Synthesis of Peracylated Derivatives of L-Ribofuranose from D-Ribose and Their Use for the Preparation of β-L-Ribonucleosides

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Abstract: A practical synthesis of peracylated derivatives of β-L-ribofuranose **13**–**15** from D-ribose was accomplished in 6 steps (total yield: 30–45%). Compound **13** was employed for the preparation of 1-(β-L-ribofuranosyl)thymine (**16**) and -cytosine (**17**), which are key intermediates for the preparation of the nucleoside derivatives with β-L-configuration. Simultaneous transformation of **17** into β-L-ddC (**19**) and β-L-3'dC (**20**) was studied.

Key words: carbohydrates, steroselective synthesis, acylations, nucleosides

Recently, a number of nucleosides with the unnatural β-L-configuration have been found to possess very potent antiviral activity.[1] These data prompted us to synthesize and to evaluate the biological properties of some β-L-nucleosides. In this paper we describe an efficient and scaleable synthesis of peracylated derivatives of β-L-ribofuranose **13**–**15** from D-ribose (**1**) and their use for the preparation of 1-(β-L-ribofuranosyl)thymine (**16**) and -cytosine (**17**) as precursors for further chemical transformations.[2]

The strategy for the preparation of β-L-nucleosides modified in the heterocyclic base and/or the sugar moiety consists in the convergent synthesis of β-L-ribofuranosyl nucleosides as the key intermediates for further chemical transformations. In this context, the practical synthesis of peracyl derivatives of β-L-ribofuranose is crucial. For the convergent synthesis of β-D-ribofuranosyl nucleosides, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (D-ABR) is the best ribosylating agent.[3–5] Its most effective synthesis comprises of three steps, (i) transformation of D-ribose into methyl α/β-ribofuranosides, (ii) benzoylation, and (iii) then acetolysis, which furnished the desired compound in 56% overall yield.[5] It should be stressed that the acetolysis requires very careful control of the reaction conditions in order to avoid the formation of acyclic derivatives of D-ribose.[6]

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (L-ABR) attracts attention as ribosylating agent for the preparation of β-L-ribofuranosyl nucleosides. Since the first synthesis of L-ABR from L-arabinose and L-xylose,[7] different approaches to this compound have been reported. Among them, three recently published schemes are of interest from the viewpoint of a large-scale preparation of L-ABR. Jung and Xu have accomplished the transformation of the readily available D-ribose into L-ABR in 7 steps in ca. 40% overall yield.[8] The most striking finding consists in the three step conversion of L-ribose to L-ABR in almost quantitative yield (*cf* Refs [5,6]). Chu and co-workers have developed another route, which starts from L-arabinose and gives L-ABR in 8 steps in ca. 20% overall yield.[9] Moyroud and Strazewski[10] have transformed L-xylose into L-ABR in 6 steps via an oxidation/reduction procedure as the key reaction. The acetolysis of methyl 2,3,5-tri-*O*-benzoyl-L-ribofuranoside afforded the crystalline L-ABR in 39% yield.[10]

In order to avoid the possible problems during acetolysis, we have developed a practical synthesis of peracylated derivatives of β-L-ribofuranose **13**–**15** from D-ribose (**1**) excluding acetolysis (Scheme 1). Treatment of D-ribose (**1**) with acetone in the presence of *p*-toluenesulfonic acid and calcium hydride gave the 2,3-*O*-isopropylidene derivative **2**. Conventional tritylation or *p*-monomethoxytritylation of **2** led to the respective 5-*O*-protected furanosides **3** and **4** in high yield. Reduction of the carbonyl function of the latter, followed by acylation without isolation of intermediary 1,4-diols resulted in the acylates **5**–**7**, which were purified by silica gel column chromatography.

Treatment of the fully blocked D-ribitol **5** with methanoic acid in diethyl ether at room temperature for 40 minutes, followed by silica gel column chromatography gave the dibenzoate **8** and the monobenzoate **9** in 60% and 5% yield based on the consumed starting **5**, 11% of which was recovered. Detritylation of **6** by reaction with trifluoroacetic acid in 1,2-dichloroethane (DCE) at room temperature for 35 minutes gave, after silica gel column chromatography, **6** (10%), **8** (87%; 55% overall yield from **1**) and **9** (10%) (the yields of benzoates **8** and **9** are based on the consumed **6**). Treatment of **6** with aqueous 90% acetic acid in THF at 35 °C for 18 hours, followed by silica gel column chromatography gave **8** (76%) and **9** (14%). Finally, detritylation of **7** with trifluoroacetic acid in DCE gave the dibenzoate **10** as the single product in 81% yield (54% overall yield from **1**) (Scheme 1).

Oxidation of the primary hydroxyl group of acylates **8** and **10** with pyridinium chlorochromate (PCC) in DCE or CH_2Cl_2 resulted in the corresponding compounds **11** (85%) and **12** (82%) containing a free aldehyde function. Deblocking of the 3,4-diol function of the aldehyde **11** with aq 85% trifluoroacetic acid at room temperature for 1 hour, followed by standard acetylation gave, after silica

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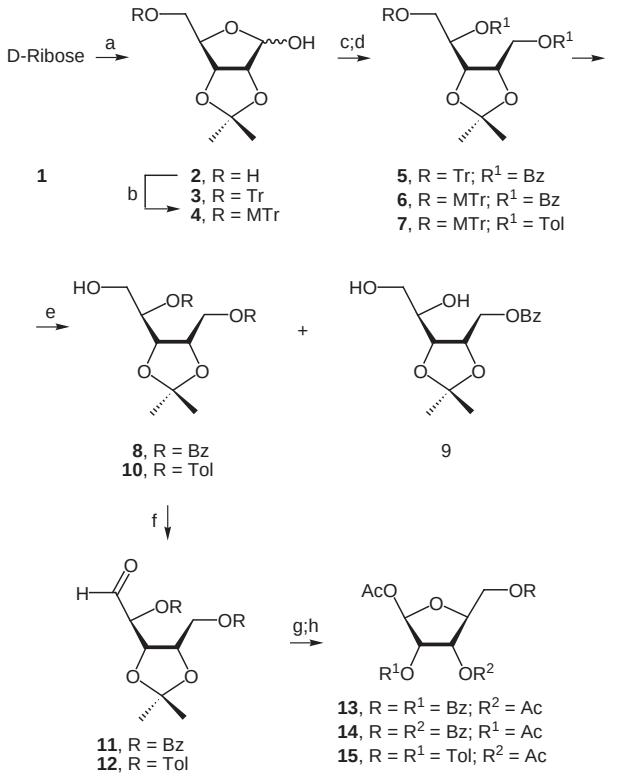
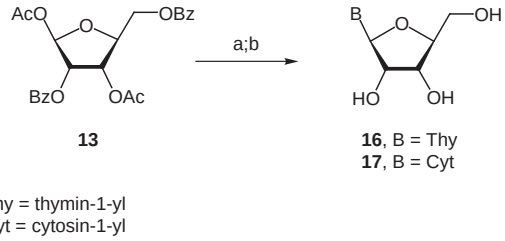


Scheme 1 *Reagents and conditions*: a) acetone, *p*-TsOH, CaH_2, (80–90%); b) TrCl or MTrCl/pyridine (80–90%); c) $NaBH_4$/EtOH; d) AcylCl/pyridine (c + d, 80–95%); e) 90% aq HOAc/THF, 35 °C, 18 h (**8**, 76%; **9**, 14%); CF_3CO_2H/CH_2Cl_2, r.t., 20–35 min (**10**, 81%); f) PCC ($PyH^+ClCrO_3^-$), CH_2Cl_2; 0 °C, 30 min; r.t., 2 h (**11**, 85%; **12**, 82%); g) 85% aq CF_3CO_2H, r.t., 40–60 min; h) Ac_2O/pyridine, r.t., 20 h (g + h, **13**, 52%; **14**, 7%; **15**, 61%)

gel column chromatography, the desired peracyl derivative of β-L-ribofuranose **13** as the main product of the reaction (52%) along with the isomeric acylate **14** (7%). Successive treatment of **12** with aqueous 85% trifluoroacetic acid at room temperature for 40 minutes followed by standard acetylation afforded peracylate **15** in 61% yield (Scheme 1). Thus, the removal of the 3,4-*O*-isopropylidene group of compound **11** is accompanied by the partial migration of 2-*O*-benzoyl group of intermediate derivatives of L-ribofuranose. As a consequence the formation of isomeric 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-ribofuranose (**14**) was observed.

Condensation of **13** with silylated thymine in the presence of tin tetrachloride in acetonitrile followed by standard deprotection with ammonia in methanol afforded β-L-nucleoside **16** (85%). In a similar way, condensation of **13** with silylated N^4-benzoylcytosine and subsequent deacylation gave β-L-cytidine (**17**) in 88% overall yield (Scheme 2).

The NMR spectral data show unequivocally the presence of a free aldehyde group in compounds **11** and **12** [δ ($CDCl_3$/TMS): ^{1}H NMR: 9.80 (s) and 9.78 (s) (CH=O);

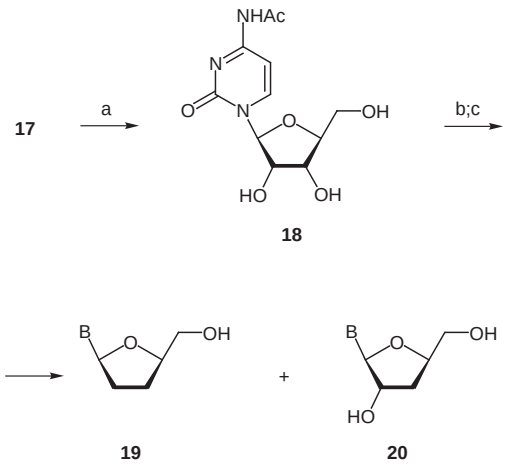


Scheme 2 *Reagents and conditions*: a) **13**-persilylated thymine or N^4-benzoylcytosine/$SnCl_4$, (molar ratio = 1.0:2.62:1.64 or 1.0:2.25:2.28, respectively), MeCN, r.t., 18 h; b) sat. methanolic ammonia (0 °C), r.t., 24 h [a + b, **16** (85%); **17** (88%)]

^{13}C NMR: 196.8 and 196.4 ($^1J_{C,H}$ = 184.9 and 179.6 Hz (CH=O)]. The spectral data for β-L-nucleosides **16** and **17** were found to be analogous to those for β-D-enantiomers except for the CD curves, which bear a mirror-image relationship with minor intensity changes.

It is obvious that chemical methods developed for the modification of natural ribonucleosides are applicable for similar transformations of L-enantiomers. Earlier, we have reported the synthesis of 3'-deoxy-2',3'-didehydro-β-L-thymidine and 3'-deoxy-3'-fluoro-β-L-thymidine from **16** employing previously developed methods for the corresponding D-enantiomer.[2] In this paper, we have studied the transformation of **17** into 2',3'-dideoxy-β-L-cytidine (β-L-ddC; **19**) and 3'-deoxy-β-L-cytidine (β-L-3'dC; **20**). The chemical literature described many approaches for the synthesis of such compounds. Among them, an universal convergent methodology[11] allows the preparation of both compounds starting from L-xylose via the intermediate formation of either 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-xylofuranose or its 3-deoxy derivative. Alternatively, Marcuccio et al. described an interesting method for the simultaneous preparation of β-D-ddC and 3'-deoxycytidine from N^4-acetylcytidine[12] (cf. Ref.[13]). We were interested in the preparation of both, β-L-ddC (**19**) and β-L-3'dC (**20**), and, therefore, this method[12] attracted our attention.

Nucleoside **17** was transformed to the N^4-acetyl derivative **18**, and the latter was treated with acetyl bromide in anhydrous acetonitrile as described.[12,14] HPLC analysis of the product, obtained as a pale yellow foam after workup of the reaction mixture, revealed the presence of three main and three minor compounds (cf. data in Ref.[12,13]). The UV spectra of all compounds were very similar to that of the starting N^4-acetyl derivative **18**. Hydrogenation of the mixture of products over 10% palladium on charcoal in methanol in the presence of potassium hydrogen carbonate[12] gave three main products, which were identified by TLC as the starting material **17**, and two desired derivatives **19** and **20** (Scheme 3). Thus, deacetylation occurred during the hydrogenation by the action of potassium hydrogen carbonate in methanol. Compounds **17** (recovered, 23%), **19** (18%) and **20** (16%) were isolated by silica gel column chromatography and characterized



Scheme 3 *Reagents and conditions*: a) Ac_2O/MeOH, 1 h (91%); b) AcBr/MeCN, 65 °C, 2 h; c) H_2, 10% Pd/C, $KHCO_3$, MeOH, r.t., 4 h [b + c, **19** (23%); **20** (17%); 24% of **17** was recovered]

by ^{1}H NMR spectroscopy as well as by UV and CD spectroscopy.

Column chromatography (CC): on silica gel 60 H (70–230 mesh ASTM; Merck, Darmstadt, Germany), except where otherwise indicated. TLC: (1) Silufol UV_{254} (Czech Republic) and (2) aluminum sheets silica gel 60 F_{254} (Merck, Germany). Solvent systems for TLC: hexane–EtOAc (1:1) (A), hexane–EtOAc (3:1) (B), hexane–EtOAc (2:1) (C), and EtOAc–MeOH–H_2O (4:1:0.2) (D) Florisil and pyridinium chlorochromate (PCC; purum) were purchased from Fluka (Switzerland). MeOH and MeCN were HPLC grade, $KHCO_3$ was purchased from Merck. Unless otherwise indicated, the reactions were carried out at 20 °C. The solutions of compounds in organic solvents were dried with anhyd Na_2SO_4 for 4 h.

UV spectra were measured with a Specord M-400 spectrometer (Carl Zeiss, Germany). CD spectra and the $[\alpha]_D^{20}$ values were obtained on a J-20 (Jasco, Japan) spectropolarimeter. ^{1}H and ^{13}C NMR Spectra were measured at 200.13 and 50.325 MHz, respectively, at 23 °C on an AC-200 spectrometer, equipped with an Aspect 3000 data system (Bruker, Germany); δ values are in ppm downfield from internal $SiMe_4$ (^{1}H, ^{13}C) (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; br s = broad signal); coupling constants *J* are given in Hz; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments. The HPLC analyses were performed on a Merck–Hitachi chromatograph (Germany): pump L-7100, UV Detector L-7400, and Integrator D-7500. The solvent employed for recording the NMR spectra was $CDCl_3$, unless otherwise stated. Mp: Boetius apparatus (Germany); not corrected. All new crystalline compounds gave satisfactory microanalyses, C ±0.38, H ±0.40.

1,4-Di-*O*-benzoyl-2,3-*O*-isopropylidene-5-*O*-trityl-D-ribitol (5), 1,4-Di-*O*-benzoyl-2,3-*O*-isopropylidene-5-*O*-monomethoxytrityl-D-ribitol (6), and 1,4-Di-*O*-(*p*-toluoyl)-2,3-*O*-isopropylidene-5-*O*-monomethoxytrityl-D-ribitol (7)

Compound **3** was prepared from D-ribose in two steps by the following modification of a known procedure.[15] A suspension of D-ribose (5.0 g, 33.3 mmol) in anhyd acetone (100 mL), containing *p*-TsOH·H_2O (19.0 g, 0.1 mol), was stirred for 30 min. To the homogeneous reaction mixture, powdered CaH_2 (2.7 g, 67.1 mol) was added; the mixture was stirred for 2 h, 1 N aq NaOH solution (100 mL) was added, the stirring was continued for an additional 20 min, and the mixture was evaporated to dryness in vacuo. The residue was purified by silica gel column (3 × 36 cm) chromatography, eluting with EtOAc–hexane (1:5, 0.4 L; 2:1, 1.1 L) mixture to give **2** (5.3 g, 84%) as a colorless oil; R_f 0.22 (A1).

A solution of compound **2** (5.3 g, 27.9 mmol) and trityl chloride (9.32 g, 33.43 mmol) in anhyd pyridine (65 mL) was stirred for 48 h, then poured into 5% aq $NaHCO_3$ (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried and evaporated to dryness. The residue was chromatographed on silica gel column (3 × 36 cm), eluting with a linear gradient (0 → 33%, v/v; 2 × 1 L) of EtOAc in hexane to afford **3** (9.6 g, 80%) as an oil; R_f 0.41 (B1).

Analogous to **3**, monomethoxytritylation of **2** (9.5 g, 50 mmol) gave **4**.

4

Colorless crystals; yield: 21.3 g (92%); mp 36–37 °C (EtOAc–hexane); R_f 0.31 (B1).

^{1}H NMR: δ = 7.44–7.20 (m, 12 H, 2 × C_6H_5 and the *ortho* protons of MTr group), 6.84 (d, 2 H, $^3J_{meta,ortho}$ = 8.5 Hz, the *meta* protons of MTr group), 5.32 (d, 1 H, $J_{1,OH}$ = 9.37 Hz, H-1), 4.80 (d, 1 H, $J_{3,2}$ = 5.52 Hz, H-3), 4.67 (d, 1 H, $J_{2,3}$ = 5.52 Hz, H-2), 4.35 (br t, 1 H, $J_{4,5}$ = 3.09 Hz, $J_{4,5'}$ = 3.31 Hz, $J_{4,3}$ = 0.8 Hz, H-4), 4.16 (d, 1 H, $J_{1,OH}$ = 9.37 Hz, 1-OH), 3.78 (s, 3 H, OCH_3), 3.42 (dd, 1 H, $J_{5,4}$ = 3.09, $J_{5,5'}$ = 10.5 Hz, H-5), 3.33 (dd, 1 H, $J_{5',4}$ = 3.31 Hz, H-5'), 1.46 and 1.30 [2 s, 2 × 3 H, =$C(CH_3)_2$].

To a solution of **3** (4.52 g, 10.46 mmol) in EtOH (150 mL) was added $NaBH_4$ (1.58 g, 41.82 mmol) and the mixture was stirred for 18 h and evaporated to dryness. The residue was partitioned between H_2O (150 mL) and EtOAc (250 mL), the organic phase was separated, and the H_2O phase was extracted with EtOAc (2 × 250 mL). The combined organic extracts were dried, evaporated, and the residue (foam, 4.50 g) was treated with benzoyl chloride (2.67 mL, 3.21 g, 23.0 mmol) in anhyd pyridine (40 mL) under stirring at 0 °C for 1 h and then at r.t. overnight. Standard workup followed by silica gel column (3 × 36 cm) chromatography [a linear EtOAc gradient (0 → 33%, v/v; 2 × 1.0 L) in hexane] afforded **5**.

5

Oil; yield: 5.41 g (80%); R_f 0.51 (B1).

^{1}H NMR: δ = 8.04 and 7.94 (2 d, 4H, $^3J_{meta,ortho}$ = 7.0, 7.0 Hz, the *ortho* protons of Bz group), 7.60–7.16 (m, 21 H_{arom}), 5.46 [m, 1 H, $J_{4,3}$ = 7.8, $J_{4,5}$ = 2.6, $J_{4,5'}$ = 3.9 Hz, C^4*H*OBz (H-4)], 4.78 (dd, 1 H, $J_{2,3}$ = 5.2 Hz, H-3), 4.61 (dd, 1 H, $J_{2,1}$ = 6.2, $J_{2,1'}$ = 4.5 Hz, H-2), 4.55 [dd, 1 H, $J_{1,1'}$ = 11.0 Hz, C$^1H_2$OBz (H-1)], 4.34 (dd, 1H, $J_{1,1'}$ = 11 Hz Hz, H-1'), 3.54 [dd, 1 H, $J_{5,5'}$ = 10.4 Hz, C$^5H_2$OTr (H-5)], 3.45 (dd, 1 H, $J_{5,5}$ = 10.4 Hz, H-5'), 1.42 and 1.38 [2 s, 2 × 3 H, =$C(CH_3)_2$].

In a similar way, compound **4** (4.73 g, 10.22 mmol) was transformed into compounds **6** and **7**.

6

Oil; yield: 6.53 g (95%); R_f 0.43 (B1).

^{1}H NMR: δ = 8.04 and 7.94 (2 dd, 4 H, $^3J_{meta,ortho}$ = 7.0, $^4J_{para,ortho}$ = 1.0 Hz, the *ortho* protons of Bz group), 7.60–7.12 (m, 18 H_{arom}), 6.68 (d, 2 H, $^3J_{meta,ortho}$ = 9.0 Hz, the *meta* protons of MTr group), 5.46 [m, 1 H, $J_{4,3}$ = 8.0, $J_{4,5}$ = 2.5, $J_{4,5'}$ = 4.2 Hz, C^4*H*OBz (H-4)], 4.78 (dd, 1 H, $J_{2,3}$ = 5.5 Hz, H-3), ≈4.60 and ≈4.55 (m, 2 H, $J_{2,1}$ = 6.0, $J_{2,1'}$ = 4.5 Hz, H-2 and H-1), 4.34 [dd, 1 H, $J_{1,1'}$ = 11.0, C$^1H_2$OBz (H-1')], 3.74 (s, 3 H, OCH_3), 3.54 [dd, 1 H, $J_{5,5'}$ = 11.0 Hz, C$^5H_2$OMTr (H-5)], 3.45 (dd, 1 H, $J_{5,5'}$ = 11.0 Hz, H-5'), 1.40 and 1.38 [2 s, 2 × 3H, =$C(CH_3)_2$].

7

Oil; yield: 6.3 g (88%); R_f 0.47 (B1).

^{1}H NMR: δ = 7.82 and 7.94 (2 d, 4 H, $^3J_{meta,ortho}$ = 8.0 and 8.0 Hz, the *ortho* protons of Tol group), 7.44–7.10 (m, 16 H_{arom}), 6.72 (d, 2 H, $^3J_{meta,ortho}$ = 9.0, the *meta* protons of MTr group), 5.45 [m, 1 H, $J_{4,3}$ = 8.0, $J_{4,5}$ = 2.5, $J_{4,5'}$ = 4.2 Hz, C^4*H*OTol (H-4)], 4.77 (dd, 1 H, $J_{2,3}$ = 5.5 Hz, H-3), ≈4.60 and ≈4.55 (m, 2 H, $J_{2,1}$ = 6.5, $J_{2,1'}$ = 4.5 Hz, H-2 and H-1), 4.32 [dd, 1 H, $J_{1,1'}$ = 11.0 Hz, C^1*H*$_2$OTol (H-1')], 3.74 (s, 3 H, OCH_3), 3.52 [dd, 1 H, $J_{5,5'}$ = 11.0 Hz, C^5*H*$_2$OMTr (H-5)], 3.42 (dd, 1 H, H-5'), 2.42 and 2.38 (2 s, 2 × 3 H, 2 × C*H*$_3$C$_{arom}$), 1.40 and 1.38 [2 s, 2 × 3 H, =C(CH_3)$_2$].

1,4-Di-*O*-benzoyl-2,3-*O*-isopropylidene-D-ribitol (8) and 1,4-Di-*O*-(*p*-toluoyl)-2,3-*O*-isopropylidene-D-ribitol (10)

Method A: To a solution of **5** (5.34 g, 8.31 mmol) in Et_2O (25 mL) was added HCO_2H (25 mL), and the mixture was stirred for 40 min. Then it was diluted with Et_2O (400 mL), washed with H_2O (2 × 60 mL), 5% aq $NaHCO_3$ solution (4 × 50 mL), and again with H_2O (2 × 80 mL), dried, and evaporated. The oily residue was chromatographed on a silica gel column (2.8 × 20 cm), using a linear EtOAc gradient (0 → 33%, v/v; 2 × 0.7 L) in hexane to give, in the order of elution: starting compound **5** (0.6 g, 11%), the monobenzoate **9**, and the dibenzoate **8**.

8

Yield: 1.78 g (60% based on the consumed **5**); mp 79–81 °C (Et_2O–hexane); R_f 0.25 (C2); $[\alpha]_D^{20}$ –43.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR: δ = 7.98 and 7.92 (2 dd, 4 H, $^3J_{meta,ortho}$ = 8.0, $^4J_{para,ortho}$ = 1.3 Hz, the *ortho* protons of Bz groups), 7.46–7.58 (m, 2 H, the *para* protons of Bz groups), 7.42–7.29 (m, 4 H, the *meta* protons of Bz groups), 5.26 (dt, 1 H, $J_{4,3}$ = 7.8, $J_{4,5}$ = 3.0 Hz, C^4*H*OBz), 4.69–4.52 [m, 3 H, C^1*H*$_2$OBz (H-1 and H-1') and H-3], 4.34 (m, 1 H, H-2), 4.08 and 3.98 (2 dd, 2 H, $J_{5,4}$ = 3.0, $J_{5',4}$ = 3.5, $J_{5,5'}$ = 12.0 Hz, C^5*H*$_2$OH), 2.52 (br s, 1 H, C^{5}H$_2$O*H*), 1.52 and 1.42 [2 s, 2 × 3 H, =C(CH_3)$_2$].

^{13}C NMR: δ = 166.2 and 165.7 (2 × C=O), 133.4 and 133.0 (2 dt, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 7.5 Hz, 2 × C$_{para}$), 129.8 and 129.7 (2 dt, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 7.6 Hz, 2 × C$_{meta}$), 129.3 (t, $^2J_{C,H}$ = 7.5, one C$_{ipso}$ resonance; the second one is overlapped by the intense line at 129.7), 128.4 and 128.2 (2 dd, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 7.5 Hz, 2 × C$_{ortho}$), 109.4 [br s, =*C*(CH_3)$_2$], 75.2 (d, $^1J_{C,H}$ = 161.0 Hz) and 74.9 (d, $^1J_{C,H}$ = 151.0 Hz) (C-2 and C-3), 72.7 (d, $^1J_{C,H}$ = 148.4 Hz, *C*^{4}H$_2$OBz), 62.8 and 62.7 (2 t, $^1J_{C,H}$ = 148.4 and 145.3, *C*^{1}H$_2$OBz and C^{5}H$_2$OH), 27.7 and 25.4 [2 × q, $^1J_{C,H}$ = 127.8 and 127.8 Hz, =C(*C*H_3)$_2$].

9

Syrup; yield: 0.1 g (5%); R_f 0.41 (C2).

^{1}H NMR: δ = 8.04 (dd, 2 H, $^3J_{meta,ortho}$ = 7.0, $^4J_{para,ortho}$ = 1.0 Hz, the *ortho* protons of Bz group), 7.50 (br t, 1 H, $^3J_{meta,para}$ = 7.0, the *para* proton of Bz group), 7.42 (br t, 2 H, $^3J_{meta,ortho}$ = $^3J_{para,meta}$ = 7.0, the *meta* protons of Bz group), 4.84–4.00 (m, 7 H, H-1,1',2,3,4,5,5'), 1.48 and 1.36 [2 s, 2 × 3 H, =C(CH_3)$_2$].

^{13}C NMR: δ = 167.1 (s, C=O), 133.2 (dt, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 7.6 Hz, C$_{para}$), 129.9 (t, $^2J_{C,H}$ ≈7.5, C$_{ipso}$), 129.7 (dt, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 6.3 Hz, C$_{meta}$), 128.4 (dd, $^1J_{C,H}$ = 161.0, $^2J_{C,H}$ = 7.6 Hz, C$_{ortho}$), 109.4 [br s, =*C*(CH_3)$_2$], 75.6 and 75.1 (2 d, $^1J_{C,H}$ ≈146 Hz, C-2 and C-3), 68.5 (d, $^1J_{C,H}$ = 145.9 Hz, C^{4}HOH), 67.6 (t, $^1J_{C,H}$ = 148.4 Hz, *C*^{1}H$_2$OBz), 63.8 (t, $^1J_{C,H}$ = 149.7 Hz, C^{5}H$_2$OH), 27.8 and 25.4 [2 q, $^1J_{C,H}$ = 131.0 Hz, =C(*C*H_3)$_2$].

Method B: A solution of **6** (2.15 g, 3.20 mmol) in anhyd DCE (96 mL) containing CF_3CO_2H (0.97 mL) was stirred for 35 min and poured into H_2O (100 mL). The organic phase was separated, washed with 5% aq $NaHCO_3$ solution (50 mL), H_2O (2 × 80 mL), dried, and evaporated. The oily residue was chromatographed on a silica gel column (2.3 × 25 cm), using a linear EtOAc gradient (0 → 33%, v/v; 2 × 0.7 L) in hexane to give, in the order of elution: starting compound **6** (0.22 g, 10%), monobenzoate **9** as a syrup (85 mg, 10%), and dibenzoate **8** (1.0 g, 87% based on **6** consumed).

Method C: A solution of **6** (1.12 g, 1.66 mmol) in a mixture of THF (3 mL) and aq 90% HOAc (8.0 mL) was stirred at 35 °C for 18 h and evaporated to dryness in vacuo. The residue was chromatographed on silica gel column (1.8 × 20 cm) as described above to afford syrupy **9** (70 mg, 14%) and crystalline **8** (0.51 g, 76%).

Method D: Similar to the one described in Method B. Starting from **7** (0.9 g, 1.28 mmol), compound **10** was prepared.

10

Yield: 445 mg (81%); mp 86–88 °C (Et_2O–hexane); R_f 0.26 (C2); $[\alpha]_D^{20}$ –62.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR: δ = 7.80 and 7.86 (2 d, 4 H, $^3J_{meta,ortho}$ = 8.0 and 8.0 Hz, the *ortho* protons of Tol group), 7.12 and 7.16 (2 d, 4 H, the *meta* protons of Tol group), 5.25 (dt, 1 H, $J_{4,3}$ = 8.0, $J_{4,5}$ = 3.5, $J_{4,5'}$ = 4.0 Hz, C^4*H*OTol), 4.50–4.68 [m, 3 H, C^1*H*$_2$OTol (H-1 and H-1') and H-3], 4.30 (m, 1 H, H-2), 4.07 and 3.96 (2 dd, 2 H, $J_{5,5'}$ = 12.0 Hz, C^5*H*$_2$OH), 2.38 (s, 6 H, 2 × ArC*H*$_3$), 1.50 and 1.42 [2 s, 2 × 3 H, =C(CH_3)$_2$].

^{13}C NMR: δ = 166.2 and 165.8 (2 s, 2 × C=O), 144.2 and 143.6 (2 m, 2 × CH_3-*C*$_{arom}$), 129.8 and 129.7 (2 dd, $^1J_{C,H}$ = 162.3, $^2J_{C,H}$ = 6.3 Hz, 2 × C$_{ortho}$), 129.1 and 128.9 (2 dm, $^1J_{C,H}$ = 156.0 Hz; 2 × C$_{meta}$), 126.9 and 126.5 (2 m, 2 × C$_{ipso}$), 109.3 [br s, =*C*(CH_3)$_2$], 75.3 (d, $^1J_{C,H}$ = 151.0 Hz) and 74.9 (d, $^1J_{C,H}$ = 147.8 Hz) (C-2 and C-3), 72.7 (d, $^1J_{C,H}$ = 145.9 Hz, *C*^{4}H$_2$OTol) 62.9 and 62.6 (2 t, $^1J_{C,H}$ = 144.7 and 148.4 Hz, *C*^{1}H$_2$OTol and C^{5}H$_2$OH), 27.7 and 25.4 [2 q, $^1J_{C,H}$ = 125.8 and 125.8 Hz, =C(*C*H_3)$_2$], 21.6 (2 q, $^1J_{C,H}$ = 125.8 Hz, 2 × *C*H_3-*C*$_{arom}$).

2,5-Di-*O*-benzoyl-3,4-*O*-isopropylidene-*aldehydo*-L-ribose (11) and 2,5-Di-*O*-(*p*-toluoyl)-3,4-*O*-isopropylidene-*aldehydo*-L-ribose (12)

To a suspension of PCC (4.2 g, 19.47 mmol) in anhyd DCE (30 mL) at 0 °C was added a solution of dibenzoyl-D-ribitol **8** (3.0 g, 7.50 mmol) in anhyd DCE (50 mL) followed by freshly dried and crushed molecular sieves 4 Å (4.2 g). The reaction mixture was stirred at 0 °C for 30 min and then at r.t. for 2 h, diluted with anhyd Et_2O (25 mL), and applied onto a column (2.3 × 19.5 cm) packed with florisil, containing crushed molecular sieves 4 Å on the top. Elution with Et_2O gave the aldehyde **11**.

11

Yield: 2.55 g (85%); mp 82–83 °C (Et_2O–hexane); R_f 0.33 (C2); $[\alpha]_D^{20}$ –34.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR: δ = 9.80 (s, 1 H, CH=O), 7.96 and 8.04 (2 br d, 4 H, $^3J_{meta,ortho}$ = 7.5 Hz, the *ortho* protons of Bz groups), 7.46–7.62 (m, 2 H, the *para* protons of Bz groups), 7.42–7.30 (m, 4 H, the *meta* protons of Bz groups), 5.52 [d, 1 H, $J_{2,3}$ = 6.5 Hz, C^2*H*OBz (H-2)], 4.40–4.80 (m, 4 H, H-3, H-4 and C^5*H*$_2$OBz], 1.56 and 1.44 [2 s, 2 × 3 H, =C(CH_3)$_2$].

^{13}C NMR: δ = 196.8 (s, $^1J_{C,H}$ = 184.9 Hz, CH=O), 166.7 and 165.7 (2 × C=O), 134.4 and 133.8 (2 dt, $^1J_{C,H}$ = 165.3, $^2J_{C,H}$ = 7.55 Hz, 2 × C$_{para}$), 130.6 and 130.3 (2 × C$_{meta}$), 130.1 (t, $^2J_{C,H}$ = 7.5 Hz, one C$_{ipso}$ resonanace, the second one is overlapped by the intense line at 130.3 ppm), 129.2 and 129.0 (2 dd, $^1J_{C,H}$ = 162.3, $^2J_{C,H}$ = 8.5 Hz, 2 × C$_{ortho}$), 110.8 [=*C*(CH_3)$_2$], 76.5 (dd, $^1J_{C,H}$ = 151.0, $^3J_{C,H}$ = 28.3 Hz, *C*^{2}HOBz), 75.9 and 75.8 (2 d, $^1J_{C,H}$ ≈150.0, C-3 and C-4), 63.0 (t, $^1J_{C,H}$ ≈149.1, *C*^{5}H$_2$OBz), 28.2 and 25.9 [2 q, $^1J_{C,H}$ = 117.0 Hz, =C(*C*H_3)$_2$].

In a similar way, starting from **10** (0.33 g, 0.77 mmol), the aldehyde **12** was prepared.

12

Yield: 0.27 g (82%); mp 83–85 °C (Et_2O–hexane); R_f 0.36 (C2); $[\alpha]_D^{20}$ –28.5 (*c* = 1.0, $CHCl_3$).

^1H NMR: δ = 9.78 (s, 1 H, CH=O), 7.96 and 7.82 (2 d, 4 H, $^3J_{meta,ortho}$ = 8.0 and 8.0 Hz, the *ortho* protons of Tol group), 7.16 and 7.12 (2 d, 4 H, the *meta* protons of Tol group), 5.52 [d, 1 H, $J_{2,3}$ = 6.75 Hz, C^2HOTol)], 4.78–4.68 (m, 2 H, H-3,4), 4.58 (dd, 1 H, $J_{5,4}$ = 4.0, $J_{5,5'}$ = 11.5 Hz, C^5H_2OTol, H-5), 4.44 (dd, 1 H, $J_{5',4}$ = 4.0 Hz, C^5H_2OTol, H-5'), 2.40 and 2.37 (2 s, 2 × 3 H, 2 × $ArCH_3$), 1.55 and 1.42 [2 s, 2 × 3 H, $=C(CH_3)_2$].

^{13}C NMR: δ = 196.4 (d, $^1J_{C,H}$ = 179.6 Hz, CH=O), 166.1 and 165.2 (2 × C=O), 144.6 and 143.9 (2 m, 2 × CH_3-C_{arom}), 130.0 and 129.7 (2 dd, $^1J_{C,H}$ = 160.5, $^2J_{C,H}$ = 7.9 Hz, 2 × C_{ortho}), 126.7 and 125.7 (2 dm, $^1J_{C,H}$ = 158.7 Hz, 2 × C_{meta}), 126.7 and 125.7 (2 m, $^2J_{C,H}$ = 7.9, 2 × C_{ipso}), 110.1 [br s, $=C(CH_3)_2$], 75.7, 75.3 and 75.2 (C-2, C-3 and C-4), 62.2 (t, $^1J_{C,H}$ ≈148, C^5H_2OTol), 27.5 and 25.2 [2 q, $^1J_{C,H}$ = 132.2 Hz, $=C(CH_3)_2$], 21.7 (2 × CH_3-C_{arom}).

1,3-Di-*O*-acetyl-2,5-di-*O*-benzoyl-β-L-ribofuranose (13) and 1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-ribofuranose (14)

A solution of the aldehyde **11** (2.55 g, 6.4 mmol) in 85% aq CF_3CO_2H (17 mL) was stirred for 1 h. The mixture was evaporated in vacuo at 35 °C, the residue was co-evaporated with toluene (3 × 30 mL) and then dissolved in anhyd pyridine (33 mL). To the stirred solution, was added Ac_2O (7.92 mL, 83.78 mmol), the mixture was stirred for 20 h, and then poured into ice-water (120 mL). After the ice had melted, the mixture was extracted with EtOAc (3 × 200 mL), the combined extracts were washed with 5% aq $NaHCO_3$ solution (100 mL), water (100 mL), dried, and evaporated. The residue was chromatographed on a silica gel column (2.8 × 43 cm) using an EtOAc–hexane (1:5, v/v) mixture as eluent to afford, in the order of elution: **13** and **14**.

13

Yield: 1.47 g (52%); mp 120–122 °C (EtOH); R_f 0.39 (C2); $[\alpha]_D^{20}$ –21.5 (*c* = 1.0, $CHCl_3$).

^1H NMR: δ = 8.10 and 8.06 (2 br d, 4 H, $^3J_{meta,ortho}$ = 7.5 Hz, the *ortho* protons of Bz groups), 7.64–7.42 (m, 6 H, two *para* and four *meta* protons of Bz groups), 6.36 (s, 1 H, H-1), ≈5.64 (m, 2 H, H-2,3), 4.72 (dd, 1 H, $J_{5,4}$ = 3.0, $J_{5,5'}$ = 11.5 Hz, H-5), 4.68 (m, 1 H, H-4), 4.44 (dd, 1 H, $J_{5',4}$ = 4.0 Hz, H-5'), 2.02 and 1.98 (2 s, 2 × 3 H, 2 × CH_3C=O).

^{13}C NMR: δ = 169.8 and 169.0 (2 × CH_3C=O), 166.0 and 165.0 (2 × C_6H_5C=O), 133.7 and 133.4 (2 × C_{para}), 129.8 and 129.7 (2 × C_{meta}), 129.6 and 128.8 (2 × C_{ipso}), 128.6 and 128.5 (2 × C_{ortho}), 98.3 (d, $^1J_{C,H}$ = 183.1 Hz, C-1), 79.3 (d, $^1J_{C,H}$ = 151.0 Hz), 74.6 (d, $^1J_{C,H}$ = 162.3 Hz) and 70.6 (d, $^1J_{C,H}$ = 151.0 Hz) (C-2, C-3 and C-4), 63.4 (t, $^1J_{C,H}$ = 149.1 Hz, C-5), 20.8 and 20.4 (2 q, $^1J_{C,H}$ = 130.8 Hz, 2 × CH_3C=O).

14

Yield: 0.19 g (7%); mp 108–110 °C (Et_2O–hexane); R_f 0.38 (C2); $[\alpha]_D^{20}$ +8.5 (*c* = 1.0, $CHCl_3$).

^1H NMR: δ = 8.08 and 8.00 (2 br d, 4 H, $^3J_{meta,ortho}$ = 7.5 Hz, the *ortho* protons of Bz groups), 7.64–7.38 (m, 6 H, two *para* and four *meta* protons of Bz groups), 6.26 (d, 1 H, $J_{1,2}$ ≈1.0 Hz, H-1), 5.76 (dd, 1 H, $J_{3,2}$ = 5.0, $J_{3,4}$ = 6.0 Hz, H-3), 5.56 (dd, 1 H, H-2), 4.76–4.64 (m, 2 H, H-4,5), 4.44 (dd, 1 H, $J_{5',4}$ = 3.0, $J_{5',5}$ = 11.0 Hz, H-5'), 2.10 and 1.98 (2 s, 2 × 3 H, 2 × CH_3C=O).

^{13}C NMR: δ = 169.3 and 169.1 (2 × CH_3C=O), 165.9 and 165.3 (2 × C_6H_5C=O), 133.7 and 133.3 (2 × C_{para}), 129.7 (2 × C_{meta} and C_{ipso}), 128.8 (C_{ipso}), 128.6 and 128.4 (2 × C_{ortho}), 98.3 (d, $^1J_{C,H}$ = 179.4 Hz, C-1), 79.8 (d, $^1J_{C,H}$ = 147.6 Hz), 76.4 (d, $^1J_{C,H}$ = 159.1 Hz) and 74.4 (d, $^1J_{C,H}$ = 159.1 Hz) (C-2, C-3 and C-4), 63.6 (t, $^1J_{C,H}$ = 144.7 Hz), C-5), 20.9 and 20.5 (2 q, $^1J_{C,H}$ = 130.2 Hz, 2 × CH_3C=O).

1,3-Di-*O*-acetyl-2,5-di-*O*-(*p*-toluoyl)- β-L-ribofuranose (15)

A solution of the aldehyde **12** (0.55 g, 1.28 mmol) in 85% aq CF_3COOH (3.7 mL) was stirred at at r.t. for 40 min. The mixture was worked up and acetylated as described above, and finally chromatographed on a silica gel column (1.8 × 20 cm) using an EtOAc–heptane (1:6, v/v) mixture as eluent to afford **15**.

15

Oil; yield: 0.37 g (61%); R_f 0.44 (C2).

^1H NMR: δ = 7.98 and 7.96 (2 d, 4 H, $^3J_{meta,ortho}$ = 8.0 and 8.0 Hz, the *ortho* protons of Tol group), 7.30 and 7.24 (2 d, 4 H, the *meta* protons of Tol group), 6.36 (s, 1 H, H-1), 5.66–5.58 (m, 2 H, H-2,3), 4.76–4.58 (m, 2 H, $J_{4,5}$ = 3.0, H-4,5), 4.40 (dd, 1 H, $J_{5',4}$ = 3.5, $J_{5',5}$ = 11.5, H-5'), 2.46 and 2.44 (2 s, 6 H, 2 × CH_3-C_{arom}), 2.02 and 2.00 (2 s, 6 H, 2 × CH_3C=O).

^{13}C NMR: δ = 169.7 and 169.0 (2 × CH_3C=O), 166.0 and 165.1 (2 × $CH_3C_6H_4C$=O), 144.6 and 144.1 (CH_3-C_{arom}), 129.9 and 129.8 (2 × C_{ortho}), 129.3 and 129.2 (2 × C_{meta}), 126.9 and 126.1 (C_{ipso}), 98.4 (C-1), 79.4, 74.5, and 70.8 (C-2, C-3 and C-4), 63.3 (C-5), 21.7, 20.9 and 20.4 (2 × CH_3C=O and 2 × CH_3-C_{arom}).

1-(β-L-Ribofuranosyl)thymine (16)

To a stirred solution of **13** (0.44 g, 0.99 mmol) and the bis(trimethylsilyl) derivative of thymine [obtained from (0.33 g, 2.59 mmol) thymine] in anhyd MeCN (23 mL) was added $SnCl_4$ (0.19 mL, 0.421 g, 1.62 mmol). The reaction mixture was stirred for 18 h and poured into 5% aq $NaHCO_3$ (60 mL). The organic phase was separated, and the H_2O phase was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried and evaporated. The residue was purified by silica gel column (2.8 × 23 cm) chromatography, eluting with an EtOAc–hexane (1:3, v/v) mixture and then $CHCl_3$, to give the acylated derivative of **16**.

Acylated Derivative of 16

Foam; yield: 0.48 g (95%); R_f 0.26 (A2).

^1H NMR: δ = 9.62 (s, 1 H, NH), 8.12 and 8.06 (2 dm, 2 × 2 H, the *ortho* protons of Bz groups), 7.58 (center of m, 2 H, the *para* protons of Bz groups), 7.46 (center of m, 4 H, the *meta* protons of Bz groups), 7.14 (d, 1 H, $J_{H6,Me}$ ≈1.0 Hz, H-6), 6.34 (d, 1 H, $J_{1',2'}$ = 5.10 Hz, H-1'), 5.72–5.63 (center of m, 2 H, H-2',3'), 4.84 (dd, 1 H, $J_{5',4'}$ = 3.5, $J_{5',5''}$ = 13.0 Hz, H-5'), 4.60–4.52 (m, 2 H, H-4',5"), 2.09 (s, 3 H, CH_3C=O), 1.58 (d, 3 H, 5-CH_3).

Deacylation of the product (0.48 g) in MeOH (50 mL), saturated with dry NH_3 gas at 0 °C for 72 h followed by a standard workup and chromatography [silica gel Woelm containing 20% H_2O; column 1.8 × 8 cm; eluents: EtOAc and EtOAc–MeOH (10:1, v/v)] gave **16.**

16

Yield: 0.22 g (90%); mp 182–184 °C (EtOH); R_f 0.62 (D2); $[\alpha]_D^{18}$ +4.5 (*c* = 1.0, H_2O) [Lit.,[16] β-D-enantiomer: mp 183–184.5 °C (EtOH); $[\alpha]_D^{27}$ –10.0 (*c* = 4.00, H_2O)].

UV (H_2O): λ_{max} (ε) = 266.8 (8100), 207 nm (8400), λ_{min} 234.7 nm (2000).

CD (H_2O): λ, nm (Θ × 10^{-3}) = 245.0 (+4.5), 272.0 (–4.5), 257 and 290 (0).

^1H NMR (DMSO-d_6): δ = 10.68 (br s, 1 H, NH), 7.76 (d, 1 H, $J_{H6,Me}$ ≈1.0 Hz, H-6), 5.68 (d, 1 H, $J_{1',2'}$ = 5.5 Hz, H-1'), 5.34 (d, $J_{OH,H3'}$ = 4.0 Hz, 3'-OH), 5.10 (t, $J_{OH,H5'}$ = $J_{OH,H5''}$ = 4.5 Hz, 5'-OH), ≈5.08 (2'-OH), 4.10–3.90 (m, 2 H, H-2' and H-3'), 3.82 (m, 1 H, $J_{3',4'}$ = 3.0, $J_{4',5'}$ = $J_{4',5''}$ = 2.5 Hz, H-4'), 3.64 (m, 1 H, H-5'), 3.54 (m, 1 H, H-5"), 1.78 (d, 3 H, 5-CH_3).

^{13}C NMR (DMSO-d_6): δ = 163.8 (C-4), 155.7 (C-2), 136.3 (C-6), 109.3 (C-5), 87.4 (C-1'), 84.7 (C-4'), 73.3 (C-2'), 69.8 (C-3'), 60.8 (C-5'), 12.1 (5-CH_3).

1-(β-L-Ribofuranosyl)cytosine (17)

A mixture of **13** (0.4 g, 0.9 mmol), the bis(trimethylsilyl) derivative of N^4-benzoylcytosine [obtained from 435 mg (2.02 mmol) of N^4-benzoylcytosine] and $SnCl_4$ (0.24 mL, 0.532 g, 2.05 mmol) in anhyd MeCN was stirred for 18 h. After standard workup, the residue was purified by silica gel (2.8 × 13 cm) column chromatography with an EtOAc–hexane (1:3, v/v) mixture and then $CHCl_3$ as eluents, to afford 0.47 g (97%) of the acylated derivative of **17**.

Acylated Derivative of 17

R_f 0.18 (A2).

^{1}H NMR: δ = 9.18 (br s, 1 H, NH), 8.18–7.94 (m, 7 H, the *ortho* protons of Bz groups and H-6), 7.60–7.38 (m, 10 H, the *para* and *meta* protons of Bz groups and H-5), 6.32 (d, 1 H, $J_{1',2'}$ = 3.7 Hz, H-1'), 5.92 (dd, 1 H, $J_{2',3'}$ = 5.7 Hz, H-2'), 6.66 (br t, 1 H, $J_{3',4'}$ = 6.0 Hz, H-3'), 4.80 (dd, 1 H, $J_{5',4'}$ = 4.5, $J_{5',5''}$ = 13.5 Hz, H-5'), 4.70–4.58 (m, 2 H, H-4',5''), 2.00 (s, 3 H, CH_3C=O).

Standard deacylation of the above product and subsequent chromatography [silica gel Woelm containing 20% H_2O (1.8 × 8 cm); eluents: EtOAc and EtOAc–MeOH (4:1, v/v)] afforded **17**.

17

Yield: 195 mg (91%); mp 207–208 °C (EtOH); R_f 0.25 (D2); $[\alpha]_D^{20}$ –40.0 (*c* = 1.0, H_2O) [Lit.,[10] $[\alpha]_{546}^{25}$ –33 ± 1 (*c* = 0.82, H_2O)].

UV (H_2O): λ_{max} (ε) = 270.6 (8100), ≈229 nm (sh, 6900), λ_{min} = 250 nm (5700).

CD (H_2O): λ, nm (Θ × 10^{-3}) = 225.0 (+10.6), 268.0 (–10.5), 238 and 300 (0).

^{1}H NMR (DMSO-d_6): δ = 7.90 (d, 1 H, $J_{5,6}$ = 7.5 Hz, H-6), 7.22 („d", 2 H, 4-NH_2), 5.76 (d, 1 H, $J_{5,6}$ = 7.5 Hz, H-5), 5.74 (d, 1 H, $J_{1',2'}$ = 3.7 Hz, H-1'), 5.36 (br s, 2'-OH), 5.11 (br m, 3'-OH and 5'-OH), 3.96 (br s, 2 H, H-2',3'), 3.84 (m, 1 H, H-4'), 3.64 (m, 1 H, H-5'), 3.48 (m, 1 H, H-5").

^{13}C NMR (DMSO-d_6): δ = 165.5 ($^3J_{C4,H6}$ = 10.1 Hz, C-4), 155.5 ($^3J_{C2,H6}$ = 5.03, $^3J_{C2,H1'}$ = <2.0 Hz, C-2), 141.4 ($^1J_{C6,H6}$ = 181.2, $^2J_{C6,H5}$ = 3.8, $^3J_{C6,H1'}$ = 3.8 Hz, C-6), 94.0 ($^1J_{C5,H5}$ = 173.8 Hz, C-5), 89.2 ($^1J_{C1',H1'}$ = 173.8 Hz, C-1'), 84.0 ($^1J_{C4',H4'}$ = 144.8 Hz, C-4'), 74.0 ($^1J_{C2',H2'}$ = 141.9 Hz, C-2'), 69.3 ($^1J_{C3',H3'}$ = 144.8 Hz, C-3'), 60.5 ($^1J_{C5',H5'}$ = 137.6 Hz, C-5').

2',3'-Dideoxy-β-L-cytidine (19) and 3'-Deoxy-β-L-cytidine (20)

N^4-Acetyl-β-L-cytidine (**18**) was prepared from **17** (4.86 g, 0.02 mol) in a yield of 91% (5.19 g) using a modification[12] of the procedure described by Watanabe and Fox.[14]

18

Mp 177–179 °C (MeOH) [Lit.,[14] β-enantiomer: mp 174–178 °C (MeOH)]; R_f 0.68 (D2).

UV (MeOH): λ_{max} (ε) = 247.8 (12340), 289.5 nm (5330).

CD (MeOH): λ, nm (Θ × 10^{-3}) = 228.0 (+24.5), 300.0 (–17.8), 214, 260, and 330 (0).

^{1}H NMR (DMSO-d_6): δ = 10.88 (s, 1 H, NH), 8.42 (d, 1 H, $J_{5,6}$ = 8.0 Hz, H-6), 7.20 (d, 1 H, *J* = Hz, H-5), 5.78 (d, 1 H, $J_{1',2'}$ = 2.0 Hz, H-1'), 5.55 (d, 1 H, $J_{OH,H2'}$ = 4.0 Hz, 2'-OH), 5.28 (t, 1 H, $J_{OH,H5'}$ = $J_{OH,H5"}$ = 4.0 Hz, 5'-OH), 5.15 (d, 1 H, $J_{OH,H3'}$ = 2.5 Hz, 3'-OH), 3.96 (center of m, 3 H, H-2',3',4'), 3.60 (center of m, 2 H, H-5',5"), 2.10 (s, 3 H, CH_3C=O).

To a stirred suspension of **18** (2.85 g, 0.01 mol) in freshly distilled anhyd MeCN (100 mL) at 65 °C, was added dropwise a solution of AcBr (3.7 mL, 0.05 mol) in anhyd MeCN (30 mL) during 1 h. The mixture was stirred for an additional 1 h, cooled to r.t. and evaporated to dryness in vacuo. The viscous yellow oily residue was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (2 × 50 mL), dried and evaporated to afford a pale yellow foam (3.88 g, ca. 90%). The HPLC analysis of this product [(column: Waters XTerra RP18, 4.6 × 150 mm; linear gradient (10 → 50%) of buffer B (0.05 M TEAA in 80% aq MeCN) in buffer A (0.05 M TEAA) at a flow rate of 1.0 mL/min (time of analysis 30 min)] revealed the following peaks [retention time (t_R, min); (%)]: 16.05 (33.6%), 18.06 (9.7%), 19.23 (23.9%), 19.80 (18.1%), 21.36 (9.2%), and 21.87 (3.7%). The UV spectra of all peaks were very similar (λ_{max} 298–300 and 247–248 in a ratio of ca. 2:1; λ_{min} 270–272 and 228–230 nm).

The aforementioned product (3.80 g) was dissolved in MeOH (50 mL), $KHCO_3$ (3.80 g) and 10% Pd/C (0.85 g) were added, and the mixture was hydrogenated for 4 h. TLC analysis (developing solvent system: D2) of the mixture showed the presence of three main products: **17** (R_f 0.25), **19** (R_f 0.33), and **20** (R_f 0.38). Catalyst and salts were filtered off, washed with MeOH (2 × 5 mL), silica gel (10 mL) was added to the combined filtrate and washings and the mixture was evaporated to dryness in vacuo. Silica gel with products was placed on the top of a column [4 × 25 cm; packed in a CH_2Cl_2–MeOH (7:1) mixture] and the column was eluted with a mixture of CH_2Cl_2–MeOH–H_2O (70:10:1, vol) to afford, in the order of elution, **19** (0.38 g, 18%), **20** (0.36 g, 16%), and **17** (0.56 g, 23%).

19

Mp 209–211 °C (Lit.[17] mp 194–196 °C; Lit.[11c] mp 220–222 °C).

UV (H_2O): λ_{max} (ε) = 270.6 (8000), ≈230 nm (sh, 6800), λ_{min} = 250.5 nm (5600).

CD (H_2O): λ, nm (Θ × 10^{-3}): 217.0 (+13.7), 272.0 (–15.3), 237.3 (0).

^{1}H NMR (CD_3OD): δ = 8.10 (d, 1 H, $J_{5,6}$ = 8.0, H-6), 6.02 (br d, 1 H, H-1'), 5.90 (d, 1 H, H-5), 4.16 (m, 1 H, H-4'), 3.90 (dd, 1 H, $J_{5',4'}$ = 4.0, $J_{5',5"}$ = 11.0 Hz, H-5'), 3.70 (dd, 1 H, $J_{5",4'}$ = 5.0 Hz, H-5"), 2.42 (m, 1 H, H-2'), 1.80–2.10 (m, 3 H, H-2",3',3").

20

White foam.

UV (H_2O): λ_{max} (ε) = 271.0 (8100), ≈230 nm (sh, 7000); λ_{min} = 250.0 nm (5750).

CD (MeOH): λ, nm (Θ × 10^{-3}) = 215.0 (+12.6), 269.0 (–18.1), 235.0 and 312.0 (0).

^{1}H NMR (CD_3OD): δ = 8.17 (d, 1 H, $J_{5,6}$ = 7.0 Hz, H-6), 5.84 (d, 1 H, H-5), 5.72 (br s, 1 H, H-1'), 4.46 (m, 1 H, H-4'), 4.28 (dd, 1 H, $J_{2',3"}$ = 4.8, $J_{2',3'}$ = 1.8 Hz, H-2'), 3.86 (dd, 1 H, $J_{5',4'}$ = 3.0, $J_{5',5"}$ = 12.7 Hz, H-5'), 3.69 (dd, 1 H, $J_{5",4'}$ = 3.75 Hz, H-5"), 2.00 (ddd, 1 H, $J_{4',3'}$ = 9.0, $J_{3',3"}$ = 13.5 Hz, H-3'), 1.83 (ddd, 1 H, $J_{3",4'}$ = 4.65 Hz, H-3").

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