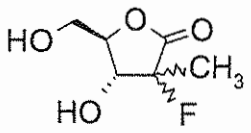
PROCESS FOR THE PREPARATION OF A FLUOROLACTONE DERIVATIVE

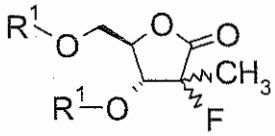
The present invention relates to a novel process for the preparation of a fluorolactone derivative of the formula



I

,

and of its acylated derivative of formula



V

.

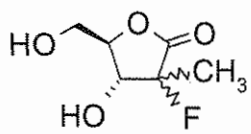
wherein R^1 stands for a hydroxy protecting group.

The acylated fluorolactones of formula V, particularly the benzoyl derivative with R^1 =benzyl are important precursors for the synthesis of prodrug compounds which have the potential to be potent inhibitors of the Hepatitis C Virus (HCV) NS5B polymerase (PCT Int. Publ. WO 2007/065829).

Object of the embodiment disclosed herein was to find a selective and scalable synthesis for the preparation of the fluorolactone of formula I and its acylated derivatives of formula V.

The object could be achieved with the synthesis of the present disclosure as described below.

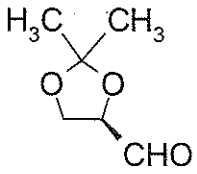
In one aspect, the process of the present disclosure comprises the preparation of a fluorolactone derivative of ~~the~~ formula I:



I

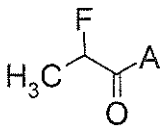
comprising ~~the steps~~:

a) reacting ~~the~~ an aldehyde of ~~the~~ formula II:



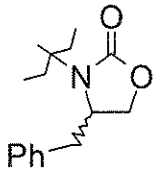
II

with a fluoropropionate derivative of formula III:

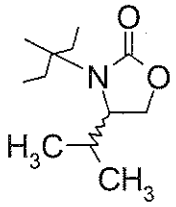


III

wherein A is selected from the chiral moieties:

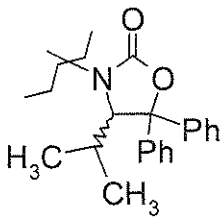


A1



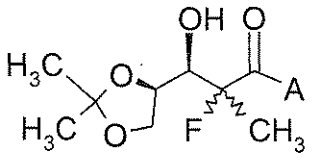
A2

and



A3

and Ph ~~stands for~~is phenyl, to form an aldol adduct of ~~the~~ formula IV:



IV

~~wherein A is as above~~; and

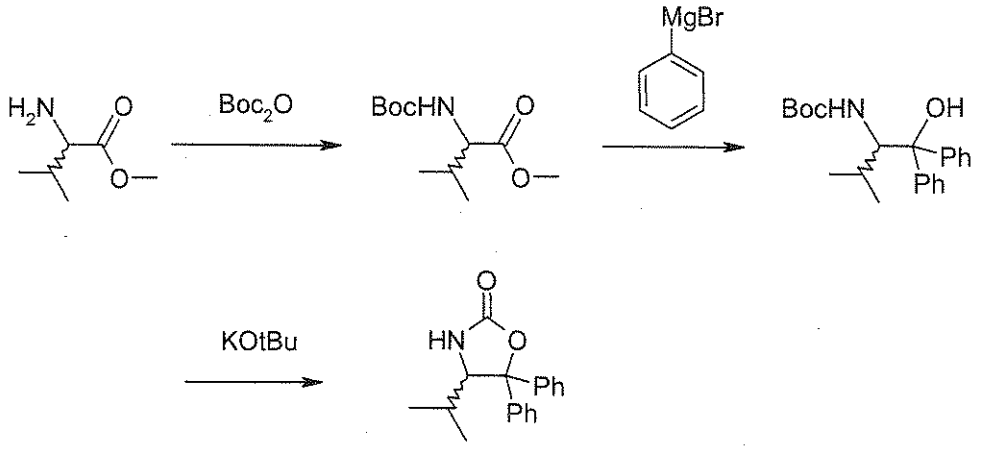
b) subjecting ~~to hydrolysis~~ the aldol adduct of formula IV to hydrolysis to ~~give~~ provide the fluorolactone derivative of ~~the~~ formula I.

The term "hydroxy protecting group" used for substituent R^1 refers to any substituents conventionally used to hinder the reactivity of the hydroxy group. Suitable hydroxy protecting groups are described in Green T., "Protective Groups in Organic Synthesis", Chapter 1 , John Wiley and Sons, Inc.,1991, 10-142 and can e.g. be selected from benzyl, acetyl, trimethyl silyl, tert-butyl, tert-butyl dimethyl silyl or dihydropyranyl, but particularly benzyl.

The wave line " ~ " indicates a chiral bond, " / "or " ····· ".

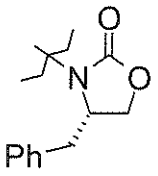
Step a)

Step a) requires the reaction of the aldehyde of the formula II with a fluoropropionate derivative of formula III to form an aldol adduct of the formula IV.

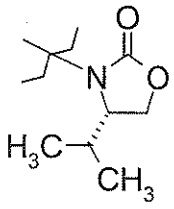


In a particular embodiment the fluoropropionate derivative of formula III wherein A is A3 is used.

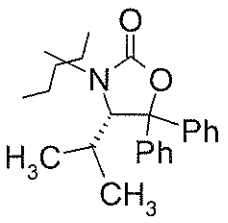
In a more particular embodiment the substituent A in the fluoropropionate derivative of formula III is selected from the chiral moieties



A1a



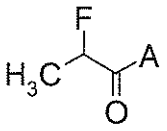
A2a



A3a

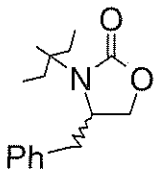
even more particularly from A3a.

The fluoropropionate derivatives of formula III

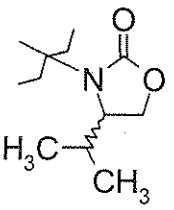


III

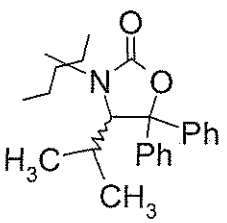
wherein A is selected from the chiral moieties



A1



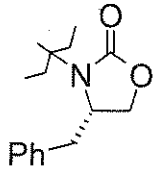
A2

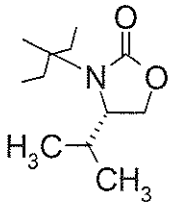


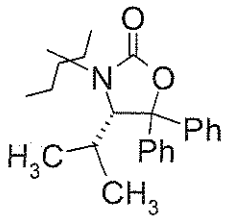
A3

wherein Ph stands for phenyl have so far have not been described in the art and therefore represent another ~~aspect~~ embodiment of the present disclosure.

In a more particular fluoropropionate derivative of formula III A is selected from

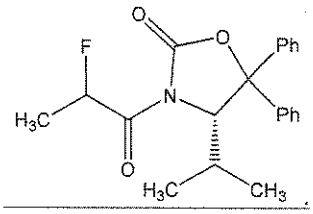

A1a


A2a


A3a

even more particularly from A3a.

In one aspect, there is provided fluoropropionate derivative of formula:



The reaction is performed in the presence of a catalyst selected from dibutylboron trifluormethanesulfonate, titanium chloride, titanium(IV) trichloride isopropoxide, titanium isopropoxide, magnesium chloride, magnesium triflate or zinc chloride.

Particularly dibutylboron trifluormethanesulfonate is used.

As a rule a base such as a tertiary amine selected from 2,6-lutidine, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine, 3,4-lutidine, 3,5-lutidine, triethyl amine, diisopropylethyl amine, diethylamine, pyridine or 1,6-dimethylpyridine and a suitable organic solvent such as methylene chloride, 1,2-dichloroethane, chloroform, acetonitrile, toluene, xylene, chlorobenzene, tetrahydrofuran, 2-methyl tetrahydrofuran or methyl isobutylether, or mixtures thereof are present.

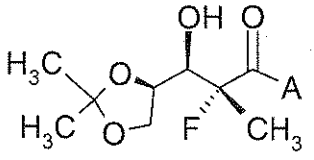
A particularly suitable tertiary amine is 2,6-lutidine and a particularly suitable organic solvent is methylene chloride.

The reaction temperature is usually held between -78°C and 50°C.

The resulting aldol adduct of formula IV can be obtained from the reaction mixture applying methods known to the skilled in the art, particularly by adding water to the reaction mixture, by separating the organic phase and removing the solvent. Further purification can be achieved by crystallization from a methylene chloride solution with hexane.

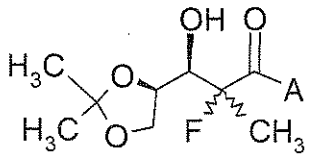
The aldol adducts of formula IV are not known in the art and therefore represent particular embodiments of the present invention.

More particular the aldol adducts have the formula


IVa

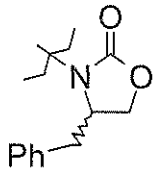
wherein the chiral moiety A is as above and selected from A1, A2 or A3, more particular from A1a, A2a or A3a and even more particular from A3a.

Hence, in another aspect, there is provided an aldol adduct of the formula IV:

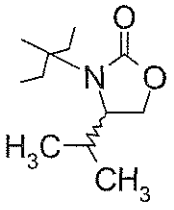


IV

wherein A is selected from the chiral moieties A1, A2 and A3:

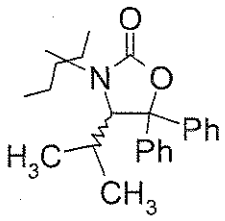


A1



A2

and



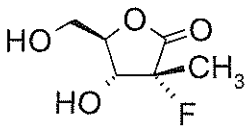
A3

wherein Ph ~~stands for~~is phenyl.

Step b)

Step b) requires subjecting to hydrolysis the aldol adduct of formula IV to give the fluorolactone derivative of the formula I.

In a particular embodiment the aldol adduct of the formula IVa with the preferences as outlined above is used resulting in the fluorolactone derivative of the formula



Ia

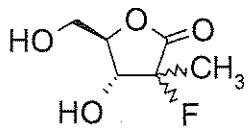
The hydrolysis is as a rule performed with an oxidizing agent selected from hydrogen peroxide, meta-chloroperoxybenzoic acid, sodium hypochlorite, sodium perchlorate or ethylene oxide in the presence of an alkali hydroxide selected from lithium-, sodium- or potassium hydroxide as base.

Hydrogen peroxide is usually selected as a suitable oxidizing agent and an aqueous solution of lithium hydroxide is particularly used as base.

The hydrolysis is usually performed at reaction temperatures between -30°C and 50°C.

Claims

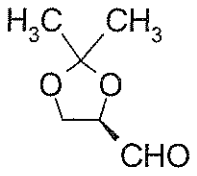
1. Process for the preparation of a fluorolactone derivative of formula I:



I

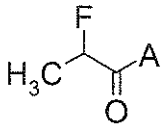
comprising:

a) reacting an aldehyde of formula II:



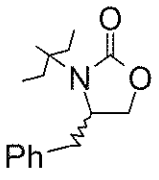
II

with a fluoropropionate derivative of formula III:

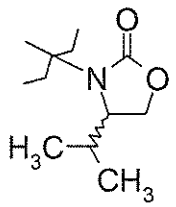


III

wherein A is selected from the chiral moieties:

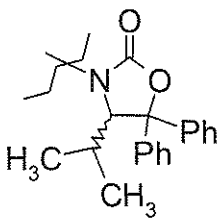


A1 ,



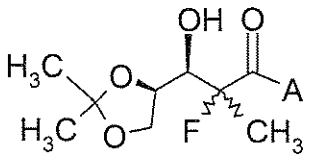
A2

and



A3

and Ph is phenyl, to form an aldol adduct of formula IV:



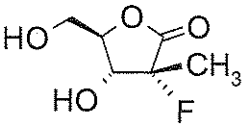
IV

; and

b) subjecting the aldol adduct of formula IV to hydrolysis to provide the fluorolactone derivative of formula I.

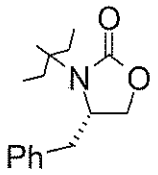
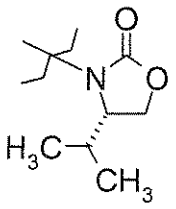
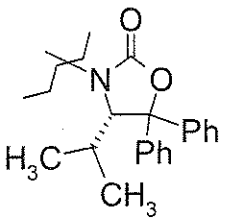
2. Process of claim 1, wherein the chiral moiety A is A3.

3. Process of claim 1, wherein the fluorolactone derivative has formula 1a:



Ia

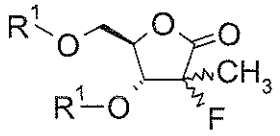
and A is selected from the chiral moieties: A1a, A2a and A3a:

 A1a ,  A2a and  A3a

and Ph is phenyl.

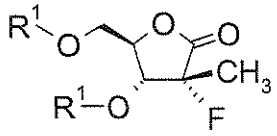
4. Process of claim 3, wherein the chiral moiety A in the fluoropropionate derivative of formula III is A3a.

5. Process of claim 1, wherein the hydroxy groups in the fluorolactone derivative of formula I are protected to form the protected fluorolactone of formula V:

 V

wherein R^1 stands for a hydroxy protecting group.

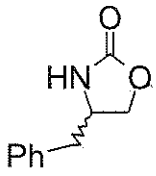
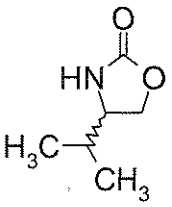
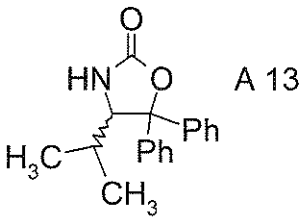
6. Process of claim 5, wherein the acylated fluorolactone has the formula

 Va

wherein R^1 stands for a hydroxy protecting group.

7. Process of claim 4, wherein the hydroxy protecting group is benzyl.

8. Process of any of the claims 1 to 5, wherein the chiral moieties A1, A2 or A3 can be recovered in the form of the respective chiral amine of formulae, A11, A12 or A13:

 A11 ,  A 12  A 13 .

9. Process of claim 1, wherein step a) comprises a catalyst selected from dibutylboron trifluormethanesulfonate, titanium chloride, titanium(IV) trichloride isopropoxide, titanium isopropoxide, magnesium chloride, magnesium triflate and zinc chloride.

10. Process of claim 9, wherein the catalyst is dibutylboron trifluormethanesulfonate.

11. Process of claim 1, 9 and 10, wherein step a) comprises a base and an organic solvent at reaction temperatures between -78 °C and 50 °C.

12. Process of claim 1, wherein step b) comprises an oxidizing agent in the presence of an alkali hydroxide base.

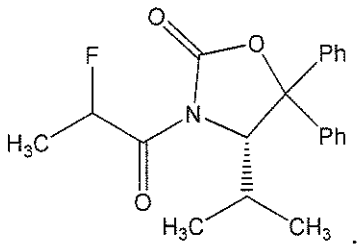
13. Process of claim 12,wherein step b) comprises hydrogen peroxide as the oxidizing agent and lithium hydroxide as the alkali hydroxide base.

14. Process of claims 1, 12 and 13, wherein step b) comprises reaction temperatures between -30°C and 50 °C.

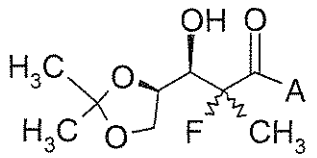
15. Process of claim 5, wherein the process further comprises a tertiary amine at reaction temperatures between -20°C and 80 °C.

16. Process of claim 15, wherein the hydroxy protecting group is benzoyl.

17. Fluoropropionate derivative of formula:

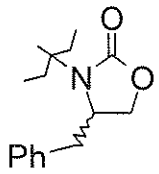


18. Aldol adduct of the formula IV:

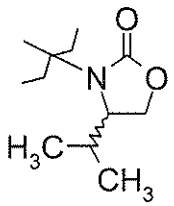


IV

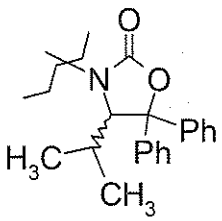
wherein A is selected from the chiral moieties A1, A2 and A3:



A1 ,



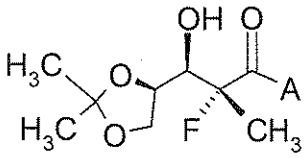
A2 and



A3 ,

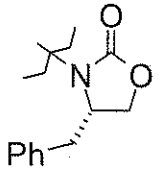
wherein Ph is phenyl.

19. Aldol adduct of claim 18 of formula IVa:

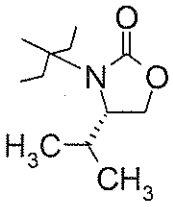


IVa

20. Aldol adduct of claims 18 and 19, wherein A is A1a, A2a or A3a:

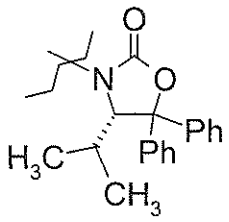


A1a



A2a

or



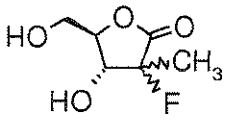
A3a

and wherein Ph is phenyl.

21. Aldol adduct of claims 18 to 20, wherein A is A3a.

Claims

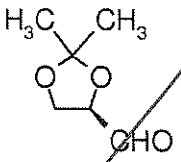
1. Process for the preparation of a fluorolactone derivative of the formula



I

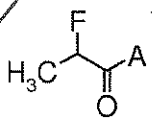
comprising the steps

a) reacting the aldehyde of the formula



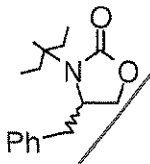
II

with a fluoropropionate derivative of formula

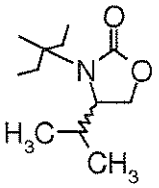


III

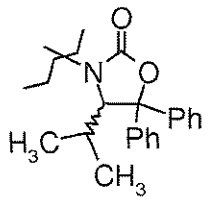
wherein A is selected from the chiral moieties



A1

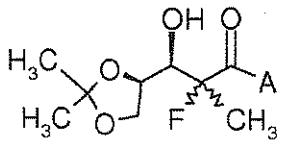


A2



A3

and Ph stands for phenyl to form an aldol adduct of the formula



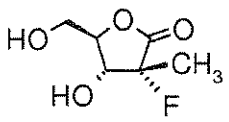
IV

wherein A is as above; and

b) subjecting to hydrolysis the aldol adduct of formula IV to give the fluorolactone derivative of the formula I.

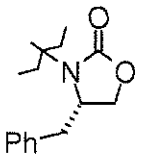
2. Process of claim 1, wherein the chiral moiety A in the fluoropropionate derivative of formula III is A3.

3. Process of claim 1, wherein the fluorolactone derivative has the formula

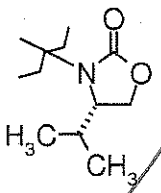


Ia

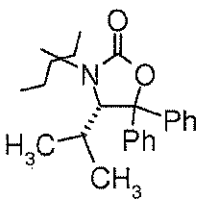
and A is selected from the chiral moieties



A1a



A2a

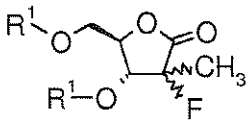


A3a

and Ph is phenyl.

4. Process of claim 3, wherein the chiral moiety A in the fluoropropionate derivative of formula III is A3a

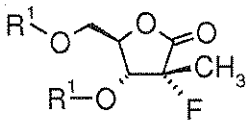
5. Process of claim 1, wherein the fluorolactone derivative of formula I is acylated to form the acylated fluorolactone of formula



V

wherein R^1 stands for a hydroxy protecting group.

6. Process of claim 5, wherein the acylated fluorolactone has the formula

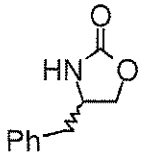


Va

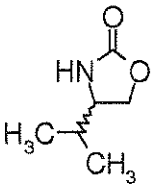
wherein R^1 stands for a hydroxy protecting group.

7. Process of claim 5 or 6, wherein the hydroxy protecting group R^1 stands for benzyl.

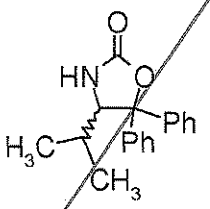
8. Process of any of the claims 1 to 7, wherein the chiral moieties A can be recovered in the form of the respective chiral amines A-H of the formulae



A11



A 12



A 13

9. Process of claim 1, wherein the reaction in step a) is performed in the presence of a catalyst selected from dibutylboron trifluormethanesulfonate, titanium chloride, titanium(IV) trichloride isopropoxide, titanium isopropoxide, magnesium chloride, magnesium triflate or zinc chloride.

10. Process of claim 9, wherein the catalyst is dibutylboron trifluormethanesulfonate.

11. Process of claim 1, 9 and 10, wherein the reaction in step a) is performed in the presence of a base and an organic solvent at reaction temperatures between -78 °C and 50 °C.

12. Process of claim 1, wherein the hydrolysis in step b) is performed with an oxidizing agent in the presence of an alkali hydroxide base.

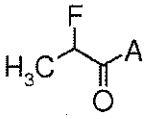
13. Process of claim 12, wherein the hydrolysis in step b) is performed with hydrogen peroxide as oxidizing agent and lithium hydroxide as alkali hydroxide base.

14. Process of claims 1, 12 and 13, wherein the hydrolysis in step b) is performed at reaction temperatures between -30°C and 50 °C.

15. Process of claim 5, wherein the acylation is performed in the presence of a tertiary amine at reaction temperatures between -20°C and 80 °C.

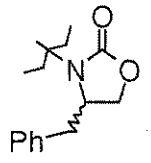
16. Process of claim 15 wherein the acylating agent is benzoyl chloride.

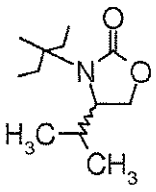
17. Fluoropropionate derivative of formula

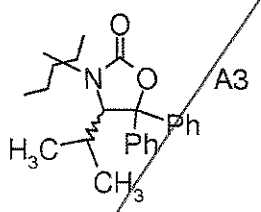


III

wherein A is selected from the chiral moieties

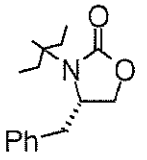

A1

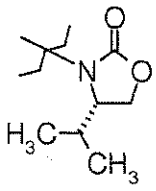

A2

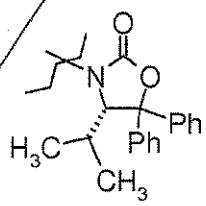

A3

wherein Ph stands for phenyl.

18. Fluoropropionate derivative of claim 17, wherein A is


A1a

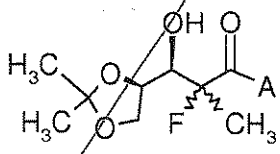

A2a


A3a

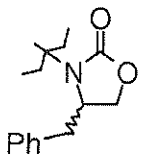
and wherein Ph stands for phenyl.

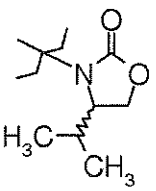
19. Fluoropropionate derivative of claim 17, wherein A is A3a.

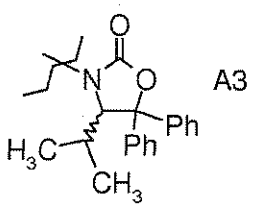
20. Aldol adduct of the formula


IV

wherein A is selected from the chiral moieties

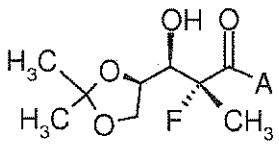

A1


A2


A3

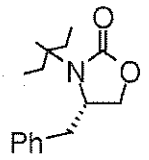
wherein Ph stands for phenyl.

21. Aldol adduct of claim 20 of the formula

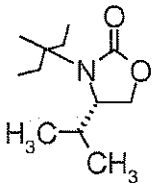

IVa

wherein A is as above.

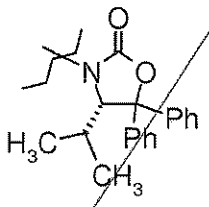
22. Aldol adduct of claims 20 and 21, wherein A is



A1a



A2a



A3a

and wherein Ph stands for phenyl.

23. Aldol adduct of claims 20 to 22 wherein A is A3a.

5