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(54) **Title:** A PROCESS FOR THE PREPARATION OF GEMCITABINE USING NOVEL INTERMEDIATES

(57) **Abstract:** The present invention provides a commercially viable process for preparing gemcitabine and its pharmaceutically acceptable acid addition salts thereof in high yield and purity using novel intermediates.

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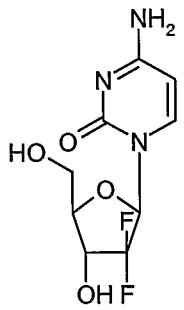
A PROCESS FOR THE PREPARATION OF GEMCITABINE USING NOVEL INTERMEDIATES

FIELD OF THE INVENTION

The present invention provides a commercially viable process for preparing gemcitabine and its pharmaceutically acceptable acid addition salts thereof in high yield and purity using novel intermediates.

BACKGROUND OF THE INVENTION

U. S. Patent No. 4,808,614 disclosed difluoro antivirals and their derivatives thereof. These compounds are antiviral agents, and are useful in the treatment of various cancers and Herpes viral infections in mammals. Among them gemcitabine, chemically 2'-deoxy-2',2'-difluorocytidine is a pyrimidine antimetabolite with broad spectrum activity against murine leukemias, murine solid tumors, and human tumor xenografts. Gemcitabine is represented by the following structure:



Processes for the preparations of gemcitabine and related compounds were disclosed in U.S. Patent No. 4,808,614, J. Org. Chem. 53, 2406 (1988), Synthesis 1992, page: 565 and Eur. Patent No. 688783 B1.

According to U.S. Patent No. 4,808,614, ethyl 2,2-difluoro-3(R)-hydroxy-3-(2,2-dimethyl-dioxolan-4-yl)propionate is treated with Dowex 50W-X12 resin to give 2-desoxy-2,2-difluoro-1-oxoribose, which is then reacted with trifluoromethylsulfonyloxy t-butyldimethylsilane followed by chromatographed on silica gel to give 3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluoro-1-oxoribose; 3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluoro-1-oxoribose is reduced with diisobutyl aluminum hydride to give 3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluororibose, which is then treated with methanesulfonyl chloride in presence of a base to give 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose; 3,5-bis(t-butyldimethylsilyloxy)-

1-methanesulfonyloxy-2-desoxy-2,2-difluororibose is reacted with bis(trimethyl silyl)-N-acetylcytosine in presence of trifluoromethanesulfonyloxytrimethylsilane, followed by treatment with ammonia to give gemcitabine.

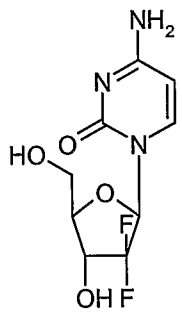
Eur. Patent No. 688783 B1 described a process for preparation of gemcitabine using benzoyl protection of intermediates.

The present invention is an improved, simple and commercially viable process that avoids multiple crystallizations and multiple chromatographic purifications that are associated with process described in the prior art.

One object of the present invention is to provide a novel process for preparing gemcitabine and pharmaceutically acceptable acid addition salts of gemcitabine in high purity and in high yield using novel intermediates.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a process for preparing gemcitabine of formula I:

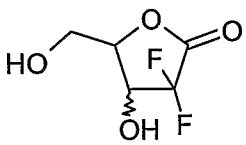


---------- I

or a pharmaceutically acceptable salt thereof:

which comprises:

a) reacting lactone compound of formula II:



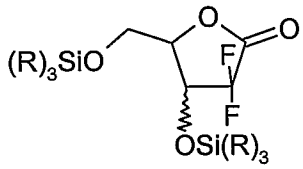
---------- II

with a silyl compound of formula III:

$(R)_3Si\text{-}Cl$ ---------- III

wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl;

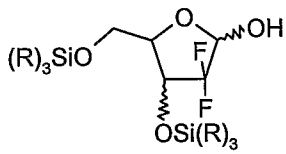
in presence of a base to give silyl protected lactone compound of formula IV:



---------- IV

wherein R is same as defined above;

b) reducing the silyl protected lactone compound of formula IV using reducing agent to give silyl protected carbohydrate of formula V:



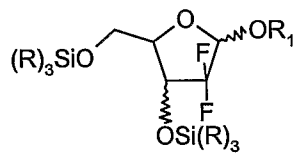
---------- V

wherein R is same as defined above;

c) reacting the silyl protected carbohydrate of formula V with the compound of formula VI:

R_1-X ----------VI

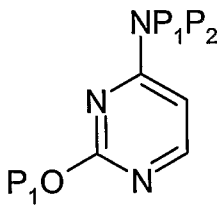
wherein X is halo and R_1 is selected from C_1 - C_6- alkylsulfonyl and unsubstituted or substituted phenylsulfonyl; in presence of a base to give the compound of formula VII:



---------- VII

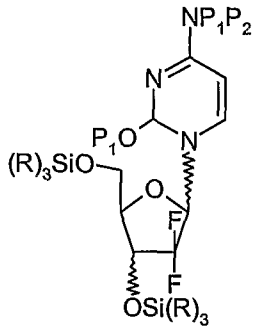
wherein R and R_1 are same as defined above;

d) reacting the compound of formula VII with the compound of formula X:



---------- X

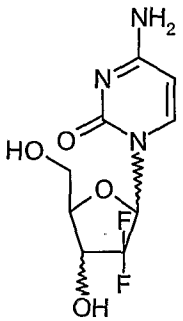
wherein P_1 is independently silyl protecting group and P_2 is H or acyl group; to give cytidine compound of formula VIII:



---------- VIII

wherein R, P_1 and P_2 are same as defined above;

e) deprotecting the cytidine compound of formula VIII using deprotecting agent/s to give the mixture of isomers of the compound of formula IX:



---------- IX

and

f) separating isomer from the mixture of isomers of the compound of formula IX obtained in step (e) by column chromatographic technique to give gemcitabine of formula I and optionally converting gemcitabine formed into the pharmaceutically acceptable acid addition salt of gemcitabine.

Preferably R is independently tert-butyl or phenyl.

Preferably the base used in step (a) is selected from imidazole, lutidine and pyridine. More preferable base is imidazole.

Preferably the reaction in step (a) is carried out in an inert solvent selected from the group consisting of hydrocarbon solvents such as toluene, xylene, n-hexane and cyclohexane; chlorinated hydrocarbon solvents such as methylene chloride, ethylene dichloride, chloroform and carbon tetrachloride; ketonic solvents such as acetone, diethyl ketone, methyl ethyl ketone, methyl propyl ketone, methyl isobutyl ketone and methyl tert-butyl ketone; ester solvents such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl

acetate, ethyl formate and methyl formate; ether solvents such as diethyl ether, diisopropyl ether and tert-butyl methyl ether; dimethylformamide; N, N-dimethyl acetamide, dimethyl sulfoxide; tetrahydrofuran. Most preferable solvent is dimethylformamide.

The reaction in step (a) is preferably carried out at ambient temperatures in the range from about -25^{0}C to 100^{0}C, more preferably at about 0^{0}C to 90^{0}C and still more preferably at about 0^{0}C to 80^{0}C.

Preferable reducing agent used in step (b) is diisobutyl aluminum hydride or lithium aluminum hydride and most preferable reducing agent is diisobutyl aluminum hydride. The reduction is preferably carried out in the temperature range of about -100^{0}C to -20^{0}C, more preferably at about -85^{0}C to -50^{0}C and still more preferably at about -80^{0}C to -65^{0}C. The reduction is preferably carried out in a solvent with a very low freezing point such as toluene and ether solvents such as diethyl ether. Most preferable solvent is toluene.

Preferable halo group used in step (c) is chloro, bromo or iodo and more preferable being chloro.

Preferable C_1 - C_6- alkylsulfonyl group is methane sulfonyl. Preferable substituents of substituted phenylsulfonyl group are C_1-C_3-alkyl and nitro; and more preferable substituted phenylsulfonyl groups are toluene sulfonyl and p-nitrobenzene sulfonyl. Most preferably R_1 is methane sulfonyl.

Preferable base used in step (c) is an amine base and most preferable amine base is triethyl amine.

The reaction in step (c) is preferably carried out in a chlorinated hydrocarbon solvent such as methylene chloride, ethylene dichloride and chloroform; and most preferable solvent is methylene chloride.

The compound of formula X is coupled with the compound of formula VII to obtain the compound of formula VIII (step- d). Preferably, P_1 is trimethylsilyl and P_2 is H or acetyl.

The reaction between the compound of formula VII and the base is preferably carried out at an elevated temperature in the range of from about 50^{0}C to about 200^{0}C. It is possible, however, to use relatively high-boiling solvents for the reaction, such as dimethylformamide and dimethylacetamide, hexamethylphosphoramide.

The coupling reaction is preferably carried out in an inert reaction solvent, as defined above, may be used to temperatures in the range of from about ambient to about 100^0C.

The preferable protected cytosine base of formula X used in step (d) is N-acetyl cytosine, bis(trimethylsilyl)-N-acetyl cytosine or bis(trimethylsilyl) cytosine. Preferable silyl protecting agent is hexamethyl disilazane.

The step (e) of the reaction is the removal of the protecting groups. Most silyl protecting groups are easily cleaved by contact with water, an alcohol, an acid or tetrabutyl ammonium fluoride. The deprotection reaction is preferably carried out in alcoholic solvents; especially aqueous alcoholic solvents; polyols such as ethylene glycol and cyclic ether solvents such as tetrahydrofuran.

The isomers of formula IX obtained after deprotection are conveniently separated by column chromatography. Usually single run can effectively separate gemcitabine from the other three isomers.

The gemcitabine obtained above can be converted to a pharmaceutically acceptable salt by a conventional method.

The protected compounds of the formulae IV, V, VII and VIII are novel and forms part of the invention.

Preferable pharmaceutically acceptable acid addition salts of gemcitabine are selected from salts obtained from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; and organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, maleic acid, fumaric acid and tartaric acid. More preferable pharmaceutically acceptable acid addition salt is hydrochloric acid.

The process of the present invention can conveniently be monitor by High Performance Liquid Chromatography (HPLC) as against the process described in U.S. Patent No. 4,808,614, which cannot be monitored by HPLC.

The invention will now be further described by the following example, which is illustrative rather than limiting.

Example

Step-I:

Acetonitrile (1000 ml), trifluoroacetic acid (10 ml) and water (260 ml) are added to ethyl 2,2-difluoro-3-hydroxy-3-(2,2-dimethyl-dioxolan-4-yl)propionate

(100 gm) and then the contents are heated to reflux for 4 hours. The solvent is distilled and co-distilled with toluene to remove water completely from the reaction mass to give 66 gm of 2-desoxy-2,2-difluoro-1-oxoribose as residue.

Step-II:

The residue obtained in step-I is added to dimethylformamide (200 ml) at 25 - 30^{0}C and then imidazole (90 gm) is added to form a clear solution. The solution is cooled to 10^{0}C, the solution of tert-butyldiphenylsilyl chloride (200 gm) in dimethylformamide (50 ml) is added drop wise and then stirred for 24 hours at reflux. The reaction mass is heated to 60 - 65^{0}C for 3 hours and then cooled to 25 - 30^{0}C. The mass is poured into water (1000 ml) and extracted with ethyl acetate (500 ml). The aqueous layer is separated and again extracted with ethyl acetate (250 ml). Then combined the two ethyl acetate layers, washed with 5% sodium bicarbonate solution (300 ml), again washed with water (200 ml) and then with saturated sodium chloride solution (200 ml). The resulting organic layer is dried on Na_2SO_4 and then distilled under vacuum to give 240 gm of residue. The residue was purified by column chromatography to give 84 gm of 3,5-bis(tert-butyldiphenylsilyloxy)-2-desoxy-2,2-difluoro-1-oxoribose.

Step-III:

The residue (24 gm, obtained in step-II) is added to toluene (300 ml), cooled to -78^{0}C and then 20% solution of diisobutylaluminum hydride (66 gm) in hexane is added drop wise for 1 hour at -75^{0}C. The reaction mass is stirred for 45 minutes at -75 to -70^{0}C to complete disappearance of starting material. To this reaction mixture methanol (60 ml) is added drop wise at -75 to -70^{0}C and then stirred for 10 minutes. Water (150 ml) is added to the reaction mass, pH is adjusted to 3 with 10% aqueous hydrochloric acid solution and the compound is extracted into toluene (200 ml). Then separated the layers and the compound is extracted with toluene (300 ml). The organic layer is washed with water (150 ml) and then washed with saturated sodium chloride solution (100 ml). The organic is layer is dried on Na_2SO_4 and distilled the toluene under reduced pressure to give 19 gm of 3,5-bis(tert-butyldiphenylsilyloxy)-2-desoxy-2,2-difluororibose as residue.

Step-IV:

The residue (19 gm, obtained in step-III) is added to methylene chloride (190 ml), cooled to 0^0C and then triethyl amine (9.5 ml) is added. To this reaction mixture methanesulfonyl chloride (3.32 ml) is added drop wise for 15 minutes, the temperature is raised to 25 - 30^0C and stirred for 2 hours. Methylene chloride is distilled off under vacuum, the residue is dissolved in ethyl acetate (500 ml) and the resulting ethyl acetate layer is washed with 5% sodium bicarbonate solution (500 ml) and water (100 ml). The ethyl acetate layer is washed with saturated sodium chloride solution (100 ml), dried on Na_2SO_4 and distilled the layer to give 20 gm of 3,5-bis(tert-butyldiphenylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose as residue.

Step-V:

The mixture of N-acetyl cytosine (18 gm) and ethylene dichloride (400 ml) is stirred for 10 minutes, hexamethyl disilazane (32 ml) and trimethylsilyl chloride (4 ml) are added and then the contents are heated to 80^0C to form a clear solution. The solution is stirred for 1 hour at 80^0C and then distilled completely to obtain a solid. To the resulting solid ethylene dichloride (125 ml) is added and stirred for 10 minutes to form a clear solution. The reaction mass is cooled to 20^0C and then the solution of trimethyl silyl triflate (20 ml) in ethylene dichloride (100 ml) is added drop wise at 20 - 25^0C for 15 minutes. The contents are stirred for 20 minutes and then the solution of the residue (20 gm, obtained in step-IV) in ethylene dichloride (100 ml) is added drop wise for 10 minutes at 20 - 25^0C. The resulting mass is heated to reflux for 18 hours and then cooled to 25 - 30^0C. To the reaction mass 5% aqueous hydrochloric acid is added at 10 - 15^0C to adjust the pH to 5.5 - 6.5. The ethylene dichloride layer is separated and then the aqueous layer is extracted with methylene chloride (400 ml). Then combined the ethylene dichloride layer and methylene chloride layer and washed with water (200 ml) and saturated sodium chloride solution (100 ml). The organic layer is dried on Na_2SO_4 and distilled to give 20 gm of 3',5'-bis(tert-butyldiphenylsilyloxy)-2',2'-difluoro-2'-deoxycytidine as residue.

Step-VI:

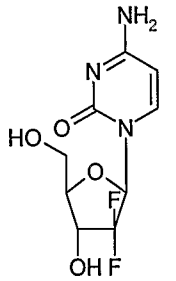
To the residue (20 gm, obtained in step-V) tetrahydrofuran (100 ml) is added and then the solution of tetrabutyl ammonium fluoride (14.7 gm) in tetrahydrofuran (50 ml) is added drop wise at 15 - 20^{0}C for 20 minutes. The reaction mass is stirred for 5 hours at 25 - 30^{0}C and then distilled the solvent under vacuum. Water (100 ml) and ethyl acetate (100 ml) are added to the residue and then stirred for 10 minutes. Separated the layers and then the aqueous layer is washed with ethyl acetate (50 ml) and hexane (50 ml). The aqueous layer is then subjected to carbon treatment at 50^{0}C and co-distillation of the filtrate with isopropyl alcohol (3 x 150 ml) under vacuum. The residue obtained is then subjected to column chromatography to obtain 3.5 gm of gemcitabine free base as residue (HPLC Purity: 92.6%).

Step-VII:

The residue (3.5 gm, obtained in step-VI) is dissolved in isopropyl alcohol (50 ml), the pH is adjusted to 2 with 20% hydrochloric acid at 0 - 5^{0}C and then distilled the solvent to get residue. To the residue acetone (60 ml) is added and stirred for 5 minutes. The separated solid is filtered, washed three times with acetone (50 ml) and then dissolved in water (1 ml). To this solution added acetone (15 ml). The separated solid is filtered and dried to give 2.5 gm of gemcitabine hydrochloride (HPLC Purity: 99.6%).

We claim:

1. A process for the preparation of gemcitabine of formula I:

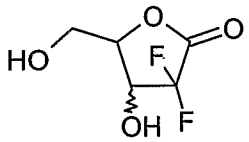


---------- I

or a pharmaceutically acceptable salt thereof:

which comprises:

a) reacting lactone compound of formula II:



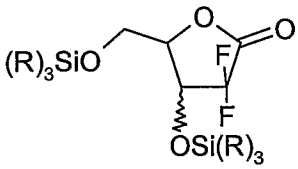
---------- II

with a silyl compound of formula III:

$(R)_3Si\text{-}Cl$ ---------- III

wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl;

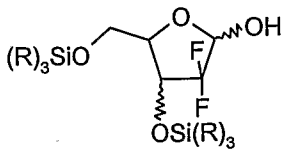
in presence of a base to give silyl protected lactone compound of formula IV:



---------- IV

wherein R is same as defined above;

b) reducing the silyl protected lactone compound of formula IV using reducing agent to give silyl protected carbohydrate of formula V:



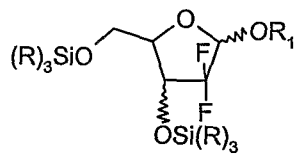
---------- V

wherein R is same as defined above;

c) reacting the silyl protected carbohydrate of formula V with the compound of formula VI:

R_1-X ----------VI

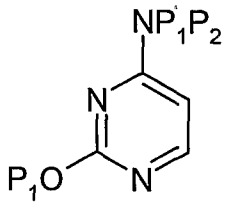
wherein X is halo and R_1 is selected from C_1 - C_6- alkylsulfonyl and unsubstituted or substituted phenylsulfonyl; in presence of a base to give the compound of formula VII:



---------- VII

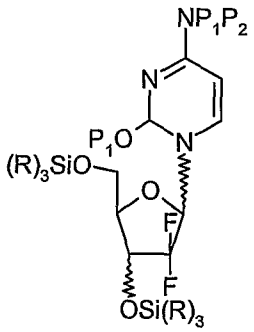
wherein R and R_1 are same as defined above;

d) reacting the compound of formula VII with the compound of formula X:



---------- X

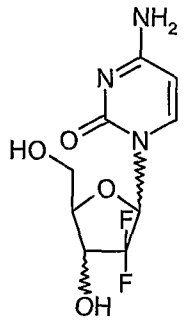
wherein P_1 is independently silyl protecting group and P_2 is H or acyl group; to give cytidine compound of formula VIII:



---------- VIII

wherein R, P_1 and P_2 are same as defined above;

e) deprotecting the cytidine compound of formula VIII using deprotecting agent/s to give the mixture of isomers of the compound of formula IX:



---------- IX

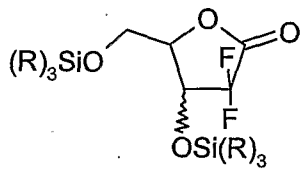
and

f) separating isomer from the mixture of isomers of the compound of formula IX obtained in step (e) by column chromatographic technique to give gemcitabine of formula I and optionally converting gemcitabine formed into the pharmaceutically acceptable acid addition salt of gemcitabine.

2. The process as claimed in claim 1, wherein the base used in step (a) is selected from imidazole, lutidine and pyridine.
3. The process as claimed in claim 2, wherein the base is imidazole.
4. The process as claimed in claim 1, wherein the reaction in step (a) is carried out in an inert solvent selected from the group consisting of hydrocarbon solvents such as toluene, xylene, n-hexane and cyclohexane; chlorinated hydrocarbon solvents such as methylene chloride, ethylene dichloride, chloroform and carbon tetrachloride; ketonic solvents such as acetone, diethyl ketone, methyl ethyl ketone, methyl propyl ketone, methyl isobutyl ketone and methyl tert-butyl ketone; ester solvents such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl acetate, ethyl formate and methyl formate; ether solvents such as diethyl ether, diisopropyl ether and tert-butyl methyl ether; dimethylformamide; N, N-dimethyl acetamide, dimethyl sulfoxide; tetrahydrofuran.
5. The process as claimed in claim 4, wherein the solvent is dimethylformamide.
6. The process as claimed in claim 1, wherein the reaction in step (a) is carried out at ambient temperatures in the range from about -25^{0}C to 100^{0}C.

7. The process as claimed in claim 6, wherein the reaction is carried out at about 0^0C to 90^0C.
8. The process as claimed in claim 7, wherein the reaction is carried out at about 0^0C to 80^0C.
9. The process as claimed in claim 1, wherein the reducing agent used in step (b) is diisobutyl aluminum hydride or lithium aluminum hydride.
10. The process as claimed in claim 9, wherein the reducing agent is diisobutyl aluminum hydride.
11. The process as claimed in claim 1, wherein the reduction in step (b) is carried out in the temperature range of about -100^0C to -20^0C.
12. The process as claimed in claim 11, wherein the reduction is carried out at about -85^0C to -50^0C.
13. The process as claimed in claim 12, wherein the reduction is carried out at about -80^0C to -65^0C.
14. The process as claimed in claim 1, wherein the reduction in step (b) is carried out in a solvent with a very low freezing point such as toluene and ether solvents such as diethyl ether.
15. The process as claimed in claim 14, wherein the solvent is toluene.
16. The process as claimed in claim 1, wherein the halo group used in step (c) is chloro, bromo or iodo.
17. The process as claimed in claim 16, wherein the halo group is chloro.
18. The process as claimed in claim 1, wherein the step (c), the C_1 - C_6-alkylsulfonyl group is methane sulfonyl.
19. The process as claimed in claim 1, wherein the step (c), substituents of substituted phenylsulfonyl group are C_1-C_3-alkyl and nitro.
20. The process as claimed in claim 19, wherein the substituted phenylsulfonyl groups are toluene sulfonyl and p-nitrobenzene sulfonyl.
21. The process as claimed in claim 1, wherein the group R_1 is methane sulfonyl.
22. The process as claimed in claim 1, wherein the base used in step (c) is an amine base.
23. The process as claimed in claim 22, wherein the amine base is triethyl amine.

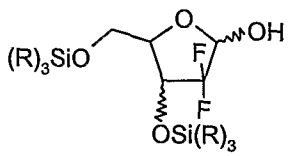
24. The process as claimed in claim 1, wherein the reaction in step (c) is carried out in a chlorinated hydrocarbon solvent such as methylene chloride, ethylene dichloride and chloroform.
25. The process as claimed in claim 1, wherein the chlorinated hydrocarbon solvent is methylene chloride.
26. The process as claimed in claim 1, wherein the protected cytosine base of formula X in step (d) is N-acetyl cytosine, bis(trimethylsilyl)-N-acetyl cytosine or bis(trimethylsilyl) cytosine.
27. The process as claimed in claim 1, wherein the reaction in step (e), the silyl protecting groups are cleaved by contact with water, an alcohol, an acid or tetrabutyl ammonium fluoride.
28. The process as claimed in claim 1, wherein the deprotection reaction in step (e) is carried out in alcoholic solvents; aqueous alcoholic solvents; polyols such as ethylene glycol, cyclic ether solvents such as tetrahydrofuran.
29. The process as claimed in claim 28, wherein the solvent is tetrahydrofuran.
30. The process as claimed in claim 1, wherein R is independently tert-butyl or phenyl.
31. Compound of formula IV:



---------- IV

wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl.

32. The compound as claimed in claim 31, wherein the R is independently tert-butyl or phenyl.
33. Compound of formula V:

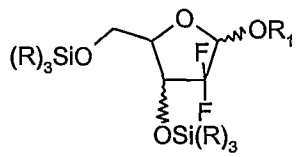


---------- V

wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl.

34. The compound as claimed in claim 33, wherein the R is independently tert-butyl or phenyl.

35. Compound of formula VII:



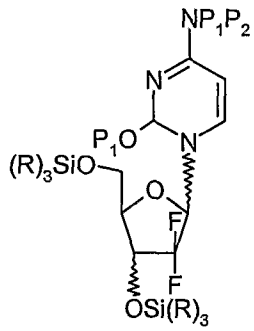
---------- VII

wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl; and R_1 is selected from C_1 - C_6- alkylsulfonyl and unsubstituted or substituted phenylsulfonyl.

36. The compound as claimed in claim 35, wherein the R is independently tert-butyl or phenyl and R_1 is toluene sulfonyl, p-nitrobenzene sulfonyl or methane sulfonyl.

37. The compound as claimed in claim 36, wherein R_1 is methane sulfonyl.

38. Compound of formula VIII:



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wherein R is C_1 - C_6- alkyl, substituted or unsubstituted phenyl provided that at least one of R groups is substituted or unsubstituted phenyl and P_1 is independently silyl protecting group and P_2 is H or acyl group.

39. The compound as claimed in claim 38, wherein the R is independently tert-butyl or phenyl, P_1 is trimethylsilyl and P_2 is H or acetyl.