Carbohydrate Research, 78 (1980) 235–242

STEREOSPECIFIC SYNTHESIS OF A NOVEL SERIES OF PYRIDINE NUCLEOSIDES

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(Received January 9th, 1979; accepted for publication, May 11th, 1979)

ABSTRACT

Condensation of 3,5-di-*O*-benzoyl-β-D-ribofuranosyl chloride severally with 3-acetyl-5-alkylpyridines, 5-alkyl-3-methoxycarbonylpyridines (alkyl = Me, Et, Pr, and ^{i}Pr), 5-isopropylnicotinamide, and 3,5-diacetylpyridine bis(ethylene acetal) in acetonitrile at −5° gave the corresponding 1-(3,5-di-*O*-benzoyl-β-D-ribofuranosyl)-3,5-disubstituted pyridinium chlorides in excellent yield (90%). From the reaction of a series of 2,3-*O*-isopropylidene-β-D-ribofuranosyl halides with 3-acetyl-5-methylpyridine at room temperature, the α-nucleosides were obtained.

INTRODUCTION

A mechanism for the enzymic reduction of ketones has been suggested by Prelog and others[1], and it is therefore of interest to determine how β-NAD^{+} analogues having a 3,5-disubstituted pyridinium moiety behave in such an enzymic system. Little attention has been paid to the preparation of this type of nucleoside[2–6], and most, relevant synthetic work has involved purine and pyrimidine nucleosides.

We have reported[7] the reaction of 1-(2,4-dinitrophenyl)-3-substituted pyridinium chlorides with 2,3-*O*-isopropylidene-D-ribofuranosylamine as a possible route to the synthesis of pyridinium nucleosides[7], and noted the failure of this method for some 3,5-disubstituted pyridinium salts. However, 3-acetyl-5-alkylpyridines are suitable[8] nucleophiles for reaction at the anomeric centre of 2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl bromide. We now report on the reaction of some ribofuranosyl halides with novel 3,5-disubstituted pyridines.

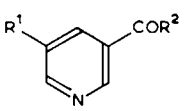
RESULTS AND DISCUSSION

The preparation of 3-acetyl-5-alkylpyridines (where alkyl is Me, Et, Pr, and ^{i}Pr) has been described elsewhere[9], and their conversion into the 5-alkyl-3-methoxycarbonylpyridines* (**5–8**) was accomplished by haloform reactions, and methylation

*According to the IUPAC-rules, the locants 3- and 5- should be inverted, but, for convenience of reading, the carbonyl group is given the locant 3- in this paper.

TABLE I

DATA FOR SOME 5-ALKYLPYRIDINE DERIVATIVES



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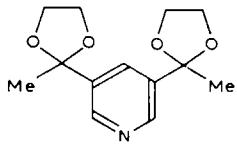

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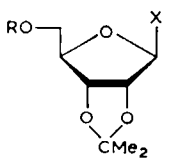
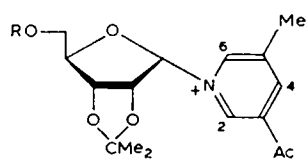
Compound	R^1	R^2	*Yield* (%)	*M.p./b.p.* *(degrees)*
1	Me	OH	61	192–195
2	Et	OH	65	150–154
3	Pr	OH	60	116–118
4	iPr	OH	80	143–147
5	Me	OMe	63	90/3 mmHg
6	Et	OMe	53	63/0.03 mmHg
7	Pr	OMe	86	110/0.5 mmHg
8	iPr	OMe	61	101/2 mmHg
9	iPr	NH_2	82	108
10			80	62

of the resulting 5-alkylnicotinic acids (**1–4**) with diazomethane. 5-Isopropylnicotinamide (**9**) was prepared by ammonolysis of 5-isopropyl-3-methoxycarbonylpyridine at 0°. Since earlier attempts to condense 3,5-diacetylpyridine with a glycosyl halide failed, the bis-acetal **10**, obtained by reaction[10] with ethylene glycol, was used.

2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (**11a**), which has been used in the synthesis of *C*-nucleosides[11-12], has the advantage that the trityl group can be removed selectively, thereby offering a route to nucleoside 5′-phosphates. 3-Acetyl-5-methylpyridine reacted with **11a** in dry acetonitrile at room temperature during 3 days, to give the α-nucleoside **12** (R = Tr). The outcome was the same when the glycosyl halides[13] **11b** and **11c** were used. Acid-catalysed detritylation of **12** (R = Tr) gave **13**.



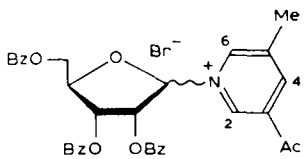
11a R = Tr, X = Cl
11b R = *p*-NO_2Ph, X = Br
11c R = Ac, X = Br



12 R = Tr
13 R = H

When the reaction of 3-acetyl-5-methylpyridine and **11a** was monitored at 30° by ^{1}H-n.m.r. spectroscopy (100 MHz), no anomerisation of the sugar halide was detected, indicating that the condensation proceeded *via* an S_N2 mechanism. The ^{1}H-n.m.r. spectrum of a solution of **11a** in CD_3CN, taken after 2 days at 30°, showed that no anomerisation had occurred, but there were additional signals which were assigned to 1,5-anhydro-2,3-*O*-isopropylidene-*β*-D-ribofuranose. This assignment was based on the proton chemical-shifts for the pure 1,5-anhydride[14]. On storage of a solution of **11a** in $CDCl_3$ for 1 week, ~80% conversion into the anhydro compound occurred. The condensations of **11b** and **11c** with 3-acetyl-5-methylpyridine, when investigated in an analogous way, were also found to be stereospecific.

The reaction of 3-acetyl-5-methylpyridine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**14**) in dry acetonitrile at −5° was also investigated. After 2 days, ^{1}H-n.m.r. spectroscopy revealed 50% reaction, and the resulting nucleoside **15** was a 1:4 mixture of *α* and *β* anomers.



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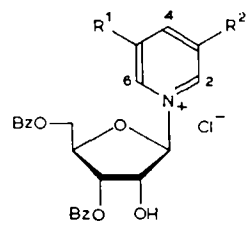
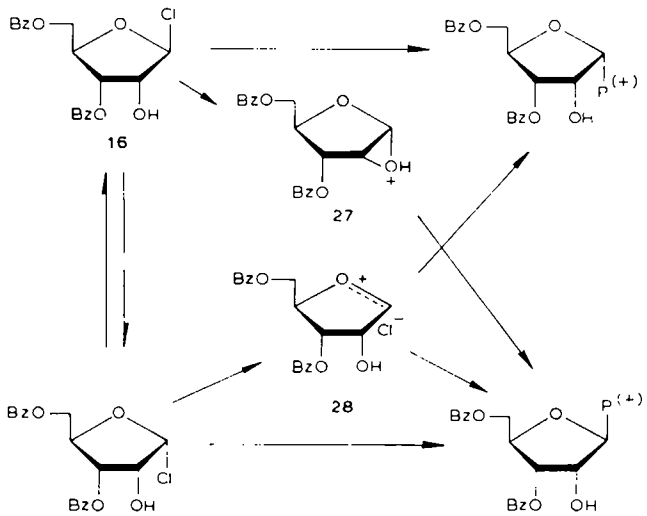


17 R^1 = Me, R^2 = Ac
18 R^1 = Et, R^2 = Ac
19 R^1 = Pr, R^2 = Ac
20 R^1 = i-Pr, R^2 = Ac
21 R^1 = Me, R^2 = CO_2Me
22 R^1 = Et, R^2 = CO_2Me
23 R^1 = Pr, R^2 = CO_2Me
24 R^1 = i-Pr, R^2 = CO_2Me
25 R^1 = i-Pr, R^2 = $CONH_2$
26 R^1 = R^2 =

Nucleosides of nicotinamide and 4-methylnicotinamide have been synthesised[6] by using crystalline 3,5-di-*O*-benzoyl-*β*-D-ribofuranosyl chloride (**16**), which can easily be obtained[15] from 1,3,5-tri-*O*-benzoyl-D-ribofuranose[6]. The reaction of **16** with 3-acetyl-5-alkylpyridines in acetonitrile at room temperature gave mixtures with an *αβ*-ratio of 1:4, but the *β* anomer was the preponderant product at −5°.

In contrast to the 2,3-*O*-isopropylideneglycosyl halides **11a–c**, 3,5-di-*O*-benzoyl-*β*-D-ribofuranosyl chloride rapidly anomerised in the presence of a pyridine compound, to give a 2:3 *αβ*-mixture. This ratio then remained constant throughout the condensation reaction. It is possible, as shown in Scheme 1, that an S_N2 mechanism could operate parallel with mechanisms involving the carboxonium ion **28** and/or an intermediate **27** formed by participation of HO-2′.

The low yields of *α*-nucleosides indicated that direct nucleophilic displacement of the halogen from **16** is not a favourable process. If the reaction proceeds *via* **27** and/or **28**, the formation of *α*-nucleosides will be dependent upon the degree of



P = pyridine derivative

Scheme 1. Possible reaction pathways in the condensation of **16** with pyridine derivatives

dissociation of the ion-pair **28**. Moreover, **16** anomerises to a 1 : 1 $\alpha\beta$-mixture in the absence of a pyridine derivative (Fig. 1). Since this equilibrium is not reached when a pyridine nucleophile is added, the α-glycosyl halide **16** must be more reactive than the β anomer. Thus, the reaction paths starting from **16** must be important in determining the composition of the product mixture. The observation that the $\alpha\beta$-ratio for the product nucleosides is 1 : 4 at room temperature, but is 7 : 3 at 70°, indicates that the formation of α-nucleosides proceeds *via* energetically less-favourable reaction-paths.

The structures **17**–**26** were confirmed by ^{1}H-n.m.r. spectroscopy.

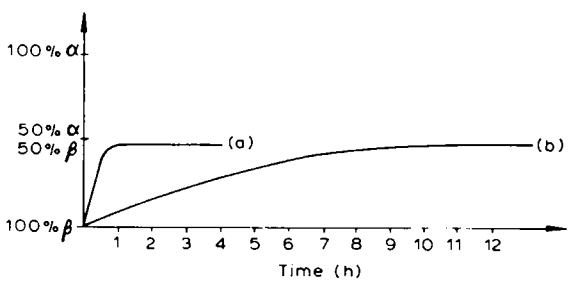


Fig. 1. Anomerisation of 3,5-di-*O*-benzoyl-β-D-ribofuranosyl chloride in CD_3CN, followed by ^{1}H-n.m.r. spectroscopy (H-1 resonances): (*a*) at 30°, (*b*) at 0°.

EXPERIMENTAL

Solvents were evaporated under diminished pressure at <5°, unless stated otherwise. The 300-MHz, ^{1}H-n.m.r. spectra were recorded for 10% solutions in organic solvents (internal Me_4Si) or D_2O (internal sodium 3-trimethylsilylpropane-1-sulphonate), using a Varian HR-300 spectrometer with an SC 8525-2 decoupler-unit and a probe temperature of 30°. The 100-MHz spectra were recorded with a Jeol-PS-100 instrument.

5-Alkylnicotinic acids (**1–4**). — To a mixture of water (300 ml), sodium hydroxide (18 g, 0.45 mol), and bromine (5.6 ml, ~0.1 mol) at ~5° was added the 3-acetyl-5-alkylpyridine (0.03 mol) with stirring. The mixture was then stored at room temperature overnight, and the aqueous layer was separated and treated with 0.6M sulphuric acid (20 ml). The pH of the solution was adjusted to 3.5 with conc. nitric acid, and the solution was continuously extracted with chloroform for 3 days. The extract was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by sublimation.

The compounds prepared by this method are shown in Table I.

5-Alkyl-3-methoxycarbonylpyridines (**5–8**). — To a solution of each 5-alkylnicotinic acid (14 mmol) in dry methanol (20 ml) was added ethereal diazomethane until evolution of nitrogen ceased. The solvent was evaporated and the residue distilled.

The compounds prepared by this method are shown in Table I.

5-Isopropylnicotinamide (**9**). — To **8** (1 g, 0.05 mol) was added conc. ammonia (10 ml), and the mixture was saturated with ammonia at 30° and then stirred at room temperature for 26 h. The resulting, clear solution was again saturated with ammonia and stored for another 4 h. The process was repeated to give **9** (see Table I).

3,5-Diacetylpyridine bis(ethylene acetal) (**10**). — A mixture of 3,5-diacetylpyridine (10 g, 61 mmol), ethylene glycol (23 g, 37 mmol), and conc. H_2SO_4 (5.4 ml) in benzene was boiled under reflux in a Dean–Stark apparatus until the theoretical amount of water was collected. The benzene solution was washed with a dilute solution of KOH in ethylene glycol, dried ($MgSO_4$), and concentrated to give **10** (see Table I).

3-Acetyl-1-(2,3-O-isopropylidene-α-D-ribofuranosyl)-5-methylpyridinium chloride (**13**). — To a solution of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride[11] (5.2 g, 11.6 mmol) in dry acetonitrile (40 ml) was added 3-acetyl-5-methylpyridine (4.7 g, 34.8 mmol). The mixture was stirred for 3 days at room temperature and then concentrated, and the residue was triturated with dry ether, to give 3-acetyl-1-(2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)-5-methylpyridinium chloride as a light-yellow solid (1.82 g, 27%), which was collected under nitrogen, and a solution of a portion (0.4 g, 0.68 mmol) in 2,2-dimethoxypropane (10 ml) and acetone (30 ml) containing 1% of HCl was stirred at room temperature for 24 h. The solution was neutralised with $NaHCO_3$, filtered, and concentrated, and the residue was triturated with dry ether, to give **13** (78%), which was isolated by centrifugation. N.m.r. data (D_2O, 300 MHz): δ 9.14 (s, 1 H, H-2), 8.91 (s, 2 H, H-4,6),

6.72 (d, 1 H, *J* 5.1 Hz, H-1′), 5.46 (dd, 1 H, *J* 5.8 and 5.1 Hz, H-2′), 5.15 (dd, 1 H, *J* 5.8 and 0.6 Hz, H-3′), 5.00 (m, 1 H, *J* 0.6, 2.9, and 3.2 Hz, H-4′), 3.94 (dd, 1 H, *J* 2.9 and −12.6 Hz, H-5′A), 3.86 (dd, 1 H, *J* 3.2 and 12.6 Hz, H-5′B), 2.70 (s, 3 H, CH_3), 2.82 (s, 3 H, Ac), 0.96 (s, 3 H, CMe), and 1.35 (s, 3 H, CMe).

Reactions of 3,5-di-O-benzoyl-β-D-ribofuranosyl chloride. — (*a*) *With 3-acetyl-5-alkylpyridines.* A mixture of the ribofuranosyl chloride[14] (0.7 g, 1.8 mmol), 3-acetyl-5-alkylpyridine (5.5 mmol), and dry acetonitrile (25 ml) was stirred for 3 days at −5°, and then concentrated *in vacuo*. A solution of the resulting syrup in dry dichloromethane was treated with dry ether, and the flocculent precipitate was collected under dry nitrogen, to give the 3-acetyl-5-alkyl-1-(3,5-di-*O*-benzoyl-β-D-ribofuranosyl)pyridinium chloride as a hygroscopic powder.

5-Methyl derivative (**17**, 92%), $[\alpha]_D^{22}$ −70.1° (*c* 5.8, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 10.19 (s, 1 H, H-2), 9.59 (s, 1 H, H-6), 8.79 (s, 1 H, H-4), 6.91 (d, 1 H, *J* 4.5 Hz, H-1′), 5.70 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-3′), 5.10 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-2′), 5.08 (m, 1 H, *J* 4.5, 3.6, and 3.6 Hz, H-4′), 4.92 (m, 1 H, *J* 3.6 and −12.7 Hz, H-5′A), 4.91 (m, 1 H, *J* 3.6 and −12.7 Hz, H-5′B), 2.78 (s, 3 H, Ac), 2.48 (s, 3 H, CH_3), and 7.8 (m, 10 H, 2 Bz).

5-Ethyl derivative (**18**, 92%), $[\alpha]_D^{22}$ −58.9° (*c* 1.8, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 10.11 (s, 1 H, H-2), 9.64 (s, 1 H, H-6), 8.84 (s, 1 H, H-4), 6.94 (d, 1 H, *J* 4.5 Hz, H-1′), 5.69 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-3′), 5.12 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-2′), 5.08 (m, 1 H, *J* 4.5, 3.8, and 3.8 Hz, H-4′), 4.93 (m, 2 H, H-5′A,5′B), 2.87 (q, 2 H, *J* 8 Hz, CH_2), 2.77 (s, 3 H, Ac), 1.23 (t, 3 H, *J* 8 Hz, CH_3), and 7.8 (m, 10 H, 2 Bz).

5-Propyl derivative (**19**, 91%), $[\alpha]_D^{22}$ −58.8° (*c* 2.8, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 10.19 (s, 1 H, H-2), 9.64 (s, 1 H, H-6), 8.84 (s, 1 H, H-4), 6.95 (d, 1 H, *J* 4.5 Hz, H-1′), 5.69 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-3′), 5.11 (dd, 1 H, *J* 4.5 and 5.5 Hz, H-2′), 5.08 (m, 1 H, *J* 4.5, 3.7, and 3.7 Hz, H-4′), 4.93 (m, 2 H, H-5′A,5′B), 2.81 (t, 2 H, *J* 8 Hz, CH_2), 1.66 (m, 2 H, *J* 8 Hz, CH_2), 0.85 (t, 3 H, *J* 8 Hz, CH_3), and 7.8 (m, 10 H, 2 Bz).

5-Isopropyl derivative (**20**, 86%), $[\alpha]_D^{22}$ −66.7° (*c* 4.6, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 10.08 (s, 1 H, H-2), 9.75 (s, 1 H, H-6), 8.99 (s, 1 H, H-4), 6.97 (d, 1 H, *J* 4.7 Hz, H-1′), 5.68 (dd, 1 H, *J* 4.5 and 5.2 Hz, H-3′), 5.11 (dd, 1 H, *J* 4.7 and 5.2 Hz, H-2′), 5.09 (m, 1 H, *J* 4.7, 3.6, and 3.6 Hz, H-4′), 4.95 (m, 1 H, *J* 3.6 and −12.5 Hz, H-5′A), 4.94 (m, 1 H, *J* 3.6 and 12.5 Hz, H-5′B), 3.25 (m, 1 H, *J* 8 Hz, CH), 1.31 (d, 6 H, *J* 8 Hz, CMe_2), and 7.8 (m, 10 H, 2 Bz).

(*b*) *5-Alkyl-3-methoxycarbonylpyridines* (**5–8**). Using essentially the procedure described in (*a*) and **5–8** severally, the 5-alkyl-1-(3,5-di-*O*-benzoyl-β-D-ribofuranosyl)-3-methoxypyridinium chlorides (**21–24**) were prepared as hygroscopic powders.

5-Methyl derivative (**21**, 82%, αβ-ratio 1:9), $[\alpha]_D^{22}$ −58.2° (*c* 3.9, methanol). N.m.r. data (acetone-d_6, 360 MHz): δ 9.89 (s, 1 H, H-2), 9.65 (s, 1 H, H-6), 8.85 (s, 1 H, H-4), 6.86 (d, 1 H, *J* 4.6 Hz, H-1′), 5.74 (dd, 1 H, *J* 4.2 and 5.2 Hz, H-3′), 5.15 (m, 1 H, H-4′), 5.14 (t, 1 H, H-2′), 4.95 (dd, 1 H, *J* 3.0 and 12.8 Hz, H-5′A),

4.85 (dd, 1 H, *J* 3.6 and −12.8 Hz, H-5′B), 3.78 (s, 3 H, OCH_3), 2.62 (s, 3 H, CH_3), and 7.4–8.2 (m, 10 H, 2 Bz).

5-Ethyl derivative (**22**, 80%, αβ-ratio 1:9), $[\alpha]_D^{22}$ −34.1° (*c* 3.7, methanol). N.m.r. data (acetone-d_6, 100 MHz): δ 9.88 (s, 1 H, H-2), 9.52 (s, 1 H, H-6), 8.72 (s, 1 H, H-4), 6.88 (d, 1 H, *J* 4.5 Hz, H-1′), 5.66 (t, 1 H, H-3′), 5.0–5.2 (2 H, H-2′,4′), 4.88 (2 H, H-5′A,5′B), 3.70 (s, 3 H, OCH_3), 2.94 (q, 2 H, *J* 7 Hz, CH_2), 1.30 (t, 3 H, *J* 7 Hz, CH_3), and 7.2–8.2 (m, 10 H, 2 Bz).

5-Propyl derivative (**23**, 78%, αβ-ratio 1:9), $[\alpha]_D^{22}$ −33.6° (*c* 4.6, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 9.94 (s, 1 H, H-2), 9.66 (s, 1 H, H-6), 8.87 (s, 1 H, H-4), 6.92 (d, 1 H, *J* 4.7 Hz, H-1′), 5.75 (dd, 1 H, *J* 4.4 and 5.3 Hz, H-3′), 5.16 (t, 1 H, H-2′), 5.15 (m, 1 H, H-4′), 4.95 (dd, 1 H, *J* 2.8 and −12.8 Hz, H-5′A), 4.86 (dd, 1 H, *J* 3.7 and −12.8 Hz, H-5′B), 3.74 (s, 3 H, OCH_3), 2.91 (t, 2 H, *J* 7.7 Hz, CH_2), 1.76 (m, 2 H, *J* 7.7 Hz, CH_2), 0.95 (t, 3 H, *J* 7.7 Hz, CH_3), and 7.4–8.2 (m, 10 H, 2 Bz).

5-Isopropyl derivative (**24**, 78%, αβ-ratio 1:9), $[\alpha]_D^{22}$ −38.6° (*c* 4.8, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 10.10 (s, 1 H, H-2), 9.60 (s, 1 H, H-6), 8.89 (s, 1 H, H-4), 6.96 (d, 1 H, *J* 4.4 Hz, H-1′), 5.72 (m, 1 H, *J* 4.3 and 5.5 Hz, H-3′), 5.14 (m, 1 H, H-4′), 5.13 (t, 1 H, H-2′), 4.96 (dd, 1 H, *J* 2.9 and −12.8 Hz, H-5′A), 4.87 (dd, 1 H, *J* 3.8 and −12.8 Hz, H-5′B), 3.70 (s, 3 H, OCH_3), 3.36 (m, 1 H, *J* 6.7 Hz, CH), 1.39 (d, 6 H, *J* 6.7 Hz, CMe_2), and 7.4–8.2 (m, 10 H, 2 Bz).

(*c*) *5-Isopropylnicotinamide* (**9**). Using essentially the procedure described in (*a*) and **9**, 3-carbamoyl-1-(3,5-di-*O*-benzoyl-β-D-ribofuranosyl)-5-isopropylpyridinium chloride (**25**, 89%) was obtained: $[\alpha]_D^{22}$ −58.3° (*c* 1.3, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 9.94 (s, 1 H, H-2), 9.38 (s, 1 H, H-6), 9.04 (s, 1 H, H-4), 6.65 (d, 1 H, *J* 4.8 Hz, H-1′), 5.79 (dd, 1 H, *J* 3.4 and 5.5 Hz, H-3′), 5.34 (dd, 1 H, *J* 4.8 and 5.5 Hz, H-2′), 5.16 (m, 1 H, *J* 3.4, 3.2, and 4.1 Hz, H-4′), 4.99 (dd, 1 H, *J* 3.2 and −12.8 Hz, H-5′A), 4.88 (dd, 1 H, *J* 4.1 and −12.8 Hz, H-5′B), 3.20 (m, 1 H, *J* 6.9 Hz, CH), 1.27 (m, 6 H, *J* 6.9 Hz, CMe_2), and 7.4–8.2 (m, 10 H, 2 Bz).

(*d*) *3,5-Diacetylpyridine bis(ethylene acetal)* (**10**). Using essentially the procedure described in (*a*) and **10**, the bis(ethylene acetal) (**26**) of 3,5-diacetyl-1-(3,5-di-*O*-benzoyl-β-D-ribofuranosyl)pyridinium chloride was obtained (75%): $[\alpha]_D^{22}$ −40.6° (*c* 4.2, methanol). N.m.r. data (acetone-d_6, 300 MHz): δ 9.25 (d, 2 H, *J* 7 Hz, H-2,6), 8.58 (t, 1 H, *J* 1.7 and 1.7 Hz, H-4), 6.74 (d, 1 H, *J* 6.6 Hz, H-1′), 5.78 (dd, 1 H, *J* 2.0 and 5.4 Hz, H-3′), 5.11 (dd, 1 H, *J* 5.4 and 6.4 Hz, H-2′), 5.07 (m, 1 H, *J* 2.0, 3.6, and 3.6 Hz, H-4′), 4.90 (m, 2 H, H-5′A,5′B), 3.8–4.1 [m, 8 H, 2 $O(CH_2)_2O$], 1.64 (s, 6 H, 2 CH_3), and 7.5–8.3 (m, 10 H, 2 Bz).

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