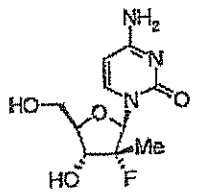
PREPARATION OF NUCLEOSIDES RIBOFURANOSYL PYRIMIDINES

This application is being filed on October 5, 2007, as a PCT International Patent application in the name of PHARMASSET, INC., a U.S. national corporation, and F. HOFFMANN LA-ROCHE AG, a Swiss national corporation, applicants for the designation of all countries except the US, and Steven D. Axt, U.S. citizen; Keshab Sarma, U.S. citizen; Justin Vitale, a U.S. citizen; Jiang Zhu, a Canadian citizen; Bruce Ross, a U.S. citizen; Suguna Rachakonda, an Indian citizen; Qingwu Jin, a Chinese citizen; and Byoung-Kwon Chun, a Korean citizen; applicants for the designation of the US only, and claims priority to U.S. Provisional patent application Serial No. 60/850,962, filed October 10, 2006.

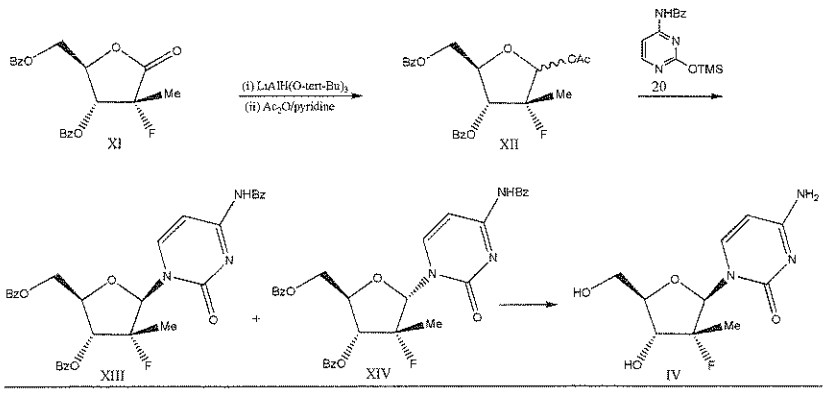
The present invention relates to an improved process for the preparation of 4-amino-1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-hydroxymethyl-3-methyl-tetrahydrofuran-2-yl)-1H-pyrimidin-2-one of the formula



(IV)

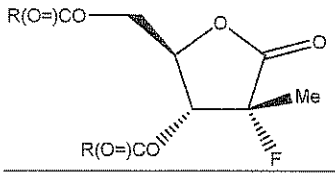
which is a potent inhibitor of Hepatitis C Virus (HCV) NS5B polymerase.

The PCT Publication WO 2006/012440 discloses a process according to the scheme below. The process requires the burdensome separation of the anomers XIII and XIV.



Summary

In one aspect, there is provided a process for the preparation of an (aryl)alkanoic acid (2R,3R,4R)-2-(aryl)alkanoyloxymethyl-4-fluoro-4-methyl-5-oxo-tetrahydro-furan-3-yl ester of formula II

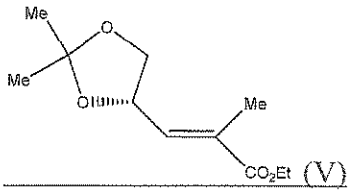


(II)

wherein R is phenyl,

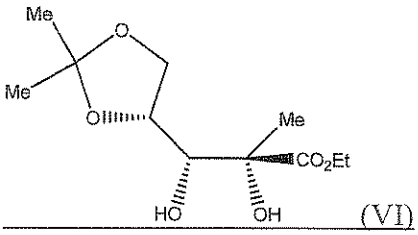
comprising the steps of

a1) transforming the (E)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-methyl-acrylic acid ethyl ester of formula V



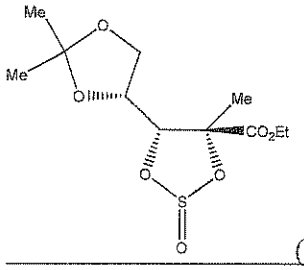
(V)

into the (2S,3R)-3-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,3-dihydroxy-2-methylpropionic acid ethyl ester of formula VI



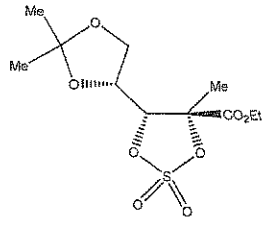
(VI)

b1) converting the (2S,3R)-3-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,3-dihydroxy-2-methyl-propionic acid ethyl ester of formula VI into the sulfite of formula VII



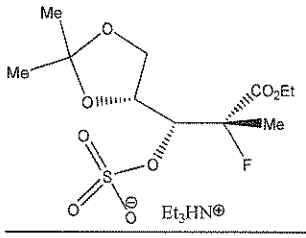
(VII)

c1) further reacting the sulfite of formula VII to the sulfate of formula VIII



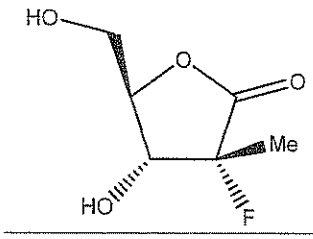
(VIII)

d1) transforming the sulfate of formula VIII into the fluorohydrin sulfate of formula IX



(IX)

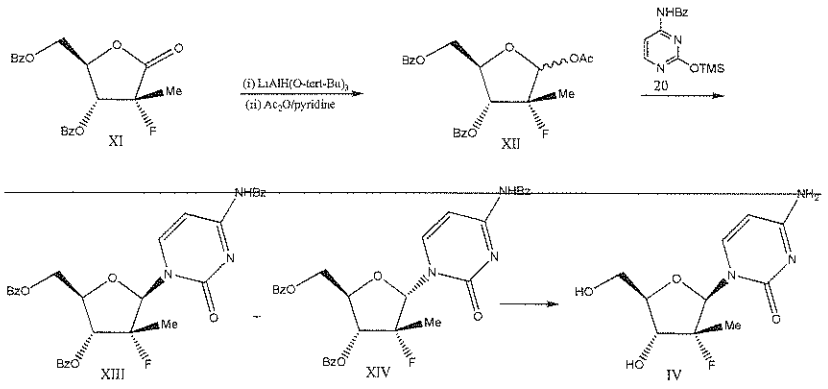
e1) decomposing the fluorohydrin sulfate of formula IX into the lactone of formula X



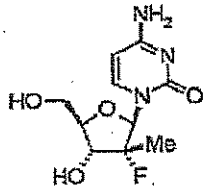
(X)

and finally

f1) acylating the lactone of formula X to form the end product of formula II wherein R is phenyl.



An object of the present invention is to provide an improved and scalable process for the preparation of 4-amino-1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-hydroxymethyl-3-methyl-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one of the formula

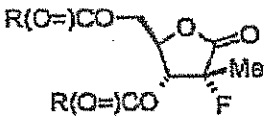


(IV)

which avoids the drawbacks known in the art.

The process of the present invention comprises

a) transforming an (aryl)alkanoic acid (2R,3R,4R)-2-(aryl)alkanoyloxymethyl-4-fluoro-4-methyl-5-oxo-tetrahydro-furan-3-yl ester of formula II



(II)