
(43) International Publication Date
3 May 2007 (03.05.2007)

(10) International Publication Number
WO 2007/049295 A2

(51) International Patent Classification:
C07D 307/26 (2006.01)

(21) International Application Number:
PCT/IN2006/000219

(22) International Filing Date:
27 June 2006 (27.06.2006)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:

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(54) Title: AN IMPROVED ONE POT PROCESS FOR MAKING KEY INTERMEDIATE FOR GEMCITABINE HCL

(57) Abstract: An improved one pot process for preparing 2-deoxy-D-erythro-2,2-difluoro-pentafuranose-l-ulose-3,5-dibenzoate of Formula (I) comprising hydrolysis of (erythro:threo) alkyl-3-dioxalan-4-yl-2,2-difluoro-3-hydroxy propionate of Formula (III) where alkyl group is having C1-C4 number of carbon atoms using a mild acid and selectively isolating 2-deoxy-D-erythro-2,2-difluoro-pentafuranose-l-ulose-3,5-dibenzoate from the mixture of erythro & threo enantiomers using ethyl acetate, ethylene dichloride and disopropyl ether as solvents with improved yield and purity.
AN IMPROVED ONE POT PROCESS FOR MAKING KEY INTERMEDIATE
FOR GEMCITABINE HCl

Field of the Invention

The present invention relates to an improved one pot process for synthesis of key intermediate of Formula (I) required for the synthesis of Gemcitabine hydrochloride.

![Formula (I)](image)

The present invention further relates to selective isolation of the erythro isomer of the intermediate using novel solvents.

Background of the Invention

Gemcitabine, a pyrimidine analog, is chemically known as 1-(2'-Deoxy-2', 2'-difluoro-D-ribofuranosyl)-4-aminopyrimidin-2-one. Although Gemcitabine is structurally similar to cytarabine, it has a wider spectrum of antitumour activity due to its different cellular pharmacology and mechanism of action. Gemcitabine belongs to the group of medicines called antimetabolites. Gemcitabine is a type of chemotherapy for treating many types of cancers including lung, pancreatic cancers. It can interfere with the growth of rapidly growing cells like cancer cells and cause cell death.

2-deoxy-D-erythro-2,2-difluoro-pentafuranose-1-ulose-3, 5-dibenzoate is a key intermediate used for synthesis of Gemcitabine hydrochloride of Formula (II).
US Patent 4,526,988, US 4808614, GB 2136425, US5015743 discloses a process for the preparation of 2-deoxy-2,2-difuoro-1-oxo ribose (lactone) shown by the Formula (IV) wherein an alkyl-3-dioxalan-4-yl-2,2-difuoro-3-hydroxy propionate of Formula (VI) where R is C₂H₅ is hydrolyzed under mild conditions using mild acidic ion exchange resin.
The above mentioned patents describe the process for the preparation of lactone intermediate of formula (IV), wherein the hydrolysis of hydroxy propionate in either form is carried out under very mild conditions using acidic ion exchange resin like Dowex 50W-X12 to form the lactone form of the carbohydrate but since reaction using resin is heterogeneous, requires more time. Further, it is specifically disclosed that it is possible to carry out the process with other hydrolytic reagents, but the main disadvantage being the formation of larger amounts of by-products. For example, aqueous acetic acid, or other relatively strong acids such as propionic acid, formic acid, chloroacetic acid, oxalic acid and the like, may be used for the hydrolysis but they do not prevent the reversion reactions.

EP Patent 0306190, EP 0688782 and EP 0630905 discloses a process for preparing lactone intermediates and 2',2'-difluoronucleosides whereby reversion back to the lactone's open chain analogue (hydroxyl acid) is minimized and the desired erythro enantiomer can be selectively isolated from an enantiomeric mixture of erythro and threo lactones in crystalline form.

EP 0306190 describes the use of monobenzyolated derivative for protection of hydroxyl group. The preparation of enantiomeric mixture of D-erythro and D-threo-2-deoxy-2, 2-difluoro-pentafuranos-1-ulose-3, 5-dibenzoate from an enantiomeric mixture of D-erythro & D-threo-2-deoxy-2, 2-difluoro pentafuranose-1-ulose-3-benzoate is described. Starting material required for monobenzoate is enantiomeric mixture containing 3R: 3S (3:1) of ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate. The hydrolytic agent used for the purpose is trifluoroacetic acid. The process results into a crystalline lactone which is stable thereby minimizing reversion back of open chain analogue as well as minimizing formation of undesirable reaction products as expected by the use of strong hydrolytic agents. The term strong acid as defined herein is acid with pKa of about -10 to 2 at room temperature (22°C). Examples of strong acid include inorganic acid such as HCl and H₂SO₄ and organic acids such as trifluoroacetic acid and p-toluene sulfonic acid. Preferred strong acids are those which have pKa value of -7 to 0. Preferred strong acids are trifluoroacetic acid and para-toluene sulfonic acid but in most of the cases
trifluoroacetic acid is used. The acid employed is in an amount sufficient to provide about 0.05 to 0.5 molar equivalents with respect to starting material. The complete removal of isoalkyldene group takes place in about 2 to 8 hours which is then followed by lactonisation with simultaneous azeotropic removal of water, it is cyclised by distilling water/alcohol, water/acetonitrile, water/acetonitrile/ aromatic solvent.

Trifluoroacetic acid (TFA) is a strong, hygroscopic, non-oxidizing, organic acid. TFA is a reagent used frequently in organic synthesis due to its nature as an organic-soluble strong acid. The present inventors have however found that trifluoroacetic acid when used as hydrolytic agent in manufacturing of Gemcitabine hydrochloride results in reversion to open chain analogue which affects the yield of the product.

The process described in EP Patent 0306190, EP 0688782 and EP 0630905 has following steps:

1. Isolation of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate.
2. Reduction of the lactone to lactol of the formula (V).

Formula (V)

Here the crude lactone containing the erythro and three isomers was crystallized from the only use of dichloromethane by dissolving it but to increase the yield, isopropanol or hexane are used as counter solvents. EP0306190 also describe about selective isolation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranose-1-ulose-3,5-dibenzoate with 95% purity.
US Patent No. 6001994 and US 5912366 discloses a process to make Gemcitabine hydrochloride wherein the improvement consists essentially of making the lactone intermediate, 2-deoxy-2,2-difluoro-D-erythro-pentafuranose-1ulose-3,5-dibenzooate of Formula (I) from D-erythro-2-Deoxy-2,2-difluoro 4,5-0- (1-ethylpropylidene) pentoic acid tertiary butyl ester which is prepared by the process of reacting S-tertiary-butyl difluoroethane thioate with 2,3-O (1-ethylpropylidene)-D-glyceraldehyde in a solvent and in the presence of a strong base; with the proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound. However, the preparation of S-tertiary-butyl difluoroethane thioate involves the use of hazardous chemical like oxalyl chloride. Also, due to their unpleasant odour thiols become unfavorable for synthesis. Beside this at various stages chromatographic purification is done which makes the process less economical.

PCT Application WO 2005/095430 discloses the use of trifluoroacetic acid as hydrolytic agent followed by cyclisation & benzyolation to get benzoylated lactone, its reduction to get benzoylated lactol. It further teaches the isolation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranose-1-ulose-3,5-dibenzooate which is achieved with the help of Methylene dichloride: Hexane & Toluene: Hexane as solvent mixtures which gives the yield in the range of 20-33%, however Methylene dichloride : Hexane as a solvent for isolation is used in most of the cases described in the prior art. In addition, hexane being highly inflammable makes its use nonviable on industrial scale. Also, it is a known fact that Toluene is a high boiling solvent which requires relative higher temperature during processing contributing to some unfavorable effects on product thereby making it a less preferred solvent.

The present inventors have found that when a strong acid like trifluoroacetic acid is used as a hydrolyzing agent, lactone formed during later part of reaction being more prone to reversion back it goes to the open chain analogue in presence of this strong acid. Even after applying reduced pressure in the procedure it is difficult to remove the water and also the strong acid present in the reaction mass further enables the reversion reaction and thus decreasing the
yield. Beside this use of toluene during the reaction requires high temperature which results in charring of the product thereby affecting the yield of the product.

As far as the solvent is concerned, the use of hexane makes this procedure very unlikely to be used at large scale. Hexane being highly inflammable makes it nonviable on industrial scale.

Isolation and crystallization of benzyolated lactone is also disclosed in US patent No. 4526988 and US Patent No. 4808614. However, the processes described in the said patents adopt laborious chromatographic purifications in different stages which make the process industrially unviable.

Therefore, the processes disclosed in the prior art for the preparation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate which is a key intermediate for the preparation of Gemcitabine hydrochloride has various disadvantages such as

- the use of mild acidic resin which prolongs the duration of process to four days thereby rendering to formation of other side products,
- the use of strong acids like trifluoroacetic acid for hydrolysis of acetals leads to formation of lactone but often causes reverse back to its open chain analogue because of its sensitivity to water,
- the relative strong acids also produce appreciable amount of undesirable side reaction products as a result of which yield of the intermediate produced is very low which affects the final yield of the Gemcitabine hydrochloride,
- the processes require isolation of product formed at every stage.

Therefore, the need of the hour is an improved process preferably an insitu or one pot process which will help in avoiding isolation of product at individual stage thereby minimizing unit operations as well as handling loss, reversion back to its open chain analogue and increasing the yield and purity significantly.

Inventors while working on suitable hydrolytic agents found that using triethyl amine salt of trifluoro acetic acid or triethyl amine salt of para toluene sulphonic acid, hydrolysis could not be completed even after 24 hours.
The inventors have surprisingly found that the use of the pyridinium salts like pyridinium trifluoroacetate or pyridinium para toluene sulphonate as a mild acid for hydrolysis in one pot, has minimized the reversion back to the lactone's open analogue thus resulting into 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulate-3,5-dibenzoate with improved yield (44% m/m) and high purity (>99.5%).

**Objects of the invention**

Therefore, it is an object of the present invention to provide an improved process for the synthesis of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulate-3,5-dibenzoate of Formula (I) that overcomes the problems associated with prior art.

It is another object of the invention to provide an improved one pot process for the synthesis of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulate-3, 5-dibenzoate.

It is yet another object of the present invention to provide an improved process for the synthesis of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulate-3, 5-dibenzoate which minimizes the reversion back to the lactone's open chain analogue.

Another object of the present invention to provide a process for selective isolation of the erythro isomer of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulate-3, 5-dibenzoate from the enantiomeric mixture of erythro and threo lactone using novel solvent system including solvent such as ethyl acetate, dichloroethane and diisopropyl ether.

Another object of the present invention to provide better hydrolytic agent required for the synthesis of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulate-3, 5-dibenzoate which minimizes the reversion back to the lactone's open chain analogue.

Another object of the present invention is to provide an improved process for the synthesis of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulate-3, 5-dibenzoate using mild acid which is a salt of organic acid such as Trifluoroacetic acid and an organic base such as Pyridine.
Yet another object of the present invention is to provide a 2-deoxy-2, 2-difluoro-D-erythro-pentafuranos-1-ulose-3, 5-dibenzoate in high yield along with high purity which in turn gives high yield of Gemcitabine hydrochloride of Formula (II).

Summary of the Invention

Thus according to an aspect of the present invention, there is provided an improved one pot process for the synthesis of a 2-deoxy-2, 2-difluoro-D-erythro-pentafuranose-1-ulose-3, 5-dibenzoate of Formula (I) comprising reaction of hydrolysis of (Erythro:Threeo) alkyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate of Formula (III) where alkyl group is having C1-C4 number of carbon atoms with hydrolyzing agent in organic solvent and water followed by formation of lactone and dibenzoylation of the lactone.

\[
\text{Formula (I)}
\]

\[
\text{Formula (III)}
\]

Where \( R = \text{Alkyl group having C1-C4 atoms} \)
According to another aspect of the present invention, there is provided a process for the selective isolation of 2-deoxy-2, 2-difluoro-D-erythro-pentafuranose-1-uloose-3, 5-dibenzoate from the enantiomeric mixture of erythro and threo isomers of 2-deoxy-2, 2-difluoro- pentafuranose-1-uloose-3, 5-dibenzoate using novel solvents such as ethyl acetate, ethylene dichloride and diisopropyl ether.

**Brief Description of Figures:**

Figure 1: DSC thermogram of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-uloose-3, 5-dibenzoate shows an endotherm at 123.69°C

Figure 2: DSC thermogram of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-uloose-3, 5-dibenzoate shows an endotherm at 123.15°C

Figure 3: DSC thermogram of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-uloose-3, 5-dibenzoate shows an endotherm at 123.19°C

DSC stands for Differential Scanning Calorimetry

**Detailed Description of the Invention**

The present invention addresses the need of a one pot process for the synthesis of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1 -uloose-3, 5-dibenzoate of Formula (I) and loss due to reversion of lactone by

![Formula (I)](image-url)
minimizing the reversion back to the lactone's open chain analogue formed which affects the overall yield of the Gemcitabine hydrochloride.

Also the present invention provides a process for exclusively isolating 2-deoxy-2, 2-difluoro-D-erythro-pentafuranose-1-ulose-3, 5-dibenzoate from the mixture of erythro and threo isomers of 2-deoxy-2, 2-difluoro-pentafuranose-1-ulose-3, 5-dibenzoate.

The inventors of the present invention have surprisingly found that use of mild acid which is salt of organic acid such as Trifluoroacetic acid and organic base such as Pyridine as a hydrolytic agent minimizing the reversion back to the lactone's open chain analogue and thus gives good yield as compared to the prior art.

The preferred mild acid according to the present invention is a Lewis acid having pKa value around 4.00 to 6.00, more preferably between 5.00-5.5. The preferred Lewis acid according to the present invention is pyridinium trifluoroacetate.

The present invention provides an improved one pot process for the hydrolysis cum lactonisation of alkyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate of formula (III) where alkyl group is having C1-C4 number of carbon atoms using acetonitrile as solvent in presence of water and pyridinium salts like pyridinium trifluoroacetate or pyridinium para toluene sulphonate as mild hydrolytic agent which also could be supporting in lactonisation to provide the required lactone in a quantitative yield, which is then taken for insitu benzoylation. However use of pyridinium para toluene sulphonate although resulted in good yield and purity but duration required for the same is more. It was found that invention also works well with other alkyl groups like methyl, isopropyl, n-propyl and butyl (Erythro:Threo)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate of Formula (III) however reaction with ethyl group yielded better results.

Alkyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate of required R isomer was charged into a round bottom flask, and acetonitrile and water and pyridinium salts like pyridinium trifluoroacetate or pyridinium para toluene sulphonate were added to it and the reaction mixture was heated to
reflux. The reaction mixture was stirred at reflux temperature for 2-15 hours preferably 3-12 hours. Mixture of Acetonitrile and water was azeotropically distilled completely to give oil. Ethyl acetate was added in the reaction mass and subjected to distillation at NTP. The obtained oil was dissolved in ethyl acetate; dry pyridine was added followed by 4,4'-dimethyl aminopyridine. The mixture was heated to 60-65°C under N2 atmosphere. Solution of benzoyl chloride in ethyl acetate for benzylation was added drop wise over 3 hours at 60-65°C. The reaction was stirred at 60-65°C for another 3 hours and then cooled to room temperature (25-30°C) and stirred for another 3 hours. The reaction mass was cooled to 0-5°C and stirred for another 1 hour and filtered. The filtrate was concentrated under vacuum at 35°-40°C to yield oil.

The preferred solvents according to present invention for the selective isolation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate from the mixture of erythro and threo isomers to get selective erythro isomer are ethyl acetate, ethylene dichloride and diisopropyl ether.

Thus, the oil obtained above was taken into ethyl acetate or ethylene dichloride followed by distillation to get a thick mass to which ethyl acetate or ethylene dichloride was then added under stirring and contents were cooled to 0-5°C and maintained for half an hour. Diisopropyl ether was then added to the contents and continued further for 10-15 min. Product so obtained is filtered off washed with diisopropyl ether and dried under vacuum at 40-45°C.

The selective erythro isomer of 2-deoxy-2,2-difluoro-D-erythro-pentafuranose-1-ulose-3,5-dibenzoate is obtained in high yield which is about 44% (m/m) along with purity >99.5%.

Entire Schematic representation for the preparation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate is shown as follows:

Step -1: Acetal formation of D-mannitol
Step -2: Preparation of 2,3-isopropylidene-D-Glyceraldehyde

Step -3: Preparation of (Erythro:Threo)Ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxypropionate

For the present invention insitu schematic representation for the conversion of (erythro:threo) ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate into 2-deoxy-2,2-difluoro-pentafuranos-1-ulose-3,5-dibenzoate is as follows:-

(Erythro:Threo)Ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate

(Erythro:Threo (3:1))

\[ \text{1. Acetonitrile,} \]

\[ \text{2. Benzoyl chloride, pyridine, DMAP in ethyl acetate} \]

(2-deoxy-2,2-difluoro-D-pentafuranose-1-ulose-3,5-dibenzoate)

(Mixture of Erythro & Threo)

\[ \chi\text{-Trifluoroacetate / Para toluene sulfonate} \]

b) Isolation of erythro isomer selectively using solvents like Ethyl acetate or Ethylene dichloride with Diisopropyl ether as solvent system.

(2-deoxy-2,2-difluoro-D-pentafuranose-1-ulose-3,5-dibenzoate)

(Mixture of Erythro & Threo)

(Erythro Isomer)

The details of the invention, its objects and advantages are explained hereunder in greater details in relation to non-limiting exemplary illustrations. The examples are merely illustrative and do not limit the teaching of this invention and it would be obvious that various modifications or changes in the procedural steps by those skilled in the art without departing from the scope of the invention and shall be consequently encompassed within the ambit and spirit of this approach and scope thereof.
Example A
Preparation of 1,2:5,6-diisopropylidene-D-mannitol:

To a 5L four neck round bottom flask fitted with Thermometer pocket, condenser with CaCl$_2$ guard tube and overhead stirrer were added 600 ml of 1,2-dimethoxy ethane, 250gm of D-mannitol and 400 ml of 2,2-dimethoxy propane. The mixture was stirred at room temperatures and 375 mg of anhydrous stannous chloride was added to the reaction mixture. The slurry was heated to reflux for approximately 50 to 90 min until mixture becomes clear. The solution was cooled below reflux temperature & pyridine (0.5ml) was added to the reaction mixture and the same was stirred for 10 minutes. The solution was concentrated below 40 to 45°C to give thick solid mass. The mixture was allowed to cool to room temperature (25°C). Methylene dichloride (500 ml) was added to it and mixture was stirred at room temperature for 30 minutes. Hexane (2.5L) was added to this mixture and cooled to 0-10°C and stirred for more 30 min and filtered off. The white solid was dried in vacuum at 35-40°C for 4 hrs. 200gm white solid obtained has GC purity 99%.

Example B
Preparation of 2,3-O-Isopropylidene-D-glyceraldehyde:

The solid (200g) 1,2:5,6-diisopropylidene-D-mannitol obtained as in example 1 was added to 2000ml of Methylene dichloride. The mixture was warmed to 30-32°C and stirred for 30 min. The resulting solution was filtered. The filtrate obtained was cooled to 15°C and 10% aqueous Sodium bicarbonate solution (80ml) was added to the reaction mass. Sodium periodate (317 gm) was added to reaction mixture and the resulting slurry is stirred at temperature between 20-25°C for another 2 hours. 100 gm of sodium sulfate was added to the reaction & the slurry is stirred for another 15 min. The reaction mass was filtered and the solid residue was washed twice with 200 ml of methylene dichloride. The resulting filtrate is collected and solvent was distilled at 40-45°C to obtain oil which was heated up to 50-52°C under vigorous stirring to remove traces of solvent. The oil weight is 180 gm with 95% (GC purity).
Example C
Preparation of (ErythroThreo) ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate:

To the 5L round bottom flask fitted with overhead stirrer, condenser, pressure equalizing dropping funnel 1.8L of tetrahydrofuran was added. Zn dust (180 gm) and trimethylsilyl chloride (28.76ml) were added to it under stirring. The mixture was stirred at room temperature for 15 min and then heated to reflux and mixture of 2,3-O-isopropylidene-D-glyceraldehyde (180gm) and Bromodifluoroethyl acetate (248 ml) was added through dropping funnel to the reaction mixture slowly over a period of 30-40 min. The reaction was stirred with reflux for another 2hrs. After 2 hours the reaction mass was cooled to room temperature and poured in mixture of 143 ml of Cone. HCl and 1100 gm ice under stirring. The mixture was stirred for 15 min and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (200mlX 3). The collective organic layer was washed with brine followed by 5% aq. Sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to yield the product (250 gm) with GC purity of desired isomer 75%.

Example D
Preparation & isolation of 2-deoxy-D-erythro-2,2-difluoro-pentafuranos-1-ulose-3,5-dibenzoate:

To a 3L four-necked round bottom flask 82g of ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate having 75% of required R isomer was charged, and acetonitrile (820ml) and water (26ml) and pyridinium trifluoroacetate (14.76g) were added to it and the reaction mixture was heated to reflux. The reaction mixture was stirred at reflux temperature for 3 hours. Mixture of Acetonitrile and water was azeotropically distilled completely to give oil. Ethyl acetate (90ml) was added in the reaction mass and subjected to distillation at NTP. The obtained oil was dissolved in ethyl acetate (328ml), dry pyridine (96ml) was added followed by 4, 4'-dimethyl aminopyridine (9.52g). The mixture was
heated to 65°C under N₂ atmosphere. Solution of benzoyl chloride (96ml) in ethyl acetate (255ml) was added drop wise over 3 hours at 65°C. The reaction was stirred at 65°C for another 3 hours and then cooled to room temperature (25-30°C) and stirred for another 3 hours. The reaction mass was cooled to 0-5°C and stirred for another 1 hour and filtered. The filtrate was concentrated under vacuum at 35°C to yield 160 g oil. Oil so obtained was taken into 164ml ethyl acetate followed by distillation to get a thick mass to which 61.5 ml ethyl acetate was then added under stirring and contents were cooled to 0-5°C followed by keeping for half an hour. Diisopropyl ether (205ml) was then added to the contents and continued further for 10-15 min. Product so obtained is filtered off washed with diisopropyl ether and dried under vacuum at 40-45°C. Yield (53.3g), HPLC purity of +99.5%, DSC thermogram has shown the endotherm in the range of 121-125°C (peak at 123.69°C), Figure 1.

**Example E**

**Preparation & isolation of 2-deoxy-D-erythro-2,2-difluoro-pentafuranos-1-ulose-3,5-dibenzoate:**

To a 3L four-necked round bottom flask 90g of ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate having 75% of required R isomer was charged, and acetonitrile (900ml) and water (29ml) and pyridinium para toluene sulphonate (19.6g) were added to it and the reaction mixture was heated to reflux. The reaction mixture was stirred at reflux temperature for 12 hours. Mixture of Acetonitrile and water was azetropically distilled completely to give oil. Ethyl acetate (100ml) was added in the reaction mass and subjected to distillation at NTP. The obtained oil was dissolved in ethyl acetate (360ml), dry pyridine (105ml) was added followed by 4, 4'-dimethyl aminopyridine (10.44g). The mixture was heated to 65°C under N₂ atmosphere. Solution of benzoyl chloride (105ml) in ethyl acetate (260ml) was added drop wise over 3 hours at 65°C. The reaction was stirred at 65°C for another 3 hours and then cooled to room temperature (25-30°C) and stirred for another 3 hours. The reaction mass was cooled to 0-5°C and stirred for another 1 hour and filtered. The filtrate was concentrated under vacuum at 35°C to yield 160 g oil. Oil so obtained was taken
into 170ml ethyl acetate followed by distillation to get a thick mass to which 61.5 ml ethyl acetate was then added under stirring and contents were cooled to 0-5°C followed by keeping for half an hour. Diisopropyl ether (210ml) was then added to the contents and continued further for 10-15 min. Product so obtained is filtered off washed with diisopropyl ether and dried under vacuum at 40-45°C. Yield (59g), HPLC purity of +99.5%. DSC thermogram has shown endotherm in the range of 121-125°C (peak at 123.15°C) Figure 2.

**Example F**

Procedure in example E was repeated with 162 g (Erythro:Threo) ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate resulting in to 290 g oil. Thick oil so obtained is taken into 300ml ethylene dichloride followed by distillation under vacuum at 55-60°C to get a thick mass to which 122 ml ethylene dichloride was then added under stirring and contents were cooled to 0-5°C followed by keeping for half an hour. Diisopropyl ether (400ml) was then added to the contents and continued further for 10-15 min. Product so obtained was filtered off washed with diisopropyl ether and dried under vacuum at 40-45°C. Yield (105.3g), HPLC purity of +99.5% & more, DSC thermogram has shown endotherm in the range of 121-125°C (peak at 123.19°C) Figure 3.

The present invention has following advantages:

- The process according to the present invention minimizes the reversion back to the lactone's open chain analogue thereby increasing the yield of lactone intermediate & overall yield of Gemcitabine hydrochloride effectively.
- Time required in the present invention for the process of hydrolysis during synthesis of 2-deoxy-2,2-difluoro-D erythro-pentafuronose-1-ulose-3,5-dibenzoate is reduced from four days to 3-12 hours.
- An in situ operation which is one of the essential features of the present invention has minimized unit operations as well as handling loss also, as isolation of individual stages is avoided.
• 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate is obtained in high yield which is about 44%(m/m) and 65%(w/w).

• Selective isolation of 2-deoxy-2,2-difluoro-D-erythro-pentafuranos-1-ulose-3,5-dibenzoate from the enantiomeric mixture of erythro and threo isomers with good purity and higher yield could be achieved with the help of solvents like ethyl acetate or ethylene dichloride with diisopropyl ether which have not been reported earlier.

• Product isolated is not only pure but also higher in yield than reported earlier.
CLAIMS

1. A process for the preparation of 2-deoxy-2,2-difluoro-D erythro-pentafuronose-1-ulose-3,5-dibenzoate of the formula (I) comprising

a) hydrolysis of (Erythro:Threo) alkyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate of formula (III) by the use of mild acid.

b) cyclisation to form lactone

c) benzoylation of lactone

d) isolation of erythro isomer using novel solvents

FORMULA (I)

FORMULA (III)

Where R = Alkyl group having C1-C4 atoms
2. The process according to claim 1 wherein said alkyl group of formula (III) is ethyl.

3. A process according to claim 1 wherein the mild acid is a salt of organic acid such as trifluoroacetic acid or para toluene sulphonic acid and organic base such as Pyridine.

4. A process according to claim 1 wherein the mild acid is selected from pyridinium trifluoroacetate or pyridinium para toluene sulphonate.

5. A process according to claim 1 wherein the preferred mild acid is pyridinium trifluoroacetate.

6. A process according to claim 1 wherein the mild acid has the pKa value around 4.00 to 6.00, more preferably between 5.00-5.50.

7. A process for selective isolation of erythro isomer of 2-deoxy-2,2-difluoro-D erythro-pentafuronose-1-ulose-3,5-dibenzoate comprising dissolving the enantiomeric mixture of erythro and threo isomers in ethyl acetate or ethylene dichloride, cooling the solution and adding diisopropyl ether followed by collecting the precipitated erythro enantiomer.

8. A process according to claim 6 wherein the selective erythro isomer of 2-deoxy-2,2-difluoro-D-erythro-pentafuronose-1-ulose-3,5-dibenzoate is obtained in yield of about 44% (m/m) along with purity >99.5%.