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(72) Inventeurs/Inventors:
HEROLD, PETER, CH;
STUTZ, STEFAN, CH;
SPINDLER, FELIX, CH;
WEISSENSTEINER, WALTER, AT;
STURM, THOMAS, AT

(73) Propriétaire/Owner:

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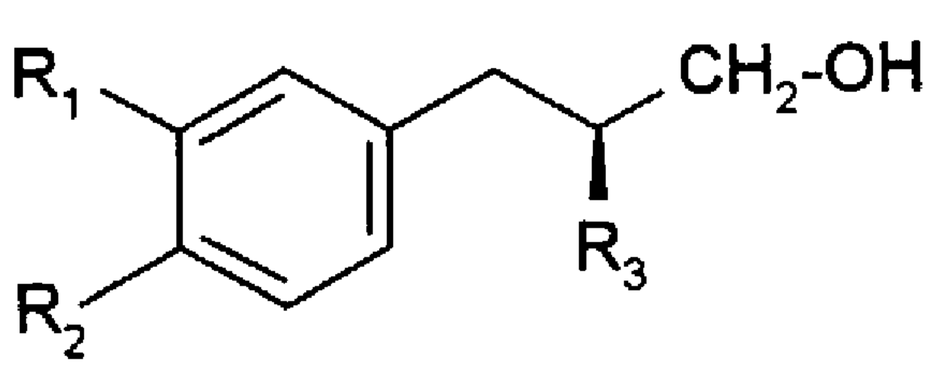

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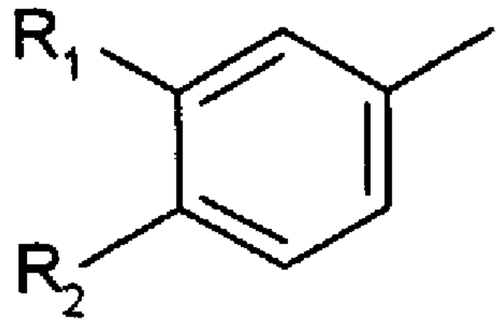

(a)

(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 yiedls 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 leaving group, subsequent regioselective elimination to form 3-R-2-R_3-propenic acid esters, and reduction to corresponding 3-R-2-R_3-allyl alcohols and their enantioselective hydrogenation, wherein R is (a).

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(73) **Propriétaires(suite)/Owners(continued)**:SPEEDEL PHARMA AG, CH

(74) **Agent**: FETHERSTONHAUGH & CO.

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(71) Applicant *(for all designated States except US)*: **SPEEDEL PHARMA AG** [CH/CH]; Hirschgässlein 11, CH-4051 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HEROLD, Peter** [CH/CH]; Unterer Rheinweg 124, CH-4057 Basel (CH). **STUTZ, Stefan** [CH/CH]; Reichensteinerstrasse 19, CH-4053 Basel (CH). **SPINDLER, Felix** [CH/CH]; Dullikerstrasse 15, CH-4656 Starrkirch-Wil (CH).

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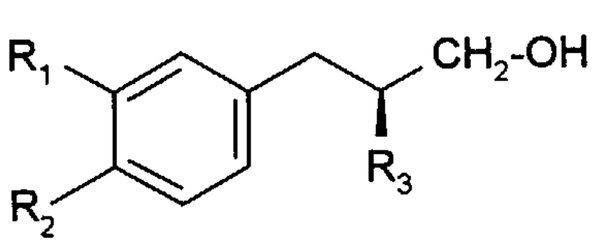
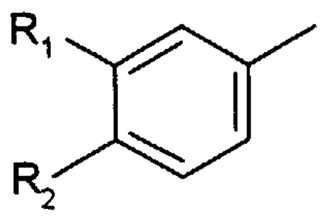
(54) Title: PROCESS FOR THE PREPARATION OF (R)-2-ALKYL-3-PHENYL-1-PROPANOLS



(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 yiedls 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 leaving group, subsequent regioselective elimination to form 3-R-2-R_3-propenic acid esters, and reduction to corresponding 3-R-2-R_3-allyl alcohols and their enantioselective hydrogenation, wherein R is (a).

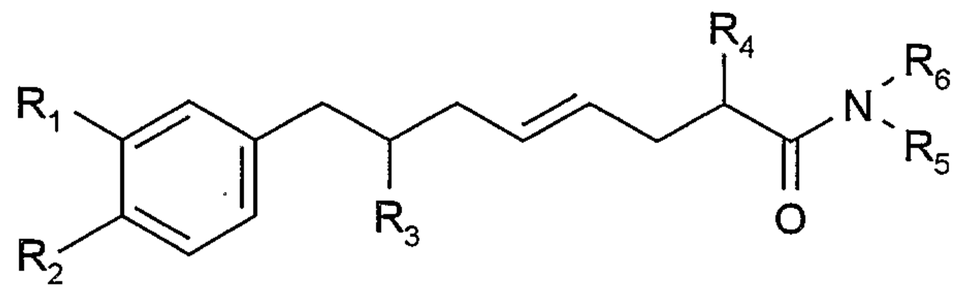
Process for the preparation of (R)-2-alkyl-3-phenyl-1-propanols

The invention relates to a stereoselective process for the preparation of (R)-2-alkyl-3-phenyl-1-propanols and new 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.

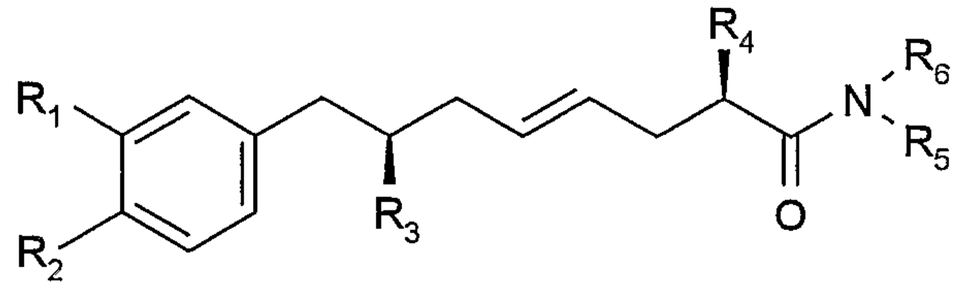
In a new process, one starts from 2,7-dialkyl-8-aryl-4-octenoyl amides, whose double bond is simultaneously halogenated in the 5-position and hydroxylated in the 4-position under lactonization, then the halogen is substituted by azide, the lactone amidated and the azide then transferred to the amine 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),

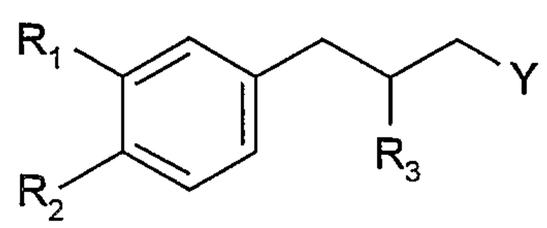
and especially to formula A1



(A1),

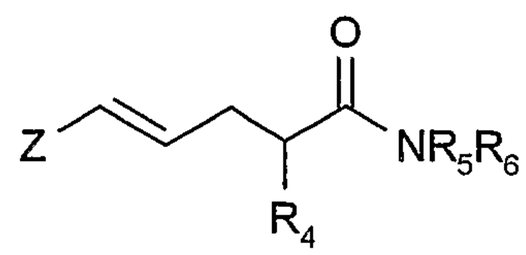
wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, R_6 is C_1-C_6alkyl, R_5 is C_1-C_6alkyl or C_1-C_6alkoxy, or R_5 and R_6 together are tetramethylene, 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 allyl alcohols obtained after hydrogenation can in turn be hydrogenated in the presence of certain catalysts to form practically enantiomer-pure 2-alkyl-3-phenyl-1-propanols. These alcohols

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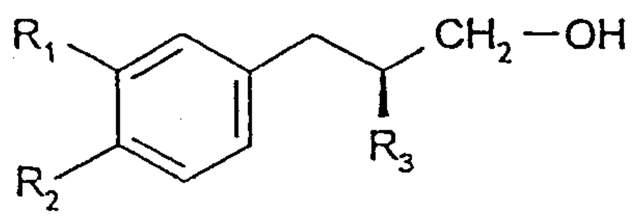
can then be converted by halogenation to the compounds of formula B in a manner known per se.

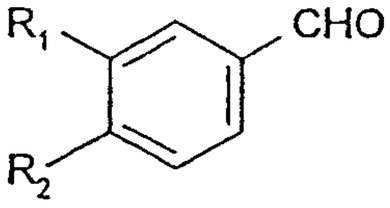
An aspect of the invention is a process for the preparation of compounds of formula I,



(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

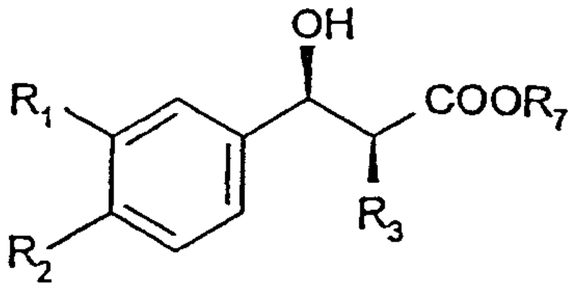


(II),

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

(III),

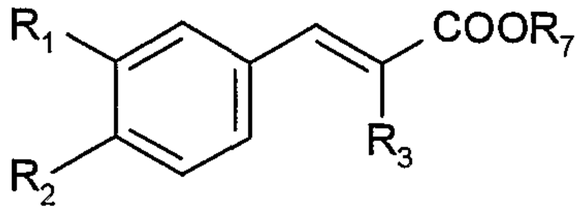
wherein R_3 is as defined above, to form a compound of formula IV,



(IV),

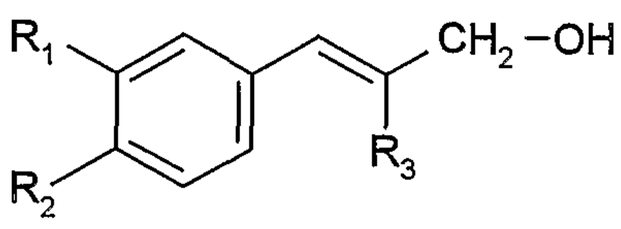
wherein R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl,

b) 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 reduction of carbonic esters of formula V to form the alcohol of formula VI,



(VI), and

d) the hydrogenation of the alcohol 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.

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%.

Process step c) is preferably carried out at low temperatures, for example -40°C to 0°C, and advantageously in a solvent. Suitable solvents are, for example, hydrocarbons (pentane, cyclohexane, methylcyclohexane, benzene, toluene and xylene). For hydrogenation, metal hydrides are expediently used in at least equimolar quantities, for example LiH, NaH, $NaBH_4$, $LiAlH_4$, and alkyl metal hydrides such as methyl, ethyl, or isopropyl aluminium dihydride or tin trihydride, dimethyl, diethyl, triisopropyl or triisobutyl aluminium hydride or tin dihydride, and tributyl tin hydride. The compounds can be isolated by means of extraction and purified by means of distillation. The yields amount to more than 90%.

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.

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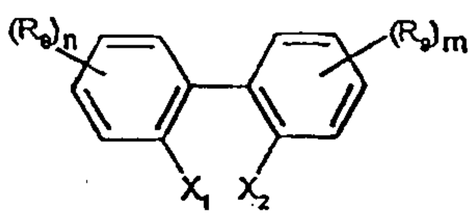
The two olefin groups of the diene are preferably linked by one or two CH_2 groups. Examples are 1,3-pentadiene, cyclopentadiene, 1,5-hexadiene, 1,4-cyclohexadiene, 1,4- or 1,5-heptadiene, 1,4- or 1,5-cycloheptadiene, 1,4- or 1,5-octadiene, 1,4- or 1,5-cyclooctadiene and norbornadiene. Y represents preferably two ethylene or 1,5-hexadiene, 1.5-cyclooctadiene or norbornadiene.

In formula VII, Z is preferably Cl or Br. Examples of E^- 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^-.

It was found that ligands with a biphenyl backbone are especially suitable for the asymmetric hydrogenation of compounds of formula VI. With these 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, wherein L represents the ligands of formula VIII,



(VIII)

wherein

m and n in each case are 0 or an integer from 1 to 4, and R_8 and R_9 are hydrogen or the same or different substituents, selected from the C_1-C_4alkyl and C_1-C_4alkoxy group; and

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

Substituents are preferably bonded in the 6 position or the 6,6' positions.

As an alkyl, R_8 and R_9 may preferably comprise 1 to 2 C atoms. Linear alkyl is preferred. Examples of R_8 and R_9 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_8 and R_9 may preferably comprise 1 to 2 C atoms. Linear alkoxy is preferred. Examples of R_8 and R_9 as an alkoxy are methoxy, ethoxy, n- and i-propoxy, n-, i- und 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 $PR_{10}R_{11}$, wherein R_{10} and R_{11} 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, wherein X_1 and X_2 are a $PR_{10}R_{11}$ group, wherein R_{10} and R_{11} in each case are cyclobutyl, cyclopentyl, cyclohexyl, phenyl or phenyl substituted with 1 or 2 methyl, methoxy or CF_3.

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.

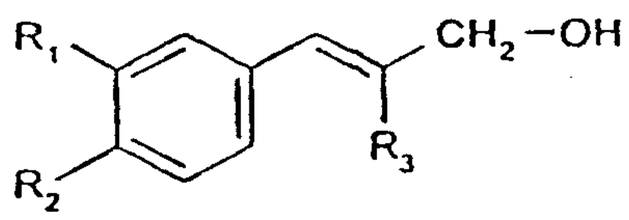
The preparation of catalysts as well as process step d) and the other process steps may be carried out in the absence or the presence of an inert solvent, wherein one solvent or a mixture of solvents may be used. Suitable solvents are, for example, aliphatic, cycloaliphatic and aromatic hydrocarbons (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 the 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.

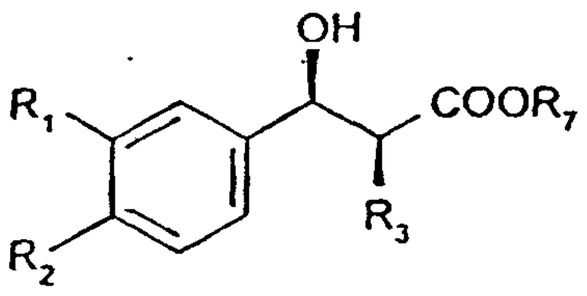
A further aspect of the invention relates to the compounds (intermediates) of formula VI,



(VI),

wherein R_1 is methoxy-C_1-C_4alkoxy or ethoxy-C_1-C_4alkoxy, R_2 is methoxy or ethoxy and R_3 is C_1-C_6 alkyl.

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



(IV),

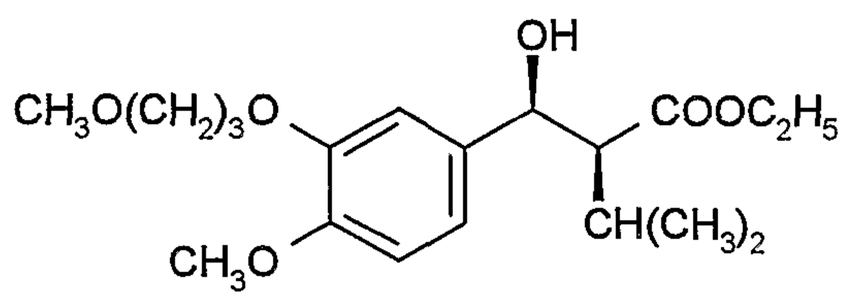
wherein R_1, R_2 and R_3 are as described for the compounds of formula VI and R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl.

The embodiments and preferences described hereinabove apply for R_1, R_2, R_3 and R_7.

The following examples explain the invention in more detail.

A) Preparation of (R)-3-[4'-CH_3O-3'-($CH_3O(CH_2)_3O$)-phen-1-yl]-2-isopropylpropan-1-ol (A4)

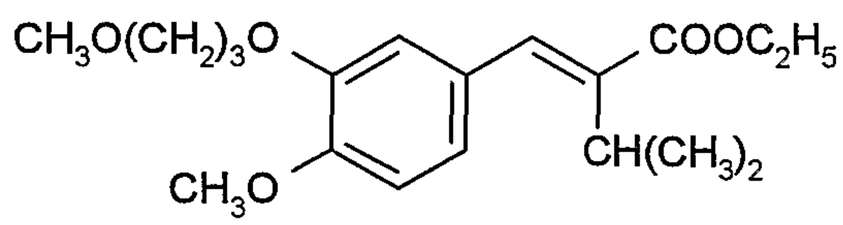
Example A1: Preparation of



(A1)

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 A1 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.

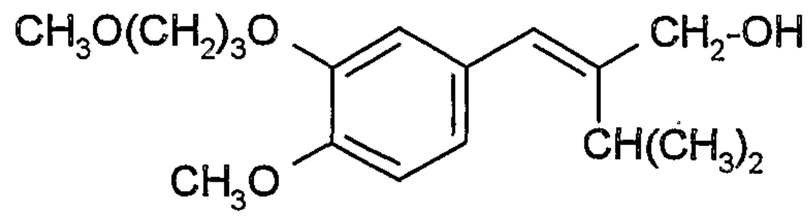
Example A2: Preparation of



(A2).

A solution of 20 g A1 and 0,4 g 4-dimethylaminopyridine in 100 ml tetrahydrofuran is cooled to 0°C, 6.3 ml acetic acid anhydride is added dropwise and the reaction mixture stirred for 1 hour. A solution of 19.0 g potassium t-butylate in 140 ml 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. Then 250 ml t-butyl methyl ether and 250 ml iced water are added to the reaction mixture. The organic phase is separated off and the aqueous phase extracted again with 250 ml t-butyl methyl ether. The organic phases are washed consecutively with 250 ml water and 250 ml brine. The combined organic phases are dried over magnesium sulfate (50 g), filtered and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F / ethyl acetate / hexane 1:4) pure title compound A2 is obtained from the residue as a colourless oil (17.45 g, 92.6 %): ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.26 (d, 6H), 1.35 (m, 3H), 2.15 (m, 2H), 3.22 (m, 1H), 3.38 (s, 3H), 3.60 (m, 2H), 3.90 (s, 3H), 4.17 (m, 2H), 4.28 (m, 2H), 6.85 - 7.0 (m, 3H), 7.49 (s, 1H) ppm.

Example A3: Preparation of

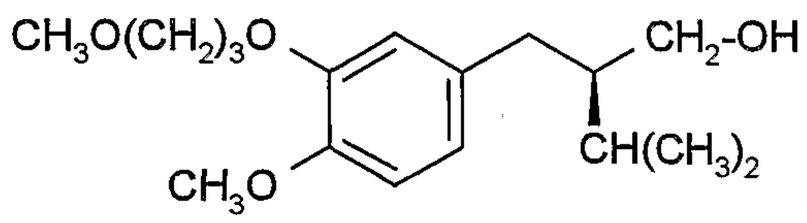


(A3).

A solution of 37.0 g A2 in 410 ml toluene is cooled to -20°C, and 229 ml diisobutyl aluminium hydride solution (1.2

M in toluene) is added over a period of 20 minutes. The reaction mixture is stirred for 1 hour at -20°C, before 220 ml methanol is slowly added. Then 1.5 l 1N HCl is added to the mixture and this is then extracted with t-butyl methyl ether (3 x 1 l). The organic phases are washed consecutively with 1.2 l water and 1.2 l brine. The combined organic phases are dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. By means of molecular distillation, title compound A3 is obtained from the residue as a colourless oil (29.7 g, 91.8 %): ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 1.08 (d, 6H), 1.93 (m, 2H), 3.02 (m, 1H), 3.28 (s, 3H), 3.50 (m, 2H), 3.85 (s, 3H), 4.02 (m, 2H), 4.10 (d, 2H), 4.77 (bs, 1H), 6.39 (s, 1H), 6.78 (m, 2H), 6.93 (m, 1H) ppm.

Example A4: Preparation of



(A4).

In a flask with a magnetic stirrer, 1.2 mg (0.0026 mmol) [Rh(norbornadiene)Cl]$_2$ and 3.83 mg (0.0054 mmol) (R)-(4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenyl-phosphine) are placed under an atmosphere of argon through repeated evacuation and purging with argon. Then 10 ml degassed toluene is added and stirred for 15 minutes, before 3.75 g (0.01275 mol) A3 and 20 ml degassed toluene are introduced into a 50 ml flask fitted with a stopcock and flushed with argon. With gentle heating, agitation is continued until a homogeneous solution is formed. The catalyst and substrate solutions are 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 1000 bar. The autoclave is heated to 30°C and hydrogenation started by switching on the stirrer. The

reaction can take place via hydrogen consumption (fall of pressure in the reservoir of hydrogen). After a reaction time of 18 hours, the reaction mixture is concentrated, and crude title compound A4 is obtained as a slightly yellowish oil (3.75 g, quantitative): The enantiomeric purity of the product (measured by HPLC: column Chiralcel™ ODH 0.46x25 cm; hexane/iPrOH: 95/5; temperature: 20°C; flow rate: 0.6 ml/min; S-product: 22.9 min; R-product: 25.3 min; educt: 27.8 min; UV: 210 nm) amounts to > 95% ee (R).

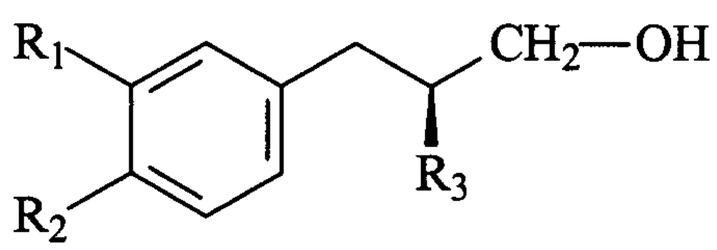
^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.96 (m, 6H), 1.2 (m, 1H), 1.67 (m, 1H), 1.90 (m, 1H), 2.12 (m, 2H), 2.48 (m, 1H), 2.68 (m, 1H), 3.40 (s, 3H), 3.60 (m, 4H), 3.89 (s, 3H), 4.12 (m, 2H), 6.70 - 6.85 (m, 3H) ppm.

Example A5: Preparation of A4

The procedure is analogous to that described under Example A4, but the ligand ((R)-(6,6'-dimethoxybiphenyl-2,2'-diyl)-bis(dicyclobutylphosphine)) is used for the catalyst. The reaction is stopped after 18 hours. The conversion amounts to 100%, and enantiomeric purity is 96.3% (R).

CLAIMS:

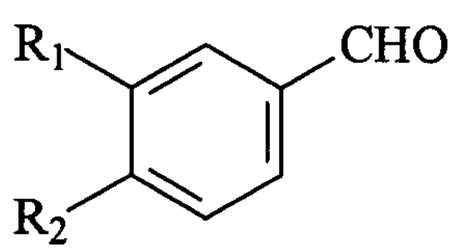
1. A process for preparation of a compound of formula I,



(I),

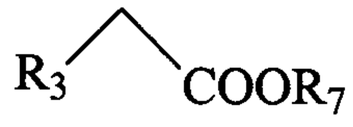
wherein R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy—C_1-C_6alkyloxy, and R_3 is C_1-C_6alkyl comprising

a) reaction of a compound of formula II



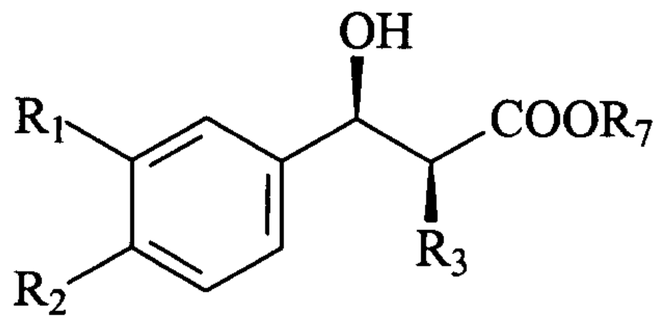
(II),

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



(III),

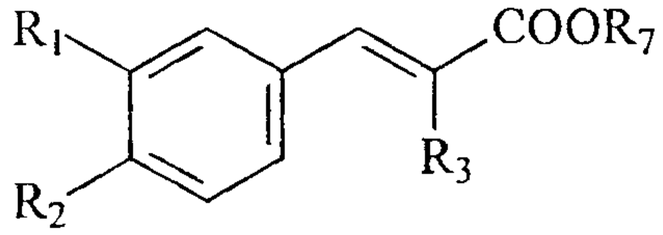
wherein R_3 is as defined for the compound of formula I and R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl to form a crystalline compound of formula IV,



(IV),

wherein R_3 and R_7 are as defined for the compound of formula III and R_1 and R_2 are as defined for the compound of formula I;

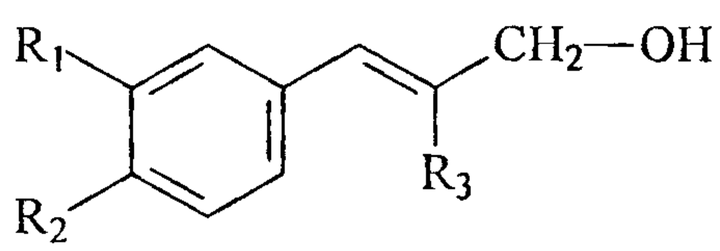
b) isolation of the crystalline compound of formula IV, conversion of the OH group in the compound of formula IV to a leaving group, and reaction of the resulting compound comprising the leaving group in the presence of a strong base to form a compound of formula V,



(V),

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

c) reduction of the compound of formula V to form an alcohol of formula VI,



(VI), and

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

d) the hydrogenation of the alcohol of formula VI in the presence of hydrogen and catalytic quantities of a metal complex as an asymmetric hydrogenation catalyst, wherein the metal complex comprises ruthenium, rhodium or iridium as the metal, to which 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 2, 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 claim 4, wherein R_3 is isopropyl.

6. A process according to any one of claims 1 to 5, wherein the reaction of 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 the conversion in step b) of the OH group into the leaving group comprises acylation of the hydroxyl group followed by elimination at a temperature of 0 to 40°C in the presence of an alkali metal alcoholate in the reaction mixture of the acylation.

8. A process according to any one of claims 1 to 6, wherein step c) is carried out at a temperature of 0 to 40°C in the presence of a metal hydride as reduction agent.

9. A process according to any one of claims 1 to 8, wherein step d) is carried out in presence of a metal complex of formula VII or VIIa as a hydrogenation catalyst,

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

wherein

Me is rhodium;

Y stands for two olefins or one diene;

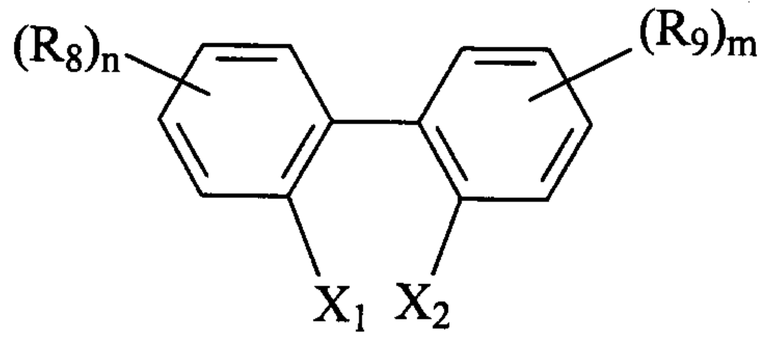
Z is Cl, Br or I;

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

L is a chiral ligand from a 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 the formula VIII,



(VIII)

wherein

m and n in each case are 0 or an integer from 1 to 4, and R_8 and R_9 are independently hydrogen, C_1-C_4alkyl 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 R_8 and R_9 when C_1-C_4alkyl or C_1-C_4alkoxy are bonded in the 6 position or the 6,6' position.

12. A process according to claim 10 or 11, wherein R_8 and R_9 are independently methyl, ethyl, methoxy or ethoxy.

13. A process according to any one of claims 10 to 12, wherein X_1 and X_2 are independently of the formula $-PR_{10}R_{11}$, wherein R_{10} and R_{11} are the same or different and are branched C_3-C_8alkyl, C_3-C_8cycloalkyl, unsubstituted phenyl or phenyl substituted with one to three C_1-C_4alkyl, C_1-C_4alkoxy, or $-CF_3$.

14. A process according to claim 10, wherein n is 0, and X_1 and X_2 are independently $PR_{10}R_{11}$, wherein R_{10} and R_{11} in each case is independently cyclobutyl, cyclopentyl,

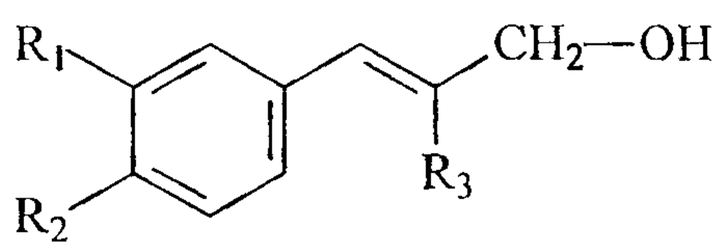
cyclohexyl, phenyl or phenyl substituted with 1 or 2 methyl, methoxy or CF_3.

15. A process according to any one of claims 1 to 14, wherein step d) is carried out at a temperature of -20 to 150°C.

16. A process according to any one of claims 1 to 15, wherein step d) is carried out under positive pressure.

17. A process according to claim 16, wherein the positive pressure is 10^5 to $2x10^7$ Pa (Pascal).

18. A compound of formula VI,



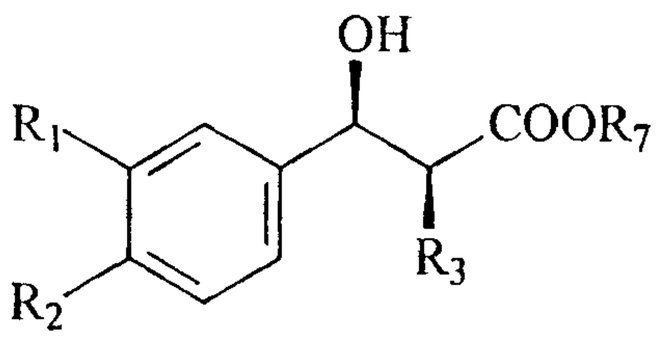
(VI),

wherein R_1 is methoxy-C_1-C_4alkyloxy or ethoxy-C_1-C_4alkyloxy, R_2 is methoxy or ethoxy, and R_3 is C_1-C_6alkyl.

19. A compound according to claim 18, wherein R_1 is methoxy-C_1-C_4alkyloxy or ethoxy-C_1-C_4alkyloxy; R_2 is methoxy or ethoxy; and R_3 is C_1-C_4alkyl.

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

21. A compound of formula IV,



(IV),

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_6alkyl, and R_7 is C_1-C_{12}alkyl, C_3-C_8cycloalkyl, phenyl or benzyl.

22. A compound according to claim 21, 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 R_7 is C_1-C_4alkyl.

23. A compound according to claim 21, wherein R_1 is 1-methoxy-n-propyloxy; R_2 is methoxy; R_3 is isopropyl, and R_7 is methyl or ethyl.

FETHERSTONHAUGH & CO.

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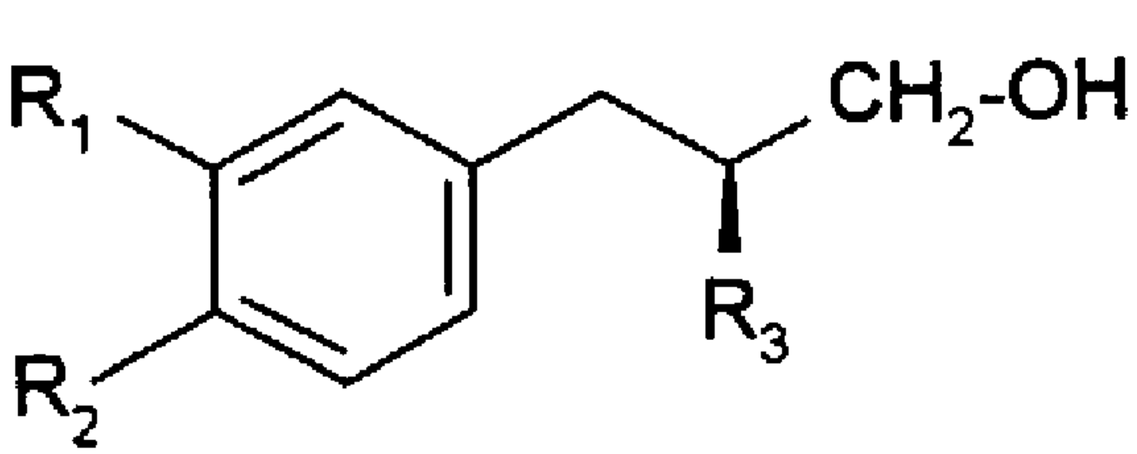
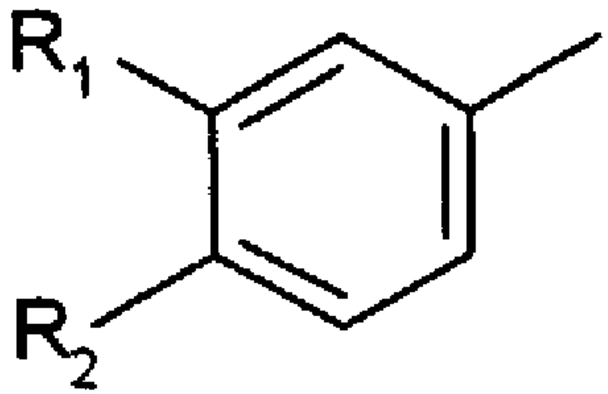


(I)



(a)