(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 02/02508 A1

(51) International Patent Classification[7]: C07C 231/02, 247/12, C07D 207/32, 303/40

(21) International Application Number: PCT/CH01/00399

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

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1329/00 5 July 2000 (05.07.2000) CH
2450/00 15 December 2000 (15.12.2000) CH

(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).

(74) Agent: **R.A. EGLI & CO.**; Horneggstrasse 4, Postfach, CH-8034 Zürich (CH).

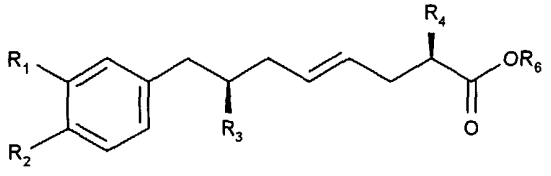
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE,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

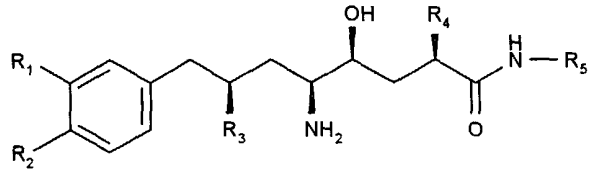
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED OCTANOYL AMIDES



(II)



(I)

(57) Abstract: Compounds of formula (II) are simultaneously halogenated in the 5 position and hydroxylated in the 4 position under lactonization, the halolactone is converted into a hydroxylactone and then the hydroxy group into a leaving group, the leaving group is replaced with azide, the lactone amidated and then the azide converted to the amine group, in order to obtain compounds of formula (I).

WO 02/02508 A1

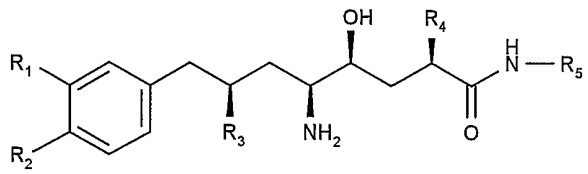
Process for the preparation of substituted octanoyl amides

The invention relates to a process for the preparation of 2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides and their physiologically acceptable salts; and the new compounds used as intermediates in the multistage process.

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 procedures 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.

It has now been surprisingly found that these alkanecarboxamides can be prepared both in high total yields and in a high degree of purity, and that selectively pure diastereomers are obtainable, if the double bond of 2,7-dialkyl-8-aryl-4-octenic acid or 2,7-dialkyl-8-aryl-4-octenic acid ester is simultaneously halogenated in the 5 position and hydroxylated in the 4 position under lactonization, the halolactone is converted to a hydroxylactone and then the hydroxy group is converted to a leaving group, the leaving group substituted with azide, the lactone amidated and then the azide converted to the amine group. Apart from the high yields and stereoselectivities in the individual process steps, particular attention is drawn to the fact that substantially fewer by-products are formed in the azidation step.

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

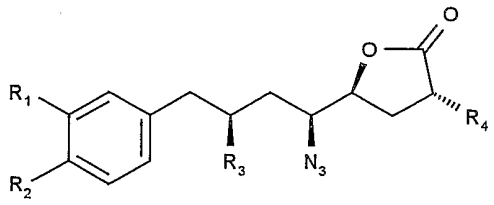


(I),

wherein

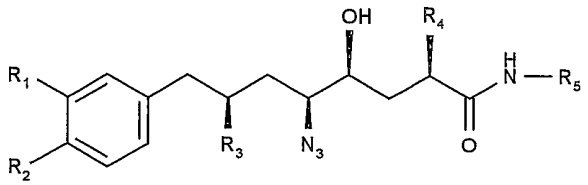
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl, comprising

a) the reaction of a compound of formula II,



(II),

with an amine of formula R_5-NH_2 to form a compound of formula III,



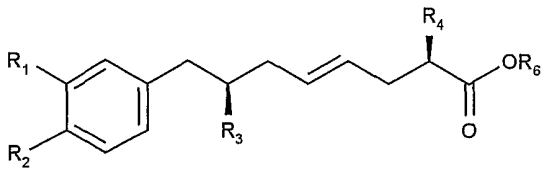
(III),

and

b) reduction of the azide group of the compound of formula III to the amine group and isolation of the compounds of

formula I, if necessary with the addition of a salt-forming acid, comprising the preparation of compounds of formula II by reacting

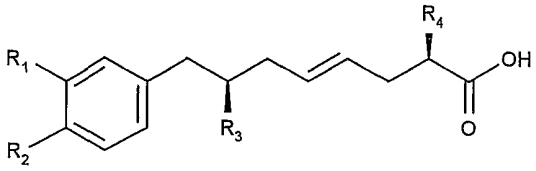
c1) a compound of formula IV,



(IV),

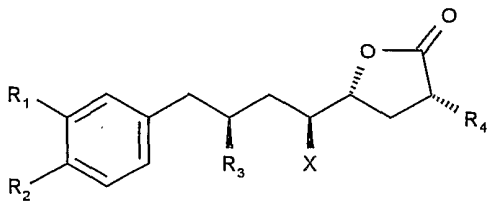
wherein R_6 is C_1-C_{20}alkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkyl-C_1-C_6alkyl, C_6-C_{10}aryl or C_6-C_{10}-aryl-C_1-C_6alkyl, with a halogenation agent to form a compound of formula VI, or

c2) a carboxylic acid of formula V, or a salt of this carboxylic acid,



(V),

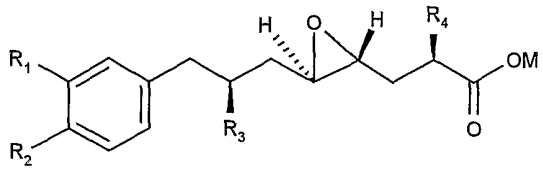
with a halogenation agent to form a compound of formula VI,



(VI),

wherein X is Cl, Br or I,

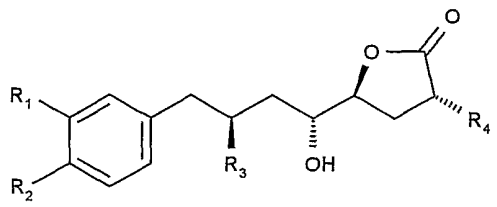
d) reaction of the compound of formula VI in the presence of an alkali metal or alkaline earth metal hydroxide or an alcohol to form a compound of formula VII,



(VII),

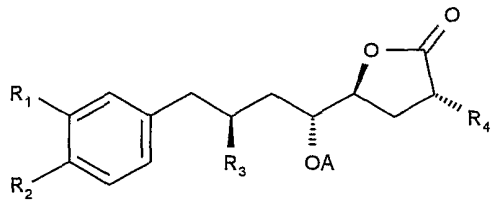
wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group,

e) hydrolysis of the compound of formula VII in the presence of an acid to form a compound of formula VIII,



(VIII),

f) substitution of the hydrogen atom of the hydroxyl group in the compound of formula VIII and conversion thereof to a leaving group AO to form compounds of formula IX,



(IX),

g) and then reaction of the compound of formula IX with an azidation agent to form a compound of formula II, or

h) reaction if the compound of formula VIII directly with a zinc azide/-bis-pyridine complex in the presence of a tertiary phosphine and an azodicarboxylate, if necessary in an organic solvent, to form a compound of formula II.

As an alkyl, R_1 and R_2 may be linear or branched and preferably comprise 1 to 4 C atoms. Examples are methyl,

ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl.

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

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

As an alkoxyalkyl, R_1 and R_2 may be linear or branched. 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.

As a C_1-C_6alkoxy-C_1-C_6alkyloxy, R_1 and R_2 may be linear or branched. The alkoxy group preferably comprises 1 to 4 and especially 1 or 2 C atoms, and the alkyoxy 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- or ethoxy-C_1-C_4alkyloxy, and R_2 is preferably methoxy or ethoxy. Particularly preferred are compounds of formula I, wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

As an alkyl, R_3 and R_4 may be linear or branched 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 and R_4 in compounds of formula I are in each case isopropyl.

As an alkyl, R_5 may be linear or branched in the form of alkyl and preferably comprise 1 to 4 C atoms. Examples of alkyl are listed hereinabove. Methyl, ethyl, n- and i-propyl, n-, i- and t-butyl are preferred.

As a C_1-C_6hydroxyalkyl, R_5 may be linear or branched and preferably comprise 2 to 6 C atoms. Some examples are 2-hydroxyethy-1-yl, 2-hydroxyprop-1-yl, 3-hydroxyprop-1-yl, 2-, 3- or 4-hydroxybut-1-yl, hydroxypentyl and hydroxyhexyl.

As a C_1-C_6alkoxy-C_1-C_6alkyl, R_5 may be linear or branched. The alkoxy group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 4 C atoms. Some examples are 2-methoxyethy-1-yl, 2-methoxyprop-1-yl, 3-methoxyprop-1-yl, 2-, 3- or 4-methoxybut-1-yl, 2-ethoxyethy-1-yl, 2-ethoxyprop-1-yl, 3-ethoxyprop-1-yl, and 2-, 3- or 4-ethoxybut-1-yl.

As a C_1-C_6alkanoyloxy-C_1-C_6alkyl, R_5 may be linear or branched. The alkanoyloxy group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 4 C atoms. Some examples are formyloxymethyl, formyloxyethyl, acetyloxyethyl, propionyloxyethyl and butyroyloxyethyl.

As a C_1-C_6aminoalkyl, R_5 may be linear or branched and preferably comprise 2 to 4 C atoms. Some examples are 2-aminoethyl, 2- or 3-aminoprop-1-yl and 2-, 3- or 4-aminobut-1-yl.

As C_1-C_6alkylamino-C_1-C_6alkyl and C_1-C_6dialkylamino-C_1-C_6-alkyl, R_5 may be linear or branched. The alkylamino group preferably comprises C_1-C_4alkyl groups and the alkyl group preferably 2 to 4 C atoms. Some examples are 2-methylaminoeth-1-yl, 2-dimethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 3-methylaminoprop-1-yl, 3-dimethylaminoprop-1-yl, 4-methylaminobut-1-yl and 4-dimethylaminobut-1-yl.

As a C_1-C_6alkanoylamido-C_1-C_6alkyl, R_5 may be linear or branched. The alkanoyl group preferably comprises 1 to 4 C atoms and the alkyl group preferably 1 to 4 C atoms. Some examples are 2-formamidoeth-1-yl, 2-acetamidoeth-1-yl, 3-propionylamidoeth-1-yl and 4-butyroylamidoeth-1-yl.

As a HO(O)C-C_1-C_6alkyl, R_5 may be linear or branched and the alkyl group preferably comprises 2 to 4 C atoms. Some examples are carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl.

As a C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, R_5 may be linear or branched, and the alkyl groups preferably comprise independently of one another 1 to 4 C atoms. Some examples are methoxycarbonylmethyl, 2-methoxycarbonyleth-1-yl, 3-methoxycarbonylprop-1-yl, 4-methoxycarbonylbut-1-yl, ethoxycarbonylmethyl, 2-ethoxycarbonyleth-1-yl, 3-ethoxycarbonylprop-1-yl, and 4-ethoxycarbonylbut-1-yl.

As a H_2N-C(O)-C_1-C_6alkyl, R_5 may be linear or branched, and the alkyl group preferably comprises 2 to 6 C atoms. Some examples are carbamidomethyl, 2-carbamidoeth-1-yl,

2-carbamido-2,2-dimethyleth-1-yl, 2- or 3-carbamidoprop-1-yl, 2-, 3- or 4-carbamidobut-1-yl, 3-carbamido-2-methylprop-1-yl, 3-carbamido-1,2-dimethylprop-1-yl, 3-carbamido-3-methylprop-1-yl, 3-carbamido-2,2-dimethylprop-1-yl, 2-, 3-, 4- or 5-carbamidopent-1-yl, 4-carbamido-3,3- or -2,2-dimethylbut-1-yl.

As a C_1-C_6alkyl-HN-C(O)-C_1-C_6-alkyl or (C_1-C_6alkyl)$_2$N-C(O)-C_1-C_6alkyl, R_5 may be linear or branched, and the NH-alkyl group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 6 C atoms. Examples are the carbamidoalkyl groups defined hereinabove, whose N atom is substituted with one or two methyl, ethyl, propyl or butyl.

A preferred subgroup of compounds of formula I is that in which R_1 is C_1-C_4alkoxy or C_1-C_4alkoxy-C_1-C_4alkyloxy, R_2 is C_1-C_4alkoxy, R_3 is C_1-C_4alkyl, R_4 is C_1-C_4alkyl and R_5 is $H_2NC(O)$-C_1-C_6alkyl which if necessary is N-monosubstituted or N-di-C_1-C_4alkyl substituted.

A more preferred subgroup of compounds of formula I is that in which R_1 is methoxy-C_2-C_4-alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4alkyl, R_4 is C_2-C_4alkyl and R_5 is $H_2NC(O)$-C_1-C_6alkyl.

An especially preferred compound of formula I is that in which R_1 is 3-methoxy-prop-3-yloxy, R_2 is methoxy, R_3 and R_4 are 1-methyleth-1-yl, and R_5 is $H_2NC(O)$-[$C(CH_3)_2$]-CH_2-.

As an alkyl, R_6 may be linear or branched and comprise preferably 1 to 12 C atoms, 1 to 8 C atoms being especially preferred. R_6 is particularly preferred as a linear C_1-C_4alkyl. Some examples are methyl, ethyl and the isomers of propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl, octacyl and eicosyl. Especially preferred are methyl and ethyl.

As a cycloalkyl, R_6 may preferably comprise 4 to 8 ring-carbon atoms, 5 or 6 being especially preferred. Some examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and cyclododecyl.

As a cycloalkyl-alkyl, R_6 may comprise preferably 4 to 8 ring-carbon atoms, 5 or 6 being especially preferred, and preferably 1 to 4 C atoms in the alkyl group, 1 or 2 C atoms being especially preferred. Some examples are cyclopropyl methyl, cyclobutyl methyl, cyclopentyl methyl or cyclopentyl ethyl, and cyclohexyl methyl or cyclohexyl ethyl.

As an aryl, R_6 is preferably phenyl or naphthyl.

As an aralkyl, R_6 is preferably benzyl or phenyl ethyl.

In formula VII, M may be an alkaline earth metal, for example Mg, Ca or Sr. Equivalent in the context of the invention means the charge equalization of cation and anion. M is preferably an alkali metal, for example Li, Na or K. Particular preference is for M as Li. If M is the residue of an alcohol minus a hydroxyl group, it may be the R_6 group, including the embodiments and preferences described hereinbefore, in particular alkyl and cycloalkyl.

Residue A in the leaving group AO is preferably the residue of an organic acid, for example C_1-C_8acyl, particular preference being for C_1-C_8sulfonyl. The acyl residue may be a carboxylic acid, such as formic acid, acetic acid, propionic acid, butyric acid and benzoic acid substituted if necessary with C_1-C_4alkyl, C_1-C_4alkoxy or halogen. The sulfonyl residue A may correspond for example to formula R_7-SO_2-, wherein R_7 is C_1-C_8alkyl, C_1-C_8halogenalkyl, C_3-C_8cycloalkyl, or phenyl or benzyl either unsubstituted or substituted with C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4hakogenalkyl or halogen. Some examples of

sulfonyl residues are methyl, ethyl, phenyl, methylphenyl, dimethyl phenyl, trimethyl phenyl, trifluoromethyl phenyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl and trifluoromethyl sulfonyl.

The individual process steps may be carried out in the presence of solvent. Suitable solvents are water and organic solvents, especially polar organic solvents, which can also be used as mixtures of at least two solvents. Examples of solvents are hydrocarbons (petroleum ether, pentane, hexane, cyclohexane, methylcyclohexane, benzene, toluene, xylene), halogenated hydrocarbon (dichloromethane, chloroform, tetrachloroethane, chlorobenzene); ether (diethyl ether, dibutyl ether, tetrahydrofuran, dioxane, ethylene glycol dimethyl or diethyl ether); carbonic esters and lactones (methyl acetate, ethyl acetate, methyl propionate, valerolactone); N,N-substituted carboxamides and lactams (dimethylformamide, dimethylacetamide, N-methylpyrrolidone); ketones (acetone, methylisobutylketone, cyclohexanone); sulfoxides and sulfones (dimethylsulfoxide, dimethylsulfone, tetramethylene sulfone); alcohols (methanol, ethanol, n- or i-propanol, n-, i- or t-butanol, pentanol, hexanol, cyclohexanol, cyclohexanediol, hydroxymethyl or dihydroxymethyl cyclohexane, benzyl alcohol, ethylene glycol, diethylene glycol, propanediol, butanediol, ethylene glycol monomethyl or monoethyl ether, and diethylene glycol monomethyl or monoethyl ether; nitriles (acetonitrile, propionitrile); tertiary amines (trimethylamine, triethylamine, tripropylamine and tributylamine, pyridine, N-methylpyrrolidine, N-methylpiperazine, N-methylmorpholine) and organic acids (acetic acid, formic acid).

Process step a)

The reaction of compounds of formula II to form compounds of formula III with a compound R_5NH_2 by opening of the lactone ring can be carried out with or without solvent. The

reaction is expediently carried out in the presence of alcohols or amines, which can form activated carbonic esters or carboxamides. Such compounds are well-known. These may be 2-hydroxypyridine, N-hydroxycarboxamides and imides, and carboximides (N-hydroxysuccinimide). Organic solvents are used as solvent, tertiary amines being of advantage, for example trimethylamine or triethylamine. The reaction temperature may range for example from approximately 40°C to 150°C and preferably from 50°C to 120°C.

Process step b)

Reduction of the azide group to the amine group in the compounds of formula III takes place in a manner known per se (see Chemical Reviews, Vol. 88 (1988), pages 298 to 317), for example using metal hydrides or more expediently using a catalytic method with hydrogen in the presence of homogeneous (Wilkinson catalyst) or heterogeneous catalysts, for example Raney nickel or precious metal catalysts such as platinum or palladium, if necessary on substrates such as carbon. The hydrogenation can also be carried out if necessary catalytically under phase transfer conditions, for example with ammonium formate as hydrogen donor. It is of advantage to use organic solvents. The reaction temperature may range for example from approximately 0°C to 200°C and preferably from 10°C to 100°C. Hydrogenation may be carried out at normal pressure or increased pressure up to 100 bar, for example, and preferably up to 50 bar.

The compounds of formula I may be converted to addition salts in a manner known per se by treatment with monobasic or polybasic, inorganic or organic acids. Hemifumarates are preferred.

Process step c1)

Suitable chlorination, bromination and iodination agents are elemental bromine and iodine, in particular N-chlorine,

N-bromine and N-iodocarboxamides and dicarboximides. Preferred are N-chloro, N-bromo and N-iodophthalimide and especially chloro, N-bromo and N-iodosuccinimide, as well as tertiary butyl hypochlorite and N-halogenated sulfonamides and sulfonimides, for example chloramine T. The reaction is advantageously carried out in organic solvents miscible with water, such as tetrahydrofuran or dioxane in the presence of at least an equivalent volume of water. The reaction takes place first at low temperatures, for example -20 to 10°C, and then at elevated temperatures, for example 30 to 100°C. The presence of inorganic or organic acids may be advantageous. Suitable acids are for example formic acid, acetic acid, methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, toluenesulfonic acid, H_2SO_4, H_3PO_4, hydrogen halides, acid ion exchange resins, and acids immobilized on solid carriers. The halolactone may be isolated for example by extraction with organic solvents.

Process step c2)

Suitable chlorination, bromination and iodination agents are elemental bromine and iodine, in particular N-chloro, N-bromo and N-iodocarboxamides and dicarboximides. Preferred are N-chloro, N-bromo and N-iodophthalimide and especially chloro, N-bromo and N-iodosuccinimide, as well as tertiary butyl hypochlorite and N-halogenated sulfonamides and sulfonimides, for example chloramine T. The reaction is advantageously carried out in organic solvents, such as halogenated hydrocarbons (chloroform, dichloromethane). The reaction temperature may range for example from approximately -70°C to ambient temperature and preferably from -30°C to 10°C. The halolactone may be isolated for example by extraction with organic solvents.

Suitable salts of carboxylic acids of formula V are for example alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, as

well as ammonium salts. The ammonium salts may derive from ammonia, primary, secondary or tertiary amines, or they may be quaternary ammonium salts. The amines may be acyclic or cyclic and comprise heteroatoms from the O and S group. The amines may comprise 1 to 18 C atoms, 1 to 12 being preferred and 1 to 8 especially preferred. Quaternary ammonium salts may comprise 4 to 18 C atoms, 4 to 12 being preferred and 4 to 8 especially preferred. Some examples of amines are methylamine, dimethylamine, triethylamine, ethylamine, diethylamine, triethylamine, propylamine, dipropylamine, Tripropylamine, isopropylamine, butylamine, dibutylamine, tributylamine, phenylamine, methylethylamine, methyldiethylamine, phenylmethylamine, benzylamine, cyclopentylamine, cyclohexylamine, piperidine, N-methylpiperidine, morpholine, pyrrolidine, and 2-phenylethylamine. Salt formation allows a more efficient purification of the carboxylic acids of formula V with regard to their optical and chemical purity, especially when crystalline salts are formed with the selection of amines. The salts may be converted before the reaction to the carboxylic acids of formula V. However, the salts may also be used directly for halolactonization. In this case, the addition of acids, for example trifluoroacetic acid or other strong acids, is recommended, as described under process step c1).

The halolactonization is surprisingly stereoselective, and the desired cis-halolactones are formed in yields of up to 90% or more.

Process step d)

The reaction of a compound of formula VI with at least equimolar quantities of alkali or alkaline earth metal hydroxides is expediently carried out in a polar organic solvent, for example alcohols such as isopropanol, and at low temperatures of, for example, -20 to 30°C. Aqueous

solutions of hydroxides are preferably used, lithium hydroxide being especially preferred. The compound of formula VII does not need to be isolated, but the reaction mixture can be used directly in process step e). The desired stereoisomer is also formed in this step at high yields of up to 90% or more.

The reaction of a compound of formula VI with at least equimolar quantities of an alcohol, especially a C_1-C_8alkanol and in particular methanol or ethanol, is expediently carried out in a polar organic solvent, for example ethers or the alkanols used for esterification, and at low temperatures of, for example -20 to 30°C. Bases are preferably used as well, for example alkali metal hydrogencarbonates or alkali metal carbonates, potassium hydrogencarbonate being especially preferred. The compound of formula VII does not need to be isolated, but the reaction mixture can be used directly in process step e). The desired stereoisomer is also formed in this reaction at high yields of up to 90% or more.

Process step e)

Lactonization of the compounds of formula VII to form compounds of formula VIII is expediently carried out at a temperature of -20 to 50°C and in the presence of a preferably polar solvent, such as an alcohol (isopropanol) or ether (tetrahydrofuran, dioxane). It is advantageous to use inorganic acids, especially mineral acids such as hydrochloric acid, hydrobromic acid or sulfuric acid. The hydroxylactone of formula VII may be isolated for example by extraction with organic solvents. The desired stereoisomer is also formed in this step at high yields of up to 90% or more.

Process step f)

Conversion of the hydroxy group to a leaving group may be carried out in organic solvents, preferably polar organic solvents, and at temperatures of -20 to 50°C. Acid halogenides, such as acid chlorides and acid bromides, are preferably used as reagents. Sulfonyl chlorides or bromides are especially preferred. The reaction is advantageously carried out in the presence of equivalent quantities of a base for bonding of the acid. Suitable bases are in particular tertiary amines, such as trimethylamine or triethylamine and dimethylaminopyridine. The hydroxylactone of a compound of formula VII may be isolated for example by extraction with organic solvents. The yields are up to 90% or more.

Process step g)

Suitable azidation agents are for example metal azides, especially alkaline earth metal azides and alkali metal azides, as well as silyl azides. Especially preferred azidation agents are lithium azide, sodium azide and potassium azide. The reaction may be carried out in organic solvents, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), dimethylformamide (DMF), 1,3-dimethylimidazolidinone (DMI), toluene or methylcyclohexane. The reaction temperature may range for example from approximately 20°C to 150°C and preferably from 50°C to 120°C. It may be expedient to include the use of phase transfer catalysts. The preparation and synthetic use of azides are described for example by E. F. V. Scriven in Chemical Reviews, Vol. 88 (1988), pages 298 to 317 The yield amounts to an outstanding 70% or more.

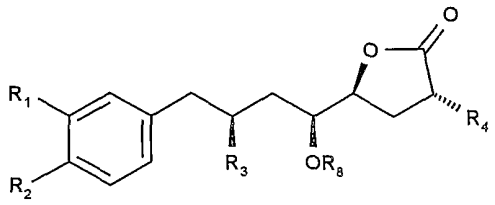
In one variant, the introduction of the leaving group in process step f) and the azidation in process step g) may be carried out simultaneously in one reaction vessel.

Process step h)

In one variant, the azidation may also be carried out directly with the hydroxyl compound of formula VIII. This reaction has been described by David. L. Hughes in Organic Preparations and Procedures Int. (1996), 28 (2), pp. 127-164 and by M. C. Viaud et al. in Synthesis (1990), pp. 130 to 131. The azidation is carried out with at least equimolar quantities of zinc azide/bis-pyridine in the presence of, for example, triphenylphosphine in quantities of 2 equivalents or more, and approximately equal quantities of an azodicarboxylate such as azodiisopropylcarboxylate. The reaction is carried out in an organic solvent, especially an aromatic hydrocarbon, such as benzene, toluene or xylene. The reaction temperature may be -20 to 80°C.

Some intermediates prepared using the process according to the invention are new and represent further objects of the invention.

A further object of the invention is thus a compound of formula X,



(X),

wherein

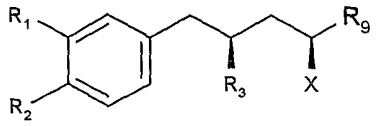
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoyl-

amido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or (C_1-C_6alkyl)$_2$N-C(O)-C_1-C_6-alkyl, and

R_8 is hydrogen or R_8O is a leaving group.

For residues R_1, R_2, R_3, and R_4 in compounds of formula X, the embodiments and preferences described hereinbefore apply.

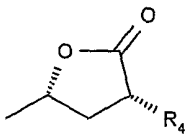
A further object of the invention is a compound of formula XI,



(XI),

wherein

X is halogen and R_9 is a residue of formula

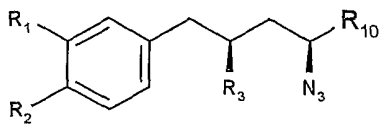


and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoyl-amido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or (C_1-C_6alkyl)$_2$N-C(O)-C_1-C_6-alkyl.

For residues R_1, R_2, R_3, and R_4, as well as for X, in compounds of formula XI, the embodiments and preferences described hereinbefore apply.

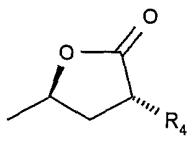
An object of the invention is also a compound of formula XII,



(XII),

wherein

R_{10} is a residue of formula

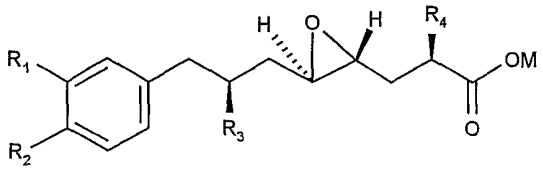


and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoyl-amido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

For residues R_1, R_2, R_3, and R_4 in compounds of formula XII, the embodiments and preferences described hereinbefore apply.

An object of the invention in a broader sense is a compound of formula VII,



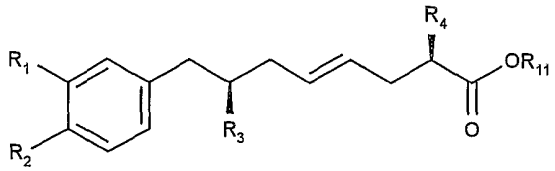
(VII),

wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group, and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoyl-amido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

For residues R_1, R_2, R_3, and R_4, as well as for M, in compounds of formula VII, the embodiments and preferences described hereinbefore apply.

An object of the invention is a compound of formula XIII



(XIII),

wherein R_{11} is an alkali metal, an equivalent alkaline earth metal, hydrogen or the residue of an alcohol minus a hydroxyl group, and

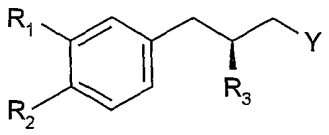
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl,

and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

For residues R_1, R_2, R_3, R_4, and R_{11} in compounds of formula XIII, the embodiments and preferences described hereinbefore apply.

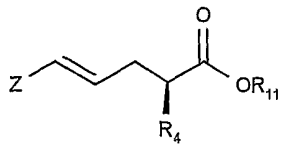
The carboxylic acids of formula V used in process step c) may be prepared in a manner known per se by hydrolysis of hydrolysable acid derivatives such as carbonic esters, carbooxamides or carboxylates. The hydrolysis may be carried out with acids or bases. Hydrolysis with a base is preferred, for example with alkali metal hydroxides (LiOH, KOH and NaOH), which can be added as aqueous solution or as a solid. The reaction is advantageously carried out in water, organic solvents (alcohols and ethers) or mixtures thereof. The reaction temperature may range up to the boiling temperature of the solvent used. After removal of the solvent, the residue of the reaction is expediently taken up with an aqueous acid, such as hydrochloric acid, and the compound of formula V is extracted (for example with ethers) and purified. The hydrolysis is quantitative, and the pure compound of formula V is obtained in yields of more than 90%. It is possible to carry out the hydrolysis at the same time as the halolactonization in one reaction vessel. The hydrolysis may also be carried out enzymatically.

The compounds of formula XIII are obtainable by reacting a compound of formula XIV



(XIV),

with a compound of formula XV,



(XV),

wherein R_1 to R_4, and R_{11} are as defined hereinbefore, including the preferences, 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 coupling of Grignard reagents with alkenyl halogenides in an ether such as tetrahydrofuran or dioxane as solvents in the presence of catalytic quantities of a soluble metal salt or metal complex, for example an iron, nickel or palladium salt or an iron, nickel or palladium complex (such as iron trichloride, iron acetonyl acetate iron benzoyl acetonate, nickel acetonyl acetate, and iron, nickel or palladium complexes with tertiary phosphines or ditertiary diphosphines such as triphenylphosphine, tricyclohexylphosphine, 1,2-diphenylphosphinoethane, 1,2-diphenylphosphinopropane, 1,2-diphenylphosphinofuran, and 1,2-diphenylphosphinobutane is known. Examples of metal complexes and metal complex salts are dichloronickel(1,2-diphenylphosphinoethane) and dichloropalladium(1,2-diphenylphosphinoethane). The presence of an additive stabilizing the metal salts or metal complexes and metal complex salts can be of advantage. Examples are DMPU, N-methylpyrrolidone, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylmorpholine, amines such as triethylamine and tetramethylethylenediamine, as well as mixtures of at least

two of these additives. When using iron acetonylacetate, the addition of a mixture of DMPU and tetramethylethylendiamine has proved successful. When using dichloronickel(1,2-diphenylphosphinoethane), the addition of triethylamine has proved to be of advantage.

The reaction is described by G. Cahiez et al. in Synthesis (1998), pp. 1199-1200. The reaction temperature may for example be -50 to 80°C, preferably -20 to 50°C. Catalytic quantities may for example be 0.1 to 20% by weight in relation to a compound of formula XIV. It is expedient to carry out the reaction so that initially a compound of formula XIV is converted to a Grignard compound (for example with magnesium) and then adding a solution of a compound of formula XV, metal salt, metal complex, or metal complex salt and the stabilizing additive, or vice versa.

It may be of advantage if only catalytic quantities of an additive stabilizing the metal complexes, for example triethylamine or DMPU, are used. Catalytic quantities may for example be 0.1 to 10 mol per cent, preferably 1 to 5 mol per cent, in relation to compounds of formula XIV or XV.

Compounds of formula XIV in the form of their racemates or enantiomers are known or capable of being prepared according to analogous processes. For example, R_1R_2phenylaldehyde may be reacted with R_3diethoxyphosphorylacetic acid ester to form 2-R_3-3-(R_1R_2phenyl)acrylic acid esters, these may then be hydrogenated to form the corresponding propionic acid esters, the ester group saponified and the carboxylic acid reduced to alcohol, and finally the hydroxyl group substituted with halogen. Enantiomers are obtainable by separating the racemates of the carboxylic acids with for example quinine or by enzymatic resolution of the racemates of the corresponding carbonic esters. Details are described

in the examples. A possible asymmetric synthesis of compounds of formula XIV is described in EP-A-0 678 503.

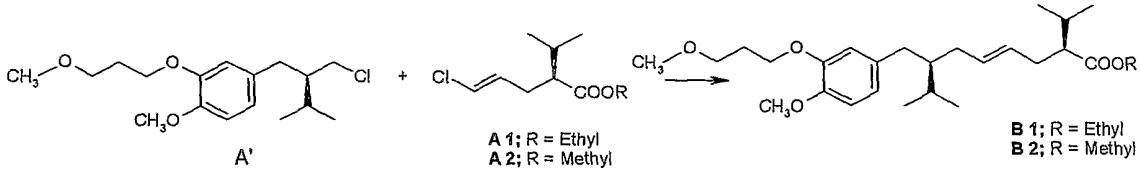
The compounds of formula XV are obtainable by reacting for example carbonic esters or derivatives of formula $R_4CH_2COOR_{11}$ with 1,3-dihalogenpropene in the presence of strong amine bases such as alkali metal amides (Li-N(i-propyl)$_2$ or lithium hexamethyldisilazane) to form compounds of formula XV, or by preparing through derivatization in a manner known per se carboxylic acids, carboxylic acid halogenides, carboxamides and carboxylic acid salts from e.g. the carbonic esters of formula XV. The desired enantiomers can be obtained from the racemates in a manner known per se by separating the racemates, for example by crystallization from addition salts of carboxylic acids using optically active bases. It is more advantageous to separate the racemates by treating esters of formula XV with esterases.

With the choice of carbonic esters and carboxylic acids of formulae IV and V, the compounds of formula I, which per se are complex compounds, can be prepared in a convergent and simple manner, which is especially true for this enantioselective or diastereoselective synthesis. The total yield from all process steps a) to h) may amount to 40% or more, which makes industrial application feasible.

The following examples explain the invention in more detail.

A) Preparation of compounds of formula IV

Example A1:



A mixture of 9.75 g magnesium powder and 100 ml tetrahydrofuran is heated to reflux, and 0.50 ml 1,2-dibromoethane then added over a period of 1 minute (visible exothermic reaction). A solution of 34.63 g A', 3.80 ml 1,2-dibromoethane and 300 ml tetrahydrofuran is added dropwise over a period of 30 minutes at 62 - 64°C. The mixture is agitated for another 30 minutes under reflux and then cooled down to ambient temperature. The reaction mixture is filtered under argon until clear and the resulting Grignard solution added dropwise over a period of 10 minutes to a solution of 20.47 g A1, 0.24 ml N-methylpyrrolidone, 0.88 g iron(III) acetylacetonate in 230 ml tetrahydrofuran at -5 to 0°C. The reaction mixture is stirred for a further 1 minute at 0°C, and 400 ml 2N hydrochloric acid is then added. The mixture is now extracted with diethyl ether (3x 300 ml) and the organic phases washed consecutively with water (1x 300 ml) and saturated aqueous sodium chloride solution (1x 200 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated by evaporation on a Rotavapor. By means of flash chromatography (SiO_2 60F; diethyl ether / hexane 1:4), title compound B1 is obtained from the residue as a slightly yellowish oil (33.8 g, 75 %): TLC R_f = 0.15 (diethyl ether - hexane 1:4).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.75 - 0.9 (m, 12H), 1.15 (t, 3H), 1.40 (m, 1H), 1.60 (m, 1H), 1.70 - 2.45 (m, 10H), 3.30 (s, 3H), 3.50 (t, 2H), 3.80 (s, 3H), 3.90 - 4.10 (m, 4H), 5.25 (m, 2H), 6.60 (m, 2H), 6.70 (d, 1H) ppm.

Example A2:

By analogy with example A1, the derivative is prepared by reacting A' with A2:

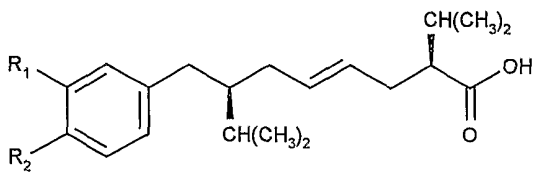
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90 - 1.00 (m, 12H), 1.40 - 2.55 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.65 (s, 3H), 3.85 (s, 3H), 4.15 (t, 2H), 5.40 (m, 2H), 6.65 - 6.75 (m, 2H), 6.80 (d, 1H) ppm.

Example A3:

A mixture of 38.9 g magnesium powder and 400 ml tetrahydrofuran is heated to reflux, and 2.0 ml 1-bromo-2-chloroethane then added over a period of 1 minute (visible exothermic reaction). A solution of 126.8 g A', 14.6 ml 1-bromo-2-chloroethane and 700 ml tetrahydrofuran is added dropwise over a period of 35 minutes at 62 - 64°C. The mixture is stirred for another 30 minutes under reflux and then cooled down to ambient temperature. The reaction mixture is filtered under argon until clear and the resulting Grignard solution added dropwise over a period of 20 minutes to a solution of 80.3 g A2, 5.58 ml triethylamine, and 2.11 g $NidppeCl_2$ in 700 ml tetrahydrofuran at 20 to 22°C. The reaction mixture is stirred for a further 1 minute at 20°C, and 1 l 1N hydrochloric acid is then added at 15°C. Extraction is now performed with tert-butyl methyl ether (2 x 1 l), and the organic phases are washed consecutively with saturated aqueous sodium chloride solution / water (1:9) (2 x 1.2 l) and saturated aqueous sodium chloride solution (1x 300 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated by evaporation on a rotary evaporator. A2 which has not been converted is distilled off from the residue at 75°C under a vacuum. Crude title compound B2 obtained in this way (171.4 g) is further reacted in example B2.

B) Preparation of compounds of formula V

Example B1: Preparation of carboxylic acid



(C1)

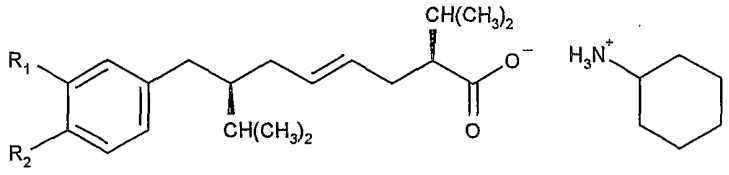
To a solution of 22.4 g B1 and 150 ml tetrahydrofuran / methanol / water (3:1:1) 3.6 g lithium hydroxide is added

and then stirred for 48 hours under reflux. The reaction mixture is concentrated by evaporation, 500 ml 1N HCl (cold) is added to the residue, and extraction performed with tert-butyl methyl ether (3x 500 ml). The organic phases are washed with saturated, aqueous NaCl solution (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F / ethyl acetate / hexane 1:1), title compound C1 is obtained from the residue as a slightly yellowish oil (19.2 g, 94 %): TLC R_t = 0.22 (diethyl ether - hexane 2:1).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80 - 1.0 (m, 12H), 1.50 (m, 1H), 1.70 (m, 1H), 1.80 - 2.60 (m, 10H), 3.40 (s, 3H), 3.65 (t, 2H), 3.85 (s, 3H), 4.15 (m, 2H), 5.45 (m, 2H), 6.70 (m, 2H), 6.80 (d, 1H) 7.60 - 9.0 (bs, 1H) ppm.

Title compound C1 can be prepared from B2 by analogy with example B1.

Example B2: Preparation of carboxylic acid-cyclohexylamine salt



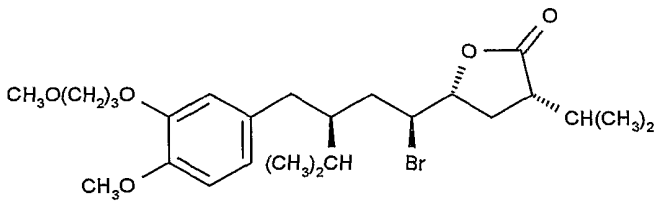
(C2)

To a solution of 171.4 g (crude) B2 and 1.07 l dioxane, 0.67 l water and 0.4 l 2N KOH are added and the mixture is then stirred under reflux for 23 hours. The reaction mixture is concentrated by evaporation, 0.6 l water is added to the residue which is washed with tert-butyl methyl ether (2 x 500 ml) (organic phases are discarded). The aqueous phase is acidified with 0.24 l 4N HCl and then extracted with tert-butyl methyl ether (2 x 0.6 l). The organic phases are washed with aqueous NaCl solution (0.6 l), dried over sodium sulfate and concentrated on a rotary evaporator. The residue

is dissolved in 2 l n-hexane, 38.5 ml cyclohexylamine is added and the mixture stirred for 20 hours at room temperature. The resulting suspension is cooled to 0°C, and title compound C2 is obtained by filtration in the form of white crystals (165.6 g, 79.6 %).

C) Preparation of compounds of formula VI

Example C1: Preparation of



(D1)

A solution of 2.66 g C1 and 26.6 ml dichloromethane is cooled to -15°C. Then 4 x 0.232 g N-bromosuccinimide is added in portions every 2 minutes. The reaction mixture is stirred for another 30 minutes at -15°C and then, over a period of 5 minutes, is introduced to 30 ml of 40% sodium hydrogen sulfite solution cooled to 0°C. The mixture is diluted with water (10 ml) and extracted with dichloromethane (2x 30 ml). The organic phases are washed consecutively with water (1x 30 ml) and concentrated aqueous NaCl solution (1x 30 ml), then dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 1:1) 2.98 g title compound D1 is obtained from the residue (content of title compound = approx. 89 %); TLC R_t = 0.34 (cis-lactone) and 0.38 (trans-lactone) with diethyl ether / hexane 2:1.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 - 1.10 (m, 12H), 1.60 - 2.65 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.55 - 3.70 (m, 1H), 3.85 (s, 3H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70 - 6.85 (m, 3H) ppm.

Example C2: Preparation from carbonic ester B1 in the presence of water

A solution of 0.449 g B 1, 3.3 ml tetrahydrofuran and 1.7 ml water is cooled to 0°C. 0.205 g N-bromosuccinimide is added to the solution and the mixture stirred for 30 minutes at 0°C and for 15 hours at 70°C. The reaction mixture is cooled to 0°C and added to 30 ml of 40% aqueous sodium hydrogen sulfite solution that has been cooled to 0°C. The mixture is extracted with ethyl acetate (3x 50 ml). The organic phases are washed consecutively with water (1x 30 ml) and concentrated aqueous NaCl solution (1x 30 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 1:1) 0.42 g title compound D1 is obtained from the residue (content of title compound = approx. 80 %); TLC R_t = 0.34 (cis-lactone) and 0.38 (trans-lactone) with diethyl ether / hexane 2:1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 - 1.10 (m, 12H), 1.60 - 2.65 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.55 - 3.70 (m, 1H), 3.85 (s, 3H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70 - 6.85 (m, 3H) ppm.

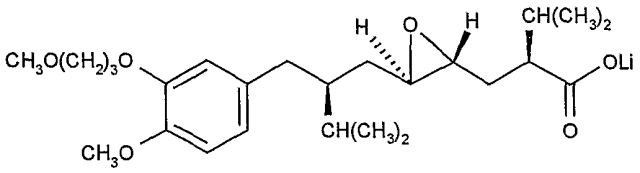
Example C3: Preparation from cyclohexylamine salt C2

A solution of 164.3 g C2 and dichloromethane is cooled to 0°C. 26.6 ml trifluoroacetic acid is added drop by drop and the mixture stirred for 1 hour. The reaction mixture is cooled to -20°C. Then 6 x 9.38 g N-bromosuccinimide is added in portions every 2 minutes. The reaction mixture is stirred for a further 2 hours at -15 to -20°C, and 160 ml 4% aqueous sodium hydrogen sulfite solution then added at 0°C. The mixture is extracted with water (1 l) and the organic phase separated off. The aqueous phase is extracted with dichloromethane (0.5 l) and the combined organic phases washed with water (1 l) and aqueous NaCl solution (0.5 l), then dried over sodium sulfate and concentrated on a rotary

evaporator. The crude title compound D1 obtained in this way (161.4 g) (content of title compound approx. 90 %) is further reacted in examples D2 and E2.

D) Preparation of compounds of formula VII

Example D1: Preparation of



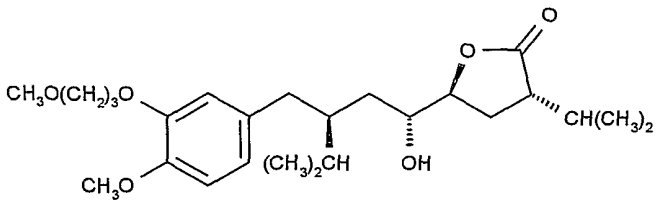
(E1)

A solution of 16.65 g D1 and 150 ml isopropanol is cooled to 0°C, then 66.6 ml 2N LiOH is added over a period of 10 minutes and the mixture stirred for 1.5 hours (the intermediate E1 is immediately reacted further in the next step).

Example D2:
Compound E1 is obtained in an analogous manner using compound D1 prepared as described under example C3 and is used in example E2.

E) Preparation of compounds of formula VIII

Example E1: Preparation of



(F1)

To the reaction mixture of example D1, 100 ml 2N HCl is added drop by drop, and the reaction mixture is stirred for 1 hour at room temperature. The reaction mixture is diluted with water (500 ml) and extracted with tert-butyl methyl ether (3x 250 ml). The organic phases are washed consecutively with water (2x 500 ml) and concentrated aqueous NaCl solution (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 2:1) 12.0 g title compound F1 is obtained from the residue (content of title compound = approx. 88 %); TLC R_t = 0.16 (diethyl ether / hexane 2:1).

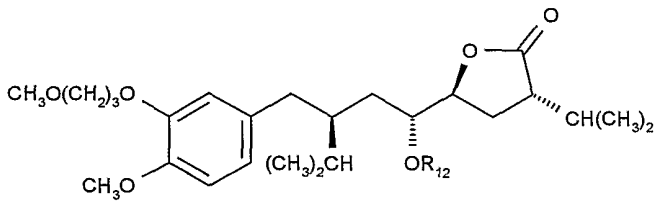
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80 - 1.05 (m, 12H), 1.10 - 2.25 (m, 10H), 2.35 (m, 1H), 2.50 - 2.75 (m, 2H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 3.80 - 3.90 (m, 1H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70 - 6.85 (m, 3H) ppm.

Example E2:

The stirred mixture of 161.4 g D1 (crude), 1.61 l tetrahydrofuran and 0.474 l water is stirred at room temperature for 20 h with 0.474 l 2N LiOH. Then 1.61 l water is added and the tetrahydrofuran (1.7 l) evaporated off on a rotary evaporator. The resulting mixture is washed with tert-butyl methyl ether (0.5 l) and the aqueous solution of the intermediate E1 is obtained and immediately reacted further. While stirring, tert-butyl methyl ether (1.0 l) and 4N HCl (0.316 l) are added. The organic phase is separated off and stirred for 2 hours under reflux (with a water separator). The solution is cooled, dried over sodium sulfate and concentrated on a rotary evaporator. The crude title compound F1 obtained in this way (136.1 g) (content of title compound approx. 90%) is further reacted in example F4.

F) Preparation of compounds of formula IX

Example F1: Preparation of

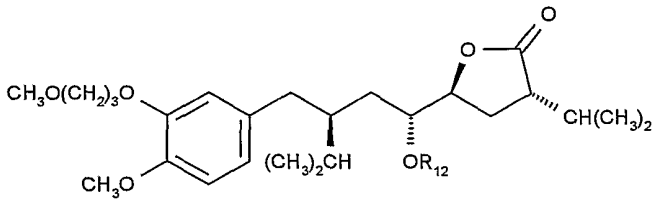


wherein R_{12} is CH_3-SO_2-(G1).

To a solution of 0.325 g F 1 and 8 ml dichloromethane, 0.156 ml triethylamine is added and the mixture cooled to 0°C. 0.087 ml methanesulfonyl chloride is added drop by drop and the mixture then stirred for 1 hour at room temperature. The reaction mixture is poured onto water (10 ml) and extracted with tert-butyl methyl ether (2x 10 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (10 ml) and concentrated aqueous NaCl solution (10 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 2:1), title compound G1 is obtained from the residue as a slightly yellowish oil (0.32 g, 82 %): TLC R_t = 0.18 (diethyl ether - hexane 2:1).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 - 1.05 (m, 12H), 1.55 - 2.25 (m, 9H), 2.40 (m, 1H), 2.60 (m, 1H), 2.75 (m, 1H), 2.95 (s, 3H), 3.40 (s, 3H), 3.60 (t, 2H), 3.85 (s, 3H), 4.15 (t, 2H), 4.45 (m, 1H), 4.80 (m, 1H), 6.70 - 6.85 (m, 3H) ppm.

Example F2: Preparation of

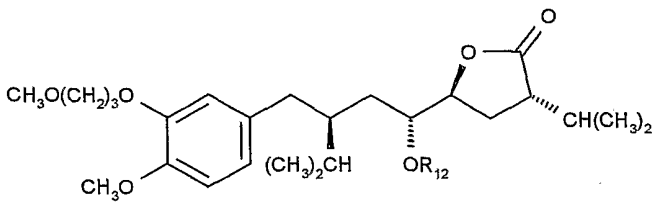


wherein R_{12} is 4-BrC_6H_5-SO_2- (G2).

To a solution of 0.437 g F 1 and 5 ml dichloromethane, 0.307 g 4-bromobenzenesulfochloride and 0.147 g 4-dimethylaminopyridine are consecutively added and the mixture then stirred for 24 hours at room temperature. The reaction mixture is poured onto iced water (30 ml) and extracted with diethyl ether (3x 30 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (30 ml) and concentrated aqueous NaCl solution (30 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 1:1), title compound G2 is obtained from the residue as a slightly yellowish oil (0.304 g, 46 %): TLC R_t = 0.36 (diethyl ether - hexane 2:1).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80 - 1.0 (m, 12H), 1.55 - 2.20 (m, 9H), 2.25 - 2.45 (m, 2H), 2.70 (m, 1H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 4.15 (m, 2H), 4.35 (m, 1H), 4.65 (m, 1H), 6.60 - 6.85 (m, 3H), 7.60 - 7.75 (m, 4H) ppm.

Example F3: Preparation of



wherein R_{12} is 4-$CH_3C_6H_5$-SO_2- (G3).

To a solution of 0.437 g F 1 and 5 ml dichloromethane, 0.229 g 4-methylbenzenesulfochloride and 0.147 g 4-dimethylaminopyridine are added and the mixture then stirred for 24 hours at room temperature. The reaction mixture is poured onto iced water (30 ml) and extracted with diethyl ether (3x 30 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (30 ml) and concentrated, aqueous NaCl solution (30 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F / diethyl ether / hexane 1:1), title compound G3 is obtained from the residue as a slightly yellowish oil (0.40 g, 68 %): TLC R_t = 0.26 (diethyl ether - hexane 2:1).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80 - 1.0 (m, 12H), 1.55 - 2.20 (m, 9H), 2.30 - 2.50 (m, 2H), 2.45 (s, 3H), 2.65 (m, 1H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 4.15 (m, 2H), 4.35 (m, 1H), 4.70 (m, 1H), 6.60 - 6.85 (m, 3H), 7.35 (d, 2H), 7.70 (d, 2H) ppm.

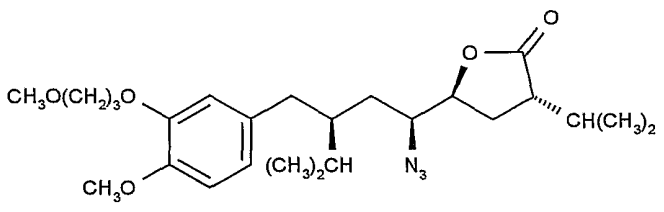
Example F4: Preparation of G1

To a solution of 136.1 g F 1 (crude), prepared as described in example E2, and 0.86 l toluene, 52.8 ml triethylamine is added and the mixture cooled to 0°C. 29.45 ml methanesulfonyl chloride is added drop by drop and the mixture then stirred for 1 hour at 15°C. The reaction mixture is cooled to 0°C, 7.88 ml 3-dimethylamino-1-propylamine is added (the excess of methanesulfonylchloride is destroyed) and the mixture stirred for 15 minutes. The reaction mixture is washed with water (1 l), the organic phase separated off and the aqueous phase extracted again with toluene (0.6 l). The organic phases are washed consecutively with water / saturated NaCl solution (5:1; 0.6 l) and saturated aqueous NaCl solution (0.6 l), dried over sodium sulfate and concentrated on a rotary evaporator. The crude title compound F1 obtained in this way (165 g)

(content of title compound approx. 90%) is further reacted in example G2.

G) Preparation of compounds of formula II

Example G1: Preparation of



(H1)

A mixture of 9.5 g G1, 2.35 g sodium azide and 100 ml 1.3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone is stirred for 20 hours at 60°C. The reaction mixture is poured onto 500 ml water and extracted with tert-butyl methyl ether (3x 200 ml). The organic phases are washed consecutively with water (3 x 500 ml), 5% aqueous sodium hydrogencarbonate solution (200 ml) and concentrated aqueous NaCl solution (200 ml). The combined organic phases are dried over sodium sulfate and concentrated on a rotary evaporator. By means of crystallization from 150 ml diisopropylether - hexane (1:2) at 0°C, title compound H 1 is obtained from the residue as white crystals (5.62 g, 67%); m.p. 61 - 62° C; TLC R_t = 0.41 (ethyl acetate - hexane 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 - 1.10 (m, 12H), 1.40 (m, 1H), 1.60 - 2.25 (m, 8H), 2.45 (m, 1H), 2.60 (m, 2H), 2.95 (m, 1H), 3.40 (s, 3H), 3.60 (t, 2H), 3.85 (s, 3H), 4.15 (t, 2H), 4.30 (m, 1H)), 6.70 - 6.85 (m, 3H) ppm.

Derivative H1 can be prepared by reaction of G2 or G3 by analogy with example G1.

Example G2: Preparation of H1

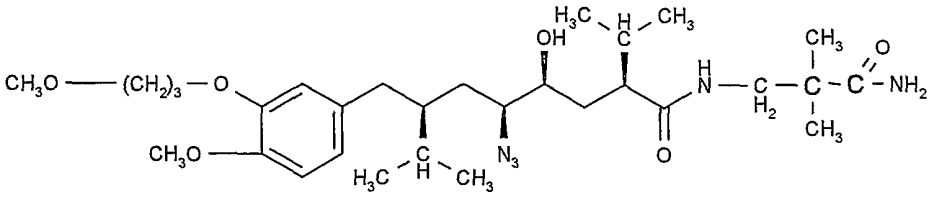
A mixture of 165 g G1 (crude), 41.1 g sodium azide and 0.8 l 1.3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone is stirred for 20 hours at 60°C. The reaction mixture is cooled, poured onto 1.5 l water and extracted with methylcyclohexane (2x 750 ml). The organic phases are washed consecutively with water (4 x 750 ml) and concentrated aqueous NaCl solution (750 ml). The combined organic phases are dried over sodium sulfate and concentrated to a volume of 900 ml on a rotary evaporator. The resulting solution is inoculated with 10 mg of title compound and stirred for 20 hours at ambient temperature. The resulting suspension is cooled to 0°C, and title compound H1 is obtained by filtration in the form of white crystals (104 g, 71 %).

Example G3: Preparation of H1

A mixture of 10.3 g G1 (crude), 50 ml methylcyclohexane, 40 ml 2N sodium azide (aqueous solution) and 0.4 g Aliquat® is stirred for 20 h at 80°C. The reaction mixture is cooled to 40°C, the aqueous phase is separated off and the organic phase washed at 40°C with (2x 40 ml). The organic phase is dried over sodium sulfate and filtered. The filtrate is inoculated with 5 mg of title compound and stirred for 20 hours at ambient temperature. The resulting suspension is cooled to 0°C, and title compound H1 is obtained by filtration in the form of white crystals (6.60 g, 71 %).

H) Preparation of compounds of formula III

Example H1: Preparation of



(J1)

A mixture of 59.1 g H1, 41.82 g 3-amino-2,2-dimethylpropionamide, 2.28 g 2-hydroxypyridine in 59.1 ml triethylamine is stirred over a period of 16 hours at 90°C. Then 33 ml triethylamine is distilled off over a period of 0.5 hours, and the residue is agitated for a further 8.5 hours at 90°C. The cooled reaction mixture is extracted between ethyl acetate (3x 500 ml), saturated aqueous sodium hydrogencarbonate solution (1x 500 ml) and saturated sodium chloride solution (1x 500 ml). The combined organic phases are dried with 100 g sodium sulfate, filtered and concentrated on the rotary evaporator. The residue is dried and crude title compound F1 is obtained as an oil (78.4g, quantitative) (HPLC assay: 88.5%): TLC R_t = 0.13 (ethyl acetate - hexane 4:1); chromatographed sample: TLC R_t = 0.13 (ethyl acetate / hexane 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 0.85 - 0.96 (m, 12H), 1.23 (s, 6H), 1.30 - 1.40 (m, 1H), 1.53 - 1.80 (m, 5H), 1.82 - 1.93 (m, 1H), 2.06 - 2.14 (m, 3H), 2.45 - 2.57 (m, 2H), 2.87 - 2.92 (m, 1H), 3.13 (d, 1H), 3.32 - 3.52 (m, 3H), 3.36 (s, 3H), 3.59 (t, 2H), 3.84 (s, 3H), 4.12 (t, 2H), 5.51 (bs, 1H), 6.01 (bs, 1H), 6.43 (t, 1H), 6.72 (dd, 1H), 6.75 (d, 1H), 6.81 (d, 1H) ppm.

Example H2: Preparation of J1

A mixture of 9.23 g H1, 6.97 g 3-amino-2,2-dimethylpropionamide, 1.90 g 2-hydroxypyridine and 5.0 ml triethylamine is stirred over a period of 24 hours at 65 °C. The cooled reaction mixture is extracted between tert-butyl methyl ether (2x 150 ml) and water (2x 150 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The residue is dried and crude title compound F1 is obtained as an oil (11.65 g, quantitative) (HPLC assay: > 95%).

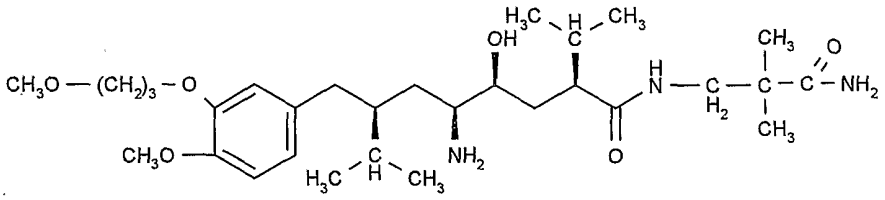
Example H3: Preparation of J1

A mixture of 4.62 g H1, 3.48 g 3-amino-2,2-dimethylpropionamide and 0.95 g 2-hydroxypyridine is stirred

over a period of 24 hours at 65 °C. The cooled reaction mixture is extracted between tert-butyl methyl ether (2x 100 ml) and water (2x 100 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The residue is dried and crude title compound J1 is obtained as an oil (5.75 g, quantitative) (HPLC assay: > 95%).

J) Hydrogenation of the azide group to form compounds of formula I

Example J1: Preparation of



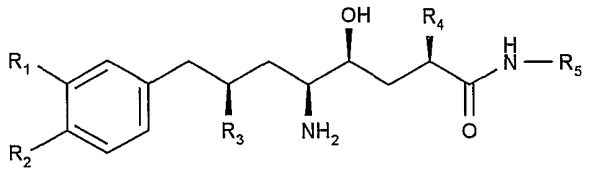
(K1)

78.4 g (HPLC assay: 88.5%) J1 (crude) is hydrogenated for 3 hours in the presence of 3.92 g Pd/C 5% and 7.2 ml ethanolamine in 700 ml tert-butyl methyl ether at ambient temperature and 3.0 bar. The reaction mixture is filtered and the catalyst washed with 300 ml tert-butyl methyl ether. The filtrate is washed consecutively with 400 ml 2N NaOH and 400 ml brine. The aqueous phases are then extracted with tert-butyl methyl ether (2 x 400 ml). The combined organic phases are dried with 100 g sodium sulfate and concentrated by evaporation. The residue is mixed with 7.31 g fumaric acid and dissolved in 200 ml ethanol and filtered until clear. The filtrate is concentrated by evaporation to a total weight of 104 g and dissolved in 1.7 l acetonitrile at 35°C. The resulting solution is inoculated with 10 mg of title compound (hemifumarate) and stirred for 17 hours at ambient temperature. The suspension is cooled to 0°C and filtered off by suction after 2 hours. The residue is washed

with acetonitrile (3 x 200 ml) and then dried in a vacuum at 35°C. The title compound K1 (hemifumarate) is obtained as white crystals (59.5 g, 81% in relation to J1): ^{1}H NMR (360 MHz, DMSO-d_6); δ 0.7 - 0.9 (m, 12H), 1.04 (s, 6H), 1.27 (m, 3H), 1.4 - 1.8 (m, 4H), 1.94 (m, 2H), 2.23 (m, 1H), 2.35 (dd, J = 8.4, 8.0 Hz, 1H), 2.45 (m, 1H), 3.08 (m, 2H), 3.2 - 3.5 (m, 2H), 3.24 (s, 3H), 3.47 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.97 (t, J = 6.4 Hz, 2H), 6.37 (s, 1H), 6.68 (dd,J = 8.0, 2.0 Hz, 1H), 6.77 (d, J = 6 Hz, 1H), 6.80 (bs, 1H), 6.83 (d, J = 8 Hz, 1H), 7.13 (bs, 1H), 7.49 (t, J = 6 Hz, 1H).

What is claimed is:

1. Process for preparation of compounds of formula I,

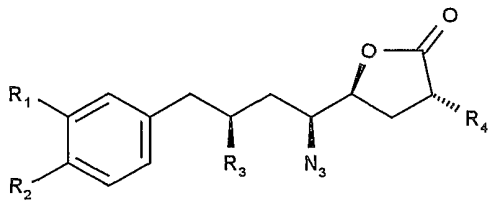


(I),

wherein

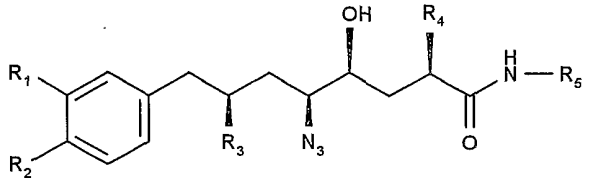
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl,

a) by reacting a compound of formula II,



(II),

with an amine of formula R_5-NH_2 to form a compound of formula III,

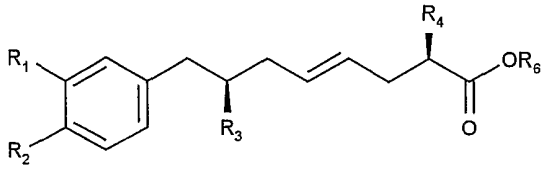


(III),

and

b) by reducing the azide group of the compound of formula III to the amine group and isolating the compounds of formula I, if necessary with the addition of a salt-forming acid, comprising the preparation of compounds of formula II by

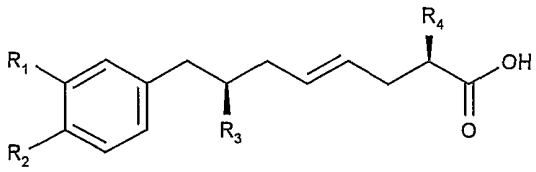
c1) reacting a compound of formula IV,



(IV),

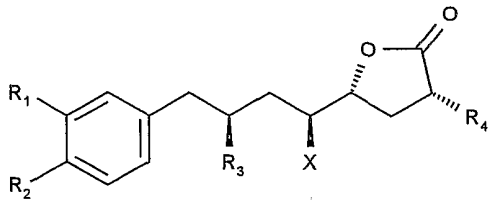
wherein R_6 is C_1-C_{20}alkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkyl-C_1-C_6alkyl, C_6-C_{10}aryl or C_6-C_{10}-aryl-C_1-C_6alkyl, with a halogenation agent to form a compound of formula VI, or

c2) reacting a carboxylic acid of formula V, or a salt of this carboxylic acid,



(V),

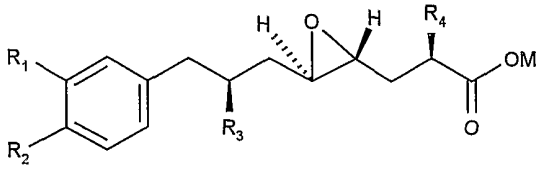
with a halogenation agent to form a compound of formula VI,



(VI),

wherein X is Cl, Br or I,

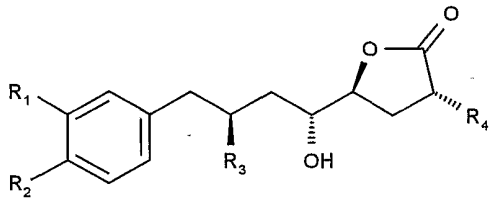
d) reacting the compound of formula VI in the presence of an alkali metal or alkaline earth metal hydroxide or an alcohol to form a compound of formula VII,



(VII),

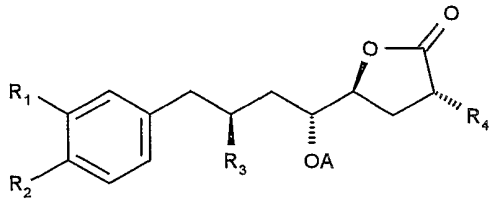
wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group,

e) hydrolysing the compound of formula VII in the presence of an acid to form a compound of formula VIII,



(VIII),

f) substituting the hydrogen atom of the hydroxyl group in the compound of formula VIII and converting it to a leaving group AO to form compounds of formula IX,



(IX),

g) and then reacting the compound of formula IX with an azidation agent to form a compound of formula II, or

h) reacting the compound of formula VIII directly with a zinc azide/-bis-pyridine complex in the presence of a

tertiary phosphine and an azodicarboxylate, if necessary in an organic solvent, to form a compound of formula II.

2. A process according to claim 1 comprising an embodiment wherein R_1 is C_1-C_4alkoxy or C_1-C_4alkoxy-C_1-C_4alkyloxy, R_2 is C_1-C_4alkoxy, R_3 is C_1-C_4alkyl, R_4 is C_1-C_4alkyl and R_5 is $H_2NC(O)$-C_1-C_6alkyl which if necessary is N-monosubstituted or N-di-C_1-C_4alkyl substituted.

3. A process according to claim 2 comprising an embodiment wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

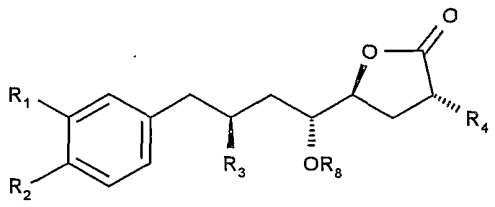
4. A process according to claim 2 comprising an embodiment wherein R_3 and R_4 are in each case isopropyl.

5. A process according to claim 2 comprising an embodiment wherein R_5 is $H_2NC(O)$-C_1-C_6alkyl.

6. A process according to claim 1 comprising an embodiment wherein R_1 is methoxy-C_2-C_4alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4alkyl, R_4 is C_2-C_4alkyl and R_5 is $H_2NC(O)$-C_1-C_6alkyl.

7. A process according to claim 1 comprising an embodiment wherein R_1 is 3-methoxy-prop-3-yloxy, R_2 is methoxy, R_3 and R_4 are each 1-methyleth-1-yl, and R_5 is $H_2NC(O)$-$[C(CH_3)_2]$-CH_2-.

8. Compounds of formula X,

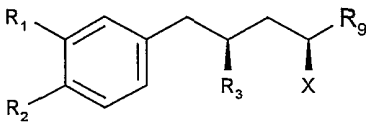


(X),

wherein

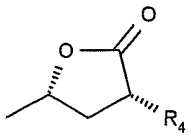
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or (C_1-C_6alkyl)$_2$N-C(O)-C_1-C_6-alkyl, and
R_8 is hydrogen or R_8O is a leaving group.

9. Compounds of formula XI,



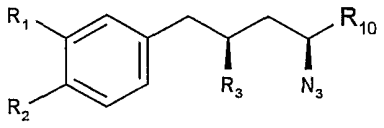
(XI),

wherein
X is halogen and R_9 is a residue of formula



and
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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or (C_1-C_6alkyl)$_2$N-C(O)-C_1-C_6-alkyl.

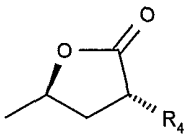
10. Compounds of formula XII,



(XII),

wherein

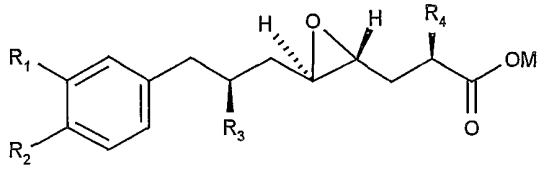
R_{10} is a residue of formula



and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

11. Compounds of formula VII,

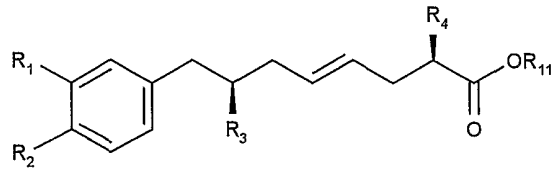


(VII),

wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group, and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

12. Compounds of formula XIII,



(XIII),

wherein R_{11} is an alkali metal, an equivalent alkaline earth metal, hydrogen or the residue of an alcohol minus a hydroxyl group, and

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, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(O)C-C_1-C_6alkyl, H_2N-C(O)-C_1-C_6alkyl, C_1-C_6alkyl-HN-C(O)-C_1-C_6alkyl or $(C_1$-C_6alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/CH 01/00399

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C231/02 C07C247/12 C07D207/32 C07D303/40

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PETER HEROLD ET AL: "A Versatile and Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosters" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 54, no. 5, 3 March 1989 (1989-03-03), pages 1178-1185, XP002149098 ISSN: 0022-3263 scheme I page 1179 ---	1-7
X	EP 0 678 514 A (CIBA GEIGY AG) 25 October 1995 (1995-10-25)	10
A	page 2, line 1 - line 10 page 5, line 18 - line 34 page 23 -page 24; claims 8,9 ---	1
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2001	02/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

INTERNATIONAL SEARCH REPORT

Intern: I Application No
PCT/CH 01/00399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 678 503 A (CIBA GEIGY AG) 25 October 1995 (1995-10-25) cited in the application page 14, line 1 - line 10 page 23	1,8-12
A	EP 0 678 500 A (CIBA GEIGY AG) 25 October 1995 (1995-10-25) page 10, line 49 -page 13, line 48	1
A	GOSCHKE R ET AL: "Design and synthesis of novel 2,7-dialkyl substituted 5(S)-amino-4(S)-hydroxy-8-phenyl-octanecar boxamides as in vitro potent peptidomimetic inhibitors of human renin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 21, 4 November 1997 (1997-11-04), pages 2735-2740, XP004136522 ISSN: 0960-894X page 2737	1
X,P	RUEGER H ET AL: "A convergent synthesis approach towards CGP60536B, a non-peptide orally potent renin inhibitor, via an enantiomerically pure ketolactone intermediate" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 51, 16 December 2000 (2000-12-16), pages 10085-10089, XP004225222 ISSN: 0040-4039	8
A	page 10087	1
X,P	SANDHAM D A ET AL: "A convergent synthesis of the renin inhibitor CGP60536B" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 51, 16 December 2000 (2000-12-16), pages 10091-10094, XP004225223 ISSN: 0040-4039	8,10
A	Scheme 4 page 10093	1
P,X	WO 01 09083 A (SPEEDEL PHARMA AG ;HEROLD PETER (CH); STUTZ STEFAN (CH); INDOLESE) 8 February 2001 (2001-02-08) page 1 -page 9	1-12

-/--

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/CH 01/00399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 09079 A (SPEEDEL PHARMA AG ;HEROLD PETER (CH); STUTZ STEFAN (CH)) 8 February 2001 (2001-02-08) page 1, line 18 - line 30	1-12

INTERNATIONAL SEARCH REPORT

nation on patent family members

Intern[illegible] Application No
PCT/CH 01/00399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0678514 A	25-10-1995	AT 183997 T	15-09-1999
		AU 1642095 A	26-10-1995
		AU 699616 B2	10-12-1998
		AU 1642195 A	26-10-1995
		AU 1642395 A	26-10-1995
		BR 1100656 A3	06-06-2000
		CA 2147044 A1	19-10-1995
		CA 2147052 A1	19-10-1995
		CA 2147056 A1	19-10-1995
		CN 1117960 A	06-03-1996
		CZ 9500976 A3	15-11-1995
		DE 59506707 D1	07-10-1999
		DK 678503 T3	20-03-2000
		EP 0678503 A1	25-10-1995
		EP 0678514 A1	25-10-1995
		EP 0678500 A1	25-10-1995
		ES 2137478 T3	16-12-1999
		FI 951771 A	19-10-1995
		FI 951772 A	19-10-1995
		FI 951773 A	19-10-1995
		GR 3031997 T3	31-03-2000
		HU 74074 A2	28-10-1996
		HU 72110 A2	28-03-1996
		HU 71701 A2	29-01-1996
		JP 8053434 A	27-02-1996
		JP 8081430 A	26-03-1996
		JP 8027079 A	30-01-1996
		NO 951441 A	19-10-1995
		NO 951442 A	19-10-1995
		NO 951443 A	19-10-1995
		NZ 270936 A	24-06-1997
		NZ 270938 A	26-11-1996
		NZ 270939 A	20-12-1996
		TW 402582 B	21-08-2000
		US 5606078 A	25-02-1997
		US 5659065 A	19-08-1997
		US 5559111 A	24-09-1996
		US 5654445 A	05-08-1997
		US 5646143 A	08-07-1997
		US 5627182 A	06-05-1997
		US 5705658 A	06-01-1998
		ZA 9503050 A	08-11-1995
		ZA 9503051 A	18-10-1995
		ZA 9503052 A	18-10-1995
EP 0678503 A	25-10-1995	AT 183997 T	15-09-1999
		AU 1642095 A	26-10-1995
		AU 699616 B2	10-12-1998
		AU 1642195 A	26-10-1995
		AU 1642395 A	26-10-1995
		BR 1100656 A3	06-06-2000
		CA 2147044 A1	19-10-1995
		CA 2147052 A1	19-10-1995
		CA 2147056 A1	19-10-1995
		CN 1117960 A	06-03-1996
		CZ 9500976 A3	15-11-1995
		DE 59506707 D1	07-10-1999
		DK 678503 T3	20-03-2000

INTERNATIONAL SEARCH REPORT

nation on patent family members

Interna l Application No
PCT/CH 01/00399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0678503 A		EP 0678503 A1	25-10-1995
		EP 0678514 A1	25-10-1995
		EP 0678500 A1	25-10-1995
		ES 2137478 T3	16-12-1999
		FI 951771 A	19-10-1995
		FI 951772 A	19-10-1995
		FI 951773 A	19-10-1995
		GR 3031997 T3	31-03-2000
		HU 74074 A2	28-10-1996
		HU 72110 A2	28-03-1996
		HU 71701 A2	29-01-1996
		JP 8053434 A	27-02-1996
		JP 8081430 A	26-03-1996
		JP 8027079 A	30-01-1996
		NO 951441 A	19-10-1995
		NO 951442 A	19-10-1995
		NO 951443 A	19-10-1995
		NZ 270936 A	24-06-1997
		NZ 270938 A	26-11-1996
		NZ 270939 A	20-12-1996
		TW 402582 B	21-08-2000
		US 5606078 A	25-02-1997
		US 5659065 A	19-08-1997
		US 5559111 A	24-09-1996
		US 5654445 A	05-08-1997
		US 5646143 A	08-07-1997
		US 5627182 A	06-05-1997
		US 5705658 A	06-01-1998
		ZA 9503050 A	08-11-1995
		ZA 9503051 A	18-10-1995
		ZA 9503052 A	18-10-1995
EP 0678500 A	25-10-1995	AT 183997 T	15-09-1999
		AU 1642095 A	26-10-1995
		AU 699616 B2	10-12-1998
		AU 1642195 A	26-10-1995
		AU 1642395 A	26-10-1995
		BR 1100656 A3	06-06-2000
		CA 2147044 A1	19-10-1995
		CA 2147052 A1	19-10-1995
		CA 2147056 A1	19-10-1995
		CN 1117960 A	06-03-1996
		CZ 9500976 A3	15-11-1995
		DE 59506707 D1	07-10-1999
		DK 678503 T3	20-03-2000
		EP 0678503 A1	25-10-1995
		EP 0678514 A1	25-10-1995
		EP 0678500 A1	25-10-1995
		ES 2137478 T3	16-12-1999
		FI 951771 A	19-10-1995
		FI 951772 A	19-10-1995
		FI 951773 A	19-10-1995
		GR 3031997 T3	31-03-2000
		HU 74074 A2	28-10-1996
		HU 72110 A2	28-03-1996
		HU 71701 A2	29-01-1996
		JP 8053434 A	27-02-1996
		JP 8081430 A	26-03-1996

INTERNATIONAL SEARCH REPORT

mation on patent family members

Interna — Application No
PCT/CH 01/00399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0678500 A		JP 8027079 A	30-01-1996
		NO 951441 A	19-10-1995
		NO 951442 A	19-10-1995
		NO 951443 A	19-10-1995
		NZ 270936 A	24-06-1997
		NZ 270938 A	26-11-1996
		NZ 270939 A	20-12-1996
		TW 402582 B	21-08-2000
		US 5606078 A	25-02-1997
		US 5659065 A	19-08-1997
		US 5559111 A	24-09-1996
		US 5654445 A	05-08-1997
		US 5646143 A	08-07-1997
		US 5627182 A	06-05-1997
		US 5705658 A	06-01-1998
		ZA 9503050 A	08-11-1995
		ZA 9503051 A	18-10-1995
		ZA 9503052 A	18-10-1995
WO 0109083 A	08-02-2001	AU 5518400 A	19-02-2001
		AU 5518500 A	19-02-2001
		WO 0109083 A1	08-02-2001
		WO 0109079 A1	08-02-2001
WO 0109079 A	08-02-2001	AU 5518400 A	19-02-2001
		AU 5518500 A	19-02-2001
		WO 0109083 A1	08-02-2001
		WO 0109079 A1	08-02-2001