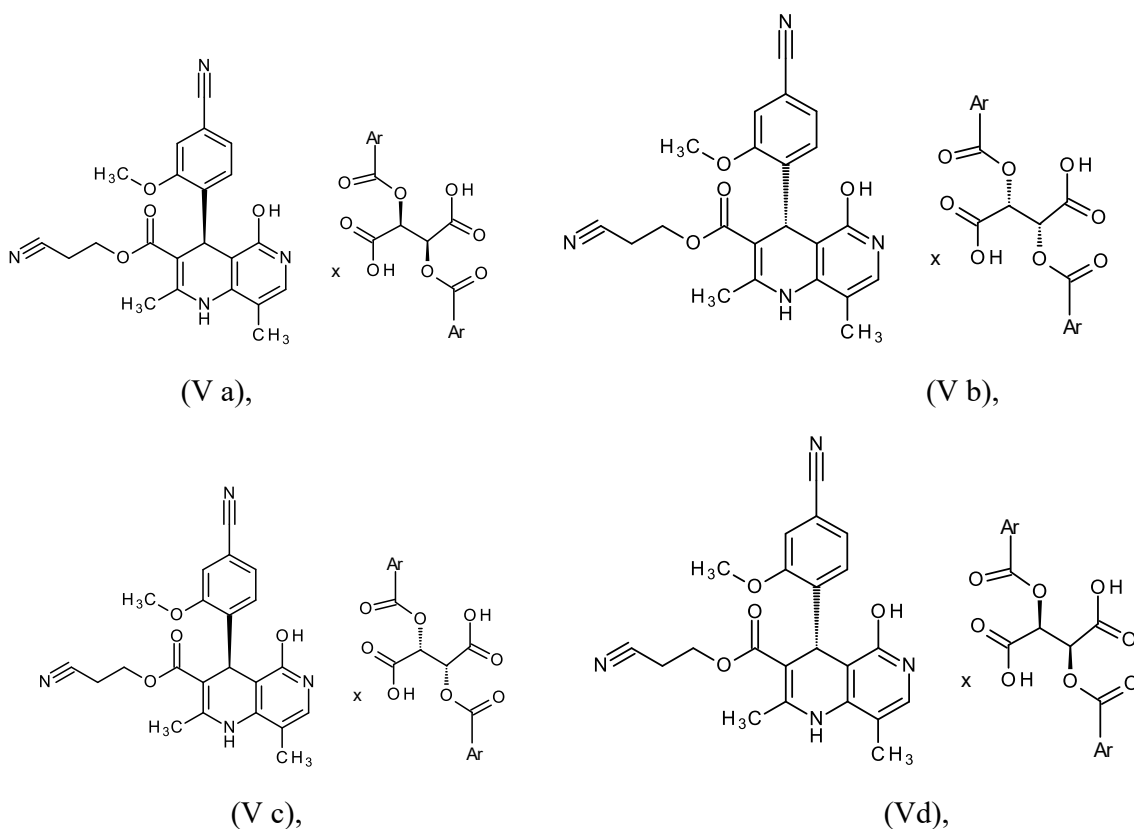


PROCESS FOR THE PREPARATION OF (2-CYANOETHYL (4S)-4-(4-CYANO-2-METHOXY-PHENYL)-5-HYDROXY-2,8-DIMETHYL-1,4-DIHYDRO-1,6-NAPHTHYRIDIN-3-CARBOXYLATE BY RACEMATE SEPARATION BY MEANS OF DIASTEREOMERIC TARTARIC ACID ESTERS

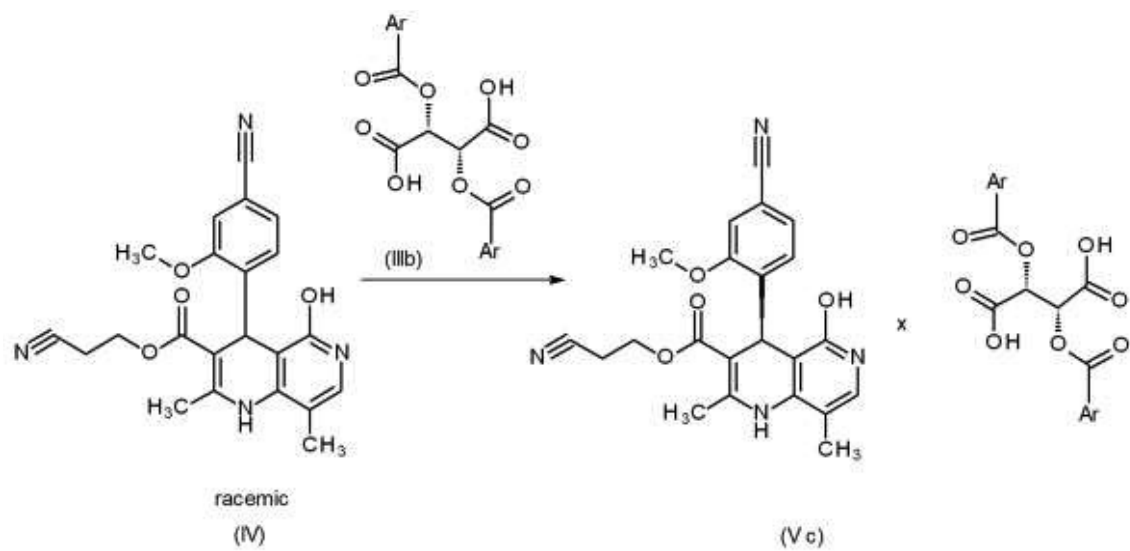
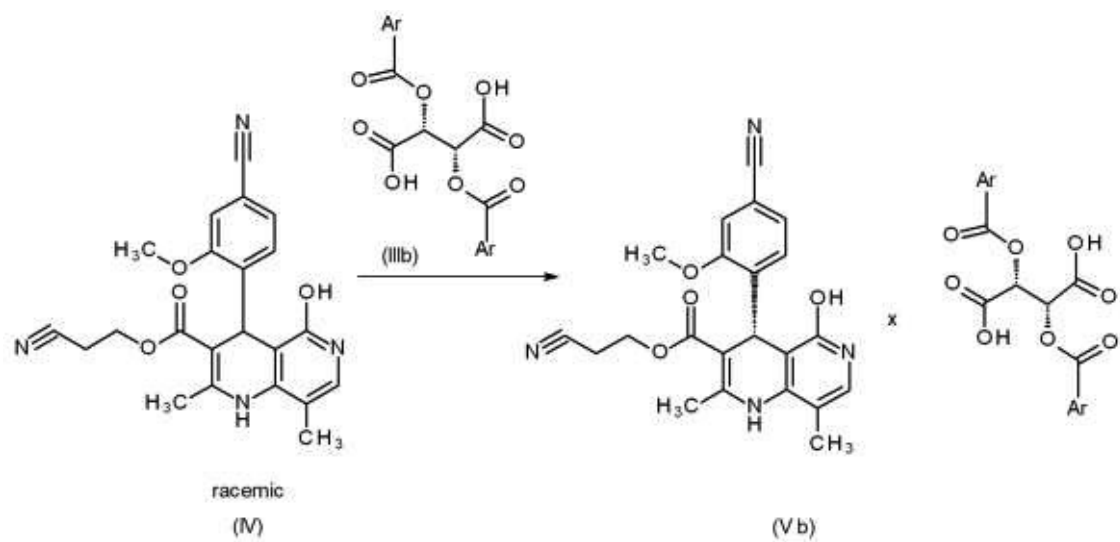
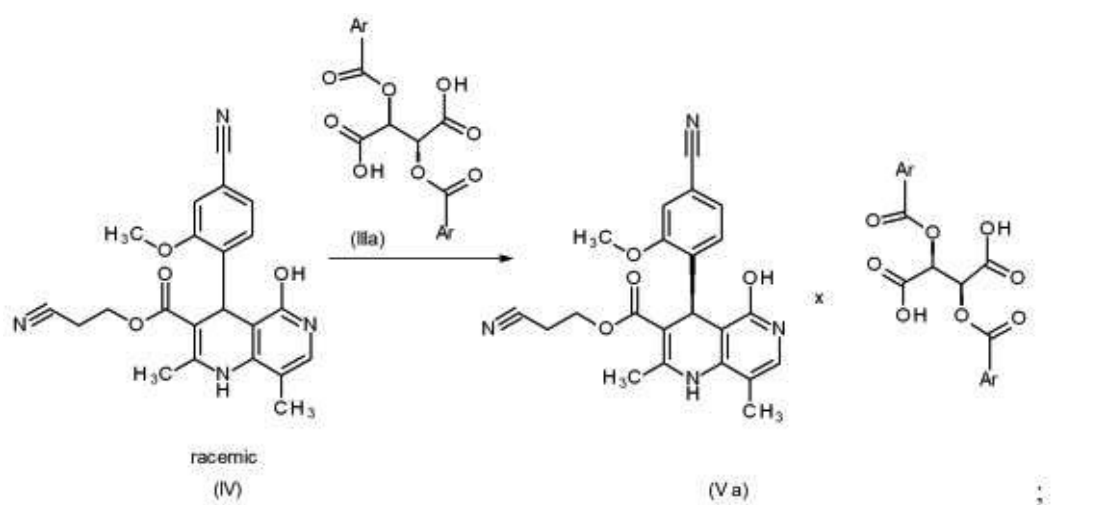
- 5 The present invention relates to a diastereomeric salt of the formula (Va), (Vb), (Vc) and/or (Vd)

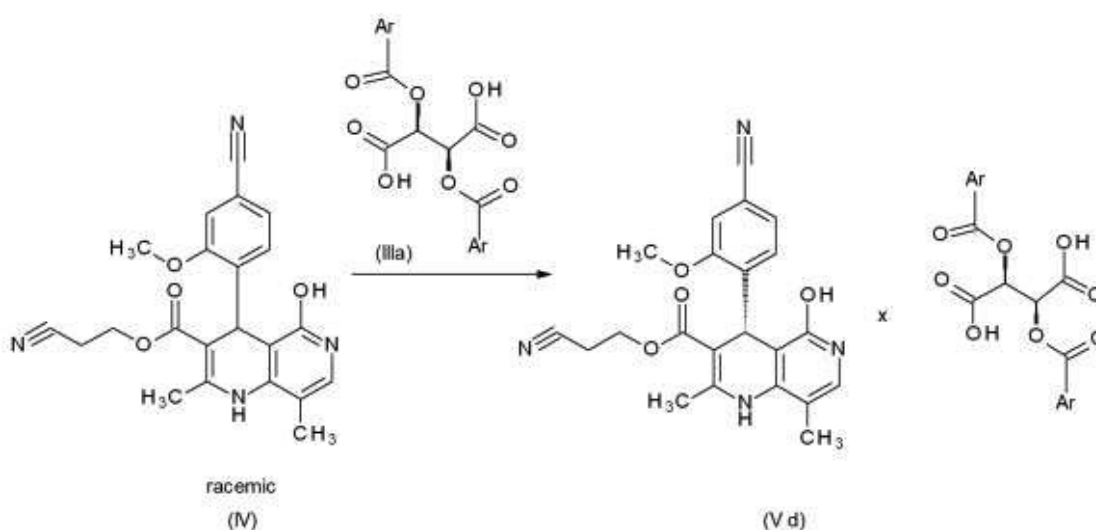


- 10 in which Ar is an unsubstituted or substituted aromatic or heteroaromatic.

The invention also relates to a process for preparing one or more diastereomeric salts of the formula (Va), (Vb), (Vc) and/or (Vd), comprising the step (i) of

- (i) optical resolution of the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb)





The invention further relates to a process for preparing the compound of the formula (IVa), comprising steps (i) and (ii):

- (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
- (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa).

The invention additionally relates to a process for preparing the compound of formula (Ia), comprising steps (i), (ii), (iii), (iv) and (v):

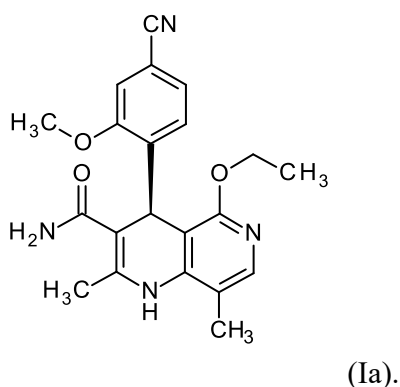
- (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
- (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa);
- (iii) reacting the compound of formula (IVa) obtained in step (ii) with an orthoester under acidic catalysis to obtain the compound of formula (VIIa);
- (iv) hydrolysing the compound of formula (VIIa) obtained in step (iii) to obtain the compound of formula (VIIIa);
- (v) converting the compound of formula (VIIIa) obtained in step (iv) to a compound of formula (Ia): reacting the product from step (iv) in THF as solvent firstly with 1,1-

carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, adding hexamethyldisilazane and then heating the mixture under reflux for 16-24 hours, and then a THF/water mixture.

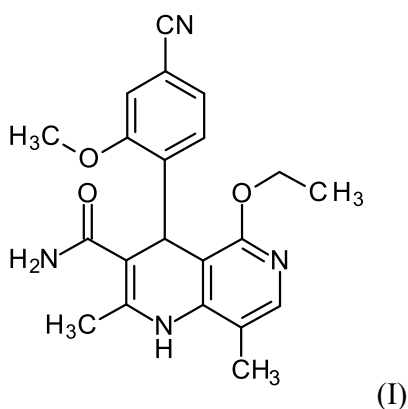
The invention further provides for the use of a tartaric ester of the formula (IIIa) or (IIIb) in a process for preparing the compound of formula (Va), (Vb), (Vc), (Vd), (IVa), and/or (Ia).

Finerenone (Ia) acts as a nonsteroidal antagonist of the mineralocorticoid receptor and can be used as an agent for prophylaxis and/or treatment of cardiovascular and renal disorders such as heart failure and diabetic nephropathy.

The term "finerenone" relates to the compound (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide or to the compound of formula (Ia)

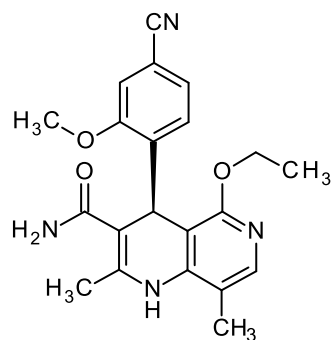


The compound of the formula (I)

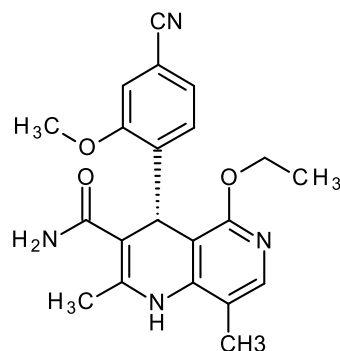


is the racemate of finerenone.

The expression "antipodes of finerenone" or "antipodes of the compound of formula (I)" concerns the compounds of formulae (Ia) and (Ib)

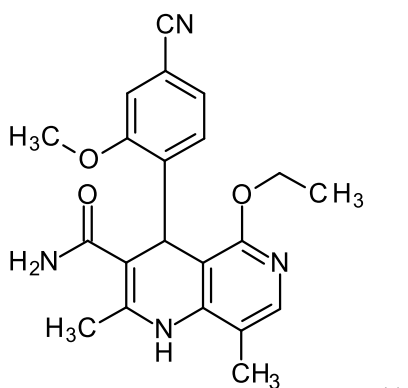


(Ia)



(Ib).

- 5 The compound of the formula (Ia) and the preparation process therefor are described in WO 2008/104306 A1 and ChemMedChem **2012**, 7, 1385, and also in WO 2016/016287 A1. In order to arrive at the compound of the formula (Ia), the racemic mixture of the amides (I)

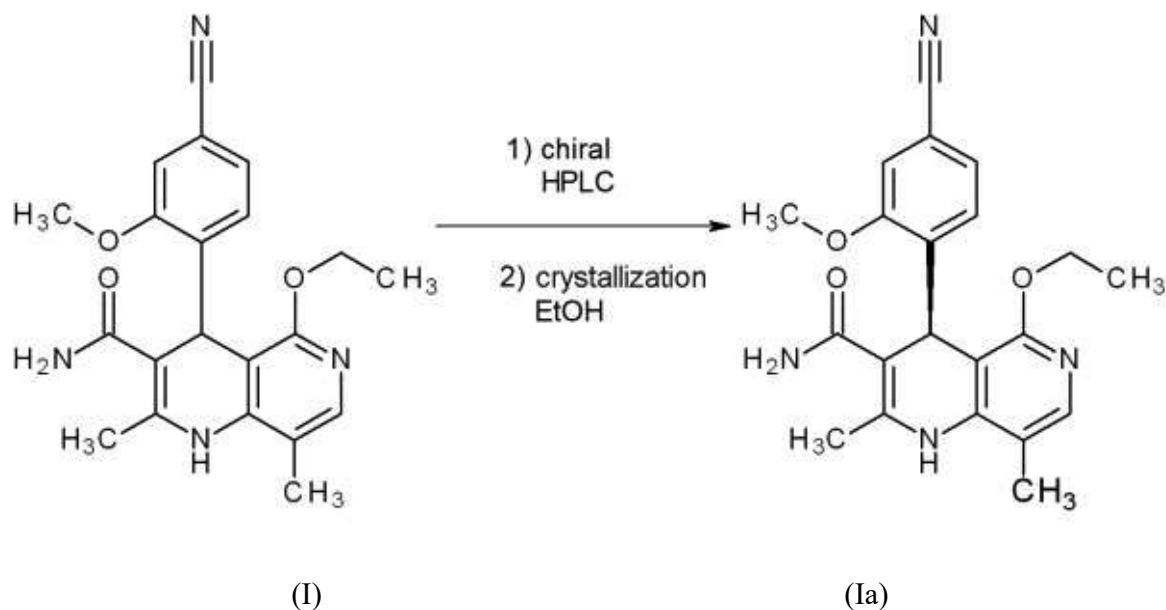


(I)

has to be separated into the antipodes since only the antipode of the formula (Ia) is active.

- 10 In the published research scale synthesis (WO 2008/104306 A1), a specifically synthesized chiral phase was used for this purpose (prepared in-house), which contained N-(dicyclopropylmethyl)-N²-methacryloyl-D-leucinamide as chiral selector. It has been found that the separation can also be performed on a readily commercially available phase. This is the Chiralpak AS-V phase, 20 μm. The eluent used was a mixture of methanol/acetonitrile 60:40. In this case, the
- 15 chromatography can be conducted on a conventional chromatography column, but preference is given to using the techniques known to those skilled in the art such as SMB (simulated moving

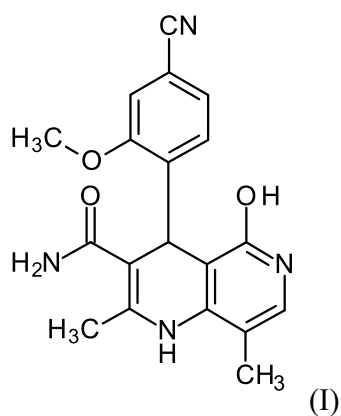
bed; G. Paredes, M. Mazotti, Journal of Chromatography A, 1142 (2007): 56-68) or Varicol (Computers and Chemical Engineering 27 (2003) 1883-1901).



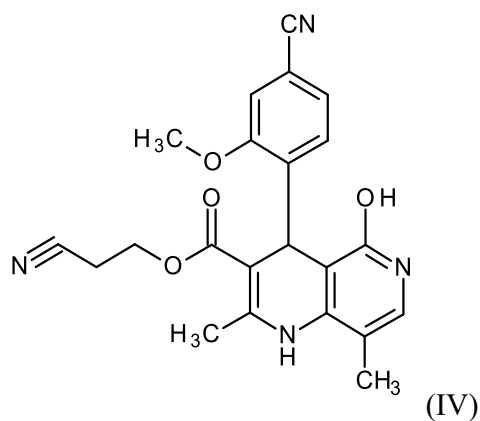
5 Although SMB separation affords a relatively good yield and optical purity, the procurement costs and the operation of such a facility under GMP conditions pose a great challenge and are associated with high costs. Even the chiral phase used in each case is very expensive and has only a limited lifespan and has to be replaced time and again in the course of production. For reasons of production engineering, this is not optimal unless there is a second plant 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 procurement of huge falling-film evaporators and is associated with the consumption of enormous amounts of energy.

15 The problem addressed was therefore to look for an alternative synthetic route to enantiomerically pure finerenone (Ia) that is significantly less costly and can be performed with conventional pilot plant equipment (stirred tanks/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.

20 In the novel process of the invention, rather than the discussed complex SMB separation of the racemic mixture of the amides (I)

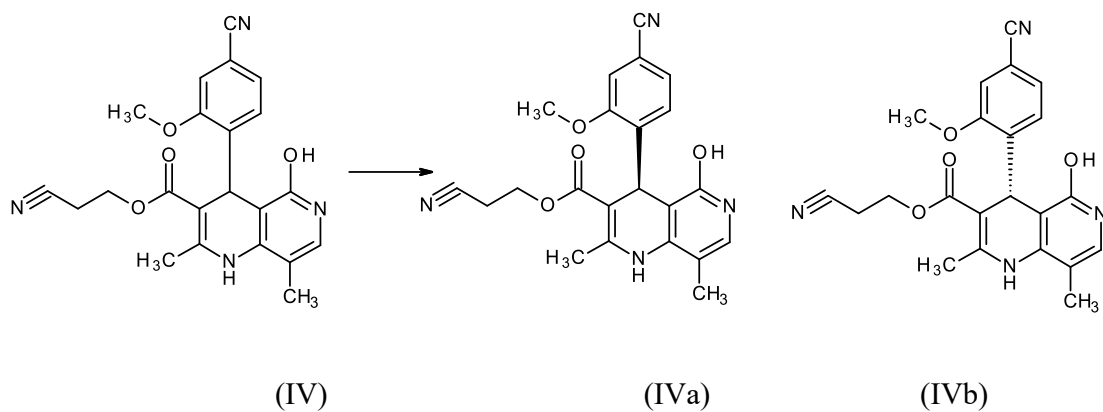


into the antipodes (Ia) and (Ib), an advantageous optical resolution is undertaken on a synthesis precursor, the racemic unit (II)



5 is undertaken.

Numerous attempts were made, using the customary conventional methods, to develop an optical resolution of the racemate IV to the antipodes IVa and IVb



10 (variation of chiral organic acid and solvent), as shown in Table 1:

Table 1:

Acid
(S)-(+)-1,1-binaphthyl-2,2-diyl hydrogenphosphate
(-)-quinic acid
(-)-O,O'-diacetyl-L-tartaric acid
(-)-O,O'-dipivaloyl-L-tartaric acid
(+)-3-bromocamphor-10-sulfonic acid
(+)-4-chlorotartranilic acid
(+)-4'-nitrotartranilic acid
(+)-camphoric acid
(+)-O-acetyl-L-mandelic acid
(1R)-(-)-camphor-10-sulfonic acid
(1S)-(-)-camphanic acid
(2R,3R)-(+)-tartaric acid
(R)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid
(S)-(-)-2-bromopropionic acid
(S)-(-)-2-chloropropionic acid
(S)-(+)-citramalic acid
(S)-(+)-mandelic acid
Ac-acid triple mix
malic acid
D-(+)-HPP monoacid
L-glutamic acid
L-lactic acid
menthoxyacetic acid

N-(3,5-dinitrobenzoyl)-(R)-(-)-2-phenylglycine
N-acetyl-L-leucine
N-acetyl-L-phenylalanine
N-Ac-proline-OH
naproxen

Table 1 lists the acids used for optical resolution. These were reacted with the racemate (IV) in various organic solvents, for example in pure alcohols (methanol, ethanol, 1-propanol, 2-propanol, butanol), and mixtures thereof with water, and also THF, acetone, ethyl acetate, 5 dichloromethane, and a further number of other solvents, and analysed for diastereomeric salt formation.

Also among the experiments conducted were those with the conventional resolution reagent (+)-tartaric acid.

However, salt formation was not observed in any of the cases; all that happens instead is that the 10 racemate precipitates out of the solution without forming a salt. This corresponds essentially to the expectations of the person skilled in the art, since it could have been inferred from the pKa of the racemic molecule (IV) that conventional optical resolution by diastereomer salt formation with organic acids should not be possible since the measured pKa (for the base) is at 4.3 and hence virtually rules out salt formation. According to the literature, for example “Handbook of 15 Pharmaceutical Salts – Properties, Selection and Use; by P. Heinrich Stahl, Camille G. Wermuth (Eds.); Wiley-VCH, p. 166”, the difference in pK should be at least 3 pK units in order to allow stable salt formation.

All efforts to obtain diastereomeric salts and then to bring the enantiomeric excess in the direction of > 99% e.e. in the course of the subsequent synthesis steps were unproductive; therefore, further 20 alternatives were sought.

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.

However, it was found that, surprisingly, aromatically or heteroaromatically substituted derivatives of tartaric acid (IIIa + IIIb) are of excellent suitability to obtain diastereomeric salts and to achieve the enantiomeric excess required.

In summary, the invention relates to the following subject-matter:

- 5 (1) Diastereomeric salt of the formula (Va), (Vb), (Vc) and/or (Vd):
- (2) Process for preparing one or more diastereomeric salts of the formula (Va), (Vb), (Vc) and/or (Vd), comprising the step (i) of
 - (i) optical resolution of the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb);
- 10 (3) Process for preparing the compound of the formula (IVa), comprising steps (i) and (ii):
 - (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
 - (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i)
15 to the compound of formula (IVa);
- (4) Process for preparing the compound of formula (Ia), comprising steps (i), (ii), (iii), (iv) and (v):
 - (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
 - 20 (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa);
 - (iii) reacting the compound of formula (IVa) obtained in step (ii) with an orthoester under acidic catalysis to obtain the compound of formula (VIIa);
 - (iv) hydrolysing the compound of formula (VIIa) obtained in step (iii) to obtain the
25 compound of formula (VIIIa);

- (v) converting the compound of formula (VIIIa) obtained in step (iv) to a compound of formula (Ia): reacting the product from step (iv) in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, adding hexamethyldisilazane and then heating the mixture under reflux for 16-24 hours, and then adding a THF/water mixture;

- (5) Use of a tartaric ester of the formula (IIIa) or (IIIb) in a process for preparing the compound of formula (Va), (Vb), (Vc), (Vd), (IVa), and/or (Ia).

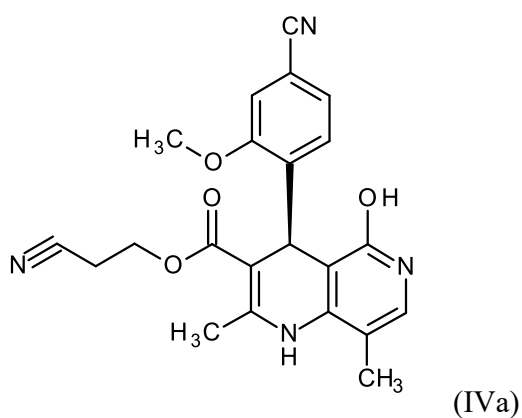
The technical effects of the invention can be summarized as follows:

- The novel processes of the invention are employable in many less expensive processes or plants by comparison with the prior art described above;
- The novel processes of the invention can be performed with conventional pilot plant equipment (stirred tanks/insulation apparatus) – such plants are traditionally part of the standard equipment in pharmaceutical production facilities and do not require any additional capital costs.
- The novel processes of the invention can be effected on an industrial scale;
- By the processes of the invention, it is possible to prepare diastereomeric salts having an enantiomeric excess of the diastereomeric salts in the range from 65% to 80% e.e.
- The diastereomeric salts obtained by processes of the invention are notable for a high enantiomeric excess, generally > 95% e.e., which is sufficient to prepare finerenone in >> 99% e.e.
- The diastereomeric salts need not necessarily be dried, but may also be used moist in the next process stage. This also enables one-pot processes;
- It has been found that, in a conversion of the acid (VIIa or VIIb) in tetrahydrofuran (THF), the amide of formula (I) or (Ia) crystallizes directly out of the solution and can be obtained in high yield and purity;
- In the synthesis of the invention, it is possible to avoid further intermediate steps, and hence the synthesis can be conducted in a time- and cost-efficient manner;

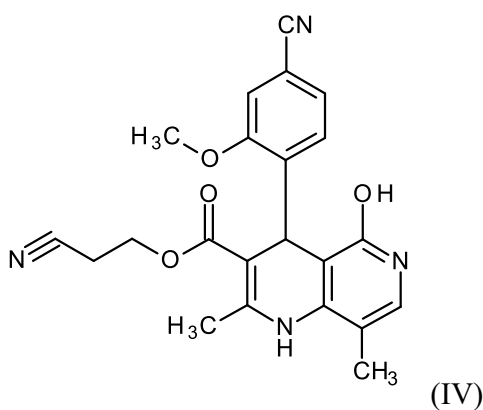
- Examples of such intermediate steps are, for example, further purifications and/or cost-/energy-intensive recovery of individual constituents, recovery or removal of solvents.

There follows a description of further embodiments and the subject-matter and further embodiments of the invention:

- 5 One embodiment also relates to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

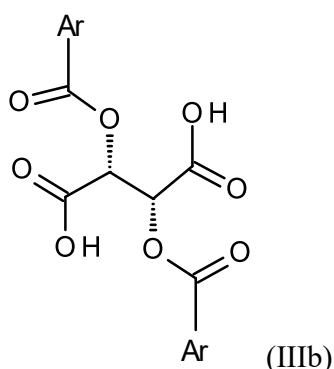


by optical resolution of the racemate (IV)



10

is reacted with a chiral substituted tartaric ester of the formula (IIIb)



where Ar is unsubstituted or substituted aryl or heteroaryl.

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
5 valency of the atom in question is not exceeded under the particular circumstances. Combinations of substituents and/or variables are permissible.

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

The heteroaryl group may be a 5-membered heteroaryl group, for example thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl,
10 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, indolizinyl or purinyl; or a 10-membered heteroaryl
15 group, for example quinolinyl, quinazolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl or pteridinyl.

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

In the context of the present application, aryl group is especially a phenyl group.

20 Substituents in the context of the present invention are halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, nitrile, nitro, cyano, trifluoromethyl, an amide group, for example -NHCOR in which R is methyl, ethyl or phenyl, an -NRCOR group in which R has the definition given above, a -CONHR group in which R has the definition given above, a -CONRR group in which R' has the same meaning

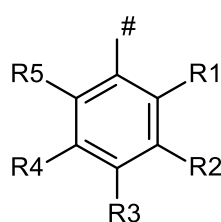
as R as defined above, or cyclic amides such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted.

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

- 5 The term “C₁-C₆-alkyl” denotes a straight-chain or branched saturated monovalent hydrocarbon group 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, 10 3,3-dimethylbutyl, 2,3-dimethylbutyl, 1,2-dimethylbutyl or 1,3-dimethylbutyl group or an isomer thereof. The group especially has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl”), e.g. a methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl or *tert*-butyl group, especially 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 15 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 or an isomer thereof.

Ar is preferably:

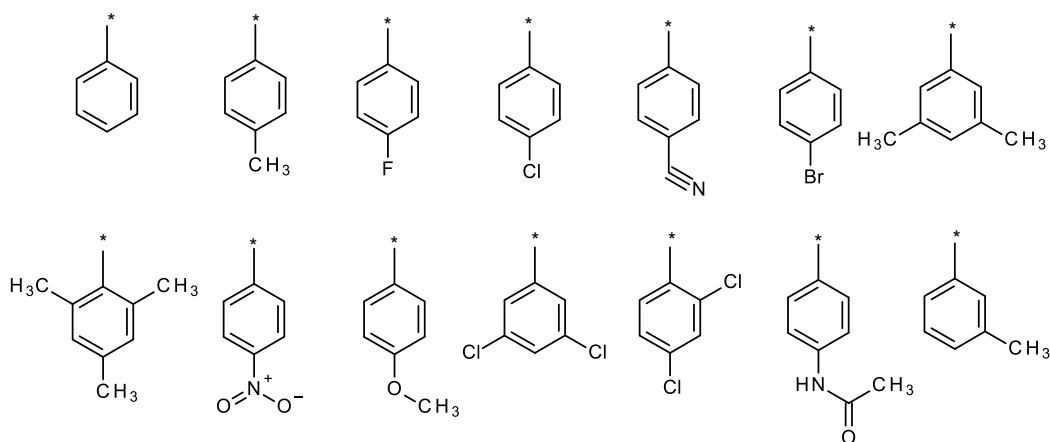


- 20 where # represents the site of attachment,

- where R₁, R₂, R₃, R₄, R₅ are each a hydrogen atom or an alkyl radical, for example methyl, ethyl, propyl, or a halogen atom, for example fluorine, chlorine, bromine or iodine, or an ether group, for example O-methyl, O-ethyl, O-phenyl, or a nitro group, or a cyano group, or a CF₃ group, or an amide group, for example -NHCOR in which R may be methyl, ethyl or phenyl, or 25 -NRCOR in which R has the meaning given above or CONHR in which R has the meaning given above or CONRR' in which R' has the same meaning as R as defined above, or cyclic amides

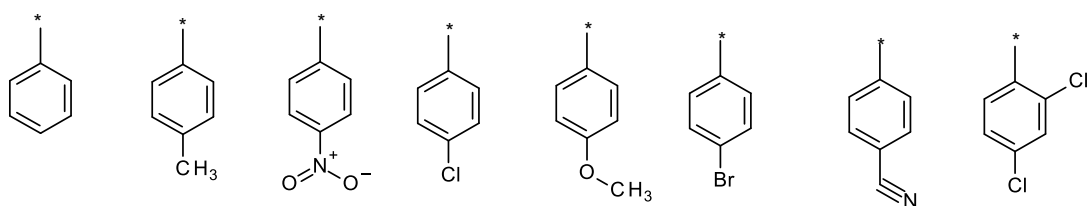
such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted. The substitution patterns may differ widely; for instance, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. Ar may alternatively be a substituted heteroaromatic radical such as, preferably, pyridine or pyrazine. Ar may alternatively be a polycyclic aromatic hydrocarbon, for example a substituted naphthalene, anthracene or quinoline.

More preferably, Ar is one of the formulae



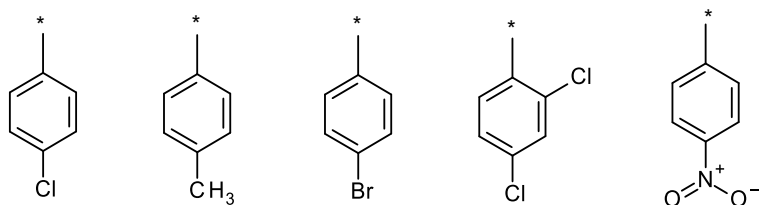
in which * represents the site of attachment.

10 Especially preferably, Ar is one of the formulae



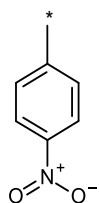
in which * represents the site of attachment.

Very particularly preferred Ar radicals are:



in which * represents the site of attachment.

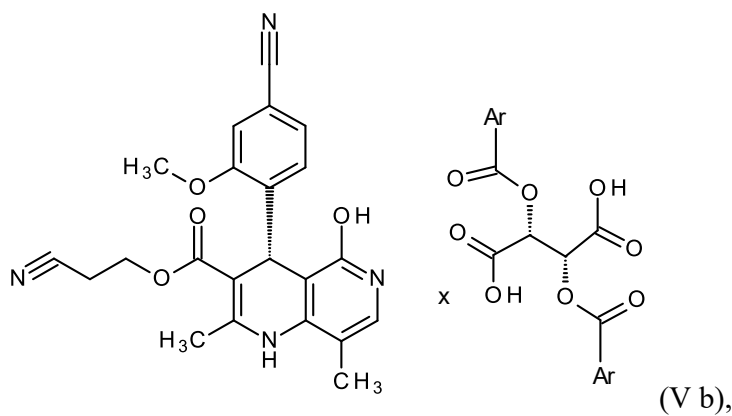
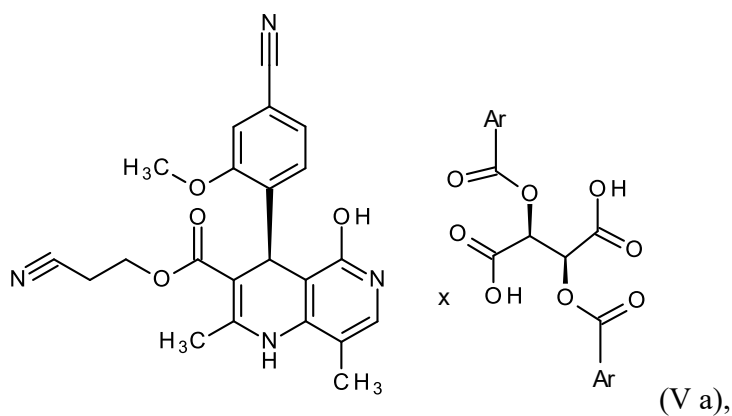
Of which the 4-nitrophenyl radical

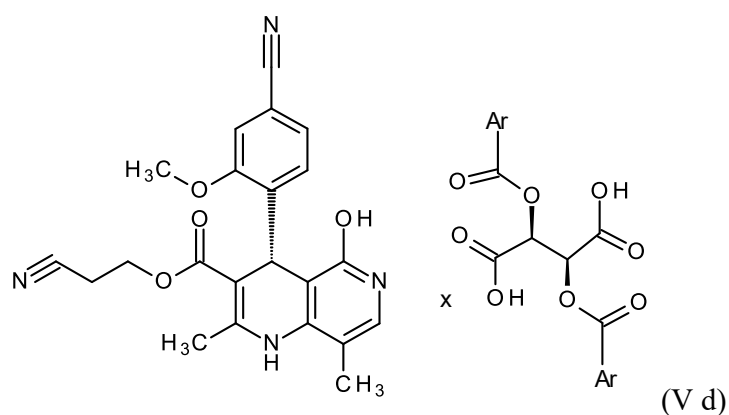
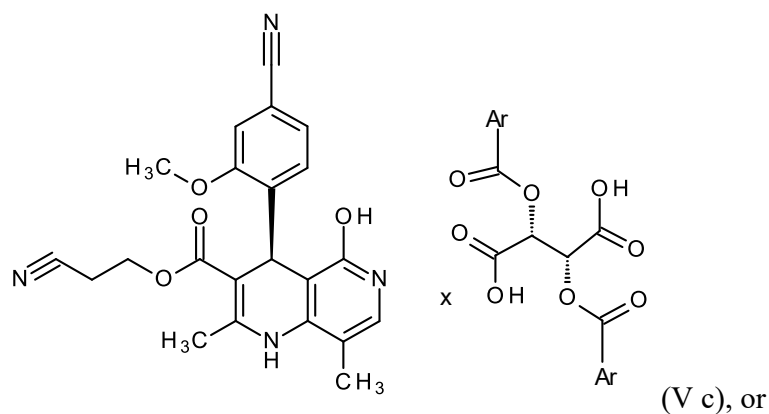


is exceptionally preferred.

- 5 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.

A further subject of the invention relates to diastereomeric salts (Va to Vd) of the formulae



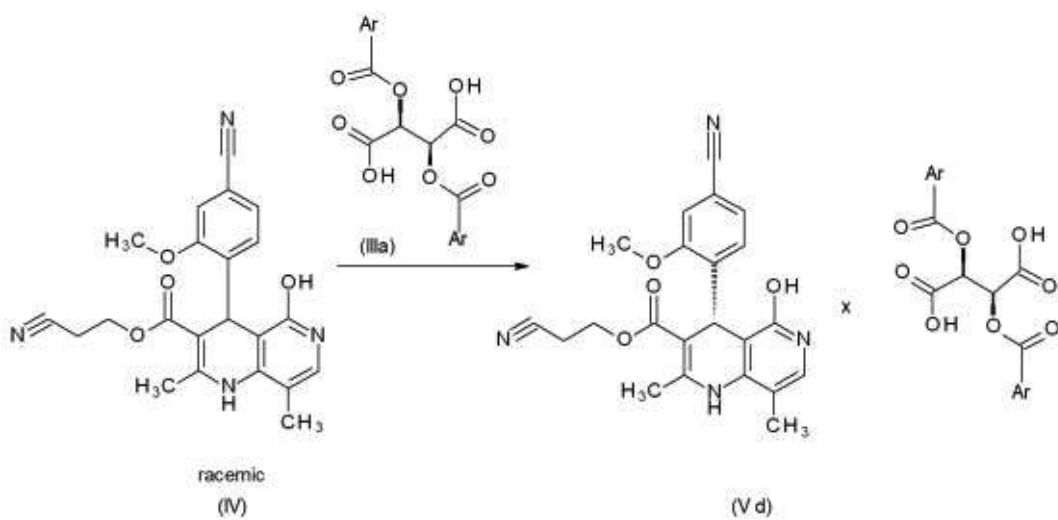
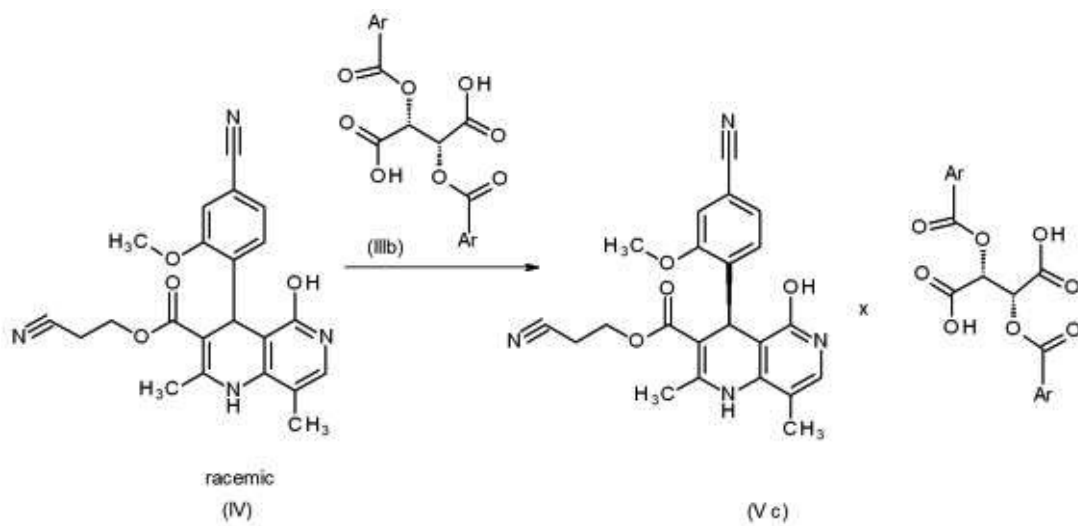
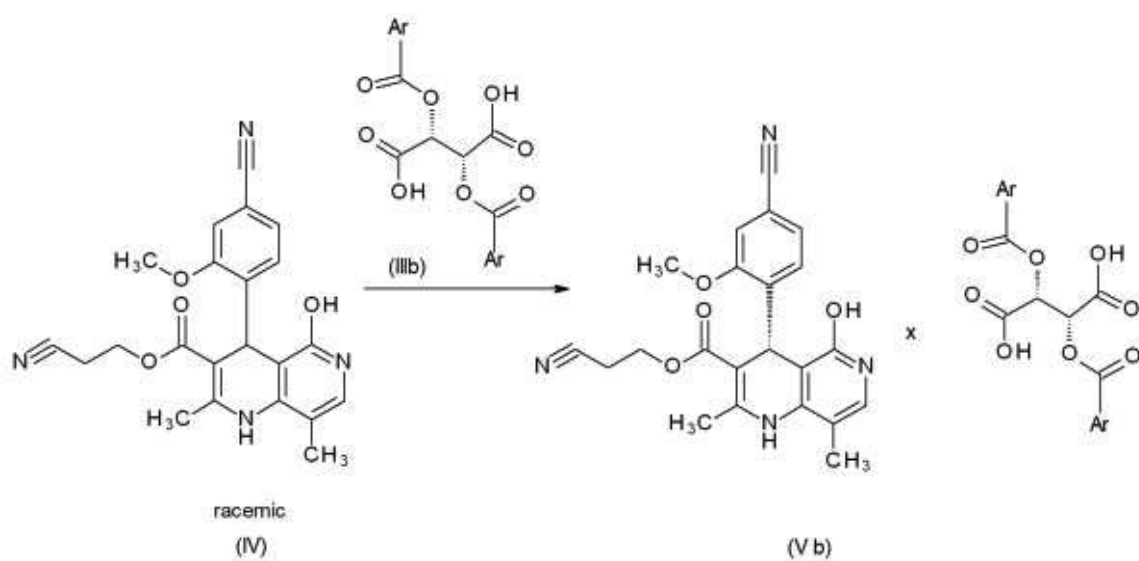


in which Ar is an unsubstituted or substituted aromatic or heteroaromatic radical and has the meaning given above.

- 5 Particular preference is given to diastereomeric salts in which Ar is 4-nitrophenyl.

Whether (Va) to (Vd) are truly conventional diastereomeric salts or 1:1 molecule complexes stabilized via hydrogen bond formation is not predictable with certainty. What is clear is that these molecular 1:1 aggregates are very stable and behave like conventional diastereomeric salts and can be isolated, and so we will use the term diastereomeric salts hereinafter. For the preparation of the diastereomeric salts, tartaric acid derivatives of the general formulae (IIIa) and (IIIb) are used:

10



The reaction of the racemic mixture (IV) with a tartaric acid derivative of the general formula (IIIa) or (IIIb) results in 4 options for diastereomeric salt formation (V a-d). Surprisingly, a preference is observed such that if rac-(IV), for example, is reacted with a tartaric acid derivative of the general formula (IIIa), what is obtained is the diastereomeric salt of the general formula (Va), with the antipode of S configuration preferentially entering into salt formation. The diastereomeric salt (Va) precipitates virtually quantitatively out of the solution, from which it can then be isolated, for example by filtration, with the antipode having R configuration remaining in solution. In a very similarly surprising manner, the mirror-image salt of the general formula (Vb) is prepared by reacting the racemate (II) with the tartaric acid derivative of the general formula (IIIb), with the antipode of R configuration preferentially entering into salt formation. The precipitated diastereomeric salts can be separated off virtually quantitatively, in which case the S antipode here remains in solution and can then be isolated therefrom.

It has been found that the stoichiometric ratio of (IV) to (IIIa)/(IIIb) and the selection of solvent can be used to optimize yield and enantiomeric purity.

Finerenone (Ia) has S configuration. Either S,S-configured or R,R-configured tartaric acid (according to substitution type) can form diastereomeric salts with the 4S-configured enantiomer of the racemate IV.

0.5 to 2.0 equivalents of tartaric ester (IIIa) or (IIIb) are used for the optical resolution, but preferably 0.7 to 1.5 equivalents, but more preferably 0.7 to 1.4 equivalents, but most preferably 0.70 -1.2 equivalents.

Diastereomeric salts are formed in organic solvents, or solvent mixtures, or from solvent mixtures consisting of water and water-miscible organic solvents.

Examples of suitable organic solvents in the context of the application include ethanol, methanol, isopropanol, 1-propanol, ethyl acetate, isobutanol, dichloromethane, 1-pentanol or acetone, but preference is given to using ethanol. The solvents may also be used in the commercial denatured form, such as the denaturing agents used in the case of ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane, which also brings great advantages for reasons of cost; therefore, spirits are suitable, especially for industrial scale use, which, in the context of the application, consist of ethanol that may optionally have been denatured with toluene or methyl ethyl ketone. In addition,

the following solvents were also used: 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; 5 cyclohexanol / water 90:10; benzyl alcohol / water 90:10; ethylene glycol; ethylene glycol / water 80:20.

Preference is given to conducting the optical resolution in ethanol/water, where the mixing ratio (v/v) is in the range of ethanol:water = 1:1 to 6:1. But preference is given to using a mixture of ethanol:water = 6:1 to 3:1. Particular preference is given to a mixture of ethanol:water = 3:1. The 10 mixture can be prepared beforehand, or else be produced *in situ*, after a pot has been charged with all the components. The solvent mixture may be used in a 10- to 60-fold excess, based on the racemate (IV), i.e. 10 l to 40 l of solvent mixture is used per 1 kg of racemate. Preference is given to a 10- to 50-fold excess.

Execution is typically effected by first initially charging all the components in the solvent mixture 15 at room temperature, then heating to 10 to 60°C, but preferably to 20-50°C, and continuing to stir at 20-50°C for 1 to 10 hours, preferably 1 to 4 hours, and then cooling down to room temperature (about 20-23°C) within 3 to 24 hours, preferably 5 to 16 hours. Thereafter, stirring is continued at room temperature for 2 to 24 hours, preferably 5-18 hours, very preferably 12-16 hours.

20 The optical resolution is typically effected by first initially charging all the components in the solvent mixture at room temperature, then heating to 10 to 60°C, but preferably to 20-50°C, and continuing to stir at 20-50°C for 1 to 10 hours, preferably 1 to 4 hours, and then cooling down to room temperature (about 20-23°C) within 3 to 24 hours, preferably 5 to 16 hours. Thereafter, stirring is continued at room temperature for 2 to 24 hours, preferably 5-18 hours, very preferably 25 12-16 hours. Optical resolution is preferably effected at a temperature of 20°C-50°C.

This is followed by the isolation of the precipitated diastereomeric salt (Va), (Vb), (Vc) and/or (Vd).

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 30 several times with a solvent or solvent mixture. This is followed by drying under reduced

pressure, preferably < 100 mbar, at elevated temperature (50- 80°C, preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous.

With the procedure outlined above, it is possible to prepare diastereomeric salts having an enantiomeric excess of the diastereomeric salts in the range from 65% to 80% e.e.

- 5 For further purification (increasing the enantiomeric excess), extractive stirring from a solvent or solvent-water mixture is repeated.

The diastereomeric salts need not necessarily be dried, but may also be used moist in the next process stage.

- Examples of suitable organic solvents in the context of the application include ethanol, methanol,
10 isopropanol, 1-propanol, ethyl acetate, isobutanol, dichloromethane, 1-pentanol or acetone, but preference is given to using dichloromethane. The solvents may also be used in the commercial denatured form, such as the denaturing agents used in the case of ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane, which also brings great advantages for reasons of cost; therefore, spirits are suitable, especially for industrial scale use, which, in the context of the application,
15 consist of ethanol that may optionally have been denatured with toluene or methyl ethyl ketone. In addition, the following solvents were also used: 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
20 80:20; cyclohexanol / water 90:10; benzyl alcohol / water 90:10; ethylene glycol; ethylene glycol / water 80:20.

Preference is given to conducting the optical resolution in dichloromethane. The solvent or solvent mixture may be used in a 10- to 60-fold excess, based on the racemate (IV), e.g. 10 l to 40 l of solvent mixture is used per 1 kg of racemate. Preference is given to a 10- to 50-fold excess.

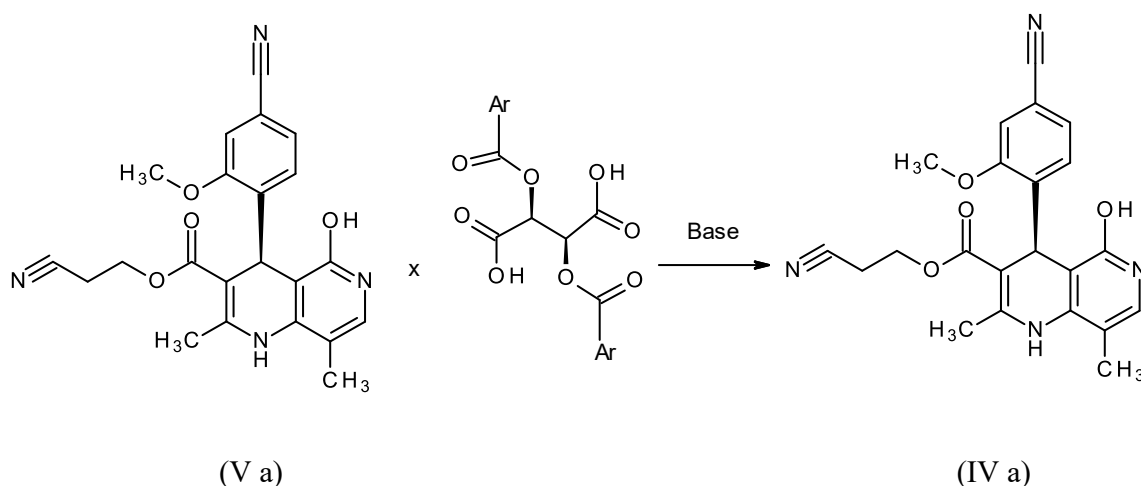
- 25 The extractive stirring is typically effected by first initially charging all the components in the solvent mixture at room temperature, then heating to 10 to 60°C, but preferably to 20-50°C, and continuing to stir at 20-50°C for 1 to 10 hours, preferably 1 to 4 hours, and then cooling down to room temperature (about 20-23°C) within 3 to 24 hours, preferably 5 to 16 hours. Thereafter, stirring is continued at room temperature for 2 to 24 hours, preferably 5-18 hours, very preferably
30 12-16 hours.

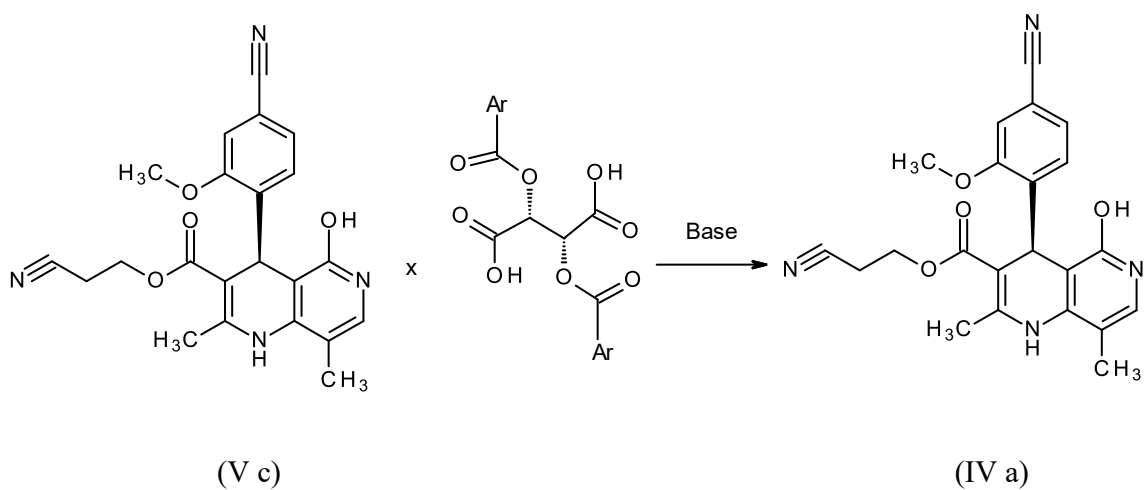
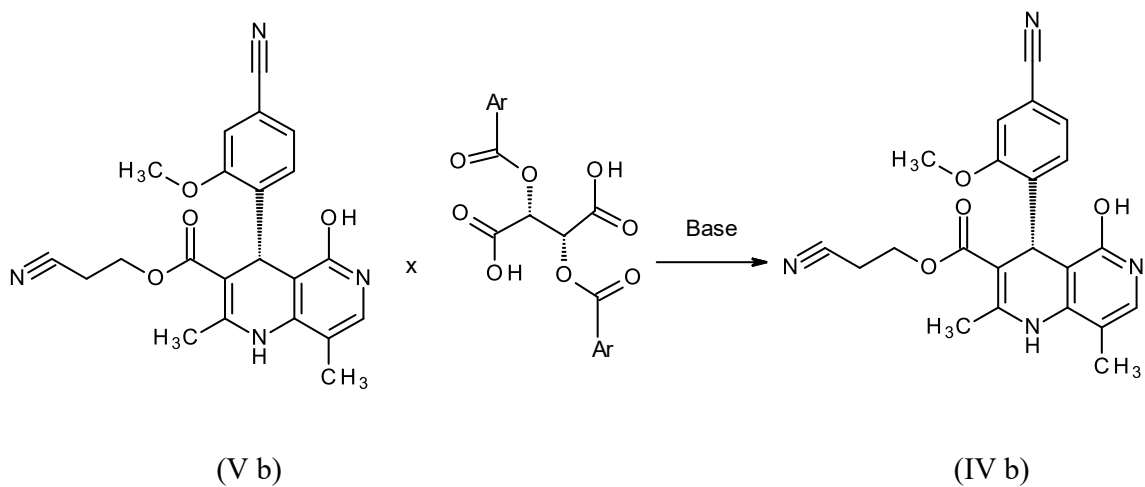
This is followed by the isolation of the precipitated diastereomeric salt (Va), (Vb), (Vc) and/or (Vd).

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 (50-80°C, preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous. The diastereomeric salts thus obtained are notable for a high enantiomeric excess, generally > 95% e.e., which is sufficient to prepare finerenone (Ia) in >> 99% e.e.

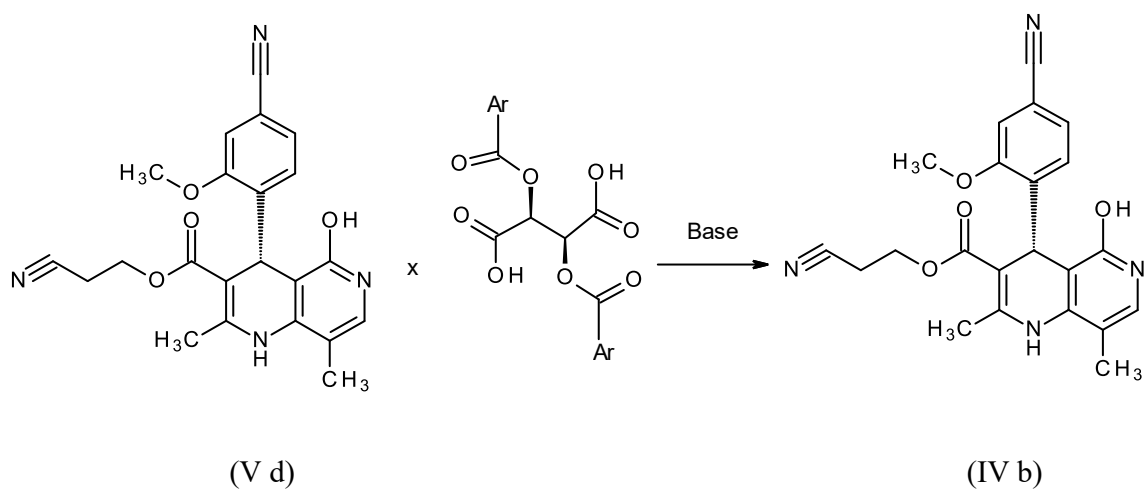
The diastereomeric salts need not necessarily be dried, but may also be used moist in the next process stage.

In the next step, the diastereomeric salt is treated with a base, and the solvent is removed. The solvent is removed by methods known to the person skilled in the art, for example by distillative removal. For preparation of the chiral compounds (IVa) and (IVb), the diastereomeric salt of the general formula (Va), (Vb), (Vc) or (Vd) has to be treated with a base; distillative removal of the organic solvent precipitates the target molecule (IVa) or (IVb) out of the solution, which is isolated – for example by filtering-off and washing on the filter – and the respective tartaric ester of formula (IIIa) or (IIIb) remains in solution in the form of a salt.





5



Suitable bases in the context of the present invention are inorganic and organic bases. In the case of inorganic bases, it is possible to use ammonia, aqueous sodium hydroxide solution, lithium

hydroxide, potassium hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium hydrogencarbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium phosphate, potassium phosphate, ammonium phosphate. However, preference is given to using sodium hydroxide, sodium phosphate or potassium phosphate.

5 Particular preference is given to using sodium phosphate or potassium phosphate. It is important to emphasize that the inorganic bases may be used either in anhydrous form or in the form of their hydrates; for example, sodium phosphate (anhydrous) and sodium phosphate hydrate may be used successfully. Organic bases used may be aliphatic or aromatic bases, for example triethylamine, imidazole, N-methylimidazole, Hünig's base, pyridine, DBU.

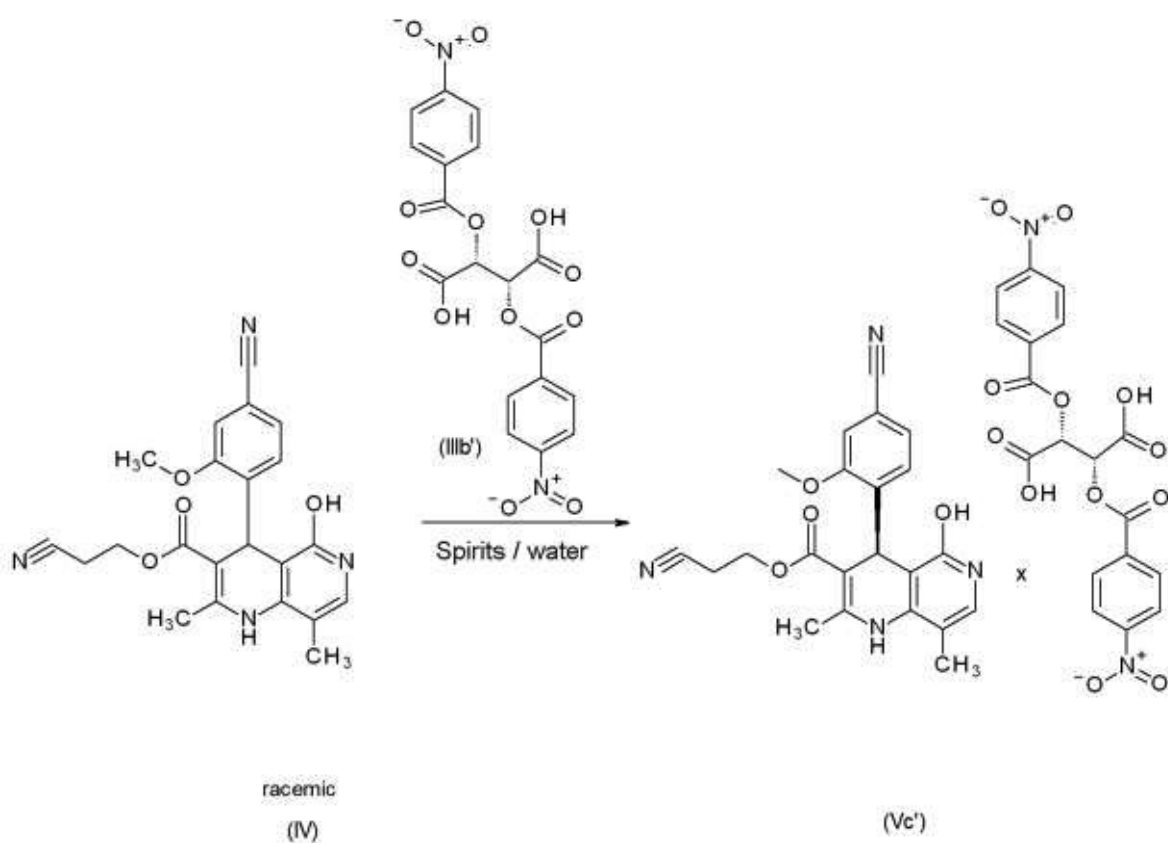
10 The target compound (IVa) or (IVb) is released in mixtures of water with water-miscible organic solvents such as ethanol, isopropanol, ethane-1,2-diol, methoxyethanol, methanol or acetone, preference being given to ethanol. The solvents may also be used in the commercial denatured form, such as the denaturing agents used in the case of ethanol, e.g. toluene, methyl ethyl ketone, thiophene, hexane; preference is given to using spirits which, in the context of the application,
15 consist of ethanol that may optionally have been denatured with toluene or methyl ethyl ketone, which brings great advantages for reasons of cost. It has been found to be advantageous to use mixtures of water and ethanol, with the mixing ratio (v/v) in the range of ethanol:water = 1:6 to 1:3. But preference is given to using a mixture of ethanol:water = 1:3. The mixture may have been prepared beforehand, or else produced in situ after a pot has been charged with all the
20 components. This mixture may be used in an amount 7 to 20 times that of the diastereomeric salt (IVa or IVb or IVc or IVd) used, i.e., for example, 1 kg in 7 l to 20 l of this mixture. Preference is given to using 8 to 15 times the amount of this mixture, more preferably 9 to 11 times the amount of this mixture, most preferably 10 times the amount of this mixture. The target compound (IVa) or (IVb) is released by initially charging the diastereomeric salt (Va or Vb or
25 Vc or Vd) in a solvent mixture at 0°C to 60°C, preferably 0°C to 50°C, followed by addition of the organic or inorganic base (either in solid form or as a solution, preferably in water) to establish a pH of 6.9 to 8.0, preferably a pH of 7.0 to 7.5, more preferably pH 7.1. Suitable bases in the context of the present invention are inorganic and organic bases. In the case of inorganic bases, it is possible to use ammonia, aqueous sodium hydroxide solution, lithium hydroxide, potassium
30 hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium hydrogencarbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium phosphate, potassium phosphate, ammonium phosphate. 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 may be used either in anhydrous form or in the form of their hydrates; for example, sodium phosphate (anhydrous) and sodium phosphate hydrate may be used successfully. Organic bases used may be aliphatic or aromatic bases, for example triethylamine, imidazole, N-methylimidazole, Hünig's base, pyridine, DBU.

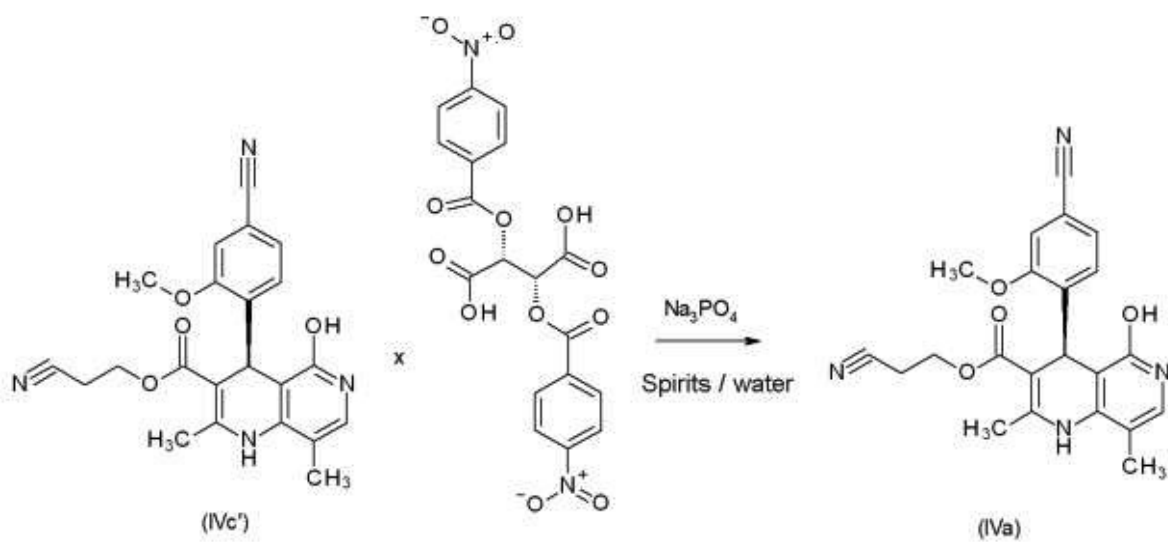
The base can be added either very quickly (within a few minutes) or else very slowly (within a few hours), for example within 5 minutes up to 3 hours. Faster addition is preferred in any case. Preference is given to metered addition within 5 min to 1 hour. This purpose may be served by a pH meter installed in the reactor, with which the adjustment is controlled and the base is gradually metered in. It is alternatively possible to add a fixed amount of base (in solid form or dissolved in a solvent) at the start, which, based on experience, ensures that the desired pH range is preferentially attained. In production, such a procedure is most preferred. It has been found to be advantageous to continue stirring after the pH has been established, again at 0°C-50°C, preferably 20°C-50°C, preferably 0°C-20°C. The period of continued stirring may be 1 to 10 hours, preferably 2-5 hours, more preferably 3-4 hours.

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 more than once with a solvent or solvent mixture. This is followed by drying under reduced pressure, preferably < 100 mbar, at elevated temperature (50-80°C, preferably 50°C). In some cases, the use of a carrier gas has been found to be advantageous.

As a particularly preferred process, especially for implementation on an industrial scale, di(4-nitrobenzoyl)tartaric acid (IIIb'), R,R configuration, is used, which may be used either in anhydrous form or in hydrate form:

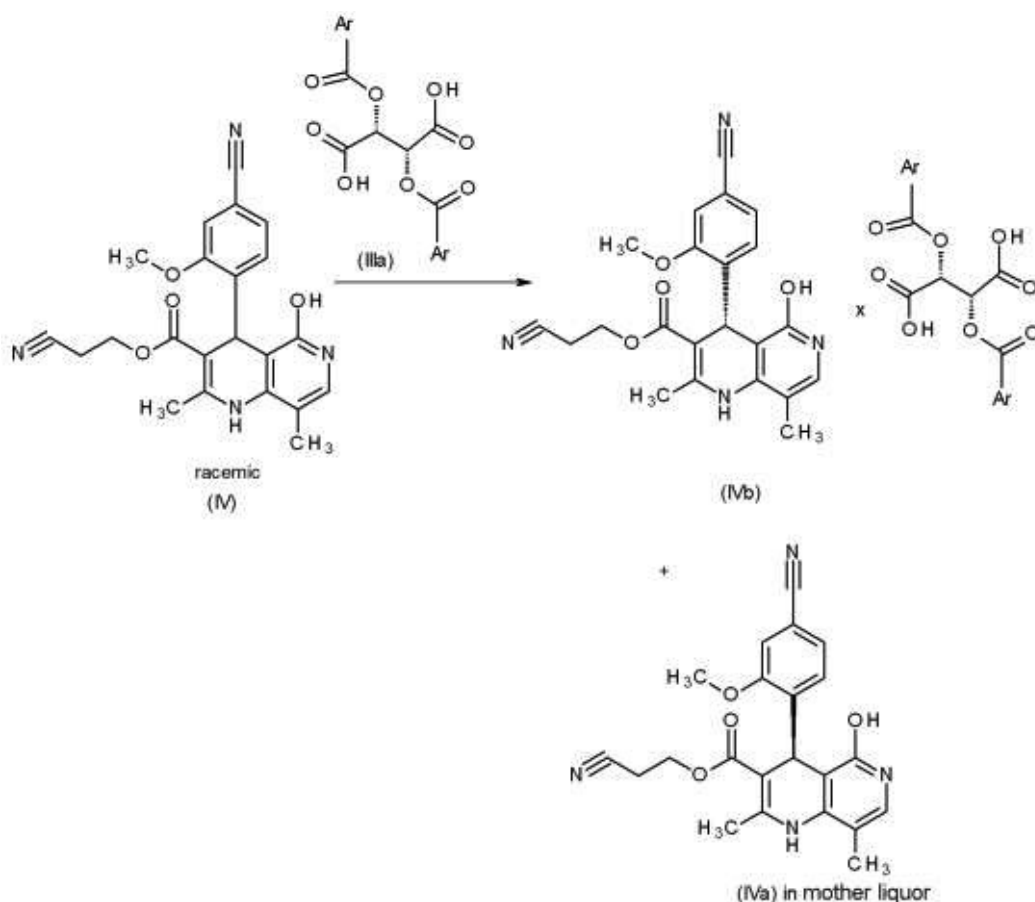


The optical resolution is preferably carried out in a spirits/water mixture. The subsequent release of (IVa)



5 is preferably effected in a spirits/water mixture using sodium phosphate as base.

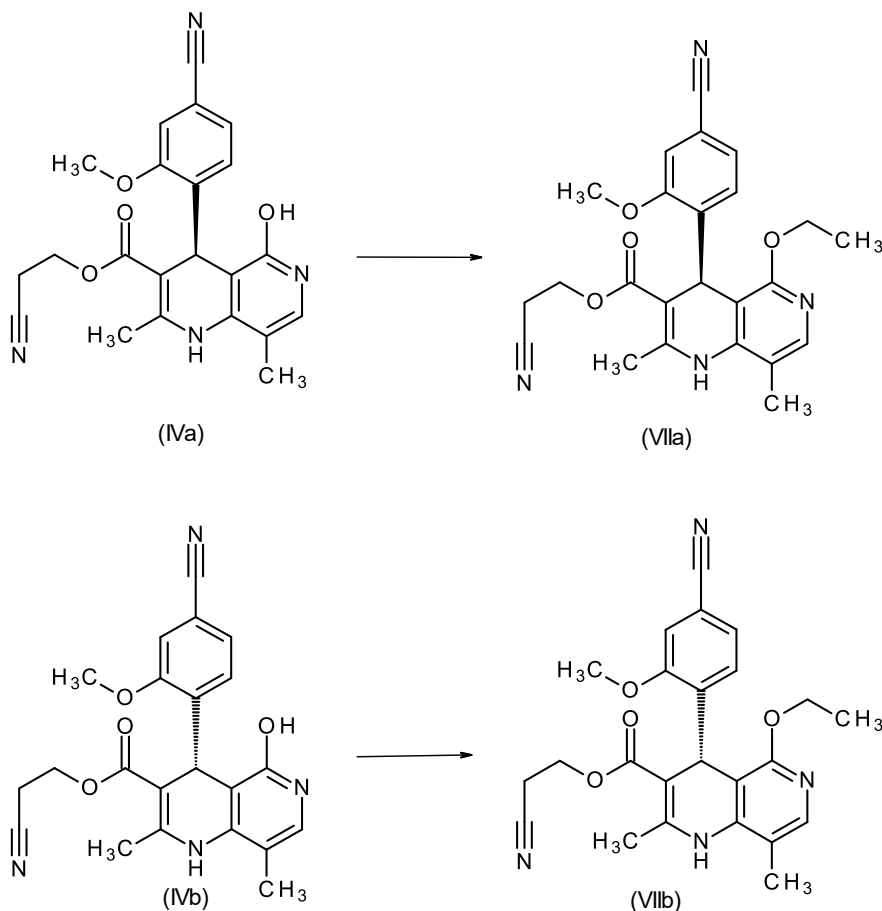
It is also possible to isolate the target enantiomer from the mother liquor. First of all, the appropriate diastereomeric salt (Va), (Vb), (Vc) or (Vd) is prepared here either from (IVa) or (IVb), then isolated by filtration, and then the pH of the mother liquor then comprising the respective antipode is adjusted to $\text{pH} > 7$, preferably $\text{pH} 7.1-8$, most preferably $\text{pH} 7.1$, by addition of a base, for example ammonia, sodium hydroxide solution, lithium hydroxide, potassium hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium hydrogencarbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium phosphate, potassium phosphate, ammonium phosphate, preferably sodium hydroxide, sodium phosphate and potassium phosphate, more preferably sodium phosphate and potassium phosphate. Subsequently, the organic solvent - preferably ethanol - is distilled off, either at atmospheric pressure or, more gently, under reduced pressure. This precipitates the corresponding antipode. 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 compounds (IVa) and (IVb) in correspondingly pure form.



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The further conversion to finerenone (Ia) or the antipode (Ib) is conducted as follows:

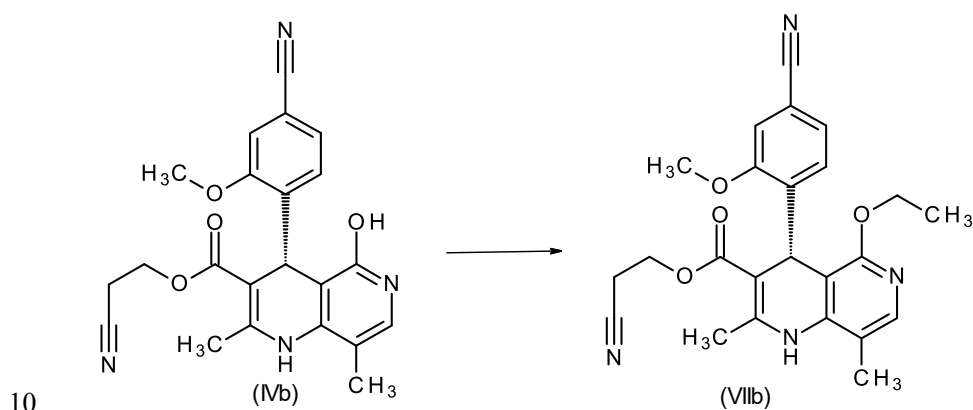
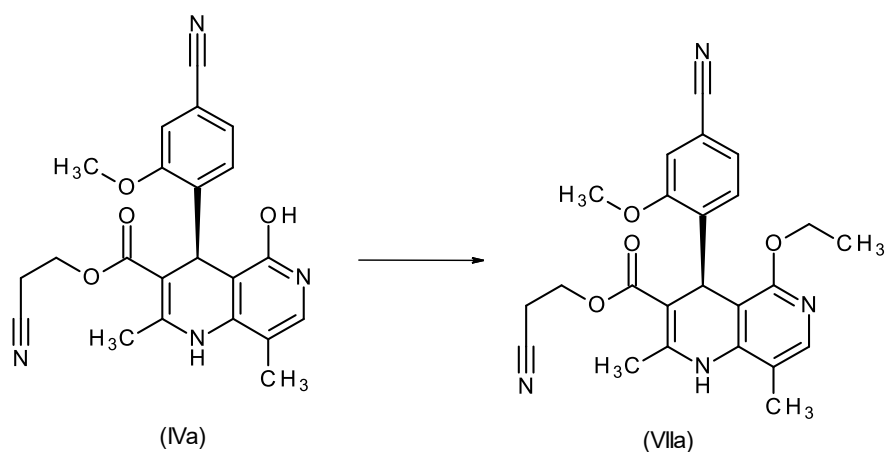
Proceeding from dihydropyridine (IVa or IVb), the ethyl ether (VIIa or VIIb) is obtained by reaction under acidic catalysis with an orthoester.



- 5 It has been found that the reaction can be conducted in relatively high concentration (up to 1.5 g of solvent per 1 g of reactant) in solvents such as dimethylacetamide, NMP (1-methyl-2-pyrrolidone) or DMF (dimethylformamide) with addition of 4-10 per cent by weight, preferably 6-8 per cent by weight, of conc. sulfuric acid. The reaction then proceeds with 2.5 equivalents-5 equivalents of orthoester (triethyl orthoacetate or triethyl orthoformate). It has been found that it
- 10 is much more convenient to use the corresponding triethyl orthoacetate in the reaction, since it firstly reacts much more cleanly and is much less inflammable, making it particularly suited to the industrial procedure. The reaction is preferably effected in DMA (dimethylacetamide) and NMP (1-methyl-2-pyrrolidone), at temperatures of 100-120°C, preferably 115°C. More preferably in NMP. Before starting the actual reaction, it has been found to be advantageous to
- 15 distil off some of the solvent (DMA or NMP) at elevated temperature (100-120°C under reduced

pressure) in order to remove any residues of isopropanol present from the precursor, since unwanted by-products otherwise occur. Reaction: Stir for 1.5 - 3 hours, preferably 2 hours. For the workup, water is added directly to the mixture, and the product crystallizes out. In order to have a particularly stable and reproducible process, a portion of the water (e.g. 1/3) is first
 5 metered in, followed by seeding, and the remaining amount of the water is added. This procedure guarantees that the same crystal polymorph which shows the best isolation characteristics is always obtained. The product is washed with water and dried. The yields are > 92% of theory.

Proceeding from the cyanoethyl ether (IVa or IVb), the acid (VIIa or VIIb) is obtained by alkaline hydrolysis and subsequent acidic workup:



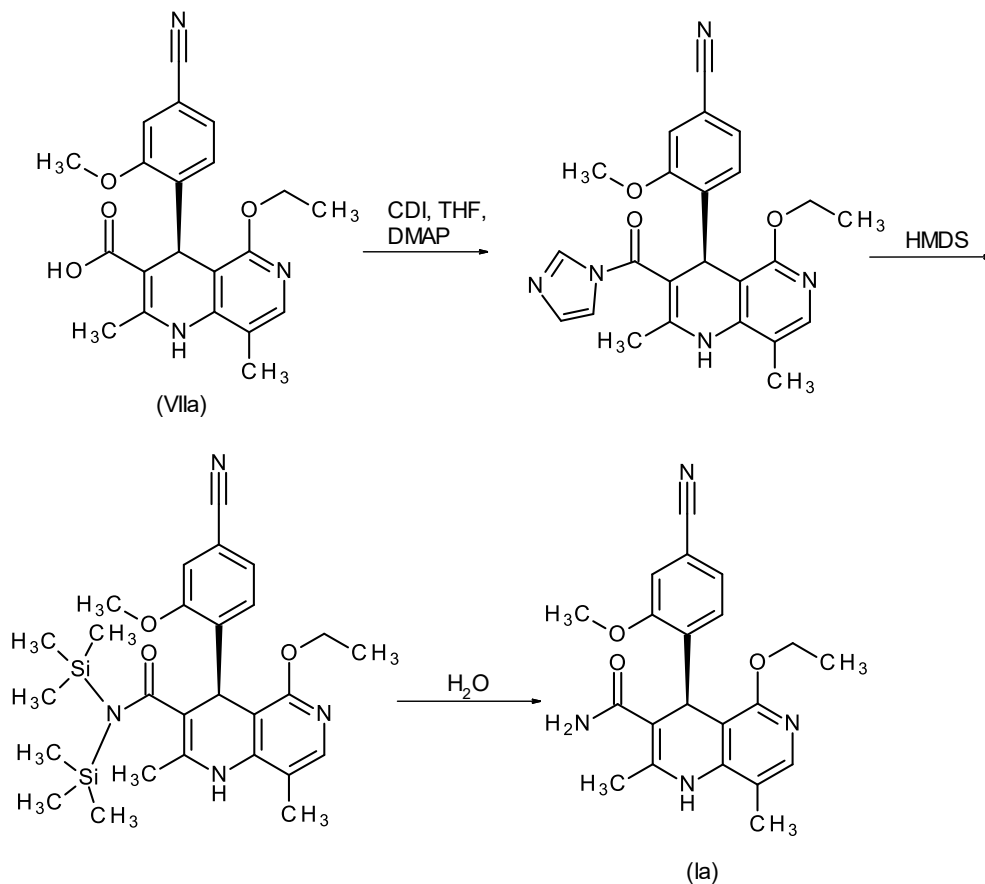
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It has been found that the reaction can be run very easily in relatively concentrated form in mixtures of THF/water. For this purpose, preference is given to working in a mixture of THF/water 2:1 (9 times the amount), metering in the aqueous sodium hydroxide solution at 0°C-5°C, then stirring the mixture at 0°C-5°C for 1-2 hours. It is also possible to use potassium
 15 hydroxide solution, but preference is given to sodium hydroxide solution. Workup is effected by

extracting with MTBE (methyl tert-butyl ether) and ethyl acetate or else toluene only, and isolation by adjusting the pH to 7 with a mineral acid such as hydrochloric acid, sulfuric acid or phosphoric acid, but preferably hydrochloric acid. It is then possible to add saturated ammonium salt solution of the corresponding acid, but preferably ammonium chloride solution, with quantitative crystallization of the product. After isolation, the product is washed with water and with ethyl acetate or with acetonitrile or with acetone, but preferably with acetonitrile, and dried under vacuum at 40°C-50°C. The yield is virtually quantitative (99%).

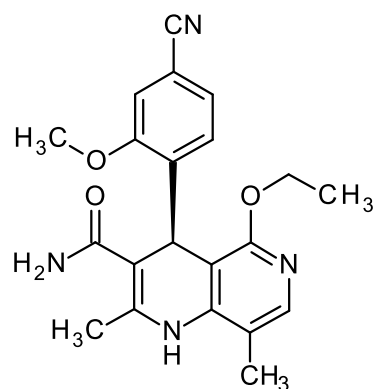
The subsequent conversion of the acid to the amide (Ia or Ib) is described as follows: It has been found that, in a conversion of the acid (VIIa or VIIb) in tetrahydrofuran (THF), the amide (I or Ia) crystallizes directly out of the solution and can be obtained in high yield and purity. For this purpose, the carboxylic acid (VIIa or VIIb) is reacted with 1.1 to 1.6 equivalents, preferably 1.3-1.4 equivalents, of 1,1'-carbodiimidazole (CDI) under 4-(dimethylamino)pyridine (DMAP) catalysis (5-15 mol%, preferably 10 mol% / in some cases it has been found that the reaction can also be conducted without addition of DMAP) in THF at temperatures between 20°C-50°C (the preferred approach has been found to be first to start at 20°C, then stir at that temperature 1 to 2 hours and then continue stirring at 50°C for 2 to 3 hours) to give the imidazolide. After the activation has ended, 3-8 equivalents, preferably 4.5 equivalents, of hexamethyldisilazane are added and the mixture is heated for 16-24 hours, but preferably for 16 hours, under reflux. The disilylamide compound formed here can optionally be isolated. However, it has been found to be more advantageous to continue in a one-pot reaction. After the reaction has ended, therefore, the mixture is cooled to 0°C-3°C and water or a mixture of water/THF is metered in. An advantageous amount of water has been found to be 0.5 to 0.7 times the amount of the reactants, and a particularly advantageous amount to be 0.52 times the amount of water. The water can be added directly or as a mixture with about one to two volume equivalents of THF. After quenching has ended, the mixture is heated to reflux for a total of 1-3 hours, preferably 1 hour. The mixture is cooled to 0°C and stirred at that temperature for a further 1-5 hours, preferably 3 hours. Subsequently, the product is isolated by filtration or centrifugation. The product is washed with THF and water and dried under vacuum at elevated temperature (30°C to 100°C, preferably at 40°C to 70°C). The yields are very high and are > 93% of theory. The purity is > 99% (HPLC, 100% method). The compound (VIIa or VIIb) can also be obtained directly by reacting with ammonia gas in an autoclave (about 25 to 30 bar). For this purpose, the preactivation described above is carried out and the reaction mixture is then heated under pressure under gaseous

ammonia. On completion of the reaction, it is cooled and the product filtered off. The yields and purities thus achieved are comparable.



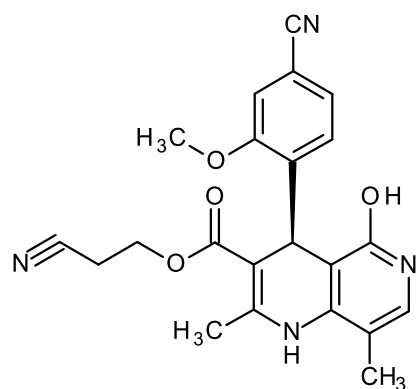
Final crystallization method (establishment of the final modification Mod A): For this purpose, (Ia) (or Ib), for GMP-related reasons, is first dissolved in ethanol and subjected to a particle filtration, and then the solvent is distilled off, either under reduced pressure or at standard temperature, preference being given to using toluene-denatured ethanol. The mixture is concentrated to about 3 to 5 times the volume of (Ia); the product crystallizes out. The mixture is cooled to 0°C and the crystals then isolated and dried at 40°C-50°C under reduced pressure. The yields are generally > 90% of theory. The chemical purity achieved is >99.8% and the content ~ 100 % correspond to the criteria for commercial products according to ICH guidelines. Residual solvent, in the case of ethanol, is < 0.02%. The optical purity is >> 99% e.e.

The present invention also relates to a 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 (Ia)



(Ia),

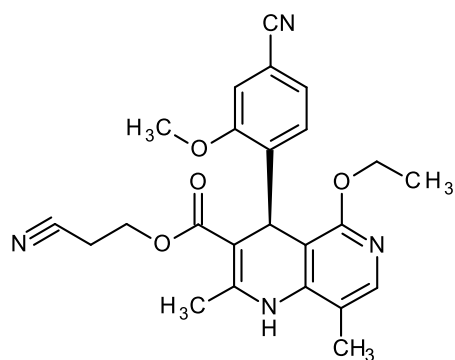
characterized in that enantiomerically pure cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)



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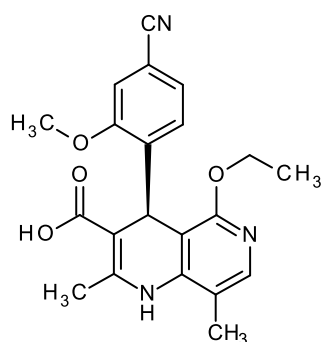
(IVa)

is converted by reacting with orthoester under acidic catalysis to the compound of the formula (VIIa)



(VIIa)

and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)

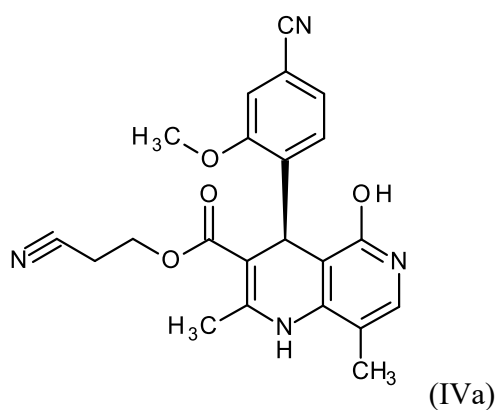


(VIIIa),

and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-
5 carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

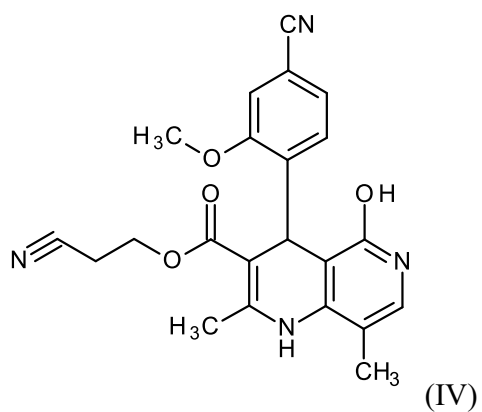
There follows a description of further embodiments of the invention:

The invention relates to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-
10 methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

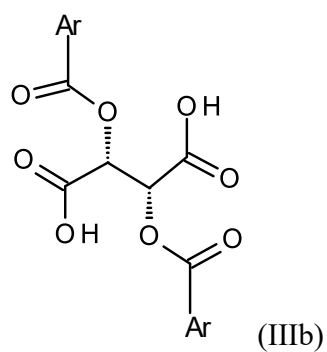


(IVa)

by optical resolution of (IV)

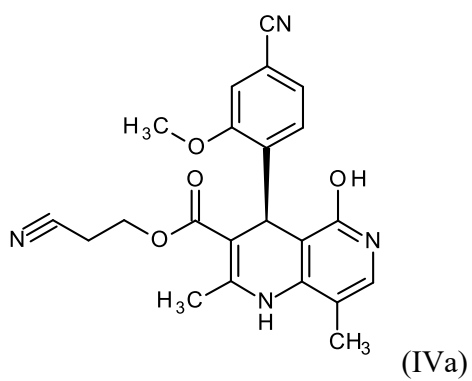


with a chiral substituted tartaric ester of the formula (IIIb)

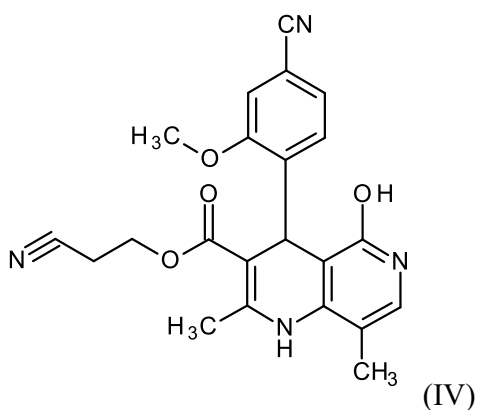


where Ar is unsubstituted or substituted aryl or heteroaryl.

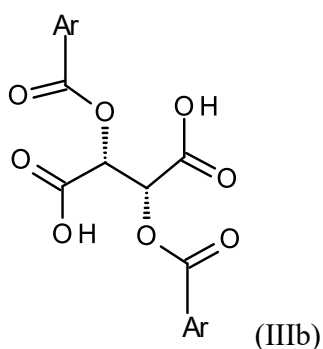
- 5 Preference is given to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)



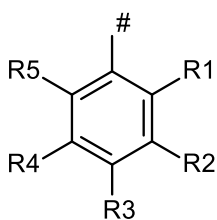
by optical resolution of (IV)



with a chiral substituted tartaric ester of the formula (IIIb)



where Ar is



5

where # represents the site of attachment,

where R₁, R₂, R₃, R₄, R₅ are each a hydrogen atom or an alkyl radical, for example methyl, ethyl, propyl, or a halogen atom, for example fluorine, chlorine, bromine or iodine, or an ether group, for example O-methyl, O-ethyl, O-phenyl, or a nitro group, or a cyano group, or a CF₃ group, or an amide group, for example -NHCOR in which R may be methyl, ethyl or phenyl, or -NRCOR in which R has the meaning given above or CONHR in which R has the meaning given above or CONRR' in which R' has the same meaning as R as defined above, or cyclic amides such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted. The

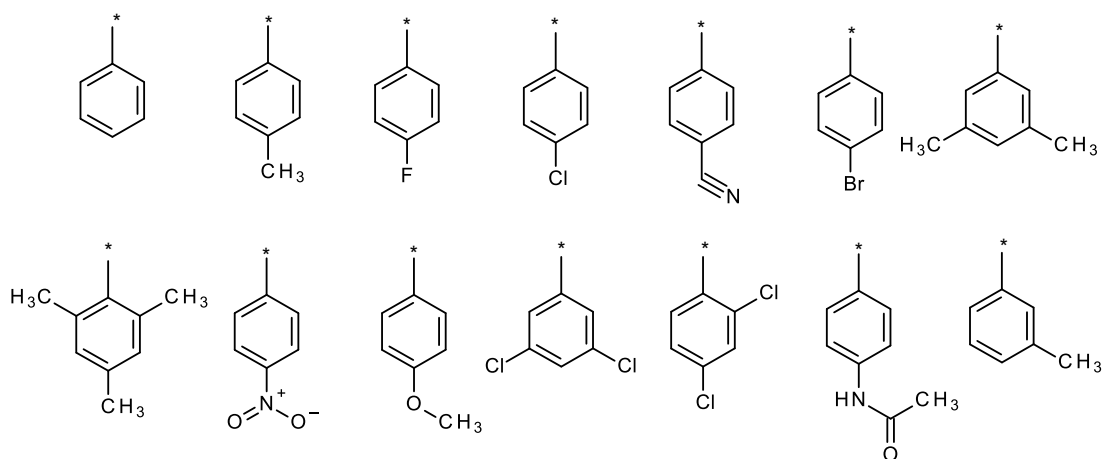
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substitution patterns may differ widely; for instance, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. Ar may alternatively be a substituted heteroaromatic radical such as, preferably, pyridine or pyrazine. Ar may alternatively be a polycyclic aromatic hydrocarbon, for example a substituted naphthalene, anthracene or quinoline.

Preference is given to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

where

Ar is one of the formulae

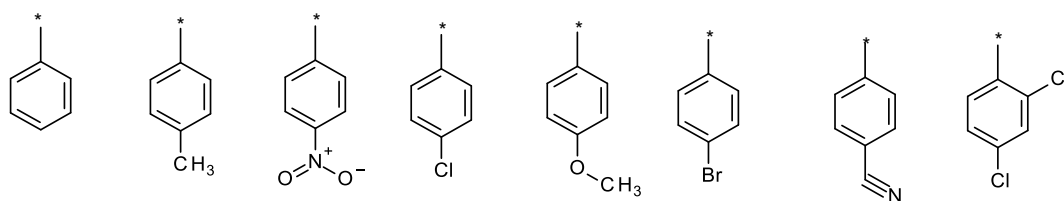


in which * represents the site of attachment.

Particular preference is given to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

where

Ar is one of the formulae

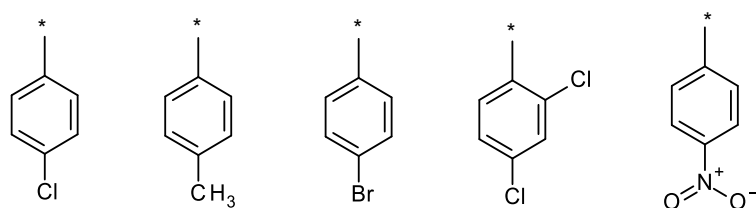


in which * represents the site of attachment.

5 Especial preference is given to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

where

Ar is one of the formulae

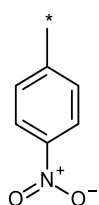


in which * represents the site of attachment.

10 Very particular preference is given to a process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

where

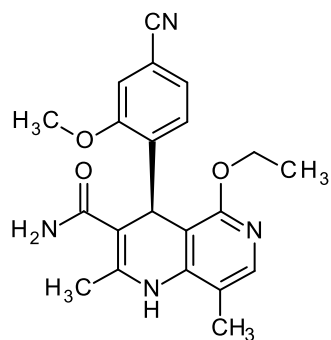
Ar is



15

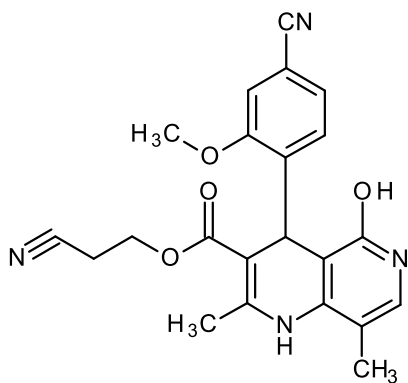
in which * represents the site of attachment.

The present invention also relates to a 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 (Ia)



(Ia),

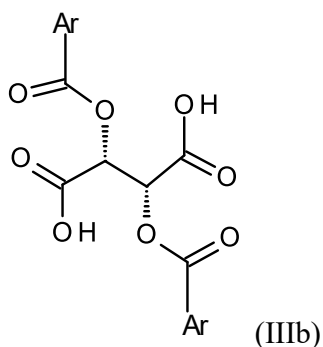
characterized in that racemic cyanoethanol ester of the formula (IV)



(IV)

5

is reacted with a chiral substituted tartaric ester of the formula (IIIb)

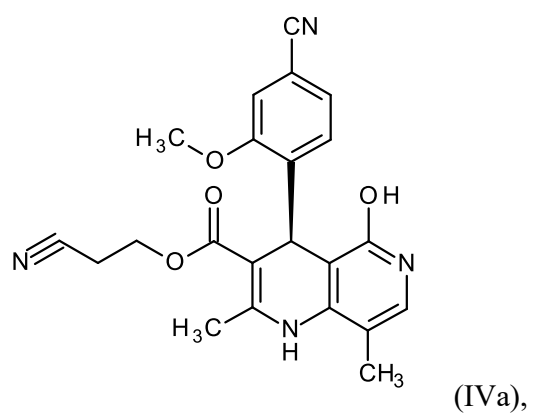


(IIIb)

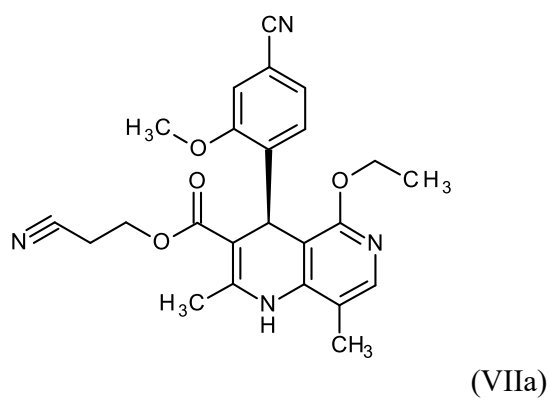
where Ar is unsubstituted or substituted aryl or heteroaryl

to give enantiomeric 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

10

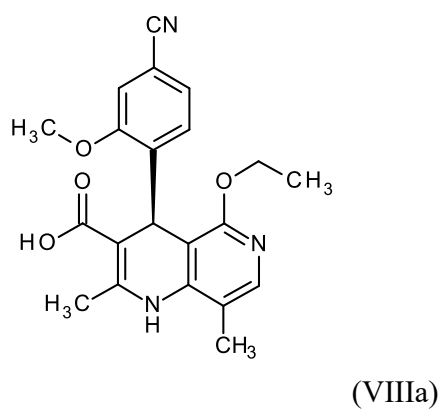


and the latter is converted by reacting with orthoester under acidic catalysis to the compound of the formula (VIIa)



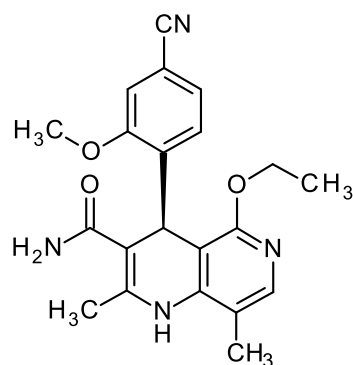
5

and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)



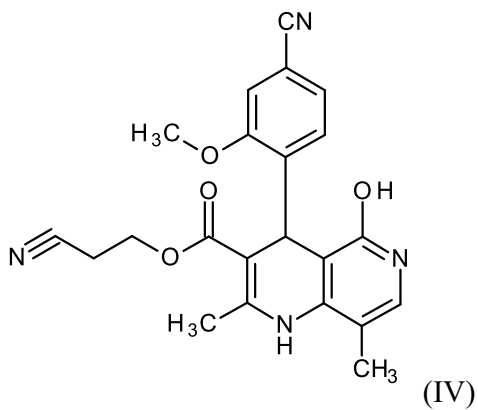
and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

- 5 Preference is given to a 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 (Ia)



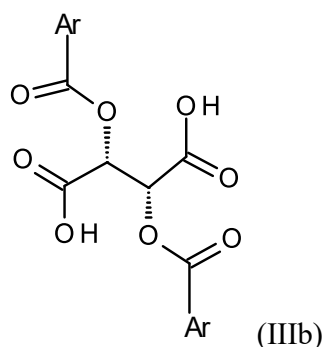
(Ia),

characterized in that racemic cyanoethanol ester of the formula (IV)

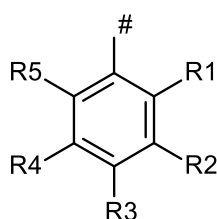


(IV)

- 10 is reacted with a chiral substituted tartaric ester of the formula (IIIb)



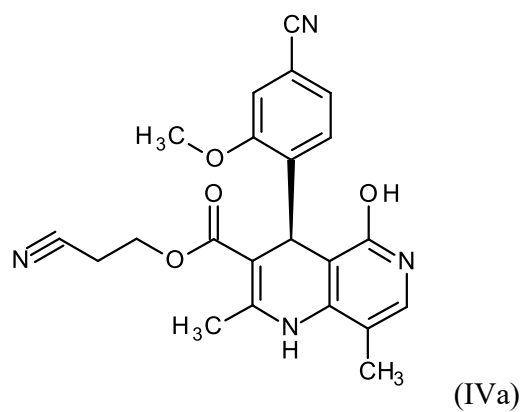
where Ar is



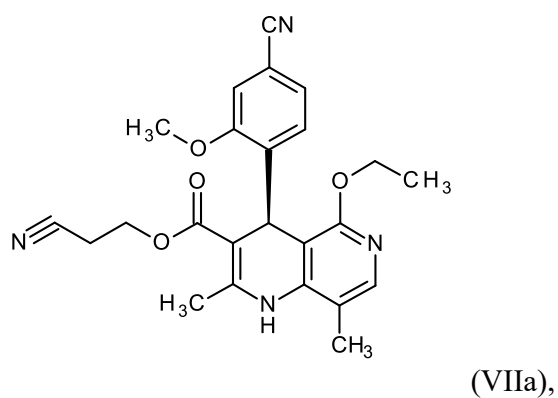
where # represents the site of attachment,

- 5 where R1, R2, R3, R4, R5 are each a hydrogen atom or an alkyl radical, for example methyl, ethyl, propyl, or a halogen atom, for example fluorine, chlorine, bromine or iodine, or an ether group, for example O-methyl, O-ethyl, O-phenyl, or a nitro group, or a cyano group, or a CF₃ group, or an amide group, for example –NHCOR in which R may be methyl, ethyl or phenyl, or –NRCOR in which R has the meaning given above or CONHR in which R has the meaning given
- 10 above or CONRR' in which R' has the same meaning as R as defined above, or cyclic amides such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted. The substitution patterns may differ widely; for instance, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. Ar may alternatively be a substituted heteroaromatic radical such as, preferably, pyridine or
- 15 pyrazine. Ar may alternatively be a polycyclic aromatic hydrocarbon, for example a substituted naphthalene, anthracene or quinoline,

to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

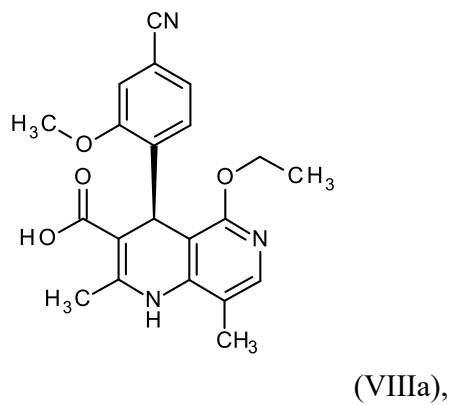


and the latter is converted by reaction with orthoester under acidic catalysis using triethyl orthoformate or triethyl orthoacetate and concentrated sulfuric acid as acidic catalyst to the compound of the formula (VIIa)



5

and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)

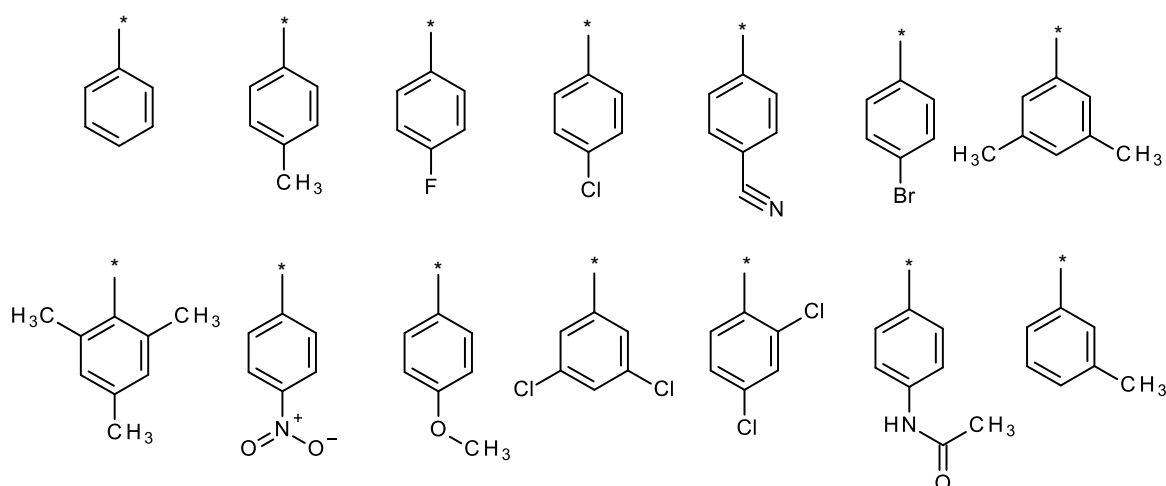


and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

- 5 Preference is given to a 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 (Ia)

where, in formula (III),

Ar is one of the formulae

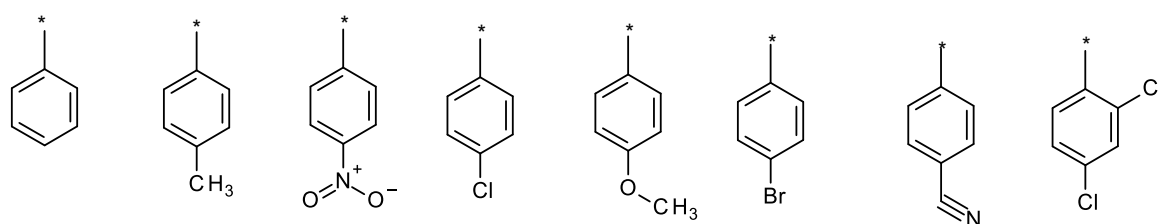


- 10 in which * represents the site of attachment.

Particular preference is given to a 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 (Ia)

where, in formula (III),

Ar is one of the formulae

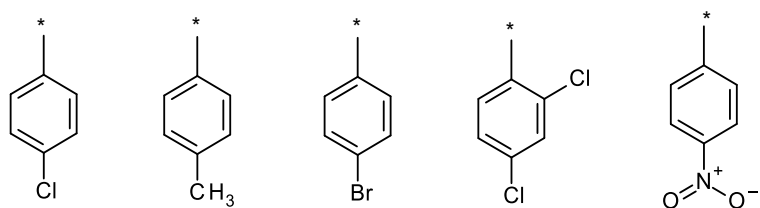


in which * represents the site of attachment.

Especial preference is given to a 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 (Ia)

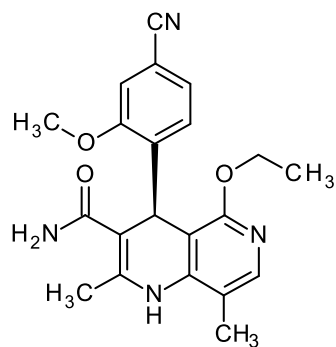
where, in formula (III),

5 Ar is one of the formulae



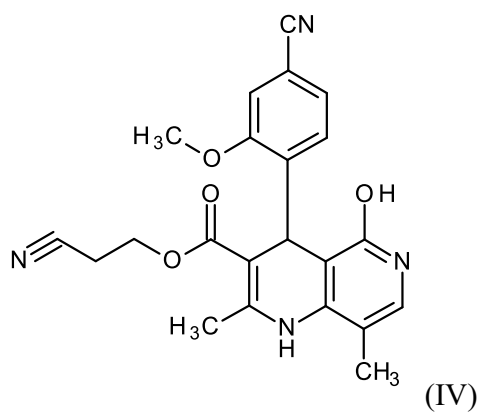
in which * represents the site of attachment.

Very particular preference is given to a process for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the
10 formula (Ia)

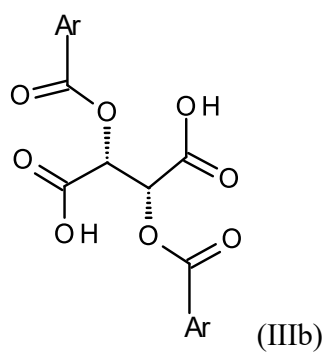


(Ia),

characterized in that racemic cyanoethanol ester of the formula (IV)

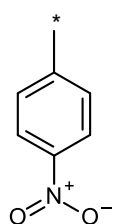


is reacted with a chiral substituted tartaric ester of the formula (IIIb)



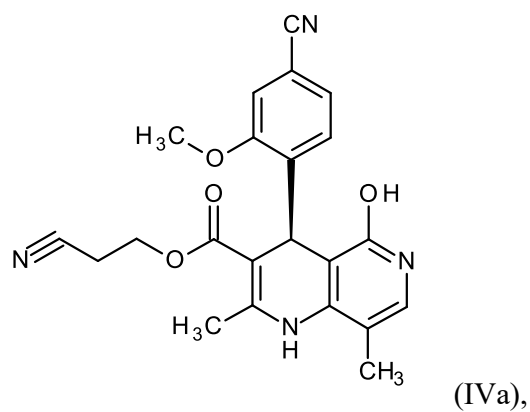
where

5 Ar is

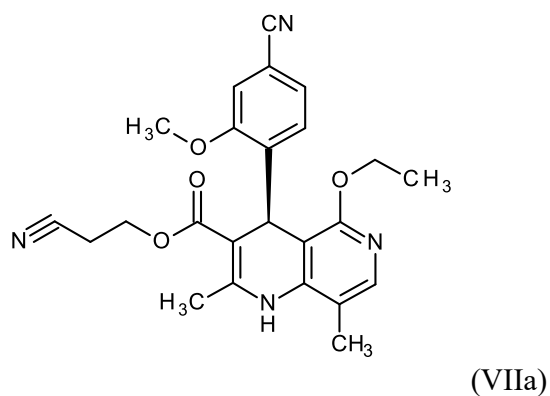


in which * represents the site of attachment

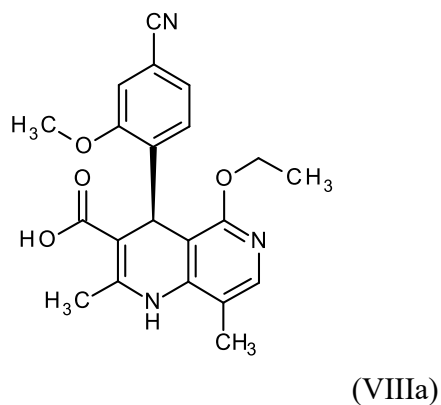
to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)



and the latter is converted by reaction with orthoester under acidic catalysis using triethyl
orthoformate or triethyl orthoacetate and concentrated sulfuric acid as acidic catalyst to the
5 compound of the formula (VIIa)



and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the
compound of the formula (VIIIa)



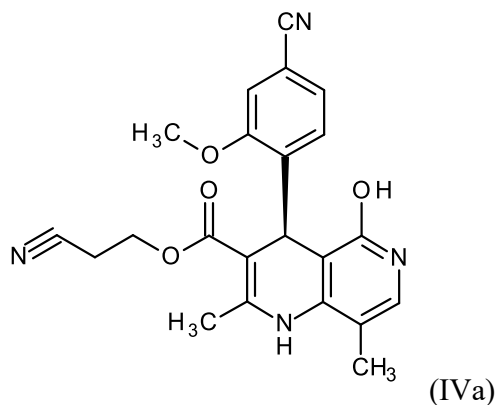
and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

- 5 The synthesis of the racemic cyanoethanol ester (IV) is described in WO 2016/016287 (Example 4). The cyanoethanol ester stages (IVa + IVb) are converted in a known manner, as described in WO 2016/016287 A1 for the racemic compound, to give the finerenone end product (Ia), or the enantiomeric (Ib). The present invention relates essentially to a novel process for preparing the cyanoethanol esters in chiral form by optical resolution by means of chiral substituted tartaric
10 esters of the general formulae (IIIa) and (IIIb).

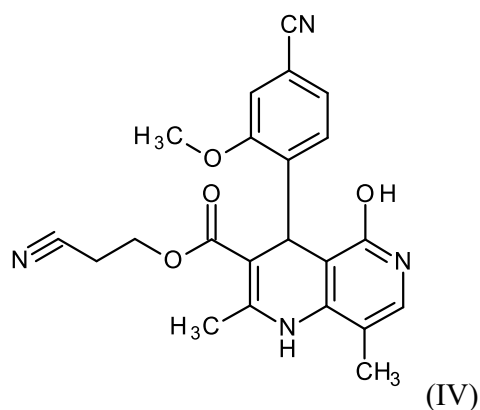
Paragraphs 1. to 14.

There follows a description of further embodiments in paragraphs 1. to 14.:

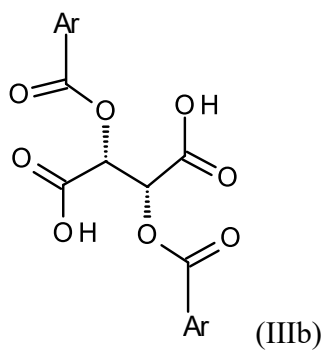
1. Process for preparing 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-
15 dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)



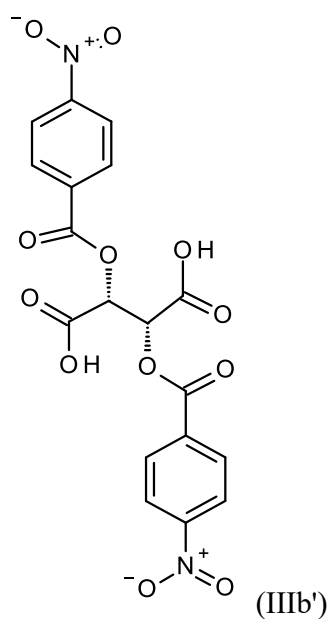
by optical resolution of (IV)



with a chiral substituted tartaric ester of the formula (IIIb)

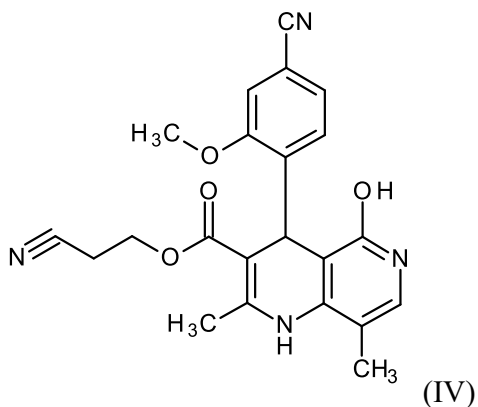


- 5 where Ar is unsubstituted or substituted aryl or heteroaryl.
2. Process according to paragraph 1, characterized in that the optical resolution is conducted in an ethanol/water mixture.
3. Process according to either of paragraphs 1 and 2, characterized in that the optical resolution is effected at a temperature in the range from 20°C to 50°C.
- 10 4. Process according to any of paragraphs 1, 2 and 3, characterized in that the optical resolution is effected at a temperature of 30°C to 50°C.
5. Process according to any of paragraphs 1, 2, 3 and 4, characterized in that (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid (IIIb')



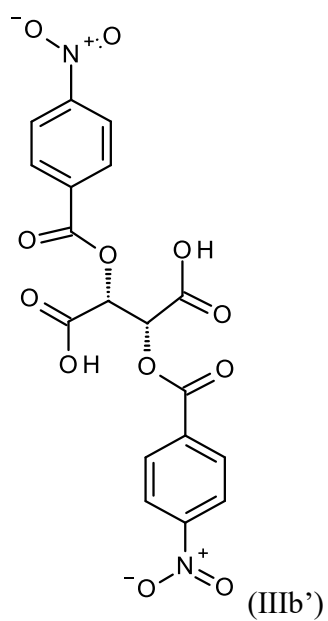
is used for optical resolution.

6. Process according to any of paragraphs 1 to 5, characterized in that the precipitated diastereomeric salt (Va), (Vb), (Vc) and/or (Vd) is isolated.
- 5 7. Process according to any of paragraphs 1 to 6, characterized in that the diastereomeric salt is treated with a base and the solvent is removed.
8. Process according to any of paragraphs 1 to 7, characterized in that the base used is potassium hydroxide, potassium phosphate or sodium phosphate.
9. Process according to any of paragraphs 1 to 8, wherein the racemate (IV)

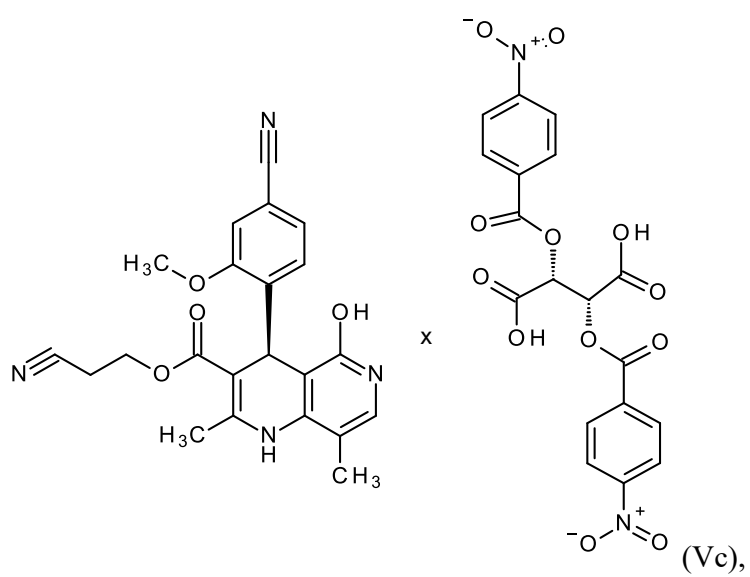


10

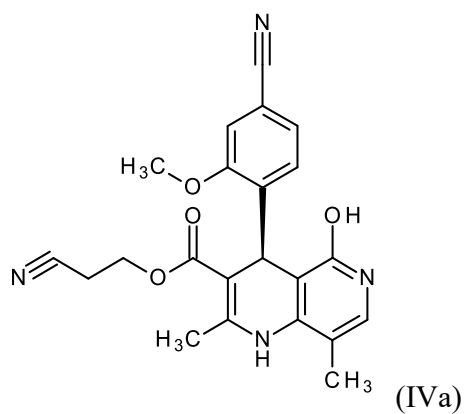
is reacted with (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid of the formula (IIIb')



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

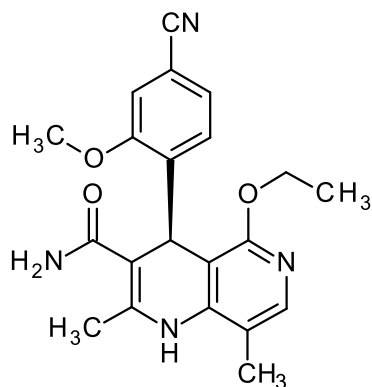


5 and then cyanoethanol ester (IVa)



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

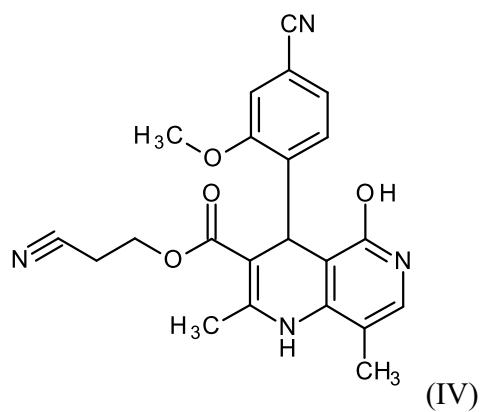
10. Process for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the formula (I)



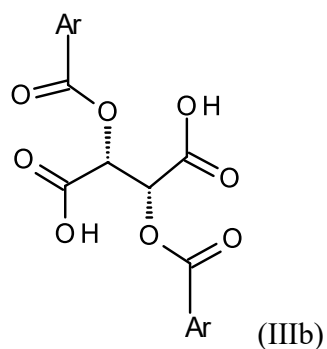
5

(Ia),

characterized in that racemic cyanoethanol ester of the formula (IV)



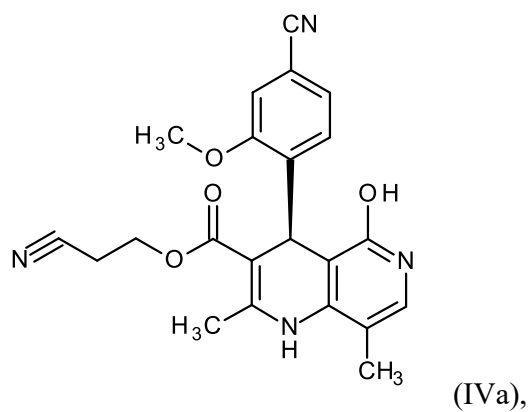
is reacted with a chiral substituted tartaric ester of the formula (IIIb)



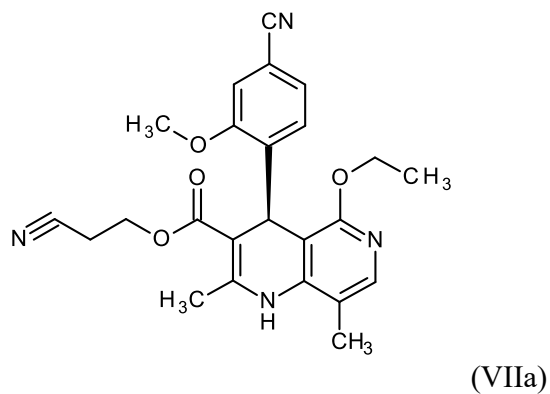
where Ar is unsubstituted or substituted aryl or heteroaryl

to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

5

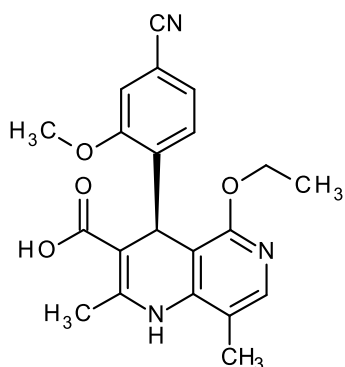


and the latter is converted by reacting with orthoester under acidic catalysis to the compound of the formula (VIIa)



10

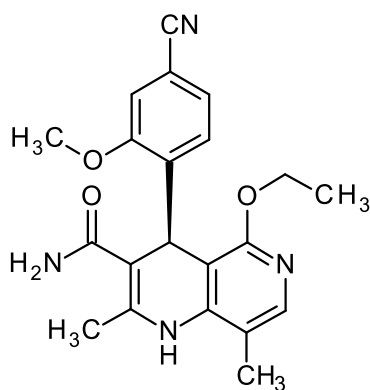
and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)



(VIIIa)

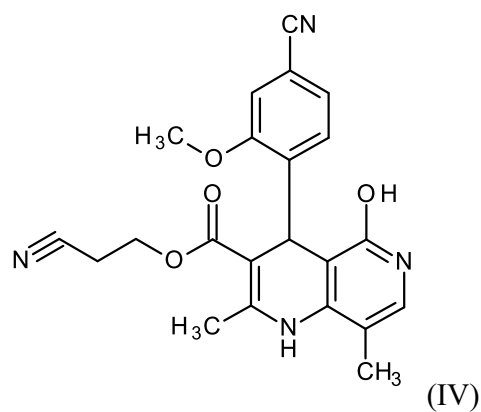
5 and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

11. Process according to paragraph 10 for preparing (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide of the formula (Ia)

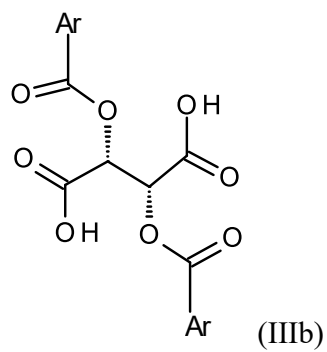


(Ia),

characterized in that racemic cyanoethanol ester of the formula (IV)

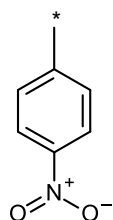


is reacted with a chiral substituted tartaric ester of the formula (IIIb)



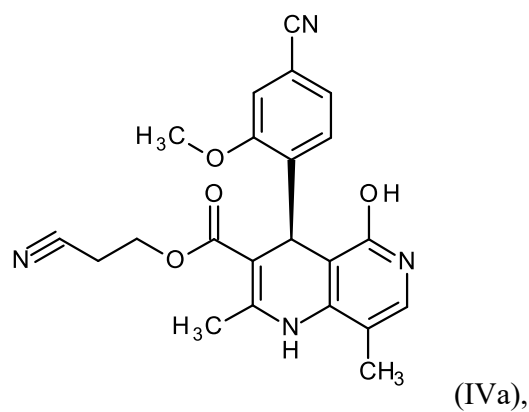
5 where

Ar is

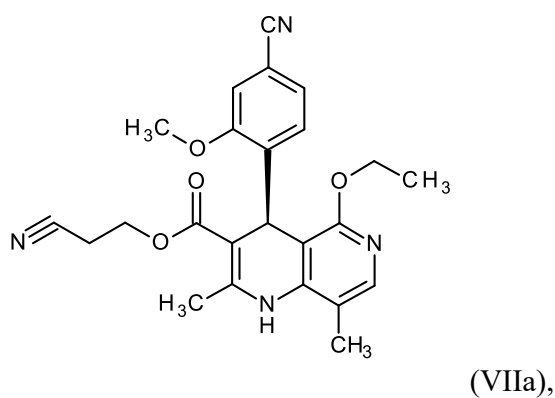


in which * represents the site of attachment

10 to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)

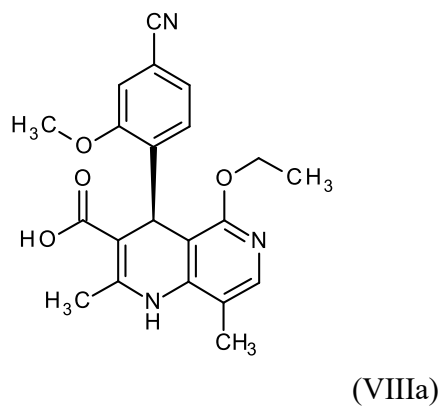


and the latter is converted by reaction with orthoester under acidic catalysis using triethyl orthoformate or triethyl orthoacetate and concentrated sulfuric acid as acidic catalyst to the compound of the formula (VIIa)



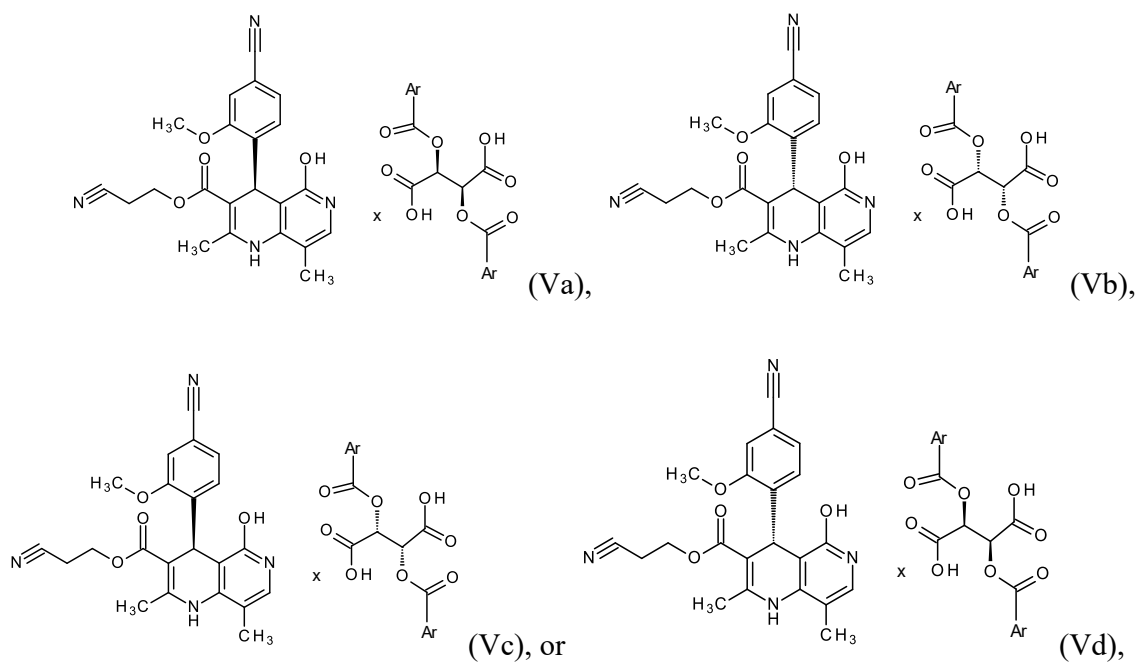
5

and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)



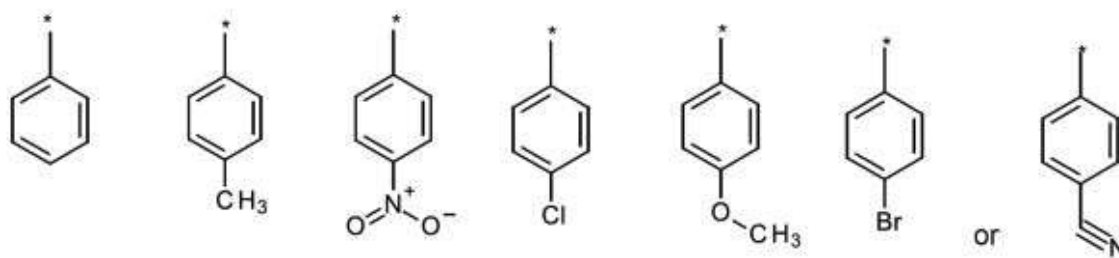
and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

5 12. Diastereomeric salts of the formula



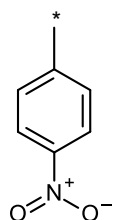
in which Ar is an unsubstituted or substituted aromatic or heteroaromatic.

13. Diastereomeric salt according to paragraph 12, characterized in that Ar is one of the formulae



in which * represents the site of attachment.

14. Diastereomeric salt according to paragraph 12 or 13, characterized in that Ar is

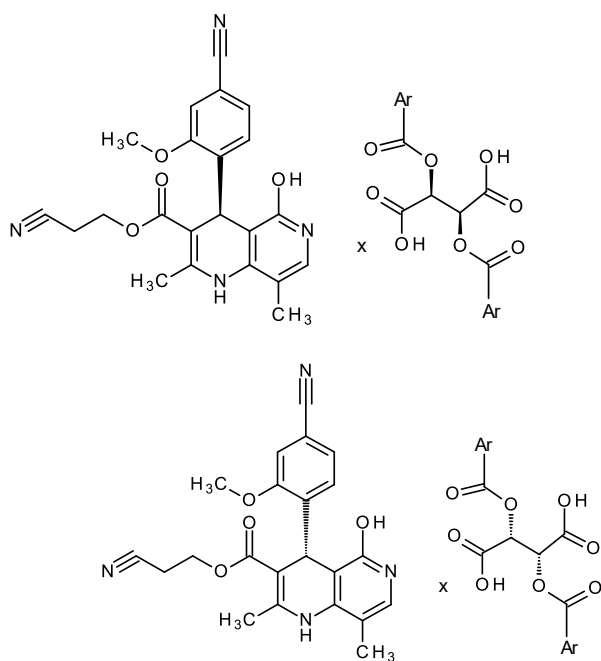


in which * represents the site of attachment.

Paragraphs (1) to (72)

5 There follows a description of further embodiments in paragraphs (1) to (72):

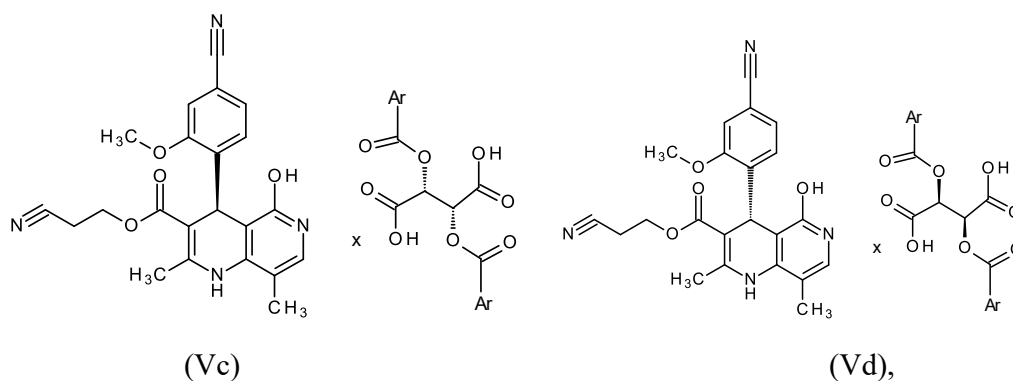
1. Diastereomeric salt of the formula (Va), (Vb), (Vc) and/or (Vd)



10

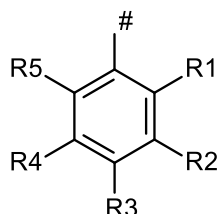
(V a)

(V b),



in which Ar is an unsubstituted or substituted aromatic or heteroaromatic.

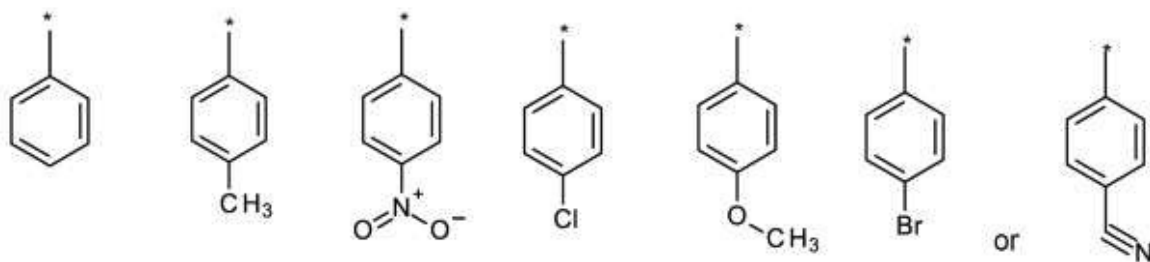
- 5 2. Diastereomeric salt according to paragraph (1), where Ar is



where # represents the site of attachment,

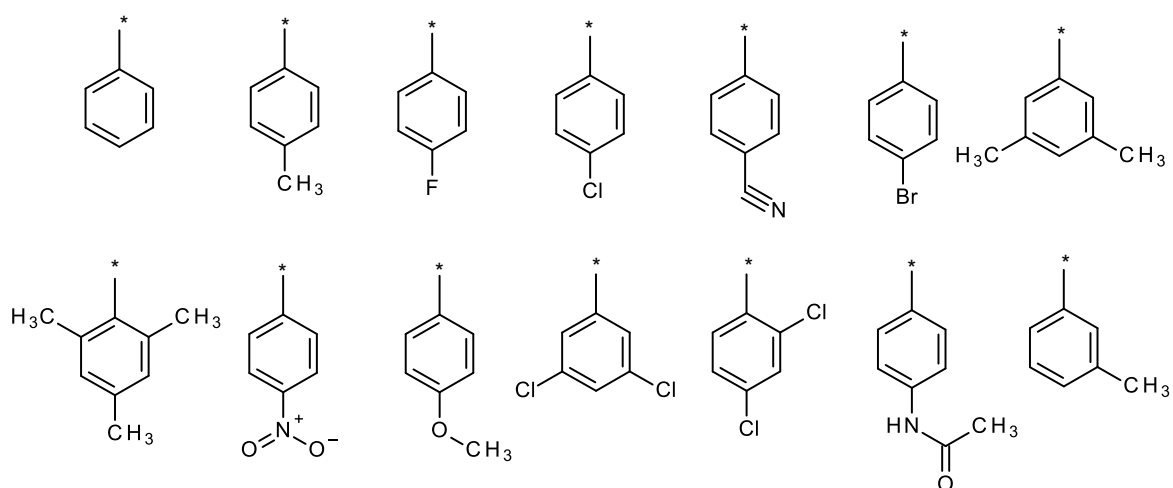
where R1, R2, R3, R4, R5 are each a hydrogen atom or an alkyl radical, for example methyl, ethyl, propyl, or a halogen atom, for example fluorine, chlorine, bromine or iodine, or an ether group, for example O-methyl, O-ethyl, O-phenyl, or a nitro group, or a cyano group, or a CF₃ group, or an amide group, for example –NHCOR in which R may be methyl, ethyl or phenyl, or –NRCOR in which R has the meaning given above or CONHR in which R has the meaning given above or CONRR' in which R' has the same meaning as R as defined above, or cyclic amides such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted. The substitution patterns may differ widely; for instance, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. Ar may alternatively be a substituted heteroaromatic radical such as, preferably, pyridine or pyrazine. Ar may alternatively be a polycyclic aromatic hydrocarbon, for example a substituted naphthalene, anthracene or quinoline.

- (3) Diastereomeric salt according to Claim 1 or 2, is one of the formulae



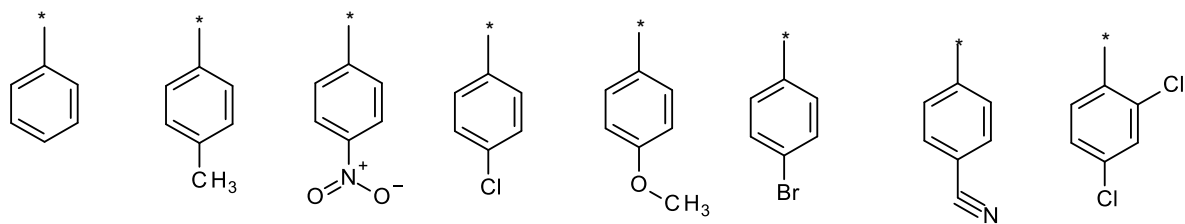
in which * represents the site of attachment.

- 5 (4) Diastereomeric salt according to any of paragraphs (1) to (3), where Ar is one of the formulae



in which * represents the site of attachment.

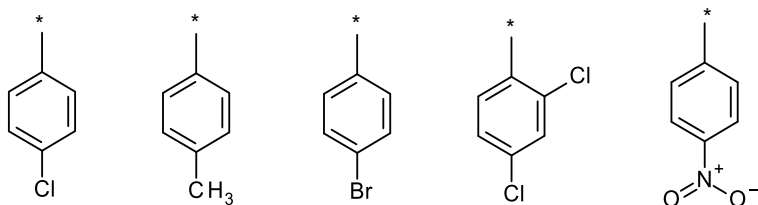
- 10 (5) Diastereomeric salt according to any of paragraphs (1) to (4), where Ar is one of the formulae



in which * represents the site of attachment.

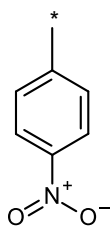
- (6) Diastereomeric salt according to any of paragraphs (1) to (5), wherein

Ar is one of the formulae



5 in which * represents the site of attachment.

- (7) Diastereomeric salt according to any of paragraphs (1) to (6), where Ar is

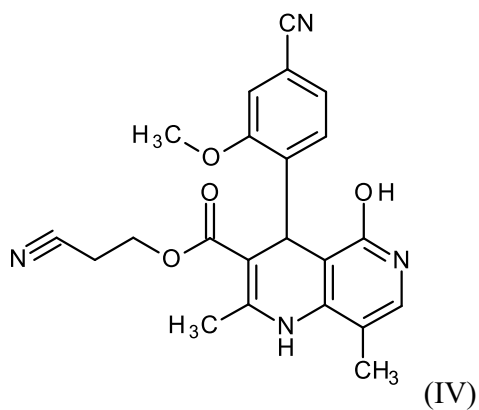


in which * represents the site of attachment.

10

- (8) Process for preparing one or more diastereomeric salts of the formula (Va), (Vb), (Vc) and/or (Vd) according to any of paragraphs (1) to (7), comprising the step (i) of

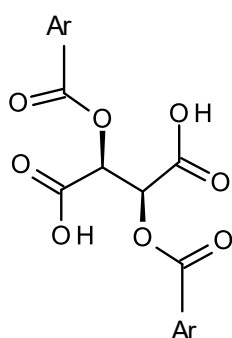
- (i) optical resolution of the compound of formula (IV)



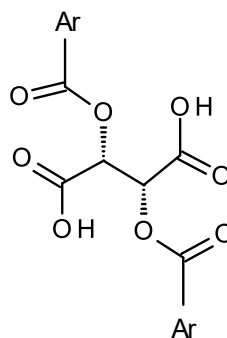
(IV)

15

by means of a tartaric ester of formula (IIIa) or (IIIb)



(IIIa)



(IIIb).

- (9) Process according to paragraph (8), wherein, in step (i), 0.5 to 2.0 equivalents of the tartaric ester (IIIa) or (IIIb) are used for the optical resolution.

5

- (10) Process according to paragraph (8) or (9), wherein, in step (i), 0.7 to 1.5 equivalents of the tartaric ester (IIIa) or (IIIb) are used for the optical resolution.

- (11) Process according to any of paragraphs (8) to (10), wherein, in step (i), 0.7 to 1.4 equivalents of the tartaric ester (IIIa) or (IIIb) are used for the optical resolution.

10

- (12) Process according to any of paragraphs (8) to (11), wherein, in step (i), 0.7 to 1.2 equivalents of the tartaric ester (IIIa) or (IIIb) are used for the optical resolution.

- (13) Process according to any of paragraphs (8) to (12), wherein in step (i) is effected in an organic solvent or insolvent mixtures consisting of water and water-miscible organic solvents.

15

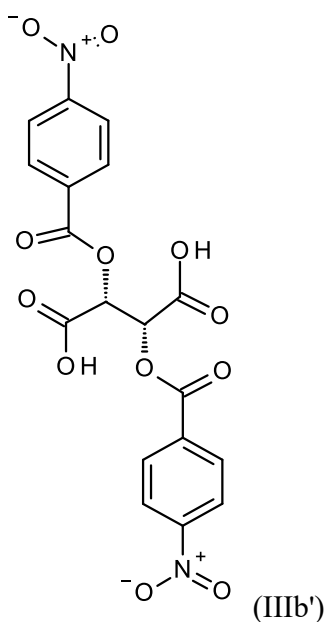
- (14) Process according to any of paragraphs (8) to (12), wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of ethanol, methanol, isopropanol,

20

1-propanol, ethyl acetate, isobutanol, dichloromethane, 1-pentanol, acetone and mixtures thereof.

- 5 (15) Process according to any of paragraphs (8) to (14), wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of 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 10 90:10; ethylene glycol; and ethylene glycol / water 80:20 and mixtures thereof, the mixing ratio being volume/volume (v/v).
- (16) Process according to any of paragraphs (8) to (15), wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of ethanol/water, where the mixing 15 ratio (v/v) is in the ethanol:water range of 1:1 to 6:1.
- (17) Process according to any of paragraphs (8) to (16), wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of ethanol:water, where the mixing ratio (v/v) is in the ethanol:water range of 6:1 to 3:1.
- 20
- (18) Process according to any of paragraphs (8) to (17), wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of ethanol:water, where the mixing ratio (v/v) is in the ethanol:water range of = 3:1.
- 25 (19) Process according to any of paragraphs (8) to (18), wherein the optical resolution in step (i) is effected at a temperature in the range from 10 to 60°C.

- (20) Process according to any of paragraphs (8) to (19), wherein the optical resolution in step (i) is effected at a temperature in the range from 20 to 50°C.
- 5 (21) Process according to any of paragraphs (8) to (20), wherein the optical resolution in step (i) is effected at a temperature in the range from 30 to 40°C.
- (22) Process according to any of paragraphs (8) to (21), wherein the optical resolution in step (i) comprises:
- 10 - initially charging the components in the solvent mixture according to any of the preceding paragraphs at room temperature,
- heating to 10 to 60°C °C or 20 to 50°C,
- continued stirring at 20-50°C for 1 to 10 hours or 1 to 4 hours, and
- cooling to room temperature within 3 to 24 hours or 5 to 16 hours.
- 15 (23) Process according to any of paragraphs (8) to (22), wherein the, in step (i), the tartaric ester of formula (IIIa) is used.
- (24) Process according to any of paragraphs (8) to (22), wherein the, in step (i), the tartaric ester of formula (IIIb) or (IIIb') (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid (IIIb')



is used for optical resolution.

5 (25) Process according to any of paragraphs (8) to (24), wherein the process in step (i) further comprises the isolating of the diastereomeric salt.

(26) Process for preparing the compound of the formula (IVa), comprising steps (i) and (ii):

- 10 (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
- (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa).

15 (27) Process according to paragraph (26), wherein step (i) is as defined in any of the preceding paragraphs (8) to (25).

(28) Process according to paragraph (26) or (27), wherein step (ii) is defined as follows:

(ii) treating the diastereomeric salt (Va) and/or (Vc) obtained in step (i) with a base to obtain the compound of the formula (IVa).

5 (29) Process according to any of paragraphs (26) to (28), wherein the base is selected from the group consisting of inorganic bases, organic bases and mixtures thereof.

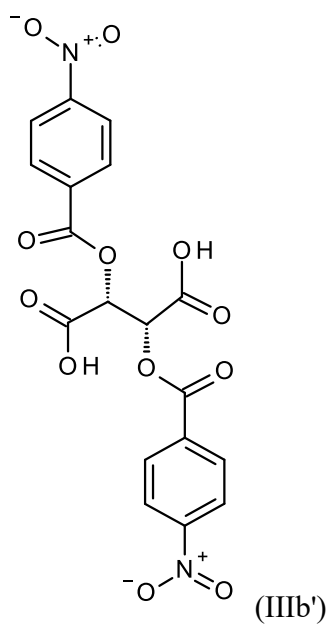
10 (30) Process according to any of paragraphs (26) to (29), wherein the base is selected from the group consisting of ammonia, sodium hydroxide solution, lithium hydroxide, potassium hydroxide, ammonium carbonate, sodium carbonate, potassium carbonate, lithium carbonate, ammonium hydrogencarbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium phosphate, potassium phosphate, ammonium phosphate and mixtures thereof.

15 (31) Process according to any of paragraphs (26) to (30), wherein the base is selected from the group consisting of sodium hydroxide, sodium phosphate, potassium phosphate and mixtures thereof.

20 (32) Process according to any of paragraphs (26) to (31), wherein the base is selected from the group consisting of aliphatic organic bases, aromatic organic bases and mixtures thereof.

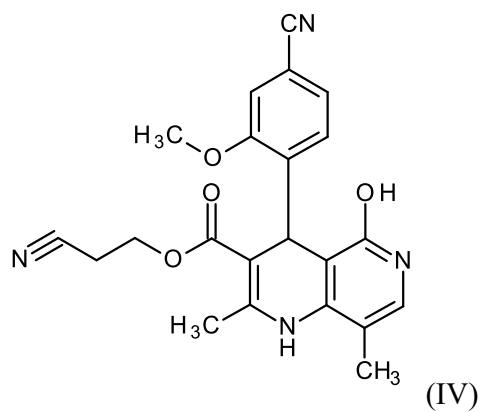
(33) Process according to paragraph (32), wherein the base is selected from the group consisting of triethylamine, imidazole, N-methylimidazole, Hünig's base, pyridine, DBU and mixtures thereof.

- (34) Process according to any of paragraphs (26) to (33), wherein a solvent or solvent mixture selected from the group consisting of water, water-miscible organic solvents or mixtures thereof is used in step (ii).
- 5 (35) Process according to any of paragraphs (26) to (34), wherein, in step (ii), the solvent or solvent mixture is selected from the group consisting of ethanol, isopropanol, ethane-1,2-diol, methoxyethanol, methanol, acetone and mixtures thereof.
- 10 (36) Process according to any of paragraphs (26) to (35), wherein, in step (ii), the organic solvent or solvent mixture is selected from the group consisting of water/ethanol, where the mixing ratio (v/v) is in the ethanol:water range of 1:6 to 1:3.
- 15 (37) Process according to any of paragraphs (26) to (36), wherein, in step (ii), the organic solvent or solvent mixture is selected from the group consisting of water/ethanol, where the mixing ratio (v/v) is in the ethanol:water range of 1:3.
- (38) Process according to any of paragraphs (26) to (37), wherein step (ii) is effected at a temperature of 0°C to 60°C.
- 20 (39) Process according to any of paragraphs (26) to (38), wherein step (ii) is effected at a temperature of 0°C to 50°C.
- (40) Process according to any of paragraphs (26) to (39), wherein step (ii) is effected at a pH of 6.9 to 8.0.
- 25 (41) Process according to any of paragraphs (26) to (40), wherein step (ii) is effected at a pH of 7.0 to 7.5.
- (42) Process according to any of paragraphs (26) to (41), wherein step (ii) is effected at a pH of 7.1.
- 30 (43) Process according to any of paragraphs (26) to (41), wherein, in step (i), (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid (IIIb')



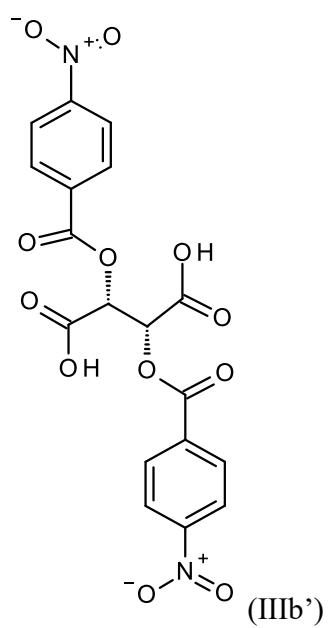
is used for optical resolution.

(44) Process according to any of paragraphs (26) to (43), wherein the racemate (IV)

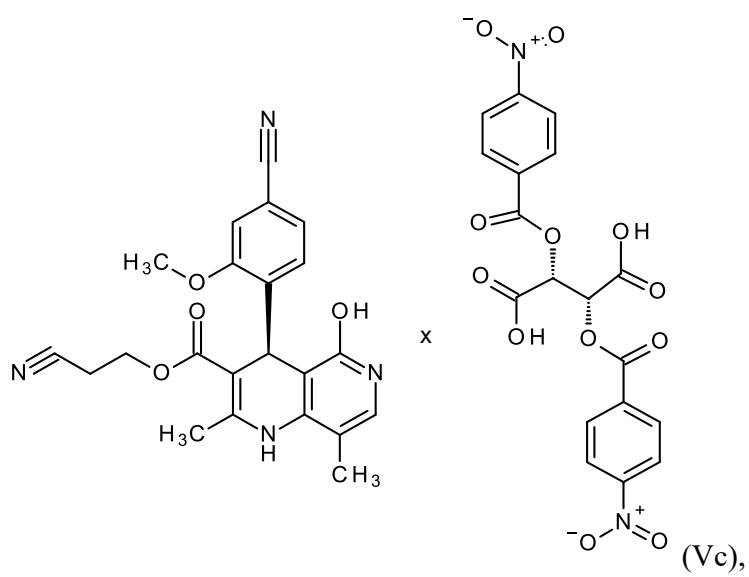


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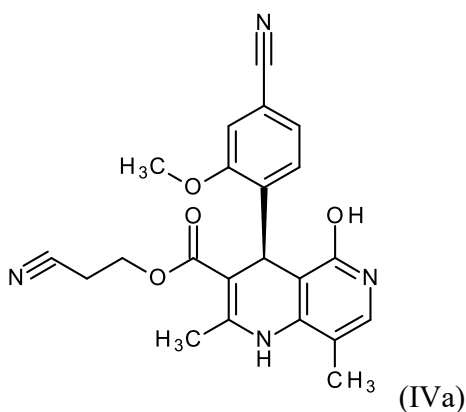
is reacted with (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid of the formula (IIIb')



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



5 and then cyanoethanol ester (IVa)



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

(45) Process for preparing the compound of formula (Ia), comprising steps (i), (ii), (iii), (iv) and (v):

- (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
- (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa) (preferably: treating the diastereomeric salt (Va) and/or (Vc) obtained in step (i) with a base to obtain the compound of the formula (IVa));
- (iii) reacting the compound of formula (IVa) obtained in step (ii) with an orthoester under acidic catalysis to obtain the compound of formula (VIIa);
- (iv) hydrolysing the compound of formula (VIIa) obtained in step (iii) to obtain the compound of formula (VIIIa);
- (v) converting the compound of formula (VIIIa) obtained in step (iv) to a compound of formula (Ia) in THF as solvent with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, then adding hexamethyldisilazane and then heating the mixture under reflux for 16-24 hours and then adding a THF/water mixture.

- (46) Process according to paragraph (45), wherein step (i) is as defined in any of paragraphs (8) to (44).
- 5 (47) Process according to paragraph (45) or (46), comprising one or more steps as defined according to any of paragraphs (8) to (44).
- (48) Process according to any of paragraphs (45) to (47), wherein the orthoester in step (iii) is an ethyl orthoester of alkyl-, aryl- or arylalkylcarboxylic acids.
- 10 (49) Process according to any of paragraphs (45) to (48), wherein the orthoester in step (iii) is selected from the group consisting of triethyl orthoacetate, triethyl orthoformate, triethyl orthoformate, triethyl orthoacetate, triethyl orthopropionate, triethyl orthobenzoate, triethyl orthobutyrate and mixtures thereof.
- 15 (50) Process according to any of paragraphs (45) to (49), wherein 2.5 to 5 equivalents of the orthoester are used.
- (51) Process according to any of paragraphs (45) to (50), wherein the acidic catalyst used in step (iii) is sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid, phosphoric acid
20 or mixtures thereof.
- (52) Process according to any of paragraphs (45) to (51), wherein, in step (iii), 4 to 10 or 6 to 8 per cent by weight (% by weight) of the acidic catalyst is used, where the percentage by weight is based on g per compound (IVa) used.

(53) Process according to any of paragraphs (45) to (52), wherein a solvent or solvent mixture selected from the group consisting of dimethylacetamide, NMP (1-methyl-2-pyrrolidone), DMF (dimethylformamide) and mixtures thereof is used in step (iii).

5 (54) Process according to any of paragraphs (45) to (53), wherein step (iii) is conducted at a temperature of 100°C to 120°C.

(55) Process according to any of paragraphs (45) to (54), wherein step (iii) is conducted at a temperature of 115°C.

10

(56) Process according to any of paragraphs (45) to (55), wherein an alkaline hydrolysis is conducted in step (iv).

15

(57) Process according to any of paragraphs (45) to (56), wherein step (iv) is conducted in a THF/water mixture.

(58) Process according to any of paragraphs (45) to (57), wherein step (iv) is conducted in a mixture of THF/water in a ratio of 2:1 (v/v).

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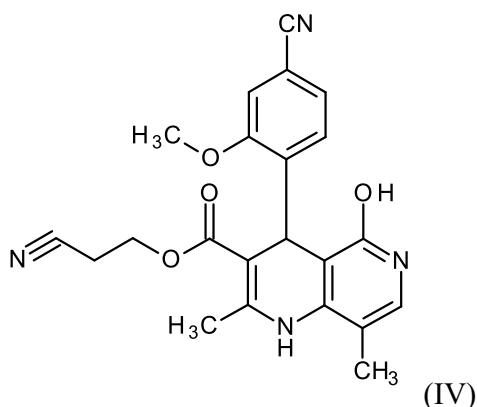
(59) Process according to any of paragraphs (45) to (58), wherein alkalization is effected with sodium hydroxide solution or potassium hydroxide solution in step (iv).

(60) Process according to any of paragraphs (45) to (59), wherein the alkalization in step (iv) is effected at a temperature of 0°C to 5°C.

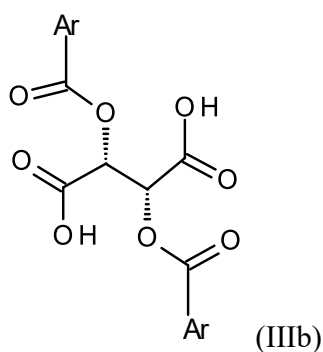
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- (61) Process according to any of paragraphs (45) to (60), wherein the converting of the compound of formula (VIIIa) obtained in step (iv) to a compound of formula (Ia) is conducted as follows: reacting the product from step (iv) in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, then adding
5 hexamethyldisilazane and then heating the mixture under reflux for 16-24 hours.

- (62) Process according to any of paragraphs (45) to (61), characterized in that racemic cyanoethanol esters of the formula (IV)

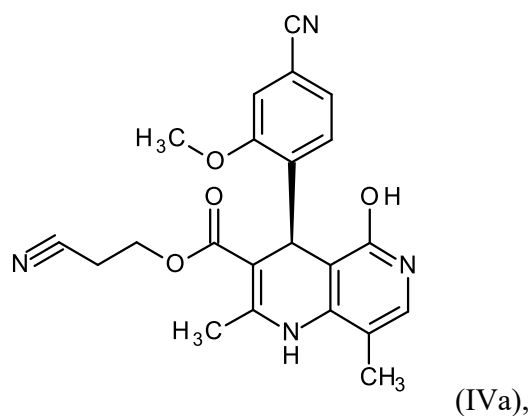


- 10 are converted using a chiral substituted tartaric ester of the formula (IIIb)

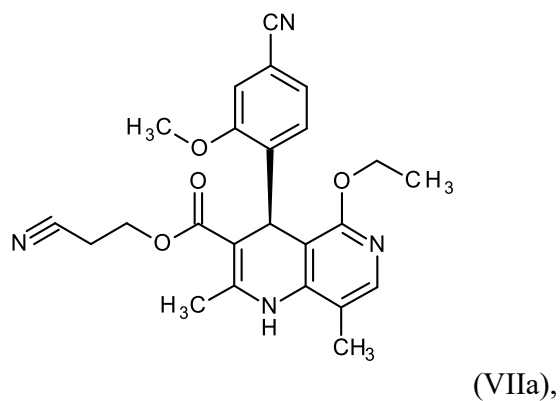


where Ar is unsubstituted or substituted aryl or heteroaryl

to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate
15 of the formula (IVa)

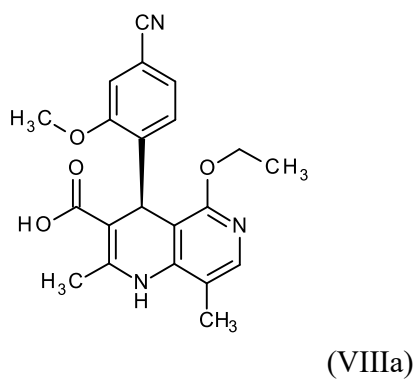


and the latter is converted by reacting with orthoester under acidic catalysis to the compound of the formula (VIIa)



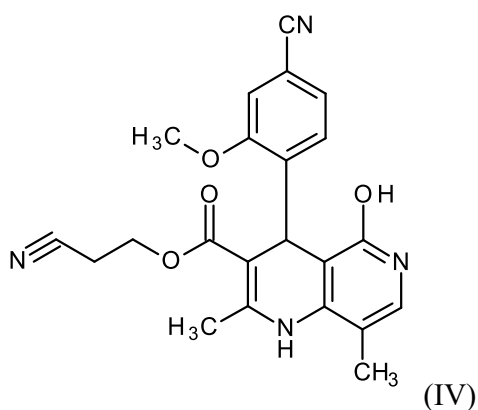
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and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)

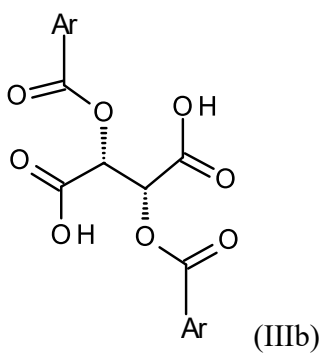


and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

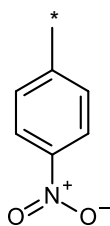
- 5 (63) Process according to any of paragraphs (45) to (62), characterized in that racemic cyanoethanol esters of the formula (IV)



are converted using a chiral substituted tartaric ester of the formula (IIIb)

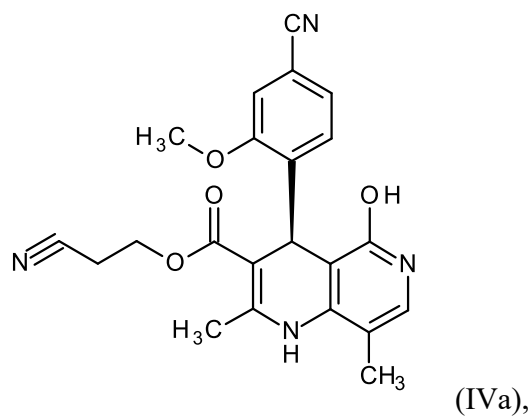


10 where Ar is



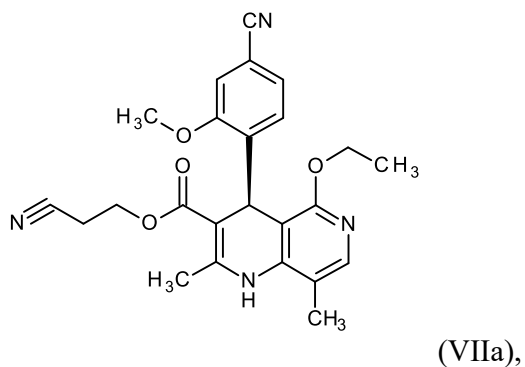
in which * represents the site of attachment

to give enantiomeric cyanoethanol ester 2-cyanoethyl (4S)-4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate of the formula (IVa)



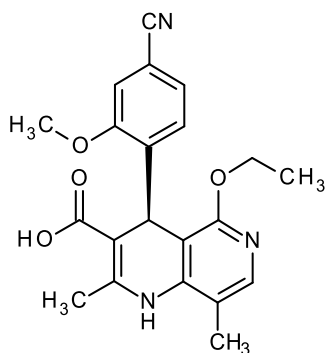
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and the latter is converted by reaction with orthoester under acidic catalysis using triethyl orthoformate or triethyl orthoacetate and concentrated sulfuric acid as acidic catalyst to the compound of the formula (VIIa)



10

and the latter is hydrolysed with sodium hydroxide in a THF/water mixture (2:1) to give the compound of the formula (VIIIa)



(VIIIa)

and the compound of the formula (VIIIa) is then reacted in THF as solvent firstly with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, hexamethyldisilazane is added and then the mixture is heated under reflux for 16-24 hours, and then a THF/water mixture is added.

(64) Use of a tartaric ester of the formula (IIIa) in a process for preparing the compound of formula (Va), (Vb), (Vc) and/or (Vd).

(65) Use of a tartaric ester of the formula (IIIb) in a process for preparing the compound of formula (Va), (Vb), (Vc) and/or (Vd).

(66) Use of a tartaric ester of the formula (IIIb') in a process for preparing the compound of formula (Va), (Vb), (Vc) and/or (Vd).

(67) Use of a tartaric ester of the formula (IIIa) in a process for preparing the compound of formula (IVa).

(68) Use of a tartaric ester of the formula (IIIb) in a process for preparing the compound of formula (IVa).

(69) Use of a tartaric ester of the formula (IIIb') in a process for preparing the compound of formula (IVa).

(70) Use of a tartaric ester of the formula (IIIa) in a process for preparing the compound of formula (Ia).

5 (71) Use of a tartaric ester of the formula (IIIb) in a process for preparing the compound of formula (Ia).

(72) Use of a tartaric ester of the formula (IIIb') in a process for preparing the compound of formula (Ia).

10 Experimental

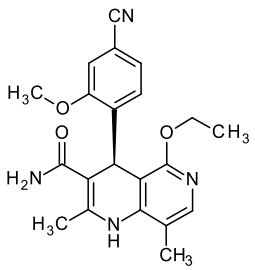
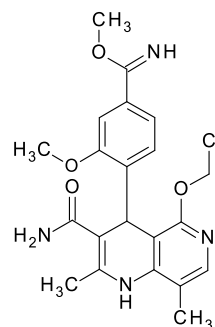
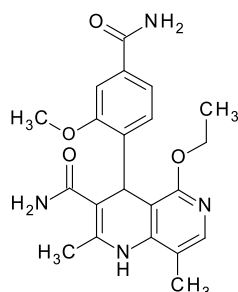
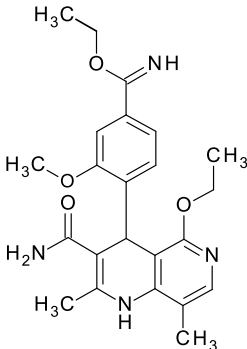
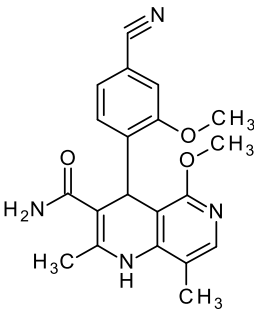
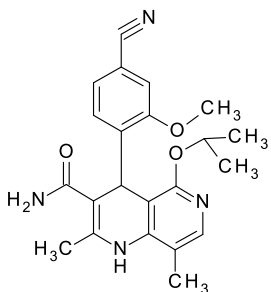
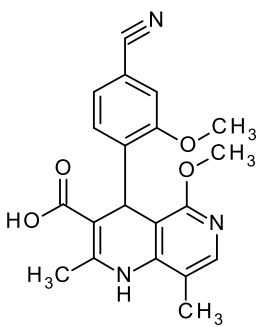
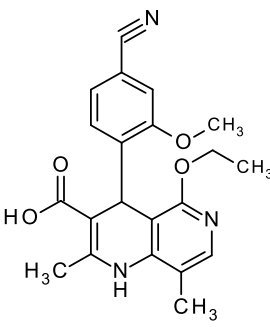
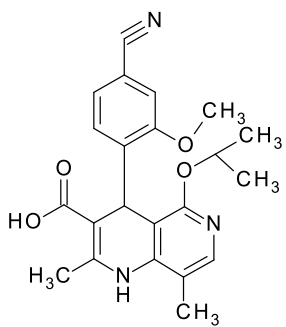
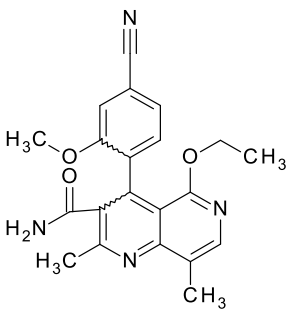
Abbreviations and acronyms:

<u>EtOH</u>	<u>ethanol</u>
<u>DB tartaric acid</u>	<u>Dibenzoyltartaric acid</u>
<u>DMSO</u>	<u>dimethyl sulfoxide</u>
<u>of th.</u>	<u>of theory (in yield)</u>
<u>HPLC</u>	<u>high-pressure, high-performance liquid chromatography</u>
<u>¹H-NMR</u>	<u>¹H nuclear magnetic resonance spectrometry</u>
<u>IT</u>	<u>internal temperature</u>
<u>MS</u>	<u>mass spectrometry</u>
<u>RT</u>	<u>room temperature</u>
<u>RRT</u>	<u>relative retention time</u>
<u>TFA</u>	<u>trifluoroacetic acid</u>
<u>TI</u>	<u>internal temperature</u>
<u>TM</u>	<u>jacket temperature</u>
<u>XRPD</u>	<u>X-ray powder diffraction (powder diffractometer)</u>
<u>Spirits</u>	<u>ethanol denatured with 2% toluene</u>

Examples

Table 3 below shows the structures of the compounds recovered in HPLC. The assignment of the
15 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 G 	impurity F 	impurity I 
impurity J 	impurity K 	

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

Content and organic		RT (min)	RRT
impurities	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

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 (%)	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</u>		RRT
<u>purity:</u>		RT (min)

Method A

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

Enantiomeric purity

Method B

	RT(min)	RRT
finerenone (I)	5.7	1.00
enantiomer (Ia)	6.8	1.19

5

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

and data evaluation system

Measurement wavelength: 252 nm

10 **Oven temperature:** 40°C

Column: Chiralpak IC

length: 150 mm, **internal diameter:** 4.6 mm, **particle size:** 3 µm

Mobile phase:

A: 50% buffer 20mM NH₄OAc pH 9

15 B: 50% acetonitrile

Flow rate: 1 ml/min.

Elution time: 8 min.

Equilibration: unnecessary, isocratic

Sample solvent: eluent

20 **Sample 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 by Method B. Some values, especially those of the batches prepared in the pilot plant, were reanalysed with Method A for comparison, and gave comparable results.

5 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.

10 HPLC conditions/methods

Method (C)

YMC Hydrosphere C18

150*4.6 mm, 3.0 µm

25°C, 1 ml/min , 270 nm, 4 nm

15 0' : 70% TFA 0.1%*; 30% acetonitrile

17': 20% TFA 0.1%; 80% acetonitrile

18': 70% TFA 0.1%; 30% acetonitrile

*: TFA in water

20 Method (D)

YMC Hydrosphere C18

150*4.6 mm, 3.0 µm

25°C, 1 ml/min , 255 nm, 6 nm

0' : 90% TFA 0.1%; 10% acetonitrile

20': 10% TFA 0.1%; 90% acetonitrile

18': 10% TFA 0.1%; 90% acetonitrile

Method (E)

5 Nucleodur Gravity C18

150*2 mm, 3.0 µm

35°C, 0.22 ml/min. , 255 nm, 6 nm

Solution A: 0.58 g of ammonium hydrogenphosphate and 0.66 g of ammonium dihydrogenphosphate in 1 l of water (ammonium phosphate buffer pH 7.2)

10 Solution B: acetonitrile

0' : 30% B ; 70% A

15' : 80% B ; 20% A

25' : 80% B ; 20% A

15 **Method (F)**

Implementation instructions

Enantiomeric purity	RT(min)	RRT
---------------------	---------	-----

Enantiomer IVa	3.8	1.00
----------------	-----	------

Enantiomer IVb	4.8	1.26
----------------	-----	------

20 Instrument/detector: high-performance liquid chromatograph with temperature-controlled column oven, UV detector

and data evaluation system

Measurement wavelength: 253 nm, range: 6 nm

Oven temperature: 40°C

Column: Chiralpak AD-H

length: 250 mm, internal diameter: 4.6 mm, particle size: 5 µm

5 Mobile phase: A: heptane

B: isopropanol +0.1% DEA (diethylamine)

Gradient programme: Time [min]

Flow rate:

	Eluent A [%]	Eluent B [%]
10 Start 2 [ml/min]	80	20

Elution time: 8 min.

Example 1a

15 Preparation of the diastereomeric salt of 2-cyanoethyl 4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate with (2S,3S)-2,3-bis(4-nitrobenzoyl)tartaric acid

2.00 g of racemic 2-cyanoethyl 4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (IV) was suspended together with 2.375 g (1.05 eq) of (2S,3S)-2,3-bis(4-nitrobenzoyl)tartaric acid in 54 ml of dichloromethane and heated to 39°C for 45 minutes, and stirred at that temperature for 4 hours. The mixture was cooled to 20°C over 20 hours and stirred at that temperature for another 18 hours. After some time, the diastereomeric salt precipitated out. This was filtered off and dried (2.1 g = 49.8% of theory), and the enantiomeric excess was measured. The measurement gave an enantiomeric excess of 84% e.e. (method F) in favour of 2-cyanoethyl (4R)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

25 MS (EIpos): m/z = 405 [M+H]⁺

¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.90 - 2.18 (m, 2 H) 2.35 (s, 2 H) 2.67 - 2.97 (m, 1 H) 3.75 (s, 2 H) 3.93 - 4.06 (m, 1 H) 4.08 - 4.34 (m, 1 H) 5.08 - 5.36 (m, 1 H) 5.98 (s, 1 H) 6.89 - 7.01 (m, 1 H) 7.07 - 7.42 (m, 2 H) 7.97 - 8.31 (m, 3 H) 8.44 (d, *J*=8.80 Hz, 2 H) 10.19 - 11.33 (m, 1 H) 12.58 - 15.01 (m, 1 H)

5

Example 1b

Preparation of the diastereomeric salt of 2-cyanoethyl 4-(4-cyano-2-methoxyphenyl)-5-hydroxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate with (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid

- 10 2.00 g of racemate (IV) was suspended together with 2.375 g (1.05 eq.) of (2S,2R)-2,3-bis(4-nitrobenzoyl)tartaric acid in 54 ml of dichloromethane and heated to 39°C for 45 minutes, and stirred at that temperature for a further 4 hours. The mixture was cooled to 20°C over two hours and stirred at that temperature for another 18 hours. After some time, the diastereomeric salt precipitated out. This was filtered off and dried (2.0 g = 47.4% of theory), and the
- 15 enantiomeric excess was measured. The measurement gave an enantiomeric excess of 85% e.e. (method F) in favour of 2-cyanoethyl (4S)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

MS (EIpos): *m/z* = 405 [M+H]⁺

- ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.90 - 2.18 (m, 2 H) 2.35 (s, 2 H) 2.67 - 2.97 (m, 1 H)
- 20 3.75 (s, 2 H) 3.93 - 4.06 (m, 1 H) 4.08 - 4.34 (m, 1 H) 5.08 - 5.36 (m, 1 H) 5.98 (s, 1 H) 6.89 - 7.01 (m, 1 H) 7.07 - 7.42 (m, 2 H) 7.97 - 8.31 (m, 3 H) 8.44 (d, *J*=8.80 Hz, 2 H) 10.19 - 11.33 (m, 1 H) 12.58 - 15.01 (m, 1 H)

Example 2a

- 25 Preparation of the diastereomeric salt of 2-cyanoethyl 4(S)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate with (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid

200 g (494.5 mmol) of racemate (IV) was suspended together with 237.5 g (1.05 eq.) of (2R,3R)-2,3-bis(4-nitrobenzoyl)tartaric acid in 5400 ml of dichloromethane and heated to 39°C for 45 minutes, and stirred at that temperature for a further 4 hours. The mixture was cooled to 20°C over two hours and stirred at that temperature for another 18 hours. After some time, the diastereomeric salt precipitated out. This was filtered off and dried (209 g), and the enantiomeric excess was measured. The measurement gave an enantiomeric excess of 83% e.e. in favour of 2-cyanoethyl (4S)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

An amount of the diastereomeric salt enriched in this way was purified further as follows:

209 g of the diastereomeric salt prepared was suspended in 2000 ml of dichloromethane and stirred at 50°C for 2 h and at room temperature overnight. The precipitated crystals were filtered off and washed twice with 300 ml of dichloromethane. The product was dried under reduced pressure at 40°C.

Yield: 163.6 g (38.8% of theory) of a colourless crystalline powder.

15 Analytical results:

Enantiomeric purity (e.e %): 98 % e.e.

MS (EIpos): $m/z = 405 [M+H]^+$

¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.90 - 2.18 (m, 2 H) 2.35 (s, 2 H) 2.67 - 2.97 (m, 1 H) 3.75 (s, 2 H) 3.93 - 4.06 (m, 1 H) 4.08 - 4.34 (m, 1 H) 5.08 - 5.36 (m, 1 H) 5.98 (s, 1 H) 6.89 - 7.01 (m, 1 H) 7.07 - 7.42 (m, 2 H) 7.97 - 8.31 (m, 3 H) 8.44 (d, $J=8.80$ Hz, 2 H) 10.19 - 11.33 (m, 1 H) 12.58 - 15.01 (m, 1 H)

Example 2b

25 Preparation of 2-cyanoethyl (4S)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate (IVa)

600 g (732.7 mmol) of the title compound from Example 2a was suspended in 6 l of a mixture of water/ethanol 3:1, and the mixture was cooled to 0°C. Then a 30% aqueous sodium phosphate solution was metered in gradually (over the course of 1 hour) and the pH was adjusted to pH 7.1. The mixture was left to stir at that temperature for a further 4 hours. The precipitated solids were
5 filtered off and washed twice with 1000 ml of a mixture (0°C) of water/ethanol 3:1. The product was dried under reduced pressure at 40°C.

Yield: 269.5 g (94.7% of theory) of a colourless crystalline powder.

Analytical results:

Enantiomeric purity (e.e %): 98 % e.e.

10

MS (EIpos): $m/z = 405 [M+H]^+$

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 2.03$ (s, 3H), 2.35 (s, 3H), 2.80 (m, 2H), 3.74 (s, 3H), 4.04 (m, 1H), 4.11 (m, 1H), 5.20 (s, 1H), 6.95 (s, 1H), 7.23 (dd, 1H), 7.28-7.33 (m, 2H), 8.18 (s, 1H), 10.76 (s, 1H).

15

Example 2c

2-Cyanoethyl (4S)-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (VIIa)

257.04 g (0.636 mol) of 2-cyanoethyl (4S)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-
20 1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate (IVa) and 282 g (1.74 mol) of triethyl orthoacetate were dissolved in 420 g of NMP (1-methyl-2-pyrrolidone), and 18.9 g of concentrated sulfuric acid was added. The mixture was heated at 115°C for 1.5 hours and then cooled to 50°C. At 50°C, 264 ml of water was added dropwise over 30 minutes. After addition had ended, 11 g of the title compound was added as seed crystals, and a further 528 ml of water
25 was added dropwise at 50°C over the course of 30 minutes. The mixture was cooled to 0°C (gradient, 2 hours) and then stirred at 0°C for 2 hours. The product was filtered off, washed twice with 480 ml each time of water and dried at 50°C under reduced pressure.

Yield: 254.3 g (92.5% of theory) of a pale yellow solid.

MS (EIpos): $m/z = 433 [M+H]^+$

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): $\delta = 1.11$ (t, 3H), 2.16 (s, 3H), 2.42 (s, 3H), 2.78 (m, 2H), 3.77 (s, 3H), 4.01-4.13 (m, 4H), 5.37 (s, 1H), 7.25 (d, 1H), 7.28-7.33 (m, 2H), 7.60 (s, 1H), 8.35 (s, 1H).

Example 2d

(4S)-(4-Cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (VIIIa)

250 g (0.578 mol) of (4S)-2-cyanoethyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (VII) was dissolved in a mixture of 1.5 l of THF and 750 ml of water, and cooled to 0°C. To this solution was added dropwise, at 0°C over the course of 15 minutes, a sodium hydroxide solution (prepared from 164 g of 45% aqueous sodium hydroxide solution (924.8 mmol) and 846 ml of water), and the mixture was stirred at 0°C for a further 1.5 hours. The mixture was extracted twice with 576 ml each time of methyl tert-butyl ether and once with 600 ml of ethyl acetate. The aqueous solution at 0°C was adjusted to pH 7 with dilute hydrochloric acid (prepared from 74.2 g of 37% HCl and 302 ml of water). The solution was allowed to warm up to 20°C, and an aqueous solution of 246 g of ammonium chloride in 665 ml of water was added. The solution was stirred at 20°C for 1 hour, and the product was filtered off and washed twice with 190 ml each time of water and once with 500 ml of acetonitrile. The product was dried at 40°C under entraining gas.

Yield: 207.7 g (94.7% of theory) of an almost colourless powder (very slight yellow tint).

HPLC Method E: RT: about 6.8 min.

MS (EIpos): $m/z = 380 [M+H]^+$

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): $\delta = 1.14$ (t, 3H), 2.14 (s, 3H), 2.37 (s, 3H), 3.73 (s, 3H), 4.04 (m, 2H), 5.33 (s, 1H), 7.26 (m, 2H), 7.32 (s, 1H), 7.57 (s, 1H), 8.16 (s, 1H), 11.43 (br. s, 1H).

Example 2e

(4S)- 4-(4-Cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide (Ia)

- 5 To an initial charge of 200 g (527.1 mmol) of 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (VIIIa) and 119.8 g (738.8 mol) of 1,1-carbodiimidazole in 1000 ml of THF was added 5.1 g (0.0417 mol) of DMAP at 20°C. The mixture was stirred at 20°C for one hour (evolution of gas!) and then heated to 50°C for 2.5 hours. 371.6 g (2.30 mol) of hexamethyldisilazane was added to this solution, which was boiled under
10 reflux for 22 hours. A further 225 ml of THF was added and the mixture was cooled to 5°C. A mixture of 146 ml of THF and 104 g of water was added over 3 hours such that the temperature remained between 5°C and 20°C. The mixture was subsequently boiled under reflux for one hour, then cooled via a gradient (3 hours) to 0°C and stirred at that temperature for one hour. The product was filtered off and washed twice with 250 ml each time of THF and twice with 400 ml
15 each time of water. The product was dried at 70°C under vacuum under entraining gas.

Yield: 186.3 g (93.4% of theory) of an almost colourless powder (very slight yellow tint).

HPLC method D: RT about 6.7 min.

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

- 20 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.05$ (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, 2H), 7.14 (d, 1H), 7.28 (dd, 1H), 7.37 (d, 1H), 7.55 (s, 1H), 7.69 (s, 1H).

Example 2f

- 25 Preparation of pure product (Ia = finerenone)

140.0 g of the crude product (I) prepared in Example 2e was suspended in 2796 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 36 ml of ethanol (denatured with toluene). The solvent was then distilled off (about 2304 ml was distilled off) until a final volume of about 4 times the substance used ($139.2\text{ g} \times 4 \sim 561\text{ ml}$) had been attained. The mixture was then cooled to internal temperature 23°C (over about 1.5 to 2 hours). The mixture was then stirred at internal temperature 3°C for 2 hours. The product was filtered off and rinsed once with 100 ml of ethanol (denatured with toluene). Wet yield: 143.70 g. The wet product was dried at 50°C over the weekend ($> 48\text{ h}$) under reduced pressure ($< 100\text{ mbar}$). Yield: 131.3 g (93.8% of theory) of a colourless crystalline powder, fine needle-like crystals.

10 Analytical results:

Finerenone (I)	Purity: 99.91 area (HPLC); Content: 99.5% by weight
Enantiomeric excess	100 % e.e.
Largest secondary component impurity E	0.05%
Residual solvents:	
EtOH	0.05%
toluene	0.00%
water (Karl Fischer)	0.00%

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

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 1.05\text{ (t, 3H)}$, 2.12 (s, 3H) , 2.18 (s, 3H) , 3.82 (s, 3H) , $3.99\text{--}4.07\text{ (m, 2H)}$, 5.37 (s, 1H) , $6.60\text{--}6.84\text{ (m (broad signal))}$, 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 the DMSO solvent and water at $\delta = 2.5\text{--}2.6$ and a very small peak at $\delta = 3.37$ (not assignable)

Modification: Mod A (as defined in WO2016/016287 A1)

Example 3

Preparation of the diastereomeric salt of 2-cyanoethyl 4(S)-(4-cyano-2-methoxyphenyl)-2,8-
dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate with (2S,3S)-2,3-bis(4-
5 nitrobenzoyl)tartaric acid

2.00 g of racemate (IV) was suspended together with 2.375 g (1.05 eq.) of (2S,3S)-2,3-bis(4-nitrobenzoyl)tartaric acid in 54 ml of propylene carbonate and heated to 39°C for 45 minutes, and stirred at that temperature for a further 4 hours. The mixture was cooled to 20°C over
10 two hours and stirred at that temperature for another 18 hours. After some time, the diastereomeric salt precipitated out. This was filtered off and dried (2.05 g = 48.6% of theory), and the enantiomeric excess was measured. The measurement gave an enantiomeric excess of 76.2% e.e. in favour of 2-cyanoethyl (4R)-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

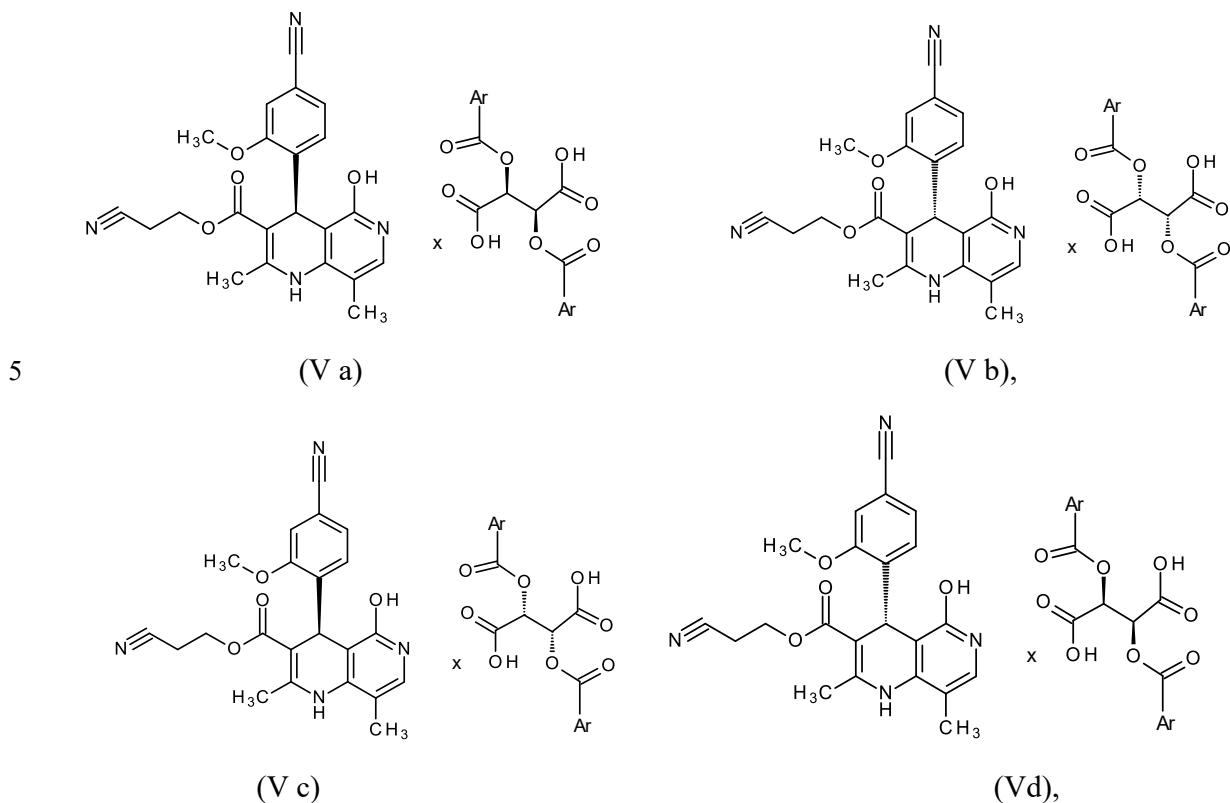
15

MS (EIpos): $m/z = 405$ $[M+H]^+$

^1H NMR (600 MHz, DMSO- d_6) δ ppm 1.90 - 2.18 (m, 2 H) 2.35 (s, 2 H) 2.67 - 2.97 (m, 1 H)
3.75 (s, 2 H) 3.93 - 4.06 (m, 1 H) 4.08 - 4.34 (m, 1 H) 5.08 - 5.36 (m, 1 H) 5.98 (s, 1 H) 6.89 -
7.01 (m, 1 H) 7.07 - 7.42 (m, 2 H) 7.97 - 8.31 (m, 3 H) 8.44 (d, $J=8.80$ Hz, 2 H) 10.19 - 11.33
20 (m, 1 H) 12.58 - 15.01 (m, 1 H).

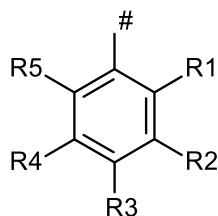
Claims

1. Diastereomeric salt of the formula (Va), (Vb), (Vc) and/or (Vd)



in which Ar is an unsubstituted or substituted aromatic or heteroaromatic.

2. Diastereomeric salt according to Claim 1, where Ar is

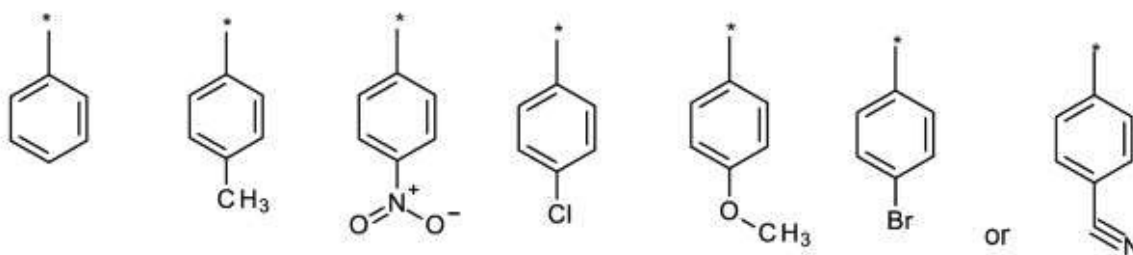


where # represents the site of attachment,

where R1, R2, R3, R4, R5 are each a hydrogen atom or an alkyl radical, for example methyl, ethyl, propyl, or a halogen atom, for example fluorine, chlorine, bromine or iodine, or an ether group, for example O-methyl, O-ethyl, O-phenyl, or a nitro group, or a

cyano group, or a CF₃ group, or an amide group, for example –NHCOR in which R may be methyl, ethyl or phenyl, or –NRCOR in which R has the meaning given above or CONHR in which R has the meaning given above or CONRR' in which R' has the same meaning as R as defined above, or cyclic amides such as 3-oxomorpholin-4-yl, 2-oxopiperidin-1-yl, which may in turn be substituted. The substitution patterns may differ widely; for instance, up to 5 different substituents are theoretically possible, but preference is generally given to the monosubstituted Ar radicals. Ar may alternatively be a substituted heteroaromatic radical such as, preferably, pyridine or pyrazine. Ar may alternatively be a polycyclic aromatic hydrocarbon, for example a substituted naphthalene, anthracene or quinoline.

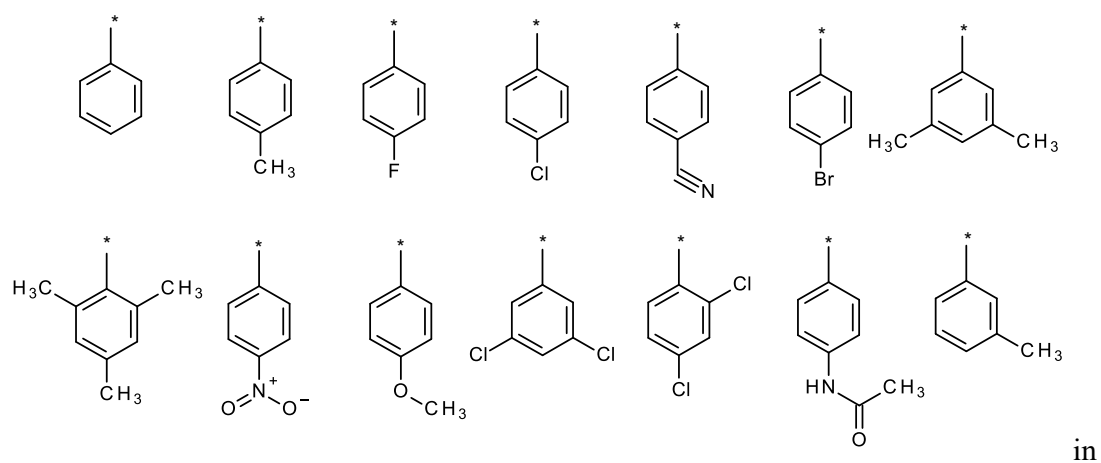
3. Diastereomeric salt according to Claim 1 or 2, is one of the formulae



in which * represents the site of attachment;

or

where Ar is one of the formulae



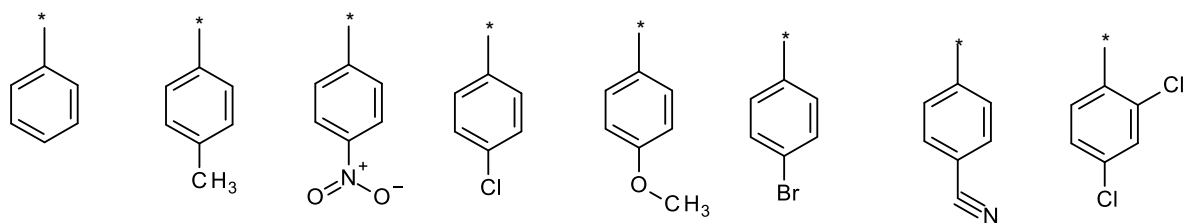
in

which * represents the site of attachment;

or

where Ar is one of the formulae

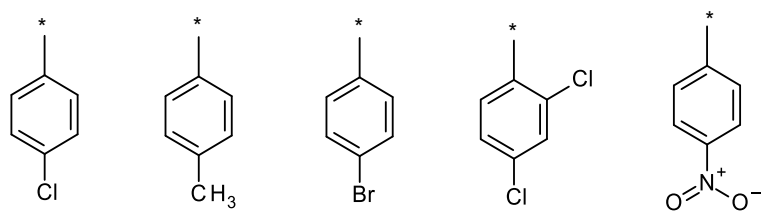
5



in which * represents the site of attachment;

or

where Ar is one of the formulae

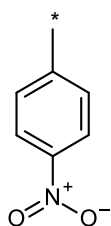


10

in which * represents the site of attachment;

or

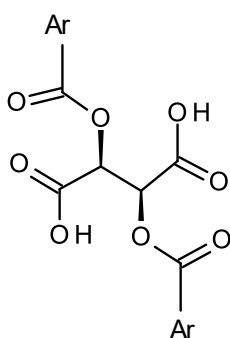
where Ar is



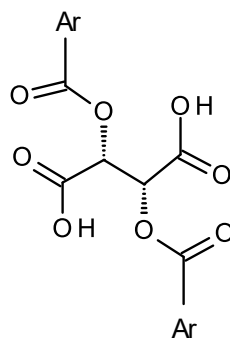
in which * represents the site of attachment.

4. Process for preparing one or more diastereomeric salts of the formula (Va), (Vb), (Vc)
5 and/or (Vd) according to any of Claims 1 to 3, comprising the step (i) of

(i) optical resolution of the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb)



(IIIa)



(IIIb).

- 10 5. Process according to Claim 4, wherein the optical resolution in step (i) is effected at a temperature of 10 to 60°C.
6. Process according to either of Claims 4 and 5, wherein, in step (i), the organic solvent or solvent mixture is selected from the group consisting of ethanol, methanol, isopropanol, 1-propanol, ethyl acetate, isobutanol, dichloromethane, 1-pentanol, acetone and mixtures thereof.
- 15 7. Process for preparing the compound of the formula (IVa), comprising steps (i) and (ii):

- (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
 - (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa).
- 8. Process according to Claim 7, wherein step (i) is as defined in any of the preceding Claims 4 to 6.
- 9. Process according to Claim 7 or 8, wherein step (ii) is defined as follows:
 - (ii) treating the diastereomeric salt (Va) and/or (Vc) obtained in step (i) with a base to obtain the compound of the formula (IVa).
- 10. Process according to any of Claims 7 to 9, wherein step (ii) is effected at a temperature of 0°C to 60°C.
- 11. Process according to any of Claims 7 to 10, wherein step (ii) is effected at a pH of 6.9 to 8.0.
- 12. Process for preparing the compound of formula (Ia), comprising steps (i), (ii), (iii), (iv) and (v):
 - (i) optically resolving the compound of formula (IV) by means of a tartaric ester of formula (IIIa) or (IIIb) to form the diastereomeric salt of formula (Va) and/or (Vc);
 - (ii) converting the diastereomeric salt of formula (Va) and/or (Vc) obtained in step (i) to the compound of formula (IVa) (preferably: treating the diastereomeric salt

(Va) and/or (Vc) obtained in step (i) with a base to obtain the compound of the formula (IVa));

(iii) reacting the compound of formula (IVa) obtained in step (ii) with an orthoester under acidic catalysis to obtain the compound of formula (VIIa);

5 (iv) hydrolysing the compound of formula (VIIa) obtained in step (iii) to obtain the compound of formula (VIIIa);

(v) converting the compound of formula (VIIIa) obtained in step (iv) to a compound of formula (Ia) in THF as solvent with 1,1-carbodiimidazole and catalytic amounts of 4-(dimethylamino)pyridine, then adding hexamethyldisilazane and
10 then heating the mixture under reflux for 16-24 hours and then adding a THF/water mixture.

13. Process according to Claim 12, wherein step (III) is conducted at a temperature of 100°C to 120°C.

15

14. Process according to either of Claims 12 and 13, wherein an alkaline hydrolysis is conducted in step (iv).

15. Use of a tartaric ester of the formula (IIIa), (IIIb) and/or (IIIb') in a process for preparing
20 the compound of formula (Va), (Vb), (Vc) and/or (Vd), the compound of formula (IVa) and/or the compound of formula (Ia).