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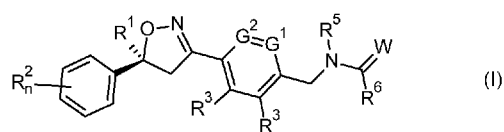
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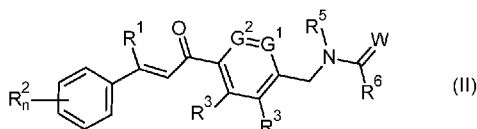
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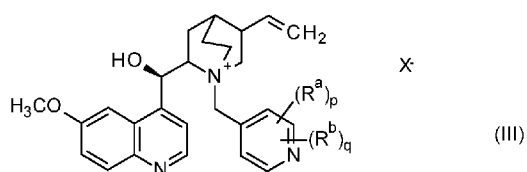
(54) Title: PROCESS FOR PREPARATION OF OPTICALLY ENRICHED ISOXAZOLINES



(I)



(II)



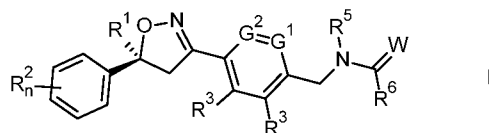
(III)

(57) Abstract: The invention relates to a process for preparing optically enriched isoxazoline compounds of formula (I), formula (I), wherein the variables are as defined in the specification, and the shown enantiomer has at least 55% ee; by oxo-Michael addition of hydroxyl amine or its salt to an enone of formula (II), formula (II), wherein the variables have the meanings given for formula (I), in the presence of a catalyst of formula (III), formula (III), and a base, the invention furthermore relates to novel compounds of formula (III).

Process for preparation of optically enriched isoxazolines

Description

- 5 The invention relates to a process for the preparation of optically enriched isoxazoline compounds of formula I



wherein

- 10 R^1 is halomethyl;
 each R^2 is independently H, halogen, CN, N_3 , NO_2 , SCN, SF_5 , C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, which groups are unsubstituted, partially or fully halogenated and/or substituted with one or more same or different R^8 , OR^9 , or $S(O)_nR^9$,
 15 n is 0, 1, or 2;
 G^1 , G^2 are each CR^3 ;
 each R^3 is independently selected from the meanings mentioned for R^2 or is $C(=O)R^8$, or two R^3 bonded to adjacent carbon atoms may form a five- or sixmembered saturated, partially or fully unsaturated carbocyclic ring, or a dihydrofurane;
 20 W is O or S;
 R^5 is independently selected from the meanings mentioned for R^2 ;
 R^6 is H, C_1 - C_{10} -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, which groups are unsubstituted, partially or fully halogenated and/or substituted with one or more same or different R^8 ; or C_1 - C_4 -alkoxy, $S(O)_nR^9$, or $C(=O)R^8$; or
 25 a 3- to 8-membered saturated, partially or fully unsaturated heterocyclic ring, which ring may contain 1, 2, 3, or 4 heteroatoms O, S, N, C=O and/or C=S as ring members, which heterocyclic ring is unsubstituted or partially or fully substituted with same or different halogen, CN, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_2 - C_6 -haloalkynyl, which groups are unsubstituted, or partially or fully substituted with same or different R^8 , or phenyl which may be partially or fully substituted with R^{11} ;
 30 each R^8 is independently CN, N_3 , NO_2 , SCN, SF_5 , C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl; $Si(R^{12})_3$, OR^9 , OSO_2R^9 , $S(O)_nR^9$, $N(R^{10a})R^{10b}$, $C(=O)N(R^{10a})R^{10b}$, $C(=S)N(R^{10a})R^{10b}$, $C(=O)OR^9$, $CH=NOR^9$,
 35 phenyl, or a 3-, 4-, 5-, 6- or 7-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2 or 3 heteroatoms N, O, and/or S as ring members, or two R^8 present on the same carbon atom of an alkyl, alkenyl, alkynyl or cycloalkyl group together form a group $=O$, $=C(R^{13})_2$, $=S$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{10a}$, $=NOR^9$; or $=NN(R^{10a})R^{10b}$; or
 40 two radicals R^8 , together with the carbon atoms of the alkyl, alkenyl, alkynyl or cycloalkyl group which they are bonded to, form a 3-, 4-, 5-, 6-, 7- or 8-membered saturated or partially unsaturated carbocyclic or heterocyclic ring, which heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms N, O, and/or S as ring members; and

R^8 as a substituent on a cycloalkyl ring may additionally be C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, and C_2 - C_6 -haloalkynyl; and

R^8 in the groups $C(=O)R^8$ and $=C(R^8)_2$ may additionally be H, halogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, or C_2 - C_6 -haloalkynyl;

5 each R^9 is independently H, C_1 - C_6 -alkyl, or C_1 - C_6 -haloalkyl;

R^{10a} , R^{10b} are independently from one another H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_2 - C_6 -haloalkynyl;

10 C_1 - C_6 -alkyl- $C(=O)OR^{15}$, C_1 - C_6 -alkyl- $C(=O)N(R^{14a})R^{14b}$, C_1 - C_6 -alkyl- $C(=S)N(R^{14a})R^{14b}$, C_1 - C_6 -alkyl- $C(=NR^{14})N(R^{14a})R^{14b}$, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $S(O)_nR^{15}$, $S(O)_nN(R^{14a})R^{14b}$, $C(=O)R^{13}$, $C(=O)OR^{15}$, $C(=O)N(R^{14a})R^{14b}$, $C(=S)R^{13}$, $C(=S)SR^{15}$, $C(=S)N(R^{14a})R^{14b}$, $C(=NR^{14})R^{13}$; phenyl; and

15 a 3-, 4-, 5-, 6- or 7-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2, 3 or 4 heteroatoms N, O, and/or S as ring members, preferably hetaryl; or

R^{10a} and R^{10b} together with the nitrogen atom they are bonded to form a 3- to 8-membered saturated, partially or fully unsaturated heterocyclic ring, which ring may additionally contain one or two heteroatoms N, O, and/or S as ring members; or

20 R^{10a} and R^{10b} together form a group $=C(R^{13})_2$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{14}$, or $=NOR^{15}$;

R^{11} is halogen, CN, N_3 , NO_2 , SCN, SF_5 , C_1 - C_{10} -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, or

25 OR^9 , $NR^{10a}R^{10b}$, $S(O)_nR^9$, $Si(R^{12})_3$; phenyl; and a 3- to 7-membered saturated, partially or fully unsaturated aromatic heterocyclic ring comprising 1, 2, 3, or 4 heteroatoms N, O, and/or S as ring members; or

two R^{11} present on the same ring carbon atom of an unsaturated or partially unsaturated heterocyclic ring may together form a group $=O$, $=C(R^{13})_2$, $=S$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{14}$, $=NOR^{15}$, or $=NN(R^{14a})R^{14b}$;

30 or two R^{11} bound on adjacent ring atoms form together with the ring atoms to which they are bound a saturated 3- to 9-membered ring, which ring may contain 1 or 2 heteroatoms O, S, N, and/or NR^{14} , and/or 1 or 2 groups $C=O$, $C=S$, $C=NR^{14}$ as ring members;

each R^{12} is independently C_1 - C_4 -alkyl and phenyl;

each R^{13} is independently CN, NO_2 , OH, SH, SCN, SF_5 , C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, SO_n - C_1 - C_6 -alkyl, SO_n - C_1 - C_6 -haloalkyl, $Si(R^{12})_3$, $C(=O)N(R^{14a})R^{14b}$,

35 C_3 - C_8 -cycloalkyl; and a 3- to 7-membered saturated, partially or fully unsaturated heterocyclic ring containing 1, 2, or 3 heteroatoms N, O, and/or S, as ring members; or

two R^{13} present on the same carbon atom of an alkyl, alkenyl, alkynyl or cycloalkyl group may together be $=O$, $=CH(C_1-C_4\text{-alkyl})$, $=C(C_1-C_4\text{-alkyl})C_1-C_4\text{-alkyl}$, $=N(C_1-C_6\text{-alkyl})$ or $=NO(C_1-C_6\text{-alkyl})$; and

40 R^{13} as a substituent of a cycloalkyl ring may additionally be C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl, which groups are unsubstituted, partially or fully halogenated, or substituted with 1 or 2 CN, C_3 - C_4 -cycloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy, and oxo; and

R^{13} in groups $=C(R^{13})_2$, $N=C(R^{13})_2$, $C(=O)R^{13}$, $C(=S)R^{13}$, and $C(=NR^{14})R^{13}$ may additionally be H, halogen, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, or C_2 - C_6 -alkynyl, and oxo;

45 each R^{14} is independently H, CN, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, SO_n - C_1 - C_6 -alkyl, SO_n - C_1 - C_6 -haloalkyl, $Si(R^{12})_3$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl; and oxo;

C₃-C₈-cycloalkyl; phenyl, benzyl, pyridyl, phenoxy; and a 3-, 4-, 5- or 6-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2 or 3 heteroatoms N, O, and/or S as ring members;

R^{14a} and R^{14b} independently of each other, have one of the meanings given for R¹⁴; or

5 R^{14a} and R^{14b}, together with the nitrogen atom to which they are bound, form a 3- to 7-membered saturated, partially, or fully unsaturated heterocyclic ring, wherein the ring may additionally contain 1 or 2 heteroatoms N, O, and/or S as ring members; or

10 R^{14a} and R¹⁴ or R^{14b} and R¹⁴, together with the nitrogen atoms to which they are bound in the group C(=NR¹⁴)N(R^{14a})R^{14b}, form a 3- to 7-membered partially, or fully unsaturated heterocyclic ring, wherein the ring may additionally contain 1 or 2 heteroatoms N, O, and/or S as ring members;

each R¹⁵ is independently H, CN, Si(R¹²)₃, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl; C₃-C₈-cycloalkyl; phenyl, benzyl, pyridyl, and phenoxy;

15 each R¹⁶ is independently halogen, NO₂, CN, OH, SH, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, SO_n-C₁-C₆-alkyl, SO_n-C₁-C₆-haloalkyl, C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-haloalkoxycarbonyl, aminocarbonyl, C₁-C₄-alkylaminocarbonyl, di-(C₁-C₄-alkyl)-aminocarbonyl, Si(R¹²)₃; C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl; C₃-C₈-cycloalkyl; or

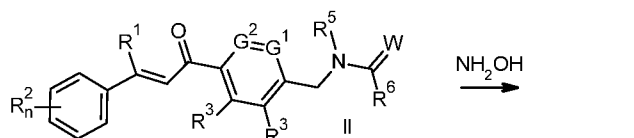
20 two R¹⁶ present together on the same atom of an unsaturated or partially unsaturated ring may be =O, =S, =N(C₁-C₆-alkyl), =NO-C₁-C₆-alkyl, =CH(C₁-C₄-alkyl), or =C(C₁-C₄-alkyl)₂; or two R¹⁶ on two adjacent carbon atoms form together with the carbon atoms they are bonded to a 4- to 8-membered saturated, partially or fully unsaturated ring, wherein the ring may contain 1 or 2 heteroatoms N, O, and/or S as ring members;

each n is independently 0, 1, or 2; and

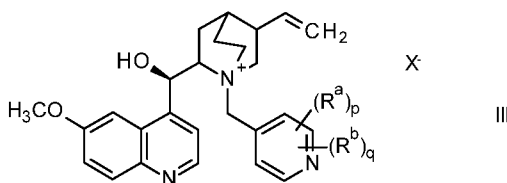
25 each m is independently 0, or 1;

wherein the shown enantiomer has at least 55% ee;

by oxo-Michael addition of hydroxyl amine or its salt to an enone of formula II,



30 wherein the variables have the meanings given for formula I, in the presence of a catalyst of formula III



wherein X is a counteranion, and

R^a is CN, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, phenyl, benzyl, and phenoxy;

35 R^b is halogen;

p is 1, 2, 3, or 4; and

q is 0, 1, 2 or 3, wherein the sum of p and q is up to 4;

and a base.

40

The isoxazoline active compounds I and their pesticidal activity are generally known from WO2007/105814.

WO2009/063910 describes asymmetric syntheses of some isooxazoline compounds of formula I by using cinchona alkaloid-based phase-transfer catalysts. The processes require relatively high catalyst loadings and yield enantiomeric excesses of formula I compounds which still leave room for improvement.

Objective task for the invention therefore is providing an economical, industrially applicable manufacturing process for optically enriched compounds of formula I. This task is achieved by the process defined in the outset. The presence of a catalyst III as defined herein in the reaction of compound II ensures a quick and effective transformation at moderate temperatures.

The formula III catalyst is novel.

In the invention this catalyst is used in asymmetric oxa-Michael addition of hydroxyl amine with an enone to form an enantioselective C-O bond. The process yields formula I compounds in good yield with at least 55% ee by using low catalyst loadings.

The reaction of an enone of formula II, wherein the variables have the meanings given in the outset, with hydroxyl amine or its salt is usually carried out at temperatures of from -30°C to 35°C, preferably from -10°C to 0°C, in an inert solvent, in the presence of a catalyst of formula III.

Suitable solvents are preferably water immiscible solvents, such as aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether, aromatic hydrocarbons such as toluene, o-, m-, and p-xylene, halogenated hydrocarbons such as methylene chloride, dichloroethane, and chloroform, ethers such as diethylether, diisopropylether, tert.-butyl-methylether (MTBE), anisole, and ketones such as methyl ethyl ketone, diethyl ketone, and tert.-butyl methyl ketone, alcohols such as, n-propanol, n-butanol, preferably halogenated hydrocarbons such as methylene chloride, dichloroethane, and chloroform. It is also possible to use mixtures of the solvents mentioned.

Suitable bases are in general, inorganic compounds, such as alkali metal and alkaline earth metal hydroxides, such as LiOH, NaOH, KOH and Ca(OH)₂, alkali metal and alkaline earth metal oxides, such as Li₂O, Na₂O, CaO, and MgO, and alkaline earth metal carbonates, such as Li₂CO₃, Na₂CO₃, K₂CO₃ and CaCO₃, and also alkali metal bicarbonates, such as NaHCO₃, moreover organic bases, e.g. tertiary amines, such as trimethylamine, triethylamine (NEt₃), diisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine, and also bicyclic amines, such as DBU (1,8-Diaza-bicyclo(5.4.0)undec-7-ene) and DBN (1,5-Diazabicyclo[4.3.0]non-5-ene). Particular preference is given to alkali metal and alkaline earth metal hydroxides, such as LiOH, NaOH, KOH, and Ca(OH)₂, such as NaOH, and KOH.

The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts or in excess. Under certain conditions an excess up to 10 mol equivalents of base to compound II may be advantageous.

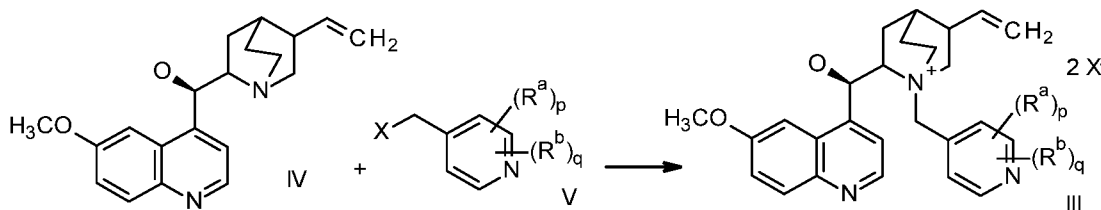
For practical reasons hydroxylamine is preferably used in the form of an aqueous solution, alternatively as acid addition salt, such as halogenide or sulfate, preferably halogenide, particularly as HCl addition salt.

Hydroxylamine is generally employed in equimolar amounts; however, it can also be used in excess. Under certain conditions an excess up to 10 mol equivalents of hydroxylamine to compound II may be advantageous.

The catalyst III is used in 0.01 to 0.5, preferably 0.01 to 0.2, particularly about 0.02 to 0.1 mol equivalents of compound II. The starting materials are generally reacted with one another in equimolar amounts. In terms of yield, it may be advantageous to employ an excess of hydroxylamine, based on II.

Starting materials of formula II required for preparing the compounds I are commercially available or known from the literature or can be prepared as outlined above, or in accordance with the literature cited.

Compounds of formula III can preferably be prepared by alkylation of (R)-(6-methyl-4-quinolyl)-(5-vinylquinuclidin-2-yl)methanol (formula IV) with a compound of formula V wherein X is a leaving group, such as hydroxy or halogen, preferably Br or Cl; and R^a, R^b, p, and q have the meaning as given for formula III.



This transformation is usually carried out at temperatures of from 20°C to 110 °C, preferably from 25°C to 80°C, in an inert solvent [cf. WO 2011/104089].

Suitable solvents are aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether, aromatic hydrocarbons such as toluene, o-, m-, and p-xylene, halogenated hydrocarbons such as methylene chloride, chloroform, and chlorobenzene, ethers such as diethylether, diisopropylether, MTBE, dioxane, anisole, and tetrahydrofurane, nitrils such as acetonitrile, and propionitrile, moreover dimethyl sulphoxide, dimethyl formamide, and dimethylacetamide (DMA), preferably toluene, or acetonitrile. It is also possible to use mixtures of the solvents mentioned.

Formula IV and V compounds are known in the art and are commercially available.

The reaction mixtures are worked up in a customary manner, for example by mixing with water, separating the phases and, if appropriate, chromatographic purification of the crude products. Some of the intermediates and end products are obtained in the form of colourless or slightly brownish viscous oils which are purified or freed from volatile components under reduced pressure and at moderately elevated temperature. If the intermediates and end products are obtained as solids, purification can also be carried out by recrystallization or digestion.

However, if the synthesis yields mixtures of isomers, a separation is generally not necessarily required since in some cases the individual isomers can be interconverted during work-up for

use or during application (for example under the action of light, acids or bases). Such conversions may also take place after use, e.g. in the treatment of plants in the treated plant.

The organic moieties mentioned in the above definitions of the variables are - like the term
5 halogen - collective terms for individual listings of the individual group members. The prefix C_n-C_m indicates in each case the possible number of carbon atoms in the group.

The term "halogen" denotes in each case fluorine, bromine, chlorine, or iodine, in particular fluorine, chlorine, or bromine.

The term "alkyl" as used herein and in the alkyl moieties of alkylamino, alkylcarbonyl, alkylthio,
10 alkylsulfinyl, alkylsulfonyl and alkoxyalkyl denotes in each case a straight-chain or branched alkyl group having usually from 1 to 10 carbon atoms, frequently from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, more preferably from 1 to 3 carbon atoms. Examples of an alkyl group are methyl ("Me"), ethyl ("Et"), n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl, tert-butyl ("tBu"), n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, n-hexyl,
15 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, and 1-ethyl-2-methylpropyl.

The term "haloalkyl" as used herein and in the haloalkyl moieties of haloalkylcarbonyl, haloalk-
20 oxycarbonyl, haloalkylthio, haloalkylsulfonyl, haloalkylsulfinyl, haloalkoxy and haloalkoxyalkyl, denotes in each case a straight-chain or branched alkyl group having usually from 1 to 10 carbon atoms, frequently from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, wherein the hydrogen atoms of this group are partially or totally replaced with halogen atoms. Preferred haloalkyl moieties are selected from C₁-C₄-haloalkyl, more preferably from C₁-C₃-haloalkyl or
25 C₁-C₂-haloalkyl, in particular from C₁-C₂-fluoroalkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, and the like.

The term "alkoxy" as used herein denotes in each case a straight-chain or branched alkyl
30 group which is bonded via an oxygen atom and has usually from 1 to 10 carbon atoms, frequently from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Examples of an alkoxy group are methoxy, ethoxy, n-propoxy, iso-propoxy, n-butyloxy, 2-butyloxy, iso-butyloxy, tert.-butyloxy, and the like.

The term "alkoxyalkyl" as used herein refers to alkyl usually comprising 1 to 10, frequently 1 to
35 4, preferably 1 to 2 carbon atoms, wherein 1 carbon atom carries an alkoxy radical usually comprising 1 to 4, preferably 1 or 2 carbon atoms as defined above. Examples are CH₂OCH₃, CH₂-OC₂H₅, 2-(methoxy)ethyl, and 2-(ethoxy)ethyl.

The term "haloalkoxy" as used herein denotes in each case a straight-chain or branched alkoxy
40 group having from 1 to 10 carbon atoms, frequently from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, wherein the hydrogen atoms of this group are partially or totally replaced with halogen atoms, in particular fluorine atoms. Preferred haloalkoxy moieties include C₁-C₄-haloalkoxy, in particular C₁-C₂-fluoroalkoxy, such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoro-ethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, pentafluoroethoxy and the like.

45 The term "alkylthio" (alkylsulfanyl: S-alkyl) as used herein refers to a straight-chain or branched saturated alkyl group having 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms (= C₁-C₄-alkylthio), more preferably 1 to 3 carbon atoms, which is attached via a sulfur atom.

The term "alkylsulfinyl" (alkylsulfoxyl: $S(=O)-C_1-C_6$ -alkyl), as used herein refers to a straight-chain or branched saturated alkyl group (as mentioned above) having 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms ($= C_1-C_4$ -alkylsulfinyl), more preferably 1 to 3 carbon atoms bonded through the sulfur atom of the sulfinyl group at any position in the alkyl group.

- 5 The term "alkylsulfonyl" ($S(=O)_2$ -alkyl) as used herein refers to a straight-chain or branched saturated alkyl group having 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms ($= C_1-C_4$ -alkylsulfonyl), preferably 1 to 3 carbon atoms, which is bonded via the sulfur atom of the sulfonyl group at any position in the alkyl group.

- 10 The term "alkylcarbonyl" refers to an alkyl group as defined above, which is bonded via the carbon atom of a carbonyl group ($C=O$) to the remainder of the molecule.

The term "alkoxycarbonyl" refers to an alkylcarbonyl group as defined above, which is bonded via an oxygen atom to the remainder of the molecule.

- 15 The term "alkenyl" as used herein denotes in each case a singly unsaturated hydrocarbon radical having usually 2 to 10, frequently 2 to 6, preferably 2 to 4 carbon atoms, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, methallyl (2-methylprop-2-en-1-yl), 2-buten-1-yl, 3-buten-1-yl, 2-penten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 1-methylbut-2-en-1-yl, 2-ethylprop-2-en-1-yl and the like.

The term "haloalkenyl" as used herein refers to an alkenyl group as defined above, wherein the hydrogen atoms are partially or totally replaced with halogen atoms.

- 20 The term "alkynyl" as used herein denotes in each case a singly unsaturated hydrocarbon radical having usually 2 to 10, frequently 2 to 6, preferably 2 to 4 carbon atoms, e.g. ethynyl, propargyl (2-propyn-1-yl), 1-propyn-1-yl, 1-methylprop-2-yn-1-yl, 2-butyne-1-yl, 3-butyne-1-yl, 1-pentyne-1-yl, 3-pentyne-1-yl, 4-pentyne-1-yl, 1-methylbut-2-yn-1-yl, 1-ethylprop-2-yn-1-yl and the like.

- 25 The term "cycloalkyl" as used herein and in the cycloalkyl moieties of cycloalkoxy and cycloalkylthio denotes in each case a monocyclic cycloaliphatic radical having usually from 3 to 10 or from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl, or cyclopropyl (C_3H_5), cyclobutyl (C_4H_7), cyclopentyl (C_5H_9), and cyclohexyl (C_6H_{11}).

- 30 The term "halocycloalkyl" as used herein and in the halocycloalkyl moieties of halocycloalkoxy and halocycloalkylthio denotes in each case a monocyclic cycloaliphatic radical having usually from 3 to 10 C atoms or 3 to 6 C atoms, wherein at least one, e.g. 1, 2, 3, 4 or 5 of the hydrogen atoms, are replaced by halogen, in particular by fluorine or chlorine. Examples are 1- and 2-fluorocyclopropyl, 1,2-, 2,2- and 2,3-difluorocyclopropyl, 1,2,2-trifluorocyclopropyl, 2,2,3,3-tetrafluorocyclopropyl, 1- and 2-chlorocyclopropyl, 1,2-, 2,2- and 2,3-dichlorocyclopropyl, 1,2,2-trichlorocyclopropyl, 2,2,3,3-tetrachlorocyclopropyl, 1,2- and 3-fluorocyclopentyl, 1,2-, 2,2-, 2,3-, 3,3-, 3,4-, 2,5-difluorocyclopentyl, 1,2- and 3-chlorocyclopentyl, 1,2-, 2,2-, 2,3-, 3,3-, 3,4-, 2,5-dichlorocyclopentyl, and the like.

- 40 The term "cycloalkenyl" as used herein and in the cycloalkenyl moieties of cycloalkenyloxy and cycloalkenylthio denotes in each case a monocyclic singly unsaturated non-aromatic radical having usually from 3 to 10, e.g. 3 or 4 or from 5 to 10 carbon atoms, preferably from 3- to 8 carbon atoms. Exemplary cycloalkenyl groups include cyclopropenyl, cycloheptenyl or cyclooctenyl.

- 45 The term "cycloalkenylalkyl" refers to a cycloalkenyl group as defined above which is bonded via an alkylene group, such as a C_1-C_5 -alkyl group or a C_1-C_4 -alkyl group, in particular a methylene group ($=$ cycloalkenylmethyl), to the remainder of the molecule.

The term "carbocycle" or "carbocyclyl" includes in general a 3- to 12-membered, preferably a 3- to 8-membered or a 5- to 8-membered, more preferably a 5- or 6-membered mono-cyclic,

non-aromatic ring comprising 3 to 12, preferably 3 to 8 or 5 to 8, more preferably 5 or 6 carbon atoms. Preferably, the term "carbocycle" covers cycloalkyl and cycloalkenyl groups as defined above.

The term "heterocycle" or "heterocyclyl" includes in general 3- to 12-membered, preferably 5- or 6-membered, in particular 6-membered monocyclic heterocyclic non-aromatic radicals. The heterocyclic non-aromatic radicals usually comprise 1, 2 or 3 heteroatoms selected from N, O and S as ring members, wherein S-atoms as ring members may be present as S, SO or SO₂. Examples of 5- or 6-membered heterocyclic radicals comprise saturated or unsaturated, non-aromatic heterocyclic rings, such as 2- and 3-azetidiny, 2- and 3-oxetanyl, 2- and 3-thietanyl, 2- and 3-thietanyl-S-oxid (S-oxothietanyl), 2- and 3-thietanyl-S-dioxid (S-dioxothietanyl), 2- and 3-pyrrolidiny, 2- and 3-tetrahydrofuranyl, 1,3-dioxolan-2-yl, thiolan-2-yl, S-oxothiolan-2-yl, S-dioxothiolan-2-yl, 4- and 5-oxazolidiny, 1,3-dioxan-2-yl, 1- and 3-thiopyran-2-yl, S-oxothiopyranyl, and S-dioxothiopyranyl.

The term "hetaryl" includes monocyclic 5- or 6-membered heteroaromatic radicals comprising as ring members 1, 2, or 3 heteroatoms selected from N, O and S. Examples of 5- or 6-membered heteroaromatic radicals include pyridyl, i.e. 2-, 3-, and 4-pyridyl, pyrimidinyl, i.e. 2-, 4- and 5-pyrimidinyl, pyrazinyl, pyridazinyl, i.e. 3- and 4-pyridazinyl, thienyl, i.e. 2- and 3-thienyl, furyl, i.e. 2- and 3-furyl, pyrrolyl, i.e. 1-, 2- and 3-pyrrolyl, oxazolyl, i.e. 2-, 4- and 5-oxazolyl, isoxazolyl, i.e. 3-, 4- and 5-isoxazolyl, thiazolyl, i.e. 2-, 3- and 5-thiazolyl, isothiazolyl, i.e. 3-, 4- and 5-isothiazolyl, pyrazolyl, i.e. 1-, 3-, 4- and 5-pyrazolyl, imidazolyl, i.e. 1-, 2-, 4- and 5-imidazolyl, oxadiazolyl, e.g. 2- and 5-[1,3,4]oxadiazolyl, thiadiazolyl, e.g. 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, triazolyl, e.g. 1,3,4-triazol-2-yl, and 1,2,4-triazol-3-yl.

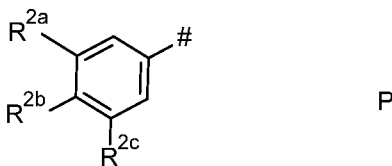
The terms "heterocyclylalkyl" and "hetarylalkyl" refer to heterocyclyl or hetaryl, resp., as defined above which are bound via a C₁-C₄-alkyl group, in particular a methyl group (= heterocyclylmethyl or hetarylmethyl, resp.), to the remainder of the molecule.

With respect to the variables, the particularly preferred embodiments of the intermediates correspond to those of the compounds of the formula I.

In a particular embodiment, the variables of the compounds of the formula I have the following meanings, these meanings, both on their own and in combination with one another, being particular embodiments of the compounds of formula I.

In the compounds of the inventive process R¹ is preferably fluoromethyl, in particular CF₃.

The phenyl ring in formula I and its sub formulae, bearing the R²_n substitution is preferably a group P



R^{2a} is preferably selected from F, Cl, Br, CF₃, and OCF₃.

R^{2b} and R^{2c} are independently preferably selected from H, F, Cl, Br, CF₃, and OCF₃.

Particularly preferred is each one of the following combinations of R^{2a}, R^{2b}, and R^{2c} wherein each line of Table A denotes a substitution pattern of the phenyl ring P bearing the R^{2a}, R^{2b}, and R^{2c} moieties.

Table A

No.		R ^{2a}	R ^{2b}	R ^{2c}
A-1		F	F	H
A-2		F	H	F
A-3		F	F	F
A-4		F	Cl	F
A-5		F	Br	F
A-6		F	H	Cl
A-7		F	H	Br
A-8		Cl	F	H
A-9		Cl	H	Cl
A-10		Cl	Cl	Cl
A-11		Cl	F	Cl
A-12		Cl	Br	Cl
A-13		Cl	H	Br
A-14		Br	F	H
A-15		Br	H	Br
A-16		Br	F	Br

No.		R ^{2a}	R ^{2b}	R ^{2c}
A-17		Br	Cl	Br
A-18		CF ₃	H	H
A-19		CF ₃	H	F
A-20		CF ₃	H	Cl
A-21		CF ₃	H	Br
A-22		CF ₃	H	CF ₃
A-23		CF ₃	F	F
A-24		CF ₃	F	Cl
A-25		CF ₃	Cl	Cl
A-26		CF ₃	F	H
A-27		OCF ₃	H	F
A-28		OCF ₃	H	Cl
A-29		OCF ₃	F	H
A-30		OCF ₃	H	CF ₃
A-31		OCF ₃	H	H

- 5 Groups A-8, A-9, and A-11 are more preferred patterns in formula I and its sub formulae compounds. A-11 is particularly preferred.

R³ is preferably H, halogen, or CH₃.

- 10 In a preferred embodiment G¹ and G² represent each CR³, wherein R³ is H, halogen, or C₁-C₄-alkyl, particularly G¹ is CH and G² is C-Cl, or C-CH₃.

In another preferred embodiment G¹ and G² represent each CR³, wherein the two R³ form a five- or sixmembered saturated carbocyclic ring, or a dihydrofurane.

15

The catalyst III is used preferably in an amount of 0.1-50 mol%, more preferred in 0.5-25 mol%, particularly in 1-10 mol% relative to formula II compounds.

- 20 The nature of the counteranion X⁻ in formula III catalyst is of minor importance. For practical reasons it is usually selected from halogen (preferably Cl, Br), BF₄, PF₆, C₁-C₁₀-alkylsulfonate, benzenesulfonate, or methylbenzenesulfonate. Preferred III is used as bromide and chloride, mesylate, and tosylate. Particularly preferred are bromide and chloride.

R^a is preferably CN, C₁-C₃-alkyl, or C₁-C₃-alkoxy, particularly CH₃, or OCH₃.

R^b is preferably Cl.

- 25 Index p is preferably 1 or 2, q is preferably 0 or 1.

Substituents R^a and R^b are preferably positioned in 2 and 6 position.

Particularly preferred are catalysts of formula III wherein the substitution of the pyridine group have the meanings as shown in Table III.1, wherein each compound corresponds to one line.

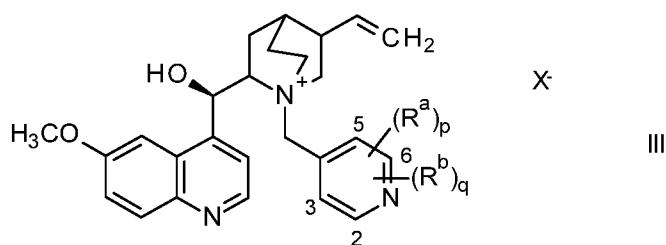


Table III.1; X is Cl or Br

No.	(R ^a) _p	(R ^b) _q
III-1	2-CN	-
III-2	3-CN	-
III-3	2-CN	6-Cl
III-4	3-CN	5-Cl
III-5	3-CN	6-Cl
III-6	2-CN,6-CH ₃	-
III-7	3-CN,5-CH ₃	-
III-8	3-CN,6-CH ₃	-
III-9	2-CN,6-OCH ₃	-
III-10	3-CN,5-OCH ₃	-
III-11	3-CN,6-OCH ₃	-
III-12	2-CH ₃	-
III-13	3-CH ₃	-
III-14	2-CH ₃	6-Cl
III-15	3-CH ₃	6-Cl
III-16	2-CF ₃	-
III-17	3-CF ₃	-
III-18	2-CF ₃	6-Cl
III-19	3-CF ₃	6-Cl
III-20	2-CH ₃	-
III-21	2,6-(CH ₃) ₂	-

No.	(R ^a) _p	(R ^b) _q
III-22	3,5-(CH ₃) ₂	-
III-23	3,6-(CH ₃) ₂	-
III-24	2-OCH ₃	-
III-25	3-OCH ₃	-
III-26	2-OCH ₃	6-Cl
III-27	2-OCH ₃ ,6-CH ₃	-
III-28	2-C ₆ H ₅	-
III-29	2-CH ₂ C ₆ H ₅	-
III-30	2-OC ₆ H ₅	-
III-31	2-OCH ₂ C ₆ H ₅	-
III-32	2-C ₆ H ₅ ,6-C ₆ H ₅	-
III-33	2-CH ₂ C ₆ H ₅ , 6-CH ₂ C ₆ H ₅	-
III-34	2-OC ₆ H ₅ ,6-OC ₆ H ₅	-
III-35	2-OCH ₂ C ₆ H ₅ , 6-OCH ₂ C ₆ H ₅	-
III-36	2-C ₆ H ₅	6-Cl
III-37	2-CH ₂ C ₆ H ₅	6-Cl
III-38	2-OC ₆ H ₅	6-Cl
III-39	2-OCH ₂ C ₆ H ₅	6-Cl

5

The bromides and chlorides of III-1, III-12, III-21, III-26, and III-27 are preferred embodiments.

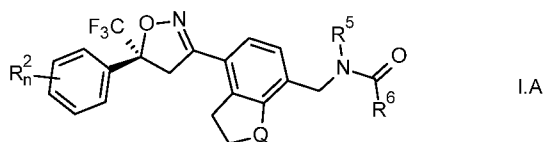
Another embodiment relates to the process for obtaining compounds I wherein R⁵ is H or CH₃, and R⁶ is H, C₁-C₆-alkyl, C₂-C₆-alkenyl, which groups are unsubstituted or substituted with one or more same or different R⁸, wherein R⁸ is as defined and preferred above.

10

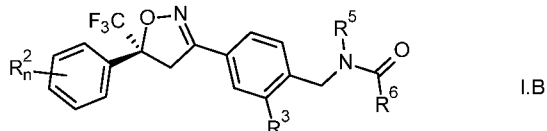
Another embodiment relates to the process for obtaining compounds I wherein R⁵ is H or CH₃, and R⁶ is H, C₁-C₆-alkyl, C₁-C₄-alkoxy, or C₂-C₆-alkenyl, which groups are unsubstituted or substituted with one or more same or different R⁸, wherein R⁸ is as defined and preferred above.

15

The process is particularly suitable for synthesis of following active compounds of formula I, which correspond to formulae I.A, and I.B, resp., wherein the variables are as defined and preferred above:



wherein Q is CH or O; and the other variables are as defined and preferred for formula I, and



- 5 wherein R³ is preferably H, CH₃, or Cl, more preferably CH₃ or Cl.

In formulae I.A and I.B group R⁵ is preferably H or CH₃, and R⁶ is preferably H, C₁-C₆-alkyl, C₁-C₂-alkoxy-C₁-C₂-alkyl, or C₂-C₆-alkenyl.

- 10 In another embodiment of formulae I.A and I.B group R⁵ is preferably H or CH₃, and R⁶ is preferably H, C₁-C₆-alkyl, or C₁-C₄-alkoxy.

- 15 Preferably the process yields in formula I compounds which obtained from the raw reaction mixture have an ee of at least 60%, more preferably 70%, even more preferably 80%, particularly at least 90% ee. Further enrichment of the S-enantiomer can be achieved by following recrystallisation.

The following examples illustrate the invention.

20 Examples

A. Preparation examples

With appropriate modification of the starting materials, the procedures given in the synthesis description were used to obtain further compounds I and III. The compounds obtained in this manner are listed in the tables that follow, together with physical data.

- 25 The products shown below were characterized by melting point determination, by NMR spectroscopy or by the masses ([m/z]) or retention time (RT; [min.]) determined by HPLC-MS or HPLC spectrometry.

HPLC-MS = high performance liquid chromatography-coupled mass spectrometry;

- 30 HPLC Method A: Agilent Series 1100, Column: Chiralpak AD-RH, 150mm * 4.6 mm ID * 5μm; Mobile Phase: A: water + 0,1vol% H₃PO₄; B: acetonitrile + 0,1vol% H₃PO₄; Temperature: 40°C; Gradient: 40% B to 70% B in 25 min; 70% B to 100% B in 5 min; 100% B 10min; 40% B 30.1 min; Flow: 1,2 mL/min; UV-detector BW = 5 nm, lambda = 240 nm.

- 35 HPLC Method B - Phenomenex Kinetex 1,7μm XB-C18 100A; 50 x 2,1 mm. Elution: acetonitrile + 0.1% trifluoroacetic acid (TFA) / water + 0.1% trifluoroacetic acid (TFA) in a ratio of from 5:95 to 95:5 in 1.5 minutes at 50°C.

Example 1: (R)-[(2S,4S,5R)-1-[(2-chloro-6-methoxy-4-pyridyl)methyl]-5-vinyl-quinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol chloride [III.2-2]

To a solution of quinine [(R)-(6-methoxy-4-quinolyl)-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol, 844 mg, 2.60 mmol] in acetonitrile (10 mL) was added 4-chloromethyl-2-chloro-6-methoxy pyridine (500 mg, 2.60 mmol) and the mixture was stirred at reflux overnight. After completion of the reaction, the mixture was diluted with MTBE (100 mL) and the resulting precipitate was collected via filtration. After drying in vacuum, the title compound was obtained (780 mg, 52%) as colorless solid.

Method B HPLC-MS: RT = 0.897 min, m/z = 480.1 [MH-Cl]

¹H-NMR (400 MHz, CDCl₃): 1.47 (m, 1H), 1.74 (m, 1H), 2.01 (s, 1H), 2.12 (m, 1H), 2.23 (m, 1H), 2.56 (m, 1H), 3.05 (m, 1H), 3.30 (m, 1H), 3.88 (s, 3H), 3.94 (s, 3H), 4.13 (m, 1H), 4.20 (m, 1H), 4.88 (m, 1H), 4.94 (d, 1H), 5.21 (d, 1H), 5.48-5.61 (m, 2H), 5.87 (d, 1H), 6.47 (s, 1H), 7.19 (m, 1H), 7.21 (s, 1H), 7.36 (s, 1H), 7.39 (s, 1H), 7.74 (m, 1H), 7.89 (d, 1H), 8.60 (m, 1H).

Example 2: (R)-(6-methoxy-4-quinolyl)-[(2S,4S,5R)-1-[(2-methyl-4-pyridyl)methyl]-5-vinylquinuclidin-1-ium-2-yl]methanol chloride [III.2-3]

To a solution of quinine [(R)-(6-methoxy-4-quinolyl)-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol, 910 mg, 2.81 mmol, 1.00 equiv.) in acetonitrile (10 mL) was added 4-chloromethyl-2-methyl pyridine (500 mg, 2.81 mmol) and the mixture was stirred at reflux overnight. After completion of the reaction, the mixture was diluted with MTBE (100 mL) and the resulting precipitate was collected via filtration. After drying in vacuum, the title compound was obtained (729 mg, 53%) as colourless solid.

Method B HPLC-MS: RT = 0.666 min, m/z = 430.1 [MH-Cl]

¹H-NMR (400 MHz, CDCl₃): 1.46 (m, 1H), 1.73 (m, 1H), 2.01 (s, 1H), 2.08-2.29 (m, 3H), 2.52 (s, 1H), 2.54 (m, 1H), 3.04 (m, 1H), 3.29 (m, 1H), 3.61 (m, 1H), 3.94 (s, 3H), 3.96 (m, 1H), 4.89-5.04 (m, 2H), 5.13 (m, 1H), 5.19 (s, 1H), 5.56 (m, 1H), 6.00 (d, 1H), 6.51 (s, 1H), 7.25 (m, 1H), 7.41 (m, 1H), 7.51 (m, 2H), 7.73 (m, 1H), 7.89 (d, 1H), 8.8.46 (m, 1H), 8.64 (m, 1H).

Example 3: (R)-[(2S,4S,5R)-1-[(2,6-dimethyl-4-pyridyl)methyl]-5-vinylquinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol bromide [III.2-4]

Step 1: Preparation of (2,6-dimethyl-4-pyridyl)methanol

Sulphuric acid (7.8 mL) and methanol (204 mL) were mixed under ice cooling. This mixture was added to a solution of ammonium persulfate (65.87 g, 289.0 mmol, 1.97 equiv.) in water (102 mL), before 2,6-lutidine (17.1 mL, 15.7 g, 147 mmol, 1.00 equiv.) was added dropwise. The resulting suspension was heated at 100°C for 24 h and became an orange solution. After cooling, the mixture was concentrated in vacuum to remove the methanol and made alkaline using aqueous NaOH (200 mL of a 1 M solution) under ice cooling. Extraction with dichloromethane (3 x 150 mL), drying the combined organic phases over Na₂SO₄ and concentration in vacuum yielded the crude product (7.7 g) which was purified via flash chromatography on silica gel using cyclohexane with 1% triethylamine and ethyl acetate to yield the title compound (2.3 g, 11%).

¹H-NMR (400 MHz, CDCl₃): 2.51 (s, 6H), 4.67 (s, 2H), 6.96 (s, 2H).

Step 2: Preparation of 4-(bromomethyl)-2,6-dimethyl-pyridine

(2,6-dimethyl-4-pyridyl)methanol (0.50 g, 3.6 mmol) in HBr (4.0 mL of a 33% solution in glacial acetic acid, 22 mmol, 6.0 equiv.) were heated at reflux for 5 h. After cooling, the mixture was concentrated in vacuum, poured onto ice-water and made alkaline with NaOH (20% in water). The resulting mixture was extracted with ethyl acetate and combined organic layers were

washed with water, brine, and dried over Na₂SO₄. After concentration in vacuum, the title compound (0.62 g, 85%) was obtained.

¹H-NMR (400 MHz, CDCl₃): 2.53 (s, 6H), 4.33 (s, 2H), 6.97 (s, 2H).

5 Step 3: Preparation of (R)-[(2S,4S,5R)-1-[(2,6-dimethyl-4-pyridyl)methyl]-5-vinyl-quinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol bromide [III.2-4]

To a solution of quinine ((R)-(6-methoxy-4-quinolyl)-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol, 445 mg, 1.37 mmol) in acetonitrile (10 mL) was added 4-(bromomethyl)-2,6-dimethylpyridine (274 mg, 1.37 mmol, 1.00 equiv.) and the mixture was stirred at reflux overnight. After
10 completion of the reaction, the mixture was diluted with MTBE (100 mL) and the resulting precipitate was collected via filtration. After drying in vacuum, the title compound was obtained (472 mg, 66%) as colourless solid.

¹H-NMR (400 MHz, CDCl₃): 1.52 (m, 1H), 1.73-1.82 (m, 2H), 2.03 (s, 1H), 2.29 (m, 2H), 2.51 (s, 6H), 2.63 (m, 1H), 3.20 (m, 1H), 3.32 (m, 1H), 3.50 (m, 1H), 3.88 (m, 1H), 3.95 (s, 3H), 4.88
15 (d, 1H), 5.02 (m, 1H), 5.09 (d, 1H), 5.13 (d, 1H), 5.60 (m, 1H), 6.06 (d, 1H), 6.50 (d, 1H), 6.63 (m, 1H), 7.24-7.32 (m, 4H), 7.71 (d, 1H), 8.00 (d, 1H), 8.71 (m, 1H).

Example 4: N-[[4-[(5S)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2,3-dihydrobenzofuran-7-yl]methyl]propanamide [I.A-1]

20 A mixture of N-[[4-[(E/Z)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-but-2-enoyl]-2,3-dihydrobenzofuran-7-yl]methyl]propenamide (1.00 g, 2.12 g; known from PCT/EP2019/079324) in dichloromethane (10 mL) was suspended at 0°C and (R)-[(2S,4S,5R)-1-[(2-chloro-6-methoxy-4-pyridyl)methyl]-5-vinyl-quinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol chloride (55 mg, 0.11
25 mmol, 5 mol-%) was added. The temperature was lowered to -10°C and a pre-cooled mixture of aqueous NaOH (1.69 g of a 20% solution in water, 8.47 mmol, 4 equiv.) and hydroxylamine (0.42 g of a 50% solution in water, 6.35 mmol, 3 equiv.) was added slowly. After 6 h at -10°C, aqueous hydrochloric acid (10 mL of a 1 M solution) was added and allowed to reach room
30 temperature. All volatile solvents were removed in vacuum, then water (20 mL) was added and sonicated. The resulting precipitate was collected by filtration and washed with water (3 x 30 mL) and pentane (3 x 15 mL) to obtain the crude product (880 mg). After recrystallization from methanol the title compound (440 mg, 41%; enantiomeric ratio > 99:1) was obtained as colorless solid.

Method A HPLC: RT = 18.615 min (S-isomer); 22.085 min (R-isomer)

35 ¹H-NMR (400 MHz, DMSO-d₆): 1.02 (t, 3H), 2.16 (q, 2H), 3.38 (m, 2H), 4.20 (m, 2H), 4.28 (d, 1H), 4.35 (d, 1H), 4.60 (m, 2H), 7.05-7.11 (m, 2H), 7.64 (s, 2H), 7.80 (s, 1H), 8.20 (m, 1H).

Example 5: tert-butyl N-[[7-[(5S)-5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]carbamate [I.A-2]

40 Step 1: Preparation of (7-acetylandan-4-yl) trifluoromethanesulfonate
To a suspension of 1-(7-hydroxyindan-4-yl)ethanone (known from WO2016/141890, 5.00 g, 28.4 mmol) in dichloromethane (50 mL) was added triethylamine (7.9 mL, 5.8 g, 2.0 equiv.) at 0-5°C. After completed addition, triflic anhydride (5.7 mL, 9.6 g, 1.2 equiv.) was added and the
45 mixture was allowed to reach 20-25°C. After 30 min, the reaction was complete and poured onto ice-water. The dichloromethane phase was separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). Combined organic layers were washed with

saturated aqueous NaHCO₃ solution (2 x 70 mL), water (70 mL) and dried over Na₂SO₄. After concentration in vacuum the title compound (8.7 g, 99%) was obtained.

Method B HPLC-MS: RT = 1.278 min, m/z = 308.7 [M+H]

¹H-NMR (400 MHz, CDCl₃): 2.19 (m, 2H), 2.61 (s, 3H), 3.02 (m, 2H), 3.35 (m, 2H), 7.16 (d, 1H), 7.75 (d, 1H).

Step 2: Preparation of 7-acetylidane-4-carbonitrile

To a solution of (7-acetylidane-4-yl) trifluoromethanesulfonate (34.50 g, 111.9 mmol) in DMA (250 mL) was added Zn(CN)₂ (19.71 g, 167.9 mmol, 1.50 equiv.) and the mixture was degassed with argon, before tetrakis(triphenylphosphine) palladium (25.87 g, 22.38 mmol, 20.0 mol-%) was added. The mixture was stirred at 140°C for 16 h, cooled and stirred into ice-water (750 mL). Ethyl acetate (300 mL) was added and all solids were removed by filtration over celite. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). Combined organic layers were washed with water (3 x 500 mL) and dried over Na₂SO₄. After concentration in vacuum, the residue was purified via flash chromatography on silica gel to yield the title compound (18.00 g, 87%).

¹H-NMR (400 MHz, CDCl₃): 2.19 (m, 2H), 2.61 (s, 3H), 3.13 (m, 2H), 3.31 (m, 2H), 7.55 (d, 1H), 7.72 (d, 1H).

Step 3: Preparation of tert-butyl N-[(7-acetylidane-4-yl)methyl]carbamate

A mixture of benzyl 7-acetylidane-4-carbonitrile (3.30 g, 17.8 mmol), Boc-anhydride (11.67 g, 53 mmol, 3 equiv.) and Raney-nickel in methanol (50 mL) was stirred under an atmosphere of hydrogen at room temperature overnight. After completion of the reaction, the mixture was filtered over a plug of celite and washed with methanol (3 x 30 mL). The filtrate was concentrated in vacuum and the resulting residue was triturated in n-pentane (15 mL) to obtain the title compound (2.70 g, 52%).

¹H-NMR (400 MHz, CDCl₃): 1.48 (s, 9H), 2.09 (m, 2H), 2.58 (s, 3H), 2.86 (m, 2H), 3.27 (m, 2H), 4.32 (m, 2H), 4.81 (br. s, 1H), 7.19 (d, 1H), 7.68 (d, 1H).

Step 4: Preparation of tert-butyl N-[[7-[(E/Z)-3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]indan-4-yl]methyl]carbamate

A mixture of tert-butyl N-[(7-acetylidane-4-yl)methyl]carbamate (12.00 g, 41.47 mmol), K₂CO₃ (8.60 g, 62.2 mmol, 1.50 equiv.), CsCl (698 mg, 4.15 mmol, 10.0 mol-%) and 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone (16.24 g, 62.20 mmol, 1.50 equiv.) and toluene (200 mL) were heated at reflux in a Dean-Stark trap for 16 h. After cooling, the solvent was removed in vacuum. Water (120 mL) was added to the residue and the resulting precipitate was collected by filtration as pure E-isomer title compound (12.5 g, 57%).

Method B HPLC-MS: RT = 1.515 min, m/z = 475.8 [M-^tbu]

¹H-NMR (500 MHz, CDCl₃): 1.49 (s, 9H), 2.09 (m, 2H), 2.85 (m, 2H), 3.12 (m, 2H), 4.31 (m, 2H), 4.82 (br. s, 1H), 7.19 (d, 1H), 7.20 (d, 2H), 7.35 (s, 1H), 7.48 (d, 1H).

Step 5: Preparation of tert-butyl N-[[7-[(5S)-5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]carbamate

A mixture of tert-butyl N-[[7-[(E/Z)-3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]indan-4-yl]methyl]carbamate (12.50 g, 23.48 mmol) and dichloromethane (120 mL) was cooled to 0°C and (R)-[(2S,4S,5R)-1-[(2,6-dimethyl-4-pyridyl)methyl]-5-vinyl-quinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol bromide (616 mg, 1.17 mmol, 5.00 mol-%) was added and the mixture was cooled to -10°C. A pre-cooled mixture of aqueous hydroxylamine (4.54 g of a

50% solution in water, 70.4 mmol, 3 equiv.) and aqueous NaOH (18.8 g of a 20% solution in water, 93.9 mmol, 4 equiv.) was added drop wise. After stirring overnight at -10°C, aqueous hydrochloric acid (120 mL) was added and allowed to reach 20-25°C. The organic solvent was removed in vacuum and the aqueous phase was extracted with ethyl acetate (3 x 80 mL).

- 5 Combined organic layers were dried over Na₂SO₄ and concentrated in vacuum. The residue was purified via flash chromatography on silica-gel to yield the title compound (12.90 g, 95% purity, 95 % yield; enantiomeric ratio = 82:18).

Method B HPLC-MS: RT = 1.590 min, m/z = 491.0 [M-^tbu]

Method A HPLC RT = 20.503 min (R-isomer); 22.260 min (S-isomer)

- 10 ¹H-NMR (400 MHz, CDCl₃): 1.45 (s, 9H), 2.14 (m, 2H), 2.92 (m, 2H), 3.18 (m, 2H), 3.73 (d, 1H), 4.11 (d, 1H), 4.32 (m, 2H), 4.80 (br. s, 1H), 7.16 (s, 2H), 7.59 (d, 2H).

Example 6: N-[[4-[(5S)-5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2,3-dihydrobenzofuran-7-yl]methyl]propanamide [I.A-3]

15

A mixture of N-[[4-[(E/Z)-3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluoro-but-2-enoyl]-2,3-dihydrobenzofuran-7-yl]methyl]propenamide (1.00 g, 2.12 g) in dichloromethane (10 mL) was suspended at 0°C and (R)-[(2S,4S,5R)-1-[(2,6-dimethyl-4-pyridyl)methyl]-5-vinyl-quinuclidin-1-ium-2-yl]-(6-methoxy-4-quinolyl)methanol bromide (53 mg, 0.10 mmol, 5 mol-%) was added.

- 20 The temperature was lowered to -10°C and a pre-cooled mixture of aq. NaOH (1.63 g of a 20% solution in water, 8.16 mmol, 4 equiv.) and hydroxylamine (0.40 g of a 50% solution in water, 6.1 mmol, 3 equiv.) was added slowly. After 6 h at -10°C, aq. HCl (10 mL of a 1 M solution) was added and allowed to reach 20-25°C. All volatile solvents were removed in vacuum, then water (20 mL) was added and sonicated. The resulting precipitate was collected by filtration and
- 25 washed with water (3 x 30 mL) and pentane (3 x 15 mL) to obtain the crude product (960 mg). Recrystallization from methanol yielded the title compound (651 mg, 70%; enantiomeric ratio = 98:2).

Method A HPLC: RT = 18.391 min (S-isomer), 19.982 min (R-isomer)

- 30 ¹H-NMR (400 MHz, CDCl₃): 1.16 (t, 3H), 2.22 (q, 2H), 3.48 (m, 2H), 3.61 (d, 1H), 4.10 (d, 1H), 6.00 (br. s, 1H), 6.79 (d, 1H), 7.15 (d, 1H), 7.58 (d, 2H).

Catalysts III

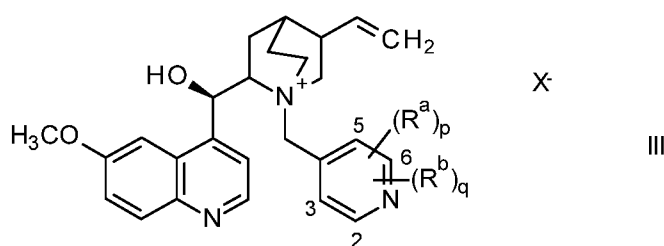
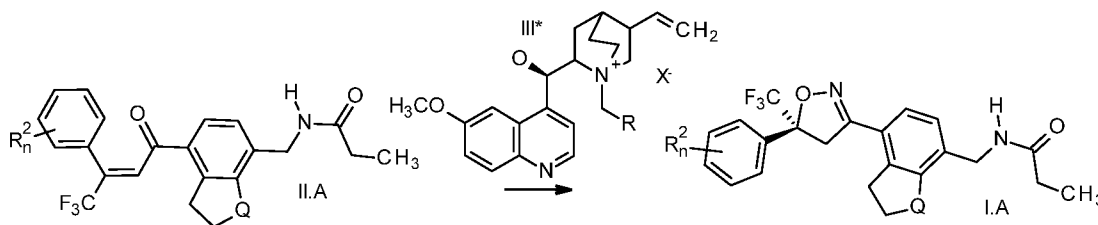


Table III.2

No.	(R ^a) _p	(R ^b) _q	X ⁻	phys. data
III.2-1	2-CN	-	Br	Method B: RT = 0.744 min; m/z = 441.1 [MH-Br]
III.2-2	2-OCH ₃	6-Cl	Cl	Example 1
III.2-3	2-CH ₃	-	Cl	Example 2
III.2-4	2,6-(CH ₃) ₂	-	Br	Example 3
III.2-5	2-OCH ₃	-	Br	Method B: RT = 0.756 min; m/z = 441.1 [MH-Br]

No.	(R ^a) _p	(R ^b) _q	X ⁻	phys. data
III.2-6	2-OCH ₃ , 6-CH ₃	-	Cl	¹ H-NMR (400 MHz, CDCl ₃): 1.45 (m, 1H), 1.72 (m, 1H), 2.00 (s, 1H), 2.15 (m, 1H), 2.24 (m, 1H), 2.39 (s, 3H), 2.58 (m, 1H), 3.15 (m, 1H), 3.41 (m, 1H), 3.54 (m, 1H), 3.87 (s, 3H), 3.94 (s, 3H), 3.97 (m, 1H), 4.96 (m, 1H), 5.04 (d, 1H), 5.11 (d, 1H), 5.58 (m, 1H), 5.93 (d, 1H), 6.54 (d, 1H), 6.84 (s, 1H), 7.13 (s, 1H), 7.24 (dd, 1H), 7.34 (d, 1H), 7.42 (d, 1H), 7.73 (d, 1H), 7.94 (d, 1H), 8.64 (d, 1H).

Preparation of formula I compounds



Compound I.A	R ² _n	Q
I.A-1	3,5-Cl ₂	O
I.A-2	3,5-Cl ₂ ,4-F	CH ₂
I.A-3	3,5-Cl ₂ ,4-F	O

Compound I.B	R ² _n	R ³	R ⁵	R ⁶
I.B-1	3,5-Cl ₂ ,4-F	H	H	OC(CH ₃) ₃

5

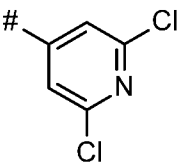
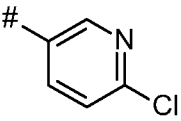
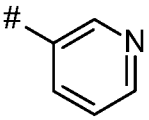
Examples according to the invention

No.	catalysts III (cf. Table III.2)	enantiomeric excess [ee]	temperature [°C]	conversion rate	formula I compound
E-1	III.2-2	60.4	-10	nearly complete	I.A-1
E-2	III.2-6	70	-10	complete	I.A-1
E-3	III.2-3	58.6	-10	complete	I.A-1
E-4	III.2-6	56	-10	nearly complete	I.A-1
E-5	III.2-4	64	-10	complete	I.A-2
E-6	III.2-4	73.2	-10	complete	I.A-3
E-7	III.2-4	68.8	-10	complete	I.B-1

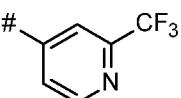
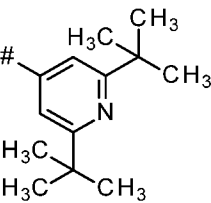
Comparisons with catalysts III* known from WO 2011/104089

10 (# being the bond to the remainder of formula III*):

No.	R	X ⁻	ee	temperature [°C]	conversion rate	formula I compound
C-1		Br	-	-10	no conversion	I.A1

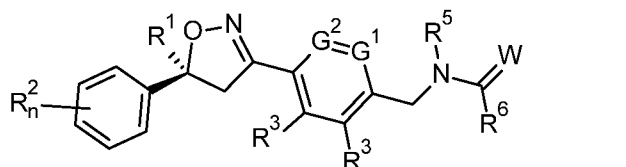
No.	R	X ⁻	ee	temperature [°C]	conversion rate	formula I compound
C-2		Cl	52.4	-10 - +10	partial	I.A1
C-3		Cl	32.8	-10	little	I.A1
C-4		Cl	32.8	-10	nearly complete	I.A1

Comparisons with other catalysts III* not according to the invention

No.	R	X ⁻	ee	temperature [°C]	conversion rate	formula I compound
C-5		Br	38.2	-10	partial	I.A1
C-6		Br	29.8	-10	partial	I.A1

Claims:

1. A process for preparing optically enriched isoxazoline compounds of formula I



wherein

R^1 is halomethyl;

each R^2 is independently H, halogen, CN, N_3 , NO_2 , SCN, SF_5 , C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, which groups are unsubstituted, partially or fully halogenated and/or substituted with one or more same or different R^8 ;

OR^9 , or $S(O)_nR^9$,

n is 0, 1, or 2;

G^1 , G^2 are each CR^3 ;

each R^3 is independently selected from the meanings mentioned for R^2 or is $C(=O)R^8$, or two R^3 bonded to adjacent carbon atoms may form a five- or sixmembered saturated, partially or fully unsaturated carbocyclic ring, or a dihydrofurane;

W is O or S;

R^5 is independently selected from the meanings mentioned for R^2 ;

R^6 is H, C_1 - C_{10} -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, which groups are unsubstituted, partially or fully halogenated and/or substituted with one or more same or different R^8 ; or C_1 - C_4 -alkoxy, $S(O)_nR^9$, or $C(=O)R^8$; or a 3- to 8-membered saturated, partially or fully unsaturated heterocyclic ring, which ring may contain 1, 2, 3, or 4 heteroatoms O, S, N, C=O and/or C=S as ring members, which heterocyclic ring is unsubstituted or partially or fully substituted with same or different halogen, CN, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_2 - C_6 -haloalkynyl, which groups are unsubstituted, or partially or fully substituted with same or different R^8 , or phenyl which may be partially or fully substituted with R^{11} ;

each R^8 is independently CN, N_3 , NO_2 , SCN, SF_5 , C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl;

$Si(R^{12})_3$, OR^9 , OSO_2R^9 , $S(O)_nR^9$, $N(R^{10a})R^{10b}$, $C(=O)N(R^{10a})R^{10b}$, $C(=S)N(R^{10a})R^{10b}$, $C(=O)OR^9$, $CH=NOR^9$,

phenyl, or a 3-, 4-, 5-, 6- or 7-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2 or 3 heteroatoms N, O, and/or S as ring members, or

two R^8 present on the same carbon atom of an alkyl, alkenyl, alkynyl or cycloalkyl group together form a group $=O$, $=C(R^{13})_2$, $=S$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{10a}$, $=NOR^9$; or $=NN(R^{10a})R^{10b}$; or

two radicals R^8 , together with the carbon atoms of the alkyl, alkenyl, alkynyl or cycloalkyl group which they are bonded to, form a 3-, 4-, 5-, 6-, 7- or 8-membered saturated or partially unsaturated carbocyclic or heterocyclic ring, which heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms N, O, and/or S as ring members; and

R^8 as a substituent on a cycloalkyl ring may additionally be C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, and C_2 - C_6 -haloalkynyl; and

R^8 in the groups $C(=O)R^8$ and $=C(R^8)_2$ may additionally be H, halogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, or C_2 - C_6 -haloalkynyl; each R^9 is independently H, C_1 - C_6 -alkyl, or C_1 - C_6 -haloalkyl;

R^{10a} , R^{10b} are independently from one another H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -halocycloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_2 - C_6 -haloalkynyl; C_1 - C_6 -alkyl- $C(=O)OR^{15}$, C_1 - C_6 -alkyl- $C(=O)N(R^{14a})R^{14b}$, C_1 - C_6 -alkyl- $C(=S)N(R^{14a})R^{14b}$, C_1 - C_6 -alkyl- $C(=NR^{14})N(R^{14a})R^{14b}$, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $S(O)_nR^{15}$, $S(O)_nN(R^{14a})R^{14b}$, $C(=O)R^{13}$, $C(=O)OR^{15}$, $C(=O)N(R^{14a})R^{14b}$, $C(=S)R^{13}$, $C(=S)SR^{15}$, $C(=S)N(R^{14a})R^{14b}$, $C(=NR^{14})R^{13}$;

phenyl; and

a 3-, 4-, 5-, 6- or 7-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2, 3 or 4 heteroatoms N, O, and/or S as ring members, preferably hetaryl; or

R^{10a} and R^{10b} together with the nitrogen atom they are bonded to form a 3- to 8-membered saturated, partially or fully unsaturated heterocyclic ring, which ring may additionally contain one or two heteroatoms N, O, and/or S as ring members; or

R^{10a} and R^{10b} together form a group $=C(R^{13})_2$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{14}$, or $=NOR^{15}$;

R^{11} is halogen, CN, N_3 , NO_2 , SCN, SF_5 , C_1 - C_{10} -alkyl, C_3 - C_8 -cycloalkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, or

OR^9 , $NR^{10a}R^{10b}$, $S(O)_nR^9$, $Si(R^{12})_3$; phenyl; and a 3- to 7-membered saturated, partially or fully unsaturated aromatic heterocyclic ring comprising 1, 2, 3, or 4 heteroatoms N, O, and/or S as ring members; or

two R^{11} present on the same ring carbon atom of an unsaturated or partially unsaturated heterocyclic ring may together form a group $=O$, $=C(R^{13})_2$, $=S$, $=S(O)_m(R^{15})_2$, $=S(O)_mR^{15}N(R^{14a})R^{14b}$, $=NR^{14}$, $=NOR^{15}$, or $=NN(R^{14a})R^{14b}$;

or two R^{11} bound on adjacent ring atoms form together with the ring atoms to which they are bound a saturated 3- to 9-membered ring, which ring may contain 1 or 2 heteroatoms O, S, N, and/or NR^{14} , and/or 1 or 2 groups $C=O$, $C=S$, $C=NR^{14}$ as ring members;

each R^{12} is independently C_1 - C_4 -alkyl and phenyl;

each R^{13} is independently CN, NO_2 , OH, SH, SCN, SF_5 , C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, SO_n - C_1 - C_6 -alkyl, SO_n - C_1 - C_6 -haloalkyl, $Si(R^{12})_3$, $C(=O)N(R^{14a})R^{14b}$, C_3 - C_8 -cycloalkyl; and a 3- to 7-membered saturated, partially or fully unsaturated heterocyclic ring containing 1, 2, or 3 heteroatoms N, O, and/or S, as ring members;

or

two R^{13} present on the same carbon atom of an alkyl, alkenyl, alkynyl or cycloalkyl group may together be $=O$, $=CH(C_1-C_4\text{-alkyl})$, $=C(C_1-C_4\text{-alkyl})C_1-C_4\text{-alkyl}$, $=N(C_1-C_6\text{-alkyl})$ or $=NO(C_1-C_6\text{-alkyl})$; and

R^{13} as a substituent of a cycloalkyl ring may additionally be C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl, which groups are unsubstituted, partially or fully halogenated, or substituted with 1 or 2 CN, C_3 - C_4 -cycloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy, and oxo; and

R^{13} in groups $=C(R^{13})_2$, $N=C(R^{13})_2$, $C(=O)R^{13}$, $C(=S)R^{13}$, and $C(=NR^{14})R^{13}$ may additionally be H, halogen, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, or C_2 - C_6 -alkynyl, and oxo;

each R^{14} is independently H, CN, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, SO_n - C_1 - C_6 -alkyl, SO_n - C_1 - C_6 -haloalkyl, $Si(R^{12})_3$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl; and oxo; C_3 - C_8 -cycloalkyl; phenyl, benzyl, pyridyl, phenoxy; and a 3-, 4-, 5- or 6-membered saturated, partially or fully unsaturated heterocyclic ring comprising 1, 2 or 3 heteroatoms N, O, and/or S as ring members;

R^{14a} and R^{14b} independently of each other, have one of the meanings given for R^{14} ; or R^{14a} and R^{14b} , together with the nitrogen atom to which they are bound, form a 3- to 7-membered saturated, partially, or fully unsaturated heterocyclic ring, wherein the ring may additionally contain 1 or 2 heteroatoms N, O, and/or S as ring members; or R^{14a} and R^{14} or R^{14b} and R^{14} , together with the nitrogen atoms to which they are bound in the group $C(=NR^{14})N(R^{14a})R^{14b}$, form a 3- to 7-membered partially, or fully unsaturated heterocyclic ring, wherein the ring may additionally contain 1 or 2 heteroatoms N, O, and/or S as ring members;

each R^{15} is independently H, CN, $Si(R^{12})_3$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl; C_3 - C_8 -cycloalkyl; phenyl, benzyl, pyridyl, and phenoxy;

each R^{16} is independently halogen, NO_2 , CN, OH, SH, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, SO_n - C_1 - C_6 -alkyl, SO_n - C_1 - C_6 -haloalkyl, C_1 - C_4 -alkylcarbonyl, C_1 - C_4 -haloalkylcarbonyl, C_1 - C_4 -alkoxycarbonyl, C_1 - C_4 -haloalkoxycarbonyl, aminocarbonyl, C_1 - C_4 -alkylaminocarbonyl, di- $(C_1$ - C_4 -alkyl)-aminocarbonyl, $Si(R^{12})_3$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl; C_3 - C_8 -cycloalkyl; or

two R^{16} present together on the same atom of an unsaturated or partially unsaturated ring may be =O, =S, =N(C_1 - C_6 -alkyl), =NO- C_1 - C_6 -alkyl, =CH(C_1 - C_4 -alkyl), or =C(C_1 - C_4 -alkyl) $_2$; or

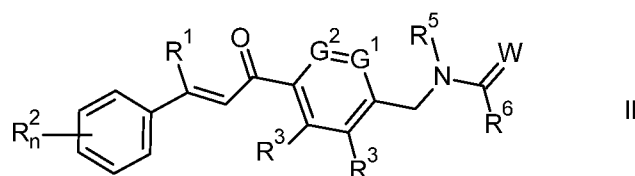
two R^{16} on two adjacent carbon atoms form together with the carbon atoms they are bonded to a 4- to 8-membered saturated, partially or fully unsaturated ring, wherein the ring may contain 1 or 2 heteroatoms N, O, and/or S as ring members;

each n is independently 0, 1, or 2; and

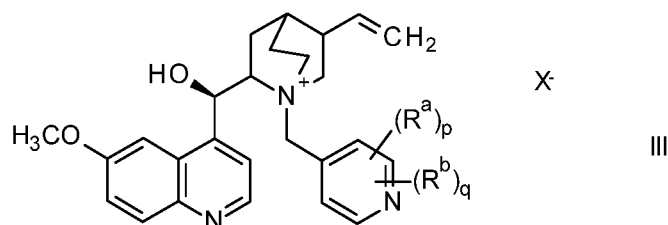
each m is independently 0, or 1;

wherein the shown enantiomer has at least 55% ee;

by oxo-Michael addition of hydroxyl amine or its salt to an enone of formula II,



wherein the variables have the meanings given for formula I, in the presence of a catalyst of formula III



wherein X is a counteranion, and

R^a is CN, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, C_1 - C_3 -alkylthio, phenyl, benzyl, and phenoxy;

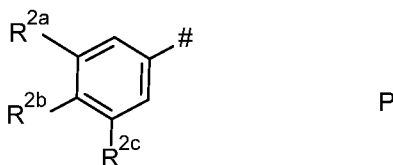
R^b is halogen;

p is 1, 2, 3, or 4; and

q is 0, 1, 2 or 3, wherein the sum of p and q is up to 4;

and a base.

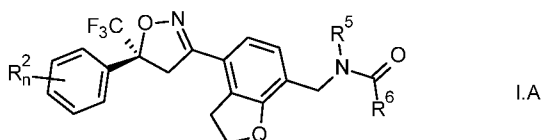
2. A process according to claim 1, wherein the phenyl ring in formula I bearing the R^{2n} substitution is a group P



wherein R^{2a} is F, Cl, Br, CF_3 , or OCF_3 , and R^{2b} and R^{2c} are H, or as defined for R^{2a} .

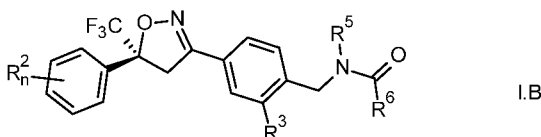
3. A process according to any of the preceding claims, wherein R^1 is CF_3 .
4. A process according to any of the preceding claims, wherein G^1 is C- CH_3 , or C-Cl, and G^2 is CH.

5. A process according to any of claims 1 to 3, wherein formula I corresponds to formula I.A,



wherein Q is CH or O, R^5 is H or CH_3 , and R^6 is H, C_1 - C_6 -alkyl, C_1 - C_2 -alkoxy- C_1 - C_2 -alkyl, or C_2 - C_6 -alkenyl.

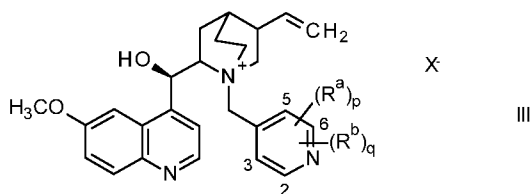
6. A process according to any of claims 1 to 4, wherein formula I is formula I.B,



wherein R^5 is H or CH_3 , and R^6 is H, C_1 - C_6 -alkyl, C_1 - C_2 -alkoxy- C_1 - C_2 -alkyl, or C_2 - C_6 -alkenyl.

7. A process according to any of the preceding claims, wherein the catalyst of formula III is applied in 0.01 to 0.5 mol equivalents of compound II.
8. A process according to any of the preceding claims, wherein an alkali metal or alkaline earth metal hydroxide is used as base in from 0.05 to 6 mol equivalents.
9. A process according to any of the preceding claims, wherein the amount of hydroxylamine is from 1 to 10 mol equivalents.

10. A compound of formula III



wherein X is halogen, BF₄, PF₆, C₁-C₁₀-alkylsulfonate, benzenesulfonate, or methylbenzenesulfonate;

R^a is CN, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, phenyl, benzyl, and phenoxy;

R^b is halogen;

p is 1, 2, 3, or 4; and

q is 0, 1, 2 or 3, wherein the sum of p and q is up to 4.

11. A compound of formula III according to claim 11, wherein (R^a)_p and (R^b)_q are selected from 2-CN, 2-OCH₃, and 3-CH₃.

12. A compound of formula III according to claim 11, wherein (R^a)_p and (R^b)_q are selected from 2-CH₃, 2-OCH₃, 6-Cl, and 2-OCH₃, 6-CH₃.

13. A compound of formula III according to claim 11, wherein (R^a)_p is 2,6-(CH₃)₂, and q is 0.

14. A compound of formula III according to any of claims 11 to 13, wherein X is halogen.

15. A compound of formula III according to claim 14, wherein X is Br or Cl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/057228

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D261/04 C07D401/14 A01N43/80
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/104089 A1 (SYNGENTA PARTICIPATIONS AG [CH]; SYNGENTA LTD [GB] ET AL.) 1 September 2011 (2011-09-01) cited in the application page 67; examples 7-8 page 79; example 17 page 82; example 20 page 86; example 24 page 96; example 31 page 101; example 33 -----	1-15
X	US 2014/350261 A1 (TOYAMA KEN-ICHI [JP] ET AL) 27 November 2014 (2014-11-27) page 27; example 4; table 2 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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