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(71) Applicant *(for all designated States except US)*: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, Massachusetts 02138-3876 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VERDINE, Gregory L.** [US/US]; 52 Hyde Avenue, Newton, Massachusetts 02458 (US). **LEE, Seongmin** [KR/US]; 928 Massachusetts Avenue, Apt. 4, Arlington, Massachusetts 02476-4624 (US).

(74) Agents: **MEIKLEJOHN, Anita L.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, MN 55440-1022 (US).

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(54) Title: SYNTHESIS OF NUCLEOSIDES

(57) Abstract: Processes for the synthesis of nucleoside analogues are provided.

# SYNTHESIS OF NUCLEOSIDES

## TECHNICAL FIELD

This disclosure relates to the synthesis of nucleoside analogues, and more particularly to the synthesis of 4'-fluoronucleoside analogues.

## BACKGROUND

In addition to encoding genetic information, nucleosides play a central role in cell metabolism. The binding motifs of these nucleosides are associated with a broad array of targets of therapeutic importance in biological systems. Thus, nucleoside analogues can be used for example as inhibitors of these processes, for example DNA biosynthesis, a process that is essential for cell growth and viral replication.

Naturally occurring nucleoside analogs demonstrate selective activities such as protein synthesis inhibition (puromycin), glycosyl transferase inhibition (tunicamycin) and methyltransferase inhibition (sinefungin). Similarly, non-naturally occurring nucleoside analogues are known to be therapeutically useful, for example as antipsychotics, cardiotonics, diuretics, analgesic, anti-inflammatory agents, anticonvulsants, antihypertensives, antibiotics, antivirals, and anticancer agents. Many of these nucleoside analogues are either on the market or in advanced clinical stages.

Substitution of hydrogen atoms for fluorine is often used in the design of synthetic analogues of natural products such as nucleosides. See, e.g., Huryn, *et al.*, *Chem. Rev.*, **1992**, *92*, 1745; Patani, et al., *Chem. Rev.*, **1996**, *96*, 3147. This substitution can dramatically affect the electronic structure of a nucleoside without significantly altering its size and shape. See Michel, *et al.*, *Tetrahedron*, **2000**, *56*, 4523; Agrofoglio, *et al.*, *Tetrahedron*, **1994**, *50*, 10611; and Scharer, et al., *J. Am. Chem. Soc.*, **1995**, *117*, 10781.

One class of fluoro-substituted nucleoside analogues that has been synthesized are 4′-fluoronucleosides. Nucleocidin, 4'-fluoro-5'-O-sulfamoyladenosine, an antimicrobial

agent effective against trypanosomes, amoebae and gram negative and gram positive bacteria is produced by cultures of *Streptomyces calvus*. Blackus, *et al.*, *Antibiot. Chemother.*, **1957**, *7*, 532; Morton, *et al*, *J. Am. Chem. Soc.*, 1969, 1535; Jenkins, *et al.*, *J. Am. Chem. Soc.*, **1971**, 93, 4323; Jenkins, *et al.*, *J. Am. Chem. Soc.*, **1976**, 98, 2346. 5′-Deoxy-4′,5-difluorouridine has been synthesized as a prodrug of the anticancer drug 5-fluorouracil. Ajmera, *et al.*, *J. Med. Chem.*, **1988**, *31*, 1094. 4′-Fluoroadenosine has been prepared as an inhibitor of S-adenosyl-L-homocysteine hydrolase, a target that has been investigated for potential antiviral agents, and inhibition of which induces immunosuppression. Guillerm, et al., *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1455-60; Wu, *et al., J. Pharmacol. Exp. Ther.*, **2005**, *313*, 705-711.

Access to 4′-fluoronucleosides has been significantly hampered by the lengthy synthetic routes (8 to 10 steps) that have previously been employed to obtain these derivatives, and also by the low overall yields of product (<5%). Previous syntheses of 4′-fluoro nucleosides employed iodofluorination of a nucleoside 4′-exo-olefin followed by hydroxide ion displacement of the iodine, which produces mixtures of 4′-epimers that can be difficult to separate. Thus, the known synthetic pathways are generally both inefficient and very difficult to implement.

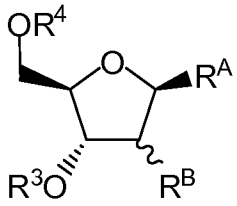
Sequential photobromination and fluorination has been used to prepare fluorinated carbohydrate derivatives. McCarter, *et al.*, *J. Am. Chem. Soc.*, **1996**, *118*, 241; Hartman, *et al.*, *J. Am. Chem. Soc.*, **2002**, *124*, 10036; Ferrier, et al., *J. Chem. Soc. Perkin Trans I*, 1984, 1675.

Improved synthetic pathways to enable access to a broader repertoire of 4′-fluoronucleoside are needed, as well as to improve access to the known compounds.

## SUMMARY

Described herein is a process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula I:



I

wherein:

$R^A$ is heterocyclic base linked via a nitrogen atom;

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $R^B$ is α or β;

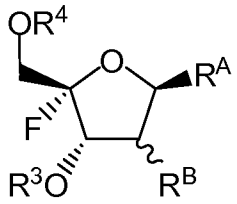
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula II:

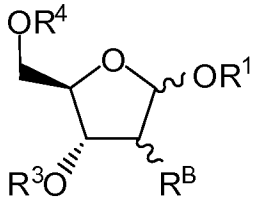


II

wherein $R^A$, $R^B$, $R^3$, and $R^4$ are as defined above for formula I.

In another aspect, there is provided a process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula III:




III

wherein:

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $OR^1$ and $R^B$ are independently α or β;

$R^1$ is selected from the group consisting of hydrogen and an alcohol protecting group;

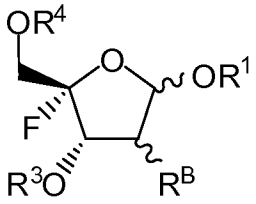
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

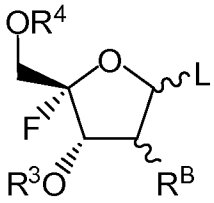
(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula IV;



IV

wherein $R^B$, $R^1$, $R^3$, and $R^4$ are as defined above for formula III;

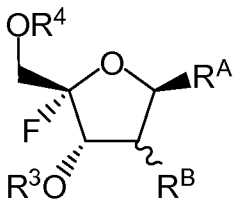
(c) optionally converting the product of step (b) into a compound according to formula V:



V

wherein L is a leaving group and $R^B$, $R^3$, and $R^4$ are as defined above for formula III;

(d) reacting the product of step (b) wherein $OR^1$ is a leaving group or the product of step (c) with a nitrogen-containing heterocyclic base to form a compound according to formula II:



II

wherein $R^A$ is a heterocyclic base linked via a nitrogen atom; and $R^B$, $R^3$, and $R^4$ are as defined above for formula III.

## DETAILED DESCRIPTION

### I. Definitions

As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The term "($C_x$-$C_y$)alkyl" (wherein x and y are integers) denotes a straight or branched hydrocarbon radical containing x to y carbons. An alkyl group formally corresponds to an alkane with a C-H bond replaced by a point of attachment of the alkylene group to the remainder of the compound. Some embodiments have 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples include methyl and ethyl. Alkyl groups having 3 or more carbon atoms may be straight-chained (e.g. n-propyl, n-butyl, n-pentyl etc.), branched (isopropyl, isobutyl, t-butyl etc.), or cyclic (e.g. cyclopropyl, cyclobutyl, cyclopropylmethyl, methylcyclopropyl, etc.).

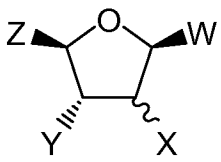
The term "($C_x$-$C_y$)alkylene" (wherein x and y are integers) denotes a straight or branched hydrocarbon diradical containing x to y carbons. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. Some embodiments have 1 or 2 to 6 carbons, some embodiments are 1 or 2 to 4 carbons, some embodiments are 1 or 2 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples include methylene -($CH_2$)- and 1,1-ethylene (-(CH($CH_3$)-) or 1,2-ethylene (-($CH_2CH_2$)-) . Alkylene groups having may be straight-chained (e.g. -($CH_2$)$_n$- where n is an integer), branched (e.g. (-(CH($CH_3$)-, -(C($CH_3$)$_2$- etc.), or cyclic (e.g. cyclopropylidene).

The term halogen means fluorine, chlorine, bromine, or iodine.

A protecting group is a derivative of a chemical functional group which is often used when the group would otherwise be incompatible with the conditions required to perform a particular reaction which, after the reaction has been carried out, can be removed to re generate the original functional group, which is thereby considered to have been "protected", but may also be useful for other purposes (such as improving the

solubility of a compound in organic solvents or facilitating purification). The person skilled in the art knows when protecting groups are indicated, is familiar with protecting groups used to protect a particular chemical functionality, how to select such groups, and knows processes that can be used for selectively introducing and selectively removing them, because methods of selecting and using protecting groups have been extensively documented in the chemical literature. Suitable protecting groups are those which are stable and thereby able to protect a particular functional group under conditions for the reaction required to be performed upon the protected compound while being able to be selectively removed when protection is no longer desired or required. Techniques for selecting, incorporating and removing chemical protecting groups may be found, for example, in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999), and Protecting Groups by Philip Kocienski, Georg Thieme Verlag (3rd Edition, 2003), the entire disclosures of which are incorporated herein by reference.

Stereochemistry is indicated herein by means of projection formulae. The stereochemistry of ring substituents herein (or, equivalently, the configuration of the carbon to which such a substituent is attached) is designated α or β by analogy to the standard designations of stereochemistry of an anomeric carbon of a carbohydrate: a substituent attached to a ring by means of a bond which projects above the plane of the ring (as indicated by the symbol —— ) is designated β while the stereochemistry of a substituent attached to a ring by means of a bond which projects below the plane of the ring (as indicated by the symbol ····· ) is designated α. A substituent which may be either α or β is indicated by the symbol ∿∿. Thus, in the following figure, the stereochemistry of W and Z is β, the stereochemistry of Y is α, and the stereochemistry of X may be either α or β.



## II. Chemical Processes

There are provided new and highly efficient synthetic processes useful for preparing 4′-fluoronucleosides.

In the processes described below may be conducted in any reactor suitable for performing chemical processes. Continuous, semi-continuous, and batch reactors can be employed. In the typical practice of the processes invention, the reagents are mixed in a batch, preferably with a solvent, and the resulting mixture is maintained at a temperature and pressure to perform the reaction. The reactions are generally preferably performed under an inert and/or dry atmosphere although rigorous exclusion of oxygen is not always necessary. If it is desirable or necessary to remove air, the solvent and reaction mixture can be sparged with a non-reactive gas, such as nitrogen, helium, or argon, or the reaction may be conducted under anaerobic conditions. The process conditions can be any operable conditions which yield the desired products.

The solvents be used in the process of the invention are selected to solubilize the reagents and not interfere with either the formation of the desired products or react with the desired products. The amount of solvent which is employed may be any amount, preferably an amount sufficient to at least partially solubilize all the reactants. A suitable quantity of solvent typically ranges from about 1 to about 100 grams solvent per gram reactants. Other quantities of solvent may also be suitable, as determined by the specific process conditions and by the skilled artisan.

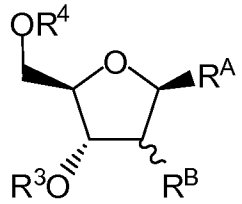
In some embodiments of the process of the following processes the final product is isolated from the reaction mixture and purified. In some embodiments it may be desirable or necessary to isolate and/or purify intermediate products before proceeding to the next step, although in some embodiments it may be acceptable to take a crude product forward to a subsequent step without purification of intermediates. The intermediates and final products can be isolated and/or purified by conventional methods known to those skilled in the art, including, for example, distillation, crystallization, sublimation, and gel chromatography. The yield of product will vary depending upon the specific

reagents and conditions used. In other embodiments of the following processes, the final product may be converted to another useful product, e.g., a monophospate, diphosphate or triphosphate nucleotide, by reaction without the intermediate isolation and/or purification of the final products of the processes.

## 1. Bromination-Fluorination of Nucleoside Analogues

In one aspect, there is provided a process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula I:




I

wherein:

$R^A$ is heterocyclic base linked via a nitrogen atom;

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $R^B$ is α or β;

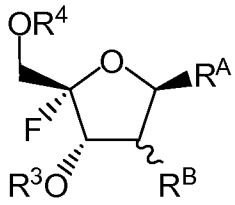
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

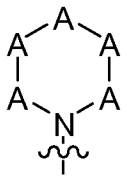
(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula II:



II

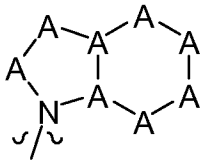
wherein $R^A$, $R^B$, $R^3$, and $R^4$ are as defined above for formula I.

The heterocyclic bases ($R^A$) of the nucleoside analogues used as reagents and made in the aforementioned process are in general the nucleobases which occur in naturally occurring nucleosides, or an analogue and/or derivative thereof, and comprise either a 6-memberered ring linked via nitrogen ("a pyrimidine" or "pyrimidine analogue") or a 5,6-fused ring system having a nitrogen at the 1-position of the 5-membered ring ("a purine or purine analogue"), i.e. a ring system defined by:



Pyrimidine/
Pyrimidine analogue

or



purine/
purine analogue

wherein each A atom independently represents either an $sp^2$-hybridized carbon or nitrogen atom.

In some embodiments of the aforementioned processes, the heterocyclic base is a nucelobase or an analogue thereof which can mimic a naturally occurring nucleobases in interations with biological molecules. In some embodiments, $R^A$ is a purine or pyrimidine, or an aza and/or deaza analogue thereof, i.e., an analogue wherein one or more carbon atoms of the ring system is replaced by nitrogen and/or one or more nitrogen atoms of the ring system is replaced by carbon.

In particular embodiments of the aforementioned process, $R^A$ is a nucleobase or nucleobase analogue selected from the group consisting of adenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3,7-dideazaadenine, 8-deazaadenine, guanine, 3-deazaguanine, 7-deaza-8-azaguanine, 3,7-dideazaaguanine, 3,7-dideaza-8-azaguanine, 7-deazaguanine, 8-azaguanine, purine, 2-aminopurine, azapurine, 2,6-diaminopurine, ethenoadenine, hypoxanthine, uracil, 5-azauracil, 6-azauracil, 5-fluorouracil, 5-bromouracil, 5-iodouracil, thymine, 6-azathymine, cytosine, 6-azacytosine, 5-azacytosine, pyrimidine, azapyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, triazolopyrimidine, imidazolopyrimidine, imidazolopyridine, pyrrolopyridine, pyrazolopyridine and triazolopyridine, and ($C_1$-$C_6$)alkyl and/or halogen-substituted and/or heteroatom-protected derivatives thereof.

A ($C_1$-$C_6$)alkyl and/or halogen-substituted derivative of one of the nucleobase or nucleobase analogues described in the preceding paragraph means that the nucleobase is derivatized by substitution with one or more ($C_1$-$C_6$)alkyl substituents and/or one or more halogen substituents. An alkyl group substituent may be attached to any substitutable position of the nucleobase or nucleobase analogue, including any substitutable heteroatom as well as substitutable carbon atoms. For example, N-($C_1$-$C_6$)alkyl and O-($C_1$-$C_6$)alkyl derivatives are included. A halogen substituent is attached to a carbon atom. By a "heteroatom-protected-derivative" it is meant that a heteroatom-containing group of the nucleobase or nucleobase analogue (or its ($C_1$-$C_6$)alkyl and/or halogen-substituted derivative)) is protected by a protecting group. The nucleobases and nucleobase analogues contain oxygen (C=O and/or OH) and/or nitrogen (NH and/or $NH_2$) containing functional groups, and protecting groups that are useful for protecting such groups are known to one skilled in the art. Examples of groups that are used for the protection of oxygen include hydroxyl protecting groups described below. Examples of groups that are used for the protection of nitrogen-containing functional groups include groups suitable for the protection of amino groups, as described, for example, in Chapter 7 of *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999). Protection of nucleosides specifically is

described in *Current Protocols in Nucleic Acid Chemistry* (John Wiley & Sons, Updated as of Supplement 30, September 2007).

In particular embodiments of the aforementioned process, $R^B$ is selected from the group consisting of $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl. In particular embodiments thereof, $R^B$ is $OR^2$.

In the aforementioned process, each of $OR^2$, $OR^3$ and $OR^4$ is an optionally protected hydroxy group. Any protecting group used to protect alcohols and which is compatible with the conditions used for the processes may be used as a protecting group, and it is not necessary that all the protecting groups be the same. Suitable protecting groups are those described in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999). Examples of protecting groups useful in the process include any suitable hydroxyl protecting group ether groups, for example methyl ether, substituted methyl ethers, benzyl ethers, silyl ethers; ester groups, for example carboxylates such as acetate and benzoate; and carbonate groups, for example methyl, ethyl and benzyl carbonates.

Typical hydroxyl protecting groups include methyl ethers, substituted methyl ethers, substituted ethyl ethers, substitute benzyl ethers, and silyl ethers, and esters, particularly carboxylates, including carbonates. Examples of substituted methyl ethers include methyoxymethyl, methylthiomethyl, t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxybenzyloxymethyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, t-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl. Examples of substituted ethyl ethers include 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-

methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, and benzyl. Examples of substituted benzyl ethers include p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, .alpha.-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4',4"-tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido. Examples of silyl ethers include trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and t-butylmethoxyphenylsilyl. Examples of esters include formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, p-phenylacetate, 3-phenylpropionate, 4-oxopentanoate(levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate(mesitoate), 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate(tigloate), o-(methoxycarbonyl)benzoate, p-benzoate, .alpha.-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, N-phenylcarbamate,

borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate. Examples of carbonate protecting groups include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, p-nitrophenyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Also useful for use in protecting some compounds of formula I and II are compounds wherein $R^2$ and $R^3$ or $R^3$ and $R^4$ are together protected by a 1,2- or 1,3-diol protecting group such that $R^2$ and $R^3$ or $R^3$ and $R^4$ form a cyclic protecting group. Examples include cyclic acetals and ketals.

Typical 1,2- and 1,3-diol protecting groups include cyclic acetals and ketals (methylene, ethylidene, 1-t-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl)ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, p-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, 2-nitrobenzylidene); cyclic ortho esters (methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidine, 1,2-dimethoxyethylidene, alpha-methoxybenzylidene, 1-(N,N-dimethylamino)ethylidene derivative, alpha-(N,N-dimethylamino)benzylidene derivative, 2-oxacyclopentylidene); and silyl derivatives (di-t-butylsilylene group, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivative, tetra-t-butoxydisiloxane-1,3-diylidene derivative, and cyclic carbonates.

In particular embodiments of the aforementioned process, each of $R^2$, $R^3$ and $R^4$ is a protecting group. In particular embodiments thereof, each of $R^2$, $R^3$ and $R^4$ is a carboxyl (i.e. an ester) protecting group. In particular embodiments thereof, each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group. The optionally benzoyl group is either unsubstituted or substituted at any substitutable position with one or more substituents by a substituent such as alkyl, heteroalkyl, fluoroalkyl, halo, or alkoxy.

Any brominating agent suitable for the bromination of aliphatic C-H bonds may be used in the aforementioned process. Free radical brominating agents are particularly useful for use as brominating agents in the process. While not being limited by theory, it is believed that such agents act via a mechanism in which bromine atoms (i.e. bromine radicals, $Br^{\cdot}$) abstract the hydrogen atom of the C-H bond to form a free radical, which then abstracts bromine from atom donor. The bromine atom donor is believed to be typically bromine which may be formed from a bromine precursor such as a compound containing an N-Br bond. Thus, in particular embodiments of the aforementioned process, the brominating agent comprises bromine atoms, or a precursor thereof.

Suitable brominating agents which are suitable for use in the aforementioned process include N-bromoimides, N-bromoimines, N-bromocarboxamides, bromine, and bromine chloride. Particular brominating agents which may be used include N-bromosuccinimide and N-bromoacetamide. N-Bromosuccinimide is preferred.

Consistent with the free radical mechanism believed to be involved in bromination by at least some of the above-mentioned brominating agents, the skilled artisan will appreciate that it may be advantageous to perform the reaction under particular conditions to promote the desired result. For example it may be desirable to perform the bromination reaction under conditions, or in the presence of reagents, that promote the formation of free radicals, such as performing the reaction in the presence of light and/or a free radical initiator, which decompose to form chain-initiating free radicals upon irradiation or heating. Light may be supplied, for example, in the form of ambient light or by irradiation with a lamp. Examples of free radical initiators include peroxides such as dibenzoyl peroxide and azo compounds such as azoisobutyronitrile. The reaction is preferably performed in a suitable solvent which is capable of dissolving the substrates and reagents and which is preferably selected to be inert under the reaction conditions. Suitable solvents include halogenated hydrocarbons, particularly perhalogenated hydrocarbons such as carbon tetrachloride and hexachloroethane. The preferred solvent is carbon tetrachloride. The reaction is preferably performed at a temperature in the

range from about 0 °C to about 150 °C, preferably about 50 °C to about 120 °C. The reaction is preferably performed in the presence of light.

Any fluorinating agent suitable for the substitution of aliphatic C-Br bonds by fluorine may be used in the aforementioned process. While not being limited by theory, it is believed that nucleophilic fluorinating agents, which donate fluorine as a fluoride anion and causing the bromine to depart as a bromide anion will be particularly useful in the above mentioned process. Particularly useful fluorinating agents are those comprising fluoride and/or tetrafluoroborate anions.

In selecting a suitable fluorinating agent, it may be beneficial to include in the reagent mixture an agent that enhances the leaving group ability of the bromine, for example agents that have an affinity for bromine, for example late transition metal ions such as silver and zinc. Therefore, in particular embodiments of the aforementioned process, suitable fluorinating agents include those that further comprise silver ions.

Particular agents that are useful as fluorinating agents for use in the aforementioned processes include metal fluoride salts, for example lithium fluoride, sodium fluoride, potassium fluoride, cesium fluoride, silver fluoride, manganese trifluoride, organic fluoride salts, for example tetraalkylammonium (e.g. tetrabutylammonium) fluoride and pyridinium hydrofluoride, and diethylaminosulfur trifluoride. The fluoride salts may be advantageously coupled with the use of Lewis acids (e.g. boron trifluoride, titanium chloride, aluminum chloride), a silver compound (e.g. silver carbonate, silver nitrate, or silver oxide) or a chelating agent which complexes the metal to increase the nucleophilicity of the fluoride (e.g. potassium fluoride / 18-crown-6).

In preferred embodiments of the aforementioned processes, the fluorinating agent comprises silver fluoride and/or silver tetrafluoroborate.

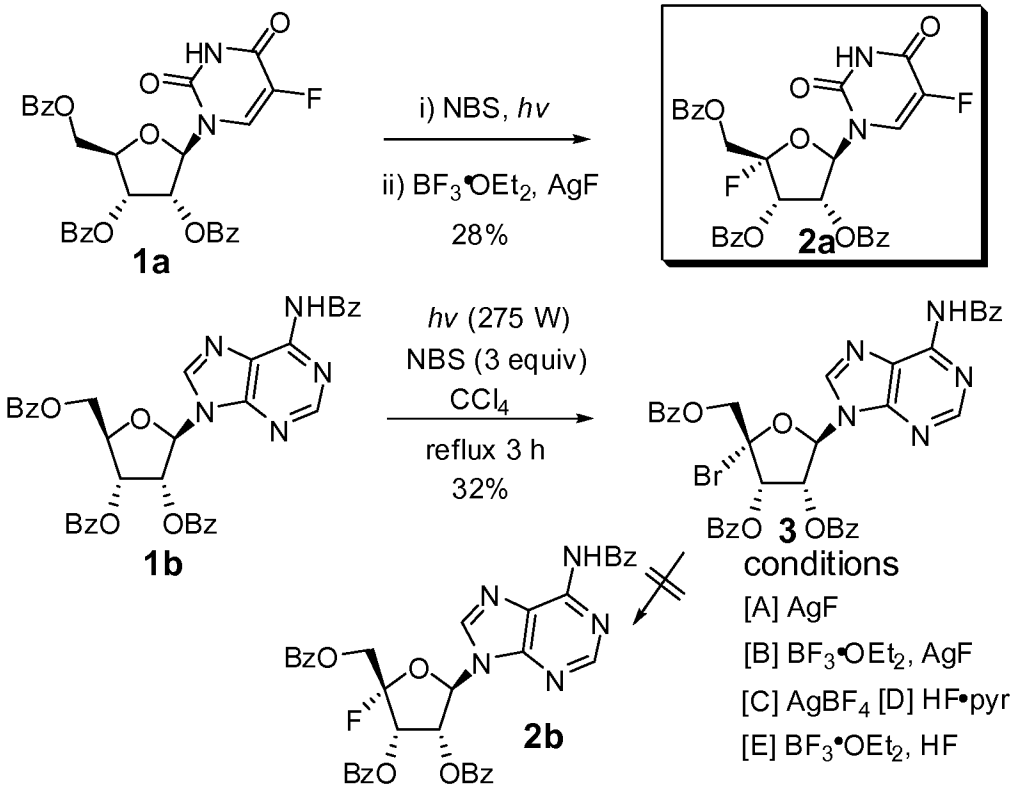
In particular embodiments of the aforementioned process, each of $R^2$, $R^3$ and $R^4$ is a carboxyl protecting group, the brominating agent an N-bromoimide, and the fluorinating agent comprises fluoride and/or tetrafluoroborate anions.

In more particular embodiments of the aforementioned process, each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group, the brominating agent an N-bromosuccinimide, and the fluorinating agent comprises silver fluoride and/or silver tetrafluoroborate.

The fluorination reaction is preferably performed in a suitable solvent which is capable of dissolving the substrates and reagents and which is preferably selected to be inert under the reaction conditions. Suitable solvents include ether solvents such as diethylether, 1,2-dimethoxyethane, 1,4-dioxane, and t-butyl methyl ether. The preferred solvent is diethyl ether. The reaction is preferably performed at a temperature in the range from about -10 °C to about 100 °C, preferably about -10 °C to about 20 °C, preferably at about 0 °C.

When a protecting group is used as $R^2$, $R^3$ and $R^4$, or for the nucleobase, the final stage of 4′-fluoro nucleoside synthesis involves the deprotection of the protecting groups. Such deprotection is performed using standard conditions for performing the deprotections, as described in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999), having due regard to selecting the protecting groups and conditions such that the reaction conditions for deprotection are compatible with the stability of the product, as described in greater detail below.

As illustrative of the process of this aspect of the invention, the synthesis of a 4′-fluoro-5-fluorouracil nucleoside by the bromination-fluorination of 5-fluorouracil ribofuranose **1a** (Scheme 1). NBS-mediated bromination of 5-fluorouracil ribofuranose **1a** followed by fluorination furnished 4′-fluoro-5-fluoronucleoside **2a**. In the case of protected adenosine **1b**, although the photobromination readily afforded 4′-bromoadenosine **3**, attempts to convert bromine to fluorine at 4′ to give **2b** were unsuccessful, generating a complex mixture of nonfluorinated compounds under the conditions tried, but it is believed that **2b** will be obtained using the route shown by routine optimization of the protecting group and/or the reaction conditions or fluorinating agents used for the fluorination step.

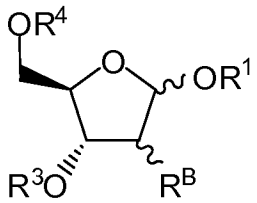



**Scheme 1**

## 2. Bromination-Fluorination-Glycosylation of Carbohydrate Analogues

In another aspect of the invention, there is provided a process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula III:



III

wherein:

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $OR^1$ and $R^B$ are independently α or β;

$R^1$ is selected from the group consisting of hydrogen and an alcohol protecting group;

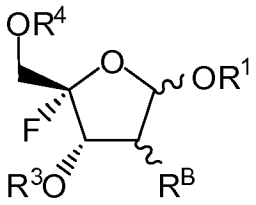
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

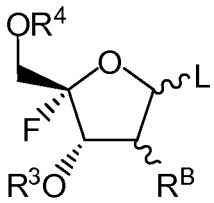
(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula IV;




IV

wherein $R^B$, $R^1$, $R^3$, and $R^4$ are as defined above for formula III;

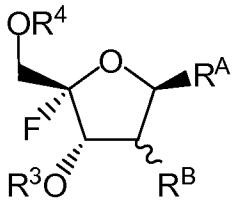
(c) optionally converting the product of step (b) into a compound according to formula V:




V

wherein L is a leaving group and $R^B$, $R^3$, and $R^4$ are as defined above for formula III;

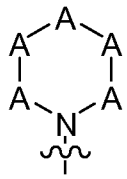
(d) reacting the product of step (b) wherein $OR^1$ is a leaving group or the product of step (c) with a nitrogen-containing heterocyclic base to form a compound according to formula II:




II

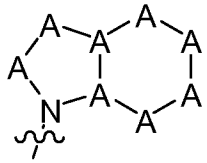
wherein $R^A$ is a heterocyclic base linked via a nitrogen atom; and $R^B$, $R^3$, and $R^4$ are as defined above for formula III.

The nitrogen-containing heterocyclic bases used as reagents in step (d) of the above process and incorporated into the synthesized nucleoside analogues as $R^A$ generally the nucleobases which occur in naturally occurring nucleosides or analogues and/or derivatives thereof and comprise either a nitrogen-containing 6-memberered ring ("a pyrimidine" or "pyrimidine analogue") or a 5,6-fused ring system having a nitrogen at the 1-position of the 5-membered ring ("a purine or purine analogue") which become linked via the nitrogen atom to yield a ring system defined by:




Pyrimidine/
Pyrimidine analogue

or




purine/
purine analogue

as $R^A$, wherein each A atom independently represents either an $sp^2$-hybridized carbon or nitrogen atom.

In some embodiments of the aforementioned processes, the heterocyclic base is a nucelobase or an analogue thereof which can mimic a naturally occurring nucleobases in interations with biological molecules. In some embodiments, $R^A$ is a purine or pyrimidine, or an aza and/or deaza analogue thereof, i.e. an analogue wherein one or more carbon atoms of the ring system is replaced by nitrogen and/or one or more nitrogen atoms of the ring system is replaced by carbon.

In particular embodiments of the aforementioned process, $R^A$ is a nucleobase or nucleobase analogue selected from the group consisting of adenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3,7-dideazaadenine, 8-deazaadenine, guanine, 3-deazaguanine, 7-deaza-8-azaguanine, 3,7-dideazaaguanine, 3,7-dideaza-8-azaguanine, 7-deazaguanine, 8-azaguanine, purine, 2-aminopurine, azapurine, 2,6-diaminopurine, ethenoadenine, hypoxanthine, uracil, 5-azauracil, 6-azauracil, 5-fluorouracil, 5-bromouracil, 5-iodouracil, thymine, 6-azathymine, cytosine, 6-azacytosine, 5-azacytosine, pyrimidine, azapyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, triazolopyrimidine, imidazolopyrimidine, imidazolopyridine, pyrrolopyridine, pyrazolopyridine and triazolopyridine, and $(C_1\text{-}C_6)$alkyl and/or halogen-substituted and/or heteroatom-protected derivatives thereof as described in greater detail for the process described for the bromination-fluorination of nucleosides described in section **(II)(1)** above.

In particular embodiments of the aforementioned process, $R^B$ is selected from the group consisting of $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl. In particular embodiments thereof, $R^B$ is $OR^2$.

In the aforementioned process, each of $OR^1$, $OR^2$, $OR^3$ and $OR^4$ is an optionally protected hydroxy group. Any protecting group used to protect alcohols and which is compatible with the conditions used for the processes may be used as a protecting group, and it is not necessary that all the protecting groups be the same. Suitable protecting groups are those described in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999). Examples of protecting groups useful in the process include any suitable hydroxyl protecting group ether groups, for example methyl ether, substituted methyl ethers, benzyl ethers, silyl

ethers; ester groups, for example carboxylates such as acetate and benzoate; and carbonate groups, for example methyl, ethyl and benzyl carbonates as described in greater detail for the process described for the bromination-fluorination of nucleosides described in section **(II)(1)** above.

In particular embodiments of the aforementioned process, each of $R^1$, $R^2$, $R^3$ and $R^4$ is a protecting group. In particular embodiments thereof, each of $R^1$, $R^2$, $R^3$ and $R^4$ is a carboxyl (i.e. an ester) protecting group. In particular embodiments thereof, $R^1$ is an acetyl group and each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group. The optionally benzoyl group is either unsubstituted or substituted at any substitutable position with one or more substituents by a substituent such as alkyl, heteroalkyl, fluoroalkyl, halo, or alkoxy.

Any brominating agent suitable for the bromination of aliphatic C-H bonds may be used in the aforementioned process. In particular, it is believed that the reagents and conditions suitable for performing the bromination step described for the bromination-fluorination of nucleosides described in section **(II)(1)** above will also in general be suitable for the bromination of carbohydrate derivatives in the process described herein. Thus, in particular embodiments of the aforementioned process, the brominating agent comprises bromine atoms, or a precursor thereof. Suitable brominating agents include N-bromoimides, N-bromoimines, N-bromocarboxamides, bromine, and bromine chloride. Particular brominating agents which may be used include N-bromosuccinimide and N-bromoacetamide. N-Bromosuccinimide is preferred.

Any fluorinating agent suitable for the substitution of aliphatic C-Br bonds by fluorine may be used in the aforementioned process. In particular, it is believed that the reagents and conditions suitable for performing the fluorination step described for the bromination-fluorination of nucleosides described in section **(II)(1)** above will also in general be suitable for the fluorination of brominated carbohydrate derivatives in the process described herein. Thus, in particular embodiments of the aforementioned process, the fluorinating agent is a nucleophilic fluorinating agent. Suitable fluorinating agents include those wherein the fluorinating agent comprises fluoride and/or

tetrafluoroborate anions. In particular embodiments of the aforementioned process, suitable fluorinating agents include those that further comprise silver ions. Particular agents that are useful as fluorinating agents for use in the aforementioned processes include metal fluoride salts, for example lithium fluoride, sodium fluoride, potassium fluoride, cesium fluoride, silver fluoride, manganese trifluoride, organic fluoride salts, for example tetraalkylammonium (e.g. tetrabutylammonium) fluoride and pyridinium hydrofluoride, and diethylaminosulfur trifluoride. The fluoride salts may be advantageously coupled with the use of Lewis acids (e.g., boron trifluoride, titanium chloride, aluminum chloride), a silver compound (e.g., silver carbonate, silver nitrate, or silver oxide) or a chelating agent which complexes the metal to increase the nucleophilicity of the fluoride (e.g., potassium fluoride / 18-crown-6). In preferred embodiments of the aforementioned process, the fluorinating agent comprises silver fluoride and/or silver tetrafluoroborate.

Completion of the 4'-fluoronucleoside synthesis then requires performing a glycosylation sequence to replace the $OR^1$ group of the carbohydrate derivative with the heterocyclic base $R^A$. This conversion is performed by converting the $OR^1$ group of the carbohydrate derivative to a leaving group as described in step (c), followed by displacement of the leaving group by the heterocyclic base as described in step (d). In general, leaving groups for displacement by the heterocyclic base are univalent groups (-L) which, when attached to hydrogen, are acids (H-L) with a pKa of about 5 or lower. Thus, a leaving group is a group which, in a nucleophilic substitution reaction may be expelled to give, typically, a stable anion while the carbon to which the leaving group was attached forms a new bond to the nucleophile. Examples of leaving groups include carboxylate, for example acetate or benzoate, halogen, for example chloride, bromide, and iodide, and sulfonate groups, for example trifluoromethanesulfonate (-OTf), arenesulfonates (such as phenylsulfonate, p-toluenesulfonate (-OTs), and naphthalenesulfonate), or alkanesulfonates (such as mesylate). The conversion of the $OR^1$ group to a suitable leaving group may be performed using conditions known to the person skilled in the art for performing such functional group transformations. See, e.g., *Comprehensive Organic Transformations* by R.C. Larock, VCH Publishers (1989). It

may be necessary or desirable to deprotect the $OR^1$ group prior to performing the conversion to the leaving group.

After converting the $OR^1$ group to a leaving group, the glycosylation reaction described in step (d) is performed. If the $OR^1$ group itself can function as a leaving group, then it may not be necessary to perform the conversion of $OR^1$ into a leaving group since the glycosylation reaction can in such cases be performed on the product of step (b) directly. The glycosylation reaction is performed by reacting the heterocyclic base, or a suitable derivative thereof, with the carbohydrate derivative from step (b) (wherein $OR^1$ is a leaving group) or step (c) under conditions suitable for effecting the glycosylation reaction. The presence of an acid or a base may promote the desired glycosylation.

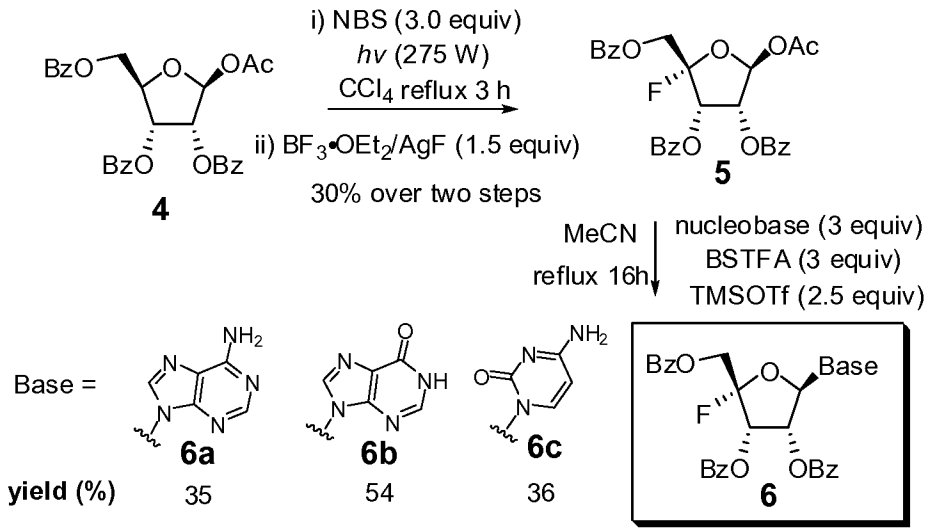
The reaction is typically performed under acidic conditions which promote the leaving group ability, particularly when $R^1$ is a carboxyl group. Therefore, in a preferred embodiment of the process is wherein $R^1$ is a carboxyl group and step (d) is performed by reacting the product of step (b) with a nucleobase, preferably a purine or pyrimidine, under acidic conditions. The acid used is preferably a Lewis acid such as tin tetrachloride, titanium tetrachloride, or trimethylsilyltriflate. When the leaving group is halogen, a Lewis acid as described herein may still be beneficial and salts with affinity for halogen (e.g. silver salts) may also be useful to promote the desired substitution. The nucleobase is preferably derivatized as a silyl derivative, preferably a trialkylsilyl derivative, most preferably a persilylated derivative. In a preferred embodiment, step (d) is performed by reacting the product of step (b), preferably wherein $OR^1$ is a carboxylate group, preferably acetate, with a purine or pyrimidine derivatized as a silylated derivative, preferably a trialkylsilyl derivative, and preferably persilylated, and the reaction is performed in the presence of a Lewis acid, preferably a trialkylsilyl triflate.

The glycosylation reaction is preferably performed in a suitable solvent which is capable of dissolving the substrates and reagents and which is preferably selected to be inert under the reaction conditions. Suitable solvents include aprotic solvents such as toluene, acetonitrile, benzene, or a mixture of any or all of these solvents. The reaction is

preferably performed at a temperature in the range from about 20 °C to about 150 °C, preferably about 50 °C to about 120 °C, preferably at about 100 °C.

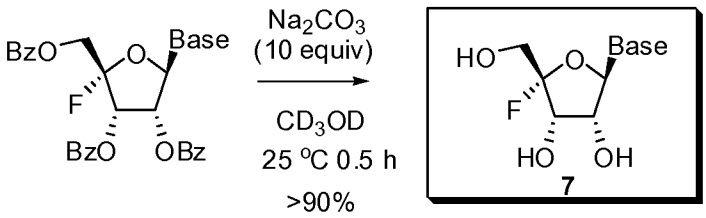
When a protecting group is used as $R^2$, $R^3$ and $R^4$, or for the nucleobase, the final stage of 4′-fluoro nucleoside synthesis involves the deprotection of the protecting groups. Such deprotection is performed using standard conditions for performing the deprotections, as described in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts, John Wiley & Sons Ltd. (3rd Edition, 1999), having due regard to selecting the protecting groups and conditions such that the reaction conditions for deprotection are compatible with the stability of the product, as described in greater detail below.

As illustrative of the process of this aspect of the invention, the synthesis of several 4′-fluoronucleosides were synthesized according to the process of the invention. Treatment of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribose **4** with N-bromosuccinimide under a sun lamp (275 W) afforded a mixture of 4-bromo-β-D-ribofuranose and 4-bromo-α-L-lyxofuranose (C4 epimer, not shown). The crude reaction mixture, without purification, was directly subjected to fluorination using silver tetrafluoroborate generated in situ from borontrifluoride-etherate and silver fluoride. The reaction provided 4-fluoro-β-D-ribofuranose **5** in 30% yield, together with an almost equal amount of 4-fluoro-α-L-lyxofuranose. Modified Hilbert-Johnson N-glycosylation (see Wright, *et al.*, *J. Med. Chem.*, **1984**, *27*, 175) of 4-fluoro-β-D-ribo furanose **5** with N,O-bis(trimethylsilyl) trifluoroacetamide (BSTFA) and TMSOTf gave 4′-fluoro adenosine (**6a**), inosine (**6b**), and cytidine (**6c**) (Scheme 2). It is noteworthy that the N-glycosylation takes place slowly (~16 h) compared to that of non-fluorinated substrate (~3 h), presumably due to retardation of the oxocarbenium intermediate for N-glycosylation, by the inductive effect of the 4′-fluoro substituent.




**Scheme 2**

Finally, as discussed above, the deprotection of the protected derivatives to give the 4′-fluoro nucleosides was performed. It was confirmed that the deprotection could be readily effected by treatment with methanolic sodium carbonate, as illustrated in Scheme 3.




**Scheme 3**

The stability of the deprotected 4′-fluoro nucleosides was then investigated by observing a solution of the nucleoside in various solvents as summarized in Table 1. It was observed that the deprotected 4′-fluoro nucleosides (**7a-d**) decomposed fairly rapidly in deuterium oxide but were stable in deuteriomethanol. However, the unprotected 4′-fluoro nucleosides were considerably more stable in 10 mM sodium phosphate buffer at pH 7.4 (mimicking physiological pH) than in unbuffered deuterium oxide.

**Table 1. Stability of 4′-fluoro nucleosides under Various Conditions**

| (base) / solvent | **7a** (adenine) | **7b** (hypoxanthine) | **7c** (cytosine) | **7d** (5-fluoruracil) |
|---|---|---|---|---|
| $CD_3OD$ | no decomposition after 1 day | no decomposition. | no decomposition. | no decomposition. |
| $D_2O$ | 80% decomposition after 1 d | 100% decomposition after 1 day | 50% decomposition after 3 h 100% decomposition after 16 h | 50% decomposition after 3 h |
| phosphate buffer (pH 7.4) | 5% decomposition after 4 days | 10% decomposition after 4 days | - | - |

## EXAMPLES

### General Methods

Reagents, such as $BF_3{\cdot}OEt_2$, TMSOTf, nucleobases, AgF, $AgBF_4$, and *N,O*-bis(trimethylsilyl)trifluoro acetamide, purchased were used as received. Methylene chloride was distilled from calcium hydride. *N*-Bromosuccinimide was recrystalized from boiling water. Sodium sulfate ($Na_2SO_4$) was anhydrous. All recrystalization, chromatographic, and workup solvents were distilled.

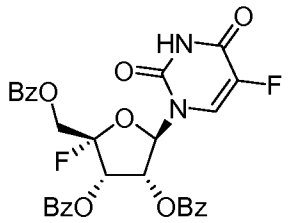
Unless otherwise indicated, all reactions were carried out under in a positive pressure of argon in anhydrous solvents and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) in comparison with the starting materials. All TLC analyses were carried out on Merck Silica Gel 60 F254 TLC plates, thickness of 0.25 mm. The plates were visualized by ultraviolet illumination at 254 nm and immersion in visualizating solution. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350 mL absolute ethanol, 50 mL concentrated $H_2SO_4$, 37 mL *p*-anisaldehyde), and (ii) permanganate solution (weight percents of 1 % $KMnO_4$ and 2 % $Na_2CO_3$ in water).

Analytical samples were obtained from flash silica gel chromatography, using silica gel of 230-400 mesh ASTM. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on

Bruker AM 500 (500 MHz). NMR spectra were determined in chloroform-$d_1$ ($CDCl_3$), DMSO-$d_6$ or methanol-$d_4$ ($CD_3OD$) solution and are reported in parts per million (ppm) from the residual chloroform (7.24 ppm and 77.0 ppm) and benzene (7.16 ppm and 128.39 ppm) standard respectively. Peak multiplicates in $^1$H-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), and/or ap (apparent) and/or br (broad). Mass spectra were all obtained on either a JEOL AX-505 or a JEOL SX-102. HPLC analyses were carried out on an HP 1090 Liquid Chromatograph equipped with a Beckman C18 Reversed-phase column.

**Example 1**

**2′,3′,5′-Tri-O-benzoyl-4′-fluoro-β-D-ribofuranosyl-5-fluoro-uracil (2a)**

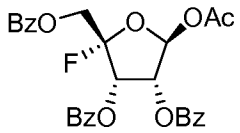



To a carbon tetrachloride solution of 2,3,5-tri-benzoyl-β-D-ribofuranose-5-fluorouracil **1a** (58 mg, 0.1 mmol) was added *N*-bromosuccinimide (53 mg, 0.3 mmol) and the mixture was stirred under sun lamp (275 W) for 6 hours at 90 °C. The reaction mixture was diluted with dichloromethane and washed with aqueous sodium thiosulfate, aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. Concentration of the solvent gave a crude product mixture (~1:1) of the 4-bromo-β-D-ribofuranose-5-fluoro-uracil and 4-bromo-α-L-lyxofuranose-5-fluoro-uracil. In a round bottom flask silver tetrafluoroborate was prepared from the reaction of silver fluoride (19 mg, 0.15 mmol) with borontrifluoride-diethyl ether (37 μL, 0.3 mmol) in anhydrous diethyl ether (2 mL) for 30 minutes at 25 °C. An ethyl acetate (1 mL) solution of the bromide mixture was added to the solution of $AgBF_4$ and the mixture was stirred for 30 minutes at 0 °C. The reaction mixture was diluted with diethyl ether, washed with aqueous saturated sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was subjected to silica gel column chromatography to give an inseparable mixture of 2′,3′,5′-

Tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl-5-fluorouracil **2a** and its 4′-epimer *epi*-**2a** (**2a**:*epi*-**2a** = 10:1 based on 1H NMR integration, 18 mg, 28% over two steps). $^1$H NMR (500 MHz, $CD_3OD$) δ 8.83 (1H, d, *J*=4.7Hz), 8.06-7.33 (15H, m, 3OBz), 6.19 (1H, dd, *J*=7.3Hz, 18.0Hz, $C_3$′-H), 5.93 (1H, dd, *J*=1.9Hz, 7.3Hz, $C_2$′-H), 5.86 (1H, d, *J*=1.9Hz, $C_1$′-H), 4.77-4.66 (2H, m, $C_5$′-H); $^{13}$C MMR (125 MHz, $CD_3OD$) δ 166.1, 165.7, 148.2, 134.3, 134.2, 133.8, 130.3, 130.1, 129.0, 128.8, 128.7, 128.4, 127.2, 126.9, 95.6, 72.3; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -118.7, 57.8; LRMS (M+H) 593.

**Example 2**

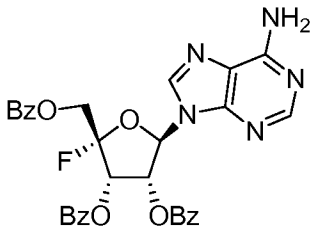
**(a) 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-4-fluoro-β-D-ribofuranose (5)**




To a carbon tetrachloride solution of 1-*O*-acetyl-2,3,5-tri-benzoyl-β-D-ribofuranose **4** (504 mg, 1 mmol) was added *N*-bromosuccinimide (534 mg, 3 mmol) and the mixture was stirred under sun lamp (275 W) for 3 hours at 90 °C. The reaction mixture was diluted with dichloromethane and washed with aqueous sodium thiosulfate, aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. Concentration of the solvent gave a crude product mixture of the 4-bromo-β-D-ribofuranose and 4-bromo-α-L-lyxofuranose. In a round bottom flask silver tetrafluoroborate was prepared from the reaction of silver fluoride (189 mg, 1.5 mmol) with borontrifluoride-diethyl ether (377 μL, 3.0 mmol) in anhydrous diethyl ether (10 mL) for 30 minutes at 25 °C. An ethyl acetate (5 mL) solution of the bromide mixture was added to the solution of $AgBF_4$ and the mixture was stirred for 30 minutes at 0 °C. The reaction mixture was diluted with diethyl ether, washed with aqueous saturated sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was subjected to silica gel column chromatography to give an inseparable mixture of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-4-fluoro-β-D-ribofuranose **5** and its 4′-epimer *epi*-**5** (**5**:*epi*-**5** = 10:1 based on $^1$H NMR integration, 310 mg, 30% over two steps). The spectral data obtained for this

compound was identical with literature data. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.10 7.30 (15H, OBz), 6.61 (s, 1H, $C_1$-H), 6.00 (1H, dd, *J*=5 Hz, 18 Hz, $C_3$-H), 5.80 (1H, d, *J*=5Hz, $C_2$-H), 4.78 (1H, $C_5$-H), 4.53 (1H, $C_5$-H), 1.98 (3H, s, OAc).

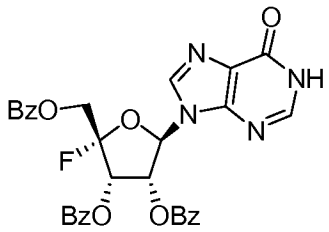
**(b) 2′,3′,5′-Tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl adenine (6a)**




To a suspension of adenine (58 mg, 0.43 mmol) in MeCN (4 mL) was added *N*,*O*-bis(trimethylsilyl)trifluoro acetamide (228 μL, 0.86 mmol) and the mixture was stirred for 1 hour at 50 °C to give silylated adenine. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-4-fluoro-β-D-ribofuranose **5** (45 mg, 0.086 mmol) and TMSOTf (72 μL, 0.43 mmol) were then added to the silylated adenine solution and the resulting mixture was stirred 24 hours at 90 °C. The reaction was quenched by adding saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by chromatography on silica gel yielded 2′,3′,5′-tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl adenine **6a** (18 mg, 35%). $^1$H NMR (500 MHz, $CD_3OD$) δ 8.79 (1H, s), 8.25 (1H, s), 8.07-7.29 (15H, m, OBz), 7.07 (1H, s, $C_1$′-H), 6.48 (1H, d, *J*=6.3Hz, $C_2$′-H), 6.24 (1H, dd, *J*=6.3Hz, 17.5Hz, $C_3$′-H), 4.84 (1H, d, *J*=12.2Hz, $C_5$′-H), 4.73 (1H, dd, *J*=5.9Hz, 12.2Hz); $^{13}$C MMR (125 MHz, $CD_3OD$) δ 166.6, 166.5, 166.1, 160.9, 154.3, 153.4, 144.3, 135.2, 135.1, 135.2, 134.7, 133.9, 131.0, 130.9, 130.6, 130.4, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 116.8, 114.9, 90.9, 71.7, 71.0, 63.0; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -118.0; LRMS (M+H) 598; HRMS calculated for $C_{31}H_{24}FN_5O_7$ (M+H): 598.1738, found 598.1766.

**Example 3**

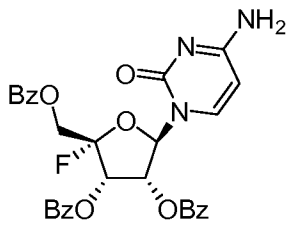
**2′,3′,5′-Tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl hypoxanthine (6b)**



2′,3′,5′-Tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl hypoxanthine **6b** was prepared by a process analogous to that used for the synthesis of **6a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 8.26 (1H, s), 8.14 (1H, s), 7.97-7.19 (15H, m), 6.87 (1H, dd, *J*=7.6Hz, 20.6Hz, $C_3$′-H), 6.53 (1H, d, *J*=2.6 Hz, $C_1$′-H), 6.04 (1H, dd, *J*=2.6Hz, 7.7Hz, $C_1$′-H), 4.87 (1H, t, *J*=12.8 Hz, $C_5$′-H), 4.77 (1H, dd, *J*=8.4Hz, 12.4Hz, $C_5$′-H); $^{13}$C MMR (125 MHz, $CD_3OD$) δ 168.3, 166.9, 166.1, 157.5, 146.5, 134.8, 134.4, 130.8, 130.3, 130.0, 129.5, 98.2, 96.5, 73.6, 72.8, 72.7, 64.8, 64.5; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -120.2; LRMS (M+H) 599; HRMS calculated for $C_{31}H_{23}FN_4O_8$ (M+H) 599.1578, found 599.1583.

**Example 4**

**2′,3′,5′-Tri-O-benzoyl-4′-fluoro-β-D-ribofuranosyl cytosine (6c)**

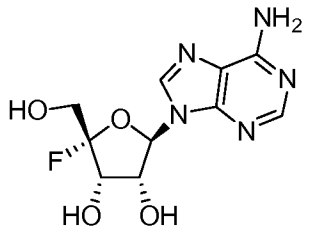


2′,3′,5′-Tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl cytosine **6c** was prepared by a process analogous to that used for the synthesis of **6a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 7.94 (2H, t, *J*=7.Hz), 7.88 (1H, d, *J*=8.3Hz), 7.69 (1H, d, *J*=7.4Hz), 7.57 (2H, m), 7.50 (1H, t, *J*=7.3Hz), 7.39 (2H, t, *J*=7.8Hz), 7.34 (2H, t, *J*=7.4Hz), 7.27 (2H, t, *J*=7.8Hz), 6.47 (1H, d, *J*=6.3Hz, 19.0Hz, $C_3$′-H), 6.10 (1H, s, $C_1$′-H), 5.90 (1H, d, *J*=7.4Hz), 4.73 (2H, d, *J*=12.7Hz, $C_5$′-H); $^{13}$C MMR (125 MHz, $CD_3OD$) δ 168.4, 166.9, 166.1, 157.5, 146.5, 134.8, 134.4, 130.8, 130.4, 130.3, 130.0, 129.6, 129.5, 98.3, 96.5, 73.6, 72.8, 72.7,

64.8, 64.5; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -118.7; LRMS (M+H) 574; HRMS calculated for $C_{30}H_{24}FN_3O_8$ (M+H) 574.1625, found 574.1639.

**Example 5**

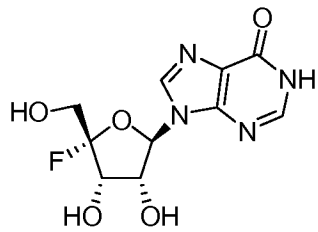
**4′-Fluoro adenosine (7a)**



To a $CD_3OD$ solution of 2′,3′,5′-tri-*O*-benzoyl-4′-fluoro-β-D-ribofuranosyl adenine **6a** was added sodium carbonate (10 equiv.) and the mixture was stirred for 30 minutes at 25 °C. The reaction mixture was filtered through sintered glass, concentrated, and subjected to silica gel chromatography to provide 4′-fluoro-β-D-ribofuranosyl adenine **7a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 8.54 (1H, s), 8.26 (1H, s), 6.15 (1H, d, *J*=4.4Hz, $C_1$′-H), 4.44 (1H, dd, *J*=7.4Hz, 14.7Hz, $C_3$′-H), 4.33 (1H, m), 3.81 (2H, m); $^{19}$F NMR (400 MHz, $CD_3OD$) -126.2; LRMS (M+H) 286; HRMS calculated for $C_{10}H_{12}FN_5O_4$ (M+H) 286.0951, found 286.0956.

**Example 6**

**4′-Fluoro inosine (7b)**

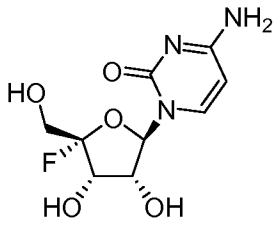


4′-Fluoro inosine **7b** was prepared by similar procedures used for the synthesis of **7a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 8.51 (1H, s), 8.02 (1H, s), 6.49 (1h, d, *J*=2.9Hz, $C_1$′-H), 4.46 (1H, dd, *J*=8.0Hz, 16.5Hz, $C_3$′-H), 4.39 (1H, m, $C_2$′-H), 3.56 (2H, m, $C_5$′-H); $^{13}$C MMR (125 MHz, $CD_3OD$) 140.5, 138.5, 133.0, 130.2, 129.3, 128.4, 115.0. 95.0, 93.1,

74.2, 48.7; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -123.8; LRMS (M+H) 286; HRMS calculated for $C_{10}H_{11}FN_4O_5$ (M + H) 287.0791, found 287.0797.

**Example 7**

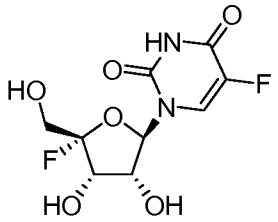
**4′-Fluoro cytidine (7c)**



4′-Fluoro cytidine **7c** was prepared by similar procedures used for the synthesis of **7a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 7.84 (1H, d, *J*=7.8Hz, $C_6$-H), 6.05 (1H, s, $C_1$′-H), 5.87 (1H, d, *J*=7.8Hz, $C_5$-H), 4.39 (1H, dd, *J*=6.3Hz, 19.0Hz, $C_3$′-H), 4.17 (1H, d, *J*=6.3Hz, $C_2$′-H), 3.75 (2H, m, $C_5$′-H); $^{13}$C MMR (125 MHz, $CD_3OD$) 141.8, 133.0, 130.1, 129.3, 128.4, 94.9, 94.2, 72.9, 69.1; $^{19}$F NMR (400 MHz, $CD_3OD$) δ -124.2; LRMS (M+H) 262; HRMS calculated for $C_9H_{12}FN_3O_5$ 262.0834, found 262.0832.

**Example 8**

**4′-Fluoro-β-D-ribofuranosyl-5-fluoro-uracil (7d)**



4′-Fluoro-β-D-ribofuranosyl-5-fluoro-uracil **7d** was prepared by similar procedures used for the synthesis of **7a**. $^1$H NMR (500 MHz, $CD_3OD$) δ 8.07 (1H, d, *J*=6.6Hz, $C_6$-H), 6.06 (1H, s, $C_1$′-H), 4.39 (1H, dd, *J*=6.1Hz, 18.0 Hz), 4.22 (1H, dd, *J*=2.2Hz, 6.6Hz, $C_2$′-H), 3.74 (2H, m, $C_5$′-H); $^{19}$F NMR (400 MHz, $CD_3OD$) δ -124.2, -77.3.

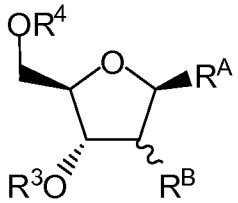
All references cited herein are incorporated by reference. A number of embodiments of the invention have been described. Nevertheless, it will be understood

that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

**WHAT IS CLAIMED IS:**

1. A process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula I:



I

wherein:

$R^A$ is heterocyclic base linked via a nitrogen atom;

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1$-$C_3)$alkyl, F, and $(C_1$-$C_3)$alkylene$O(C_1$-$C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $R^B$ is α or β;

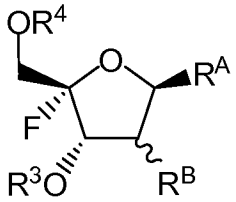
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula II:




II

wherein $R^A$, $R^B$, $R^3$, and $R^4$ are as defined above for formula I.

2. A process according to claim 1 wherein $R^A$ is a purine or pyrimidine.

3. A process according to claim 1 wherein $R^A$ is a nucleobase or nucleobase analogue selected from the group consisting of adenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3,7-dideazaadenine, 8-deazaadenine, guanine, 3-deazaguanine, 7-deaza-8-azaguanine, 3,7-dideazaaguanine, 3,7-dideaza-8-azaguanine, 7-deazaguanine, 8-azaguanine, purine, 2-aminopurine, azapurine, 2,6-diaminopurine, ethenoadenine, hypoxanthine, uracil, 5-azauracil, 6-azauracil, 5-fluorouracil, 5-bromouracil, 5-iodouracil, thymine, 6-azathymine, cytosine, 6-azacytosine, 5-azacytosine, pyrimidine, azapyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, triazolopyrimidine, imidazolopyrimidine, imidazolopyridine, pyrrolopyridine, pyrazolopyridine and triazolopyridine, and $(C_1\text{-}C_6)$alkyl and/or halogen-substituted and/or heteroatom-protected derivatives thereof.

4. A process according to claim 1 wherein $R^B$ is selected from the group consisting of $OR^2$, $O(C_1\text{-}C_3)$alkyl, F, and $(C_1\text{-}C_3)$alkylene$O(C_1\text{-}C_3)$alkyl.

5. A process according to claim 1 wherein each of $R^2$, $R^3$ and $R^4$ is a protecting group.

6. A process according to claim 5 wherein each of $R^2$, $R^3$ and $R^4$ is a carboxyl protecting group.

7. A process according to claim 6 wherein each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group.

8. A process according to claim 1 wherein the brominating agent comprises bromine atoms, or a precursor thereof.

9. A process according to claim 1 wherein the brominating agent is selected from the group consisting of N-bromoimides, N-bromoimines, N-bromocarboxamides, and bromine.

10. A process according to claim 10 wherein the brominating agent is an N-bromoimide.

11. A process according to claim 11 wherein the brominating agent is N-bromosuccinimide.

12. A process according to claim 1 wherein the fluorinating agent is a nucleophilic fluorinating agent.

13. A process according to claim 12 wherein the fluorinating agent comprises fluoride and/or tetrafluoroborate anions.

14. A process according to claim 13 wherein the fluorinating agent further comprises silver ions.

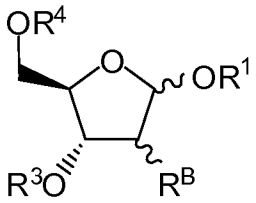
15. A process according to claim 12 wherein the fluorinating agent comprises silver fluoride and/ or silver tetrafluoroborate.

16. A process according to claim 1 wherein each of $R^2$, $R^3$ and $R^4$ is a carboxyl protecting group, the brominating agent an N-bromoimide, and the fluorinating agent comprises fluoride and/or tetrafluoroborate anions.

17. A process according to claim 1 wherein each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group, the brominating agent an N-bromosuccinimide, and the fluorinating agent comprises silver fluoride and/or silver tetrafluoroborate.

18. A process useful for the synthesis of 4'-fluoronucleosides and analogues thereof, the process comprising:

(a) reacting a compound according to formula III:




III

wherein:

$R^B$ is selected from the group consisting of hydrogen, $OR^2$, $O(C_1$-$C_3)$alkyl, F, and $(C_1$-$C_3)$alkyleneO$(C_1$-$C_3)$alkyl;

the symbol ∿∿ indicates that the stereochemistry of $OR^1$ and $R^B$ are independently α or β;

$R^1$ is selected from the group consisting of hydrogen and an alcohol protecting group;

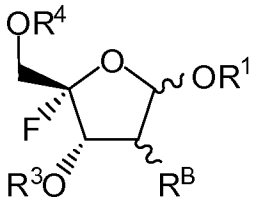
$R^2$ is selected from the group consisting of hydrogen and an alcohol protecting group;

$R^3$ is selected from the group consisting of hydrogen and an alcohol protecting group; and

$R^4$ is selected from the group consisting of hydrogen and an alcohol protecting group;

with a brominating agent; and

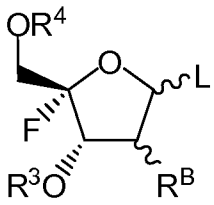
(b) reacting the product of step (a) with a fluorinating agent to form a compound according to formula IV;




IV

wherein $R^B$, $R^1$, $R^3$, and $R^4$ are as defined above for formula III;

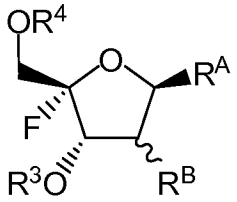
(c) optionally converting the product of step (b) into a compound according to formula V:




V

wherein L is a leaving group and $R^B$, $R^3$, and $R^4$ are as defined above for formula III;

(d) reacting the product of step (b) wherein $OR^1$ is a leaving group or the product of step (c) with a nitrogen-containing heterocyclic base to form a compound according to formula II:




II

wherein $R^A$ is a heterocyclic base linked via a nitrogen atom; and $R^B$, $R^3$, and $R^4$ are as defined above for formula III.

19. A process according to claim 18 wherein $R^A$ is a purine or pyrimidine.

20. A process according to claim 18 wherein $R^A$ is a nucleobase or nucleobase analogue selected from the group consisting of adenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3,7-dideazaadenine, 8-deazaadenine, guanine, 3-deazaguanine, 7-deaza-8-azaguanine, 3,7-dideazaaguanine, 3,7-dideaza-8-azaguanine, 7-deazaguanine, 8-azaguanine, purine, 2-aminopurine, azapurine, 2,6-diaminopurine, ethenoadenine, hypoxanthine, uracil, 5-azauracil, 6-azauracil, 5-fluorouracil, 5-bromouracil, 5-iodouracil, thymine, 6-azathymine, cytosine, 6-azacytosine, 5-azacytosine, pyrimidine, azapyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, triazolopyrimidine, imidazolopyrimidine, imidazolopyridine, pyrrolopyridine, pyrazolopyridine and triazolopyridine, and ($C_1$-$C_6$)alkyl and/or halogen-substituted and/or heteroatom-protected derivatives thereof.

21. A process according to claim 1 wherein $R^B$ is selected from the group consisting of $OR^2$, O($C_1$-$C_3$)alkyl, F, and ($C_1$-$C_3$)alkyleneO($C_1$-$C_3$)alkyl.

22. A process according to claim 18 wherein each of $R^1$, $R^2$, $R^3$ and $R^4$ is a protecting group.

23. A process according to claim 18 wherein each of $R^1$, $R^2$, $R^3$ and $R^4$ is a carboxyl protecting group.

24. A process according to claim 23 wherein $R^1$, is an acetyl group and each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group.

25. A process according to claim 18 wherein the brominating agent comprises bromine atoms, or a precursor thereof.

26. A process according to claim 16 wherein the brominating agent is selected from the group consisting of N-bromoimides, N-bromoimines, N-bromocarboxamides, and bromine.

27. A process according to claim 22 wherein the brominating agent is an N-bromoimide.

28. A process according to claim 23 wherein the brominating agent is N-bromosuccinimide.

29. A process according to claim 16 wherein the fluorinating agent is a nucleophilic fluorinating agent.

30. A process according to claim 25 wherein the fluorinating agent comprises fluoride and/or tetrafluoroborate anions.

31. A process according to claim 26 wherein the fluorinating agent further comprises silver ions.

32. A process according to claim 27 wherein the fluorinating agent comprises silver fluoride and/ or silver tetrafluoroborate.

33. A process according to claim 16 wherein $R^1$ is a carboxyl group and step (d) is performed by reacting the product of step (b) with a purine or pyrimidine under acidic conditions.

34. A process according to claim 33 wherein step (d) is performed by reacting the product of step (b) with a purine or pyrimidine derivatized as a trialkylsilyl derivative and the reaction is performed in the presence of a trialkylsilyl triflate.

35. A process according to claim 30 wherein each of $R^1$, $R^2$, $R^3$ and $R^4$ is a carboxyl protecting group, the brominating agent an N-bromoimide, and the fluorinating agent comprises fluoride and/or tetrafluoroborate anions and step (d) is performed by reacting the product of step (b) with a purine or pyrimidine under acidic conditions.

36. A process according to claim 1 wherein each of $R^2$, $R^3$ and $R^4$ is an optionally substituted benzoyl protecting group, the brominating agent an N-bromosuccinimide, and the fluorinating agent comprises silver fluoride and/or silver tetrafluoroborate and step (d) is performed by reacting the product of step (b) with a purine or pyrimidine derivatized as a trialkylsilyl derivative and the reaction is performed in the presence of a trialkylsilyl triflate.