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CA 2414839 C 2010/02/16

(11)(21) 2 414 839

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2001/06/26
(87) Date publication PCT/PCT Publication Date: 2002/01/10
(45) Date de délivrance/Issue Date: 2010/02/16
(85) Entrée phase nationale/National Entry: 2003/01/02
(86) N° demande PCT/PCT Application No.: CH 2001/000397
(87) N° publication PCT/PCT Publication No.: 2002/002500
(30) Priorité/Priority: 2000/07/03 (CH1317/00)

(51) Cl.Int./Int.Cl. *C07C 67/293* (2006.01), *C07C 51/36* (2006.01), *C07C 59/66* (2006.01)

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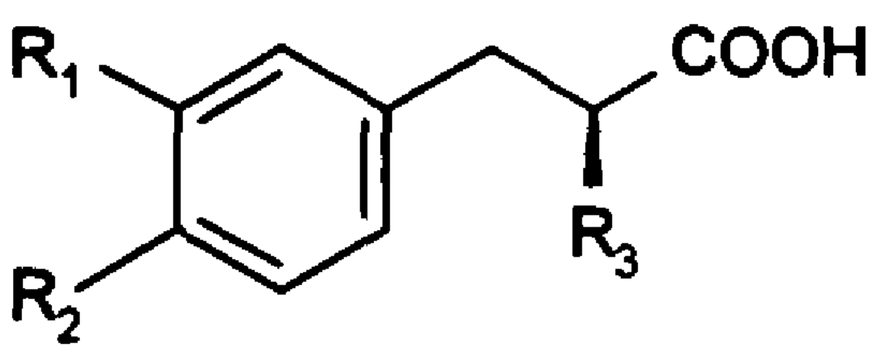
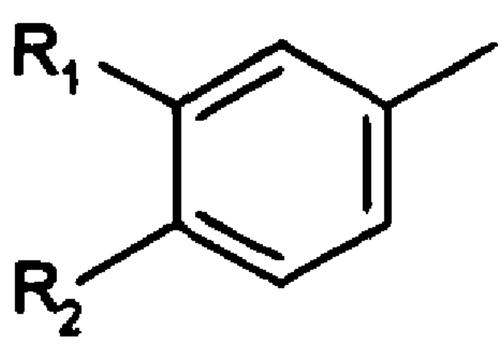
(54) Titre : PREPARATION D'ACIDES (R)-2-ALKYL-3-PHENYLPROPIONIQUES
(54) Title: PREPARATION OF (R)-2-ALKYL-3-PHENYLPROPIONIC ACIDS



(I)



(a)

(57) Abrégé/Abstract:
Compounds of formula (I), wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl, are obtainable in high yields by stereoselective addition of R_3-substituted propionic acid esters to R_1- and R_2-substituted benzaldehydes of formula R-CHO to form corresponding 3-R-3-hydroxy-2-R_3-propionic acid esters, conversion of the OH group to a leavaing group, subsequent regioselective elimination to form 3-R-2-R_3-propenic acid esters, and their hydrolysis to form corresponding propenic carboxylic acids and their enantioselective hydrogenation, wherein R is (a).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02500 A1

(51) International Patent Classification[7]: C07C 67/293, 51/36, 59/66

(21) International Application Number: PCT/CH01/00397

(22) International Filing Date: 26 June 2001 (26.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1317/00 3 July 2000 (03.07.2000) CH

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

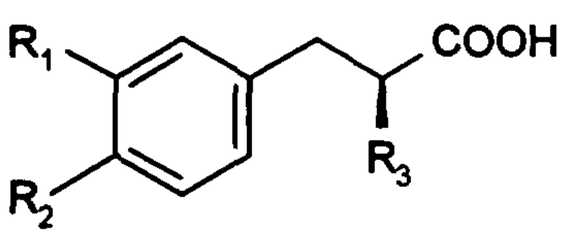
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

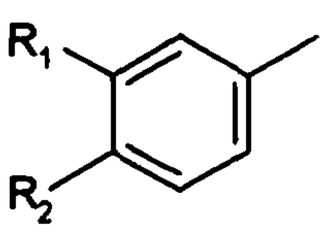
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/02500 A1

(54) Title: PREPARATION OF (R)-2-ALKYL-3-PHENYLPROPIONIC ACIDS



(I)



(a)

(57) Abstract: Compounds of formula (I), wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl, are obtainable in high yields by stereoselective addition of R_3-substituted propionic acid esters to R_1- and R_2-substituted benzaldehydes of formula R-CHO to form corresponding 3-R-3-hydroxy-2-R_3-propionic acid esters, conversion of the OH group to a leavaing group, subsequent regioselective elimination to form 3-R-2-R_3-propenic acid esters, and their hydrolysis to form corresponding propenic carboxylic acids and their enantioselective hydrogenation, wherein R is (a).

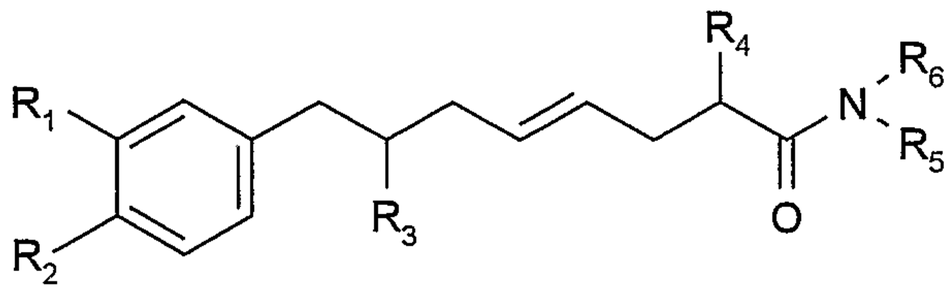
Preparation of (R)-2-alkyl-3-phenylpropionic acids

The invention relates to a stereoselective process for the preparation of (R)-2-alkyl-3-phenyl-propionic acids and intermediate products obtained in the process steps.

In EP-A-0 678 503, δ-amino-γ-hydroxy-ω-aryl-alkanecarboxamides are described which exhibit renin-inhibiting properties and could be used as antihypertensive agents in pharmaceutical preparations. The manufacturing processes described are unsatisfactory in terms of the number of process steps and yields and are not suitable for an industrial process. A disadvantage of these processes is also that the total yields of pure diastereomers that are obtainable are too small.

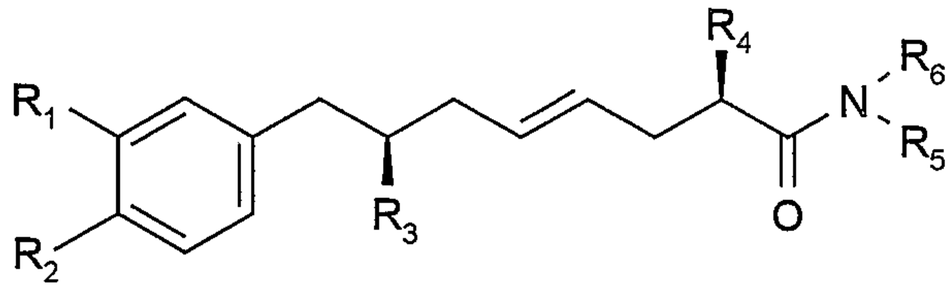
In a new process, one starts from 2,7-dialkyl-8-aryl-4-octenoyl amides, whose double bond is simultaneously halogenated in the 5-position and hydroxylated in the 4-position under lactonization, then the halogen is substituted by azide, the lactone amidated and the azide then transferred to the amine group. The desired alkanecarboxamides are obtained with the new process both in high total yields and in a high degree of purity, and selectively pure diastereomers can be prepared. The halolactonization of process step a), the azidation of process step b), and the azide reduction of process step d) are described by P. Herold in the Journal of Organic Chemistry, Vol. 54 (1989), pages 1178-1185.

The 2,7-dialkyl-8-aryl-4-octenoyl amides may correspond for example to formula A,



(A),

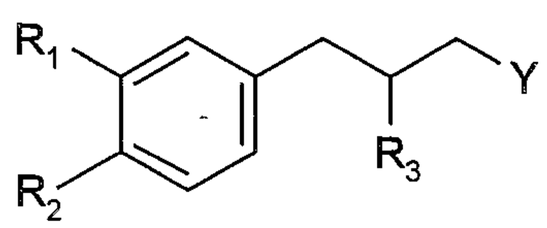
and especially to formula A1



(A1),

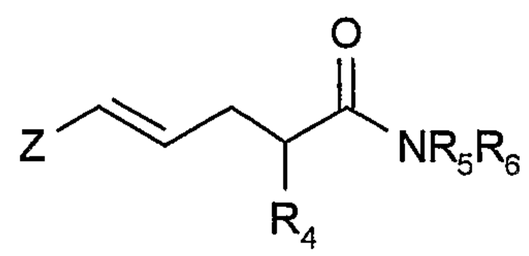
wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, R_6 is C_1-C_6alkyl, R_5 is C_1-C_6alkyl or C_1-C_6alkoxy, or R_5 and R_6 together are tetramethylene, pentamethylene, 3-oxa-1,5-pentylene or $-CH_2CH_2O-C(O)-$ substituted if necessary with C_1-C_4alkyl, phenyl or benzyl.

The compounds of formulae A and A1 are obtainable by reacting a compound of formula B



(B),

as racemate or enantiomer, with a compound of formula C, as racemate or enantiomer,



(C),

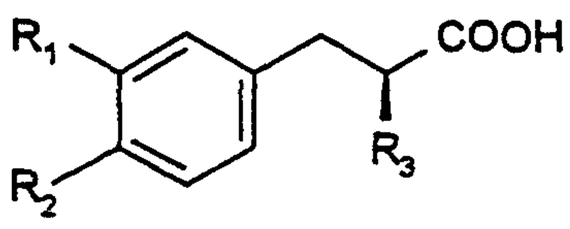
wherein R_1 to R_4, R_5 and R_6 are as defined above, Y is Cl, Br or I and Z is Cl, Br or I, in the presence of an alkali metal or alkaline earth metal. Y and Z are preferably Br and especially Cl.

The compounds of formula B are known from EP-A-0 678 503. The compounds of formula C may be prepared from amidation of the corresponding carbonic esters, amides, or halides. The formation of carboxamides from carbonic esters and amines in the presence of trialkyl aluminium or dialkyl aluminium halide, for example using trimethyl aluminium or dimethyl aluminium chloride, is described by S. M. Weinreb in Org. Synthesis, VI, page 49 (1988). The carbonic esters are obtainable by the reaction of trans-1,3-dihalogenpropene (for example, trans-1,3-dichlorepropene) with corresponding carbonic esters in the presence of strong bases, for example alkali metal amides.

A satisfactory solution for the stereoselective preparation of compounds of formula B has not yet been found, especially with regard to an industrial process. Surprisingly it has now been found that 2-alkyl-3-phenylpropionic acids can be stereoselectively prepared with high yields in only three process steps. When suitably substituted benzaldehydes are condensed with carbonic esters to form 2-alkyl-3-hydroxy-3-phenylpropionic acid esters, the desired diastereomers are obtainable in surprisingly high yields mostly as crystalline compounds which can be readily isolated. After conversion of the hydroxy group to a leaving group, 2-alkylcinnamic acid esters are then formed by elimination with strong bases with surprisingly high regioselectivity. The carboxylic acids obtained after saponification can in turn be surprisingly hydrogenated in the presence of homogeneous, asymmetric hydrogenation catalysts to form practically enantiomer-pure 2-alkyl-3-phenylpropionic acids. These acids can then be

reduced in a manner known per se to form enantiomer-pure alcohols, from which the compounds of formula B are obtainable by halogenation.

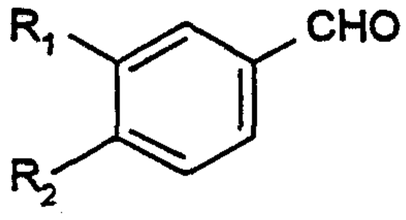
The object of the invention is a process for the preparation of compounds of formula I,



(I),

wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6-alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl, comprising

a) the reaction of a compound of formula II



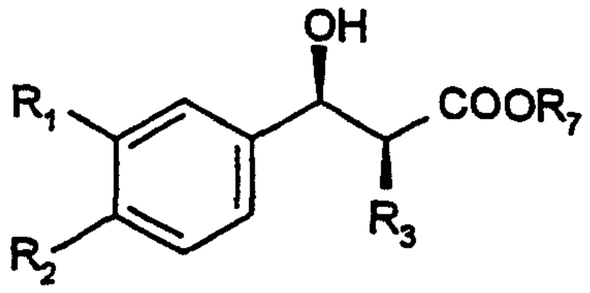
(II),

wherein R_1 and R_2 are as defined above, with a compound of formula III,

(III),

R_3-CH_2-CO_2R_7

wherein R_3 is as defined above, to form a compound of IV,



(IV),

wherein R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl,

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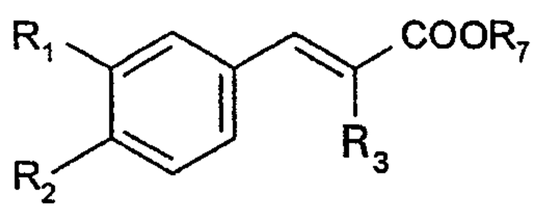
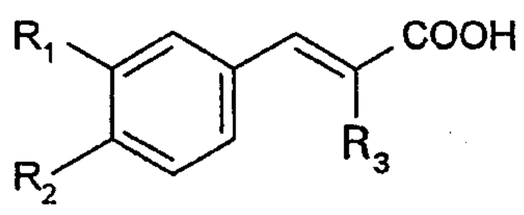
b) the isolation of the crystalline compound of formula IV, the conversion of the OH group to a leaving group, and the reaction of a compound containing a leaving group in the presence of a strong base to form a compound of formula V,



(V),

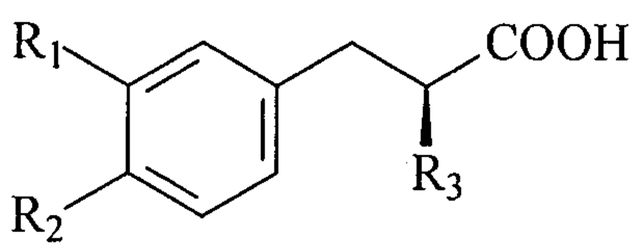
c) the hydrolysis of carbonic esters of formula V to form the carboxylic acid of formula VI,



(VI), and

d) the hydrogenation of the carboxylic acid of formula VI in the presence of hydrogen and catalytic quantities of a metal complex as asymmetric hydrogenation catalyst, comprising metals from the group of ruthenium, rhodium and iridium, to which the chiral bidentate ligands are bonded, to form a compound of formula I.

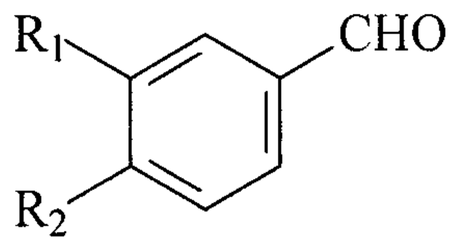
According to one aspect of the present invention, there is provided a process for the preparation of a compound of formula I,



(I),

wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl comprising

a) reaction of a compound of formula II

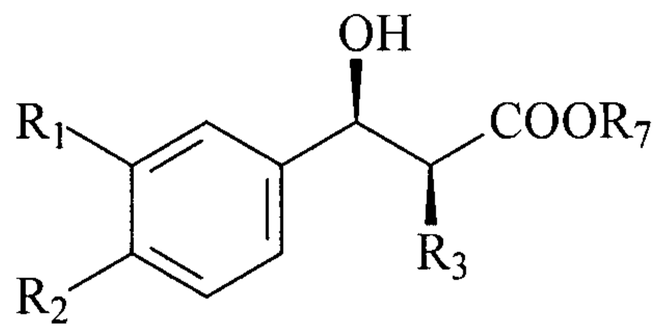


(II),

wherein R_1 and R_2 are as defined for the compound of formula I, with a compound of formula III,

$$R_3\text{-}CH_2\text{-}CO_2R_7 \qquad \text{(III)},$$

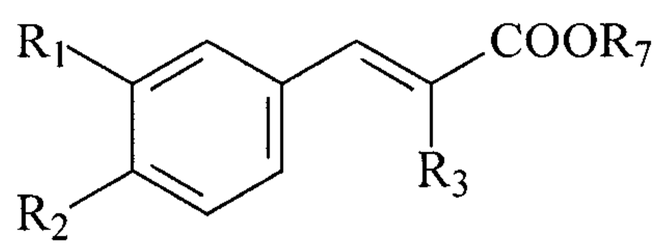
wherein R_3 is as defined for the compound of formula I, to form a compound of formula IV,



(IV),

wherein R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl;

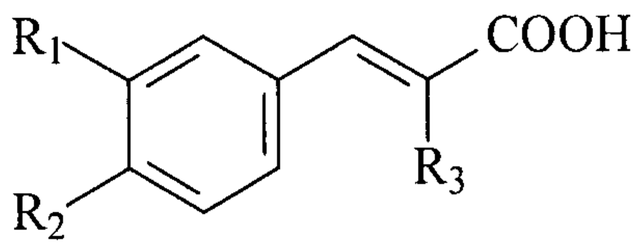
b) isolation of the crystalline compound of formula IV, conversion of the OH group to a leaving group, and reaction of the compound containing the leaving group in presence of a strong base to form a compound of formula V,



(V)

wherein R_1, R_2, R_3 and R_7 are as defined for the compound of formula IV;

c) hydrolysis of the carbonic ester of formula V to form the carboxylic acid of formula VI,

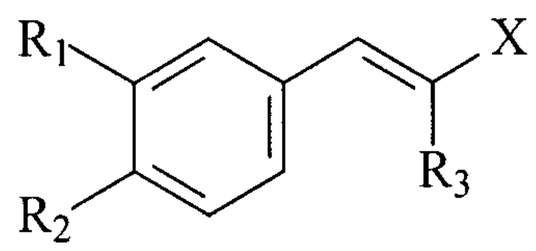


(VI)

wherein R_1, R_2 and R_3 are as defined for the compound of formula V; and

d) hydrogenation of the carboxylic acid of formula VI in the presence of hydrogen and catalytic quantities of a metal complex as asymmetric hydrogenation catalyst, wherein the metal complex comprises ruthenium, rhodium or iridium, to which a chiral bidentate ligand is bonded, to form the compound of formula I.

According to another aspect of the present invention, there is provided a compound of formula IX,



(IX),

wherein

R_1 and R_2, independently of one another, are C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, and X is -COOH.

R_1 and R_2 may be a linear or branched alkyl and preferably comprise 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl.

R_1 and R_2 may be a linear or branched halogenalkyl and preferably comprise 1 to 4 C atoms, 1 or 2 C atoms being especially preferred. Examples are fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-chloroethyl and 2,2,2-trifluoroethyl.

R_1 and R_2 may be a linear or branched alkoxy and preferably comprise 1 to 4 C atoms. Examples are methoxy, ethoxy, n- and i-propyloxy, n-, i- and t-butyloxy, pentyloxy and hexyloxy.

R_1 and R_2 may be a linear or branched alkoxyalkyl. The alkoxy group preferably comprises 1 to 4 and especially 1 or 2 C atoms, and the alkyl group preferably comprises 1 to 4 C atoms. Examples are methoxymethyl, 1-methoxyeth-2-yl, 1-methoxyprop-3-yl, 1-methoxybut-4-yl, methoxypentyl, methoxyhexyl, ethoxymethyl, 1-ethoxyeth-2-yl, 1-ethoxyprop-3-yl, 1-ethoxybut-4-yl, ethoxypentyl, ethoxyhexyl, propyloxymethyl, butyloxymethyl, 1-propyloxyeth-2-yl and 1-butyloxyeth-2-yl.

R_1 and R_2 may be linear or branched C_1-C_6alkoxy-C_1-C_6alkyloxy. The alkoxy group preferably comprises 1 to 4 and especially 1 or 2 C atoms, and the alkyloxy group preferably comprises 1 to 4 C atoms. Examples are methoxymethyloxy, 1-methoxyeth-2-yloxy, 1-methoxyprop-3-yloxy, 1-methoxybut-4-yloxy, methoxypentyloxy, methoxyhexyloxy, ethoxymethyloxy, 1-ethoxyeth-2-yloxy, 1-ethoxyprop-3-yloxy, 1-ethoxybut-4-yloxy, ethoxypentyloxy, ethoxyhexyloxy, propyloxymethyloxy, butyloxymethyloxy, 1-propyloxyeth-2-yloxy and 1-butyloxyeth-2-yloxy.

In a preferred embodiment, R_1 is methoxy-C_1-C_4alkyloxy or ethoxy-C_1-C_4alkyloxy, and R_2 is preferably methoxy or ethoxy. Quite especially preferred are compounds of formula I, wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

R_3 may be a linear or branched alkyl and preferably comprise 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl. In a preferred embodiment, R_3 in compounds of formula I is isopropyl.

Especially preferred are compounds of formula I wherein R_1 is methoxy-n-propoxy, R_2 is methoxy and R_3 is isopropyl.

R_7 is preferably C_1-C_6alkyl, C_1-C_4alkyl being especially preferred; some examples are methyl, ethyl, n-propyl and n-butyl.

The starting compounds of formulae II and III used in process step a) are known or can be prepared in a manner similar to known processes. Compounds of formula II are described in EP-A 0 678 503. The reaction is advantageously carried out at low temperatures, for example 0-40°C, in the presence of at least equivalent quantities of strong bases. The reaction is further expediently carried out in a solvent, ethers such as diethyl ether, tetrahydrofuran and dioxane being especially suitable. Suitable strong bases are in particular alkali metal alcoholates and secondary amides, such as lithium diisopropylamide.

The desired diastereomer of formula IV is surprisingly formed up to about 75%. The compounds of formula IV are surprisingly crystalline and can therefore be readily isolated without any substantial losses by means of extraction and crystallization.

The conversion of the OH group to a leaving group in reaction step b) is known per se. Reaction with carboxylic acids or sulfonic acids, or their anhydrides (acylation), is especially suitable. Some examples of carboxylic acids are formic acid, acetic acid, propionic acid, benzoic acid, benzenesulfonic acid, toluenesulfonic acid, methylsulfonic acid and trifluoromethylsulfonic acid. The use of acetic acid anhydride has proved especially successful. The elimination is expediently carried out in the presence of strong bases, alkali metal alcoholates such as potassium t-butylate being especially suitable. The presence of solvents

such as ethers is expedient. The reaction is advantageously carried out at low temperatures, for example 0-40°C. It is of advantage to conduct the elimination reaction directly in the reaction mixture for acylation. The elimination leads to the desired Z isomers with surprisingly high regioselectivity. These isomers are crystalline and can therefore be readily isolated without any substantial losses by means of extraction and crystallization. The yields are above 80%.

Hydrolysis of the ester of formula V to form the carboxylic acids of formula VI in process step c) is a generally known reaction. The hydrolysis may be carried out after isolation and purification of the compound of formula III. It is expedient to add water to the reaction mixture of process step b), to evaporate off the solvent and then to carry out alkaline or acidic hydrolysis. The carboxylic acids of formula VI are crystalline and can be readily isolated in yields of 80% or more.

The asymmetric hydrogenation in process step d) of α,β-unsaturated carboxylic acids with homogeneous, asymmetric hydrogenation catalysts is known per se and described for example by John M. Brown in E. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis I to III, Springer Verlag, 1999, pages 121 to 182. Especially effective are ruthenium and rhodium catalysts. Chiral ditertiary diphosphines whose phosphine groups in the 1,2, 1,3 or 1,4 position are bonded to a C_2-C_4carbon chain are often used as ligands. The skeletal structures of the chiral ditertiary diphosphines may be acyclic, monocyclic or polycyclic. The phosphine groups may be substituted with the same or with different, preferably the same, substituents selected from the group of C_1-C_8alkyl, C_3-C_8cycloalkyl, C_6-C_{12}aryl, and C_6-C_{12}aryl- C_1-C_4alkyl. Cycloalkyl and aryl may be unsubstituted or substituted with C_1-C_4alkyl, C_1-C_4alkoxy,

C_1-C_4fluoroalkyl or C-C_{12}secondary amino. Suitable phosphine groups are also phosphanyl, preferably five-member phosphanyl, which if necessary is substituted in one or both α-positions with C_1-C_4alkyl or C_1-C_4alkoxy.

Some examples of chiral ditertiary diphosphines are ($R"_2P$ is for example diphenylphosphino or dicyclohexylphosphino, substituted if necessary) 1,2-Di-$R"_2P$-propane, 2,3-Di-$R"_2P$-butane, 1,2-Di-$R"_2P$-norbornane or -norbornadiene, 1,2-Di-$R"_2P$-cyclopentane, 1,2-Di-$R"_2P$-N-methylpyrrolidine, 2,2'-Di-$R"_2P$-biphenyl or -binaphthyl, 2,2'-Di-$R"_2P$-6-methyl or -6,6'-dimethylbiphenyl, 2,2'-Di-$R"_2P$-6-methoxy or -6,6'-dimethoxy-biphenyl, and 1-(α-$R"_2P$-ethyl)-2-$R"_2P$-ferrocene.

Good optical yields are achieved using metal complexes of formula VII or VIIa,

$[LMeYZ]$ (VII), $[LMeY]^+E^-$ (VIIa),

wherein

Me is rhodium;

Y stands for two olefins or one diene;

Z is Cl, Br or I;

E^- is the anion of an oxygen acid or a complex acid; and

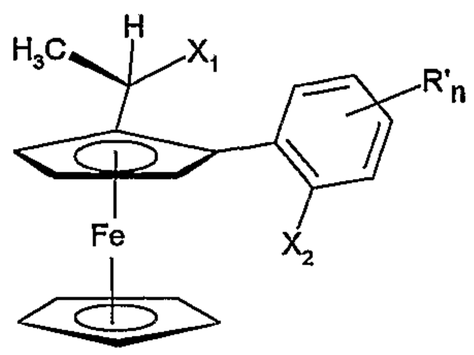
L is a chiral ligand from the group of ditertiary diphosphines, in which the phosphine groups are bonded to a C_2-C_4 chain of the diphosphine backbone chain, and the diphosphine forms a five to seven-member ring together with the rhodium atom.

Where Y stands for two olefins, they may be C_2-C_{12} olefins, C_2-C_6olefins being preferred and C_2-C_4olefins being especially preferred. Examples are propene, but-1-ene and especially ethylene. The diene may comprise 5 to 12 and preferably 5 to 8 C atoms and may be an acyclic, cyclic or polycyclic diene. The two olefin groups of the diene are preferably linked by

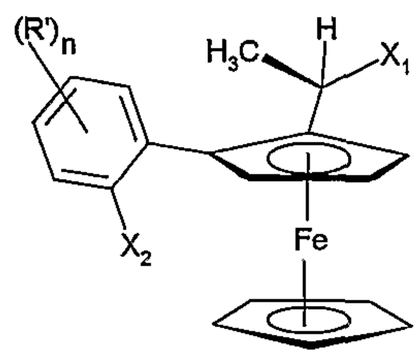
one or two CH_2 groups. Examples are 1,3-pentadiene, cyclopentadiene, 1,5-hexadiene, 1,4-cyclohexadiene, 1,4- or 1,5-heptadiene, 1,4- or 1,5-cycloheptadiene, 1,4- or 1,5-octadiene, 1,4- or 1,5-cyclooctadiene and norbornadiene. Y represents preferably two ethylene or 1,5- hexadiene, 1,5-cyclooctadiene or norbornadiene.

In formula VII, Z is preferably Cl or Br. Examples of E_1 are ClO_4^-, $CF_3SO_3^-$, $CH_3SO_3^-$, HSO_4^-, BF_4^-, $B(phenyl)_4^-$, PF_6^-, $SbCl_6^-$, AsF_6^- or SbF_6^-.

With known ligands for asymmetric catalysts, optical yields of up to about 80% ee can be achieved under optimized conditions. It was surprisingly found that new ligands with a ferrocenyl backbone are especially suitable for asymmetric hydrogenation of the compounds of formula VI. With these new ligands in the metal complexes of formulae VII and VIIa, optical yields of at least 95% ee can be achieved, which represents a substantial cost saving for manufacture on an industrial scale. In process step d), therefore, it is preferred to use metal complexes of formulae VII and VIIa which comprise ligands of formula VIII or VIIIa,



(VIII)



(VIIIa),

wherein

n is 0 or an integer from 1 to 4 and R' represents the same or different substituents selected from the C_1-C_4alkyl, $-CF_3$ and C_1-C_4alkoxy group; and

X_1 and X_2 are, independently of one another, secondary phosphino.

As an alkyl, R' may preferably comprise 1 to 2 C atoms. Linear alkyl is preferred. Examples of R' as an alkyl are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl. Methyl and ethyl are preferred, and methyl is especially preferred.

As an alkoxy, R' may preferably comprise 1 to 2 C atoms. Linear alkoxy is preferred. Examples of R' as an alkoxyl are methoxy, ethoxy, n- and i-propoxy, n-, i- and t-butoxy. Methoxy and ethoxy are preferred and methoxy is especially preferred.

The X_1 and X_2 groups may be different or preferably the same and correspond to formula PR_8R_9, wherein R_8 and R_9 are the same or different and represent branched C_3-C_8alkyl, C_3-C_8cycloalkyl, or unsubstituted or phenyl substituted with one to three C_1-C_4alkyl, C_1-C_4-alkoxy, or $-CF_3$.

Special preference is for ligands of formulae VIII and VIIIa, wherein n is 0, and X_1 and X_2 are a PR_8R_9 group, wherein R_8 and R_9 in each case are cyclohexyl, phenyl or phenyl substituted with 1 or 2 methyl, methoxy or CF_3.

The new ligands are prepared by means of reactions that are known per se or analogous to known reactions, such as those described in US-A-5,371,256, US-A-5,446,844 and US-A-5,583,241. Ligands with other phosphine groups may be prepared in a manner analogous to the method described in the example.

The metal complexes used as catalysts may be added as separately prepared isolated compounds, or also formed in situ before the reaction and then mixed with the substrate to be hydrogenated. It may be advantageous in the reaction using isolated metal complexes to add additional ligands, or in the in situ preparation to use surplus ligands. The surplus may for example be up to 10 moles and preferably

0.001 to 5 moles, based on the metal complexes used for the preparation.

Process step d) may be carried out at low or elevated temperatures, for example at temperatures from -20 to 150°C, preferably from -10 to 100°C, temperatures of 10 to 80°C being especially preferred. The optical yields are generally better at low temperatures than at high temperatures.

The process according to the invention may be carried out at normal pressure or preferably under positive pressure. The pressure may for example range from 10^5 to $2x10^7$ Pa (Pascal).

Catalysts are preferably used in quantities from 0.0001 to 10 mol-% based on the compound to be hydrogenated, the range 0.001 to 10 mol-% being especially preferred and the range 0.01 to 5 mol-% being preferred in particular.

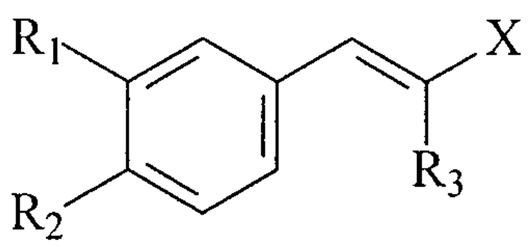
The preparation of catalysts as well as process step d) and the other process steps may be carried out in the absence or the presence of an inert solvent, wherein one solvent or a mixture of solvents may be used. Suitable solvents are, for example, aliphatic, cycloaliphatic and aromatic hydrocarbons (pentane, hexane, petroleum ether, cyclohexane, methylcyclohexane, benzene, toluene, xylene), aliphatic halogenated hydrocarbons (dichloromethane, chloroform, di- and tetrachloroethane), nitriles (acetonitrile, propionitrile, benzonitrile), ethers (diethyl ether, dibutyl ether, t-butyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, tetrahydrofuran, dioxane, diethylene glycol monomethyl or monoethyl ether), ketones (acetone, methyl isobutyl ketone), carbonic esters and lactones (ethyl or methyl acetate, valerolactone), N-substituted lactams (N-methylpyrrolidone), carboxamides (dimethylamide, dimethylformamide), acyclic ureas (dimethylimidazoline), and

sulfoxides and sulfones (dimethyl sulfoxide, dimethyl sulfone, tetramethylene sulfoxide, tetramethylene sulfone) and alcohols (methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, diethylene glycol monomethyl ether) and water. The solvents may be used alone or in a combination of at least two solvents.

The reaction may be carried out in the presence of co-catalysts, for example quaternary ammonium halogenides (tetrabutylammonium iodide) and/or in the presence of protonic acids, for example mineral acids.

Using the regioselective and enantioselective process according to the invention, the intermediate products of formula (B) may be prepared via all process steps in yields of at least 50% by weight, based on the compounds of formula II. The high total yields make the process suitable for industrial use.

A further aspect of the invention relates to the compounds (intermediates) of formula IX,



(IX),

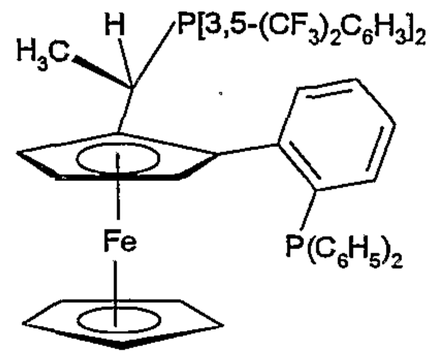
wherein

R_1 and R_2, independently of one another, are C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, and X is -COOH.

The embodiments and preferences described hereinabove apply for R_1, R_2, and R_3.

The following examples explain the invention in more detail.

A) Preparation of the ligands

Example A1: Preparation of  (L1)

a) Preparation of (R_C,S_P)-2-(2-bromophenyl)-1-[1-N,N-dimethylamino)ethyl]ferrocene, L2

At 0°C, 33 ml (43 mmol) of a 1.3 molar solution of s-butyl lithium in cyclohexane is added dropwise to a degassed solution of 10 g (38.9 mmol) *(+)-(R)*-1-N,N-dimethyl-aminoethyl ferrocene (L1) in 32 ml tetrahydrofuran (THF). After 30 minutes, still at 0°C, 44 ml of a 1 molar solution of $ZnCl_2$ in diethyl ether is added drop by drop. The reaction mixture is then stirred for one hour at room temperature. After the addition of 1.4 g (2 mmol) bis-diphenylphosphino-palladium(II) chloride and a solution of 22.64 g (80 mmol) 2-bromo-1-iodobenzene in 50 ml THF, the reaction mixture is heated for 3 days under reflux. The solvent is removed on a rotary evaporator, the residue taken up in CH_2Cl_2 and extracted with water. The aqueous phase is extracted 3 times with 30 ml CH_2Cl_2 and the combined organic phases are washed twice with 20 ml water. After drying over $MgSO_4$ and removal of the solvent in a vacuum, the residue is chromatographed on aluminium oxide 90. A mixture of petroleum ether, ether and triethylamine in a ratio of 60 : 1 : 3 is used as the mobile phase. The yield amounts to 4.65 g (11.3 mmol, 30%).

^{1}H-NMR: δ 1.61 (d, *J*=7.0 Hz, 3H), 1.75 (s, 6H), 3,54 (q, *J*=7.0 Hz, 1H), 4.13 (s, 5H, Cp), 4.23-4.25 (m, 1H, Cp), 4.32-4.34 (m, 1H, Cp), 4.59-4.61 (m, 1H, Cp), 7.07-7.11 (m, 1H, Ph), 7.30-7.35 (m, 1H, Ph), 7.51-7.53 (m, 1H, Ph), 7.85-7.87 (m, 1H, Ph).

$[\alpha]^{20}$ (nm): +75.9 ° (589), + 61.4 ° (578), -45.4 ° (546) (c = 1, $CHCl_3$)

b) Preparation of (R_C,S_P)-1-[1-(N,N-dimethylamino)ethyl]-2-(2-diphenylphosphinophenyl)-ferrocene, L3

At -40°C, 4.5 ml of a 1.3 molar solution of s-butyl lithium in cyclohexane is slowly added drop by drop to a degassed solution of 2 g (4.87 mmol) of L2 in 25 ml THF. After 40 minutes, the reaction mixture is allowed to warm up to room temperature, and then 1.1 ml (6.6 mmol) diphenylchlorophosphine is added drop by drop. After 18 hours, 30 ml saturated $NaHCO_3$ solution is added. The organic phase is separated off and the aqueous phase is extracted twice with 20 ml CH_2Cl_2. The combined organic phases are washed twice with 20 ml water and dried over $MgSO_4$. After removal of the solvent in a vacuum and chromatography on silica gel 60 (petroleum ether / diethylamine = 95 : 5) a yield of 2.15 g (4.16 mmol, 85.4 %) of the product is obtained.

^{1}H-NMR: δ 1.64 (d, *J*=7.0 Hz, 3H), 1.86 (s, 6H), 3.72 (q, *J*=7.0 Hz, 1H), 4.04-4.06 (m, 1H, Cp), 4.08 (s, 5H, Cp), 4.22 (m, 1H, Cp), 4.25 (m, 1H, Cp), 6.93-6.98 (m, 2H, Ph), 6.99-7.02 (m, 1H, Ph), 7.15-7.20 (m, 4H, Ph), 7.31-7.40 (m, 6H, Ph), 7.94-7.98 (m, 1H, Ph).

^{31}P-NMR: δ -14.09.

$[\alpha]^{20}$ (nm): -23.7 ° (589), -47.5 ° (578), -203.2 ° (546) (c = 1, $CHCl_3$).

c) Preparation of (R_C,S_P)-1-[1-(N,N-dimethylamino)ethyl]-2-(2-diphenylphosphinylphenyl)-ferrocene, L4

To a solution of 1 g (1.93 mmol) L3 in 15 ml acetone, 0.8 ml 30% H_2O_2 is added dropwise. The solution is stirred for 45 minutes at room temperature, and then 20 ml saturated $Na_2S_2O_5$ solution is added. After extraction 3 x 25 ml CH_2Cl_2 the combined organic phases are washed with 2 x 20 ml water and dried over $MgSO_4$. The solvent is removed in a vacuum and the product purified by chromatography on aluminium oxide 90.

Non-polar impurities are removed by elution with a mixture of petroleum ether and ethyl acetate in a ratio of 80 : 20, and the product is then eluted with methanol. A yield of 990 mg (1.86 mmol, 96%) product is obtained.

^{1}H-NMR: δ 1.67 (d, *J*=7.0 Hz, 3H), 2.03 (s, 6H), 4.04 (s, 5H, Cp), 4.04 (q, *J*=7,0 Hz, 1H), 4.09-4.11 (m, 1H, Cp), 4.21-4.23 (m, 1H, Cp), 4.26 (m, 1H, Cp), 7.05-7.11 (m, 1H, Ph), 7.18-7.23 (m, 1H, Ph), 7.28-7.33 (m, 2H, Ph), 7.34-7.43 (m, 3H, Ph), 7.48-7.60 (m, 4H, Ph), 7.65-7.71 (m, 2H, Ph), 8.10-8.13 (m, 1H, Ph).

^{31}P-NMR: δ 31.67.

$[\alpha]^{20}$ (nm): -160° (589), -200.6° (578), -449.4° (546) (c = 0.5, $CHCl_3$).

d) Preparation of (R_C,S_P)-1-{1-[bis-(bis-3,5-trifluoromethylphenyl)phosphino]ethyl}-2-(2-diphenylphosphinylphenyl)ferrocene, L6

To a degassed solution of 1.25 g (2.35 mmol) L4 in 15 ml freshly distilled acetic acid, 1.6 g (3.5 mmol) bis-(3,5-trifluoromethylphenyl)phosphine is added. The reaction mixture is then agitated for 3 days at 100°C. The solvent is removed in a vacuum, the residue dissolved in CH_2Cl_2 and chromatographed on aluminium oxide 90. Non-polar impurities are removed by elution with hexane, and subsequent elution with a mixture of CH_2Cl_2 and methanol in a ratio of 99 : 1 yields 2.09 g (2.21 mmol, 88.9%) of product. Two diastereomers are formed in a ratio of 6 : 1 (determined by ^{31}P-NMR), but these are not separated. The ^{1}H-NMR data are those of the principal isomer.

^{1}H-NMR: δ 1.32 (dd, J_1=6.1 Hz, J_2=6.8 Hz, 3H), 3.47 (m, 1H, Cp), 3.79 (dq, J_1=2.8 Hz, J_2=7.1 Hz, 1H), 3.96 (t, *J*=2.8 Hz, Cp), 4.08 (s, 5H, Cp), 5.03 (m, 1H, Cp), 7.1-7,15 (m, 2H, Ph), 7.20-7.30 (m, 3H, Ph), 7.42-7.53 (m, 3H, Ph), 7.56-7.75 (m, 8H, Ph), 7.86 (s, 2H, Ph), 8.24-8.28 (m, 1H, Ph).

^{31}P-NMR: main component: δ 4.63, 30.29; secondary component: δ 4.77, 29.67.

e) Preparation of title compound (R_C,S_P)-1-{1-[bis-(bis-3,5-trifuoromethylphenyl)phosphino]-ethyl}-2-(2-diphenylphosphinophenyl)ferrocene, L1

To a degassed solution of 1.97 g (2.08 mmol) L6 in 20 ml THF, 9.2 ml polymethyl hydrosiloxane and 5.04 ml Ti(O*i*-Propyl)$_4$ are added. The reaction mixture is heated under reflux for 18 hours, during which the solution turns a dark violet colour. Then 15 ml hexane is added and heated for a further 2 hours under reflux. The reaction mixture is applied to an aluminium oxide column without any further preparation, and the product is eluted with a mixture of petroleum ether, ethyl acetate and methanol in a ratio of 90 : 10 : 1. The yield amounts to 1.78 g (1.91 mmol, 91.8%). The two diastereomers are separated by chromatography on silica gel. A mixture of petroleum ether and CH_2Cl_2 in a ratio of 80:20 is used as the mobile phase.

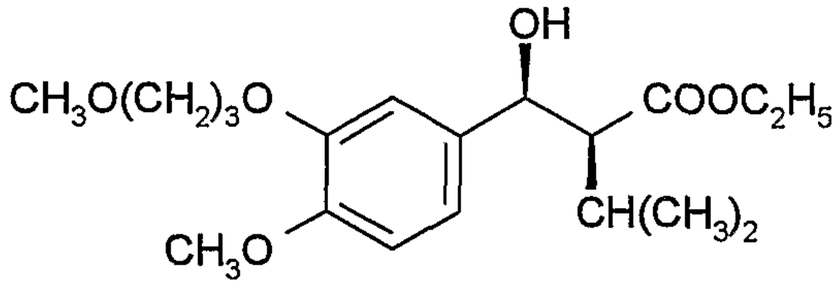
^{1}H-NMR: δ 1.32 (dd, J_1=6.1 Hz, J_2=6.8 Hz, 3H), 3.29 (s, 1H, Cp), 3.66 (dq, J_1=J_2=7.1 Hz, 1H), 3.86 (m, 1H, Cp), 4.02 (t, J=2.5 Hz, 1H, Cp), 4.16 (s, 5H, Cp), 7.06-7.11 (m, 2H, Ph), 7.13-7.19 (m, 3H, Ph), 7.25-7.29 (m, 2H, Ph), 7.38-7.50 (m, 6H, Ph), 7.59 (d, J=4.0 Hz, 2H, Ph), 7.80 (s, 1H, Ph), 7.90 (s, 1H, Ph), 7.97 (d, J=6.1 Hz, 2H, Ph), 8.12-8.15 (m, 1H, Ph).

^{31}P-NMR: main component: δ -14.04 (d, J=23.5 Hz), 3.55 (d, J=23.5 Hz); secondary component: δ -15.19 (d, J=28.5 Hz), -5.16 (d, J=28.5 Hz).

$[\alpha]_{20}$ (nm): -0.88 (589), -7.72 (578), -52.8 (546) (c=0.57, $CHCl_3$).

B) Preparation of (R)-3-[4'-CH_3O-3'-($CH_3O(CH_2)_3O$)-phen-1-yl]-2-isopropylpropionic acid

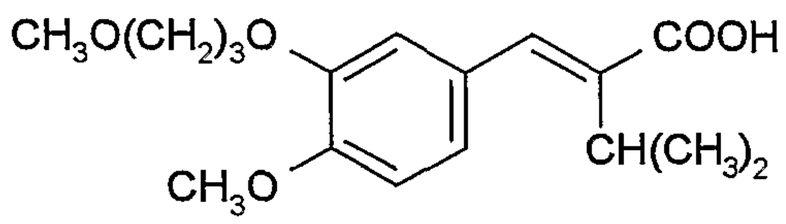
Example B1: Preparation of



(B1)

A solution of 436 ml diisopropylamine and 2.6 l tetrahydrofuran is cooled to -20°C, and 1.234 l n-hexyl lithium (2.5 M in hexane) is added dropwise over a period of 15 minutes. A solution of 368 g ethyl isovalerate in 1.7 l tetrahydrofuran is added dropwise over a period of 15 minutes at -20°C. After a further 10 minutes, a solution of 584 g 4-methoxy-3-(3-methoxy-propoxy)benzaldehyde (EP 0 678 503) in 1.7 l tetrahydrofuran is added drop by drop and stirred for 40 minutes at -20°C. Then 2.15 l saturated aqueous ammonium chloride solution is added drop by drop and extracted with ethyl acetate (2 x 8 l). The organic phases are washed consecutively with 0.5 N hydrochloric acid (1x 4.3 l), water (1x 4.4 l) and brine (1x 4.4 l). The combined organic phases are dried over sodium sulfate (1.6 kg), filtered and boiled down in a rotary evaporator. By means of crystallization from ethyl acetate (1 l) and hexane (11 l), title compound B1 is obtained from the residue as a white solid (656 g, 72 %): ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 0.90 - 1.04 (m, 9H), 1.97 (m, 2H), 2.32 (m, 1H), 2.58 (m, 1H), 3.28 (s, 3H), 3.50 (m, 2H), 3.74 (s, 3H), 3.82 (q, 2H), 3.98 (m, 2H), 4.57 (m, 1H), 5.30 (d, 1H), 6.75 - 6.90 (m, 3H) ppm.

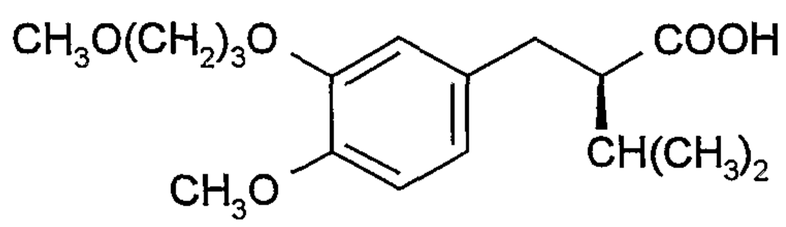
Example B2: Preparation of



(B2).

A solution of 649 g (content: 98.3 %) B1 and 11.0 g 4-dimethylaminopyridine in 3.2 l tetrahydrofuran is cooled to 0°C, 187.2 ml acetic acid anhydride is added dropwise and the reaction mixture then stirred for 1 hour. A solution of 606 g potassium t-butylate in 4.4 l tetrahydrofuran is added drop by drop over a period of 30 minutes at -2°C to 0°C and then stirred for 2 hours at 0°C. After the addition of 2 l water and distilling off 7.6 l tetrahydrofuran at 35 °C, 6.5 l ethanol and 0.9 l 2N KOH are added to the aqueous residue. The mixture obtained is stirred for 20 hours under reflux. The reaction solution is cooled off and concentrated by evaporation. At 0°C, 7.2 l t-butyl methyl ether and 3 l 2N HCl are added to the residue. The organic phase is separated off and the aqueous phase extracted again with 7.2 l t-butyl methyl ether. The organic phases are then washed consecutively with 7.2 l water and 7.2 l brine. The combined organic phases are dried over magnesium sulfate (2 kg), filtered and concentrated in a rotary evaporator. By means of crystallization from diisopropyl ether (2.4 l) and hexane (2.4 l), 470 g of crude title compound is obtained from the residue. After recrystallization from diisopropyl ether (2 l) and Hexan (2 l), pure title compound B2 (454.3 g, 81.8 %) is obtained: ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 1.22 (d, 6H), 1.97 (m, 2H), 3.14 (m, 1H), 3.28 (s, 3H), 3.50 (m, 2H), 3.82 (s, 3H), 4.02 (m, 2H), 6.90 - 7.05 (m, 3H), 7.42 (s, 1H), COOH (exchanged) ppm.

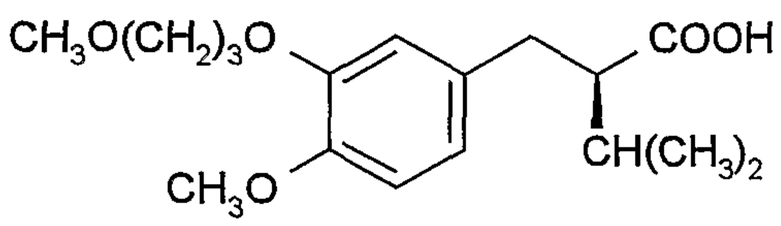
Example B3: Preparation of



(B3).

In a flask with a magnetic stirrer, 5.83 mg (0.0156 mmol) $[Rh(NBD)_2]BF_4$ and 15.3 mg (0.0164 mmol) L1 are placed under an atmosphere of argon through repeated evacuation and purging with argon. Then 20 ml degassed methanol is added and stirred for 15 minutes, before 24 g (0.078 mol) B2 and 140 ml degassed methanol are introduced into a 250 ml flask fitted with a side stopcock and flushed with argon. With gentle heating, agitation is continued until a homogeneous solution is formed. The solution is forced under pressure via a steel capillary tube into a 300 ml steel autoclave under cover of argon. In 3 purge cycles (argon 20 bar / hydrogen 20 bar) the hydrogen pressure is eventually increased to 50 bar. Hydrogenation is started by switching on the stirrer and carried out at room temperature. The reaction takes place via hydrogen consumption (fall of pressure in the reservoir of hydrogen). After a reaction time of 8 hours, a full conversion is measured by HPLC (method 1). The reaction mixture is concentrated by evaporation and crude title compound B3 obtained as a slightly yellowish oil (24 g , quantitative): HPLC (method 2) optical yield > 95% R-Isomer; ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.03 (m, 6H), 1.95 (m, 1H), 2.07 (m, 2H), 2.48 (m, 1H), 2.81 (m, 2H), 3.40 (s, 3H), 3.60 (m, 2H), 3.85 (s, 3H), 4.10 (m, 2H), 6.70 - 6.80 (m, 3H) ppm.

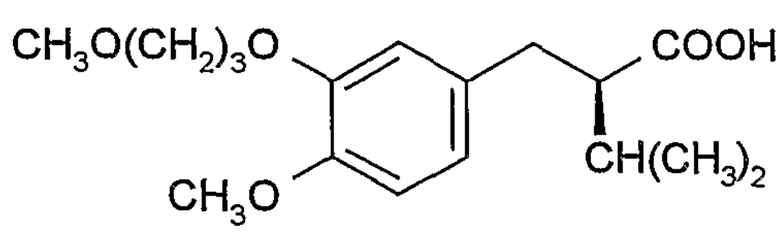
Example B4: Preparation of



(B3).

In a flask with a magnetic stirrer, 1.50 mg (0.0024 mmol) $[Rh(NBD)(OOCCF_3]_2$ and 4.75 mg (0.0051 mmol) L1 are placed under an atmosphere of argon through repeated evacuation and purging with argon. Then 5 ml degassed methanol is added and stirred for 15 minutes, before 3.0 g (9.73 mmol) B2 and 15 ml degassed methanol are introduced into a 50 ml flask fitted with a side stopcock and flushed with argon. With gentle heating, agitation is continued until a homogeneous solution is formed. The solution is forced under pressure via a steel capillary tube into a 50 ml steel autoclave under cover of argon. In 3 purge cycles (argon 20 bar / hydrogen 20 bar) the hydrogen pressure is eventually increased to 20 bar. Hydrogenation is started by switching on the stirrer and carried out at room temperature. The reaction takes place via hydrogen consumption (fall of pressure in the reservoir of hydrogen). After a reaction time of 20 hours, a full conversion is measured. The optical yield amounts to >95% (R)-compound.

Example B5: Preparation of

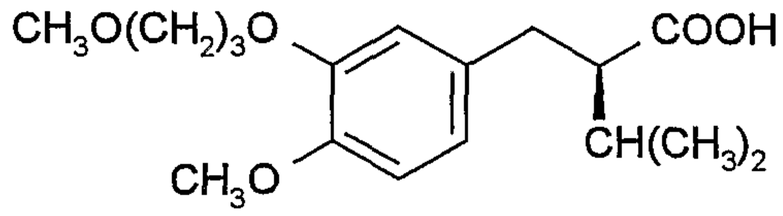


(B3).

In a flask with a magnetic stirrer, 1.50 mg (0.0024 mmol) $[Rh(NBD)(OOCCF_3]_2$ and 4.75 mg (0.0051 mmol) L1 are placed under an atmosphere of argon through repeated evacuation and purging with argon. Then 5 ml degassed toluene is added and

stirred for 15 minutes, before 150 mg (0.486 mmol) B2 and 15 ml degassed toluene are introduced into a 50 ml flask fitted with a side stopcock and flushed with argon. With gentle heating, agitation is continued until a homogeneous solution is formed. The solution is forced under pressure via a steel capillary tube into a 50 ml steel autoclave under cover of argon. In 3 purge cycles (argon 20 bar / hydrogen 20 bar) the hydrogen pressure is eventually increased to 100 bar. Hydrogenation is started by switching on the stirrer and carried out at room temperature. The reaction takes place via hydrogen consumption (fall of pressure in the reservoir of hydrogen). After a reaction time of 72 hours, a full conversion is measured. The optical yield amounts to 95% (R)-compound.

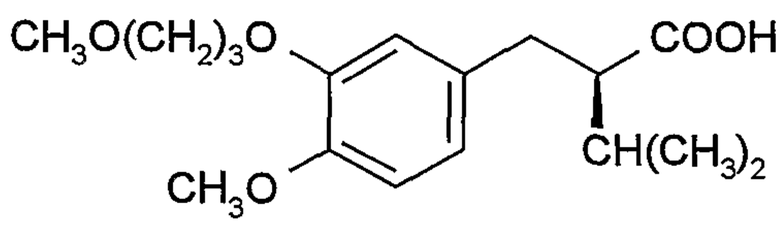
Example B6: Preparation of



(B3).

The procedure is analogous to that described under Example B5. For preparation of the catalyst, 1.5 mg (0.004 mmol) $[Rh(NBD)Cl]_2$ and 3.86 mg (0.004 mmol) (2S,4S)-N-(t-butyloxycarbonyl)-4-(dicyclohexylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine are used. 0.205 g (0.65 mmol) of educt B2 is hydrogenated in 10 ml toluene. After 20 hours at 60 bar hydrogen and 50°C, the reaction is stopped and the conversion and enantiomeric purity are determined. The conversion amounts to 98.9% and the optical yield is 80% ee.

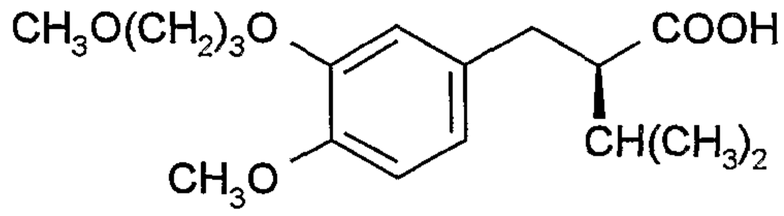
Example B7: Preparation of



(B3).

The procedure is analogous to that described under Example B6, and 2.2 mg (0.01 mmol) $[Rh(NBD)Cl]_2$ and 9.6 mg (0.01 mmol) (R)-1,1'-(di-3,4,5-methoxyphenylphosphino)-6,6'-dimethoxybiphenyl are used for the preparation of the catalyst. 0.304 g (0.99 mmol) of educt B2 is hydrogenated in 10 ml toluene. After a reaction time of 18 hours at 60 bar hydrogen and 50°C, the conversion amounts to 93.5% and the optical yield is 73.5% ee.

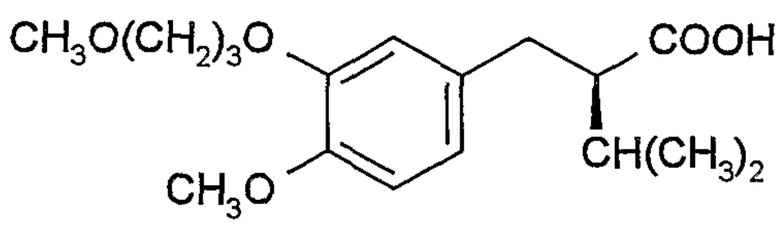
Example B8: Preparation of



(B3).

The procedure is analogous to that described under Example B6, and 3.0 mg (0.01 mmol) $[Rh(NBD)Cl]_2$ and 6.19 mg (0.01 mmol) (R)-(S)-1-{1-[bis-(bis-t-butylphenyl)phosphino]ethyl}-2-(diphenylphosphino)ferrocene are used for the preparation of the catalyst. 0.227 g (0.74 mmol) of educt B2 is hydrogenated in 10 ml toluene. After a reaction time of 90 hours at 60 bar hydrogen and 30°C, the conversion amounts to 98.6 % and the optical yield is 49% ee.

Example B9: Preparation of



(B3)

In a 50 l steel autoclave are placed 25 l of methanol under an atmosphere of argon through repeated evacuation and purging with argon. Then 12.00 kg B2 are added under argon. The suspension is heated under argon (2 bar) to 50° C, cooled to 35° C and degassed. 2.634 g (6.486 mmol) $[Rh(COD)_2]BF_4$ and 6.337 g (6.810 mmol) L1 are placed in a flask with magnetic stirrer under an atmosphere of argon through repeated evacuation and purging with argon. Then 700 ml degassed methanol are added and stirred for 45 minutes. This catalyst solution is forced under argon atmosphere through a steel capillary in the autoclave. In 3 purge cycles (argon 20 bar / hydrogen 20 bar) the hydrogen pressure is increased to 50 bar. The hydrogenation is started by switching on the stirrer and carried out at 35° C. The reaction is monitored via hydrogen consumption (decrease of pressure in the reservoir of hydrogen). After a reaction time of 21 hours (15 hours take-up of hydrogen) a full conversion is measured according to HPLC (methode 1). The reaction mixture is concentrated by evaporation and crude title compound B3 obtained as slightly yellowish oil (12,08 kg, quantitative): HPLC (Methode 2) optical yield > 95% R-Isomer.

Determination of conversion and optical yield:

For the HPLC analysis, B1 and B2 are derivatized (preparation of the respective methyl esters): a sample of the residue in diethyl ether is mixed with excess diazo methane in diethyl ether. The solvent is then evaporated off, and the residue obtained is the corresponding methyl ester.

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Method 1 (determination of conversion): column HP Hypersil™ BDS-C 18 125 x 4mm ; acetonitrile and water 5% to 100%; 40 minutes flow: 0.8 ml.

Method 2 (determination of optical yield): column: Daicel™ OJ-R 0.45 x 15 cm; solvent 30% acetonitrile and 70% water.

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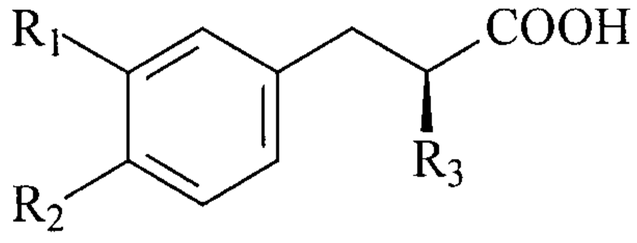
CLAIMS:

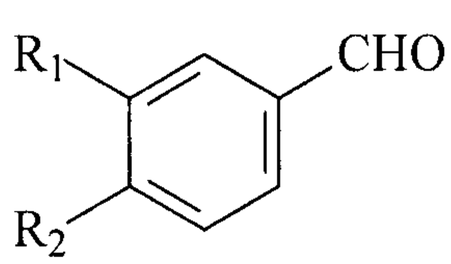
1. A process for the preparation of a compound of formula I,



(I),

wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl comprising

a) reaction of a compound of formula II

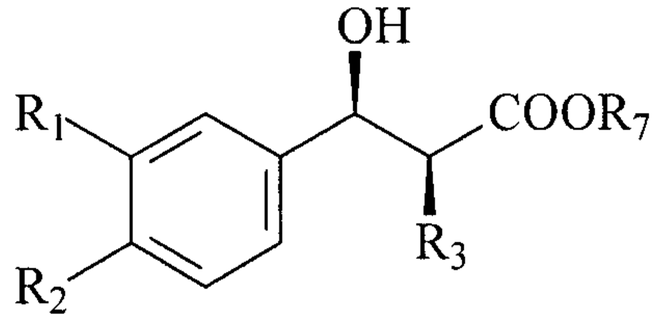


(II),

wherein R_1 and R_2 are as defined for the compound of formula I, with a compound of formula III,

$$R_3\text{-}CH_2\text{-}CO_2R_7 \qquad \text{(III)},$$

wherein R_3 is as defined for the compound of formula I, to form a compound of formula IV,

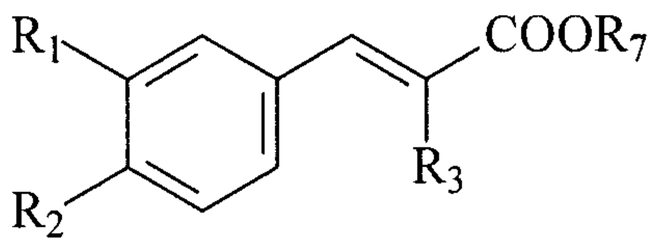


(IV),

wherein R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl;

b) isolation of the crystalline compound of formula IV, conversion of the OH group to a leaving group,

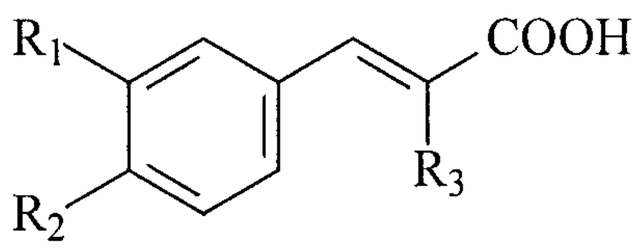
and reaction of the compound containing the leaving group in presence of a strong base to form a compound of formula V,



(V)

wherein R_1, R_2, R_3 and R_7 are as defined for the compound of formula IV;

c) hydrolysis of the carbonic ester of formula V to form the carboxylic acid of formula VI,



(VI)

wherein R_1, R_2 and R_3 are as defined for the compound of formula V; and

d) hydrogenation of the carboxylic acid of formula VI in the presence of hydrogen and catalytic quantities of a metal complex as asymmetric hydrogenation catalyst, wherein the metal complex comprises ruthenium, rhodium or iridium, to which a chiral bidentate ligand is bonded, to form the compound of formula I.

2. A process according to claim 1, wherein R_1 is methoxy-C_1-C_4alkyloxy or ethoxy-C_1-C_4alkyloxy and R_2 is methoxy or ethoxy.

3. A process according to claim 1, wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

4. A process according to any one of claims 1 to 3, wherein R_3 is a linear or branched C_1-C_4alkyl.

5. A process according to any one of claims 1 to 3, wherein R_3 is isopropyl.

6. A process according to any one of claims 1 to 5, wherein step a) takes place at a temperature of 0 to 40°C in the presence of a secondary lithium amide.

7. A process according to any one of claims 1 to 6, wherein step b) comprises first acylation of the OH group and then elimination at a temperature of 0 to 40°C in the presence of an alkali metal alcoholate in the reaction mixture of the acylation process.

8. A process according to any one of claims 1 to 7, wherein step c) is carried out in the reaction mixture of step b).

9. A process according to any one of claims 1 to 8, wherein the metal complex of step d) is of formula VII or VIIa

[LMeYZ] (VII), $[LMeY]^+E^-$ (VIIa),

wherein

Me is rhodium;

Y stands for two olefins or one diene;

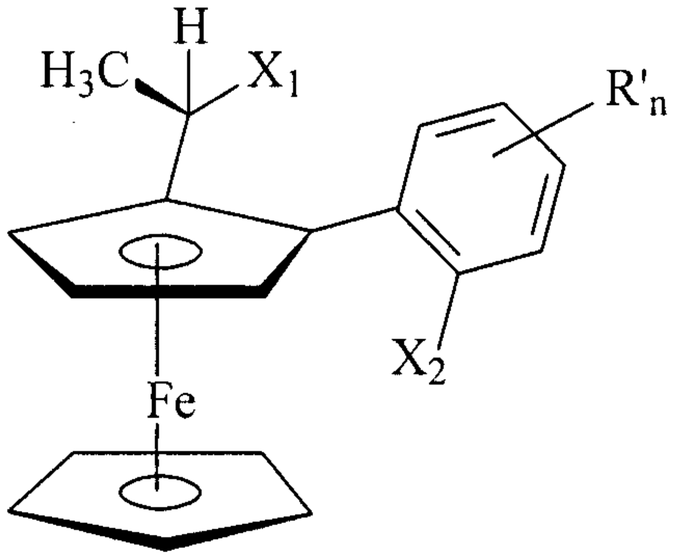
Z is Cl, Br or I;

E^- is an anion of an oxygen acid or a complex acid; and

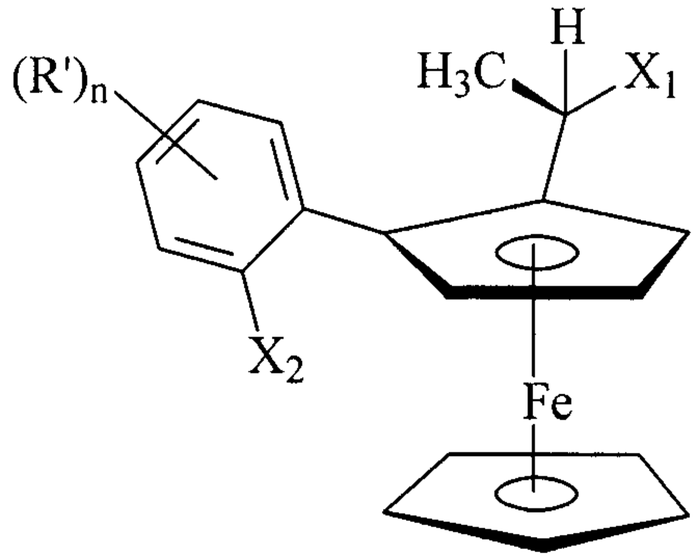
L is a chiral ligand from the ditertiary diphosphine group, in which the phosphine groups are bonded to a C_2-C_4 chain of the diphosphine backbone chain, and the

diphosphine forms a five to seven-member ring together with the rhodium atom.

10. A process according to claim 9, wherein L has formula VIII or VIIIa,



(VIII)



(VIIIa),

wherein

n is 0 or an integer from 1 to 4 and each R' independently is C_1-C_4alkyl, -CF_3 or C_1-C_4alkoxy; and

X_1 and X_2 are, independently of one another, secondary phosphino.

11. A process according to claim 10, wherein X_1 and X_2 are each independently of formula -PR_8R_9, wherein R_8 and R_9 are independently branched C_3-C_8alkyl, C_3-C_8cycloalkyl, unsubstituted phenyl or phenyl independently substituted with one to three C_1-C_4alkyl, C_1-C_4alkoxy, or -CF_3.

12. A process according to claim 11, wherein n is 0, and R_8 and R_9 are each independently cyclohexyl, phenyl or phenyl substituted with 1 or 2 methyl, methoxy or CF_3.

13. A process according to any one of claims 1 to 12, wherein step d) is carried out at temperatures of -20 to 150°C.

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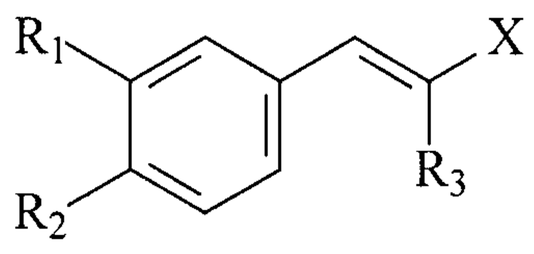
14. A process according to any one of claims 1 to 13, wherein step d) is carried out under positive pressure.

15. A process according to any one of claims 1 to 14, wherein the process is carried out under pressure conditions of 10^5 to $2x10^7$ Pa (Pascal).

16. A compound of formula IX,



(IX),

wherein

R_1 and R_2, independently of one another, are C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, and X is -COOH.

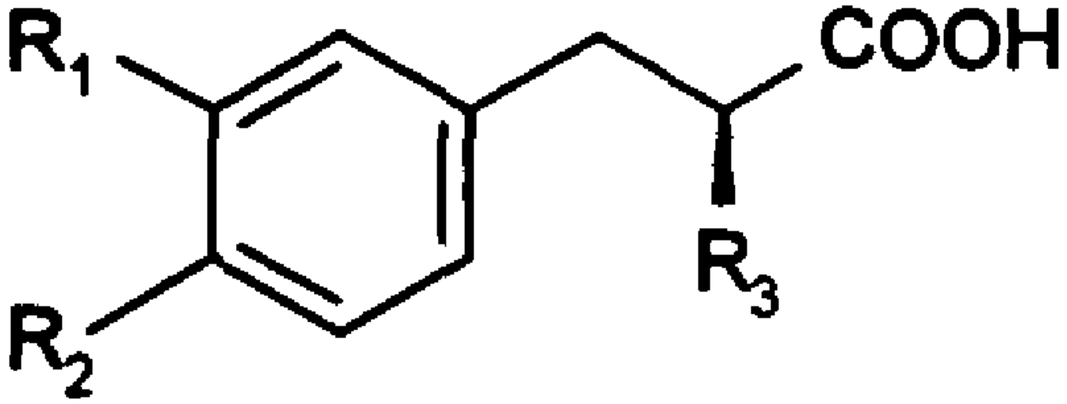
17. A compound according to claim 16, wherein R_1 is methoxy-C_1-C_4alkyloxy or ethoxy-C_1-C_4alkyloxy; R_2 is methoxy or ethoxy; R_3 is C_1-C_4alkyl; and X is -COOH.

18. A compound according to claim 16, wherein R_1 is 1-methoxy-n-propyloxy; R_2 is methoxy; R_3 is isopropyl; and X is -COOH.

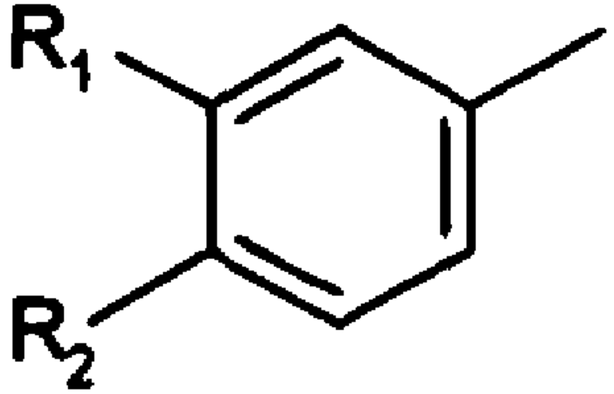
FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS



(I)



(a)