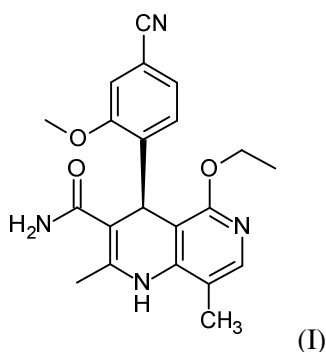
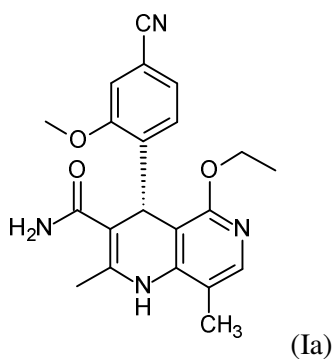
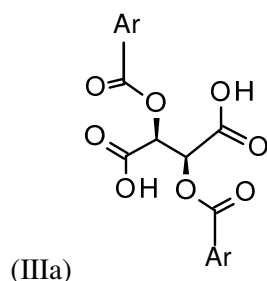
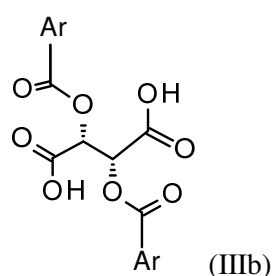


Method for the preparation of (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide by racemate separation by means of diastereomeric tartaric acid esters

The present invention relates to a novel and improved process for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the formula (I)



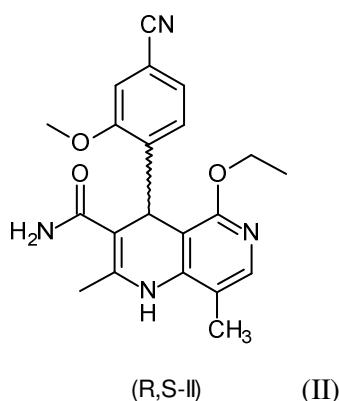
- 5 and also to the preparation of the enantiomer (Ia) by racemate resolution using chiral substituted tartaric acid esters of the general formulae (IIIa) and (IIIb)



where Ar represents a substituted or unsubstituted aromatic or heteroaromatic radical.

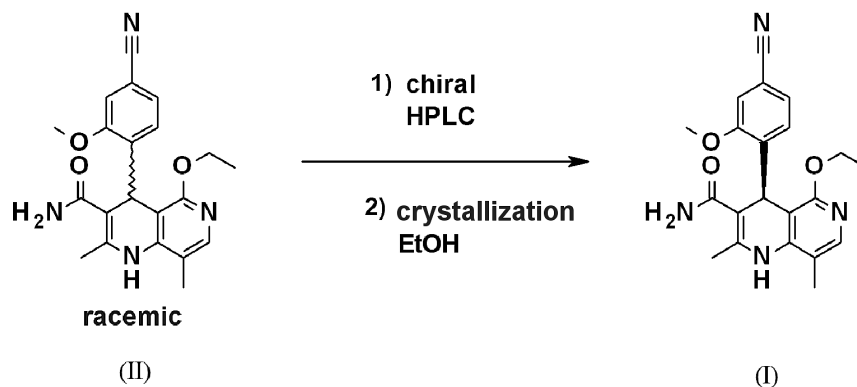
Finerenone (I) acts as a non-steroidal antagonist of the mineralocorticoid receptor and may be used as an agent for prophylaxis and/or treatment of cardiovascular and renal disorders such as heart failure and diabetic nephropathy, for example.

The compound of the formula (I) and their preparation process are described in WO 2008/104306 and ChemMedChem **2012**, 7, 1385, and also in WO 2016/016287 A1. To obtain the compound of the formula (I), the racemic mixture of the amides (II)



has to be separated into the enantiomers since only the enantiomer of the formula (I) is active.

In the published research scale synthesis (WO 2008/104306), a specifically synthesized chiral phase was used for this purpose (prepared in-house), which comprised poly(*N*-methacryloyl-D-leucine-dicyclopropylmethylamide) as chiral selector. It has been found that the separation can also be performed on a readily commercially available phase. This takes the form of the phase Chiralpak AS-V, 20 μ m. The eluent used was a mixture of methanol/acetonitrile 60:40. In this case, the chromatography may be carried out on a conventional chromatography column, but preferably the techniques known to those skilled in the art such as SMB (simulated moving bed; G. Paredes, M. Mazotti, Journal of Chromatography A, 1142 (2007): 56-68) or Varicol (Computers and Chemical Engineering 27 (2003) 1883-1901) are used.



Although SMB separation affords a relatively good yield and optical purity, the acquisition costs and the

operation of such a facility under GMP conditions poses a great challenge and is associated with high costs. The respective chiral phase employed, too, is very expensive and has only a limited life span and has to be frequently replaced during continuous production. For reasons of production engineering, this is not optimal unless there is a second plant present to ensure continuous operation, which is associated with additional costs. Furthermore, especially in the case of products produced on a ton scale, solvent recovery is the time-limiting step and requires the acquisition of gigantic falling-film evaporators and is associated with the consumption of huge amounts of energy.

Accordingly, it was an object to search for alternatives for separating the enantiomer mixture, which alternatives are significantly more cost-effective and can be carried out using conventional pilot plant equipment (stirred vessel/isolation apparatuses). Such facilities are traditionally standard equipment of pharmaceutical production plants and do not require additional investments. Moreover, qualification and validation of batch processes is considerably easier than that of chromatographic processes, which is an additional advantage.

Numerous attempts were carried out to develop a separation using the classic methods of racemate resolution (variation of chiral organic acid and solvent), as shown in Table 1:

Table 1:

Acid	Solvent
(S)-(+)-1,1-bisnaphthyl-2,2-diyl hydrogenphosphate	methanol
(-)-quinic acid	ethanol
(-)-O,O'-diacetyl-L-tartaric acid	1-propanol
(-)-O,O'-dipivaloyl-L-tartaric acid	2-propanol
(+)-3-bromocamphor-10-sulfonic acid	1-butanol
(+)-4-chlorotartranilic acid	isobutanol
(+)-4'-nitrotartranilic acid	1-pentanol
(+)-camphoric acid	cyclohexanol
(+)-O-acetyl-L-mandelic acid	benzyl alcohol
(1R)-(-)-camphor-10-sulfonic acid	acetone
(1S)-(-)-camphanic acid	ethylene glycol
(2R,3R)-(+)-tartaric acid	chlorobenzene
(R)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid	dichloromethane
(S)-(-)-2-bromopropionic acid	ethyl acetate
(S)-(-)-2-chloropropionic acid	dimethylacetamide

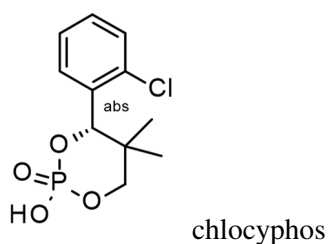
(S)-(+)-citramalic acid	THF
(S)-(+)-mandelic acid	toluene
Ac-acid triple mix	toluene / ethyl acetate 95:5
malic acid	toluene / ethyl acetate 90:10
chlocyphos	toluene / ethyl acetate 80:20
D-(+)-HPP monoacid	toluene / ethyl acetate 50:50
L-glutaminic acid	toluene / ethanol 95:5
L-lactic acid	methanol / water 90:10
menthoxyacetic acid	methanol / water 80:20
N-(3,5-dinitrobenzoyl)-(R)-(-)-2-phenylglycine	methanol / water 50:50
N-acetyl-L-leucine	ethyl acetate / MeOH 90:10
N-acetyl-L-phenylalanine	ethanol / water 90:10
N-Ac-proline-OH	ethanol / water 85:15
naproxen	ethanol / water 80:20
phencyphos	ethanol / water 75:25
	ethanol / water 70:30
	ethanol / water 50:50
	methanol / water 90:10
	methanol / water 80:20
	methanol / water 50:50
	1-propanol / water 80:20
	isopropanol / water 80:20
	1-butanol / water 90:10
	2-butanol / water 80:20
	2-butanol / water 90:10
	1-pentanol / water 90:10
	cyclohexanol / water 90:10
	benzyl alcohol / water 90:10
	ethylene glycol / water 80:20

Inter alia, we also carried out experiments with the classic resolving agent (+)-tartaric acid.

However, in none of the cases salt formation was observed; instead, in each case only the racemate precipitates from the solution, without having formed a salt. This corresponds essentially to the expectations of the person skilled in the art which can be derived from the pKs of molecule (II), i.e. that

classic racemate resolution by diastereomer salt formation with organic acids should not be possible since the measured pKs (for the base) is at 4.3, which virtually excludes salt formation, so that salt formation would only be possible using preferably very strong inorganic or organic mineral acids such as chiral sulfonic acids or phosphonic acids. According to the literature, for example “Handbook of Pharmaceutical

5 Salts – Properties, Selection and Use; by P. Heinrich Stahl, Camille G. Wermuth (Eds.); Wiley-VCH, p. 166”, the pK difference should be at least 3 pK units to allow stable salt formation. Indeed, this is found using, for example, the cyclic phosphoric ester chlocyphos below:



The reaction of 3 eq. of this cyclic phosphoric ester with the racemate (II) gives a diastereomeric salt in which (I) is present with an enantiomeric excess of only 44% e.e.

10

All efforts to push the enantiomeric excess towards > 99% e.e. were unsuccessful; in addition, chlocyphos was not commercially available in large amounts; accordingly, we investigated other alternatives.

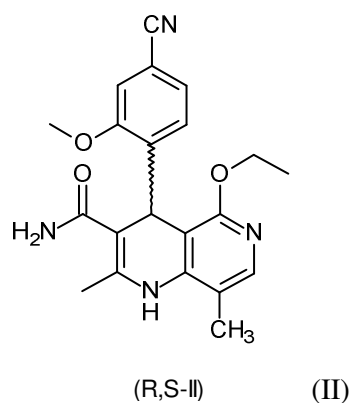
No salt formation was observed in reactions with alkyl-substituted tartaric acid derivatives such as (-)-O,O'-dipivaloyl-L-tartaric acid or (-)-O,O'-diacetyl-L-tartaric acid.

On further investigation of the subject, we found, surprisingly, that aromatically or heteroaromatically substituted derivatives of tartaric acid are highly suitable for forming “diastereomeric salts” from racemate (II).

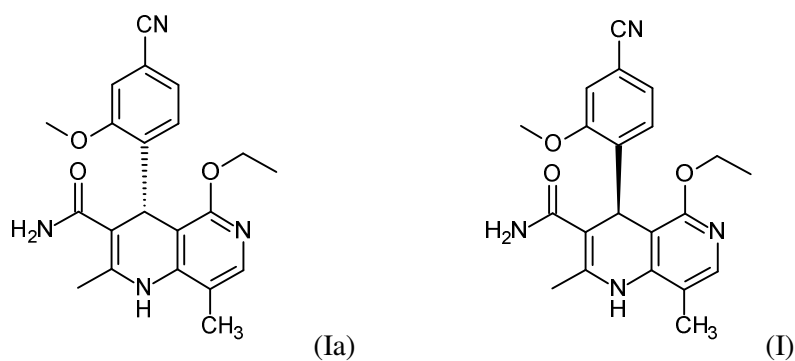
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- 6 -

Accordingly, the present application provides the racemate resolution of (II)

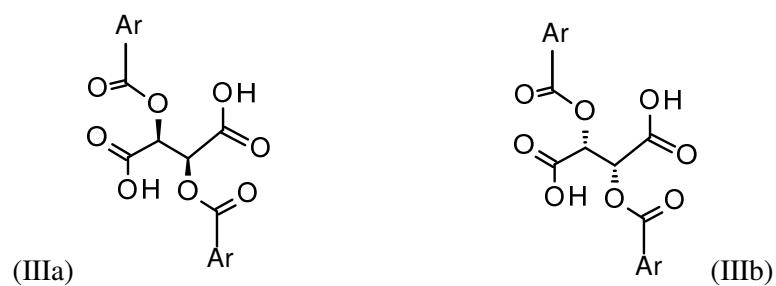


into (Ia) and/or (I)



5

using chiral substituted tartaric esters of the general formulae (IIIa) or (IIIb)

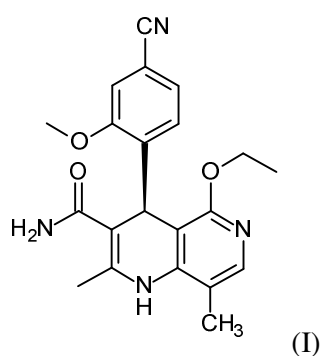


where Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical.

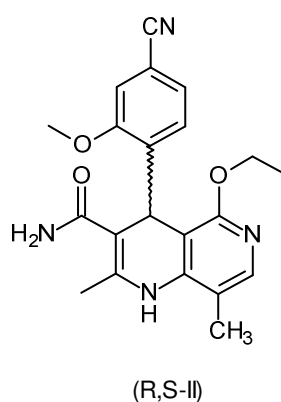
The invention further provides processes for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the formula (I)

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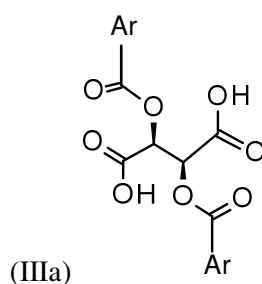
- 7 -



by racemate resolution of (II)



using a chiral substituted tartaric ester of the formula (IIIa)



where Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical.

The term “substituted” means that one or more hydrogen atoms on the atom or group in question has/have been replaced by a selection from the group specified, with the proviso that the normal valency of the atom in question is not exceeded under the circumstances present. Combinations of substituents and/or variables are permissible.

The term “unsubstituted” means that none of the hydrogen atoms have been replaced.

The heteroaryl group or the heteroaromatic radical may be a 5-membered heteroaryl group, for example thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl or tetrazolyl; or a 6-membered heteroaryl group, for example pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl; or a tricyclic heteroaryl group, for example carbazolyl, acridinyl or phenazinyl; or a 9-membered heteroaryl group, for example benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzothiazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, indoliziny

5 or purinyl; or a 10-membered heteroaryl group, for example quinolinyl, quinazolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl or pteridinyl.

The heteroaryl group is in particular a pyridinyl, pyrazinyl, pyrrolyl, pyrazolyl or pyrimidinyl group.

10 For the purposes of the present application, an aryl group is in particular a phenyl group.

Suitable substituents for the purposes of the present invention are halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, nitrile, a nitro group, cyano group, CF₃ group or amide group such as, for example, NHCOR in which R represents methyl, ethyl or phenyl, or a -NRCOR group in which R has the meaning mentioned above, or a CONHR group in which R has the meaning mentioned above, or a CONRR' group in which R' has the

15 same meaning as R as defined above, or cyclic amides such as the -CO-morpholine radical or the -CO-piperidine radical.

The term "halogen atom" refers to a fluorine, chlorine, bromine or iodine atom, preferably a fluorine, chlorine or bromine atom.

The term "C₁-C₆-alkyl" denotes a straight-chain or branched saturated monovalent hydrocarbon group

20 having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neopentyl, 1,1-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2,3-dimethylbutyl, 1,2-dimethylbutyl or 1,3-dimethylbutyl group or an isomer thereof. The group has in particular 1, 2, 3 or 4

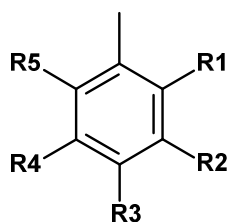
25 carbon atoms ("C₁-C₄-alkyl"), e.g. a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl or tert-butyl group, in particular 1, 2 or 3 carbon atoms ("C₁-C₃-alkyl"), e.g. a methyl, ethyl, n-propyl or isopropyl group.

The term "C₁-C₆-alkoxy" denotes a straight-chain or branched saturated monovalent group of the formula (C₁-C₆-alkyl)-O- in which the term "C₁-C₆-alkyl" is as defined above, e.g. a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy or n-hexyloxy group

30 or an isomer thereof.

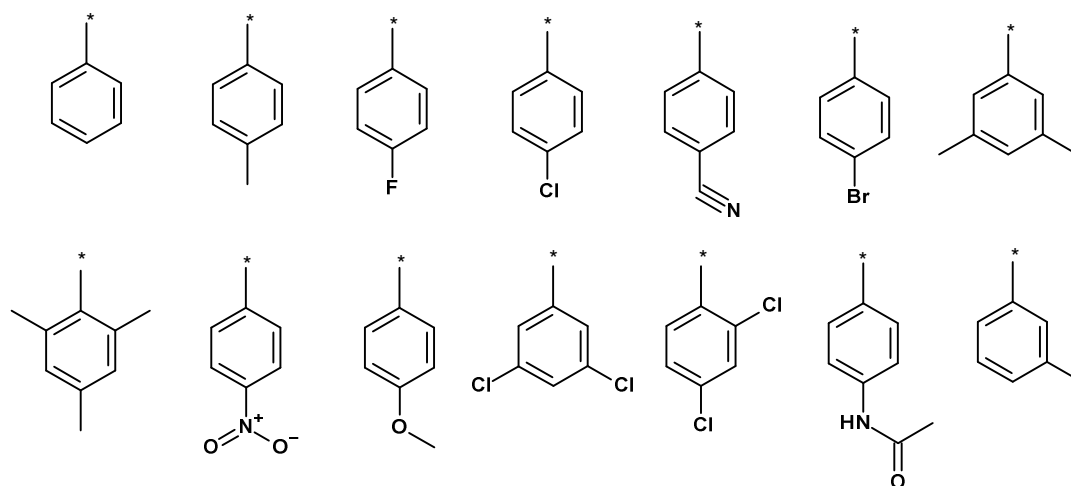
Preferably, Ar represents:

- 9 -



where R1, R2, R3, R4, R5 each represent a hydrogen atom or an alkyl radical such as, for example, methyl, ethyl, propyl, or a halogen atom such as, for example, fluorine, chlorine, bromine or iodine, or an ether group such as, for example, O-methyl, O-ethyl, O-phenyl, or a nitro group, cyano group, CF₃ group or amide group such as, for example, NHCOR in which R may represent methyl, ethyl or phenyl, or a -NRCOR group in which R has the meaning mentioned above, or a CONHR group in which R has the meaning mentioned above, or a CONRR' group in which R' has the same meaning as R as defined above, or represent cyclic amides such as the -CO-morpholine radical or the -CO-piperidine radical. The substitution patterns may differ widely; thus, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. However, Ar may also be a substituted heteroaromatic radical such as, preferably, pyridine or pyrazine. It may also be a polycyclic aromatic hydrocarbon such as a substituted naphthalene, anthracene or quinoline.

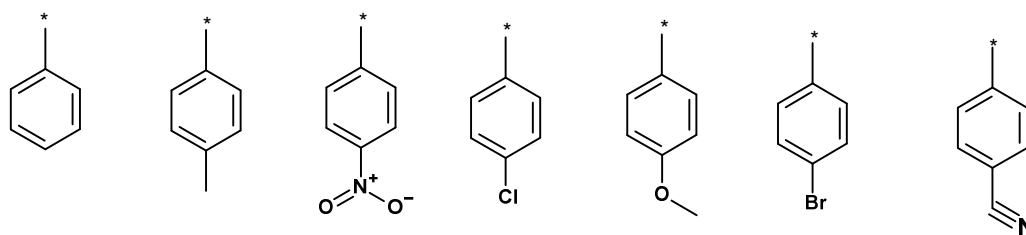
Particularly preferred Ar are:



where * represents the point of attachment.

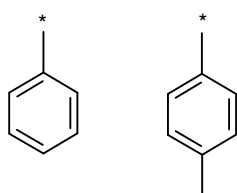
With particular preference, Ar represents:

- 10 -



where * represents the point of attachment.

Very particularly preferred Ar radicals are:



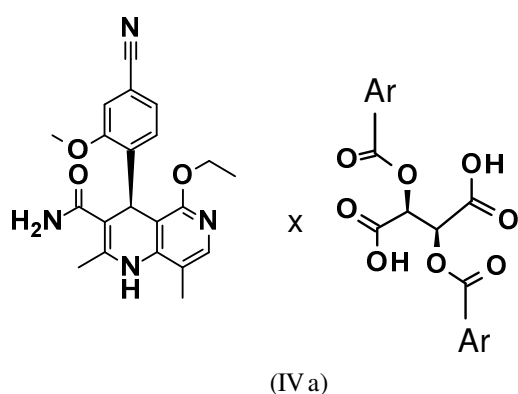
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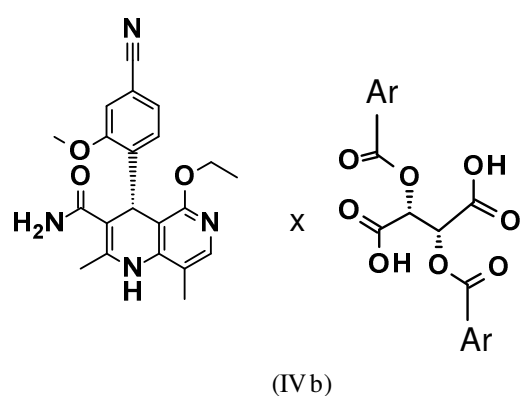
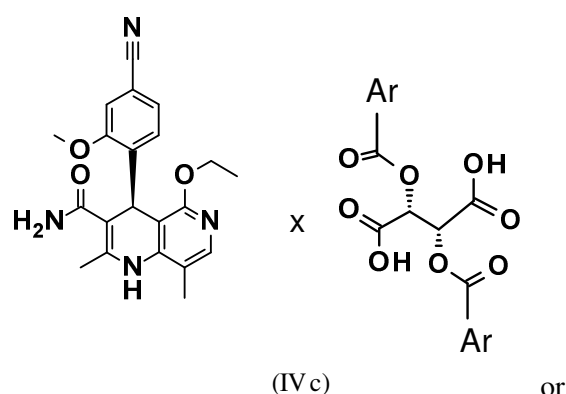
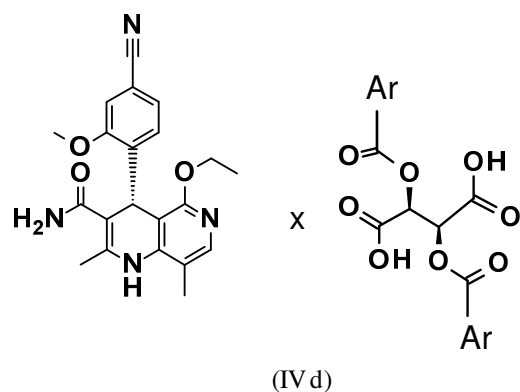
where * represents the point of attachment.

Of these, the unsubstituted ring (phenyl) is especially preferred.

The preparation of the tartaric esters is known from the literature, as described, for example, in Organic Synthesis, Coll. Vol. 9, p.722 (1998); Vol. 72, p.86 (1995), and in Chirality 2011 (23), 3, p.228.

10 The invention furthermore relates to diastereomeric salts of the formulae

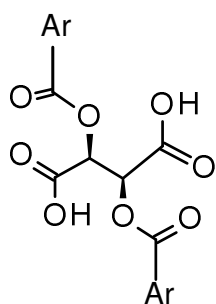




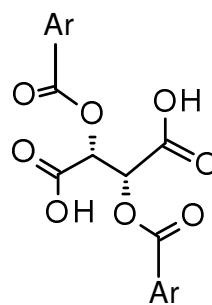
in which Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical and has the
 5 meaning given above.

Particular preference is given to diastereomeric salts in which Ar represents phenyl.

Whether this is really a classic diastereomeric salt or a molecular 1:1 complex stabilized by hydrogen
 bonds cannot be predicted with certainty. What is clear is that these molecular 1:1 aggregates are highly
 stable, behave like classic diastereomeric salts and can be isolated; so hereinbelow we still use the term
 10 diastereomeric salts. For the preparation of the diastereomeric salts, tartaric acid derivatives of the general
 formulae (IIIa) and (IIIb) are used:



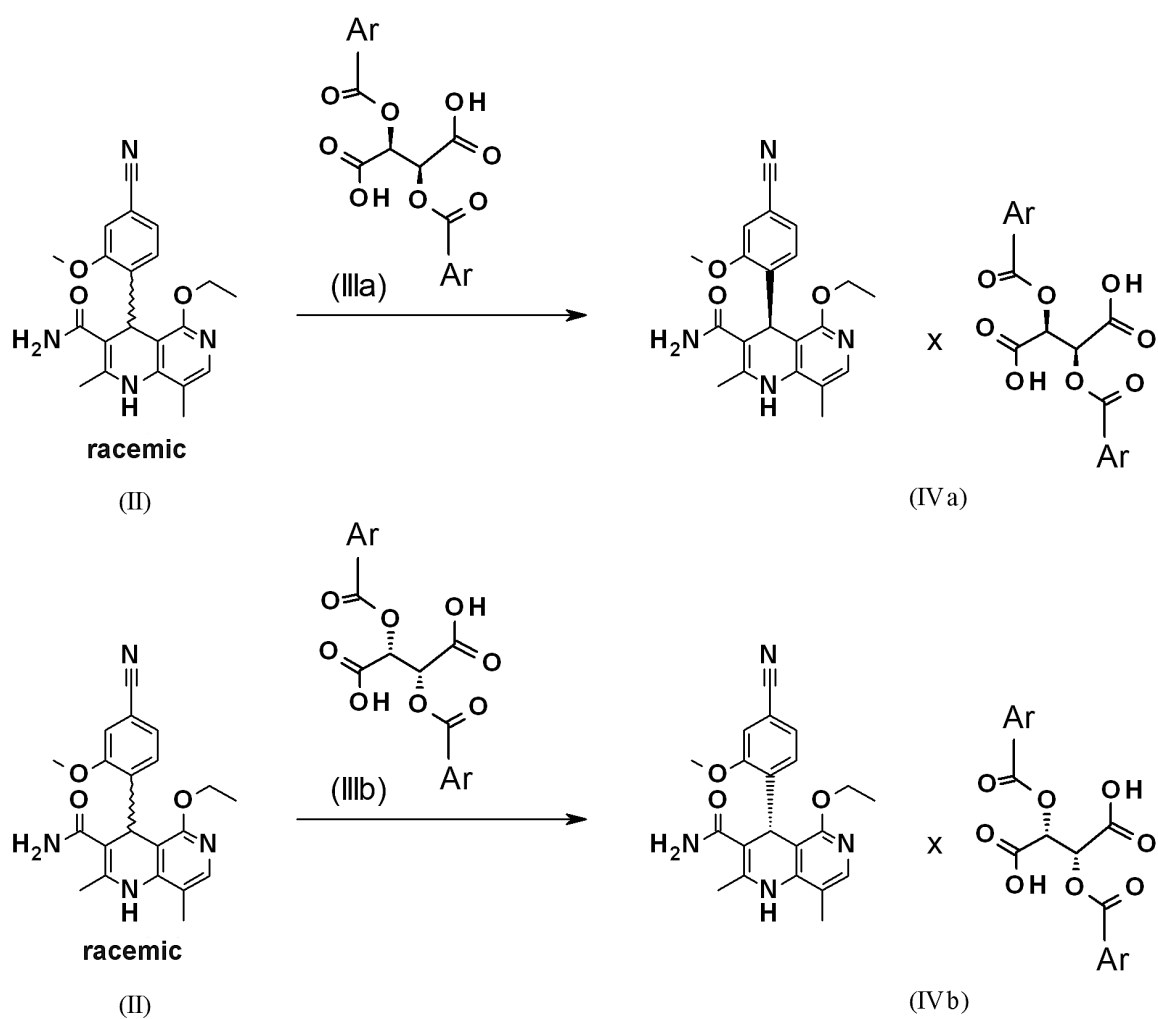
(IIIa)

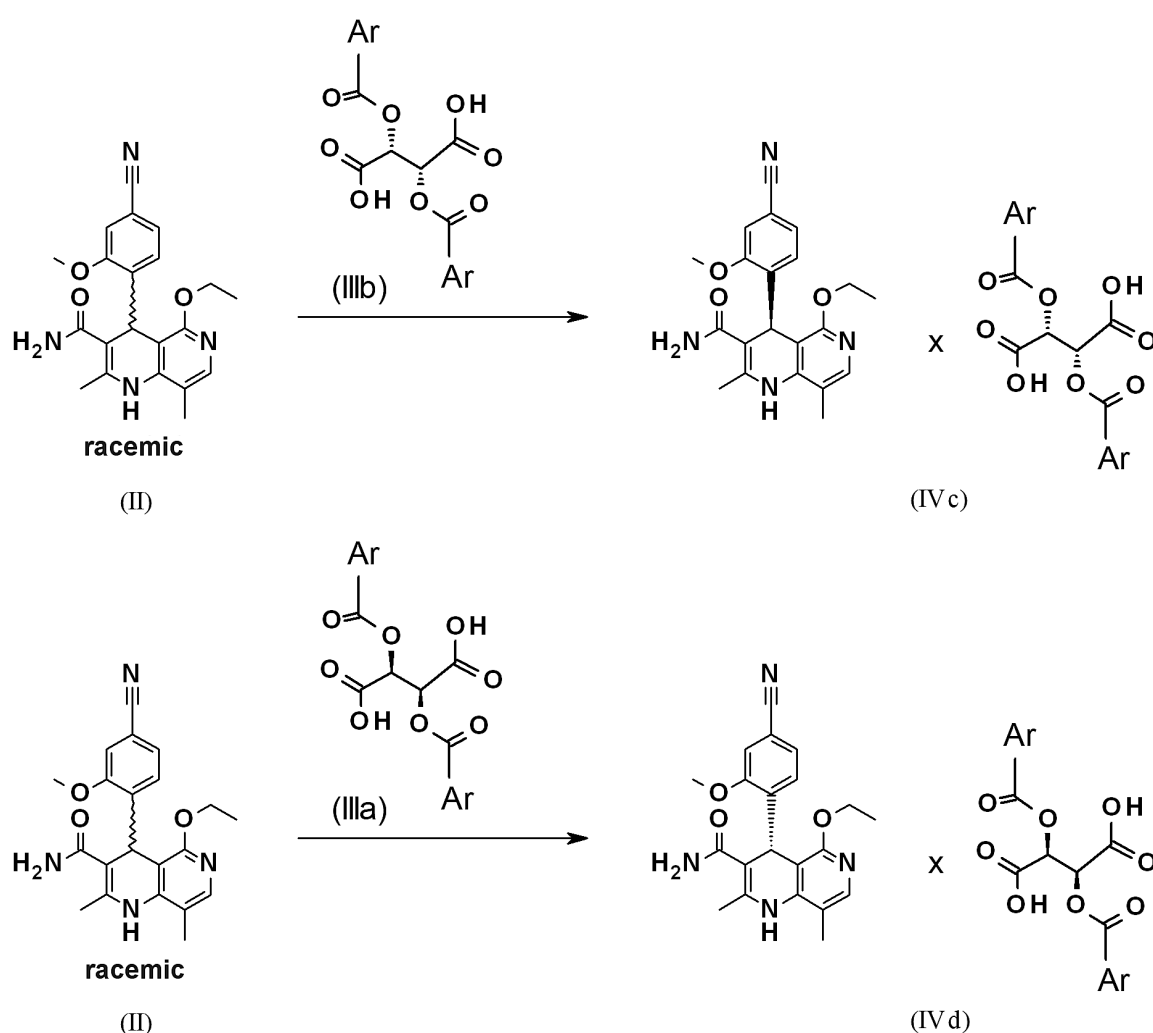


(IIIb)

where Ar represents a substituted or unsubstituted aromatic or heteroaromatic radical.

5 The preparation of the diastereomeric salts is carried out as follows:





The reaction of the racemic mixture (II) with a tartaric acid derivative of the general formula (IIIa) or (IIIb) yields 4 possibilities of diastereomeric salt formation (IV a-d). Surprisingly, a certain preference is observed such that, if, for example, rac-(II) is reacted with a tartaric acid derivative of the general formula (IIIa), in most cases the diastereomeric salt of the general formula (IVa) is obtained, with the enantiomer having the S configuration preferably forming the salt. Nearly quantitatively, the diastereomeric salt (IVa) precipitates from the solution from which it can then be isolated e.g. by filtration, the enantiomer having the R configuration remaining in solution. In a very similar manner, the mirror-image salt of the general formula (IVb) is prepared by reacting the racemate (II) with the tartaric acid derivative of the general formula (IIIb), with the enantiomer having the R configuration preferably forming the salt. The precipitated diastereomeric salts can be separated off nearly quantitatively, and here the S-enantiomer remains in solution.

Via the stoichiometric ratio of (II) to (IIIa) and (IIIb), respectively, and by the selection of solvent, yield and enantiomeric purity can be optimized.

Since finerenone (I) has the S configuration, the S,S-configured tartaric acid derivatives are preferably used for racemate resolution since in this case the diastereomeric salt of the S-enantiomer is formed with preference.

For racemate resolution, 0.4 to 1.2 eq. of tartaric ester (IIIa) or (IIIb) are employed, preferably 0.4 to 0.7 eq., particularly preferably 0.45 to 0.6 eq., very particularly preferably 0.50 - 0.55 eq.

The formation of diastereomeric salts takes place in solvent mixtures consisting of water and water-miscible organic solvents.

For the purposes of the application, suitable organic solvents are, for example, ethanol, methanol, isopropanol, 1-propanol, ethyl acetate, isobutanol, dichloromethane, 1-pentanol or acetone; however, preference is given to using ethanol. The solvents can also be employed in the commercially available denatured form, such as the denaturing agents usually employed for ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane, which has great economic advantages; accordingly, in particular for industrial scale use, spirits may be used which, for the purposes of the application, consist of ethanol optionally denatured with toluene or methyl ethyl ketone. Accordingly, for the purposes of the present application, if mention is made hereinbelow of ethanol as solvent, this is to be understood to mean, in addition to pure ethanol, also spirits in the sense of the above definition, in particular for industrial scale use. In addition, use was also made of the following solvents: ethyl acetate / methanol 90:10; methanol / water 80:20; ethanol / water 90:10; ethanol / water 85:15; ethanol / water 80:20; ethanol / water 75:25; ethanol / water 70:30; dichloromethane; 1-propanol / water 80:20; 1-pentanol; 1-pentanol / water 90:10; isopropanol; isopropanol / water 80:20; isobutanol / water 90:10; isobutanol / water 80:20; cyclohexanol / water 90:10; benzyl alcohol / water 90:10; ethylene glycol; ethylene glycol / water 80:20.

Preferably, the racemate resolution is carried out in an ethanol/water mixture, the mixtures (v/v) being in the range of ethanol:water = 1:1 to 6:1. However, preference is given to a mixture of ethanol:water = 4:1 to 3:1. Particular preference is given to a mixture of ethanol: water = 3:1. The mixture can be prepared beforehand or else be produced *in situ*, once all the components have been charged into a pot. The solvent mixture can be employed in an excess of from 10- to 40-fold, based on the racemate (II), e.g. 10 l to 40 l of solvent mixture are employed per 1 kg of racemate. Preference is given to a 10- to 20-fold excess, in particular a 13- to 16-fold excess – particular preference is given to a 14- to 15-fold excess.

Usually, the racemate resolution is carried out by initially charging all components into the solvent mixture at room temperature, then heating to 60 to 80°C, but preferably to 75°C, stirring at 75°C for 2 to 10 hours, preferably 3 to 4 hours, and then cooling to room temperature (about 20 to 23°C) over 3 to 10 hours, preferably 4 to 5 hours (using a temperature ramp). The mixture is then allowed to stir at room temperature

for another 2 to 24 hours, preferably 5 to 18 hours, particularly preferably 12 to 16 hours. Racemate resolution is preferably carried out at a temperature of 75°C.

Subsequently, the precipitated diastereomeric salt (IVa), (IVb), (IVc) and/or (IVd) is isolated.

5 The isolation is carried out by methods known to the person skilled in the art, for example by filtration or using a centrifuge. The filter cake obtained in this manner can be washed once or several times with a solvent or solvent mixture. This is followed by drying under reduced pressure, preferably < 100 mbar, at elevated temperature (50 to 80°C, preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous.

10 Using the procedure described above, it is possible to prepare diastereomeric salts of very high chemical purity. The enantiomeric excess of the diastereomeric salts is generally > 97% e.e. (see examples)

The diastereomeric salts do not have to be dried necessarily but may also be employed moist in the next process stage.

In addition to the customary procedure mentioned above, the process steps may also be combined or their sequence may be changed, as shown in Table 2 below:

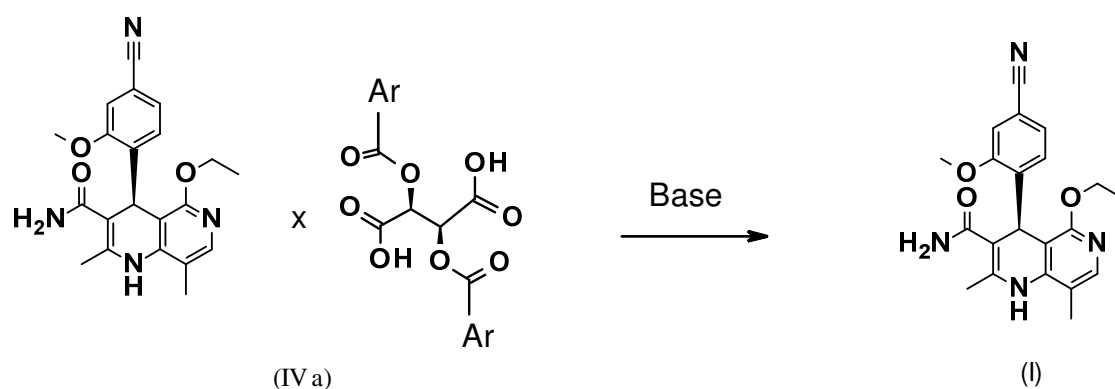
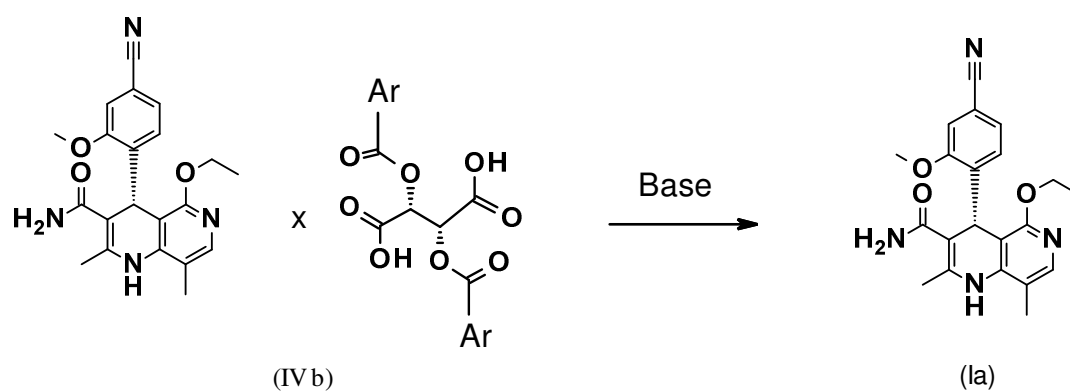
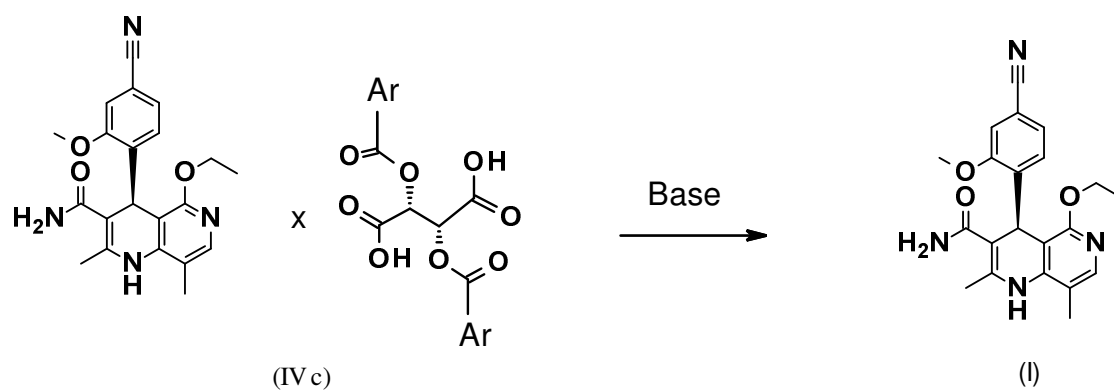
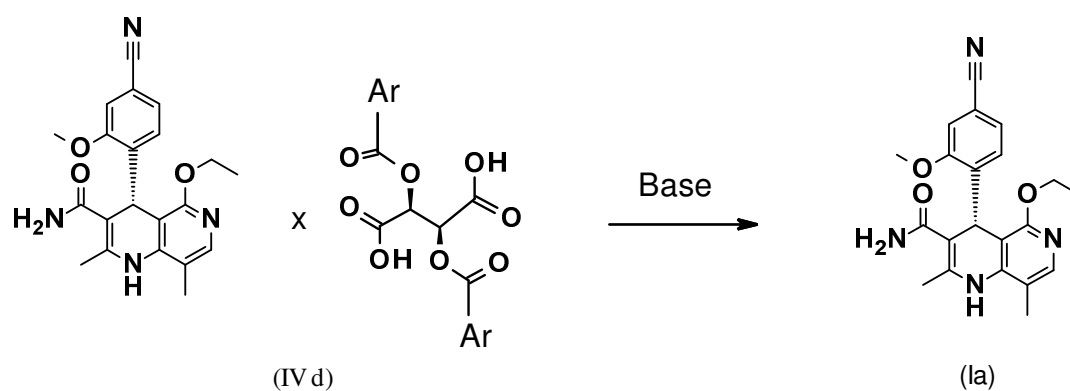
15 **Table 2**

1st Step	2nd Step	3rd Step	4th Step	5th Step
initial charging of racemate (II) and diaryltartaric acid (IIIa or b)	addition of ethanol	addition of water	heating	
initial charging of racemate (II)	addition of ethanol	addition of diaryltartaric acid (IIIa or b)	addition of water	heating
initial charging of racemate (II)	addition of water	addition of diaryltartaric acid (IIIa or b)	addition of ethanol	heating
initial charging of diaryltartaric acid (IIIa or b)	addition of ethanol	addition of racemate (II)	addition of water	heating
initial charging of diaryltartaric acid (IIIa or b)	addition of water	addition of racemate (II)	addition of ethanol	heating
initial charging of racemate (II) and	addition of the ethanol/water mixture	heating		

diaryltartaric acid (IIIa or b)				
initial charging of racemate (II)	addition of the ethanol/water mixture	addition of diaryltartaric acid (IIIa or b)	addition of ethanol	heating
initial charging of diaryltartaric acid (IIIa or b)	addition of the ethanol/water mixture	addition of racemate (II)	addition of water	heating
initial charging of the ethanol/water mixture	addition of racemate (II)	addition of diaryltartaric acid (IIIa or b)	heating	
initial charging of the ethanol/water mixture	addition of diaryltartaric acid (IIIa or b)	addition of racemate (II)	heating	
initial charging of ethanol	addition of racemate (II)	addition of water	addition of diaryltartaric acid (IIIa or b)	heating
initial charging of water	addition of racemate (II)	addition of ethanol	addition of diaryltartaric acid (IIIa or b)	heating
initial charging of ethanol	addition of diaryltartaric acid (IIIa or b)	addition of water	addition of racemate (II)	heating
initial charging of water	addition of diaryltartaric acid (IIIa or b)	addition of ethanol	addition of racemate (II)	heating

Depending on the type of plant in the pilot plant or in the production, one variant or the other may be advantageous.

5 In the next step, the diastereomeric salt is treated with a base and the solvent is removed. Removal of the solvent is carried out using methods known to the person skilled in the art, for example removal by distillation. To produce the chiral compounds (I) and (Ia), the diastereomeric salt of the general formula (IVa), (IVb), (IVc) or (IVd) has to be treated with a base, following distillative removal of the organic solvent, the target molecule (I) or (Ia) then precipitates from the solution and is isolated – for example by filtration and washing – and the respective tartaric ester according to formula (IIIa) or (IIIb) then remains
10 in solution in the form of a salt.



- 5 For the purposes of the present invention, suitable bases are inorganic and organic bases. Ammonia, aqueous sodium hydroxide solution, lithium hydroxide, potassium hydroxide, ammonium carbonate,

sodium carbonate, potassium carbonate, lithium carbonate, ammonium bicarbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate, potassium phosphate, ammonium phosphate may be employed as inorganic bases. However, preference is given to using sodium hydroxide, sodium phosphate or potassium phosphate. Particular preference is given to using sodium phosphate or potassium phosphate.

5 It is important to emphasize that the inorganic bases can be employed both in anhydrous form and in the form of their hydrates; thus, for example, sodium phosphate (anhydrous) and sodium phosphate hydrate may be used successfully. Aliphatic or aromatic bases such as triethylamine, imidazole, N-methylimidazole, Hünig base, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) may be employed as organic base.

10 Release of the target compound (I) or (Ia) takes place in mixtures of water, water-miscible organic solvents such as ethanol, isopropanol, 1,2-ethanediol, methoxyethanol, methanol or acetone; however, preference is given to using ethanol. The solvents may also be employed in the commercially available denatured form, such as the denaturing agents employed for ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane, preferably, spirits may be used which, for the purposes of the application, consist of ethanol
15 optionally denatured with toluene or methyl ethyl ketone, which has great economic advantages. It has been found to be advantageous to use mixtures of water and ethanol, with mixtures (v/v) in the range of ethanol:water = 1:6 to 1:3. However, preference is given to a mixture of ethanol:water = 1:4. The mixture can be prepared beforehand or else be produced *in situ*, once all the components have been charged into a pot. These mixtures may be used in an amount 7 to 20 times that of the diastereomeric salt (IVa or IVb or
20 IVc or IVd) employed, i.e., for example, 1 kg in 7 l to 20 l of this mixture. Preferably, the amount of the mixture used is 8 to 12 times, particularly preferably 9 to 11 times, very particularly preferably 10 times the amount of the salt.

The target compound (I) or (Ia) is released by initially charging the diastereomeric salt (IVa or IVb or IVc or IVd) in a solvent mixture at from 0 to 80°C, preferably 20 to 50°C, followed by addition of the organic
25 or inorganic base (either in solid form or as a solution, preferably in water) to adjust the pH to from 6.9 to 9.5, preferably from 7.0 to 8.0, particularly preferably to pH 7.5. Optionally, the base may be added very rapidly (over a few minutes) or else very slowly (over several hours), for example over 5 minutes to 3 hours. In any case, a more rapid addition is preferred; with preference, the metered addition is carried out over 5 min to 1 hour. For this purpose, use may be made of a pH meter installed in the reactor which
30 checks the setting and slowly adds the base. However, it is also possible to initially add a fixed amount of base (solid or dissolved in a solvent) which, based on experience, ensures that the desired pH range is reached. In production, such a procedure is particularly preferred. It has been found to be advantageous to continue stirring, after the pH has been set, at 10 to 80°C, preferably 20 to 60°C, with preference 40-60°C. The additional stirring period may be from 1 to 10 hours, preferably 2-5 hours, particularly preferably 3-
35 4 hours. The mixture is then allowed to cool to 15 to 25°C, e.g. using a ramp, and may then again be

stirred for 1 to 64 hours (the 64 hours serve to demonstrate the robustness of the process, see Example 3b); however, the extra stirring time is preferably between 3 and 24 hours, and 10 to 20 hours are generally sufficient.

5 The isolation is carried out by methods known to the person skilled in the art, for example by filtration or using a centrifuge. The filter cake obtained in this manner can be washed once or several times with a solvent or solvent mixture. This is followed by drying under reduced pressure, preferably < 100 mbar, at elevated temperature (50 to 80°C, preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous.

10 However, it is also possible to dissolve the material obtained from the filter using ethanol or mixtures of water and ethanol and then, after adjustment of the amount of water/ethanol in the eluate, immediately proceed to the next process step (see below). This procedure is preferred in particular when working on an industrial scale as a drying step can be dispensed with.

Using the procedure described above, it is possible to prepare crude products of very high chemical purity. The enantiomeric excess of the crude products (I) and (Ia) is generally > 96.5% e.e.

15 During up-scaling, it was found that complete removal of the tartaric esters (IIIa) and (IIIb) from the crude products (I) and (Ia) is technically not always simple and that the content of these components is close to the specification limit. Since the specification requirements for the final active compound are very high (< 0.1% (IIIa) in the final active compound), it has been found to be advantageous in some cases to add a further process step which ensures that the content of tartaric ester (IIIa) is reduced to below 0.15%,
20 preferably below 0.1% and in particular below 0.05% and the final active compound is reproducibly obtained in a quality conforming to specifications. In the final crystallization yielding the pure product, the tartaric ester (IIIa) is hardly depleted, or virtually not at all, so that such a subsequent process step guarantees that robust operation of the entire process is ensured, moreover, the operation is virtually without loss. This process step, which ensures that compound (IIIa) is depleted to below 0.15%, preferably
25 to below 0.1% and in particular to below 0.05% in the active compound, also forms part of the subject matter of the present invention. The process for reducing the amount of (IIIa) is carried out as follows. The starting material employed for the process is the dried or, advantageously, the still moist crude product of (I) or (Ia). Again, a base is used. Inorganic or organic bases may be employed for removing tartaric esters of the formula (IIIa) or (IIIb). Ammonia, aqueous sodium hydroxide solution, lithium hydroxide,
30 potassium hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium bicarbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate, potassium phosphate, ammonium phosphate may be employed as inorganic bases. However, preference is given to using sodium hydroxide, sodium phosphate or potassium phosphate. Particular preference is given to using sodium phosphate or potassium phosphate. It is important to emphasize that the inorganic bases can be

employed both in anhydrous form and in the form of their hydrates; thus, for example, sodium phosphate (anhydrous) and sodium phosphate hydrate may be used successfully. Aliphatic or aromatic bases such as triethylamine, imidazole, N-methylimidazole, Hünig base, pyridine, DBU may be employed as organic base.

- 5 Practice of the depletion of (IIIa) or (IIIb) is carried out in mixtures of water, with water-miscible organic solvents such as ethanol, isopropanol, 1,2-ethanediol, methoxyethanol, methanol or acetone; however, preference is given to using ethanol. The solvents may also be employed in the commercially available denatured form, such as the denaturing agents employed for ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane, which has great economic advantages. It has been found to be advantageous to use
- 10 mixtures of water and ethanol, with mixtures (v/v) in the range of ethanol:water = 30:10 to 10:10. However, preference is given to a mixture of ethanol:water = 20:10. The mixture can be prepared beforehand or else be produced *in situ*, once all the components have been charged into a pot. It is possible to use 10 to 20 times the amount of the solvent mixture, based on the diastereomeric salt (IVa), (IVb), (IVc) or (IVd) employed, i.e., for example, 1 kg in 10 l to 20 l of this mixture. Preferably, the amount of
- 15 the mixture used is 10 to 14 times, particularly preferably 11 to 12 times, the amount of this mixture.

The practice of the depletion of (IIIa) or (IIIb) is carried out such that the mixture is initially charged in a solvent mixture as described above at from 40 to 80°C, preferably 50 to 70°C, followed by addition of the organic or inorganic base (either in solid form or as a solution, preferably in water) to adjust the pH to from 6.9 to 9.5, preferably from 7.5 to 9.0, particularly preferably to pH 8.5. Optionally, the base may be

20 added very rapidly (over a few minutes) or else very slowly (over several hours), for example over 1 minute to 3 hours. In any case, a more rapid addition is preferred; with preference, the metered addition is carried out over 1 min to 1 hour. For this purpose, use may be made of a pH meter installed in the reactor which checks the setting and slowly adds the base. However, it is also possible to initially add a fixed amount of base (solid or dissolved in a solvent) which, based on experience, ensures that the desired pH

25 range is reached. In production, such a procedure is most preferred. It has been found to be advantageous to continue stirring, after the pH has been set, at 40-80°C, preferably 50-75°C, with preference 60-70°C. The additional stirring period may be from 1 to 24 hours, preferably 2-10 hours, particularly preferably 2-4 hours. The organic solvent is then substantially distilled off; this may be carried out at atmospheric pressure or, in a more gentle manner, under reduced pressure. Once the organic solvent has been

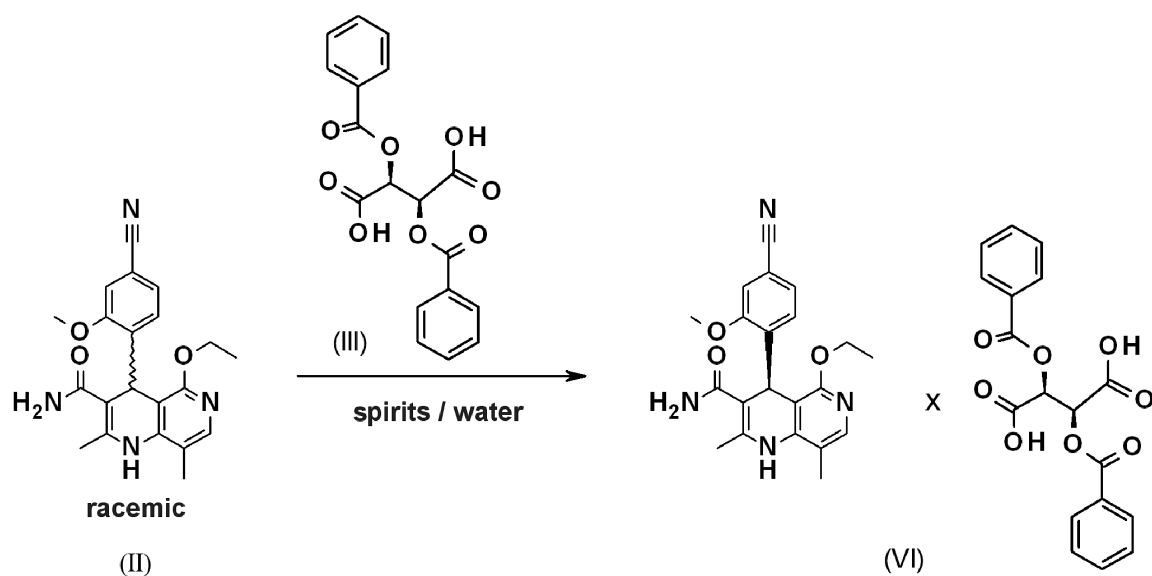
30 substantially distilled off, the mixture is allowed to cool to 15-25°C, e.g. using a ramp, and may then again be stirred for 1 to 64 hours (the 64 hours serve to demonstrate the robustness of the process, see Example 3b); however, the extra stirring time is preferably between 1 and 24 hours, and 1-5 hours are generally sufficient.

The isolation is carried out by methods known to the person skilled in the art, for example by filtration or using a centrifuge. The filter cake obtained in this manner can be washed once or several times with a solvent or solvent mixture. This is followed by drying under reduced pressure, preferably < 100 mbar, at elevated temperature (50 to 80°C , preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous.

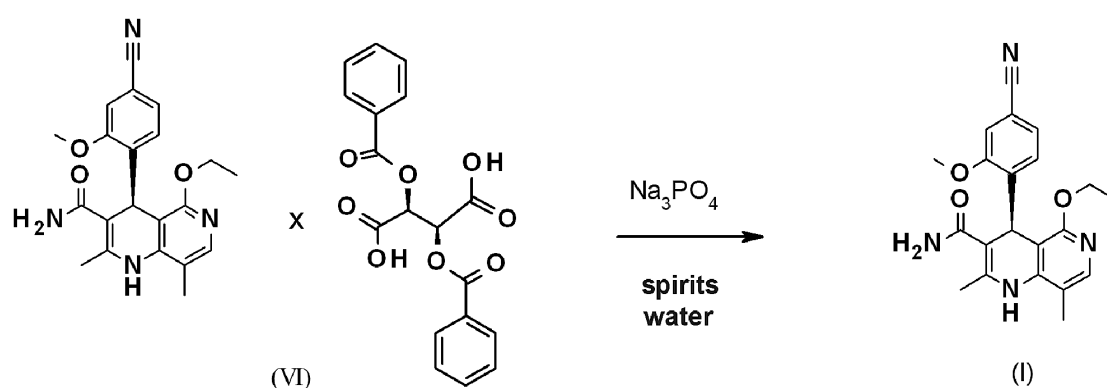
It is also possible, prior to the distillative removal of the solvent, to re-adjust the pH to pH 5-7 using an organic acid, for example formic acid, citric acid, acetic acid, or an inorganic acid, for example hydrochloric acid, sulfuric acid, phosphoric acid, or an acidic salt, for example sodium dihydrogen phosphate, potassium bisulfate or sodium bisulfate, and then to carry on as described above.

- 10 Using the procedure described above, it is possible to prepare crude products of very high chemical purity. The enantiomeric excess of the crude products (I) and (Ia) is generally $> 97\%$ e.e. The content of (IIIa) or (IIIb) has been reduced to below 0.15%, preferably below 0.1% and in particular below 0.05%.

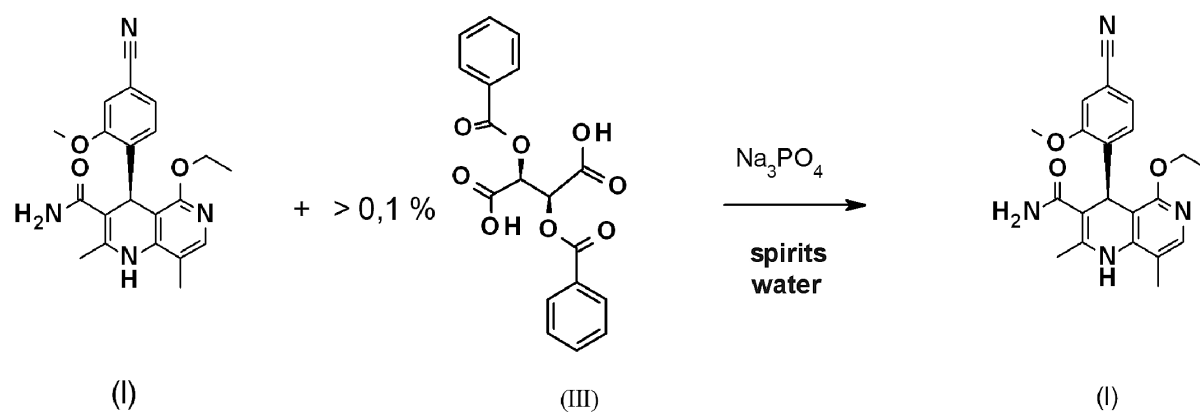
- 15 It has been found to be advantageous to subject a crude product obtained in this manner of the formula (I) or (Ia) to an additional crystallization to improve both chemical and especially optical purity, since the enantiomeric excesses of the crude products are generally $> 97\%$ e.e. To this end, a final crystallization process was developed: For reasons of GMP, the crude product (I) or (Ia) is dissolved in ethanol (if required with heating) and then subjected to particle filtration, preferably using spirits or ethanol denatured with toluene. In some cases, depending on the technical equipment, the crystallization can also be carried out under pressure, at elevated temperature (advantage: less solvent); however, recrystallization from aqueous ethanol solutions (under elevated pressure or at atmospheric pressure) is also possible. Under atmospheric pressure or reduced pressure, the mixture is then concentrated to about 1/3 to 1/6 of the original volume, preferably 1/4 to 1/5; this results in the crystallization of the product. In some cases, for example when large volumes have to be distilled off over long periods of time, it has been found to be advantageous to carry out the distillative removal under reduced pressure, keeping the internal temperature low to avoid decomposition and byproduct formation. After the distillation has ended, the mixture is cooled to 0°C and the crystals then isolated and dried at 40 to 50°C under reduced pressure. The yields are generally $> 88\%$ of theory. The chemical purity and the content achieved correspond to the criteria for commercial products according to ICH guidelines. In pilot plant batches, the residual solvent content, in the present case ethanol content, is generally $< 0.05\%$. The optical purity is $>> 99\%$ e.e.
- 20
- 25
- 30 In a particularly preferred process, in particular for operation on an industrial scale, (+)-dibenzoyltartaric acid (III) is used; both the anhydrous form and the hydrate may be employed:



The racemate resolution is preferably carried out in a spirits/water mixture. The subsequent release of crude finerenone



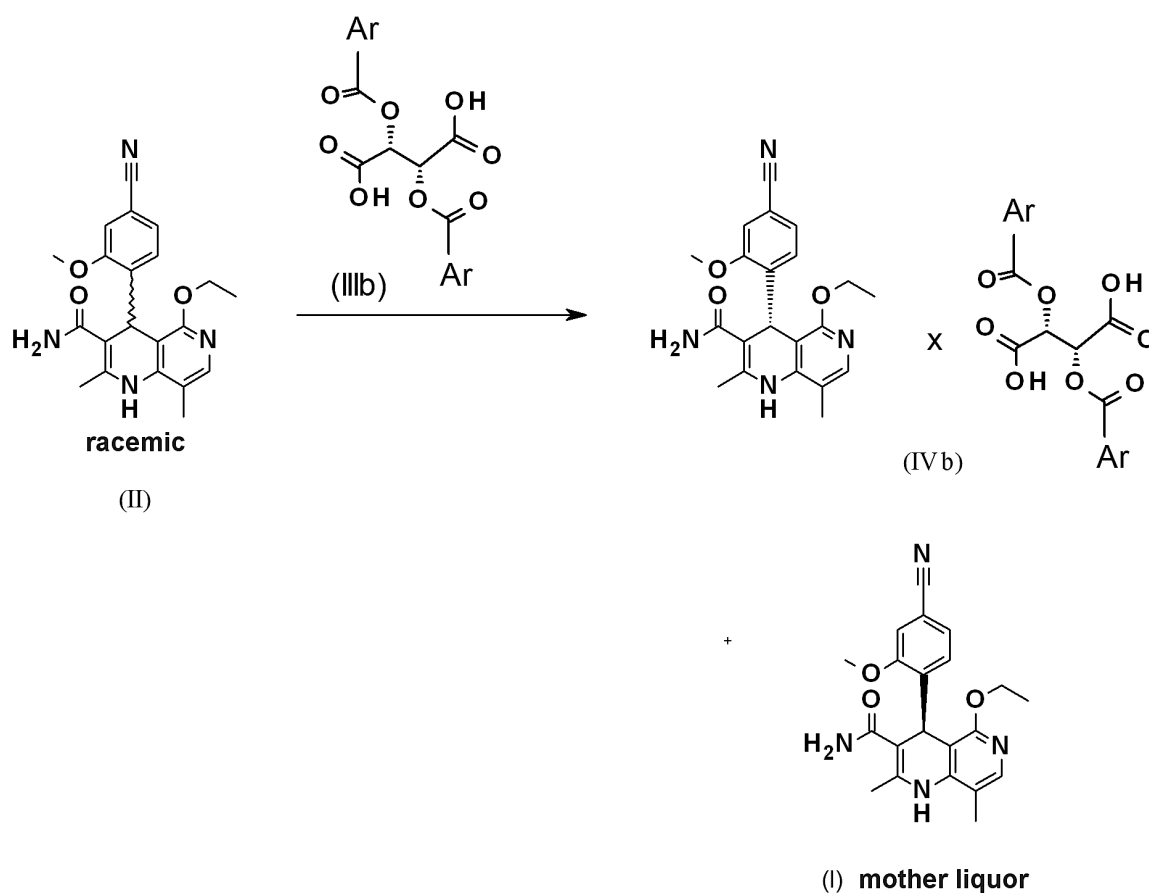
- 5 is preferably carried out in a spirits/water mixture using sodium phosphate as base. In cases requiring reprocessing, if the proportion of (+)-dibenzoyltartaric acid (III) is $> 0.15\%$,



reprocessing is preferably carried out in a spirits/water mixture using sodium phosphate as base. Final

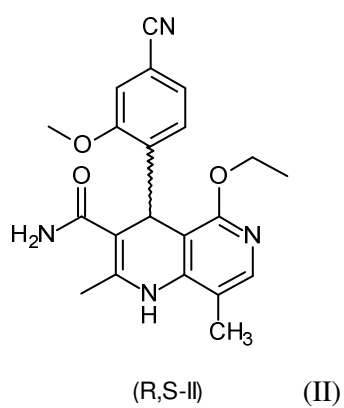
crystallization to afford pure finerenone is preferably carried out using spirits as solvent. Here, a purity of 0.15%, preferably 0.1%, particularly preferably less than 0.05% impurities is achieved.

It is also possible to isolate the target enantiomer from the mother liquor. Here, initially, the appropriate diastereomeric salt (IVa), (IVb), (IVc) or (IVd) is prepared either from (I) or (Ia) and then isolated by
 5 filtration, and the mother liquor comprising the respective other diastereomer is then adjusted to a pH of pH > 7, preferably pH 7.5, by addition of a base such as, for example, ammonia, aqueous sodium hydroxide solution, lithium hydroxide, potassium hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium bicarbonate, sodium bicarbonate, potassium
 10 bicarbonate, sodium phosphate, potassium phosphate, ammonium phosphate, preferably sodium hydroxide, sodium phosphate and potassium phosphate, particularly preferably sodium phosphate and potassium phosphate. The organic solvent, preferably ethanol, is then distilled off, either at atmospheric pressure or, more gently, under reduced pressure; this results in the precipitation of the corresponding other enantiomer. The product is filtered off, washed with water or water/solvent mixtures and dried. An appropriate final crystallization from spirits as described, for example, in Example 1c affords the
 15 compounds (I) and (Ia) in appropriate pure form.

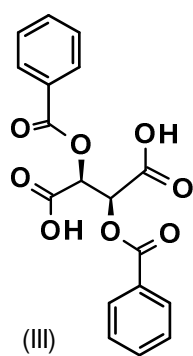


Accordingly, the present application furthermore provides finerenone (I) having a dibenzoyltartaric acid content of $\leq 0.15\%$, obtained by reacting the racemate (II)

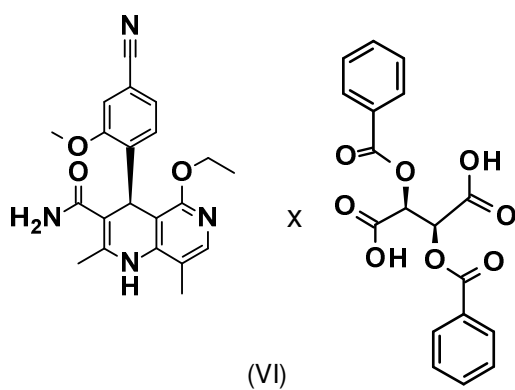
- 24 -



with dibenzoyltartaric acid of the formula (III)



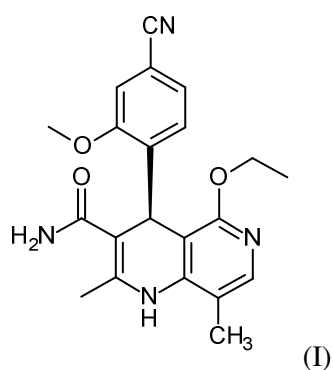
in a spirits/water mixture to give the diastereomeric salt (VI)



5

and subsequently releasing finerenone (I)

- 25 -



using sodium phosphate, also in a spirits/water mixture, and then again reacting with sodium phosphate in a spirits/water mixture and then crystallizing pure finerenone having a dibenzoyltartaric acid content of $\leq 0.15\%$; in a particularly preferred embodiment, finerenone having a dibenzoyltartaric acid content of $\leq 0.1\%$, in particular less than 0.05% , is obtained.

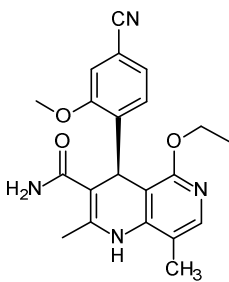
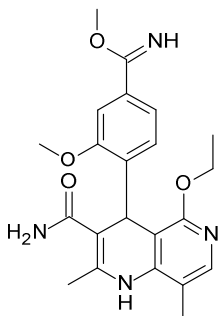
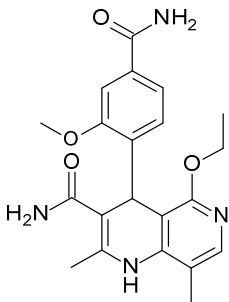
Experimental section**Abbreviations and acronyms:**

EtOH	ethanol
DB tartaric acid	dibenzoyltartaric acid
DMSO	dimethyl sulfoxide
HPLC	high-pressure, high-performance liquid chromatography
¹H-NMR	¹H nuclear magnetic resonance spectrometry
IT	internal temperature
MS	mass spectrometry
RT	retention time
RRT	relative retention time
TFA	trifluoroacetic acid
TM	mantle temperature
XRPD	X-ray powder diffraction
spirits	ethanol denatured with 2% toluene

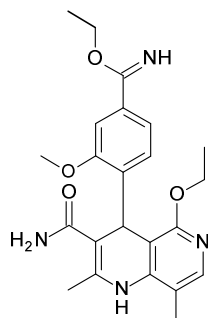
Examples

Table 3 below shows the structures of the compounds recovered in HPLC. Assignment of the retention times in HPLC is shown below.

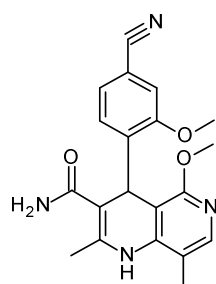
Table 3

finerenone (I) 
impurity A 
impurity B 
impurity C (unknown structure, always significantly less than 0.1%)

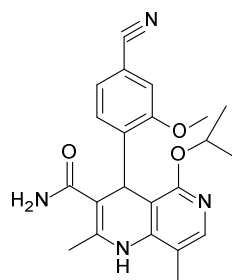
impurity D



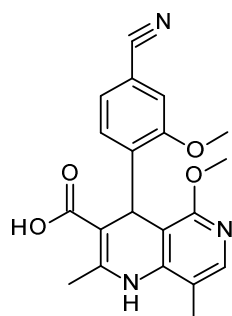
impurity E



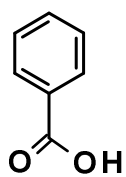
impurity F



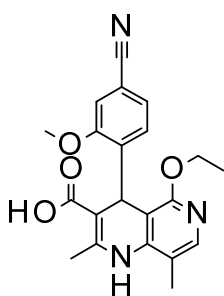
impurity G



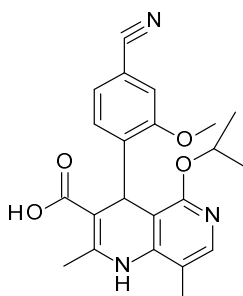
impurity H



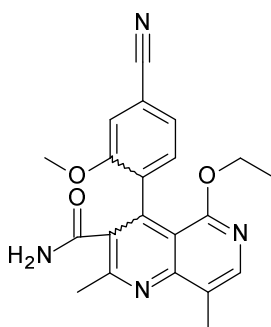
impurity I



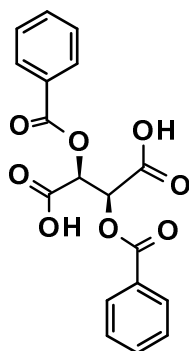
impurity J



impurity K



impurity N (III)



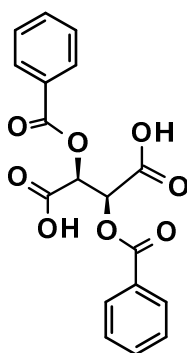
- 1) Analytical method for checking the content of impurities and the enantiomeric purity at the stage of the dibenzoyltartaric acid

**Content and organic
impurities**

RT (min) RRT

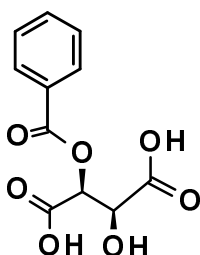
dibenzoyltartaric acid

approx. 1.00
11.1



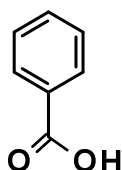
monobenzoyltartaric acid

Approx. 0.46
5.1



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benzoic acid

Approx. 0.69
7.6**Instrument:**

ultrahigh-performance liquid chromatograph
(having a pressure range of up to 1200 bar with
temperature-controlled column oven and UV detector)

Column:

YMC Triart C8

length: 100 mm, internal diameter: 3.0 mm, particle size: 1.9 μm
max pressure: 1000 bar

Conditions:20°C; 0.50 ml/min; 1.7 μl (10°C); 240 nm/6 nm**Eluent:**

A: 0.1% TFA in water; B: acetonitrile

Gradient:

time (min)	A (%)	B (%)
0.0	90.0	10.0
15.0	35.0	65.0
16.0	20.0	80.0
20.0	20.0	80.0

Enantiomeric purity:

	RT (min)	RRT
(+)-dibenzoyltartaric acid	2.1	1.00
(-)-dibenzoyltartaric acid	3.9	1.86

Instrument:

high-performance liquid chromatograph with temperature-
controlled column oven and UV detector

Column:**Chiralpak IC**

length: 250 mm, internal diameter: 4.6 mm, particle size: 5.0 μm
max pressure: 300 bar

Conditions: 40°C; 2.0 ml/min; 5 µl; 234 nm/6 nm

Eluent: A: heptane; B: 0.1% TFA in ethanol

isocratic: A(%) 80: B (%) 20

2) Analytical method for checking the content of impurities and the enantiomeric purity at the stage of the diastereomeric salt

<u>Content and organic</u>		RT (min)	RRT
<u>impurities</u>	finerenone (I)	6.2	1.00
	impurity A	3.3	0.53
	impurity B	3.7	0.60
	impurity C	3.9	0.62
	impurity D	4.4	0.70
	impurity E	5.5	0.89
	impurity F	6.8	1.10
	impurity G	7.2	1.17
	impurity H	7.7	1.25
	impurity I	7.8	1.27
	impurity J	8.4	1.36
	impurity K	10.4	1.69
	impurity N	11.1	1.80

Instrument: ultrahigh-performance liquid chromatograph (having a pressure range of up to 1200 bar with temperature-controlled column oven and UV detector)

Column: YMC Triart C8

length: 100 mm; internal diameter: 3.0 mm; particle size: 1.9 µm
max pressure: 1000 bar

Conditions: 20°C; 0.50 ml/min; 3.5 µl (10°C); 242 nm/6 nm

Eluent: A: 0.1% TFA in water; B: acetonitrile

Gradient:	time (min)	A (%)	B (%)
	0.0	90.0	10.0
	15.0	35.0	65.0
	16.0	20.0	80.0
	20.0	20.0	80.0

<u>Enantiomeric purity:</u>	RT (min)	RRT
finerenone (I)	5.34	1.00
(Ia)	6.14	1.15
Instrument:	high-performance liquid chromatograph with temperature-controlled column oven and UV detector	
Column:	Lux 3µm i-Cellulose-5 length: 150 mm, internal diameter: 4.6 mm, particle size: 3.0 µm max pressure: 300 bar	
Conditions:	40°C; 1.0 ml/min; 10 µl (20°C); 252 nm/6 nm	
Eluent:	A: 20 mmol ammonium acetate buffer pH 9.0 (1.54 g ammonium acetate in 1l of Milli-Q water, adjusted to pH 9.0 with ammonia) B: acetonitrile	
isocratic:	A(%) 50: B (%) 50	

3) Analytical method for checking the content of impurities and the enantiomeric purity at the stage of crude finerenone (I).

<u>Content and organic</u>	RT (min)	RRT
<u>impurities</u>		
finerenone (I)	6.2	1.00
impurity A	3.3	0.53
impurity B	3.7	0.60
impurity C	3.9	0.62
impurity D	4.4	0.70
impurity E	5.5	0.89
impurity F	5.6	0.91
impurity G	6.8	1.10
impurity H	7.6	1.23
impurity K	10.4	1.68
impurity N	11.1	1.79

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Instrument: ultrahigh-performance liquid chromatograph (having a pressure range of up to 1200 bar with temperature-controlled column oven and UV detector)

Column: YMC Triart C8
length: 100 mm; internal diameter: 3.0 mm; particle size: 1.9 µm
max pressure: 1000 bar

Conditions: 20°C; 0.50 ml/min; 1.7 µl (10°C); 252 nm/6 nm and 230 nm/6 nm for the evaluation of DB-tartaric acid

Eluent: A: 0.1% TFA in water; B: acetonitrile

Gradient:	time (min)	A (%)	E
	0.0	90.0	1
	15.0	35.0	6
	16.0	20.0	8
	20.0	20.0	8

<u>Enantiomeric purity:</u>	RT (min)	RRT
<u>Method A</u>		
finerenone (I)	about 11	1.00
(Ia)	about 9	0.82

Instrument: high-performance liquid chromatograph with temperature-controlled column oven and UV detector

Column: **Chiralpak IA**
length: 250 mm, internal diameter: 4.6 mm, particle size: 5.0 µm
max pressure: 300 bar

Conditions: 40°C; 0.8 ml/min; 5 µl (20°C); 255 nm/6 nm

Eluent: A: acetonitrile; B: methyl tert-butyl ether (MTBE)

isocratic: A(%) 90; B (%) 10

<u>Enantiomeric purity:</u>	RT (min)	RRT
<u>Method B</u>		
finerenone (I)	5.7	1.00
enantiomer (Ia)	6.8	1.19

Instrument/detector: high-performance liquid chromatograph with temperature-controlled column oven, UV detector and data evaluation system.

5 **Measurement wavelength:** 252 nm

	Oven temperature:	40°C
	Column:	Chiralpak IC
	length:	150 mm, internal diameter: 4.6 mm, particle size: 3 µm
	Mobile phase:	A: 50% buffer 20 mM ammonium acetate pH 9
5		B: 50% acetonitrile
	Flow rate:	1 ml/min
	Elution time:	8 min
	Equilibration:	not required, isocratic
	Sample solvent:	mobile phase
10	Test solution:	about 0.5 mg/ml of the substance racemate, dissolved in sample solvent
	Comparative solution:	A comparative solution analogous to the sample solution is prepared
	Injection volume:	10 µl

The measured values stated in the examples below for enantiomer determination were all determined according to Method B. Some values, especially those of the batches prepared in the pilot plant, were, for comparison, measured again using Method A, and gave comparable results.

The HPLC analysis data given in the examples which follow with respect to purity and content of the end product pure finerenone (I) refer only to impurities present in the product in an amount of > 0.05%. This is essentially impurity E. All other impurities shown in the Table listed above are generally < 0.05%. The structure of such impurities was determined by isolation from enriched mother liquors.

Example 1

Laboratory batch using anhydrous (+)-O,O-dibenzoyl-D-tartaric acid (III)

Example 1a

25 Tartrate salt (IV) preparation

250 g (660.616 mmol) of finerenone (II) racemate were initially charged into 3500 ml of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v) at room temperature (about 23°C). 130.2 g (363.339 mmol) of (+)-O,O-dibenzoyl-D-tartaric acid (III) were added using a funnel for solids, subsequently rinsing with 250 ml of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v). The resulting suspension was heated to an internal temperature of 75°C over 0.75 hours and then stirred at this temperature for 3.0 hours. Subsequently, using a cooling ramp, the mixture was cooled to 23°C over 5.0 hours and then stirred at this temperature overnight (about 16 hours). The suspension

was filtered off through a frit, rinsing once with 250 ml of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v). Wet yield: 334.7 g. The wet product was then dried overnight (about 16 hours) at 50°C under reduced pressure (< 100 mbar). Yield: 250.2 g (100.08% of theory) of a colourless crystalline powder.

5 Analytical results:

Finerenone (I)	47.2% by weight (HPLC)
Enantiomeric excess	97.68 % e.e.
Largest unknown secondary component at RT 5.606 min.	0.47 %
Residual solvents:	
EtOH	2.24 %
toluene	0.0 %

MS (EIpos): $m/z = 379 [M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): $\delta = 1.05$ (t, 3H), 2.12 (s, 3H), 2.18 (s, 3H), 3.82 (s, 3H), 3.99-4.07 (m, 2H), 5.39 (s, 1H), 5.89 (s, 2H), 6.60-6.84 (m (broad signal), 2H), 7.14 (d, 1H), 7.28 (dd, 1H), 7.37 (d, 1H), 7.55 (s, 1H), 7.61 (t, 4H), 7.69 (s, 1H), 7.75 (t, 2H), 8.04 (d, 4H), 12.50-15.40 (very broad signal, 2H) and signal of the solvent DMSO and increased water signal: $\delta = 2.5$ -2.6, as well as smaller peaks at $\delta = 3.40$ – 3.50 (q) and $\delta = 1.05$ - 1.10 (t), superimposed signals from residual solvent ethanol.

The colourless crystalline powder (finerenone - (+)-O,O-dibenzoyl-D-tartaric acid complex (VI)) obtained according to Example 1a was examined by XRPD under the following conditions at 25°C:

Sample preparation: The powder is prepared as a thin layer between two films (e.g. polyacetate)

15 Apparatus: X-ray powder diffractometer X'Pert Pro

Generator: 40 kV / 40 mA

Detector: PIXcel

Radiation: CuK α radiation

Wavelength: 1.5406Å

20 Technique: transmission

Scanning range: 2° $\leq$ 2Q $\leq$ 40°

Stepwidth: 0.013° 2Q

Measuring time: 25 s/step

The results are shown in Figure 1 and Table 1.

25 Table 1:

No.	Position	No.	Position	No.	Position	No.	Position
1	7.1576	18	18.3972	35	25.6188	52	31.8820
2	8.3525	19	18.8961	36	25.7895	53	32.2890
3	8.6020	20	19.2638	37	25.9996	54	32.6173
4	11.2018	21	20.3404	38	26.3410	55	32.9586
5	11.7664	22	20.6556	39	27.0106	56	34.5343
6	12.5279	23	20.9182	40	27.8510	57	35.7291
7	13.6703	24	21.6141	41	28.0873	58	36.6614
8	13.9066	25	22.0474	42	28.3237	59	37.7381
9	14.3399	26	22.2049	43	28.5863	60	38.1976
10	14.5631	27	22.5332	44	28.8620	61	38.7228
11	14.7863	28	22.8221	45	29.2034	62	39.6026
12	14.9702	29	23.2554	46	29.4003		
13	16.1650	30	23.6361	47	29.7942		
14	16.3488	31	24.0300	48	30.0306		
15	16.7427	32	24.5947	49	30.1356		
16	17.2548	33	24.8179	50	30.5164		
17	17.4912	34	25.2118	51	30.9497		

Example 1b

Preparation crude product (I)

At room temperature, 248 g of the compound (IV) prepared in Example 1a were suspended in 2480 ml of a mixture consisting of ethanol (denatured with toluene)/water = 20:80 (v/v) (the pH was determined to be pH=4). Subsequently, 819.6 g of an aqueous sodium phosphate solution (100 g of sodium phosphate dissolved in 1000 ml of water) were added dropwise over 60 minutes and the pH was adjusted to pH=7.2. The mixture was stirred at 23°C for a further 50 minutes (pH=7.1). Subsequently, 98.3 g of an aqueous sodium phosphate solution (100 g of sodium phosphate dissolved in 1000 ml of water) were added dropwise over 10 minutes and the pH was adjusted to pH=7.5. Over one hour, the mixture was heated to an internal temperature of 50°C and stirred at this temperature for 3.0 hours. The mixture was cooled to 22°C over one hour and stirred at this temperature for another hour. The crystals are filtered off through a frit and washed once with 200 ml and once with 100 ml of a mixture consisting of ethanol (denatured with toluene)/water = 20:80 (v/v) and twice with 200 g of water. Wet yield: 263.4 g. The wet product was then dried over the weekend (> 48 hours) at 50°C under reduced pressure (< 100 mbar). Yield: 116.9 g (93.52% of theory) of a colourless crystalline powder.

Analytical results:

Finerenone (I)	Purity: 99.86 area % (HPLC); Content: 100.0% by weight
enantiomeric excess	97.02 % e.e.
Largest secondary component impurity E	0.07 %
Residual solvents:	
EtOH	0.19 %
toluene	0.13 %
Water (Karl-Fischer)	0.042 %

MS (EIpos): $m/z = 379$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 1.05$ (t, 3H), 2.12 (s, 3H), 2.18 (s, 3H), 3.82 (s, 3H), 3.99-4.07 (m, 2H), 5.37 (s, 1H), 6.60-6.84 (m (broad signal), 2H), 7.14 (d, 1H), 7.28 (dd, 1H), 7.37 (d, 1H), 7.55 (s, 1H), 7.69 (s, 1H) and signal of the solvent DMSO and significantly increased water signal: $\delta = 2.5$ -2.6, and also very small peak at $\delta = 3.38$ (not assigned)

Example 1c

10 Preparation pure product (I)

116.0 g of the crude product (I) prepared in Example 1b were suspended in 2330 ml of ethanol (denatured with toluene) and then heated to reflux. On heating, the product went into solution. Stirring was continued at this temperature for one hour. The solution was filtered off through a heated pressure filter ($T=75^\circ\text{C}$) and the pressure filter was then rinsed with 30 ml of ethanol (denatured with toluene). The solvent was then distilled off to the point where a final volume of about 4-fold (with respect to the substance employed: 116 g x 4 ~ 484 ml) had been achieved (about 1920 ml were distilled off). The mixture was then cooled to an internal temperature of 23°C (duration about 1.5 to 2 hours). The mixture was then stirred at an internal temperature of 3°C for 2 hours. The product was filtered off and rinsed once with 100 ml of ethanol (denatured with toluene). Wet yield: 124 g. The wet product was dried at 50°C over the weekend (> 48 h) under reduced pressure (< 100 mbar). Yield: 112.6 g (97.07% of theory) of a colourless crystalline powder, fine needle-like crystals.

Analytical results:

Finerenone (I)	Purity: 99.86 area % (HPLC); Content: 99.5% by weight
enantiomeric excess	100 % e.e.
Largest secondary component impurity E	0.07 %
Residual solvents:	
EtOH	0.05 %
toluene	0.00 %
Water (Karl-Fischer)	0.00 %

MS (EIpos): $m/z = 379$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 1.05$ (t, 3H), 2.12 (s, 3H), 2.18 (s, 3H), 3.82 (s, 3H), 3.99-4.07 (m, 2H), 5.37 (s, 1H), 6.60-6.84 (m (broad signal), 2H), 7.14 (d, 1H), 7.28 (dd, 1H), 7.37 (d, 1H), 7.55 (s, 1H), 7.69 (s, 1H) and small signals of solvents DMSO and Wasser at $\delta = 2.5$ -2.6 and a very small peak at $\delta =$
5 3.38 (not assigned)

Modification: Mod A (according to the definition in WO2016/016287 A1 where the absolute configuration was determined by X-ray)

Example 2

10 Laboratory batch using (+)-O,O-dibenzoyl-D-tartaric acid hydrate (III)

Example 2a

Tartrate preparation

350.0 g racemate (II) were initially charged at room temperature and 3112 g of spirits were then added. 1200 g of water were then added. 191.4 g of (+)-O,O-dibenzoyl-D-tartaric acid monohydrate (III) were
15 added using a funnel for solids, subsequently rinsing with 113 g of water. The suspension was heated to an internal temperature of 75°C over one hour and then stirred at 75°C for 3 hours. Subsequently, using a cooling ramp, the mixture was cooled to 23°C over 5.0 hours and then stirred at this temperature overnight (about 18 hours). The suspension was filtered off through a frit and washed twice with a mixture consisting of 332.3 g of spirits and 140.2 g of water. Wet yield: 487.6 g. The wet product was then dried over the
20 weekend (> 48 hours) at 50°C under reduced pressure (< 100 mbar). Yield: 351.0 g (100.29% of theory) of a colourless crystalline powder.

Finerenone (I)	Content: 47.92% by weight
enantiomeric excess	97.84 % e.e.
Largest secondary component at RT 5.86 min	0.22 %
Residual solvents:	
EtOH	2.594 %
toluene	0.003 %

In a manner analogous to that described in Examples 1b and 1c, pure finerenone (I) can be prepared from this tartrate salt.

5 Example 3

Preparation of 3 batches of pure finerenone (I) in a pilot plant, starting with 2 kg of racemate (II).

Example 3a

Tartrate preparation (IV)

- 10 2.00 kg (5.285 mol) of racemic finerenone (II) were initially charged into 28.0 l of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v) at room temperature (about 23°C). 1.042 kg (2.907 mol) of (+)-O,O-dibenzoyl-D-tartaric acid (III) were added using a funnel for solids, subsequently rinsing with 2 l of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v). The resulting suspension was heated to an internal temperature of 75°C over 45 minutes and then stirred at this
- 15 temperature for 3.0 hours. Subsequently, using a cooling ramp, the mixture was cooled to 23°C over 5.0 hours and then stirred at this temperature overnight (about 16 hours). The suspension was filtered off via a frit, rinsing once with 2 l of a mixture consisting of ethanol (denatured with toluene)/water = 75:25 (v/v) and sucked dry for 10 minutes. Wet yield: 2.69 kg. The wet product was then dried at 50°C under reduced pressure (< 100 mbar) until the mass remained constant (after about 17 hours). Yield: 2.009 kg (~ 100 %
- 20 of theory) of a colourless crystalline powder.

Example 3b

Preparation crude product (I)

- At room temperature (about 23°C), 2.006 kg of the compound (IV) prepared in Example 3a were
- 25 suspended in 20.0 l of a mixture consisting of ethanol (denatured with toluene)/water = 1:4 (v/v) (the pH

was determined to be pH=4). 6.05 kg of a 9.09% strength aqueous sodium phosphate solution was then added dropwise and the pH was adjusted to pH=7.2. The mixture was stirred at 23°C for approx. a further 50 minutes (pH=7.17). 0.65 kg of a 9.09% strength aqueous sodium phosphate solution was then added dropwise and the pH was adjusted to pH=7.5. Over one hour, the mixture was heated to an internal temperature of 50°C and stirred at this temperature for 3.0 hours. The mixture was cooled to 22°C over one hour and stirred at this temperature over the weekend (about 64 hours*). The crystals are filtered off through a K800 Seitz filter plate and washed once with 1.6 l and once with 0.8 l of a mixture consisting of ethanol (denatured with toluene)/water = 20:80 (v/v) and twice with in each case 1.6 l of water. Wet yield: 1.82 kg. The wet product was then dried at 50°C under reduced pressure (< 100 mbar) until the mass remained constant (after about 17 hours). Yield: 0.978 kg (97.8% of theory) of a colourless crystalline powder.

*) for technical reasons, the mixture was stirred over the weekend; usually, 14 hours of stirring are sufficient.

15 Example 3c

Preparation pure product (I)

250 g of the crude product (I) prepared in Example 3b were suspended in 5000 ml of ethanol (denatured with toluene) and then heated to reflux. On heating, the product went into solution. Stirring was continued at this temperature for one hour. The solution was filtered off through a heated pressure filter (T=85°C) and the pressure filter was then rinsed with 200 ml of ethanol (denatured with toluene). The solvent was then distilled off to the point where a final volume of about 4-fold (with respect to the substance employed: 250 g x 4 ~ 1000 ml) had been achieved (about 4200 ml were distilled off). The mixture was then cooled to an internal temperature of 4-5°C (ramp: duration about 4 hours). The mixture was then stirred at an internal temperature of 4-5°C for one hour. The product was filtered off and rinsed once with 220 ml of ethanol (denatured with toluene). Wet yield: 251.2 g. The wet product was dried at 50°C over the weekend (> 48 h) under reduced pressure (< 100 mbar). Yield: 223.0 g (89.2% of theory) of a colourless crystalline powder.

The results of 3 batches starting in each case with 2 kg of the racemate of finerenone (II) are summarized in Table 4 below:

Table 4: Tartrate salt (IV)

Batch	Racemate (II) employed kg	Yield: kg	Yield: % of theory
Batch 1 (Example 3a)	2	2.009	~ 100
Batch 2	2	2.025	~ 100
Batch 3	2	2.027	~ 100

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 3a)	49.20	Largest secondary compound at RT 5.606 min: 0.22%	97.69	ethanol: 2.55% toluene: 0.01%
Batch 2	49.80	Largest secondary compound at RT 5.606 min: 0.11%	97.49	ethanol: 2.74% toluene: 0.00%
Batch 3	50.06	Largest secondary compound at RT 5.606 min: 0.14%	97.64	ethanol: 2.58% toluene: 0.004%

Crude product (I)

Batch	Tartrate salt (IV) employed: kg	Yield: kg	Yield: % of theory
Batch 1 (Example 3b)	2.009	0.978	97.8
Batch 2	2.025	0.985	98.5
Batch 3	2.027	0.987	98.7

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 3a)	98.10	finerenone (I): 99.85% Largest secondary compound impurity E: 0.07%	98.15	ethanol: 0.203% toluene: 0.117%
Batch 2	99.00	finerenone (I): 99.83% Largest secondary compound impurity E: 0.08%	97.93	ethanol: 0.110% toluene: 0.073%

Batch 3	99.70	finerenone (I): 99.84% Largest secondary compound impurity E: 0.07%	97.97	ethanol: 0.118% toluene: 0.076%
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In all 3 batches, the (+)-O,O-dibenzoyl-D-tartaric acid content was: 0.00%

Pure product (I)

Batch	Crude product (I) g	Yield: g	Yield: % of theory
Batch 1 (Example 3c)	250	223	89.2
Batch 2	250	235	94.0
Batch 3	250	226	91.8

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 3a)	99.40	finerenone (I): 99.82% impurity E 0.08 %	100.00	ethanol: 0.074% toluene: 0.000%
Batch 2	99.80	finerenone (I): 99.94% impurity E 0.08 %	100.00	ethanol: 0.037% toluene: 0.000%
Batch 3	99.50	finerenone (I): 99.85% impurity E 0.08 %	99.92	ethanol: 0.033% toluene: 0.000%

In all 3 batches, the (+)-O,O-dibenzoyl-D-tartaric acid content (III) was 0.00%

5

Example 4

Industrial realization of the process. The examples which follow describe the realization of the process on an industrial scale. The results, such as yield and analytic data, of 2 batches of pure finerenone (I) are then represented in tables:

10

Example 4a

Tartrate salt (IV) preparation

The batch size was 80 kg of racemic finerenone (II).

- In a 1600 l stirred vessel, 711.0 kg of spirits were initially charged at an IT of 20°C, following by addition of 300 kg of water, then 80.0 kg of racemate (II) and finally 41.7 kg of (+)-dibenzoyltartaric acid (III).
- 5 • The mixture was heated to an IT of 75°C and stirred for 3 h.
- The mixture was cooled to an IT of 23°C over 5 h (ramp) and stirred for another 16 h.
- For centrifugation, the suspension was transferred into the inverting centrifuge, centrifuged, rinsed with a mixture consisting of 10.7 kg of spirits and 4.5 kg of water, then tumble-dried and removed.
- 10 • Drying was carried out in a 300 l spherical drier at a mantle temperature of 50°C and at 30 mbar. Drying was terminated at an internal temperature of 45°C (duration about 6 h).
- The product was cooled to 15°C and then removed.

Example 4b

15 Crude product (I)

The batch size was 89.3 kg of tartrate salt (IV) starting material

- Preparation of a sodium phosphate solution
- In a 630 l stirred vessel, 360.0 kg of fully demineralized water were initially charged at 20°C
- 36.0 kg of sodium phosphate were added and dissolved
- 20 • In a 1600 l stirred vessel, 141.1 kg of spirits were initially charged at 20°C
- 714.2 kg of water and 89.3 kg of tartrate salt (IV) were then added
- The mixture was heated to an internal temperature of 50°C
- 295.1 kg of a sodium phosphate solution were then metered in
- After 1.5 h, the pH was adjusted to pH=7.5 (+/-0.1) by addition of 35.4 kg of sodium phosphate
- 25 solution
- The mixture was left to stir and cooled via a ramp (3 h) to IT=22°C.
- Stirring was then continued at IT=22°C (18 h)
- In a receiver, a mixture of 129.6 kg of water and 25.6 kg of spirits was prepared (for washing)
- The suspension was metered into the inverting centrifuge (about 4 batches + residual batch) and,
- 30 a little at a time, washed once with the mixture of 129.6 kg of water and 25.6 kg of spirits and once with 288.0 kg of fully demineralized water.
- The product was removed and dried in a spherical drier (TM=50°C, 30 mbar, terminated at IT=45°C, about 6 h)

- The product was cooled and removed at $<30^{\circ}\text{C}$.

Example 4c

Reprocessing of the crude product (I)

- 5 In some cases, if the specification limit for (+)-dibenzoyltartaric acid (III) in the crude product is $> 0.1\%$, it has been found to be advantageous to carry out reprocessing (see Example 6) to ensure that the limit $< 0.1\%$ is reproducibly achieved. In addition, the reprocessing process is virtually loss-free and generally affords the crude product in a yield of $> 95\%$.

Reprocessed crude product (I)

- 10 The batch size was 30 kg of crude product (I).
- Preparation of a sodium phosphate solution: At room temperature, 2.3 kg of sodium phosphate were dissolved in 147.8 kg of water in a 250 l stirred receiver
 - At 20°C , 198.8 kg of spirits were initially charged in a 630 l stirred vessel and 120 kg of water were added, followed by the addition of 30 kg of crude product (containing (+)-dibenzoyltartaric acid (III) as stated in Table 5).
 - The mixture was heated to an internal temperature of 70°C and stirred for 30 minutes.
 - At 70°C , 14.1 kg of the sodium phosphate solution prepared above were metered in, adjusting the pH to pH 8.9 (± 0.1), and the mixture was stirred at 70°C for 20 hours.
 - Using a ramp, the mixture was cooled to 44°C over 60 minutes and 300 g of pure finerenone (I) seed crystals were added
 - The solvent was then distilled off at 200 mbar and an internal temperature of at most 60°C and at the same time 369 kg of water were metered into the stirred vessel.
 - Finally, the mixture was cooled to 22°C over 1.5 hours and the product was isolated on a pressurized suction filter and, in 3 portions, washed with a total of 180 l of water
 - At a mantle temperature of 50°C and under reduced pressure (30 mbar), the product was then dried to weight constancy.
 - The product was allowed to cool to 15°C and then removed.
- 15
- 20
- 25

Example 4dPure product (I)

The batch size was 26 kg (2 times 13 kg) of reprocessed crude product (I)

- 5 • In a 250 l stirred vessel, 13 kg of reprocessed crude product (I) were initially charged in 184.9 kg of spirits at 20°C, with the stirred vessel having been inertized beforehand
- The solution was heated to a mantle temperature of 80°C and stirred at 78°C for 30 minutes (with dissolution of the product).
- The solution was filtered through a 0.65 µm filter element (PP element Sartorius) (GMP filtration)
- 10 and the filtrate was transferred into a 630 l stirred vessel.
- The product was washed with 18.5 kg of spirits
- This was repeated in 2 subdivided portions (2 times 13 kg of product) and the solutions were combined
- The solvent was distilled off at atmospheric pressure to a final filling level of about 130 l (in two
- 15 portions, mantle temperature: 104°C, duration about 6 hours)
- The solution was cooled to 0°C over 4 hours using a linear temperature ramp and then stirred for another hour.
- The product suspension was isolated on a pressurized suction filter and washed with 45.9 kg of spirits
- 20 • The wet product was then dried under reduced pressure (30 mbar) at 50°C to weight constancy (about 12 h). The mixture was cooled to 15°C and the product was removed.

A summary of yield and analytical results of 3 industrial batches for the preparation of pure finerenone (I) is given in Table 5

Tartrate salt (IV)

Table 5:

Batch	Racemate employed (II) kg	Yield tartrate salt (IV): kg	Yield: % of theory (not corrected for content)
Batch 1 (Example 4a)	80	77.3	100
Batch 2	80	81.2	105
Batch 3	80	80.2	103

5

Batch	Content tartrate salt (IV) % by weight	Content of finerenone (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %
Batch 1 (Example 4a)	94.2	48.4	(+)-dibenzoyltartaric acid: 44.98%	98.6
Batch 2	95.4	49.0	(+)-dibenzoyltartaric acid: 44.98%	98.6
Batch 3	94.2	48.4	(+)-dibenzoyltartaric acid: 44.98%	98.6

Crude product (I)

Batch	Tartrate salt (IV) employed: kg	Yield (I, crude): kg	Yield: % of theory
Batch 1 (Example 4b)	89.3	36.6	80
Batch 2	89.3	44.2	96
Batch 3	89.3	45.7	99

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 4b)	98.5	finerenone (I): 99.71% impurity E: 0.08% Sum of all organic secondary components: 0.29% (+)- dibenzoyltartaric acid: 0.71%	98.8	ethanol: 0.098% toluene: 0.048%
Batch 2	98.2	finerenone (I): 97.70% impurity E: 0.08% Sum of all organic secondary components: 0.30% (+)- dibenzoyltartaric acid: 0.39%	98.9	ethanol: 0.151% toluene: 0.088%
Batch 3	100	finerenone (I): 99.76% impurity E: 0.07% Sum of all organic secondary components: 0. 0.24% (+)- dibenzoyltartaric acid: 0.46%	98.7	ethanol: 0.102% toluene: 0.066%

Crude product (I) after reprocessing

Batch	Input (I): kg	Yield (I): kg	Yield: % of theory
Batch 1 (Example 4c)	30	29.8	99.33
Batch 2	30	29.8	99.33

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 4c)	99.6	finerenone (I): 99.70% (+)-dibenzoyltartaric acid: < 0.05 % Largest secondary component impurity E: 0.08% Sum of all organic secondary components: 0.3%	98.8	ethanol: n.d. toluene: n.d.
Batch 2	99.6	finerenone (I): 99.70% (+)-dibenzoyltartaric acid: < 0.05 % Largest secondary component impurity E: 0.08% Sum of all organic secondary components: 0.3%	98.8	ethanol: n.d. toluene: n.d.

Pure product, pure finerenone (I)

Batch	Input kg	Yield: kg	Yield: % of theory
Batch 1 (Example 4d)	26	23.1	88.85
Batch 2	26	22.9	88.08

Batch	Content (I) % by weight	Purity (HPLC)	Enantiomeric excess e.e. %	Residual solvents:
Batch 1 (Example 4d)	100	finerenone (I): 99.8% Sum of all organic secondary components: 0.2% Largest secondary component impurity E: 0.08% (+)-dibenzoyltartaric acid: < 0.05	100	ethanol: 0.044 toluene: 0.00 water: < 0.2
Batch 2	100	finerenone (I): 99.8% Sum of all organic secondary components: 0.2% Largest secondary component impurity E: 0.08% (+)-dibenzoyltartaric acid: < 0.05%	100	ethanol: 0.063 toluene: 0.00 water: < 0.2

Example 5

Several variants analogously to the procedure of Example 1b are suitable for releasing crude finerenone (I). Here, it was the objective to keep the proportion of (+)-O,O-dibenzoyl-D-tartaric acid (III) in the crude product as small as possible (0.15% or less). Specifically, final pH after the metered addition of the sodium phosphate solution, temperature, time of the metered addition of the sodium phosphate solution and additional stirring time were varied and the effect on the content of (+)-O,O-dibenzoyl-D-tartaric acid in the crude product was investigated.

Batch size: 100 g of tartrate salt (IV) in 158.0 g of spirits and 799.8 g of water

10 Analytical data for the tartrate salt (IV) employed:

Finerenone (I)	48.05% by weight (HPLC)
enantiomeric excess	97.71 % e.e.
Largest unknown secondary component at Rt 5.606 min.	0.28 %
Residual solvents: EtOH	2.576 %

toluene	0.006 %
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The results are summarized in Table 6 below:

Table 6

Batch	pH	Amount of Na ₃ PO ₄ sol. (g) (100 g/l of water)	T (°C)	Time of metered addition (min.)	Additional stirring time (min.)	Purity of finerenone (I) HPLC (%)	Yield (% of theory)	Proportion of (+)-dibenzoyltartaric acid (% by weight)
1	7.5	400	50	30	180	99.17	97.2	0.0996
2	7.5	400	60	30	180	99.74	97.2	0.1101
3	8.0	444.9	50	30	180	99.86	97.0	0.0986
4	8.5	467.7	50	30	180	99.73	96.6	0.1298
5	9.0	480.3	50	30	180	99.85	97.4	0.1027
6	7.5	400	50	30	60	99.86	96.8	0.1010
7	7.5	400	50	30	300	99.87	97.2	0.1058
8	7.5	400	50	8	180	99.73	97.6	0.1294

5 Example 6

Reprocessing process

Example 6a

Reprocessed crude product Reduction of the proportion of (+)-O,O-dibenzoyl-D-tartaric acid < 0.1%

This experiment served to demonstrate the robustness of the reprocessing process by intentionally employing a batch having an elevated proportion of (+)-O,O-dibenzoyl-D-tartaric acid (III).

A crude product which, according to analysis, still contained 0.77% (+)-O,O-dibenzoyl-D-tartaric acid (III) was used for reprocessing

Crude finerenone (I)	Purity: 99.67 area % (HPLC); Content: 98.69% by weight
(+)-O,O-Dibenzoyl-D-tartaric acid	0.77 %

Largest secondary component impurity E	0.07 %
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Reprocessing of the crude product: Reduction of the proportion of (+)-O,O-dibenzoyl-D-tartaric acid (III) < 0.1%

5 A crude product which, according to analysis, still contains 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III) was used for reprocessing. The following procedure was adopted:

150 g of crude product (I) (containing 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III)) were added into 600 g of water and 953.9 g of spirits and heated to 70°C. Over a period of one hour, the entire solid went into solution. The mixture was then stirred at 70°C for 30 minutes. The pH is pH=5.0. By addition of 44.6 g of an aqueous sodium phosphate solution (15 g of sodium phosphate per 985 g of water), the pH was
 10 adjusted to pH=8.5 and the mixture was then stirred at 70°C for 2 hours. Over a period of 30 minutes, the mixture was cooled to 53°C and seeded with pure material (seed crystals). Stirring was then continued at 50-52°C for 30 minutes. At 200 to 155 mbar and an internal temperature, the ethanol was distilled off virtually completely, and at the same time 1845 ml of water were metered in (the filling level was kept constant: amount distilled off = amount of water added). Heating was switched off and the suspension
 15 was stirred at 23°C overnight. The crystals were filtered off via a frit and washed three times with 300 ml of water in each case. Wet yield: 218.9 g. The wet product was dried at 50°C over the weekend (> 48 hours) under reduced pressure (< 100 mbar). Yield: 146.7 g (97.8% of theory)

Finerenone (I)	Purity: 99.87 area % (HPLC); Content: 100.3% by weight
enantiomeric excess	97.87 % e.e.
(+)-O,O-Dibenzoyl-D-tartaric acid	0.00 %
Largest secondary component impurity E	0.07 %
Residual solvents: EtOH	0.286 %

Example 6b

20 Demonstration of stability, 20 h of stirring at 70°C

Reprocessing of the crude product: Reduction of the proportion of (+)-O,O-dibenzoyl-D-tartaric acid (III) < 0.1%

A crude product which, according to analysis, still contains 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III) was used for reprocessing. The following procedure was adopted:

150 g of crude product (I) (containing 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III)) were added into 600 g of water and 953.9 g of spirits and heated to 70°C. Over a period of one hour, the entire solid went into solution. The mixture was then stirred at 70°C for 30 minutes. The pH is pH=5.0. By addition of 45.2 g of an aqueous sodium phosphate solution (15 g of sodium phosphate per 985 g of water), the pH was adjusted to pH=8.5 and the mixture was then stirred at 70°C for 20 hours. Over a period of 30 minutes, the mixture was cooled to 53°C and seeded with pure material (seed crystals). Stirring was then continued at 50-52°C for 30 minutes. At 200 to 155 mbar and an internal temperature, the ethanol was distilled off virtually completely, and at the same time 1845 ml of water were metered in (the filling level was kept constant: amount distilled off = amount of water added). Heating was switched off and the suspension was stirred at 23°C overnight. The crystals were filtered off via a frit and washed three times with 300 ml of water in each case. Wet yield: 194.3 g. The wet product was dried at 50°C overnight (about 16 hours) under reduced pressure (< 100 mbar). Yield: 143.1 g (95.4% of theory)

Finerenone (I)	Purity: 99.86 area % (HPLC); Content: 101.3% by weight
enantiomeric excess	97.85 % e.e.
(+)-O,O-Dibenzoyl-D-tartaric acid	0.00 area % (0.024% by weight)
Largest secondary component impurity E	0.07 %
Residual solvent: EtOH	0.128 %

Example 6c

Reprocessing of the crude product: Reduction of the proportion of (+)-O,O-dibenzoyl-D-tartaric acid (III) < 0.1% Backtitration of the pH to pH 7.0 with sodium dihydrogen phosphate

A crude product which, according to analysis, still contains 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III) was used for reprocessing. The following procedure was adopted:

375.0 g of crude product (I) (containing 0.77% of (+)-O,O-dibenzoyl-D-tartaric acid (III)) were added into 1500 g of water and 2384.8 g of spirits and heated to 70°C. Over a period of one hour, the entire solid went into solution. The mixture was then stirred at 70°C for 30 minutes. The pH is pH=4.9. By addition of 101.4 g of an aqueous sodium phosphate solution (15 g of sodium phosphate per 985 g of water), the pH was adjusted to pH=8.5 and the mixture was then stirred at 70°C for 20 hours. Subsequently, the pH

was adjusted to pH=7 using a sodium dihydrogen phosphate solution (50 g of sodium dihydrogen phosphate in 200 ml of water). Over a period of 30 minutes, the mixture was cooled to 53°C and seeded with pure material (seed crystals). Stirring was then continued at 50-52°C for 30 minutes. At 200 to 155 mbar and an internal temperature, the ethanol was distilled off virtually completely, and at the same time 4610 ml of water were metered in (the filling level was kept constant: amount distilled off = amount of water added). Finally, the mixture was cooled to 23°C over 90 minutes. Then the reaction mixture was stirred at 22°C over the weekend (about 70 h). The crystals were filtered off via a frit and washed three times with 750 ml of water in each case. Wet yield: 402.3 g. The wet product was dried at 50°C overnight (about 16 hours) under reduced pressure (< 100 mbar). Yield: 336.6 g (89.76% of theory)

Crude finerenone (I)	Purity: 99.84 area % (HPLC); Content: 99.2% by weight
enantiomeric excess	98.02 % e.e.
(+)-O,O-Dibenzoyl-D-tartaric acid	0.00 area % (0.0068% by weight)
Largest secondary component impurity E	0.07 %
Residual solvents:	
EtOH	0.107 %
toluene	0.001 %

Example 6d

Final crystallization of the batch from Example 6c

80.0 g of the crude product (I) prepared in Example 6c were suspended in 1600 ml of ethanol (denatured with toluene) and then heated to reflux. On heating, the product went into solution. Stirring was continued at this temperature for one hour. The solution was filtered off through a heated pressure filter (T=75°C) and the pressure filter was then rinsed with 100 ml of ethanol (denatured with toluene). The solvent was then distilled off as gently as possible under reduced pressure (mantle temperature 45-47°C) until an end volume of about 5-fold (with respect to the substance employed: 80 g x 5 ~ 400 ml) had been achieved. Then, over one hour, the mixture was cooled to an internal temperature of 2°C and stirred at this temperature for 1 h. The product was filtered off and rinsed once with 80 ml of ethanol (denatured with toluene). Wet yield: 83.3 g. The wet product was dried at 50°C overnight (about 16 h) under reduced pressure (< 100 mbar). Yield: 71.4 g (89.3% of theory) of a colourless crystalline powder, fine needle-like crystals.

Analytical results:

Finerenone (I)	Purity: 99.82 area % (HPLC); Content: 98.7% by weight
enantiomeric excess	99.87 % e.e.
Largest secondary component impurity E	0.08 %
Residual solvents:	
EtOH	0.489 %
toluene	0.005 %

Example 7

Isolation of the finerenone enantiomer (Ia)

5 Example 7a

Preparation of the (-)-O,O-dibenzoyl-L-tartaric acid salt

187.2 g racemate (II) were initially charged at room temperature and 1662.5 g of spirits were then added. 485.5 g of water were then added. 97.5 g of (-)-O,O-dibenzoyl-L-tartaric acid (IIIa) were added using a funnel for solids, subsequently rinsing with 156.0 g of water. The suspension was heated to an internal
 10 temperature of 75°C over one hour and then stirred at 75°C for 3 hours. Subsequently, using a cooling ramp, the mixture was cooled to 23°C over 5.0 hours and then stirred at this temperature overnight (about 18 hours). The suspension was filtered off through a frit and washed twice with a mixture consisting of 178 g of spirits and 75 g of water. Wet yield: 255.4 g. The wet product was then dried overnight (about 16 hours) at 50°C under reduced pressure (< 100 mbar). Yield: 188.6 g (100.73% of theory) of a colourless
 15 crystalline powder. The mother liquor and the wash solution were combined (about 3200 ml of a yellowish solution, pH = 4.6) and the crude finerenone (I) was isolated therefrom (Example 7b)

Finerenone enantiomer (Ia)	49.3% by weight (HPLC)
enantiomeric excess	97.35 % e.e.
Residual solvents:	
EtOH	1.847 %
toluene	0.00 %

In a manner analogous to that described in Examples 1b and 1c, the enantiomer of finerenone (Ia) can be prepared from this tartrate salt.

Example 7bIsolation of crude finerenone (I) from the mother liquor

At room temperature, combined mother liquor and wash solution from Example 7a (about 3200 ml of a yellowish solution, pH = 4.6) were adjusted to pH = 7.6 by addition of 43.3 g of an aqueous sodium phosphate solution (100 g dissolved in 1 l of water). Under reduced pressure (85 to 65 mbar, internal temperature 38 to 20°C), the spirits were then substantially distilled off and the mixture was reduced to an end volume of about 0.8 l. The mixture was cooled to room temperature and the precipitated suspension was stirred at 22°C for 2 hours. The suspension was filtered off with suction and washed twice with in each case 150 ml of water. Wet yield: 159.1 g. The wet product was dried at 50°C overnight (about 16 h) under reduced pressure (< 100 mbar). Yield: 86.3 g (92.2% of theory based on the racemate (II) employed in Example 7a).

Finerenone (I)	Purity: 99.48 area % (HPLC); Content: 99.39% by weight
enantiomeric excess	98.14 % e.e.
Largest secondary component impurity E	0.13 %
(-)-O,O-Dibenzoyl-L-tartaric acid	0.14 % (0.05% by weight)

In an analogous manner, as described in Example 1c, this crude product can be employed to produce finerenone (I) in pure form.

15

Example 8**Example 8a**Isolation of the wrong enantiomer (Ia) from the mother liquor

At room temperature, combined mother liquor and wash solution from Example 1a (about 3750 ml of a yellowish solution, pH = 4.5) were adjusted to pH = 7.5 by addition of 101.1 g of an aqueous sodium phosphate solution (100 g dissolved in 1 l of water). Under reduced pressure (85 to 65 mbar, internal temperature 38 to 20°C), the spirits were then substantially distilled off and the mixture was reduced to an end volume of about 0.85 l. The mixture was cooled to room temperature and the precipitated suspension was stirred over the weekend (> 48 hours) and then at 22°C for a further 2 hours. The suspension was filtered off with suction and washed twice with in each case 200 ml of water. Wet yield:

25

139.1 g. The wet product was dried at 50°C overnight (about 16 h) under reduced pressure (< 100 mbar).

Yield: 103.1 g (82.48% of theory based on the racemate (II) employed in Example 1a).

Finerenone enantiomer (Ia)	Purity: 99.75 area % (HPLC); Content: 99.2% by weight
enantiomeric excess	99.34 % e.e.
Largest secondary component impurity E	0.12 %
(+)-O,O-Dibenzoyl-D-tartaric acid	0.14 % (0.05% by weight)
Water	0.102 %

Example 8b

5 Industrial batch for isolation of the finerenone enantiomer (Ia)

A combined mother liquor and wash solution from Example 4 (tartrate preparation on an industrial scale) was worked up as follows: Amount about 1165 kg of solution

- Preparation of a sodium phosphate solution: At 20°C, 7.3 kg of sodium phosphate were dissolved in 73.1 kg of water
- 10 • In a 1600 l stirred vessel, 1165 kg of mother liquor (including wash solution) were initially charged at 20°C and adjusted to pH 7.5 (+/- 0.1) using 28 kg of the sodium phosphate solution prepared above
- The mixture was stirred for 0.25 h, and subsequently spirits were distilled off under reduced pressure (65 mbar, IT about 22°C) to a filling level of about 310 l
- 15 • The mixture was then stirred at 20°C for 2 h and the suspension was isolated using an inverting centrifuge, washing with 20 kg of water in each case.
- The wet product was then dried in a spherical dryer at 50°C under reduced pressure (30 mbar; about 6 h)
- The mixture was cooled to 15°C and the product was removed

20

Analytical data of the mother liquor (incl. wash solution) employed for Batch 1

Finerenone enantiomer (Ia)	92.4 % (HPLC)
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Enantiomeric excess	95.92
Largest secondary component impurity E	0.26 %
(+)-O,O-Dibenzoyl-D-tartaric acid	5.38 % (HPLC)
Residual solvents:	
ethanol	0.319 %
toluene	0.001 %

Analytical data of the mother liquor (incl. wash solution) employed for Batch 2

Finerenone enantiomer (Ia)	92.03 %
enantiomeric excess	99.03
Largest secondary component impurity E	0.15 %
(+)-O,O-Dibenzoyl-D-tartaric acid	5.94 %
Residual solvents:	
ethanol	0.177 %
toluene	0.001 %

Batch	Input kg	Yield: kg	Yield: % of theory
Batch 1	~ 1165 of mother liquor (incl. wash solution)	38,2	96
Batch 2	~ 1165 of mother liquor (incl. wash solution)	37,1	93

5

Analytical data Batch 1

Finerenone enantiomer (Ia)	Purity: 99.71%
enantiomeric excess	96.56 % e.e.
Largest secondary component impurity E	0.106 %
(+)-O,O-Dibenzoyl-D-tartaric acid	0.081 %

Analytical data Batch 2

Finerenone enantiomer (Ia)	Purity: 99.446%
enantiomeric excess	99.5 % e.e.
Largest secondary component impurity E	0.107 %
(+)-O,O-Dibenzoyl-D-tartaric acid	0.33 %

Example 9

Examples of further tartaric acid derivatives and further solvents

5 Example 9a(+)-O,O-Di-p-anisoyl-D-tartaric acid

100 mg of racemate and 111 mg of (+)-O,O-di-p-anisoyl-D-tartaric acid were dissolved in 5 ml of dichloromethane and allowed to stand. After some time, the diastereomeric salt precipitated out. The salt was filtered off and the enantiomeric excess was measured. The measurement showed an enantiomeric excess of 68% e.e. for (Ia)

Example 9b(-)-O,O'-Di-p-toluyyl-L-tartaric acid

100 mg of racemate and 0.55 eq. of (-)-O,O-di-p-toluyyl-L-tartaric acid were dissolved in 4 ml of solvent and allowed to stand. After some time, the diastereomeric salt precipitated out. The salt was filtered off and the enantiomeric excess was measured. The measurement showed an enantiomeric excess of y% e.e. for (Ia). The results are summarized in Table 7 below.

Table 7:

4 ml of solvent/solvent mixture	Enantiomeric excess e.e. % (Ia)
n-propanol / water 80:20	85.35
n-pentanol / water 90:10	89.10
methanol / water 80:20	84.47
methanol	93.18
isopropanol / water 80:20	81.20
isobutanol / water 90:10	79.25

ethylene glycol / water 80:20	93.68
ethylene glycol	68.50
ethanol / water 80:20	85.87
ethanol	85.96
2-butanol / water 80:20	83.92
1-butanol / water 90:10	88.93

Example 9c(+)-O,O-Dibenzoyl-D-tartaric acid

100 mg of racemate and 0.55 eq. of (+)-O,O-dibenzoyl-D-tartaric acid were dissolved in 4 ml of solvent
 5 and allowed to stand. After some time, the diastereomeric salt precipitated out. The salt was filtered off and the enantiomeric excess was measured. The measurement showed an enantiomeric excess of y% e.e. for (I). The results are summarized in Table 8 below.

Table 8:

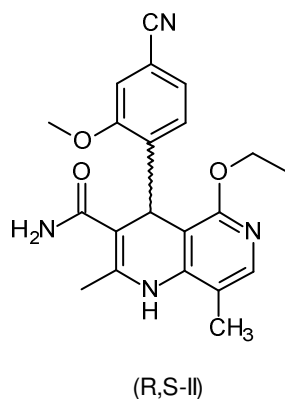
4 ml of solvent/solvent mixture	Enantiomeric excess e.e. % (I)
n-propanol / water 80:20	94.01
n-pentanol / water 90:10	94.59
methanol / water 80:20	89.09
methanol	91.21
isopropanol / water 80:20	90.92
isobutanol / water 90:10	85.42
ethyl glycol	92.08
ethanol / water 80:20	94.64
ethanol	93.64
cyclohexanol / water 90:10	84.33
benzyl alcohol / water 90:10	88.83
2-butanol / water 80:20	92.49
1-pentanol	80.99
1-butanol / water 90:10	94.02

Description of the figure

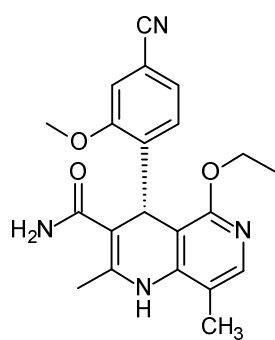
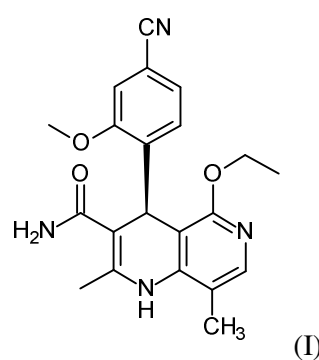
Figure 1: XRPD of compound (VI) obtained as a colourless crystalline powder according to Example 1a

Claims

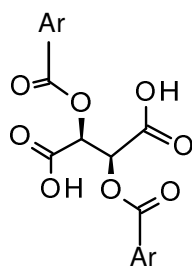
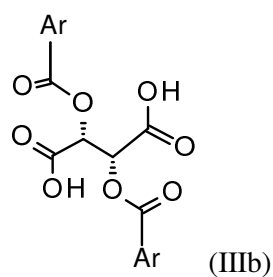
1. Racemate resolution of (II)



5 into (Ia) and/or (I)

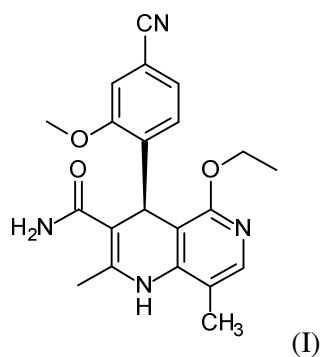


using chiral substituted tartaric ester of the general formulae (IIIa) or (IIIb)

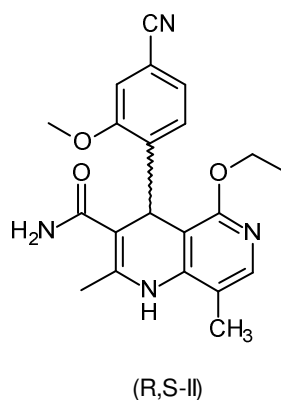


where Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical.

2. Process for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the formula (I)

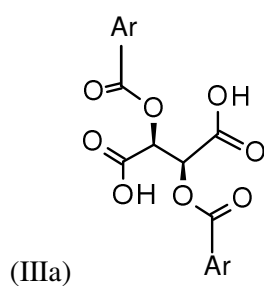


by racemate resolution of (II)



5

using a chiral substituted tartaric ester of the formula (IIIa)



where Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical.

- 10 3. Process according to Claim 1 or 2, characterized in that the racemate resolution is carried out in an ethanol/water mixture.

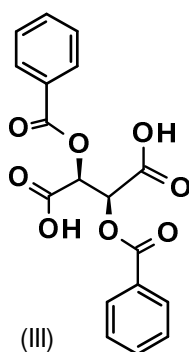
- 64 -

4. Process according to any of Claims 1 to 3, characterized in that the racemate resolution is carried out at a temperature in the range from 60 to 80°C.

5. Process according to any of Claims 1 to 4, characterized in that Ar represents phenyl.

5

6. Process according to any of Claims 1 to 5, characterized in that dibenzoyltartaric acid (III)



is employed for the racemate resolution.

10 7. Process according to any of Claims 1 to 6, characterized in that the precipitated diastereomeric salt (IVa), (IVb), (IVc) and/or (IVd) is isolated.

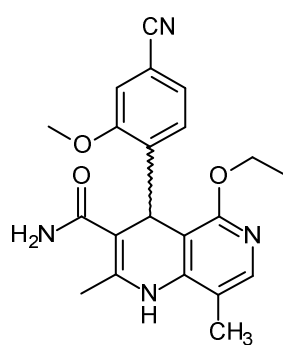
8. Process according to any of Claims 1 to 7, characterized in that the diastereomeric salt is treated with a base and the solvent is removed.

15

9. Process according to any of Claims 1 to 8, characterized in that the base used is potassium hydroxide, potassium phosphate or sodium phosphate.

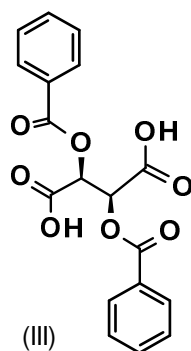
10. Process according to any of Claims 1 to 9, wherein the racemate

- 65 -



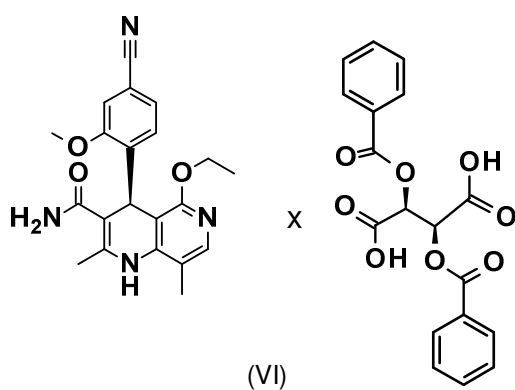
(R,S-II)

is reacted with dibenzoyltartaric acid of the formula (III)



(III)

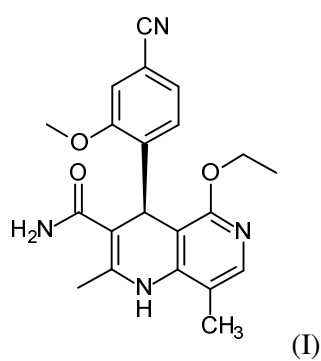
in a spirits/water mixture to give the diastereomeric salt (VI)



(VI)

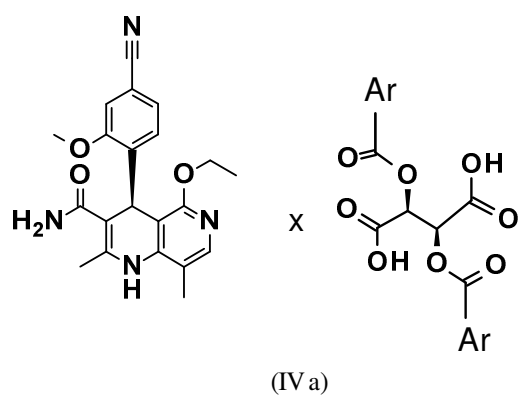
5

and subsequently finerenone (I)

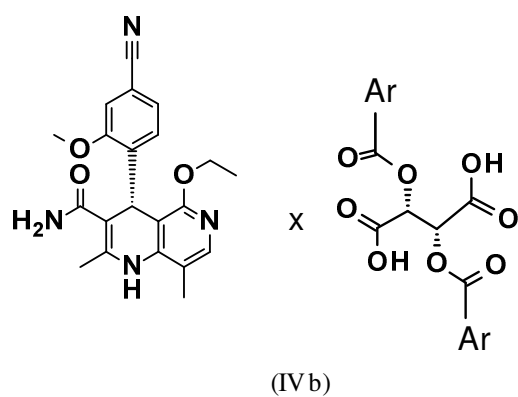


is released using sodium phosphate, likewise in a spirits/water mixture.

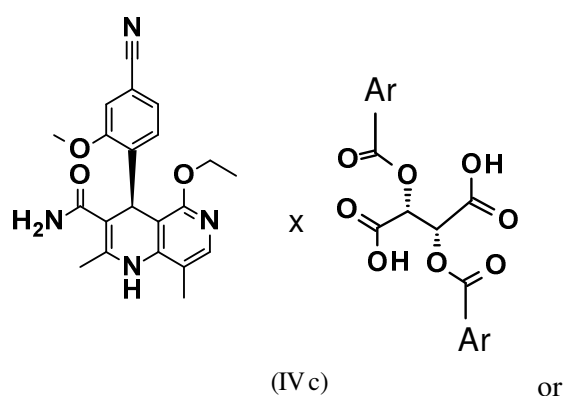
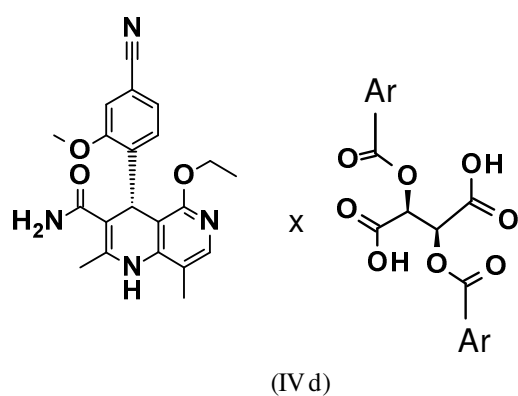
11. Diastereomeric salts of the formula



5

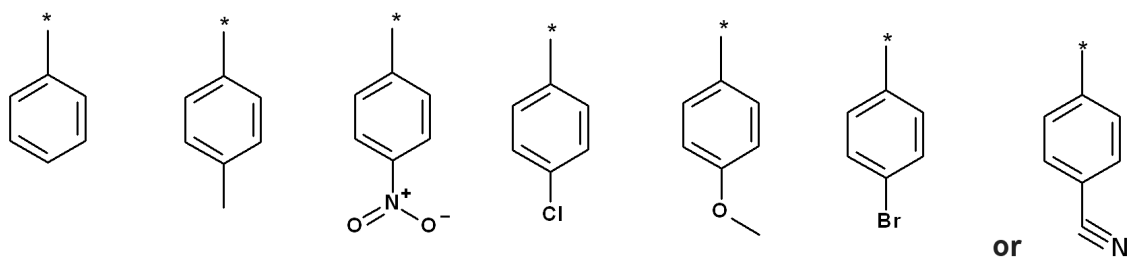


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where Ar represents an unsubstituted or substituted aromatic or heteroaromatic radical.

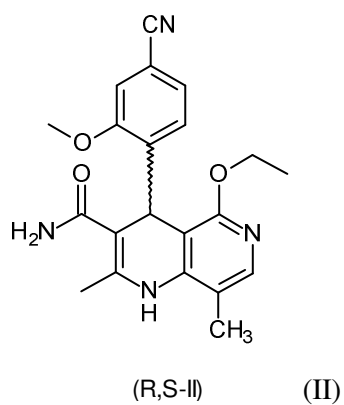
- 5 12. Diastereomeric salt according to Claim 11, characterized in that Ar represents



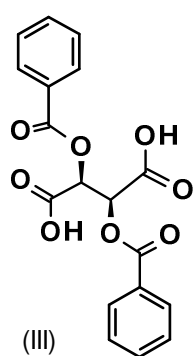
where * represents the point of attachment.

13. Diastereomeric salt according to Claim 11 or 12, characterized in that Ar represents phenyl.

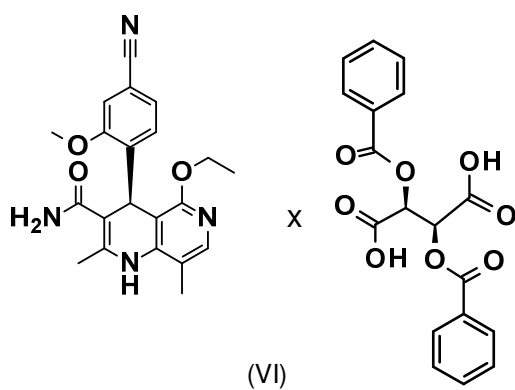
14. Finerenone (I) having a dibenzoyltartaric acid content of $\leq 0.15\%$, obtained by reacting the racemate (II)



- 5 with dibenzoyltartaric acid of the formula (III)



in a spirits/water mixture to give the diastereomeric salt (VI)



and subsequently releasing finerenone (I)

