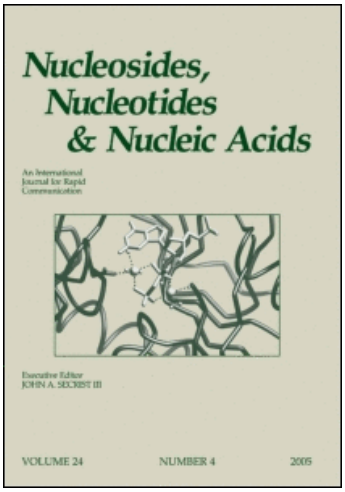


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# Synthesis of 4'-Trifluoromethyl Nucleoside Analogs

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# SYNTHESIS OF 4'-TRIFLUOROMETHYL NUCLEOSIDE ANALOGS

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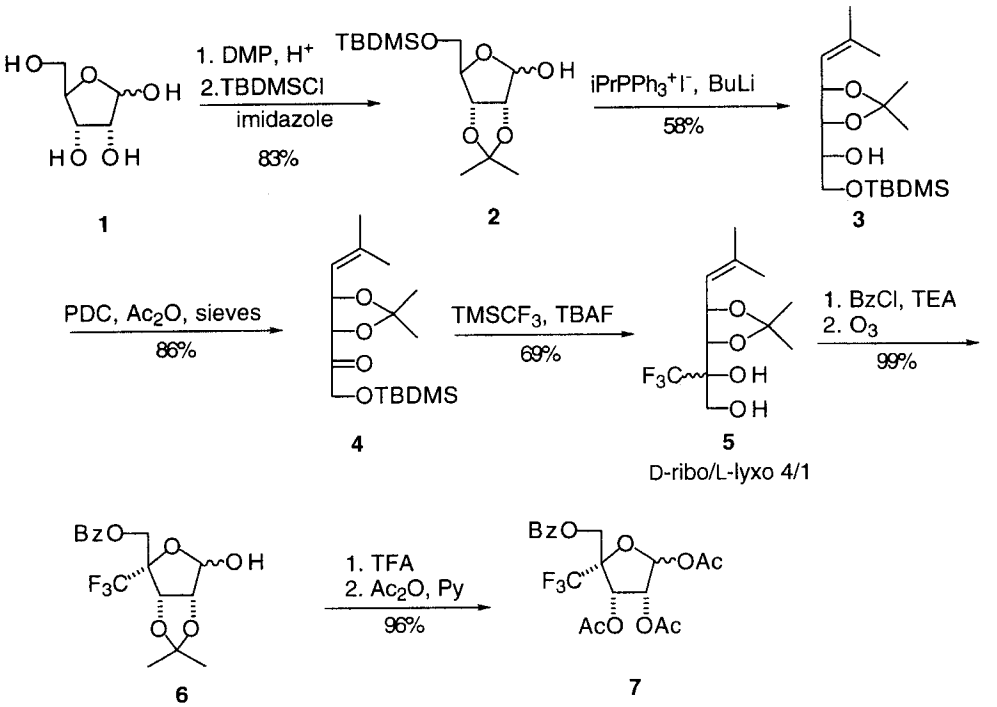
**ABSTRACT:** A strategy based on the use of (trifluoromethyl)trimethylsilane for introduction of the trifluoromethyl group at the C-4 of ribose has been developed and utilized in the synthesis of various novel 4'-trifluoromethylated nucleoside analogs. Screening of these analogs against HIV did not reveal significant biological activity.



The search for methods allowing substituent incorporation at C-4' in nucleosides began with the isolation of nucleocidin, a broad spectrum antibiotic, active against trypanosomes,[1] with fluorine at this position on the carbohydrate ring.[2] Although several methods have been developed which allow incorporation of fluorine,[3,4] various alkoxyl groups,[5,6,7,8] and hydroxymethyl,[9,10,11] carbon-carbon bond formation at C-4' remains challenging. We have developed a method for introduction of the trifluoromethyl group at the 4-position of ribose. In this paper we describe the synthesis of 4'-trifluoromethyl analogs of nucleosidic HIV reverse transcriptase (RT) inhibitors.

It is well established in various areas of medicinal chemistry that the introduction of fluoride into selected molecules has a profound effect on their biological activity.[12] Of specific interest to this work were reports that fluorinated nucleosides showed activity against human immunodeficiency virus (HIV)[13] and human cytomegalovirus (HCMV).[14] The latter is one of the leading opportunistic infections in acquired immunodeficiency syndrome (AIDS).[15]

Modifications of the sugar portion of 2'-deoxy nucleosides has resulted in some very potent RT inhibitors. Recent reports by Maag et al. described novel 4'-azido and 4'-methoxy nucleosides.[8] Some nucleoside analogs with a methyl substituent in that position also appeared to inhibit HIV replication in vitro.[16]




**Scheme 1**



It had been previously shown that the C-4' hydroxymethyl functionality as well as the β-D-configuration of the sugar moiety are essential for the preservation of biological activity.[17] A major challenge was the synthesis of the 4'-trifluoromethylated sugar portion with exclusive, natural D-*ribo* stereochemistry.

## Results and Discussion

*Synthesis of the sugar portion.* As a starting material we used D-ribose (**1**), which was converted into the known 5-*t*-butyldimethylsilyl-2,3-isopropylidene derivative (**2**)[18] (Scheme 1). To introduce the trifluoromethyl group into 4-position of the sugar, we adapted Townsend's protocol[19] for the synthesis of the 4-deuterated ribose and lyxose analogs.

Masking of the aldehyde moiety as an olefin[20] and subsequent pyridinium dichromate (PDC) oxidation[21] of the resulting secondary alcohol **3** offered ribulose derivative **4** in 61% overall yield. Treatment of the ketone **4** with Rupperts reagent ($CF_3SiMe_3$),[22] a source of the nucleophilic $CF_3^-$ group, in the presence of the catalytic

amount of tetrabutylammonium fluoride (TBAF), gave the diol **5** as an inseparable mixture of D-*ribo* and L-*lyxo* (ca 4:1, by NMR) isomers. Regioselective protection of the primary alcohol functionality, followed by ozonolytic cleavage of the olefinic bond, yielded the ribose derivative **6**. The latter upon acidolysis and peracetylation afforded the triacetate **7** in 88% yield. At this stage **6** and **7** were still contaminated with the *lyxo* isomers.

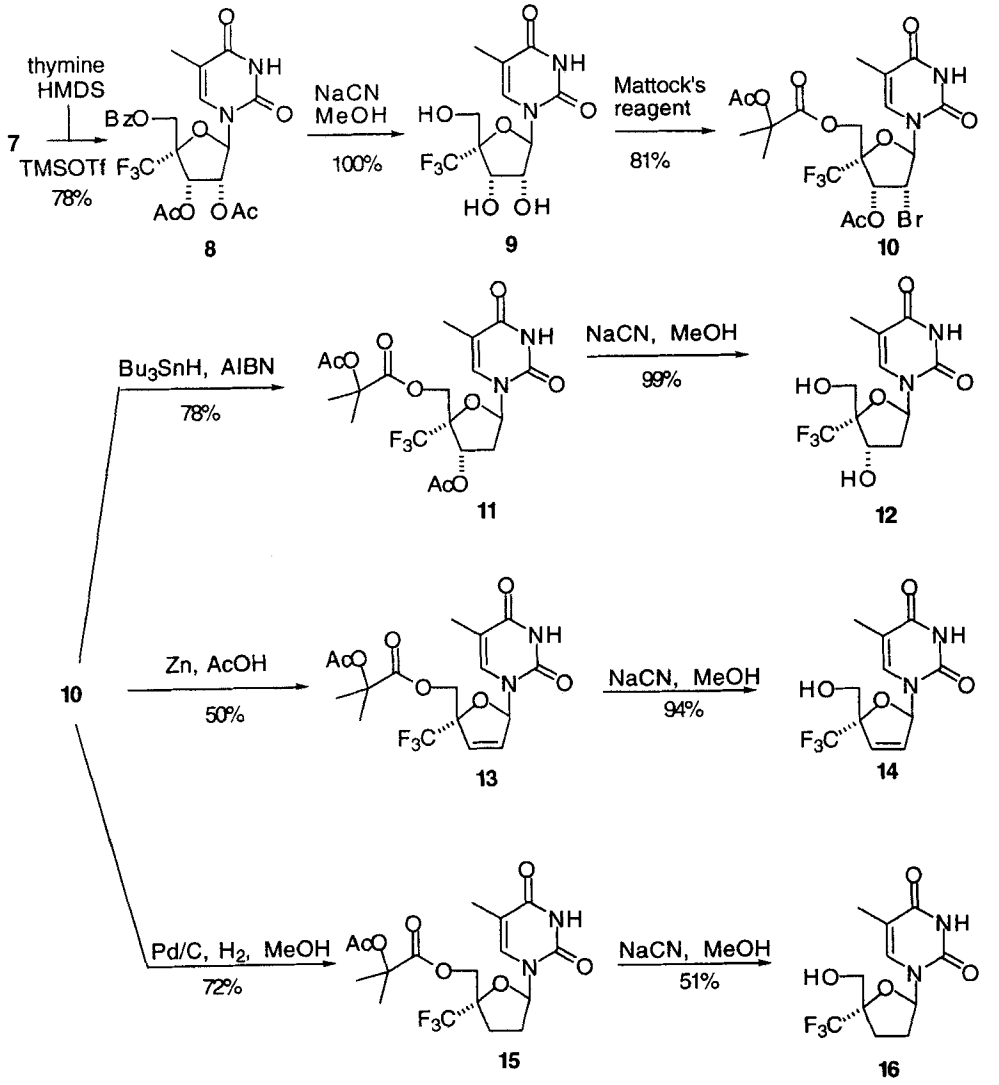
*Synthesis of the nucleosides.* The 4-trifluoromethyl-D-ribose derivative **7** was coupled with various bases according to the Vörbrugen protocol.[23] The condensation products were obtained, after separation of the 4'-epimers (*lyxo* isomers), with high chemical yields as β-nucleosides.

Our first targets were analogs of thymidine, dideoxythymidine (ddT) and dideoxydidehydrothymidine (d4T). 4'-$CF_3$-thymidine (**12**), 4'- $CF_3$-ddT (**16**), and 4'-$CF_3$-d4T (**14**) were obtained from the thymine coupling product **8** (Scheme 2). Removal of the ester type protecting groups of **8** with a catalytic amount of NaCN in methanol[24] and treatment of the resulting triol **9** with Mattock's reagent[25] (α-acetoxyisobutyryl bromide) led to the 2'-bromo-2'-deoxy derivative **10**.[26] The assignment of **9** was secured by x-ray crystal structure analysis.[27]

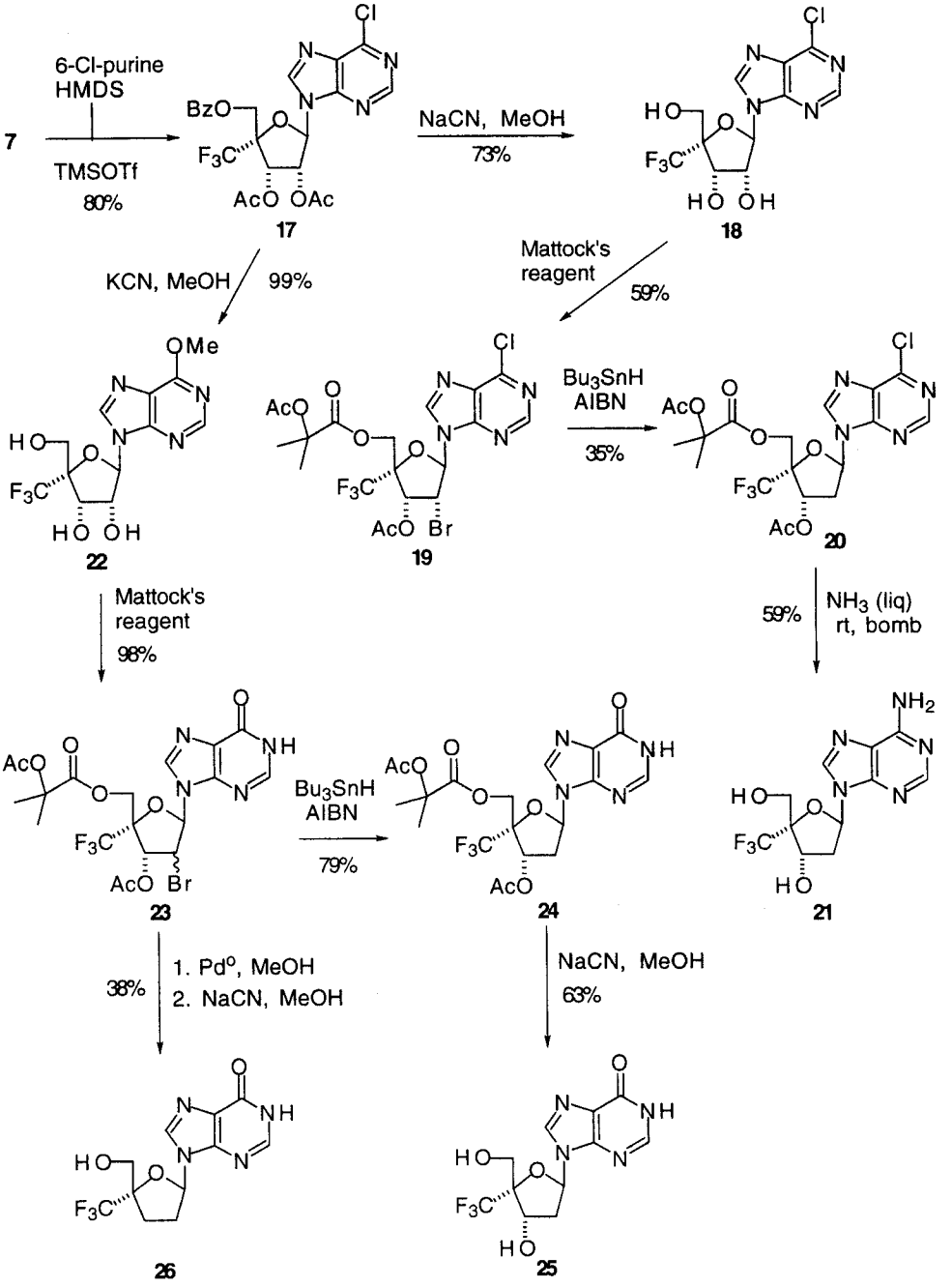
When **10** was treated with $Bu_3SnH$ under free radical conditions[28] the thymidine analog **11** was formed. Compound **11** was deprotected with NaCN in methanol[24] to give 4'-$CF_3$-thymidine (**12**) in 62% overall yield from the thymine coupling product **8**. Reductive elimination of **10** with Zn-Cu[29] couple led to the intermediate **13** which, after methanolysis,[24] gave 4'-$CF_3$-d4T (**14**) in 60% yield. Reduction of **10** with hydrogen and palladium catalyst[30] gave, after deprotection, the trifluoromethylated ddT analog **16** along with the 2'-deoxy derivative **12**.

6-Chloropurine coupling product **17**, obtained in 80% yield, served as a precursor for the synthesis of both adenosine and inosine analogs (**21**, **25** and **26**). Methanolysis of **17** in the presence of cataylic amount of NaCN[24] afforded triol **18**, which was then converted into bromide **19** by treatment with Mattock's reagent.[25] Free radical dehalogenation with tributyltin hydride in the presence of AIBN,[28] gave 2'-deoxy derivative **20** in moderate yield.

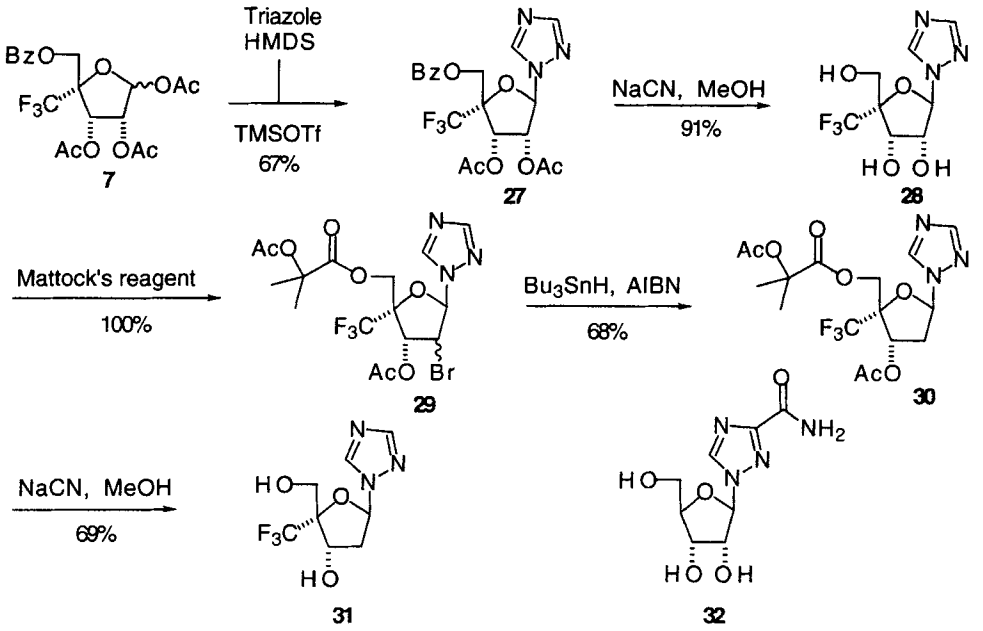
Nucleoside **20**, when subjected to ammonolysis at room temperature overnight in a bomb[31] yielded the 4'-substituted 2'-deoxyadenosine **21** in 60% yield. Treatment of **17** with an excess of KCN (10 fold)[32] in methanol yielded the 6-methoxy derivative **22**. Treatment of **22** with Mattock's reagent[25] according to the Moffatt's protocol[26] gave the 2'-bromo-2'-deoxyinosine derivative **23**. The latter when dehalogenated with $Bu_3SnH$[28] and deprotected gave 2'-deoxy inosine analog **25** in 50% overall yield. Intermediate **23**, when subjected to the hydrogenolysis over palladium catalyst[30] and subsequent methanolysis[24] provided the final ddI (dideoxyinosine) analog **26** in 38% yield. Triazole analog **31**, was




**Scheme 2**




**Scheme 3**




**Scheme 4**



chosen as a target for this work, based on the biological activity of ribavirin (**32**)[13] (Scheme 4).

Vörbrugen product **27** was solvolyzed with NaCN in methanol[25] to give triol **28** in good yield. Moffatt's protocol,[26] followed by free radical dehalogenation[28] of the bromide **29**, and methanolysis of the analog **30** gave 4'-trifluoromethylated ribavirin analog **31** in 40% yield from triol **28**.

## Conclusions

A method for introduction of the trifluoromethyl group into the D-ribose derivatives[33] have been developed and utilized to synthesize various novel 4'-trifluoromethylated nucleoside analogs. The National Cancer Institute screened analogs **9**, **12**, **14**, **16**, **21**, **22**, **25**, and **31** against HIV; all were confirmed inactive. Racemic 4'- fluoromethyl-3'-deoxythymidine analog recently has been reported[34] and shown to be biologically inactive.

## Experimental Section

**5-*O*-*tert*-Butyldimethylsilyl-2,3-isopropylidene-D-*ribo*-furanose (2).** D-Ribose (**1**) (2.0 g, 133.3 mmol) was dissolved in DMF (25 mL) containing 2,2-dimethoxypropane (DMP) (5 mL). Dowex - 50X ($H^+$-type) resin (2. 0 g) was then added

and the reaction mixture was vigorously stirred overnight. The resin was filtered off and the filtrate was evaporated *in vacuo*. The oily residue was purified by column chromatography on silica gel ($CHCl_3$-methanol, 8:2), then dissolved in dichloromethane (100 mL) containing triethylamine (2.04 mL, 146.6 mmol), and 4-(dimethylamino)pyridine (DMAP) (65 mg, 5.332 mmol). *tert*-Butyldimethylsilyl chloride (TBDMSCl) (2.01g, 133.3 mmol) in dichloromethane (50 mL) was added dropwise over the period of 4 h. The mixture was stirred at ambient temperature overnight. After that time the mixture was concentrated under reduced pressure. The residue was partially dissolved in diethyl ether, and washed successively with sat. $NaHCO_3$ (3 x 50 mL), $NH_4Cl$ (50 mL) and brine (50 mL). The etheral solution was dried over $MgSO_4$, filtered and evaporated to give desired product **2** (3.4 g, 83%) as an oil, which crystallized, after standing: mp 48-50 °C (lit.[18] 52-54 °C); $[\alpha]_D$: -17.0 (c 1.0, $CHCl_3$) (lit.[18] $[\alpha]_D$: -17.0 ); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.28 (d, J = 11.65 Hz, 1 H), 4.76 (d, J = 11.65 Hz, 1 H), 4.70 (d, J = 6.07 Hz, 1 H), 4.50 (d, J = 6.08 Hz, 1 H), 4.36 (dd, J = 2.03, 2.03 Hz, 1 H), 3.77 (dd, J = 11.14, 2.03 Hz, 1 H), 3.74 (dd, J = 11.15, 2.02 Hz, 1 H), 1.49 (s, 3H), 1.32 (s, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 112.03, 103.47, 99.29, 87.64, 86.98, 81.73, 64.80, 26.45, 25.82, 24.92, 18.22, -5.67, -5.70.

**(2*R*,3*S*,4*S*)-1-*tert*-Butyldimethylsilyloxy-3,4-isopropylidenedioxy-6-methyl-5-hepten-2-ol (3).** Isopropyltriphenylphosphonium iodide[20] (9.59 g, 22.2 mmol) was suspended in dry THF (50 mL) and cooled down to 0 °C. BuLi solution (2.5M in THF, 8.8 mL, 22.2 mmol) was added dropwise over 0.5 h. The deep red solution was maintained at 0 °C for additional 0.5 h and the ribose **2** in THF (10 mL) was introduced slowly over 2 h. The reaction mixture was allowed to warm to ambient temperature, stirred overnight and quenched with sat. $NaHCO_3$ (20 mL). The precipitated solids were removed by filtration. The filtrate was diluted with diethyl ether (300 mL) and washed with aqueous sat. $NaHCO_3$ (3 x 60 mL), $NH_4Cl$ (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by chromatography on silica gel (hexanes - ethyl acetate, 9:1 and then 8:2) to give starting material (942 mg, 24%) and 2.21 g (58%) of **3** as colorless oil: $[\alpha]_D$ +7.8 (c 2.2, $CHCl_3$) (lit.[19] $[\alpha]_D$ +5.0 (c 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.37 (dqq, J = 9.46, 1.22, 1.22 Hz, 1H), 4.95 (dd, J = 9.76, 6.10 Hz, 1H), 4.00 (dd, J = 8.55, 6.11 Hz, 1H), 3.82 (dd, J = 12.51, 5.46 Hz, 1H), 3.68 (m, 2H), 2.54 (d, J = 4.28 Hz, 1H), 1.79 (d, J = 1.20 Hz, 3H), 1.74 (d, J = 1.20 Hz, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 138.34, 120.15, 108.12, 74.53, 69.82, 64.47, 28.10, 26.19, 25.89, 25.54, 18.36, 18.17, -5.34, -5.41.

**(3*S*,4*S*)-1-*tert*-Butyldimethylsilyloxy-3,4-isopropylidenedioxy-6-methyl-5-heptene-2-one (4).** Alcohol **3** (1.331g, 4.033 mmol) was dissolved in dry dichloromethane (50 mL), containing acetic anhydride (0.57 mL, 6.05 mmol). PDC (2.27

g, 6.05 mmol) and crushed molecular sieves (3.0 g) were added and the mixture was vigorously stirred until all substrate was consumed (ca. 5 h). The solids were filtered off and the filtrate was concentrated. The residue was purified by column chromatography (hexanes - ethyl acetate, 8:2), to give the product **4** (1.135 g, 86%) as a colorless oil: $[\alpha]_D$ +4.2 (c 0.8, $CHCl_3$) (lit.[19] $[\alpha]_D$ +4.0 (c 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.15 (dd, J = 8.87, 8.10 Hz, 1H), 5.00 (dd, J = 9.37, 1.26 Hz, 1H), 4.78 (d, J = 7.59 Hz, 1H), 4.46 (d, J = 18.99 Hz, 1H), 4.23 (d, J = 18.74 Hz, 1H), 1.70 (s, 6H), 1.58 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 206.46, 139.99, 119.14, 109.71, 81.36, 74.54, 68.52, 27.11, 25.97, 25.79, 24.89, 18.41, -5.43, -5.50.

**(2*R*,3*S*,4*S*)-3,4-Isopropylidenedioxy-6-methyl-2-trifluoromethyl-5-hepten-1,2-diol (5).** Ketone **4** (2.705 g, 8.25 mmol) and trifluoromethyltrimethylsilane (1.405 g, 9.90 mmol) were placed in dry THF (80 mL). The mixture was cooled to 0 °C and the tetrabutylammonium fluoride (TBAF) solution (1M in THF, 9.896 mL) was slowly added (ca. 0.5 h). The reaction mixture was stirred at 0 °C for 0.5 h and then at rt for additional 2 h. The solvent was then evaporated. The residue was taken up in the dichloromethane (100 mL) and washed with $NaHCO_3$ (3 x 20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The dark oil was purified by flash chromatography (hexanes - ethyl acetate, 8:2) to give yellow oily product **5** (1.608 g, 69%) as a mixture of diastereoisomers at C-2 (D-*ribo* /L-*lyxo* = 4:1 by NMR): $[\alpha]_D$ -65.9 (c 0.7, $CHCl_3$); MS (+VE CI) *m/z* 285 (M+H, 1), 267 (M-$H_2O$+H, 18), 227 (M-$OC(CH_3)_2$+H, 100); HRMS (EI) calcd for $C_{11}H_{16}F_3O_4$ (M-$CH_3$): 269.1001, Found: 269.1001.

**5-*O*-Benzoyl-2,3-isopropylidene-4-*C*-trifluoromethyl-D-*ribo*-furanose (6).** The diol **5** (943 mg, 3.32 mmol) was dissolved in dry dichloromethane (33 mL). Triethylamine (485 μL, 3.49 mmol), followed by benzoyl chloride (404 μL, 3.49 mmol) and DMAP (1 crystal) were added; the mixture was stirred under ambient conditions overnight. Aqueous sodium bicarbonate (20 mL) was added and vigorous stirring was continued over additional 0.5 h. The phases were separated. The organic phase was dried over $MgSO_4$ and concentrated. The residue was redissolved in dichloromethane (33 mL) and ozonized at -78 °C over 10 min (until the mixture became blue). The reaction mixture was flushed with a stream of oxygen and the ozonide was quenched with an excess of dimethylsulfide. The mixture was allowed to warm to room temperature and stirred overnight. Solvents were evaporated under reduced pressure and the oily residue was co-evaporated with toluene (5 mL) to give desired furanose **6** (1.18 g, 99%), as a mixture of diastereoisomers: MS (+VE CI) *m/z* 363 (M+H, 2), 347 (M-$CH_3$, 7), 305 (M-$OC(CH_3)_2$+H, 18), 241 (4), 182 (4), 105 (100); HRMS (EI) calcd for $C_{15}H_{14}F_3O_6$ (M-$CH_3$): 347.0742, Found: 347.0743.

**1,2,3-Tri-*O*-acetyl-5-*O*-benzoyl-4-*C*-trifluoromethyl-D-*ribo*-furanose (7).** The furanose **6** (1.133 g, 3.13 mmol) was dissolved in 90% trifluoroacetic acid (6 mL) and stirred overnight. The solvent was evaporated and the oily residue was evaporated with toluene (3 x 5 mL). The pale solid was suspended in dichloromethane (31 mL). Triethylamine (2.61 mL, 18.78 mmol) followed by acetic anhydride (1.177 mL, 12.52 mmol) and DMAP (few crystals) was added. The mixture was stirred at ambient temperature overnight, diluted with ethyl acetate (100 mL), washed with $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Product **7** (1.34 g, 96%) was isolated by column chromatography on silica gel (hexanes-ethyl acetate, 7:3), as a pale yellow oil. $^1H$ and $^{13}C$ NMR spectra revealed signals doubled due to presence of C-4 diastereoisomers (D-*ribo* and L-*lyxo* ca. 4:1).
MS (+FAB, thioglycerol) *m/z* 471 (M+Na, 12), 389 (M-AcOH+H, 17), 136 (12), 105 (100).

**2',3'-Di-*O*-acetyl-5'-*O*-benzoyl-4'-*C*-trifluoromethyl-5-methyluridine (8).** Thymine (630 mg, 1 mmol) was placed in hexamethyldisilazane (HMDS) (6 mL) containing a catalytic amount of TMSCl (100 µL). The mixture was then refluxed until all solids dissolved (ca. 2 h). The solvent was then carefully evaporated *in vacuo* and the residue co-evaporated several times with absolute toluene to dryness. The colorless, viscous oil of bis-silylated thymine was then dissolved in dry acetonitrile (10 mL), the acetate **7** (448 mg, 1 mmol) was added followed by TMS triflate (965 µL, 5 mmol). The mixture was stirred under reflux overnight. The mixture was poured into sat. $NaHCO_3$ (50 mL) and extracted with dichloromethane (3 x 30 mL). The collected extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was chromatographed on a silica gel column (hexanes-ethyl acetate, 5:5) to give product **8** (399 mg, 78%) as a mixture of two diastereoisomers (see above).

**4'-*C*-Trifluoromethyl-5-methyluridine (9).** The protected nucleoside **8** (215 mg, 0.419 mmol) was dissolved in methanol (4 mL). NaCN (few crystals) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the oily residue was purified by column chromatography (chloroform - methanol, 8:2), to give free uridine **9** (137 mg, 100%) as a mixture of D-*ribo* and L-*lyxo* isomers ca. 4:1.
The analytical sample of pure β-D-*ribo* isomer **9** was isolated by fractional crystallization from ethyl acetate: mp 207-210 °C (needles): $[\alpha]_D$ -32.14 (c 0.8, methanol); $^1H$ NMR (500 MHz, $CD_3OD$) δ 7.67 (q, J = 1.52 Hz, 1H), 6.13 (d, J = 8.10 Hz, 1H), 4.44 (d, J = 6.08 Hz, 1H), 4.38 (dd, J = 5.57, 7.60, 1H), 3.81 (d, J = 11.65 Hz, 1H), 3.76 (d, J = 11.64 Hz, 1H), 1.89 (d, J = 1.53 Hz, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ: 164.73, 151.42, 136.30, 125.60 (q, J = 283.5 Hz, $CF_3$), 111.07, 88.08, 87.1 (q, J = 25.75 Hz, C-4'), 72.62, 70.88, 61.42, 11.01; MS (+FAB, thioglycerol) *m/z* 349 (M+Na, 49), 327 (M+H,

30), 176 (30), 136 (88), 127 (base+H, 100). The structure and absolute configuration of **9** was confirmed by single crystal x-ray analysis.[27]

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-3'-*O*-acetyl-2'-bromo-2'-deoxy-4'-*C*-trifluoromethyl-5-methyluridine (10):** Uridine **9** (163 mg, 0.5 mmol) was dissolved in 1 mL of α-acetoxyisobutyryl bromide (Mattocks' reagent)[25] and stirred at 100 °C for 2 h. After all substrate was consumed, the mixture was diluted with ethyl acetate (5 mL) and neutralized with aqueous $NaHCO_3$ (5 mL). The organic phase was washed again with bicarbonate (5 mL) and brine (5 mL), dried over MgSO4, filtered and evaporated. The crude material was purified by column chromatography (hexanes - ethyl acetate, 1:1) to give **10** as a colorless oil (227 mg, 81%): $^1$H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.12 (q, J = 1.22 Hz, 1H), 6.32 (d, J = 9.47 Hz, 1H), 5.79 (d, J = 5.80 Hz, 1H), 4.62 (dd, J = 5.80, 9.47 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 12.51, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 1.93 (d, J = 1.1 Hz, 3H), 1.56 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.68, 170.59, 168.28, 163.38, 150.29, 134.51, 126.8 (q, J = 280.0 Hz, CF3), 112.77, 89.77, 83.75 (q, J = 23.5 Hz, C-4'), 77.82, 69.77, 63.45, 44.81, 24.64, 24.12, 20.84, 20.34, 12.24.

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-3'-*O*-acetyl-4'-*C*-(trifluoromethyl)thymidine (11):** Bromouridine **10** (191.7 mg, 0.343 mmol) was dissolved in toluene (10 mL), along with catalytic amount of 2,2'-azobisisobutyronitrile (AIBN). Tributyltin hydride (199.6 mg, 0.686 mmol) was added and the mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated and the product **11** (129 mg, 78%) was isolated by column chromatography (hexanes - ethyl acetate, 7:3) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.18 (q, J = 1.2 Hz, 1H), 6.38 (t, J = 6.6 Hz, 1H), 5.68 (d, J = 6.3 Hz, 1H), 4.49 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 2.50 (dd, J = 6.9, 6.3, 2H), 2.11 (s, 3H), 2.05 (s, 3H), 1.94 (d, J = 1.2 Hz, 3H), 1.56 (s, 3H), 1.55 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.73, 170.20, 169.26, 163.47, 150.01, 134.95, 122.90 (q, J = 284.6 Hz, $CF_3$), 112.05, 86.18, 84.61 (q, J = 28.7 Hz, C-4'), 77.80, 71.49, 63.12, 37.19, 24.60, 24.18, 20.82, 20.57, 12.25.

**4'-*C*-(Trifluoromethyl)thymidine (12):** Acylated thymidine **11** (129 mg, 0.268 mmol) was dissolved in methanol (2.5 mL) and solvolyzed in the presence of catalytic amount of NaCN (1 crystal) overnight. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (chloroform - methanol, 8:2) to give **12** (82 mg, 99%) as white crystals: mp 105-107 °C; $[\alpha]_D$ +9.37 (c 0.64, methanol); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.71 (d, J = 1.01 Hz, 1H), 6.42 (t, J = 6.84, 1H), 4.87 (m, 1H), 3.85 (d, J = 11.64 Hz, 1H), 3.83 (d, J = 11.90, 1H), 2.44 (m, 2H), 1.87 (d, J = 1.00 Hz, 1H); $^{13}$C NMR (75 MHz,

$CD_3OD$) δ 168.50, 152.31, 138.12, 125.62 (q, J = 284.6, CF3), 112.02, 88.00 (q, C-4'), 86.52, 71.80, 61.20, 40.45, 12.45; MS (+FAB, thioglycerol) *m/z* 333 (M+Na, 13), 311 (M+H, 34), 225 (14), 127 (base+H, 100).

A small ammount of the L-lyxo (4'-epimer of 11) nucleoside was also isolated: mp 120-122 °C; $[\alpha]_D$ -14.9 (c 0.84, methanol); $^1H$ NMR (300 MHz, $CD_3OD$) δ 7.31 (d, J = 1.22 Hz, 1H), 6.48 (t, J = 6.72 Hz, 1H), 4.81 (dd, J = 5.49, 7.32 Hz, 1H), 4.02 (d, J = 12.54 Hz, 1H), 3.83 (d, J = 12.21 Hz, 1H), 2.48 (m, 2H), 1.88 (d, J = 1.00 Hz, 3H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 164.70, 150.87, 135.64, 123.2, 110.86, 85.07, 70.97, 59.80, 39.20, 11.11.

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-2',3'-didehydro-3'-deoxy-4'-*C*-(trifluoromethyl)thymidine (13).** Bromide **10** (100 mg, 0.179 mmol) was dissolved in methanol (7 mL) and freshly activated[30] Zn-Cu couple (300 mg, Aldrich) was added. The mixture was vigorously stirred until no starting material was detected on TLC (ca. 1 h). The solids were filtered on Celite and the filtrate concentrated. The residue oil was purified by flash column chromatography (hexanes - ethyl acetate, 1:1) to give **13** (378 mg, 50%) as colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.02 (bs, 1H), 7.17 (d, J = 2.45 Hz, 1H), 7.16 (q, J = 1.22 Hz, 1H), 6.28 (dd, J = 6.11, 2.44 Hz, 1H), 6.15 (d, J = 6.11 Hz, 1H), 4.70 (d, J = 12.21 Hz, 1H), 4.29 (d, J = 12.82 Hz, 1H), 2.03 (s, 3H), 1.95 (d, J = 1.22 Hz, 3H), 1.57 (s, 3H), 1.55 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.91, 134.65, 131.87, 129.97, 112.27, 90.47, 78.02, 62.93, 24.71, 24.21, 21.02, 12.34.

**2',3'-Didehydro-3'-deoxy-4'-*C*-(trifluoromethyl)thymidine (14).** Ester **13** (38 mg, 0.09 mmol) was placed in methanol (1 mL) containing 1 crystal of NaCN. The mixture was stirred overnight, concentrated under reduced pressure and purified by column chromatography (chloroform - methanol, 8:2) to give **14** (25 mg, 94%) as a colorless oil: $[\alpha]_D$: +49.7 (c 0.4, methanol); $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.40 (bs, 1H), 7.48 (d, J = 1.03 Hz, 1H), 7.12 (dd, J = 1.71, 1.37 Hz, 1H), 6.28 (dd, J = 2.00, 6.05 Hz, 1H), 6.17 (dd, J = 0.78, 6.13 Hz, 1H), 4.03 (s, 2H), 1.85 (d, J = 0.90 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 163.90, 150.54, 138.48, 136.72, 131.64, 130.51, 91.08, 60.96, 12.27; MS (EI) *m/z* 292 (M, 2), 218 (7), 167 (M-base, 5), 126 (base, 100); HRMS (EI) calcd for $C_{11}H_{11}F_3N_2O_4$: 292.0671, Found: 292.0665.

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-2',3'-dideoxy-4'-*C*-(trifluoromethyl)thymidine (15).** Bromide **10** (313 mg, 0.56 mmol) was dissolved in methanol (20 mL) containing triethylamine (156 μL, 1.12 mmol). The mixture was hydrogenated in the presence of palladium catalyst (10% on charcoal, 110 mg) until no starting material was detected on TLC (ca. 2 h). The catalyst was filtered off and the filtrate evaporated to give the crude product (171 mg, 72%) contaminated with the 2'-deoxy analog **11**. An

analytical sample of the main product **15** was isolated by column flash chromatography (hexanes - ethyl acetate, 1:1) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.75 (bs, 1H), 7.27 (q, J = 1.2 Hz, 1H), 6.28 (dd, J = 6.02, 7.82 Hz, 1H), 4.54 (d, J = 12.14 Hz, 1H), 4.32 (d, J = 12.17 Hz, 1H), 2.53 (m, 1H), 2.30 (m, 3H), 2.05 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H), 1.59 (s, 6H); MS (EI) *m/z* 422 (M, 9), 297 (36), 278 (27), 237 (56), 127 (base, 49), 69 ($CF_3$, 100); HRMS (EI): calcd for $C_{17}H_{21}F_3N_2O_7$: 422.1301, Found: 422.1305.

**3'-Deoxy-4'-*C*-(trifluoromethyl)thymidine (16)**: Crude compound **15** (171 mg, 0.41 mmol) was dissolved in methanol (4 mL) and NaCN (1 crystal) was added. The mixture was stirred at room temperature for 10 h. The solvent was then removed under reduced pressure and the oily residue was chromatographed on a silica gel column. Two products were isolated. The 2'-deoxy analog (**12**) (57 mg, 46%) was obtained along with the desired dideoxy compound **16** (oil) (61 mg, 51%): $[\alpha]_D$ -6.5 (c 0.2, methanol); +5.8 (c 0.2, $CDCl_3$) (lit.[34] $[\alpha]_D$ +2.8 (c 0.4, $CDCl_3$)); $^1$H NMR (300 MHz, $CDCl_3$) δ 9.20 (bs, 1H), 7.35 (q, J = 1.20 Hz, 1H), 6.05 (t, J = 6.72 Hz, 1H), 4.00 (d, J = 11.59 Hz, 1H), 3.76 (d, J = 11.59 Hz, 1H), 2.48 (m, 2H), 2.25 (m, 2H), 1.85 (d, J = 1.20, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.85, 150.39, 137.43, 124.97 (q, J = 284.80 Hz, $CF_3$); 111.45, 90.04, 86.29 (q, J = 27.80 Hz, C-4'); 61.75, 30.41, 26.12, 12.35; MS (+FAB, thioglycerol) *m/z* 295 (M+H, 65), 250 (15), 169 (M-base, 100).

**9-(2,3-Di-*O*-acetyl-5-*O*-benzoyl-4-*C*-trifluoromethyl-β-D-*ribo*-furanosyl)-6-chloropurine (17).** 6-Chloropurine (1.06 g, 6.86 mmol) was silylated with HMDS (10 mL) under reflux for 2 h. After removal of solvent, the oily residue was dissolved in dry acetonitrile (22 mL), triacetate **7** (1.02 g, 2.29 mmol) was added, followed by TMS triflate (1.33 mL, 6.86 mmol). The reaction mixture was refluxed overnight. After cooling to the room temperature, the mixture was poured into sat. $NaHCO_3$ (100 mL) and extracted with chloroform (3 x 20 mL). The combined chloroform extracts were washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over MgSO4, filtered and evaporated. Final purification by column chromatography afforded title compound **17** (581 mg, 47%) as a colorless oil along with the L-lyxo isomer (130 mg, 11%) and a mixture of N-7 coupled product (195 mg, 16%).

D-ribo **17**: $[\alpha]_D$: -28.1 (c 1.45, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.20 (s, 1H), 8.05 (d, J = 7.60 Hz, 2H), 7.58 (t, J = 7.60 Hz, 1H), 7.43 (t, J = 7.60 Hz, 2H), 6.45 (dd, J = 6.58, 6.58 Hz, 1H), 6.32 (d, J = 6.59 Hz, 1H), 6.29 (d, J = 6.59, 1H), 4.90 (d, J = 12.16 Hz, 1H), 4.54 (d, J = 12.15 Hz, 1H), 2.17 (s, 3H), 1.99 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 168.94, 168.51, 165.28, 152.19, 144.31, 133.71, 132.29, 129.76, 128.58, 123.05 (q, J = 286.12 Hz, $CF_3$), 87.31, 84.72 (q, J = 27.75, C-4'), 70.78, 69.04, 62.36, 20.19, 20.01; MS (+VE CI) *m/z* 543 (M+H, 100),

483 (M-AcOH+H, 2), 389 (85), 155 (base+H, 11); HRMS (EI) calcd for $C_{20}H_{15}ClF_3N_4O_5$ (M-$CH_3CO_2$): 483.06831, Found: 483.0694.

L-lyxo isomer (4'-epimer of **17**): $[\alpha]_D$: -5.6 (c 1.13, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.25 (s, 1H), 8.02 (d, J = 7.63 Hz, 2H), 7.58 (t, J = 7.32 Hz, 1H), 7.44 (t, J = 7.33 Hz, 2H), 6.43 (d, J = 4.88, 1H), 6.31 (d, J = 6.11 Hz, 1H), 6.12 (dd, J = 5.49, 6.11 Hz, 1H), 5.07 (d, J = 12.82 Hz, 1H), 4.60 (d, J = 12.20 Hz, 1H), 2.11 (s, 3H), 2.01 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.95, 168.25, 165.59, 152.47, 151.72, 151.29, 143.37, 133.66, 132.04, 129.75, 128.60, 123.43 (q, J = 283.50 Hz, $CF_3$), 87.13, 84.11 (q, J = 29.77, C-4'), 72.47, 69.52, 60.01, 20.06, 20.01. The N-7 coupled product was isomerized to the desired *N*-9 regioisomer **17** by refluxing overnight with 1 equiv. of TMS triflate in acetonitrile.

**9-(4-*C*-Trifluoromethyl-β-D-*ribo*-furanosyl)-6-chloropurine (18):** The nucleoside **17** (571.4 mg, 1.053 mmol) was dissolved in methanol (10 mL). A catalytic amount of NaCN (1 crystal) was added and the mixture was stirred at ambient temperature overnight. The solvent was evaporated and the product was isolated by column flash chromatography (chloroform - methanol, 9:1) to give 272.5 mg (73%) of the product **18** as a yellowish oil: $[\alpha]_D$ -40.5 (c 1.8, methanol); $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.78 (s, 1H), 8.75 (s, 1H), 6.26 (d, J = 7.93 Hz, 1H), 5.00 (dd, J = 6.10, 7.94 Hz, 1H), 4.62 (d, J = 5.50 Hz, 1H), 3.87 (s, 2H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 151.80, 151.60, 150.55 , 145.59, 131.74, 124.09 (q, J = 285.92 Hz, $CF_3$), 89.12, 88.14 (q, J = 25.99 Hz, C-4'), 73.42, 71.23, 61.66; MS (+VE CI) *m/z* 355 (M+H, 73), 197 (22), 183 (39), 155 (base+H, 100); HRMS (EI) caldcd for $C_{11}H_{11}ClF_3N_4O_4$ (M+H): 355.0421, Found: 355.0426.

**9-[5-*O*-(2-Acetoxy-2-methylpropanoyl)-3-*O*-acetyl-2-bromo-2-deoxy-4-*C*-trifluoromethyl-β-D-*ribo*-furanosyl]-6-chloropurine (19)**: Triol **18** (272.5 mg, 0.7698 mmol) was heated in Mattock's reagent (3 mL) at 100 °C for 2 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (30 mL), and treated with sat. aqueous $NaHCO_3$ (10 mL) followed by solid bicarbonate until no more gases are evolved. The organic phase was then separated and washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. Final purification by column chromatography gave **19** (267 mg, 59%) as a yellowish oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.40 (s, 1H), 6.68 (d, J = 6.72 Hz, 1H), 6.30 (d, J = 7.33 Hz, 1H), 5.00 (dd, J = 7.33, 7.33 Hz, 1H), 4.82 (d, J = 12.21 Hz, 1H), 4.50 (d, J = 12.82 Hz, 1H), 2.17 (s, 3H), 2.01 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.36, 170.07, 168.76, 152.33, 150.79, 149.53, 143.33, 134.48, 123.30 (q, J = 286.802 Hz, $CF_3$), 84.83, 83.30 (q, J = 28.65 Hz, C-4'), 77.71, 76.62, 62.47, 48.49, 24.15, 24.30, 20.91, 20.25.

**9-[5-*O*-(2-Acetoxy-2-methylpropanoyl)-3-*O*-acetyl-2-deoxy-4-*C*-trifluoromethyl-β-D-*ribo*-furanosyl]-6-chloropurine (20)**: Bromide **19** (267 mg, 0.45 mmol) was dissolved in toluene (7 mL) containing tributyltin hydride (401.0 mg, 0.91 mmol) and catalytic amount of AIBN. The mixture was stirred at 100 °C for 2 h (no more starting material was detected on TLC). The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes - ethyl acetate, 3:7) to give 80.7 mg (35%) of **20** as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.31 (s, 1H), 6.55 (dd, J = 6.08, 7.09 Hz, 1H), 6.08 (dd, J = 5.57, 7.59 Hz, 1H), 4.52 (d, J = 12.16 Hz, 1H), 4.46 (d, J = 12.15 Hz, 1H), 3.32 (ddd, J = 6.08, 7.60, 13.68 Hz, 1H), 2.78 (ddd, J = 6.59, 6.59, 13.17 Hz, 1H), 2.16 (s, 3H), 2.01 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.66, 170.20, 169.26, 152.36, 151.71, 150.83, 143.94, 132.46, 124.21 (q, J = 287.0 Hz, $CF_3$), 85.26, 84.41 (q, J = 28.70 Hz, C-4'), 77.72, 71.73, 62.78, 36.75, 24.34, 24.34, 20.87, 20.62.

**2'-Deoxy-4'-*C*-(trifluoromethyl)adenosine (21)**: The chloropurine nucleoside **20** (98.6 mg, 0.194 mmol) was placed in the steel bomb and covered with liquid ammonia. The bomb was tightly closed and left at ambient temperature overnight. After that time it was carefully opened and the solid residue was subjected to the column chromatography (chloroform - methanol, 8:2) to give free adenosine analog **21** (36.4 mg, 58.9%): mp 104-105 °C; $[\alpha]_D$: -15.0 (c 0.2, methanol); $^1$H NMR (300 MHz, $CD_3OD$) δ 8.29 (s, 1H), 8.18 (s, 1H), 6.56 (dd, J = 6.72, 6.72 Hz, 1H), 5.06 (dd, J = 6.10, 6.10 Hz, 1H), 3.86 (s, 2H), 3.01 (ddd, J = 6.72, 6.72, 14.04 Hz, 1H), 2.59 (dd, J = 6.71, 6.71, 12.82 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 156.19, 152.22, 148.45, 140.12, 123.46 (q, J = 287.0 Hz, $CF_3$), 119.32, 88.29 ((q, J = 24.30 Hz, C-4'), 85.60, 71.20, 60.81, 39.71; MS (EI) *m/z* 319 (M, 2), 164 (29), 162 (37), 135 (base, 100); HRMS (EI) calcd for $C_{11}H_{12}F_3N_5O_3$: 319.0892, Found: 319.0900.

**9-(4-*C*-Trifluoromethyl-β-D-*ribo*-furanosyl)-6-methoxypurine (22)**: The chloropurine nucleoside **17** (95 mg, 0.208 mmol) was placed in methanol (5 mL) containing potassium cyanide (110 mg, 1.66 mmol) and stirred overnight. The mixture was concentrated and filtered through a short column of silica gel (chloroform - methanol, 8:2), to give **22** (72 mg, 99%) as white crystals: mp 198-203 °C (dec.), $[\alpha]_D$: -51.7 (c 1.7, methanol); $^1$H NMR (500 MHz, $CD_3OD$) δ 8.53 (s, 1H), 8.48 (s, 1H), 6.18 (d, J = 8.10 Hz, 1H), 4.98 (dd, J = 5.57, 8.11 Hz, 1H), 4.58 (d, J = 5.57 Hz, 1H), 4.19 (s, 3H), 3.90 (d, J = 12.16 Hz, 1H), 3.84 (d, J = 12.16 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 161.19, 151.92, 151.02, 142.62, 124.09 (q, J = 284.07 Hz, $CF_3$), 121.64, 89.86, 88.29 (q, J = 25.99 Hz, C-4'), 73.12, 71.31, 61.99, 53.61; MS (+FAB, thioglycerol) *m/z* 351 (M+H, 56), 193 (12), 151 (base+H, 100); Anal. calcd for $C_{12}H_{13}F_3N_4O_5$: %C 41.13, %H 3.71, Found: %C41.07, %H 3.76.

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-3'-*O*-acetyl-2'-bromo-2'-deoxy-4'-*C*-(trifluoromethyl)inosine (23).** The methoxy nucleoside **22** (54 mg, 0.155 mmol) was placed in α-acetoxyisobutyryl bromide (1.5 mL) and stirred at 100 °C overnight. The reaction mixture was cooled down, diluted with ethyl acetate 5 mL and quenched with sat. $NaHCO_3$ (5 mL), followed by solid $NaHCO_3$ until no evolution of gases was observed. The organic phase was then separated and washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The dark oily residue was purified by column chromatography on silica gel (chloroform - methanol, 9:1) to give **23** (86 mg, 98%) as a mixture of diastereoisomers at C-2': $^1$H NMR (300 MHz, $CDCl_3$) δ 13.00 (bs, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 6.62 (d, J = 7.09 Hz, 1H), 6.28 (d, J = 7.33 Hz, 1H), 5.98 (dd, J = 7.32, 7.31 Hz, 1H), 4.77 (d, J = 12.21 Hz, 1H), 4.48 (d, J = 12.66 Hz, 1H), 2.13 (s, 3H), 1.99 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.42, 170.20, 168.87, 158.71, 148.22, 146.33, 146.24, 138.69, 125.01, 123.66 (q, J = 286.25 Hz, $CF_3$), 84.71, 83.05 (q, J = 27.63 Hz, C-4'), 77.71, 76.87, 62.66, 48.54, 24.40, 24.21, 20.94, 20.27; MS (+FAB, thioglycerol) *m/z* 569 (M+H, 63), 491 (M-Br+H, 1), 137 (base+H, 100).

**5'-*O*-(2-Acetoxy-2-methylpropanoyl)-3'-*O*-acetyl-2'-deoxy-4'-*C*-(trifluoromethyl)inosine (24).** The bromide **23** (208 mg, 0.366 mmol) was dissolved in toluene (4 mL) containing catalytic amount of AIBN. Tributyltin hydride (213 mg, 0.731 mmol) was added and the mixture was kept at 100 °C over 2 h. The mixture was cooled down and concentrated. The residue was purified by column flash chromatography (chloroform - methanol, 9:1) to give 142 mg (79%) of **24** as a colorless oil: $[\alpha]_D$: +1.4 (c 1.5, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 13.02 (bs, 1H), 8.26 (s, 1H), 8.01 (s, 1H), 6.50 (t, J = 7.09 Hz, 1H), 6.05 (t, J = 7.09 Hz, 1H), 4.50 (s, 2H), 3.20 (ddd, J = 7.09, 7.09, 14.18 Hz, 1H), 2.75 (ddd, J = 7.09, 7.09, 14.18 Hz, 1H), 2.15 (s, 3H), 2.03 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.67, 170.25, 169.23, 158.81, 148.29, 146.02, 139.02, 125.48, 123.35 (q, J = 284.38 Hz, $CF_3$), 85.09, 84.09, 84.67 (q, J = 27.62 Hz, C-4'), 77.75, 72.03, 63.07, 37.00, 24.29, 24.29, 20.86, 20.61; MS (+FAB, thioglycerol) *m/z* 981 (2M+H, 1), 491 (M+H, 22), 295 (10), 137 (base+H, 100).

**2'-Deoxy-4'-*C*-(trifluoromethyl)inosine (25):** The acylated inosine **24** (44.8 mg, 0.091 mmol) was dissolved in methanol (1 mL) with catalytic amount of NaCN (1 crystal). After overnight stirring, the mixture was concentrated under reduced pressure and the residue was filtered though short silica gel column (chloroform - methanol, 9:1), to give 18.3 mg (63%) of 2'-deoxyinosine **25** as white crystals: mp 253-256 °C; $[\alpha]_D$: -14.3 (c 0.7, methanol); $^1$H NMR (500 MHz, $CD_3OD$) δ 8.31 (s, 1H), 8.08 (s, 1H), 6.56 (dd, J = 5.06, 7.09 Hz, 1H), 5.10 (t, J = 6.58 Hz, 1H), 3.86 (d, J = 12.15 Hz, 1H), 3.83 (d, J = 12.16 Hz, 1H), 2.94 (ddd, J = 5.57, 7.09, 13.17 Hz, 1H), 2.66 (ddd, J = 7.09, 7.09,

13.67 Hz, 1H); $^{13}C$ NMR (75 MHz, $CD_3OD$) δ 159.03, 147.00, 140.77, 125.77, 89.31(q, J = 27.0 Hz, C-4'), 86.16, 72.17, 61.58, 41.01; MS (+FAB, thioglycerol) *m/z* 343 (M+Na, 31), 321 (M+H, 11), 291 (28), 137 (base+H, 100); HRMS (EI) calcd for $C_{11}H_{11}F_3N_4O_4$: 320.0732, Found: 320.0727.

**2',3'-Dideoxy-4'-*C*-(trifluoromethyl)inosine (26):** The bromide **23** (128.8 mg, 0.226 mmol) was dissolved in methanol (20 mL) containing triethylamine (78 μL, 0.5660 mmol). The mixture was then hydrogenated under ambient conditions in the presence of palladium catalyst (10% on charcoal, 50 mg). After 2.5 h there was no substrate detected on TLC. The catalyst was filtered onto Celite and the filtrate concentrated *in vacuo*. The residue was passed through silica gel column (ethyl acetate - methanol, 9:1). The solvents were evaporated and resulting oil was redissolved in methanol (10 mL) with catalytic amount of NaCN. The mixture was stirred overnight, concentrated and filtered through silica gel (chloroform - methanol, 8:2) to give dideoxyinosine **26** (26.3 mg, 38%) as white crystals: mp 245-247 °C; $[\alpha]_D$: -18.7 (c 0.9, methanol); $^1H$ NMR (500 MHz, $CD_3OD$) δ 8.29 (s, 1H), 8.04 (s, 1H), 6.43 (t, J = 5.82 Hz, 1H), 3.88 (d, J = 11.90 Hz, 1H), 3.72 (d, J = 11.90 Hz, 1H), 2.67 (m, 3H), 2.35 (m, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 145.41, 139.20, 87.04, 61.30, 31.77, 26.33; MS (+FAB, NBA with traces of NaCl) *m/z* 609 (2M+H, 3), 327 (M+Na, 6),305 (M+H, 25), 169 (M-base, 7), 137 (base+H, 100).

2'-Deoxyinosine (**25**) (16.9 mg, 24.6%) was also isolated.

**1-(2,3-Di-*O*-acetyl-5-*O*-benzoyl-4-*C*-trifluoromethyl-β-D-*ribo*-furanosyl)triazole (27).** Triazole (115.5 mg, 1.67 mmol) was silylated with refluxing HMDS (2 mL) over 2 h. The solvent was then evaporated to dryness and the colorless, oily residue was dissolved in acetonitrile (5 mL) containing triacetate **7** (250 mg, 0.558 mmol) and TMS triflate (323.6 μL, 1.67 mmol). The mixture was refluxed overnight, poured into sat. $NaHCO_3$ (20 mL) and extracted with chloroform (3 x 10 mL). The combined chloroform extracts were dried over $MgSO_4$, filtered and evaporated. Column chromatography (chloroform, methanol, 9:1) afforded a mixture (250 mg, 98%) of diastereoisomers at C-4'. The major, D-ribo isomer **27** was isolated by a second chromatography on silica gel column (hexanes - ethyl acetate, 15:85) as colorless oil (165.0 mg, 67%): $[\alpha]_D$: -57.1 (c 0.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.06 (d, J = 7.50 Hz, 2H), 7.86 (s, 1H), 7.56 (t, J = 7.20 Hz, 1H), 7.43 (t, J = 7.20 Hz, 2H), 6.24 (d, J = 6.10 Hz, 1H), 6.20 (d, J = 4.27 Hz, 1H), 5.97 (dd, J = 4.27, 6.11 Hz, 1H), 4.69 (d, J = 12.82 Hz, 1H), 4.60 (d, J = 12.21 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.04, 168.54, 165.37, 153.12, 144.23, 133.51, 129.90, 128.45, 123.01 (q, J = 284.55 Hz, $CF_3$), 89.38, 85.09 (q, J = 27.60 Hz, C-4'), 73.05, 69.96, 62.83, 20.14, 19.97; MS (+VE CI) *m/z* 458 (M+H, 61), 389 (M-base, 100), 105 (35), 70 (base+H, 5); HRMS (EI) calcd for $C_{19}H_{18}F_3N_3O_7$: 457.1097, Found: 457.1106.

**1-(4-*C*-Trifluoromethyl-β-D-*ribo*-furanosyl)triazole (28).** The nucleoside **27** (165 mg, o.361 mmol) was dissolved in methanol (3 mL) and a single crystal of NaCN was added. The mixture was stirred under ambient conditions for 10 h. The solvent was evaporated and the product **28** (88 mg, 91%) was isolated by column flash chromatography (chloroform - methanol, 8:2) as white crystals: mp 172-174 °C; $[\alpha]_D$: -54.4 (c 1.45, methanol); $^1$H NMR (500 MHz, $CD_3OD$) δ 8.76 (s, 1H), 8.10 (s, 1H), 6.00 (d, J = 7.09 Hz, 1H), 4.82 (dd, J = 5.57, 7.09 Hz, 1H), 4.56 (d, J = 5.57 Hz, 1H), 3.81 (d, J = 12.16 Hz, 1H), 3.74 (d, J = 12.15 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 151.48, 144.55, 124.75 (q, J = 281.25 Hz, $CF_3$), 91.46, 87.72 (q, J = 27.50 Hz, C-4'), 73.75, 71.07, 61.60; MS (+VE CI) *m/z* 270 (M+H, 82), 201 (M-base, 10), 112 (27), 70 (base+H, 100); HRMS (EI) calcd for $C_7H_8F_3N_3O_3$ (M-$CH_2O$): 239.0517, Found: 239.0517.

**1-[5-*O*-(2-Acetoxy-2-methylpropanoyl)-3-*O*-acetyl-2-bromo-2-deoxy-4-*C*-trifluoromethyl-β-D-*ribo*-furanosyl]triazole (29).** The triol **28** (73.5 mg, 0.273 mmol) was dissolved in Mattocks' reagent (2 mL) and heated at 100 °C for 2 h. The mixture was diluted with ethyl acetate (20 mL) and neutralized with aqueous sodium bicarbonate. The organic phase was separated, dried ($MgSO_4$) and concentrated on the rotary evaporator. The dark, oily residue was purified by flash chromatography (chloroform - methanol, 9:1) to give 2'-bromo derivative **29** (137 mg, 100%) as a mixture of diastereoisomers at C-2': $^1$H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.06 (s, 1H), 6.36 (d, J = 10.22 Hz, 1H), 6.29 (d, J = 6.48 Hz, 1H), 4.86 (dd, J = 6.78, 10.01 Hz, 1H), 4.79 (d, J = 12.45 Hz, 1H), 4.58 (d, J = 12.39 Hz, 1H), 2.16 (s, 3H), 1.97 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.47, 169.97, 168.97, 153.18, 144.50, 86.26, 77.75, 63.95, 62.61, 45.99, 24.27, 24.17, 20.83, 20.32.

**1-[5-*O*-(2-Acetoxy-2-methylpropanoyl)-3-*O*-acetyl-2-deoxy-4-*C*-trifluoromethyl-β-D-*erythro*-pentofuranosyl]triazole (30).** The bromide **29** (137.1 mg, 0.273 mmol) was placed into dry toluene (3 mL) and treated with tributyltin hydride (159 mg, 0.546 mmol) in the presence of AIBN at 100 °C. After 2 h the mixture was concentrated and subjected to column chromatography (hexanes - ethyl acetate, 1:1). The deoxy- derivative **30** (78.5 mg, 68%) was isolated as colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.98 (s, 1H), 6.28 (dd, J = 3.05, 6.71 Hz, 1H), 6.00 (dd, J = 7.33, 7.33 Hz, 1H), 4.40 (d, J = 12.21 Hz, 1H), 4.32 (d, J = 12.21 Hz, 1H), 3.08 (ddd, J = 2.45, 7.33, 12.82 Hz, 1H), 2.72 (ddd, J = 7.93, 7.93, 14.65 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.56, 170.03, 169.25, 152.82, 143.57, 123.51 (q, J = 284.55 Hz, $CF_3$), 86.49, 84.43 (q, J = 26.47 Hz, C-4'), 77.74, 72.09, 63.08, 36.52, 24.28, 24.22, 20.83, 20.50.

**1-(2-Deoxy-4-*C*-trifluoromethyl-β-D-*erythro*-pentofuranosyl)triazole (31).** The acylated nucleoside **30** (78.5 mg, 0.186 mmol) was dissolved in methanol (2

mL) and a catalytic amount of NaCN was added. The mixture was stirred at room temperature overnight. The solvent was evaporated and the product **31** (32.5 mg, 69%) was isolated by column flash chromatography (ethyl acetate - methanol, 95:5) as white crystals: mp 143-145 °C; $[\alpha]_D$: -34.2 (c 0.5, methanol); $^1$H NMR (500 MHz, $CD_3OD$) δ 8.66 (s, 1H), 8.02 (s, 1H), 6.40 (dd, J = 3.04, 7.60 Hz, 1H), 5.07 (dd, J = 7.60, 7.60 Hz, 1H), 3.82 (d, J = 13.17 Hz, 1H), 3.78 (d, J = 13.67 Hz, 1H), 2.80 (ddd, J = 2.53, 7.60, 13.17 Hz, 1H), 2.65 (dd, J = 8.10, 8.10, 14.18 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 151.20, 143.77, 124.70 (q, J = 285.25 Hz, $CF_3$), 86.92, 86.72 (q, J = 24.75 Hz, C-4'), 70.87, 60.77, 38.57; MS (+FAB, thioglycerol) *m/z* 276 (M+Na, 73), 254 (M+H, 100), 185 (M-$CF_3$+H, 23), 176 (49), 137 (51).

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## References

1. Hewitt, R. W.; Gumble, A. R.; Taylor, L. W.; Wallace, W. S. *Antibiot. Annu.*, 722, 1956-1957.
2. Morton, G. O.; Lancaster, J. E.; Van Lear, G. E.; Fulmor, W.; Meyer, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 1535.
3. Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 4323.
4. Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 3346-3357.
5. Verheyden, J. P. H.; Jenkins, I. D.; Owen, G. R.; Dimitrijevich, S. D.; Richards, C. M.; Srivastava, P. C.; Le-Hong, N.; Moffatt, J. G. *Ann. N. Y. Acad. Sci.* **1975**, *255*, 151-165.
6. Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4386-4395.
7. Cook, S. L.; Secrist III, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1554-1564.
8. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440-1451.
9. Secrist III, J. A.; Winter, Jr., W. J. *J. Am. Chem. Soc.* **1978**, *100*, 2554-2555.
10. O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37-40.
11. O-Yang, C.; Kurz, W.; Eugui, E. M. McRoberts, M. J.; Verheyden, J. P. H.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 41-44.

12. Maquire, A. R.; Meng, W-D.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin I*, **1993**, 1795-1808.
13. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768.
14. Bhattacharya, B. K.; Ojwang, J. O.; Rando, R. F.; Huffman, J. H. *J. Med. Chem.* **1995**, *38*, 3957-3966.
15. Bronson, J. J.; Kim, C. U.; Ghazzouli, I.; Hitchcock, M. J. M.; Kern, E. R.; Martin, J. C. Synthesis and Antiviral Activity of Phosphonylmethoxyethyl Derivatives of purine and Pyrimidine Bases, in *Nucleotide Analogues as Antiviral Agents*, Martin J. C. ed., American Chemical Society, Washington, D.C., 1989, pp.72-87.
16. Waga, T.; Ohrui, H.; Meguro, H. *Nucleosides Nucleotides* **1996**, *15*, 287-304.
17. Hrebabecky, H.; Holy, A.; *Collect. Czech. Chem. Commun.* **1993**, *58*, 409-420.
18. (a) Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1976**, *52*, 95-101. (b) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99-102.
19. De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Org. Chem.* **1994**, *59*, 2715-2723.
20. Wittig, G.; Wittenberg, D. *Liebigs Ann. Chem.* **1957**, *606*, 1-23.
21. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399-402.
22. Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195-2198.
23. Vorbrugen, H.; Krolikiewich, K.; Bennua, B. *Chem. Berichte* **1981**, *114*, 1234-1255.
24. Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790-701.
25. Mattocks, A. R. *J. Chem. Soc.* **1964**, 1918, 4840-4845.
26. Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016-4025.
27. Johnson, C. R.; Kozak, J.; Heeg, M. J., unpublished results.
28. Kuivila, H. G. *Synthesis* **1970**, 499-509.
29. Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *25*, 367-370.
30. Russell, A. F.; Greenberg, S.; Moffatt, J. G. . *J. Am. Chem. Soc.* **1973**, *95*, 4025-4030.
31. Maruyama, T.; Utzumi, K.; Sato, Y.; Richman, D. D. *Nucleosides Nucleotides* **1994**, *13*, 527-538.
32. Wells, G.W.; C. R. Johnson, unpublished results.
33. Johnson, C.R.; Bhumaralkar, D. R. . *Nucleosides Nucleotides* **1995**, *14*, 185-194.
34. Bravo, P.; Mele, A.; Salani, G. *Gazz. Chim. Ital.* **1995**, *125*, 295-303.

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