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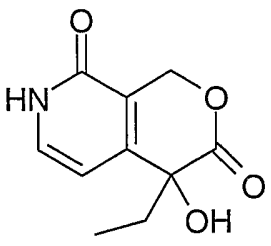
(54) Title: NEW SYNTHESIS OF A CAMPTOTHECIN SUBUNIT

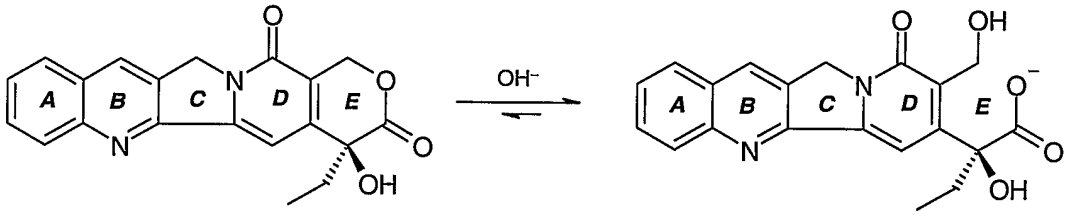


(1)

(57) Abstract: The present invention provides a process for the manufacture of the compound of formula (1) which is a key intermediate in the manufacture of camptothecin (CPT). This compound continues to serve as attractive and promising lead structure for the development of new anti-cancer drugs.

New synthesis of a camptothecin subunit

The alkaloid camptothecin (CPT, 3), which has been isolated in 1958 by Wani and Wall from the Chinese tree *Camptotheca accuminata*, shows potent antiproliferative activity (M. E. Wall in *Chronicles of Drug Discovery*, D. Lednicer (Ed.), Am. Chem. Soc.: Washington D.C., 1993; *Vol. 3*, p. 327). The structure of the pentacyclic skeleton, which was also determined by Wani and Wall eight years after its discovery, contains a highly electrophilic α-hydroxy-δ-lactone ring (ring E, scheme 1), which contains the only stereocenter in form of a tertiary alcohol.



CPT (3) (4)

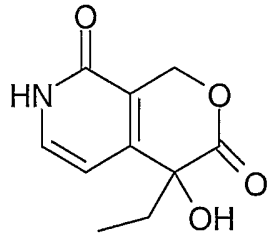
scheme 1

Despite its shortcomings, due to rapid hydrolysis in basic and neutral media towards the open chain carboxylate form (4, scheme 1), CPT continues to serve as an attractive and promising lead structure for the development of new anti-cancer drugs (see for example C. J. Thomas, N. J. Rahier, S. M. Hecht, *Bioorg. Med. Chem.* 2004, *12*, 1585–1604).

Despite numerous attempts to develop a practical synthesis of camptothecin and derivatives thereof, up to now no really efficient synthesis is available. This is mainly because the currently known synthetic approaches suffer either from very low yields, expensive or commercially not available reagents or highly toxic reagents which may cause health hazard and environmental problems. Another major drawback of most current synthesis routes is an extensive need for column chromatographies during the reaction sequence.

The present invention addresses this problem by providing a novel synthesis route for the bicyclic "DE-Fragment" (s. scheme 1 for nomenclature), a key intermediate in the manufacture of CPT and derivatives thereof. The synthesis according to the present invention is based on simple, easily available and harmless starting materials and reagents, and uses straightforward carbonyl chemistry. Furthermore the synthesis according to the present invention avoids laborious chromatography and therefore provides improved yields of the desired product.

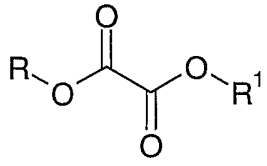
In particular, the present invention provides a process for the manufacture of the compound of formula (1)



(1),

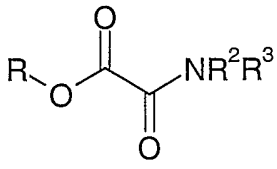
wherein

a) a compound of formula (I)



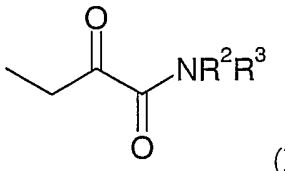
(I)

is reacted in the presence of an amine of formula HNR^2R^3 to give a compound of formula (II)

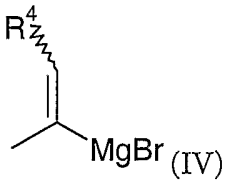


(II);

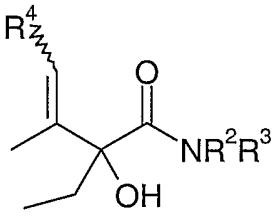
b) said compound of formula (II) is further reacted in the presence of an ethyl-base to give a compound of formula (III),


(III);

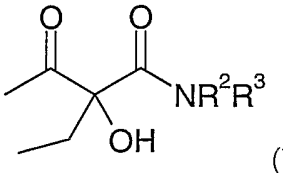
c) said compound of formula (III) is further reacted with a compound of formula (IV)


(IV)

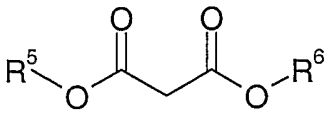
to give a compound of formula (V)


(V);

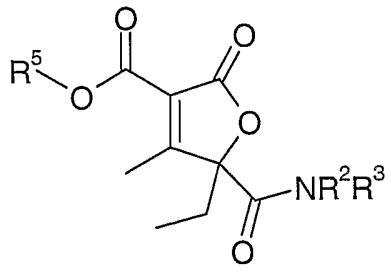
d) said compound of formula (V) is further reacted in the presence of ozone to give a compound of formula (VI)


(VI);

e) said compound of formula (VI) is further reacted in the presence of a compound of formula (VII)

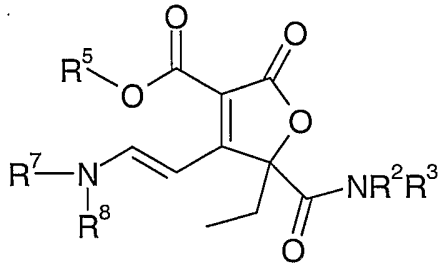

(VII),

and a base, to give a compound of formula (VIII)



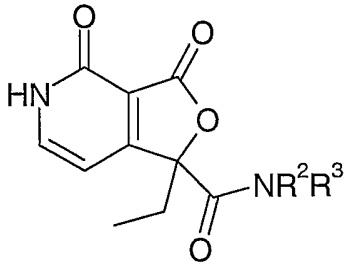
(VIII);

f) said compound of formula (VIII) is further reacted in the presence of di(C_1-C_6)-alkylformamide di(C_1-C_6)-alkylacetal or a compound of the formula $(R^7R^8N)_3$-CH to give a compound of formula (IX)



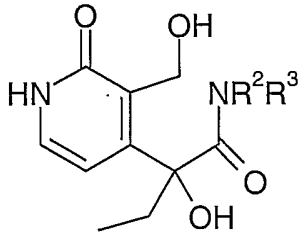
(IX)

g) said compound of formula (IX) is further reacted in the presence of ammonium acetate to give a compound of formula (X)



(X);

h) said compound of formula (X) is further reacted in the presence of alkali metal borohydrides and rare earth metal salts to give a compound of formula (XI)



(XI); and

j) said compound of formula (XI) is further reacted in the presence of concentrated mineral acids to give the compound of formula (1);

wherein

R, R^1, R^7 and R^8 independently from each other are (C_1-C_6)-alkyl;

R^2, R^3 and R^4 independently represent (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl; and

R^5 and R^6 are both either the same or different (C_1-C_6)-alkyl, or an aryl group.

The term "(C_1-C_6)-alkyl" as used herein means a straight chain or branched hydrocarbon, having from one to six, preferably from one to four carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, 2-butyl, *tert*-butyl and the like.

The term "(C_3-C_{12})-alkyl" as used herein means a straight chain, branched, mono-, di- or tri-cyclic saturated hydrocarbon, having from three to twelve, preferably from three to ten carbon atoms. Preferably said "(C_3-C_{12})-alkyl" is attached via a tertiary carbon atom. Preferred examples are *tert*-butyl or adamantyl.

The term (C_3-C_7)-cycloalkyl as used herein means a monocyclic, saturated hydrocarbon, having from three to seven, preferably five or six carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "aryl" as used herein means a mono-, bi- or tricyclic, aromatic hydrocarbon, having from six to fourteen, preferably from six to ten, carbon atoms such as phenyl, biphenyl, naphthyl or antracenyl.

The term "ethyl-base" as used herein refers to basic organometal compounds, such as for example *Grignard-reagents* (Et MgHal), wherein "Hal" means halide, preferably Et MgBr; or ethyl-alkali-metal compounds such as EtLi; or mixed organometal compounds such as Et_3AlLi or Et_3ZnLi.

The "base", as mentioned under reaction step e) above means preferably an alkali-metal carbonate or –hydride, such as Na_2CO_3, K_2CO_3 or Cs_2CO_3; or NaH or KH. The use of Cs_2CO_3 is especially preferred.

The term "alkali metal borohydrides" as used in reaction step h) above, means preferably $LiBH_4$ or $NaBH_4$. The use of $NaBH_4$ is especially preferred.

The term "rare earth metal salts" as used in reaction step h) above, means conventional salts of rare earth metals, preferably halides such as chlorides and bromides; or triflates. Especially preferred is the use of $EuCl_3$ or $CeCl_3$.

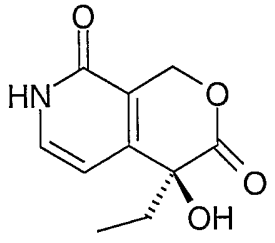
The term "mineral acids" as used under reaction step j) above is well known to the skilled artisan and represents inorganic acids, such as HCl, HBr, HNO_3, H_2SO_4 and the like. According to the present invention the use of HCl is especially preferred.

The symbol  or  means that the group R^4 or $R^{4'}$, when attached to a double bond, may be present in (Z)- or (E)-configuration.

The term "alkali metal- or earth alkali metal hydroxide", as mentioned herein under reaction step cc) means LiOH, NaOH, KOH, $Ca(OH)_2$ or $Ba(OH)_2$. The use of LiOH is especially preferred.

The term "tertiary amine" as used herein under reaction step dd) is well known to the skilled artisan and means a basic amine, preferably a trialkyl amine. Examples of such tertiary amines are ethyl di-isoproylamine, triethyl amine and the like.

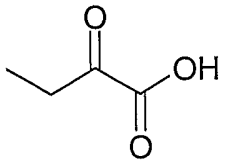
A preferred embodiment of the present invention is the process as described above, for the manufacture of the compound of formula (1a)



(1a),

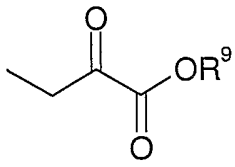
wherein

aa) the compound of formula (2)



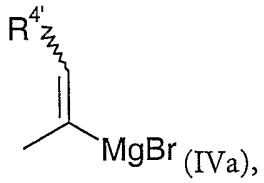
(2),

is reacted in the presence of a chiral secondary alcohol of the formula R^9OH to give an ester of formula (IIIa)



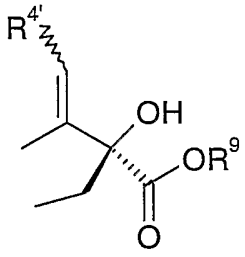
(IIIa);

bb) said ester of formula (IIIa) is further reacted with a compound of formula (IVa)



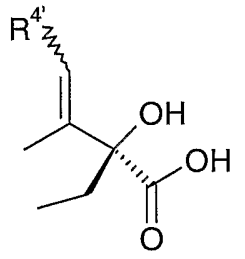
(IVa),

to give a compound of formula (Va)



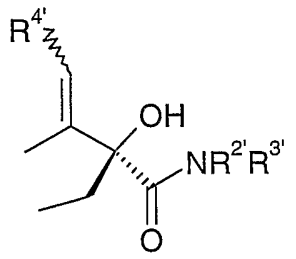
(Va);

cc) ester cleavage from a compound of formula (Va) is carried out in the presence of an alkali metal- or earth alkali metal hydroxide, optionally in the presence of hydrogen peroxide, to give the compound of formula (Vb)



(Vb);

dd) said compound of formula (Vb) is further reacted in the presence of a tertiary amine and thionyl chloride, prior to addition of an amine of formula $HNR^{2'}R^{3'}$ to give a compound of formula (Vc)



(Vc); and

further reaction is carried out according to the reaction steps d) to j) as described hereinbefore, to give the compound of formula (1a),

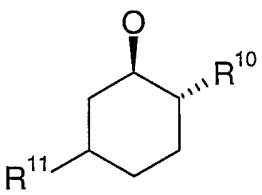
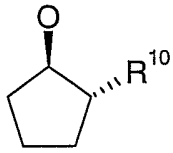
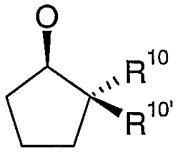
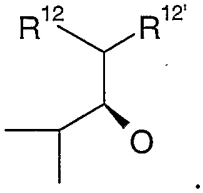
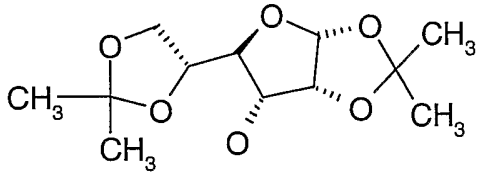
wherein

$R^{2'}$ has the meaning of R^2 as defined above;

$R^{3'}$ has the meaning of R^3 as defined above;

$R^{4'}$ has the meaning of R^4 as defined above;

$-OR^9$ represents

or ; and

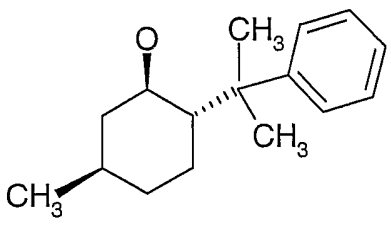
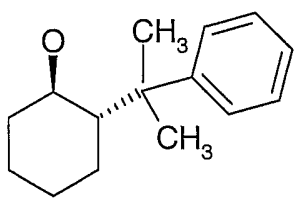
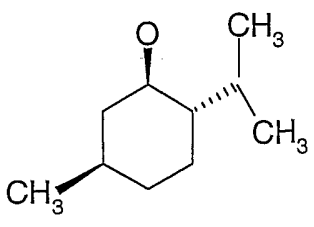
R^{10} and $R^{10'}$ independently represents an aryl group, or a $(C_3\text{-}C_{12})$alkyl group, which is unsubstituted or substituted by phenyl;

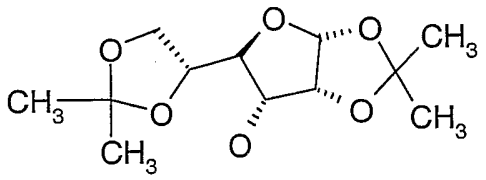
R^{11} is hydrogen or $(C_1\text{-}C_6)$alkyl; and

R^{12} and $R^{12'}$ independently represent an aryl group.

The transformation of the compounds of formula (Va) into the compounds of formula (Vc) via the compounds of formula (Vb) as described above, can also be carried out in a one step reaction, directly from the compounds of formula (Va) to the compounds of formula (Vc) without the intermediate of formula (Vb). Such modification of the reaction sequence as described above is within the ordinary skill of an organic chemist.

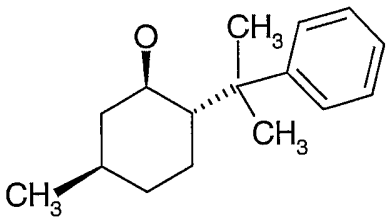
Another preferred embodiment of the present invention is the process as described above, wherein $-OR^9$ represents

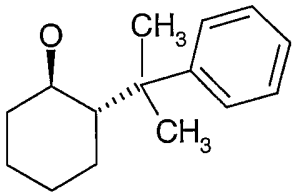


; or .

Another preferred embodiment of the present invention is the process as described above, wherein $-OR^9$ represents



or



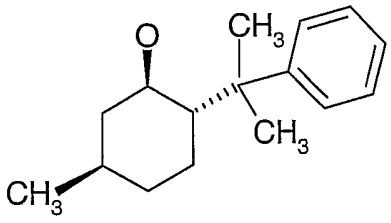
.

Still another preferred embodiment of the present invention is the process as described above, wherein

$R^{2'}$ and $R^{3'}$ are ethyl;

$R^{4'}$ is hydrogen or methyl; and

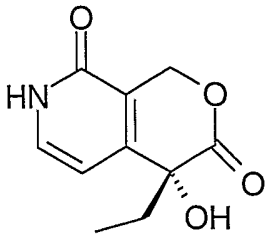
$-OR^9$ is



.

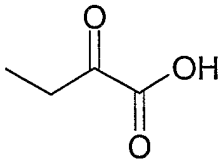
The asymmetric reaction as described above can also be carried out using the enantiomers of the alcohols R^9OH, which are designated $R^{18}OH$ hereinafter, to furnish the enantiomer of the compound of formula (1a) which is designated 1b hereinafter.

Therefore, still another embodiment of the present invention is the process as described above, for the manufacture of the compound of formula (1b)

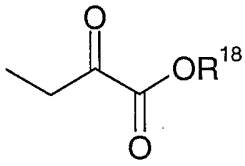

(1b),

wherein

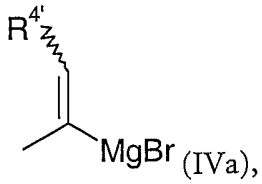
aaa) the compound of formula (2)


(2),

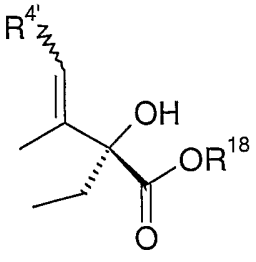
is reacted in the presence of a chiral secondary alcohol of the formula $R^{18}OH$ to give an ester of formula (IIIb)


(IIIb);

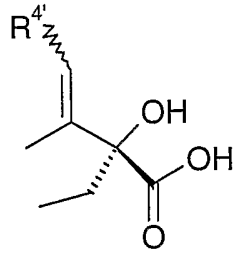
bbb) said ester of formula (IIIb) is further reacted with a compound of formula (IVa) as defined above


(IVa),

to give a compound of formula (Vd)

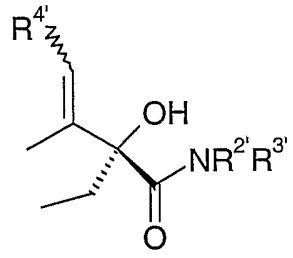

(Vd);

ccc) ester cleavage from a compound of formula (Vd) is carried out in the presence of an alkali metal- or earth alkali metal hydroxide, optionally in the presence of hydrogen peroxide, to give the compound of formula (Ve)



(Ve);

ddd) said compound of formula (Ve) is further reacted in the presence of a tertiary amine and thionyl chloride, prior to addition of an amine of formula $HNR^{2'}R^{3'}$ as defined above to give a compound of formula (Vf)



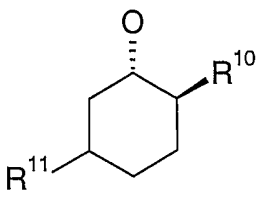
(Vf); and

further reaction is carried out according to the reaction steps d) to j) as described hereinbefore, to give the compound of formula (1b),

wherein

$R^{2'}$, $R^{3'}$, $R^{4'}$ R^{10}, $R^{10'}$, R^{11}, R^{12} and $R^{12'}$ have the meanings as defined above; and

$-OR^{18}$ represents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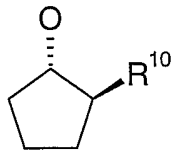
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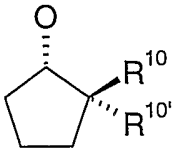
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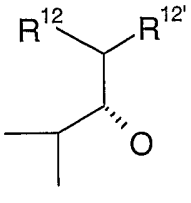
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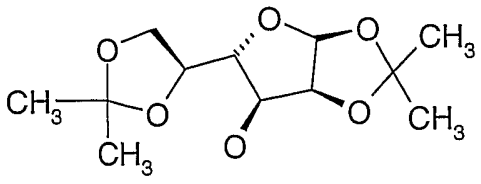
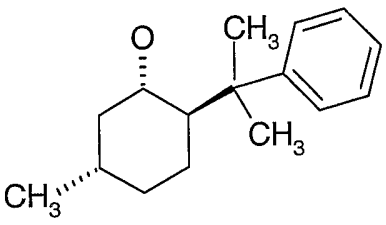


or .

The transformation of the compounds of formula (Vd) into the compounds of formula (Vf) via the compounds of formula (Ve) as described above, can also be carried out in a one step reaction, directly from the compounds of formula (Vd) to the compounds of formula (Vf) without the intermediate of formula (Ve). Such modification of the reaction sequence as described above is within the ordinary skill of an organic chemist.

Another preferred embodiment of the present invention is the process as described above, wherein $-OR^{18}$ represents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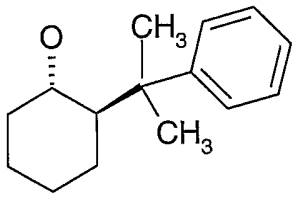
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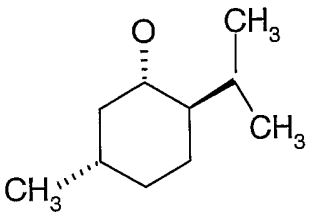
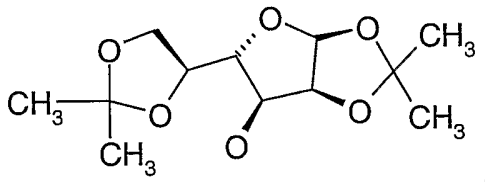
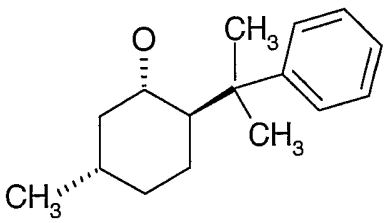
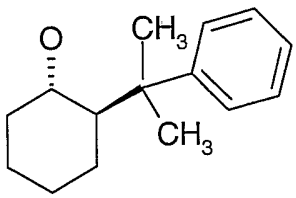



; or .

Another preferred embodiment of the present invention is the process as described above, wherein $-OR^{18}$ represents


or

.

Another preferred embodiment of the present invention is the process as described above, wherein

R, R^1, R^2, R^3, R^5 and R^6 are ethyl; and

R^4, R^7 and R^8 are methyl.

Still another preferred embodiment of the present invention is the process as described above, wherein the ethyl-base of reaction step b) is ethyl magnesium bromide.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step b) is carried out in diethyl ether at temperatures between -30 °C and 0 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step c) is carried out in di-isopropyl ether at temperatures between -78 °C and -40 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step d) is carried out in the presence of dimethyl sulfide and at a temperature between -90 °C and -50 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step e) is carried out in ethanol and in the presence of cesium carbonate at temperatures between 0 °C and 40 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step f) is carried out in dimethylformamide and in the presence of dimethylformamide dimethylacetal at temperatures between 0 °C and 40 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step g) is carried out in dimethylformamide at temperature between 60 °C and 100 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step h) is carried out in the presence of sodium borohydride and cerium chloride at temperatures between 0 °C and 40 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein said reaction step h) is carried out in ethanol and in the presence of excess sodium borohydride.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step j) is carried out in the presence of concentrated hydrochloric acid in dimethoxyethane at temperatures between 0 °C and 40 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step cc) is carried out in the presence of aqueous lithium hydroxide in methanol in a pressure tube, and at a temperature between 100 °C and 120 °C.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step cc) is carried out in the presence of hydrogen peroxide.

Still another preferred embodiment of the present invention is the process as described above, wherein the reaction step dd) is carried out in the presence of ethyl di-isopropylamine and thionyl chloride, and at a temperature between -40 °C and 0 °C.

The reactions of steps aaa) to ddd) as defined herein can generally be carried out according to those of steps aa) to dd) as described above.

In accordance with the present invention, the above processes can generally be carried out according to the following specifications , wherein unless explicitly otherwise stated all substituents and definitions have the significances given herein before.

Racmic approach towards the compound of formula (1):

The general reaction sequence as described above starts from the dialkyl oxalate of formula (I), which is used to prepare α-ketoamides of formula (III) over two steps applying a modified literature procedure for steps a) and b) (M. A. Ciufolini, F. Roschangar, *Targets in Heterocyclic Systems*, **2000**, *4*, 25–55). Reaction step a) can be carried out using any amine of the formula HNR^2R^3 as defined herein before. Preferably, said reaction step a) is carried out at temperatures between 40 °C and 140 °C, more preferably between 80 °C and 100 °C.

Reaction step b) is carried out in the presence of an ethyl base as defined herein before, in an organic solvent such as alkanes or ethers, preferably diethyl ether, methyl *tert*-butyl ether or tetrahydrofuran and at temperatures between -78 °C and 35 °C, preferably between -40 °C and room temperature, and more preferably between -30 °C and 0 °C.

During the subsequent *Grignard addition* of step c), an (*E*/*Z*)-1-Methyl-1-alkenyl-magnesium bromide of formula (IV), preferably (*E*/*Z*)-1-Methyl-1-propenyl-magnesium bromide is added at temperatures between -100 °C and room temperature, preferably between -78 °C and 0 °C, more preferably between -30 °C and 0 °C, in suitable organic

solvents, preferably in ethers, more preferably in tetrahydrofuran, diethyl ether, di-isopropyl ether or methyl *tert*-butyl ether.

In reaction step d), ozonolysis of the C=C double bond in the compounds of formula (V) smoothly furnished the α-hydroxy-β-keto amides of formula (VI). This reaction is carried out in polar organic solvents, preferably in methanol, dichloromethane, ethyl acetate or pure acetic acid or aqueous mixtures of acetic acid, and at temperatures between -100 °C and room temperature, preferably between -90 °C and -50 °C. When acetic acid is used, the reaction is preferably carried out at temperatures between 10 °C and 20 °C. The five-membered, cyclic intermediate of the ozonolysis reaction is cleaved according to methods well known to the skilled artisan, preferably under conditions of reductive cleavage, more preferably using triphenylphosphine or dimethyl sulfide.

The subsequent reaction step e) is a tandem *Knoevenagel* condensation / lactonization reaction of the compounds of formula (VI) with the malonates of formula (VII), providing the α,β-unsaturated γ-lactones of formula (VIII). This reaction is preferably carried out in the presence of alkali metal carbonates or –hydrides as defined herein before in suitable organic solvents such as lower alcohols, alkanes or ethers. Especially preferred is the use of methanol, ethanol or tetrahydrofuran. Said reaction step e) takes place at temperatures between -20 °C and 80 °C, preferably between 0 °C and 40 °C

The reaction step f) is a condensation reaction of the compounds of formula (VIII) with tris(dialkylamino)methanes, preferably tris(dimethylamino)methane in dimethyl formamide furnishing the respective enamines of formula (IX). As an alternative reaction according to the present invention dialkylformamide dialkylacetals, preferably dimethyl formamide dimethylacetal (DMFDMA), can be used to replace the more expensive tris(dimethylamino)methane. Said reaction step f) takes place at temperatures between -20 °C and 100 °C, preferably between 0 °C and 40 °C.

In reaction step g) the crude compounds of formula (IX) are further reacted with ammonium acetate in dimethylformamide or acetic acid and at temperatures between room temperature and 160 °C, preferably between 60 °C and 100 °C, to result in the pyridones of formula (X).

The reaction step h) is the chemoselective reduction of the lactone ring in the compounds of formula (X) to give the diols of formula (XI). This reaction is accomplished by a modification of conditions previously reported by Ciufolini *et al* for a related, but different substrate (M. A. Ciufolini, F. Roschangar, *Tetrahedron* 1997, *53*, 11049–11060). The reduction with alkali metal borohydrides as defined herein before, preferably sodium

borohydride, required Lewis acid activation by rare earth metal salts as defined above. The use of chlorides, preferably cerium chloride, and an excess of sodium borohydride are especially preferred. The reduction did not run to completion even under these conditions and the crude product still contained 2 to 5% of both lactol diastereomers, which were efficiently removed by trituration with dichloromethane / methyl *tert*-butyl ether (2 : 1). Without cerium chloride, the reaction proceeded very slowly and resulted largely in decomposition of starting material of formula (X). Said reaction step h) takes place at temperatures between -20 °C and 80 °C, preferably between 0 °C and 40 °C.

The final reaction step j) is a cyclization reaction, giving rise to the α-hydroxylactone of formula (1). This reaction is preferably carried out at room temperature in the presence of concentrated mineral acids in ethereal solvents, preferably in dimethoxyethane, methyl *tert*-butyl ether, tetrahydrofuran and dioxane. Especially preferred according to the present invention is the use of concentrated hydrochloric acid in dimethoxyethane. The side products of this reaction are the respective ammonium halides, which result from the cleavage of the NR^2R^3-group during the cyclization reaction, especially diethylammonium chloride. Such side products can be removed by trituration with methanol, resulting in the purified racemic compound of formula (1) ("DE fragment") without any chromatographic purification. Said reaction step j) takes place at temperatures between -20 °C and 80 °C, preferably between 0 °C and 40 °C.

Asymmetric approach: Synthesis of the compound of formula (1a):

The asymmetric version as described hereinbefore is mainly based on the racemic approach as described above. The first reaction steps are different in such a way that they require a stereoselective synthesis of the respective (*S*)-enantiomers of the compounds of formula (VI). This is achieved starting from reaction step aa) with the preparation of enantiomerically pure α-ketoesters of the formula (IIIa) by reacting the 2-oxobutyric acid (2) with a chiral alcohol of the formula R^9OH, preferably (−)-8-phenylmenthol, as auxiliary reagent and according to conditions known from literature (D. L. Comins, M. F. Baevsky, H. Hong, *J. Am. Chem. Soc.* 1992, *114*, 10971–10972). This reaction is carried out in the presence of aromatic solvents such as benzene, toluene, mesitylene or xylene, and in the presence of acids such as sulfuric acid or para-toluene sulfonic acid. The use of benzene and para-toluene sulfonic acid is especially preferred. Said reaction step aa) takes place at temperatures between 80 °C and 160 °C, preferably between 80 °C and 130 °C.

The following, stereodeterminig reaction step bb) is a diastereoselective *Grignard addition* using an alkenyl magnesium bromide of formula (IVa), preferably isopropenyl

magnesium bromide. Like the *Grignard addition* reaction under step c) above, the present reaction step also requires temperatures between -100 °C and room temperature, preferably between -90 °C and -60 °C, as well as suitable organic solvents such as ethers, alkanes or aromatic solvents, preferably tetrahydrofuran, diethyl ether, di-isopropyl ether, methyl *tert*-butyl ether or toluene. The use of tetrahydrofuran is especially preferred.

The subsequent reaction step cc) is the cleavage of the auxiliary (chiral alcohol of formula R^9OH) in the presence of aqueous alkali metal- or earth alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide or barium hydroxide, preferably lithium hydroxide, and in the presence of hydrogen peroxide. The reaction takes place in suitable organic solvents such as lower alcohols and ethers, or mixtures thereof, preferably in methanol. This reaction requires heating in an autoclave to temperatures between room temperature and 180 °C, preferably between 80 °C and 130 °C, more preferably between 100 °C and 120 °C. The separation of the resulting carboxylic acids of formula (Vb) and the auxiliary is achieved by pH-dependent extraction, thus allowing a facile recycling of the expensive chiral auxiliary, which can be reused several times.

The subsequent formation of the amides of formula (Vc) according to step dd) is based on a known protocol for the formation of related α-hydroxy amides derived from pyrrolidine (L. Tan, C.-y. Chen, W. Chen, L. Frey, A. O. King, R. D. Tillyer, F. Xu, D. Zhao, E. J. J. Grabowski, P. J. Reider, P. O'Shea, P. Dagneau, X. Wang, *Tetrahedron* 2002, *58*, 7403–7410). In contrast to the known procedure, the present amide formation requires deprotonation of the carboxylic acids of formula (Vb), preferably by a tertiary amine, more preferably by ethyl di-isoproylamine, prior to the exposure to thionyl chloride. This reaction takes place at temperatures between -78 °C and 20 °C, preferably between -40 °C and 0 °C. The subsequent addition of the secondary amine of the formula $HNR^{2'}R^{3'}$ takes place at temperatures between -20 °C and 40 °C, preferably between -10 °C and 30 °C. Preferably this reaction is carried out in polar organic solvents like lower alcohols or alkyl halides, more preferably in dichloromethane.

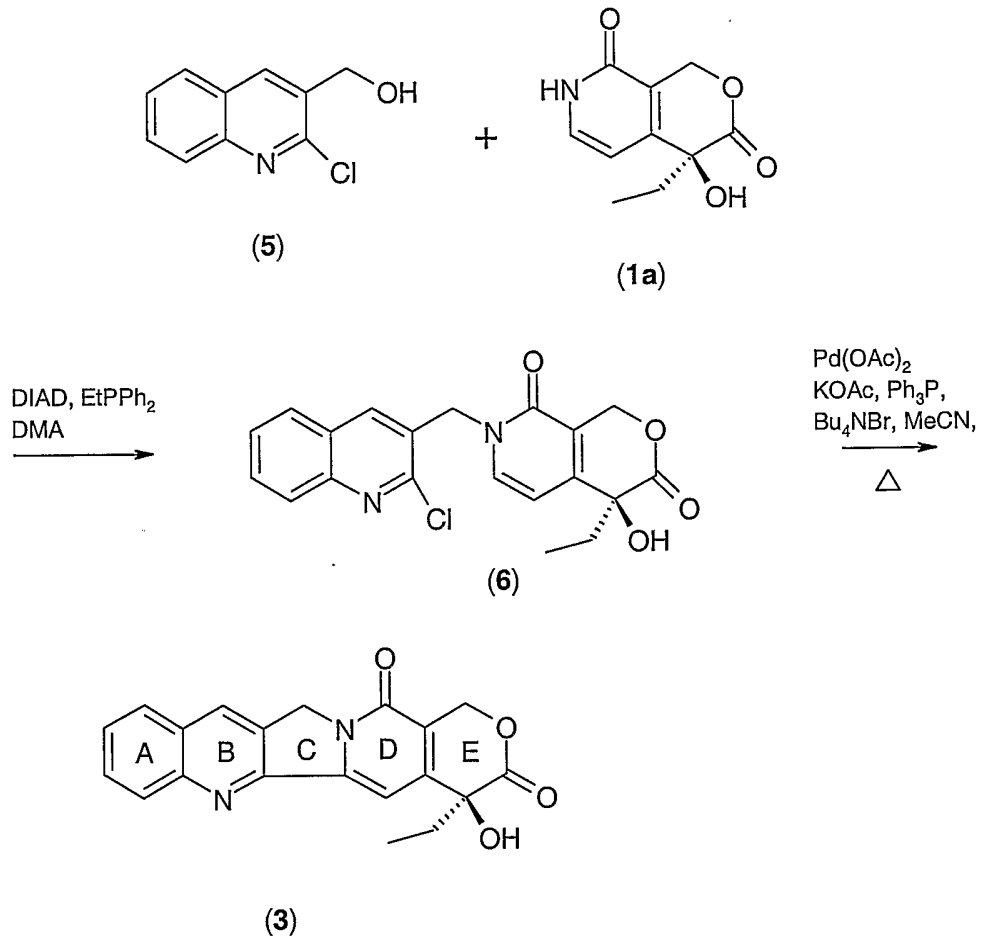
Further reaction of the compounds of formula (Vc) towards the compound of formula (1a) can be carried out according to the reaction conditions described above for reaction steps d) to j).

The reactions of steps aaa) to ddd) as defined herein only differ from the reaction steps aa) to dd) as defined herein before by using the second enantiomeric forms of the respective chiral alcohols of formula R^9OH, which enantiomeric forms are designated $R^{18}OH$. Therefore the reaction conditions of reactions aaa) to ddd) can generally be carried out according to those of steps aa) to dd) as described above.

Subsequent synthesis of camptothecin and derivatives thereof

Subsequent to the synthesis of the compound of formula (1), (1a) or (1b) according to the present invention, the final reaction steps in order to obtain racemic, (R)- or (S)-camptothecin, or derivatives thereof, require the coupling of the compound of formula (1), (1a) or (1b) to the quinoline derivative (5, scheme 2) via a *Mitsunobu-alkylation* and subsequent *Heck-cyclisation* (D.L. Comins, H. Hong, J.K. Saha, G. Jinkua, *J. Org. Chem* 1994, *59*, 5120-5121; or D.L. Comins, H. Hong, J.K. Saha, G. Jinkua, *Tetrahedron Lett* 1994, *35*, 5331-5334). This procedure can generally be performed under the conditions which are suitable for said *Mitsunobu-alkylation* and said *Heck-cyclisations*, and which are well known to the person skilled in the art.

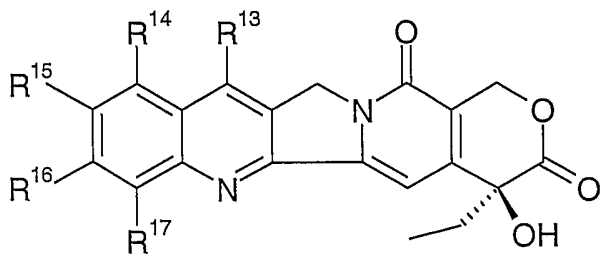
One preferred example of suitable reaction conditions for said reactions is given by the synthesis route described in scheme 2. The synthesis according to scheme 2 leads to (S)-camptothecin, but can also be carried out as a racemic route to provide (rac)-camptothecin, or starting from (1b) to furnish (R)-camptothecine. It is understood that such modifications are within the ordinary knowledge of the skilled artisan, and therefore need not to be further exemplified in all details.



scheme 2

The "AB-ring" of formula (3) can be optionally substituted. It is within the ordinary knowledge of the person skilled in the art that the process according to the present invention can also be used in the manufacture of derivatives of formula (3) wherein the "AB-ring" is further substituted.

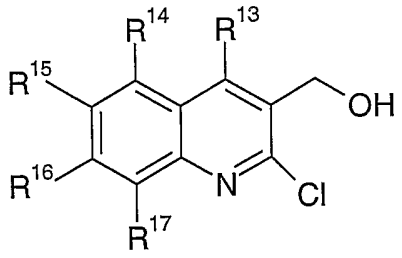
Consequently a further embodiment of the present invention is the process as described above, wherein said compound of formula (1a) is transformed into a compound of formula (A)



(A),

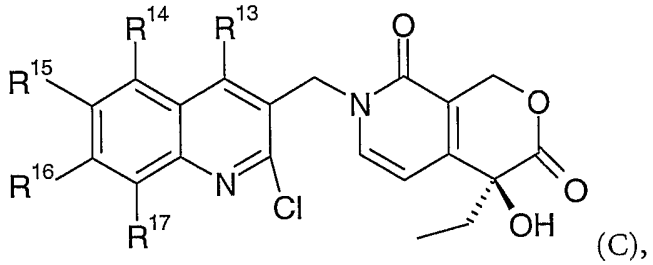
by:

a) further reacting said compound of formula (1a) with a compound of formula (B)



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C)



(C),

and

b) said compound of formula (C) is further reacted in the presence of palladium (II) acetate ($Pd(OAc)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P), tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A),

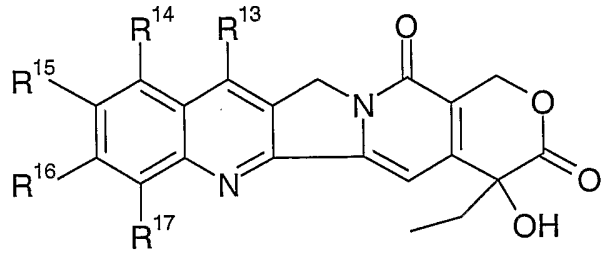
wherein

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from hydrogen; halogen; cyano; $(C_1\text{-}C_6)$alkyl; -O-$(C_1\text{-}C_6)$alkyl; -S-$(C_1\text{-}C_6)$alkyl; hydroxyl; amino; mono $(C_1\text{-}C_6)$alkyl amino; di$(C_1\text{-}C_6)$alkyl amino; nitro; trifluoromethyl; and

R^{13} and R^{14} together with the carbon atoms to which they are attached can also form a six-membered, unsaturated cyclic hydrocarbon, wherein one or two carbon atoms are

optionally replaced be nitrogen and which is unsubstituted or once substituted by $(C_1\text{-}C_6)$alkyl.

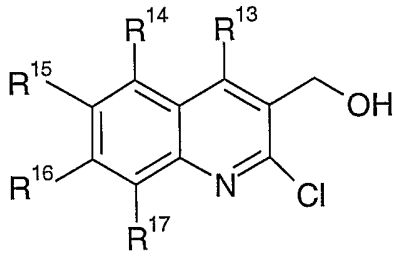
Still another embodiment of the present invention is the process as described above, wherein the compound of formula (1) is transformed into a compound of formula (A-1)



(A-1),

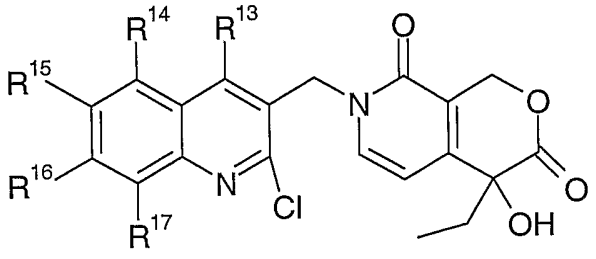
by:

a) further reacting said compound of formula (1) with a compound of formula (B) as defined above



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C-1)



(C-1),

and

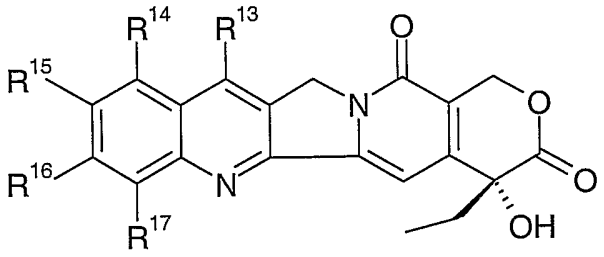
b) said compound of formula (C-1) is further reacted in the presence of palladium (II) acetate ($Pd(OAc)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P),

tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A-1),

wherein

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} have the significances given above.

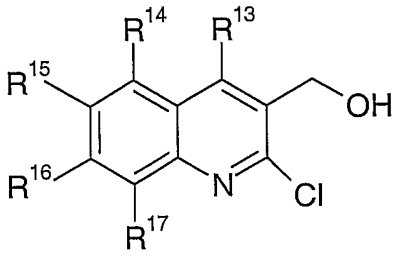
A further embodiment of the present invention is the process as described above, wherein said compound of formula (1b) is transformed into a compound of formula (A-2)



(A-2),

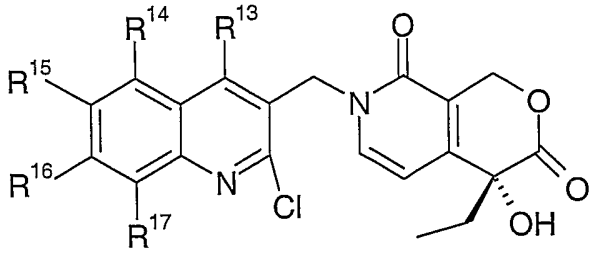
by:

a) further reacting said compound of formula (1b) with a compound of formula (B) as defined above



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C-2)



(C-2),

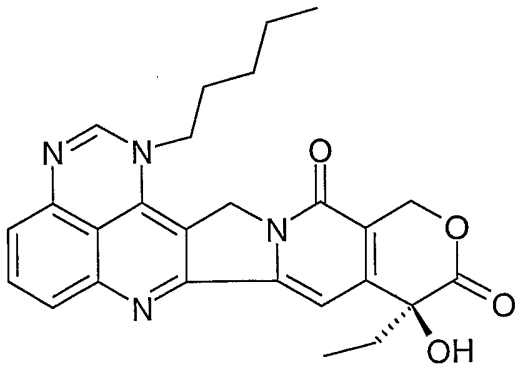
and

b) said compound of formula (C-2) is further reacted in the presence of palladium (II) acetate ($Pd(OAc)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P), tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A-2),

wherein

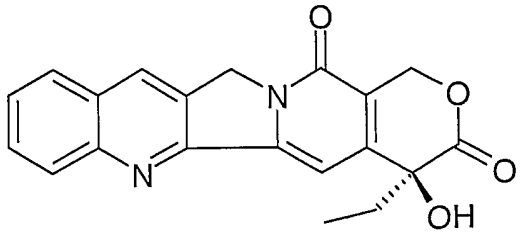
R^{13}, R^{14}, R^{15}, R^{16} and R^{17} have the significances given above.

Still another embodiment of the present invention is the process as described above wherein the compound of formual (1a) is transformed into the compound of formula (3a)



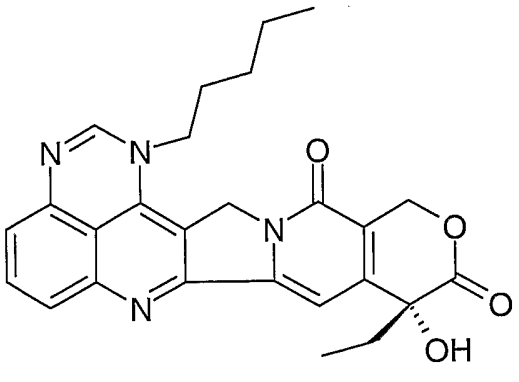
(3a).

Still another embodiment of the present invention is the process as described above wherein the compound of formula (1a) is transformed into the compound of formula (3)



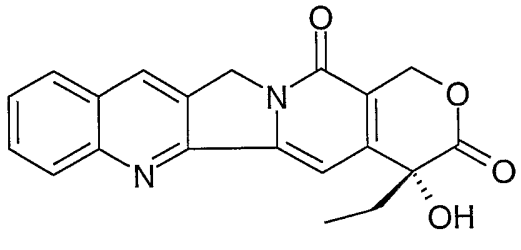
(3).

Still another embodiment of the present invention is the process as described above wherein the compound of formual (1b) is transformed into the compound of formula (3b)



(3b).

Still another embodiment of the present invention is the process as described above wherein the compound of formula (1b) is transformed into the compound of formula (3c)



(3c).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (A).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (A-1).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (A-2).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (3a).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (3).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (3b).

Still another embodiment of the present invention is the use of the process as described above in the manufacture of the compound of formula (3c).

The following examples are provided to aid the understanding of the present invention. It is understood that modifications can be made without departing from the spirit of the invention.

If not explicitly otherwise stated, the following abbreviations are used:

min	minute(s)
h	hour(s)
rt	room temperature
NMR	nuclear magnetic resonance
GC	gas chromatography
TLC	thin layer chromatography
HPLC	high performance liquid chromatography
dr	distereosiomer ratio
er	enantiomer ratio
ee	enantiomeric excess
mp	melting point

Examples

Example 1:

Synthesis of *N,N*-diethyl-oxalamic acid ethyl ester (8)

To

30.00 g diethyloxalate (7, 203.2 mmol) were added at room temperature
42.2 mL diethylamine (406.4 mmol, 2.0 eq). The colorless clear solution was heated to reflux (oil bath temperature: 90°C) and the reaction was monitored by HPLC. After 2.5 h, the resulting yellow-orange liquid was cooled to room temperature and all volatile compounds (ethanol, diethylamine) were removed in a rotary evaporator (50°C, 10 mbar) furnishing the

crude product (35.073 g, 100% by weight) as a yellow liquid. Purification was achieved using a high vacuum distillation (bp 85°C at 0.08 mbar) furnishing the title compound (30.22 g, 174.4 mmol, 86% by weight) as colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34 (q, 2H, J = 7.1 Hz), 3.43 (q, 2H, J = 7.2 Hz), 3.29 (q, 2H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.1 Hz), 1.23 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz) ppm.

Example 2

Synthesis of *N,N*-diethyl-2-oxo butyramide (9)

63.95 mL ethyl magnesium bromide solution (191.8 mmol, 1.10 eq) were diluted with
182.6 mL diethylether. The solution was cooled to -15°C and a solution of
30.20 g of compound (8) as obtained from example 1 (174.4 mmol) in
60.4 mL diethylether was added dropwise. The resulting viscous suspension was stirred for additional 75 min at -15°C. Subsequently, the reaction was quenched by addition of
14.96 mL acetic acid (261.6 mmol, 1.5 eq). Then,
35 mL water were added to dissolve all salts and the cooling bath was removed. After 15 min, the mixture was washed twice with 200 mL, pH-7-buffer and the organic phase was dried over

20 g sodium sulfate and was filtered. The filter cake was washed with
40 mL diethylether. After evaporation of solvent in a rotary evaporator (40°C/10 mbar), the crude product (26.33 g, 96% by weight) was obtained as a yellow liquid. Purification was achieved using a high vacuum distillation (bp 86°C at 2.5 mbar) furnishing the title compound (18.66 g, 118.7 mmol, 68% by weight) as colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (q, 2H, J = 7.1 Hz), 3.25 (q, 2H, J = 7.2 Hz), 2.78 (q, 2H, J = 7.3 Hz), 1.12 – 1.18 (m, 9H, J = 7.0 Hz, J = 7.0 Hz) ppm.

Example 3

Synthesis of 2-ethyl-2-hydroxy-3-methyl-pent-3-enoic acid diethylamide (10)

500 mL 1-methyl-1-propenyl magnesium bromide solution (250.0 mmol, 3.0 eq) were cooled to -78°C prior to slow addition of a precooled solution (-78°C) of
13.10 g of compound (9) as obtained from example 2 (83.2 mmol) in
262 mL diisopropylether *via* a canula. After 60 min,
250 mL saturated aqueous ammonium chloride were added and the mixture was extracted 3 times with 250 mL, dichloromethane. The combined organic phases were dried over
25 g sodium sulfate and filtered. The filter cake was washed with
50 mL dichloromethane. After removal of solvent in a rotary evaporator (40°C, 10 mbar), the crude product (18.05 g, 102% by weight) was obtained as a yellow liquid, which was purified by high vacuum distillation (bp 65°C at 0.28 mbar) furnishing the title compound (8.145 g, 38.18 mmol) as light yellow liquid in form of *E*/*Z* isomers (*E*/*Z* = 5.1:1). An analytical sample of the (*E*)-isomer was obtained by column chromatography with hexane/ethyl acetate (4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (m, 1H), 5.28 (s, 1H), 3.40 (m, 4H), 1.96 (dq, 1H, J = 13.8 Hz, J = 7.5 Hz), 1.87 (dq, 1H, J = 13.7 Hz, J = 7.2 Hz), 1.67 (d, 3H, J = 6.8 Hz), 1.57 (br. s, 3H), 1.15 (t, 3H, J = 6.8 Hz), 1.08 (t, 3H, J = 6.9 Hz), 0.86 (t, 3H, J = 7.3 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) of the (*E*)-isomer: δ 173.0, 137.7, 120.1, 78.5, 41.4, 41.2, 28.1, 13.5, 13.3, 12.8, 12.4, 8.0 ppm.

Example 4

Synthesis of 2-*N*,*N*-triethyl-2-hydroxy-3-oxo-butyramide (11)

Through a stirred solution of
8.000 g of compound (**10**) as obtained from example 3 (37.50 mmol) in
400 mL dichloromethane at -78°C,
ozone was bubbled (150 L/h) until a blue colour appeared. Subsequently, argon was bubbled through the solution for 10 min.
28 mL dimethylsulfide (375 mmol, 10.0 eq) were subsequently added and the solution was allowed to slowly warm up to room temperature overnight. The mixture was washed three times with 250 mL water. The organic phase was dried over
20 g sodium sulfate and was filtered. The solid was washed with
40 mL dichloromethane. After evaporation of solvent in a rotary evaporator (40°C/10 mbar), the crude product (7.85 g, 104% by weight) was obtained as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (s, 1H), 3.41 (m, 2H), 3.29 (q, 2H, J = 7.1 Hz), 2.19 (s, 3H), 2.01 (dq, 1H, J = 14.7 Hz, J = 7.4 Hz), 1.96 (dq, 1H, J = 15.3 Hz, J = 7.2 Hz), 1.15 (t, 3H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 0.83 (t, 3H, J = 7.5 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 170.2, 84.8, 43.1, 42.9, 28.9, 26.1, 15.0, 13.6, 8.6 ppm.

Example 5

Synthesis of 5-diethylcarbamoyl-5-ethyl-4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (12)

To a solution of
2.500 g of compound (11) as obtained from example 4 (12.42 mmol) and
9.73 mL diethylmalonate (62.10 mmol, 5.0 eq) in
100 mL ethanol were added at room temperature,
16.27 g cesium carbonate (49.68 mmol, 4.0 eq). After 26 h the yellow suspension was cooled to 0°C and
200 mL aqueous hydrochloric acid (0.5 M, 65.25 mmol, 5.0 eq) were added dropwise over 60 min. 95 mL ethanol were subsequently removed in a rotary evaporator (50°C, 5 mbar) and then,

200 mL ethylacetate were added. The organic phase was washed twice with 150 mL brine, dried over
20 g sodium sulfate and filtered. The filter cake was washed with
40 mL ethylacetate. After evaporation of the solvent in a rotary evaporator (50°C, 5 mbar), volatile components were removed in a *Kugelrohr* apparatus (55°C, 0.08 mbar). The crude product (6.758 g, 183% by weight) was obtained as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (q, 2H, J = 7.1 Hz), 3.58 (m, 1H), 3.12-3.48 (m, 3H), 2.50 (s, 3H), 2.35 (dq, 1H, J = 14.4 Hz, J = 7.1 Hz), 2.00 (dq, 1H, J = 14.4 Hz, J = 7.3 Hz), 1.38 (t, 3H, J = 7.1 Hz), 1.21 (m, 3H), 1.15 (m, 3H), 0.86 (t, 3H, J = 7.4 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 166.5, 164.8, 160.5, 119.0, 90.9, 60.8, 42.2, 42.1, 29.1, 14.5, 13.8, 13.4, 11.8, 6.5 ppm.

Example 6

Synthesis of 5-diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (13)

To a solution of
500.0 mg of compound (12) as obtained from example 5 (22.73 mmol) in
3.0 mL dimethyl formamide were added at room temperature
3.0 mL tris(dimethylamino)methane (17.3 mmol, 10.3 eq). The color of the reaction mixture changed from orange to brown and further to green. After 17 h, the mixture was diluted with
50 mL dichloromethane, washed with
25 mL aqueous hydrochloric acid (1.0 M) and washed again three times with 50 mL brine. The organic phase was dried over
2 g sodium sulfate and was filtered. The filter cake was washed with
4 mL dichloromethane. After evaporation of the solvent in a rotary evaporator (50°C, 5 mbar), the crude product was obtained as an orange oil (627.0 mg, 106% by weight), which was liberated from residual dimethyl formamide in a high vacuum rotary evaporator (50°C, 0.5 mbar) yielding the title product (536.0 mg, 1.517 mmol, 90% by weight) as orange crystals.

Mp: 105°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (br., 1H), 6.47 (br., 1H), 4.32 (m, 2H), 3.52 (dq, 1H, J = 13.2 Hz, J = 6.6 Hz), 3.18 (s, 3H), 3.17 (m, 2H), 3.00 (s, 3H), 2.99 (m, 1H), 2.41 (dq, 1H, J = 14.3 Hz, J = 7.0 Hz), 2.03 (dq, 1H, J = 14.3 Hz, J = 7.1 Hz), 1.39 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.0 Hz), 1.08 (t, 3H, J = 7.0 Hz), 0.84 (t, 3H, J = 7.3 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 169.6, 168.0, 164.4, 154.3, 99.3, 91.9, 87.7, 60.1, 45.7, 43.0, 42.4, 36.8, 34.6, 14.4, 14.0, 12.3, 7.3 ppm.

Example 7

Alternative synthesis of 5-diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (13) using DMFDMA

To a solution of

6.758	g	of compound (12) as obtained from example 5 (22.73 mmol) in
40	mL	dimethyl formamide were added at room temperature
40	mL	dimethyl formamide dimethylacetal (DMFDMA, 285.1 mmol, 12.5 eq). The color of the reaction mixture changed from orange to brown and further to green. After 2.5 h, the mixture was diluted with
150	mL	dichloromethane and washed with
150	mL	aqueous hydrochloric acid (1.0 M) and subsequently three times with 150 mL brine. The organic phase was dried over
20	g	sodium sulfate and was filtered. The filter cake was washed with
40	mL	dichloromethane. After evaporation of the solvent in a rotary evaporator (50°C, 5 mbar), the crude product was obtained as a red-brown liquid.

Example 8

Synthesis of 1-ethyl-3,4-dioxo-1,3,4,5-tetrahydro-furo[3,4-*c*]pyridine-1-carboxylic acid diethylamide (14)

To a solution of

10.63	g	of compound (13) as obtained from example 6 or 7 (29, 30.17 mmol) in
85	mL	dimethyl formamide were added at room temperature
23.7	g	ammonium acetate (301.7 mmol, 10.0 eq) resulting in the formation of a shiny red solution, which was heated to 80°C. After 19.25 h, the mixture was diluted with
150	mL	dichloromethane and successively washed with

130 mL water,
130 mL aqueous hydrochloric acid (0.5 M) and subsequently three times with 130 mL brine. The organic phase was dried over
20 g sodium sulfate and was filtered. The filter cake was washed with
40 mL dichloromethane. After evaporation of the solvent in a rotary evaporator (50°C, 5 mbar), the crude product was obtained as a red liquid (6.611 g, 79% by weight). All volatile components were removed in a *Kugelrohr* distillation apparatus. The residue was purified by trituration for 18 h at room temperature with
12 mL heptane / methyl *tert*-butyl ether (1:1), then with
8 mL heptane / methyl *tert*-butyl ether (1:1) and finally with
10 mL methyl *tert*-butyl ether furnishing the title compound (1.797 g, 6.46 mmol, 21% by weight), as violet crystals.

Mp: 177°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 13.03 (br. s, 1H), 7.78 (d, 1H, J = 6.6 Hz), 6.93 (d, 1H, J = 6.6 Hz), 3.94 (dq, 1H, J = 13.7 Hz, J = 7.4 Hz), 3.50 (dq, 1H, J = 13.4 Hz, J = 7.0 Hz), 3.28 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 3.17 (dq, 1H, J = 13.6 Hz, J = 7.0 Hz), 2.39 (dq, 1H, J = 14.5 Hz, J = 7.4 Hz), 2.09 (dq, 1H, J = 14.4 Hz, J = 7.3 Hz), 1.24 (t, 3H, J = 6.9 Hz), 1.14 (t, 3H, J = 6.9 Hz), 0.89 (t, 3H, J = 7.3 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 166.6, 166.2, 160.3, 141.9, 112.7, 104.5, 89.0, 42.7, 31.7, 14.7, 12.4, 7.6 ppm.

Example 9

Synthesis of *N,N*-diethyl-2-hydroxy-2-(3-hydroxymethyl-2-oxo-1,2-dihydro-pyridin-4-yl)-butyramide (15)

To a solution of
1.000 g of compound (14) as obtained from example 8 (3.595 mmol) in
40 mL ethanol were added at room temperature
2.215 g cerium (III) chloride (grinded, 8.99 mmol, 2.5 eq). The suspension was placed in an ultrasonic bath for 10 min and was then cooled to 15°C by a water bath.
2.40 g sodium borohydride (61.1 mmol, 17 eq) were added in 6 portions over 3 h. After additional 2 h at room temperature, the suspension was poured onto

800 mL saturated aqueous sodium hydrogencarbonate / brine (1:1) and the mixture was vigorously stirred for 13 h prior to extraction with five times 400 mL, dichloromethane / ethanol (4:1). The combined organic extracts were evaporated in a rotary evaporator (50°C, 5 mbar). The crude product was obtained as a purple-red solid (879.6 mg, 87% by weight), which was purified by trituration with

5.25 mL dichloromethane / methyl *tert*-butyl ether (2:1) yielding the title compound (623.2 mg, 2.21 mmol, 61% by weight) as a white solid.

Mp: 193°C;

^{1}H NMR (300 MHz, DMSO): δ 11.68 (br. s, 1H), 7.32 (d, 1H, J = 7.1 Hz), 6.41 (d, 1H, J = 7.0 Hz), 6.06 (s, 1H), 4.68 (t, 1H, J = 5.9 Hz), 4.37 (d, 2H, J = 5.9 Hz), 3.05-3.40 (m, 4H), 2.07 (dq, 1H, J = 14.3 Hz, J = 7.3 Hz), 1.86 (dq, 1H, J = 14.3 Hz, J = 7.3 Hz), 1.01 (t, 3H, J = 7.0 Hz), 0.74 (t, 3H, J = 7.0 Hz), 0.68 (t, 3H, J = 7.4 Hz) ppm;

^{13}C NMR (100 MHz, DMSO): δ 171.5, 163.3, 152.5, 132.3, 126.8, 103.8, 77.9, 55.6, 40.9, 32.8, 12.6, 12.2, 7.5 ppm.

Example 10

Synthesis of 4-ethyl-4-hydroxy-1,7-dihydro-4H-pyrano[3,4-c]pyridine-3,8-dione (16)

To a suspension of

560.0 mg of compound (15) as obtained from example 9 (1.983 mmol) in

11.2 mL dimethoxyethane were added dropwise at 0°C

1.68 mL concentrated aqueous hydrochloric acid (36.5%) (19.83 mmol, 10.0 eq). The ice bath was removed after 15 min and the triphasic mixture was vigorously stirred. After 4 h, the mixture was evaporated to dryness in a rotary evaporator (27°C, 5 mbar, then 1 mbar). The crude product was obtained as a lightly yellow semisolid (805.4mg, 194% by weight).

333.3 mg crude product were purified by trituration with

0.7 mL methanol at room temperature for 18 h furnishing the title compound (168.7 mg, 0.425 mmol, 98% by weight) as white crystals.

Mp: 227°C (decomposition).

^{1}H NMR (300 MHz, $CDCl_3$ / MeOH (1 : 1)): δ 7.18 (d, 1H, J = 6.8 Hz), 6.44 (d, 1H, J = 7.0 Hz), 5.31 (d, 1H, J = 16.2 Hz), 4.97 (d, 1H, J = 16.2 Hz), 1.65 (m, 2H), 0.76 (t, 3H, J = 7.3 Hz) ppm;

^{13}C NMR (100 MHz, DMSO): δ 171.9, 158.2, 149.2, 134.0, 118.4, 101.4, 71.3, 64.5, 29.8, 7.0 ppm.

Example 11

Synthesis of 2-oxo-butyric acid (*1R,2S,5R*)-5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester (17)

A solution of

2.28	g	2-oxobutyric acid (2, 22.11 mmol, 1.3 eq),
4.04	g	(-)-8-phenylmenthol (18, 17.02 mmol, 1.0 eq) and
169.9	mg	para-toluenesulfonic acid monohydrate (0.884 mmol, 0.52 eq) in
48	mL	benzene was heated to reflux for 20 h 35 min. After cooling down to room temperature, the solution was washed twice with 50 mL saturated aqueous sodium hydrogencarbonate solution, and subsequently with
50	mL	water and
50	mL	brine.The organic phase was dried over
5	g	sodium sulfate and was filtered. The filter cake was washed with
10	mL	benzene. The organic phase was evaporated to dryness in a rotary evaporator (40°C, 20 mbar) yielding the title compound (4.98 g, 92% by weight) as colorless solid.

$[\alpha]_D^{20}$ (c = 0.827 g/dL, $CHCl_3$) = +1.3;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.27 (m, 4H), 7.09 (m, 1H), 4.95 (td, 1H, J = 10.7 Hz, J = 4.5 Hz), 2.36 (dq, 1H, J = 19.4 Hz, J = 7.1 Hz), 2.19 (dq, 1H, J = 19.4 Hz, J = 7.1 Hz), 2.14 (m, 1H), 1.84 (m, 2H), 1.69 (m, 1H), 1.50 (m, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.10-1.40 (m, 3H), 0.94 (t, 3H, J = 7.1 Hz), 0.89 (d, 3H, J = 6.4 Hz) ppm.

Example 12

Synthesis of (*2S*)-2-ethyl-2-hydroxy-3-methyl-but-3-enoic acid (*1R,2S,5R*)-5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester (19)

To a solution of
4.200 g of compound (17) as obtained from example 11 (13.27 mmol) in
168 mL tetrahydrofuran were added dropwise at -78°C
39.8 mL isopropenylmagnesium bromide (19.91 mmol, 1.5 eq).
After additional 50 min, the reaction mixture was quenched by addition of
110 mL saturated aqueous ammonium chloride solution, and was extracted twice with 110 mL ethyl acetate. The combined organic phases were washed with
110 mL brine, dried over
15 g sodium sulfate and were filtered. The filter cake was washed with
30 mL ethyl acetate. The organic phase was evaporated to dryness in a rotary evaporator (40°C, 8 mbar) yielding the title compound (4.790 g, 101% by weight, *dr* = 93 : 7)as a yellow oil.

$[\alpha]_D^{20}$ (c = 0.615 g/dL, $CHCl_3$) = −44.0;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.29 (m, 5H), 5.11 (br. s, 1H), 4.97 (m, 1H), 4.84 (td, 1H, *J* = 10.8 Hz, *J* = 4.2 Hz), 2.83 (br. s, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.74 (s, 3H), 1.31 (s, 3H), 1.21 (s, 3H), 0.90-1.80 (m, 8H), 0.87 (d, 3H, *J* = 6.4 Hz), 0.80 (t, 3H, *J* = 7.4 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 151.0, 144.5, 128.2, 125.4, 125.4, 113.1, 79.7, 77.8, 49.9, 41.0, 39.9, 34.5, 31.4, 28.8, 27.3, 27.1, 26.4, 21.7, 19.3, 7.8 ppm.

Example 14

Synthesis of (*S*)-2-ethyl-2-hydroxy-3-methyl-but-3-enoic acid (20)

A solution of
3.025 g of compound (19) as obtained from example 12 (8.435 mmol) in
40 mL methanol / tetrahydrofuran (1:1) was treated with
16.9 mL aqueous lithium hydroxide (1.0 M, 16.9 mmol, 2.0 eq). The resulting colorless suspension was heated to 110° for 18.5 h providing a slightly brown solution. After cooling down to room temperature, the reaction mixture was diluted with
150 mL methyl *tert*-butyl ether and
150 mL aqueous lithium hydroxide. The aqueous phase was extracted one more time with
150 mL methyl *tert*-butyl ether to remove the auxiliary (-)-8-phenylmenthol. Subsequently, the aqueous phase was adjusted to pH 2 by addition of 10% aqueous potassium hydrogensulfate. The aqueous phase was extracted four times with 100 mL of a mixture of chloroform / ethanol (4:1). The combined organic phases were evaporated to dryness in a rotary evaporator (40°C, 10 mbar) and the title compound (931.4 mg, 77% by weight) was obtained as a yellow solid.

$[\alpha]_D^{20}$ (c = 0.251 g/dL, $CHCl_3$) = −11.9;

mp: 77°C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (s, 1H), 5.06 (br. s, 1H), 2.04 (dq, 1H, J = 14.2 Hz, J = 7.2 Hz), 2.04 (dq, 1H, J = 14.3 Hz, J = 7.4 Hz), 1.85 (s, 3H), 0.94 (t, 3H, J = 7.4 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 144.3, 113.5, 79.9, 29.1, 19.1, 7.7 ppm.

Example 15

Synthesis of (*S*)-2-ethyl-2-hydroxy-3-methyl-but-3-enoic acid diethylamide (21)

To a solution of

1.000	g	of compound (20) as obtained from example 14 (6.95 mmol) in
30	mL	dichloromethane were added dropwise at -15°C
2.5	mL	*N*-ethyldiisopropyl amine (14.60 mmol, 2.1 eq) and after additional 8 min.
1.53	mL	thionyl chloride (20.85 mmol, 3.0 eq). After 50 min., a solution of
7.22	mL	diethylamine (69.5 mmol, 10.0 eq) in
20	mL	dichloromethane was added dropwise using a syringe pump (addition time: 60 min.). The reaction mixture was allowed to slowly warm up to room temperature overnight. The reaction mixture was diluted with
50	mL	dichloromethane and was then washed with
50	mL	aqueous hydrochloric acid (1.0 M). The organic phase was dried over
5	g	sodium sulfate and was filtered. The solid was washed with
10	mL	dichloromethane. After evaporation of solvent in a rotary evaporator (40°C/10 mbar), the crude product (1.36 g, 98% by weight) was obtained as a yellow oil, which was purified by column chromatography with heptane / ethyl acetate (9:1) yielding the title compound (0.900 g, 4.515 mmol, 65% by weight, *er* = 93.4 : 6.6) as yellow oil.

$[\alpha]_D^{20}$ (c =0.990 g/dL, $CHCl_3$) = +63.3;

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (s, 1H), 5.12 (br. s, 1H), 5.03 (m, 1H), 3.42 (m, 4H), 2.00 (dq, 1H, J = 13.9 Hz, J = 7.4 Hz), 1.91 (dq, 1H, J = 14.0, Hz, J = 6.9 Hz), 1.71 (s, 3H), 1.16 (t, 3H, J = 6.9 Hz), 1.12 (t, 3H, J = 6.9 Hz), 0.88 (t, 3H, J = 7.4 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 146.9, 111.5, 77.5, 41.4, 41.1, 28.2, 18.9, 13.1, 12.2, 7.8 ppm.

Example 16

Synthesis of (*S*)-2-*N*,*N*-triethyl-2-hydroxy-3-oxo-butyramide (22)

Through a stirred solution of
595.0 mg of compound (21) as obtained from example 15 (2.985 mmol) in
29.8 mL dichloromethane at -78°C,
ozone was bubbled (150 L/h) until a blue colour appeared. Subsequently, argon was bubbled through the solution for 20 min.
2.21 mL dimethylsulfide (200.7 mmol, 10.0 eq) were subsequently added and the solution was allowed to slowly warm up to room temperature overnight. The mixture was washed three times with 20 mL water. The organic phase was dried over
5 g sodium sulfate and filtered. The solid was washed with
10 mL dichloromethane. After evaporation of solvent in a rotary evaporator (24°C/10 mbar), the title compound (587.3 mg, 98% by weight) was obtained as a yellow oil.

$[\alpha]_D^{20}$ (c = g/dL, $CHCl_3$) = +77.1. The other analytical data are in accordance with the racemic form of Example 4.

Example 17

Synthesis of (*S*)-5-diethylcarbamoyl-5-ethyl-4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (23)

According to procedure described in Example 5,
587.3 mg of compound (22) as obtained from example 16 (2.918 mmol) and
2.29 mL diethylmalonate (14.59 mmol, 5.0 eq) in
23 mL ethanol were treated with
3.822 g cesium carbonate (11.67 mmol, 4.0 eq) yielding the crude product (1.224 g, 141% by weight) as a yellow liquid (*er* = 94.15 : 5.85).

$[\alpha]_D^{20}$ (c = 1.025 g/dL, $CHCl_3$) = −134.8. The other analytical data are in accordance with the racemic form of Example 5.

Example 18

Synthesis of (*S*)-5-diethylcarbamoyl-4-((*E*)-2-dimethylamino-vinyl)-5-ethyl-2-oxo-2,5-dihydro-furan-3-carboxylic acid ethyl ester (24)

According to the procedure described in Example 6

1.220 g of compound (23) as obtained from example 17 (4.103 mmol) in
7.3 mL dimethyl formamide were treated with
7.55 mL tris(dimethylamino)methane (42.26 mmol, 10.3 eq) yielding the crude product as an orange oil (1.463 mg, 101% by weight).

$[\alpha]_D^{20}$ (c = 1.020 g/dL, $CHCl_3$) = −238.9. The other analytical data are in accordance with the racemic form of Example 6.

Example 19

Synthesis of (*S*)-1-ethyl-3,4-dioxo-1,3,4,5-tetrahydro-furo[3,4-*c*]pyridine-1-carboxylic acid diethylamide (25)

According to the procedure as described in Example 8

1.462 g of compound (24) as obtained from example 18 (4.148 mmol) in
11.7 mL dimethyl formamide were treated with
3.263 g ammonium acetate (41.48 mmol, 10.0 eq) yielding the crude product as a red liquid (3.175 g, 275% by weight). All volatile components were removed in a *Kugelrohr* distillation apparatus (50°C, 0.05 mbar). The residue (402.8 mg, 35% by weight) was purified by trituration for 18 h at room temperature with
4.8 mL methyl *tert*-butyl ether furnishing the title compound (329.2 mg, 1.18 mmol, 29% by weight, *er* = 93.26 : 6.74) as yellow crystals.

mp: 199°C;

$[\alpha]_D^{20}$ (c = 0.364 g/dL, $CHCl_3$) = −67.9.

The other analytical data are in accordance with the racemic form of Example 8.

Example 20

Synthesis of (*S*)-*N*,*N*-diethyl-2-hydroxy-2-(3-hydroxymethyl-2-oxo-1,2-dihydro-pyridin-4-yl)-butyramide (26)

According to the procedure described in Example 9

694.0 mg of compound (25) as obtained from example 19 (2.494 mmol) in
28 mL ethanol were treated with
1.537 g cerium (III) chloride (grinded, 6.235 mmol, 2.5 eq) and
1.081 g sodium borohydride (27.4 mmol, 11 eq) yielding the crude product as a beige solid (576.0 mg, 82% by weight), which was redissolved in
10 mL methanol at 60°C. The solution was poured on
88 mL saturated aqueous sodium hydrogencarbonate / brine (1:1) and the resulting suspension was stirred for additional 24 h prior to extraction with five times 88 mL dichloromethane / ethanol mixture (4:1). The combined organic extracts were evaporated in a rotary evaporator (50°C, 5 mbar) yielding the title compound (461.5 mg, 1.63 mmol, 66% by weight) as an off-white solid.

mp: 174°C (decomposition);

$[\alpha]_D^{20}$ (c = 0.253 g/dL, $CHCl_3$) = −81.8.

The other analytical data are in accordance with the racemic form of Example 9.

Example 21

Synthesis of (*S*)-4-ethyl-4-hydroxy-1,7-dihydro-4H-pyrano[3,4-c]pyridine-3,8-dione (27)

According to the procedure described in Example 10

461.0 mg of compound (26) as obtained from example 20 (1.633 mmol) in
9.2 mL dimethoxyethane were treated with
1.38 mL concentrated aqueous hydrochloric acid (36.5%, 16.33 mmol, 10.0 eq) yielding the crude product as a lightly yellow solid (722.8 mg, 212% by weight), which was stirred with
2.2 mL methanol at room temperature overnight. The mixture was filtered and the title compound was washed with additional
2.2 mL methanol furnishing the purified product as white crystals (117.4 mg, 34% by weight, *er* = 95.0 : 5.0 by chiral HPLC).

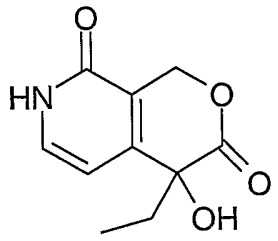
mp: 226°C (decomposition);

$[\alpha]_D^{20}$ (c = 0.168 g/dL, MeOH) = +102.6 (for a sample with *er* = 98.1 : 1.9).

The other analytical data are in accordance with the racemic form of Example 10.

Claims

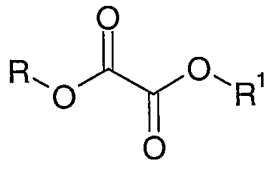
1. A process for the manufacture of the compound of formula (1)



(1),

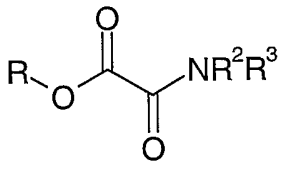
wherein

a) a compound of formula (I)



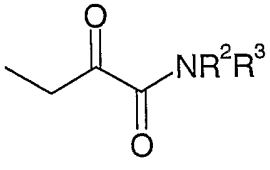
(I)

is reacted in the presence of an amine of formula HNR^2R^3 to give a compound of formula (II)



(II);

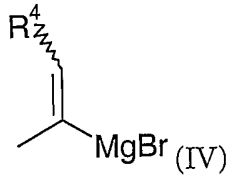
b) said compound of formula (II) is further reacted in the presence of an ethyl-base to give a compound of formula (III),



(III);

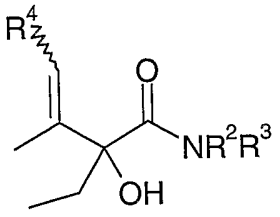
c) said compound of formula (III) is further reacted with a compound of

formula (IV)



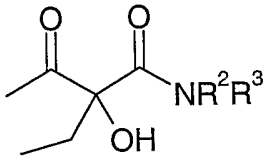
(IV)

to give a compound of formula (V)



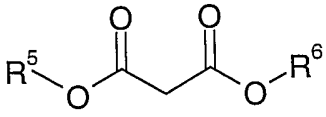
(V);

d) said compound of formula (V) is further reacted in the presence of ozone to give a compound of formula (VI)



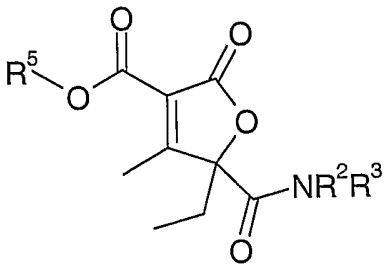
(VI);

e) said compound of formula (VI) is further reacted in the presence of a compound of formula (VII)



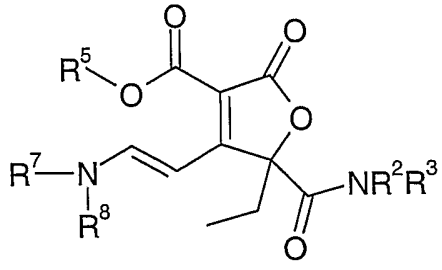
(VII),

and a base, to give a compound of formula (VIII)



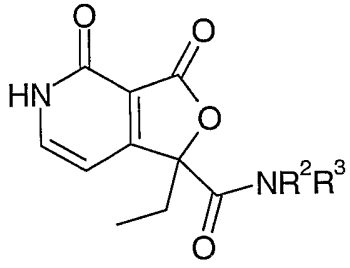
(VIII);

f) said compound of formula (VIII) is further reacted in the presence of di(C_1-C_6)-alkylformamide di(C_1-C_6)-alkylacetal or a compound of the formula $(R^7R^8N)_3$-CH to give a compound of formula (IX)



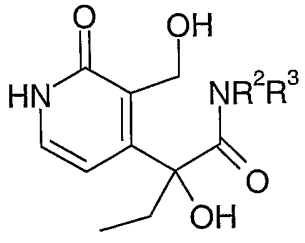
(IX)

g) said compound of formula (IX) is further reacted in the presence of ammonium acetate to give a compound of formula (X)



(X);

h) said compound of formula (X) is further reacted in the presence of alkali metal borohydrides and rare earth metal salts to give a compound of formula (XI)



(XI); and

j) said compound of formula (XI) is further reacted in the presence of concentrated mineral acids to give the compound of formula (1);

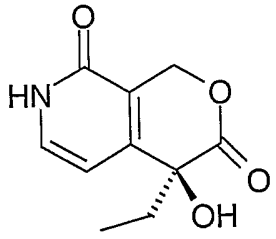
wherein

R, R^1, R^7 and R^8 independently from each other are (C_1-C_6)-alkyl;

R^2, R^3 and R^4 independently represent (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl; and

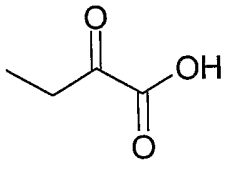
R^5 and R^6 are both either the same or different (C_1-C_6)-alkyl, or an aryl group.

2. The process according to claim 1, for the manufacture of the compound of formula (1a)

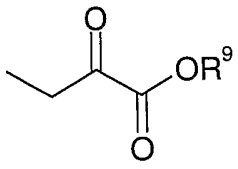

(1a),

wherein

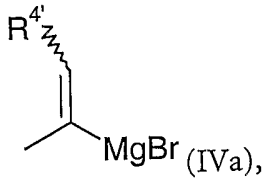
aa) the compound of formula (2)


(2),

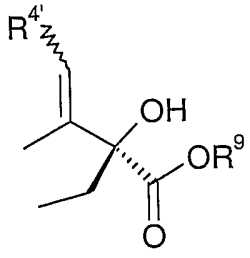
is reacted in the presence of a chiral secondary alcohol of the formula R^9OH to give an ester of formula (IIIa)


(IIIa);

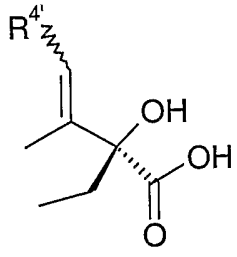
bb) said ester of formula (IIIa) is further reacted with a compound of formula (IVa)


(IVa),

to give a compound of formula (Va)

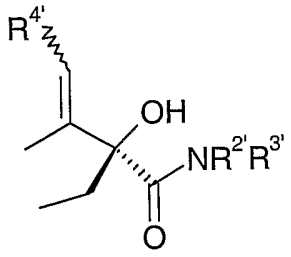

(Va);

cc) ester cleavage from a compound of formula (Va) is carried out in the presence of an alkali metal- or earth alkali metal hydroxide, optionally in the presence of hydrogen peroxide, to give the compound of formula (Vb)



(Vb);

dd) said compound of formula (Vb) is further reacted in the presence of a tertiary amine and thionyl chloride, prior to addition of an amine of formula $HNR^{2'}R^{3'}$ to give a compound of formula (Vc)



(Vc); and

further reaction is carried out according to the reaction steps d) to j) according to claim 1, to give the compound of formula (1a),

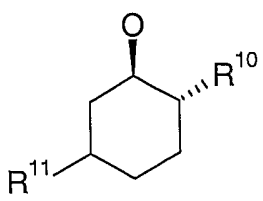
wherein

$R^{2'}$ has the meaning of R^2 according to claim 1;

$R^{3'}$ has the meaning of R^3 according to claim 1;

$R^{4'}$ has the meaning of R^4 according to claim 1;

$-OR^9$ represents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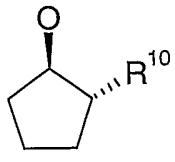
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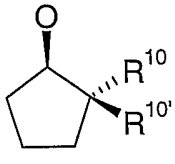
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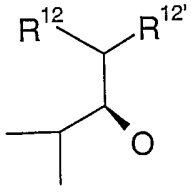
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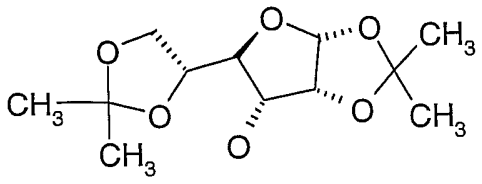


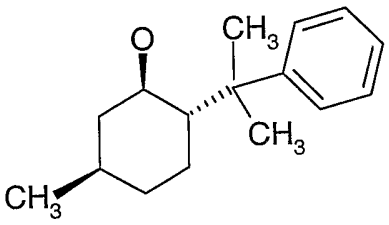
or ; and

R^{10} and $R^{10'}$ independently represents an aryl group, or a $(C_3$-$C_{12})$alkyl group, which is unsubstituted or substituted by phenyl;

R^{11} is hydrogen or $(C_1$-$C_6)$alkyl; and

R^{12} and $R^{12'}$ independently represent an aryl group.

3. The process according to claim 2, wherein $-OR^9$ represents



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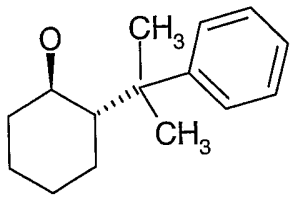
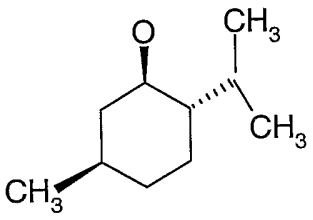
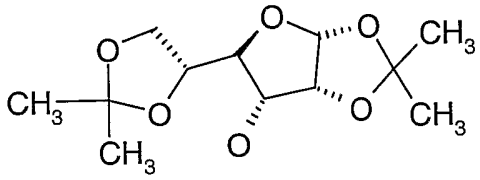


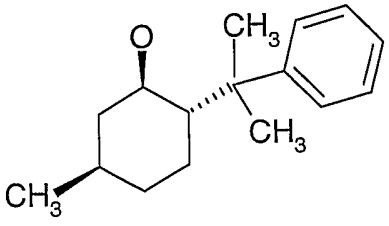
;

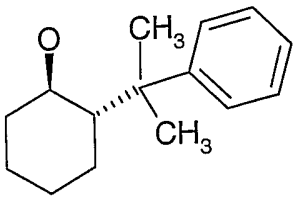




; or .

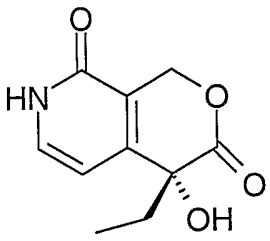
4. The process according to claim 2, wherein $-OR^9$ represents





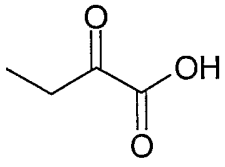
or .

5. The process according to claim 1, for the manufacture of the compound of formula (1b)

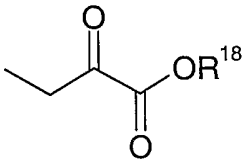

(1b),

wherein

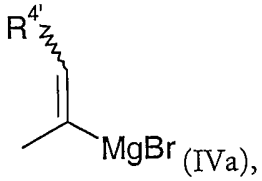
aaa) the compound of formula (2)


(2),

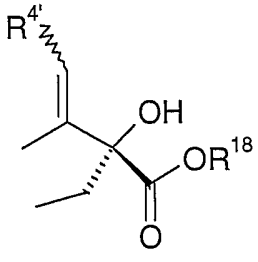
is reacted in the presence of a chiral secondary alcohol of the formula $R^{18}OH$ to give an ester of formula (IIIb)


(IIIb);

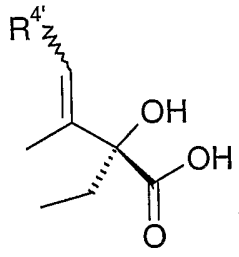
bbb) said ester of formula (IIIb) is further reacted with a compound of formula (IVa) according to claim 2


(IVa),

to give a compound of formula (Vd)

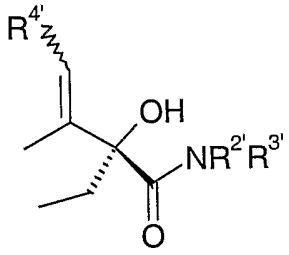

(Vd);

ccc) ester cleavage from a compound of formula (Vd) is carried out in the presence of an alkali metal- or earth alkali metal hydroxide, optionally in the presence of hydrogen peroxide, to give the compound of formula (Ve)



(Ve);

ddd) said compound of formula (Ve) is further reacted in the presence of a tertiary amine and thionyl chloride, prior to addition of an amine of formula $HNR^{2'}R^{3'}$ according to claim 2 to give a compound of formula (Vf)



(Vf); and

further reaction is carried out according to the reaction steps d) to j) according to claim 1, to give the compound of formula (1b),

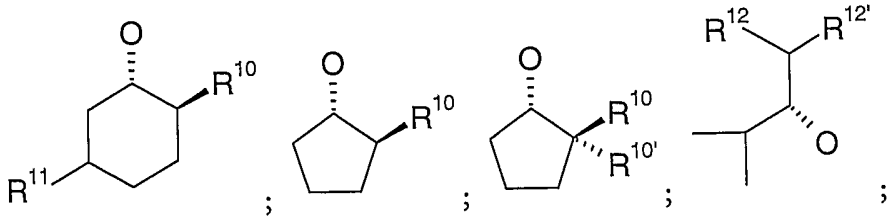
wherein

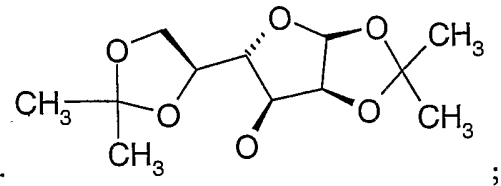
$R^{2'}$ has the meaning according to claim 2;

$R^{3'}$ has the meaning according to claim 2;

$R^{4'}$ has the meaning according to claim 2;

$-OR^{18}$ represents





or ; and

R^{10} and $R^{10'}$ independently represents an aryl group, or a (C_3-C_{12})alkyl group, which is unsubstituted or substituted by phenyl;

R^{11} is hydrogen or (C_1-C_6)alkyl; and

R^{12} and $R^{12'}$ independently represent an aryl group.

6. The process according to claim 1, wherein

R, R^1, R^2, R^3, R^5 and R^6 are ethyl; and

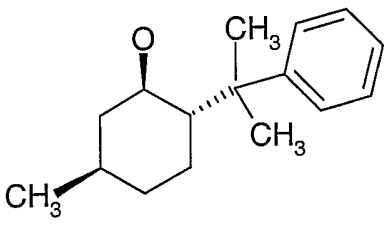
R^4, R^7 and R^8 are methyl.

7. The process according to claim 2, wherein

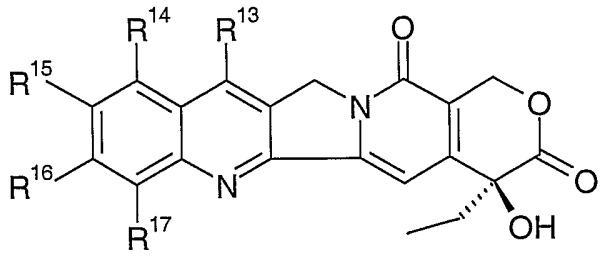
$R^{2'}$ and $R^{3'}$ are ethyl;

$R^{4'}$ is methyl; and

$-OR^9$ is



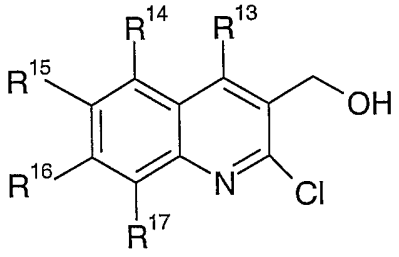
8. The process according to claim 2, wherein said compound of formula (1a) is transformed into a compound of formula (A)



(A),

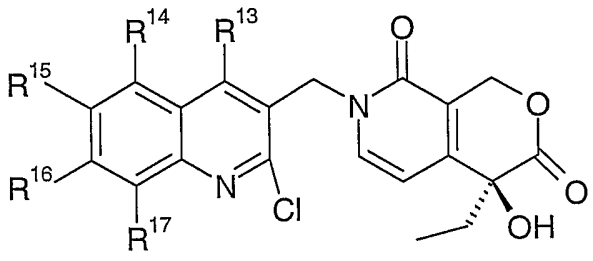
by:

a) further reacting said compound of formula (1a) with a compound of formula (B)



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C)



(C),

and

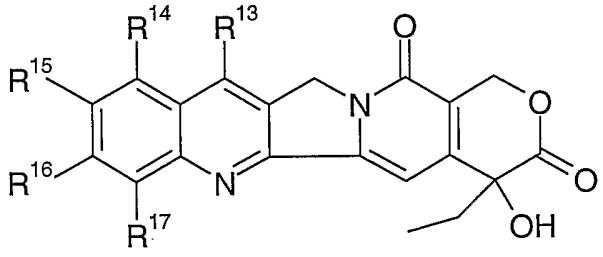
b) said compound of formula (C) is further reacted in the presence of palladium (II) acetate ($Pd(OAc)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P), tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A),

wherein

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from hydrogen; halogen; cyano; $(C_1\text{-}C_6)$alkyl; -O-$(C_1\text{-}C_6)$alkyl; -S-$(C_1\text{-}C_6)$alkyl; hydroxyl; amino; mono $(C_1\text{-}C_6)$alkyl amino; di$(C_1\text{-}C_6)$alkyl amino; nitro; trifluoromethyl; and

R^{13} and R^{14} together with the carbon atoms to which they are attached can also form a six-membered, unsaturated cyclic hydrocarbon, wherein one or two carbon atoms are optionally replaced be nitrogen and which is unsubstituted or once substituted by $(C_1\text{-}C_6)$alkyl.

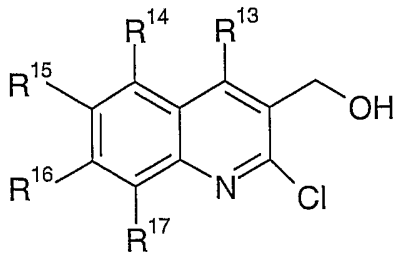
9. The process according to claim 1, wherein the compound of formual (1) is transformed into a compound of formula (A-1)



(A-1),

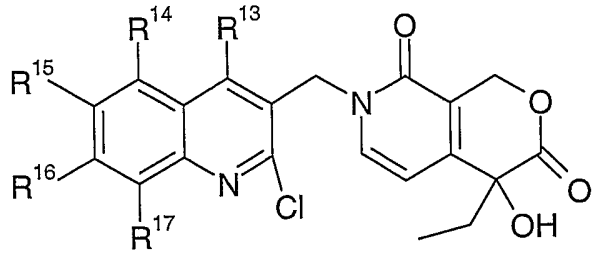
by:

a) further reacting said compound of formula (1) with a compound of formula (B) according to claim 8



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C-1)



(C-1),

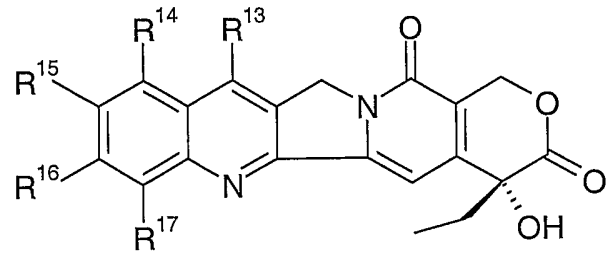
and

b) said compound of formula (C-1) is further reacted in the presence of palladium (II) acetate ($Pd(OAc)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P), tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A-1),

wherein

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} have the significances given in claim 8.

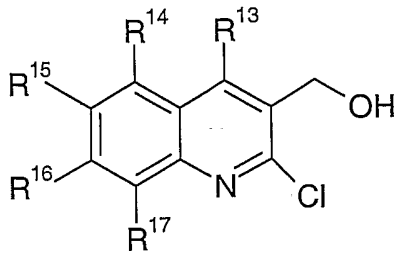
10. The process according to claim 5, wherein said compound of formula (1b) is transformed into a compound of formula (A-2)



(A-2),

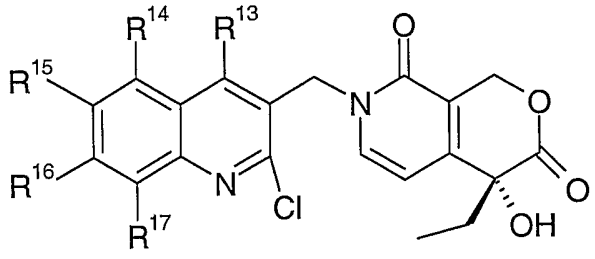
by:

a) further reacting said compound of formula (1b) with a compound of formula (B) according to claim 8



(B),

in the presence of diisopropyl azodicarboxylate (DIAD), ethyldiphenylphosphine ($EtPPh_2$) and dimethylacetamide (DMA), to give a compound of formula (C-2)



(C-2),

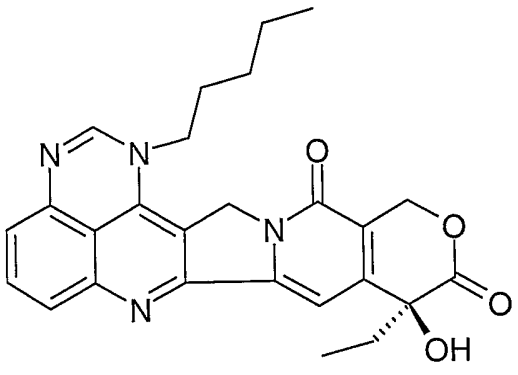
and

b) said compound of formula (C-2) is further reacted in the presence of palladium (II) acetate ($Pd(Oac)_2$), potassium acetate (KOAc), triphenylphosphine (Ph_3P), tetrabutyl ammonium bromide (Bu_4NBr) and acetonitrile(MeCN) to give the corresponding compound of formula (A-2),

wherein

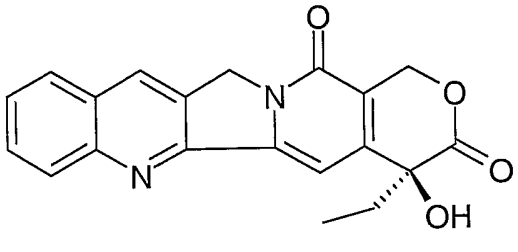
R^{13}, R^{14}, R^{15}, R^{16} and R^{17} have the significances given in claim 8.

11. The process according to claim 8, wherein the compound of formula (1a) is transformed into the compound of formula (3a)



(3a).

12. The process according to claim 8, wherein the compound of formula (1a) is transformed into the compound of formula (3)



(3).

13. The use of the process according to claim 2 in the manufacture of the compound of formula (A) according to claim 8.

14. The use of the process according to claim 1 in the manufacture of the compound of formula (A-1) according to claim 9.

15. The use of the process according to claim 5 in the manufacture of the compound of formula (A-2) according to claim 10.

16. The use of the process according to claim 2 in the manufacture of the compound of formula (3) according to claim 12.

17. The use of the process according to claim 2 in the manufacture of the compound of formula (3a) according to claim 11.

18. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001306

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/04 C07D491/22

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	R. PETERS, M. ALTHAUS AND A. -L. NAGY: "Practical formal total synthesis of (rac)- and (s)-camptothecin" ORGANIC&BIOMOLECULAR CHEMISTRY, vol. 4, no. 3, 2006, pages 498-509, XP002378337 Schemes 4-6 (pages 500-502).	1-10, 12-16,18
A	D. L. COMINS, H. HONG, J. K. SAHA AND G. JIANHUA: "A six-step synthesis of camptothecin" JOURNAL OF ORGANIC CHEMISTRY, vol. 59, 1994, pages 5120-5121, XP002378338 cited in the application Scheme 1 and 2 (pages 5120-5121)	1,13-18

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

☐ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2006	01/06/2006

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