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(54) **PROCESS FOR THE MANUFACTURE OF IVABRADINE AND OF INTERMEDIATES OF SYNTHESIS THEREOF**

VERFAHREN ZUR HERSTELLUNG VON IVABRADIN UND ZWISCHENPRODUKTEN ZU SEINER SYNTHESE

PROCÉDÉ DE FABRICATION DE L'IVABRADINE ET DE SES INTERMÉDIAIRES DE SYNTHÈSE

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(56) References cited:
EP-A1- 0 534 859 EP-A1- 1 598 333
WO-A1-2008/070909 WO-A1-2010/072409

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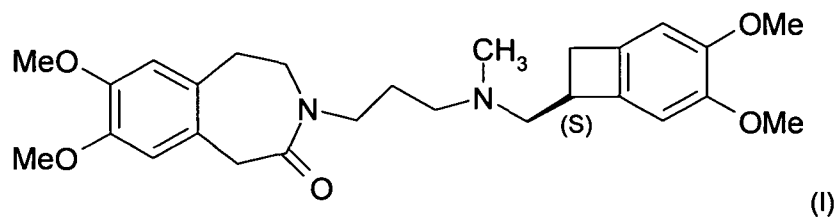
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DescriptionSummary of the invention

[0001] The present invention concerns a new process for the manufacture of ivabradine and of intermediates of synthesis thereof, in particular a new process for resolution of the corresponding racemic mixtures of said compounds.

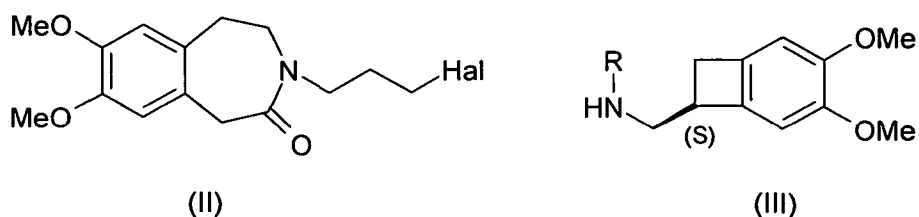
Technical background

[0002] Ivabradine or 3-[3-({[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino) propyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepine-2-one has the formula (I)



and is used in cardiology for heart failure, hypertension, angina and post-infarction treatment.

[0003] Ivabradine is therefore in an enantiomeric form, in particular in the (S) form. The most common synthesis of ivabradine entails condensation between the compounds (II) and (III) shown in the following diagram:



in which R is hydrogen or methyl and Hal is an atom of halogen.

[0004] Preparation of the intermediate amine (III) in enantiomerically pure form is the subject of numerous patents.

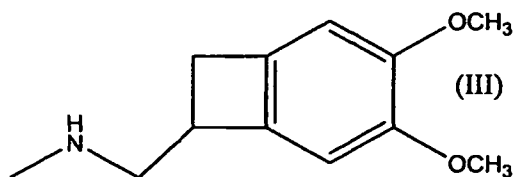
[0005] EP 0 534 859 describes preparation of the compound (III) in which R is methyl, by means of a resolution with camphorsulphonic acid with a yield of 2-3% while EP 1 598 333 describes resolution of the compound (III) in which R is hydrogen with N-acetyl-L-glutamic acid, obtaining better yields. Although said process produces good yields, it must be performed controlling the operating conditions accurately and carefully both during its use as a resolving agent and during its recovery and re-use, since the N-acetyl-L-glutamic acid can give rise to intramolecular reactions, degrading and therefore no longer being available as a reagent for the resolution.

Objects of the invention

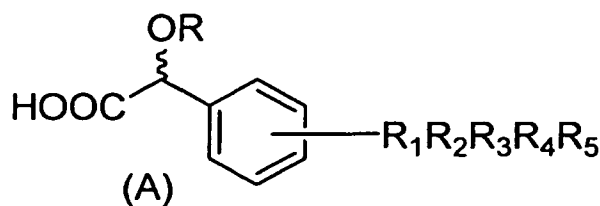
[0006] The object of the present invention is to provide a new process for the resolution of ivabradine or of its intermediates of formula (III) which is industrially applicable, and easy to be performed and cost effective.

[0007] Another object of the present invention is to provide a new process for the resolution of ivabradine or its intermediates of formula (III) which allows a simple recycling of the resolution reagent.

[0008] WO2010/072409 discloses the optical resolution of the compound having the following formula



with an optically active acid of formula



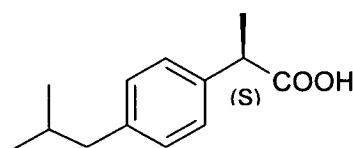
especially with (S)-mandelic acid.

10 **[0009]** D2 discloses the separation of the (S) form of salbutamol with (S)-ibuprofen.

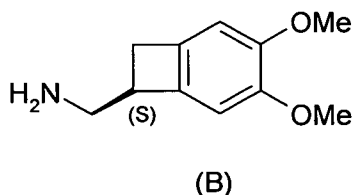
[0010] None of the two documents disclose or suggest the resolution of a primary amine with (S)-ibuprofen.

Description of the invention

15 **[0011]** The (S)-ibuprofen has the following structural formula



25 **[0012]** Thus, according to one of its aspects, the invention concerns a process for the preparation of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane of formula (B)



which comprises

- 35 (i) reacting the 4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane in racemic form with (S)-ibuprofen in an organic solvent;
 (ii) stirring the solution at ambient temperature until a precipitate is obtained;
 (iii) treating the precipitate formed in step (vi) with a base to release the compound (B) in the (S) form; and
 40 (iv) optionally isolating the compound of formula (B) in the (S) form.

Brief description of the drawings

45 **[0013]**

Figure 1 shows the ¹H-NMR spectrum of the intermediate (C).

Figure 2 shows the X ray diffraction spectrum of the intermediate (C).

Figure 3 shows the DSC graph of the intermediate (C).

Figure 4 shows the TGA graph of the intermediate (C).

50 **[0014]** According to the invention, the (S)-ibuprofen is used in an at least equimolar quantity, advantageously in a molar quantity at least double with respect to the racemic starting compounds. According to a preferred embodiment, the (S)-ibuprofen is used in a molar quantity approximately triple that of the racemic starting compounds.

55 **[0015]** As organic solvent, any organic solvent able to dissolve the racemic starting compounds can be used according to the invention; preferred organic solvents are apolar solvents, for example chosen from among the aromatic hydrocarbons, aliphatic hydrocarbons, acetonitrile and their mixtures.

[0016] Suitable solvents include toluene, hexane, heptane, cyclohexane, acetonitrile and their mixtures.

[0017] The expression "reacting" here indicates mixing the racemic starting compounds and the (S)-ibuprofen in the

chosen organic solvent. The racemic starting compounds and the (S)-ibuprofen can be previously and separately dissolved in the chosen organic solvent.

[0018] The reaction between the racemic starting compounds and the (S)-ibuprofen does not require heating and can be performed at ambient temperature. If desired or necessary, the mixture of step (i) can also be heated, up to a temperature of approximately 50-60°C, preferably up to 40-50°C, for example around 40-45°C.

[0019] After mixing it is stirred for a few hours, for example 10-30 hours, advantageously approximately 24 hours, after which the precipitation of a compound occurs.

[0020] The compound obtained in step (ii) can be isolated according to the known techniques, for example by filtering.

[0021] In step (iii), the compound obtained in step (ii) can be treated with a basic aqueous solution and the desired compound can be obtained by extraction with a water-immiscible organic solvent.

[0022] In practice, it is possible to suspend the compound obtained in step (ii) in water, add a base up to basic pH, then extract the compound (B) in the (S) form with a water-immiscible organic solvent. The organic solution containing the desired compound can be used as is for any subsequent reactions or the desired compound can be isolated according to the methods known to a person skilled in the art.

[0023] The base used in step (iii) can be organic, for example triethylamine, or inorganic, for example sodium bicarbonate, sodium or potassium hydroxide, etc.

[0024] The organic solvent can be any water-immiscible organic solvent, for example toluene, ethyl acetate, dichloromethane, etc.

[0025] The (S)-ibuprofen remaining in the aqueous phase can be simply recovered and reused via techniques known to a person skilled in the art such as extraction of the (S)-ibuprofen with water-immiscible organic solvents or by precipitation and filtering of the (S)-ibuprofen from the aqueous phase after acidification of the solution with strong inorganic acids, for example hydrochloric acid, sulphuric acid, etc., or organic acids, for example trifluoroacetic acid, methanesulphonic acid, p-toluenesulphonic acid, etc.

[0026] It has been unexpectedly observed that when a quantity higher than the stoichiometric quantity of (S)-ibuprofen is used (i.e. when the ratio in moles between (S)-ibuprofen and the racemic starting compound (B) is higher than 1, for example equal to or higher than 2), the precipitate that forms is not a simple salt of the compound (B) in the (S) form with the (S)-ibuprofen but is a co-crystal which comprises the compound (B) in the (S) form and the (S)-ibuprofen in the proportion 1:2, which contains a molecule of compound (B) in the (S) form and two molecules of (S)-ibuprofen.

[0027] In particular, the co-crystal is formed of a salt of compound (B) in the (S) form and a molecule of (S)-ibuprofen, solvated with a further molecule of (S)-ibuprofen.

[0028] Said co-crystal can be isolated according to the known methods, for example by filtering and, if necessary or desired, can be further purified, for example by re-suspension in a solvent and subsequent filtering or crystallisation.

[0029] It has been noted that said co-crystal precipitates with good yields and is a stable and easily workable compound. If desired or necessary, the product can be purified, for example by means of one or more crystallisations, to increase the enantiomeric excess.

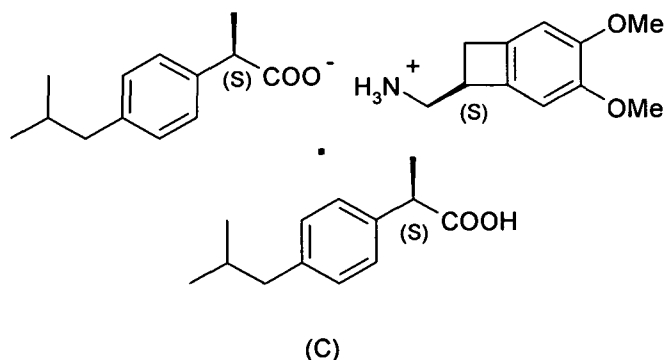
[0030] According to a preferred embodiment, in order to directly obtain the crystal with a good enantiomeric excess, it is expedient to include a small quantity of crystal in pure form in the reaction solution. In this way the desired crystalline compound is obtained with excellent yields and high enantiomeric purity.

[0031] The co-crystal formed in step (vi), i.e. the co-crystal formed of a molecule of compound of formula (B) in the (S) form and two molecules of (S)-ibuprofen, was characterised by ¹H NMR, X ray diffraction, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The results of these characterisations are reported in the experimental section of the present description and in the attached figures.

[0032] Said co-crystal, formed as described above in step (ii) reported above and better explained in the experimental section, is therefore composed of the salt formed of a molecule of the compound of formula (B) in the (S) form and a molecule of (S)-ibuprofen, co-crystallised with another molecule of (S)-ibuprofen, and is the compound:

(S)-ibuprofenate of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane

(S)-ibuprofen, having the following formula (C)



[0033] Figure 1 shows the ^1H NMR spectrum of the compound (C) and Figure 2 shows the X ray powder diffraction (XRPD) spectrum of the compound (C).

[0034] The co-crystal of formula (C) is a new compound and constitutes a further subject of the present invention, as does its use for the preparation of a compound chosen from (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane and ivabradine.

[0035] The process of the invention therefore unexpectedly and surprisingly allows, for example, the compound (B) to be obtained using the molecule of the (S)-ibuprofen (which is normally used in therapy as an anti-inflammatory drug, rather than as a resolution agent) with excellent yields and in a simple industrially feasible manner, as also illustrated in the experimental section of the present description.

[0036] The invention will now be better described via the following illustrative non-limiting examples.

Experimental section

Proton nuclear magnetic resonance

[0037] The ^1H NMR spectra were recorded in deuterated dimethyl sulphoxide with a Varian Mercury 400 spectrophotometer, equipped with a 5 mm ATB 1H/19F/X broadband probe. The spectra were acquired by dissolving 5-10 mg of sample in 0.6 ml of deuterated solvent.

X ray diffraction

[0038] The XRPD analysis was performed using a Philips XPert diffractometer with Cu K α radiations in Bragg-Brentano geometry. The system is equipped with RTMS (Real Time Multiple Strip) multidetector. The diffraction pattern was recorded from 3° to 40° (2 θ) at a scanning speed of 17.7° per minute.

DSC

[0039] The DSC analysis was recorded with a Mettler DSC822°. A 5.3140 mg sample was weighed in a 40 microl aluminium crucible with perforated cover and heated under nitrogen (50ml/min) at 10°C/minute from 30 to 200°C. The endothermic peak corresponding to the melting point begins at 117.82°C (melting enthalpy - 95.11J/g). The graph is shown in Figure 3.

TGA

[0040] The thermogravimetric analysis was recorded in a Mettler TGA/SDTA851° thermogravimetric analyser. A sample of 6.2067 mg was weighed in a 70 microl aluminium crucible with perforated cover and heated under nitrogen (50ml/min) at 10°C/minute from 30 to 200°C. The analysis did not show loss of water at temperatures below the melting point. The graph is shown in Figure 4.

Chiral high performance liquid chromatography (chiral HPLC)

Direct analysis of the co-crystal

[0041] The samples were prepared by dissolving the co-crystal in methanol (2mg/ml). The enantiomeric excess (e.e.) was measured with Agilent Technologies HP1100 apparatus equipped with UV/vis photodiode array detector. Ethanol

containing 0.1% diethylamine at a flow speed of 0.4 ml/minute through a Chiralpack IA column was used as the mobile phase. The samples were analysed at 220 nm:

Rt = 12.1 min (1R)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane

Rt = 12.3 min (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane (Compound (B))

Analysis of (1R) and derivatized (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane

[0042] The co-crystal was treated with a biphasic mixture of dichloromethane and aqueous NaOH. The aqueous phase was extracted with dichloromethane and the reunited organic extracts were dry-evaporated. The derivatization of the compound was performed by reaction with methyl chloroformate in toluene-methanol-water in the presence of sodium bicarbonate.

[0043] The samples were prepared by dissolving a compound derivatized in heptane: isopropyl alcohol (95:5.2 mg/ml). The enantiomeric excess (e.e.) was measured with Agilent Technologies HP1100 apparatus equipped with UV/vis photodiode array detector. Heptane:IPA (95:5) at a flow speed of 0.4 ml/minute through a Chiralpack IA column was used as the mobile phase. The samples were analysed at 220 nm:

Rt = 16.2 min derivatized (1R)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane

Rt = 20.3 min derivatized (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane (Compound (B)).

Example 1

Preparation of (S)-ibuprofenate of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane • (S)-ibuprofen

Example 1a: preparation of the title compound

[0044] A solution of 5.65 g (29.2 mmoles) of 4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane racemate in 30 ml of acetonitrile is added at ambient temperature, in 25 minutes, to a 100 ml three-necked flask with mechanical stirrer, metering funnel and thermometer, containing 18.12 g (87.8 mmoles) of S-ibuprofen dissolved in 27 ml of acetonitrile. A slight exothermic reaction is noted during the addition. At the end, the mixture is stirred for 24 hours at ambient temperature, after which the resulting precipitate is filtered, washed with acetonitrile and dried in a vacuum at ambient temperature to obtain the title compound as a white solid (7.12 g, yield 40%).

Example 1b: crystallization

[0045] 1 g (1.65 mmoles) of the compound obtained in example 1a is dissolved in 6 ml of acetonitrile by heating in a bath at 58°C. The solution is then stirred at ambient temperature for 18 hours. The resulting solid is filtered and washed with acetonitrile, then dried in a vacuum at ambient temperature to give the title compound. The crystallization is repeated until the title compound is obtained with an e.e. of 98.0% HPLC.

Example 2

Preparation of (S)-ibuprofenate of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane • (S)-ibuprofen

[0046] The procedure is the same as in Example 1a, but after stirring the mixture for 19 hours, instead of 24 hours, it is heated to 42°C (internal) for one hour, seeded with a crystal of the title compound and then stirred for 4 hours at ambient temperature. In this way the title compound is obtained as a white solid with yield of 38% (e.e. 86.6% HPLC).

Example 3

Preparation of (S)-ibuprofenate of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane • (S)-ibuprofen

Example 3a

[0047] 4.35 g (21.1 mmoles) of (S)-ibuprofen are added, at ambient temperature, to a 100 ml three-necked flask with mechanical stirrer and thermometer, containing a suspension of 1.36 g (7.04 mmoles) of 4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane racemate in cyclohexane, and seeded with a crystal of the title compound. The mixture is stirred for 24 hours at ambient temperature, after which the resulting precipitate is filtered, washed with cyclohexane

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and dried in a vacuum at ambient temperature to obtain the title compound as a white solid (1.82 g, yield 43%, e.e. 74.6% HPLC).

Example 3b

[0048] The compound thus obtained is purified by re-suspension in acetonitrile, stirring for 24 hours, and subsequent filtering to obtain the title compound as a white solid (e.e. 96.6% HPLC).

¹H NMR (dmso, 400 MHz): d = 7.18-7.13 (m, 4H); 7.07-7.02 (m, 4H); 6.86 (s, 1H); 6.75 (s, 1H); 3.67 (s, 6H); 3.52 (q, *J* = 7.0 Hz, 2H); 3.44-3.36 (m, 1H); 3.09 (dd, *J* = 4.7 Hz, *J* = 13.7 Hz, 1H); 2.89 (dd, *J* = 6.6 Hz, *J* = 12.5 Hz, 1H); 2.80 (dd, *J* = 7.8 Hz, *J* = 12.5 Hz, 1H); 2.70 (dd, *J* = 1.9 Hz, *J* = 13.7 Hz, 1H); 2.38 (d, *J* = 7.0 Hz, 4H); 1.84-1.71 (m, 2H); 1.29 (d, *J* = 7.0 Hz, 6H); 0.83 (d, *J* = 6.6 Hz, 12H) (Figure 1).

[0049] X ray diffraction, peaks with intensity equal to or higher than 1%

Position [°2Th.]	d-spacing [Å]	Relative intensity [%]
4.95	17.84	33
6.06	14.59	100
6.40	13.81	5
8.98	9.85	2
9.70	9.12	7
9.88	8.95	4
12.7	7.33	1
13.21	6.70	13
14.00	6.32	3
14.52	6.10	2
14.79	5.99	3
14.96	5.92	2
15.64	5.67	1
16.38	5.41	3
16.91	5.24	8
17.13	5.18	7
17.49	5.07	5
17.84	4.97	5
18.63	4.76	1
19.20	4.62	14
19.61	4.53	3
20.00	4.44	2
20.38	4.36	18
21.99	4.04	12
22.51	3.95	4
23.00	3.86	6
23.08	3.85	7
23.48	3.79	4
23.67	3.76	2
24.24	3.67	3

(continued)

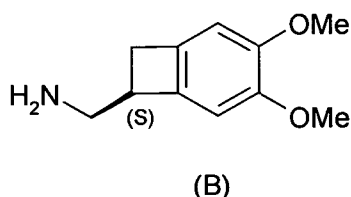
Position [°2Th.]	d-spacing [Å]	Relative intensity [%]
25.37	3.51	2
26.85	3.32	1
27.25	3.27	5
28.42	3.14	1
29.13	3.07	2
29.83	2.99	1
33.55	2.67	1

Example 5**Preparation of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane**

[0050] An aqueous solution of 10% sodium hydroxide is added to a suspension of 1.00 g (5.18 mmoles) of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane in 10 ml of water up to pH 8. Ethyl acetate is then extracted (3x10 ml). The reunited organic phases are dried on sodium sulphate and the solvent is evaporated in a vacuum. In this way 0.30 g of title compound are obtained.

Claims

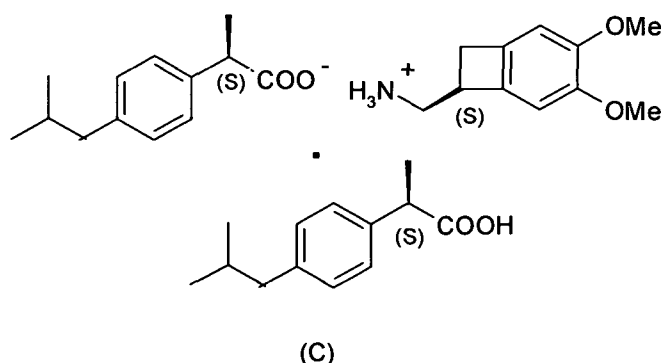
1. Process for the preparation of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane of formula (B)



which comprises:

- (i) reacting racemic 4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane with (S)-ibuprofen in an organic solvent;
 - (ii) stirring the solution at room temperature until a precipitate occurs;
 - (iii) treating the precipitate formed in step (ii) with a base to release compound (B) in its (S) form; and;
 - (iv) optionally isolating compound of formula (B) in its (S) form.
2. Process according to claim 1, wherein (S)-ibuprofen is used in an at least double amount with respect to the racemic starting compounds.
 3. Process according to claim 2, wherein (S)-ibuprofen is used in an at least triple amount with respect to the racemic starting compounds.
 4. Process according to any one of claims 1 to 3, wherein said organic solvent is selected from acetonitrile and cyclohexane.
 5. Process according to any one of claims 1 to 4, wherein the precipitate formed in step (ii) is treated with a aqueous basic solution and extracted with a water immiscible organic solvent.
 6. (S)-ibuprofenate of (1S)-4,5-dimethoxy-1-(ammoniummethyl)-benzocyclobutane · (S)-ibuprofen having the following

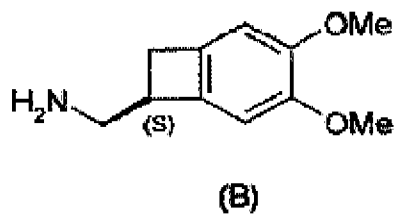
formula (C)



7. Use of compound (C) of claim 6, for the preparation of a compound selected from (1S)-4,5-dimethoxy-1-(aminomethyl)-benzocyclobutane and ivabradine.

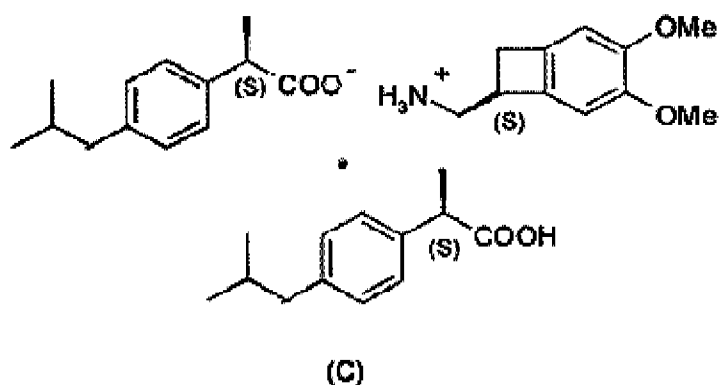
Patentansprüche

1. Verfahren zur Herstellung von (1S)-4,5-Dimethoxy-1-(aminomethyl)-benzocyclobutan der Formel (B)



umfassend

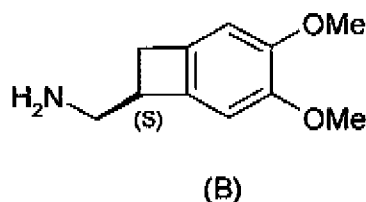
- (i) Umsetzen racemisches 4,5-Dimethoxy-1-(aminomethyl)-benzocyclobutan mit (S)-Ibuprofen in einem organischen Lösungsmittel;
 - (ii) Rühren der Lösung bei Raumtemperatur bis ein Niederschlag auftritt;
 - (iii) Behandlung des in Schritt (ii) gebildeten Niederschlags mit einer Base, um die Verbindung (B) in ihrer (S)-Form freizusetzen; und;
 - (iv) gegebenenfalls Isolieren der Verbindung der Formel (B) in ihrer (S)-Form.
2. Das Verfahren gemäß Anspruch 1, wobei (S)-Ibuprofen in einer wenigstens doppelten Menge bezogen auf die racemischen Ausgangsverbindungen eingesetzt wird.
 3. Das Verfahren gemäß Anspruch 2, wobei (S)-Ibuprofen in einer wenigstens dreifachen Menge bezogen auf die racemischen Ausgangsverbindungen eingesetzt wird.
 4. Das Verfahren gemäß irgendeinem der Ansprüche 1 bis 3, wobei das organische Lösungsmittel ausgewählt ist aus Acetonitril und Cyclohexan.
 5. Das Verfahren gemäß irgendeinem der Ansprüche 1 bis 4, wobei der in Schritt (ii) gebildete Niederschlag mit einer wässrigen basischen Lösung behandelt und mit einem mit Wasser nicht mischbaren organischen Lösungsmittel extrahiert wird.
 6. (S)-Ibuprofen-Salz von (1S)-4,5-Dimethoxy-1-(aminomethyl)-Benzocyclobutan · (S)-Ibuprofen mit der folgenden Formel (C)



7. Verwendung der Verbindung (C) gemäß Anspruch 6 zur Herstellung einer Verbindung ausgewählt aus (1S)-4,5-Dimethoxy-1-(aminomethyl)-benzocyclobutan und Ibuprofen.

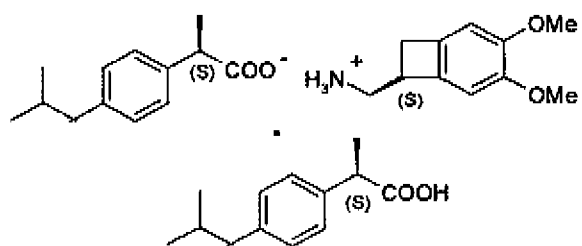
Revendications

1. Procédé de préparation du (1S)-1,5-diméthoxy-1-(ammoniumméthyl)-benzocyclobutane de formule (B)



qui comprend :

- (i) la réaction de 4,5-diméthoxy-1-(ammoniumméthyl)-benzocyclobutane racémique avec du (S)-ibuprofène dans un solvant organique ;
 - (ii) l'agitation de la solution à la température ambiante jusqu'à ce qu'un précipité se forme ;
 - (iii) le traitement du précipité formé dans l'étape (ii) avec une base pour libérer le composé (B) sous sa forme (S) ; ; et
 - (iv) éventuellement l'isolement du composé de formule (B) sous sa forme (S).
2. Procédé selon la revendication 1, dans lequel le (S)-ibuprofène est utilisé au moins en une quantité double de celle des composés racémiques de départ.
3. Procédé selon la revendication 2, dans lequel le (S)-ibuprofène est utilisé au moins en une quantité triple de celle des composés racémiques de départ.
4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel ledit solvant organique est choisi parmi l'acétonitrile et le cyclohexane.
5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le précipité formé dans l'étape (ii) est traité avec une solution aqueuse basique et extraite avec un solvant organique immiscible avec l'eau.
6. (S)-Ibuprofénate de (1S)-4,5-diméthoxy-1-(ammoniumméthyl)-benzocyclobutane - (S)-ibuprofène ayant la formule (C)



(C)

7. Utilisation du composé (C) selon la revendication 6, pour la préparation d'un composé choisi parmi le (1S)-4,5-diméthoxy-1-(ammoniumméthyl)-benzocyclobutane et l'ivabradine.

Fig. 1

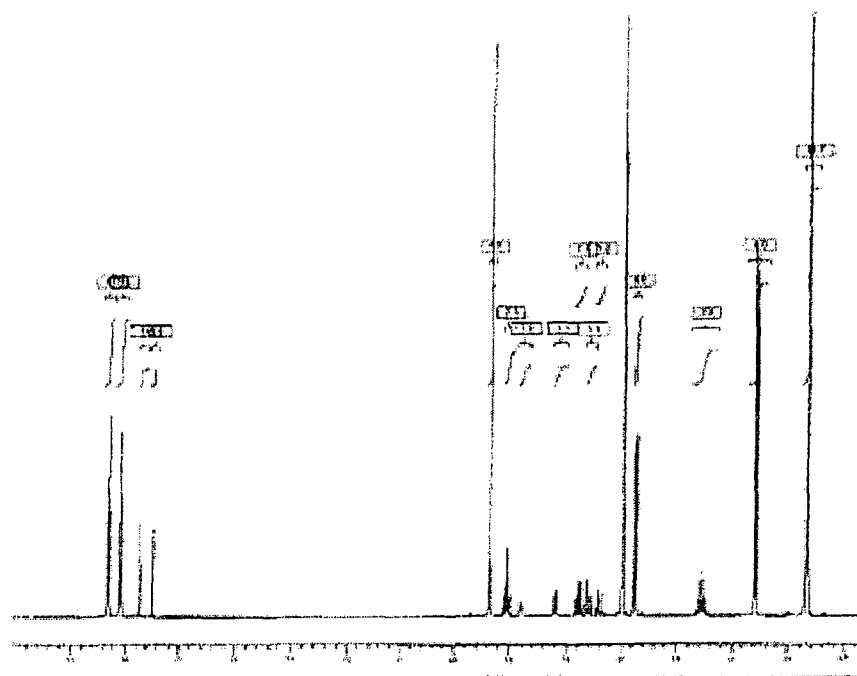


Fig. 2

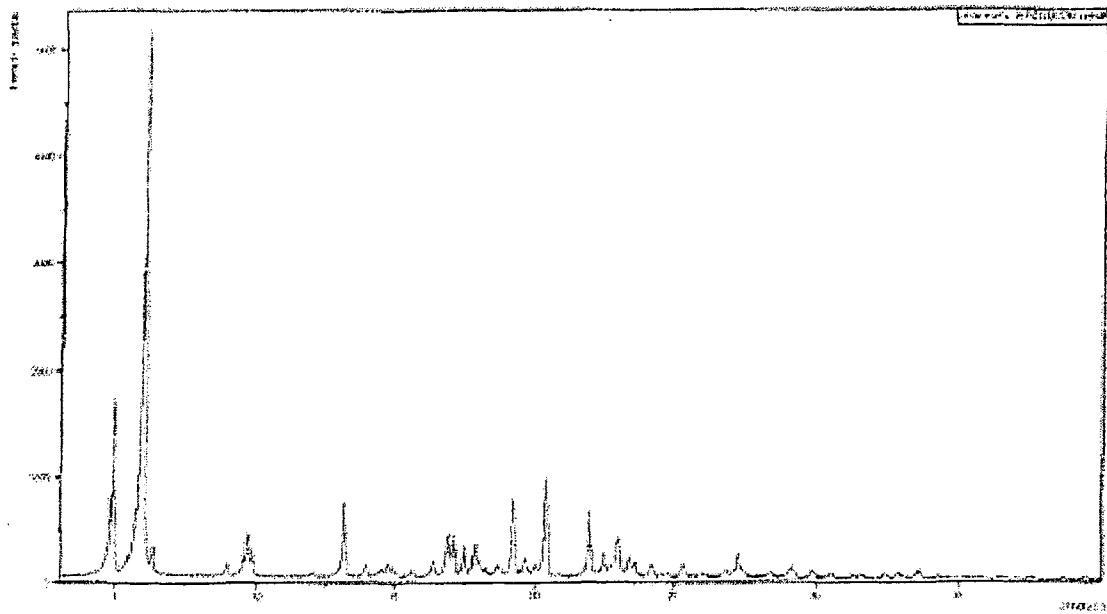


Fig. 3

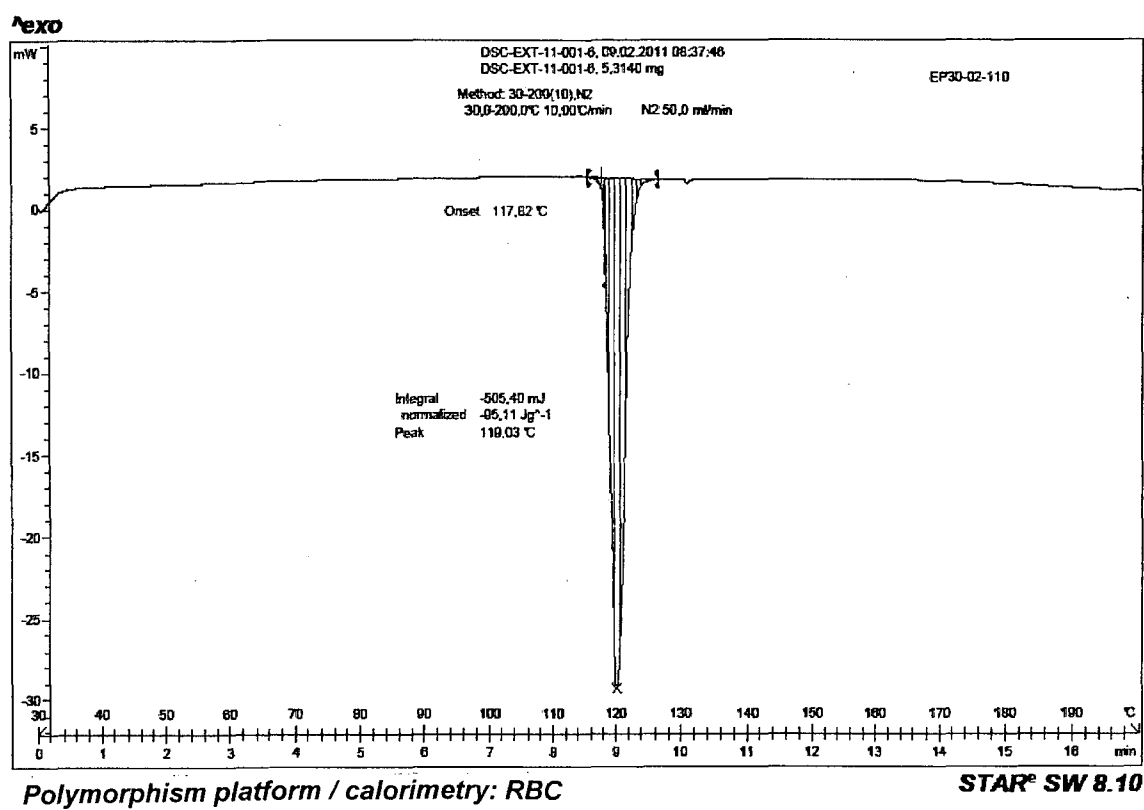
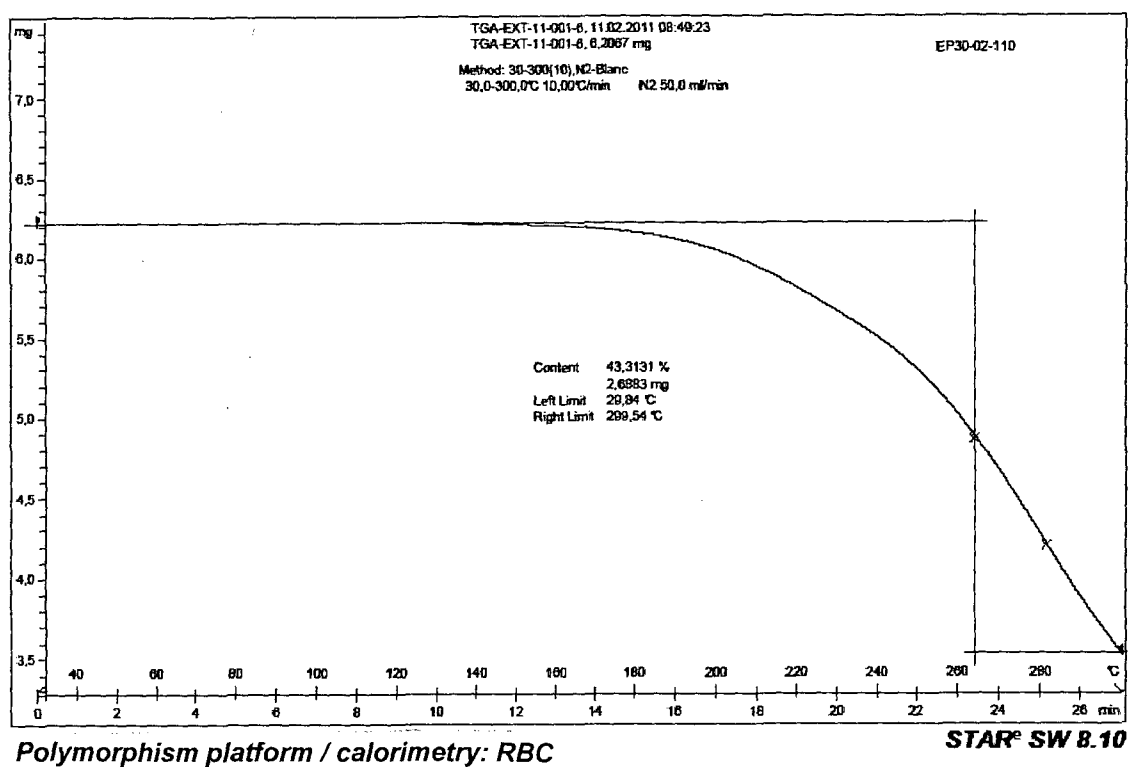


Fig. 4



REFERENCES CITED IN THE DESCRIPTION

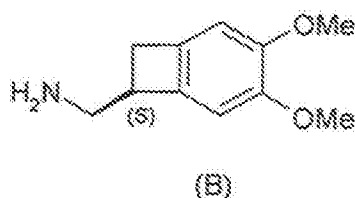
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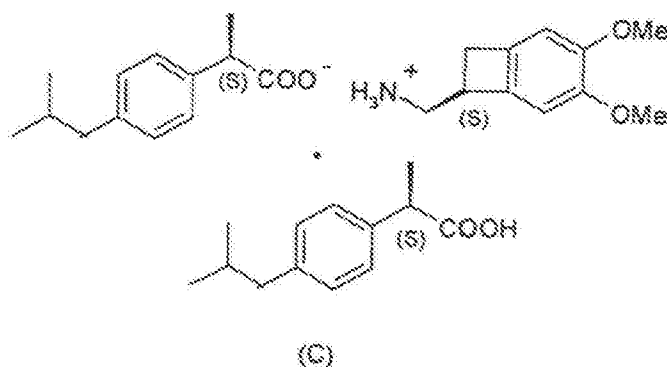
**ELJÁRÁS IVABRADIN ELŐÁLLÍTÁSÁRA, ÉS ELJÁRÁS SZINTÉZISE KÖZTES TERMÉKÉNEK ELŐÁLLÍTÁSÁRA
SZABADALMI IGÉNYPONTOK**

1. Eljárás a (B) képletű (1S)-4,5-dimetoxi-1-(ammónium-metil)-benzociklobután előállítására



amely eljárás a következő lépéseket tartalmazza:

- (i) reagáltatunk racém 4,5-dimetoxi-1-(ammónium-metil)-benzociklobutánt (S)-ibuprofénnel egy szerves oldószerben;
 - (ii) az oldatot kevertetjük szobahőmérsékleten, amíg csapadék nem jön létre;
 - (iii) a (ii) lépésben kialakult csapadékokat kezeljük egy bázissal, hogy a (B) vegyületet (S) formájában bocsássa ki, és
 - (iv) kívánt esetben izoláljuk a (B) képletű vegyületet (S) formájában.
2. Az 1. igénypont szerinti eljárás, ahol az (S)-ibuprofént legalább kétszeres mennyiségben alkalmazzuk a racém kiindulási vegyületekre vonatkoztatva.
3. Az 1. igénypont szerinti eljárás, ahol az (S)-ibuprofént legalább háromszoros mennyiségben alkalmazzuk a racém kiindulási vegyületekre vonatkoztatva.
4. Az 1-3. igénypontok bármelyike szerinti eljárás, ahol az említett szerves oldószer a következők közül választható ki: acetonitril és ciklohexán.
5. Az 1-4. igénypontok bármelyike szerinti eljárás, ahol az (ii) lépésben keletkezett csapadékot vizes bázisos oldattal keverjük, és vízzel nem elegyedő szerves oldószerrel extraháljuk.
6. (1S)-4,5-dimetoxi-1-(ammónium-metil)-benzociklobután (S)-ibuprofenáttal, (S)-ibuprofénnel, amely a következő (C) képlettel bír:



7. Alkalmazása a 6. igénypont szerinti (C) vegyületnek egy vegyület előállítására, amely a következők közül választható ki: (1S)-4,5-dimetoxi-1-(ammónium-metil)-benzociklobután és ivabradin.