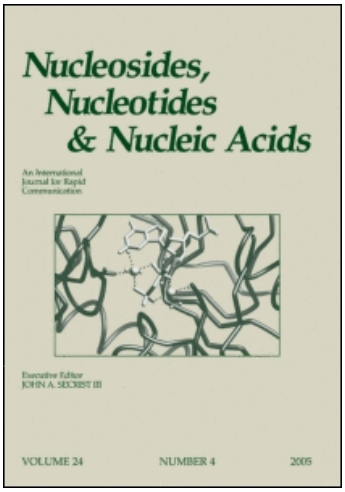

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis of Novel Carbohydrates Amenable to the Synthesis of 2',3'-Dideoxy-3'-Branched Nucleosides

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To cite this Article Pudlo, Jeffrey S. and Townsend, Leroy B.(1992) 'The Synthesis of Novel Carbohydrates Amenable to the Synthesis of 2',3'-Dideoxy-3'-Branched Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 11: 2, 279 — 293
To link to this Article: DOI: 10.1080/07328319208021703
URL: http://dx.doi.org/10.1080/07328319208021703

NUCLEOSIDES & NUCLEOTIDES, 11(2-4), 279-293 (1992)

THE SYNTHESIS OF NOVEL CARBOHYDRATES AMENABLE TO THE SYNTHESIS OF 2',3'-DIDEOXY-3'-BRANCHED NUCLEOSIDES

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Abstract. The facile synthesis of several substituted carbohydrates that are amenable for the preparation of 2',3'-dideoxy-3'-hydroxymethyl nucleosides are reported. Elaboration of a previously reported analog, 5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-1,2-O-isopropylidene-α-D-ribofuranose (**4**) has provided two 2,3-dideoxy-3-branched ribose derivatives 5-O-benzoyl-2,3-dideoxy-3-(benzyloxy)methyl-1-O-methyl-β-D-ribofuranose (**7**) and 1,5-di-O-benzoyl-2,3-dideoxy-3-(benzyloxy)methyl-(α,β)-D-ribofuranose (**10**). Due to problems involved with the separation of anomeric mixtures when these carbohydrates were condensed with an heterocycle, another versatile synthon 5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-2-O-*t*-butyldimethylsilyl-1-O-methyl-β-D-ribofuranose (**12**) was synthesized. The utility of this compound (**12**) is demonstrated in the total synthesis of 1-[3-deoxy-3-hydroxymethyl-β-D-ribofuranosyl]thymine (**20**).

INTRODUCTION

2',3'-Dideoxy-3'-hydroxymethyl ribofuranosides (2'-deoxy-3'-branched ribosides, **1**, figure 1) are a known class of compounds but there has been limited information published concerning the synthetic methodology used to prepare this class of compounds. To the best of our knowledge, only the uridine[1a,b] (**2**) and the thioguanosine[1c] (**3**) analogs

This paper is dedicated to the memory of Professor Tohru Ueda.

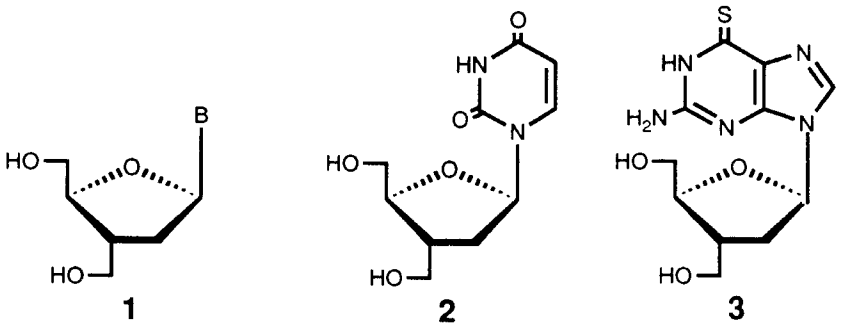


Figure 1

have been reported[2]. The synthesis of **2** was achieved *via* a ring expansion-ring contraction methodology from uridine *via* a 2',3'-dideoxy-3'-aminopyranosyl nucleoside[1a] or ring-opening of a 2',3'-lyxo-epoxide derivative.[1b] These methodologies were complicated by epimeric mixtures about the 3'-center[1a] and a limited synthetic approach.[1b] Another reported example of a total synthetic approach to these analogs was published by Acton[1c] and was based upon the methodology of Rosenthal.[3] Anomeric mixtures, obtained by the condensation of an heterocycle to a suitably substituted 2,3-dideoxy-3-hydroxymethyl ribofuranose derivative, presented a problem with this methodology and glycosylation was reported to proceed in poor yield (calc 22% yield of the desired β-anomer). Due to the paucity of expedient synthetic approaches into this class of compounds and the close structural similarity of compound **1** to the known antiviral agents 9-[(1,3-dihydroxypropoxy)methyl]guanine (ganciclovir) and oxetanocin,[4] we elected to initiate a new total synthetic approach to these 2'-deoxy-3'-branched nucleosides.

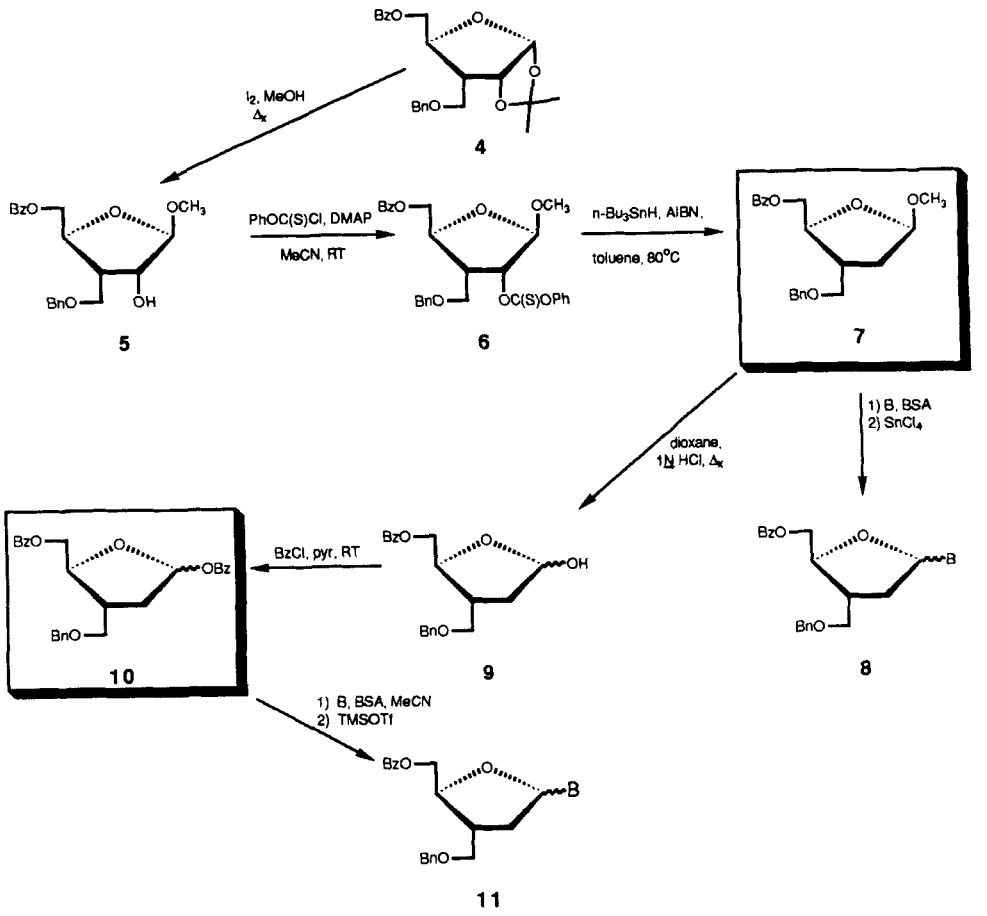
RESULTS AND DISCUSSION

The most expedient route into these analogs involves the synthesis of a properly substituted carbohydrate that may be appended to a number of aglycones and deprotected in

a minimum number of steps. To this end, we chose 5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-1,2-O-isopropylidene-α-D-ribofuranose (**4**, scheme 1) as our starting material. We have recently published an improved synthetic route for the preparation of **4** in excellent overall yield.[5]

An examination of the structure of compound **4** revealed that removal of the acetonide could be followed by a functionalization of the 1- and 2-hydroxyls such that the 2-hydroxyl group could be selectively removed. This preferential removal of the acetonide would then allow us to deoxygenate the 2-position and provide an expedient route for the preparation of the desired carbohydrate. A review of the literature furnished an appropriate method[6] which would substitute the anomeric oxygen with an O-methyl while leaving the 2-hydroxyl free for further elaboration. Compound **4** was dissolved in 1% I_2/MeOH (w/v) and heated at reflux to provide the desired product **5**. The ^{1}H NMR spectrum of **5** revealed that we had obtained only one anomer. This anomer was assigned as β due to the appearance of a peak for the anomeric proton as a singlet which is indicative of β-anomers. If we had obtained the α-anomer, a larger coupling constant ($J_{1,2}$ of >3Hz) would have been observed.

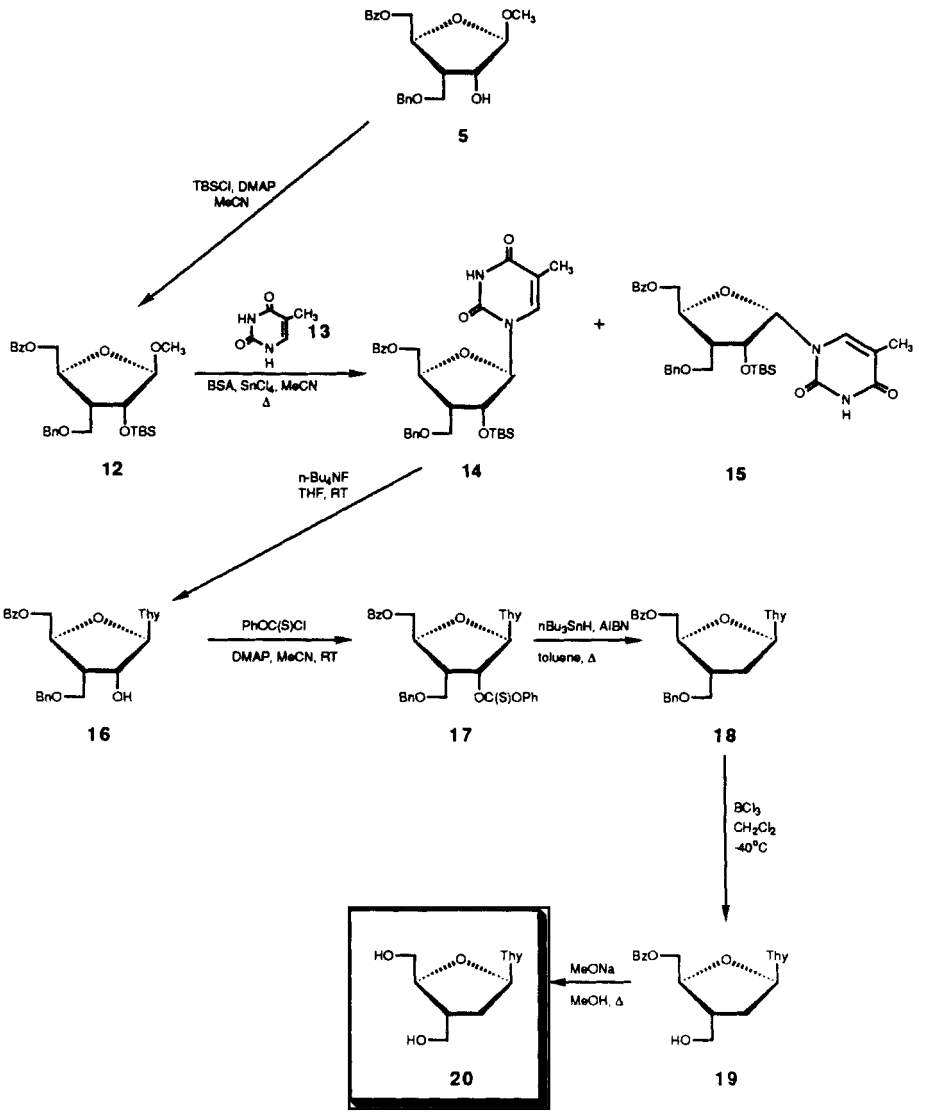
Selective deoxygenation of the 2-hydroxyl of compound **5** was accomplished *via* a modified Barton procedure. Treatment of **5** (scheme 1) with phenoxythiocarbonyl chloride in acetonitrile (MeCN)/dimethylaminopyridine (DMAP) yielded 5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-2-O-phenoxythiocarbonyl-1-O-methyl-β-D-ribofuranose (**6**). Treatment of compound **6** with tri-*n*-butyltin hydride[7] (Bu_3SnH) furnished 2,3-dideoxy-3-(benzyloxy)methyl-1-O-methyl-β-D-ribofuranose (**7**) which was appropriately substituted for condensation with an heterocycle. However, when **7** was subjected to glycosylation procedures, we obtained inconsistent yields of anomeric mixtures (**8**). The poor yields we obtained were attributed to the fact that the OMe present at the anomeric center was a rather poor leaving group. Therefore, a replacement of this ether by a benzoyl group was effected to yield 1,5-di-O-benzoyl-2,3-dideoxy-3-(benzyloxy)methyl-α,β-D-ribofuranose (**10**) as a 1:1 (α:β) mixture. Compound **10** did provide consistently good yields of nucleoside



Scheme 1

material, but, again, anomeric mixtures were obtained (**11**) that were not easily separable by column chromatography. Due to the complications associated with the use of compounds **7** and **11**, an alternative route to the 2',3'-dideoxy-3'-branched nucleosides was initiated .

Compound **5** was viewed as a divergence point in the synthetic methodologies. If a protecting group was substituted at the 2-hydroxyl that could be selectively removed subsequent to condensation with an heterocycle, a viable approach would result. Also, if a



Scheme 2

bulky protecting group for the 2-hydroxyl could be appended, steric hindrance might favor formation of the desired β-anomer. The *tert*-butyldimethylsilyl ether (TBS) was chosen due to its large size and ability to be selectively removed in subsequent steps. Therefore, compound **5** was treated with TBSCl in dimethylformamide (DMF)/imidazole, according to a literature method,[8] to afford the 2-silyl protected compound **12**.

With the appropriate carbohydrate (**12**) in hand, the utility of compound **12** was demonstrated by the synthesis of the branched thymidine analog. Thymine (**13**) was suspended in MeCN and silylated with bis(trimethylsilyl)acetamide (BSA) followed by the addition of a solution of **12** and stannic chloride ($SnCl_4$). Although the β-anomer was the target compound, unfortunately the reaction furnished a 1:1 anomeric mixture of **14** and **15**, albeit in good overall yield (calc 45% of the desired β-anomer **14**). However, these anomers were easily separated by column chromatography. A selective removal of the 2'-protecting group was then achieved to furnish 1-[5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-β-D-ribofuranosyl]thymine (**16**) by treatment of **14** with tetra-n-butyl ammonium fluoride (Bu_4NF). Compound **16** was deoxygenated, as described before, by treatment with phenoxythiocarbonyl chloride to afford 1-[5-O-benzoyl-3-deoxy-3-(benzyloxy)methyl-2-O-phenoxythiocarbonyl-β-D-ribofuranosyl]thymine (**17**). This was followed by treatment with Bu_3SnH to provide 1-[5-O-benzoyl-2,3-dideoxy-3-(benzyloxy)methyl-β-D-ribofuranosyl]thymine (**18**).

A removal of the carbohydrate protecting groups was achieved in a stepwise manner. Treatment of **18** with boron trichloride (BCl_3) in CH_2Cl_2 at -40°C gave a good yield of **19**. Compound **19** was heated in MeOH with sodium methoxide (NaOMe, catalytic) to effect debenzoylation which provided the target nucleoside 1-[2,3-dideoxy-3-hydroxymethyl-β-D-ribofuranosyl]thymine (**20**). The site of glycosylation was established by a comparison of the UV spectral data of **20** to the spectral data of some known N-1 substituted thymine compounds.

Unlike the previous synthetic approach employing compound **10**, anomeric mixtures obtained when compound **12** was employed could be separated easily by column chromatographic techniques. The 3-branched ribofuranose **12** is thus a general starting material for the synthesis of other 2',3'-dideoxy-3'-hydroxymethyl nucleosides.

EXPERIMENTAL

General Methods. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Bruker WP-270SY or an IBM AM-300 or an IBM WM-360 spectrophotometer (solutions in dimethylsulfoxide-d_6 (DMSO-d_6) or deuteriochloroform ($CDCl_3$)) with chemical shift values reported in δ, parts per million, relative to the internal standard. Ultraviolet (UV) spectra were recorded on a Hewlett-Packard model 8450A U. V./Vis spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. E. Merck silica gel (230-400 mesh) was used for column chromatography (amount of silica gel used (g) and column inner diameter (id) are specified for each column). Thin layer chromatography was performed on silica gel GHLF-254 plates. R_f's were determined using the solvent systems recorded. Solvent systems are reported in volume:volume ratios. Compounds of interest were detected by either ultraviolet lamp (254 nm) or treatment with 10% H_2SO_4 in MeOH followed by heating (charred). "Reduced" refers to evaporations which were performed under reduced pressure with a bath temperature < 50°C with a rotary evaporator using a water aspirator unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

5-Q-Benzoyl-3-deoxy-3-[(benzyloxy)methyl]-1-Q-methyl-β-D-ribofuranose (**5**).

Compound **4** (9.30 g, 23.3 mmol) was dissolved in I_2/MeOH (1%, W:V, 130 mL) and the solution was heated at reflux for 4 hours. The solution was cooled and poured into a solution of $Na_2S_2O_4$ (200 mL) and this solution was extracted with Et_2O (1 x 200 mL, 1x50 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered, and reduced to an orange oil. This oil was subjected to column chromatography (130 g, 3" id) and eluted with 40% EtOAc/hexane. Fractions (50 mL) were obtained and evaporation of fractions 7-14 yielded a clear, colorless oil; yield=7.80 g (90%); R_f=0.45 (45% EtOAc/hexane); ^{1}H NMR ($CDCl_3$): δ 2.58 (m, 1H, *H*-3); 2.96 (bs,

1H, D_2O exchangeable, 2-OH); 3.33 (s, 3H, OCH_3); 3.82 (m, 2H, H-3'); 4.11-4.61 (m, 6H, H-2, H-4, H-5, $O\underline{CH_2}Ph$; 4.83 (s, 1H, H-1); 7.29-8.07 (complex, 10H, Ph, Bz); *Anal.* Calc. for $C_{21}H_{24}O_6$: C, 67.72; H, 6.51. Found: C, 67.80; H, 6.42.

5-Q-Benzoyl-3-deoxy-3-[(benzyloxy)methyl]-2-Q-phenoxythiocarbonyl-1-Q-methyl-β-D-ribofuranose (**6**).

Compound **5** (4.19 g, 11.2 mmol) was dissolved in MeCN (dry, 60 mL) and DMAP (6.0 g, 49 mmol) and phenoxythiocarbonyl chloride (3.1 mL, 22 mmol) were added. The solution was stirred at room temperature for 2 hours after which time the solution was diluted with EtOAc (100 mL) and washed with 1% HCl (3x70 mL) and brine (50 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and reduced to a yellow oil that was subjected to column chromatography (80 g, 3" id) and eluted with 10% EtOAc/hexane. Fractions (40 mL) were obtained and the title compound crystallized from fractions 7-15 to yield white needles; yield=4.03 g (70%); mp=93-93.5°C; R_f=0.46 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 3.03 (m. 1H, H-3); 3.37 (s, 3H, OCH_3); 3.65 (t, 1H, H-3'); 3.79 (t, 1H, H-3'); 4.34-4.64 (complex, 5H, H-4, H-5, $O\underline{CH_2}Ph$); 5.13 (s, 1H, H-1); 5.66 (d, 1H, $J_{2,3}$=4.7 Hz; H-2); 7.04-8.11 (complex, 15H, Bn, Bz, OPh); *Anal.* Calc. for $C_{28}H_{28}O_7S$: C, 66.12; H, 5.56. Found: C, 65.99; H, 5.63.

5-Q-Benzoyl-2,3-dideoxy-3-[(benzyloxy)methyl]-1-Q-methyl-β-D-ribofuranose (**7**).

Compound **6** (17.22 g, 33.9 mmol) was dissolved in toluene (dry, 400 mL) and the solution was heated to 80°C and argon was bubbled through the solution for 15 minutes. A solution of Bu_3SnH (30 mL, 110 mmol) and AIBN (1.5 g, 9 mmol) in toluene (20 mL) was then added dropwise. After complete addition the solution was stirred for 5 hours. The solution was cooled and the solvent removed *in vacuo* to yield a yellow oil. This oil was subjected to column chromatography (380 g, 4" id) and eluted with 10% EtOAc/hexane. Fractions (100 mL) were obtained and evaporation of fractions 17-34

yielded a clear, colorless oil; yield=10.89 g (90%); R_f=0.24 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 1.83 (m, 1H, H-2 a); 2.12 (dd, 1H, H-2 b); 2.67 (m, 1H, H-3); 3.31 (s, 3H, OCH_3); 3.55 (m, 2H, H-3'); 4.23 (m, 1H, H-4); 4.33-4.54 (complex, 4H, H-5, O$\underline{CH_2}$Ph); 5.01 (d, 1H, $J_{1,2\alpha}$=4.7 Hz, H-1); 7.30-8.18 (complex, 10H, Bn, Bz).

5-$\underline{O}$-Benzoyl-2,3-dideoxy-3-[(benzyloxy)methyl]-α,β-D-ribofuranose (**9**).

Compound **7** (8.16 g, 22.9 mmol) was dissolved in dioxane (120 mL) and HCl (1N, 50 mL) and the solution was heated at reflux for 60 minutes. The solution was cooled to 0°C and neutralized the by addition of saturated $NaHCO_3$ (pH=5). The solvent was then removed *in vacuo* until a phase separation was observed. The solution was then diluted with EtOAc (150 mL) and washed with H_2O (2x100 mL) and brine (50 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and reduced to a yellow oil that was subjected to column chromatography (100 g, 3.5" id) and eluted with 30% EtOAc/hexane. Fractions (100 mL) were obtained and evaporation of fractions 8-15 yielded a clear, colorless oil as an α,β mixture (1:1); yield=5.17 g (66%); R_f=0.24 (30% EtOAc/hexane); ^1H NMR (DMSO-$\underline{d_6}$): d 1.45-2.55 (complex, 3H, H-2, H-3); 3.50 (complex, 2H, H-3'); 4.00-4.50 (complex, 5H, H-4, H-5, O$\underline{CH_2}$Ph); 5.32 (t, 0.5H; H-1); 5.39 (m, 0.5H, H-1); 6.14 (d, 0.5H, D_2O exchangeable, $J_{1\text{-}OH,1}$=4.4 Hz, 1-OH); 6.23 (d, 0.5H, D_2O exchangeable, $J_{1\text{-}OH,1}$=4.4 Hz, 1-OH); 7.28-7.97 (complex, 10H, Bn, Bz); *Anal.* Calc. for $C_{20}H_{22}O_5$•0.5 H_2O: C, 68.74; H, 6.01. Found: C, 68.89; H, 6.13.

1,5-Di-$\underline{O}$-benzoyl-2,3-dideoxy-3-[(benzyloxy)methyl]-α,β-D-ribofuranose (**10**).

Compound **9** (4.90 g, 14.3 mmol) was dissolved in pyridine (dry, 50 mL) and BzCl (2.5 mL, 22 mmol) was added. The solution was stirred at room temperature for 3 hours. The solvent was then removed *in vacuo* to yield a white slurry. This slurry was dissolved in Et_2O (200 mL) and washed with H_2O (100 mL), 1% HCl (2x100 mL), and brine (50 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and reduced

to a yellow oil that was subjected to column chromatography (80 g, 2.5" id) and eluted with 15% EtOAc/hexane. Fractions (50 mL) were obtained and evaporation of fractions 10-18 yielded a clear, colorless syrup as an α,β mixture (1:1); yield=4.65 g (73%); R_f=0.29 (15% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 1.95-2.58 (complex, 3H, H-2, H-3); 3.61 (complex, 2H, H-3'); 4.24-4.53 (complex, 5H, H-4, H-5, O$\underline{CH_2}$Ph); 6.40 (d, 1H, $J_{1,2}$=4.6 Hz, H-1); 6.48 (d, 1H, $J_{1,2}$=4.5 Hz, H-1); 7.30-7.97 (complex, 15H, Bn, Bz); *Anal.* Calc. for $C_{27}H_{26}O_6 \cdot 1.5H_2O$: C, 68.47; H, 6.18. Found: C, 68.49; H, 6.18.

5-Q-Benzoyl-2-Q-(t-butyldimethyl)silyl-3-deoxy-3-[(benzyloxy)methyl]-1-Q-methyl-β-D-ribofuranose (**12**).

Compound **5** (17.91 g, 48.1 mmol) was dissolved in DMF (dry, 80 mL) and then imidazole (9.77 g, 140 mmol) and TBSCl (10.99 g, 73 mmol) were added. The solution was stirred at room temperature for 19 hours. The solvent was removed *in vacuo* and the resultant yellow slurry was dissolved in Et_2O (300 mL) and washed with H_2O (150 mL), 1% HCl (2x150 mL), and brine (50 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and reduced to a yellow oil that was subjected to column chromatography (250 g, 4" id) and eluted with 5% EtOAc/hexane. All charring fractions were combined and reduced to a clear, colorless oil; yield=19.03 g (81%); R_f=0.46 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$): δ 0.07 (d, 6H, $SiCH_3$); 0.89 (s, 9H, t-Bu); 2.64 (m, 1H, H-3); 3.29 (s, 3H, OCH_3); 3.54 (dd, 1H, $J_{3',3'}$=9.0 Hz, H-3'a); 3.75 (dd, 1H, $J_{3',3'}$=9.0 Hz, H-3'b); 4.22-4.61 (complex, 6H, H-2, H-4, H-5, O$\underline{CH_2}$Ph); 4.72 (s, 1H, H-1); 7.28-8.11 (complex, 10H, Bn, Bz); *Anal.* Calc. for $C_{27}H_{38}O_6Si$: C, 66.62; H, 7.89. Found: C, 66.69; H, 7.75.

1-[5-Q-Benzoyl-2-Q-(t-butyldimethyl)silyl-3-deoxy-3-(benzyloxy)methyl-β-D-ribofuranosyl]thymine (**14**).

Thymine (1.15 g, 9.12 mmol, **13**) was suspended in MeCN (40 mL) and heated to 80°C (external) and BSA (7.5 mL, 30 mmol) was added. The solution was stirred for 15

minutes, **12** (3.67 g, 7.54 mmol in 5 mL MeCN) and $SnCl_4$ (2.5 mL, 21 mmol) were then added and the reaction was stirred for 11 hours. The solution was cooled to 0°C and MeOH (10 mL) was added. The solution was stirred for 10 minutes and diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (3x25 mL) and brine (25 mL). All aqueous extracts were combined and re-extracted with EtOAc (25 mL). All organic extracts were combined, dried over $MgSO_4$, filtered, and reduced to a yellow syrup. This syrup was subjected to column chromatography (80 g, 2.5" id) and eluted with 35% EtOAc/hexane. Evaporation of all charring fractions yielded a white foam which proved to be the β-anomer (further elution of the column provided the α-anomer); yield=1.94 g (44%, β-anomer, α:β=1:1); R_f=0.60 (60% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 0.02 (s, 3H, $SiCH_3$); 0.20 (s, 3H, $SiCH_3$); 0.89 (s, 9H, t-Bu); 1.61 (s, 3H, CH_3); 2.44 (s, 1H, H-3'); 3.59 (dd, 1H, $J_{3'',3''}$=6.9 Hz, H-3''); 3.76 (dd, 1H, $J_{3'',3''}$=6.9 Hz, H-3''); 4.43-4.80 (complex, 6H, H-2', H-4', H-5', O$\underline{CH_2}$Ph); 5.66 (d, 1H, $J_{1',2'}$=1.1 Hz, H-1'); 7.26-8.06 (complex, 10H, Bn, Bz); 8.42 (bs, 1H, D_2O exchangeable, NH); *Anal.* Calc. for $C_{31}H_{40}N_2O_7Si$: C, 64.10; H, 6.70; N, 4.82. Found C, 63.86; H, 7.05; N, 4.55.

1-[5-O-Benzoyl-3-deoxy-3-(benzyloxy)methyl-β-D-ribofuranosyl]thymine (**16**).

Compound **14** (1.10 g, 1.89 mmol) was dissolved in THF (dry, 20 mL) and Bu_4NF (1 M in THF, 2.8 mL) was added. The solution was stirred at room temperature for 4 hours, diluted with EtOAc (15 mL), and washed with saturated NH_4Cl (2x10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and reduced to a white foam that was crystallized from Et_2O/MeOH to yield a white powder; yield=0.63 g (72%); R_f=0.21 (60% EtOAc/hexane); mp 127-128°C; ^1H NMR (DMSO-d_6): δ 1.57 (s, 3H, CH_3); 2.60 (m, 1H, H-3'); 3.59 (t, 1H, H-3''); 3.74 (dd, 1H, H-3''); 4.34 (m, 2H, H-2', H-4'); 4.42-4.70 (complex, 4H, H-5', O$\underline{CH_2}$Ph); 5.71 (s, 1H, H-1'); 5.75 (d, 1H, D_2O exchangeable, $J_{2'\text{-}OH,2'}$=5.1 Hz, 2'-OH); 7.23-8.00 (complex, 11H, H-6, Bn, Bz);

11.34 (s, 1H, D_2O exchangeable, NH); *Anal.* Calc. for $C_{25}H_{26}N_2O_7$: C, 64.36; H, 5.63; N, 6.01. Found: C, 64.12; H, 5.57; N, 5.91.

1-[5-O-Benzoyl-3-deoxy-3-(benzyloxy)methyl-2-O-phenoxythiocarbonyl-β-D-ribofuranosyl]thymine (**17**).

Compound **16** (1.42 g, 3.04 mmol) was dissolved in MeCN (30 mL) and DMAP (1.23 g, 10.1 mmol) and phenoxythiocarbonyl chloride (0.63 mL, 4.55 mmol) were added. The solution was stirred at room temperature for 9 hours, diluted with EtOAc (50 mL), and washed with 1% HCl (2x50 mL), H_2O (50 mL), and brine (25 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and reduced to a white foam that was subjected to column chromatography (30 g, 2.5" id) and eluted with 40% EtOAc/hexane. Fractions (25 mL) were obtained and evaporation of fractions 7-13 yielded a white foam that was crystallized from MeOH to yield a white powder; yield=1.56 g (85%); R_f=0.71 (60% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 1.64 (s, 3H, CH_3); 3.17 (m, 1H, H-3'); 3.72 (m, 2H, H-3") 4.45-4.82 (complex, 5H, H-4', H-5', OCH_2Ph); 6.06 (m, 2H, H-1', H-2'); 7.04 (complex, 16H, H-6, Bn, Bz, Ph); 8.55 (s, 1H, D_2O exchangeable, NH); *Anal.* Calc. for $C_{32}H_{30}N_2O_8S$: C, 63.77; H, 5.03; N, 4.65. Found: C, 63.90; H, 5.14; N, 4.72.

1-[5-O-Benzoyl-2,3-dideoxy-3-(benzyloxy)methyl-β-D-ribofuranosyl]thymine (**18**).

Compound **17** (0.51 g, 0.85 mmol) was dissolved in toluene (dry, 18 mL), the solution was heated to 80°C and argon was bubbled through the solution for 15 minutes. A solution of Bu_3SnH (0.68 mL, 2.5 mmol) and AIBN (0.04 g, 0.24 mmol) in toluene (2 mL) was added dropwise. After complete addition, the solution was stirred for 2.5 hours after which time the solvent was removed *in vacuo*. The resultant yellow oil was subjected to column chromatography (15 g, 1.5" id) and eluted with 50% EtOAc/hexane. Fractions (10 mL) were obtained and evaporation of fractions 15-23 yielded a clear, colorless syrup that was crystallized from EtOAc/hexane to yield a white powder; yield=0.32 g (84%);

R_f=0.34 (60% EtOAc/hexane); mp=101-103°C; ^{1}H NMR (DMSO-d_6): δ 1.60 (s, 3H, CH_3); 2.18 (m, 2H, H-2'); 2.71 (m, 1H, H-3'); 3.56 (m, 2H, H-3''); 4.12 (m, 1H, H-4'); 4.41-4.65 (complex, 4H, H-5', OCH_2Ph); 6.08 (t, 1H, H-1'); 7.24-7.99 (complex, 11H, H-6, Bn, Bz); 11.27 (s, 1H, D_2O exchangeable, NH); *Anal.* Calc. for $C_{25}H_{26}N_2O_6$: C, 66.64; H, 5.83; N, 6.22. Found: C, 66.48; H, 5.81; N, 6.21.

1-[5-O-Benzoyl-2,3-dideoxy-3-hydroxymethyl-β-D-ribofuranosyl]thymine (**19**).

Compound **18** (0.74 g, 1.64 mmol) was dissolved in CH_2Cl_2 (15 mL), cooled to -40°C, and BCl_3 (5 mL) was added. The solution was stirred for 30 minutes and additional BCl_3 (2 mL) was added. The solution was stirred for 15 minutes, MeOH (5 mL) was added, and the solution was immediately neutralized by the addition of saturated $NaHCO_3$ (pH=6). The organic layer was decanted and washed with brine (10 mL), dried over $MgSO_4$, filtered, and reduced to a white foam that was crystallized from Et_2O/MeOH to yield white needles; yield=0.49 g (83%); R_f=0.26 (5% MeOH/$CHCl_3$); mp 121-122°C; ^{1}H NMR (DMSO-d_6): δ 1.59 (s, 3H, CH_3); 2.13 (m, 2H, H-2'); 2.49 (m, 1H, H-3'); 3.53 (m, 2H, H-3''); 4.10 (m, 1H, H-4'); 4.42 (dd, 1H, H-5'); 4.58 (dd, 1H, H-5'); 4.98 (t, 1H, D_2O exchangeable, $J_{3''\text{-}OH,3''}$=5.1 Hz, 3''-OH); 6.05 (dd, 1H, H-1'); 7.43 (s, 1H, H-6); 7.50-7.99 (complex, 5H, Bz); 11.29 (s, 1H, D_2O exchangeable, NH); *Anal.* Calc. for $C_{18}H_{20}N_2O_6$: C, 59.98; H, 5.60; N, 7.77. Found: C, 59.79; H, 5.73; N, 7.67.

1-[2,3-Dideoxy-3-hydroxymethyl-β-D-ribofuranosyl]thymine (**20**).

Compound **19** (0.12 g, 0.33 mmol) was dissolved in MeOH (dry, 4 mL) and heated to 60°C (external) and NaOMe (trace) was added. The solution was then stirred for 3 hours after which time the solution was cooled to 0°C and the solution was neutralized by addition of Dowex 50X8-100 (50-100 mesh, H^+ form). The resin was filtered and the filtrate reduced to a syrup that was triturated with $CHCl_3$ (2 x 2mL). The residue was subjected to low-bar chromatography (25 mL/min) and eluted with 10% MeOH/$CHCl_3$.

Fractions (25 mL) were obtained and evaporation of fractions 8-12 yielded a syrup that was crystallized from Et_2O/MeOH to yield white needles; yield=0.029 g (34%); R_f=0.16 (10% MeOH/$CHCl_3$); mp 130-131°C; ^1H NMR (DMSO-d_6): δ 1.16 (s, 3H, CH_3); 1.98 (m, 1H, H-2'a); 2.12 (m, 1H, H-2'b); 2.34 (hex, 1H, H-3'); 3.42 (m, 2H, H-3''); 3.55 (m, 1H, H-5'a); 3.68 (m, 1H, H-5'b); 3.76 (m, 1H, H-4'); 4.76 (t, 1H, D_2O exchangeable, 3''-OH); 5.04 (t, 1H, D_2O exchangeable, 5'-OH); 5.96 (dd, 1H, H-1'); 7.83 (s, 1H, H-6); 11.23 (bs, 1H, D_2O exchangeable, NH). UV λ_{max} nm (ε): pH 1, 268(9200); pH 7, 267(8400); pH 11, 267(7500); MS (DCI with NH_3): m/e 257 (M+H, 23%), 131 (sugar, 100%); *Anal.* Calc. for $C_{11}H_{16}N_2O_5$: C, 51.55; H, 6.31; N, 10.93. Found: C, 51.66; H, 6.33; N, 11.04.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs. Rae L. Herrst for her expert preparation of this manuscript. This research was supported by funds from the Department of Health and Human Services research grant number NO1-AI-25739 and the National Institutes of Health Training grant number 5-T32-GM-07767.

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Received 7/29/91
Accepted 11/25/91