# Stereoselectivity in the Synthesis of 3′-Deoxy-3′-*C*-(hydroxymethyl)uridines by Hydroboration and Conversion into a Building Block for Various 3′-Deoxy-3′-*C*-(methylene)uridine Analogues

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The stereoselectivity in hydroboration of 3′-deoxy-3′-*C*-(methylene)uridine derivatives has been studied. Hydroboration of 3′-deoxy-3′-*C*-(methylene)uridine derivatives gave two 3′-deoxy-3′-*C*-hydroxymethyl stereoisomers (with *ribo* or *xylo* configuration). The influence of reagent ($BH_3$·$Me_2S$, or 9-borabicyclo[3.3.1]nonane (9-BBN-H)) and solvent (THF, toluene, or hexane) was investigated. Use of $BH_3$·$Me_2S$ gave the *xylo* isomer as the main product. The highest preference for the *ribo* isomer was obtained by use of 9-BBN-H in hexane. Furthermore, 4-methoxytrityl protection of the hydroxy function at the 5′-position resulted in better stereoselectivity than that obtained by *tert*-butyldimethylsilyl protection, when 9-BBN-H was used as reagent. At best, hydroboration of 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-methylene-5-*O*-(4-methoxytrityl)-β-D-*erythro*-pentofuranosyl]uracil (**3b**) using 9-BBN-H in hexane gave a *ribo* to *xylo* (**4b** to **5b**) isomer ratio of 82:18. The *ribo* isomer was converted into the corresponding mesylate **6** to allow for further functionalization. Subsequent substitution with azide and reduction afforded 1-[3-*C*-aminomethyl-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-5-*O*-(4-methoxytrityl)-β-D-*ribo*-pentofuranosyl]uracil (**8**) in good overall yield (43% over 6 steps).

## Introduction

Antisense oligonucleotides are oligonucleotide analogues typically intended to bind to RNA (such as a mRNA of a disease-related protein) in a sequence-specific fashion through Watson−Crick base-pairing, to suppress gene expression.[1,2,3] In the design of antisense oligonucleotides with good pharmacological properties, several aspects have to be considered. Two important properties are resistance to degradation by nucleases and high hybridization affinity towards complementary RNA. From a general point of view, RNA:RNA duplexes, which give rise to a helix of A-type, are thermodynamically more stable than DNA:RNA duplexes. Hence, a more stable duplex is in general obtained if the antisense oligonucleotides are of RNA type. The first generation antisense oligonucleotides were, however, of the DNA type, in the form of phosphorothioate oligodeoxyribonucleotides.[1−7]

In order to increase duplex stability, conformational preorganisation in a single-stranded antisense oligonucleotide can be achieved through structural modification. One approach is to introduce a modification into the furanose moieties. The gauche-effect from an electronegative group at the 2′-position has been shown to shift the conformational equilibrium toward the North conformers (largely 3′-*endo*),[8,9] which in general results in oligonucleotide analogues with increased hybridization affinity towards complementary RNA.[10,11] Recent studies of oligonucleotide analogues containing 3′-*N*-modified (phosphoramidates[12,13]) and 3′-*C*-branched internucleoside linkages [amide linkages[14−19] or methylene methylimino (MMI) linkages[20,21]] have shown that they display enhanced binding to complementary RNA. Analysis of these modifications suggest that a substituent less electronegative than oxygen in the 3′-position gives a sugar conformation typical of A-type helixes.[12,16,22,23]

To the best of our knowledge, only a little work has been done with 3′-*C*-branched analogues with 2′-hydroxyl functions.[19] To investigate oligoribonucleotide analogues containing 3′-*C*-branched internucleoside linkages further, development of a convenient synthesis of a general building block capable of being converted into differently functionalized 3′-deoxy-3′-*C*-methylene ribonucleoside analogues would be valuable. In this paper, a novel method for preparation of a uridine analogue with its 3′-hydroxyl function replaced by a hydroxymethyl group and further conversion into the corresponding mesylate is presented. Furthermore, conversion into the corresponding aminomethyl analogue, which is a building block for synthesis of the 3′-*C*-branched internucleoside amide linkage, is described.

## Results and Discussion

Several synthetic strategies have been used in the past to introduce a hydroxymethyl group as a substitute for the 3′-hydroxyl function in deoxyribonucleosides[24−27] and ribonucleosides.[28] This paper evaluates a strategy involving introduction of the hydroxymethyl group by hydroboration of 3′-deoxy-3′-*C*-(methylene)uridine analogues. This strategy also provides for early introduction of appropriate protecting groups prior to synthesis of building blocks for oli-

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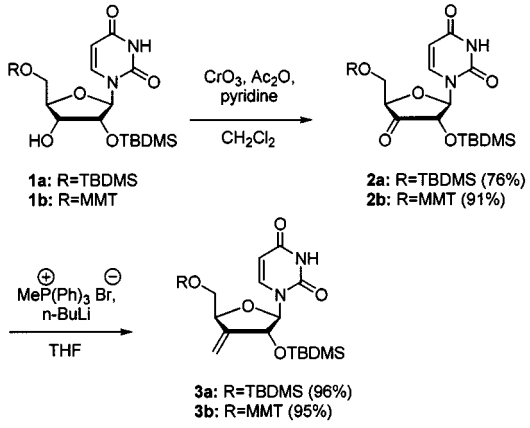
gomer synthesis: the 4-methoxytrityl (MMT) group for protection of the 5′-hydroxyl function and the *tert*-butyldimethylsilyl (TBDMS) group for protection of the 2′-hydroxyl function.

Stereoselectivity and yield of the hydroboration step were conceivable limiting features, due to the possibility of the formation of two stereoisomers with *ribo* or *xylo* pentofuranosyl configurations. Influences on stereoselectivity through the use of different boranes and solvents were investigated for the 5′-*O*-TBDMS-protected 3′-deoxy-3′-*C*-methylene derivative **3a**, with the goal of obtaining the *ribo* isomer in an adequate ratio over the *xylo* isomer. The best conditions were then used for hydroboration of the 5′-*O*-MMT-protected derivative **3b**.

In view of the fact that the stereoselectivity in hydroboration reactions can be directed by steric influences, we assumed that a large protecting group, such as the TBDMS group, for protection of the 2′-hydroxyl functions of **3a** and **3b** would increase the steric hindrance at the *Re* face, and consequently direct the borane reagent to the *Si* face. A disadvantage in the use of the TBDMS group or the MMT group for protection of the hydroxyl function at the 5′-positions of **3a** and **3b** is that a large group can reduce stereoselectivity by shielding the *Si* face. However, initial protection by the MMT group, which is commonly used in oligonucleotide synthesis, provides for a substantial advantage in the synthesis of building blocks.

Compounds **3a** and **3b** were prepared essentially according to the procedure of Samano et al.[29] Oxidation of the 2′,5′-*O*-protected uridines **1a** and **1b** (Scheme 1) gave **2a** and **2b** in yields of 76% and 91%, respectively. Wittig reactions were then carried out on **2a** and **2b**, using *n*-butyllithium and methyltriphenylphosphonium bromide in THF, to afford the corresponding 3′-deoxy-3′-*C*-methylene derivatives **3a** (96%) and **3b** (95%). It is worth mentioning that no less than equimolar amounts of base relative to phosphonium salt are preferred. When an excess of phosphonium salt was used, a polar side product was obtained; this did not decompose to give the 3′-deoxy-3′-*C*-methylene derivative, even upon heating. Similarly to results reported by Matsuda et al.,[30] the polar side product converted into **3a**/**3b** when treated with NaH, and is suggested to be the corresponding 3′-hydroxy-3′-*C*-methyltriphenylphosphonium salt.




Scheme 1

The influence of reagent and solvent on the stereoselectivity (Table 1) of the hydroboration step (Scheme 2) was investigated for **3a** using 9-borabicyclo[3.3.1]nonane (9-BBN-H) and $BH_3{\cdot}Me_2S$ in THF, toluene, or hexane. Subsequent oxidative treatment was carried out using $NaBO_3{\cdot}4H_2O$, since the use of $H_2O_2$ in alkaline solution caused side reactions, in particular the loss of TBDMS protecting groups. The use of $H_2O_2$ as oxidizing agent also gave an unidentified, UV-inactive side product. However, this problem was negligible when $NaBO_3{\cdot}4H_2O$ was used. Oxidative treatment with $NaBO_3{\cdot}4H_2O$ was complete within 30 hours; after longer reaction times partial loss of the TBDMS groups was observed. This problem was most noticeable with the primary TBDMS group.

Hydroboration of the 5′-*O*-TBDMS-protected derivative **3a** using $BH_3{\cdot}Me_2S$ in THF, toluene, or hexane gave the *xylo* isomer **5a** as the main product (entries 1−3). On the other hand, treatment with 9-BBN-H gave a considerably higher proportion of the *ribo* isomer **4a**. Furthermore, when 9-BBN-H was used as reagent, a solvent effect was observed on changing from THF to toluene or hexane (entries 4−6). A less polar solvent favored the formation of isomer **4a**. In conclusion, then, 9-BBN-H in hexane was the best combination in the synthesis of the *ribo* isomer; **4a** and **5a** were obtained in a ratio of 61:39 (entry 6). The desired product **4a** was isolated by silica gel chromatography in a yield of 35%.

Hydroboration of the 5′-*O*-MMT-protected derivative **3b**, using 9-BBN-H in hexane and subsequent oxidative treatment with $NaBO_3{\cdot}4H_2O$, resulted in further improved stereoselectivity; isomers **4b** and **5b** were obtained in a ratio of 82:18 (entry 8). The *ribo* isomer **4b** was isolated by silica gel chromatography in a yield of 64%. The configurations of isomers **4a/4b** and **5a/5b** were established by rotating-frame Overhauser effect spectroscopy (ROESY) experiments. Selected ROE contacts are outlined in Figure 1.

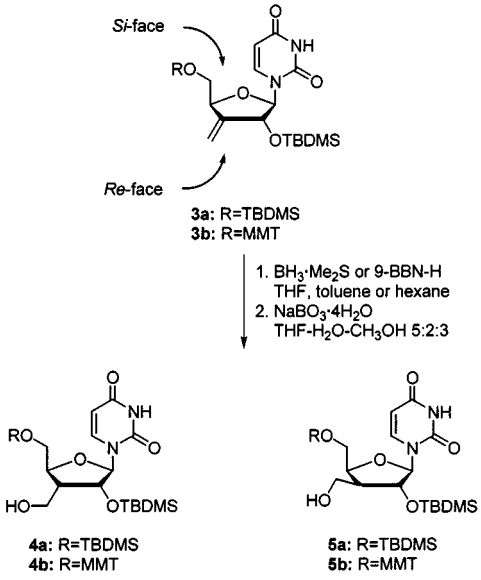
A comparison of the results from hydroboration of **3a** and **3b** using 9-BBN-H in THF or hexane suggests that even switching between two relatively large protecting groups for the hydroxyl function at the 5′-position has a significant effect on the stereoselectivity (entry 4 vs.7 and entry 6 vs. 8). A relatively small 5′-*O*-protecting group might then be expected to improve the selectivity even further. However, as stated earlier, this would imply a strategy with extra protection and deprotection steps, which would be less desirable overall.

Conversion of the hydroxyl function in **4b** into a leaving group enables further functionalization to be achieved through substitution. Different nucleophiles can be used in order to obtain building blocks for various 3′-*C*-branched backbone modified oligoribonucleotides, such as amide-linked nucleosides etc. Treatment of **4b** with methanesulfonyl chloride gave the mesylate **6** in 88% yield. Treatment of **6** with lithium azide in DMF gave **7** (94%), and subsequent reduction of the azide using triphenylphosphane in

Table 1. Results from hydroboration of **3a** and **3b** with $BH_3{\cdot}Me_2S$ or 9-BBN-H in various solvents.

| Entry | Reaction of compound | Reagent | Reaction conditions | Ratio of *ribo* and *xylo* isomers[a] | Yield of the *ribo* isomer **4** (**a** or **b**)[b] |
|---|---|---|---|---|---|
| 1 | **3a** | $BH_3{\cdot}Me_2S$ | THF, 0 °C, 120 h. | 7:93 | 6% |
| 2 | **3a** | $BH_3{\cdot}Me_2S$ | Toluene, 0 °C, 120 h | 13:87 | 7% |
| 3 | **3a** | $BH_3{\cdot}Me_2S$ | Hexane, 0 °C, 120 h | 9:91 | 8% |
| 4 | **3a** | 9-BBN-H | THF, 20 °C, 20 h | 46:54 | 41% |
| 5 | **3a** | 9-BBN-H | Toluene, 20 °C, 20 h | 53:47 | 43% |
| 6 | **3a** | 9-BBN-H | Hexane, 20 °C, 20 h | 61:39 | 45% (35%)[c] |
| 7 | **3b** | 9-BBN-H | THF, 20 °C, 20 h | 75:25 | 63% |
| 8 | **3b** | 9-BBN-H | Hexane, 20 °C, 20 h | 82:18 | 71% (64%)[c] |

[a] Isomeric ratios of *ribo* and *xylo* isomers, established by $^1$H NMR experiments on crude product mixtures after oxidative treatment with $NaBO_3{\cdot}4H_2O$ and workup. – [b] Yield of the *ribo* isomer **4** (**a** or **b**), established by $^1$H NMR, taking traces of remaining starting material and side products into account. – [c] Isolated yield after purification by silica gel chromatography.




Scheme 2

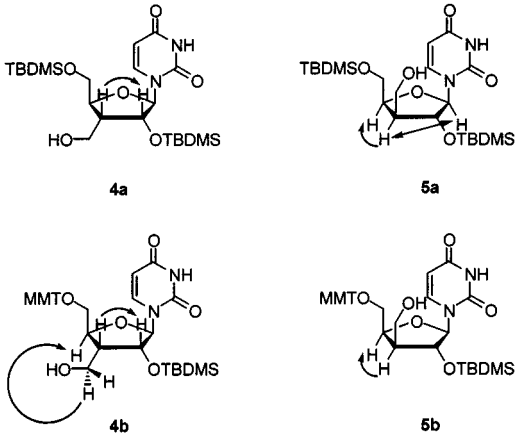
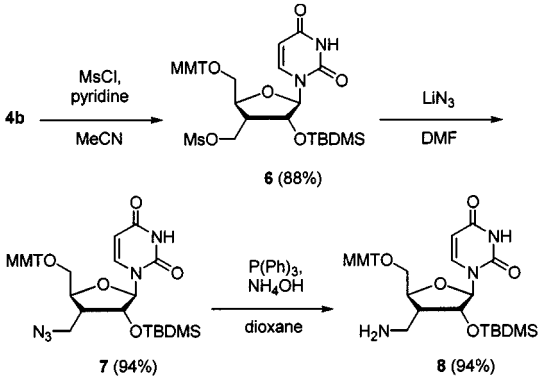



Figure 1. Informative ROE contacts observed for compounds **4a**, **4b**, **5a**, and **5b**, which confirms the total configurations.

dioxane and aqueous ammonia afforded the 3′-deoxy-3′-*C*-aminomethyl derivative **8** in a yield of 94% (Scheme 3). The overall yield of **8**, over 6 steps from **1b**, was a respectable 43%.




Scheme 3

## Conclusions

We have developed an efficient method, involving highly stereoselective hydroboration of 2′,5′-*O*-protected 3′-deoxy-3′-*C*-(methylene)uridine derivatives, for preparation of a uridine analogue with its 3′-hydroxyl function replaced by a hydroxymethyl group. A study of the stereoselectivity of the hydroboration showed that by changing to 9-BBN-H and a less polar solvent, the proportion of *ribo* isomer could be increased from 7 to 61%. A change in the 5′-protection further increased the proportion of *ribo* isomer to 82%. The overall method proved to be fully compatible with the standard protecting group strategy normally adopted in oligoribonucleotide synthesis, thus avoiding further protecting group manipulation. The synthesis of the hydroxymethyl analogue requires only three additional steps compared to that of a ribonucleoside bearing the same standard RNA synthesis protection, and it is produced in good yield. Conversion of the hydroxymethyl group of **4b** into the corresponding mesylate readily allowed further functionalization through substitution, and this derivative is therefore valuable as a general building block in the synthesis of various 3′-*C*-branched uridine analogues. As an example, substitution with azide and reduction afforded 3′-*C*-aminomethyl-3′-deoxy derivative **8**, part of the building block for amide-linked nucleotides, in good overall yield. Use of this strategy for synthesis of other 3′-*C*-branched nucleoside analogues,

and extension of the methodology for the other common ribonucleosides, is in progress.

## Experimental Section

**General Remarks and Methods:** NMR spectra were recorded using a Bruker AVANCE DRX 400 instrument (400.13 MHz in $^1$H and 100.62 MHz in $^{13}$C). Chemical shifts are given in ppm, downfield from external TMS. Most assignments in $^1$H and $^{13}$C NMR spectra were made by standard $^1$H-$^1$H-COSY and $^1$H-$^{13}$C-HMQC experiments; uridine numbering is used. ROESY experiments were carried out in $CD_3CN$ at 20 °C, using a mixing time of 250 ms. − Silica gel column chromatography was generally carried out using Matrex silica, 60Å (35−70 μm, Amicron). Isomeric mixtures were purified by column chromatography on silica gel 60 (40−63 μm, Merck). − TLC analysis was carried out on pre-coated 60 $F_{254}$ silica gel plates (Merck), with detection by UV light and/or by charring with 8% sulfuric acid in methanol. Solutions were concentrated under reduced pressure using temperatures not exceeding 40 °C, unless otherwise stated. Reagents and solvents were of ordinary commercial grade unless otherwise stated. THF was distilled at atmospheric pressure over $CaH_2$ prior to use. DMF was distilled over $CaH_2$ at reduced pressure and was stored over 4-Å molecular sieves. Acetonitrile (Labscan p.a.) and methanol were dried over 3-Å molecular sieves. Hexane, pyridine (Labscan p.a.), and $CH_2Cl_2$ were dried over 4-Å molecular sieves. Toluene was dried with and stored over sodium. 2′-*O*-(*tert*-Butyldimethylsilyl)-5′-*O*-(4-methoxytrityl)-uridine (**1b**) was synthesized essentially according to standard procedures.[31] $LiN_3$ was prepared as follows: a solution of $NaN_3$ (1.8 equiv.) in 0.16 M aqueous $Li_2SO_4$ (135 mL) was stirred at 40 °C until a clear solution was obtained. Ethanol (96%, 675 mL) was added dropwise. The mixture was filtered to remove the precipitate and the filtrate was concentrated. The residue was further dried by evaporation of added toluene, and was then dried over $P_2O_5$ at 40 °C in vacuum.

**1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-3-pentofuran-3-ulosyl]uracil (2a):** A solution of 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-uridine[32] (**1a**, 4.55 g, 9.63 mmol) in dry $CH_2Cl_2$ (60 mL) was added to a mixture of $CrO_3$ (4.33 g, 43.3 mmol, 4.5 equiv.), acetic anhydride (4.36 mL, 46.2 mmol, 4.8 equiv.), and dry pyridine (7.78 mL, 96.3 mmol, 10 equiv.) in dry $CH_2Cl_2$ (60 mL). The reaction mixture was stirred at room temperature for 40 minutes. Ethyl acetate (60 mL) was added with vigorous stirring. The mixture was filtered through silica gel (5 cm layer packed in a minimum volume of ethyl acetate), into saturated aqueous $NaHCO_3$ (150 mL), which gave a colorless filtrate. The silica gel was carefully washed with ethyl acetate (ca 300 mL) until no additional product could be observed by TLC analysis. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (150 mL). The organic layer was dried ($Na_2SO_4$) and concentrated (<25 °C to avoid depyrimidination). The residue was taken up in diethyl ether (10 mL) and was then triturated by addition of hexane (100 mL) to give **2a** (3.45 g, 76%): $R_f$ = 0.27 (toluene/ethyl acetate, 5:1, v/v); NMR spectroscopic data were in agreement with published data.[33]

**1-[2-*O*-(*tert*-Butyldimethylsilyl)-5-*O*-(4-methoxytrityl)-β-D-*erythro*-3-pentofuran-3-ulosyl]uracil (2b):** A mixture of $CrO_3$ (7.2 g, 72 mmol, 4.5 equiv.), $Ac_2O$ (7.26 mL, 76.9 mmol, 4.8 equiv.), and dry pyridine (12.93 mL, 160 mmol, 10 equiv.) in dry $CH_2Cl_2$ (100 mL) was cooled to 0 °C and a solution of 2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-(4-methoxytrityl)uridine (**1b**, 10.10 g, 16 mmol) in dry $CH_2Cl_2$ (100 mL) was added. The reaction mixture was stirred at 0 °C for 1 h. Ethyl acetate (100 mL) was added with vigorous stirring. The mixture was filtered through silica gel (6 cm layer packed in a minimum volume of ethyl acetate), into saturated aqueous $NaHCO_3$ (250 mL), which gave a colorless filtrate. The silica gel was carefully washed with ethyl acetate (ca 500 mL) until no remaining product could be observed by TLC analysis. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (250 mL). The organic layer was dried ($Na_2SO_4$), concentrated (< 25 °C to avoid depyrimidination). The residue was further dried by evaporation of added toluene, and was then purified by silica gel column chromatography (toluene/ethyl acetate, 2:1, v/v) to give crystalline **2b** (9.35 g, 91%): $R_f$ = 0.31 (toluene/ethyl acetate, 5:1, v/v). − $^1$H NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 9.25 (s, 1 H, NH), 7.62 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-6), 7.39−7.24 and 6.89 (14 H, MMT), 6.13 (d, $J_{1',2'}$ = 7.8 Hz, 1 H, H-1′), 5.59 (d, 1 H, H-5), 4.58 (d, 1 H, H-2′), 4.39 (m, 1 H, H-4′), 3.77 (s, 3 H, $OCH_3$), 3.48 (dd, $J_{5'a,5'b}$ = 10.8 Hz, $J_{4',5'a}$ = 3.7 Hz, 1 H, H-5′a), 3.30 (dd, $J_{4',5'b}$ = 2.0 Hz, 1 H, H-5′b), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.15 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$). − $^{13}$C NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 209.8 (C-3′), 163.6, 160.1, 151.7, 145.1, 144.9, 140.6 (C-6), 135.6, 131.4, 129.3, 129.2, 129.1, 128.5, 128.4, 114.4, 104.4 (C-5), 88.1, 86.5 (C-1′), 81.6 (C-4′), 77.3 (C-2′), 64.2 (C-5′), 56.1 ($OCH_3$), 25.9 [$SiC(CH_3)_3$], 19.0 [$SiC(CH_3)_3$], −4.33 ($SiCH_3$), −4.92 ($SiCH_3$).

**1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl]uracil (3a):** *n*-Butyllithium in hexane (2 M, 5.55 mL, 11.1 mmol, 3 equiv.) was added to a slurry of methyltriphenylphosphonium bromide (3.97 g, 11.1 mmol, 3 equiv.) in dry THF (20 mL). The mixture was stirred for 2 h and then cooled to 0 °C. A solution of **2a** (1.74 g, 3.7 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, and was then poured into saturated aqueous ammonium chloride (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with brine (100 mL). The combined water layers were washed with ethyl acetate (50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude product was purified by silica gel column chromatography (stepwise gradient of 10−20% v/v ethyl acetate in toluene) to give **3a** (1.66 g, 96%): $R_f$ = 0.33 (toluene/ethyl acetate, 5:1, v/v); NMR spectroscopic data were in agreement with published data.[29]

**1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-5-*O*-(4-methoxytrityl)-3-*C*-methylene-β-D-*erythro*-pentofuranosyl]uracil (3b):** *n*-Butyllithium in hexane (2 M, 21.2 mL, 42.4 mmol, 3 equiv.) was added to a slurry of methyltriphenylphosphonium bromide (15.13 g, 42.4 mmol, 3 equiv.) in dry THF (80 mL). The mixture was stirred for 2 h, and then cooled to 0 °C. A solution of compound **2b** (8.88 g, 14.12 mmol) in dry THF (80 mL) was added dropwise. The reaction mixture was stirred at room temperature for 20 h, and was then poured into saturated aqueous ammonium chloride (200 mL) and extracted with ethyl acetate (400 mL). The organic layer was washed with brine (200 mL). The combined water layers were washed with ethyl acetate (100 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude product was purified by silica gel column chromatography (stepwise gradient of 10−50% v/v ethyl acetate in toluene) to give **3b** (8.45 g, 95%): $R_f$ = 0.31 (toluene/ethyl acetate, 5:1, v/v). − $^1$H NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 9.16 (br. s, 1 H, NH), 7.68 (d, $J_{5,6}$ = 8.1 Hz, 1 H, H-6), 7.44−7.13, 6.89 (14 H, MMT), 5.79 (d, $J_{1',2'}$ = 6.9 Hz, 1 H, H-1′), 5.39 (d, 1 H, H-5), 5.33 (br. s, 1 H, 3′-$CH_2$), 5.21 (br. s, 1 H, 3′-$CH_2$), 4.84 (m, 1 H, H-2′), 4.74 (m, 1 H, H-4′), 3.78 (s, 3 H, $OCH_3$), 3.42 (dd, $J_{5'a,5'b}$ = 10.5 Hz, $J_{4',5'a}$ = 3.8 Hz, 1 H, H-5′a), 3.21 (dd, $J_{4',5'b}$ = 2.5 Hz, H-5′b), 0.91 [s, 9 H, $SiC(CH_3)_3$], 0.14 (s,

3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$). – $^{13}C$ NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 163.8, 160.0, 151.8, 148.4, 145.6, 145.2, 141.2 (C-6), 136.0, 131.5, 129.3, 129.08, 129.06, 128.80, 128.76, 128.29, 128.27, 114.3, 109.9 (3′-$CH_2$), 103.6 (C-5), 88.3 (C-1′), 87.9, 80.4 (C-4′), 77.1 (C-2′), 67.3 (C-5′), 56.1 ($OCH_3$), 26.1 [SiC($CH_3$)$_3$], 18.8 [Si*C*($CH_3$)$_3$], −4.36 ($SiCH_3$), −4.66 ($SiCH_3$). – $C_{36}H_{42}N_2O_6Si$: calcd. C 68.98, H 6.75, N 4.47; found C 68.82, H 6.67, N 4.42.

**1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-β-D-*ribo*-pentofuranosyl]uracil (4a):** A solution of compound **3a** (0.29 g, 0.62 mmol) in dry hexane (8 mL) was cooled to 0 °C, and 9-BBN-H (0.43 g, 3.71 mmol, 6 equiv.) was added. The reaction mixture was left on a melting ice-water bath, and was then stirred at 20 °C for 20 hours. The mixture was concentrated and the residue was dissolved in dry THF (8 mL). The solution was cooled to 0 °C, and methanol (3.2 mL) was added dropwise. When gas evolution had ceased, water (4.8 mL) was added, followed by $NaBO_3$·$4H_2O$ (2.33 g, 11.1 mmol, 24 equiv.). The ice-water bath was removed and the mixture was stirred vigorously at room temperature for 30 hours. The mixture was filtered to remove the precipitate. The filtrate was diluted with ethyl acetate (50 mL) and washed with brine (2× 25 mL). The organic layer was dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$/methanol, 98:2, v/v) to give the product as an isomeric mixture. The two isomers were separated by column chromatography on silica gel (30 g, Merck 40−63 μm) using a stepwise gradient of 5%-40% v/v ethyl acetate in toluene (the ethyl acetate concentration was increased by 5% v/v per 100 mL eluent), to give **4a** (106 mg, 35%) and **5a** (94 mg, 31%). **4a**: $R_f$ = 0.33 (hexane/ethyl acetate, 6:4, v/v). – $^1H$ NMR ($CDCl_3$, 20 °C, δ = 7.26): δ = 9.96 (s, 1 H, NH), 8.08 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-6), 5.88 (d, $J_{1',2'}$ = 1.1, 1 H, H-1′), 5.62 (d, 1 H, H-5), 4.39 (dd, $J_{2',3'}$ = 4.9 Hz, 1 H, H-2′), 4.25 (m, 1 H, H-4′), 4.07 (dd, $J_{5'a,5'b}$ = 11.6 Hz, $J_{4',5'a}$ = 2.3 Hz, 1 H, H-5′a), 3.83−3.72 (m, 3 H, H-5′b and C$H_2$OH), 2.39 (br. s, 1 H, $CH_2OH$), 2.32 (m, 1 H, H-3′), 0.90 [s, 9 H, SiC($CH_3$)$_3$], 0.88 [s, 9 H, SiC($CH_3$)$_3$], 0.19 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$). – $^{13}C$ NMR ($CDCl_3$, 20 °C, δ = 77.01): δ = 163.8 (C-4), 150.4 (C-2), 140.3 (C-6), 101.3 (C-5), 91.0 (C-1′), 82.8 (C-4′), 78.4 (C-2′), 62.6 (C-5′), 58.9 ($CH_2OH$), 43.1 (C-3′), 25.8 [SiC(*C*$H_3$)$_3$], 25.6 [SiC(*C*$H_3$)$_3$], 18.3 [Si*C*($CH_3$)$_3$], 17.9 [Si*C*($CH_3$)$_3$], −4.06, −5.00 and −5.08 (4 × $SiCH_3$). – $C_{22}H_{42}N_2O_6Si_2$: calcd. C 54.29, H 8.70, N 5.76; found C 54.29, H 8.84, N 5.70.

**1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-β-D-*xylo*-pentofuranosyl]uracil (5a):** $R_f$ = 0.28 (hexane/ethyl acetate, 6:4, v/v). – $^1H$ NMR ($CDCl_3$, 20 °C, δ = 7.26): δ = 9.62 (s, 1 H, NH), 7.74 (d, $J_{5,6}$ = 8.1 Hz, 1 H, H-6), 5.86 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1′), 5.71 (d, 1 H, H-5), 4.23 (m, 1 H, H-4′), 4.25 (t, 1 H, H-2′), 3.95 (dd, $J_{5'a,5'b}$ = 11.7 Hz, $J_{4',5'a}$ = 3.0 Hz, 1 H, H-5′a), 3.88−3.74 (m, 3 H, H-5′b and C$H_2$OH), 3.06 (dd, 1 H, $CH_2OH$), 2.59 (m, 1 H, H-3′), 0.92 [s, 9 H, SiC($CH_3$)$_3$], 0.82 [s, 9 H, SiC($CH_3$)$_3$], 0.124 (s, 3 H, $SiCH_3$), 0.116 (s, 3 H, $SiCH_3$), −0.01 (s, 3 H, $SiCH_3$), −0.10 (s, 3 H, $SiCH_3$). – $^{13}C$ NMR ($CDCl_3$, 20 °C, δ = 77.01): δ = 163.3 (C-4), 150.6 (C-2), 140.5 (C-6), 102.6 (C-5), 88.8 (C-1′), 78.8, 75.3, 62.9 (C-5′), 59.6 ($CH_2OH$), 49.7 (C-3′), 25.7 [SiC(*C*$H_3$)$_3$], 25.4 [SiC(*C*$H_3$)$_3$], 18.1 [Si*C*($CH_3$)$_3$], 17.6 [Si*C*($CH_3$)$_3$], −4.23, −4.27 and −4.93 (4× $SiCH_3$).

**1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-(4-methoxytrityl)-β-D-*ribo*-pentofuranosyl]uracil (4b):** A solution of compound **3b** (0.50 g, 0.798 mmol) in dry hexane (10 mL) was cooled to 0 °C, and 9-BBN-H (0.58 g, 4.79 mmol, 6 equiv.) was added. The reaction mixture was left on a melting ice-water bath, and was stirred at 20 °C for 20 hours. The mixture was concentrated and the residue was dissolved in dry THF (10 mL). The solution was cooled to 0 °C, and methanol (4 mL) was added dropwise. When gas evolution had ceased, water (6 mL) was added, followed by $NaBO_3$·$4H_2O$ (2.91 g, 18.9 mmol, 24 equiv.). The ice-water bath was removed and the mixture was stirred vigorously at room temperature for 30 hours. The mixture was filtered to remove the precipitate. The filtrate was diluted with ethyl acetate (50 mL) and washed with brine (2× 25 mL). The organic layer was dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$/methanol, 98:2, v/v, containing 0.1% v/v triethylamine) to give the product as an isomeric mixture. The two isomers were separated by column chromatography on silica gel (30 g, Merck 40−63 μm) using a stepwise gradient of 0−3% (v/v) acetone in $CHCl_3$ containing 0.8± 0.2% v/v ethanol and 0.1% v/v triethylamine (the acetone concentration was increased by 0.5% v/v per 100 mL eluent), to give **4b** (330 mg, 64%) and **5b** (81 mg, 16%). **4b**: $R_f$ = 0.14 (acetone/$CHCl_3$ containing 0.8± 0.2% v/v ethanol, 5:95 v/v). – $^1H$ NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 8.88 (s, 1 H, NH), 7.90 (d, $J_{5,6}$ = 8.1 Hz, 1 H, H-6), 7.48−7.26 and 6.90 (14 H, MMT), 5.63 (d, $J_{1',2'}$ = 1.5 Hz, 1 H, H-1′), 5.12 (dd, 1 H, H-5), 4.44 (dd, $J_{2',3'}$ = 4.8 Hz, 1 H, H-2′), 4.14 (m, 1 H, H-4′), 3.78 (s, 3 H, $OCH_3$), 3.69 (m, 1 H, C$H_2$OH), 3.53 (m, 1 H, C$H_2$OH), 3.47 (dd, $J_{5'a,5'b}$ = 2.2, Hz, $J_{4',5'a}$ = 11.2 Hz, 1 H, H-5′a), 3.40 (dd, $J_{4',5'b}$ = 3.7 Hz, 1 H, H-5′b), 2.71 (t, 1 H, $CH_2OH$), 2.45 (m, 1 H, H-3′), 0.90 [s, 9 H, SiC($CH_3$)$_3$], 0.17 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$). – $^{13}C$ NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 164.3, 160.0, 151.5, 145.6, 145.3, 141.5 (C-6), 136.1, 131.6, 129.5, 129.1, 128.3, 114.3, 101.9 (C-5), 92.4 (C-1′), 88.0, 83.1 (C-4′), 78.5 (C-2′), 64.3 (C-5′), 59.1 ($CH_2OH$), 56.1 ($OCH_3$), 45.4 (C-3′), 26.3 [SiC(*C*$H_3$)$_3$], 18.8 [Si*C*($CH_3$)$_3$], −4.26 ($SiCH_3$), −5.07 ($SiCH_3$). – $C_{36}H_{44}N_2O_7Si$: calcd. C 67.05, H 6.88, N 4.34; found C 66.93, H 6.77, N 4.32.

**1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-(4-methoxytrityl)-β-D-*xylo*-pentofuranosyl]uracil (5b):** $R_f$ = 0.18 (acetone/$CHCl_3$ containing 0.8± 0.2% v/v ethanol, 5:95 v/v). – $^1H$ NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 9.00 (s, 1 H, NH), 7.55 (d, $J_{5,6}$ = 8.1 Hz, 1 H, H-6), 7.44−7.24 and 6.89 (14 H, MMT), 5.74 (d, $J_{1',2'}$ = 5.3 Hz, 1 H, H-1′), 5.32 (dd, 1 H, H-5), 4.43 (m, 1 H, H-4′), 4.25 (m, 1 H, H-2′), 3.78 (s, 3 H, $OCH_3$), 3.60 (m, 1 H, C$H_2$OH), 3.52 (m, 1 H, C$H_2$OH), 3.42−3.41 (ABX, 2 H, H-5′a and b), 2.80 (t, 1 H, $CH_2OH$), 2.47 (m, 1 H, H-3′), 0.86 [s, 9 H, SiC($CH_3$)$_3$], 0.07 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$). – $^{13}C$ NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 163.8, 160.0, 151.8, 145.4, 145.3, 141.5 (C-6), 136.1, 131.6, 129.5, 129.1, 128.3, 114.3, 102.9 (C-5), 90.6 (C-1′), 88.3, 79.8 (C-4′), 77.2 (C-2′), 64.4 (C-5′), 59.9 ($CH_2OH$), 56.1 ($OCH_3$), 50.7 (C-3′), 26.0 [SiC(*C*$H_3$)$_3$], 18.5 [Si*C*($CH_3$)$_3$], −4.46 ($SiCH_3$), −4.47 ($SiCH_3$).

**1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-*C*-methanesulfomethyl-5-*O*-(4-methoxytrityl)-β-D-*ribo*-pentofuranosyl]uracil (6):** Compound **4b** (130 mg, 0.20 mmol) was dissolved in dry acetonitrile/pyridine, 9:1 (2 mL) and the solution was cooled to 0 °C. Methanesulfonyl chloride (18.6 μL, 0.24 mmol, 1.2 equiv.) was added. The ice-water bath was removed and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was partitioned between $CH_2Cl_2$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The water layer was washed with $CH_2Cl_2$ (20 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. The residue was further dried by evaporation of added toluene. The crude product was purified by silica gel column chromatography (toluene/ethyl acetate, 2:1 v/v), to give crystalline **6** (128 mg, 88%): $R_f$ = 0.08 (toluene/ethyl acetate, 5:1, v/v). – $^1H$ NMR ($CD_3CN$, 20 °C, δ =

1.94): δ = 9.66 (s, 1 H, NH), 7.86 (d, $J_{5,6}$ = 8.1, 1 H, H-6), 7.47−7.26 and 6.90 (14 H, MMT), 5.64 (d, $J_{1',2'}$ = 0.9 Hz, 1 H, H-1′), 5.14 (d, 1 H, H-5), 4.53 (dd, $J_{2',3'}$ = 4.9 Hz, 1 H, H-2′), 4.37 (dd, $J$ = 7.0, $^2J$ = 10.1 Hz, 1 H, C$H_2$OMs), 4.23 (dd, $J$ = 6.3, $^2J$ = 10.1 Hz, 1 H, C$H_2$OMs), 4.20 (m, 1 H, H-4′), 3.78 (s, 3 H, $OCH_3$), 3.49 (dd, $J_{5'a,5'b}$ = 11.3 Hz, $J_{5'a,4'}$ = 2.3 Hz, 1 H, H-5′a), 3.43 (dd, $J_{5'b,4'}$ = 3.5 Hz, 1 H, H-5′b), 2.98 [s, 3 H, $CH_3S(O)_2O$], 2.80 (m, 1 H, H-3′), 0.91 [s, 9 H, SiC$(CH_3)_3$], 0.19 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$). − $^{13}$C NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 164.2, 160.1, 151.6, 145.5, 145.2, 141.4 (C-6), 135.9, 131.7, 129.5, 129.2, 129.1, 128.8, 114.4, 102.1 (C-5), 92.4 (C-1′), 88.1, 82.4 (C-4′), 80.0 (C-2′), 67.7 (*C*$H_2$OMs), 63.8 (C-5′), 56.1 ($OCH_3$), 42.9 (C-3′), 37.8 [$CH_3S(O)_2O$], 26.3 [SiC(*C*$H_3)_3$], 18.8 [Si*C*$(CH_3)_3$], −4.12 ($SiCH_3$), −5.10 ($SiCH_3$). − $C_{37}H_{46}N_2O_9SSi$: calcd. C 61.47, H 6.41, N 3.88, S 4.44; found C 61.58, H 6.58, N 3.77, S 4.56.

**1-[3-*C*-Azidomethyl-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-5-*O*-(4-methoxytrityl)-β-D-*ribo*-pentofuranosyl]uracil (7):** Compound **6** (25 mg, 0.035 mmol) was dissolved in dry DMF (1 mL). $LiN_3$ (10.1 mg, 0.207 mmol, 6 equiv.) was added and the reaction mixture was stirred at 60 °C for 20 hours. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with water (2× 15 mL) and brine (15 mL). The organic layer was dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel column chromatography (stepwise gradient of 0−35% v/v ethyl acetate in toluene) to give **7** (22 mg, 94%): $R_f$ = 0.29 (toluene/ethyl acetate, 5:1, v/v). − $^1$H NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 9.09 (s, 1 H, NH), 7.92 (d, $J_{5,6}$ = 8.1, 1 H, H-6), 7.47−7.26 and 6.90 (14 H, MMT), 5.62 (br. s, 1 H, 1 H, H-1′), 5.17 (d, 1 H, H-5), 4.44 (d, $J_{2',3'}$ = 4.6 Hz, 1 H, H-2′), 4.08 (m, 1 H, H-4′), 3.78 (s, 3 H, $OCH_3$), 3.57 (dd, $J_{5'a,5'b}$ = 11.5 Hz, $J_{5'a,4'}$ = 1.8 Hz, 1 H, H-5′a), 3.52 (dd, $^3J$ = 7.9, $^2J$ = 12.4 Hz, 1 H, $CH_2N_3$), 3.37 (dd, $J_{5'b,4'}$ = 3.4 Hz, H-5′b), 3.22 (dd, $^3J$ = 6.2, $^2J$ = 12.4 Hz, 1 H, $CH_2N_3$), 2.52 (m, 1 H, H-3′), 0.90 [s, 9 H, SiC$(CH_3)_3$], 0.19 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$). − $^{13}$C NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 164.3, 160.0, 151.5, 145.4, 145.2, 141.4 (C-6), 135.9, 131.6, 129.5, 129.4, 129.1, 128.3, 114.3, 102.0 (C-5), 92.4 (C-1′), 88.1, 83.1 (C-4′), 78.2 (C-2′), 63.4 (C-5′), 56.1 ($OCH_3$), 48.6 ($CH_2N_3$), 42.5 (C-3′), 26.3 [SiC(*C*$H_3)_3$], 18.8 [Si*C*$(CH_3)_3$], −4.09 ($SiCH_3$), −5.16 ($SiCH_3$).

**1-[3-*C*-Aminomethyl-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-5-*O*-(4-methoxytrityl)-β-D-*ribo*-pentofuranosyl]uracil (8):** Compound **7** (21.5 mg, 0.032 mmol) was dissolved in dioxane (0.3 mL). Triphenylphosphane (18 mg, 0.069 mmol, 2 equiv.) and 32% aqueous ammonia (0.24 mL) were added, and the mixture was stirred for 10 hours. The reaction mixture was concentrated, and traces of water were removed by lyophilization. The residue was purified by silica gel column chromatography (stepwise gradient of 0−10% v/v methanol in $CHCl_3$ containing 0.5% v/v triethylamine) to give **8** (19 mg, 94%): $R_f$ = 0.47 ($CHCl_3$/methanol, 9:1, v/v, containing 0.5% v/v $Et_3N$). − $^1$H NMR ($CD_3CN$, 20 °C, δ = 1.94): δ = 7.98 (d, $J_{5,6}$ = 8.1, 1 H, H-6), 7.48−7.27 and 6.90 (14 H, MMT), 5.60 (br. s, 1 H, H-1′), 5.14 (d, 1 H, H-5), 4.44 (d, $J_{2',3'}$ = 4.4 Hz, 1 H, H-2′), 4.05 (m, 1 H, H-4′), 3.77 (s, 3 H, $OCH_3$), 3.51 (dd, $J_{5'a,5'b}$ = 11.3 Hz, $J_{5'a,4'}$ = 2.0 Hz, 1 H, H-5′a), 3.37 (dd, $J_{5'b,4'}$ = 3.5 Hz, 1 H, H-5′b), 2.79 (dd, $^3J$ = 8.5, $^2J$ = 12.5 Hz, 1 H, C$H_2NH_2$), 2.55 (dd, $^3J$ = 5.1, $^2J$ = 12.5 Hz, 1 H, C$H_2NH_2$), 2.30 (m, 1 H, H-3′), 0.89 [s, 9 H, SiC$(CH_3)_3$], 0.20 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$). − $^{13}$C NMR ($CD_3CN$, 20 °C, δ = 118.41 and 1.40): δ = 164.4, 159.9, 151.5, 145.5, 145.3, 141.4 (C-6), 136.0, 131.6, 129.5, 129.4, 129.1, 129.0, 128.2, 114.2, 101.7 (C-5), 92.2 (C-1′), 88.0, 83.4 (C-4′), 78.2 (C-2′), 63.7 (C-5′), 56.0 ($OCH_3$), 45.8 (C-3′), 38.4 ($CH_2NH_2$), 26.2 [SiC(*C*$H_3)_3$], 18.8 [Si*C*$(CH_3)_3$], −4.00 ($SiCH_3$), −5.07 ($SiCH_3$). − $C_{36}H_{45}N_3O_6Si$: calcd. C 67.16, H 7.04, N 6.53; found C 66.72, H 7.19, N 6.35.

**Experimental Procedure for the Determination of the Stereoselectivity in Hydroboration of 3a and 3b with Different Reagents ($BH_3$·$Me_2S$ or 9-BBN-H) in Various Solvents (THF, toluene, or hexane):** Test reactions for hydroboration by $BH_3$·$Me_2S$ (3 equiv.) were carried out on a 43 μmol scale (of **3a**) in 0.51 mL of THF, toluene, and hexane. The reaction mixtures were kept at 0 °C for 120 h. Test reactions for hydroboration by 9-BBN-H (6 equiv.) were carried out on a 43 μ mol scale of the 1-[2,5-*O*-protected 3-deoxy-3-*C*-methylene-β-D-*erythro*-pentofuranosyl]uracil derivatives (**3a** and **3b**) in 0.51 mL THF, toluene, and hexane. The reaction mixtures were stirred at 20 °C for 20 h. All reaction mixtures were concentrated. Subsequent oxidative treatments of the reactions with $NaBO_3$·$4H_2O$ (18 equiv.) in 1.2 mL THF/methanol/$H_2O$ (5:2:3 v/v). The mixtures were stirred vigorously for 30 h at 20 °C, and were then centrifuged. The supernatant was removed, diluted with ethyl acetate, extracted with brine, and the organic layers were then concentrated. The residues were further dried by evaporation of added acetonitrile, and were then analyzed by $^1$H NMR. Isomeric ratios were determined by integration of signals originating from H-6 in the respective isomers. The chemical shifts for H-6 of the products **4a**, **5a**, **4b**, and **5b** are given above.

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