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Carbohydrate Research 320 (1999) 161–166

CARBOHYDRATE RESEARCH

Stereoselective synthesis of 3′-*C*-methylene- and 2′-methyl-3′-*C*-methylene-3′-deoxythymidine

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Received 22 March 1999; accepted 9 June 1999

Abstract

Stereoselective synthesis of 3′-*C*-methylene- and 2′-methyl-3′-*C*-methylene-3′-deoxythymidine is described, the key reaction being the formation of 3-*C*-methylene function by catalytic isomerization of a chiral epoxyalcohol, prepared from commercially available 3-methyl-2-butenal and 3-methyl-2-pentenal.

Keywords: Dideoxynucleoside; Asymmetric epoxidation; 3′-Substituted thymidine

1. Introduction

Monosaccharides with an exocyclic double bond are essential components in the synthesis of the branched glycoside moieties of 3′-substituted nucleosides with antiretroviral activity [1,2]. It is known that 3′-*C*-methylene-2′,3′-dideoxycytidine not only inhibits the reversed HIV transcriptase, but also exhibits a pronounced antitumor effect, which induced us to synthesize new thymine analogs of this compound. The synthetic availability of this class of nucleosides depends to a great extent upon the availability of the corresponding 2-deoxypentose derivatives. The objective of this study was the development of a method for the enantio- and stereoselective synthesis of derivatives of 2-deoxy-D-pentose branched at C-3 and their use in nucleoside synthesis (see Scheme 1).

2. Results and discussion

The starting compounds in this synthesis were the corresponding methyl derivatives of 2-butenal (**1a**,**b**). Silylation of **1a**,**b** was accomplished by reaction with chlorotrimethylsilane and triethylamine in the presence of sodium iodide in an acetonitrile–pentane binary system, according to the method described earlier [3], which led to 1-trimethylsilyloxy-3-methyl-1,3-butadiene (**2a**) and 1-trimethylsilyloxy-3,4-dimethyl-1,3-butadiene (**2b**) in 72 and 70% yields, respectively. Condensation of these compounds with ethyl orthoformate in the presence of $ZnCl_2$ [4] gave 5,5-diethoxy-3-methyl-2-pentenal (**3a**) and 5,5-diethoxy-3,4-dimethyl-2-pentenal (**3b**). Compounds **3a,b** were obtained as mixtures of E and Z isomers with ratios of 3:1 and 4:1, respectively, as

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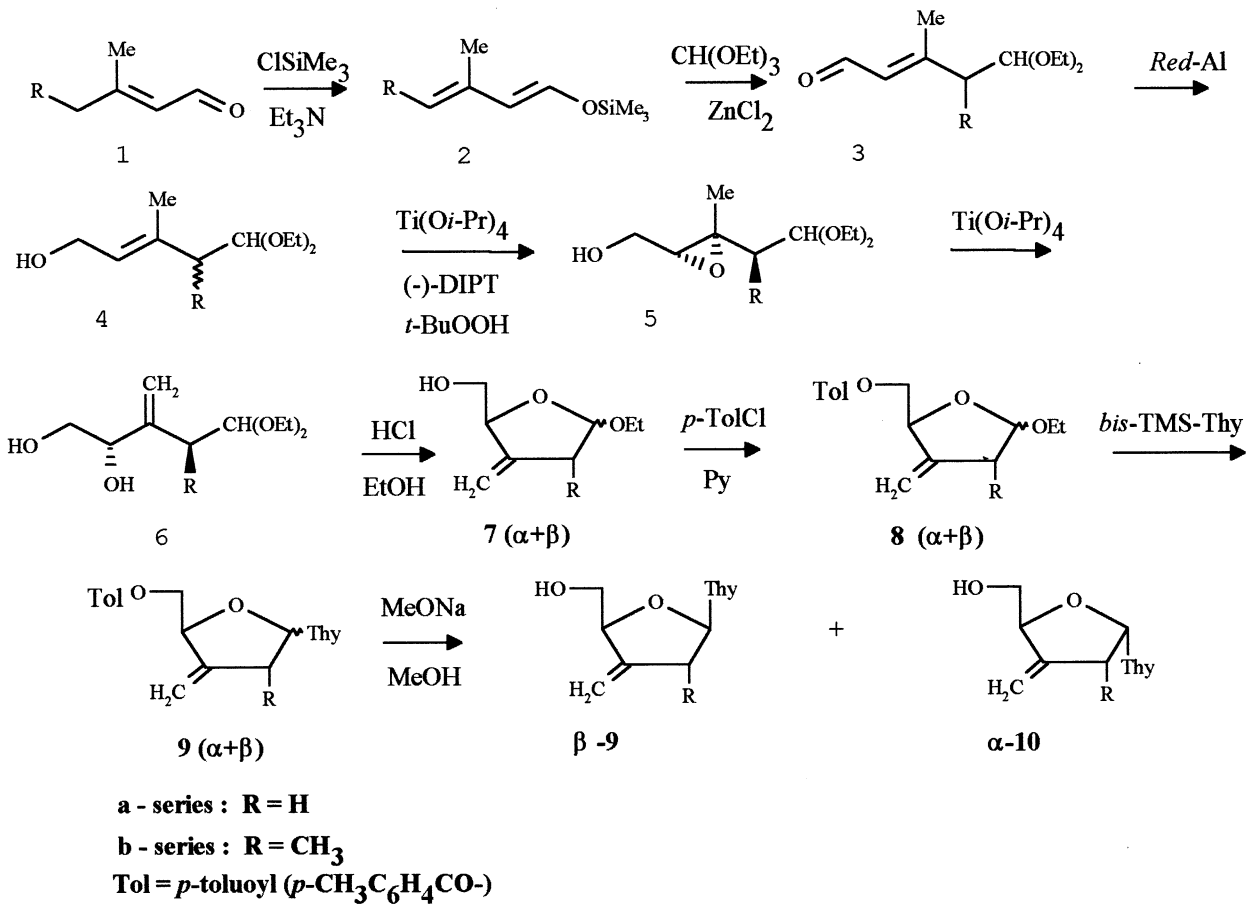
0008-6215/99/$ - see front matter
PII: S0008-6215(99)00149-4

found by ^{13}C NMR spectroscopy. Reduction of E and Z isomers of pentenal (**3a**) by Red-Al® (sodium bis(2-methoxyethoxy)aluminum hydride) led to 5,5-diethoxy-3-methyl-2-penten-1-ol (**4a**) in 81% yield. Pentenal (**3b**) was reduced according to a similar procedure, which led to 5,5-diethoxy-3,4-dimethyl-2-penten-1-ol (**4b**) in 87% yield. The ratio of the isomers in pentenols **4a,b** remained unchanged.

As our intention was to prepare nucleosides with D configurations in the sugar part, D-(−)-diisopropyl tartrate was used for the subsequent catalytic asymmetric epoxidation of the pentenols **4a,b** [5]. Epoxidation of the double E bond in allylic alcohols is known to be much faster, as compared with that of the Z bond [6]; hence allylic alcohol **4a** was epoxidated without previous separation of E and Z isomers. The ratio of E and Z isomers in epoxide (**5a**) was 49:1, respectively, as determined by NMR spectroscopy. (2*R*,3*R*)-2,3-Epoxy-3-methylpentanol (**5a**) was separated by column chromatography in 90% yield (based on E alcohol (**4a**)). The enantiomeric purity of **5a**, determined by NMR spectroscopy of the Mosher ester derivative [7] was 95%.

Asymmetric epoxidation of alcohol **4b** with an asymmetric C_2 atom affords a mixture of erythro- and threodiastereomers of epoxide **5b**. It is known that asymmetric epoxidation of chiral primary allylic alcohols is accomplished with high stereo- (predominantly erythro) and enantioselectivity, if the conditions of kinetic resolving were applied [8,9]. If the difference between epoxidation rates for the two enantiomers was insignificant, a high enantiomeric purity is observed at 50% conversion of the starting alcohol, which in its turn is achieved by decreasing the amount of oxidative agent.

In accordance with this, asymmetric epoxidation of alcohol **4b** with D-(−)-diisopropyl tartrate and 0.6 molar equivalent of *t*-butyl hydroperoxide led to *erythro*-(2*R*,3*R*)-2,3-



Scheme 1.

Table 1
^{1}H NMR data (δ, ppm) for **3a**,**b**–**8a**,**b**

Compound	C-1	C-2	C-3	C-4	C-5	C-3′	C-2′
E-**3a** [a]	101.7	45.1	159.7	129.9	191.1	18.1	
Z-**3a** [a]	102.2	38.0	159.0	130.3	191.2	26.2	
E-**3b** [a]	102.2	42.3	153.9	134.1	191.3	18.3	11.0
Z-**3b** [a]	102.9	37.3	153.6	134.5	191.2	23.3	11.2
E-**4a** [a]	102.8	44.3	133.4	128.5	58.9	16.9	
Z-**4a** [a]	102.6	37.5	134.3	128.5	58.7	21.6	
E-**4b** [a]	103.2	40.1	131.7	127.2	63.1	19.0	16.4
Z-**4b** [a]	103.4	36.8	132.6	127.4	62.9	20.2	16.6
5a [a]	101.3	43.6	58.3	64.8	61.5	17.7	
5b [a]	101.7	40.2	64.9	62.3	65.5	19.1	16.8
6a	103.3	37.4	146.1	75.6	66.2	113.4	
6b	104.0	36.8	150.0	75.6	69.7	112.4	25.0
7a-α	103.2	40.6	148.5	81.1	65.6	105.7	
7b-β	103.5	40.7	147.9	82.8	67.0	105.2	
7b-α	102.2	41.6	152.9	85.8	70.0	105.4	24.7
7b-β	102.3	40.7	152.2	86.3	71.2	105.7	24.2
8a-α	103.5	41.2	148.3	81.3	66.2	105.5	
8a-β	103.8	41.7	148.1	82.4	67.8	106.1	
8b-α	102.3	40.5	152.7	85.6	70.9	105.3	24.5
8b-β	102.6	40.7	152.1	86.4	71.2	105.8	24.3

[a] Atom numbering corresponds to numbering of the sugar atoms in **6a**,**b**–**8a**,**b**.

epoxy-3,4-dimethylpentanol (**5b**) in 85% yield, if only one enantiomer of alcohol **4b** was taken into consideration. The enantiomeric purity of **5b**, determined by NMR spectroscopy of the Mosher ester derivative, was 93%.

Epoxides **5a,b** were used as starting compounds for the synthesis of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentoses. Acyclic acetals **6a,b** were formed as a result of epoxide–allylic rearrangement of epoxyalcohols **5a,b**. The optimal yield was achieved by refluxing **5a,b** in benzene in the presence of catalytic amounts of titanium(IV) isopropoxide; the reaction was completed in 1–2 h. Subsequent cyclization of acetals **6a,b** in ethanol in the presence of a trace amount of HCl led to α- and β-ethylglycosides of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentofuranoses (**7a,b**).

Reaction of **7a,b** with *p*-toluoylchloride in the presence of pyridine under mild conditions afforded 5-*O*-toluoyloxy derivatives of the ethylfuranosides **8a,b** with 76 and 78% yields, respectively. ^{13}C NMR spectral data for **3a**,**b**–**8a**,**b** are presented in Table 1.

N-Glycosylation of *p*-toluoyloxyfuranosides **8a,b** with bis(trimethylsilyloxy)thymine was conducted in acetonitrile at 20 °C in the presence of trimethylsilyl triflate as a catalyst. After separation by column chromatography on silica gel, 5′-O-protected nucleosides **9a,b** were obtained as anomeric mixtures. Treating of anomeric mixtures **9a,b** with sodium methoxide–methanol and subsequent separation of anomers by column chromatography on silica gel afforded the desired nucleosides β-(**10a**,**b**) and α-(**11a**,**b**) with 54, 60, 22, and 19% yields, respectively. ^{1}H NMR spectral data for **9a**,**b**–**11a**,**b** are presented in Table 2.

3. Experimental

General methods.—NMR spectra were recorded in $(CD_3)_2CO$ on either Bruker AM-360 (90.56 MHz,) or Varian Gemini-300 (75 MHz) spectrometers. Optical rotations were determined with a Jasco polarimeter in MeOH. The progress of reaction was monitored by TLC on Silufol$_{254}$ (Cavalier, Czechoslovakia) silica gel plates in 10:1 $CHCl_3$–CH_3OH with spot detection by UV or by heating at 300–400 °C. Column chromatography was carried out on Silica Gel 60 (63–100 μm, E. Merck), and the systems are indicated in the text. Melting points were determined in open capillary tubes and are uncorrected. For NMR data, see Tables 1 and 2.

1-Trimethylsilyloxy-3-methyl-1,3-butadiene (**2a**).—To a suspension of anhyd NaI (180.0

g, 1.2 mol) in dry MeCN (300 mL), triethylamine (112.0 g, 1.1 mol), 3-methyl-2-butenal (**1a**) (84.0 g, 1.0 mol) and pentane (400 mL) were added at room temperature (rt). The mixture was cooled to 0 °C and $ClMe_3Si$ (109.0 g, 1.0 mol) was added dropwise, followed by heating at 40 °C. This temperature was maintained for 4 h, the resulting solid was filtered and washed with pentane (200 mL), and the solvent was evaporated at atmospheric pressure. Distillation of the residue gave **2a** (112.0 g, 72%): bp 56–60 °C/25 mmHg; n_D^{20} 1.4496. Anal. Calcd for $C_8H_{16}OSi$: C, 61.48; H, 10.32; Si, 17.97. Found: C, 61.52; H, 10.38; Si, 17.88.

1-Trimethylsilyloxy-3,4-dimethyl-1,3-butadiene (**2b**).—Prepared similarly to **2a**, but starting from **1b**. Yield: 70%; bp 68–72 °C/25 mmHg; n_D^{20} 1.4534. Anal. Calcd for $C_9H_{18}OSi$: C, 63.47; H, 10.65; Si, 16.49. Found: C, 63.52; H, 10.58; N, 16.52.

5,5-Diethoxy-3-methyl-2-pentenal (**3a**).—To a mixture of ethyl orthoformate (118.0 g, 0.80 mol) and 15% soln of $ZnCl_2$ in EtOAc (700 mL) **2a** was added (109.0 g, 0.70 mol) dropwise with stirring at rt. After 1 h at rt, satd aq $NaHCO_3$ (600 mL) was added. The resulting precipitate was filtered and washed with ether (600 mL). The aq phase was separated, the organic layer was washed with water (200 mL), dried (K_2CO_3), and concd in vacuo. Distillation of the residue gave **3a** (78.3 g, 60%): bp 88–90 °C/0.1 mmHg; n_D^{20} 1.4592. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.55; H, 9.70.

5,5-Diethoxy-3,4-dimethyl-2-pentenal (**3b**).—Prepared similarly to **3a**, but starting from **2b**. Yield: 40%; bp 98–100 °C/0.1 mmHg; n_D^{20} 1.4601. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.92; H, 10.12.

5,5-Diethoxy-3-methyl-2-penten-1-ol (**4a**).—Red-Al® (200 mL of a 30% soln in toluene, Aldrich) was added dropwise with stirring at 0 °C to a soln of **3a** (50.0 g, 0.27 mol) in ether (50 mL), and the mixture was stirred for 1 h at 0–5 °C. Satd aq NH_4Cl (150 ml) was then added dropwise at 0–5 °C, and the mixture was stirred for 1 h at 0–5 °C. The precipitated solid was filtered and washed with ether (200 mL). The organic phase was separated, dried (K_2CO_3), and concd in vacuo. Distillation of the residue gave **4a** (41.2 g, 81%); bp 95–96 °C/0.1 mmHg; n_D^{20} 1.4548. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.84; H, 10.63.

5,5-Diethoxy-3,4-dimethyl-2-penten-1-ol (**4b**).—Prepared similarly to **4a**, but starting from **3b**. Yield: 87%; bp 106–107 °C/0.1 mmHg; n_D^{20} 1.4538. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.40; H, 11.01.

(2R,3R)-5,5-Diethoxy-2,3-epoxy-3-methylpentan-1-ol (**5a**).—A mixture of powdered activated 4 Å molecular sieves (5 g) and CH_2Cl_2 (300 mL) was cooled to −20 °C. D-(−)-Diisopropyl tartrate (3.51 g, 15.0 mmol), Ti(IV) isopropoxide (2.84 g, 10.0 mmol), and *t*-butyl hydroperoxide (45.5 mL, 4.4 M in CH_2Cl_2) were added sequentially at −20 °C, and the resulting mixture was stirred for 30 min. A soln of **4a** (18.8 g, 100.0 mmol) in CH_2Cl_2 (20 mL) was then added dropwise, and stirring was maintained for 8 h at −20 °C; water (200 mL) was then added and the mixture was stirred for 1 h. The resulting suspension was filtered through a Celite pad, dried ($MgSO_4$), and evaporated. Column chromatography (hexane–ether, gradient elution) of the residue on silica gel gave **5a** (13.7 g, 67%): R_f 0.36; n_D^{20} 1.4465; $[\alpha]_D$ +19.0° (*c* 3.5, CH_3OH). Anal.

Table 2
^{1}H NMR (δ, ppm) data for **9a,b–11a,b**

Compound	H′-1	H′-2	H′-2′	H′-4	H′-5	H′-5′	2′-CH_3	=CH_2	H-6	5-CH_3	NH
9a-α	5.11	2.44	2.70	4.45	3.49	3.60		4.95	7.55	1.86	8.52
9a-β	5.15	2.47	2.71	4.30	3.61	3.62		4.97	7.64	1.87	8.55
9b-α	5.08	2.41		4.39	3.40	3.33	1.25	4.94	7.54	1.85	8.54
9b-β	5.10	2.43		4.31	3.42	3.40	1.27	4.98	7.61	1.86	8.55
10a-β	5.24	2.47	2.68	4.44	3.51	3.64		5.01	7.57	1.85	8.57
10b-β	5.18	2.40		4.32	3.60	3.32	1.26	4.98	7.56	1.88	8.55
11a-α	5.25	2.49	2.72	4.39	3.41	3.66		4.96	7.65	1.86	8.54
11b-α	5.20	2.43		4.38	3.43	3.38	1.25	4.98	7.67	1.85	8.56

Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.72; H, 9.91.

Erythro-*(2R,3R)-5,5-diethoxy-2,3-epoxy-3,4-dimethylpentan-1-ol* (**5b**).—Prepared similarly to **5a**, but starting from **4b** and with 0.6 mol equiv of *t*-butyl hydroperoxide. Yield: 85%; R_f 0.38; n_D^{20} 1.4445; $[\alpha]_D$ +9.8° (*c* 4.2, CH_3OH). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.57; H, 10.19.

2,3-Dideoxy-3-C-methylene-D-glycero-pentose diethyl acetal (**6a**).—To a soln of **5a** (2.04 g, 10.0 mmol) in dry benzene (100 mL) Ti(IV) isopropoxide (1.42 g, 5.0 mmol) was added. The mixture was stirred at 80 °C for 2 h, then satd aq $NaHCO_3$ (20 mL) was added. The precipitate was separated and washed with ether (3 × 20 mL). The organic layer was dried (K_2CO_3) and the solvent was evaporated. The residue was subjected to column chromatography with $CHCl_3$–CH_3OH (20:1, v/v), to give **6a** (1.78 g, 87%) (oil); R_f 0.36; $[\alpha]_D$ +12.2° (*c* 2.2, CH_3OH). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.84. Found: C, 58.77; H, 9.86.

2,3-Dideoxy-3-C-methylene-2-methyl-D-glycero-pentose diethyl acetal (**6b**).—Prepared similarly to **6a**, but starting from **5b**. Yield: 85% (oil); R_f 0.28; $[\alpha]_D$ +6.2° (*c* 4.2, CH_3OH). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.58; H, 10.11.

Ethyl-2,3-dideoxy-3-C-methylene-α,β-D-glycero-pentofuranoside (**7a**).—To a soln of **6a** (1.75 g, 8.6 mmol) in dry EtOH (230 mL) a 10% soln of HCl in EtOH (0.22 mL) was added at rt. The mixture was stirred for 30 min, then $NaHCO_3$ (0.8 g) was added, and the mixture was stirred for an additional 1 h. The precipitate was filtered, and the filtrate was concd in vacuo. The residue was purified by column chromatography with $CHCl_3$, which afforded **7a** (1.14 g, 84%) (oil) as an anomeric mixture; R_f 0.55 (β anomer) and 0.60 (α anomer). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.70; H, 8.95.

Ethyl-2,3-dideoxy-3-C-methylene-2-methyl-α,β-D-glycero-pentofuranoside (**7b**).—Prepared similarly to **7a**, but starting from **6b**; R_f 0.62 (β anomer) and 0.70 (α anomer). Yield: 87%. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.81; H, 9.33.

Ethyl-2,3-dideoxy-3-C-methylene-5-O-toluoyl-α,β-D-glycero-pentofuranoside (**8a**).—A cold (0 °C) soln of **7a** (1.58 g, 10 mmol) in dry pyridine (10 mL) was treated with *p*-toluoylchloride (2.07 g, 13.0 mmol). The mixture was stirred at constant temperature for 3 h, then it was concd in vacuo. The soln of the residue in $CHCl_3$ (100 mL) was washed in succession with satd aq $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried (Na_2SO_4) and concd in vacuo. The residue was purified by column chromatography with $CHCl_3$, which afforded **8a** (2.11 g, 76%) as an anomeric mixture; R_f 0.75. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.48; H, 7.32.

Ethyl-2,3-dideoxy-3-C-methylene-2-methyl-5-O-toluoyl-α,β-D-glycero-pentofuranoside (**8b**).—Prepared similarly to **8a** but starting from **7b**. Yield: 78%; R_f 0.83. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.41; H, 7.59.

1-(2,3-Dideoxy-3-C-methylene-5-O-toluoyl-α,β-D-glycero-pentofuranosyl)thymine (**9a**).—A soln of **8a** (1.39 g, 5.0 mmol) and bis(trimethylsilyloxy)thymine (1.44 g, 10 mmol) in dry MeCN (60 mL) was treated with trimethylsilyl triflate (2.1 mL, 10 mmol). The mixture was stirred at ambient temperature for 16 h, then cooled to 0 °C; the reaction was quenched with satd aq $NaHCO_3$ (20 mL) and $CHCl_3$ (100 mL) was added. The precipitate was filtered, the filtrate was dried (Na_2SO_4), and was then concd in vacuo. The residue was purified by column chromatography with 100:1 $CHCl_3$–CH_3OH, which afforded oily **9a** (1.14 g, 64%) as an anomeric mixture; R_f 0.47. Anal. Calcd for $C_{19}H_{20}O_5N_2$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.11; H, 5.62; N, 7.84.

1-(2,3-Dideoxy-3-C-methylene-2-methyl-5-O-toluoyl-α,β-D-glycero-pentofuranosyl)-thymine (**9b**).—Prepared similarly to **9a**, but starting from **8b**; R_f 0.53. Yield: 59% (oil). Anal. Calcd for $C_{20}H_{22}O_5N_2$: C, 64.88; H, 5.99; N, 7.56. Found: C, 64.79; H, 6.01; N, 7.51.

1-(2,3-Dideoxy-3-C-methylene-α-D-glycero-pentofuranosyl)thymine (**11a**) *and 1-(2,3-dideoxy-3-C-methylene-β-D-glycero-pentofuranosyl)thymine* (**10a**).—A soln of **9a** (1.79 g, 5.0 mmol) in dry CH_3OH (40 mL) was treated with 0.2 M methanolic CH_3ONa (20 mL). The

mixture was maintained at ambient temperature for 4 h and neutralized with Dowex® 50W × 1 (H^+-form, 10 mL). The mixture was then filtered and the filtrate was concd in vacuo. The residue was purified by column chromatography with 40:1 $CHCl_3$–CH_3OH, which afforded **11a** (0.65 g, 54%): mp 124–125 °C (C_2H_5OH); R_f 0.25; $[\alpha]_D$ +9.1° (*c* 0.77, CH_3OH) and oily **10a** (0.26 g, 22%): R_f 0.38. Anal. Calcd for $C_{11}H_{14}O_4N_2$ (**11a**): C, 55.46; H, 5.92; N, 11.76. Found: C, 55.41; H, 5.95; N, 11.72.

*1-(2,3-Dideoxy-3-*C*-methylene-2-methyl-α-*D*-glycero-pentofuranosyl)thymine* (**11b**) *and 1-(2,3-dideoxy-3-*C*-methylene-2-methyl-β-*D*-glycero-pentofuranosyl)thymine* (**10b**).—Prepared similarly to **11a** and **10a**, but starting from **9b**. α Anomer **11b**: yield 20%; oil; R_f 0.22. β Anomer **10b**: yield 59%; mp 130–131 °C (C_2H_5OH); R_f 0.29; $[\alpha]_D$ +11.4° (*c* 0.85, CH_3OH). Anal. Calcd for $C_{12}H_{16}O_4N_2$ (**10b**): C, 57.13; H, 6.39; N, 11.10. Found: C, 57.16; H, 6.35; N, 11.13.

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