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Jung et al.

[54] PROCESS FOR THE SYNTHESIS OF 2',3'-DIDEOXYNUCLEOSIDES

[75] Inventors: Michael E. Jung, Los Angeles, Calif.; John M. Gardiner, Birmingham, England

[73] Assignee: The Regents of the University of California, Oakland, Calif.

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536/28.2, 536/28.5

[58] Field of Search 536/23, 24, 26

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Primary Examiner—Johnnie R. Brown
Assistant Examiner—L. Eric Crane
Attorney, Agent, or Firm—Christie, Parker & Hale

ABSTRACT

Methods are provided for preparing 3'-substituted-2', 3'-dideoxynucleosides, and the like, from non-carbohydrate, non-nucleoside starting materials.

8 Claims, No Drawings
OTHER PUBLICATIONS


PROCESS FOR THE SYNTHESIS OF 2',3'-DIDEOXYNUCLEOSIDES

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FIELD OF THE INVENTION

This invention is directed to processes for making 2',3'-dideoxynucleosides, 2',3'-dideoxy-2',3'-didehydroxynucleosides, 3'-substituted-dideoxynucleosides, and the like.

BACKGROUND OF THE INVENTION

Modified nucleosides (e.g., 3'-substituted, deoxy-, dideoxy-, and dideoxy-didehydroxynucleosides) are known to exhibit actual or potential activity against a variety of contagions, antitumor activity, and/or usefulness as chemotherapeutic agents. For example, 3'-azido-3'-deoxythymidine (AZT) is effective in treating infection by the HTLV III virus (see, e.g., U.S. Pat. No. 4,724,232 to Rideout, et al.), feline leukemia virus (U.S. Pat. No. 4,780,453 to Rideout, et al.) and gram-negative bacteria (U.S. Pat. No. 4,874,751 to Beacham III, et al.). In order to make these compounds available on a large scale, chemists have worked for years on the development of new methods for their preparation.

The synthesis of AZT is illustrative. AZT was prepared by Horowitz in 1964 using a six-step process starting with the naturally occurring nucleoside, thymidine. J. R. Horowitz, et al., J. Org. Chem. 1964, 20, 2076. A shorter route is described in several U.S. patents to Rideout, et al. (assigned to Burroughs-Wellcome Co.) and entails converting thymidine to 2',3'-anhydrothymidine, followed by reaction with sodium azide to give AZT. A similar route was reported by a Russian group in 1984. V. E. Zaitseva, et al., Bioorg. Khim. 1984, 10, 670.

A different approach, starting with a sugar, was described by Fleet in 1988. G. W. J. Fleet, et al. Tetrahedron 1988, 44, 625 (incorporated herein by reference). Fleet's synthesis entails conversion of D-xylene to methyl-5-O-tert-butylideneethyl-2-deoxy-a-D-threo-pentofuranoside, reaction with sodium azide to give an azido-pentofuranoside, and subsequent coupling with silylated thymine in the presence of trialkysilyl triflates to give AZT. A similar route, based on the condensation of methyl-3-azido-2,3-dideoxy-5-O-p-tolyl-a-D-ribofuranoside with silylated thymine (or other heterocyclic bases) was described by the same Russian group in 1986 N. B. Dyatkina, et al., Bioorg. Khim. 1986, 12, 1046.


To date, nearly every approach to the synthesis of modified nucleosides has begun with chemical compounds such as naturally occurring nucleosides or sugars. With limited exception, most of these material are quite expensive. Thymidine, for example, costs approximately $6.60 per gram. Accordingly, a need exists for an inexpensive, straightforward process for making modified nucleosides. The present invention fulfills that need.

SUMMARY OF THE INVENTION

This invention provides novel synthetic routes to modified nucleosides such as 3'-azido-3'-deoxythymidine (AZT), dideoxycytidine (ddC), dideoxydidehydrothymidine (ddT), and the like, starting with simple organic compounds that are neither carbohydrates nor nucleosides. Asymmetry is introduced at what becomes the 3' and 4' positions by using a Sharpless epoxidation.

More specifically, crotonaldehyde, or a silyl enol ether derivative thereof, is converted to a modified ribofuranoside, and a purine or pyrimidine base is coupled thereto to yield the modified nucleoside. Key intermediates include an epoxy alcohol and various diols. The modified ribofuranosides are formed by treating the diols with dilute acid.

In an exemplary embodiment of the invention, D-3'-azido-3'-deoxythymidine (AZT) is synthesized from crotonaldehyde by the following steps: (a) silylation of crotonaldehyde to yield a silyl enol ether; (b) condensation of the silyl enol ether with trimethyl orthoformate to yield an enal; (c) reduction of the enal to yield an allicic acid; (d) Sharpless epoxidation of the allicic acid to yield an epoxy alcohol of desired configuration; (e) reaction of the epoxy alcohol with diethylaluminum fluoride and azidotrimethylsilane to yield a five-carbon azido diol; (f) cyclization of the azido diol, using dilute acid, to yield a 3'-azido-2,3'-dideoxyribonucleoside; and (g) preparation of AZT by (i) protecting the primary hydroxyl group, (ii) reacting the hydroxy-protected azido-ribonucleoside with silylated thymine, and (iii) de-protecting the hydroxyl group to yield AZT.

Dideoxycytidine (ddC) is prepared in a similar manner: crotonaldehyde is converted to the epoxy alcohol as in the above paragraph, and the epoxy alcohol is converted to 5,5-dimethyloxepane-1,2-diol by reaction with diisobutylaluminum hydride. The diol is then converted to a 2,3-dideoxyribonucleoside by treatment with dilute acid. Protection of the hydroxyl group, treatment with silylated cytosine, and de-protection yields ddC.

Dideoxydidehydrothymidine (ddT) is prepared by converting the above-mentioned epoxy alcohol to 3-thiophenoxy-5,5-dimethyloxepane-1,2-diol, using thionophenol and a metal catalyst. The diol is then cyclized using dilute acid, and the resulting 3-thiophenoxy-2,3'-dideoxyribonucleoside is hydroxyl-protected, then oxidatively eliminated to obtain a 2,3'-dideoxy-2,3'-didehydroribonucleoside using MCPBA or NaIO.

The present invention also provides an inexpensive route to L-2'-deoxynucleosides, which in turn are polymerizable to enantio-DNA ("anti-sense" DNA), which is presently being investigated for its ability to prevent gene expression. L-2'-deoxynucleosides are prepared by converting crotonaldehyde to an enantiomer of the above-mentioned epoxy alcohol, converting the epoxy alcohol to a hydroxy-protected L-ribofuranoside, and coupling the L-ribofuranoside with a purine or pyrimidine base in a manner similar to that described above.

By starting with crotonaldehyde, an inexpensive ($14/liter) commodity chemical, the present invention provides a low-cost route to AZT and other modified nucleosides. The invention is also marked by great versatility. Preparation of 3'-substituted nucleosides, 2',3'-
dideoxynucleosides and 2',3'-dideoxy-2',3'-didehydro-
dronucleosides from crotonaldehyde proceeds in each 
case by formation of a common intermediate, namely, 
an epoxide alcohol. Similarly, the synthesis of AZT de-
scribed herein is equally useful in preparing modified 
nucleoside analogues of AZT, e.g., AZI, AZU, AZC, 
and the like, since the base is added after the furanoside 
is prepared.

**DETAILED DESCRIPTION**

The present invention provides new processes for 
preparing modified nucleosides. As used herein, the 
term "modified nucleoside" means a compound struc-
turally analogous to a naturally occurring nucleo-
side—adenosine, cytidine, guanosine, thymidine, 
uridine, and the like—i.e., a compound comprising a 
pyrimidine or purine base, or derivative thereof, 
linked to a ribose, deoxyribose, dideoxyribose, or similar moi-
ety. In particular, the term includes 3'-substituted-2',3'- 
dideoxynucleosides, 2,3'-dideoxynucleosides, and 2',3'- 
dideoxy-2',3'-didehydrodronucleosides. Both L- and D-
enantiomers are included.

Modified nucleosides are prepared by first converting 
a silyl enol ether, (1,3-butadien-1-yl)oxytrimethylsilane 
(commercially available from Aldrich or prepared from 
crotonaldehyde) to an epoxy alcohol having the desired 
configuration. For D-modified nucleosides, the epoxy 
alcohol is (2R,3R) 3-(2,2-dimethoxyethyl)oxiranemethan-
ol:

\[
\begin{align*}
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\end{align*}
\]

For L-modified nucleosides, the epoxy alcohol is 
(2S,3S) 3-(2,2-dimethoxyethyl)oxiranemethanol:

\[
\begin{align*}
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\end{align*}
\]

The epoxy alcohol is prepared in the following manner: A solution of crotonaldehyde is heated with tri-
methylsilyl chloride, zinc chloride and triethylamine, in 
benzene, to obtain a mixture of (E) and (Z) (1,3-butadi-
en-1-yl)oxytrimethylsilane:

\[
\text{OTMS}
\]

The silyl enol ether is mixed with trimethyl orthofo-
rmate and zinc chloride and heated in dichloromethane 
to obtain 5,5-dimethoxypent-2-enal:

\[
\begin{align*}
\text{OH} & \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{OCH}_3 & \\
\end{align*}
\]

The enal is dissolved in diethyl ether and reduced with 
diisobutylaluminum hydride (Dibal-H) to obtain 
5,5-dimethoxypent-2-en-1-ol as a mixture of and Z iso-
mers, in which the desired isomer greatly predominates 
(> 95%):

\[
\begin{align*}
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\text{OCH}_3 & \\
\end{align*}
\]

Sharpless epoxidation of the allylic alcohol yields 
the epoxy alcohol, with stereoconfiguration being con-
trolled by the particular enantiomer of tartrate used. 
More specifically, the allylic alcohol is added, with 
tert-butylhydroperoxide, to a cooled (−20°C) solution of 
D-(−)-diisopropyl tartrate and titanium (IV) tetra-
sopropoxide to obtain (2S,3R) 3-(2,2-dimethoxyethyl)oxi-
ranemethanol (> 95% enantiomeric excess). Alternatively, 
(2S,3S) 3-(2,2-dimethoxyethyl)oxiranemethanol is obtained by using L-(−)-diisopropyl tartrate.

The epoxy alcohol is converted to a 3-substituted-2,3-
dideoxyribosofuranose, a 2,3-dideoxyribosofuranose, or 
a 2,3-dideoxy-2,3-didehydrodoribofuranose by a series of 
steps that will now be described.

**3'-Substituted-2'3'-Dideoxynucleosides**

A mixture of the epoxy alcohol (2R,3R) 3-(2,2-dime-
thoxyethyl)oxiranemethanol and azidotrimethylsilane 
in dichloromethane is reacted with diethylaluminum 
fluoride to obtain (2S,3S) 3-azido-5,5-dimethoxypenta-
tane-1,2-diol:

\[
\begin{align*}
\text{OH} & \\
\text{OCH}_3 & \\
\text{N}_3 & \\
\end{align*}
\]

The azido diol is dissolved in dichloromethane and 
treated with dilute acid, e.g., 1.5% hydrochloric acid in 
methanol, to obtain a mixture of two anomers—methyl 
α- and β-D-3-azido-2,3-dideoxyribofuranoside:

\[
\begin{align*}
\text{OH} & \\
\text{OCH}_3 & \\
\text{N}_3 & \\
\end{align*}
\]

By keeping the concentration of the azido diol low, 
cyclization to the ribose (five-membered ring) predomi-
nates over cyclization to the hexose (six-membered 
ring).

The above-described ribofuranoside is converted to a 
modified nucleoside, i.e., a 3'-azido-2',3'-dideoxynucleo-
side, using Vorbrüggen or Hilbert-Johnson technology.
(i.e., coupling with a silylated base in the presence of a trialkylsilyl triflate, as described in the Fleet reference, supra.). First, the primary hydroxyl group is protected by reacting the anomeric mixture of methyl α- and β-D-3-azido-2,3-dideoxy-ribofuranoside with tert-butyldiphenylsilyl chloride (TPSCl) in DMF, along with imidazole, to obtain a hydroxy-protected D-3-azido-2,3-dideoxyribosfuranoside, e.g., methyl α- and β-D-3-azido-2,3-dideoxy-5-{[1(1,1-dimethylethyl)di-phenylsilyl]oxy}ribosfuranoside:

The hydroxy-protected D-3’-azido-2,3-dideoxyribosfuranoside is reacted with a silylated purine or pyrimidine base, in the presence of a trialkylsilyl triflate, and the hydroxyl group on the primary carbon is deprotected, to obtain a D-3’-azido-2,3-dideoxynucleoside of the formula:

wherein B is a purine or pyrimidine base.

As desired, the modified nucleoside is then separated into its α and β anomers by flash chromatography or similar technique. (Optionally, the hydroxy-protected, as well as the unprotected 3-azido-2,3-dideoxyribosfuranoside are separated into α- and β-anomers using silica gel chromatography or TLC prior to conversion to the nucleoside. Regardless of whether a pure anomer or mixture is used, one obtains an α β mixture of the nucleoside. Typically, only one anomer (usually β) is bioactive.)

Methyl α- and β-L-3′-azido-2′,3′-dideoxynucleosides are prepared in a manner identical to that just described, except that (2S,3S) 3-(2,2-dimethoxyethyl)oxiranemethanol is employed as the epoxy alcohol.

In addition to 3′-azido-2′,3′-dideoxynucleosides, other 3′-substituted-2′,3′-dideoxynucleosides are prepared in accordance with the present invention by substituting other nucleophiles, e.g., -halo, -cyano, -thioal-kyl, -phosphono derivatives, and the like, for azide in the conversion of the epoxy alcohol to the diol.

2′-Dideoxynucleosides

The epoxy alcohol (2R,3R) 3-(2,2-dimethoxyethyl)oxiranemethanol is reacted with diisobutylaluminum hydride, in benzene, to obtain 5,5-dimethoxypentane-1,2-diol:

The diol is dissolved in dichloromethane and treated with dilute acid to obtain a dideoxyribosfuranoside, i.e., methyl α- and β-D-2,3-dideoxyribosfuranoside:

The dideoxyribosfuranoside is converted into a 2′,3′-dideoxynucleoside having the formula:

by the same process used in converting a 3-azido-2,3-dideoxyribosfuranoside to a 3′-azido-2′,3′-dideoxynucleoside. Thus, dideoxycytidine (ddC) is prepared by protecting the hydroxyl group on the primary carbon of the dideoxyribosfuranoside, reacting the resulting hydroxyprotected dideoxyribosfuranoside with silylated cytosine, and de-protecting the hydroxyl group to obtain ddC.

As desired, a 2′,3′-dideoxynucleoside prepared in the above manner is resolved into α- and β-anomers using flash chromatography or a similar technique.

2′-Dideoxy-2′-Didehydronucleosides

The epoxy alcohol (2R,3R) 3-(2,2-dimethoxyethyl)oxiranemethanol is reacted with thiophenol in the presence of a metal catalyst to obtain 3-thiophenoxy-5,5-dimethoxy pentane-1,2-diol:
alcohol (2S,3S) 3-(2,2-dimethoxyethyl)oxiranemethanol is reacted with benzyl alcohol in the presence of titanium (IV) tetraisopropoxide to obtain 3-benzyloxy-5,5-dimethoxypentane-1,2-diol:

The benzyloxy diol is dissolved in dichloromethane and treated with dilute acid (in a manner similar to that described above) to obtain a 2,3-deoxy-3-benzylribofuranoside having the formula:

This compound is treated with benzyl bromide, in the presence of a base, to obtain a hydroxy-protected L-ribofuranoside having the formula:

where R is a protecting group (e.g., TPS).

The hydroxy-protected 2,3-deoxy-2,3-didehydroribofuranoside is converted to a 2,3-deoxy-2,3-didehydro-ribofuranoside:

wherein B is a purine or pyrimidine base, in a manner similar to that described above, i.e., it is reacted with a silylated base in the presence of a trialkylsilyl triflate and then de-protected. For example, dideoxydideoxyhydrothymidine (d4T) is prepared by reacting the above-described hydroxy-protected 2,3-deoxy-2,3-didehydroriborofuranoside with silylated thymine, and deprotecting the hydroxyl group on the primary carbon to obtain d4T.

Those skilled in the art will appreciate that the compounds described above—3'-substituted-2,3'-dideoxyribonucleosides; 2',3'-dideoxyribonucleosides; 2',3'-dideoxy-2',3'-didehydroribonucleosides; the modified ribofuranoside precursors thereof; and the like—can be prepared as both the D- and L-enantiomers, and that the compounds are separable into α- and β-anomers.

L-2'-dideoxyribonucleosides

The present invention also provides a synthetic route to L-2'-dideoxyribonucleosides, which can be polymerized to enanti-DNA ("anti-sense" DNA). Synthesis of L-2'-dideoxyribonucleosides proceeds as follows: The epoxy...
and is polymerized into enantio-DNA using known techniques.

The following examples describe in detail syntheses illustrative of the present invention. It will be apparent to those skilled in the art that many modifications, both of material and methods, may be practiced without departure from the purpose and intent of this disclosure.

**EXAMPLE 1**

(E) and (Z) (1-3-butanedi-1-yl)oxytrimethylsilane

To a solution of crotonaldehyde (31.8 g, 0.454 mole) and triethylamine (51.4 g, 1 eq) in benzene at 25°C, was added hydroquinone (0.95 g) and zinc chloride (0.75 g) rapidly with efficient stirring. This was followed by the addition of freshly distilled trimethylsilyl chloride (46 ml, 0.9 eq) over 1–2 minutes, whereupon a white precipitate rapidly formed. After stirring the mixture for 30 minutes at 25°C, a further 0.2 eq of trimethylsilyl chloride were added. The reaction was then warmed to 70°C and stirred at this temperature for 12 hours. It was then cooled to 0°C, quenched by addition of saturatedaq. NaHCO₃ (75 ml), poured into a separatory funnel, and the organic layer separated. The aqueous layer was extracted with further portions of benzene (3×50 ml), the organic extracts combined, washed with 10% KHSO₄, and the benzene removed in vacuo to leave a dark brown liquid. Distillation through a small Vigreux column yielded 28.4 g (46%) of pure 1-trimethylsilyloxy-1,3-butadiene as a colorless liquid (bp 38°C/65 mm Hg). ¹H NMR (200 MHz, CDCl₃): δ 6.66 (1H,d,d,J=11.9 Hz), 6.35 (1H,d,t,J=17.1, 10.6Hz), 5.84 (1H, t, J=11.4 Hz), 5.11 (1H, dd, J=16.8, 1.8 Hz), 4.94 (1H, dd, J=10.3, 1.8 Hz), 0.37 (9H, s).

¹C NMR (50 MHz, CDCl₃): δ 8144.56, 133.22, 114.44, 111.96, –0.53.

**EXAMPLE 2**

(E)-5,5-Dimethoxypentyl-2-enal

To a mixture of 1-trimethylsilyloxy-1,3-butadiene (14.57 g, 0.1 mol) and trimethyl orthoformate (10.855 g, 0.1 mol) stirring in dichloromethane (500 ml) was added ZnCl₂ (1.75 g, 10% mol), and the mixture stirred vigorously at 25°C for 18 h. The reaction mixture was then poured into saturated NaHCO₃ (100 ml), and the organic layer collected. The aqueous layer was reextracted with dichloromethane (100 ml), the combined organic extracts dried over MgSO₄ and the solvents removed in vacuo. The resulting brown oil was taken up in hexane/ethyl acetate (1:1) and filtered through a pad of flash silica gel, washing through with a further 400 ml of the solvent mixture. The solvents were removed in vacuo and the crude product Kugelrohr distilled at 0.4 mm Hg/100°C to provide the pure enol (7.065 g, 49%).

¹H NMR (200 MHz, CDCl₃): δ 9.38 (1H,d,J=7.9 Hz), 6.63 (1H,d,t,J=15.7, 7 Hz), 5.96 (1H,dd,J=15.8, 1.4, 7.9Hz), 4.32 (1H,td,J=5.44 Hz), 3.18 (6H,s), 2.46 (2H,dd,J=7, 5.5, 1.4 Hz).

¹C NMR (50 MHz, CDCl₃): δ 193.4, 152.3, 134.7, 102.5, 53.0, 36.1.

IR (neat): 2990, 2960, 2930, 2900, 2830, 2740, 1718 cm⁻¹.

**EXAMPLE 3**

(E)-5,5-Dimethoxypentyl-2-en-1-ol

To a stirring solution of the enal (5.17 g, 0.036 mol) in diethyl ether (350 ml) cooled in an ice-acetone bath was added disobutylationum hydrate (39 ml, 1.0 M in hexanes, 1.08 eq) in portions over 5 minutes. The solution was allowed to warm to 25°C and was stirred for further 10 hours. The reaction was quenched by slow addition of saturated sodium chloride solution (75 ml), stirred further 2 hours, and the organic layer separated. The aqueous layer was reextracted with ethyl acetate (2×100 ml), and the combined organic phases dried over Na₂SO₄, filtered, and the solvents removed in vacuo to yield 4.6 g (87%) of the crude alcohol. Chromatography on silica gel (30:1 CH₂Cl₂/MeOH) yields 3.6 g (70%) of the pure allylic alcohol.

¹H NMR (200 MHz, CDCl₃): δ 5.44–5.69 (2H, m), 4.29 (1H,d,J=5.7 Hz), 3.78 (2H,d,J=3.9 Hz), 3.22 (6H,s), 2.27 (2H, t,J=5.7 Hz).

¹C NMR (50 MHz, CDCl₃): δ 132.3, 126.2, 103.8, 63.0, 52.8, 35.6.

IR (neat): 3400 (OH), 2925, 2895, 2820 cm⁻¹.

**EXAMPLE 4**

(2R,3R) 3-(2,2-Dimethoxyethyl)oxiranemethanol

To a solution of D(-)-disopropyl tartrate (0.78 g, 3.33 mmol) in dichloromethane (25 ml), cooled to -20°C, was added titanium tetraisopropoxide (0.9 ml, 2.8 mmol), and the mixture stirred at -20°C for 15 minutes. The allylic alcohol (0.4 g, 2.7 mmol) was then added as a solution in dichloromethane (10 ml) and stirred for a further 10 minutes stirring at -20°C to -25°C. t-butyl hydroperoxide (2 ml, 2.0 M, 2 eq) was added. The reaction mixture was stored in a refrigerator at -20°C for 2 days and then quenched by addition of 30% NaOH in saturated sodium chloride. The mixture was allowed to warm to 25°C and stirred a further 4 hours, when MgSO₄ (3 g) and Celite (1 g) were added, and the resultant well-stirred mixture was filtered through a pad of Celite. After removal of the solvents in vacuo, the residue was chromatographed on silica gel (30:1 CH₂Cl₂/MeOH), yielding the epoxy alcohol (R, R) (326 mg, 74%) as a colorless oil.

¹H NMR (200 MHz, CDCl₃): δ 4.50 (1H,dd,J=6.5, 4.9 Hz), 3.82 (1H,dd,J=12.5, 2.5 Hz), 3.57 (1H,dd,J=12.5, 4.4 Hz) 3.30 (3H,s), 3.27 (3H,s), 2.96 (1H,m), 2.96 (1H,m), 1.83–1.90 (1H, m), 1.69–1.79 (1H,m).

¹C NMR (50 MHz, CDCl₃): δ 102.2(d), 61.7(t), 58.3(d), 53.4(q), 52.9(q), 52.2(d), 35.2(t).

IR (neat): 3440, 2980, 2920, 2825 cm⁻¹.

**EXAMPLE 5**

(2S, 3S) 3-Azido-5,5-dimethoxypentene-1,2-diol

To a stirred mixture of the epoxy alcohol (R, R) (200 mg, 1.26 mmol) and azidotrimethylenesilane (340 mg, 2.3 eq) in dichloromethane (12 ml) cooled to 0°C, was added diethyaluminum fluoride (2 ml, 25% solution, 4 eq), and the mixture allowed to warm to 25°C and stir for a further 48 h. The reaction was quenched by addition of saturated NaHCO₃ (10 ml), the organic layer collected, and the aqueous layer washed with dichloromethane (2×10 ml). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and the solvents removed in vacuo. The crude diol was chromatographed on silica gel (eluting first with CH₂Cl₂ then with 2% MeOH/CH₂Cl₂) yielding 161.8 mg (64%) of the pure azido diol.

¹H NMR (200 MHz, CDCl₃): δ 4.56 (1H,dd,J=11.1, 4.5 Hz), 3.58–3.76 (3H, m), 3.44–3.55 (1H m) 3.37 (6H s) 1.95–2.05 (1H, m), 1.73–1.87 (1H, m).
EXAMPLE 6
Methyl α- and β-D-3-Azido-2,3-dideoxyribofuranoside

To a solution of 67 mg (0.33 mmol) of the azido diol in dichloromethane (60 ml) at 25 °C was added 10 drops of approximately 1.5% HCl in aqueous MeOH, and the mixture stirred for 5 min. TLC showed complete conversion to a mixture of the anomeric products. The reaction was quenched by addition of 1 ml saturated NaHCO3, and vigorously stirred for 2 min. Sodium sulfate was added, the solution filtered, and the solvents removed in vacuo. Chromatography on silica gel (eluting first with CH2Cl2, then with 1% MeOH/CH2Cl2) yielded 46.8 mg (81%) of the pure mixture of the two anomeric products. Samples of the pure α or β anomer were obtained by either further silica gel chromatography or preparative TLC (eluting with 24:1 CH2Cl2/MeOH).

β-anomer

1H NMR (200 MHz, CDCl3): δ 5.50 (1H, dd, J = 5.2, 1.4 Hz), 3.84-4.02 (3H, m), 3.69 (1H, m), 3.39 (3H's, OMe), 2.40 (1H, dd, J = 14.1, 8.7, 5.3 Hz), 2.03 (1H, dd, J = 14.2, 3.6, 1.4 Hz), 1.82 (1H, dd, J = 7.9, 4.6 Hz, OMe).

mixture of α- and β-anomers

13C NMR (50 MHz, CDCl3): δ 105.2 (β), 104.9 (α), 85.2 (β), 82.3 (α), 63.5 (β), 62.2 (α), 60.6 (β), 59.8 (α), 55.6 (β), 55.1 (α), 39.5 (β), 39.1 (α). lit. (Fleet)

EXAMPLE 9
(2S, 3S)-3-(2,2-Dimethoxyethyl)oxirane-2-methanol

To a solution of L-(+)
diisopropyl tartrate (0.962 g, 4.1 mmol) in dichloromethane (50 ml), cooled to −20°C, was added titanium tetraisopropoxide (1.2 g, 4.2 mmol), and the mixture stirred at −20°C for 15 min. The allylic alcohol (0.6 g, 4.1 mmol) was then added as a solution in dichloromethane (10 ml) and after a further 10 min stirring at −20°C, t-butyl hydroperoxide (2.8 ml, 3.0 M, 2 eq) was added. The reaction mixture was stored in a refrigerator at −20°C for 5 days and then quenched by addition of 30% NaOH in saturated sodium chloride. The mixture was allowed to warm to 25°C and stirred a further 4 h, when MgSO4 (3 g) and Celite (1 g) were added, and the resultant well-stirred mixture was filtered through a pad of Celite. After removal of the solvents in vacuo, the residue was chromatographed on silica gel (30:1; CH2Cl2/MeOH), yielding the epoxy alcohol (S, S) (491 mg, 75%) as a colorless oil.

1H NMR (200 MHz, CDCl3): δ 4.50 (1H, dd, J = 6.5, 4.9 Hz), 3.82 (1H, dd, J = 12.6, 2.5 Hz), 3.57 (1H, dd, J = 12.5, 4.4 Hz), 3.30 (3H's), 3.27 (3H's), 2.98 (1H, m), 2.96 (1H, m), 1.83-1.90 (1H, m), 1.69-1.79 (1H, m). 13C NMR (50 MHz, CDCl3): δ 102.2 (d), 61.7 (t), 58.3 (d), 53.4 (q), 52.9 (q), 52.5 (d), 35.2 (t).
IR (neat): 3440, 2980, 2920, 2825 cm−1.

EXAMPLE 10
(2R, 3R)-3-Azido-5,5-dimethoxypentane-1,2-diol

To a stirred mixture of the epoxy alcohol (S, S) (151 mg, 0.983 mmol) and azidomethylsilane (245 mg, 2.1 eq) in dichloromethane (10 ml) cooled to 0°C, was added diethylaluminum chloride (2 ml, 25% solution 4 eq), and the mixture allowed to warm to 25°C and stir a further 48 h. The reaction was quenched by addition of saturated NaHCO3 (10 ml), the organic layer collected, and the aqueous layer washed with dichloromethane (×10 ml). The combined organic extracts were washed with brine, dried over Na2SO4, filtered, and the solvents removed in vacuo. The crude diol was chromatographed on silica gel (eluting first with CH2Cl2, then with 2% MeOH/CH2Cl2) yielding 116 mg (61%) of the pure azido diol.

1H NMR (200 MHz, CDCl3): δ 8.56 (1H, dd, J = 11.1, 4.5Hz), 3.58-3.76 (3H, m), 3.44-3.5 (1H, m), 3.37 (6H, s), 1.95-2.05 (1H, m), 1.73-1.87 (1H, m). 13C NMR (50 MHz, CDCl3): δ 102.3 (d), 73.5 (d), 63.2 (d), 60.4 (d), 53.8 (q), 53.5 (q), 35.6 (t), IR (neat): 3440 (v br), 2920, 2825, 2100 (N3 sharp) cm−1.

EXAMPLE 11
Methyl α- and β-L-3-Azido-2,3-dideoxyribofuranoside

To a solution of 14 mg (0.07 mmol) of the azido diol in dichloromethane (8 ml) at 25°C was added 3 drops
of approximately 1.5% HCl in aqueous MeOH, and the mixture stirred for 5 min. TLC showed complete conversion to a mixture of the anomic products. The reaction was quenched by addition of 0.2 ml saturated aq. NaHCO₃ and vigorously stirred for 2 min. Sodium sulfate was added, the solution filtered, and the solvents removed in vacuo. Chromatography on silica gel (eluting first with CH₂Cl₂, then with 1% MeOH/CH₂Cl₂) yielded 10.1 mg (85%) of the pure mixture of the two anomic products. Samples of the pure α or β anomer were obtained by either further silica gel chromatography or preparative TLC (eluting with 24:1 CH₂Cl₂/MeOH).

β-anomer

¹H NMR (200 MHz, CDCl₃): δ 5.10 (1H, dd, J = 5.4, 1.7 Hz), 4.09-4.28 (2H, m), 3.78 (1H, dd, J = 12 Hz), 3.63 (1H, m, J = 8.9 Hz), 3.40 (1H, d, J = 7.9 Hz), 2.52 (1H, dd, J = 9.0, 3.7 Hz, OH), 2.35 (1H, d, dd, J = 13.9, 7.4, 1.8 Hz), 2.17 (1H, dd, J = 13.8, 6.4, 5.5 Hz).

α-anomer

¹H NMR (200 MHz, CDCl₃): δ 5.08 (1H, dd, J = 5.2, 1.4 Hz), 3.84-4.02 (3H, m), 3.69 (1H, m), 3.39 (3H, s, OMe), 2.40 (1H, d, dd, J = 14.1, 8.7, 5.3 Hz), 2.03 (1H, dd, J = 14.2, 3.6, 1.4 Hz), 1.82 (1H, d, dd, J = 7.9, 4.6 Hz, OH).

mixture of α- and β-anomers

¹³C NMR (50 MHz, CDCl₃): δ 105.2 (β), 104.9 (α), 85.2 (β), 82.3 (α), 63.5 (β), 62.2 (α), 60.6 (β), 59.8 (α), 55.6 (β), 55.1 (α), 39.5 (β), 39.1 (α), lit. (Fleet) ¹³C NMR (CDCl₃): δ 105.1, 104.8, 85.2, 82.5, 63.5, 62.4, 60.6, 60.0, 55.5, 55.2, 39.5, 39.2.

IR (neat): 3250-3500 (v br), 2925, 2100 (v strong, sharp, N₃), 1435, 1365, 1325, 1255, 1100, 1040 cm⁻¹.

EXAMPLE 12

3-Azido-5,5-dimethoxy-1-[(1,1-dimethyl)ethyl]dimethylsilyloxy]-2-pentanol

This compound was prepared from the azido-dideoxyribofuranoside of Example 11 by the normal method using t-butyl dimethylsilyl chloride, 4-(dimethylamino)pyridine, and triethylamine in dichloromethane. ¹H NMR (200 MHz, CDCl₃): δ 4.6 (1H, dd, J = 4.1, 7.6 Hz), 3.71 (2H, d, J = 3.5 Hz), 3.55 (2H, m), 3.368 (3H, s), 3.365 (3H, s), 2.62 (1H, d, J = 5.0 Hz), 2.07 (1H, d, dd, J = 2.8, 7.5, 14.47 Hz), 1.66-1.80 (1H, m), 0.90 (9H, s), 0.095 (6H, s). IR (neat): 3445, 2940, 2920, 2840, 2100 (N₃), 1455, 1250 cm⁻¹.

What is claimed is:

1. A process for making a 2',3'-dideoxyribonucleoside of the formula (I)

wherein X is H and B is a purine or pyrimidine base, comprising the steps of

(a) converting a diol having the formula (II)

wherein X is H and B are as defined above.

2. 2',3'-dideoxyribonucleoside of the formula (I) obtained by the process of claim 1.

3. A process for preparing a 2',3'-dideoxyribonucleoside of the formula (I) comprising the steps of

(a) reacting a parent 2',3'-dideoxyribonucleoside (III)

wherein X is H, and

(b) coupling a purine or pyrimidine base to the dideoxyribofuranoside having the formula (III) to obtain the 2',3'-dideoxyribonucleoside of formula (I) defined above.

4. A process as recited in claim 1, wherein the diol of formula II is converted to the dideoxyribofuranoside of formula III by treating the diol with dilute acid.

5. A process as recited in claim 1, wherein the step of coupling the purine or pyrimidine base to the dideoxyribofuranoside comprises substeps of (i) forming a hydroxy-protected dideoxyribofuranoside having the formula (IV)

wherein X is H and R is a hydroxy-protecting group, (ii) reacting the hydroxy-protected dideoxyribofuranoside of formula IV with a silylated purine or pyrimidine base in the presence of a trialkylsilyl triflate, and (iii) removing the hydroxy-protecting group to obtain the 2',3'-dideoxyribonucleoside of formula I defined above.

6. A process as recited in claim 1, further comprising the step of separating the 2',3'-dideoxyribonucleoside of formula I into α and β anomers having the formulas Ia and Ib, respectively.
5. A process as recited in claim 1, wherein X is H, and the diol of formula II is prepared by reacting an epoxy alcohol having the formula (V) with diisobutylaluminum hydride.

6. A process as recited in claim 1, wherein B is thymine.

7. A process as recited in claim 1, wherein B is cytosine.

8. A process for making a 2',3'-dideoxynucleoside of the formula (I) wherein B is a purine or pyrimidine base, comprising the steps of:

(a) reacting (1,3-butadien-1-yl)oxytrimethylsilane with trimethyl orthoformate to form 5,5-dimethoxypent-2-enal;

(b) reducing 5,5-dimethoxypent-2-enal with diisobutylaluminum hydride to form 5,5-dimethoxypent-2-en-1-ol;

(c) forming (2R,3R) 3-(2,2-dimethoxyethyl)oxiranemethanol by Sharpless epoxidation of 5,5-dimethoxypent-2-en-1-ol;

(d) reacting (2R,3R) 3-(2,2-dimethoxyethyl)oxiranemethanol with diisobutylaluminum hydride to form 5,5-dimethoxypentane-1,2-diol;

(e) treating 5,5-dimethoxypentane-1,2-diol with dilute acid to form a 2,3-dideoxyribofuranoside having the formula II; and

(f) coupling a purine or pyrimidine base to the dideoxyribofuranoside of formula II to obtain the 2',3'-dideoxynucleoside of formula I defined above.