INSTRUCTIONS

(a) If Convention application insert "Convention"

672533

USSN 152,803

(a) CONVENTION

AUSTRALIA

Patents Act 1990

(b) Delete one

REQUEST FOR A (b) STANDARD/~~PETTY~~ PATENT

(c) Insert FULL name(s) of applicant(s)

I/We being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying Standard/~~Petty~~ (b) Complete Patent Specification.

~~I am~~/We are (b) not an opponent or eligible person described in Sections 33-36 of the Act.

[70,71] Applicant and Nominated Person (c): BRISTOL-MYERS SQUIBB COMPANY

(d) Insert FULL address(es) of applicant(s)

of (d) Lawrenceville-Princeton Road, Princeton, New Jersey 08543-4000
United States of America

(e) Insert TITLE of invention

[54] Invention Title (e) PROCESS FOR PREPARING AZT AND DERIVATIVES THEREOF

(f) Insert Names of actual Inventors.

[72] Names of Actual Inventors (f)

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[74] Address for Service:

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000
Attorney Code: PO

(Note: The following applies only to Convention applications)

Basic Convention Application Details

(g)	[31] Application No.	[33] Country	Country Code	[32] Date of Application
	152,803	US United States of America	US	November 15, 1993

(g) Insert number, country and filing date for the/or each basic application

(h) Signature of applicant(s) (For body corporate see headnote*)

(i) Insert date of signing

(j) Corporate seal if any

Note: No legalization or other witness required

(j)

MO 6203 14 11 94

(h) Signature of Applicant

(i) Date September 19, 1994

Nicholas P. Malatestinic
Assistant Secretary

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

AUSTRALIA

USSN 152,803

Patents Act 1990

NOTICE OF ENTITLEMENT

INSTRUCTIONS
(a) Name of person making statement
(b) Position of that person.
(c) Name of applicant
(d) Address of applicant
(e) Delete as necessary
(f) Insert details if not covered by (i) or (ii)
(g) Delete as necessary
(h) Delete for non-convention applications
(i) Insert DATE of signing
(j) Signature(s) of person making statement

I (a) Nicholas P. Malatestinic

(b) Assistant Secretary

of (c) BRISTOL-MYERS SQUIBB COMPANY

of (d) Lawrenceville-Princeton Road,
Princeton New Jersey, USA

State the following

1. The nominated person (applicant) is entitled to the grant of a patent

(e) (i) as assignee of the actual inventor(s)

~~(ii) by contract of employment of the actual inventor(s)~~

or (iii) (f)

2. The nominated person (applicant) is entitled to claim priority from the basic convention application(~~s~~)

(g) ~~(i) as applicants of the said application(s)~~

(ii) as the assignee of the applicants of the said application(~~s~~)

~~(iii) with the consent of the applicants of the said application(s)~~

3. The basic convention application(~~s~~) was/~~were~~ the first made in a Convention country in respect of the invention the subject of the application. (h)

Dated (i) September 19, 1994

(j) BRISTOL-MYERS SQUIBB COMPANY

Nicholas P. Malatestinic
Assistant Secretary

Note: No legalization or other witness required

To: The Commissioner of Patents

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

AU9478805

(12) PATENT ABRIDGMENT (11) Document No. AU-B-78805/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 672533

(54) Title
PROCESS FOR PREPARING AZT AND DERIVATIVES THEREOF

(51)[5] International Patent Classification(s)
C07H 019/073

(21) Application No. : **78805/94** (22) Application Date : **14.11.94**

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152803	**15.11.93**	**US UNITED STATES OF AMERICA**

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(71) Applicant(s)
BRISTOL-MYERS SQUIBB COMPANY

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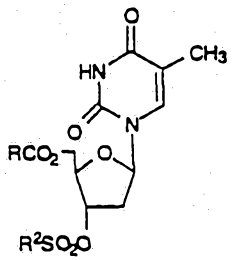
(57) Claim

1. A process for reduction of a pyrimidinyl 2'-deoxyribonucleoside compound comprising contacting a 2'α-halo-5'-protected pyrimidinyl ribonucleoside compound having a 3'α-sulfonyl group with a tri C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initiator in an ether, ester or ketone solvent under conditions to result in a dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound.

31. A compound of the formula



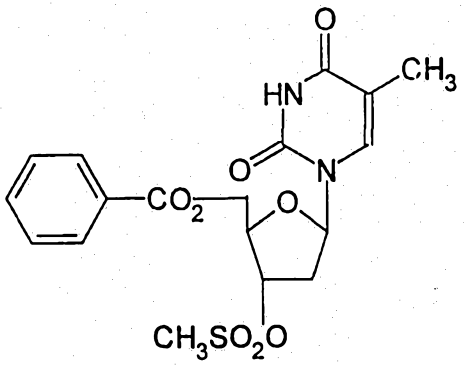
wherein

R hydrogen, C_1-C_{12} alkyl or C_6-C_{30} aryl and

R^2 is C_1-C_{12} alkyl or C_6-C_{30} aryl.

.../2

33. A compound of the formula



AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Name of Applicant:

Bristol-Myers Squibb Company

Actual Inventor(s):

Bang-Chi Chen
Sandra L. Quinlan

Address for Service:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Invention Title:

PROCESS FOR PREPARING AZT AND DERIVATIVES THEREOF

Our Ref : 386862
POF Code: 140109/140109

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

The present invention concerns a process for preparing AZT and derivatives thereof.

The compound AZT (3'-azido-3'-deoxythymidine) and derivatives thereof are known to be useful for treating viral and bacterial infections, most notably in the treatment of AIDS (see, for example, U.S. Patents 4,724,232, 4,828,838, 4,847,244, 4,874,609, 4,874,751, 4,818,750, 5,093,114 and 5,145,840). In the past, AZT has been made from an expensive starting material, thymidine (see Horwitz, J. P., et al., J. Org. Chem., 1964, 29, 2076; Maillard, M. Farag, A., Frappier, F., Florent, J. C., Grierson, D. S., Monneret, C., Tetrahedron Lett., 1989, 30, 1955; U.S. Patent 5,041,543 and DE 3,705,794).

Another known approach for preparing AZT features the coupling between an azido substituted carbohydrate precursor with an activated thymine base (see, Chu, C. K., Beach, J. W., Ullas, G. V., Kosugi, Y., Tetrahedron Lett., 1988, 29, 5349; Chu, C. K., WO 9001492 A1, Feb. 1990; Fleet, G. W. J., Son, J. C., Derome, A. E., Tetrahedron, 1988, 44, 625; Wengel, J., Pedersen, E. B., Synthesis, 1991, 451; Hager, M. W., Liotta, D. C., J. Am. Chem. Soc., 1991, 113, 5117; Jung, M. E., Gardiner, J. M., J. Org. Chem., 1991, 56, 2614; and Sugimura, H., Osumi, K., Yamazaki, T., Yamaya, T., Tetrahedron Lett., 1991, 32, 1813).

A third approach employs D-xylose (see, U.S. Patent 4,916,218, Japanese Patent 63255295, European Patent 295090, and U.S. Patent 4,921,950) or D-glucofuranose (see, Hrebabecky, H., Holy, A., Carbohydr. Res., 1991, 216, 179) as starting material, using the 2'-α-hydroxy group (in carboxylic ester form) to direct the base coupling to give the required β-anomer. Although the glycosidic stereoselectivity of this reaction is high, the lengthy selective protection and deprotection of the sugar moieties remained a problem, in addition to the expensive reagents used in these processes.

The inventors have discovered a new, economical and highly efficient process for producing AZT and derivatives thereof as well as key intermediates. The process involves novel intermediate compounds and can be adapted to produce other pharmaceutically useful nucleosides.

The present invention makes use of key intermediate steps. One such intermediate step can be described as a process for reduction of a pyrimidinyl 2'-deoxyribonucleoside compound comprising contacting a 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside compound having a 3'α-sulfonyl group with a tri-C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initiator in an ether, ester or ketone solvent under conditions to result in a dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound (referred to herein as the "reduction step").

The reduction step is optionally followed by another key intermediate step which can be described as a one-step process for displacing a 3'α-sulfonyl group of a pyrimidinyl 2'-deoxyribonucleoside compound comprising contacting a pyrimidinyl 2'-deoxyribonucleoside compound having a 3'α-sulfonyl group with a base, a lithium salt, and an azide salt under conditions to result in formation of a 5'-protected pyrimidinyl 2',3'-dideoxyribonucleoside compound having a 3'α-azido group (referred to herein as the "displacement step").

The displacement step is optionally followed by a step to remove the 5'-protecting group in order to produce AZT or an active derivative thereof.

Use of the intermediates and processes of the invention yield AZT and other useful nucleosides via reactions having good yields and relatively few undesired by-products.

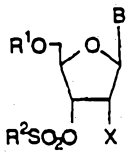
The use of 5-methyluridine instead of thymidine as a starting material is less costly.

Further advantages and various other aspects of the invention will be apparent after consideration of the following description and claims.

Unless otherwise indicated, all percentages recited are weight percentages, based upon total composition weight.

All previously published materials referred to herein are hereby incorporated by reference in their entirety.

A key intermediate for use herein is a 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside compound. A preferred such compound is of the formula



(I)

wherein

R^1 is hydrogen or an OH- protecting group,

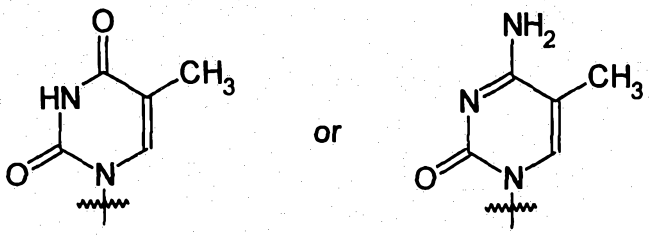
R^2 is C_1-C_{12} alkyl (preferably C_1-C_6 alkyl) or C_6-C_{30} aryl,

B is a pyrimidine base; and

X is Cl, Br or I.

Unless otherwise indicated, as used herein the term "alkyl" or derivative forms thereof refers to straight chain or branched alkyl groups of 1 to 12 carbon atoms, the term "aryl" or derivative forms thereof refers to aryl groups of 6 to 30 carbon atoms, the term "acyl" refers to acyl groups of 1 to 12 carbon atoms, and the term "halo" refers to Cl, Br and I. Examples of alkyl groups include methyl, ethyl, propyl, butyl, isobutyl, pentyl, hexyl, and the like. Examples of aryl groups include phenyl, naphthyl, anthryl, biphenyl and the like. Examples of acyl groups include acetyl, benzoyl, and the like.

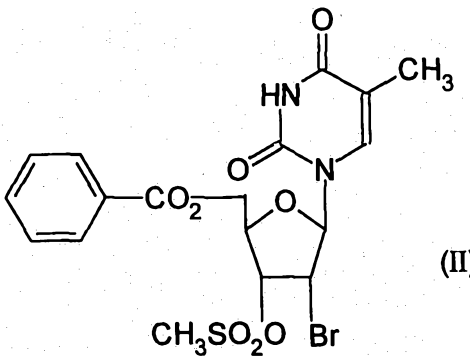
The pyrimidine base ("B group") is typically a nucleobase group containing a keto group in the 2-position, especially a thymine, uracil or cytosine group. Preferred B groups include



By "hydroxyl-protecting group" or "OH-protecting group" is meant a group which protects the hydroxyl group, is capable of being introduced and removed, and does not substantially interfere with the desired reactions. Preferred OH-protecting groups are carboxylic ester groups, carbonate groups, silyl groups, acetal and ketal groups and ether groups. Examples of such OH-protecting groups include RC(O)-, ROC(O)-, R_3Si-, $ROCH_2$ and R-, when R is alkyl or aryl. Preferred OH-protecting groups are ester (i.e., RC(O)-) groups. The benzoyl groups (PhC(O); sometimes abbreviated herein as "Bz") is highly preferred.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, integers or process steps.

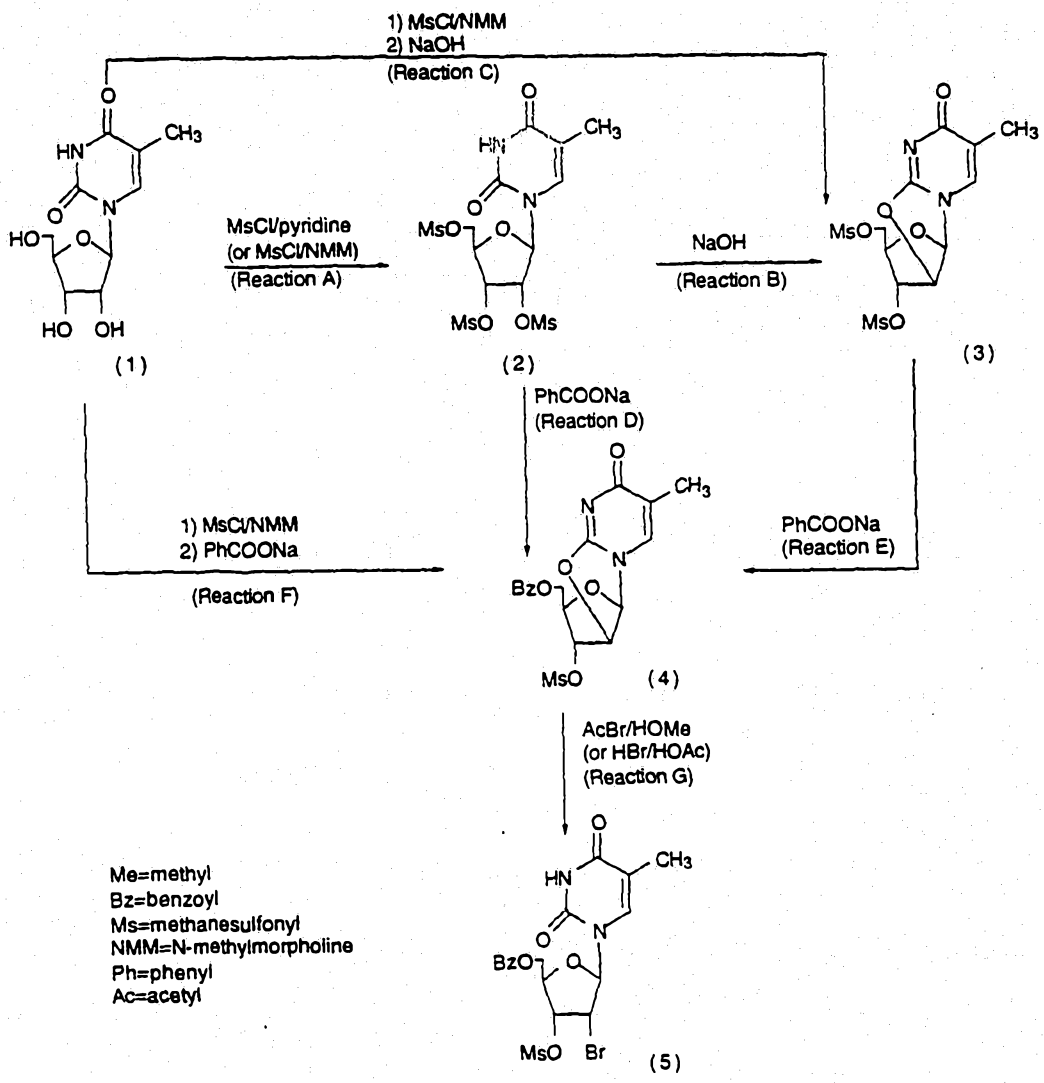
The compound of formula II is preferred. Formula II is:



(II)

This compound is produced via the reactions set out schematically on the following page.

Scheme 1



Me=methyl
Bz=benzoyl
Ms=methanesulfonyl
NMM=N-methylmorpholine
Ph=phenyl
Ac=acetyl

The compound of formula II (i.e., compound 5 in Scheme 1) can be made via several routes. Scheme 1 shows a variety of such routes. Among the routes illustrated are reaction sequences as follows:

1. Reactions A, D, and G;
2. Reactions F and G;
3. Reactions A, B, E and G;
4. Reactions C, E and G.

Other conventional reactions, as well as modifications of those discussed here, may be used to produce compound 5.

A preferred process for producing the 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside intermediate can be described as a process comprising the steps of:

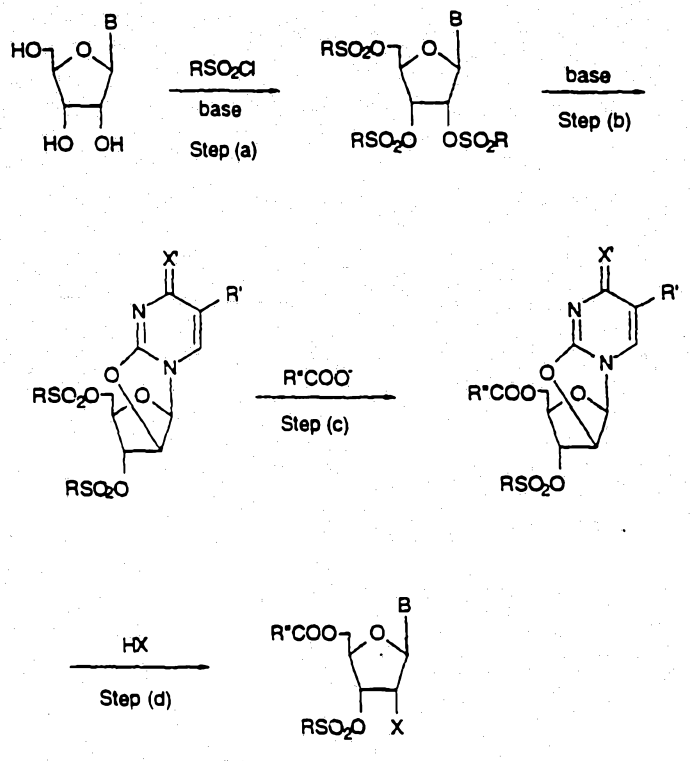
(a) contacting a 2'α,3'α,5'-trihydroxy pyrimidinyl ribonucleoside with a C_1-C_{12} alkyl or C_6-C_{30} aryl sulfonyl chloride and a base under conditions to form a tris(alkylsulfonyl) or tris(arylsulfonyl) compound;

(b) contacting the compound formed in step (a) with a base under conditions to form a 2,2'-anhydro compound;

(c) contacting the compound formed in step (b) with a metal carboxylate to yield a 5'-carboxylic ester compound;

(d) contacting the compound formed in step (c) with a hydrohalic acid to produce a 2'-halo-3'-sulfonyl-5'-carboxylic diester compound.

The schematic representation of this series of reactions is:



In step (a), useful alkyl and arylsulfonyl halides include methanesulfonyl chloride, phenylsulfonyl chloride and the like. Methanesulfonyl chloride (CH_3SO_2Cl) is highly preferred.

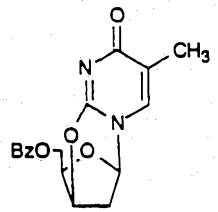
The base used in step (a) is generally an organic amine. Preferred compounds include pyridine, N-methyl-morpholine and the like.

The basic reagent used in step (b) is typically a strong base. Preferred compounds are one or more inorganic bases such as sodium or potassium hydroxide and sodium and potassium carbonate. Sodium hydroxide, NaOH, is highly preferred.

Step (c) is generally carried out using as the metal carboxylate, alkali metal salts of carboxylic acids. Sodium and potassium benzoate are preferred agents.

The hydrohalic acid used in step (d) is generally selected from HCl, HBr and HI, with HBr preferred. The hydrohalic acid can be generated and used in situ.

The reduction step of the invention is performed using the 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside intermediate as a starting material. The pyrimidinyl 2'-deoxyribonucleoside starting compound for the reduction step has a 3'α-sulfonyl group. Examples of 3'α-sulfonyl groups include C_1-C_{12} alkylsulfonyl, C_6-C_{30} arylsulfonyl, and the like. The pyrimidinyl 2'-deoxyribonucleoside starting compound of the reduction step is preferably a thymidine derivative. The reduction step requires the use of a radical initiator such as azobisisobutyronitrile (AIBN), diacetyl peroxide, t-butyl peracetate, di-t-butyl peroxide, benzoyl peroxide, or any other suitable compounds known in the art to initiate free radical formation. It is important to the invention that a the solvent used in the reduction step is an ether, ester, or ketone. It has been found that use of such a solvent avoids substantial formation of an anhydro impurity. An example of such an anhydro impurity has the following formula



We have found that when the 3'-sulfonyl group is in the α-position, then use of certain solvents such as dimethylformamide (DMF) results in substantial formation of the anhydro impurity. The anhydro impurity problem does not arise in prior art processes such as described in U.S. Patent 4,921,950 since the 3'-sulfonyl group is in the β-position. Solvents which consistently provide low levels of the anhydro impurity are within the scope of the present invention. Such solvents are ethers, esters, and ketones which use results in low

levels of the anhydro impurity, for example, less than 0.5% anhydro impurity formation, preferably less than 0.05%.

Suitable ether solvents for the reduction step contain two to ten carbon atoms. Such ethers may contain more than one oxygen atom (e.g., two or three). Examples of such ethers include C_1-C_6 dialkyl ethers, preferably C_1-C_4 dialkyl ethers, such as dibutyl ether, diethyl ether, methyl t-butyl ether, and the like. Other examples of suitable ethers include C_4-C_6 cyclic ethers such as tetrahydrofuran (THF), dioxane, and the like.

Suitable ester solvents for the reduction step are alkyl esters and contain two to ten carbon atoms, preferably two to six carbon atoms. Examples include methyl acetate, ethyl acetate (sometimes abbreviated herein as "EtOAc"), butyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, s-butyl acetate, ethyl formate, and the like.

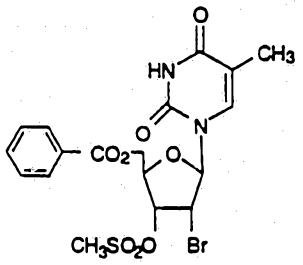
Suitable ketone solvents for the reduction step are dialkyl ketones containing three to ten carbon atoms, preferably three to six carbon atoms. Examples include acetone, butanone, pentanone, methyl isobutyl ketone, and the like.

The reduction step also requires a tri C_1-C_{12} alkyl tin hydride reducing agent (preferably a C_1-C_4 alkyl tin hydride reducing agent). Most preferred is tri-butyl tin hydride (Bu_3SnH). Preferred 5'-protecting groups are carboxylic esters especially benzoyl. The most preferred 2'-halo group is bromine. The process conditions for the reduction step are not particularly critical and can vary considerably. For example, a temperature of about 40°C to about 155°C (preferably about 50°C to about 125°C) for about 0.25 to about 5 hours is typically adequate.

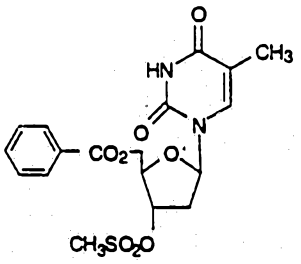
The amount of reducing agent should be sufficient to allow the reaction to proceed to completion, typically about 1 to about 5 moles of reducing agent per mole of pyrimidinyl 2'-deoxyribonucleoside is sufficient. Similarly, the amount of radical initiator should be sufficient to allow the reaction to proceed at a reasonable rate, typically about 0.005 to about 0.25 mole of radical initiator per mole of pyrimidinyl 2'-

deoxyribonucleoside is sufficient, preferably about 0.01 to about 0.1 mole.

A preferred reduction step of the invention can be described as a process comprising contacting a compound of the formula



with tributyl tin hydride and a catalytic amount of azobisisobutyronitrile in ethyl acetate under conditions which result in formation of a compound of the formula

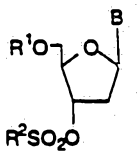


After the dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound is obtained by the reduction step of the invention, it can be used as a starting material for the displacement step of the invention. The displacement step wherein the 3'-sulfonyl group has the α configuration is facile and provides superior yields as compared with prior art processes. The displacement reaction of the invention is a one-step process which avoids the need for more than one isolation and, thus, also results in improved yields. In addition, protection of the 5'-hydroxyl is optional for the displacement step. As is the case for the reduction step of the invention, the starting material for the displacement step is preferably a thymidine derivative. The displacement step requires a lithium

salt as a catalyst and an azide salt to use as the displacing group. Examples of lithium salts include lithium perchlorate, lithium chloride, lithium bromide, lithium iodide, and the like. Preferred azide salts are alkali metal salts, especially NaN_3. The displacement step also requires the presence of a base, preferably a metal carbonate base. Preferably and conveniently, the lithium salt catalyst and the base are embodied in a single compound such as Li_2CO_3. Conditions for the displacement reaction are not particularly critical; for example, a temperature of about 100°C to about 155°C for about 2 to about 20 hours are typically adequate. The displacement reaction is performed in a solvent, preferably a polar aprotic solvent such as DMF, dimethyl sulfoxide (DMSO), N,N-dimethyl acetamide (DMAC), N-methylpyrollidinone and the like. Preferred is DMF.

The amount of lithium salt for the displacement step can be a catalytic amount. Typically, about 0.1 to about 10 moles of lithium salt (preferably about 1 to about 5 moles) are used per mole of pyrimidinyl 2'-deoxyribonucleoside. Similarly, the amount of base used is typically from about 1 to about 5 moles per mole of pyrimidinyl 2'-deoxyribonucleoside. The amount of azide salt is typically at least about 1 mole per mole of pyrimidinyl 2'-deoxyribonucleoside, preferably about 1 to about 10 moles, and more preferably about 1 to about 2 moles.

A preferred displacement step can be described as a process comprising contacting a compound of the formula



wherein

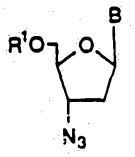
R^1 is hydrogen or an OH - protecting group,

R^2 is a C_1-C_{12} alkyl, or C_6-C_{30} aryl, and

B is a pyrimidine base,

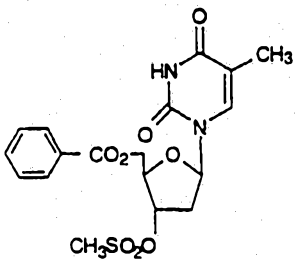
with

a base, a lithium salt, and an azide salt under conditions to result in formation of a compound of the formula

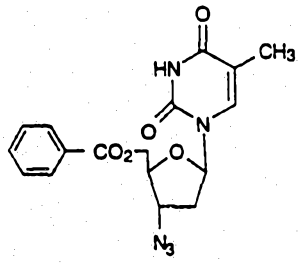


wherein R^1 and B are as defined hereinbefore.

An even more preferred displacement step can be described as a process comprising contacting a compound of the formula



with NaN_3 and Li_2CO_3
under conditions to result in formation of the compound



After the displacement step is performed, the 5'-protecting group can be removed by any procedure known in the art such as methanolysis to form the desired compounds, i.e., AZT or a biologically active derivative thereof. Typical methanolysis agents include sodium methoxide (NaOMe), or a mixture of methanol and a base such as trialkyl amines, NaOH and the like.

A preferred process of the invention can be described as a process comprising the steps of:

(a) contacting a 2'α,3'α,5' trihydroxy pyrimidinyl ribonucleoside with a C_1-C_{12} alkyl or C_6-C_{30} aryl sulfonyl chloride and a base under conditions to form a tris(alkylsulfonyl) or tris(arylsulfonyl) compound;

(b) contacting the compound formed in step (a) with a base under conditions to form a 2,2'-anhydro compound;

(c) contacting the compound formed in step (b) with a metal carboxylate to yield a 5'-carboxylic ester compound;

(d) contacting the compound formed in step (c) with a hydrohalic acid to produce a 2'-halo-3'-sulfonyl-5'-carboxylic diester compound;

(e) contacting the compound formed in step (d) with a tri-C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initiator in an ether, ester or ketone solvent to produce a 2'-deoxy-3'-sulfonyl-5'-carboxylic diester compound

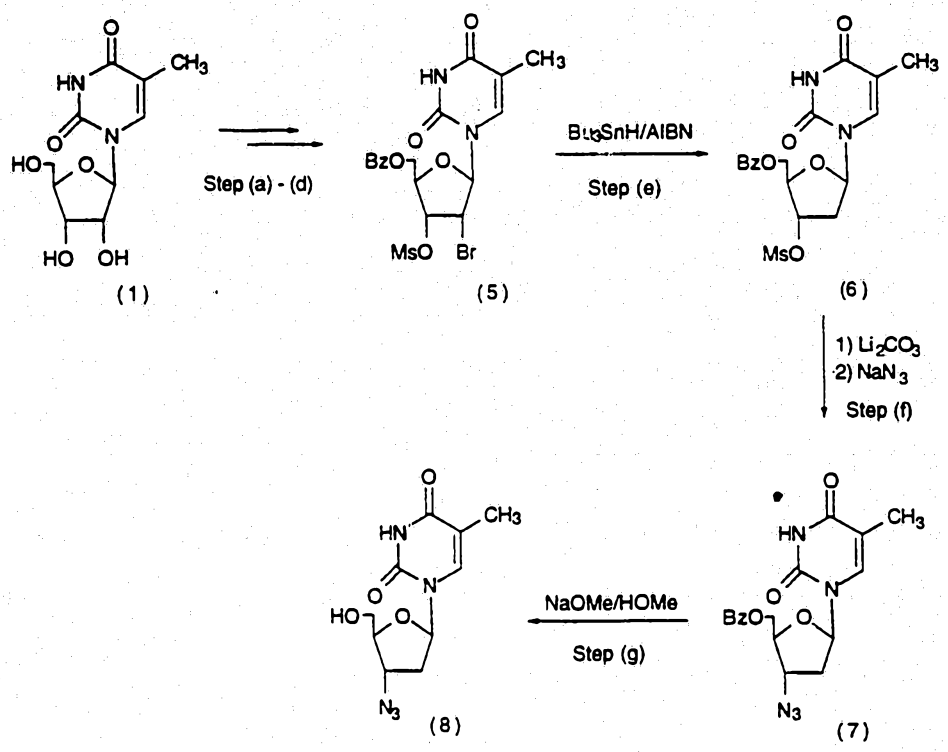
followed by the optional step of

(f) contacting the dehalogenated compound produced in step (e) with a base, a lithium salt, and an azide salt to produce a 3'α-azido compound

followed by the optional step of

(g) deprotecting the compound formed in step (f) to form a compound having a 5' hydroxyl group and a 3'α azido group.

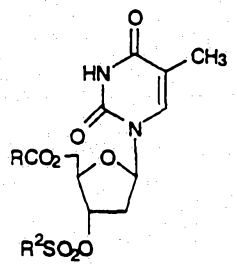
A preferred process of the invention can be depicted schematically as follows:



(1) (5) (6) (7) (8)

Me=methyl
Bz=benzoyl
Ms=methanesulfonyl
Bu=butyl

Some of the intermediates produced in the process of the invention are novel and, thus, the present invention also concerns these intermediates. Thus, the invention also is directed to a compound of the formula

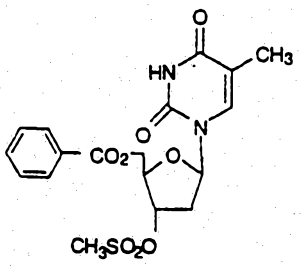


wherein

R is hydrogen, C_1-C_{12} alkyl or C_6-C_{30} aryl and

R^2 is C_1-C_{12} alkyl or C_6-C_{30} aryl.

A preferred R group is a C_6-C_{30} aryl, especially phenyl. A preferred compound of the invention has the formula



The following examples illustrate the invention but should not be interpreted as a limitation thereon.

EXAMPLE 1

2',3',5'-Tris(methanesulfonyl)-5-methyluridine (2)

To a stirred mixture of 5-methyluridine (12.8g, 50 mmol) in pyridine (75 mL) at 0°C was added methanesulfonyl chloride (17.4 mL, 225 mmol). The reaction mixture was stirred at 0°C for five hours then poured into ice-water (500 mL) with stirring. Trimethanesulfonyl-5-methyluridine (2) precipitated and the mixture was stirred for 5 min. The solid product was collected

by filtration and washed with water (3x200 mL) and dried. Yield, 21.6 g, 89%.

^{1}H-NMR (DMSO-d_6) δ 1.77 (s, 3H), 3.24 (s, 3H), 3.34 (s, 3H), 3,36 (s, 3H), 4.47-4.60 (m, 2H), 5.33 (m, 1H), 5.54 (m, 1H), 5.97 (d, J=4.5 Hz, 1H), 7.56 (s, 1H), 11.56 (s, 1H).

EXAMPLE 2

2',3',5'-Tris(methanesulfonyl)-5-methyluridine (2)

N-Methylmorpholine (29.6 mL, 266 mmol) was added to a slurry of 5-methyluridine hemihydrate (15.64 g, 58.5 mmol) in acetone (68 mL) and the resulting mixture was cooled to 5°C. A solution of methanesulfonyl chloride (20.1 mL, 255 mmol) in acetone (30 mL) was added over 45 minutes, causing the reaction temperature to rise to 45-50°C. After stirring an additional 1.4 hours the N-methylmorpholine hydrochloride was removed by filtration and the cake was washed with acetone (2 x 30 mL). The combined filtrate and washes were then added to water (1 L) at 10-15°C. After stirring for 1.1 hours the white precipitate was filtered, washed with water (2x75 mL), and dried under vacuum. Yield, 27.95 g (97%).

EXAMPLE 3

5'-Benzoyl-3'-methanesulfonyl-2,2'-anhydro-5-methyluridine (4)

To a stirred slurry of sodium benzoate (10 g, 69.3 mmol) in acetamide (50 g) at 115°C was added trimethanesulfonyl-5-methyluridine (2) (10 g, 20.3 mmol). The reaction mixture was stirred at 115°C for 65 min. and then poured into ice-water (2L). The mixture was stirred at 0°C for 15 min. The white solid was filtered, washed with water (2x50 mL) and dried. Yield, 7.76 g, 90%.

^{1}H-NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.44 (s, 3H), 4.16-4.33 (m, 2H), 4.78 (m, 1H), 5.63 (s, 1H), 5.68 (d, J=5.7 Hz, 1H), 6.45 (d, J=5.7Hz, 1H), 7.79 (s, 1H), 7.47-7.89 (m, 5H).

EXAMPLE 4

5'-Benzoyl-3'-methanesulfonyl-2'-bromo-thymidine (5)

To a stirred mixture of 5'-benzoyl-3'-methanesulfonyl-2,2'-anhydro-5-methyluridine (4) (4.0 g, 9.5 mmol) in ethyl acetate (100 mL) and methanol (10 mL) was added acetyl bromide (5 mL, 67.7 mmol). The reaction mixture was refluxed for one hour and then cooled. The reaction mixture was transferred to a separatory funnel. Ethyl acetate (150 mL) was added. The solution was washed with saturated sodium bicarbonate (100 mL) followed by brine (100 mL). The organic layer was separated and dried over MgSO4. Removal of solvent gave the solid product 5. Yield, 4.86g, 100%.

^{1}H-NMR (DMSO-d_6) δ 1.63 (s, 3H), 3.37 (s, 3H), 4.50-4.55 (m, 2H), 4.60-4.64 (m, 2H), 5.09 (t, J=6.0 Hz, 1H), 5.47 (m, 1H), 6.14 (d, J=7.2 Hz, 1H), 7.49 (s, 1H), 7.50-8.04 (m, 5H), 11.56 (s, 1H).

EXAMPLES 5-11

5'-Benzoyl-3'-methanesulfonylthymidine (6) (reduction step)

General Procedure: To a 50 ml round-bottom flask equipped with condenser, nitrogen inlet, and thermometer was added 5'-benzoyl-3'-methanesulfonyl-2'-bromo-thymidine (5) (3.0 g, 5.96 mmol) and 30 ml of the specified solvent (see the table below). Bu_3SnH (3.0 ml, 11.15 mmol; 1.9 equiv) was then added. The reaction mixture was heated to reflux or to the temperature specified in the table, to give a clear, homogeneous solution. The reaction mixture was then cooled slightly and 300 mg AIBN was added. The mixture was heated to reflux or the temperature specified in table for 45 minutes at which time the reaction was complete by HPLC (or for a period of time as specified in the table). The mixture was then cooled to 25°C and concentrated to give a residue. The residue was purified by silica gel column chromatography (Kiesgel 60, 230-400 mesh silica gel, 2.5 x 23 cm column, 3/1 EtOAc/hexane as eluent) or by methylene chloride trituration to afford 5'-benzoyl-3'-methanesulfonylthymidine (6). These results were summarized in the table.

Table: Reductions of 5'-benzoyl-3'-methanesulfonyl-2'-bromo-thymidine (5) to 5'-benzoyl-3'-methanesulfonylthymidine (6):

EXAMPLE	Solvent	Temp (°C)	Time	Impurity (%)[a]	Yield (%)
5	THF	67°C	45 min	<0.05	94[b]
		67°C	2.0 h	<0.05	76[c]
6	EtOAc	78°C	45 min	<0.05	87[c]
		78°C	2.0 h	<0.05	d
7	Acetone	56°C	2.0 h	0.20	84[b]
8 (comparative)	EtOH	76°C	45 min	6.70	79[b]
			2.5 h	7.20	48[c]
9 (comparative)	Toluene	80-90°C	45 min	1.20	91[b]
			2.0 h	12.6	d
			6.0 h	21.6	100[c,e]
10 (comparative)	DMAC	80-90°C	45 min	6.90	56[b]
11 (comparative)	DMF	80-90°C	45 min	17.3	83[b]
		125-130°C	2.5 h	24.2	d

a) Impurity (%) represents HPLC area % of the impurity in the reaction mixture. The impurity was identified as 5'-benzoyl-2,3'-anhydrothymidine.

b) Weight yield (%) isolated by silica gel column chromatographic separation.

c) Weight yield (%) isolated by methylene chloride trituration. This isolation method did not purge the impurity from the desired product (6). This preferred isolation method was only practical for those cases where

the reaction (reduction step) was clean (little or no impurity formation).

d) Product (6) not isolated.

e) High yield also due to tributyltin bromide contamination.

The following are additional information for the results given in the table:

Example #5

Use of THF (tetrahydrofuran) resulted in <0.05% of the impurity by HPLC even after 2 h at reflux (67°C). The product (6) was isolated by silica gel column chromatography in 94% yield. Isolation by methylene chloride trituration gave a 76% yield.

^{1}H-NMR (DMSO-d_6) δ 1.57 (s, 3H), 2.55 (m, 2H), 3.32 (s, 3H), 4.45 (s, 1H), 4.48-4.60 (m, 2H), 5.47 (m, 1H), 6.22 (t, J=6.9 Hz, 1H), 7.41 (s, 1H), 7.52-8.02 (m, 5H), 11.40 (s, 1H).

Example #6

Use of ethyl acetate resulted in <0.05% of the impurity by HPLC even after 2.5 h at reflux (78°C). The product (6) was isolated by methylene chloride trituration in 87% yield.

Example #7

Use of acetone resulted in 0.20% HPLC area of the impurity after 2 hours at reflux (56°C). The product (6) was isolated by silica gel column chromatography in 84% yield.

Example #8 (comparative)

Use of ethanol resulted in 6.7% HPLC area of the impurity in 45 minutes at reflux (76°C). At 2.5 h, the level of impurity increased to 7.2%. The product (6) was isolated by silica gel column chromatography in 79%. Isolation by methylene chloride trituration resulted in a 48% yield of product (6) containing 7.0% (HPLC area) of the impurity.

Example #9 (comparative)

Use of toluene as solvent in the reduction resulted in 1.2% HPLC area of the impurity at 80-90°C in 45 minutes. The product was isolated by column chromatography giving a 91% yield. In a separated experiment using toluene, the reaction mixture contained 12.6% HPLC area of the impurity at 80-90°C in 2 hours and 21.6% area after 4 additional hours. The product was isolated by methylene chloride trituration in essentially a quantitative yield but the product contained 26.3% (HPLC area) of the impurity. The product was also contaminated with tributyltin bromide, as indicated by ^{1}H-NMR.

Example #10 (comparative)

Use of dimethylacetamide (DMAC) resulted in 6.9% HPLC area of the impurity in 45 minutes at 80-90°C. The product was isolated by silica gel column chromatography in 56% yield.

Example #11 (comparative)

Use of DMF (dimethylformamide) resulted in 17.3% HPLC area of the impurity at 80-90°C in 45 minutes. The product was isolated by silica gel column chromatography in 83% yield. In a separated experiment using DMF, a 24.2% HPLC area of the impurity was detected at 2.5h at 125-130°C.

EXAMPLE 12

5'-Benzoyl-3'α-azido-3'-deoxythymidine (7) (displacement step)

To the stirred solution of 5'-benzoyl-3'-methanesulfonylthymidine (6) (0.5 g, 1.18 mmol) in DMF (3 ml) was added lithium carbonate (0.2 g, 2.7 mmol). The reaction mixture was placed in a preheated oil bath at 125°C and stirred for 100 minutes. Sodium azide (0.2 g, 3.1 mmol) was then added and the reaction was stirred at 125°C for five hours. The reaction mixture was then cooled to room temperature and poured into ice-water (5 ml). The pH was adjusted to ca. 6 by adding acetic acid. The resulting precipitate was collected by

filtration and dried to give 5'-benzoyl-3'α-azido-3'-deoxythymidine (7). Yield, 0.37 g (82%).

^{1}H-NMR ($CDCl_3$): δ 1.64 (s, 3H), 2.32-2.55 (m, 2H), 4.18 (m, 1H), 4.32 (m, 1H), 4.50-4.67 (m, 2H), 6.15 (t, J=6.4 Hz, 1H), 7.16 (s, 1H), 7.41-8.01 (m, 5H), 9.54 (s, 1H).

EXAMPLE 13

3'α-Azido-3'-deoxythymidine (8)

To the stirred solution of 5'-benzoyl-3'α-azido-3'-deoxythimidine (7) (0.20 g, 0.54 mmol) in methanol (3 ml) was added 25% sodium methoxide solution in methanol (0.4 ml, 1.75 mmol). The reaction was stirred at room temperature for one hour and the mixture was then neutralized by strong acidic resin (Dowex 50-200X8, prewashed with methanol) to a pH of ca. 6. The resin was filtered off and washed with methanol (2x10 ml). The solvent was removed to give AZT which was dried under vacuum. Yield, 0.10 g (71%).

^{1}H-NMR (D_2O) δ 1.70 (s, 3H), 2.32 (t, J=6.5 Hz, 2H), 3.58-3.71 (m, 2H), 3.83 (q, J=4.7 Hz, 1H), 4.18 (q, J=6.4 Hz, 1H), 6.02 (t, J=6.5 Hz, 1H), 7.46 (s, 1H).

~~What is Claimed is~~

The claims defining the invention are as follows:

1. A process for reduction of a pyrimidinyl 2'-deoxyribonucleoside compound comprising contacting a 2'α-halo-5'-protected pyrimidinyl ribonucleoside compound having a 3'α-sulfonyl group with a tri C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initiator in an ether, ester or ketone solvent under conditions to result in a dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound.

2. The process of Claim 1 wherein the pyrimidinyl 2'-deoxyribonucleoside compound is a thymidine derivative.

3. The process of Claims 1 or 2 wherein the solvent is an ether containing two to ten carbon atoms, an ester containing two to ten carbon atoms, or a ketone containing three to ten carbon atoms.

4. The process of Claim 3 wherein the solvent is a C_1-C_4 dialkyl ether, a C_4-C_6 cyclic ether, a C_2-C_6 alkyl ester, or a C_3-C_6 dialkyl ketone.

5. The process of Claims 1 or 2 wherein the solvent is methyl acetate, ethyl acetate, butyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, s-butyl acetate, ethyl formate, THF, dibutyl ether, diethyl ether, methyl t-butyl ether, acetone, butanone, pentanone, or methyl isobutyl ketone, amyl acetate, cyclohexanone, dioxane, 1,2-dimethoxyethane, 1,2-diethoxyethane and diethoxymethane.

6. The process of Claims 1 or 2 wherein the solvent is selected from the group consisting of ethyl acetate, butyl acetate, acetone, and THF.

7. The process of any one of Claims 1-6 wherein the radical initiator is azobisisobutyronitrile, di-t-butyl peroxide, benzoyl peroxide, t-butyl peracetate or diacetyl peroxide.

any one of 1-7

8. The process of Claims wherein the tri C_1-C_{12} alkyl tin hydride reducing agent is Bu_3SnH and the radical initiator is azobisisobutyronitrile.

any one of 1-8

9. The process of Claims wherein the 5'-protecting group is a carboxylic ester.

any one of 1-8

10. The process of Claims wherein the 5'-protecting group is benzoyl.

any one of 1-10

11. The process of Claims wherein the 3'α-sulfonyl group is C_1-C_{12} alkylsulfonyl, C_6-C_{30} arylsulfonyl.

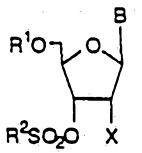
any one of 1-11

12. The process of Claims wherein the 2'-halo group is Br.

any one of 1-12

13. The process of Claim carried out at a temperature of about 50°C to about 125°C for about 0.25 to about 5 hours.

14. A process comprising contacting a compound of the formula



wherein

R^1 is hydrogen or an OH - protecting group,

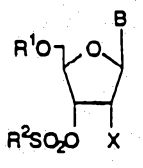
R^2 is a C_1-C_{12} alkyl or C_6-C_{30} aryl,

B is a pyrimidine base; and

X is Cl, Br or I;

with

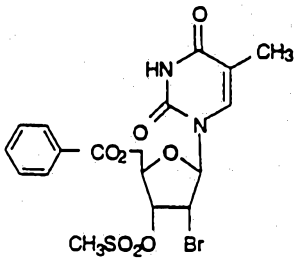
a tri C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initator in an ether, ester, or ketone solvent under conditions to result in a compound of the formula



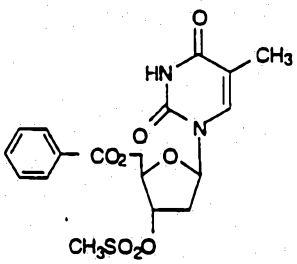
wherein

R^1, R^2 and B are as defined hereinabove.

15. A process comprising contacting a compound of the formula



with tributyl tin hydride and a catalytic amount of azobisisobutyronitrile in ethyl acetate under conditions which result in formation of a compound of the formula



16. A one-step process for displacing a 3'α-sulfonyl group of a pyrimidinyl 2'-deoxyribonucleoside compound comprising contacting a pyrimidinyl 2'-deoxyribonucleoside compound having a 3'α-sulfonyl group with a base, a lithium salt, and an azide salt under conditions to result in formation of a 5'-protected pyrimidinyl 2',3'-dideoxyribonucleoside compound having a 3'α-azido group.

17. The process of Claim 16 wherein the pyrimidinyl 2'-deoxyribonucleoside compound is a thymidine derivative.

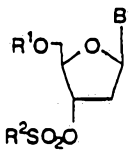
18. The process of Claim 16 or 17 wherein the base is a metal carbonate.

19. The process of Claim 18 wherein said base and lithium salt are Li_2CO_3 and the azide salt is an alkali metal salt.

20. The process of Claim 19 wherein the azide salt is NaN_3.

21. The process of any one of Claims 16-20 carried out at a temperature of about 90°C to about 155°C from about 2 to about 20 hours.

22. A one-step process comprising contacting a compound of the formula



wherein

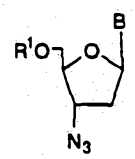
R^1 is hydrogen or an OH-protecting group,

R^2 is a C_1-C_{12} alkyl or C_6-C_{30} aryl, and

B is a pyrimidine base;

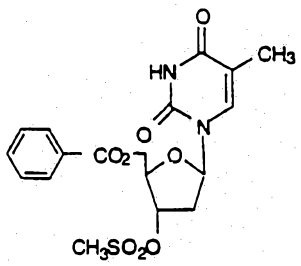
with

a base, a lithium salt, and an azide salt under conditions to result in formation of a compound of the formula



wherein R^1 and B are as defined hereinbefore.

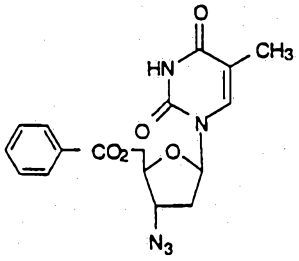
23. A one-step process comprising contacting a compound of the formula



with

NaN_3 and Li_2CO_3

under conditions to result in formation of the compound



24. The process of any one of Claims 16-21 followed by the additional step of removing any 5'-protecting group to form a compound having a 5'-hydroxyl group and a 3'α-azido group.

25. The process of Claim 24 wherein the 5'-protecting group is a carboxylic ester and the deprotecting step is accomplished by methanolysis.

26. A process comprising the steps of:

(a) contacting a 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside compound having a 3'α-sulfonyl group with a tri C_1-C_{12} alkyl tin hydride reducing agent and a catalytic amount of a radical initiator in an ether, ester, or ketone solvent under conditions to

result in a dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound; followed by

(b) contacting the dehalogenated pyrimidinyl 2'-deoxyribonucleoside compound formed in step (a) with a base, a lithium salt, and an azide salt under conditions to result in formation of a 5'-protected pyrimidinyl 2',3'-dideoxyribonucleoside compound having a 3'α-azido group.

27. The process of Claim 26 followed by additional step (c):

(c) deprotecting the 5'-protected pyrimidinyl 2',3'-dideoxyribonucleoside compound formed in step (b) to form a compound having a 5'-hydroxyl group and a 3'α-azido group.

28. A process comprising the steps of:

(a) contacting a 2'α,3'α,5'-trihydroxy pyrimidinyl ribonucleoside with a C_1-C_{12} alkyl or C_6-C_{30} aryl sulfonyl chloride and a base under conditions to form a tris(alkylsulfonyl) or tris(arylsulfonyl) compound;

(b) contacting the compound formed in step (a) with a base under conditions to form a 2,2'-anhydro compound;

(c) contacting the compound formed in step (b) with a metal carboxylate to yield a 5'-carboxylic ester compound;

(d) contacting the compound formed in step (c) with a hydrohalic acid to produce a 2'α-halo-3'-sulfonyl-5'-carboxylic diester compound;

(e) contacting the compound formed in step (d) with a tri C_1-C_{12} alkyl tin hydride reducing

agent and a catalytic amount of a radical initiator in an ether, ester, or ketone solvent to produce a 2'-deoxy-3'-sulfonyl-5'-carboxylic diester compound.

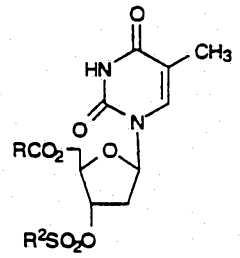
29. The process of Claim 28 followed by additional step (f):

(f) contacting the dehalogenated compound produced in step (e) with a base, a lithium salt, and an azide salt to produce a 3'α-azido compound.

30. The process of Claim 29 followed by additional step (g):

(g) deprotecting the compound formed in step (f) to form a compound having a 5'-hydroxyl group and a 3'α-azido group.

31. A compound of the formula



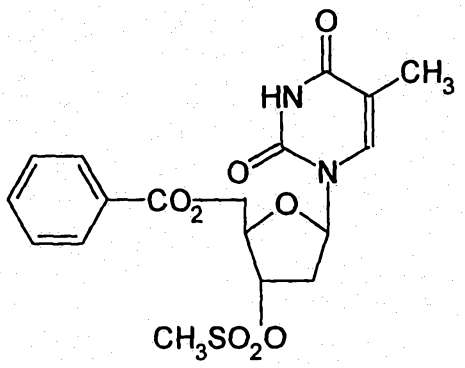
wherein

R hydrogen, C_1-C_{12} alkyl or C_6-C_{30} aryl and

R^2 is C_1-C_{12} alkyl or C_6-C_{30} aryl.

32. The compound of Claim 31 wherein R is C_6-C_{30} aryl.

33. A compound of the formula



34. A process for reduction of a pyrimidinyl 2'- deoxyribonucleoside compound substantially as hereinbefore described with reference to any one of the examples.

DATED: 24 April, 1996

PHILLIPS ORMONDE & FITZPATRICK

Attorneys for:

BRISTOL-MYERS SQUIBB COMPANY

ABSTRACT CT2258

PROCESS FOR PREPARING AZT AND DERIVATIVES THEREOF

Disclosed is a process for producing AZT (3'-azido-3'-deoxythymidine) and derivatives thereof. The process makes use of a reduction step wherein a 2'-halo-5'-protected pyrimidinyl 2'-deoxyribonucleoside compound is reduced in an ether, ester, or ketone solvent. Also, the process makes use of a displacement step wherein a 3'α-sulfonyl group is displaced with an azido group in the presence of a lithium salt and a base.