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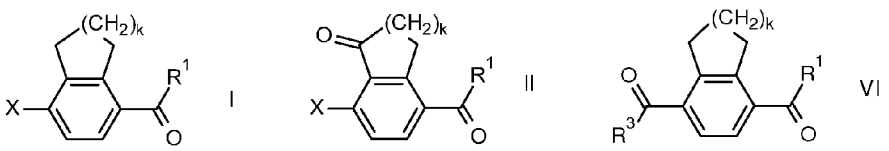
(54) Title: PARA-SUBSTITUTED INDANYL AND TETRALINYL DERIVATIVES

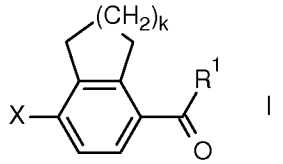


(57) Abstract: Compounds of formula I, wherein the substituents R^1, X, and the index k are as defined in the specification; a process for preparation of compounds of formula I, a process for preparation of its precursor compounds II, wherein the substituents R^1, X, and the index k are as defined in the specification; intermediates for the production of compounds I, or II; use of compounds of formula I for the production of compounds of formula VI wherein the substituents R^1, R^3, and the index k are as defined in the specification; the use of compounds I, or II, for the production of active compounds.

Para-substituted Indanyl and Tetralinyl derivatives

Description

The present invention relates to intermediate compounds of formula I



I

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wherein the variables have the following meaning:

X halogen;

R^1 H, OR^{11}, or $NR^{12}R^{13}$;

R^{11} a) H;

b) C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl; which groups are unsubstituted, or substituted by halogen, CN, NO_2, $S(O)_mR^A$, OR^B, NR^BR^C, $S(O)_mNR^BR^C$, $Si(R^B)_2R^C$, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$, $C(=S)R^B$, $C(=S)NR^BR^C$, $C(=S)OR^B$, $C(=S)SR^B$, $C(=NR^B)R^C$, $C(=NR^B)NR^CR^D$;

c) phenyl, which is unsubstituted, or substituted by R^A; or

d) a 3-, 4-, 5-, 6-, or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle comprises one or more, same, or different heteroatoms O, $N(O)_n$, or $S(O)_m$;

wherein

R^A a) C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_1-C_4-alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl; which groups are unsubstituted, or substituted by halogen, CN, OH, NO_2, phenyl, or C_1-C_6-alkyl-phenyl; or

b) a 3-, 4-, 5-, 6-, or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle comprises one or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, wherein none, one, or more ring members are replaced by C(=O), or C(=S), and which heterocycle is unsubstituted, or substituted with halogen, CN, N_3, NO_2, SCN, SF_5, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, or C_2-C_6-haloalkynyl;

R^B, R^C, R^D are independently from one another, as defined for R^A, or H; or two substituents R^B, R^C, or R^D, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, or $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S);

R^{12} H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

R^{13} a) H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

b) a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2, or C=O; and A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle is unsubstituted, or substituted by R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

c) a group $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $N(R^B)C(=O)OR^C$, $N(R^B)C(=O)N(R^C)R^D$, $N(R^B)C(=S)OR^C$, $N(R^B)C(=S)N(R^C)R^D$, $C(=O)N(R^B)R^C$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$, $C=NR^BR^C$; or

wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a group $=S(R^B)R^C$, $=NR^B$, $=NOR^B$, or $=NN(R^B)R^C$;

R^E a) halogen, CN, N_3, NO_2, SCN, SF_5, 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, $Si(R^B)_2R^C$, OR^{11}, OSO_2R^A, $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=O)N(R^B)N(R^C)R^D$, $C(=O)NOR^B$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$;

b) phenyl, which is unsubstituted, or substituted by R^A; or

c) two substituents R^E, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

R^F a) halogen, CN, N_3, NO_2, SCN, SF_5, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $Si(R^B)_2R^C$, OR^{11}, OSO_2R^A, $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=O)N(R^B)N(R^C)R^D$, $C(=O)NOR^B$, $N(R^B)R^C$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$;

b) phenyl, which is unsubstituted, or substituted by R^A; or

c) two substituents R^F, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully un-

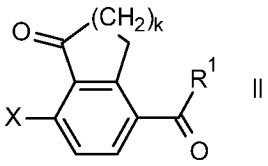
saturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

k 1, or 2

m 0, 1, or 2; and

n 0, or 1.

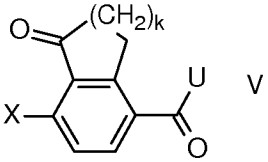
The invention also relates to a process for the production of compounds I by reaction of compounds II with a reducing agent



II

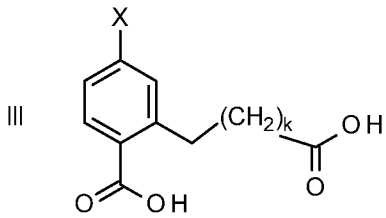
wherein all variables have a meaning as defined for compounds I.

The invention also relates to the production of compounds II by reaction of compounds V



V

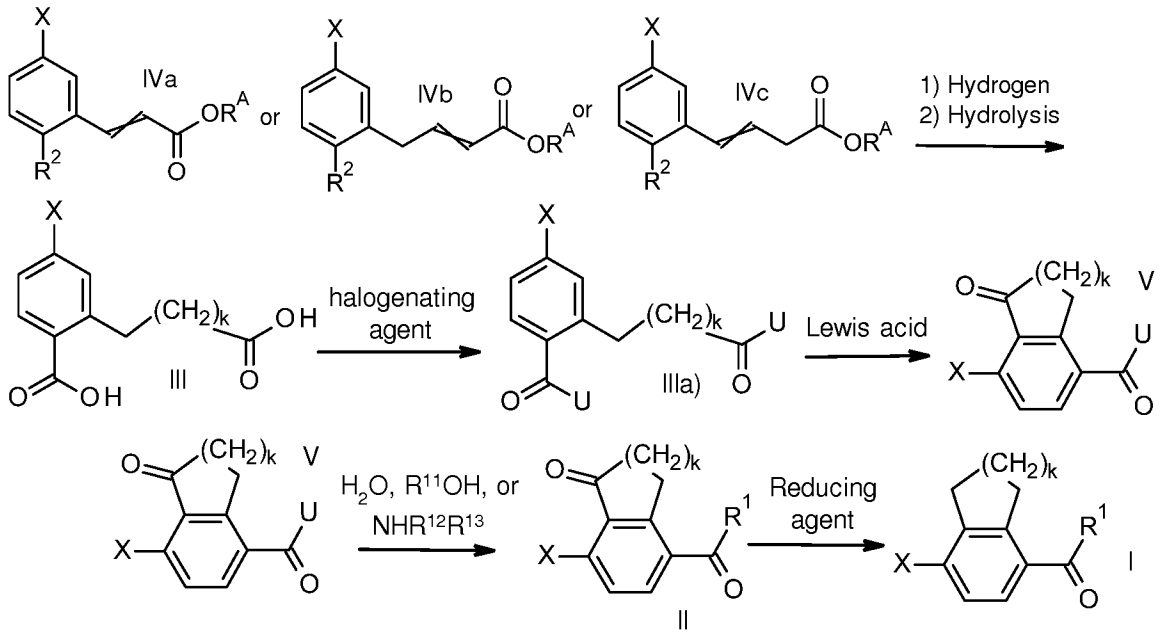
with H_2O, $R^{11}OH$, or $NHR^{12}R^{13}$; wherein compounds V are produced by reaction of compounds III



III

with a halogenating agent, followed by cyclization in the presence of a Lewis acid; wherein all substituents in compounds of formulae II, III, and V are defined as for compounds of formula I, and wherein U is halogen.

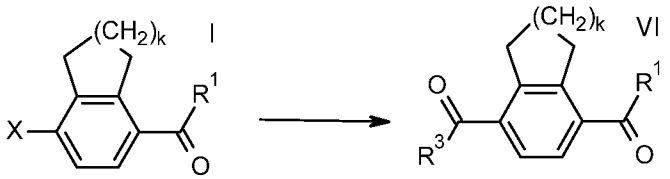
The invention also relates to the production of compounds III by reaction of compounds IVa, IVb, or IVc with hydrogen, followed by hydrolysis.



R^2 in compounds IVa, IVb, and IVc is CN, or C(=O)OR^A; U in compounds IIIa), and V is halogen; and all other substituents in compounds I, II, III, IIIa, IVa, IVb, IVc, and V have a meaning as defined for compounds I. The invention further relates to compounds III, wherein X is halogen, preferably Cl, Br, or I, in particular Br, or I, and especially Br.

The invention further relates to intermediate compounds V, which are intermediates in the production of compounds II from compounds III.

The invention also relates to the use of compounds I for the production of compounds VI,



wherein R^1 and k have a meaning as defined for compounds I, and R^3 is H or CH_3.

All other variables in formulae II to VI have a meaning as defined for compounds I. If not otherwise stated, this shall be the case of all depicted structures - in case the variables are present - throughout this text. Embodiments and preferences of variables defined for specific compounds are also embodiments and preferences of the variables of same nomenclature in all other compounds.

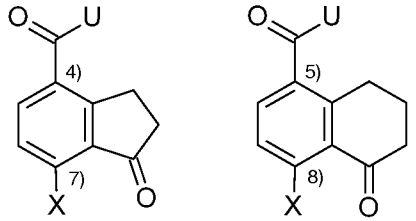
Throughout the text, the expressions “compounds”, and “compounds of formula” are equivalent expressions with the same meaning.

The invention also relates to production processes, wherein the reaction steps for the preparation of compounds I, of compounds II, or of compounds VI are carried out in a one-pot synthesis.

Indanyl and tetralinyl derivatives of formulae I and V are novel. They are valuable intermediates for the manufacture of active ingredients and fine chemicals.

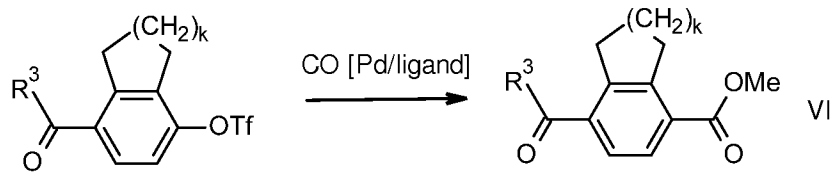
Compounds V enable further conversion to a large variety of 4,7-disubstituted indane and 5,8-disubstituted tetralinyl derivatives by reaction of the activated acid moiety C(=O)U in a one-step

process. Exemplary for the range of accessible compound classes are carboxylic acids, esters, amides, aldehydes, ketones, and halogens, at the carbon 4 of the indane, or the carbon 5 position of the tetralinyl derivatives.



Compounds I representing the aldehyde, carboxylic acid, ester, and amide conversion products of compounds V, are equally versatile intermediates for the manufacture of active ingredients and fine chemicals. Their asymmetric substitution pattern allows for a directed manipulation to key building blocks in industrial scale manufacture of active ingredients, such as compounds VI.

Compounds VI are known from prior art WO2015/128358, where the production of compounds VI involves precursor molecules, which are derivatives of trifluoromethane sulfonic acid (hereinafter named triflates):



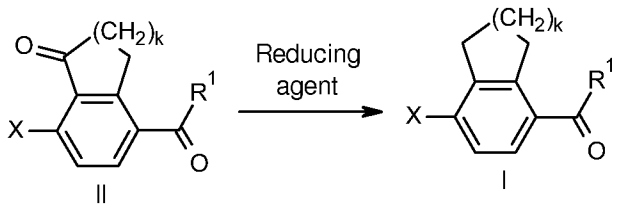
Triflates are expensive to produce and corrosive towards production plants. Triflates also hold a poor atom economy in chemical reactions, which translates to an increased amount of waste and a low environmental sustainability. The production process involving triflates is also not versatile in terms of a broad product spectrum, as only esters and carboxylates can be produced, whereas amides afford an additional coupling step.

It was therefore the objective of the invention to supply reaction intermediates, processes for their production, as well as processes for their conversion to compounds VI, which are suitable for industrial-scale production and where the abovementioned disadvantages of prior art are avoided. It was also an object of the invention to supply a versatile method and intermediates for making accessible a broad spectrum of downstream active ingredients and fine chemicals.

The objective was solved by compounds I, and V, as described above, which may be produced and further converted to compounds VI without application of triflates. Compounds I, V, and VI are key intermediates for a broad range of indanyl and tetralinyl derivatives that are crucial for active ingredient manufacture.

The reactions are economically advantageous i.a. by being characterized in high yield, high selectivity, little side products, cost effectiveness, industrial scale applicability, and little amount of waste material.

Compounds I are produced by reaction of compounds of formula II with a reducing agent.



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wherein all variables have a meaning as defined for compounds I.

Typical reducing agents are metals, metal salts, inorganic hydrides, and alcohols, preferably metals and inorganic hydrides, more preferably transition metals and inorganic hydrides. In another embodiment, reducing agents are metals, inorganic hydrides, and alcohols, preferably metals and inorganic hydrides, more preferably transition metals and inorganic hydrides.

In one embodiment, compounds I can be directly produced from compounds II. In another embodiment, compounds I are first reacted with a reducing agent, and then dehydroxylated, as described below.

In one embodiment, compounds I are produced by reduction of compounds II with a metal, or a metal salt, at a pH below 7.0, preferably with Zn, or a Sn(II)-salt. In another embodiment, compounds I are produced by reduction of compounds II with a metal, at a pH below 7.0, preferably with Zn.

This process is usually carried out at temperatures of from 0 to 60 °C, preferably from 15 to 35 °C, in a protic solvent, in the presence of an acid.

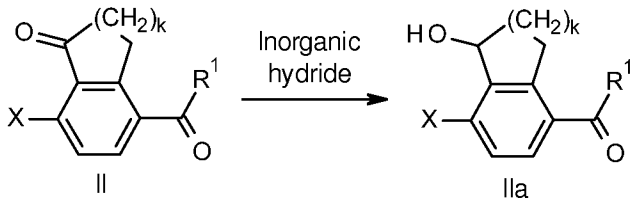
Suitable protic solvents are H_2O, or aliphatic C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$, preferably H_2O, or CH_3OH. It is also possible to use mixtures of the solvents mentioned.

Suitable acids are in general inorganic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulphuric acid und perchloric acid, as well as organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, toluene sulphonic acid, benzene sulphonic acid, camphor sulphonic acid, citric acid, and trifluoro acetic acid.

In a first step, the metal, which may be applied as powder, is usually amalgamated with a mercury salt under acidic conditions in H_2O. Usually, the molar ratio of the metal to compounds II is from 1:1 to 50:1, preferably from 5:1 to 20:1, and most preferably from 10:1 to 20:1. The reaction system may then be acidified with an acid to a pH below 5.0, preferably below 3.0, more preferably below 1.0. The pH may range from -3 to 5, preferably from -2 to 3, and especially preferably from -2 to 0.

Subsequently, compounds II may be added and reacted under reflux to yield compounds I.

In another embodiment, compounds II are reduced by reaction with an inorganic hydride to compounds IIa:



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wherein all variables have a meaning as defined for compounds II.

This process is usually carried out at temperatures of from -10 to 50 °C, preferably from -5 to 40 °C, in a protic, or apolar solvent. In one embodiment, the reaction temperature is kept from -10 to 10 °C, and then raised to 20 to 25 °C, where it is kept for at least 60 minutes before reaction work-up

Suitable protic, or apolar solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbon, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, tert-butylmethylether (MTBE), ethylene glycol dimethylether (DME), dioxane, anisole, and tetrahydrofurane (THF); alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; or H_2O.

Preferred solvents are protic solvents, more preferably H_2O, or C_1-C_4-alcohols, such as H_2O, CH_3OH, CH_3CH_2OH, $CH_3CH(OH)CH_3$, most preferably H_2O, CH_3OH, or CH_3CH_2OH, especially preferably H_2O, or CH_3OH, and in particular CH_3OH. It is also possible to use mixtures of the solvents mentioned.

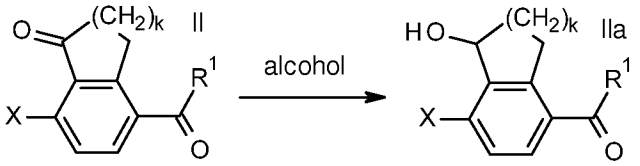
Suitable inorganic hydrides are $NaBH_4$, $LiAlH_4$, diisobutylaluminium hydride (DIBAL-H), or its homogeneous salts, preferably $NaBH_4$ and DIBAL-H, more preferably $NaBH_4$.

Preferably, the reaction with an inorganic hydride may involve the addition of a Lewis acid. Lewis acids are protic acids, such as trifluoroacetic acid, CH_3SO_3H, or polyphosphoric acid; aprotic inorganic salts of metals of groups 13 or 14, and transition metals of period 4, such as $FeCl_3$, $FeBr_3$, AlF_3, $AlCl_3$, $AlBr_3$, SbF_5, $SbCl_5$, BiF_3, $BiCl_3$, $TiCl_4$, $ZnCl_2$, $SnCl_4$, BF_3, BCl_3, BBr_3, $ZrCl_4$; or aprotic and metalorganic compounds metals of groups 13 or 14, and transition metals of period 4, such as $Al(CH_3)_3$, $Al(CH_2CH_3)_3$, $B(CH_3)_3$; moreover polyphosphate ester, trimethylsilyl polyphosphate. Preferred Lewis acids are trifluoroacetic acid and $AlCl_3$, more preferably trifluoroacetic acid.

Preferably, the reaction with an inorganic hydride may involve the previous conversion of compounds II to a hydrazone by reaction with hydrazine, or a derivative. Suitable hydrazine derivatives are p-toluene sulfone hydrazine, or methyl sulfone hydrazine, preferably p-toluene sulfone hydrazine.

Compounds II and the inorganic hydride are generally reacted with one another in equimolar amounts. It may be advantageous to employ an excess of the inorganic hydride, e.g. with a ratio from 1:1 to 10:1, preferably from 1:1 to 5:1, more preferably from 1:1 to 2:1.

In another embodiment, compounds II are reduced by reaction with an alcohol to compounds IIa.



Production processes of this type are generally known as Meerwein-Ponndorf-Verley-Reductions, whose general reaction conditions are described i.a. in Jin et al., Org. Process Res. Dev., 2006, 10 (5), pp 1032–1053.

This production is usually carried out by reaction of compounds II with an alcohol, optionally in an inert solvent, in the presence of a metal alcoholate.

Suitable alcohols are C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, or $C(CH_3)_3OH$, preferably $CH_3CH_2CH_2OH$ or $CH_3CH(OH)CH_3$, more preferably $CH_3CH(OH)CH_3$.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes or halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles such as CH_3CN, and propionitrile. Preferred solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether, or aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene. It is also possible to use mixtures of the solvents mentioned. In one embodiment, the production is carried out with an alcohol and without a solvent.

Suitable metal alcoholates are usually the C_1-C_6-alcoholates of transition metals of the 4th period, such as $Zn(OCH_3)_2$, $Zn(OCH_3CH_2)_2$, $Zn[OCH(CH_3)_2]_2$, $Fe(OCH_3)_3$, $Fe(OCH_2CH_3)_3$, $Fe(OCH(CH_3)_2)_3$ or metals of group 13, such as $Al(OCH_3)_3$, $Al(OCH_2CH_3)_3$, $Al(OCH(CH_3)_2)_3$. Preferably, metal alcoholates are C_1-C_6-alcoholates, preferably C_1-C_4-alcoholates of metals of group 13, preferably $Al(OCH(CH_3)_2)_3$.

Dehydroxylation of compounds IIa to compounds I may be achieved by standard methods of organic chemistry as described in Hartwig et al., Tetrahedron 1983 (16), 2609-2645; Kirwan et al., and Tetrahedron 1990 (31), 5093-5096.

Dehydroxylation of compounds IIa to compounds II may comprise the reaction of compounds IIa with a metal hydride, or with a hydrosilane, preferably with a hydrosilane.

In one embodiment, compounds IIa are dehydroxylated by esterfication with a strong organic acid that is optionally dissolved in an inert solvent, followed by reaction with a hydrosilane. The process is usually carried out at temperatures of from 0 to 40 °C, preferably from 15 to 35 °C, in an aprotic solvent, in the presence of an organic acid.

Suitable aprotic solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{12}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones such as C_1-C_6-alkyl-C_1-C_6-alkyl ketones, C_1-C_6-alkyl-C_6-C_{10}-aryl ketones, and C_6-C_{10}-aryl-C_6-C_{10}-aryl-ketones, $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and tert-butyl methyl ketone (MTBK); moreover dimethyl sulphoxide (DMSO), dimethyl formamide (DMF), and dimethylacetamide (DMA), preferably halogenated hydrocarbons, such as preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, more preferably chlorinated hydrocarbons, and in particular CH_2Cl_2. It is also possible to use mixtures of the solvents mentioned. In one embodiment, no solvent is used.

Suitable acids are carboxylic acids (preferably C_1-C_{10}-carboxylic acids), such as formic acid, acetic acid and propionic acid, or halogenated carboxylic acids (preferably halogenated C_1-C_{10}-carboxylic acids), such as mono-, di-, and trifluoroacetic acid, mono-, di-, and trichloroacetic acid, or pentafluorobenzoic acid; preferably mono-, di-, and trifluoroacetic acid, more preferably trifluoroacetic acid. In one embodiment, the acid is used as a solvent.

The process may involve an activating agent and/or a coupling agent. Suitable activating agents are halogenating agents, which are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride. Suitable coupling agents are selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7- azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP ((benzotriazol-1-yloxy)-tris(dimethylamino) phosphonium hexafluorophosphate), PyBOP ((benzotriazol-1-yloxy)-tripyrrolidinphosphonium hexafluorophosphate) and PyBrOP (bromotripyrrolidinphosphonium hexafluorophosphate). Generally, the activator is used in excess. Usually, no activating agent and/or coupling agent is necessary.

In one embodiment, the process is carried out in the presence of a base. Typical bases applied are organic bases, such as pyridine, 4-N,N-dimethylamino-pyridine, tetramethylene diamine, piperidine, diisopropylamine, morpholine, and triethylamine, preferably pyridine, 4-N,N-dimethylaminopyridine, and diisopropylamine. Usually, esterfication can be achieved without a base.

The resulting ester may then be reduced with a hydrosilane. This process is usually carried out at temperatures of from 0 to 80 °C, preferably from 10 to 50 °C, more preferably from 15 to 30 °C, in an aprotic solvent.

Suitable aprotic solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes or halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, C_1-C_6-alkyl-C_6-C_{10}-aryl ketones, and C_6-C_{10}-aryl-C_6-C_{10}-aryl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK. Preferred solvents are $CH_3C(O)CH_3$, CH_3CN, $CHCl_3$, CH_2Cl_2, CCl_4, 1,2-dichloro ethane, benzene, xylene, toluene, $CH_3CH_2OCH_2CH_3$, CH_3OCH_3, petroleum ether, C_5-C_{12}-alkanes, preferably CH_2Cl_2 and benzene, more preferably CH_2Cl_2. It is also possible to use mixtures of the solvents mentioned.

Suitable hydrosilanes are C_1-C_6-alkyl silanes, C_6-C_{10}-arylsilanes, and mixed (C_1-C_6-alkyl)(C_6-C_{10}-aryl) silanes,, such as trimethylsilane, triethylsilane, diphenylsilane, diphenylmethylsilane, dimethylphenylsilane, phenyldimethylsilane, or polymethylhydrosiloxane. Preferred hydrosilanes are C_1-C_6-alkyl silanes, such as trimethylsilane and triethylsilane, and C_6-C_{10}-arylsilanes, such as triphenylsilane and diphenylsilane, more preferred trimethylsilane and triethylsilane, and in particular triethylsilane.

The conditions for the above type of reductions are known from WO2012/0209005.

Compounds I with R^1 being OH may be reacted with an amine $NHR^{12}R^{13}$ to the corresponding amide (as described in WO2015128358).

This process may be carried out in an inert solvent, in the presence of a base and by activation with an activating agent, or a coupling agent.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkane, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMSO, DMF, and DMA, preferably DMF. It is also possible to use mixtures of the solvents mentioned.

Suitable activating agents are halogenating agents, which are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride. Suitable coupling agents are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7- azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate)

and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP, PyBOP, and PyBrOP. Generally, the activator is used in excess.

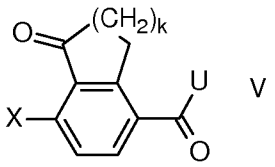
As a further alternative, compounds I with R^1 being OR^{11} and R^{11} being not H (ester form) can also be directly converted to the corresponding amide. This process is usually carried out at temperatures from 20 to 80 °C, preferably from 30 to 70 °C, more preferably from 40 to 60 °C, and in particular from 45 to 55 °C, in the presence of a catalyst, such as a metalorganic compound. Such reactions have been described by Levin et al., Synthetic Communications, 1982, (12) 989-993.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkane, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. Preferred solvents are $CH_3C(O)CH_3$, CH_3CN, CH_3NO_2, $CHCl_3$, CH_2Cl_2, CCl_4, CH_2ClCH_2Cl, benzene, toluene, xylene $CH_3CH_2OCH_2CH_3$, CH_3OCH_3, and C_5-C_{12}-alkanes, preferably CH_2Cl_2 and benzene, more preferably benzene. In one embodiment, the solvent is a C_1-C_6-alkyl-C_1-C_6-alkyl ether, C_1-C_6-alkyl-C_6-C_{10}-aryl ether, C_1-C_6-nitrile, halogenated C_1-C_6-alkane, halogenated C_6-C_{10}-aromatic hydrocarbon, C_5-C_{16}-alkane, or C_6-C_{10}-aromatic hydrocarbon. It is also possible to use mixtures of the solvents mentioned.

Suitable metalorganic compounds are metal alkyl (e.g. C_1-C_6-alkyl metal) or metal aryl compounds (e.g. C_6-C_{10}-aryl metal), preferably of Fe, Ti, Zr, Al, more preferably Al, such as $Al(CH_3)_3$, $Al(CH_2CH_3)_2$, $Al(CH_2CH_2CH_3)_3$, $Al(CH(CH_3)_2)_3$, $Al(CH_2CH_2CH_2CH_3)_3$, $Al(CH(CH_3)(CH_2CH_3)_3$, $Al(C(CH_3)_3)_3$, or $Al(C_6H_5)_3$, preferably $Al(CH_3)_3$.

Alternatively, compounds I, or compounds VI, wherein R^1 is OR^{11}, can be further reacted to compounds XIV-A, or compounds XV-A, as described below, which may then be converted to the amides XIV-A, and XV-A, wherein R^1 is $NR^{11}R^{12}$. It is thus possible to alter R^1 in compounds I, II, V, VI, XIV-A, or XV-A, by amidation, esterfication, hydrolysis, or a combination of these reactions, to introduce a suitable group R^1 that may be present in the final compounds XIV-A, or XV-A. Thus, R^1 may have the same meaning for all compounds I, II, V, VI, XIV-A, and XV-A, or may have a different meaning between said compounds, depending on the reaction step in which R^1 is altered.

Compounds II are produced by reaction of compounds V



V

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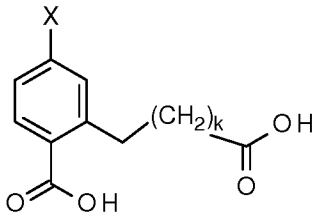
with H_2O, $R^{11}OH$, or $NHR^{12}R^{13}$; wherein X is halogen, and U is halogen; and wherein compounds V are produced by reaction of compounds III

III 

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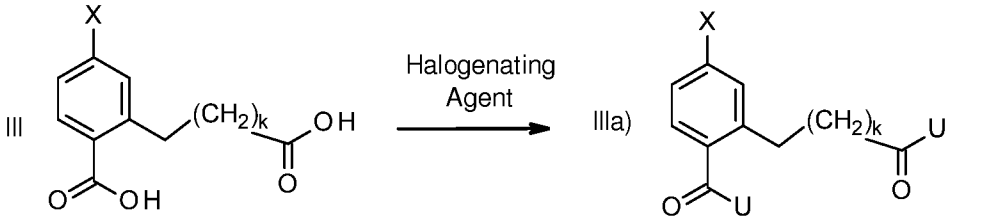
with a halogenating agent, followed by cyclization in the presence of a Lewis acid.

Compounds III are first activated by the conversion to an acid halogenide of formula IIIa



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wherein each U is independently a halogen, preferably both U are the same halogen, and all other variables have a meaning as defined for compounds I. In one embodiment, U is Cl, Br, or I. In another embodiment, U is Br, or I. In yet another embodiment, U is Br. In yet another embodiment, U is Cl.

This process is usually carried out at temperatures of from 0 to 50 °C, preferably from 10 to 30 °C, in an inert solvent with a halogenating agent, optionally in the presence of a base.

Suitable inert solvents are aprotic solvents, such as aliphatic hydrocarbons, preferably C_1-C_{16}-alkanes, e.g. pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, e.g. toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated aliphatic C_1-C_6-alkanes, or halogenated aromatic C_6-C_{10}-hydrocarbons, e.g. CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, e.g. $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles e.g. CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, e.g. $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMSO, DMF, and DMA. Preferred solvents are DMF, $CH_3C(O)CH_3$, $CHCl_3$, CH_2Cl_2, CCl_4, benzene, toluene, xylene, 1,2-dichlorobenzene, CH_2ClCH_2Cl, $CH_3CH_2OCH_2CH_3$, CH_3OCH_3, petroleum ether, C_5-C_{12}-alkanes, preferably CH_2Cl_2, benzene and DMF, more preferably CH_2Cl_2 and DMF, most preferably CH_2Cl_2. It is also possible to use mixtures of the solvents mentioned. In one embodiment, the inert solvent is a mixture of CH_2Cl_2 and DMF, preferably with an excess of CH_2Cl_2. In one embodiment, the inert solvent is DMF, a halogenated aliphatic C_1-C_6-alkane, a halogenated aro-

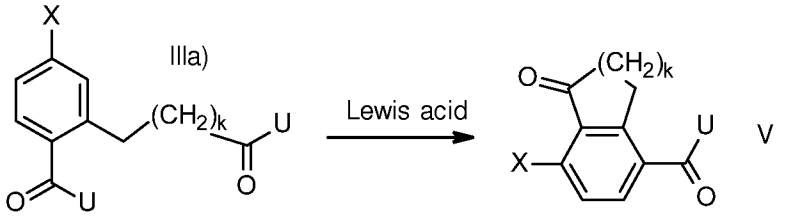
matic C_6-C_{10}-hydrocarbon, a C_1-C_6-alkyl-C_1-C_6-alkyl ether, a C_1-C_6-alkyl-C_1-C_6-alkyl ketone, or a C_1-C_{16}-alkane. In one embodiment, the inert solvent is DMF, a halogenated hydrocarbon, an ether, a ketone, or an aliphatic hydrocarbon. In another embodiment, the inert solvent is DMF, or a halogenated hydrocarbon.

Suitable bases are, in general, organic bases, for example tertiary amines, such as trimethylamine, diisopropylethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also bicyclic amines. Particular preference is given to diisopropylethylamine. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent.

Halogenating agent are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride.

The ratio of chlorinating agent to compounds III usually depends on number of halogen atoms that can be transferred from the chlorinating agent. Usually, the halogenating agent (preferably the number of transferable halogen atoms) is applied in an excess of compounds III. The molar ratio of transferrable halogen atoms to the dicarboxylic acid III is usually from 1:1 to 20:1, more preferably from 2:1 to 15:1, and most preferably from 5:1 to 10:1.

Compounds IIIa are then cyclized to compounds V:



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wherein X and U are independently halogen.

This process is usually carried out in the presence of Lewis acid in an inert solvent at low temperatures e.g. from -100 to 20 °C, preferably from -80 to 10 °C, more preferably from -20 to 5 °C, which are then raised after mixture of the reactants to the boiling temperature of the solvent, e.g. to a range from 20 to 100 °C, preferably from 25 to 50 °C, more preferably from 30 to 50 °C.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2 $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMF, and DMA; preferably DMF, $CH_3C(O)CH_3$, $CHCl_3$, CH_2Cl_2, CCl_4, benzene, toluene, xylene, 1,2-dichlorobenzene, CH_2ClCH_2Cl, $CH_3CH_2OCH_2CH_3$, CH_3OCH_3,

petroleum ether, or C_5-C_{12}-alkanes, more preferably CH_2Cl_2, benzene, or DMF, especially preferably CH_2Cl_2 or DMF, and in particular CH_2Cl_2. It is also possible to use mixtures of the solvents mentioned.

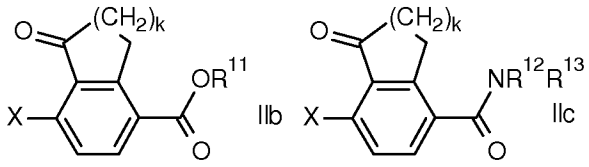
Lewis acids are protic acids, such as trifluoroacetic acid, CH_3SO_3H, or polyphosphoric acid; aprotic inorganic salts of metals of groups 13 or 14, and of transition metals of period 4, such as $FeCl_3$, $FeBr_3$, AlF_3, $AlCl_3$, $AlBr_3$, SbF_5, $SbCl_5$, BiF_3, $BiCl_3$, $TiCl_4$, $ZnCl_2$, $SnCl_4$, BF_3, BCl_3, BBr_3, $ZrCl_4$; or aprotic and metalorganic compounds of metals of groups 13 or 14, and of transition metals of period 4, such as $Al(CH_3)_3$, $Al(CH_2CH_3)_3$, $B(CH_3)_3$; moreover polyphosphate ester, and trimethylsilyl polyphosphate. Preferred Lewis acids are $FeCl_3$, $FeBr_3$, $AlCl_3$, and $AlBr_3$, more preferably $AlCl_3$.

Usually, an excess of a Lewis acid compared to compounds IIIa is applied, e.g. with a ratio from 1 to 5, preferably from 1 to 2, more preferably from 1.2 to 1.7 equivalents of the Lewis acid.

Cyclization reactions of the above described Friedel-Crafts-type are known, e.g. from England K. et al, Tetrahedron Letters, 2010 (51) 2849-2851, where a fluorine compound is used in ortho position to the carboxylic acid moiety of the phenyl ring. However, this would not lead to the desirable substitution pattern that is suitable for producing compounds I.

By the inventive method, compounds II are usually produced at high purity, although the cyclization could in theory also yield dimers, intramolecular anhydrides, and other side products.

Compounds V are then quenched with an alcohol $R^{11}OH$, or H_2O to yield compounds IIb, or with an amine $NHR^{12}R^{13}$ to yield compounds IIc



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wherein all variables have a meaning as described form compounds I.

Compounds IIb with R^{11} being not H can be hydrolyzed to the respective carboxylic acid. This process is usually carried out in the presence of a base or an acid in an inert solvent, and optionally H_2O.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. It is also possible to use mixtures of the solvents mentioned.

Suitable acids are mineral acids, such as hydrochloric acid, sulfuric acid, and organic acids, such as trifluoroacetic acid. Suitable bases are alkali metal hydroxides and earth alkali metal hydroxides, such as LiOH, NaOH or KOH.

Compounds IIb with R^{11} being H may be reacted with an amine $NHR^{12}R^{13}$ to the compounds IIc (as described in WO2015128358).

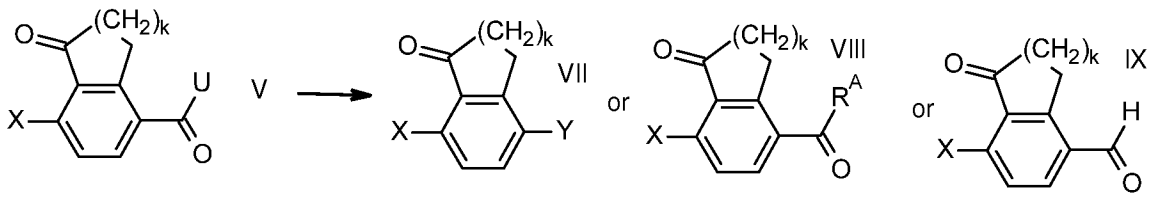
This process may be carried out in an inert solvent, in the presence of a base and by activation with an activating agent, or a coupling agent.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkane, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMSO, DMF, and DMA, preferably DMF. It is also possible to use mixtures of the solvents mentioned.

Suitable activating agents are halogenating agents, which are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride. Suitable coupling agents are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7- azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP, PyBOP, and PyBrOP. Generally, the activating agent, or coupling agent is used in excess.

As a further alternative, compounds IIb with R^1 being OR^{11} and R^{11} being not H (ester form) can also be directly converted to the corresponding amide, as described for compounds I above.

For illustration of the versatility of compounds V, they may alternatively be converted to compounds VII, VIII, or IX



wherein X, Y, and U are each independently halogen, R^A has a meaning as defined for compounds I, and k is 1, or 2.

Typically compounds VII are produced by radical decarboxylation of compounds V, followed by halogenation. Such reactions are generally known as Hunsdiecker-Borodin reactions. This transformation is usually carried out in an inert solvent, in the presence of a radical formation agent, such as a Ag(I)halogenide, e.g. AgCl, AgBr, AgI, $AgNO_3$, $AgSO_4$, $AgCO_3$, and a halogen source such as halogen gas, or an inorganic halogenide, preferably an alkali halogenide, such as sodium chloride, sodium bromide, potassium chloride, potassium bromide. Alternatively, compounds V are reacted with compounds that are both a halogen source and a radical formation agent, such as N-bromsuccinimide, N-chlorsuccinimide, or selectfluor.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as methylene chloride, chloroform, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, dioxane, anisole, and tetrahydrofurane; nitriles, preferably C_1-C_6-nitriles, such as acetonitrile, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and tert-butyl methyl ketone; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; preferably halogenated hydrocarbons, more preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as methylene chloride, chloroform, and chlorobenzene, as well as nitriles such as acetonitrile, and propionitrile.

Compounds VII can also be produced by Curtius rearrangement of compounds V to the urethane, followed by hydrolysis to the amine, and followed by a Sandmeyer reaction, which are all reactions known to the skilled person and comprised in the above mentioned text books.

The Curtius rearrangement is usually carried out at temperatures of from 100 to 200 °C, in an inert solvent, in the presence of an azide, e.g. sodium azide.

Hydrolysis is then usually carried out in the presence of a base or an acid in water. The Sandmeyer reaction usually requires reaction of the resulting amine with a nitrite, such as sodium nitrite, potassium nitrite or nitrous acid, in the presence of a halogenide, such as sodium halogenide, potassium halogenide, HF, HCl, or HBr.

Compounds VIII can be produced i.a. by reaction of compounds V with a Gillman reagent, or by conversion to a Weinreb-amide followed by reaction with a Grignard reagent, such as a metal-halogen-exchange reagent.

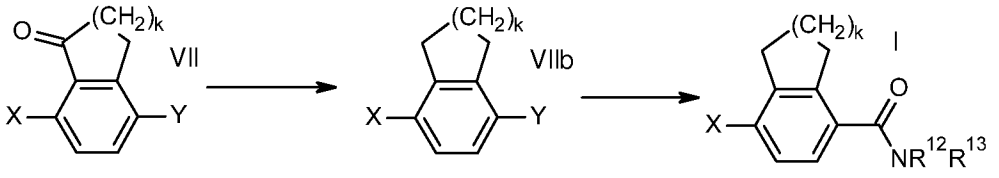
Suitable Gillman reagents are C_1-C_6-alkyl-Li compounds, C_1-C_6-alkyl-Cu compounds, or mixtures thereof. Examples of Gilman reagents are CH_3-Li or $(CH_3)_2CuLi$, CH_3CH_2-Li or $(CH_3CH_2)_2CuLi$, $CH_3CH_2CH_2$-Li or $(CH_3CH_2CH_2)_2CuLi$, $(CH_3)_2CH$-Li or $(CH_3)_2CH$ CuLi, $(CH_3)C$-Li or $(CH_3)C$-CuLi, C_6H_6-Li or C_6H_6CuLi.

Suitable hydroxylamines for reaction with compounds V to the Weinreb-amide are hydroxylamine, N,O-dimethylamine, N,O-diethylamine, N,O-diisopropylamine, N,O-dipropylamine, N,O-dibutylamine, N,O-diisobutylamine, preferably N,O-dimethylamine.

Suitable Grignard reagents are C_1-C_6-alkyl metal and C_6-C_{10}-aryl metal compounds, such as C_1-C_6-alkyl lithium, C_6-C_{10}-aryl lithium, C_1-C_6-alkyl magnesium halogenide, C_6-C_{10}-aryl magnesium halogenide. Examples of Grignard reagents are, for example, C_6H_5-Li, CH_3-Li, CH_3CH_2-Li, $CH_3(CH_2)_3$-Li, $(CH_3)_3C$-Li, C_6H_5-MgCl, C_6H_5-MgCl, CH_3-MgCl, CH_3-MgBr, CH_3-MgI, CH_3CH_2-MgCl, CH_3CH_2-MgBr, CH_3CH_2-MgI, $CH_3CH_2CH_2$-MgCl, $CH_3CH_2CH_2$-MgBr, $CH_3CH_2CH_2$-MgI, $(CH_3)_2CH$-MgCl, $(CH_3)_2CH$-MgBr, $(CH_3)_2CH$-MgI, $CH_3(CH_2)_3$-MgCl, $CH_3(CH_2)_3$-MgBr, $CH_3(CH_2)_3$-MgI, $CH_3CH(CH_2CH_3)$-MgCl, $CH_3CH(CH_2CH_3)$-MgBr, $CH_3CH(CH_2CH_3)$-MgI, $(CH_3)_3C$-MgCl, $(CH_3)_3C$-MgBr, $(CH_3)_3C$-MgI, $(CH_3)_2CHCH_2$-MgCl, $(CH_3)_2CHCH_2$-MgBr, and $(CH_3)_2CHCH_2$-MgI.

Compounds IX can be produced i.a. by reaction of compounds V with hydrogen catalyzed by a Lindlar catalyst, or by conversion to the Weinreb amide, as described above, and subsequent reduction with an inorganic hydride as listed above, preferably with lithium aluminium hydride.

Compounds VII may be converted to compounds VIIb,



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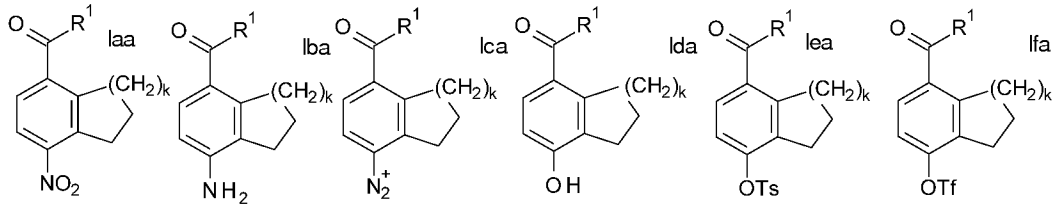
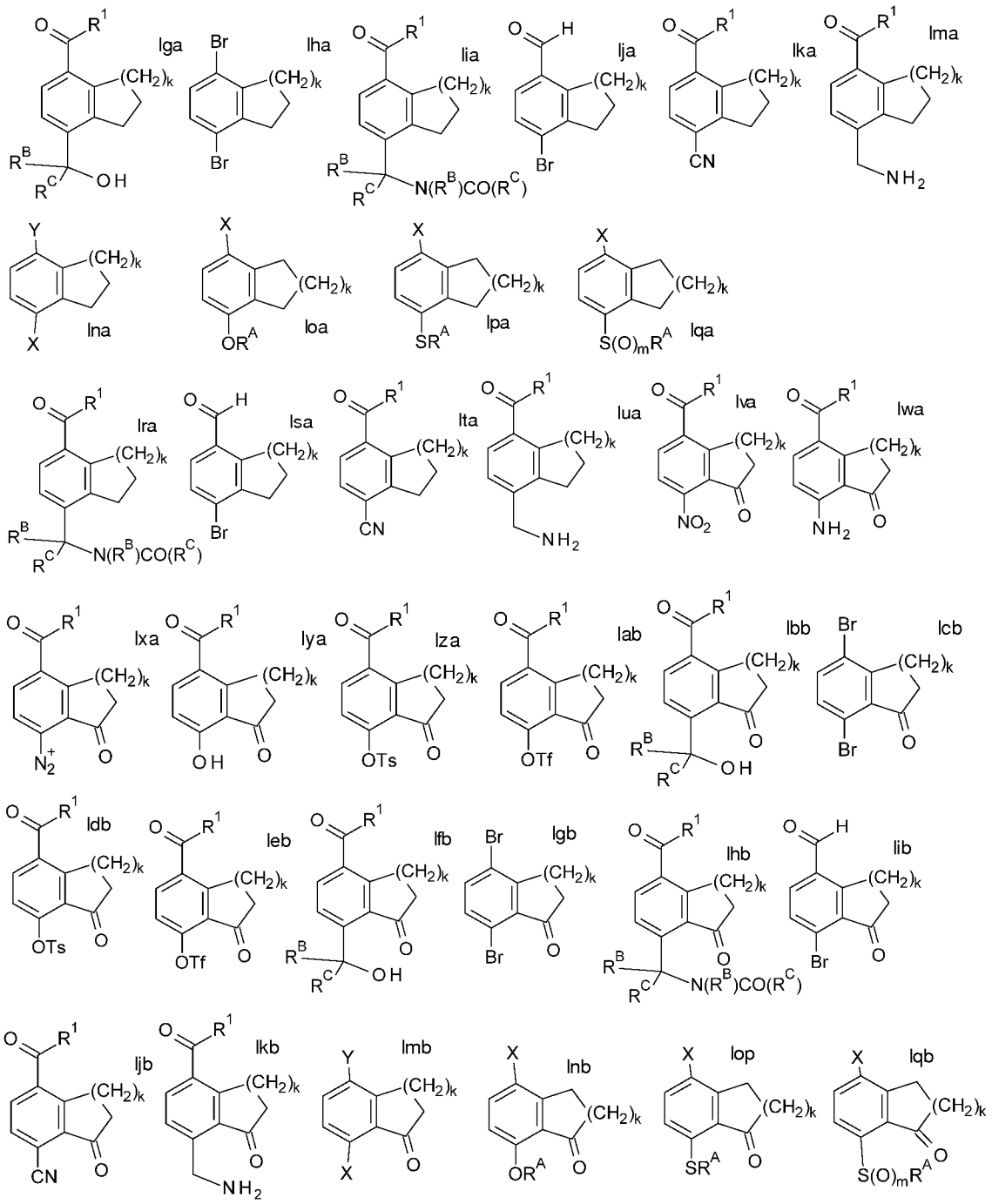
by processes as described above for the conversion of compounds II to compounds I, wherein X, and Y are independently from one another halogen, and k, R^{12}, and R^{13} have a meaning as defined for compounds I. Compounds VIIb may then again be further processed to compounds I with R^1 being $NR^{12}R^{13}$, by aminocarbonylation, as described in WO2008/145740.

Compounds I, IIb, IIc, VII, VIIb, VIII, and IX are precursors for a wide range of indane and tetralinyl derivatives. Examples of such derivatives are compounds Iaa to Ifd. The skilled person is able to devise suitable methods for the conversion of compounds IIb, IIc, VII, VIIb, VIII, and IX to compounds Iaa to Ifd by applying standard techniques of organic chemistry.

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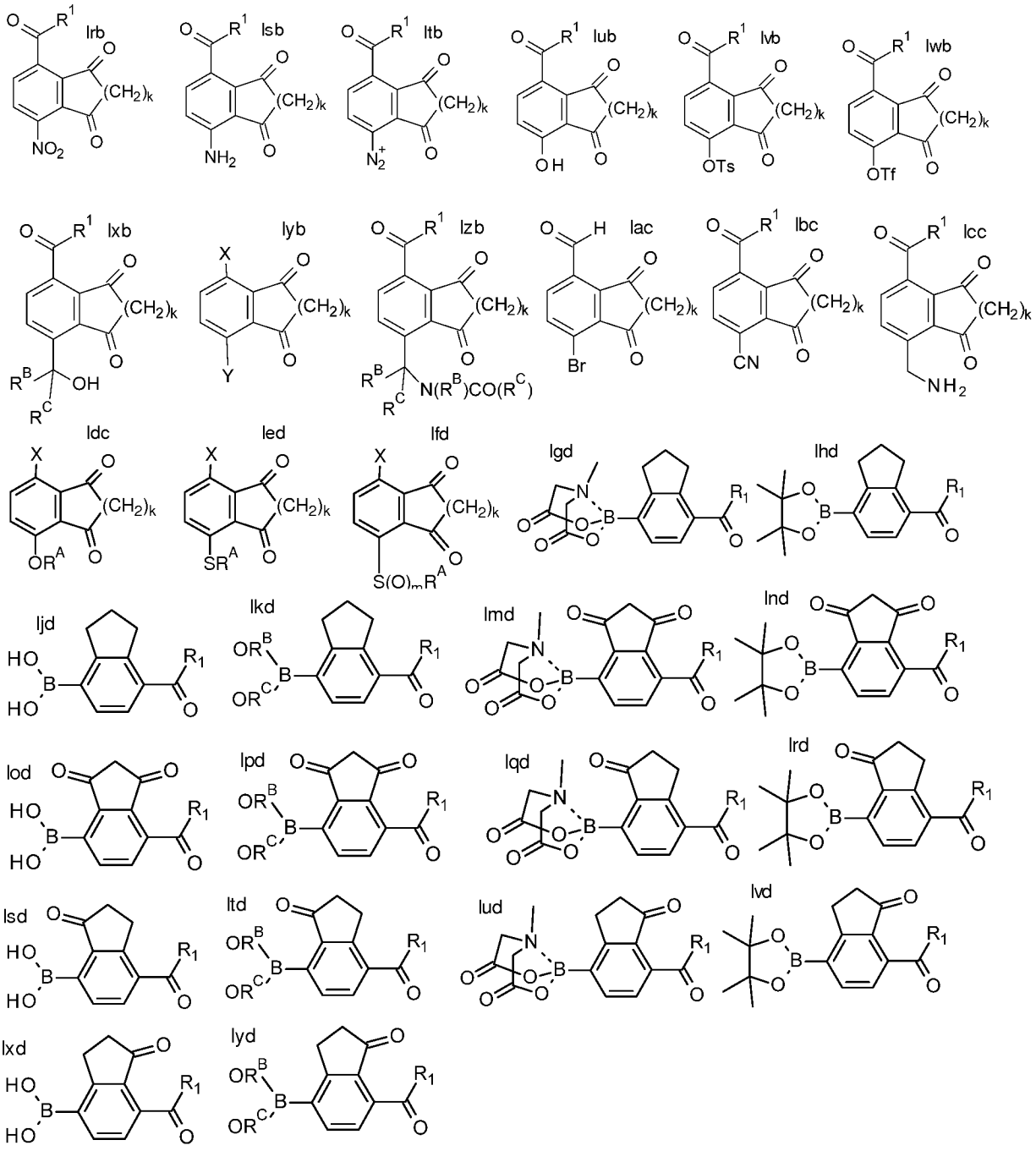
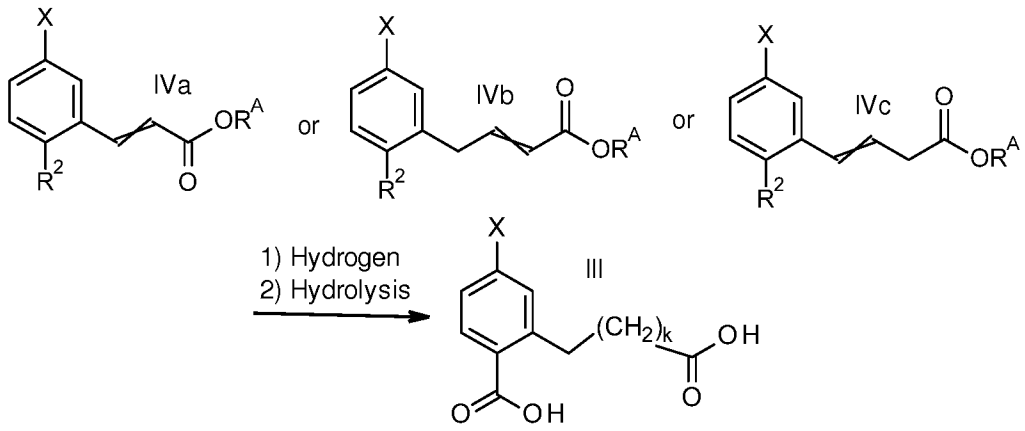


wherein all variables have a meaning as defined for compounds I.

Compounds III are produced by reaction of compounds IVa), IVb), or IVc) (collectively referred to as compounds IV) with hydrogen, followed by hydrolysis



wherein R^2 is CN, or C(=O)OR^A, as defined for compounds I. The crossed bond in the above depicted structures IVa, IVb, and IVc relates to both an E- and a Z-configuration. The process usually involves either a reducing metal or hydrogen gas, and a base, such as an inorganic base, or an acid, such as a mineral acid. Preferably, the process involves a transition metal and an acid.

The term "reaction with hydrogen" may relate to hydrogen gas, which is introduced into the reaction mixture.

The process is usually carried out at a pressure from 1 to 100 psi, preferably 10 to 60 psi, in an inert solvent, in the presence of a catalyst.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$, preferably CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3C(O)CH_3$, CH_3OCH_3, $CH_3CH_2OCH_2CH_3$, MTBE, and THF, $CHCl_3$, CH_2Cl_2, CCl_4.It is also possible to use mixtures of the solvents mentioned.

Suitable catalysts are metals or their salts, preferably transition metals or their salts, which may be poisoned, e.g. by addition of sulfur-containing compounds. Preferred metals are platinum, palladium, nickel, as well as their salts and oxides, such as PtO_2, Pd on active coal, or Raney-nickel. Reactions of this type have been described in England K. et al, Tetrahedron Letters, 2010 (51) 2849-2851.

The term "reaction with hydrogen" may also relate to an embodiment, wherein compounds IVa to IVc are reacted with hydrogen gas and/or nascent hydrogen that is produced in situ.

Surprisingly, it has been found that processes according to this embodiment show a lower amount of side reactions, e.g. dehalogenation, compared to other methods, e.g. reaction with hydrogen gas in the presence of a catalyst, wherein the hydrogen is introduced into the reaction mixture.

This process is usually carried out at temperatures of from 70 to 90 °C, more preferably from 75 to 85 °C, more preferably from 78 to 82 °C, in a protic solvent, in presence of a metal, and optionally at acidic pH, e.g. from 0 to 3.

The process may be carried out at temperatures of at least 65 °C, preferably 75 °C. The process may be carried out at temperatures up to 95 °C, preferably up to 85 °C.
Surprisingly, the reaction does not take place at temperatures below 60 °C, or only with a reduced speed, therefore making it less economically effective. Furthermore, it was unexpectedly discovered that at temperatures above 95 °C, major side reactions occur, thereby again making the process less economically effective.

On top, it was surprisingly found that this process does not lead to dehalogenation, which is a major side reaction under other reduction conditions, e.g. those involving hydrogen gas, which is introduced into the reaction mixture.

Suitable metals are selected from alkali metals, and alkaline earth metals, such as Li, Na, K, Rb, Cs, Mg, Ca, Sr, or Ba, metals of group 13, such as Al, and transition metals, such as Mn, Zn, Cr. In one embodiment, the metal is selected from alkali metals, alkaline earth metals, and transition metals.

Typical protic solvents are H_2O; C_1-C_4-alcohols, preferably CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, and $CH_3CH(OH)CH_3$; or an acid, preferably acetic acid, formic acid, HCl, H_2SO_4, or HNO_3. In one embodiment, the solvent is H_2O. In another embodiment, the solvent is acetic acid or HCl. In another embodiment, the solvent is an acid. It is also possible to use mixtures of the solvents mentioned.

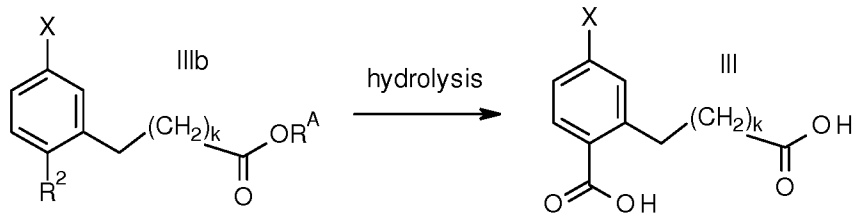
Preferably, the metal has a standard electrode potential below 0 at a pH below 7.0. For clarification, the redox potential at a pH below 7.0 relates to a setup of half-cells, wherein all conditions except for the pH are the same as for the measurement of the common standard electron potential. Hence, a metal with a redox potential at a pH below 7.0 will be able to donate electrons to protons and thus produce hydrogen. Preferred metals are Li, Na, K, Zn, more preferably Zn.

It has furthermore surprisingly been found, that repeated addition of metal leads to economic advantages, such as an enhanced kinetic profile, or higher yields. Thus, in one embodiment, the metal is added repeatedly portionwise after several points of time, preferably once at the beginning and once after 3 to 20 hours, preferably 5 to 15 hours.

Preferably, the hydrogen gas and/or nascent hydrogen is produced in situ from either a metal selected from alkali metals and alkaline earth metals, or a metal with a redox potential below 0 at a pH below 7.0.

In one embodiment, the process is carried out at temperatures from 75 to 85 °C, more preferably from 78 to 82 °C, in a protic solvent, in presence of a Zn.

The resulting compounds IIIb



may then be hydrolyzed to compounds III by alkaline or acidic hydrolysis.

This transformation is usually carried out at temperatures of from 50 to 200 °C, preferably from 80 to 150 °C, more preferably from 100 to 150 °C in the presence of a base, or an acid.

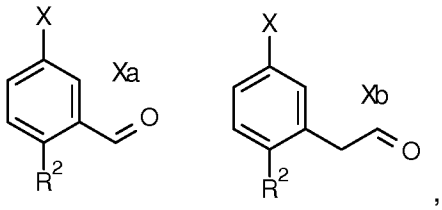
Suitable bases are, in general, inorganic bases, such as alkali metal and alkaline earth metal hydroxides, such as LiOH, NaOH, KOH and $Ca(OH)_2$, alkali metal and alkaline earth metal oxides, such as lithium oxide, sodium oxide, calcium oxide, and magnesium oxide, alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride, alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate, and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine, and also bicyclic amines.

Particular preference is given to inorganic bases, such as LiOH, NaOH, KOH, more preferably NaOH. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent.

Suitable acids and acidic catalysts are in general inorganic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulphuric acid und perchloric acid; Lewis acids, such as boron tri fluoride, aluminium tri chloride, iron-(III) chloride, tin-(IV) chloride, titanium-(IV) chloride and zinc-(II) chloride; moreover organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, toluene sulphonic acid, benzene sulphonic acid, camphor sulphonic acid, citric acid, and trifluoro acetic acid. Particular preference is given to inorganic acids and organic acids, most preferably mineral acids and acetic acid, and in particular sulfuric acid, and acetic acid.

The acids are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent.

Compounds IVa, or IVc, may be produced by olefination of compounds Xa, and compounds IVb may be produced by olefination of compounds Xb,



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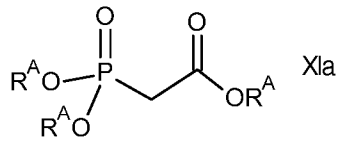
wherein X is halogen, and R^2 is CN or $C(=O)OR^A$, and R^A has a meaning as defined for compounds I. Typical olefination reactions include Peterson-olefinations, Wittig-reactions (as described in WO 2010/125130), Horner-Wadsworth-Emmons-reactions, or Julia-olefination, which

are all known to the skilled person. Compounds IVa and IVc can be produced by olefination of compounds Xa, while compounds IVb can be produced by olefination of compounds Xb.

This process is usually carried out by reaction with a phosphine, or a phosphonate in the presence of a base at temperatures of -100 to 20 °C, preferably from -80 to 10 °C, more preferably from -50 to 0 °C.

Suitable phosphonates are compounds of formula XIa



XIa

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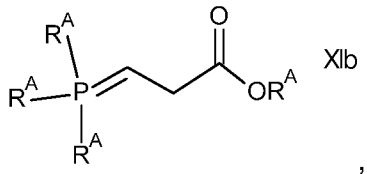
wherein each R^A may be independently selected and has a meaning as described for compounds I. Preferred phosphonates are di-C_1-C_6-alkylesters, di-C_6-C_{10}-arylesters, or mixed C_1-C_6-alkyl- and C_6-C_{10}-arylesters of phosphonates, e.g. dimethylphosphonates.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene, halogenated hydrocarbons, preferably halogenated C-C_6-alkanes and halogenated C_6-C_{10}-aromats, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF. Preferred solvents are ethers, such DME. It is also possible to use mixtures of the solvents mentioned.

Suitable phosphines are compounds of formula XIb



XIb

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wherein each R^A may be independently selected and has a meaning as described for compounds I. Preferred phosphines are phosphines with R^A bound to phosphorous being C_1-C_6-alkyl, mixed C_1-C_6-alkyl and C_6-C_{10}-aryl, such as triphenylphosphines, trimethylphosphines, triisopropylphosphines, preferably triphenylphosphines.

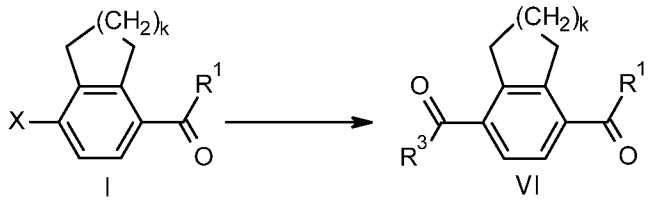
Suitable bases are, in general, inorganic compounds, such as alkali metal and alkaline earth metal hydroxides, such as LiOH, NaOH, KOH and $Ca(OH)_2$; alkali metal and alkaline earth metal oxides, such as lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate, and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine, and also bicyclic amines; and metalorganic bases, such as n-butyl lithium, tert-butyl lithium, phenyl lithium, lithium diisopropylamide (LDA), or lithium bis(trimethylsilyl)amide. Particular preference is given to n-butyl

lithium. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent.

Olefinations of the Horner-Wadsworth-Emmons-type are known from Li et al., Organic Letters 2013, (15) 6086-6089, Suppl. Inf.

Compounds XIa and XIb are either commercially available or can be produced from commercially available compounds by transesterfication, electrophilic substitution of a halogenide precursor etc.

The invention also relates to the production of compounds VI from compounds I,



wherein R^3 is H or CH_3.

In case R^3 is CH_3, compounds I are either reacted with a vinyl alcohol derivative, or magnesium, or a metal-halogen-transfer-reagent; and whereas in case R^3 is H, compound V is either reacted with magnesium, or a metal-halogen-transfer-reagent, or with carbon monoxide.

In particular, in case R^3 is CH_3, compounds I are

a) reacted with a vinyl alcohol derivative in the presence of a transition metal; or
b) they are reacted with magnesium or a metal-halogen-transfer-reagent, and an acetic acid derivative;

and in case R^3 is H, compounds I are

c) reacted with carbon monoxide, and a reducing agent; or
d) they are reacted with magnesium, or a metal-halogen-transfer-reagent, and a formamide.

In case R^3 is CH_3, compounds VI can be produced by either a cross-coupling reaction a), or by a Grignard reaction b) of compounds I.

Cross coupling reactions a) involve the reaction with a vinyl alcohol derivative.

Such cross coupling reactions are usually carried out in the presence of a catalyst, e.g. a transition metal such as Ni, Zn, Pd, Pt, preferably Pd, and a ligand L in an inert solvent by reaction with a vinyl alcohol derivative, and optionally in the presence of a base, preferably in the presence of a base. The transition metals are usually applied as salts, e.g. inorganic salts, or organic salts. In another embodiment, the cross coupling reactions are carried out in the presence of a base, a catalyst, e.g. a transition metal such as Ni, Zn, Pd, Pt, preferably Pd, and a ligand L in water by reaction with a vinyl alcohol derivative.

Suitable vinyl alcohol derivatives are vinyl alcohol, vinyl ethers, vinyl esters, vinyl amides, wherein the vinyl moiety may be substituted with a C_1-C_6-alkyl alkyl, C_1-C_6-haloalkyl, C_6-C_{10}-aryl, C_6-C_{10}-haloaryl, C_6-C_{10}-hetaryl, C_1-C_6-alkyl-C_6-C_{10}-aryl moiety. Preferred vinyl alcohol derivatives are vinyl alcohol, vinyl ethers and vinyl esters, such as vinyl alcohol, vinyl methyl ether, vinyl ethyl ether, vinyl isopropyl ether, vinyl n-propyl ether, vinyl n-butyl ether, vinyl tert-butyl

ether, vinyl sec.-butyl ether, 1-vinyloxypropan-1-ol, 2-vinyloxypropan-1-ol, 3-vinyloxypropan-1-ol, 1-vinyloxypropan-2-ol, 2-vinyloxypropan-2-ol, 3-vinyloxypropan-2-ol, 1-vinyloxypropan-3-ol, 2-vinyloxypropan-3-ol, 3-vinyloxypropan-3-ol, vinylacetate, and vinyl propionate, preferably vinyl alcohol, vinyl methyl ether, vinyl n-butyl ether, 3-vinyloxypropan-1-ol, and vinyl acetate, more preferably vinyl alcohol, 3-vinyloxypropan-1-ol, vinyl acetate, most preferably 3-vinyloxypropan-1-ol. In another embodiment, the vinyl alcohol derivative is a vinyl ether, preferably a ethylene glycol vinyl ether.

Suitable inert solvents for the reaction are aprotic polar and non-polar solvents. Typical solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF. The reaction is preferably carried out in aromatic hydrocarbons, (more preferably C_6-C_{10}-aromatic hydrocarbons), such as benzene, toluene, xylenes, cumene, or tert-butylbenzene, aprotic polar solvents, for example cyclic, or acyclic ethers, such as diethyl ether, tert-butyl methyl ether (MTBE), cyclopentyl methyl ether, THF or dioxane. In another embodiment, the reaction is carried out in water, thereby including aqueous mixtures with at least 10 wt% water with regard to the total mass of the reaction mixture.

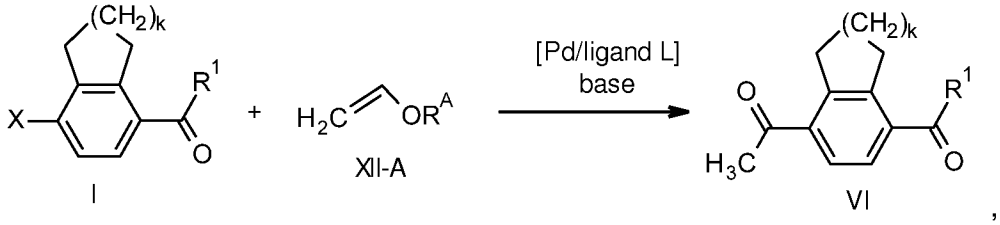
Typical Pd(II)-salts, which are converted to the catalytically active Pd(0) complex during the reaction, are PdO, $PdCl_2$, $PdBr_2$, PdI_2, $Pd(NO_3)_2$, $PdSO_4$, or $Pd(OAc)_2$, preferably $PdCl_2$ or $Pd(OAc)_2$, more preferably $Pd(OAc)_2$.

Suitable ligands L are phosphine derivatives, such as preferably mono-, bi- or tridentate phosphine derivatives, e.g. triphenylphosphine, tricyclohexylphosphine, phosphinooxazolines, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bis(diphenylphosphino) methane, bis(diphenylphosphino) ethane, diphenyl-2-pyridylphosphine, and 1,3-bis(di-iso-propylphosphino)propane, preferably triphenylphosphine, diphenyl-2-pyridylphosphine, and 1,3-bis(di-iso-propylphosphino)propane. In one embodiment, the ligand L is bis(diphenylphosphino) propane.

Suitable bases are inorganic bases and organic bases. Inorganic bases are usually 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; alkali metal bicarbonates, such as sodium bicarbonate; and silver hydroxides or silver carbonates. Organic bases are usually tertiary amines, such as trimethylamine, triethylamine, 4-N,N-dimethylaminopyridine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylamino-pyridine, and also bicyclic amines; alkali metal acetates, such as NaOAc, KOAc; moreover secondary amines, such as, tetramethylethylendiamine, tetramethylene diamine, piperidine, diisopropylamine, morpholine, preferably pyridine, 4-N,N-dimethylaminopyridine, diisopropylamine, Na_2CO_3, K_2CO_3, NaOAc, KOAc, Ag_2CO_3 and triethylamine, and most preferably K_2CO_3.

Typical cross-coupling reactions are Heck reactions, Stille reactions, Suzuki reactions, Negishi reaction, and Kumada reactions, which are known to the skilled person, also including typical reaction parameters, reactants etc, and which may be found in Metal-Catalyzed Cross-Coupling Reactions and More, de Meijere A., Wiley VCH, 2014.

In one embodiment compounds VI are produced by the following Heck reaction of compounds I with compounds XII-A



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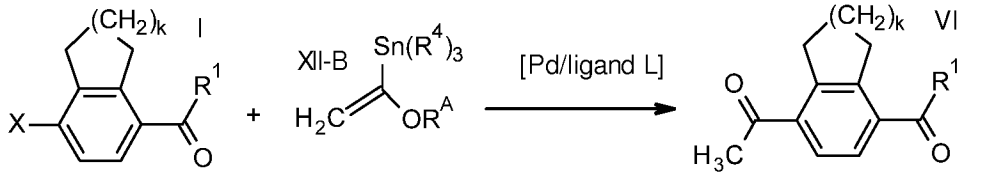
wherein R^A has the same meaning as defined for compounds I, preferably C_1-C_6-alkyl, which may be partially or fully substituted by OH, preferably C_1-C_4-alkyl, which may be partially substituted by OH, more preferably CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, or CH_2CH_2OH, and in particular CH_2CH_2OH.

The temperature for such cross coupling reactions is typically from 70 to 120 °C, preferably from 80 to 110 °C, most preferably from 85 to 95 °C. In one embodiment, the temperature is at least 60 °C. In another embodiment, the temperature is at most 110 °C.

In another embodiment compounds VI with R^3 being CH_3 are produced by the following Stille reaction of compounds I with compounds XII-B



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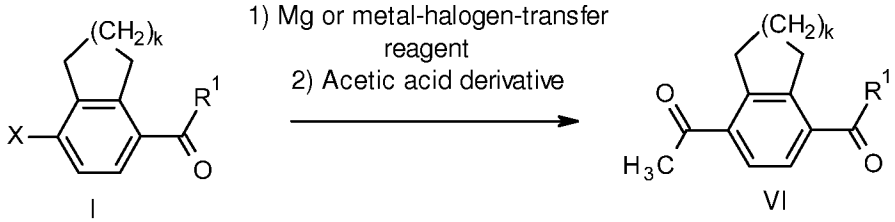
wherein R^A has the same meaning as defined for compounds I, preferably methyl or ethyl; and wherein each R^4 is independently a C_1-C_6 alkyl, C_1-C_6-cycloalkyl, or phenyl, preferably methyl, butyl, and phenyl, more preferably butyl.

Compounds VI with R^3 being CH_3 may also be produced via a Grignard reaction of compounds I:



This transformation is usually carried an aprotic polar or non-polar solvent in the presence of Mg, or a metal-halogen-transfer reagent, as well as of an acetic acid derivative, in a two-step process.

The reaction is preferably carried out at temperatures of from -78 to 110 °C. In general, the upper temperature limits the boiling point of the solvent in question when the reaction is carried out under atmospheric pressure. The first step of the reaction is preferably carried out at temperatures of -30 to 110 °C. The second step (electrophile addition) is preferably carried out at temperatures of -78 to 50 °C.

Suitable solvents for the reaction are aprotic polar and non-polar solvents. Typical solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF. The reaction is preferably carried out in aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as benzene, toluene, xylenes, cumene, chlorobenzene, nitrobenzene, or tert-butylbenzene, aprotic polar solvents, for example cyclic, or acyclic ethers, such as diethyl ether, tert-butyl methyl ether (MTBE), cyclopentyl methyl ether, THF or dioxane.

In case the reaction is carried out in the presence of magnesium, the magnesium can be activated by halogens organohalogenides, such as like iodine, bromine, dibromo ethane, monobromo ethane.

Metal-halogen-transfer reagents suitable for the reaction are C_1-C_6-alkyl metal and C_6-C_{10}-aryl metal compounds, such as C_1-C_6-alkyl lithium, aryl lithium, C_1-C_6-alkyl magnesium halogenide, C_6-C_{10}-aryl magnesium halogenide. In one embodiment, the metal-halogen-transfer reagent is C_1-C_6-alkyl lithium, or aryl lithium. Examples of metal-halogen-transfer reagents are, for example, C_6H_5-Li, CH_3-Li, CH_3CH_2-Li, $CH_3(CH_2)_3$-Li, $(CH_3)_3C$-Li, C_6H_5-MgCl, C_6H_5-MgCl, CH_3-MgCl, CH_3-MgBr, CH_3-MgI, CH_3CH_2-MgCl, CH_3CH_2-MgBr, CH_3CH_2-MgI, $CH_3CH_2CH_2$-MgCl, $CH_3CH_2CH_2$-MgBr, $CH_3CH_2CH_2$-MgI, $(CH_3)_2CH$-MgCl, $(CH_3)_2CH$-MgBr, $(CH_3)_2CH$-MgI, $CH_3(CH_2)_3$-MgCl, $CH_3(CH_2)_3$-MgBr, $CH_3(CH_2)_3$-MgI, $CH_3CH(CH_2CH_3)$-MgCl, $CH_3CH(CH_2CH_3)$-MgBr, $CH_3CH(CH_2CH_3)$-MgI, $(CH_3)_3C$-MgCl, $(CH_3)_3C$-MgBr, $(CH_3)_3C$-MgI, $(CH_3)_2CHCH_2$-MgCl, $(CH_3)_2CHCH_2$-MgBr, and $(CH_3)_2CHCH_2$-MgI.

The reaction is preferably carried out with CH_3-MgCl, CH_3-MgBr, CH_3CH_2-MgCl, CH_3CH_2-MgBr, $CH_3CH_2CH_2$-MgCl, $CH_3CH_2CH_2$-MgBr, $(CH_3)_2CH$-MgCl, $(CH_3)_2CH$-MgBr, $CH_3(CH_2)_3$-MgCl, $CH_3(CH_2)_3$-Br, $CH_3CH(CH_2CH_3)$-MgCl, $CH_3CH(CH_2CH_3)$-MgBr, $(CH_3)_3C$-MgCl, $(CH_3)_3C$-MgBr, $(CH_3)_2CHCH_2$-MgCl, or $(CH_3)_2CHCH_2$-MgBr.

The reaction is more preferably carried out with CH_3-MgCl, CH_3-MgBr, CH_3CH_2-MgCl, CH_3CH_2-MgBr, $CH_3CH_2CH_2$-MgCl, $CH_3CH_2CH_2$-MgBr, $(CH_3)_2CH$-MgCl, $(CH_3)_2CH$-MgBr, $CH_3(CH_2)_3$-MgCl, or $CH_3(CH_2)_3$-Br,

The reaction is most preferably carried out with CH_3-MgCl, CH_3-MgBr, $(CH_3)_2CH$-MgCl, $(CH_3)_2CH$-MgBr, $(CH_3)_3C$-MgCl, or $(CH_3)_3C$-MgBr, and in particular with $(CH_3)_2CH$-MgCl, or $(CH_3)_2CH$-MgBr.

In case the reaction is carried out with a C_1-C_6-alkyl magnesium halogenide, or a C_6-C_{10}-aryl magnesium halogenide, a lithium salt may be added, preferably LiCl.

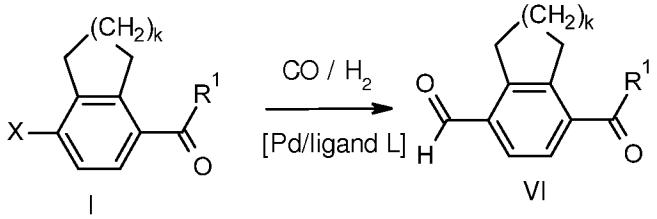
The acetic acid derivative may be an acetic acid ester (e.g. methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, phenyl ester), an acetic acid halogenide, e.g. chloride, acetic acid

bromide, or CH_3CN, preferably an acetic acid ester or acetic acid chloride, more preferably methyl acetate, ethyl acetate or acetic acid chloride, most preferably acetic acid chloride.

The magnesium, or the metal-halogen-transfer reagent is preferably employed in a molar ratio of from 0.9 to 2 mol per mol of the compounds I. Preferably, from 0.9 to 1.2 mol, in particular from about 0.95 to 1.1 mol, of magnesium or a metal-halogen-transfer reagent are employed per mol of compounds I.

The acetic acid derivatives are preferably employed in a molar ratio of from 0.9 to 5 mol per mol of compounds I. Preferably, from 0.9 to 2 mol, in particular from about 0.95 to 1.5 mol, of acetic acid derivatives are employed per mol of the compounds I.

Compounds VI with R^3 being H may be produced form compounds I by various methods, which were generally described in Natte et. al., Angewandte Chemie, 2014, (53) 10090-10094; Neumann et al, Chemistry Asian Journal, 2012, (7) 2213-2216; Ashfield et al, Organic Process Research and Development, 2007, (11) 39-43; Pétrier et al., Tetrahedron Letters, 1982, (23) 3361-3364, and Jiang et al., Journal of Chemical Research, 2014, (38) 218-222, such as reductive carbonylation a) or the Bouveault-aldehyde formation b).



I VI

Reductive carbonylation c) is carried out by reaction with carbon monoxide (CO). Usually, reductive carbonylation is carried out in the presence of a metal, preferably a transition metal, a ligand L, carbon monoxide, as well as a reducing agent.

Typical reducing agents are H_2, formic acid or its salts. The total gas pressure is usually from 1 to 20 bar, preferably from 2 to 15 bar, more preferably from 2 to 7 bar and the temperature is from 50 to 150 °C, preferably from 70 to 130 °C.

For example, compounds VI may be produced by reductive carbonylation of compounds I with carbon monoxide (CO) and hydrogen (H_2) by palladium catalysis.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; preferably aromatic solvents such as benzene or toluene. It is also possible to use mixtures of the solvents mentioned.

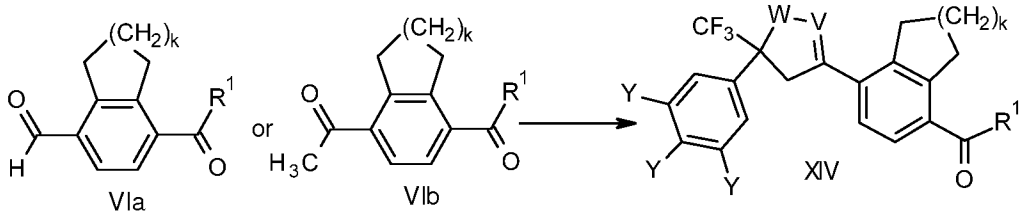
Suitable gas ratios of CO to H_2 are from 40: 60 to 60:40, preferably 50:50. The gas pressure may be from 1 to 20 bar, preferably 1 to 10 bar. Suitable Pd(II)-salts and ligands L are those described for the cross couplings above.

Bouveault-aldehyde formation d) usually involves the reaction with magnesium, or a metal-halogen transfer agent, as described above in an inert solvent, and the subsequent reaction with a formamide.

Suitable formamides are formamide and N-akylformamides, such as methylformamide, DMF, phenylformamide.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; preferably C_5-C_{16}-alkanes, or C_6-C_{10}-aromatic hydrocarbons.
It is also possible to use mixtures of the solvents mentioned.

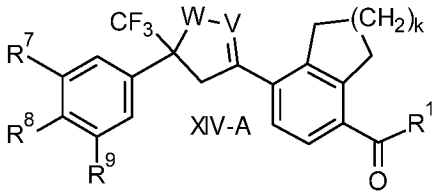
Compounds I, or compounds VI are intermediates for the manufacture of the insecticidal compounds XIV



,

wherein each Y is independently a halogen, V is selected from CH and N, W is selected from O, S and CH_2, and R^1 and k have a meaning as defined for compounds I.

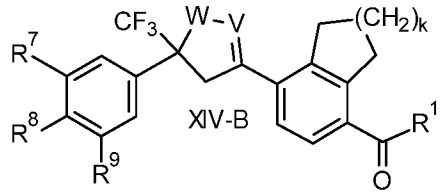
In one embodiment, compounds I, or compounds VI are intermediates for the manufacture of insecticidal compounds XIV-A



,

wherein V is selected from CH, N, and NO, W is selected from O, S and CH_2, R^1 and k have a meaning as defined for compounds I, and R^7, R^8, and R^9 are independently hydrogen, halogen, halomethyl, or halomethoxy, wherein at most two substituents R^7, R^8, and R^9 are H.

In yet another embodiment, compounds I and VI are intermediates for the manufacture of insecticidal compounds XIV-B



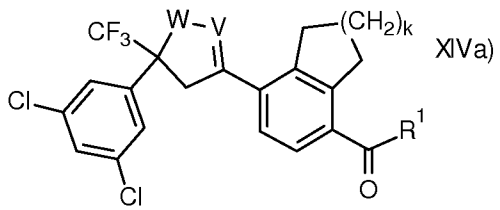
wherein R^7, R^8, and R^9 correspond to a line A-1 to A-31 of Table 1:

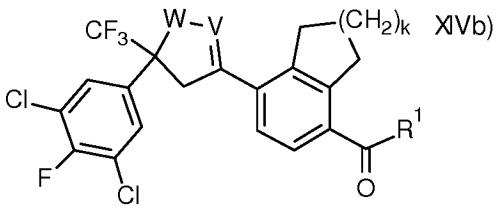
Table 1:

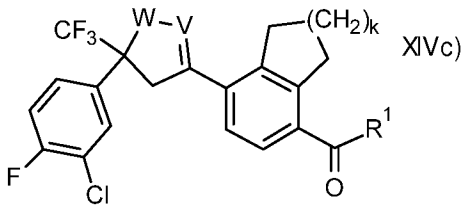
No.	R^7	R^8	R^9
A-1	F	H	F
A-2	F	F	F
A-3	F	Cl	F
A-4	F	Br	F
A-5	F	H	Cl
A-6	F	H	Br
A-7	Cl	H	Cl
A-8	Cl	Cl	Cl
A-9	Cl	F	Cl
A-10	Cl	Br	Cl
A-11	Cl	H	Br
A-12	Br	H	Br
A-13	Br	F	Br
A-14	Br	Cl	Br
A-15	CF_3	H	F
A-16	CF_3	H	Cl
A-17	CF_3	H	Br
A-18	CF_3	H	CF_3
A-19	CF_3	F	F
A-20	CF_3	Cl	Cl
A-21	CF_3	Br	Br
A-22	OCF_3	H	F
A-23	OCF_3	H	Cl
A-24	OCF_3	H	Br
A-25	OCF_3	H	CF_3
A-26	OCF_3	H	H
A-27	CF_3	H	H
A-28	Br	H	H
A-29	Cl	H	H
A-30	F	H	H
A-31	Cl	F	H

In one embodiment, compounds of lines A-19, A-22, A-23, and A-24 are manufactured from compounds I and VI. Compounds XV, and XV-B, fall under the definition of compounds XV-A and are thus preferred embodiments of XV-A for all compounds and reactions disclosed herein.

In one embodiment, insecticidal compounds XIV-A that are manufactured from compounds I, or compounds VI are selected from


XIVa)

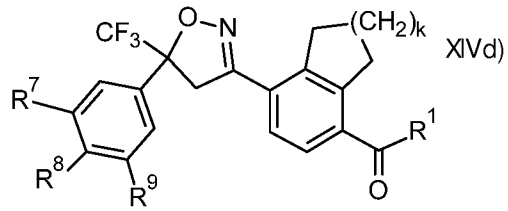

XIVb)

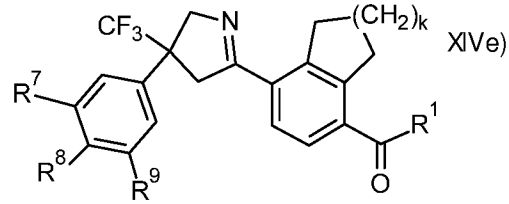

XIVc)

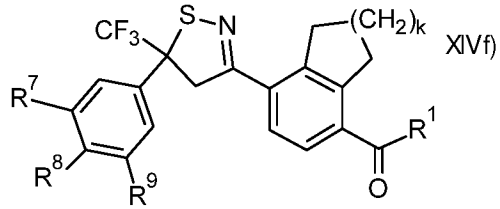
,

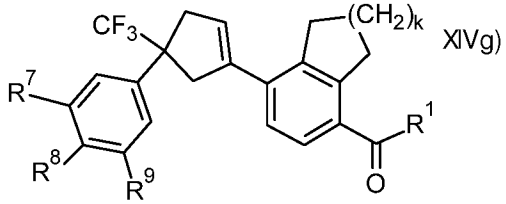
wherein all variables have a meaning as defined for compounds XIV.

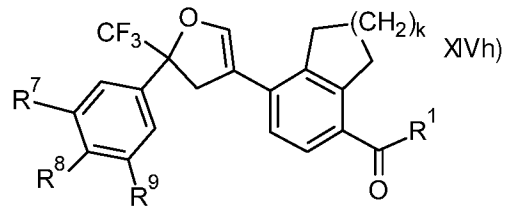
In another embodiment, insecticidal compounds XIV-A that are manufactured from compounds I, or compounds VI are selected from

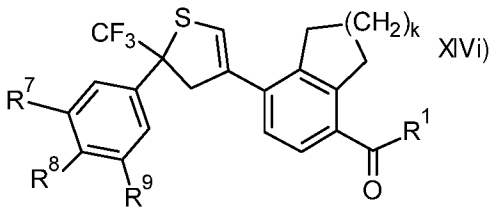

XIVd)


XIVe)


XIVf)


XIVg)


XIVh)

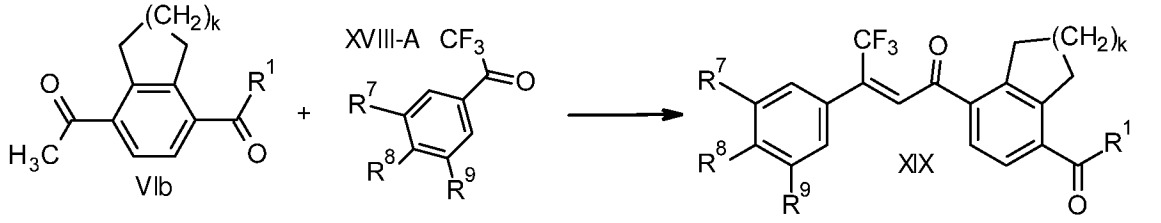

XIVi)

where all variables have a meaning as defined for compounds XIV-A. In one embodiment, R^7, R^8, and R^9 are independently selected from halogen.

In yet another embodiment, insecticidal compounds XIV-A are selected from compounds XIVd, XIVe, XIVf, and XIVg. In yet another embodiment, insecticidal compounds XIV-A are selected from compounds XIVd to XIVi. In yet another embodiment, insecticidal compounds XIV-A are compounds XIVj. In yet another embodiment, insecticidal compounds XIV-A are compounds XIVh.

Suitable manufacture processes to yield insecticidal compounds XIV-A from compounds VI are disclosed in WO2010/125130 and WO2015128358, WO2014206908, EP2172462, and WO2014206910.

The process for the production of compounds XIV-A from compounds I, or compounds VI may involve the condensation of compounds I, or compounds VI, with acetophenone compounds XVIII-A to compounds XIX.



,

where all the variables have a meaning as defined for compounds XIV-A.

This transformation is usually carried out at temperatures of from 100 to 140 °C, preferably from 110 to 130 °C, in an inert solvent, in the presence of a base.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; preferably halogenated hydrocarbons, in particular dichloroethane. 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also bicyclic amines. Particular preference is given to alkali metal and alkaline earth metal carbonates, as well as tertiary amines, in particular K_2CO_3, and triethylamine. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

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 XIII, based on Vib).

Compounds XIX may then be reacted with hydroxylamine to the isoxazoline compounds XIV-A, wherein V is N, and W is O. This transformation is usually carried out at temperatures of from 10 to 50 °C, preferably from 20 to 30 °C, in an inert solvent, in the presence of a catalyst, and a base.

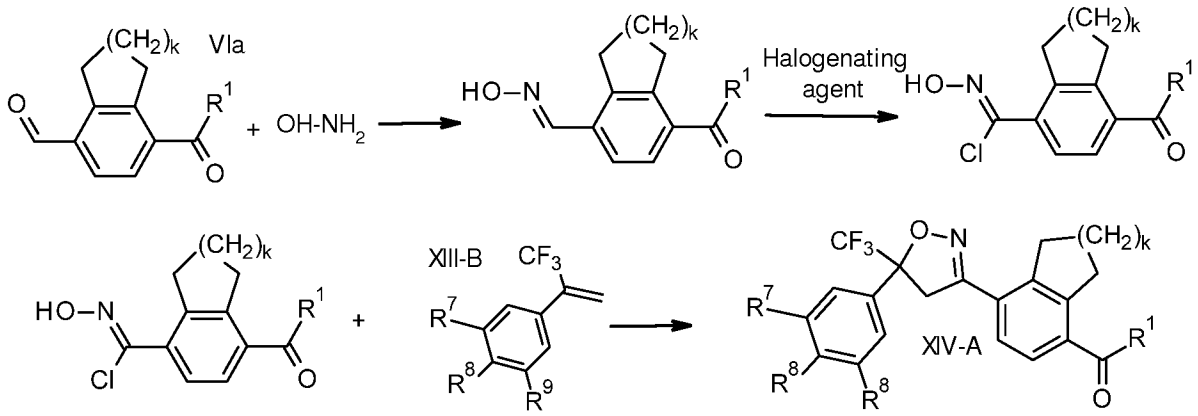
Suitable solvents are aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons such as methylene chloride, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; preferably halogenated hydrocarbons, in particular dichloroethane. 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also bicyclic amines. Particular preference is given to alkali metal and alkaline earth metal hydroxides, such as LiOH, NaOH and KOH, preferably NaOH. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

Suitable catalysts are phase transfer catalysts, such as quaternary amines, for example tetra-n-butyl ammonium chloride, benzalkonium chloride, cetyl alkonium chloride, cetyl pyridinium chloride; and crown ethers, for example 12-crown-4, 15-crown-5, 18-crown-6, dibenzo-18-crown-6, and diaza-18-crown-6. Particular preference is given to quaternary amines, preferably tetra-n-butyl ammonium chloride.

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 XIX.

Alternatively, aldehyde compounds VIa may be reacted with hydroxylamine directly, followed by reaction with a halogenating agent, and a 1,3-bipolar addition reaction with compounds XIII-B to isoxazoline compounds XIV-A, as described in Example S.6 of WO2010/125130.



wherein all variables have a meaning as defined for compounds XIV-A.

Preparation of the oxime from compounds VIa) is usually carried out at temperatures of from 10 to 40 °C, preferably from 20 to 30 °C, in an inert solvent in the presence of hydroxylamine, as described in Galvis et al., Org. Biomol. Chem., 2013, (11) 407-411, Supplementary Information.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover water DMSO, DMF, and DMA; preferably alcohols and water, in particular ethanol and water. It is also possible to use mixtures of the solvents mentioned.

Halogenation of the oxime to the hydroxamic acid is usually carried out at temperatures of from 50 to 90 °C, preferably from 60 to 80 °C, in an inert solvent in the presence of a halogenating agent.

Typical halogenating agents are oxalylchloride, thionylchloride, phorphortri- and pentachloride, phosphortri- and pentabromide, N-chlor- and N-bromosuccinimide, preferably thionylchloride, or N-chlor succinimmide.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; moreover DMSO, DMF, and DMA; preferably DMF. It is also possible to use mixtures of the solvents mentioned.

Reaction of the hydroxamic acid halogenide with compounds XIII-B is usually carried out at temperatures of from -10 to 20 °C, preferably from -5 to 5 °C, in an inert solvent in the presence of a base.

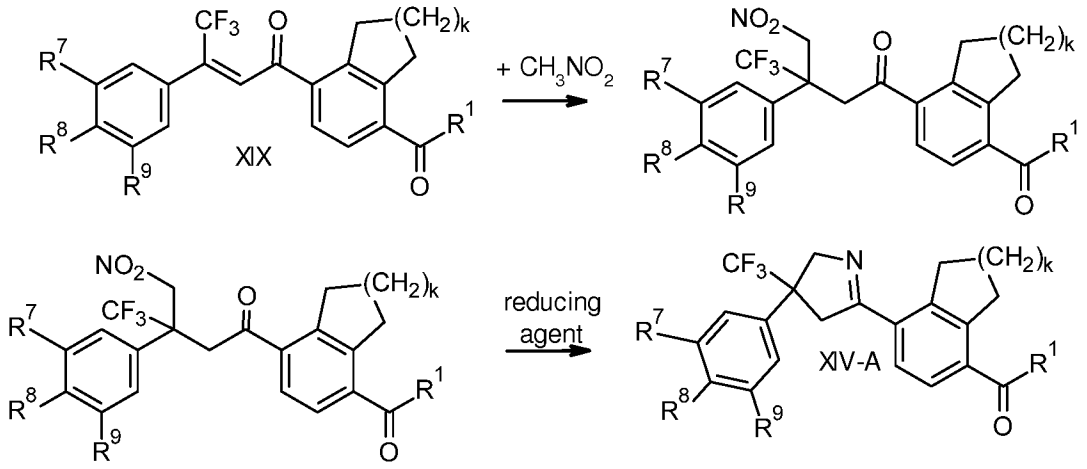
Suitable solvents are aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons such as toluene, o-, m-, and p-xylene; halogenated hydrocar-

bons such as methylene chloride, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; moreover DMF, and DMA; preferably DMF. 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also bicyclic amines. Particular preference is given to organic bases, in particular tertiary amines. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

Isothiazoline compounds XIV-A, wherein V is N, and W is S, may be manufactured by the methods disclosed in WO2014/206911, Synthesis Example S.1.

Pyrroline compounds XIV-A, wherein V is N, and W is CH_2, may be manufactured by reacting compounds XIX with nitromethane, followed by reduction with a suitable reducing agent.



wherein all variables have a meaning as defined for compounds XIV-A.

The reaction of compounds XIX with nitromethane is usually carried out at temperatures of from -10 to 20 °C, preferably from -5 to 5 °C, in an inert solvent in the presence of a base.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane;

nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMF, and DMA; preferably nitriles, and in particular acetonitrile. 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also polycyclic amines, such as 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo[5.4.0]un-dec-7-ene. Particular preference is given to organic bases, in particular polycyclic amines, such as 1,8-diazabicyclo[5.4.0]un-dec-7-ene. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

Reduction of the nitromethylated product to compounds XIV-A is usually carried out at temperatures of from 60 to 100 °C, preferably from 70 to 90 °C, in an inert solvent in the presence of an acid, and a reducing agent.

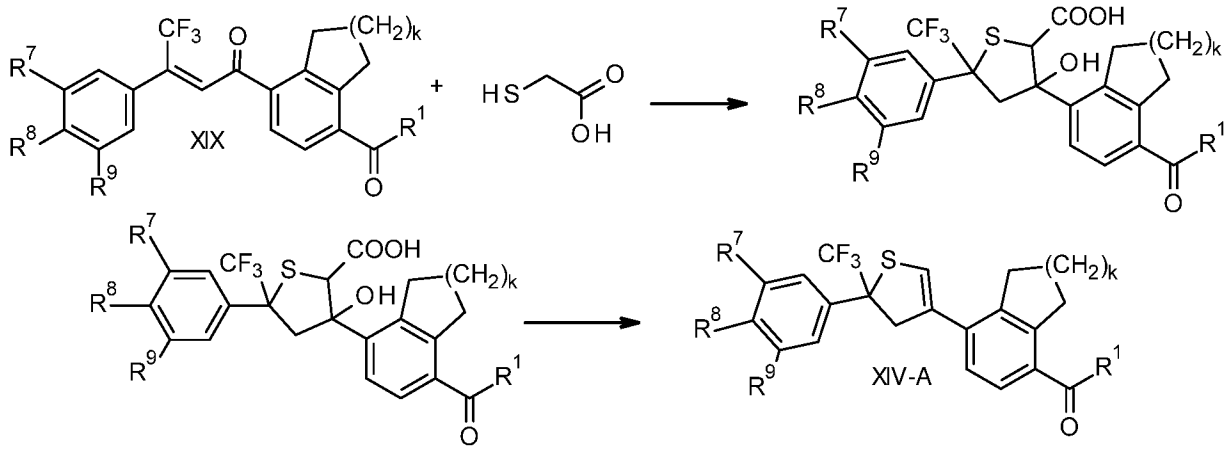
Suitable solvents are aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons such as methylene chloride, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover water, DMSO, DMF, and DMA; preferably alcohols, and in particular CH_3OH. It is also possible to use mixtures of the solvents mentioned.

Suitable reducing agents are metals, for example alkaline metals, earth alkaline metals, and transition metals of period 4, metal salts metal oxides, such as salts or oxides of copper, tin, and lead; inorganic hydrides, such as NaH, $NaBH_4$, and $LiAlH_4$, alcohols, such as CH_3OH, CH_3CH_2OH, and $CH_3CH(OH)CH_3$; phosphines, such as triphenylphosphine, and trimethylphosphine; and other such as sulfite, dithionite, thiosulfate, hydrazine, aldehydes, preferably metals and inorganic hydrides, more preferably transition metals, such as Fe, Al, or Zn, in particular Fe.

Suitable acids are in general inorganic acids, such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulphuric acid und perchloric acid; moreover organic acids, such as formic acid, acetic acid, propionic acid, oxalic acid, toluene sulphonic acid, benzene sulphonic acid, camphor sulphonic acid, citric acid, and trifluoro acetic acid; preferably organic acids, and in particu-

lar acetic acid. The acids are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent.

Dihydrothiphene compounds XIV-A, wherein V is CH, and W is S, may be manufactured by reacting compounds XIX with 2-sulfanylacetic acid, followed by an elimination reaction.



wherein all variables have a meaning as defined for compounds XIV-A.

Reaction of compounds XIX with 2-sulfanylacetic acid is usually carried out at temperatures of 10 to 40 °C, preferably from 15 to 30 °C in an inert solvent in the presence of a base.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; preferably ethers, and in particular THF. 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also polycyclic amines, such as 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo[5.4.0]un-dec-7-ene. Particular preference is given to organic bases, in particular tertiary amines, such as trimethylamine. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

The subsequent elimination reaction to dihydrothiophene compounds XIV-A is usually carried out in two steps. Step one may be carried out at temperatures of -20 to 40 °C, preferably from -10 to 10 °C in an inert solvent in the presence of a base and an acid halgenide.

Suitable acid halogenides are halogenides of organic acids with a pKa below 5, preferably below 2, such as mesyl chloride, tosyl chloride.

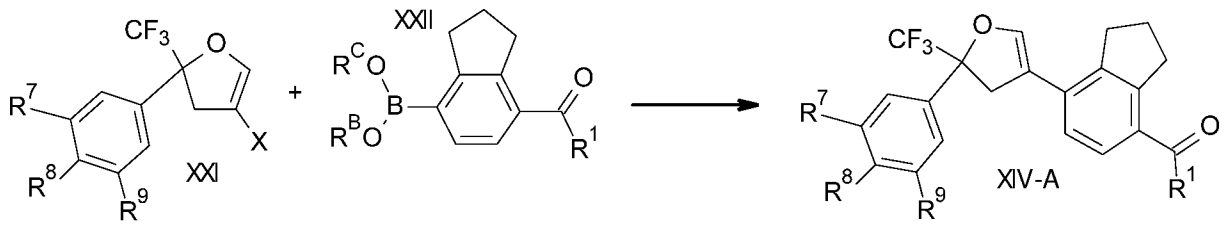
Suitable solvents in step one are aliphatic hydrocarbons such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons such as methylene chloride, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. In one embodiment, no solvent is used apart from the base.

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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; and also alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine; substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine; and also polycyclic amines, such as 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo[5.4.0]un-dec-7-ene. Particular preference is given to organic bases, in particular tertiary amines, such as pyridine. The bases are generally employed in catalytic amounts; however, they can also be used in equimolar amounts, in excess or, if appropriate, as solvent. It is also possible to use mixtures of the bases mentioned.

Step two may be carried out at temperatures of 100 to 150 °C, preferably from 110 to 130 °C in an inert solvent.

Suitable solvents in step two 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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; in particular DMF. It is also possible to use mixtures of the solvents mentioned.

Dihydrofurane compounds XIV-A may be produced by reaction of compounds XXI with compounds XXII



wherein X, R^1, and R^C have a meaning as defined for compounds I, and wherein all other variables have a meaning as defined for compounds XIV-A.

The reaction of compounds XXI and compounds XXII to compounds XIV-A is usually carried out in the presence of a transition metal, such as Ni, Zn, Pd, Pt, preferably Pd, and a ligand L in an inert solvent in the presence of a base. The transition metals are usually applied as salts, e.g. inorganic salts organic salts.

Suitable inert solvents for the reaction are aprotic polar and non-polar solvents. Typical solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_6-C_{10}-aromatic hydrocarbons, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF, nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones such as C_1-C_6-alkyl-C_1-C_6-alkyl ketones, C_1-C_6-alkyl-C_6-C_{10}-aryl ketones, and C_6-C_{10}-aryl-C_6-C_{10}-aryl-ketones, $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; DMSO, DMF, water, and DMA, preferably DMF, or water, most preferably a mixture of DMF and water, or DMF, and in particular DMF.

Typical Pd(II)-salts, which are converted to the catalytically active Pd(0) complex during the reaction, are PdO, $PdCl_2$, $PdBr_2$, PdI_2, $Pd(NO_3)_2$, $PdSO_4$, or $Pd(OAc)_2$, preferably $PdCl_2$ or $Pd(OAc)_2$, more preferably $Pd(OAc)_2$.

Suitable ligands L are phosphine derivatives, such as preferably mono-, bi- or tridentate phosphine derivatives, e.g. triphenylphosphine, tricyclohexylphosphine, phosphinooxazolines, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bis(diphenylphosphino) methane, bis(diphenylphosphino) ethane, diphenyl-2-pyridylphosphine, and 1,3-bis(di-iso-propylphosphino)propane, preferably triphenylphosphine, diphenyl-2-pyridylphosphine, and 1,3-bis(di-iso-propylphosphino)propane. In one embodiment, the ligand L is bis(diphenylphosphino) ethane.

Suitable bases are inorganic bases and organic bases. Inorganic bases are usually 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate; alkali metal bicarbonates, such as sodium bicarbonate; and silver hydroxides or silver carbonates. Organic bases are usually tertiary amines, such as trimethylamine, triethylamine, 4-N,N-dimethylaminopyridine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylamino-pyridine, and also bicyclic amines; alkali

metal acetates, such as NaOAc, KOAc; moreover secondary amines, such as, tetramethylethylendiamine, tetramethylene diamine, piperidine, diisopropylamine, morpholine, preferably alkali metal and alkaline earth metal hydroxides.

Compounds XXI are available by the methods described in WO2013/026726, or by derivatization of the compounds disclosed in therein. Compounds XXII may be produced from compounds I by processes described in WO2013/026726.

Typically, the reaction of compounds I to compounds XII is carried out in the presence of a boronic acid, a base, a transition metal such as Ni, Zn, Pd, Pt, preferably Pd, and a ligand L in an inert solvent. The transition metals are usually applied as salts, e.g. inorganic salts organic salts.

Suitable inert solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-hydrocarbons, such as toluene, o-, m-, and p-xylene; ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles such as CH_3CN, and propionitrile; ketones such as C_1-C_6-alkyl-C_1-C_6-alkyl ketones, C_1-C_6-alkyl-C_6-C_{10}-aryl ketones, and C_6-C_{10}-aryl-C_6-C_{10}-aryl-ketones, $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover dimethyl sulphoxide (DMSO), dimethyl formamide (DMF), and dimethylacetamide (DMA), preferably DMF.

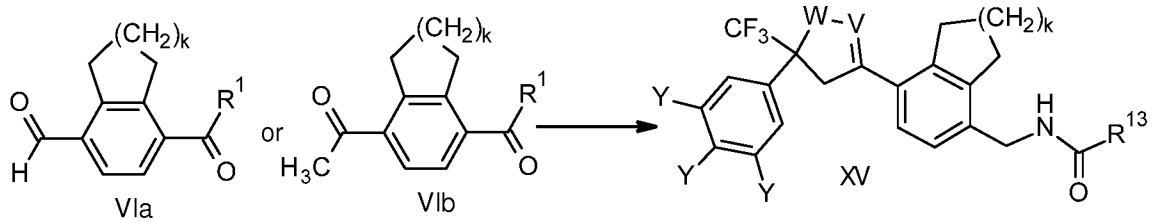
Typical Pd(II)-salts, which are converted to the catalytically active Pd(0) complex during the reaction, are PdO, $PdCl_2$, $PdBr_2$, PdI_2, $Pd(NO_3)_2$, $PdSO_4$, or $Pd(OAc)_2$, preferably $PdCl_2$ or $Pd(OAc)_2$, more preferably $PdCl_2$.

Suitable ligands L are phosphine derivatives, such as preferably mono-, bi- or tridentate phosphine derivatives, e.g. triphenylphosphine, tricyclohexylphosphine, phosphinooxazolines, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bis(diphenylphosphino) methane, bis(diphenylphosphino) ethane, diphenyl-2-pyridylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, and 1,3-bis(di-iso-propylphosphino)propane, preferably 1,1'-bis(diphenylphosphino)ferrocene.

Suitable bases are inorganic bases and organic bases. Inorganic bases are usually 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide; alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal and alkaline earth metal carbonates, such as lithium carbonate, sodium carbonate, potassium carbonate and calcium carbonate; alkali metal bicarbonates, such as sodium bicarbonate; and silver hydroxides or silver carbonates. Organic bases are usually tertiary amines, such as trimethylamine, triethylamine, 4-N,N-dimethylaminopyridine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylamino-pyridine, and also bicyclic amines; alkali metal acetates, such as NaOAc, KOAc; moreover secondary amines, such as, tetramethylethylendiamine, tetramethylene diamine, piperidine, diisopropylamine, morpholine, preferably alkali metal and alkaline earth metal carbonates, such as sodium carbonate.

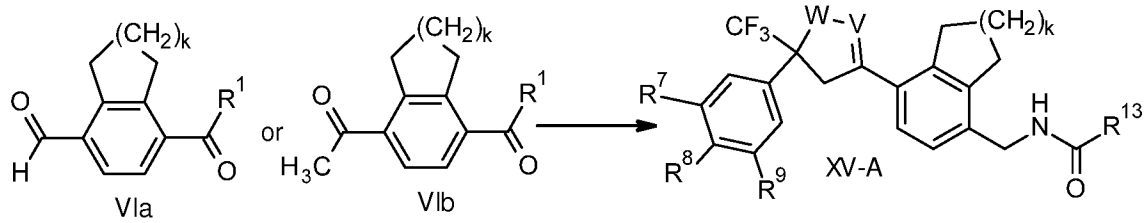
Suitable boronic acids are derivatives of hypodiboric acid, such as bis(pinacolato)diboron, or tetramethyldiboron, preferably bis(pinacolato)diboron.

Compounds I, VI, and XIV are also intermediates for the manufacture of insecticidal compounds of formula XV



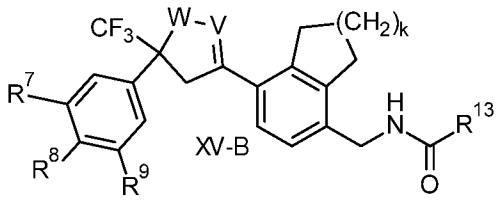
wherein each Y is independently a halogen, V is selected from CH and N, W is selected from O, S and CH_2, and R^1, R^{13} and k have a meaning as defined for compounds I. The meaning of the variables V, W, and Y, may have a meaning as defined for compounds XIV.

Compounds I, VI, and XIV-A are also intermediates for the manufacture of insecticidal compounds of formula XV-A



wherein V is selected from CH, N, and NO, W is selected from O, S and CH_2, and R^1, and R^7, R^8, and R^9 are independently H, halogen, halomethyl, or halomethoxy, wherein at most two substituents R^7, R^8, and R^9 are H, and R^{13} and k have a meaning as defined for compounds I. The meaning of the variables V, W, R^7, R^8, or R^9, may have a meaning as defined for compounds XIV, or XIV-A.

Compounds I and VI, and XIV-B are also intermediates for the manufacture of insecticidal compounds XV-B



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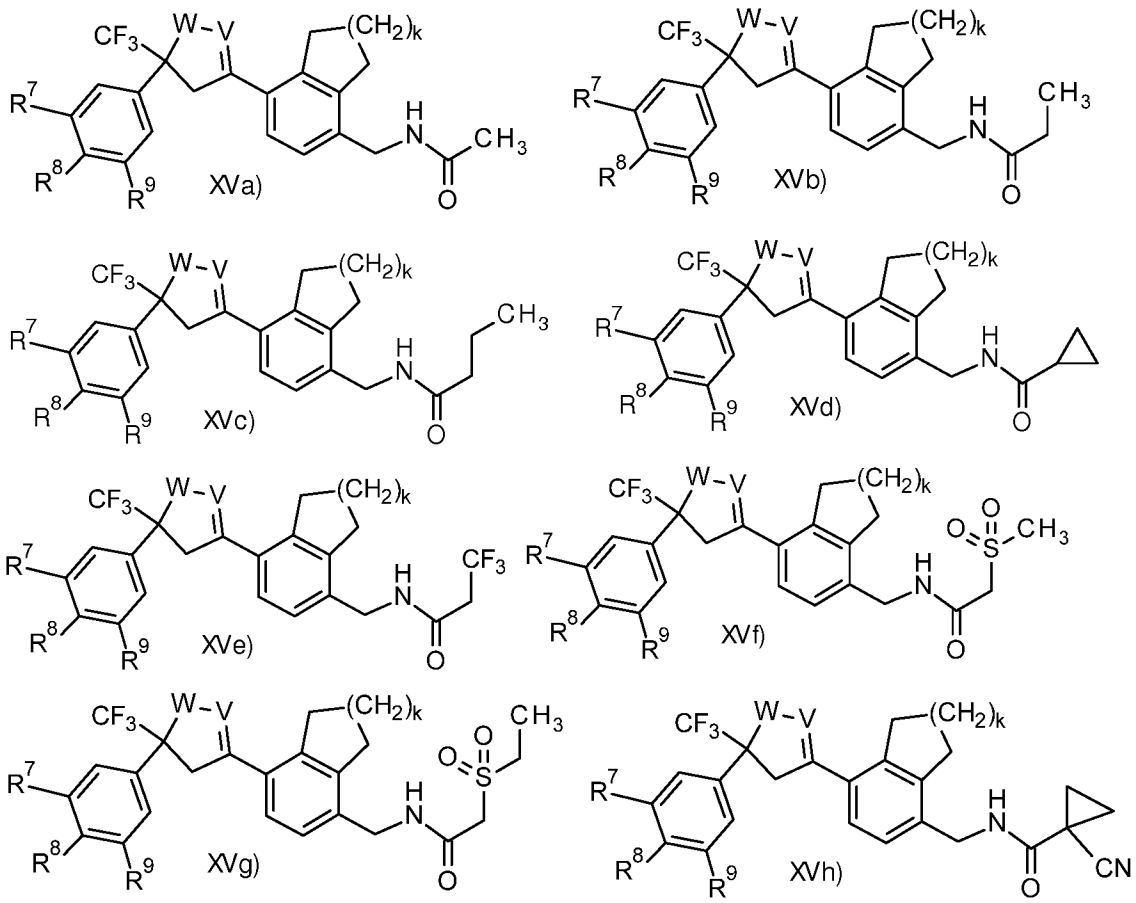
wherein V is selected from CH, N, and NO, W is selected from O, S and CH_2, R^{13} and k have a meaning as defined for compounds I, and R^7, R^8, and R^9 are selected from a line A-1 to A-31 of Table 1. Compounds XV, and XV-B fall under the definition of compounds XV-A and are thus preferred embodiments of XV-A for all compounds and reactions disclosed herein.

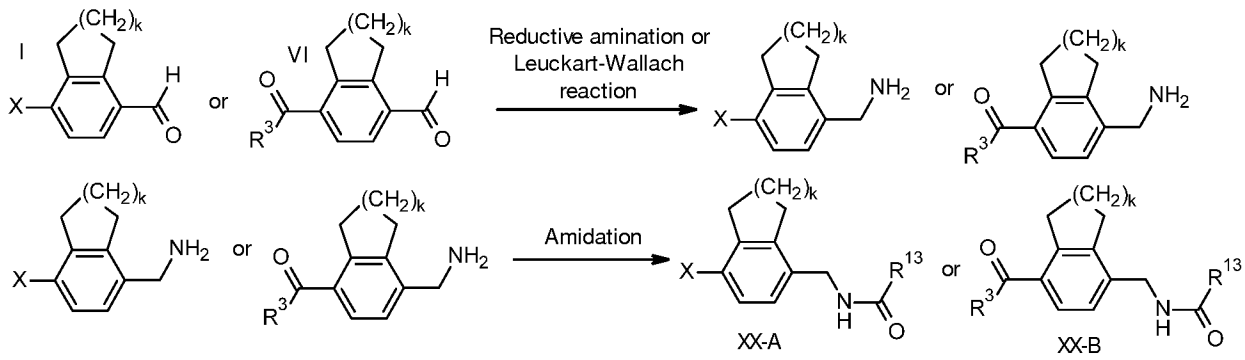
In one embodiment, compounds XV-A are selected from



where all variables have a meaning as defined form compounds XV-A. In another embodiment, R^7, R^8, and R^9 are independently halogen.

In another embodiment, compounds XV-A are selected from compounds XVa to XVg. In another embodiment, compounds XV-A are compounds XVh.

Suitable manufacture processes including suitable reaction conditions of insecticidal products XV-A by reaction of compounds VI, or compounds I are disclosed in US 62/095073 and US62/095071, e.g. in case R^1 is H, reductive amination, or Leuckart-Wallach-reaction, followed by amidation:



Reductive amination of compounds I, or compounds VI, is usually carried out in the presence of NH_3, or an ammonium salt, and a reducing agent, in an inert solvent.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-hydrocarbons, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes or halogenated C_6-C_{10} aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; and alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, and tert-butanol, moreover DMSO, DMF, and DMA.

Suitable ammonium salts are ammonium halogenides, such as NH_4F, NH_4Cl, NH_4Br, or NH_4I, preferably NH_4Cl.

Suitable reducing agents are H_2, inorganic hydrides, such as NaH, $NaBH_4$, and $LiAlH_4$, BH_3, or its salts, such as $NaBH_3CN$, and formic acid. In case H_2 is used, it may be used in combination with a catalyst, such as Pd on active coal, or Raney Nickel, preferably Raney Nickel.

Amidation of the resulting amine to compounds XX-A, or compounds XX-B, is usually carried out by reaction with R^{13}-COOH in the presence of an activating agent, or a coupling agent in an inert solvent. Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromats, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMSO, DMF, and DMA, preferably DMF. It is also possible to use mixtures of the solvents mentioned.

Suitable activating agents are halogenating agent, which are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride. Suitable coupling agents are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7- azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP, PyBOP, and PyBrOP, preferably PyBrOP. Generally, the activating agent, or the coupling agent is used in excess.

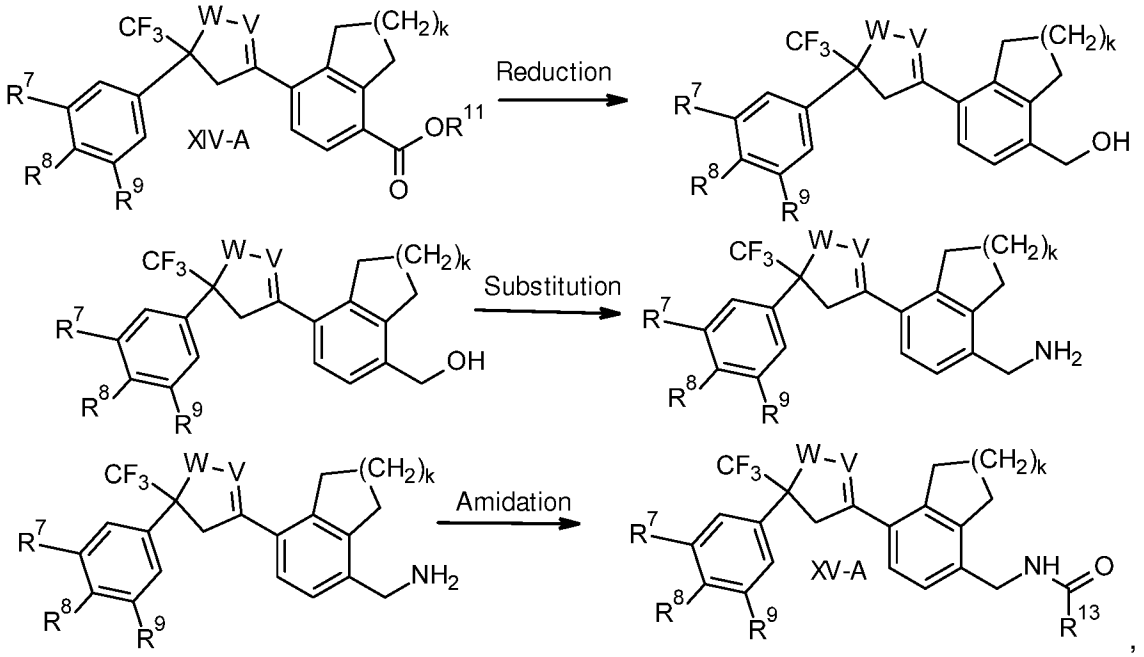
Alternatively, amidation of the resulting amine to compounds XX-A, or compounds XX-B, may also be carried out by reaction with an ester derivative of R^{13}-COOH at temperatures from 20 to 80 °C, preferably from 30 to 70 °C, more preferably from 40 to 60 °C, and in particular from 45 to 55 °C, in the presence of a catalyst, such as a metalorganic compound. Such reactions have been described by Levin et al., Synthetic Communications, 1982, (12) 989-993.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene, halogenated hydrocarbons, preferably halogenated C-C_6-alkanes and halogenated C_6-C_{10}-aromats, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. Preferred solvents are $CH_3C(O)CH_3$, CH_3CN, CH_3NO_2, $CHCl_3$, CH_2Cl_2, CCl_4, CH_2ClCH_2Cl, benzene, toluene, xylene $CH_3CH_2OCH_2CH_3$, CH_3OCH_3, petroleum ether, C_5-C_{12}-alkanes, preferably CH_2Cl_2 and benzene, more preferably benzene. It is also possible to use mixtures of the solvents mentioned.

Suitable metalorganic compounds are C_1-C_6-alkyl metal or C_6-C_{10}-aryl metal compounds, preferably of Fe, Ti, Zr, Al, more preferably Al, such as $Al(CH_3)_3$, $Al(CH_2CH_3)_2$, $Al(CH_2CH_2CH_3)_3$, $Al(CH(CH_3)_2)_3$, $Al(CH_2CH_2CH_2CH_3)_3$, $Al(CH(CH_3)(CH_2CH_3)_3$, tri-tert-butyl aluminium, or $Al(C_6H_5)_3$, preferably $Al(CH_3)_3$.

Compounds XX-A may then be converted to compounds XIV-A, as described for the reaction of compounds I to compounds VI. Compounds XX-B may be converted to compounds XV-A, as described for the conversion of compounds VI to compounds XV-A.

Compounds XV-A may also be produced by reduction of the ester or carboxylic acid group of compounds XIV-A with R^1 being OR^{11}, followed by substitution of the resulting hydroxyl with an amine, and finally an amidation reaction:



wherein all variables have a meaning as defined for compounds XV-A.

Reduction of the ester, or carboxylic acid group in compounds XIV-A is usually carried out at temperatures of from 10 to 30 °C, in an inert solvent, in the presence of a reducing agent.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; in particular ethers, such as THF. It is also possible to use mixtures of the solvents mentioned.

Suitable reducing agents are metals, for example alkaline, and earth alkaline metals, metal salts metal oxides, such as salts or oxides of copper, tin, and lead; inorganic hydrides, such as NaH, $NaBH_4$, and $LiAlH_4$, alcohols, such as CH_3OH, CH_3CH_2OH, and $CH_3CH(OH)CH_3$; and other such as sulfite, dithionite, thiosulfate, hydrazine, aldehydes, preferably inorganic hydrides, and in particular $LiBH_4$.

Substitution of the hydroxyl with an amine is usually a process consisting of the activation of the hydroxyl group in step one, followed by nucleophilic substitution in step two.

Activation of the hydroxyl group is usually carried out at temperatures of from -10 to 50 °C, in an inert solvent, in the presence of an acid halogenide and a base.

Suitable acid halogenides are halogenides of organic acids with a pKa below 5, preferably below 2, such as mesyl chloride, or tosyl chloride.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; in particular halogenated hydrocarbons, for example methylene chloride.

Suitable bases are, in general, inorganic bases, 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 lithium oxide, sodium oxide, calcium oxide, and magnesium oxide, alkali metal and alkaline earth metal hydrides, such as lithium hydride, sodium hydride, potassium hydride and calcium hydride, alkali metal and alkaline earth metal carbonates, such as lithium carbonate, potassium carbonate and calcium carbonate, and also
alkali metal bicarbonates, such as sodium bicarbonate; moreover organic bases, for example tertiary amines, such as trimethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine, and also bicyclic amines; in particular tertiary amines, such as triethylamine.

Nucleophilic substitution is then is usually carried out at temperatures of from 10 to 50 °C, preferably from 20 to 30 °C, in an inert solvent, in the presence of a nitrogen source.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA; in particular DMF.

Suitable nitrogen sources are NH_3, primary- and secondary amines, and azides, preferably azide salts, and in particular NaN_3.

In case an azide is used in the nucleophilic substitution, reduction of the resulting azide product by a reducing agent in an inert solvent at temperatures of from 60 to 120 °C, preferably 70 to 90 °C.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover water, DMSO, DMF, and DMA; in particular water and THF.

Suitable reducing agents are metals, for example alkaline, and earth alkaline metals, metal salts metal oxides, such as salts or oxides of copper, tin, and lead; inorganic hydrides, such as NaH, $NaBH_4$, and $LiAlH_4$, alcohols, such as CH_3OH, CH_3CH_2OH, and $CH_3CH(OH)CH_3$; phosphines, such as triphenylphosphine, and trimethylphosphin; and other such as sulfite, dithionite, thiosulfate, hydrazine, aldehydes, preferably phosphines, and in particular triphenylphosphine.

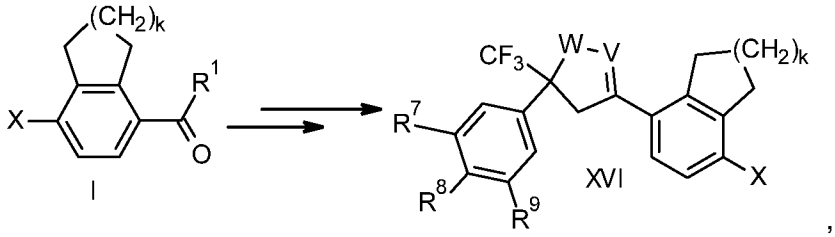
Amidation reaction of the resulting amines to compounds XV-A is usually carried out at temperatures of from 10 to 50 °C, preferably from 20 to 30 °C, in an inert solvent, in the presence of a base, and an carboxylic acid halogenide derivative of R^{13}-COOH, or a carboxylic acid R^{13}-COOH and a coupling agent.

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, dichloroethane, chloroform, and chlorobenzene; ethers such as diethylether, diisopropylether, tert-butylmethylether, dioxane, anisole, and tetrahydrofurane; nitriles such as acetonitrile, and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone, and tert-butyl methyl ketone; alcohols such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover water, DMSO, DMF, and DMA; ethers and DMF, and in particular ethers, such as THF.

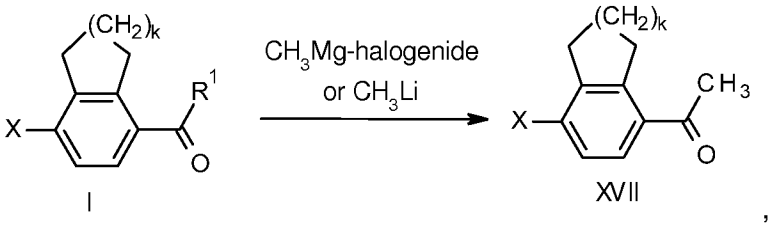
Suitable coupling agents selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP ((benzotriazol-1-yloxy)-tris(dimethylamino) phosphonium hexafluorophosphate), PyBOP ((benzotriazol-1-yloxy)-tripyrrolidinphosphonium hexafluorophosphate) and PyBrOP (bromotripyrrolidinphosphonium hexafluorophosphate), preferably PyBrOP. Generally, the coupling agent is used in excess.

Typical bases applied are organic bases, such as pyridine, 4-N,N-dimethylamino-pyridine, tetramethylene diamine, piperidine, diisopropylamine, morpholine, and triethylamine, preferably pyridine, 4-N,N-dimethylaminopyridine, and diisopropylamine, in particular tertiary amines, such as trimethylamine, diisopropylethylamine, triethylamine, triisopropylethylamine and N-methylpiperidine, pyridine, substituted pyridines, such as collidine, lutidine and 4-dimethylaminopyridine, especially triethylamine.

Compounds I are also suitable intermediates for the manufacture of insecticidal compounds of formula XVI



wherein X is halogen, and all other variables have a meaning as defined for compounds XIV-A. This process usually involves the conversion of compounds I to compounds XVII



where all variables have a meaning as defined for compounds I.

This transformation is usually carried an aprotic polar or non-polar solvent in the presence of CH_3Mg-halogenide, or CH_3Li.

The reaction is preferably carried out at temperatures of from -78 to 110°C, preferably at temperatures from -50 to 20 °C, more preferably from -20 to 0 °C.

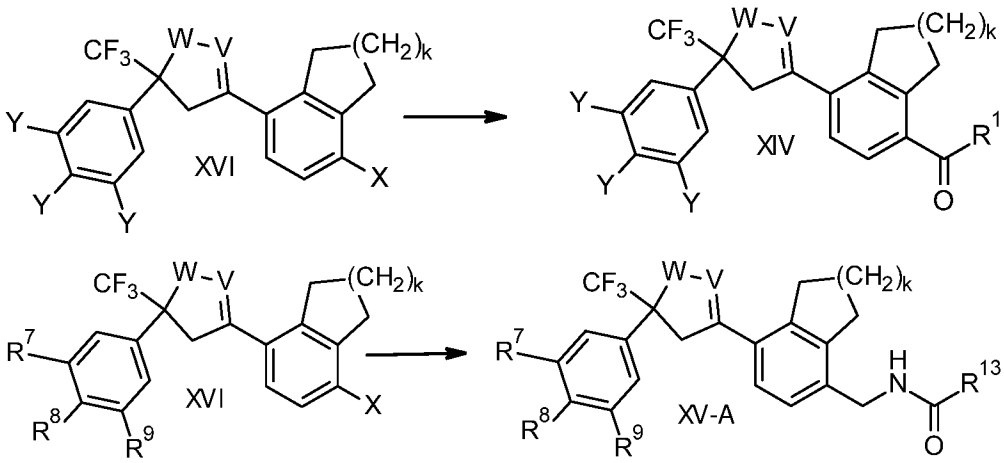
Suitable solvents for the reaction are aprotic polar and non-polar solvents. Typical solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF.

The reaction is preferably carried out in aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as benzene, toluene, xylenes, cumene, chlorobenzene, nitrobenzene, or tert-butylbenzene, aprotic polar solvents, for example cyclic, or acyclic ethers, such as diethyl ether, tert-butyl methyl ether (MTBE), cyclopentyl methyl ether, THF or dioxane.

The CH_3Mg-halogenide may be CH_3MgF, CH_3MgCl, CH_3MgBr, or CH_3MgI, preferably CH_3MgBr.

The molar ratio of the CH_3Mg-halogenide, or CH_3Li to compounds I is usually from 1:1 to 5:1, preferably from 1:1 to 2:1, and most preferably from 1:1 to 1:1.5.

Compounds XVII may then be converted to compounds XVI by methods disclosed in WO 2010/125130, WO2015128358, WO2014206908, and WO2014206910. Compounds XVI may be converted to compounds XIV, or compounds XV-A, by the reactions listed above, which are also described in WO2015128358.



where X, R^1, and R^{13} have a meaning as defined for compounds I, Y is independently halogen, and wherein all other variables have a meaning as defined for compounds XV-A.

Another aspect of the invention is the use of compounds I or II for the manufacture of such insecticidal compounds XIV-A, or XV-A; and methods for the manufacture of insecticidal products XIV-A, or XV-A from compounds I or II.

Suitable processes for the production of compounds VI from compounds I or II have been described above. Further conversion of compounds VI to compounds XIV-A, or XV-A can be carried out by the methods described above.

Compounds VI, and insecticidal compounds XIV-A with R^1 being OR^{11} and R^{11} being not H can be hydrolyzed to the respective carboxylic acid.

This process is usually carried out in the presence of a base or an acid in an inert solvent, and optionally H_2O.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromats, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, pref-

erably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. Preferred solvents are C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, in particular dioxane and THF. It is also possible to use mixtures of the solvents mentioned.

Suitable acids are mineral acids, such as hydrochloric acid, sulfuric acid organic acids, such as trifluoroacetic acid. Suitable bases are alkali metal hydroxides and earth alkali metal hydroxides, such as LiOH, NaOH or KOH.

Compounds VI, and insecticidal compounds XIV-A, or XV-A with R^1 being OH may be reacted with an amine $NHR^{12}R^{13}$ to the amide.

This process is usually carried out in an inert solvent, in the presence of a base and by activation with an activating agent, or a coupling agent.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene; halogenated hydrocarbons, preferably halogenated C_1-C_6-alkanes and halogenated C_6-C_{10}-aromatic hydrocarbons, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; moreover DMSO, DMF, and DMA, preferably DMF. It is also possible to use mixtures of the solvents mentioned.

Suitable activating agents are halogenating agent, which are usually selected from chlorinating agents and brominating agents, such as oxalylchloride, thionylchloride, phosphortri- and pentabromide, phorphortri- and pentachloride, preferably from thionylchloride and oxalylchloride. Suitable coupling agents are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzotriazole derivatives, such as HATU (O-(7- azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((Obenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP, PyBOP, and PyBrOP, preferably PyBrOP. Generally, the activating agent is used in excess.

As a further alternative insecticidal compounds VI, and insecticidal compounds XIV-A, or XV-A with R^1 being OR^{11} and R^{11} being not H (ester form) can also be directly converted to the corresponding amide.

This process is usually carried out at temperatures from 20 to 80 °C, preferably from 30 to 70 °C, more preferably from 40 to 60 °C, and in particular from 45 to 55 °C, in the presence of a catalyst, such as a metalorganic compound. Such reactions have been described by Levin et al., Synthetic Communications, 1982, (12) 989-993.

Suitable solvents are aliphatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as pentane, hexane, cyclohexane, and petrol ether; aromatic hydrocarbons, preferably C_5-C_{16}-alkanes, such as toluene, o-, m-, and p-xylene, halogenated hydrocarbons, preferably halogenated C-C_6-alkanes and halogenated C_6-C_{10}-aromats, such as CH_2Cl_2, $CHCl_3$, and chlorobenzene; ethers, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ethers and C_1-C_6-alkyl-C_6-C_{10}-aryl ethers, such as $CH_3CH_2OCH_2CH_3$, $(CH_3)_2CHOCH(CH_3)_2$, MTBE, DME, dioxane, anisole, and THF; nitriles, preferably C_1-C_6-nitriles, such as CH_3CN, and propionitrile; ketones, preferably C_1-C_6-alkyl-C_1-C_6-alkyl ketones, such as $CH_3C(O)CH_3$, $CH_3C(O)CH_2CH_3$, $CH_3CH_2C(O)CH_2CH_3$, and MTBK; alcohols, preferably C_1-C_4-alcohols, such as CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$, $CH_3CH(OH)CH_3$, $CH_3(CH_2)_3OH$, and $C(CH_3)_3OH$; moreover DMSO, DMF, and DMA. Preferred solvents are $CH_3C(O)CH_3$, CH_3CN, CH_3NO_2, $CHCl_3$, CH_2Cl_2, CCl_4, CH_2ClCH_2Cl, benzene, toluene, xylene $CH_3CH_2OCH_2CH_3$, CH_3OCH_3, petroleum ether, C_5-C_{12}-alkanes, preferably CH_2Cl_2 and benzene, more preferably benzene. It is also possible to use mixtures of the solvents mentioned.

Suitable metalorganic compounds are C_1-C_6-alkyl metal or C_6-C_{10}-aryl metal compounds, preferably of Fe, Ti, Zr, Al, more preferably Al, such as $Al(CH_3)_3$, $Al(CH_2CH_3)_2$, $Al(CH_2CH_2CH_3)_3$, $Al(CH(CH_3)_2)_3$, $Al(CH_2CH_2CH_2CH_3)_3$, $Al(CH(CH_3)(CH_2CH_3)_3)$, $Al(C(CH_3)_3)_3$, or triphenylaluminium, preferably $Al(CH_3)_3$.

The initial starting compounds Xa and Xb are commercially available. Compounds of formula XII-A are commercially available, or may be produced by commercially available stannane chlorides with Grignard reagents. Compounds XII-B are commercially available, or can be produced from vinyl alcohol by a Williamson ether synthesis. Compounds XIII-A can be produced as described in CN103224447, or Raja et al., Tetrahedron Letters, 2011, 52(40), p.5170-5172. Compounds XIII-A are also commercially available. Compounds XIII-B may be produced as described in WO2010/125130. In case any educts for the reactions disclosed herein are not commercially available, or directly obtainable by the methods described in the prior art given above, they can be produced by derivatization of these compounds.

The reaction mixtures are worked up in a customary manner, for example by mixing with H_2O, separating the phases and, if appropriate, chromatographic purification of the crude products. Some of the intermediates and end products are produced in the form of colorless 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 produced as solids, purification can also be carried out by recrystallization or digestion.

If individual compounds I, II, or VI cannot be produced by the routes described above, they can be produced by derivatization of other compounds I, II, or VI.

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, for example in the treatment of plants in the treated plant, or in the harmful fungus to be controlled.

The terms for organic groups used in the definition of the variables, such as, for example, the term "halogen", are collective terms which represent the individual members of these groups of organic moieties. In each case, the prefix C_x-C_y denotes the number of possible carbon atoms.

The term "halogen" refers in each case to fluorine, chlorine, bromine or iodine, especially fluorine or chlorine. In another embodiment, the term halogen refers to chlorine, bromine, or iodine. In yet another embodiment, the term halogen refers to bromine, or iodine. In yet another embodiment, the term halogen refers to bromine.

In all above cases C_5-C_{12} alkanes means n-pentane, n-hexane, n-heptane, n-octane, n-nonane, n-decane, n-undecane, n- dodocane, isopentane, neopentane, 2-methyl pentane, 3-methyl pentane, 2,2,-dimethylpentane, as well as all isomers of heptane, octane, nonane, decane, undecane, and dodecane, and the mixture of the aforementioned C_5-C_{12} alkanes.

The term "alkyl", as used in C_1-C_6-alkyl, C_1-C_4-alkyl and in the terms C_1-C_6-alkoxy, refers to a saturated straight-chain or branched hydrocarbon group, for example methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-ethylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 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, 1-ethyl-2-methylpropyl. The term "C_2-C_6-alkenyl" refers to monounsaturated straight-chain or branched hydrocarbon radicals having 2 to 6 carbon atoms, and a C-C double bond in any position, such as ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, or 3-butenyl.

The term "C_2-C_6-alkynyl" refers to monounsaturated straight-chain or branched hydrocarbon radicals having 2 to 6 carbon atoms, and a C-C triple bond in any position, for example C_2-C_6-alkynyl, such as ethynyl, 1-propynyl, and 2-propynyl.

The term "C_1-C_6-alkoxy" refers to straight-chain or branched saturated alkyl groups comprising 1 to 6 carbon atoms, which groups are attached via an oxygen atom. Examples include C_1-C_6-alkoxy, such as, for example, methoxy, ethoxy, OCH_2-C_2H_5, $OCH(CH_3)_2$, n-butoxy, $OCH(CH_3)$-C_2H_5, OCH_2-$CH(CH_3)_2$ and $OC(CH_3)_3$.

The term "C_1-C_6-haloalkyl", as used herein and in the haloalkyl moieties of C_1-C_6-haloalkoxy and C_1-C_6-haloalkylthio, refers to straight-chain or branched alkyl groups having 1 to 6 carbon atoms, wherein some or all of the hydrogen atoms of these groups are replaced by halogen atoms, such as chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl, heptafluoroisopropyl, etc.

The term "C_2-C_6-haloalkenyl" as used herein, which is also expressed as "C_1-C_6-alkenyl which is partially or fully halogenated", and the haloalkenyl moieties in haloalkenyloxy, haloalkenylcarbonyl and the like refers to unsaturated straight-chain or branched hydrocarbon radicals 2 to 6 carbon atoms and a double bond in any position (as mentioned above), wherein some or all of

the hydrogen atoms in these groups are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine, for example chlorovinyl, chloroallyl and the like.

The term "C_2-C_6-haloalkynyl" as used herein, which is also expressed as "C_1-C_6-alkynyl which is partially or fully halogenated", and the haloalkynyl moieties in haloalkynyloxy, haloalkynylcarbonyl and the like refers to unsaturated straight-chain or branched hydrocarbon radicals having 2 to 6 ("C_2-C_6-haloalkynyl") carbon atoms and one or two triple bonds in any position (as mentioned above), wherein some or all of the hydrogen atoms in these groups are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine. The term "C_1-C_6-haloalkoxy" refers to C_1-C_6-haloalkyl groups, as defined above, which are attached via an oxygen atom. Examples include mono-, di- and trifluoromethoxy, mono-, di- and trichloromethoxy, 2,2,2-trifluoroethoxy, or heptafluoroisopropoxy.

The term "C_3-C_8-cycloalkyl", as used herein, describes cyclic hydrocarbon radicals comprising 3 to 8 carbon atoms. Examples of cyclic radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "C_3-C_8-halocycloalkyl" as used herein, which is also expressed as "C_3-C_8-cycloalkyl which is partially or fully halogenated", and the halocycloalkyl moieties in halocycloalkoxy, halocycloalkylcarbonyl and the like refers to mono- or bi- or polycyclic saturated hydrocarbon groups having 3 to 8 ("C_3-C_8-halocycloalkyl") carbon ring members (as mentioned above) in which some or all of the hydrogen atoms are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine.

The term “carbocycle” or “carbocyclyl” includes, unless otherwise indicated, 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, for example cyclopropane, cyclobutane, cyclopentane and cyclohexane rings.

The term “heterocycle” or "heterocyclyl" includes, unless otherwise indicated, in general 3- to 12-membered, preferably 3- to 8-membered, 3- to 7-membered, or 5- to 8-membered, more preferably 5- or 6-membered, in particular 6-membered monocyclic heterocyclic non-aromatic radicals. The heterocyclic non-aromatic radicals usually comprise 1, 2, 3, 4 or 5, preferably 1, 2 or 3 heteroatoms selected from N, O and S as ring members, where S-atoms as ring members may be present as S, SO or SO_2. Examples of 5- or 6-membered heterocyclic radicals comprise saturated, or unsaturated, non-aromatic heterocyclic rings, such as oxiranyl, oxetanyl, thietanyl, thietanyl-S-oxide (S-oxothietanyl), thietanyl-S-dioxide (S-dioxothiethanyl), pyrrolidinyl, pyrrolinyl, pyrazolinyl, tetrahydrofuranyl, dihydrofuranyl, 1,3-dioxolanyl, thiolanyl, S-oxothiolanyl, S-dioxothiolanyl, dihydrothienyl, S-oxodihydrothienyl, S-dioxodihydrothienyl, oxazolidinyl, oxazolinyl, thiazolinyl, oxathiolanyl, piperidinyl, piperazinyl, pyranyl, dihydropyranyl, tetrahydropyranyl, 1,3- and 1,4-dioxanyl, thiopyranyl, S.oxothiopyranyl, S-dioxothiopyranyl, dihydrothiopyranyl, S-oxodihydrothiopyranyl, S-dioxodihydrothiopyranyl, tetrahydrothiopyranyl, S-oxotetrahydrothiopyranyl, S-dioxotetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl, S-dioxothiomorpholinyl, thiazinyl and the like. Examples for heterocyclic ring also comprising 1 or 2 carbonyl groups as ring members comprise pyrrolidin-2-onyl, pyrrolidin-2,5-dionyl,

imidazolidin-2-onyl, oxazolidin-2-onyl, thiazolidin-2-onyl and the like.

The substituent “OTf" refers to a triflate substituent (trifluoromethane sulfonate), which is bonded to the rest of the molecule by a single bond to one oxygen atom of the sulfonic acid moiety.

The substituent “OTs" refers to a tosylate substituent (p-toluenesulfonate), which is bonded to the rest of the molecule by a single bond to one oxygen atom of the sulfonic acid moiety.

The term “substituted” refers in each case to a substitution by one, or more, same or different substituents.

If not otherwise stated, the preferred definitions of the different substituents relate to all compounds and processes where these are applicable. Combinations of embodiments with other embodiments, independent of their nature or preference, are within the scope of the invention.

In one embodiment, the substituents and indices in formula I have the following meaning:

X halogen;

R^1 OR^{11} or $NR^{12}R^{13}$;

R^{11} a) H;

b) C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl; which groups are unsubstituted, or substituted by halogen, CN, NO_2, $S(O)_mR^A$, OR^B, NR^BR^C, $S(O)_mNR^BR^C$, $Si(R^B)_2R^C$, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$, $C(=S)R^B$, $C(=S)NR^BR^C$, $C(=S)OR^B$, $C(=S)SR^B$, $C(=NR^B)R^C$, or $C(=NR^B)NR^CR^D$

c) phenyl, which is unsubstituted, or substituted by R^A; or

d) a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which ring comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$;

wherein

R^A a) C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_1-C_4-alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl; which groups are unsubstituted, or partially, or fully substituted by halogen, CN, OH, NO_2;

b) a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which ring comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$;

R^B,R^C, R^D have a meaning, independently from one another, as defined for R^A, or H;

R^{12} H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl; which groups are unsubstituted, or substituted by R^F;

R^{13} a) H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl; which groups are unsubstituted, or substituted by R^F;

b) a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2 or C=O; and A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which ring is unsubstituted, or substituted with one, or more, same, or differ-

ent substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$;

c) a group $S(O)_mR^A$, $S(O)_nN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$, $C=NR^BR^C$;

R^F a) halogen, CN, N_3, NO_2, SCN, SF_5, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $Si(R^B)_2R^C$, OR^{11}, OSO_2R^A, $S(O)_mR^A$, $S(O)_nN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$;

b) phenyl, which is unsubstituted, or substituted by R^A;

k 1 or 2

m 0, 1, or 2; and

n 0 or 1.

In one embodiment, k is 1. In another embodiment k is 2.

X is usually a halogen, preferably Cl or Br, more preferably Br. In one embodiment, X is Cl, Br, or I. In another embodiment, X is Br or I. In another embodiment, X is Cl. In another embodiment, X is I.

U is usually a halogen, preferably Cl or Br, more preferably Cl. In another embodiment, U is Cl, Br, or I. In yet another embodiment, U is Br, or I. In yet another embodiment, U is Br. In yet another embodiment, U is I.

In one embodiment, V is N, and W is CH_2. In another embodiment, V is N, and W is O. In another embodiment, W is CH_2 and V is CH. In another embodiment, W is O and V is CH. In another embodiment, W is S and V is CH. In another embodiment, W is S and V is N.

In one embodiment, R^1 is H.

In another embodiment, R^1 is OR^{11} and R^{11} is not H (ester form). The ester form is advantageously utilized in the production steps described herein due to higher yields, and less side reactions. Finally, protective groups are usually not required for the ester form.

R^{11} is preferably R^{11}a), b), or c), more preferably R^{11}a) or R^{11}b). More preferably, R^{11} is R^{11}a). Also more preferably, R^{11} is R^{11}b), especially preferably C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl; which groups are unsubstituted, or substituted by selected from halogen, CN, NO_2, $S(O)_mR^A$, OR^B, NR^BR^C, $S(O)_mNR^BR^C$, $Si(R^B)_2R^C$, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$, $C(=S)R^B$, $C(=S)NR^BR^C$, $C(=S)OR^B$, $C(=S)SR^B$, $C(=NR^B)R^C$, $C(=NR^B)NR^CR^D$.

In particular, R^{11} is C_1-C_6-alkyl or C_3-C_8-cycloalkyl; which groups are unsubstituted, or substituted by selected from halogen, CN, NO_2, $S(O)_mR^A$, OR^B, NR^BR^C, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$.

In one embodiment, R^{11} is C_1-C_6-alkyl or C_3-C_8-cycloalkyl, preferably C_1-C_6-alkyl, more preferably C_1-C_4 alkyl (such as CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$), preferably CH_3.

In another embodiment, R^{11} is C_1-C_6-alkyl, which is fully substituted with halogen, such as CF_3, CF_2CF_3, $CF(CF_3)_2$, CCl_3, CCl_2CCl_3, $CCl(CCl_3)_2$. In yet another embodiment, R^{11} is C_1-C_6-alkyl,

which is partially substituted with CN, NO_2, or OR^B, such as CH_2CN, CH_2CH_2CN, CH_2NO_2, $CH_2CH_2NO_2$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, CH_2OCH_3, $CH_2OCH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OC(CH_3)_3$, $CH_2CH_2OCH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH(CH_3)_2$, $CH_2CH_2OC(CH_3)_3$, CF_2OCF_3, $CF_2OCF_2CF_3$, $CF_2OCF(CF_3)_2$, $CF_2OC(CF_3)_3$, $CF_2CF_2OCF_3$, $CF_2CF_2OCF_2CF_3$, $CF_2CF_2OCF(CF_3)_2$, $CF_2CF_2OC(CF_3)_3$.

In one embodiment, R^{11} is H, C_1-C_6-alkyl or C_3-C_8-cycloalkyl, preferably H, C_1-C_6-alkyl, more preferably H, C_1-C_4 alkyl (such as CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$). In another embodiment, R^{11} is C_1-C_4-alkyl.

In one embodiment, R^{11} is H, C_1-C_4 alkyl, preferably H, or CH_3, in particular CH_3.

In another embodiment, R^{11} is C_1-C_6-alkyl, which is fully substituted with halogen, such as CF_3, CF_2CF_3, $CF(CF_3)_2$, CCl_3, CCl_2CCl_3, $CCl(CCl_3)_2$.

In yet another embodiment, R^{11} is C_1-C_6-alkyl, which is partially substituted with CN, NO_2, or OR^B, such as CH_2CN, CH_2CH_2CN, CH_2NO_2, $CH_2CH_2NO_2$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, CH_2OCH_3, $CH_2OCH_2CH_3$, $CH_2OCH(CH_3)_2$, $CH_2OC(CH_3)_3$, $CH_2CH_2OCH_3$, $CH_2CH_2OCH_2CH_3$, $CH_2CH_2OCH(CH_3)_2$, $CH_2CH_2OC(CH_3)_3$, CF_2OCF_3, $CF_2OCF_2CF_3$, $CF_2OCF(CF_3)_2$, $CF_2OC(CF_3)_3$, $CF_2CF_2OCF_3$, $CF_2CF_2OCF_2CF_3$, $CF_2CF_2OCF(CF_3)_2$, $CF_2CF_2OC(CF_3)_3$.

Also more preferably, R^{11} is R^{11}c) or R^{11}d), especially preferably unsubstituted phenyl, or a 3-, 4-, 5, or 6-membered saturated, or fully unsaturated heterocycle, which heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and in particular phenyl.

In one embodiment, R^1 is OR^{11} and R^{11} is H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl; which groups are unsubstituted, or substituted by selected from halogen, CN, NO_2, $S(O)_mR^A$, OR^B, NR^BR^C, $S(O)_mNR^BR^C$, $Si(R^B)_2R^C$, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$, $C(=S)R^B$, $C(=S)NR^BR^C$, $C(=S)OR^B$, $C(=S)SR^B$, $C(=NR^B)R^C$, $C(=NR^B)NR^CR^D$.

In another embodiment, R^1 is OR^{11} and R^{11} is H, C_1-C_6-alkyl, preferably H or CH_3, more preferably CH_3. In another embodiment, R^1 is OR^{11} and R^{11} is H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl, especially preferably C_1-C_6-alkyl. In yet another embodiment, R^{11} is H, C_1-C_6-alkyl, phenyl, or benzyl. In yet another embodiment, R^{11} is C_1-C_6-alkyl, phenyl, or benzyl.

R^A is usually C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_1-C_4-alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl; which groups are unsubstituted, or partially, or fully substituted by halogen, CN, OH, NO_2. Preferably, R^A is C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_1-C_4-alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl, more preferably C_1-C_6-alkyl.

In another embodiment of the invention, R^1 is $NR^{12}R^{13}$.

Preferably, R^{12} is H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $C(=O)CH_3$, or $C(=O)OCH_3$, more preferably H, CH_3, CH_2CH_3, or $CH_2CH_2CH_3$, even more preferably H or CH_3, and most preferably H. In another embodiment, R^{12} is H, or C_1-C_6-alkyl.

In one embodiment, R^{13} is H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, preferably CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $CHCH_2$, CH_2CHCH_2, $CHCHCH_3$, CCH, CH_2CCH, isopropyl, isobutyl, isopentyl, isohexyl, phenyl, more preferably CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $(CH_2)_2CH(CH_3)_2$, $(CH_2)_3CH(CH_3)_2$, phenyl.

In another embodiment, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which groups are fully substituted with R^F. In another embodiment, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which groups are partially (e.g. 1, 2, 3, 4, 5 times) substituted with R^F.

In another embodiment, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkyl, which groups are partially (e.g. 1, 2, 3, 4, 5 times) substituted with halogen or C_3-C_8-cycloalkyl.

In another embodiment, R^{13} is C_1-C_6-alkyl, C_3-C_8-cycloalkyl, which groups are partially (e.g. 1, 2, 3, 4, 5 times) substituted with R^F, preferably with halogen, or $S(O)_mR^A$.

In another embodiment, R^{13} is C_1-C_6-alkyl, which is partially substituted with halogen or C_3-C_8-cycloalkyl, preferably with C_3-C_8-cycloalkyl.

In another embodiment, R^{13} is a) H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

b) a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2 or C=O; and A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle is unsubstituted, or substituted with one, or more, same, or different substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

c) a group $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $N(R^B)C(=O)OR^C$, $N(R^B)C(=O)N(R^C)R^D$, $C(=O)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$;

or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted with one, or more, same, or different substituents R^F, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O);

or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a group $=S(R^B)R^C$.

In another embodiment, R^{13} is a) H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

b) a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2 or C=O; and A is selected from A-1 to A-31;

c) a group $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $N(R^B)C(=O)OR^C$, $N(R^B)C(=O)N(R^C)R^D$, $C(=O)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$;

or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocy-

cle is unsubstituted, or substituted with one, or more, same, or different substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O);
or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a group $=S(R^B)R^C$.

In another embodiment, R^{13} is a) H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl; which groups are unsubstituted, or substituted by R^E;
b) a group Z-A, wherein Z is a chemical bond, CH_2, or CH_2CH_2; and A is selected from A-1 to A-31;
c) a group $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $N(R^B)C(=O)OR^C$, $N(R^B)C(=O)N(R^C)R^D$, $C(=O)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$;
or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle is unsubstituted, or substituted with one, or more, same, or different substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O);
or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a group $=S(R^B)R^C$.

In another embodiment, R^{13} is

a) H;
b) C_1-C_6-alkyl, C_2-C_6-alkynyl; which groups are unsubstituted, or substituted by R^E;
c) C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl; which groups are unsubstituted, or substituted by R^E, C_1-C_2-alkyl, or C_1-C_2-haloalkyl;
d) a group Z-A, wherein Z is a chemical bond, CH_2, or CH_2CH_2;

wherein A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocycle is unsubstituted, or substituted with one, or more, same, or different substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S);

In one embodiment, R^F is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $S(O)_mR^A$, $C(=O)OR^A$, phenyl, or pentafluorophenyl, more preferably halogen, CN, 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, C_2-C_6-haloalkynyl, most preferably 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, C_2-C_6-haloalkynyl, and especially preferably halogen.

In another embodiment, R^F is a) halogen, CN, N_3, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-halocycloalkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_2-

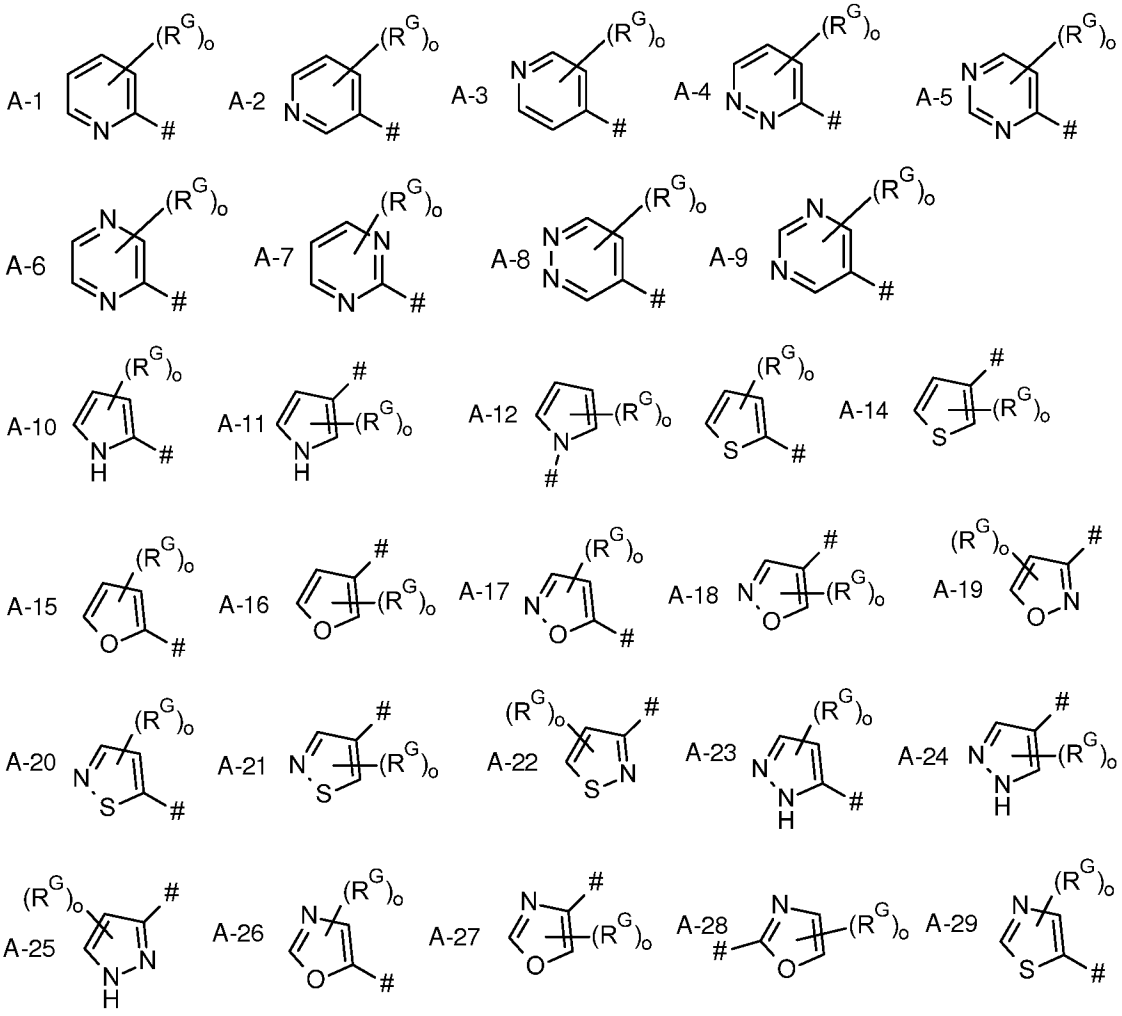
C_6-alkynyl, C_2-C_6-haloalkynyl, OR^{11}, $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=O)N(R^B)N(R^C)R^D$, $C(=O)NOR^B$, $N(R^B)R^C$, $C(=O)OR^A$;

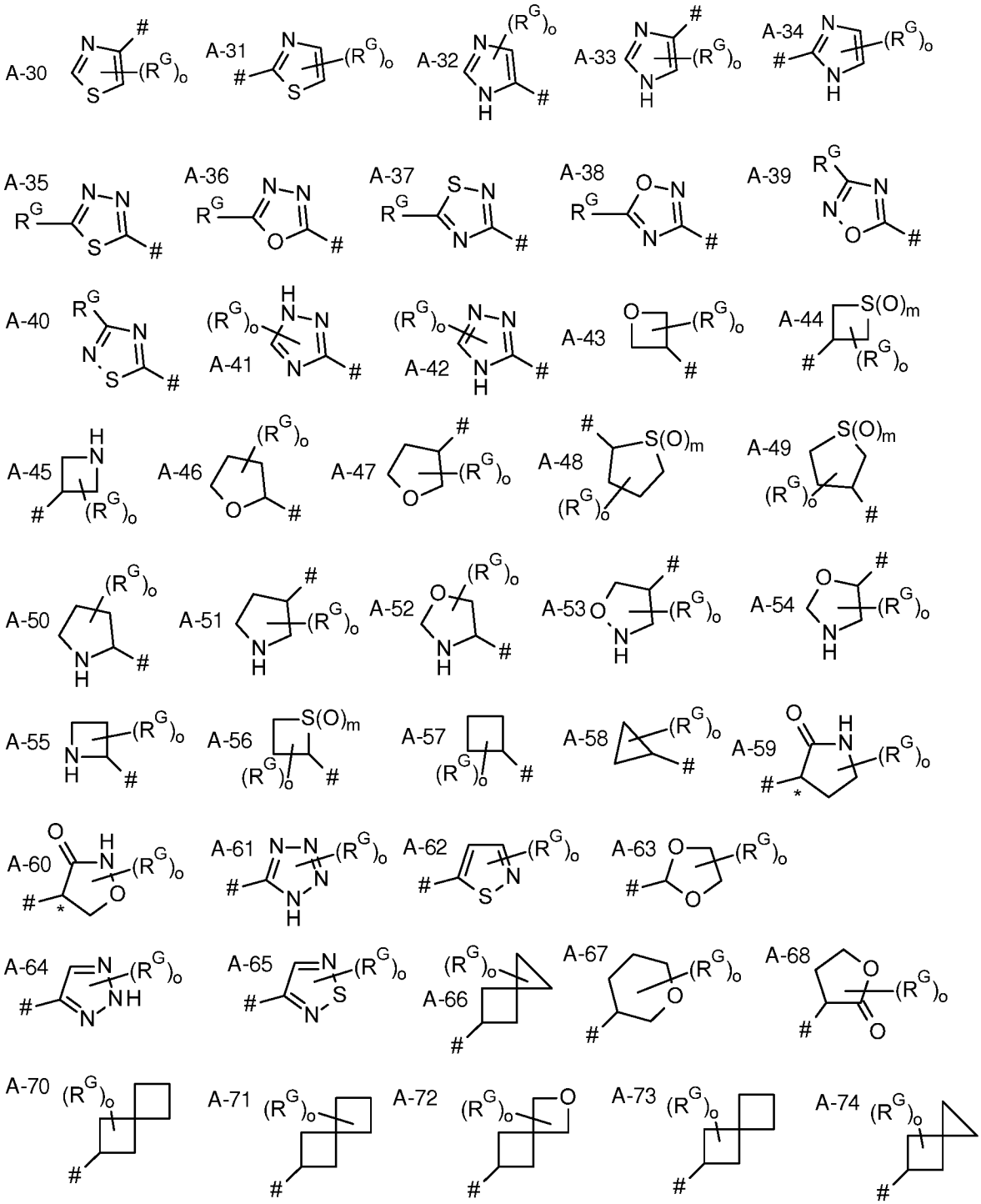
b) phenyl, which is unsubstituted, or substituted by R^A; or

c) two substituents R^F, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted with one, or more, same, or different substituents R^A and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

In yet another embodiment, R^{13} is a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2 or C=O; and A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated, or fully unsaturated heterocycle, which heterocyle is unsubstituted, or substituted with one, or more, same, or different substituents R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$.

Preferably, A is selected from





wherein # stands for the connection to Z. In case of A-59 and A-60, the chirality center marked with an asterisk usually has two stable stereoisomers, which may be supplied in their isolated, or racemic form. In one embodiment, A-59 and/or A-60 are supplied as the S-diastereomer (or enantiomer). In another embodiment, A-59 and/or A-60 are supplied as the R-diastereomer (or enantiomer). For the avoidance of doubt, the chirality center is localized at the carbon that is directly linked to Z by a single bond. In one embodiment, A is selected from A-1 to A-60.

Substituents R^G are usually same or different substituents selected from halogen, CN, NO_2, C_1-C_6-alkyl, N(C_1-C_6-alkyl)(C_1-C_6-alkyl), C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkyl-S(O)$_m$, C_1-C_6-haloalkyl-S(O)$_m$, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_2-C_6-alkynyl, C_2-C_6-haloalkynyl, C_1-C_4-alkyl-C(O), C_1-C_4-haloalkyl-C(O), C(=O)NR^BR^C; or two R^G present on the same carbon atom of a saturated ring may form together =O or =S.

In one embodiment, R^E are same or different substituents selected from halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkyl-S(O)$_m$, C_1-C_6-haloalkyl-S(O)$_m$, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_2-C_6-alkynyl, C_2-C_6-haloalkynyl, C_1-C_4-alkyl-C(O), C_1-C_4-haloalkyl-C(O), C(=O)NR^BR^C; or two R^E present on the same carbon atom of a saturated ring may form together =O or =S.

In one embodiment, R^G is halogen, CN, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkyl-S(O)$_m$, C_1-C_4-haloalkyl-S(O)$_m$, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_2-C_4-alkenyl, C_2-C_4-haloalkenyl, C_2-C_4-alkynyl, C_2-C_4-haloalkynyl, more preferably halogen, CN, C_1-C_4-alkyl, most preferably halogen or C_1-C_4-alkyl.
The index o is usually 0, 1, or 2, preferably 0 or 1. In one embodiment, the index o is 0. In another embodiment, the index o is 1.

In one embodiment, A is selected from A-1 to A-9. In another embodiment, A is selected from A-10 to A-16. In yet another embodiment, A is selected from A-17 to A-42. In yet another embodiment, A is selected from A-43 to A-60, preferably A-55 to A-60. In yet another embodiment, A is selected from A-1, A-7, A-56, and A-58. In yet another embodiment, A is selected from A-59 and A-60. In yet another embodiment, A is selected from A-1, A-7, and A-56 to A-60. In yet another example, A is selected from A-7 and A-56. In yet another embodiment, A is selected from A-1, A-4 to A-7. In yet another embodiment, A is selected from A-1, A-4 to A-7, A-10, A-19, A-22, A-23, A-25, A-27, A-28, A-30, A-31, A-32 to A-42, A-50, A-52, and A-55.

Preferably, Z is a chemical bond, CH_2, or CH_2CH_2, more preferably a chemical bond, or CH_2.

In one embodiment, R^{13} is a group S(O)$_m$$R^A$, S(O)$_n$N($R^B$)$R^C$, N($R^B$)$R^C$, C(=O)N($R^B$)$R^C$, C(=S)N($R^B$)$R^C$, C(=O)O$R^A$, C=NO$R^A$, C=N$R^A$$R^B$, C=N$R^B$$R^C$, preferably S(O)$_m$$R^A$, S(O)$_n$N($R^B$)$R^C$, N($R^B$)$R^C$, C(=O)N($R^B$)$R^C$, C=NO$R^A$, C=N$R^A$$R^B$, C=N$R^B$$R^C$. In another embodiment, R^{13} is a group C=NOR^A, C=N$R^A$$R^B$, C=N$R^B$$R^C$, preferably C=NO$R^A$. In another embodiment, R^{13} is a group N(R^B)R^C, C(=O)N(R^B)R^C, C(=S)N(R^B)R^C, C=NOR^A, C=N$R^A$$R^B$, C=N$R^B$$R^C$, preferably N($R^B$)$R^C$, C=NO$R^A$, C=N$R^A$$R^B$, C=N$R^B$$R^C$.

In one embodiment, R^1 is N$R^{12}$$R^{13}$, R^{12} is H or CH_3, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl.
In another embodiment, R^1 is N$R^{12}$$R^{13}$, R^{12} is H, R^{13} is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, isopropyl, isobutyl, isopentyl, isohexyl, phenyl, in particular CH_3, CH_2CH_3, phenyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which is fully substituted with R^F,
wherein R^F is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $S(O)_mR^A$, $C(=O)OR^A$, phenyl, or pentafluorophenyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which is fully substituted with R^F,
wherein R^F is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $S(O)_mR^A$, $C(=O)OR^A$, phenyl, or pentafluorophenyl

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which is once substituted with R^F, wherein R^F is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $S(O)_mR^A$, $C(=O)OR^A$, phenyl, or pentafluorophenyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl, which is once substituted with R^F, wherein R^F is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $S(O)_mR^A$, $C(=O)OR^A$, phenyl, or pentafluorophenyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkyl, which groups are partially substituted with halogen, C_3-C_8-cycloalkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is C_1-C_6-alkyl, which is partially substituted with halogen or C_3-C_8-cycloalkyl, preferably with C_3-C_8-cycloalkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-10 to A-16, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-10 to A-16, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-10 to A-16, the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-43 to A-60, preferably A-55 to A-60, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-43 to A-60, preferably A-55 to A-60, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-43 to A-60, preferably A-55 to A-60, and the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-7, A-56, and A-58, and the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-7, A-56, and A-58, and the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-7, A-56, and A-58, and the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, A-10, A-19, A-22, A-23, A-25, A-27, A-28, A-30, A-31, A-32 to A-42, A-50, A-52, and A-55, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, A-10, A-19, A-22, A-23, A-25, A-27, A-28, A-30, A-31, A-32 to A-42, A-50, A-52, and A-55, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-4 to A-7, A-10, A-19, A-22, A-23, A-25, A-27, A-28, A-30, A-31, A-32 to A-42, A-50, A-52, and A-55, and the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-1, A-7, A-56, and A-58, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H or CH_3, R^{13} is Z-A, Z is a chemical bond, CH_2, or CH_2CH_2, A is selected from A-59 and A-60, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, A is selected from A-59 and A-60, the index o is 0.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, A is selected from A-59 and A-60, the index o is 1, 2, or 3, R^G is halogen, CN, C_1-C_4-alkyl.

In another embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} is Z-A, Z is a chemical bond, A is selected from A-59 and A-60, the index o is 1, R^G is C_1-C_4-alkyl.

In a preferred embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} selected from is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkyl, which groups are unsubstituted, or substituted by R^F; wherein R^F is selected from halogen, C_3-C_8-cycloalkyl, $S(O)_mR^A$; and wherein R^{13} is further selected from Z-A, wherein Z is a chemical bond, or CH_2, and wherein A is selected from A-1, A-7, A-56 to A-60; and wherein R^{13} is further selected from $C{=}NOR^A$.

In a preferred embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} selected from is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkyl, which groups are unsubstituted, or substituted by R^F; wherein R^F is selected from halogen, C_3-C_8-cycloalkyl; and wherein R^{13} is further selected from Z-A, wherein Z

is a chemical bond, or CH_2, and wherein A is selected from A-1, A-7, A-56 to A-60; and wherein R^{13} is further selected from C=NOR^A.

In another preferred embodiment, R^1 is $NR^{12}R^{13}$, R^{12} is H, R^{13} selected from is C_1-C_6-alkyl, which is unsubstituted; and wherein R^{13} is further selected from Z-A, wherein Z is a chemical bond, or CH_2, and wherein A is selected from A-7 and A-56.

The following examples illustrate the invention.

Examples

I. Characterization

The characterization can be done by coupled High Performance Liquid Chromato-graphy / mass spectrometry (HPLC/MS), by NMR or by their melting points.

HPLC/MS. The gradient was 5-95% B in 0.7 min, 95-95% B in 0.45 min, 95-5% B in 0.01 min, and then hold at 0% B for 0.44 min (1.5 mL/min flow rate). Mobile phase A was 0.0375% TFA in water, mobile phase B was 0.018% TFA (trifluoroacetic acid) in MeCN (acetonitrile). Column temperature was 40°C. The column used for the chromatography was a Chromolith Flash RP-18e 25-2mm column. MS-method: ESI positive.

NMR data of compounds and intermediates are summarized in Table 2.

HPLC-MS data of compounds and intermediates are summarized in Table 3 to 5. HPLC devices, solvents, columns, and gradients are listed in Table 7.

^{1}H-NMR: The signals are characterized by chemical shift (ppm) vs. tetramethylsilane, by their multiplicity and by their integral (relative number of hydrogen atoms given). The following abbreviations are used to characterize the multiplicity of the signals: m = multiplett, q = quartett, t = triplett, d = doublet and s = singlet.

Abbreviations used are: h for hour(s), min for minute(s), eq for equivalent(s).

Preparation Examples

Example 1: Production of ethyl (E)-3-(5-bromo-2-cyano-phenyl)prop-2-enoate (IVa.1).

A mixture of NaH (1.05 g / 60 wt% in mineral oil) and DME (7 mL) was produced and cooled to -30 °C. Subsequently, a solution of ethyl 2-diethoxyphosphorylacetate (5.9 g) in DME (47 mL) was added dropwise to the mixture over 15 minutes and stirred at -30 °C for further 35 minutes. Then, a solution of 4-bromo-2-formylbenzonitrile (5 g) in DME (43 mL) was added at about -30 °C dropwise over 20 minutes, and the mixture was stirred for additional 2 h. The reaction was quenched by addition of H_2O (70 mL), which was extracted with ethyl acetate. The organic extracts were combined and the solvent was evaporated. Compound IVa.1 was isolated by silica chromatography, resulting in a final yield of 88%. No impurities were detectable by H-NMR.

Example 2: Production of 4-bromo-2-(2-carboxyethyl)benzoic acid (III.1).

A mixture of compound IVa (1 g) from Example 1 with 25 mL of acetic acid was produced. Subsequently Zn powder (2 g) was added and the mixture stirred for 3 h at 80 °C. The mixture was filtrated and the filtrate concentrated by evaporation of the solvent. Ethyl 3-(5-bromo-2-cyano-phenyl)propanoate was obtained with a yield of 100%, no impurities were detectable by H-NMR.

In turn, a premix of H_2SO_4 (2.1 g) with 1 mL of H_2O and 2.6 mL acetic acid was produced. Ethyl 3-(5-bromo-2-cyano-phenyl)propanoate (400 mg) was added to the premix and the resulting reaction mixture was stirred for 20 h at about 139 °C. The reaction was then cooled by addition of 25 g of ice. The precipitated compound III.1 was filtrated, washed with H_2O, and the resulting crystals were dried. The final yield was 75%.

Example 3: Production of methyl 7-bromo-1-oxo-indane-4-carboxylate (II.1).

Step 1: A mixture of compound III.1 (600 mg) from Example 2 with 26 mL of CH_2Cl_2 and a few drops of DMF was produced. Oxalylchloride (1.9 g) was added dropwise at about 25 °C and the mixture was stirred for 35 minutes. The solvent and remaining oxalylchloride were evaporated and 4-bromo-2-(3-chloro-3-oxo-propyl)benzoyl chloride (compound III.1) was instantly further converted by Friedel-Crafts acylation.

Step 2: A mixture of $AlCl_3$ (469 mg) and CH_2Cl_2 (10 mL) was produced. A solution of compound III.1 (692 mg) in CH_2Cl_2 (20 mL) was added to the mixture at about 0 °C over 12 minutes. The mixture was then heated to about 40 °C and stirred under reflux.

Chemical shifts, multiplicity, and peak intensity for 7-bromo-1-oxo-indane-4-carbonyl chloride (compound V.1) are summarized in Table 2.

Compound V.1 was then esterified by addition of CH_3OH (10 mL) to the mixture at about 15 °C. The solvent was evaporated, 5 mL of H_2O was added and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined and the solvent was evaporated. Compound II.1 was isolated from the reaction mixture via silica chromatography.

Example 4: Production of 7-bromo-N-(cyclopropylmethyl)-1-oxo-indane-4-carboxamide (II.2).

Compound III.1 was cyclized to compound V.1 as described in Example 3. Compound V.1 was then amidated by addition of 172 mg cyclopropylmethanamine to the mixture to yield compound II.2.

Example 5: Production of 7-bromo-1-oxo-indane-4-carboxylic acid (II.3).

Compound III.1 was cyclized to compound V.1 as described in Example 3. Compound V.1 was then treated with water to yield compound II.3.

Example 6: Production of methyl 7-bromoindane-4-carboxylate (I.1).

A mixture of $HgCl_2$ (28 mg), H_2O (3 mL), concentrated aqueous HCl (0.025 mL) and Zn powder (370 mg) was produced. The mixture was stirred for 5 minutes at about 20-25 °C, the supernatant was decanted. A premix of 3 mL of H_2O and 9 mL of concentrated aqueous HCl was added to the mixture, resulting in the production of gas. Compound II.1 (100 mg) from Example 3 was added to the mixture and stirred for 1.5 h under reflux. Workup was achieved by addition of brine and extraction with ethyl acetate. The organic phases were combined and the solvent was evaporated. Compound I.1 was isolated by silica chromatography with a purity above 90% (determined by ^{1}H-NMR).

Example 7: Production of compound I.1 from compound II.1 by reduction with $NaBH_4$, followed by dehydroxylation.

A mixture of compound II.1 (180 mg) from Example 3 with CH_3OH (10 mL) was produced and cooled to 0 °C. $NaBH_4$ (28 mg) was added to the mixture and stirred for 40 minutes at about 0 °C, followed by 40 minutes at 20-25 °C. Aqueous HCl (1M) was added to a final pH of 7.0 and

the solvent was evaporated. Methyl 7-bromo-1-hydroxy-indane-4-carboxylate (IIa.1) was produced at high purity (95%, determined by ^{1}H-NMR) with a yield of 89%.

A mixture of compound IIa (65 mg) with CH_2Cl_2 and trifluoroacetic acid (160 mg) was produced. The mixture was stirred at about 25 °C for 70 h. Methyl 7-bromo-1-(2,2,2-trifluoroacetyl)oxy-indane-4-carboxylate was isolated by silica chromatography.

A mixture of methyl 7-bromo-1-(2,2,2-trifluoroacetyl)oxy-indane-4-carboxylate with 3 mL of trifluoroacetic acid and triethyl silane (67 mg) was produced. The mixture was stirred at 20-25 °C for 64 h, upon which the solvent was evaporated. Compound I.1 was produced in pure form with a yield of 92% (determined by ^{1}H-NMR).

Example 8: Characterization of compound V.1 by NMR spectroscopy

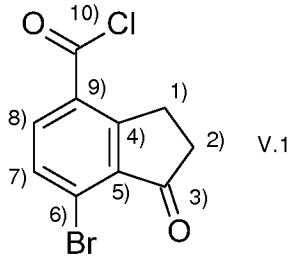
Compound V.1 was synthesized as described in Example 3. Before quenching, the reaction mixture was complemented with perdeuterated DMSO. The sample was measured by ^{1}H-NMR and ^{1}H-decoupled ^{13}C-NMR at 500 MHz.

The following peaks were detected in the

a) ^{13}C-spectrum [ppm]: 27.58, 38.64, 162.27, 166.55, 223.00.

b) ^{1}H-spectrum [ppm]: 3.02, 3.14, 7.49 (d), 8.07 (d).

The sample was also measured by ^{1}H-Correlation Spectroscopy (COSY) ^{1}H,^{13}C-heteronuclear single quantum coherence (HSQC), and ^{1}H,^{1}H-heteronuclear multiple bond correlation (HMBC), resulting in the following peaks and their structural correlation:



V.1

Assignment: 1) (3.14/27.58); 2) (3.02/38.64); 3) (223.00), 4) (162); 5) (139.6), 6) (121.0); 7) (7.49/131.6); 8) (8.07/134.0); 9) (130.6), 10) (167.0).

Example 9: Production of methyl 7-acetylindane-4-carboxylate (VI.1)

A mixture of methyl 7-bromoindane-4-carboxylate (compound I.1, 46 mg), ethylene glycol vinyl ether (79.5 mg), $Pd(OAc)_2$ (1 mg), 1,3-bis(diphenylphosphino)propane (3.7 mg), K_2CO_3 (74.5 mg) and 1 mL of water was stirred at 90 °C for 80 minutes under reflux. The mixture was cooled to about 25 °C and concentrated aqueous HCl (0.3 mL) was added. The resulting mixture was stirred at about 25 °C for one hour. Workup was achieved by addition of K_2CO_3 (10 wt% aqueous solution) and extraction by ethyl acetate. Then the organic phase was dried and concentrated. Compound VI.1 was isolated from the extract by silica column chromatography.

Example 10: Production of methyl 7-[(Z)-3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]indane-4-carboxylate (XIX.1).

A solution of methyl 7-acetylindane-4-carboxylate (compound VI.1, 50.00 g) in 1 liter 1,2-dichloroethane (DCE) was added to a mixture of 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone (119.59 g), K_2CO_3 (38.00 g), and triethylamine (27.82 g). Then the mixture was stirred

at about 120 °C under nitrogen for 12 h. Water (500 mL) was added to the mixture, which was in turn extracted with dichloromethane (DCM). Then the organic phase was dried and concentrated. Compound IX.1 was isolated by from the residue by silica column chromatography.

Example 11: Production of methyl 7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indane-4-carboxylate (XIV.1).

A mixture of a solution of compound XIX.1 of example 10 (100.00 g) in two liters DCE, NH_2OH/HCl (30.13 g), and tetra-n-butylammonium bromide (10.48 g) was produced. A solution of NaOH (34.69 g) in 400 mL water was admixed dropwise at about 25 °C. Then the mixture was stirred at about 25 °C for 12h. Water (200 mL) was added to the mixture, which was in turn extracted with DCM. The organic phase was washed with water, dried, filtered and concentrated by evaporation of the solvent. Compound XIV.1 was isolated from the residue by silica column chromatography with a yield of 96.8%.

Example 12: Production of 7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indane-4-carboxylic acid (XIV.2).

A solution of compound XIV.1 of example 11 (110.00 g) in THF/dioxane (500 mL/500 mL), and a solution of $LiOH \cdot H_2O$ (48.46 g) in 150 mL water was mixed at about 25 °C. Then the mixture was stirred at about 80 °C for 18 h, cooled to about 25°C, and concentrated under reduced pressure at about 50 °C. Water (400 mL) was added to the mixture, which was subsequently extracted with petroleum ether (400 mL). The pH of the aqueous phase was then adjusted to about 2.0 with aqueous HCl. The aqueous phase was subsequently extracted with ethyl acetate. The ethyl acetate extract was dried, and concentrated in vacuo. The residue was washed with hexane (600 mL), resulting in compound XIV.2 with a yield of 93.7% as a white solid.

Example 13: Production of 7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.3).

A solution of compound XIV.2 of example 12 (230 mg), the HCl salt of pyrimidin-2-ylmethanamine (65 mg), and PyBrop (279 mg), in DCM (15 mL) was produced. Di-isopropyl ethyl amine (258 mg) was admixed at 20 to 25 °C. The mixture was stirred overnight under nitrogen. The reaction was extracted with water, and the organic phase was concentrated in vacuo. Compound XIV.3 was isolated from the residue via silica column chromatography.

Example 14: Production of methyl 7-[(Z)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-but-2-enoyl]indane-4-carboxylate (XIX.2)

A mixture of 1-[7-(1-methoxyvinyl)indan-4-yl]ethanone (27 g), 1-(3,5-dichlorophenyl)-2,2,2-trifluoro-ethanone (60 g), K_2CO_3 (22 g), triethylamine (16 g) and dichloroethane (600 mLl) was produced. The mixture was stirred at 110 °C under nitrogen for 12 h. Water (500 mL) was added to the mixture. The mixture was subsequently extracted with DCM. The organic phase was dried over N_2SO_4 and concentrated in vacuo. Compound XIX.2 was isolated from the residue via silica column chromatography with a yield of 87.8%.

Example 15: Production of methyl 7-[3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-(nitromethyl)butanoyl]indane-4-carboxylate

A mixture of compound XIX.2 of example 14 (40 g), MeCN (400 mL), 1,8-diazabicyclo[5.4.0]un-dec-7-ene (41 g) and nitromethane (27 g) was produced. The mixture was stirred for 40 min at 20 °C and subsequently adjusted to pH 5-6 with aqueous HCl. The mixture

was then extracted with ethyl acetate. The organic phase was concentrated in vacuo. Methyl 7-[3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-(nitromethyl)butanoyl]indane-4-carboxylate was isolated from the residue via silica column chromatography with a yield of 80%.

Example 16: Production of Methyl 7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxylate (XIV.4).

Iron powder (10.4 g) was added at about 25 °C to a mixture of methyl 7-[3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-(nitromethyl)butanoyl]indane-4-carboxylate of example 15, CH_3OH (300 mL), and CH_3COOH (300 mL). The mixture was stirred at 80 °C for 12h. The mixture was concentrated in vacuo and subsequently poured into a saturated solution of aqueous $NaHCO_3$. The resulting mixture was extracted with ethyl acetate. The organic phase was concentrated in vacuo. Compound XIV.4 was isolated from the residue via silica column chromatography.

Example 17: Production of 7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxylic acid (XIV.5)

A mixture of compound XIV.4 of example 16 (19 g), THF (200 mL) and CH_3OH (100 mL) was produced. A solution of $LiOH \cdot H_2O$ (8.4 g) in water (100 mL) was added to the mixture at 25 °C, which was subsequently stirred at 20 °C for 12h. The pH of the mixture was then adjusted to pH 9 with aqueous HCl. The mixture was subsequently reduced in vacuo, upon which the pH was again adjusted to pH 5 with aqueous HCl. The resulting mixture was then extracted with ethyl acetate. The organic phase was concentrated in vacuo. Compound XIV.5 was isolated from the residue via silica column chromatography.

Example 18: Production of 7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.6)

A solution of compound XIV.5 (1.0 eq), pyrimidin-2-ylmethanammoniumchloride (1.2 eq), PyBrOP (1.2 eq) in DCM (10 mL) was produced. Diisopropylethylamine (3-4 eq) was added to the mixture at 20 to 25 °C. The mixture was stirred under nitrogen for several hours. The mixture was extracted with water, and the organic phase was reduced in vacuo. Compound XIV.6 was isolated from the residue via silica column chromatography.

Example 19: Production of 7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.7)

Compound 7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxylic acid was produced in analogy to examples 14 to 17. A solution of 7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxylic acid (2.5 g), pyrimidin-2-ylmethanammoniumchloride (0.95 g), PyBrOP (3.04 g) in DCM (100 mL) was produced. Diisopropylethylamine (2.25 g) was added to the mixture at 20 to 25 °C. The mixture was stirred under nitrogen for several hours. The mixture was extracted with water, and the organic phase was reduced in vacuo. Compound XIV.7 was isolated from the residue via silica column chromatography.

Example 20: Production of 5-(3,5-dichlorophenyl)-3-hydroxy-3-(7-methoxycarbonylindan-4-yl)-5-(trifluoromethyl)tetrahydrothiophene-2-carboxylic acid

2-sulfanylacetic acid (2.2 g) and triethylamine (2.4 g) were added to a mixture of compound XIX.2 of example 14 (2.2 g) and THF (35 mL). The resulting mixture was stirred at 20 °C for 16h

and reduced in vacuo. Subsequently, the pH was adjusted to pH 2 with aqueous HCl. The mixture was extracted with methyl-tert-butyl-ether (50 mL). Subsequently, the pH of the aqueous phase was adjusted to pH 8 with a saturated solution of $NaHCO_3$. The aqueous phase was then extracted with ethyl acetate and reduced in vacuo to dryness, thereby yielding 3-(7-carboxyindan-4-yl)-5-(3,5-dichlorophenyl)-3-hydroxy-5-(trifluoromethyl)tetrahydrothiophene-2-carboxylic acid.

Example 21: Production of methyl 7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]indane-4-carboxylate (XIV.8)

Mesyl chloride (3 g) was added to a mixture of 5-(3,5-dichlorophenyl)-3-hydroxy-3-(7-methoxycarbonylindan-4-yl)-5-(trifluoromethyl)tetrahydrothiophene-2-carboxylic acid of example 20 (6.2 g) and pyridine (60 mL) at 0 °C. The mixture was subsequently stirred at 20 °C for 16 h, then poured into H_2O (100 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried, and reduced in vacuo. DMF (20 mL) was added to the residue, and the resulting mixture was stirred at 120 °C for 1 h. The mixture was reduced in vacuo and then poured into H_2O (100 mL) and extracted with methyl tert-butyl ether. The organic phase was reduced in vacuo. Compound XIV.8 was isolated from the residue via silica column chromatography.

Example 22: Production of 7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]indane-4-carboxylic acid (XIV.9)

A mixture of compound XIV.8 of example 21 (1.1 g), and THF (15 mL) was produced. A solution of $LiOH \cdot H_2O$ (0.3 g) in water (1 mL) was added to the mixture, which was subsequently stirred at 20 °C for 16h. The pH of the mixture was then adjusted to pH 2 with aqueous HCl. The resulting mixture was then extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated in vacuo. Compound XIV.9 was isolated from the residue via silica column chromatography.

Example 23: Production of dihydrothiophene compounds XIV.10 to XIV.13

A solution comprising compound XIV.9 of example 22 (1.0 eq), PyBrOP (1.2 eq), DCM (10 mL), and an ammonium chloride compound selected from pyrimidin-2-ylmethanammonium chloride, 2-pyridylmethanammonium chloride, 2-ammonium-N-(2,2,2-trifluoroethyl)acetamide chloride, or 1,1-dioxothietan-3-ammonium chloride (1.2 eq) was produced. Diisopropylethylamine (3-4 eq) was added to the mixture at 20 to 25 °C. The mixture was stirred under nitrogen for several hours. The mixture was extracted with water, and the organic phase was reduced in vacuo. Depending on the ammonium chloride compound used, a compound XIV.10 to XIV.13 was isolated from the residue via silica column chromatography.

Example 24: Production of dihydrothiophene compounds XIV.15 to XIV.20

7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]indane-4-carboxylic acid (XIV.14) was produced in analogy to compound XIV.9 in examples 20 to 22.

A solution comprising compound XIV.14 (1.0 eq), PyBrOP (1.2 eq), DCM (10 mL), and an ammonium chloride compound selected from 1,1-dioxothietan-3-ammonium chloride, (4R)-4-ammonium-2-ethyl-isoxazolidin-3-one chloride, pyrimidin-2-ylmethanammonium chloride, 2-ammonium-N-(2,2,2-trifluoroethyl)acetamide chloride, thietan-3-ammonium chloride, and 2-methylsulfanylethanammonium chloride (1.2 eq) was produced. Diisopropylethylamine (3-4 eq)

was added to the mixture at 20 to 25 °C. The mixture was stirred under nitrogen for several hours. The mixture was extracted with water, and the organic phase was reduced in vacuo. Depending on the ammonium chloride compound used, a compound XIV.15 to XIV.20 was isolated from the residue via silica column chromatography.

Example 25: Production of [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanol

$LiBH_4$ (0.44 g) was added to a mixture of compound XIV.1 of example 11 (2 g), and THF (50 mL) at 25 °C. The mixture was stirred at 70 °C for 15 h and subsequently diluted with a saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate. The organic phases were dried, reduced in vacuo. [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanol was isolated from the residue by silica column chromatography.

Example 26: Production of 3-[7-(chloromethyl)indan-4-yl]-5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoro-methyl)-4H-isoxazole

To a solution of [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanol (2.0 g) in DCM (60 mL) was admixed triethylamine (3 mL) and mesylchloride (1 g) at 0°C. The mixture was stirred at 25 °C for 10h. The mixture was subsequently diluted with a saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate. The organic phases were dried, reduced in vacuo. [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanol was isolated from the residue by silica column chromatography with a yield of 94%.

Example 27: Production of [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine

A mixture of 3-[7-(chloromethyl)indan-4-yl]-5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoro-methyl)-4H-isoxazole of example 26 (3.8 g), NaN_3 (0.95 g), and DMF (50 mL) was stirred at 25 °C under nitrogen for 13h. The mixture was diluted with water (100 mL) and extracted with methyl tert-butyl ether. The organic phases were dried and reduced in vacuo. The residue was dissolved in THF (80 mL) and H_2O (80 mL). Triphenylphosphine (2 g) was added, and the mixture was stirred at 85 °C under nitrogen for 2h. The mixture was extracted with ethyl acetate and the organic phases were dried and concentrated. [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine was isolated from the residue by silica column chromatography.

Example 27: Production of inverted amides XV.1 to XV.6

A mixture of [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine of example 26 (1.0 eq) in THF (10 mL) and TEA (3.0 eq.) was stirred at 20 to 25 °C. An acid chloride (1.2 eq.) selected from 2-methylsulfonylacetyl chloride, propanoyl chloride, 3,3,3-trifluoropropanoyl chloride, acetyl chloride, cyclopropanecarbonyl chloride was added dropwise. The reaction mixture was stirred at 20 to 25 °C, followed by dilution with H_2O and extraction with ethyl acetate. The organic phases were dried and reduced in vacuo. Depending on the acid chloride compound used, a compound XV.1 to XIV.6 was isolated from the residue via silica column chromatography.

Example 28: Production of inverted amides XV.7 to XV.8

Compound [7-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine was produced in analogy to [7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine in examples 25 to 27.

A mixture of [7-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methanamine (1.0 eq) in THF (10 mL) and TEA (3.0 eq.) was stirred at 20 to 25 °C. An acid chloride (1.2 eq.) selected from 2-methylsulfonylacetyl chloride, and propanoyl chloride, was added dropwise. The reaction mixture was stirred at 20 to 25 °C, followed by dilution with H_2O and extraction with ethyl acetate. The organic phases were dried and reduced in vacuo. Depending on the acid chloride compound used, a compound XV.7 or XIV.8 was isolated from the residue via silica column chromatography.

Example 29: Production of further compounds XIV-A and XV-A

Tables 3, 4, 5 and 6 list further compounds XIV-A and XV-A from the classes of isoxazazoles, pyrrolines, dihydrothophenes, and dihydrofuranes. These were produced in analogy to examples 1 to 28, or in accordance to the general description of the reactions above from compounds I.1 and VI.1 with the respective amines, acid chlorides, 2,2,2-trifluoroacetophenone, and 4-halogen-2-phenyl-2-(trifluoromethyl)-3H-furan derivatives.

Table 2: Characterization of compounds by NMR spectroscopy

Compound	Solvent / frequency	Chemical shift ^{1}H-NMR (ppm)	Chemical shift ^{13}C-NMR (ppm)
I.1	DMSO-d6 / 500 MHz	2.04 (m, 2H), 2.9 (t, 2H), 3.3 (t, 2H), 3.8 (s, 3H), 7.52 (d, 1H), 7.64 (d, 1H)	23.3, 33.9, 34.77, 52.04, 124.36, 125.36, 129.65, 129.68, 145.68, 147.9, 166.12.
II.1	DMSO-d6 / 500 MHz	2.71 (m, 2H), 3.34 (m, 2H), 3.9 (s, 3H), 7.78 (d, 1H), 8.06 (d, 1H).	25.82, 36.44, 52.21, 123.48, 126.29, 132.66, 134.58, 136.14, 159.27, 165.06, 203.05.
II.2	$CDCl_3$ / 500 MHz	0.31 (q, 4H), 1.06 (m, 1H), 2.77 (m, 2H), 3.3 (m, 4H), 6.22 (t, 1H), 7.59 (d, 1H), 7.60 (d,1H)	3.60 (2C), 10.70, 24.94, 36.94, 44.90, 122.21, 132.42, 132.62, 132.75, 134.97, 156.89, 166.38, 203.68
II.3	DMSO-d6 / 500 MHz	2.69(m, 2H), 3.35 (m, 2H), 7.74 (d, 1H), 8.04 (d, 1H), 13.4 (s, broad, 1H)	26.09, 36.63, 123.14, 128.20, 132.66, 134.59, 136.61, 159.56, 166.42, 203.36
III.1	DMSO-d6 / 500 MHz	2.51 (t, 2H), 3.12 (t, 2H), 7.5 (s, 1H), 7.6 (d, 1H), 7.7 (d, 1H), 12.5 (s, broad, 2H)	28.59, 34.84, 125.26, 129.24, 129.42, 132.27, 133.33, 144.39, 167.72, 173.46
V.1	DMSO-d6 / 500 MHz	3.02 (m, 2H), 3.14 (m, 2H), 7.49 (d, 1H), 8.07 (d, 1H)	27.58, 38.64, 121.0, 130.6, 131.6, 134.0, 139.6, 162.27, 167.0, 223.00
VI.1	$CDCl_3$ / 500 MHz	2.09 (m, J=7.7 Hz, 2 H) 2.62 (s, 3 H) 3.26 (m, 4 H) 3.93 (s, 3 H) 7.7 (d, J=8.1 Hz, 1 H) 7.90 (d, J=8.1 Hz, 1 H)	24.85, 28.74, 33.36, 33.64, 52.07, 127.11, 128.15, 129.47, 136.65, 146.96, 148.77, 166.95, 199.85
XIV.1	$CDCl_3$ / 400 MHz	7.809-7.789 (d, J=8 Hz, 1 H) 7.527-7.513 (d, J=5.6 Hz, 1 H) 7.187-7.141 (t, J= 9.2 Hz, 1H) 4.099-4.056 (d, J= 17.2 Hz, 1H) 3.84 (s, 3H), 3.704-3.662 (d, J= 16.8 Hz), 3.264-3.226 (m, 2H), 3.137-3.120 (m, 2 H)	-

		2.068-2.030 (m, 2 H).	
XIV.2	DMSO-d6 / 500 MHz	13.10 (s, 1H, very broad), 7.84 (d, 2H, J=6Hz), 7.81 (d, 1H, J=8Hz), 7.50 (d, 1H, J=8Hz), 4.41 (d, 1H, J=18.3Hz), 4.33 (d, 1H, J=18.3Hz), 3.23 (t, 2H, J=7.7Hz), 3.09 (m 2H), 2.03 (m, 2H)	167.60, 157.84, 153.74, 146.97, 144.57, 132.95, 129.69, 128.05, 128.05, 128.05, 126.88, 126.34, 123.68, 121.59, 121.59, 85.63, 43.95, 34.05, 33.25, 24.01
XIV.3	DMSO-d6 / 500 MHz	8.75 (d, 2H, J=4.9Hz), 7.65 (d, 1H, J=8Hz), 7.61 (d, 2H, J=6Hz), 7.45 (t, 1H, J=4.5Hz), 7.27 (m, 2H), 4.91 (d, 2H, J=4.5Hz), 4.17 (d, 1H, J=17Hz), 3.79 (d, 1H, J=17Hz), 3.28 (t, 2H, J=7.7Hz), 3.22 (q, 2H, J=7.7Hz), 2.15 (m, 2H)	167.74, 165.55, 157.29, 157.29, 156.32, 154.76, 145.91, 144.94, 133.55, 133.08, 127.57, 127.57, 126.32, 125.91, 125.79, 123.77, 123.06, 123.06, 119.73, 86.14, 45.68, 45.29, 34.93, 33.03, 25.00
XIV.4	$CDCl_3$ / 400 MHz	7.82 (d, J=8.38 Hz, 1 H), 7.39 (d, J=7.94 Hz, 1 H), 7.31 (t, J=1.54 Hz, 1 H), 7.19 (d, J=1.32 Hz, 2 H), 4.87 (dd, J=17.20, 1.32 Hz, 1 H), 4.40 (d, J=17.20 Hz, 1H), 3.85 (s, 3 H), 3.73 (dd, J=17.42, 1.54 Hz, 1 H), 3.42 (d, J=17.20 Hz, 1H), 3.12 - 3.29 (m, 4 H), 2.03 (t, J=7.28 Hz, 2H)	
XIV.5	DMSO-d6 / 500 MHz	13.0 (s, 1H, broad), 7.82 (d, 1H, J=8Hz), 7.69 (m, 2H), 7.60 (d, 2H, J=1.4Hz), 4.91 (d, 1H, J=17.3Hz), 4.45 (d, 1H, J=17.3Hz), 3.88 (d, 1H, J=17.9Hz), 3.77 (d, 1H,	171.09, 167.52, 147.14, 145.16, 141.08, 134.15, 134.15, 132.62, 128.33, 128.1, 127.9, 127.9, 127.9, 127.36, 127.18, 67.22, 54.81, 43.78, 33.62, 33.12, 24.21

		J=17.9Hz), 3.21 (m, 2H), 2.01 (m, 2H)	
XIV.6	DMSO-d6 / 500 MHz	8.75 (d, 2H, J=5Hz), 7.66 (d, 1H, J=8Hz), 7.51 (d, 1H, J=8Hz), 7.45 (t, 1H, J=4.3Hz), 7.38 (t, 1H, J=1.7Hz), 7.27 (m, 3H), 4.94 (d, 1H, J=17.3Hz), 4.92 (d, 2H, J=4.3Hz), 4.47 (d, 1H, J=17.3Hz), 3.81 (d, 1H, J=17.3Hz), 3.51 (d, 1H, J=17.3Hz), 3.26 (m, 4H), 2.13 (m, 2H)	135.29, 135.29, 133.3, 131.57, 128.57, 127.15, 127.13, 127.13, 126.88, 125.52, 119.63, 68.43, 55.12, 45.61, 45.05, 34.24, 32.78, 25.23
XIV.8	$CDCl_3$ / 400 MHz	7.84 (d, J=8.03 Hz, 1H) 7.37 - 7.46 (m, 3H) 7.11 (d, J=8.28 Hz, 1H) 6.45 (s, 1H) 3.87 - 3.94 (m, 4H) 3.70 - 3.77 (m, 1H) 3.29 - 3.36 (m, 2H) 2.96 - 3.02 (m, 2H) 2.08 - 2.16 (m, 2H)	
XIV.9	$CDCl_3$ / 400 MHz	7.94 (d, J=8.38 Hz, 1H) 7.38 - 7.45 (m, 3 H) 7.15 (d, J=7.94 Hz, 1H) 3.87 - 3.97 (m, 1H), 3.68 - 3.80 (m, 2H) 3.32 - 3.42 (m, 2H) 3.01 (td, J=7.39, 2.43 Hz, 2H) 2.06 - 2.19 (m, 3H)	
XIV.56	DMSO-d6 / 500 MHz	7.6 (d, 2H, J=6Hz), 7.44 (d, 1H, J=8Hz), 7.2 (d, 1H, J=8Hz), 7.11 (d, 1H, J=6.7Hz), 4.86 (m, 1H), 4.59 (m, 2H), 4.11 (m, 3H), 3.77 (d, 1H, J=17.3Hz), 3.15 (m, 4H), 2.1 (m, 2H)	168.17, 156.11, 154.73, 146.15, 145.47, 132.84, 131.68, 127.5, 127.5, 126.22, 126.5, 125.33, 123.66, 123.02, 123.02, 86.24, 71.48, 71.48, 45.08, 34.74, 32.83, 32.25, 24.79
XIX.1	DMSO-d6 / 500	7.86 (d, 1H, J=8Hz), 7.49 (d, 1H, J=8Hz),	192.26, 166.51, 154.67, 149.11, 147.63,

	MHz	7.32 (q, 1H, J=1.1Hz), 7.19 (d, 2H, J=6Hz), 3.92 (s, 3H,), 3.24 (t, 2H, J=7.6Hz), 3.1 (t, 2H, J= 7.6Hz), 2.07 (quin-tet, 2H, J=7.6Hz)	135.88, 135.23, 133.35, 130.46, 129.64, 129.64, 128.25, 127.63, 127.16, 122.63, 122.63, 122.18, 52.22, 33.33, 32.25, 24.86
XIX.2	$CDCl_3$ / 400 MHz	7.81 (d, 1H, J=8.38Hz), 7.44 (d, 1H, J=7.94Hz), 7.25 (d, 2H, 7.06Hz), 7.07 (d, 2H, 0.88 Hz), 3.89 (s, 3H), 3.21 (t, 2H, J=7.72Hz), 3.06 (t, 2H, J=7.5 Hz), 2.05 (d, 2H, J=7.5 Hz)	

Table 3: Characterization of dihydrothiophene compounds by HPLC-MS

Compound	HPLC set-up	Reten-tion time	Mass over charge (m/z)
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.10)	A	1.440	550.0
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(2-pyridylmethyl)indane-4-carboxamide (XIV.11)	A	1.267	549.0
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]indane-4-carboxamide (XIV.12)	A	1.432	596.9
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(1,1-dioxothietan-3-yl)indane-4-carboxamide (XIV.13)	A	1.416	561.9
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(1,1-dioxothietan-3-yl)indane-4-carboxamide (XIV.15)	B	1.428	579.6
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-[(4R)-2-ethyl-3-oxo-isoxazolidin-4-yl]indane-4-carboxamide (XIV.16)	A	1.464	590.4
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.17)	A	1.429	568.0
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]indane-4-carboxamide (XIV.18)	A	1.451	614.6
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(thietan-3-yl)indane-4-carboxamide (XIV.19)	B	1.467	548.0
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(2-methylsulfanylethyl)indane-4-carboxamide (XIV.20)	A	1.462	550.0

Table 4: Characterization of inverted amide compounds by HPLC-MS

Compound	HPLC set-up	Retention time	Mass over charge (m/z)
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]-2-methylsulfonyl-acetamide (XV.1)	A	1.367	567.0
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]propanamide (XV.2)	A	1.421	503.0
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]-3,3,3-trifluoro-propanamide (XV.3)	A	1.455	557.0
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]acetamide (XV.4)	A	1.384	488.9
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]cyclopropanecarboxamide (XV.5)	A	1.423	514.9
N-[[7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indan-4-yl]methyl]propanamide (XV.6)	A	1.421	503.0
N-[[7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indan-4-yl]methyl]propanamide (XV.7)	A	1.270	483.1
N-[[7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indan-4-yl]methyl]-2-methylsulfonyl-acetamide (XV.8)	C	1.222	547.1

Table 5: Characterization of amide compounds by HPLC-MS

Compound	HPLC set-up	Retention time	Mass over charge (m/z)
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.7)	A	1.284	550.9

7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(2-methylsulfanylethyl)indane-4-carboxamide (XIV.21)	A	1.405	535.0
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.22)	A	1.284	550.9
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(thietan-3-ylmethyl)indane-4-carboxamide (XIV.23)	A	1.527	544.8
N-(cyclopropylmethyl)-7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxamide (XIV.24)	A	1.393	514.6
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[(1,1-dioxothietan-3-yl)methyl]indane-4-carboxamide (XIV.25)	A	1.265	576.9
N-cyclopropyl-7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carboxamide (XIV.26)	A	1.347	481.0
7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(thiazol-4-ylmethyl)indane-4-carboxamide (XIV.27)	A	1.319	538.0
7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[1-methyl-2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]indane-4-carboxamide (XIV.28)	A	1.357	594.0
7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(1-oxothietan-3-yl)indane-4-carboxamide (XIV.29)	A	1.232	529.0
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[(E)-methoxyiminomethyl]indane-4-carboxamide (XIV.30)	A	1.468	515.8
1-[[7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]indane-4-carbonyl]amino]-3-(2,2,2-trifluoroethyl)urea (XIV.31)	A	1.286	581.3
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(2-methylsulfonylethyl)indane-4-carboxamide (XIV.32)	A	1.271	565.3
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[[1-	A	1.433	565.0

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(difluoromethyl)cyclopropyl]methyl]indane-4-carboxamide (XIV.33)			
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-prop-2-ynyl-indane-4-carboxamide (XIV.34)	A	1.358	498.9
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[(2,2-difluorocyclopropyl)methyl]indane-4-carboxamide (XIV.35)	A	1.411	549.3
7-[3-(3,5-dichlorophenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-[[5-(difluoromethyl)pyrimidin-2-yl]methyl]indane-4-carboxamide (XIV.36)	A	1.308	583.1
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(1,1-dioxothiolan-3-yl)indane-4-carboxamide (XIV.37)	A	1.269	577.2
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-(2-oxotetrahydrofuran-3-yl)indane-4-carboxamide (XIV.38)	A	1.324	543.1
7-[3-(3,5-dichloro-4-fluoro-phenyl)-3-(trifluoromethyl)-2,4-dihydropyrrol-5-yl]-N-tetrahydrothiophen-3-yl-indane-4-carboxamide (XIV.39)	A	1.510	546.0
N-allyl-7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indane-4-carboxamide (XIV.40)	A	1.440	500.8
7-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N'-pyrimidin-2-yl-indane-4-carbohydrazide (XIV.41)	A	1.317	535.9
7-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-[(4S)-2-ethyl-3-oxo-isoxazolidin-4-yl]indane-4-carboxamide (XIV.42)	A	1.396	556.0
7-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(thietan-3-ylmethyl)indane-4-carboxamide (XIV.43)	A	1.446	529.0
N-[(2,2-dichlorocyclopropyl)methyl]-7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]indane-4-carboxamide (XIV.44)	A	1.526	584.9
7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-[(2-methyltetrazol-5-yl)methyl]indane-4-	A	1.373	557.0

carboxamide (XIV.45)			
7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(1,2,4-oxadiazol-3-ylmethyl)indane-4-carboxamide (XIV.46)	A	1.375	542.9
7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(1,3-dioxolan-2-ylmethyl)indane-4-carboxamide (XIV.47)	A	1.399	547.1
7-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(diethyl-λ⁴-sulfanylidene)indane-4-carboxamide (XIV.48)	A	1.349	549.0
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-[(4R)-2-ethyl-3-oxo-isoxazolidin-4-yl]indane-4-carboxamide (XIV.49)	A	1.464	590.4
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(1,1-dioxothietan-3-yl)indane-4-carboxamide (XIV.50)	A	1.461	561.9
7-[2-(3,5-dichloro-4-fluoro-phenyl)-2-(trifluoromethyl)-3H-thiophen-4-yl]-N-(1,1-dioxothietan-3-yl)indane-4-carboxamide (XIV.51)	B	1.428	579.6

Table 6: Characterization of dihydrofurane compounds by HPLC-MS

Compound	HPLC set-up	Retention time	Mass over charge (m/z)
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-furan-4-yl]-N-[(4R)-2-ethyl-3-oxo-isoxazolidin-4-yl]indane-4-carboxamide (XIV.52)	A	1.388	555.1
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-furan-4-yl]-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]indane-4-carboxamide (XIV.53)	A	1.370	581.0
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-furan-4-yl]-N-(2-methylsulfanylethyl)indane-4-carboxamide (XIV.54)	A	1.451	516.0

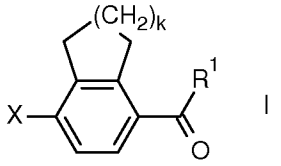
7-[2-(3,5-dichlorophenyl)-2-(trifluoromethyl)-3H-furan-4-yl]-N-(pyrimidin-2-ylmethyl)indane-4-carboxamide (XIV.55)	A	1.378	534.0

Table 7: HPLC set-up and equipment

Code used in Tables 3, 4, and 5	HPLC set-up	Equipment
A	Mobile phase A: water + 0.1% TFA; mobile phase B: MeCN; gradient: 5% B to 100% B in 1.50 min, 100% B for 0.25 min; flow 0.8 mL/min to 1 mL/min in 1.51 min; temperature 60 °C; ESI positive; range (m/z) 100-700	MSD4/5: Shimadzu Nexera UHPLC and Shimadzu LCMS 20-20, ESI; Column: Phenomenex Kinetex 1.7 µm XB-C18 100A, 50 x 2.1 mm
B	Mobile phase A: water + 0.1% TFA; mobile phase B: MeCN; gradient: 5% B to 100% B in 1.50 min, 100% B for 0.25 min; flow 0.8 mL/min to 1 mL/min in 1.51 min; temperature 60 °C; ESI positive; range (m/z) 50-700	
C	Mobile phase A: water + 0.1% TFA; mobile phase B: MeCN; gradient: 5% B to 100% B in 1.50 min, 100% B for 0.25 min; flow 0.8 mL/min to 1 mL/min in 1.51 min; temperature 60 °C; ESI positive; range (m/z) 100-1400	

Claims

1. Compounds of formula I



I

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wherein the variables have the following meaning:

X Cl, Br, or I;

R^1 H, OR^{11}, or $NR^{12}R^{13}$;

R^{11} a) H;

b) C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_2-C_6-alkynyl;

which groups are unsubstituted, or substituted by halogen, CN, NO_2, phenyl, $S(O)_mR^A$, OR^B, NR^BR^C, $S(O)_mNR^BR^C$, $Si(R^B)_2R^C$, $C(=O)R^B$, $C(=O)NR^BR^C$, $C(=O)OR^B$, $C(=S)R^B$, $C(=S)NR^BR^C$, $C(=S)OR^B$, $C(=S)SR^B$, $C(=NR^B)R^C$, $C(=NR^B)NR^CR^D$;

c) phenyl, which is unsubstituted, or substituted by R^A; or

d) a 3-, 4-, 5-, 6-, or 7-membered saturated, partially unsaturated or fully unsaturated heterocycle, which heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, or $S(O)_m$;

wherein

R^A a) C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, C_1-C_4-alkyl-C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, phenyl; which groups are unsubstituted, or substituted by halogen, CN, OH, NO_2, phenyl, or C_1-C_6-alkyl-phenyl;

b) a 3-, 4-, 5-, 6-, or 7-membered saturated, partially unsaturated or fully unsaturated heterocycle, which heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, wherein none, one, or more ring members are replaced by C(=O), or C(=S), and which heterocycle is unsubstituted, or substituted by halogen, CN, N_3, NO_2, SCN, SF_5, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, or C_2-C_6-haloalkynyl;

R^B, R^C, R^D are independently from one another, as defined for R^A, or H; or

two substituents R^B, R^C, or R^D, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, or $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S);

R^{12} H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

R^{13} a) H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl; which groups are unsubstituted, or substituted by R^E;

b) a group Z-A, wherein Z is a chemical bond, CH_2, CH_2CH_2 or C=O; and A is a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or fully unsaturated heterocycle, which heterocycle is unsubstituted or substituted by R^F and comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

c) a group $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $N(R^B)C(=O)OR^C$, $N(R^B)C(=O)N(R^C)R^D$, $N(R^B)C(=S)OR^C$, $N(R^B)C(=S)N(R^C)R^D$,$C(=O)N(R^B)R^C$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$, $C=NOR^A$, $C=NR^AR^B$, $C=NR^BR^C$; or

wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^F, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

or wherein R^{12} and R^{13}, together with the N-atom to which they are bound, form a group $=S(R^B)R^C$, $=NR^B$, $=NOR^B$, or $=NN(R^B)R^C$;

R^E a) halogen, CN, N_3, NO_2, SCN, SF_5, 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, $Si(R^B)_2R^C$, OR^{11}, OSO_2R^A, $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=O)N(R^B)N(R^C)R^D$, $C(=O)NOR^B$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$;

b) phenyl, which is unsubstituted, or substituted by R^A; or

c) two substituents R^E, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or

fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, or $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

R^F a) halogen, CN, N_3, NO_2, SCN, SF_5, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, 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, $Si(R^B)_2R^C$, OR^{11}, OSO_2R^A, $S(O)_mR^A$, $S(O)_mN(R^B)R^C$, $N(R^B)R^C$, $C(=O)N(R^B)R^C$, $C(=O)N(R^B)N(R^C)R^D$, $C(=O)NOR^B$, $C(=S)N(R^B)R^C$, $C(=O)OR^A$;

b) phenyl, which is unsubstituted, or substituted by R^A; or

c) two substituents R^F, together with the atom, or the atoms to which they are bound, form a 3, 4, 5, 6, or 7-membered saturated, partially unsaturated, or fully unsaturated carbocycle, or heterocycle, which cycles are unsubstituted, or substituted by R^A, and wherein the heterocycle comprises one, or more, same, or different heteroatoms O, $N(O)_n$, and $S(O)_m$, and wherein none, one, or more ring members are replaced by C(=O), or C(=S), $C(=NR^B)$, or $C(=NOR^B)$;

k 1, or 2

m 0, 1, or 2;

n 0, or 1.

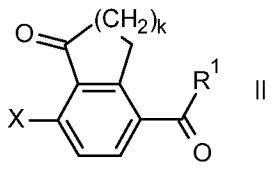
2. The compounds according to claim 1, wherein k is 1.

3. The compounds according to claim 1, wherein k is 2.

4. The compounds according to any of claims 1 to 3, wherein R^1 is OR^{11}, and R^{11} is H, C_1-C_6-alkyl, phenyl, or benzyl.

5. The compounds according to claim 4, wherein R^{11} is C_1-C_4-alkyl.

6. A process for the production of compounds I, as defined in any of claims 1 to 5, by reaction of compounds II with a reducing agent.



II

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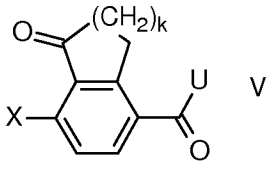
7. The process according to claim 6, wherein compounds II are produced by reaction of compounds V



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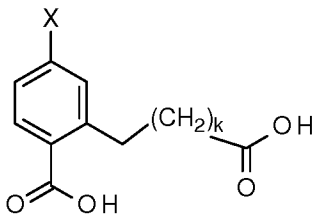
with H_2O, $R^{11}OH$, or $NHR^{12}R^{13}$; wherein X is Cl, Br, or I, and U is halogen; and wherein compounds V are produced by reaction of compounds III

III



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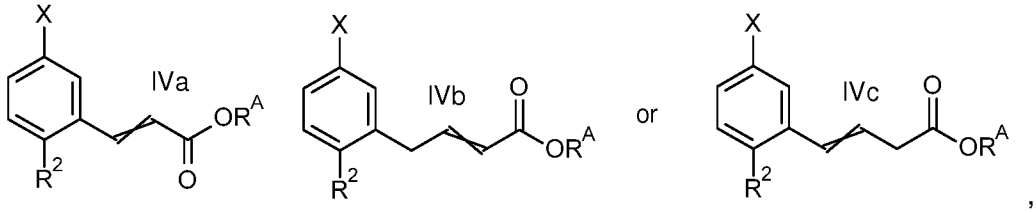
with a halogenating agent, followed by cyclization in the presence of a Lewis acid.

8. The process of claim 7, wherein compounds III are produced by reaction of compounds IV selected from IVa, IVb, or IVc.



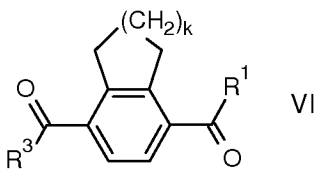
,

with hydrogen, followed by hydrolysis; wherein R^2 is CN, or $C(=O)OR^A$;

9. The process of claim 8, wherein the hydrogen is produced *in situ* from
   a) a metal selected from alkali metals, and alkaline earth metals, or
   b) a metal with a redox potential below 0 at a pH below 7.0.

10. Intermediate compounds V, as defined in claim 7.

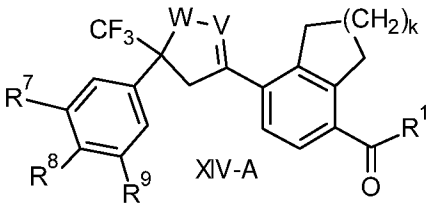
11. Use of compounds I, as defined in any of claims 1 to 5, for the production of compounds VI



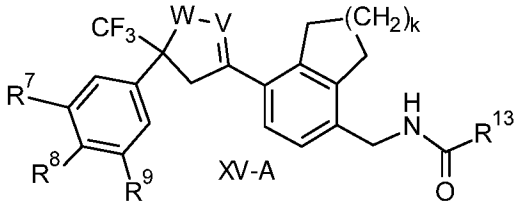
,

wherein R^3 is H, or CH_3, and k and R^1 have a meaning as defined in claims 1 to 5.

12. Use of a compound I as defined in any of claims 1 to 5, or the use of a compound II as defined in claim 6, for the production of insecticidal compounds of formula XIV-A or XV-A



XIV-A



XV-A

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wherein V is selected from CH, N, and NO, W is selected from O, S and CH_2, and R^7, R^8, and R^9 are independently hydrogen, halogen, halomethyl, or halomethoxy, wherein at most two substituents R^7, R^8, and R^9 are H, and R^1, R^{13}, and k have a meaning as defined in any of claims 1 to 5.

13. A process for the production of compounds II from compounds III by a reaction as defined in claim 7.

14. The process of claim 13, wherein compounds III are produced from compounds IV by a process as defined in claims 8 or 9.

15. A process for the production of compounds III from compounds IVa or IVb as defined in claims 8 or 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/066603

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C63/36 C07C63/49
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)
C07C

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, INSPEC, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 362 846 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 19 November 2003 (2003-11-19) [0221]-[0223] -----	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2016	24/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hacking, Michiel

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/066603

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5

   Compounds of formula I

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2. claims: 6-9

   Process for the production of compounds of formula I from compounds of formula II

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3. claim: 10

   Compounds of formula V

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4. claim: 11

   Process for the production of compounds of formula VI from compounds of formula I

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5. claims: 12, 14

   Use of compounds of formula I or II for the production of XIV or XV

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6. claim: 13

   Process for the production of compounds of formula II from compounds of formula III

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7. claim: 15

   Process for the production of compounds of formula III from compounds of formula IVa or IVb

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/066603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1362846 A1	19-11-2003	EP 1362846 A1	19-11-2003
		US 2004127574 A1	01-07-2004
		WO 02059077 A1	01-08-2002