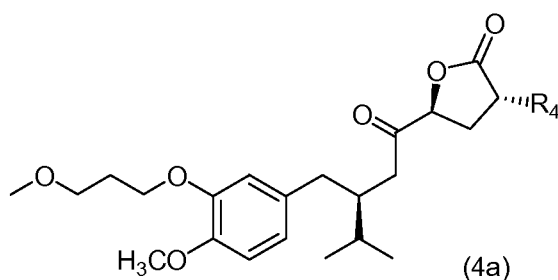


SYNTHESIS ROUTES TO 2(S),4(S),5(S),7(S)-2,7-DIALKYL-4-HYDROXY-5-AMINO-8-ARYL-OCTANOYL AMIDES

The invention relates to a process for the preparation of compound  
5 according to formula (13) or its ring-closed form according to formula (2), which  
compound is an important building block in convergent synthesis routes to  
2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides (compounds  
according to formula 13 with X stands for  $\text{NHR}_5$ ), or pharmaceutically acceptable salts  
thereof, such as the compound Aliskiren, and to a process for the preparation of these  
10 octanoyl amides, comprising reacting said building block.

From a paper by Rueger et al, Tetrahedron letters 41 (2000) p.10085-  
10089, it is known that a ketone containing compound according to formula (4a)



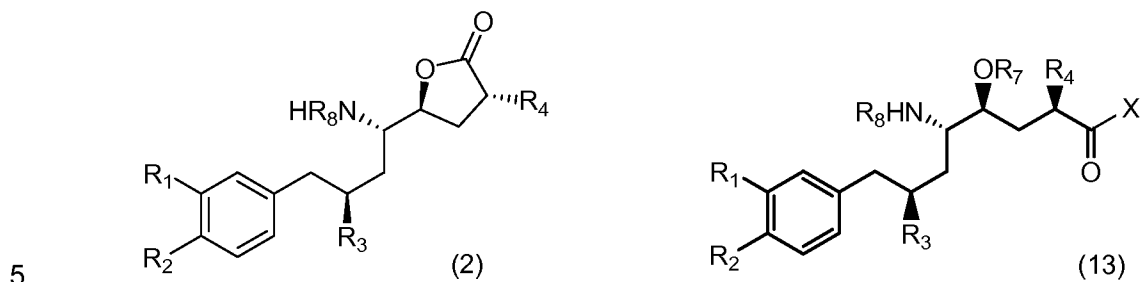
with  $\text{R}_4$  being 2-propyl is a potentially interesting building block for use in a convergent  
15 synthesis route to Aliskiren. However, the conversion of the ketone according to  
formula (4a) to the corresponding enantio-enriched amine (according to formula 2), and  
subsequently to the compound Aliskiren or related compounds has so far remained  
unsatisfactory with respect to yield and/or stereoselectivity.

From a paper by Sandham et al, Tetrahedron letters 41 (2000)  
20 p.10091-10094, it is known that compounds according to formula (13) with X stands for  
 $\text{NHR}_5$  are prepared by the corresponding 5(R) hydroxy compound using substitution  
chemistry with sodium azide. The corresponding 5(R) hydroxy compound had been  
prepared in a inseparable mixture of diastereomers, which only could be purified at the  
end stage of the synthesis (the crystallization of the hemifumarate salt) or with a high  
25 diastereomeric ratio of 96:4 but at the expense of a low yield (33%).

The invention now provides a novel route for converting the ketone  
containing compound according to formula (4) or its open form according to formula  
(11), or a mixture thereof, to the desired 5(S)-amino compound according to formula (2)  
or its open form according to formula (13). It is an advantage of the new process that  
30 the products are obtained in a small number of scalable steps, in a high yield and with

the desired 5(S)-amino or 5(S)-amine-derivative configuration.

Thus, the invention is aimed at providing an alternative process for the preparation of a compound according to formula (13) or its ring-closed form according to formula (2), or a mixture thereof,



wherein  $R_1$  being selected from the group consisting of F, Cl, Br, I,  $C_{1-6}$ halogenalkyl,  $C_{1-6}$ alkoxy  $C_{1-6}$ alkoxy- $C_{1-6}$ alkoxy, and  $C_{1-6}$ alkoxy- $C_{1-6}$ alkyl;

$R_2$  being selected from the group consisting of F, Cl, Br, I,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy;

$R_1$  and  $R_2$  may be linked together to form a ring structure

10  $R_3$  and  $R_4$  each independently being branched  $C_{3-6}$ alkyl;

X stands for  $NHR_5$  or  $OR_6$  wherein

$R_5$  is  $C_{1-12}$ cycloalkyl,  $C_{1-12}$ alkyl,  $C_{1-12}$ hydroxyalkyl,  $C_{1-6}$ alkoxy- $C_{1-6}$ alkyl,  $C_{1-6}$ alkanoyloxy- $C_{1-6}$ alkyl,  $C_{1-12}$ aminoalkyl,  $C_{1-6}$ alkylamino- $C_{1-6}$ alkyl,  $C_{1-6}$ dialkylamino- $C_{1-6}$ alkyl,  $C_{1-6}$ alkanoylamino- $C_{1-6}$ alkyl,  $HO-(O)C-C_{1-12}$ alkyl,  $C_{1-6}$ alkyl- $O-(O)C-C_{1-6}$ alkyl,  $H_2N-C(O)-C_{1-12}$ alkyl,  $C_{1-6}$ alkyl- $HN-C(O)-C_{1-6}$ alkyl,  $(C_{1-6}alkyl)_2-N-C(O)-C_{1-6}alkyl$ ; saturated,

15 unsaturated, or partially saturated  $C_{1-12}$ heterocyclyl bonded via a carbon atom to the N-atom, and which heterocyclyl is optionally substituted one or more times by  $C_{1-6}$ alkyl, trifluoromethyl, nitro, amino, *N*-mono- or *N,N*-di- $C_{1-6}$ alkylated amino,  $C_{1-6}$ alkanoyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxycarbonylamino,  $C_{0-6}$ alkylcarbonylamino,  $C_{1-6}$ alkylcarbonyloxy,  $C_{1-12}$ aryl, *N*-mono or *N,N*-di- $C_{1-6}$ alkylated carbamoyl, optionally esterified carboxyl, cyano, halogen, halo- $C_{1-6}$ alkoxy, halo- $C_{1-6}$ alkyl,  $C_{1-12}$ heteroaryl, saturated, unsaturated or partially saturated  $C_{1-6}$ heterocyclyl, hydroxyl, nitro;

20 and  $R_6$  represents H, or optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl;

25  $R_7$  represents H, or is an O-protecting group;

Any two of  $R_7$ ,  $R_8$ , or X are optionally linked together to form a ring structure. In particular  $R_7$  and X may be linked together to form an optionally substituted  $C_{1-12}$  heterocyclic compound.

30  $R_8$  denotes H; optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl; optionally substituted  $C(O)C_{1-6}$ alkyl;

optionally substituted  $C(O)OC_{1-6}alkyl$ ; optionally substituted  $C(O)NHC_{1-6}alkyl$ ; or optionally substituted  $C(O)N(C_{1-6}alkyl)_2$ ; or  $R_8$  denotes

$-NHR_9$ ;

$-S(O)_2R_9$ ;  $SOR_9$ ;  $S(O)_3R_9$ ;  $S(O)_2N(R_9)$ ;

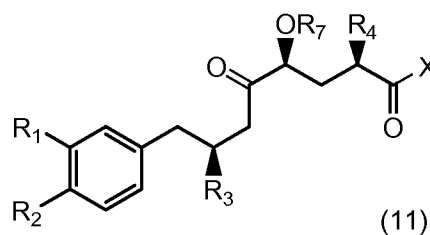
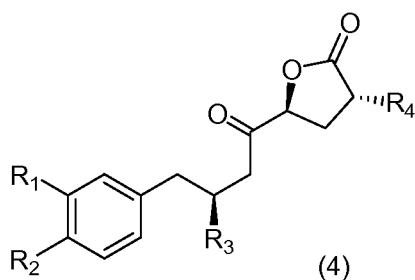
5  $-P(O)(R_9)_2$ ;

$-OR_{10}$ , with  $R_{10}$  standing for H, optionally substituted  $C_{1-6}alkyl$ ,  $C(O)C_{1-6}alkyl$ ,  $S(O)_2R_9$  or  $R_8$  stands for  $(R_9)_2Y$  with Y being an anion such as acetate, or halogen;

and wherein each  $R_9$  group individually represents H, optionally substituted  $C_{1-12}alkyl$ , optionally substituted  $C_{1-12}alkylaryl$ , or optionally substituted  $C_{1-12}aryl$

10 comprising the following steps,

- a) reacting a compound according to formula (11), or its ring-closed form according to formula (4), or mixture thereof,



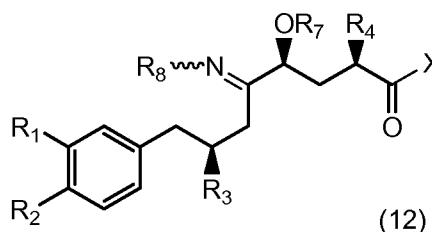
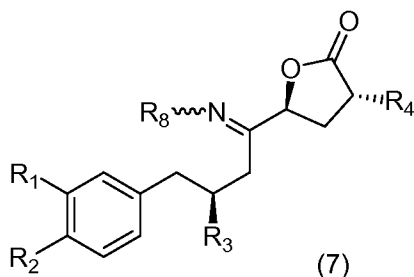
wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_7$ , and X are as described above for formula (2) and (13),

15 with a compound according to formula (5)

$R_8-NH_2$  (5)

wherein  $R_8$  is as described above for formula (2) and (13)

which reaction results in a compound according to formula (7) or a compound according to formula (12) or a mixture thereof,



20

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_7$ ,  $R_8$  and X are as described above for formula (2) and (13),

- b) further reacting compound according to formula (7) or (12) or a mixture thereof, in the presence of a reducing reagent, and optionally in the presence of a catalyst, and optionally in the presence of 1 or more additives,

25

which reaction results in the formation of compound according to formula (2) or

formula (13) or a mixture thereof.

So the invention provides a process in which the 5(S)-amino functionality is introduced from the corresponding ketone containing compounds in fewer steps than in the processes known so far.

5 Preferably, in the process for the preparation of the octanoyl amides according to formula (13) with X stands for  $\text{NHR}_5$ , such as the compound Aliskiren,  $\text{R}_1$  is 3-methoxypropoxy;  $\text{R}_2$  is methoxy, and  $\text{R}_3$  and  $\text{R}_4$  are 2-propyl.

In the framework of this invention, an O-protecting group is a group as described in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; or in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999; and defined as a customary group for protecting the oxygen atom, for instance a tosylate, mesylate, benzoylate, benzoate, trialkylsilyl or carboxylic acid group, such as the acetate group, etc., and all other protecting groups customary for alcohols or oxygen atoms.

15 In the framework of this invention optionally substituted means that any hydrogen present in the description of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{R}_7$ ,  $\text{R}_8$ ,  $\text{R}_9$ ,  $\text{R}_{10}$ ,  $\text{R}'$  and  $\text{R}''$  (and X can be replaced by another atom, hydrocarbon, or functional group known to a person skilled in the art, provided that the substituents are inert with respect to the processes carried out. For example, one, up to all hydrogens in an optionally substituted  $\text{C}_{1-12}$ alkyl, can be replaced by e.g. halogen, or other functional groups.

20 In the framework of this invention, an inert substituent is defined as a substituent that does not react itself when the desired reaction according to the invention is carried out, and that does not prevent in any other way the desired reaction from being carried out.

25 For example, it is known to a person skilled in the art that some substituents are very large and may sterically hinder the desired reaction from taking place, although the substituents themselves will not react.

It is understood that wherever aryl is mentioned this aryl group can also be a heteroaryl.

30 For all structural formulas shown in the framework of the invention, the most desired configuration is that configuration ultimately allowing the synthesis of compound according to formula (13) wherein X is  $\text{NHR}_5$ , having a 2(S), 4(S), 5(S), 7(S) configuration. However, unless specifically stated otherwise in the text, the invention also relates to racemic mixtures or scalemic mixtures of the desired compounds, whereby 35 the desired isomer is present in excess to the undesired isomer. Preferably, the ratio of

the desired isomer to the undesired isomer for any individual stereogenic centre is at least 70:30, more preferably at least 90:10, and still more preferably at least 95:5.

In an aspect of this invention the diastereomeric ratio of the compounds according to formula (2) or (13) can be improved by classical purification methods known to the person skilled in the art, such as preferential crystallization, optionally with an auxiliary, distillation, or chromatographic techniques such as simulating moving beds (SMB).

The formation of compounds according to formula (7) or (12) or a mixture thereof, from the corresponding ketone compounds formula (11), or its ring-closed form according to formula (4), or mixture thereof, using the compound according to formula (5) are performed using methods known to the person skilled in the art to prepare C=N bonds from a ketone. Suitable references can be found in March, Jerry, Chapter 6, (1985) *Advanced Organic Chemistry reactions, mechanisms and structure* (3rd ed.), New York: John Wiley & Sons; or other general Organic Chemistry textbooks and Comprehensive Reviews. More specific examples are given in Organic Syntheses, Coll. Vol. 9, p.610 (1998); Vol. 70, p.35 (1992) and Organic Syntheses, Coll. Vol. 6, p.818 (1988); Vol. 54, p.93 (1974). In particular these preparations of compounds according to formula (7) or (12), or a mixture thereof, are catalyzed by the addition of a Bronsted or Lewis acid, and conditions are employed in which the reaction for the preparation of the C=N bond is driven to completion by removal of water. More particular these preparations are performed by azeotropic distillation, and/or the addition of molecular sieves and/or the addition of titanium tetrachloride.

The compounds according to formula (7) or (12) or a mixture thereof, can be in the *Z* or *E* configuration, or a mixture thereof.

Preferably  $R_8$  is a group which can be easily removed subsequently to obtain compounds according to formula (2) or formula (13) or a mixture thereof, with  $R_8$  is equal to H. Examples of such compounds according to formula (5) with  $R_8$  which are easily removed are optionally substituted benzylamines, electron rich anilines such as 4-methoxy aniline, optionally substituted sulfonamides, hydrazones, and phosphinylimines. Preferably, such compounds according to formula (5) with  $R_8$  which are easily removed are optionally substituted benzylamines, more preferably  $\alpha$ -methyl benzylamines.

Alternatively, the  $R_8$  group is not removed, which leads to compounds according to formula (2) or formula (13) or a mixture thereof, in which  $R_8$  is equal to  $R_8$  in the compound according to formula (5).

The reaction of the compound according to formula (7) or (12) or a mixture thereof resulting in the formation of compound according to formula (2) or formula (13) or a mixture thereof, in the presence of a reducing reagent, and optionally in the presence of a catalyst, and optionally in the presence of an additive, can be  
5 conducted stereoselectively or non-stereoselectively. When both isomers will be formed in the same amount one speaks of a non-stereoselective reaction. Preferably the isomer of compounds according to formula (2) or formula (13) or a mixture thereof, with a (S)-configuration at the C-5 stereogenic center is formed in excess. For clarity reasons the obtained compounds are depicted in one configuration (C-5 stereogenic  
10 center), but it will be appreciated that the other isomer of the C-5 stereogenic center can be formed as well.

When the reaction of the compound according to formula (7) or (12) or a mixture thereof resulting in the formation of compound according to formula (2) or formula (13) or a mixture thereof, in the presence of a reducing reagent, and optionally  
15 in the presence of a catalyst, and optionally in the presence of 1 or more additives is performed non-stereoselectively, the formed isomers can be separated by methods known to the person skilled in the art, such as crystallization; classical resolution; using chromatographic techniques like simulating moving beds, optionally with a optically pure stationary phase; or by an enzymatic resolution for example with a lipase or  
20 amidase.

Preferably a stereoselective synthesis, i.e. with an excess of the (S)-configuration at the C-5 stereogenic center, preferably at least a 70:30 selectivity, more preferably at least 90:10 selectivity, most preferably a 95:5 selectivity or higher, of the compound according to formula (2) or formula (13) or a mixture thereof, in the  
25 presence of a reducing reagent, and optionally in the presence of a catalyst, and optionally in the presence of one or more additives, is performed.

Stereoselective reactions may be obtained:

- A.) due to using compounds according to formula (7) or (12) or a mixture thereof with a high optical purity at the C-2, the C-4 and the C-7 stereogenic center, the  
30 formation of compound according to formula (2) or formula (13) or a mixture thereof, is stereoselective,
- B.) as A but additionally by using a compound according to formula (5) which is optically enriched, hence introducing more directing chirality in the compound according to formula (7) or formula (12) or a mixture thereof. Suitable  
35 compounds are any optically enriched compound according to formula (5),

preferably optically enriched amines and phenyl glycine amide are used, more preferably optically enriched  $\alpha$ -methyl benzyl amine is used,

C.) as described under A or B but additionally in the presence of an optically enriched reducing agent,

5 D.) as described under A, B or C but additionally in the presence of an optically enriched catalyst.

It will be understood by the person skilled in the art that any combination of the above methods to perform a stereoselective reaction is possible.

The reducing agent can be any reducing agent, known to the person  
10 skilled in the art.

A reducing agent, also called a reductant or reducer is the element or a compound in a redox reaction that reduces another species. Here reductions refer to the addition of hydrogen ( $H_2$ ), or the transfer of a hydride to a molecule.

In particular the reducing agent may be molecular hydrogen in the  
15 presence of a transition metal catalyst; alkali-metal hydrides, such as  $NaBH_4$ ,  $NaCNBH_3$ ,  $BH_3-THF$ ,  $B_2H_6$ , 9-borabicyclo[3.3.1]nonane (9-BBN) or lithium tri-sec-butylborohydride (L-selectride); or hydrogen donating compounds, such as alcohols and amines, for example iso-propanol and isopropylamine, or carboxylic acids in the presence of triethylamine, for example formic acid, and salts thereof, or a Hantzsch  
20 ester; or NADPH (Nicotinamide adenine dinucleotide phosphate) and NADH (Nicotinamide adenine dinucleotide); or hydrogen donating compounds in the presence of a catalyst.

Preferably molecular hydrogen in the presence of a transition metal catalyst is used, or a hydrogen donating compound, optionally in the presence of a  
25 catalyst is used.

The reduction reaction may be carried out in the presence of one or more additives. Suitable additives are any compound which will facilitate the reduction reaction with respect to yield and/or stereoselectivity. Suitable additives are for example Lewis acids, Lewis bases, Bronsted acids, Bronsted bases, or salts, such as  
30 quaternary ammonium salts, e.g. tetrabutylammonium iodide.

The reducing agents can itself also be optically enriched, as such facilitating stereoselective reaction. Optically enriched reducing agents may be obtained by combining reducing agents like alkali-metal hydrides, such as boron hydrides, e.g.  $BH_3$ , with an optically enriched compound which can coordinate to the  
35 reducing agent, such as optionally substituted amino alcohols, and optionally

substituted diamines, e.g. t-BuMe<sub>2</sub>SiOCH(Me)CH(NH<sub>2</sub>)CPh<sub>2</sub>OH, PhS(O)<sub>2</sub>NHCH(Ph)CH(Ph)OH, or by a preformed optically enriched alkali-metal hydride, such as a chiral boron hydride compound as for example described by E. J. Corey, S. Shibata, R. K. Bakshi, in J. Org. Chem., **1988**, 53, 2861-2863. The amount  
5 of optically enriched compound to be added to the reducing agent can be in excess, stoichiometric or catalytical amounts. Preferably stoichiometric or catalytic amounts are used, more preferably catalytical amounts are used.

In the case of molecular hydrogen as reducing agent a transition metal based catalyst is added. These transition metal based catalyst can be any  
10 source of transition metal, whether homogeneous, or heterogeneous of origin, and can be supported and non-supported, and can be non-chiral or optically enriched. Suitable catalysts are any transition metal based catalyst, preferably group VIII based catalyst, more preferably Ni, Pd, Ru, Rh, Ir and Pt based catalysts. Any support that is known in the field can be used. Suitable catalysts and conditions are for example described in  
15 Larock, R.C. *Comprehensive Organic Transformations* 2<sup>nd</sup> ed., Wiley-VCH, NY, 1999, pp 835-840; and by Spindler, F. and Blaser, H.U. in *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, p. 1193-1214; and by Clarke, M.L. and Roff, G.J. in *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, p. 437-439, and in *Organic Syntheses*,  
20 Coll. Vol. 3, p.827 (1955); Vol. 21, p.108 (1941).

Suitable catalyst are for example RhCl(PPh<sub>3</sub>)<sub>3</sub>, Pd/C, PtO<sub>2</sub>, Raney Nickel, Ru/C, RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>(ampy) wherein ampy stands for aminomethylpyridine or Crabtree's catalyst: [Ir(1,5-cyclooctadiene)(tris-cyclohexylphosphine)(pyridine)]<sup>+</sup> PF<sub>6</sub><sup>-</sup>.

In the case of the reducing agent being a hydrogen donating  
25 compound the presence of a catalyst is preferred. Such catalyst can be any metal, for example sodium or magnesium, or Al(OEt)<sub>3</sub>; a transition metal based catalyst, such as H<sub>2</sub>IrCl<sub>6</sub>; an organic compound (so-called organocatalyst), such as a Bronsted acid; or a biocatalyst with oxidoreductase activity (EC class 1).

Suitable catalysts and conditions are for example described by  
30 Klomp, D., Hanefeld, U. and Peters, J. in *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, p. 585-632.

In the case of the use of an optically enriched catalyst in the reduction of the compound according to formula (7) or (12) or a mixture thereof resulting in the formation of compound according to formula (2) or formula (13) or a mixture thereof,  
35 the optically enriched catalyst is a transition metal based catalyst, an organocatalyst, or

a biocatalyst.

Suitable transition metal based catalysts are homogeneous or heterogeneous of origin, and can be supported and non-supported. Examples of these catalysts and conditions are for example described by Spindler, F. and Blaser, H.U. in  
5 *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, p. 1193-1214 in the case of molecular hydrogen as reducing agent.

In the case of hydrogen donating compounds as reducing agents, suitable optically enriched transition metal based catalysts, as well as conditions, are for example described by Blacker, A.J. in *Handbook of Homogeneous Hydrogenation*,  
10 J.G. de Vries and C. Elsevier (Eds.) Wiley-VCH, Weinheim, p. 1215; by Noyori et al, in *Org. Biomol. Chem.* **2006**, 4, 393-406. Optically enriched metallocycles, such as iridacycles, and ruthenacycles are also suitable. Suitable optically enriched organocatalysts are bronsted acids, for example described by Rueping, M., Antonchick, A.P. and Theissmann, T. in *Angew. Chem. Int. Ed.* **2006**, 45, 3683 –3686 and  
15 references therein, and suitable biocatalysts are those with oxidoreductase activity (EC class 1), for example amino dehydrogenases. In the case of biocatalysts hydrogen donating compounds are in particular NADPH (Nicotinamide adenine dinucleotide phosphate) and NADH (Nicotinamide adenine dinucleotide).

The catalyst is preferably used in quantities from 0.0001 to 10 mol-%  
20 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.

When an enzyme is used as the catalyst the amount of enzyme used depends on the activity of the enzyme and it may vary between wide ranges. Preferably, the amount of enzyme is as low as possible. Preferably the amount of  
25 enzyme is less than 0.1 g per gram of compound to be hydrogenated, more preferably the amount of enzyme is less than 0.01 g per gram of compound to be hydrogenated, most preferably the amount of enzyme is less than 0.001 g per gram of compound to be hydrogenated.

The reduction may be carried out at low or elevated temperatures, in  
30 particular at a temperature in the range of -20 to 150 °C. Preferably, the temperature is at least 10 °C, more preferably at least ambient temperature (for instance about 20°C). Preferably, the temperature is up to 120°C or less, more preferably 90°C or less.

The processes according to the invention may be carried out at atmospheric pressure or at elevated pressure. In particular the hydrogen pressure, if  
35 hydrogen gas is used as a hydrogen source, may be in the range of atmospheric to

200 bars of Hydrogen, more in particular in the range of atmospheric to 50 bars of Hydrogen.

The reduction reaction of step b) may be carried out in the absence or the presence of a solvent, wherein one solvent or a mixture of solvents may be used.

5 Suitable solvents include 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  
10 ether, diethylene glycol dimethyl ether, tetrahydrofuran, dioxan, 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  
15 sulfone, tetramethylene sulfoxide, tetramethylene sulfone) and alcohols (methanol, ethanol, trifluoro ethanol, propanol, butanol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, diethylene glycol monomethyl ether) and water.

In the case of a hydrogen donating compound, preferably the solvent is also used as hydrogen donating compound.

20 The transition metal based catalyst, optionally required for the reducing reaction with molecular hydrogen or a hydrogen donating compound, can be prepared beforehand, and added as such (vide supra), or the transition metal based catalyst can be prepared in situ, i.e. by addition of the transition metal precursor and the suitable ligands to the reaction vessel.

25 Suitable transition metal precursors are any available transition metal salt or complex. Preferably group VIII transition metal precursors are used, such as the one derived from Ru, Ir, Rh. Suitable precursor examples are bis(1,5-cyclooctadiene)iridium tetrafluoroborate, bis[chloro-1,5-cyclooctadiene-iridium], bis(1,5-cyclooctadiene)-rhodium tetrafluoroborate, bis(2-methylallyl)(1,5-  
30 cyclooctadiene)ruthenium, dichlorobis[(p-cymene)chlororuthenium, dichloro(1,5-cyclooctadiene)ruthenium.

Suitable ligands are any compound with possibility to donate electrons to the metal center, as known to the person skilled in the art. The ligands can be monodentate, bidentate, tridentate or tetradentate. More than one ligand can be  
35 used. The ligands can be a mixture of non chiral and chiral ligands. The amount of

ligand with respect to the metal is not crucial. Preferably the amount of ligand is between 0.1 and 10, more preferably between 0.5 and 5 mol equivalents.

Suitable ligands are for example ligands described in *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, 2007 or *Comprehensive Asymmetric Catalysis I to III*, Jacobsen, E., Pfaltz, A. and Yamamoto, H. (Eds.), Springer Verlag, 1999

The invention also relates to a process for the preparation of a compound according to formula (13) or its ring-closed form according to formula (2), or a mixture thereof by reacting a compound according to formula (11), or its ring-closed form according to formula (4), or mixture thereof, with a compound according to formula (5), in the presence of a reducing reagent, and optionally in the presence of a catalyst, and optionally in the presence of an additive, without the isolation of the compounds (7) or (12). This process resulting in direct formation of the amine moiety from the ketone moiety is also often referred to as reductive amination. The same compounds according to formula (5), conditions and catalysts are used as described for the separate reaction steps as above. In general one can say that the direct reductive amination is performed with reducing agents and/or under reaction conditions that are more reactive toward imines than ketones, such as sodium cyanoborohydride ( $\text{NaBH}_3\text{CN}$ ) or sodium triacetoxyborohydride ( $\text{NaBH}(\text{OCOCH}_3)_3$ ). In the case of molecular hydrogen or hydrogen donating compounds as reducing agent, preferably a catalyst is added. Suitable catalysts and conditions are the same as described for the indirect reductive amination. Preferably transition metal based catalysts and biocatalysts are used. In the case of biocatalysts, enzymes like aminotransferases or aminodehydrogenases can be used. These aminotransferase enzymes can be obtained from various microorganisms for example, but not limited to, *Vibrio sp.*, *Arthrobacter sp.*, *Bacillus sp.*, *Pseudomonas sp.*, *Paracoccus sp.*, *Rhodobacter sp.*. Genes for these enzymes can be transferred and over expressed in host microorganisms like *E-Coli*. Conditions and examples of suitable aminodehydrogenases are described by Itoh et al. in *J. Mol. Catal. B Enzymatic*, **2000**, 10, 281, in particular in combination with ammonia as compound according to formula (5).

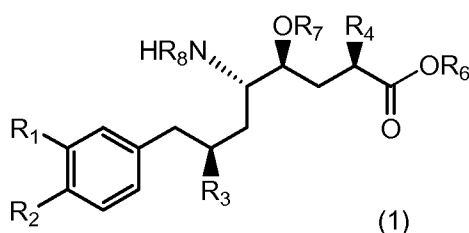
Where an enzyme is used in the processes according to the invention, the enzyme is preferably used in combination with a suitable cofactor regeneration system for the enzyme which is known to those skilled in the art. Examples are the use of formate dehydrogenase combined with formate, or the use of

glucose dehydrogenase combined with glucose. Catalytic amounts of cofactor generally suffice in these cofactor recycling systems.

In the case that amines are used as reducing agents (hydrogen donating compound), preferably the amine is the compound of formula (5), the solvent, and the reducing agent. Suitable amines for this triple use are for example phenylethylamine and 2-propylamine. When the amine is used triple (as compound according to formula (5), solvent, and reducing agent), preferably, phenylethylamine or 2-propylamine are used as compound according to formula (5), preferably an enzyme is used as catalyst, and preferably the  $R_8$  group in the obtained compounds according to formula (2) and (13) stands for H.

The invention also relates to a process for the preparation of a compound according to formula (13) or its ring-closed form according to formula (2), or a mixture thereof by reacting a compound according to formula (11), or its ring-closed form according to formula (4), or mixture thereof, with an amine of a general formula  $R_8-NH_2$ , in the presence of a reducing agent and catalyst, preferably an enzyme, and optionally in the presence of one or more additives.

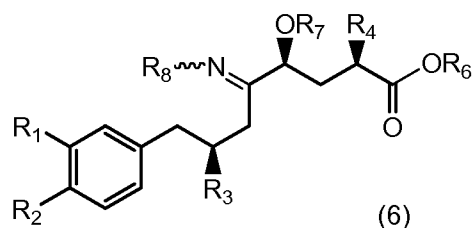
The invention also relates to a process for the preparation of 2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides, (compounds according to formula (13) wherein X stands for  $NHR_5$ ), or pharmaceutically acceptable salts thereof, such as the compound aliskiren, comprising reacting the compound of formula (1),



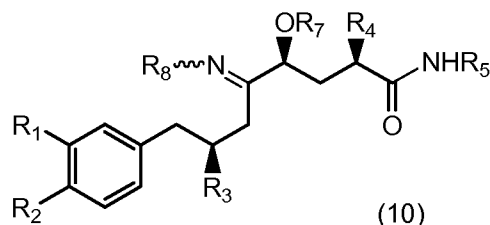
or (2) obtained by the process according to the invention with an appropriate amine, i.e. of a general formula  $R_5-NH_2$ , under conditions sufficient to form an amide bond, optionally followed by purification in order to obtain the desired configuration of the C-5 stereogenic center. Suitable conditions for the amide bond formation are known to the person skilled in the art, and are for example described in Sandham et al (Tetrahedron Letters, 2000, 41, 10091-10094).

It will be appreciated that the order of reactions to obtain certain 2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides, or pharmaceutically acceptable salts thereof, such as the compound aliskiren, is not

crucial, so the compound according to formula (6)

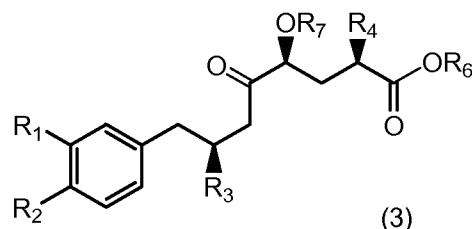


or the compound according to formula (7) can be reacted with the appropriate amine  
i.e. of a general formula  $H_2N-R_5$ , under conditions sufficient to form an amide bond,  
5 optionally followed by protecting the alcohol moiety at the C-4 center, resulting in the  
formation of compound according to formula (10),



prior to the reduction reaction of the invention.

10 It will also be appreciated that reacting the compounds according to  
formula (3)



or the compound according to formula (4), or a mixture thereof, with at least two  
equivalents of the amine of general formula  $R_8-NH_2$  could result in the formation of  
compounds according to formula (10), in which in this case  $R_5$  is equal to  $R_8$ . In this  
15 case, the amine of general formula  $R_8-NH_2$  is preferably the amine needed to obtain  
certain 2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides, or  
pharmaceutically acceptable salts thereof, such as the compound aliskiren.

It will also be appreciated that the compound according to formula (4)  
can be reacted with alcohols, of a general formula of  $HO-R_6$  under conditions known to  
20 the person skilled in the art, optionally followed by protection of the alcohol moiety at  
the C-4 center, resulting in the formation of compounds of formula (3), prior to the  
reaction or reactions of the invention.

It will also be appreciated that the compound according to formula (7)

can be reacted with alcohols, of a general formula of HO-R<sub>6</sub> under conditions known to the person skilled in the art, optionally followed by protection of the alcohol moiety at the C-4 center, resulting in the formation of compounds of formula (6), prior to the reduction reaction of the invention.

5                   The invention also relates to new processes for the preparation of compounds according to formula (4) and (11) as described below.

                  The compound according to formula (4), with R<sub>1</sub> is methoxypropoxy, R<sub>2</sub> is methoxy, and R<sub>3</sub> and R<sub>4</sub> are 2-propyl can be obtained by a method known in the literature, as described in Rueger et al referred to above.

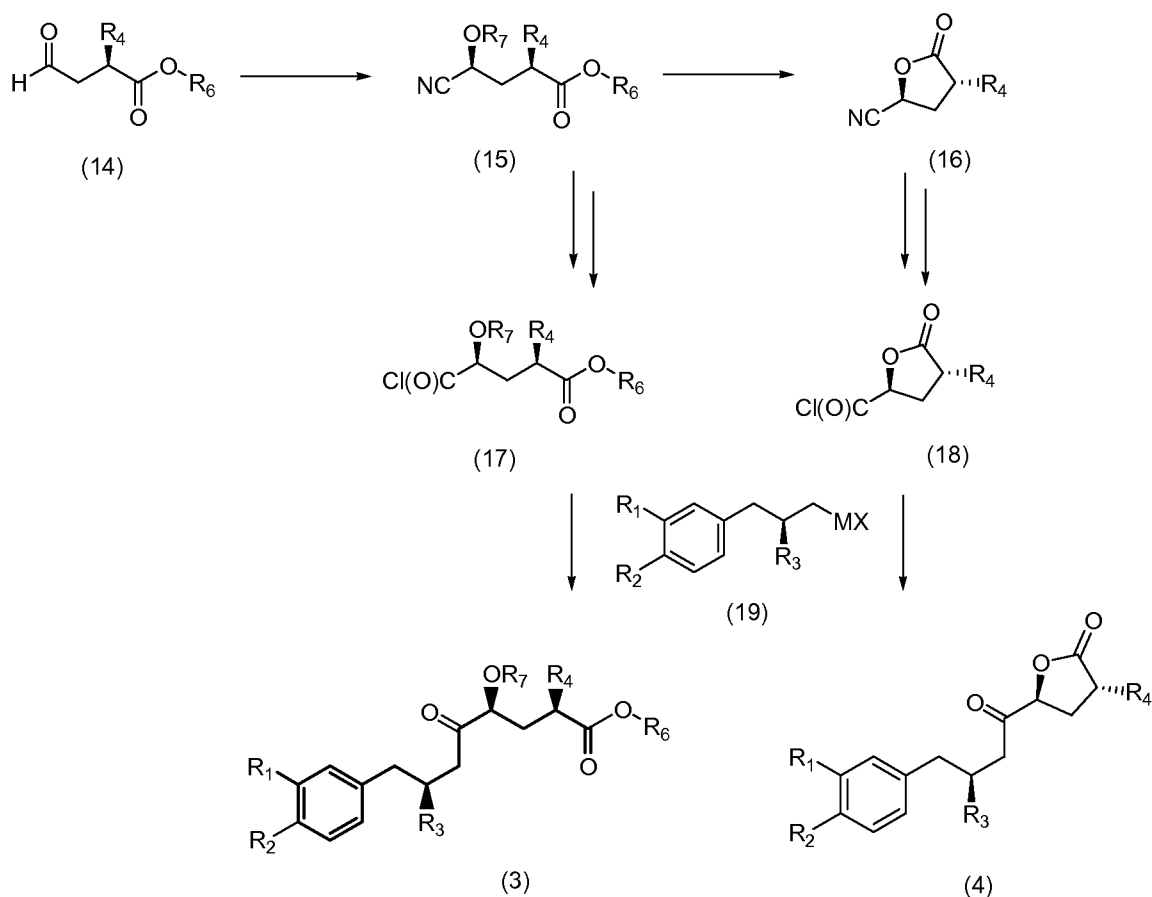
10                  This lengthy route has several drawbacks, of which the use of stoichiometric amounts of chiral auxiliaries, a low diastereoselectivity, and hence a cumbersome separation, are the most striking ones.

                  An other aspect of the invention is a new process to compounds according to formula (3) or formula (4) or mixture thereof, which are relatively short,  
15                  high yielding and with high selectivities.

                  The surprisingly short and efficient synthesis for the compounds according to formula (3) and (4), comprises the steps of

- a) an addition reaction of a cyanide to the enantiomerically enriched compound according to formula (14), wherein R<sub>4</sub> is as described in claim 1, followed by
- 20                  b) a hydrolysis of the nitrile group followed by acid chloride synthesis
- c) a coupling reaction of the acid chloride compounds with compound according to formula (19).

                  For clarity reasons the syntheses are depicted in scheme I:



Scheme I.

The coupling reaction of the compounds according to formula (18) and (19), with R<sub>1</sub> is methoxypropoxy, R<sub>2</sub> is methoxy, R<sub>3</sub> and R<sub>4</sub> are 2-propyl and MX is MgCl, leading to compound according to formula (4) has been described in Rueger et al, as referred to earlier. Similar conditions could be used to achieve the coupling between compounds according to formula (17) and (19), leading to compound according to formula (3), wherein M is chosen from the group of Mg, Li, Ce, Ti, Cu, Zn, Mn, Fe, B, Si, or Al, and X is an anion, in general a halide. Preferably M is Mg, and X is chloride.

Compounds according to formula (17) and (18) or mixture thereof can be easily obtained from the corresponding nitrile containing compounds according to formula (15) and (16) or mixture thereof, using methods known to the person skilled in the art (hydrolysis of nitriles and acid chloride formation, respectively).

Compounds according to formula (15) and (16) (as disclosed in WO2009/080773) or mixture thereof are prepared by reacting the chiral aldehyde of formula (14) with a cyanide, preferably with HCN, NaCN, KCN, (R)<sub>3</sub>SiCN (with R

selected from C<sub>1-6</sub>alkyl, C<sub>1-10</sub>alkylaryl, and C<sub>1-10</sub>aryl), optionally in the presence of a chiral catalyst. Said catalyst can be a chiral organic compound, a chiral metal complex, or an enzyme, as described in by F.X. Chen and X.M. Feng in "Asymmetric synthesis of cyanohydrins" Current Organic Synthesis 2006, 3, 77-97, and references therein; and by P. Poechlauer, W. Skranc, and M. Wubbolts in "The large-scale biocatalytic synthesis of enantiopure cyanohydrins" in Asymmetric Catalysis on Industrial Scale; H.U. Blaser and E. Schmidt, Eds. Wiley-VCH, 2004, pp 151-164. Preferably HCN, or (R)<sub>3</sub>SiCN in the presence of a suitable chiral catalyst is used. More preferred HCN and the enzyme HNL (hydroxynitrile lyase) are used. Suitable conditions for the synthesis of compound of formula (15) or compound according to formula (16), or a mixture thereof, are known to the person skilled in the art and are described in the references above, and references therein.

The compound according to formula (15) with R<sub>7</sub> is equal to H is ring-closed relatively easily to the compound according to formula (16) by employing acidic conditions e.g. catalytic amount of para-toluene sulfonic acid, all in analogy with lactonization methods known to the person skilled in the art. For the lactone formation, R<sub>6</sub> is preferentially C<sub>1-6</sub>alkyl, more preferentially R<sub>6</sub> is methyl.

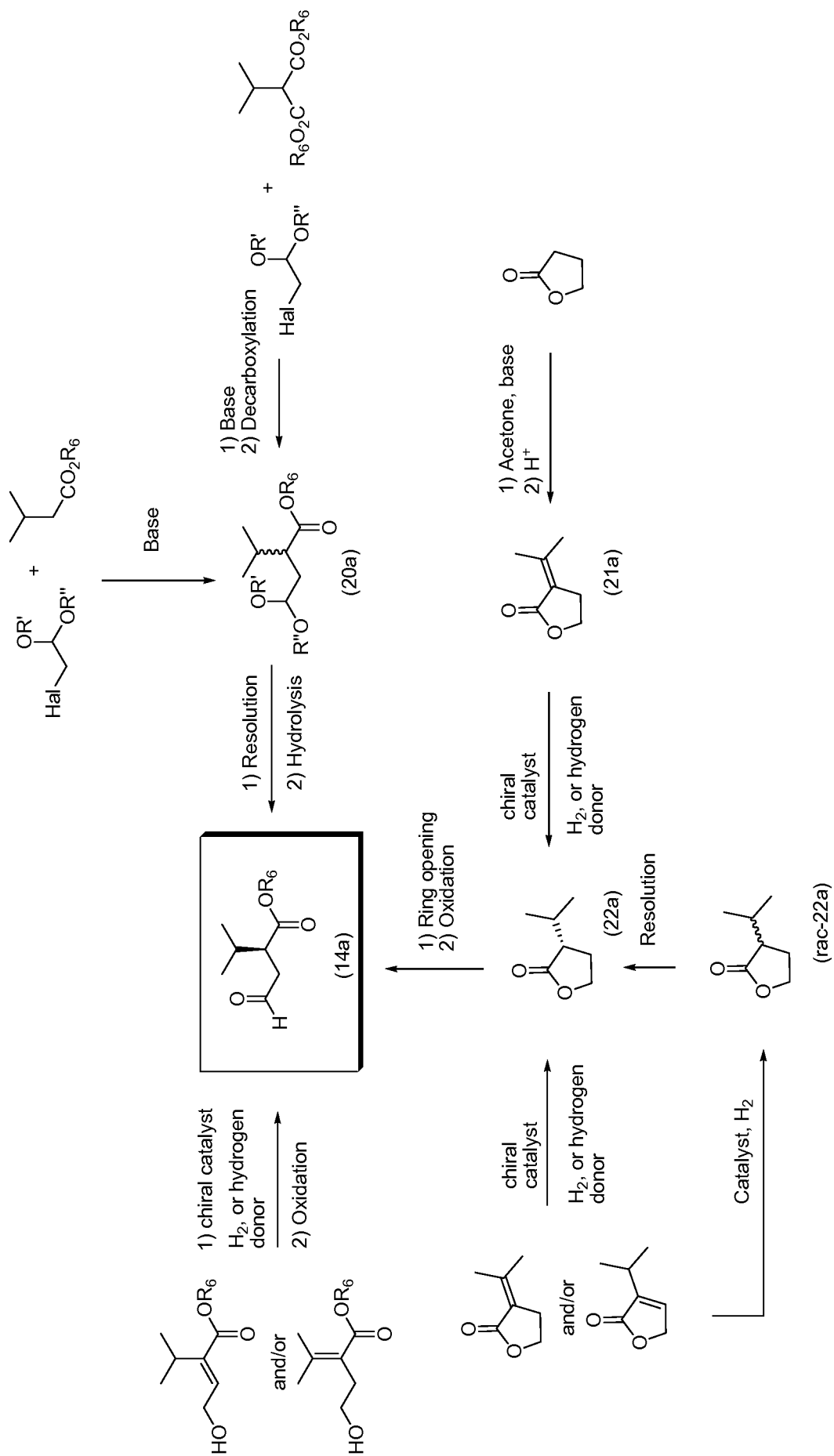
The compound according to formula (16) in the diastereochemically desired configuration can be obtained by ring-closing the compound according to formula (15) in the desired configuration, or by ring-closing both diastereomers of the compound according to formula (15) with fixed configuration at C-2 stereogenic center, followed by epimerization of the C-4 stereogenic center to the thermodynamically preferred diastereomer, also being the desired diastereomer. Said epimerisation can be conducted by heating the compound according to formula (16), optionally in a suitable solvent, and optionally in the presence of a base or other suitable additives. Alternatively, the diastereoisomer with the desired configuration can be separated from the other diastereoisomer making use of their different physical properties (e.g. preferential crystallization), or by means of classic or separating moving beds (SMB) chromatography. Suitable examples of SMB chromatography can be found in Schulte and Strube J. Chromatogr. A 2001, 906, 399-416 and references therein.

Preferably the compound according to formula (16) in the diastereochemically desired configuration is obtained by ring-closing an optically pure compound according to formula (15) with R<sub>7</sub> is equal to H and R<sub>6</sub> is C<sub>1-6</sub>alkyl.

Alternatively, diastereomeric mixtures of compounds according to formula (15) or (16) can be hydrolysed to the corresponding acids and then purified

with respect to the undesired diastereomer by using purification methods known to the person skilled in the art, e.g. preferential crystallization, optionally in the presence of a chiral auxiliary, or chromatographic techniques such as SMB.

In another aspect, the invention provides new routes to the useful  
5 building block according to formula (14), which was disclosed in WO2009/080773. The compound according to formula (14) can be obtained in various alternative ways, all surprisingly short, and atom-efficient, as illustrated in Scheme II for the compound according to formula (14) with R<sub>4</sub> is equal to 2-propyl (numbered as 14a), wherein R<sub>6</sub> is as described for compounds according to formula (13), R' and R'' are equal or  
10 independently stand for an optionally substituted C<sub>1-8</sub>alkyl, or form together an optionally substituted ring of maximal 10 carbon atoms, and Hal stands for Halogen.



Scheme II

As part of the invention new routes to compounds according to formula (14) are disclosed.

In one of the new routes, the compound according to formula (14) is obtained by resolution methods of the corresponding acetal, the compound according to formula (20) (depicted in the scheme for compound of formula (20a)), followed by hydrolysis of the acetal moiety to the aldehyde moiety, for example with acid such as aqueous HCl. Suitable resolution methods are those known to the person skilled in the art, such as preferential crystallization, optionally with the aid of chiral auxiliaries; classical resolution; chromatographic techniques such as SMB; or enzymatic resolution methods. In particular, enzymatic resolution methods are used. Suitable enzymes to be used in resolution processes as described above are for example hydrolases. Examples of suitable hydrolases are esterases, lipases, proteases, peptidases or acylases. These enzymes may be obtained from animals, for example pig liver esterase, or from microorganisms, such as bacteria or fungi or from plants.

Examples of suitable enzymes are disclosed in e.g. WO2006/117057, in particular on p.4 line 25 to p.7, line 6. Preferably, enzymes are used of non-animal origin.

The racemic compound according to formula (20) can be obtained in several ways, for example by alkylating the substituted malonate ester with an  $\alpha$ -halogenated acetal, followed by hydrolysis and decarboxylation as depicted on the right side of Scheme II. Conditions and reagents for these steps are known to the person skilled in the art.  $\alpha$ -alkylating an appropriate ester with the  $\alpha$ -halogenated acetal, as depicted on the top of Scheme II is another viable option.

Other new routes to compound according to formula (14) are based on catalytic asymmetric reductions of cyclic or non cyclic precursors in which the C=C double bond can be a tetrasubstituted one, or the isomerized tri-substituted one, or a mixture thereof, optionally followed by ring opening of the lactone, and subsequent oxidation.

For the cyclic compounds according to formula (21a) this reaction sequence is depicted on the center-bottom of Scheme II. For the isomerized cyclic compound, or a mixture thereof with compound according to formula (21a) this is depicted on the center-left of scheme II for the compounds with  $R_4$  is 2-propyl. For the non cyclic precursors this reaction sequence is depicted on the top-left of scheme II (for  $R_4$  is 2-propyl).

Suitable conditions and reagents for the catalytic asymmetric

reductions of the C=C bond are similar as described above for the reduction of the C=N bond. More specific examples are described in chapters 23-31 of *Handbook of Homogeneous Hydrogenation*, de Vries and Elsevier (Eds.); Wiley-VCH, Weinheim, 2007

5                                      Preferably molecular hydrogen in combination with optically enriched transition metal based catalysts are used for the reduction of the C=C bond.

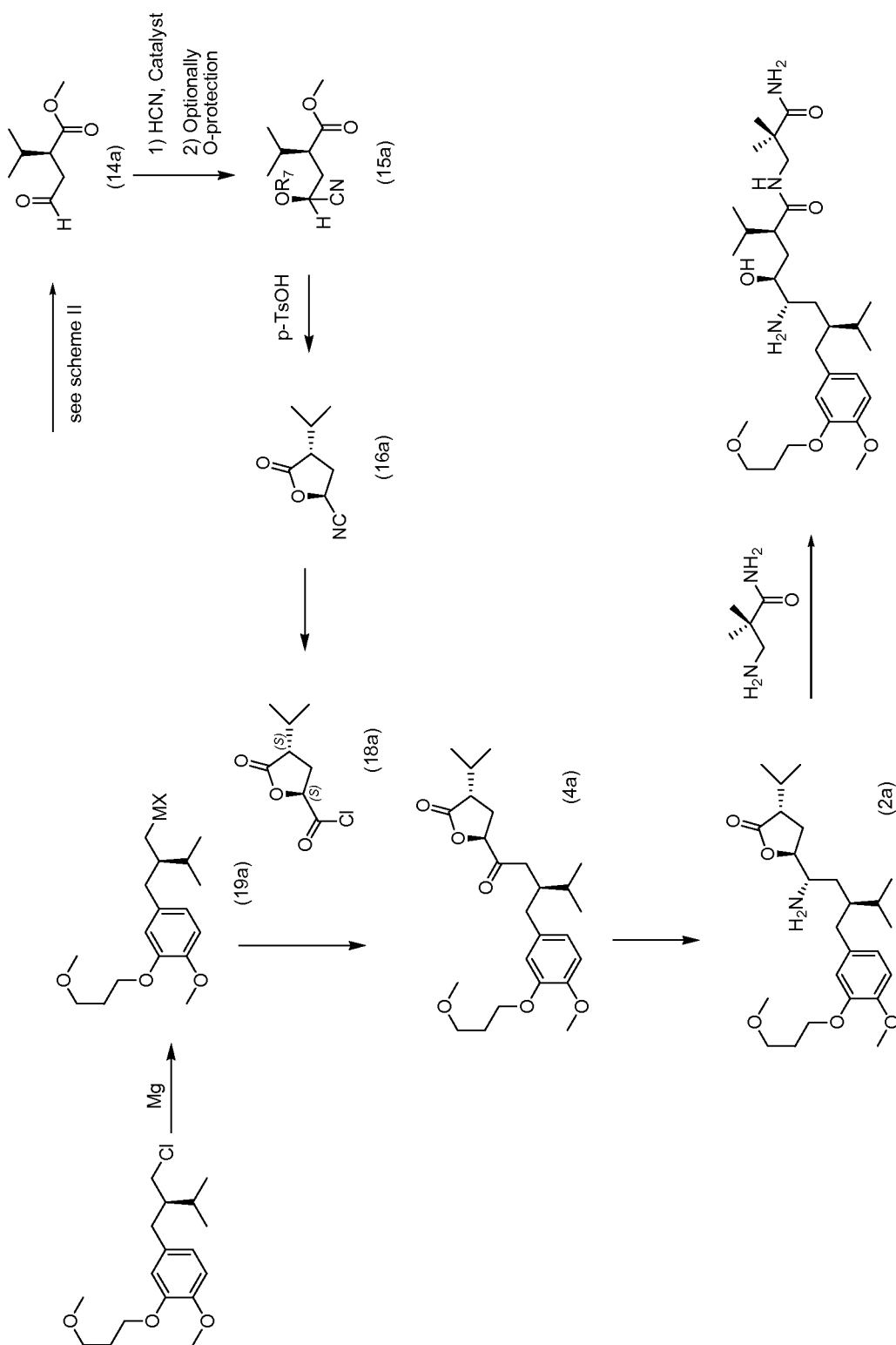
                                         Suitable conditions and reagents for the ring-opening of the lacton, and subsequent oxidation of the alcohol moiety are known to the person skilled in the art. Preferably the ring-opening of the lacton (the compound with R<sub>4</sub> is 2-propyl is  
10        depicted in the scheme with formula 22a) is performed in non alcoholic solvents.

                                         Another new route to compound according to formula (14) is any resolution method of the racemic lacton (a compound according to formula (22)), itself easily obtained by reduction of the compound according to formula (21), or its isomerised compound, or a mixture thereof, as depicted at the left-bottom corner of  
15        Scheme II for the compounds with R<sub>4</sub> is 2-propyl. Suitable resolution methods for this route are similar ones as described above for compound according to formula (20).

                                         For the synthesis of the compound according to formula (14), preferably,

- 20                                      a.    resolution methods of the compound according to formula (20), followed by hydrolysis of the acetal moiety to the aldehyde moiety, and
- b.    the catalytic asymmetric reduction of compound according to formula (21), followed by ring opening and oxidation,
- are used.

25                                      More specific, and without being limited thereto, the synthesis to Aliskiren (2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumaraat) using reactions of the invention, is as depicted in scheme III.



Scheme III

The processes and compounds according to the invention are particularly useful for the preparation of 2(S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides (compounds according to formula 13 with X stands for  $\text{NHR}_5$ ), or pharmaceutically acceptable salts thereof, such as disclosed in

5 WO02/02508, WO 2006/061427 and WO 2006/095020, which are hereby incorporated by reference. In particular, the processes and compounds according to the invention are useful in the preparation of compounds according to formula (I) of claim 1 of WO02/02508 A1 and the pharmaceutically acceptable salt thereof.

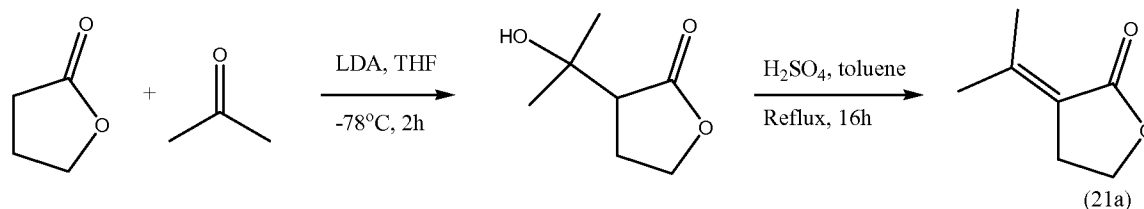
Salts, including pharmaceutically acceptable salts of compounds  
10 according to formula (13), wherein X is  $\text{HNR}_5$ , means salts that are generally safe, non-toxic and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound. These salts are derived from an inorganic or organic acid or base.

Pharmaceutically acceptable salts of the compounds according to  
15 formula (13), are for example disclosed in US5,559,111 which is hereby incorporated by reference and in particular in column 11 line 50 to column 12 line 33, of said document, which paragraph is also explicitly incorporated by reference.

All compounds according to the invention may be isolated by methods known to the person skilled in the art, such as crystallization, distillation, or  
20 chromatographic techniques. Some specific isolations, but not limited hereto, are described in the examples.

The amount of reagents and additives used in the processes of the invention are in principal known to the person skilled in the art and may vary between wide limits. Depending on the nature of the reagent (reactivity, costs, etc.), it can be  
25 used in large excess, or in stoichiometric amounts, or less than stoichiometric amounts, for example, it will be understood that catalysts and certain additives will only be used in less than stoichiometric amounts, in particular in catalytic amounts.

The following examples illustrate the invention, without however being limited hereto.

**EXAMPLE 1**Preparation of 2-isopropylidene- $\gamma$ -butyrolactone from acetone and  $\gamma$ -butyrolactone:

Diisopropylamine (41.0 mL, 292 mmol, 1.15 eq.) was dissolved in

5 THF (140 mL) and cooled to  $-70^{\circ}\text{C}$ . *n*-BuLi (2.9 M in hexanes, 95.8 mL, 278 mmol, 1.1 eq.) was added dropwise at  $-70^{\circ}\text{C}$  and the resulting yellow solution was stirred at  $0^{\circ}\text{C}$  for 30 minutes. The solution was then cooled to  $-70^{\circ}\text{C}$ , after which a solution of  $\gamma$ -butyrolactone (19.3 mL, 253 mmol, 1.0 eq.) in THF (100 mL) was added dropwise over 20 minutes. The solution was stirred for 1 hour at  $-70^{\circ}\text{C}$  and then acetone (37.2 mL,

10 506 mmol, 2.0 eq.) was added dropwise over 20 minutes. Subsequently, the reaction was stirred for 4 hours at  $-70^{\circ}\text{C}$  and then allowed to reach room temperature while stirring overnight. The reaction was quenched with water and diluted with MTBE. The organic layer was extracted with HCl (aq. 1N, 6x) and the combined aqueous layers were extracted with chloroform (9x). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ),

15 filtered and concentrated *in vacuo* to give the alcohol as a yellow liquid/oil which was used in the next step without further purification.

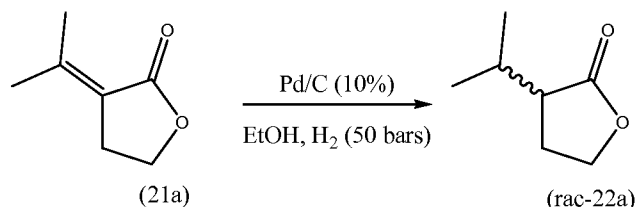
The crude alcohol was dissolved in toluene (500 mL) and  $\text{H}_2\text{SO}_4$  (95-97%, 1.75 mL, 32.8 mmol, 13 mol%) was added. The resulting reaction mixture was heated under reflux overnight. Subsequently, the reaction mixture was allowed to reach

20 room temperature. The organic layer was diluted with MTBE and washed with HCl (aq. 1N),  $\text{NaHCO}_3$  (sat. aq.) and brine (sat. aq.), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give a brown liquid. The aqueous layers were combined and the pH was adapted to 7. The aqueous layer was then extracted with dichloromethane (3x) and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to

25 give a yellow liquid that was added to the previously obtained brown fraction. The product was purified by vacuum distillation ( $65^{\circ}\text{C}$ , 1 mbar) to give a slightly yellow liquid. After further purification by column chromatography (heptane-EtOAc 7:3) the desired product (21a) (22.0 g, 174 mmol, 69%) was obtained as a colorless liquid.

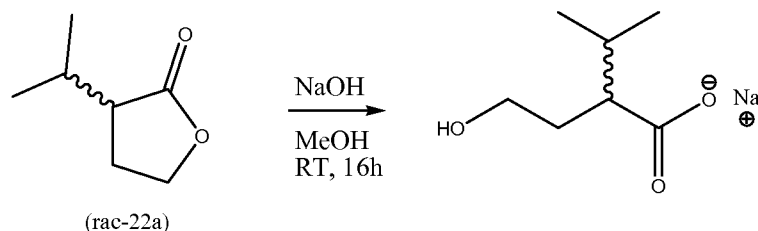
$^1\text{H}$ -NMR of compound according to formula (21a) ( $\text{CDCl}_3$ , 300 MHz)  $\delta$

30 = 1.89 (s, 3H,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 2.88 (m, 2H, C3- $\text{H}_2$ ), 4.29 (t,  $J = 7.5$  Hz), C4- $\text{H}_2$ ) ppm.

**EXAMPLE 2**Racemic 2-isopropyl- $\gamma$ -butyrolactone from 2-isopropylidene- $\gamma$ -butyrolactone:

The tetrasubstituted alkene (21a) (5.0 g, 40 mmol) was dissolved in  
 5 ethanol (100 mL) and stirred in an autoclave under an hydrogen atmosphere (50 bars)  
 in the presence of Pd/C (500 mg) for 16 hours at room temperature. Subsequently, the  
 suspension was filtered over dicalite and the resulting clear solution was concentrated  
*in vacuo* to give the saturated lacton (3.1 g, 24 mmol, 61%) as a colorless liquid.

<sup>1</sup>H-NMR of compound according to formula (rac-22a) (CDCl<sub>3</sub>, 300  
 10 MHz)  $\delta$  = 0.94 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>), 1.05 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>), 2.08 (m, 1H, C3-H),  
 2.21 (m, 2H, C2-H and C3-H), 2.48 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CH), 4.18 (ddd,  $J$  = 7.2, 9.0, 9.0  
 Hz, 1H, C4-H), 4.31 (ddd,  $J$  = 3.3, 8.7, 8.7 Hz, 1H, C3-H) ppm.

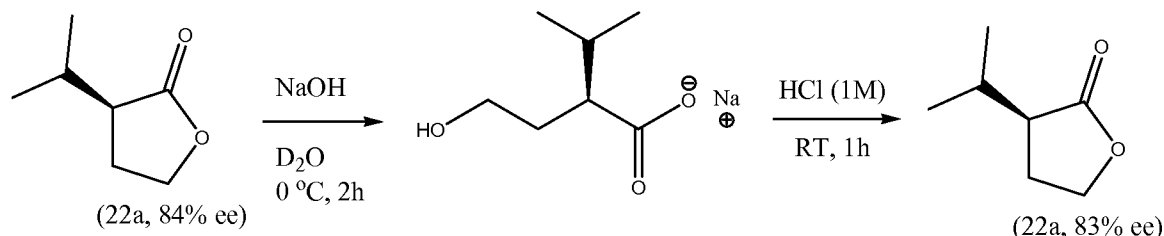
**EXAMPLE 3**Opening of racemic 2-isopropylidene- $\gamma$ -butyrolactone to the sodium salt:

To a solution of compound (rac-22a) (1.5 g, 12 mmol) in MeOH (10  
 mL) was added a solution of NaOH (0.47 g, 12 mmol, 1.0 eq.) in MeOH (20 mL). The  
 resulting solution was stirred at room temperature for 16 hours and then concentrated  
 20 *in vacuo* to give the corresponding racemic sodium salt in quantitative yield as an off-  
 white foam.

<sup>1</sup>H-NMR of sodium salt (CD<sub>3</sub>OD, 300 MHz)  $\delta$  = 0.94 (d,  $J$  = 6.4 Hz,  
 3H, CH<sub>3</sub>), 0.98 (d,  $J$  = 6.4 Hz, 3H, CH<sub>3</sub>), 1.70-1.87 (m, 3H, C2-H and C3-H<sub>2</sub>), 1.95 (m,  
 1H, (CH<sub>3</sub>)<sub>2</sub>CH), 3.58 (m, 2H, C4-H<sub>2</sub>) ppm.

**EXAMPLE 4**

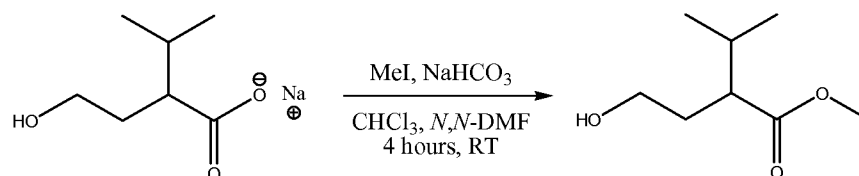
Opening of optically enriched 2-isopropylidene- $\gamma$ -butyrolactone to the sodium salt, followed by ring closure to determine the e.e. (of the sodium salt)



- 5 Optically enriched lactone (22a) (110 mg, 0.86 mmol, 84% ee) is dissolved in D<sub>2</sub>O (1.0 mL) and a solution of NaOH (34.4 mg, 0.86 mmol, 1.0 eq.) in D<sub>2</sub>O (1.0 mL) is added at 0 °C over 30 minutes in three portions. The reaction mixture is stirred for an additional 90 minutes at 0 °C. <sup>1</sup>H-NMR shows complete conversion into the linear ring opened compound. The pH of the reaction mixture is adapted to 0-1
- 10 using aqueous HCl (1M) and the reaction mixture is stirred for 1 hour at ambient temperature. The aqueous layer is extracted with chloroform (2x) and the combined organic layers are dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. Chiral GC shows that the enantiomeric excess of compound according to formula (22a) is 83%.

**EXAMPLE 5**

Alkylation of the sodium salt to the methylester:



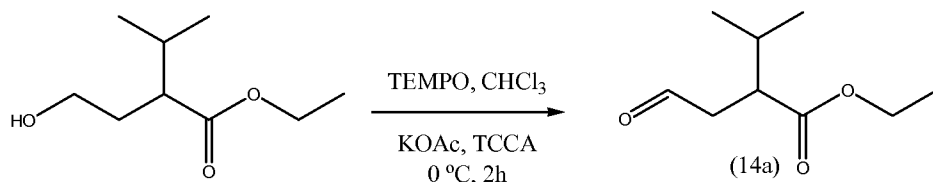
- The sodium salt of 4-hydroxy-2-isopropylbutanoate (56 mg, 0.33 mmol) and NaHCO<sub>3</sub> (s, 277 mg, 3.3 mmol, 10 eq.) were suspended in a mixture of chloroform (2.5 mL) and DMF (1.0 mL). The resulting suspension was stirred at room temperature for 4 hours and then quenched by addition of water. The aqueous layer was extracted with chloroform (3x) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. Residual DMF was removed by co-evaporation with toluene to give the desired methyl ester as a colourless oil
- 25 (quantitative).

<sup>1</sup>H-NMR of methyl ester (CDCl<sub>3</sub>, 300 MHz)  $\delta$  = 0.93 (d,  $J$  = 5.4 Hz, 3H, CH<sub>3</sub>), 0.95 (d,  $J$  = 5.4 Hz, 3H, CH<sub>3</sub>), 1.65-1.93 (m, 4H, C2-H, C3-H<sub>2</sub> and OH), 2.32 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CH), 3.64 (m, 2H, C4-H<sub>2</sub>), 3.69 (s, 3H, CH<sub>3</sub>OCO) ppm.

$^{13}\text{C}$ -NMR of methyl ester ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  = 20.0, 20.4, 30.5, 32.2, 49.3, 51.4, 61.4, 176.3 ppm.

#### EXAMPLE 6

##### 5 Oxidation of the 4-hydroxy-ethyl ester to the corresponding aldehyde (14):



To a solution of the 4-hydroxy ethyl ester (50 mg, 0.29 mmol) in chloroform (2.5 mL) was added KOAc (42 mg, 0.43 mmol, 1.5 eq.). The resulting suspension was cooled to  $0\text{ }^\circ\text{C}$  and then TEMPO (1.0 mg, 6.4  $\mu\text{mol}$ , 2.2 mol%) and finally trichlorocyanuric acid (TCCA, 34 mg, 0.15 mmol, 0.50 eq.) were added in a single portion. The resulting reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 90 minutes and then quenched with  $\text{Na}_2\text{S}_2\text{O}_3$  (aq. 10% w/w). The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with  $\text{NaHCO}_3$  (sat. aq.), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give compound (14a) (30 mg, 0.17 mmol, 61%) as a yellow oil.

$^1\text{H}$ -NMR of (14a) ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  = 0.92 (d,  $J$  = 6.6 Hz, 3H,  $\text{CH}_3$ ), 0.94 (d,  $J$  = 6.6 Hz, 3H,  $\text{CH}_3$ ), 1.26 (t,  $J$  = 7.2 Hz, 3H,  $\text{CH}_3\text{CH}_2\text{OCO}$ ), 2.03 (m, 1H,  $(\text{CH}_3)_2\text{CH}$ ), 2.53 (m, 1H, C4-H), 2.78 (m, 1H, C2-H), 2.88 (m, 1H, C4-H), 4.16 (m, 2H,  $\text{CH}_3\text{CH}_2\text{OCO}$ ), 9.79 (s, 1H) ppm.

20

#### EXAMPLE 7

##### Preparation of methyl-4,4-diethoxy-2-isopropylbutanoate (a compound according to formula 20a)

Sodium hydride (32.0 g of a 60% dispersion in mineral oil; 0.8 mole) was suspended in 1 L dry DMF and cooled to  $0\text{--}5\text{ }^\circ\text{C}$  by external cooling. Next dimethyl 2-isopropylmalonate (139.2 g; 0.8 mole) was added in 1 hour at  $5\text{--}10\text{ }^\circ\text{C}$  and stirred for another hour at  $10\text{ }^\circ\text{C}$ , whereafter no further evolution of hydrogen could be detected. Next bromoacetaldehyde diethylacetal (157.6 g; 0.8 mole) was added to the reaction mixture to give a red-brown solution, which was then heated to  $130\text{ }^\circ\text{C}$  for 18 hrs with stirring. GC analysis (HP-5, 30m \* 0.32 mm \* 0.25  $\mu\text{m}$ ;  $T_{\text{init}}=80\text{ }^\circ\text{C}$  (1 min), rate  $20\text{ }^\circ\text{C}/\text{min}$ ,  $T_{\text{end}}=300\text{ }^\circ\text{C}$ (3 min)) showed complete conversion of the malonate.

30

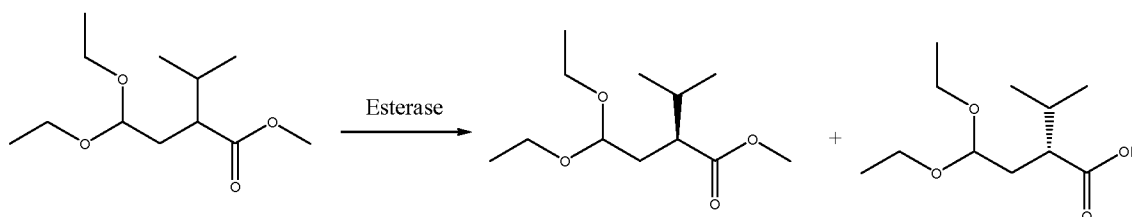
This mixture is cooled to room temperature methanol (32 g; 1 mole)

and lithiumchloride (34 g; 0.8 mol) was added. The mixture was stirred under nitrogen and heated to 130°C for 8 hours. GC analyses showed complete conversion. Next, the reaction mixture is concentrated in vacuo (70°C, 25 mbar, ~500 ml distillate), cooled and after addition of water (500 ml) and methyl-tert.butylether (300 ml), filtered over a  
5 precoated filter. The phases were separated and the water layer was extracted with methyl-tert.butylether (2 x 300 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by evaporation of the solvent under reduced pressure (70°C, 25 mbar). The residual liquid was subjected to fractional distillation (60°C, 1 mbar) to give 82 g of colorless oil of the racemic compound according to formula (20a). Overall  
10 yield = 45%.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : 0.9 (d, 6H); 1.2 (m, 6H); 1.7 (m, 1H); 1.8-2.1 (m, 2H); 2.3 (m, 1H); 3.4-3.7 (m, 4H); 3.7 (s, 3H); 4.4 (m, 1H)

#### EXAMPLE 8

15 Enzymatic resolution of methyl-4,4-diethoxy-2-isopropylbutanoate (a compound according to formula 20a)



In a round-bottom flask equipped with a pH-STAT apparatus 47 g of the purified methyl 4,4-diethoxy-2-isopropylbutanoate (202.3 mmol) were added to  
20 2.265 l of Phosphate Buffer pH 7.5 (100 mM). 85 ml of the cell-free extract of the enzyme (Diversa 13665, 5.35 g of enzyme) were then added and the solution was stirred at room temperature until one of the enantiomers was totally consumed (monitored by the consumption of NaOH used to keep the pH constant).

After 72 hours (e.e. > 99% of the remaining methyl 4,4-diethoxy-2-isopropylbutanoate), MTBE (500 ml), Charcoal (20 g) and Celite (20 g) were added and  
25 the mixture was stirred for 10 minutes. The suspension is then filtered and the water phase extracted three times with MTBE (3 X 500 ml). The combined organic phases were filtered over Celite to eliminate the residual biomass, and the organic phase was dried over anhydrous sodium sulphate. After filtration the solvent was evaporated *in*  
30 *vacuo* to give the desired enantiomer of methyl 4,4-diethoxy-2-isopropylbutanoate (e.e. > 99%) as a pale yellow oil (20.5 g, 88.2 mmol, 95% pure – based on GC analysis).

EXAMPLE 9Preparation of methyl 2-(formylmethyl)-3-methylbutanoate (14a)

Methyl-4,4-diethoxy-2-isopropylbutanoate (e.e. > 99%, 25.6 g; 110 mmol) is dissolved in 220 ml 0.5N HCl and stirred for 2 hrs at room temperature. The mixture is extracted with methyl-t-butylether (2 x 100 ml) and concentrated by

evaporation of the solvent under reduced pressure to yield 16.3 g of colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : 0.95 (dd, 6H); 1.85-2.00 (m, 1H); 2.35-2.45 (dd, 1H); 2.65-2.70 (m, 1H); 2.75-2.90 (m, 1H); 3.60 (s, 3H); 9.70 (s, 1H)

10 EXAMPLE 10Preparation of 2-isopropyl-γ-butyrolactone (compound according to formula 22a) by catalytic asymmetric hydrogenation of dihydro-3-(propan-2-ylidene)furan-2(3h)-one (21a)

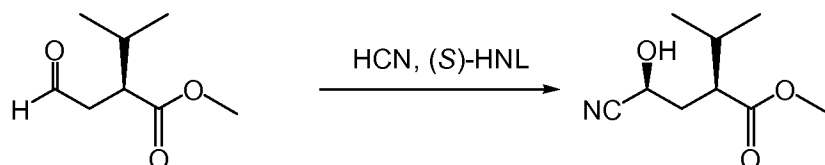
5.7 mg (11 μmol) (R)-1-[(S)-2-(Di-2-furfurylphosphino)-ferrocenyl]ethyl-di-tert-butylphosphine and 250 μl 0.04 M (10 μmol) Ru(COD)(methylallyl)<sub>2</sub> solution in dichloromethane were placed in a vial followed by 1.4 μl (10 μmol) HBF<sub>4</sub>·OEt<sub>2</sub>, 5 ml dichloromethane and 35 μl (320 μmol) dihydro-3-(propan-2-ylidene)furan-2(3H)-one. This solution was transferred to the hydrogenation apparatus and was hydrogenated for 1 h 30 min at 50 °C and 25 bar hydrogen. GC-analysis showed 100% conversion and 93% enantiomeric excess.

GC CONDITIONS:

Column ChiralDEX G-TA (30 m x 0.25 mm ID x 0.13 μm)  
Oventemperature 80°C (1min) → 5°C/min → 180°C (5 min)  
Carrier gas He flow rate 1.2 ml/min  
Split ratio 1: 50  
Injection volume 1 μL  
Enantiomer 1: 10.3 min  
Enantiomer 2: 10.8 min  
Substrate: 11.7 min

**EXAMPLE 11**

Synthesis of enantiomerically enriched cyanohydrin: (S)-methyl 2-((S)-2-cyano-2-hydroxyethyl)-3-methylbutanoate (a compound according to formula 15)

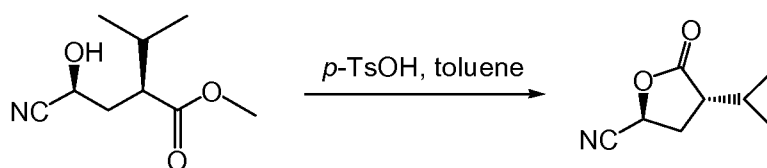


5 A mixture of 72 ml S-HNL in 18 ml K-Phosphate buffer (20 mM, pH=5.6) and 360 ml MTBE is charged to the reactor. The 2 phases are mixed by stirring and at a temperature of 0°C 20 ml pure HCN (0.53 mol) is added. Methyl 2-(formylmethyl)-3-methylbutanoate (16.5 g) diluted with 95 ml MTBE are dosed to the reactor in 20 minutes. The mixture is stirred for 3 hours at 0°C. The conversion of the  
10 aldehyde is >95% and e.e. >95%.

The reaction mixture is diluted with 200 ml MTBE. After phase separation the water layer is extracted with MTBE (2 x 100 ml), acidified with 0.2 ml concentrated H<sub>3</sub>PO<sub>4</sub> and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration the MTBE is evaporated under reduced pressure yielding 21.0 g of the cyanohydrin of formula (15) (e.e. of C-4  
15 center is 97%).

**EXAMPLE 12**

Synthesis of the lactone nitrile: (2S,4S)-tetrahydro-4-isopropyl-5-oxofuran-2-carbonitrile (a compound according to formula 16)



20 The cyanohydrin of example 11 (12.4 g) was diluted with 120 mL of toluene and 25 g of mol sieves 5Å were added. To this mixture, 250 mg of *p*-toluenesulfonic acid was added and, whilst stirring, the mixture was heated at 70 °C for 1 hour. After cooling to RT, the molecular sieves were filtered off and washed with  
25 toluene. The collected organic phase was washed with a saturated aqueous solution of sodium bicarbonate and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtering off the Na<sub>2</sub>SO<sub>4</sub>, the organic phase was concentrated under reduced pressure yielding 10.7 g of crude lactone. Purification by flash column chromatography on silica gel yielded the title compound with >98% purity.

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.11 (dd,  $J = 8.4, 2.3$  Hz, 1H), 2.84-2.74 (m, 1H), 2.62-2.41 (m, 2H), 2.31-2.16 (m, 1H), 1.10 (d,  $J = 6.9$  Hz, 3H), 0.97 (d,  $J = 6.9$  Hz, 3H).

#### 5 EXAMPLE 13

Synthesis of the TBS-protected cyanohydrin: (S)-methyl 2-[(S)-2-cyano-2-(*t*-butyldimethylsilyl)oxyethyl]-3-methylbutanoate, compound according to formula (15)



Imidazole (7.35 g, 108 mmol) was added at 0 °C to a solution of the  
 10 cyanohydrin (10 g) in DMF (180 mL), followed by TBDMSiCl (9.77 g, 64.8 mmol). The mixture was stirred at room temperature overnight. Subsequently, the reaction mixture was poured over an ice-cold aqueous HCl solution (1 M, 80 mL). After the addition of diethyl ether (100 mL), the organic layer was separated and the aqueous layer was further extracted with diethyl ether (2x100 mL). The combined organic layers were  
 15 washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over  $\text{Na}_2\text{SO}_4$  and the solvent was then removed under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel yielding the title compound.

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.26 (dd,  $J = 9.2, 3.4$  Hz, 1H), 3.50 (s, 3H), 2.37-2.29 (m, 1H), 2.08-1.96 (m, 1H), 1.86-1.68 (m, 2H), 0.81-0.68 (m, 15H), 0.00  
 20 (s, 3H), -0.08 (s, 3H).

#### EXAMPLE 14

Hydrolysis of tetrahydro-4-isopropyl-5-oxofuran-2-carbonitrile (a compound according to formula 16) to the corresponding acid: tetrahydro-4-isopropyl-5-oxofuran-2-carboxylic acid  
 25 acid

Tetrahydro-4-isopropyl-5-oxofuran-2-carbonitrile (19.7 g, 128.7 mmole) was dissolved in 200 ml 6N HCl and stirred at reflux for 18 hrs. The mixture was cooled to room temperature and extracted with methyl-tert.butylether (3 x 100 ml). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated by  
 30 evaporation of the solvent under reduced pressure to yield 16.8 g of yellow oil (97.7 mmol).

Purification via the dicyclohexylamine-salt:

The yellow oil is dissolved in 240 ml heptane/ methyl-tert.butylether (1 : 2 v/v). Next dicyclohexylamine (17.7 g; 97.7 mmole) is added dropwise. Spontaneous crystallization occurs. The precipitate is isolated by filtration, washed with heptane and dried in vacuo to yield 17.6 g of a white solid. Next, this white solid is suspended in 200 ml methyl-tert.butylether and 4.9 ml (58.8 mmole) of conc HCl is added drop wise at room temperature. The mixture is stirred for another 0.5 hrs. The precipitate is filtered off and the filtrate is concentrated in vacuo to yield 9.8 g of the acid (57.0 mmol) as a light brown oil which crystallizes after a few hours standing.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) : 0.95 (d, 3H); 1.05 (dd, 3H); 2.2-2.7 (3 x m, together 4H); 9.2 (broad s, 1H)

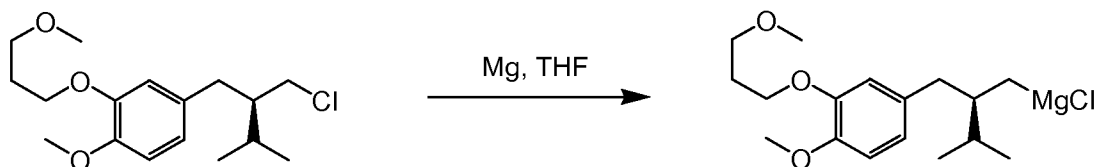
#### EXAMPLE 15

Synthesis of tetrahydro-4-isopropyl-5-oxofuran-2-carbonyl chloride (a compound according to formula 18)

A dry and nitrogen gas filled 3 necked round bottom flask (250 ml) equipped with magnetic stirrer, nitrogen gas inlet, septum and thermocouple, was filled with 7.12 g (38.08 mmol, 1.00 eq) carboxylic acid lactone (of example 14) and 45 ml toluene (dry, degassed). 5 ml (7.5 g, 59.09 mmol, 1.6 eq) oxalylchloride was added and subsequently 22 µl dimethylformamide (dry) resulting in gas evolution. The solution was stirred at room temperature for 3.5 h after which a sample quenched in ethanol showed no starting material by TLC. The solvent was removed in vacuum at room temperature and giving the desired acid chloride.

#### EXAMPLE 16

Preparation of compound according to formula (19a)



A dry, nitrogen gas filled, 3 necked round bottom flask (500 ml) equipped with reflux condenser, dropping funnel, magnetic stirrer and nitrogen gas inlet was filled with 4.680 g (192.5 mmol, 1.1 eq) Mg powder, 10 ml tetrahydrofuran (THF, dry, degassed)) and a crystal of iodine. A solution of 54.930 g (174.5 mmol, 1.0 eq) 2-(3-methoxypropoxy)-4-((R)-2-(chloromethyl)-3-methylbutyl)-1-methoxybenzene, and

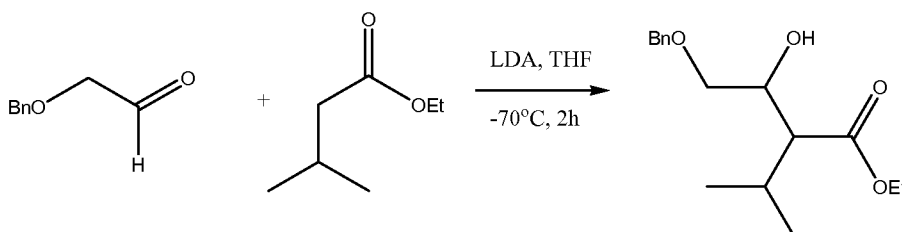
0.6 ml 1,2-dibromomethane in 163 ml THF was prepared and 20 ml of this solution was added to the Mg slurry. This mixture was heated to boil, and while keeping it refluxing, the remaining solution of above was added drop wise in 1.5 h. The mixture was then heated under reflux conditions for another 3.5 h, after which analysis by TLC showed  
5 no starting material. The concentration of the Grignard solution was 0.763 M determined by titration with *s*-butanol using phenantroline as indicator.

### EXAMPLE 17

Synthesis of compound according to formula (4a): Coupling of compound according to formula (19a) with the compound according to formula (18a).  
10

The in example 15 prepared acid chloride (18a) was dissolved in 45 ml THF (dry, degassed) and cooled with an ice/water bath. To this cooled solution was added drop wise in 30 min in total 51 ml (38.91 mmol, 1.02 eq) of the Grignard solution of example 16, keeping the inside temperature below 22 °C. The reaction mixture was cooled in ice and 25 ml water was added slowly. The formed slurry was filtered and the precipitate was washed with 50 ml ethyl acetate. The combined filtrates were washed with water (50 ml and 100 ml) and brine (100 ml), dried on Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under vacuum to yield 17.19 g crude product as an oil. This was purified by column chromatography to giving compound according to formula (4a) as pure  
15  
20 diastereoisomer.

### EXAMPLE 18

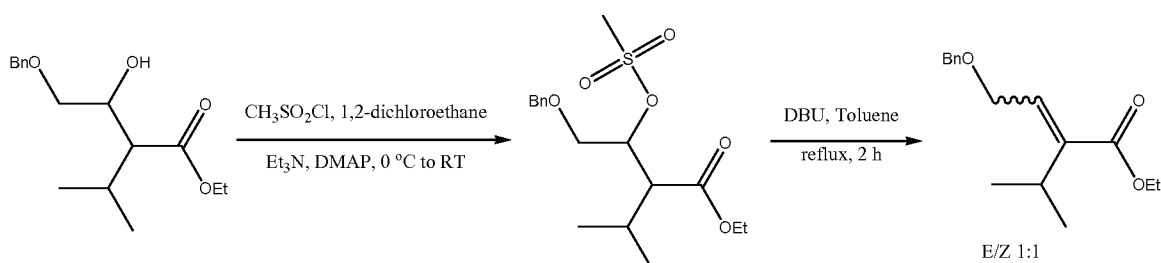


Diisopropylamine (3.56 mL, 25.3 mmol, 1.05 eq.) was dissolved in THF (14 mL) and cooled to -70 °C. *n*-BuLi (1.6 M in hexanes, 15.2 mL, 24.2 mmol, 1.0 eq.) was added dropwise at -70 °C and the resulting yellow solution was stirred at 0 °C for 30 minutes. The solution was then cooled to -70 °C, after which a solution of ethyl isovalerate (3.65 mL, 24.2 mmol, 1.0 eq.) in THF (15 mL) was added drop wise over 20 minutes. The solution was stirred for 1 hour at -70 °C and then  
25  
30 benzyloxyacetaldehyde (3.74 mL, 26.6 mmol, 1.1 eq.) was added drop wise. Subsequently, the reaction was stirred for 3 hours at -70 °C and then allowed to reach

room temperature while stirring overnight. The reaction was quenched with  $\text{NH}_4\text{Cl}$  (sat. aq.) and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (sat. aq.) dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give the desired products (4.9 g, 17.5 mmol, 72%, mixture of diastereomers) as a yellow oil which was used in the next step without further purification.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  = 0.98 (m, 6H, 2  $\text{CHCH}_3$ ), 1.24 (t, 3H,  $\text{OCH}_2\text{CH}_3$ ), 2.08-2.35 (m, 1H), 2.60 (m, 1H), 3.52 (m, 2H,  $\text{BnOCH}_2$ ), 4.11 (m, 3H, C3-H and  $\text{OCH}_2\text{CH}_3$ ), 4.54 (m, 2H,  $\text{PhCH}_2$ ), 7.32 (m, 5H, Ph) ppm.

## 10 EXAMPLE 19



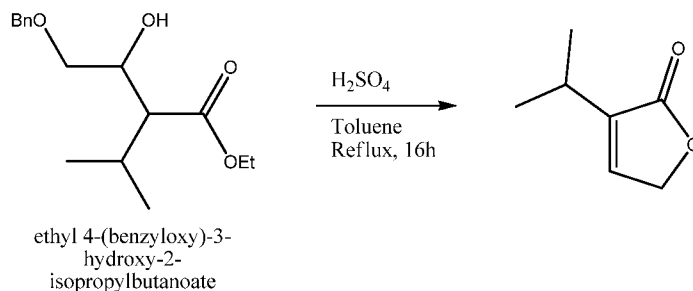
To a solution of the alcohol compound of example 18 (1.0 g, 3.56 mmol) in 1,2-dichloroethane and triethylamine (5.0 mL, 1:1 v/v) at  $0\text{ }^\circ\text{C}$  was added *N,N*-4-dimethylaminopyridine (44 mg, 0.36 mmol, 10 mol%) and then methanesulfonylchloride (0.83 mL, 10.7 mmol, 3.0 eq.) in a dropwise fashion. The resulting solution was stirred for 48 hours while warming to room temperature. The reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  (sat. aq.) and diluted with water. The layers were separated and the aqueous layer was extracted with chloroform (3x). The combined organic layers were washed with  $\text{NaHCO}_3$  (sat. aq.) and brine (sat. aq.), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give the mesylated product as a yellow/brown oil, which was used in the next step without further purification.

The mesylated compound was dissolved in toluene (10 mL) and diazabicyclo-undecene (DBU, 0.64 mL, 4.3 mmol, 1.2 eq.) was added. The resulting solution was heated under refluxing conditions for two hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc. Subsequently, the organic solution was washed with  $\text{NH}_4\text{Cl}$  (sat. aq.) and brine (sat. aq.), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (heptane-EtOAc 95:5 v/v) giving 0.88 g of product (3.36 mmol, 94% over 2 steps, 1:1 E/Z-mixture) as a yellow oil.

$^1\text{H-NMR}$  of product (1:1 E/Z mixture) ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  = 1.09 (d, J

= 6.6 Hz, 3H, CHCH<sub>3</sub>), 1.18 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>), 1.30 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.77 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.12-4.26 (m, 3H, C4-H, OCH<sub>2</sub>CH<sub>3</sub>), 4.41 (m, 1H, C4-H), 4.55 (m, 2H, PhCH<sub>2</sub>), 6.01 (dt, *J* = 1.2, 5.1 Hz, 1H, C3-H), 6.69 (t, *J* = 5.7 Hz, 1H, C3-H), 7.34 (m, 5H, Ph) ppm.

5

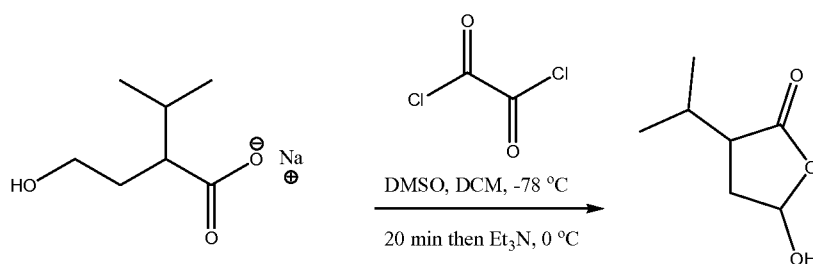
**EXAMPLE 20**

Ethyl 4-(benzyloxy)-3-hydroxy-2-isopropylbutanoate (3.9 g, 14 mmol) was dissolved in toluene (25 mL) and the resulting solution was heated under reflux overnight in the presence of stoichiometric sulfuric acid (96%, 0.74 mL, 14 mmol). The reaction mixture was allowed to cool to room temperature after which the reaction was quenched with NaHCO<sub>3</sub> (sat. aq.). The aqueous layer was extracted with chloroform (3x) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. Subsequently, the product was diluted with pentane and extracted with

15 acetonitrile. The acetonitrile layer was washed with pentane (2x) and then concentrated *in vacuo*. The product was further purified by column chromatography (heptane-EtOAc 4:1 v/v) and Kugelrohr distillation to give the unsaturated lactone (1.3 g, 10 mmol, 74%) as a colorless liquid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ = 1.19 (d, *J* = 6.9 Hz, 6H, 2 CH<sub>3</sub>), 2.69 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.76 (m, 2H, C4-H<sub>2</sub>), 7.07 (m, 1H, C3-H) ppm.

20

**EXAMPLE 21**

A solution of DMSO (0.41 mL, 5.8 mmol, 3.8 eq.) in DCM (7.5 mL) was added to a solution of oxalylchloride (0.24 mL, 2.9 mmol, 1.9 eq.) in DCM (7.5 mL)

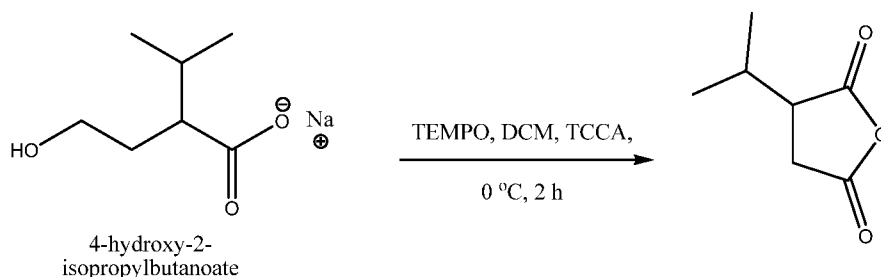
25

at -78 °C under a nitrogen atmosphere. The resulting solution was stirred at -78 °C for 20 minutes after which first 250 mg of the sodium salt depicted in the equation (1.49 mmol) in DCM (7.5 mL) and then acetic acid (0.20 mL, 3.5 mmol, 2.3 eq.) were added. The resulting suspension was stirred for another 20 minutes at -78 °C after which

5 triethylamine (2.5 mL, 18 mmol, 12 eq.) was added. The reaction mixture was allowed to reach 0 °C and stirred at this temperature for 4 hours and then at room temperature overnight. The reaction was quenched with water and the pH of the aqueous layer was adjusted to pH 3-4 with HCl (1M, aq.). The aqueous layer was extracted with DCM (4x) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. <sup>1</sup>H-NMR of the crude product showed a mixture of products. The desired hemiacetal was identified by a characteristic peak at 5.77 ppm (C4-H). Importantly, no overoxidation to the di-carboxylic acid or the corresponding anhydride was observed. The presence of the hemiacetal was confirmed by GC-MS: m/z = 144.

10

15 EXAMPLE 22



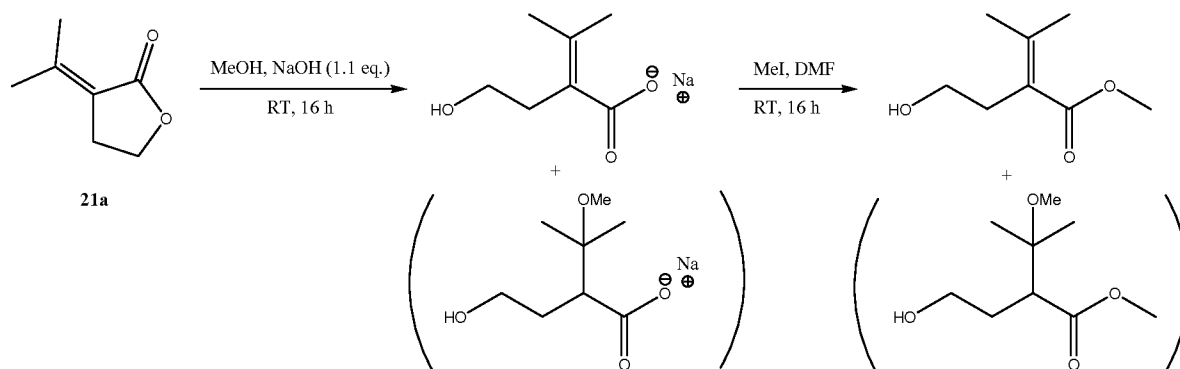
TEMPO (1.8 mg, 12 μmol, 2 mol%) was added to a suspension of the sodium salt of 4-hydroxy-2-isopropylbutanoate (100 mg, 0.60 mmol) in DCM (5.0 mL) at 0 °C. Subsequently, trichlorocyanuric acid (152 mg, 0.65 mmol, 1.1 eq.) was added

20 upon which the suspension turned yellow. The reaction mixture was stirred at 0 °C for 2 hours and then diluted with water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give the anhydride as the sole product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ = 0.99 (d, J = 6.9 Hz, 3H, CH<sub>3</sub>), 1.04 (d, J = 6.9 Hz, 3H, CH<sub>3</sub>), 2.30 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.76 (dd, J = 5.4, 18.6 Hz, 1H, C2-H),

25 3.05 (m, 2H, C3-H<sub>2</sub>) ppm.

## EXAMPLE 23



Unsaturated lactone **21a** (5.0 g, 40 mmol) was dissolved in methanol (50 mL) and NaOH (1.8 g, 44 mmol, 1.1 eq.) was added. The resulting solution was stirred overnight at room temperature and then concentrated *in vacuo* to give the desired ring-opened salt as an off-white solid. <sup>1</sup>H-NMR shows that the desired compound was contaminated with a side product (approximately 20%) which was identified as the salt depicted in the equation formed by 1,4-addition of methanol

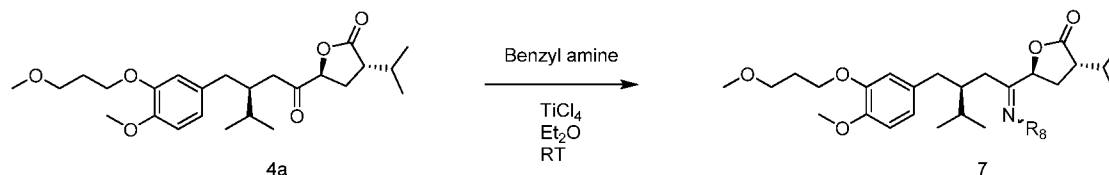
<sup>1</sup>H-NMR of desired salt (CD<sub>3</sub>OD, 300 MHz)  $\delta$  = 1.70 (s, 3H, CH<sub>3</sub>), 1.83 (s, 3H, CH<sub>3</sub>), 2.49 (t, *J* = 6.6 Hz, 2H, C3-H<sub>2</sub>), 3.63 (t, *J* = 6.6 Hz, 2H, C4-H<sub>2</sub>) ppm.

<sup>1</sup>H-NMR of side product (CD<sub>3</sub>OD, 300 MHz)  $\delta$  = 1.25 (s, 3H, CH<sub>3</sub>), 1.28 (s, 3H, CH<sub>3</sub>), 2.49 (m, 2H, C3-H<sub>2</sub>), 2.60 (dd, *J* = 3.0, 11.4 Hz, 1H, C2-H), 3.21 (s, 3H, CH<sub>3</sub>O), 3.60 (t, 2H, C4-H<sub>2</sub>) ppm.

The mixture of salts obtained above (4:1 mol/mol, 720 mg, 4.2 mmol) was dissolved in DMF (3.0 mL) and MeI (0.32 mmol, 5.0 mmol, 1.2 eq.) was added. The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was quenched with water and the resulting homogeneous mixture was extracted with chloroform (2x). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. Residual DMF was removed by co-evaporation with toluene to give a mixture of the desired ester and the ester derived from the side-product (4:1 mol/mol, 600 mg, 3.6 mmol, 87%) as a yellow oil.

<sup>1</sup>H-NMR of desired ester (CDCl<sub>3</sub>, 300 MHz)  $\delta$  = 1.79 (s, 3H, CH<sub>3</sub>), 1.93 (s, 3H, CH<sub>3</sub>), 2.51 (t, *J* = 6.3 Hz, 2H, C3-H<sub>2</sub>), 3.62 (m, 2H, C4-H<sub>2</sub>), 3.67 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>1</sup>H-NMR of ester of side product (CDCl<sub>3</sub>, 300 MHz)  $\delta$  = 1.14 (s, 3H, CH<sub>3</sub>), 1.16 (s, 3H, CH<sub>3</sub>), 2.51 (m, 2H, C3-H<sub>2</sub>), 2.74 (dd, *J* = 3.3, 10.5 Hz, 1H, C2-H), 3.14 (s, 3H, CH<sub>3</sub>O), 3.60 (t, 2H, C4-H<sub>2</sub>), 3.67 (s, 3H, C(O)OCH<sub>3</sub>) ppm.

**EXAMPLE 24**Preparation of a compound according to formula (7)

- 5 A solution of the compound according to formula (4a) with  $R_4=2$ -propyl (868 mg) and benzyl amine (1.07 g) in diethyl ether (4.4 mL) was degassed with  $N_2$ . To the solution, a 1 M solution of  $TiCl_4$  in toluene (1.1 mL) was slowly added under vigorous stirring. After stirring for 1 h at room temperature, the heterogeneous reaction mixture was diluted with diethyl ether (5.4 mL) and filtrated. Extraction of the filtrate by
- 10 0.5 N NaOH (2 x 50 mL), drying the solution over  $Na_2SO_4$  anhydrous, filtration and subsequent evaporation gave the corresponding imine, a compound according to formula (7) ( $R_8$ =benzyl) in 0.8 g yield.
- GCMS: M/z: 524.

15 **EXAMPLE 25-27**Hydrogenation experiments of compound according to formula (7). Preparations of a compound according to formula (2)Method A

- The imine compound as obtained in example 24 (0.052 g) was
- 20 dissolved in a solvent (5 mL).  $[Ir(COD)Cl]_2$  (0.0016 g) was added and dissolved. After preconditioning of the homogeneous catalyst mixture by 5 cycles of  $N_2$  (3 bar) and by 5 cycles of  $H_2$  (25 bar), the solution was stirred for 3 h at 50°C and 25 bar  $H_2$ .

Method B

- 25 A solution of benzyl amine (0.021 g) in  $CH_2Cl_2$  (5 mL) was prepared. Under an atmosphere of  $N_2$ ,  $[Ir(COD)Cl]_2$  (0.0034 g) was dissolved in the benzyl amine solution (1 mL) giving a catalyst solution. The catalyst solution (0.1 mL) was placed in a reaction vessel and the  $CH_2Cl_2$  removed in vacuo and the remaining complex subsequently dissolved in 5 mL of a 0.01 M methanol solution of the imine compound
- 30 as obtained in example 24. After preconditioning of the methanol reaction mixture by 5 cycles of  $N_2$  (3 bar) and by 5 cycles of  $H_2$  (25 bar), the solution was stirred for 3 h at 50°C and 25 bar  $H_2$ .

Results:

| Exp. | Method | Solvent       | Product (area %) |           |
|------|--------|---------------|------------------|-----------|
|      |        |               | (4S,5S)-2        | (4S,5R)-2 |
| 25   | A      | Isopropanol   | 52               | 40        |
| 26   | A      | Ethyl acetate | 53               | 28        |
| 27   | B      | Methanol      | 69               | 23        |

Up to ca 10% of the undesired 4(R)-2 stereoisomers are also detected.

#### EXAMPLE 28

- 5 Preparation of a compound according to formula (2) from the compound according to formula (4) – 2 steps.

A solution of ketone (compound according to formula (4a) with R<sub>4</sub>=2-propyl) (359 mg) and benzyl amine (443 mg) in diethyl ether (2 mL) was degassed by N<sub>2</sub>. Then, (0.5 mL) of 1 M solution of TiCl<sub>4</sub> in toluene was slowly added at room  
 10 temperature and the heterogeneous mixture was allowed to stir for 0.1 hour. The reaction mixture subsequently was diluted by diethyl ether (5 mL) followed by filtration of the precipitates and the residue washed with 5 portions of 1 mL diethyl ether. According to GC analysis, the ketone was completely converted to the imine and the excess of benzyl amine remains in the diethyl ether solution. Due to evaporation of  
 15 diethyl ether during the filtration step, the total volume of the imine solution was adjusted with diethyl ether to a total amount of 10 mL.

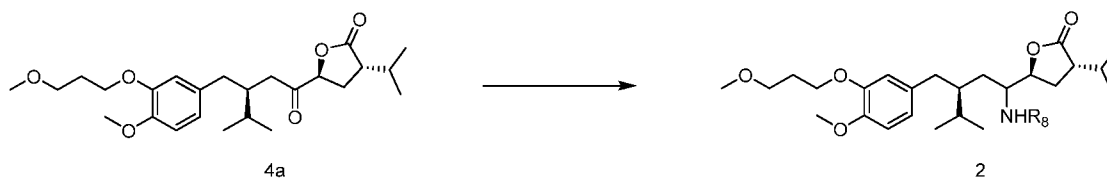
For hydrogenation, (2.5 mL) of the diethyl ether solution of the imine solution was placed in a vessel, and the diethyl ether was evaporated by a stream of N<sub>2</sub>. The residue was subsequently dissolved in methanol (10 mL). Meanwhile,  
 20 [Ir(COD)Cl]<sub>2</sub> (0.0024 g) was dissolved in a solution of a 0.03 M solution of benzyl amine in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and allowed to stand for 0.25 h. After removal of the CH<sub>2</sub>Cl<sub>2</sub> by a stream of N<sub>2</sub>, the remaining complex was dissolved in the previously prepared solution of the imine in methanol (10 mL) and subsequently the reaction mixture was subjected to hydrogenation. Prior to hydrogenation, the reaction mixture was degassed by 5  
 25 cycles of N<sub>2</sub> (3 bar) and by 5 cycles of H<sub>2</sub> (25 bar) and the hydrogenation was conducted for 3 h at 50°C and 25 bar H<sub>2</sub>.

After hydrogenation, the reaction mixture was filtrated and treated with 1 N HCl (1 mL) overnight. The methanol was removed in vacuo and the residue dissolved in isopropanol (10 mL) followed by removal of water by azeotropic distillation

to dryness. The residue was dissolved in a 1:1 mixture of heptane and ethyl acetate, filtrated over SiO<sub>2</sub> and the SiO<sub>2</sub> washed by the 1:1 heptane/ethyl acetate mixture (3 x 15 mL). Then, the SiO<sub>2</sub> was washed by methanol giving the HCl-salt solution in methanol. The methanol was distilled and the residue dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and triethylamine (0.2 mL) followed by extraction with sat. NaHCO<sub>3</sub> (2 x 1 mL). The CH<sub>2</sub>Cl<sub>2</sub> was dried over Na<sub>2</sub>SO<sub>4</sub> anhydrous, filtrated, followed by removal of CH<sub>2</sub>Cl<sub>2</sub> by distillation. According to GC, the product was obtained in 60 area % of the 4(S), 5(S)-stereoisomer (R<sub>8</sub>=benzyl).

#### 10 EXAMPLE 29

Preparation of a compound according to formula (2) from the compound according to formula (4) Reductive amination protocol - 1-pot.



Placed in a reaction vessel, [((S)-tol-BINAP)RuCl<sub>2</sub> (DMF)<sub>x</sub>] (10 mg), ketone according to formula (4a) (40 mg) ammonium formate (189 mg) and dissolved in 7 N NH<sub>3</sub> in methanol. The reaction mixture was degassed by N<sub>2</sub> and heated at 85 °C. After 2 hours, a sample of the reaction mixture was analysed by GC and the formation of product (4S,5S)-2 (R<sub>8</sub> = H) has been demonstrated in comparison to a standard.

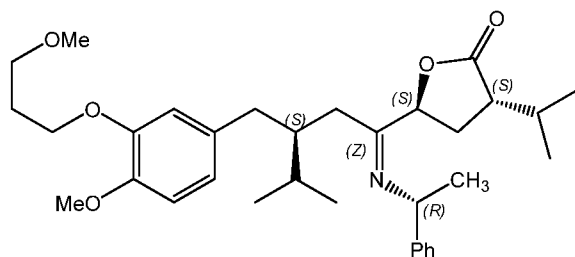
#### 20 EXAMPLE 30

Preparation of a compound according to formula (2) from the compound according to formula (7) using NaBH<sub>4</sub> as reducing agent.

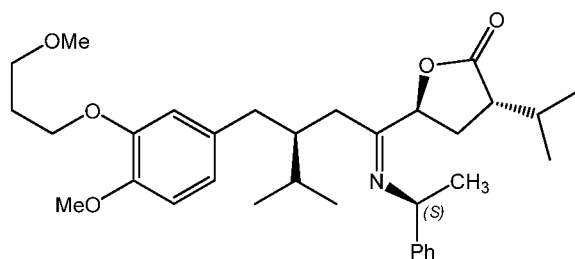
A sample of the imine obtained as in example 24, was dissolved in methanol, treated with excess of NaBH<sub>4</sub> for 1 h and subsequently quenched by 6 N HCl. The methanol was removed in vacuo and the residue dissolved in water. After basifying the water layer to pH 11 with 32 % NaOH in water, the product was extracted by CH<sub>2</sub>Cl<sub>2</sub>. According to GC, the product was obtained in 60 area % of the 4(S), 5(S)-stereoisomer of compound according to formula (2) with (R<sub>8</sub> = benzyl).

**EXAMPLE 31**Racemisation of the 4-(S) center of the keton according to formula (4a)

A solution of (4S)-4a with  $R_4=2$ -propyl (2.17 g) in isopropanol (20 mL) was stirred for 2 h at 70°C in the presence of  $\text{KHCO}_3$  (0.5 g). The reaction mixture was cooled to room temperature and isopropanol removed in vacuo at 40°C and the residue dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL). Extraction of the  $\text{CH}_2\text{Cl}_2$  solution with water (3 x 50 mL), dried over  $\text{Na}_2\text{SO}_4$  anhydrous, filtration and evaporation of the solvent gave a viscous oil. Analysis showed full racemisation of the 4-C stereogenic center, while the other stereocenters (2-(S) and 7-(S)) are still optically pure.

**EXAMPLE 32**Preparation of a compound according to formula (7) using (R)- $\alpha$ -methyl benzyl amine.

A solution of ketone 4a (178 mg) and (R)- $\alpha$ -methyl benzyl amine (264  $\mu\text{L}$ ) in ether (2 mL) was degassed by  $\text{N}_2$ . To the solution, a 1 M solution of  $\text{TiCl}_4$  in toluene (0.25 mL) was slowly added under vigorous stirring. The reaction mixture was allowed to stir for 2 hours, filtrated and the residue washed extensively with excessive amounts of ether. In order to remove residual amounts of  $\alpha$ -methyl benzyl amine the ether solution was extracted with diluted  $\text{NaHCO}_3$  (3 x 5 mL) and water (5 mL). The ether layer was separated, dried over  $\text{Na}_2\text{SO}_4$  anhydrous, and concentrated. The residue was used as such in the subsequent reactions.

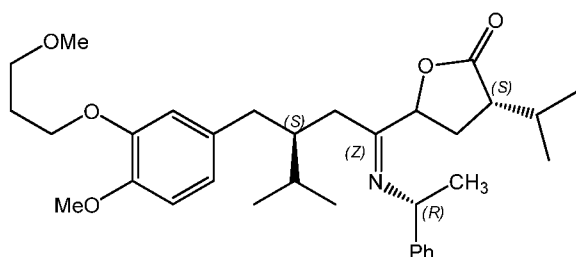
**EXAMPLE 33**Preparation of a compound according to formula (7) using (S)- $\alpha$ -methyl benzyl amine.

A solution of ketone 4a (178 mg) and (S)- $\alpha$ -methyl benzyl amine (264

μL) in ether (2 mL) was degassed by N<sub>2</sub>. To the solution, a 1 M solution of TiCl<sub>4</sub> in toluene (0.25 mL) was slowly added under vigorous stirring. The reaction mixture was allowed to stir for 2 hours, filtrated and the residue washed extensively with excessive amounts of ether. In order to remove residual amounts of α-methyl benzyl amine the ether solution was extracted with diluted NaHCO<sub>3</sub> (3 x 5 mL) and water (5 mL). The ether layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> anhydrous, and concentrated. The residue was used as such in the subsequent reactions.

#### EXAMPLE 34

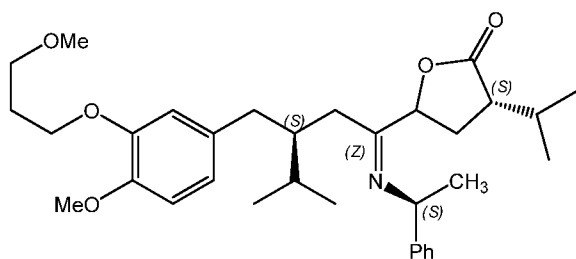
10 Preparation of a compound according to formula (7) using (R)-α-methyl benzyl amine and the ketone of formula 4a with the 4-C center being racemic.



A solution of ketone 4a (178 mg) and (R)-α-methyl benzyl amine (264 μL) in ether (2 mL) was degassed by N<sub>2</sub>. To the solution, a 1 M solution of TiCl<sub>4</sub> in toluene (0.25 mL) was slowly added under vigorous stirring. The reaction mixture was allowed to stir for 2 hours, filtrated and the residue washed extensively with excessive amounts of ether. In order to remove residual amounts of α-methyl benzyl amine the ether solution was extracted with diluted NaHCO<sub>3</sub> (3 x 5 mL) and water (5 mL). The ether layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> anhydrous, and concentrated. The residue was used as such in the subsequent reactions.

#### EXAMPLE 35

Preparation of a compound according to formula (7) using (S)-α-methyl benzyl amine and the ketone of formula 4a with the 4-C center being racemic.



A solution of ketone 4a (178 mg) and (S)-α-methyl benzyl amine (264

μL) in ether (2 mL) was degassed by N<sub>2</sub>. To the solution, a 1 M solution of TiCl<sub>4</sub> in toluene (0.25 mL) was slowly added under vigorous stirring. The reaction mixture was allowed to stir for 2 hours, filtrated and the residue washed extensively with excessive amounts of ether. In order to remove residual amounts of α-methyl benzyl amine the ether solution was extracted with diluted NaHCO<sub>3</sub> (3 x 5 mL) and water (5 mL). The ether layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> anhydrous, and concentrated. The residue was used as such in the subsequent reactions.

#### EXAMPLE 36 - 39

##### 10 Reduction of the imines of examples 32-35 using NaBH<sub>4</sub>, and subsequent hydrogenolysis (preparation of compound according to formula 2 with R<sub>8</sub> = H)

Methanol (5 mL) was added to the residue of example 32, 33, 34, and 35. In each vessel NaBH<sub>4</sub> (40 mg) was added and after complete conversion, the reaction mixtures were quenched with 1 N HCl (1 mL), the solvents removed in vacuo and water (2 mL) added to the residue. In the presence of CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the pH was adjusted to 13 with 32 % NaOH under vigorous stirring and cooling. The CH<sub>2</sub>Cl<sub>2</sub> was separated and the water layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> layers dried over Na<sub>2</sub>SO<sub>4</sub> anhydrous, filtrated and the CH<sub>2</sub>Cl<sub>2</sub> removed.

##### 20 Hydrogenolysis

For this purpose, 45 mg of the above obtained amines were dissolved in methanol (5 mL). The reaction mixture was treated by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar) in the presence of wet 10 % Pd/C (80 mg). The hydrogenolysis subsequently was performed at 50°C and 25 bar of H<sub>2</sub> for 2 hours. Analysis of the reaction mixtures by GC, see table below.

| Example | Imine      | Product (area %) |           |        |
|---------|------------|------------------|-----------|--------|
|         |            | (4S,5S)-2        | (4S,5R)-2 | (4R)-2 |
| 36      | Example 32 | 14               | 80        | 6.5    |
| 37      | Example 33 | 75               | 12        | 13     |
| 38      | Example 34 | 15               | 39        | 46     |
| 39      | Example 35 | 46               | 7         | 46     |

EXAMPLE 40 - 43

Synthesis of compounds according to formula 2 ( $R_8 = \alpha$ -methyl benzyl) by preparing the imine of compound 4a and  $\alpha$ -methyl benzyl amine and subsequent reduction using different hydrides.

- 5 To a solution of (4S)-4 (2.17 g) in THF ( 8 mL) was respectively added  $\alpha$ -methyl benzyl amine (1.45 g) and  $Ti(O^iPr)_4$  (2.98 g) and the mixture was allowed to stir overnight. A fraction of the obtained solution (1.37 g) was placed in a 5 mL vial, degassed by  $N_2$  and subsequently a 1 eq. of the hydride source was introduced. The mixture was allowed to stir for 40 hours at room temperature. For
- 10 HPLC analysis, a sample was prepared by hydrolysis of the reaction mixture (0.2 mL) in 1 N HCl (0.3 mL). Extraction was carried out by a mixture of  $CH_2Cl_2$  (1 mL) and triethylamine (0.1 mL) in the presence of an additional amount of water (1 ml). The  $CH_2Cl_2$  layer was separated and dried over  $Na_2SO_4$  anhydrous, filtrated and the volatiles removed giving a residue containing the product. The obtained residue was
- 15 dissolved in the HPLC-eluent and the solution subjected to HPLC-analysis, see table below.

| Ex. | [H]                | Product                                    | Product (area %) |         |      |
|-----|--------------------|--------------------------------------------|------------------|---------|------|
|     |                    |                                            | (4S,5S)          | (4S,5R) | (4R) |
| 40  | 2M $LiBH_4$ in THF | 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl) | 82               | 12      | 6    |
| 41  | $NaCNBH_3$         | 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl) | 73               | 25      | 2    |
| 42  | $NBu_4BH_4$        | 2 ( $R_8 = (S)$ - $\alpha$ -methyl benzyl) | 72               | 21      | 7    |
| 43  | $BH_3$             | 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl) | 22               | 72      | 5    |

EXAMPLE 44 - 47

- 20 Synthesis of compounds according to formula 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl) by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pt/C in different solvents.

- (R)- $\alpha$ -methyl benzyl amine (0.66 g) and  $Ti(O^iPr)_4$  (2.99 g) was slowly added to a solution of (4S)-4 (2.17 g) in dry THF (6.4 mL) and the mixture was allowed
- 25 to stir for 40 hours at room temperature. The reaction mixture was diluted with a solution of water (1 mL) in THF (50 mL) and after stirring for 1 night the solids were filtrated. Then removal of THF in vacuo at 30°C and the residue was immediately dissolved in EtOAc (35 mL) followed by azeotropic distillation of water giving the crude

product in 2.48 g yield. The crude product was dissolved in MTBE (10mL) and the obtained solution used as such in hydrogenation reactions.

For hydrogenations, the substrate solution in MTBE (1.25 mL) was evaporated to dryness and dissolved in a solvent (5 mL). To the obtained substrate solution, 5 % Pt/C wet (140 mg) was added and the mixture prepared for hydrogenation by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar). The hydrogenations were carried out at room temperature and 25 bar H<sub>2</sub> for 24 hours. According to GC, complete conversion of the imine-derivative was achieved. The stereomeric ratios of product 2 (R<sub>8</sub> = (R)- $\alpha$ -methyl benzyl amine) was determined by HPLC, see table below.

| Example | Solvent | Product 2 (R <sub>8</sub> = (R)- $\alpha$ -methyl benzyl) (area %) |         |      |
|---------|---------|--------------------------------------------------------------------|---------|------|
|         |         | (4S,5S)                                                            | (4S,5R) | (4R) |
| 44      | THF     | 26                                                                 | 61      | 12   |
| 45      | IPA     | 20                                                                 | 66      | 13   |
| 46      | MTBE    | 22                                                                 | 66      | 12   |
| 47      | EtOAc   | 32                                                                 | 55      | 13   |

#### EXAMPLE 48 and 49

Synthesis of compounds according to formula 2 (R<sub>8</sub> = (R)- $\alpha$ -methyl benzyl) by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pt/C in different solvents.

(R)- $\alpha$ -methyl benzyl amine (1.21 g) and Ti(O<sup>i</sup>Pr)<sub>4</sub> (5.98 g) were slowly added to a solution of (4S)-4 (4.34 g) in dry THF (16 mL) and the mixture was allowed to stir for 40 hours at room temperature.

For hydrogenation, the imine-derivative solution in THF (1 mL) was placed in a reaction vessel and after removal of the solvent the residue was dissolved in a solvent (5 mL), then addition of Pt/C wet (140 mg) and the mixture prepared for hydrogenation by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar). The hydrogenations were carried out at 50°C and 25 bar H<sub>2</sub> overnight. According to GC, complete conversion of the imine-derivative was achieved. The stereomeric ratios of compound according to formula 2 (R<sub>8</sub> = (R)- $\alpha$ -methyl benzyl amine) was determined by HPLC, see table below

| Example | solvent | Product 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl amine) (area %) |         |      |
|---------|---------|-------------------------------------------------------------------|---------|------|
|         |         | (4S,5S)                                                           | (4S,5R) | (4R) |
| 48      | MeOH    | 25                                                                | 61      | 15   |
| 49      | IPA     | 24                                                                | 61      | 15   |

EXAMPLE 50 and 51

Synthesis of compounds according to formula 2 ( $R_8 = H$ ) by preparing the imine of compound 4a and  $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C.

- 5 A solution of ketone (4S)-4 (1.09 g), the  $\alpha$ -methyl benzyl amine (363 mg) and triethyl amine (1.01 g) in ether (12 mL) was degassed by  $N_2$ . Then, slow addition of 1 M of  $TiCl_4$  in toluene (1.5 mL) at room temperature and the mixture allowed to stir for 3 hour. From the obtained reaction mixture, 1.2 mL was diluted by ether (2 mL) and extracted with a  $NaHCO_3$  solution in water (3 x 1 mL), the ether layer
- 10 separated, dried over  $Na_2SO_4$ , filtrated and the ether removed. The obtained residue was dissolved in methanol and the obtained solution prepared for hydrogenation by 5 cycles of  $N_2$  (3 bar) and 5 cycles of  $H_2$  (25 bar). The hydrogenation was carried out in the presence of wet 10 % Pd/C (80 mg) at 50°C and 25 bar of  $H_2$  for 2 hours. After hydrogenation, a sample was filtrated and the stereomeric ratios of compound
- 15 according to formula 2 ( $R_8 = H$ ) was determined by GC-analysis, see table below

| Example | amine                              | Product 2 ( $R_8 = H$ ) (area %) |         |      |
|---------|------------------------------------|----------------------------------|---------|------|
|         |                                    | (4S,5S)                          | (4S,5R) | (4R) |
| 50      | (R)- $\alpha$ -Methyl benzyl amine | 95                               | 5       |      |
| 51      | (S)- $\alpha$ -Methyl benzyl amine | 63                               | 32      | 5    |

EXAMPLE 52

- Synthesis of compound according to formula 2 ( $R_8 = H$ ) by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C in isopropanol.
- 20

A solution of ketone (4S)-4 (434 mg) in THF (1.6 mL) was degassed by  $N_2$ . Then slow addition of (R)- $\alpha$ -methyl benzyl amine (308  $\mu$ L) and  $Ti(O^iPr)_4$  (0.63 mL) and the reaction mixture allowed to stir for 24 hours.

- 25 The imine product was isolated by means of column chromatography. For this purpose, a column was charged with  $SiO_2$  and heptane (10 mL). In the clear

heptane phase, 1 mL of the reaction mixture was dissolved and eluted on top of the SiO<sub>2</sub>. The elution was continued by a mixture of EtOAc/heptane and 3 fractions of 10 mL were collected. Fraction 1 and 2 were combined and residual amounts of TiO<sub>2</sub> filtrated following by removal of the solvent in vacuo at 30°C. The residue (0.14 g) was dissolved in isopropanol and according to GC-analysis, the solution was free from (R)- $\alpha$ -Methyl benzyl amine.

For hydrogenation, 5 mL of the isopropanol solution was placed in a reaction vessel and conditioned by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar). The hydrogenation was conducted in the presence of dry 5 % Pd/C (20 mg) at 50°C and 25 bar of H<sub>2</sub> for 20 hours giving the compound according to formula 2 (R<sub>8</sub> = H) in stereomeric ratios of (4S,5S)-2 (74 area %), (4S,5R)-2 (6 area %), (4R)-2 (20 area %) according to GC-analysis.

#### EXAMPLE 53

Synthesis of compound according to formula 2 (R<sub>8</sub> = H) by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C in MTBE.

(R)- $\alpha$ -methyl benzyl amine (1.30 g) and Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (5.98 g) were slowly added to a solution of ketone (4S)-4 (4.34 g) in dry THF (13 mL) and the mixture was allowed to stir for 40 hours at room temperature. The reaction mixture was slowly added to a vigorous stirring solution of water (2 mL) and triethyl amine (305 mg) in THF (100 mL) and after 0.75 hours the reaction mixture was filtrated. The volatiles were removed in vacuo at 30°C and the obtained residue dissolved in EtOAc (85 mL) followed by azeotropic distillation of residual amounts of water under reduced pressure at 30°C. The obtained residue was dissolved in MTBE (20 mL).

For hydrogenation, the MTBE solution (1 mL) was placed in a reaction vessel and the MTBE removed. The obtained residue was dissolved in THF (5 mL) followed by the addition of dry 5 % Pd/C (200 mg). After conditioning the solution by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar), the reaction mixture was subjected to hydrogenation overnight at 50°C and 25 bar of H<sub>2</sub> giving compound according to formula 2 (R<sub>8</sub> = H) in stereomeric ratios of (4S,5S)-2 (72 area %), (4S,5R)-2 (9.7 area %), (4R)-2 (18.5 area %) according to HPLC-analysis.

EXAMPLE 54

Synthesis of compound according to formula 2 ( $R_8 = H$ ) by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C in THF.

5                      Stock solution of imine compound: A solution of the imine compound was prepared by slow addition of (R)- $\alpha$ -methyl benzyl amine (3.63 g) and  $Ti(O^iPr)_4$  (9.38 g) to a solution of (4S)-4 (13.02 g) in dry THF (50 mL). The mixture was allowed to stir at room temperature and monitored by GC-analysis until complete conversion.

10                      1.18 g of this imine solution was treated with water (20.6 mg) for 0.25 h at 50°C and the precipitate removed by filtration at room temperature. The clear THF solution was diluted by THF to a total volume of 5 mL and after addition of dry 5 % Pd/C (200 mg) conditioned for hydrogenation by 5 cycles of  $N_2$  (3 bar) and 5 cycles of  $H_2$  (25 bar). The mixture was subjected to hydrogenation at 50°C and 25 bar of  $H_2$  to full conversion of the starting material giving compound according to formula 2 ( $R_8 = H$ )  
15 in stereomeric ratios of (4S,5S)-2 (78 area %), (4S,5R)-2 (9.5 area %), (4R)-2 A (11.9 area %) according to HPLC-analysis.

EXAMPLE 55

20                      Synthesis of compound according to formula 2 by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C and LiH as an additive.

                         1.18 g of the imine solution of example 54 was placed in a reaction vessel and diluted with THF anhydrous (3.3 g) under an atmosphere of  $N_2$ . Then, LiH (8 mg) and dry 5 % Pd/C (200 mg) was added and after conditioning by 5 cycles of  $N_2$   
25 (3 bar) and 5 cycles of  $H_2$  (25 bar) the mixture was subjected for hydrogenation at 50°C and 25 bar of  $H_2$  for 20 hours giving, according to GC, a mixture of the compound according to formula 2 ( $R_8 = H$ ) (23 area %) and compound according to formula 2 ( $R_8 = (R)$ - $\alpha$ -methyl benzyl amine) (49 area %). According to HPLC, the optical purity of the compound according to formula 2 ( $R_8 = H$ ) was as follows: (4S,5S) (90 area %),  
30 (4S,5R) (4.8 area %), (4R) (5.5 area %).

EXAMPLE 56

Synthesis of compound according to formula 2 by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd(OH)<sub>2</sub>/C.

11.8 g of the imine solution of example 54 was placed in a reaction vessel and diluted with THF anhydrous (33 g) and heated to 50°C. To the obtained warm solution, water (200  $\mu$ L) was added and the mixture stirred for 0.25 hours. Then, the mixture was cooled to room temperature followed by filtration of the formed precipitate. From the obtained clear solution, 4.5 g was placed in a reaction vessel containing dry 20 % Pd(OH)<sub>2</sub>/C (75 mg). The reaction mixture was degassed by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar) and the hydrogenation was carried out at 50°C and 25 bar of H<sub>2</sub> for 38 hours giving complete conversion according to GC. According to HPLC, the compound according to formula 2 (R<sub>8</sub> = H) was obtained in stereomeric ratios of (4S,5S)-2 (53 area %), (4S,5R)-2 (22 area %), (4R)-2 (24 area %).

EXAMPLE 57

Large scale synthesis of compound according to formula 2 by preparing the imine of compound 4a and (R)- $\alpha$ -methyl benzyl amine and subsequent hydrogenation using Pd/C.

23.7 g of the imine solution of example 54 was placed in a reaction vessel and diluted with THF (52 g) and heated to 50°C. To the obtained warm solution, sat. NaHCO<sub>3</sub> (400  $\mu$ L) was added and the mixture stirred for 0.25 hours. To the heterogeneous mixture, Na<sub>2</sub>SO<sub>4</sub> anhydrous (10 g) and active carbon (6.9 g) was respectively added under vigorous stirring. Then, the mixture was cooled to room temperature followed by filtration of the reaction mixture under N<sub>2</sub> and the wet cake was washed by THF (4 x 8 mL). The obtained clear solution, was placed in the autoclave containing dry 5 % Pd/C (4 g). The autoclave was degassed by 5 cycles of N<sub>2</sub> (3 bar) and 5 cycles of H<sub>2</sub> (25 bar) and the hydrogenation was carried out at 50°C and 25 bar of H<sub>2</sub> for 15 hours giving complete conversion according to GC.

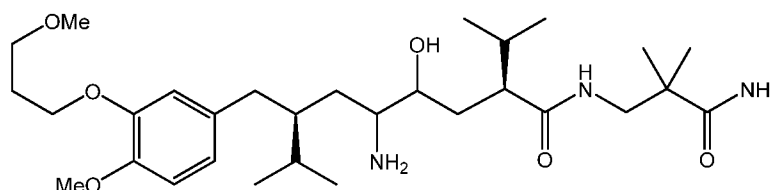
The product was isolated by filtration of the catalyst and subsequent removal of the solvent under reduced pressure. The residue was treated with 1 N HCl (20 mL) and water (50 mL) and the water layer extracted by heptane (3 x 50 mL). The water layer was separated and the pH was increased to 13 by the addition of 32 % NaOH (~ 3 g) in the presence of MTBE (40 mL) under vigorous stirring. The MTBE layer was separated followed by an additional extraction of the remaining water layer

with MTBE (40 mL). The combined MTBE layers were dried over  $\text{Na}_2\text{SO}_4$  anhydrous, filtrated and the MTBE evaporated giving the compound according to formula 2 ( $R_8 = \text{H}$ ) in stereomeric ratios of (4S,5S)-2 (82 area %), (4S,5R)-2 (8.3 area %) and (4R)-2 (10.2 area %) according to GC.

5

#### EXAMPLE 58

Preparation of compound according to formula 13 with  $X = \text{NHR}_5$ , obtained by reacting a compound according to formula 2 ( $R_8 = \text{H}$ ) with 3-amino-2,2-dimethylpropanamide.



10

A round bottom flask was charged with compound according to formula 2 ( $R_8 = \text{H}$ ) (8.8 g), 3-amino-2,2-dimethylpropanamide (7.08 g) and triethylamine (3.50 g) and the viscous mixture was stirred at reflux in the presence of MTBE in order to obtain a homogeneous mixture. Under slow heating to  $65^\circ\text{C}$ , the MTBE was removed by distillation and the remaining residue allowed to stir for 20 hours at  $65^\circ\text{C}$  in the presence of 2-hydroxypyridine (1.94 g). At complete conversion of compound according to formula 2, the reaction mixture was dissolved in MTBE (71 mL) and the MTBE layer extracted by 5 % NaCl in water (2 x 71 mL). The combined water layers were washed by MTBE (3 X 71 mL) and the combined MTBE layers (total of 4 fractions) dried over  $\text{Na}_2\text{SO}_4$  anhydrous, filtrated and the MTBE evaporated in vacuo giving the crude product in 10.29 g. The crude product was dissolved in MTBE (71 mL) followed by extraction with 1 N HCl (15 mL) and water (2 x 15 mL). The combined water layers washed with MTBE (71 mL) and the combined MTBE layers washed with water (2 x 14 mL). Under cooling and vigorous stirring, the pH of the combined water layers was adjusted to pH 11 by 32 % NaOH in the presence of MTBE (71 mL), MTBE separated and the remaining basic water layer washed with MTBE (5 x 71 mL). The combined MTBE layers were dried over  $\text{Na}_2\text{SO}_4$  anhydrous, filtrated and removal of MTBE in vacuo affording compound according to formula 13 in with stereomeric ratios of (4S,5S)-13 (71 area %) and other stereoisomers of 13 (29 area %) according to HPLC.

30

EXAMPLE 59

Purification of compound according to formula 13, obtained in example 58, by crystallization with fumaric acid.

A solution of the compound according to formula 13, as obtained in example 58 (1.48 g), and fumaric acid (155.4 mg) in EtOH (15 mL) were heated to 40°C and subsequently the ethanol removed by distillation under reduced pressure to a total weight of 3.21 g. The concentrated ethanol solution was dissolved in CH<sub>3</sub>CN (37 mL) at 37°C. The solution slowly was cooled to room temperature and seeded by a few crystals of aliskiren · fumarate salt and the mixture was allowed to stir for 19 hours. The precipitated aliskiren · fumarate salt was filtrated and dried giving the product.

According to <sup>1</sup>H NMR the compound is pure besides a trace of acetonitril left, see Figure 1.

The all (S) purity of the aliskiren fumarate-salt (2.8 g) obtained as such was 93 area % according to HPLC.

EXAMPLE 60

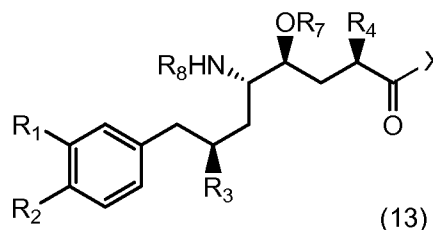
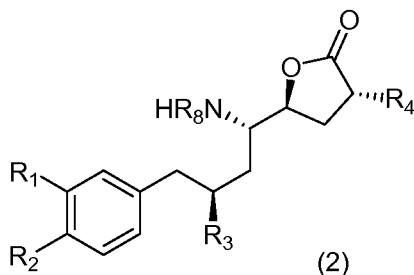
Purification of compound according to formula 13, obtained in example 59, by double re-crystallization

The acetonitril containing product 7 · fumarate-salt (2.8 g) obtained from first crystallisation was dissolved in ethanol (40 mL) and the total amount reduced to 5.8 g by partial distillation of ethanol. The concentrated ethanol solution was dissolved in CH<sub>3</sub>CN (80 mL). The solution was slowly cooled to room temperature and seeded by a few crystals of the aliskiren · fumarate-salt and the mixture was allowed to stir for 19 hours. The precipitated aliskiren · fumarate-salt was filtrated and dried giving the product in 2.4 g yield in a stereomeric purity of 98.2% of (4S,5S)-Aliskiren fumarate salt.(98.2 area %).

This isolated aliskiren · fumarate-salt was redissolved in ethanol and the ethanol partially distilled to a total amount of of the residue of 5.0 g. The obtained residue was dissolved in CH<sub>3</sub>CN (80mL) and cooled to room temperature. At room temperature, the solution was seeded by a few crystals of Aliskiren · fumarate-salt and the mixture was allowed to stir for 5 hours. The precipitated Aliskiren · fumarate-salt was filtrated and dried giving the product in 2.2 g yield in a stereomeric purity of (4S,5S)-7 (98.8 area %), according to HPLC. From the isolated product, a <sup>1</sup>H NMR spectrum was recorded, see Figure 2.

CLAIMS

1. Process for the preparation of a compound according to formula (13) or its ring-closed form according to formula (2), or a mixture thereof,



5

wherein  $R_1$  being selected from the group consisting of F, Cl, Br, I,  $C_{1-6}$ halogenalkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy- $C_{1-6}$ alkyloxy, and  $C_{1-6}$ alkoxy- $C_{1-6}$ alkyl;  $R_2$  being selected from the group consisting of F, Cl, Br, I,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy;

10

$R_1$  and  $R_2$  may be linked together to form a ring structure;

$R_3$  and  $R_4$  each independently being branched  $C_{3-6}$ alkyl;

X stands for  $NHR_5$  or  $OR_6$  wherein

15

$R_5$  is  $C_{1-12}$ cycloalkyl,  $C_{1-12}$ alkyl,  $C_{1-12}$ hydroxyalkyl,  $C_{1-6}$ alkoxy- $C_{1-6}$ alkyl,  $C_{1-6}$ alkanoyloxy- $C_{1-6}$ alkyl,  $C_{1-12}$ aminoalkyl,  $C_{1-6}$ alkylamino- $C_{1-6}$ alkyl,  $C_{1-6}$ dialkylamino- $C_{1-6}$ alkyl,  $C_{1-6}$ alkanoylamino- $C_{1-6}$ alkyl,  $HO-(O)C-C_{1-12}$ alkyl,  $C_{1-6}$ alkyl- $O-(O)C-C_{1-6}$ alkyl,  $H_2N-C(O)-C_{1-12}$ alkyl,  $C_{1-6}$ alkyl- $HN-C(O)-C_{1-6}$ alkyl,  $(C_{1-6}alkyl)_2-N-C(O)-C_{1-6}alkyl$ ; saturated, unsaturated, or partially saturated  $C_{1-12}$ heterocyclyl bonded via a carbon atom, and which heterocyclyl is optionally substituted one or more times by  $C_{1-6}$ alkyl, trifluoromethyl, nitro, amino, *N*-mono- or *N,N*-di- $C_{1-6}$ alkylated amino,  $C_{1-6}$ alkanoyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxycarbonylamino,  $C_{0-6}$ alkylcarbonylamino,  $C_{1-6}$ alkylcarbonyloxy,  $C_{1-12}$ aryl, *N*-mono or *N,N*-di- $C_{1-6}$ alkylated carbamoyl, optionally esterified carboxyl, cyano, halogen, halo- $C_{1-6}$ alkoxy, halo- $C_{1-6}$ alkyl,  $C_{1-12}$ heteroaryl, saturated, unsaturated or partially saturated  $C_{1-6}$ heterocyclyl, hydroxyl, nitro;

20

25

and  $R_6$  represents H, or optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl;

$R_7$  represents H, or is an O-protecting group;

and wherein any two of  $R_7$ ,  $R_8$ , or X are optionally linked together to form a ring structure;

30

$R_8$  denotes H; optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl; optionally substituted  $C(O)C_{1-6}$ alkyl; optionally substituted  $C(O)OC_{1-6}$ alkyl; optionally substituted  $C(O)NHC_{1-6}$ alkyl; or optionally substituted  $C(O)N(C_{1-6}alkyl)_2$ ; or  $R_8$  denotes

-NHR<sub>9</sub>,

-S(O)<sub>2</sub>R<sub>9</sub>; SOR<sub>9</sub>; S(O)<sub>3</sub>R<sub>9</sub>; S(O)<sub>2</sub>N(R<sub>9</sub>);

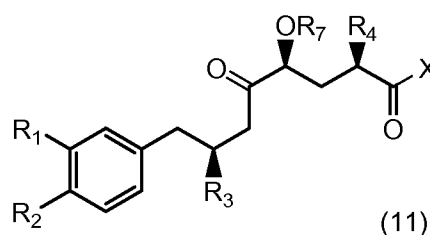
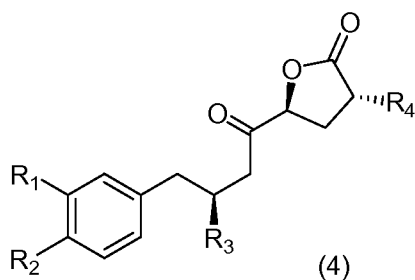
-P(O)(R<sub>9</sub>)<sub>2</sub>

or  $R_8$  stands for (R<sub>9</sub>)<sub>2</sub>Y with Y being an anion such as acetate, or halogen;

and wherein each R<sub>9</sub> independently represents H, optionally substituted  $C_{1-12}$ alkyl,

optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl; comprising the following steps,

a) reacting a compound according to formula (11), or its ring-closed form according to formula (4), or a mixture thereof,



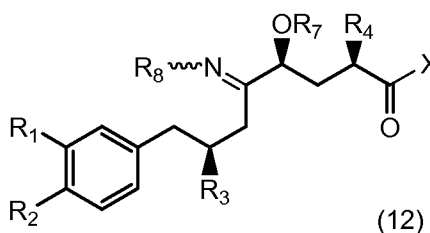
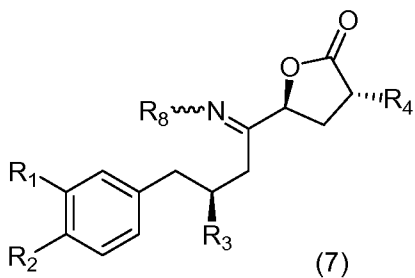
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>7</sub> and X are each as described above for formula (2) and (13)

with a compound according to formula (5)

$R_8-NH_2$  (5)

wherein  $R_8$  is as described above for formula (2) and (13)

which reaction results in a compound according to formula (7) or a compound according to formula (12) or a mixture thereof,



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub> and X are each as described above for formula (2) and (13)

b) further reacting compound according to formula (7) or (12) or a mixture

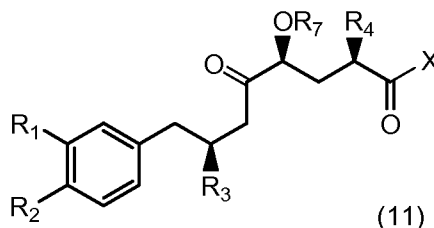
thereof, in the presence of a reducing reagent, and optionally in the presence of a catalyst, and optionally in the presence of one or more additives,

which reaction results in the formation of compound according to formula (2) or formula (13) or a mixture thereof.

- 5 2. A process according to claim 1, wherein the compounds according to formula (7) or formula (12) are not isolated from the reaction mixture before carrying out step b).
3. A process according to any one of claims 1-2, wherein step b) is performed in  
10 the presence of a catalyst and wherein said catalyst is a transition metal based catalyst.
4. A process for the preparation of a compound according to formula (13) or its ring-closed form according to formula (2), or a mixture thereof, comprising reacting the compound according to formula (11), or its ring-closed form  
15 according to formula (4), or mixture thereof, with a compound according to formula (5) in the presence of a reducing agent and a catalyst.
5. A process according to claim 4, wherein the reducing agent is selected from the group of molecular hydrogen or a hydrogen donating compound; and wherein when the molecular hydrogen is used it is used in the presence of a  
20 transition metal catalyst and when a hydrogen donating compound is used it is used optionally in the presence of a catalyst.
6. A process according to claim 4 or 5 wherein said catalyst is an enzyme, preferably an aminotransferase.
7. A process according to any one of claims 4-6 wherein compound according to  
25 formula (5) is also the reducing agent.
8. Process according to any one of claims 1-7, wherein X in the compound according to formula (11), and also in resulting compounds according to formula (12), if it is formed, and the compound according to formula (13), respectively, stands for  $OR_6$  and wherein  $R_6$  is as described in Claim 1.
- 30 9. Process according to any one of claims 1-7, wherein X in the compound according to formula (11), and also in resulting compounds according to formula (12), if it is formed, and the compound according to formula (13), respectively, stands for  $NHR_5$ , and wherein  $R_5$  is as described in Claim 1.
10. Process for the preparation of a compound according to formula (13) or any  
35 pharmaceutically acceptable salt thereof, wherein X represent  $NHR_5$ , wherein

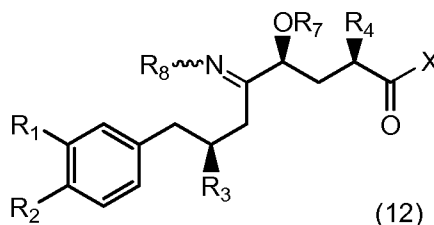
the process comprises a process according to any one of claims 1-9 and wherein  $R_5$  is as described in claim 1.

11. A compound according to formula (11)



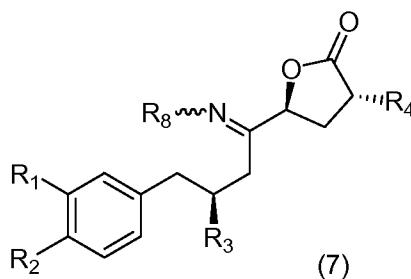
- 5 wherein all the R-groups are defined as in Claim 1, and wherein X is selected from the group of  $OR_6$  and  $NHR_5$ , and wherein  $R_6$  and  $R_5$  are as described in Claim 1.

12. A compound according to formula (12)



- 10 wherein all the R-groups are defined as in Claim 1 and wherein X is selected from the group of  $OR_6$  and  $NHR_5$ , and wherein  $R_6$  and  $R_5$  are as described in Claim 1.

- 13 A compound according to formula (7)



- 15 wherein  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$ , are defined as in Claim 1, and wherein  $R_8$  denotes H; optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl; optionally substituted  $C(O)C_{1-6}$ alkyl; optionally substituted  $C(O)OC_{1-6}$ alkyl; optionally substituted  $C(O)NHC_{1-6}$ alkyl; or optionally substituted  $C(O)N(C_{1-6}alkyl)_2$ ; or  $R_8$  denotes
- 20 - $NHR_9$ ,  
 - $S(O)_2R_9$ ;  $SOR_9$ ;  $S(O)_3R_9$ ;  $S(O)_2N(R_9)$ ;  
 - $P(O)(R_9)_2$ ;

or  $R_8$  stands for  $(R_9)_2Y$  with Y being an anion such as acetate, or halogen;  
and wherein each  $R_9$  independently represents H, optionally substituted  $C_{1-12}$ alkyl, optionally substituted  $C_{1-12}$ alkylaryl, or optionally substituted  $C_{1-12}$ aryl.

14. Process according to any of claims 1-10, wherein the compound according to  
5 formula (2) is further reacted with 3-amino-2,2-dimethylpropanamide to obtain  
a compound according to formula (13) with  $X=NHR_5$ , or pharmaceutically  
acceptable salts thereof.
15. Process according to any of claims 1-10 and 14, wherein the compound  
according to formula (2) or formula (13) is further reacted to obtain  
10 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-  
diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide or any  
pharmaceutically acceptable salt thereof.