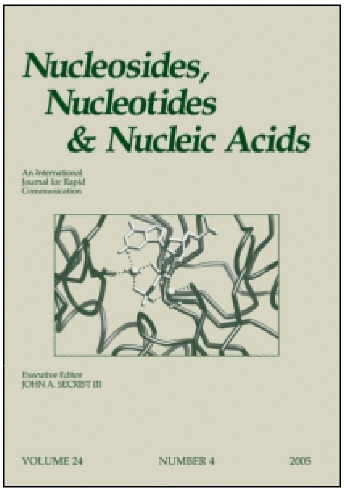

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Reinvestigation of the Synthesis of 1-Deazauridine

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REINVESTIGATION OF THE SYNTHESIS OF 1-DEAZAURIDINE

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□ *A thorough study for the synthesis of 1-deazauridine is described. 3-Bromo-2,6-dimethoxy-5-(β-D-ribofuranosyl)pyridine, a synthetic precursor for 1-deazauridine, was prepared in seven steps from 2,6-dimethoxypyridine and D-ribose via the ribonolactone approach. Subsequent demethylation was unsuccessful but led to presumable anomerization and isomerization. The effort concluded that the synthesis of 1-deazauridine remained unachieved.*

Keywords 1-deazauridine; *C*-nucleoside; D-ribonolactone; 2,6-dimethoxypyridine

INTRODUCTION

Pyridine *C*-nucleosides featuring a carbon-carbon glycosyl bond could be considered as 1-deaza analogs of naturally occurring pyrimidine *N*-nucleosides. They are comparatively more stable toward chemical and enzymatic hydrolysis than their pyrimidine *N*-nucleoside counterparts.[1–6] The structural resemblance and the intrinsic stability have made the pyridine *C*-nucleosides useful isosteres for investigating the interactions with biological targets.[7–11] As part of our research interest, we embarked on a study to investigate feasible synthetic routes for 1-deazauridine (**2**) and its derivatives as potential mechanistic probes for uridine-related enzymes.

RESULTS AND DISCUSSION

A review of the literature disclosed that the synthesis of 1-deazauridine (**2**) is a challenging task. The first attempt to synthesize 1-deazauridine (**2**) was reported by M. P. Mertes et al. in 1967, in which 3-(β-D-ribofuranosyl)-2,6-dibenzyloxypyridine was prepared by the direct condensation of bis (2,6-dibenzyloxypyrid-3-yl)cadmium with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl

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chloride followed by debenzoylation. Subsequent hydrogenolysis to remove the benzyl groups gave chemically unstable l-deazauridine (**2**). Mertes rationalized that the instability of 1-deazauridine (**2**) was attributed to spontaneous air-oxidation of the base to the corresponding 2,5,6-trihydroxypyri dine or azaquinone derivatives.[12]

Several 1-deazauridine analogs have also been reported in the literature, including 2,6-dihydroxy-5-phenyldiazo-3-D-ribopyranosylpyridine (**5**),[13] 5-(β-D-ribofuranosyl)-2,6-dihydroxynicotinamide (**6**),[14] (D-ribofuranosyl)glutarimides **3a** and **3b** (4,5-dihydro-1-deazauridines),[15,16] and (*E*)-3-(D-ribofuranosylidene)piperidine-2,6-dione (**4**).[17] (Figure 1) Some of the analogs were claimed to be unstable and, thus far, there is no confirmative synthesis of 1-deazauridine (**2**). It is noticeable that both Knackmuss's and Watanabe's examples possessed deactivating substituents at the 5-position of the base, the most nucleophilic site of the base, which might stabilize the 2,6-dihydroxypyridine nucleosides against air-oxidation.

These facts have prompted us to re-investigate an alternative synthetic route to 1-deazauridine derivatives. 5-Bromo-1-deazauridine (**7**) was selected as the target molecule. The bromo-substituent at 5-position (the most nucleophilic site) of 1-deazauridine (**2**) was anticipated to prevent 2,6-dihydroxypyridine from air-oxidation and could also be used for chemical manipulation afterwards. We opted to adopt the ribonolactone approach for the synthesis of 1-deazauridine derivatives,[18–20] whereas the addition of an organometallic heterocycle to a protected ribonolactone has been one of the most straightforward approaches for the synthesis of *C*-nucleosides.[21–25]

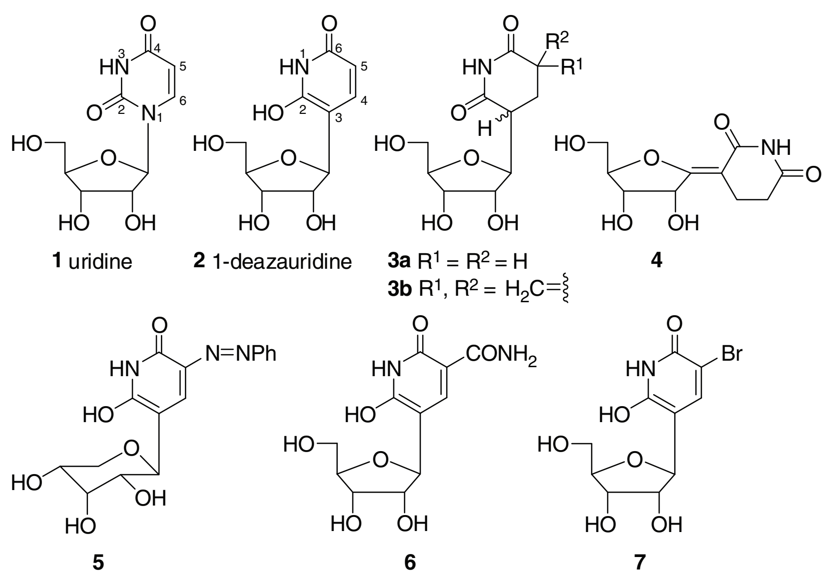
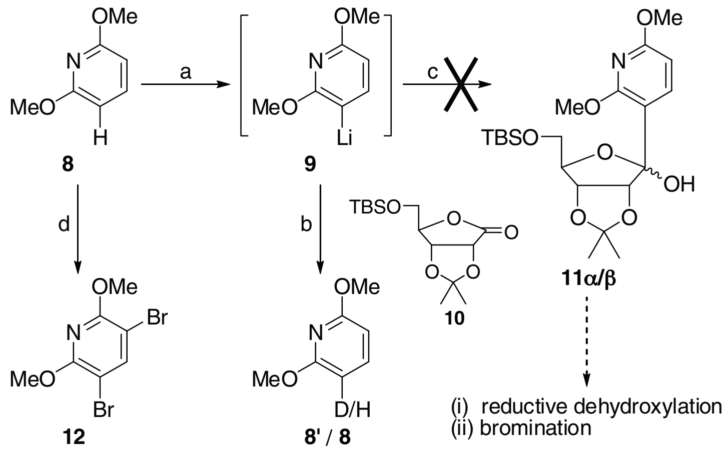


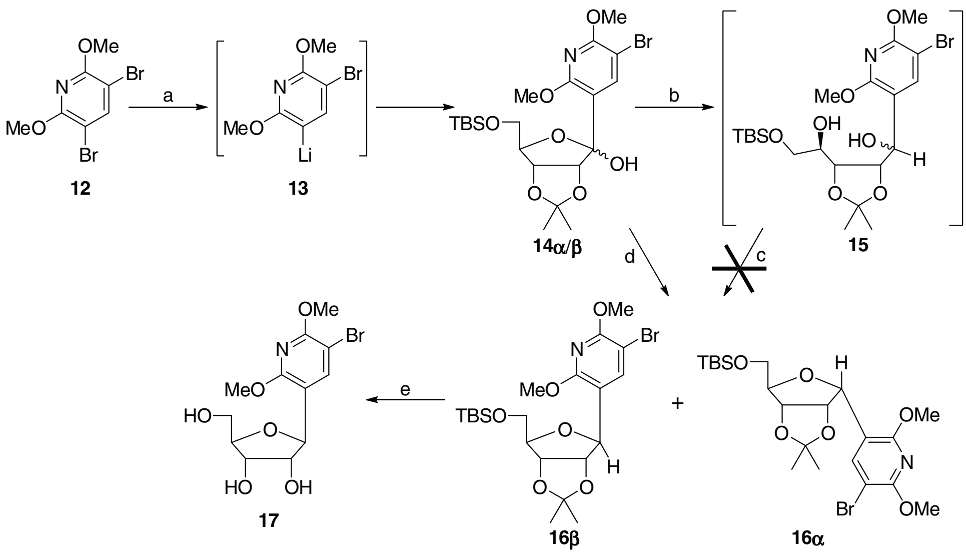
FIGURE 1 Uridine and synthetic 1-deazauridine analogs reported in the literature.



SCHEME 1 Direct lithiation and bromination of 2,6-dimethoxypyridine (**8**). *Reagents and conditions:* a) *n*-BuLi, THF, −78°C, 4 hours; b) D_2O, THF, 0°C ~ room temperature; c) 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (**10**), THF, 0°C ~ room temperature; d) Br_2, $CHCl_3$, room temperature, 4 hours, 80%.

Direct lithiation of 2,6-dimethoxypyridine (**8**) was achieved with *n*-butyllithium in THF at −78°C. The formation of the lithiated intermediate **9** was confirmed by quenching the reaction with D_2O to give 3-deutero-2,6-dimethoxypyridine (**8**′, 75–80%, based on the ^{1}H NMR integration). However, the addition of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-1,4-ribonolactone[26,27] (**10**) to the lithiated 2,6-dimethoxypyridine (**9**) did not yield the expected ribonolactol **11** (Scheme 1). Hence, 3,5-dibromo-2,6-dimethoxypyridine[12,28] (**12**) was prepared by dibromination of 2,6-dimethoxypyridine (**8**), and was subjected to the metal-halogen exchange with *n*-butyllithium in THF at −78°C. The resulting lithiated pyridine derivative **13** was treated with the protected ribono-1,4-lactone **10** to afford an anomeric mixture (in a ratio of 2.5 : 1 determined by ^{1}H NMR) of the ribonolactol **14**α/β in a good yield. Individual anomers could be separated by flash column chromatography, but the anomeric configuration remained undetermined. It is notable that, during the prolonged NMR experiments, gradual epimerization of the single anomeric ribonolactol **14** in solution was observed.

A literature survey on the reduction of the aryl ribonolactols suggested that two major approaches could be employed, including Wilcox's[18] and Watanabe's[19] reductive ring opening/reclosing approach and Czernecki's directly reductive dehydroxylation.[20] In our attempts to utilize an improved method by S. Hanessian et al.,[29] reductive ring-opening of ribonolactol **14** with K-selectride in the presence of zinc(II) chloride led to a diastereomeric mixture of diols **15**. Immediate ring-closure by Mitsunobu reaction, however, gave a complex result and the desired product was not observed (Scheme 2).



SCHEME 2 Synthesis of 3-bromo-2,6-dimethoxy-5-(*β*-D-ribofuranosyl) pyridine (**17**). *Reagents and conditions:* a) (i) *n*-BuLi, THF, −78°C, 30 minutes; (ii) 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribonolactone (**10**), THF, −78°C ~ room temperature, 2 hours, 73%; b) (i) $ZnCl_2$/ether, CH_2Cl_2, −78°C, 30 minutes; (ii) K-Selectride, THF, −78°C ~ room temperature; c) DIRD, PPh_3, THF; d) toluene, Et_3SiH, BF_3·OEt_2, −78 ~ 0°C, 2.5 hours, 56%; e) (i) TBAF, THF, room temperature, 1 hour; (ii) Dowex H^+, H_2O, 70°C, 1 hour, 35%.

Alternatively, the direct reductive dehydroxylation of ribonolactol **14** using triethylsilane in the presence of boron trifluoride etherate, an improved protocol by S. A. Benner et al.,[6] was then investigated. It is worth noting that, in the initial trials, the reduction gave approximately the same α/β ratio regardless of whether the ribonolactol **14** was purified as a single anomer or obtained as a mixture of anomeric diastereoisomers from the glycosylation step. Since the stereoselectivity of the glycosylation was lost during the reduction step, the anomeric mixture of **14** was subjected to the subsequent optimization study without further separation. Under the tested conditions, a mixture of α- and β-anomeric diastereoisomers (**16**α and **16**β) was obtained and the α-isomer (**16**α) always appeared to be predominant. (Table 1) The desired β-isomer (**16**β) was separated from the α-isomer (**16**α) by repeated flash column chromatography.

The structural elucidation of nucleosides **16**α and **16**β was carried out by intensive NMR studies including ^1H, ^{13}C, DEPT-135, COSY, HMQC, and NOESY experiments. The α-anomeric configuration of **16**α was established on the basis of the NOE correlation between H-1′ and H-5′ observed in 2D NOESY, whereas the β-isomer **16**β showed the NOE correlation between H-1′ and H-4′. Furthermore, the chemical shift differences ($\Delta\delta$) of two isopropylidene methyl groups in **16**α and **16**β are 0.11 (< 0.15) and 0.25 (> 0.15) ppm, which suggest the α- and β-anomeric configuration, respectively, based on Imbach's empirical rule.[30] These predictions are consistent with

TABLE 1 Optimization for the reductive dehydroxylation of **14**

Entry	Solvent	Et_3SiH (equiv.)	Lewis acid[a]	T (°C)	t (hour)	Yield[b]	α/β[c]
1	THF	10	$BF_3 \cdot Et_2O$	0	4.5	no reaction	
2	CH_2Cl_2	10	$BF_3 \cdot Et_2O$	0	4	27%	9.8/1
3	CH_2Cl_2/toluene (1 : 1, v/v)	10	$BF_3 \cdot Et_2O$	0	4	34%	7.9/1
4	toluene	3	$BF_3 \cdot Et_2O$	0	2.5	trace	
5	toluene	10	$BF_3 \cdot Et_2O$	−78 ~ 0	3.5	trace	
6	toluene	10	$BF_3 \cdot Et_2O$	−40 ~ 0	1	31%	1.9/1
7	toluene	10	$BF_3 \cdot Et_2O$	−40 ~ 0	2	46%	1.5/1
8	toluene	10	$BF_3 \cdot Et_2O$	−40 ~ 0	2.5	56%	1.25/1
9	toluene	10	$BF_3 \cdot Et_2O$	−40 ~ 0	3.3	45%	2.2/1

[a]1.2 equivalent of $BF_3 \cdot Et_2O$.
[b]Isolated yields; during the optimization process, the α- and β-anomers were isolated as a mixture.
[c]During the optimization process, the α/β ratio were determined by ^{1}H NMR.

the NOESY results and, therefore, the anomeric configurations of **16**α and **16**β were determined unambiguously (Figures 2 and 3).

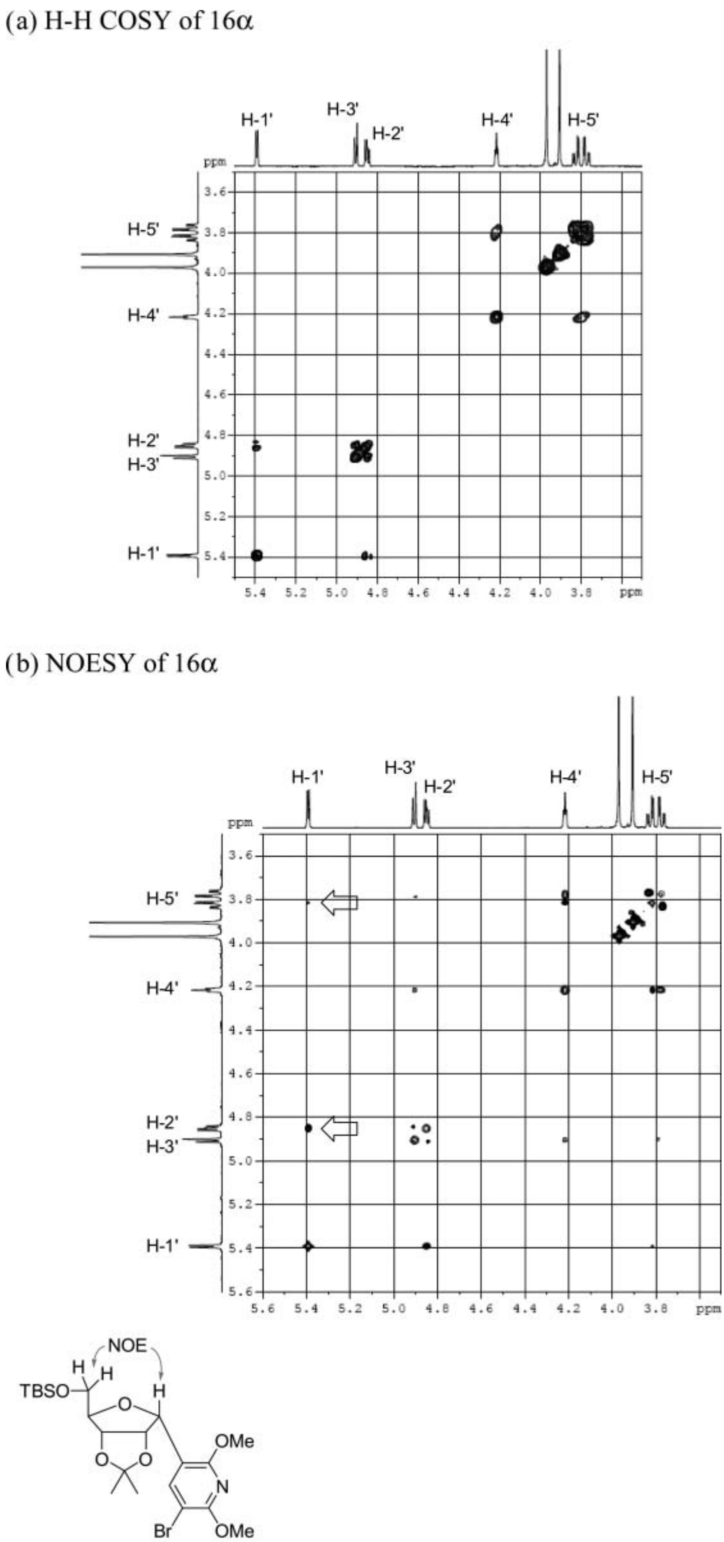
The *t*-butyldimethylsilyl (TBS) group of **16**β was deprotected by tetrabutylammonium fluoride (TBAF) in THF and the removal of isopropylidene group was accomplished by DOWEX H^+ resin in H_2O to give 3-bromo-2,6-dimethoxy-5-(β-D-ribofuranosyl)pyridine (**17**). Attempts to remove the methyl groups from the base with trimethylsilyl iodide or boron tribromide were unsuccessful but led to a mixture of several possible isomerized products. The demethylation was then monitored by mass spectrometry and ^{1}H NMR. The results indicated that no oxidation products were observed during the reaction. However, the isomerization/anomerization occurred prior to the demethylation, which resulted in several possible isomeric products (**7**, **17–21**) proposed in Scheme 3.

In conclusion, our efforts have shown that the instability of 1-deazauridine was due to the anomerization/isomerization caused by the keto -enol tautomerism of the base. Since many 3-(D-ribofuranosl)-2-pyridone derivatives have been previously synthesized and characterized,[2,4,31–36] including 1-deazacytidine,[2] we rationalized that the additional hydroxyl group at 6-position enhanced the tautomerism and, therefore, accelerated the anomerization and isomerization. Accordingly, the synthesis of 1-deazauridine (**2**) still remained unachieved.

EXPERIMENTAL

3-Bromo-2,6-dimethoxy-5-(5-*O*-*tert*-butyldimethylsilyl-1-hydroxy-2,3-*O*-isopropylidene-α/β-D-ribofuranosyl)pyridine (14α/β)

3,5-Dibromo-2,6-dimethoxypyridine[12,28] (**12**, 7.20 g, 24.0 mmol) was dissolved in anhydrous THF (70 mL) and the solution was stirred under an



16α

FIGURE 2 a) H-H COSY of 16α; b) NOESY of 16α.

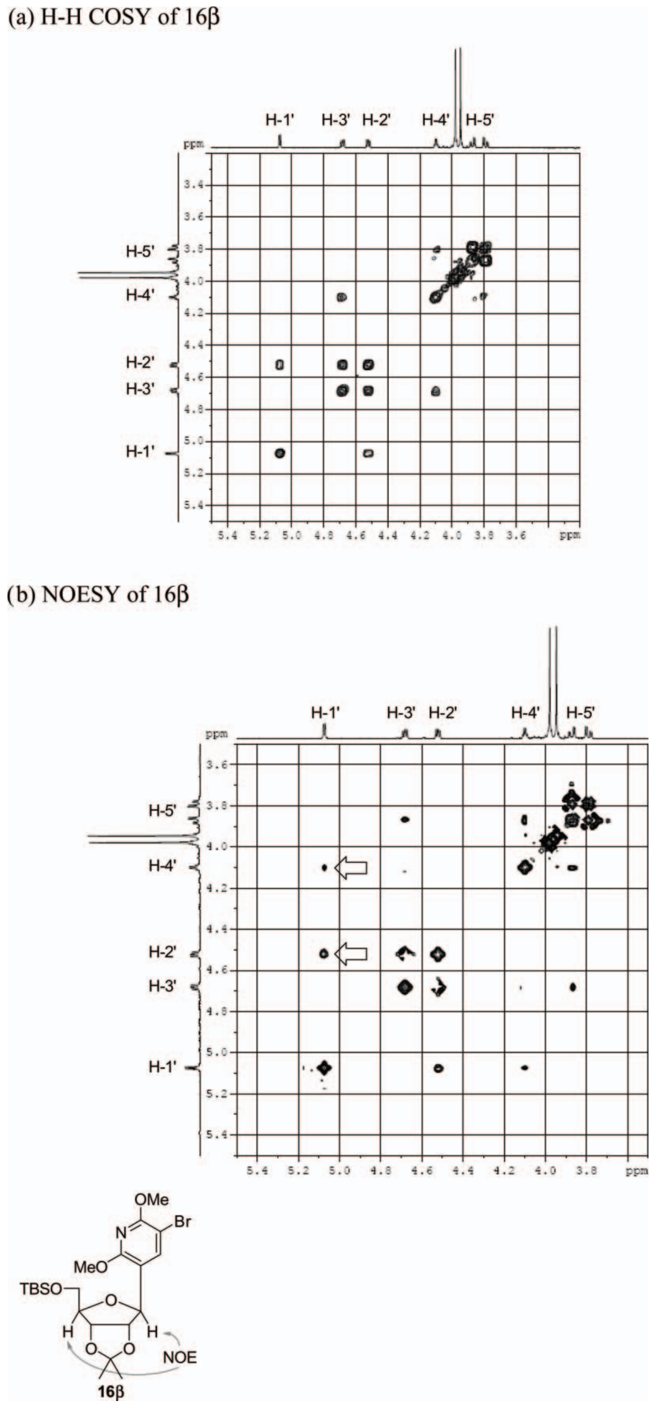
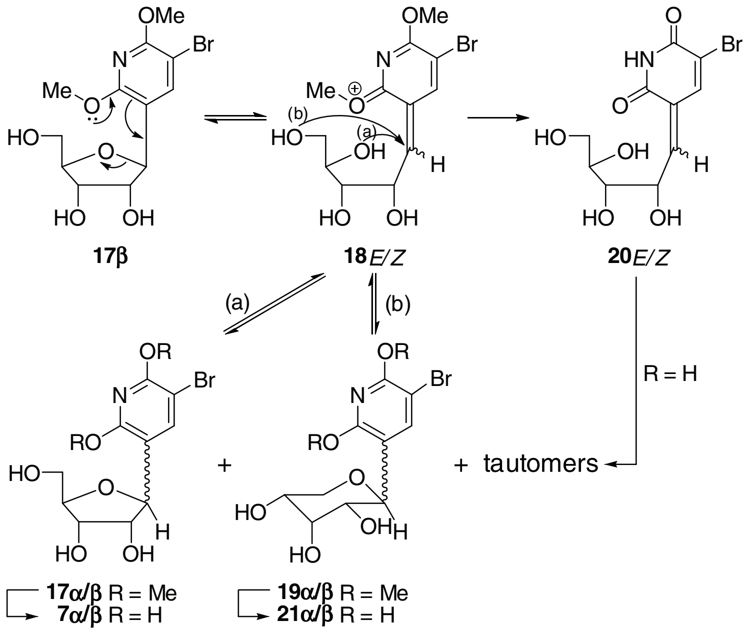


FIGURE 3 a) H-H COSY of 16β; (b) NOESY of 16β.



SCHEME 3 Proposed mechanism for the isomerization/anomerization during the demethylation of 3-bromo-2,6-dimethoxy-5-(β-D-ribofuranosyl) pyridine (**17**).

argon atmosphere at −78°C. *n*-Butyllithium (1.6 M, 18.0 mL, 28.8 mmol, 1.2 equiv.) was added to the solution and the reaction mixture was kept stirring for 30 minutes at the same temperature. To the reaction mixture was then added a solution of 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-1,4-ribonolactone[26,27] (**10**, 7.28 g, 24.0 mmol, 1 equiv.) in anhydrous THF (50 mL). The reaction mixture was stirred for an additional 2 hours while the temperature was allowed to raise to room temperature. H_2O (20 mL) was added to quench the reaction. The reaction mixture was extracted with EtOAc (100 mL) and the organic layer was washed with saturated NaCl solution (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 9 : 1, Rf = 0.16) to give a product mixture containing α/β anomers (**14**α/β, in a ratio of 2.5 : 1 approximately, determined by ^{1}H NMR) as light yellow oil (7.93 g, 15.2 mmol, 63%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 0.28 H), 8.03 (s, 0.72 H), 4.90 (d, 0.72 H), 4.87 (m, 1.44 H), 4.75 (m, 0.56 H), 4.72 (m, 0.28 H), 4.36 (m, 0.72 H), 4.28 (m, 0.28 H), 3.993 (s, 2.16 H), 3.990 (s, 2.16 H), 3.98 (s, 0.84 H), 3.95 (s, 0.84 H), 3.94–3.78 (m, 2 H), 1.65 (s, 0.84 H), 1.41 (s, 0.84 H), 1.27 (s, 2.16 H), 1.25 (s, 2.16 H), 0.94 (s, 6.48 H), 0.83 (s, 2.52 H), 0.15 (s, 2.16 H), 0.14 (s, 2.16 H), 0.05 (s, 0.84 H), 0.02 (s, 0.84 H).

The major anomer of 14 (14α): The major anomer was collected by recrystallization from Hex. Attempts to determine the anomeric configuration by NOE were unsuccessful. Thus, the anomeric configuration was assigned as α, based on Imbach's empirical rule[30] without spectroscopic support. m.p. 106–108°C (Hex); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (s, 1 H, H-4), 4.90 (d, 1 H, J = 5.8 Hz), 4.87 (d, 1 H, J = 4.9 Hz), 4.87 (s, 1 H, OH), 4.36 (m, 1 H), 3.993 (s, 3 H, OCH_3), 3.990 (s, 3 H, OCH_3), 3.88 (dd, 1 H, J = 4.0 and 10.9 Hz, H-5′), 3.82 (dd, 1 H, J = 3.0 and 10.9 Hz, H-5′), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 0.94 (s, 9 H, *t*-Bu), 0.15 (s, 3 H, CH_3), 0.14 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 158.0, 142.0 (CH), 115.4, 112.4, 105.5, 94.7, 87.6 (CH), 86.2 (CH), 81.9 (CH), 64.7 (CH_2), 54.3 (CH_3), 54.0 (CH_3), 26.7 (CH_3), 25.8 (3 × CH_3), 25.6 (CH_3), 18.4, −5.51 (2 × CH_3); MS (ES) m/z 502 (90, M–OH), 504 (100, M–OH + 2), 542 (19, M + Na), 544 (32, M + Na + 2); HRMS Calcd for $C_{21}H_{34}NO_7SiBr.Na$ (M + Na): 542.1186. Found: 542.1156; Anal. Calcd. for $C_{21}H_{34}NO_7SiBr$: C, 48.46; H, 6.58; N, 2.69. Found: C, 48.36; H, 6.71; N, 2.47.

3-Bromo-2,6-dimethoxy-5-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-α/β-D-ribofuranosyl)pyridine (16α/β)

Compound **14**α/β (0.51 g, 0.99 mmol) was dissolved in dry toluene (20 mL) and the solution was stirred under an argon atmosphere at −40°C. To the solution was added triethylsilane (1.6 mL, 1.15 g, 9.9 mmol, 10 equiv.), followed by boron trifluoride etherate (0.15 mL, 0.168 g, 1.18 mmol, 1.2 equiv.) and the reaction mixture was kept stirring for an additional 2 hours while the temperature was allowed to raise to 0°C. The reaction mixture was quenched at 0°C with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with saturated NaCl solution (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 9.7 : 0.3, Rf = 0.2, the α-anomer is slightly less polar than the β-anomer) to give compounds **16**α and **16**β (syrup, 0.23 g, 0.45 mmol, 45%).

α-**anomer (16**α**):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (s, 1 H, H-4), 5.39 (d, 1 H, J = 4.0 Hz, H-1′), 4.91 (d, 1 H, J = 6.0 Hz, H-3′), 4.85 (dd, 1 H, J = 4.1 & 5.9 Hz, H-2′), 4.22 (t, 1 H, J = 3.2 Hz, H-4′), 3.97 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.83 (dd, 1 H, J = 3.4 & 10.9 Hz, H-5′), 3.77 (dd, 1 H, J = 3.1 & 11.0 Hz, H-5′), 1.40 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 0.93 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, CH_3), 0.07 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 157.4, 142.6 (CH), 112.6, 112.1, 95.2, 83.7 (CH), 83.3 (CH), 81.5 (CH), 78.2 (CH), 65.3 (CH_2), 54.2 (CH_3), 53.5 (CH_3), 26.1 (CH_3), 25.8 (3 × CH_3), 24.8 (CH_3), 18.0, −5.68 (CH_3), −5.71 (CH_3); MS (ES) m/z 504 (70, M + 1), 506 (73, M + 3), 526 (93, M + Na), 528 (100, M + Na + 2); HRMS Calcd for $C_{21}H_{35}NO_6SiBr$ (M+1): 504.1417. Found: 504.1451.

β-anomer (16β): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (s, 1 H, H-4), 5.07 (d, 1 H, J = 4.2 Hz, H-1′), 4.68 (dd, 1 H, J = 6.4 and 4.4 Hz, H-3′), 4.52 (dd, 1 H, J = 6.4 and 4.2 Hz, H-2′), 4.10 (dd, 1 H, J = 3.7 and 7.5 Hz, H-4′), 3.98 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.87 (dd, 1 H, J = 3.2 and 11.2 Hz, H-5′), 3.79 (dd, 1 H, J = 3.8 and 11.2 Hz, H-5′), 1.60 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 0.91 (s, 9 H, *t*-Bu), 0.10 (s, 3 H, CH_3), 0.09 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 157.8, 141.5 (CH), 115.3, 113.9, 95.3, 86.3 (CH), 84.6 (CH), 81.2 (CH), 80.1 (CH), 63.2 (CH_2), 54.3 (CH_3), 53.8 (CH_3), 27.7 (CH_3), 26.0 (3 × CH_3), 25.7 (CH_3), 18.4, −5.3 (CH_3), −5.4 (CH_3); MS (ES) *m/z* 504 (46, M + 1), 506 (47, M + 3), 526 (92, M + Na), 528 (100, M + Na + 2); HRMS Calcd for $C_{21}H_{35}NO_6SiBr$ (M+1): 504.1417. Found: 504.1456.

3-Bromo-2,6-dimethoxy-5-(β-D-ribofuranosyl)pyridine (17)

To a solution of compound **16β** (0.59 g, 1.17 mmol) in THF (8 mL) at room temperature was added tetra-*n*-butylammonium fluoride (TBAF; 1 M solution in THF with approximately 5% of H_2O, 1.3 mL; containing 1.3 mmol of TBAF, 1.1 equiv.) and the solution was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was redissolved in H_2O (30 mL) and the aqueous solution was extracted with $CHCl_3$ (2 × 60 mL). The organic portions were combined and washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous Na_2SO_4, and the solvent was then evaporated under reduced pressure to give the crude product that was used without further purification. A mixture of the crude product and Dowex-H^+ 50W × 8 (2.30 g) in H_2O (6 mL) was stirred at 70°C for 1 hour. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (Hex/EtOAc = 3 : 7, Rf = 0.16) to give compound **17** (solid, 0.14 g, 0.40 mmol, 35%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.02 (s, 1 H, H-4), 4.94 (d, 1 H, J = 4.4 Hz, H-1′), 3.98 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.00–3.91 (m, 3 H, H-2′, H-3′ and H-4′), 3.85 (dd, 1 H, J = 2.9 and 12.0 Hz, H-5′), 3.72 (dd, 1 H, J = 4.4 and 12.0 Hz, H-5′); ^{13}C & DEPT135 NMR ($CDCl_3$, 100 MHz) δ 160.3, 159.3, 143.1 (CH), 116.9, 96.2, 85.0 (CH), 80.8 (CH), 77.7 (CH), 72.3 (CH), 63.1 (CH_2), 54.9 (CH_3), 54.4 (CH_3); MS (ES) *m/z* 350 (92, M + 1), 352 (100, M + 3), 372 (46, M + Na), 374 (45, M + Na + 2); HRMS Calcd for $C_{12}H_{17}NO_6Br$ (M+1): 350.0239. Found (M): 350.0218.

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