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(54) Title: PROCESS FOR THE PREPARATION OF ELAFIBRANOR AND NOVEL SYNTHESIS INTERMEDIATES

(57) Abrégé/Abstract:

The present invention relates to a process for the preparation of elafibranor and novel synthesis intermediates.

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(54) Title: PROCESS FOR THE PREPARATION OF ELAFIBRANOR AND NOVEL SYNTHESIS INTERMEDIATES

(57) Abstract: The present invention relates to a process for the preparation of elafibranor and novel synthesis intermediates.

WO 2019/025017 A1

procedure can only be carried out when the carboxylic group of compound (b) is esterified. Of course, this implies the additional hydrolyzing step in order to obtain elafibranor.

WO2005/005369 discloses a process for the manufacture of elafibranor which also comprises the process of Scheme 2, wherein R is a protecting group cleavable in acidic conditions, followed by the necessary acidic hydrolysis of said protecting group.

As it will be shown in the following description and examples, the known processes involve many drawbacks.

There is a need to provide novel processes for the preparation of elafibranor, which imply short reactions, limited side reaction, limited reaction steps and give high overall yields.

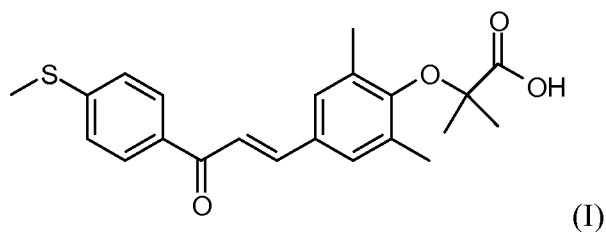
Objects of the invention

It is an object of the invention to provide a new and effective process for the preparation of elafibranor, which implies few reaction steps and which is industrially feasible and cost-effective.

It is a further object of the invention to provide novel synthesis intermediates and their use in the preparation of elafibranor.

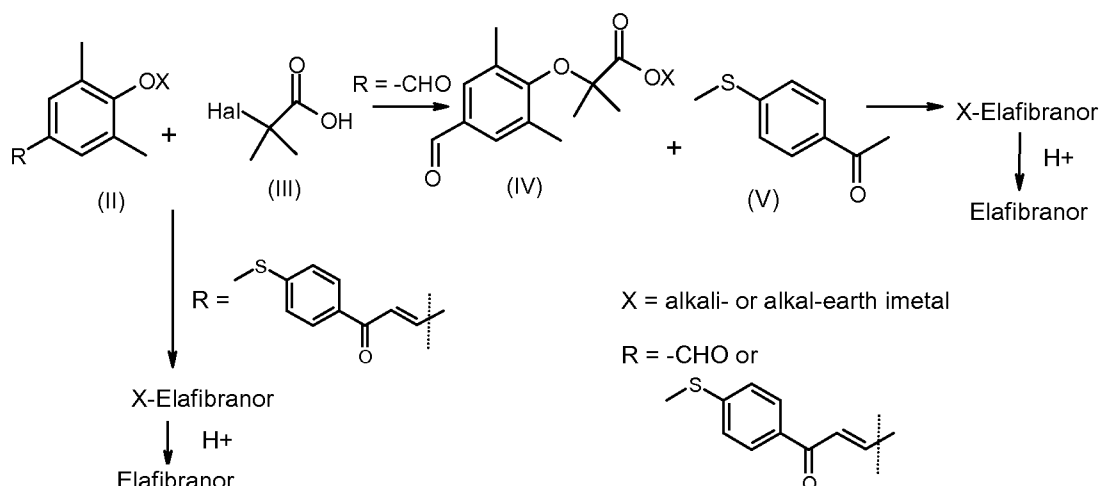
Description of the invention

According to one of its aspects, the present invention relates to a process for the manufacture of elafibranor of formula (I)



according to the following Scheme 2:

Scheme 2

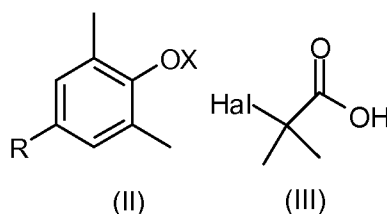


wherein the dotted line indicates the bond by which said group is linked to the remaining part of the molecule.

According to Scheme 2, it is possible to carry out the alkylation reaction on compound (II) when R is $-\text{CHO}$ or on compound (II) wherein R is 4-methylthiophenyl-propenyl-2-one. In the first case, a second reaction with compound (V) must be carried out. In this case, it was surprisingly found out that the above synthesis may be performed as a one-pot reaction wherein all compounds (II), (III) and (V) are loaded in the same reaction mixture. The process is carried out in an aprotic solvent which is optionally in admixture with a polar co-solvent. Except for the conversion of elafibranor salt into elafibranor, the process is carried out in basic conditions using a strong base.

So, according to Scheme 2, the invention provides a process for the preparation of elafibranor and its salts, which comprises:

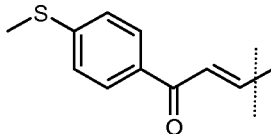
- 15 a. mixing compounds (II) and (III)



wherein

- X is an alkali—or a alkali-earth metal

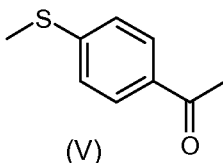
- R is -CHO or



wherein the dotted line indicates the bond by which said group is linked to the remaining part of the molecule; in an aprotic solvent, which is optionally in admixture with a protic co-solvent, in the presence of a strong base;

5

- b. preferably heating the mixture of step (a) and, when R is -CHO, adding 4' (methylthio)acetophenone of formula (V)



to the mixture;

10

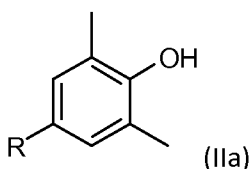
- c. acidifying the mixture after step (b) with an acidic solution to achieve elafibranor; and
d. optionally isolating and optionally purifying elafibranor thus obtained.

Intermediate compound (IV) does not need to be isolated, however, if needed or desired, it can be prepared, isolated and optionally purified according to the methods known in the art.

15

Compounds (IIa), (III) and (V) are known in the art.

According to a preferred embodiment, compound (II) is prepared by dissolving a compound of formula (IIa)



20

wherein R is as defined in Scheme 2, in an aprotic solvent, in the presence of a strong base, to obtain the compound of formula (II).

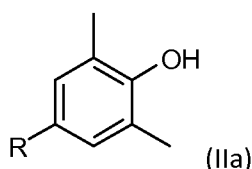
According to a preferred embodiment, the process of the invention is a one-pot reaction and comprises the following steps:

- a'. in an aprotic solvent comprising (II) or (IIa), optionally in the presence of a protic co-solvent and in the presence of a strong base, preferably sodium or potassium hydroxide;
- b'. preferably heating the mixture (a') and adding (III) and, when R is –CHO, also (V);
- c'. acidifying the mixture after step (b') with an acidic solution to achieve elafibranor; and
- d'. optionally isolating and optionally purifying elafibranor thus obtained.

According to a preferred embodiment, step (b) and (b') is carried out at a temperature of 20 to 70°C, preferably of 45 to 60°C, more preferably of 50 to 55°C.

According to a preferred embodiment, the process of the invention comprises the following steps:

- a''. dissolving a compound of formula (IIa)



- wherein R is as defined in Scheme 2, in an aprotic solvent, optionally in the presence of a protic co-solvent and in the presence of a strong base preferably selected from sodium hydroxide and potassium hydroxide, to obtain the compound of formula (II) as herein defined;

- b''. heating the mixture of step (a'') at a temperature of 20 to 70°C, preferably of 45 to 60°C, more preferably of 50 to 55°C, and adding a solution of 2-halo-2-methylpropanoic acid (III) and, when R is –CHO, also 4'-(methylthio)acetophenone (V);
- c''. acidifying the mixture after step (b'') with an acidic solution to achieve elafibranor, and
- d''. optionally isolating and optionally purifying elafibranor thus obtained.

The purification of elafibranor is preferably carried out by crystallization, more preferably from toluene or from a mixture of toluene and heptane.

According to a preferred embodiment, aprotic solvents are selected from hydrocarbons C₅- C₁₂- alkanes, alkenes, cycloalkanes and cycloalkenes; aromatic
 5 solvents such as toluene and xylenes; halogenated solvents; ketones; esters; heterocyclic solvents such as pyridine; and ethers such as tetrahydrofuran (THF), diethyl ether (Et₂O), methyl *tert*-butyl ether (MTBE), diisopropyl ether (DIPE), dibutyl ether (Bu₂O), 1,2-dimethoxyethane (DME). Ethers such as 1,4-dioxane, THF and their mixtures are preferred, THF being most preferred.

10 A polar solvent may be present in the reaction mixture of the process of the invention, as a co-solvent. Preferably, polar aprotic solvents are selected from dimethylformamide (DMF), dimethylacetamide (DMA), acetonitrile, dimethyl sulfoxide (DMSO), sulfolane, N-methyl-2-pyrrolidone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI), hexamethylphosphoramide (HMPA), N,N'-
 15 dimethylpropyleneurea (DMPU). Preferably, polar protic solvents are selected from water, alcohols, diols and their mixtures, acetonitrile, sulfolane. n-propanol and 1,4-butandiol are preferred, n-propanol being more preferred.

According to a preferred embodiment, when R is -CHO, a polar co-solvent is also present in the reaction mixture, preferably a polar aprotic co-solvent.

20 Ratios (vol/vol) of aprotic solvent to polar solvent are preferably, but not limited to, approx. 4:1 for n-propanol, approx. 9:1 for 1,4-butandiol and approx. 20:1 for water, acetonitrile and sulfolane.

The strong base used in the process of the invention is selected from hydroxides, alkoxydes, hydrides, amides, diethylamides, diisopropylamides,
 25 tetramethylpiperidides and hexamethyl disilazides of alkali metals and alkaline earth metals or strong organic bases such as N,N-diisopropylethylamine, DBU, DBN, quinuclidine, DABCO, Barton base or other guanidine derivatives, and phosphazene bases.

Sodium and potassium hydroxides are preferred strong bases, preferably sodium
 30 hydroxide, advantageously solid sodium hydroxide, such as powdered, pellets,

flakes, and bead sodium hydroxide; particularly preferred is pulverized solid sodium hydroxide.

According to a preferred embodiment, the process is carried out under vigorous stirring.

- 5 The reaction is completed in a very short time, such as 1 to 6 hours, generally 2-3 hours. The skilled man is anyway perfectly able to check the development of the reaction, for instance by using chromatographic techniques.

According to a preferred embodiment, when the reaction of step (b), (b') and (b'') is completed, a basic aqueous solution is added, for instance an aqueous solution of
10 sodium hydroxide and the organic solvent is distilled off.

The mixture is then worked up according to the methods known in the art to provide elafibranol sodium or potassium salt, which is converted to elafibranol by acidification. Examples of work up techniques are provided in the Experimental Section, as illustrative examples of the invention.

- 15 With respect to the starting compound (IIa) wherein R is 4-methylthiophenyl-propenyl-2-one, the base, preferably a hydroxide, is preferably used in a molar excess, such as for example in a 2.5-5 molar excess, more preferably in about a 3.5 molar excess, while compound (III) is preferably used in a 1.5-5 molar excess, more preferably in about a 2-3 molar excess.

- 20 When in compound (IIa) R is -CHO, the same above mentioned molar excesses can be used for the hydroxide and for compound (III), whereas compound (V) is preferably used in an equimolar amount.

The process of the invention gives high yields and a very pure final product.

According to a preferred embodiment, R is -CHO.

- 25 According to a preferred embodiment, R is -CHO and the strong base is sodium hydroxide.

According to a preferred embodiment, R is -CHO, the strong base is sodium hydroxide and the solvent is THF, optionally with a polar co-solvent, preferably n-propanol.

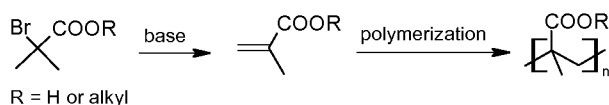
- 30 With respect to the prior art processes, the process of the invention provides the following advantages:

- less steps, thus being cost-effective;
 - lower excess of alkylation reagent (1.7 3.0 equiv. of 2-bromo-2-methylpropanoic acid vs. 6-10 equiv. of alkyl 2-bromo-2-methylpropanoate equivalents used in WO2004/005233, General method 4.
- 5
- avoiding poly(alkyl methacrylate) formation;
 - shorter reaction times;
 - higher overall yields.

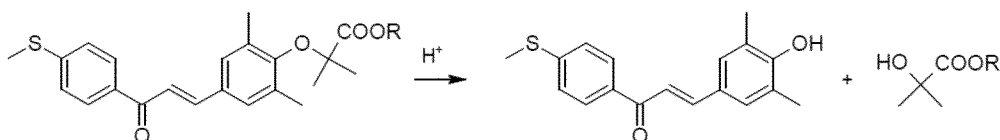
Also, compared to the known processes, the process of the invention provides limited side reactions, such as elimination, oxidative dimerization, ether hydrolysis, Nazarov

10 reaction, which may occur with the prior art processes, such as the following:

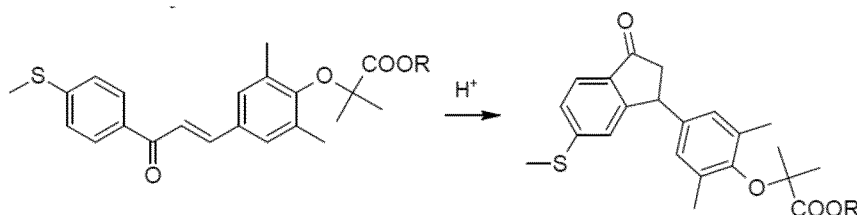
- Elimination and polymerization



- Ether hydrolysis



- 15
- Nazarov cyclization



Indeed, without willing to be bound to any theory, applicant deems that the basic principle of new process is limited solubility of phenolates and salts of organic acids in non-polar (hydrocarbons, toluene) and borderline polar solvents (ethers, ketones, esters, halogenated solvents). In the first step, sodium phenolate is precipitated from solution of phenol (IIa) by sodium hydroxide and forms suspension. Then solution of 2-bromo-2-methylpropanoic acid (together with (V)) is added and sodium salt of this acid precipitates from the solvent and suspension of sodium phenolate and sodium 2-bromo-2-methylpropanoate is formed.

20

When a weaker base (for example potassium carbonate) is used, formation of phenolate does not take place but the weaker base is usually still strong enough to trigger main side reaction – elimination, which is a severe inconvenience, either for the good outcome of the process and due to health hazard issues. In fact, the repeated exposure can lead to serious health problems.

As already mentioned the solubility of phenolate and salt of acid is limited. It means that most of the stuff is in unreactive solid form but little part remains dissolved and ready to perform formation of intermediate (IV). Intermediate (IV) is also salt of carboxylic acid and precipitates from non-polar and borderline polar solvents even more willingly than phenolate (II) and salt of (III). Precipitation of intermediate (IV) is a driving force of the reaction as it shifts the equilibrium towards the desired product.

It is therefore evident that the process of the invention provides a great technical improvement when compared to the prior art.

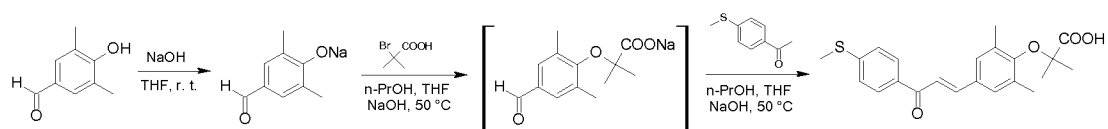
According to another of its aspects, the invention relates to the compounds of formula (II) and (IV) wherein X is Na, preferably compounds of formula (II) and (IV) wherein R is –CHO. Said compounds may be prepared as above disclosed and are particularly useful in, but not limited to, the preparation of elafibranor.

The invention will be illustrated in the following examples, which are not at all to be considered as limitative.

Experimental Section

Example 1

One pot synthesis of 1-[(4-methylthio)phenyl]-3-[(3,5-dimethyl-4-carboxydimethyloxy)phenyl]prop-2-en-1-one (Elafibranor) performed as a multicomponent reaction



4-hydroxy-3,5-dimethylbenzaldehyde (300 mg; 2.0 mmol) was dissolved in THF (6 mL), pulverized NaOH (360 mg 9.0 mmol; 4.5 equiv.) was added and mixture was stirred until sodium phenolate was formed as a greenish yellow suspension. 1-

propanol (2 mL) was added, suspension was heated to 50 °C and a solution of 2-bromo-2-methylpropanoic acid (1002 mg, 6.0 mmol; 3 equiv.) and 4-(methylthio)acetophenone (332 mg; 2.0 mmol; 1 equiv.) in THF (2 mL) was added over approximately 20 minutes. After the addition, the mixture was held at 50 °C for 2 h and solution of NaOH (400 mg; 10 mmol; 5.0 equiv.) in water (10 mL) was added. Reaction mixture was heated to reflux (66 – 67 °C), THF was distilled off and reaction was quenched by addition of 1M HCl to pH = 3.0-3.5. The mixture was taken up into MTBE and extracted with 1M Na₂CO₃. The sodium salt of product, obtained by salting out after addition of appropriate amount of NaCl, was dissolved in water, acidified with 1M HCl to pH 2.0 and extracted with toluene. The product was obtained after concentration of toluenic solution under vacuum and crystallization as a yellow solid. Isolated yield: 61%, HPLC purity: 99.4%.

¹H NMR (DMSO): δ 1.42 (s, 6H, C(CH₃)₂), 2.25 (s, 6H, Ph-CH₃), 2.57 (s, 3H, S-CH₃), 7.40 (m, 2H, H_{Ar}), 7.56 (s, 2H, H_{Ar}), 7.64 (d, *J* = 15.5 Hz, 1H, CO-CH=CH-Ph), 7.82 (d, *J* = 15.7 Hz, 1H, CO-CH=CH-Ph), 8.11 (m, 2H, H_{Ar}), 12.95 (s, 1H, COOH).

¹³C NMR (DMSO): δ 13.94 (S-CH₃), 17.53 (2Ph-CH₃), 24.98 (C(CH₃)₂), 80.68 (O-C(CH₃)₂-COOH), 120.82 (CO-CH=CH-Ph), 124.90 (2C_{Ar}H), 128.98 (2C_{Ar}H), 129.30 (2C_{Ar}H), 130.19 (C_{Ar}), 133.13 (2C_{Ar}), 133.89 (C_{Ar}), 143.31 (CO-CH=CH-Ph), 145.37 (C_{Ar}-S), 154.93 (C_{Ar}-O), 174.96 (COOH), 187.77 (C=O).

HRMS (ESI+) *m/z* [C₂₂H₂₅O₄S]⁺: calcd 385.1474; found 385.1470.

Comparative Examples according to WO2004/005233 (General method 4)

Comparative Example A

Preparation of methyl 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoate according to WO2004/005233

4-hydroxy-3,5-dimethylbenzaldehyde (150 mg; 1.0 mmol) was dissolved in acetonitrile (5 mL), potassium carbonate (691 mg; 5.0 mmol; 5 equiv.) and a solution of methyl 2-bromo-2-methylpropanoate (543 mg; 3.0 mmol; 3 equiv.) in acetonitrile (5 mL) were added. The reaction mixture was briskly stirred under reflux for 3 hrs, then the second portion of methyl 2-bromo-2-methylpropanoate (543 mg; 3.0 mmol; 3 equiv.) was added and the reaction mixture was stirred for additional 3 hrs. LC-MS

analysis showed almost complete conversion to methyl 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoate.

Comparative Example B

Preparation of 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoic acid according to WO2004/005233

4-hydroxy-3,5-dimethylbenzaldehyde (150 mg; 1.0 mmol) was dissolved in acetonitrile (5 mL), potassium carbonate (691 mg; 5.0 mmol, 5 equiv.) and a solution of 2-bromo-2-methylpropanoic acid (1002 mg; 6.0 mmol; 6 equiv.) in acetonitrile (5 mL) were added. The reaction mixture was briskly stirred under reflux for 3 hrs, then water (5 mL) was added to homogenize the mixture. LC-MS analysis showed that 2-bromo-2-methylpropanoic acid is completely converted to 2-methylacrylic acid, required product – 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoic acid – was not found in the reaction mixture.

Comparative Example C

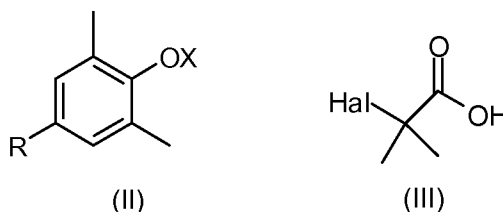
Preparation of 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoic acid according to WO2004/005233

4-hydroxy-3,5-dimethylbenzaldehyde (150 mg; 1.0 mmol) was dissolved in acetonitrile (5 mL), potassium carbonate (691 mg; 5.0 mmol; 5 equiv.) and a solution of 2-bromo-2-methylpropanoic acid (1670 mg; 10.0 mmol; 10 equiv.) in acetonitrile (5 mL) were added. The reaction mixture was briskly stirred under reflux for 3 hrs, then water (5 mL) was added to homogenize the mixture. LC-MS analysis showed that 2-bromo-2-methylpropanoic acid is completely converted to 2-methylacrylic acid, required product – 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoic acid – was not found in the reaction mixture.

Claims

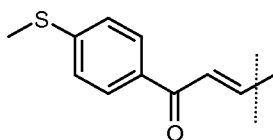
1. A process for the preparation of elafibranor which comprises:

a. mixing compounds (II) and (III)



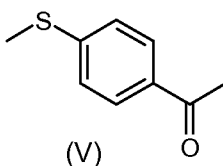
wherein

- 5 - X is an alkali—or a alkali-earth metal
 - R is –CHO or



10 wherein the dotted line indicates the bond by which said group is linked to the remaining part of the molecule; in an aprotic solvent, which is optionally in admixture with a protic co-solvent, in the presence of a strong base;

b. preferably heating the mixture of step (a) and, when R is –CHO, adding 4' (methylthio)acetophenone of formula (V)

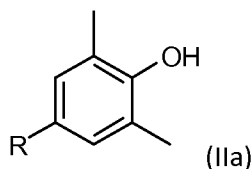


15 to the mixture;

- c. acidifying the mixture after step (b) with an acidic solution to achieve elafibranor; and
 d. optionally isolating and optionally purifying elafibranor thus obtained.

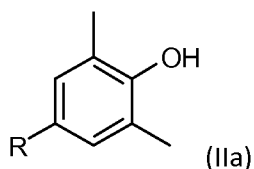
2. A one-pot process comprising the following steps:

20 a'. in an aprotic solvent comprising compound (II) or (IIa),



optionally in the presence of a protic co-solvent and in the presence of a strong base, preferably sodium or potassium hydroxide,;

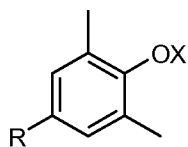
- b'. preferably heating the mixture and adding (III) and, when R is $-CHO$, also (V);
- c'. acidifying the mixture after step (b') with an acidic solution to achieve elafibranor; and
- d'. optionally isolating and optionally purifying elafibranor thus obtained.
3. The process according to claims 1 or 2, characterized in that step (b) and (b') are carried out at a temperature of 20 to 70°C, preferably of 45 to 60°C, more preferably of 50 to 55°C.
4. The process according to claims 2 or 3, characterized in that it comprises:
- a''. dissolving a compound of formula (IIa)



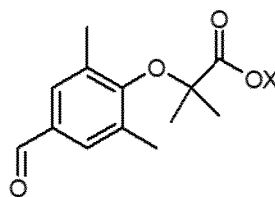
- wherein R is as defined in claim 1, in an aprotic solvent, optionally in the presence of a protic co-solvent and in the presence of a strong base preferably selected from sodium hydroxide and potassium hydroxide, to obtain the compound of formula (II) as defined in claim 1;
- b''. heating the mixture of step (a'') at a temperature of 20 to 70°C, preferably of 45 to 60°C, more preferably of 50 to 55°C, and adding a solution of 2-halo-2-methylpropanoic acid (III), when R is $-CHO$, also 4'-(methylthio)acetophenone (V);
- c''. acidifying the mixture after step (b'') with an acidic solution to achieve elafibranor, and
- d''. optionally isolating and optionally purifying elafibranor thus obtained.

5. The process according to any one of the preceding claims, characterized in that the aprotic solvent is selected from hydrocarbons C₅- C₁₂- alkanes, alkenes, cycloalkanes and cycloalkenes; aromatic solvents such as toluene and xylenes; halogenated solvents; ketones; esters; heterocyclic solvents such as pyridine; and ethers such as tetrahydrofuran (THF), diethyl ether (Et₂O), methyl *tert*-butyl ether (MTBE), diisopropyl ether (DIPE), dibutyl ether (Bu₂O) and 1,2-dimethoxyethane (DME).
6. The process according to claim 5, characterized in that the aprotic solvent is THF or 1,4-dioxane.
7. The process according to any one of the preceding claims, characterized in that the polar solvent is selected from dimethylformamide (DMF), dimethylacetamide (DMA), acetonitrile, dimethyl sulfoxide (DMSO), sulfolane, N-methyl-2-pyrrolidone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI), hexamethylphosphoramide (HMPA), N,N'-dimethylpropyleneurea (DMP, water, alcohols, diols and their mixtures, acetonitrile, sulfolane.
8. The process according to claim 7, characterized in that the protic solvent is n-propanol or 1,4-butanediol.
9. The process according to any one of the preceding claims, characterized in that R is -CHO.
10. The process according to any one of the preceding claims, characterized in that the strong base is selected from hydroxides, alkoxides, hydrides, amides, diethylamides, diisopropylamides, tetramethylpiperidides and hexamethyl disilazides of alkali metals and alkaline earth metals or strong organic bases such as N,N-diisopropylethylamine, DBU, DBN, quinuclidine, DABCO, Barton base or other guanidine derivatives, and phosphazene bases.
11. The process according to claim 10, characterized in that the strong base is sodium or potassium hydroxide.
12. The process according to claim 11, characterized in that the strong base is solid sodium salt.
13. The process according to claim 12, characterized in that said solid sodium hydroxide, is in the form of powder, pellets, flakes, or beads.

14. A compound selected from formula (II) and (IV)



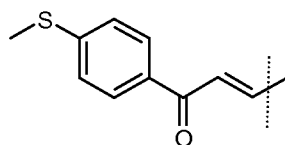
(II)



(IV)

wherein

- 5 - X is Na
 - R is -CHO or



15. The compound according to claim 14, wherein R is -CHO.
16. Use of at least a compound according to claim 14 or 15, as a synthesis
 10 intermediate.
17. Use according to claim 16 as a synthesis intermediate for the preparation of
 elafibranor.