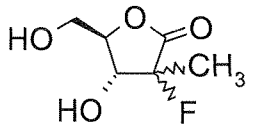
PROCESS FOR THE PREPARATION OF A FLUOROLACTONE DERIVATIVE

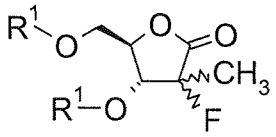
The present invention relates to a novel process for the preparation of a fluorolactone derivative of the formula



I

,

and of its acylated derivative of formula



V

.

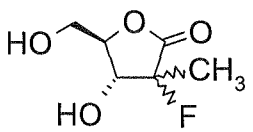
wherein R^1 stands for a hydroxy protecting group.

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 ~~present invention~~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 ~~invention~~ disclosure as described below.

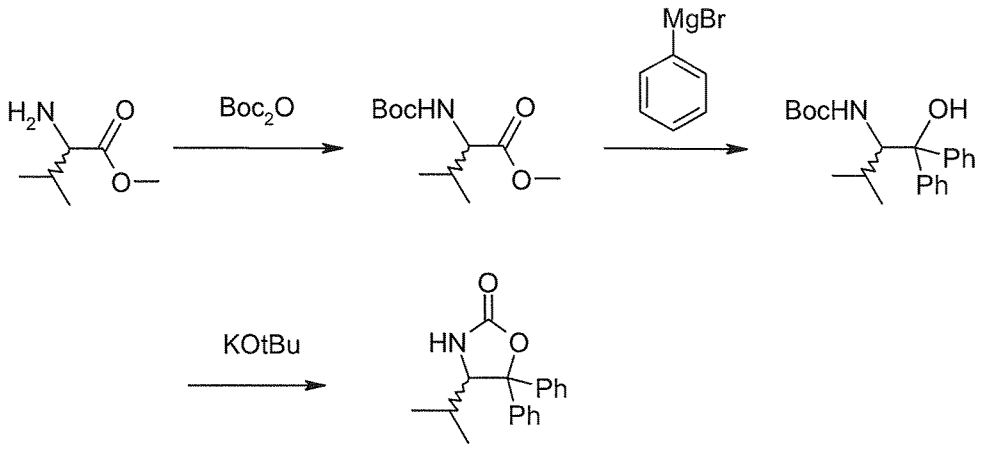
In one aspect, the ~~The~~ process of the present ~~invention~~ disclosure comprises the preparation of a fluorolactone derivative of the formula



I

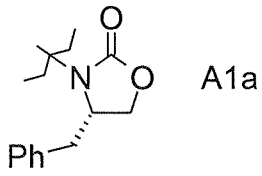
comprising the steps

a) reacting the aldehyde of the formula

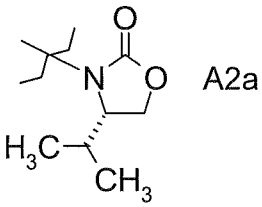


In a particular embodiment the fluoropropionate derivative of formula III wherein A is A3 is used.

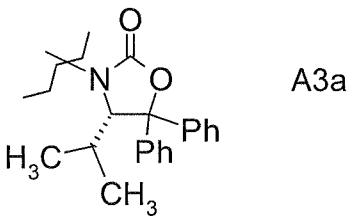
In a more particular embodiment the substituent A in the fluoropropionate derivative of formula III is selected from the chiral moieties



A1a



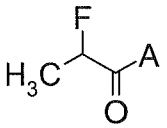
A2a



A3a

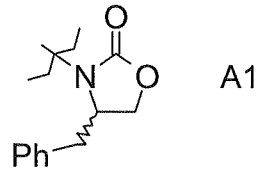
even more particularly from A3a.

The fluoropropionate derivatives of formula III

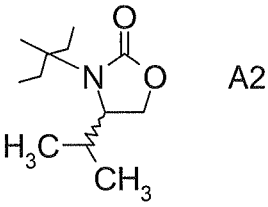


III

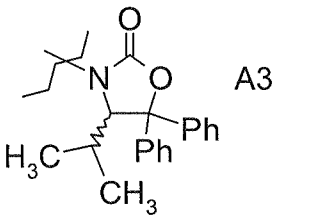
wherein A is selected from the chiral moieties



A1



A2

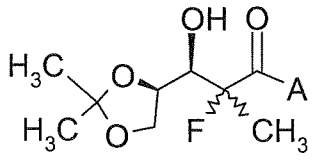


A3

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

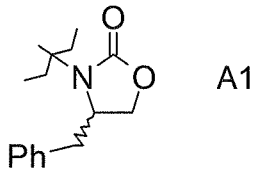
wherein the chiral moiety A is as above and selected from A1, A2 or A3, more particular from A1a, A2a or A3a and even more particular from A3a.

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

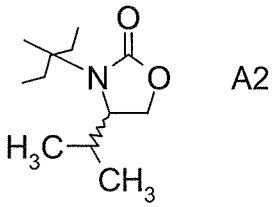


IV

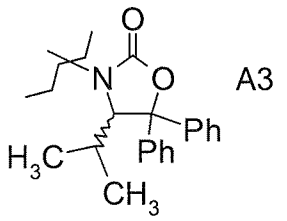
wherein A is selected from the chiral moieties



A1



A2



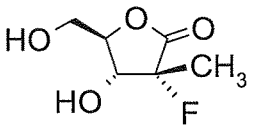
A3

wherein Ph stands for 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



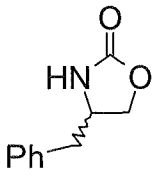
Ia

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.

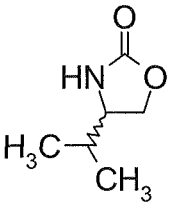
Hydrogen peroxide is usually selected as a suitable oxidizing agent and an aqueous solution of lithium hydroxide is particularly used as base.

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

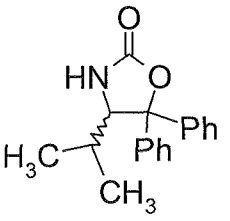
It is a particular embodiment of the present invention that the chiral moieties A are cleaved off with the hydrolysis and can be recovered in the form of the respective chiral amine A-H of the formulae



A11

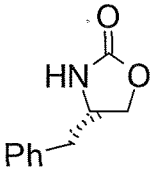


A 12

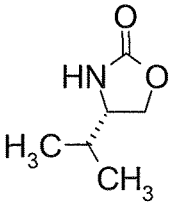


A 13

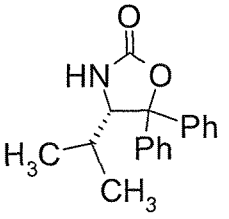
or more particularly of the formulae



A11a



A12a



A13a