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Carbohydrate Research 270 (1995) 77–83

CARBOHYDRATE RESEARCH

Note

Synthesis of (3′*R*)-3′-deoxy-3′-*C*-nitromethylthymidine

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Received 22 September 1994; accepted 10 November 1994

Keywords: (3′*R*)-3′-Deoxy-3′-*C*-nitromethylthymidine; Anti-AIDS drug

After the discovery of 3′-azido-3′-deoxythymidine (AZT), an effective anti-AIDS drug, many structurally related nucleoside analogs targeted as inhibitors of HIV reverse transcriptase have been prepared. Among the thymidine derivatives reported, modified at the 3′-substituent supposedly modeled after the 3′-azide group of AZT, are the following ones as having the indicated groups at C-3′: $-CH_2CH=CH_2$ [1], $-CH_2-C\equiv CH$ [2], $-CH_2-C\equiv N$ [2], $-C\equiv N$ [3–8], $-CH_2N_3$ [9,10], $-CH_2NH_2$ [10], $-NHC\equiv N$ [11], –NHCHO [11–13], $-NHCO_2CH_3$ [11], $-N\equiv C$ [6,11,12,14], $-N=C=O$ [15], $-NHCONH_2$ [15], $-NHCH_2C\equiv N$ [11], $-N=C=S$ [6,12], –OCHO [16], $-SC\equiv N$ [6,17], –SEt [17,18], and $-SCOCH_3$ [19]. None of them showed activity surpassing that of AZT. Here, we have undertaken the preparation of a related compound, (3′*R*)-3′-deoxy-3′-*C*-nitromethylthymidine (**1**).

In the first synthetic attempt, 3′-deoxy-3′-oxo-5′-*O*-tritylthymidine (**3**) [20–22] was treated with nitromethane anion, with the expectation of obtaining the corresponding 3′-nitromethyl derivative. However, the reaction only gave 3-oxoglycal (**4**) [6,20,22] quantitatively. Recently Chattopadhyaya and co-workers [23] prepared 1-[3-deoxy-3-*C*-(nitromethyl)-β-D-*ribo*-pentofuranosyl]thymine (**2**) and its 3′-epimer by reaction of a 1-[2-*O*-protected-3-deoxy-5-*O*-(4-monomethoxytrityl)-β-D-*erythro*-pentofuran-3-

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SSDI 0008-6215(95)00003-8

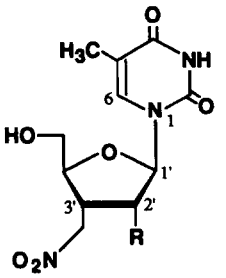
ulosyl]thymine with nitromethane anion (to give the corresponding 3′-*C*-nitromethyl-D-xylo derivative), with subsequent dehydration [giving the 3′-(nitromethylene) derivative] and $NaBH_4$ reduction. Our lack of success is ascribed to the absence of a 2′-hydroxy group; in the 2′-deoxy structure, nitromethane anion may abstract the 2′-hydrogen preferentially to give the C-2′ carbanion, which is then converted into glycal **4** with the loss of a thymine fragment.

We searched for an alternative route for **1** not utilizing a 3′-oxo compound as the starting material. Branchaud and co-workers reported [24–28] a C–C bond formation reaction using of cobaloxime-mediated radical alkyl–alkenyl or alkyl–nitroalkyl cross coupling. These authors transformed 3-deoxy-1,2;5,6-di-*O*-isopropylidene-3-iodo-D-glucofuranose into the $Co^{III}(dmgH)_2py$ complex (dmgH = dimethylglyoxime monoanion) by treatment with $[Co^{I}(dmgH)_2py]^-$ [24,27], and the complex was treated with nitromethane anion under photolysis. Cross coupling occurred [28] to give 3-deoxy-1,2;5,6-di-*O*-isopropylidene-3-*C*-(nitromethyl)-D-gluco-furanoses and -allo-furanoses (1 : 1, 48% isolated yield). We attempted to apply their procedure to our case.

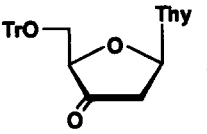
3′-Deoxy-3′-iodothymidine (**5**) [29–31] was converted into its 5′-*O*-(*tert*-butyldimethylsilyl) derivative **6** and this was treated with $Na^+[Co^{I}(dmgH)_2py]^-$ according to the procedure of Branchaud and co-workers [24,27]. The orange-colored Co complex **7** was isolated in 30% yield after flash column chromatography, along with the 3′-eno **8**, 2′-eno **9** [32,33], and 3′-deoxy derivatives **10** [34], in the ratio of 1 : 1.15 : 1.4 according to NMR analysis of the product mixture. When, however, this reaction was performed with the 5′-hydroxy compound **5**, complex formation similar to **7** was minor, and a mixture of the known 3′-eno [35], 2′-eno [17,36], and 3′-deoxy [6,29,30,32,34–37] derivatives were the major products. The structure of **7** was determined by NMR analysis. High-field resonances of H-3′ (δ 1.80 in CD_2Cl_2), and C-3′ (δ 37.3, broad, in $CDCl_3$) in the ^1H and ^{13}C NMR spectra, respectively, indicate that Co is attached to C-3′. The 3′*S* absolute configuration (that is, Co approaches C-3′ from the α-face) was determined by ^1H NOE difference spectroscopy (saturation of H-6 showed 0.8% signal enhancement of H-3′) as well as by phase-sensitive ^1H NOESY, where cross peaks were observed between H-6 and H-3′, and between H-3′ and H-5′a. All of the other functional groups present in **7** including pyridine, were confirmed by the ^1H and ^{13}C NMR spectra.

Cross coupling of **7** with nitromethane anion was then carried out under visible light in 3 : 1 ethanol–water at 10–20°C, essentially according to the method of Branchaud and co-workers [26,28]. The desired (3′*R*)-3′-(nitromethyl) derivative **11** was produced in 47% yield, together with **8** and **9** and without formation of the 3′*S*-isomer of **11**. Exclusive formation of the 3′*R*-isomer **11** may be ascribed to the presence of the bulky thymine and *tert*-butyldimethylsilyl groups on the β-face. Raising or lowering the reaction temperature, or scale-up of the preparation (more than 100 mg at one time) markedly decreased the yield of **11**. It is noteworthy that the 3′-deoxy compound **10** was not produced in this reaction. Final deprotection by acidic cleavage of the silyl group afforded **1**.

Compound **1** was inactive in an in vitro anti-HIV test, using HIV-1 infected T4 lymphocytes (CEM cell line).



1 R = H
2 R = OH



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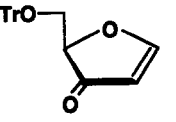

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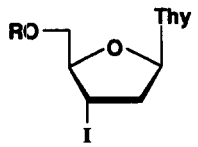
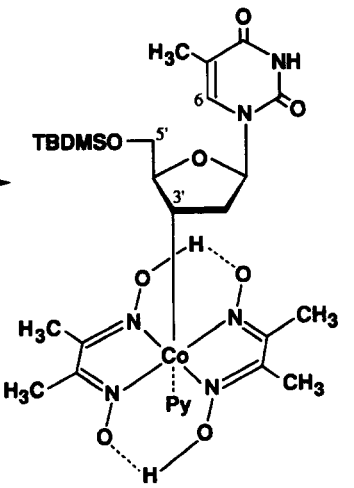


5 R = H
6 R = TBDMS



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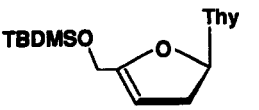

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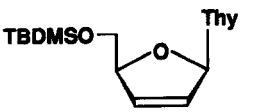

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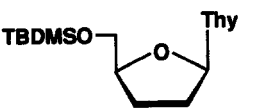
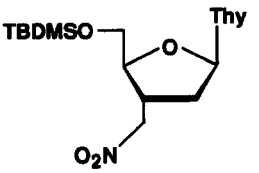


10

Tr : Ph_3C
Py : pyridine
Thy : thymin-1-yl
TBDMS : t-$Bu(Me)_2Si$



11

Experimental

General methods.—Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. IR spectra were recorded with a Jasco A-202 grating spectrophotometer. Mass spectra were recorded with a Jeol SX-102 spectrometer. NMR spectra (^{1}H at 500 MHz and ^{13}C at 125.8 MHz) were recorded, unless otherwise stated, with a Bruker AMX 500 spectrometer, using Me_4Si as the internal reference. TLC was performed on Kieselgel 60 F_{254} (Merck), and column chromatography on Wakogel C-200.

5′-O-(tert-Butyldimethylsilyl)-3′-deoxy-3′-iodothymidine (**6**).—To a solution of **5** (4.83 g, 13.7 mmol) in pyridine (48 mL) was added *tert*-butylchlorodimethylsilane (2.49 g, 16.5 mmol) and the solution was kept overnight at room temperature. Addition of water (1.5 mL) followed by evaporation gave a syrup. A chloroform extract was washed with water, dried (Na_2SO_4), and concentrated to a syrup that was purified on a short column of silica gel (4 : 1 $CHCl_3$–EtOAc) to give **6** as an amorphous solid (6.01 g, 94%). An analytical sample was prepared by crystallization from acetone–water to give needles, mp 133–134°C, $[\alpha]_D^{22}$ + 42° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}IN_2O_4Si$: C, 41.20; H, 5.84; I, 27.21; N, 6.01. Found: C, 41.37; H, 5.95; I, 26.91; N, 5.81.

Reaction of **6** *with* $Na^+[Co^I(dmgH)_2py]^-$ *to prepare [(3′S)-5′-O-tert-butyldimethylsilyl-3′-deoxythymidin-3′-yl]bis(dimethylglyoximato)(pyridine)cobalt* (**7**).—A solution of $CoCl_2 \cdot 6H_2O$ (620 mg, 2.61 mmol) and dimethylglyoxime (610 mg, 5.25 mmol) in methanol (15 mL, predeoxygenated by Ar) was cooled to −10°C and Ar was bubbled through for 30 min. To the resulting suspension were added aq 50% NaOH (210 mg as net NaOH, 5.25 mmol) and pyridine (0.21 mL, 2.60 mmol). Aqueous $NaBH_4$ (1 mL, 50 mg, 1.32 mmol) was added to the resulting dark-brown suspension and the mixture was stirred under Ar for 30 min at the temperature. Subsequently **6** (1.01 g, 2.17 mmol) in MeOH (10 mL) was added to the dark-blue suspension, followed by aq $NaBH_4$ (1 mL, 50 mg) (after 1 h a similar amount of aq $NaBH_4$ was added) and the mixture was stirred for 2 h at room temperature. TLC (1 : 1 $CHCl_3$–EtOAc) of the mixture showed several spots at R_f 0.55 (**8**), 0.5 (**9** and **10**), 0.35 − 0.3 (slight), 0.15 (**7**), and 0 (cf. **6**: R_f 0.65). Concentration of the mixture gave a residue that was extracted with $CHCl_3$. The organic solution was washed with aq 1% pyridine, dried (Na_2SO_4), and concentrated. The yellow residue was subjected to flash-column chromatography [Wakogel C-300, 1 : 1 $CHCl_3$–EtOAc (by-products containing Co (R_f 0.35 ~ 0.3) were eluted) → 3 : 1 $CHCl_3$–acetone] to afford **7** as an orange solid (453 mg, 30%), together with a mixture of **8**, **9**, and **10** (402 mg, ~ 55%). An analytical sample of **7** was prepared by reprecipitation from $CHCl_3$–hexane; $[\alpha]_D^{23}$ + 25° (*c* 1, $CHCl_3$); FAB-MS: *m/z* 629 ($M^+ - C_5H_5N$); ^{1}H NMR ($CDCl_3$): δ 0.04 and 0.05 [each s, 3 H, $(CH_3)_2Si$], 0.89 [s, 9 H, $(CH_3)_3CSi$], 1.11 (dt, 1 H, H-2′β), ~ 1.86 (dt, 1 H, H-3′; δ 1.80, dt in CD_2Cl_2), 1.87 (s, 3 H, CH_3-5), 1.93 (ddd, 1 H, H-2′α), 2.17 and 2.22 (each s, 6 H, 2 CH_3 in Co complex), 3.41 (dd, 1 H, H-5′a), 3.71 (br s, 1 H, H-4′), 3.83 (dd, 1 H, H-5′b), 5.58 (dd, 1 H, H-1′), 7.30 (m, 2 H, 2 *meta*-H of pyridine), 7.62 (deformed q, 1 H, H-6), 7.71 (m, 1 H, *para*-H of pyridine), 8.03 (br s, 1 H, NH-3), 8.54 (m, 2 H, 2 *ortho*-H of pyridine), and 18.08 (sl. br s, 2 H, 2 OH in Co complex); $J_{1',2'\alpha}$ 5.5, $J_{1',2'\beta}$ 8,

$J_{2'\alpha,2'\beta}$ 15.5, $J_{2'\alpha,3'}$ 2.5, $J_{2'\beta,3'}$ 8, $J_{3',4'} \sim 3$, $J_{4',5'a} \sim 3$, $J_{4',5'b}$ 2, and $J_{5'a,5'b}$ 11 Hz. The observation of NOE between H-6 and H-1′ suggests that the thymine ring undergoes relatively free pseudorotation, although the probability of a *syn* relationship between H-6 and H-1′ is expected to be low. Signal enhancement (%) by saturation of H-6 in CD_2Cl_2: $Si(CH_3)_2$ (1.1), CH_3-5 (6.7), H-1′ (1.3), H-2′β (3.7), H-3′ (0.8), H-5′a (0.8), and H-5′b (0.6). ^{13}C NMR ($CDCl_3$): δ −5.3 and −5.2 [$(CH_3)_2Si$], 12.2 and 12.3 (each 2 CH_3 in Co complex), 12.5 (CH_3-5), 18.6 [$(CH_3)_3CSi$], 26.0 [$(CH_3)_3CSi$], 37.3 (br, C-3′), 40.9 (C-2′), 65.8 (C-5′), 85.9 (C-1′), 86.1 (C-4′), 110.0 (C-5), 125.3 (2 *meta*-C in pyridine), 136.3 (C-6), 137.7 (*para*-C in pyridine), 150.0 (2 *ortho*-C in pyridine), 150.4 (C-2), 150.6 and 150.9 (each 2 CH_3C=N in Co complex), and 163.8 (C-4; confirmed by $^1H-^{13}C$ HMBC between CH_3-5 and C-4). All signals were confirmed by $^1H-^{13}C$ COSY. Anal. Calcd for $C_{29}H_{46}CoN_7O_8Si$: C, 49.21; H, 6.55; N, 13.85. Found: C, 49.18; H, 6.54; N, 13.76.

Separation of **8**, **9**, *and* **10**.—Column chromatography (silica gel 70 g) of the mixture of **8**–**10** (380 mg) just described, with 3 : 2 hexane–EtOAc, gave **8** as a solid (102 mg, 15%) and a mixture of **9** and **10**. In TLC (3 : 2 hexane–EtOAc), **8** had R_f 0.20, and **9** and **10**, R_f 0.15. Rechromatography of the latter mixture (silica gel, 80 g, with 5 : 1 toluene–CH_3CN) gave **9** as a solid (87.2 mg) and **10** as a solid (37.4 mg), plus a mixture of **9** and **10** (135 mg) [TLC (3 : 1 toluene–CH_3CN, three-time developments): **9**, R_f 0.4 and **10**, R_f 0.35].

*(*R*)-1-(5-*O*-tert-Butyldimethylsilyl-2,3-dideoxy-pent-3-enofuranosyl)thymine* (**8**).—Mp 87–88°C ($CHCl_3$–hexane), $[\alpha]_D^{23}$ −69° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.106 and 0.113 [each s, 3 H, $(CH_3)_2Si$], 0.93 [s, 9 H, $(CH_3)_3CSi$], 1.92 (d, 3 H, CH_3-5), 2.58 (ddq, 1 H, H-2′a), 3.23 (ddq, 1 H, H-2′b), 4.23 (sl. br s, 2 H, 2 H-5′), 5.01 (sl. br s, 1 H, H-3′), 6.70 (dd, 1 H, H-1′), 7.14 (q, 1 H, H-6), and 8.42 (br s, 1 H, NH-3); $J_{CH_3\text{-}5,6}$ 1.2, $J_{1',2'a}$ 4, $J_{1',2'b}$ 9.5, $J_{2'a,2'b}$ 17, $J_{2'b,3'}$ 2, and $J_{2'b,5'}$ 2 Hz (confirmed by irradiation of H-5′). Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.27. Found: C, 56.89; H, 7.85; N, 8.17.

*1-(5-*O*-tert-Butyldimethylsilyl-2,3-dideoxy-β-*D*-glycero-pent-2-enofuranosyl)thymine* (**9**).—Mp 174–175°C (EtOAc–hexane), lit. [32] 169–171°C, [33] 173–175°C; $[\alpha]_D^{18}$ −33° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.09 [s, 6 H, $(CH_3)_2Si$], 0.91 [s, 9 H, $(CH_3)_3CSi$], 1.90 (d, 3 H, CH_3-5), 3.85 (d, 2 H, 2 H-5′), 4.87 (ddq, 1 H, H-4′), 5.84 (ddd, 1 H, H-2′), 6.29 (dt, 1 H, H-3′), 6.97 (ddd, 1 H, H-1′), 7.33 (q, 1 H, H-6), and 8.38 (br s, 1 H, NH-3); $J_{CH_3\text{-}5,6}$ 1.2, $J_{1',2'}$ 1.5, $J_{1',3'}$ 2, $J_{1',4'}$ 4, $J_{2',3'}$ 6, $J_{2',4'}$ 2.5, $J_{3',4'}$ 2, and $J_{4',5'}$ 4 Hz. ^{13}C NMR ($CDCl_3$): δ −5.3 and −5.2 [$(CH_3)_2Si$], 12.5 (CH_3-5), 18.6 [$(CH_3)_3CSi$], 26.0 [$(CH_3)_3CSi$], 64.7 (C-5′), 87.1 (C-4′), 89.8(C-1′), 110.8 (C-5), 126.4 (C-2′), 134.6 (C-3′; confirmed by $^1H-^{13}C$ HMBC between H-5′ and C-3′), 135.9 (C-6), 150.7 (C-2), and 163.6 (C-4; confirmed by $^1H-^{13}C$ HMBC between CH_3-5 and C-4). Assignments of signals were further confirmed by $^1H-^{13}C$ COSY. Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.27. Found: C, 57.07; H, 7.69; N, 8.45.

*5′-*O*-tert-Butyldimethylsilyl-3′-deoxythymidine* (**10**).—Mp 132–133°C (needles from EtOAc–hexane), lit. [34] 125–128°C; $[\alpha]_D^{23}$ + 7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.11 and 0.12 [each s, 3 H, $(CH_3)_2Si$], 0.93 [s, 9 H, $(CH_3)_3CSi$], 1.92 (d, 3 H, CH_3-5), 1.95 ~ 2.03 (m, 3 H, H-2′a, 3′a, and 3′b), 2.31 ~ 2.42 (m, 1 H, H-2′b), 3.71 (dd, 1 H, H-5′a), 3.98 (dd, 1 H, H-5′b), 4.15 (m, 1 H, H-4′), 6.07 (unresolved dd, *J* 5 and 6.5 Hz,

1 H, H-1′), 7.57 (q, 1 H, H-6), and 8.30 (br s, 1 H, NH-3); $J_{CH_3\text{-}5,6}$ 1.2, $J_{4',5'a} = J_{4',5'b}$ 3, and $J_{5'a,5'b}$ 11.5 Hz. Anal. Calcd for $C_{16}H_{28}N_2O_4Si$: C, 56.44; H, 8.29; N, 8.23. Found: C, 56.69; H, 8.37; N, 8.48.

(3′R)-5′-O-tert-Butyldimethysilyl-3′-deoxy-3′-C-nitromethylthymidine (**11**).—To a suspension of **7** (51.0 mg, 72.1 μmol) in ethanol–water (3:1, 3 mL, predeoxygenated by Ar) in Pyrex glass vessel was added nitromethane anion [prepared by mixing CH_3NO_2 (40 μL) and 1 M NaOEt in EtOH (0.75 mL)] and the mixture was irradiated by 300 W visible light under an atmosphere of Ar with gentle stirring for 4 h at or near room temperature (10 ~ 20°C). TLC (1:1 $CHCl_3$–EtOAc) of the resulting orange solution showed spots at R_f 0.55 (**8**), 0.5 (**9**), 0.4 (**11**), and 0.3–0 (cf. **7**: R_f 0.15). Neutralization with AcOH followed by concentration gave a residue that was extracted with 3:1 $CHCl_3$–EtOAc. The soluble products isolated were chromatographed with 3:1 $CHCl_3$–EtOAc to afford **11** as a solid (13.6 mg, 47%) and a mixture of **8** and **9** (4.9 mg, 20%, the ratio being 1:0.6 as judged by the ^{1}H NMR spectrum). Compound **11**: mp 150–151°C (benzene), $[\alpha]_D^{22}$ + 6° (*c* 0.5, $CHCl_3$); IR (KBr): 1380 (ν_s NO_2), 1550 (ν_{as} NO_2), and 1680 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ 0.12 and 0.13 [each s, 3 H, $(CH_3)_2Si$], 0.93 [s, 9 H, $(CH_3)_3CSi$], 1.93 (d, 3 H, CH_3-5), 2.30 (dd, 2 H, 2 H-2′), 3.14 (apparent sextet, 1 H, H-3′), 3.78 (dd, 1 H, H-5′a), 3.91 (dt, 1 H, H-4′), 3.95 (dd, 1 H, H-5′b), 4.45 and 4.56 [each dd, 1 H, H-3″a, 3″b (CH_2NO_2-3′)], 6.14 (t, 1 H, H-1′), 7.43 (deformed q, 1 H, H-6), and 8.98 (br s, 1 H, NH-3); $J_{1',2'}$ 6, $J_{2',3'}$ 7, $J_{3',4'}$ 6, $J_{3',3''a} = J_{3',3''b}$ 7.5, $J_{3''a,3''b}$ 13, $J_{4',5'a} = J_{4',5'b}$ 3, and $J_{5'a,5'b}$ 11 Hz. Signal enhancement (%) by saturation of H-3′ (measured by a Bruker WM 250 spectrometer): H-6 (2.0), H-2′ (4.6), H-5′a (1.4), H-3″a (2.6), and H-3″b (2.4). Anal. Calcd for $C_{17}H_{29}N_3O_6Si$: C, 51.11; H, 7.32; N, 10.52. Found: C, 51.38; H, 7.19; N, 10.27.

(3′R)-3′-Deoxy-3′-C-nitromethylthymidine (**1**).—A solution of **11** (100 mg) in aq 80% AcOH (1.0 mL) was heated for 3 h at 70°C. Concentration followed by chromatography (7:1 $CHCl_3$–MeOH) of the product gave **1** as a solid (62.5 mg, 88%), $[\alpha]_D^{25}$ + 27° (*c* 0.5, H_2O); IR (KBr): 1380 ($\nu_s NO_2$), 1550 ($\nu_{as} NO_2$), and 1685 cm^{-1} (C=O). ^{1}H NMR (D_2O): δ 1.92 (d, 3 H, CH_3-5), 2.45 (ddd, 1 H, H-2′a), 2.49 (ddd, 1 H, H-2′b), 3.15 (apparent double quintets, 1 H, H-3′), 3.78 (dd, 1 H, H-5′a), 3.93 (dd, 1 H, H-5′b), 4.05 (ddd, 1 H, H-4′), 4.73 (dd, 1 H, H-3″a), 4.78 (dd, 1 H, H-3″b), 6.18 (dd, 1 H, H-1′), and 7.77 (q, 1 H, H-6); $J_{CH_3\text{-}5,6}$ 1.1, $J_{1',2'a}$ 7, $J_{1',2'b}$ 4, $J_{2'a,2'b}$ 14, $J_{2'a,3'}$ 9, $J_{2'b,3'}$ 8.5, $J_{3',4'}$ 8, $J_{4',5'a}$ 4.5, $J_{4',5'b}$ 3, $J_{5'a,5'b}$ 13, $J_{3',3''a}$ 8, $J_{3',3''b}$ 6, and $J_{3''a,3''b}$ 14 Hz. ^{13}C NMR (D_2O): δ 12.4 (CH_3-5), 36.1 (C-2′), 36.8 (C-3′), 61.9 (C-5′), 77.0 (C-3″), 83.8 (C-4′), 85.8 (C-1′), 112.0 (C-5), 138.5 (C-6), 152.5 (C-2), and 167.4 (C-4). Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.30; N, 14.73. Found: C, 46.04; H, 5.47; N, 14.67.

Acknowledgment

Anti-HIV testing was carried out by the Anti-HIV Drug Testing System in the National Cancer Institute (Bethesda, Maryland), for which the authors express deep thanks.

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