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SYNTHESIS AND EVALUATION OF A SERIES OF 1-(3-ALKYL-2,3-DIDEOXY-α,β-D-*erythro*-PENTOFURANOSYL)THYMINES

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ABSTRACT

A series of 1-(3-alkyl-2,3-dideoxy-α,β-D-*erythro*-pentofuranosyl)thymines (3′-alkyl-3′-deoxythymidines) has been prepared from 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pent-2-enono-1,4-lactone {(*S*)-5-[(*tert*-butyldiphenylsilyl)oxymethyl]-2(5*H*)-furanone} by Michael addition of the appropriate organocopper reagent, followed by reduction of the lactone, acetylation of the resulting hemiacetal, and trimethylsilyl triflate-catalyzed coupling with 2,4-di-*O*-(trimethylsilyl)thymine. The protected nucleosides were desilylated by using tetrabutylammonium fluoride to give anomeric mixtures of the free nucleosides. The unsubstituted 2′,3′-dideoxynucleoside analog was similarly prepared from 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pentono-1,4-lactone{(*S*)5-[(*tert*-butyldiphenylsilyl)-oxymethyl]-dihydro-2(3*H*)-furanone}.

INTRODUCTION

The selection of azidothymidine [1-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine, AZT, Retrovir^R][1–3]as the first approved drug for use against acquired immune deficiency syndrome (AIDS)[4,5] has piqued an interest in evaluating a number of nucleosides for activity against the HIV virus complex, a retrovirus that is the causative agent of the disease[6,7]. Although the evidence is not firm, the 3′-azido group appears, perhaps through a slight alteration in the conformation of the furanose ring, to facilitate the conversion of AZT in to AZT triphosphate[8], the intermediate required for incorporation of the compound into DNA, where it presumably acts as a chain terminator. A natural extension of congener development based on the AZT lead is the synthesis and evaluation of other thymidine nucleosides having alkyl or other groups in place of the azido group.

One route to 3′-alkyl-2′,3′-dideoxynucleosides, which would provide an alternative to direct replacement of a 3′-hydroxyl group on an intact nucleoside, would be

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TABLE 1

200-MHz, ^{1}H-N.M.R. SPECTRAL DATA FOR COMPOUNDS **5**, **6**, AND **11a–12d**

Compound No.	*Chemical shifts (δ scale) and multiplicity[a] (apparent first-order couplings in Hz)*											
	H-1'	*H-2'a,2'b*	*H-3'*	*H-4'*	*H-5'a,5'b*[b]	C_nH_{2n}	CH_3	tert-*Bu*	*Ar*	*H-6 (Thy)*	*5-CH_3 (Thy)*	*Others*
5[c]	6.09m	2.46m[d] 1.89–2.11m		4.16m[e] 4.45m[f]	3.71m 4.03dd[g] (J_1 2.8 Hz, J_2 11.4 Hz)			1.07s[f] 1.10s[e]	7.35–7.69m	7.15a[f] 7.48s[e]	1.64s[e] 1.66s[f]	8.58s N*H*
6[c]	5.99m	2.05		4.38m,α[f] 4.02m,β[e]	3.45m					7.45s,α[f] 7.80s,β[e]	1.77s,β[e] 1.80,α[f]	4.78t O*H*-5',α 5.04t O*H*-5',β 11.24s N*H*, α,β
11a[c]	6.07m	2.09–2.80m		3.61–3.85m	4.06dd[g] (J_1 2.4Hz, J_2 11.6Hz)		1.03m[h]	1.07s[f] 1.10s[e]	7.42m 7.68m	7.22s,α[f] 7.15s,β[f]	1.61s,β[e] 1.95s,α[f]	8.36 (s, broad) NH, α,β
11b[c]	6.07m	1.54m 2.09–2.36m 2.70m[d]		3.70–3.87m	4.06dd[g] (J_1 2.2 Hz, J_2 11.4 Hz)	1.39m [n = 1]	0.93m	1.07s[f] 1.10s[e]	7.42m 7.68m	7.22s,α[f] 7.53s,β[e]	1.62s,β[e] 1.95s,α[f]	8.26s N*H*, α,β
11c[c]	6.07m	1.53m[f,d] 2.09–2.35m 2.69m[d]		3.80m	4.07m[g]	1.31m [n = 2]	0.89m	1.07s[f] 1.10s[e]	7.43m 7.68m	7.22s,α[f] 7.53s,β[e]	1.62s,β[e] 1.95s,α[f]	8.60m N*H*
11d[c]	6.08m	1.53[f,d] 2.08–2.33 m 2.70m[d]		3.67–3.91	4.06dd[g] (J_1 2.3 Hz, J_2 11.7 Hz)	1.23m [n = 3]	0.87	1.07s[f] 1.10s[e]	7.42m 7.61m	7.23s,β[f] 7.52s,α[e]	1.62s,β[e] 1.95s,α[f]	8.87s N*H*

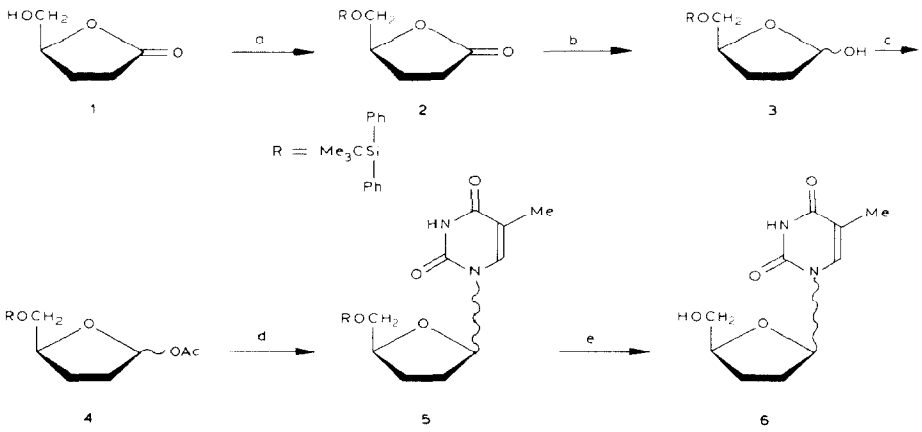
12a[c]	5.98m	1.90–2.41m		3.34–3.88m[j]		0.99d (*J* 6.2 Hz) 1.05d (*J* 6.4 Hz)	7.59s,α[f] 7.89s,β[e]	1.76s,α[e] 1.81s,β[f]	4.76 *OH*-5',α 5.09t, *OH*-5',β 11.24s, 11.27s, N*H*
12b[c]	6.11m[i]	1.65m 2.06–2.41 m 2.67m	4.00m	3.72m	1.31m [*n* = 1]	0.97ψt (*J* 7.1 Hz)	7.20d,α[f] (*J* 1.0 Hz) 7.59d,β[e] (*J* 0.98 Hz)	1.91s,β[e] 1.95s,α[f]	8.8 (s, broad) N*H* 3.90,[k] *OH*-5'
12c[c]	6.11m	1.60m[i] 2.06–2.36m 2.65m[i]	3.99m[k]	3.75m	1.36m [*n* = 2]	0.94ψt (J_1 6.4 Hz) (J_2 6.8 Hz)	7.20d,α[f] (*J* 1.1 Hz) 7.58s,β[e]	1.19s,β[e] 1.95s,α[f]	8.75 (s, broad) N*H* 4.02[l] *OH*-5'
12d[c]	6.12m	1.57m[i] 2.07–2.96m		3.43–4.15m	1.40m [*n* = 3]	0.90m[m]	7.20d,α[f] (*J* 0.93 Hz) 7.61d,β[e] (*J* 1.03 Hz)	1.90s,β[e] 1.95s,α[f]	9.15 (s, broad) N*H*

[a]Spectra were recorded for solutions in deuterated chloroform (except compounds **6** and **12a**, which were obtained in deuterated dimethyl sulfoxide) with tetramethylsilane as the internal standard. Chemical shifts (δ) are downfield from Me_4Si. Spin–spin splittings are apparent, first-order values reported in Hz: d = doublet; dd, doublet of doublets; m = multiplet; t = triplet; ψ = pseudo. [b]AB of an ABX system. [c]Mixture of anomers. [d]Part of minor product. [e]Major component. [f]Minor component. [g]H-5'b of minor component. [h]Partially overlaps with *tert*-Bu. [i]Partially overlaps with $-CH_2-$. [j]Overlaps with water. [k]Overlaps with H-5'a,5'b. [l]Overlaps with H-4'. [m]Partially overlaps with H-2'a,2'b, major component.

the Michael addition of an appropriate organocopper reagent to a protected α,β-unsaturated furanone [*e.g.*, 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pent-2-enono-1,4-lactone, i.e. (*S*)-5-(*tert*-butyldiphenylsilyl)oxymethyl)-2(5*H*)-furanone (**7**)], followed by reduction, acetylation, and nucleoside coupling. Deprotection should then afford the free nucleoside.

RESULTS AND DISCUSSION

Synthesis. — For the purpose of evaluating the strategy just outlined, use was made of optically pure 2,3-dideoxy-D-*glycero*-pentono-1,4-lactone [(*S*)-dihydro-5-(hydroxymethyl)-2(3*H*)furanone (**1**)], which is easily obtained from L-glutamic acid[9]. The 5-OH group was protected with a *tert*-butyldiphenylsilyl (TBDPS) group[10] to give **2** (ref. 11), which was then reduced with diisobutylaluminum hydride, to afford 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pentofuranose (**3**). Acetylation of **3** to give **4**, followed by coupling of the acetate **4** with 2,4-di-*O*-(trimethylsilyl)thymine, gave an anomeric mixture (α:β 1:1.2) of the protected nucleosides **5**, as determined by ^{1}H-n.m.r. spectroscopy using the resonance of H-6 or CH_3 of the thymine moiety as definitive signals, because the H-1′ resonances of the anomers were invariably overlapping. Assignments were made based on resonances reported for the known β-D anomers of similar thymidine nucleosides[12]. Another singlet located 0.33 p.p.m. upfield of H-6 of the β anomer was assigned to that of the α anomer (see Table I). The TBDPS group, which imparted u.v. activity to the carbohydrate moiety, thus facilitating the monitoring of the reactions by t.l.c., was well tolerated under the conditions of Lewis acid-catalyzed nucleoside coupling. However, these nucleosides could not be separated, either by adsorption chromatography on silica gel or reverse-phase chromatography on C_{18}-derivatized silica gel operated under high-perfor-



a, Me_3CPh_2SiCl-imidazole b, *i*-Bu_2AlH c, Ac_2O-pyridine
d, Me_3Si triflate-$(Me_3Si)_2$Thy e, Bu_4NF

mance liquid chromatography (h.p.l.c.) conditions. Deprotection of **5** was readily effected by tetrabutylammonium fluoride in tetrahydrofuran to give the mixture of anomeric nucleosides (**6**), again established in the α:β ratio of 1:1.2 by ^{1}H-n.m.r. spectroscopy (established as for **5** either by the H-6 or CH_3 resonances of the thymine moiety) and found inseparabale by h.p.l.c. The compounds were otherwise fully characterized by spectroscopic means and by elemental analysis.

In order to extend the foregoing process to the synthesis of 3′-alkyl-2′,3′-dideoxynucleosides, use was made of the Michael addition of organocopper reagents to the α,β-unsaturated lactone, 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pent-2-enono-1,4-lactone[13,14](**7**). Addition of the lithium dimethylcuprate–chlorotrimethylsilane reagent of Alexakis and coworkers[15] gave only one isomer, known [14] to be the product of stereospecific addition on the α-face of the molecule, which is in line with that earlier reported for the trityl-protected lactone[16,17].

Attempts to extend the lithium dimethylcuprate chemistry (Method A, Experimental section) to other alkyl groups met, however, with discouraging results. Addition of the lithium dialkylcuprate–chlorotrimethylsilane reagent[15] to **7** gave only poor yields of C_2–C_4 alkyl adducts[18]. However, experimentation with the phenylthiocuprate–Grignard reagent complex described by Behforouz and coworkers[19], which was developed for additions to α,β-unsaturated esters, showed that good yields

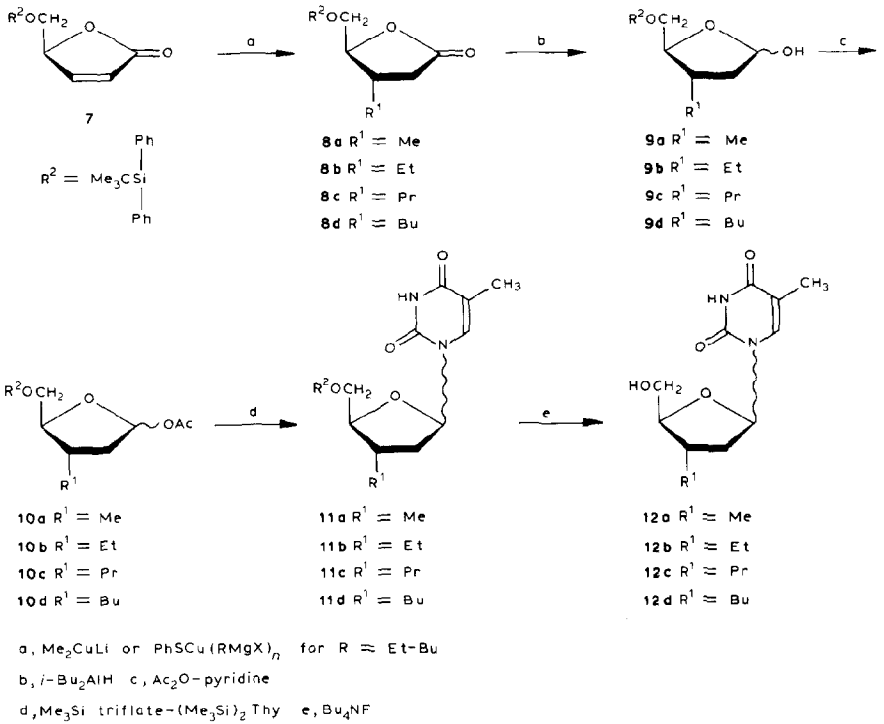


TABLE II

200-MHz, ^{1}H N.M.R. SPECTRAL DATA FOR COMPOUNDS **2–4**, **8–10**, AND **13**

Compound No.	*Chemical shifts (δ scale) and multiplicity[a] (apparent first-order couplings in Hz)*											
	H-1	*H-2a*	*H-2b*	*H-3*	*H-4*	*H-5a*	*H-5b*	C_nH_{2n}	CH_3	tert-*Bu*	*Ar*	*Others*
2		2.60m		2.28m	4.60m	3.68d[b] (J_1 3.3 Hz, J_2 11.3 Hz)	3.87dd[b] (J 3.2 Hz, J_2 11.3 Hz)			1.05s	7.35–7.73m	
3	5.48m	1.65–2.20m			4.30m	3.49–3.90m				1.05s 1.08s	7.37–7.69m	3.37d O*H*
4	6.33d	1.90–2.30m			4.38m	3.65d (J 4.3 Hz)				1.05s	7.33–7.69m	2.04s CH_3CO
8a		2.17dd[b] (J_1 6.8 Hz, J_2 17.1 Hz)	2.82dd[b] (J_1 8.6 Hz, J_2 17.1 Hz)	2.57m	4.11m	3.71dd[b] (J_1 3.5 Hz, J_2 11.5 Hz)	3.87dd[b] (J_1 3.2 Hz, J_2 11.5 Hz)		1.12d (J 6.9 Hz)	1.05s	7.35–7.69m	
8b		2.21dd[b] (J_1 6.0 Hz, J_2 17.3 Hz)	2.81dd[b] (J_1 8.8 Hz, J_2 17.3 Hz)	2.40m	4.20m	3.68dd[b] (J_1 3.5 Hz, J_2 11.4 Hz)	3.88dd[b] (J_1 3.2 Hz, J_2 11.4 Hz)	1.49m [n = 1]	0.92t (J 7.3 Hz)	1.05s	7.37–7.68m	
8c		2.20dd[b] (J_1 6.4 Hz, J_2 17.3 Hz)	2.79dd[b] (J_1 9.0 Hz, J_2 17.3 Hz)	2.47m	4.18m	3.69dd[b] (J_1 3.6 Hz, J_2 11.4 Hz)	3.87dd[b] (J_1 3.1 Hz, J_2 11.3 Hz)	1.35m [n = 2]	0.91t (J 6.8 Hz)	1.06s	7.35–7.69m	
8d		2.20dd[b] (J_1 6.4 Hz, J_2 17.3 Hz)	2.80dd[b] (J_1 8.8 Hz, J_2 17.3 Hz)	2.47m	4.19m	3.68d[b] (J_1 3.5 Hz, J_2 11.4 Hz)	3.87dd[b] (J_1 3.2 Hz, J_2 11.4 Hz)	1.29m [n = 3]	0.92t (J 6.9 Hz)	1.05s	7.32–7.73m	
9a[c]	5.41q[d] 5.55m[f]	1.61m	2.46m	2.10m	3.73m				1.03d[e] (J 8.9 Hz)	1.05s[f] 1.08s[d]	7.34–7.72m	3.29d O*H*
9b[c]	5.41q[d]	1.56m[d,g]		2.13m	3.54–3.99m			1.40m[h]	0.87m	1.06s[f]	7.32–7.72m	2.77d O*H*[f]
	5.56m[f]	1.97m[i]	2.30m					[n = 1]		1.08s[d]		3.31d O*H*[d]

9c[c]	5.41q[d] 5.55m[f]		1.59m[d,g] 2.23m[f,i]	2.13m[j]		3.53–3.96m		1.34m[h] [n = 2]	0.88m	1.06s[f] 1.08s[d]	7.35–7.71m	2.74d OH[f] 3.30d OH[d]
9d[c]	5.30m[f]		1.4–1.70m[d,g]			3.55–3.95m		1.30m[h] [n = 3]	0.87t[f] (J 6.5 Hz)	1.06s[d]	7.32–7.71m	3.22d OH[e]
	5.42m[d]		1.92–2.50m						1.04t[d,e] (J 3.8 Hz)	1.08s[f]		3.60d OH[d]
10a[c]	6.29m	1.67m[k]	2.45m[i]	2.36m	3.87m	3.71ψd (J 4.2 Hz)		—	1.10d[e] 1.14d (J 6.7 Hz)	1.05s	7.35–7.70m	2.05s CH_3CO
10b[c]	6.28m	1.57m[g]	2.37m[i]	2.14m	3.98m[f]	3.68–3.81m		1.21[h] 1.63m[h] [n = 1]	0.94m	1.05s[f] 1.06s[d]	7.35–7.70m	1.90s CH_3CO[f] 2.04s CH_3CO[d]
10c[c]	6.27m	1.71m	2.37m[i]	2.18m	3.96m[f]	3.68–3.81m		1.20 1.63	0.90t (J 6.7 Hz)	1.05s[f] 1.06s[d]	7.33–7.71m	1.90s[d] CH_3CO[d] 2.05s CH_3CO[e]
10d[c]	6.28m	1.75m[g]	2.38m[i]	2.19m	3.89m[f]	3.76m		1.13 1.59m	0.92m	1.06s[d] 1.08s[f]	7.39–7.73m	1.92s CH_3CO[d] 2.06s[f] CH_3CO
13	—	1.62m[g]	2.48d (J 9.0 Hz)	2.22m	4.17m	3.68dd[b] (J_1 4.7 Hz, J_2 11.7 Hz)	3.86dd (J_1 3.1 Hz, J_2 11.6 Hz)	1.35m [n = 3]	0.87t (J 6.8 Hz)	1.06s	7.35–7.70m	—

[a]Spectra were recorded for solutions in deuterated chloroform with tetramethylsilane as the internal standard. Chemical shifts (δ) are downfield from Me_4Si. Spin-spin splittings are apparent, first-order values reported in Hz: d = doublet; dd, doublet of doublets; m = multiplet; t = triplet; ψ = pseudo. [b]AB of an ABX system. [c]Mixture of anomers. [d]Major component. [e]Partially overlaps with *tert*-Bu. [f]Minor component. [g]Partially overlaps with -CH_2-. [h]Partially overlaps with H-2a,2b, major component. [i]Partially overlaps with H-3. [j]Partially overlaps with H-2a,2b, minor component. [k]Partially overlaps with water.

TABLE III

PHYSICOCHEMICAL DATA FOR COMPOUNDS **2–6** AND **8–13**

Compound	*Yield (%)*	R_f[a] *(Solvent)*	*Physical state*	*m.p. (°)*	$[\alpha]_D$, c *in* $CHCl_3$ *(temp.)*	*Formula*	*Elemental analysis*					
							Calculated			*Found*		
							C	*H*	*N*	*C*	*H*	*N*
2	81	0.60 *(A)*	cryst.	70–72	+28.3°, 1.8 (21)	$C_{21}H_{26}O_3Si$	71.15	7.39		71.23	7.39	
3	88	0.31 *(A)*	syrup			$C_{21}H_{28}O_3Si$	70.74	7.92		70.81	7.92	
4	92	0.49 0.54 *(B)*	syrup			$C_{23}H_{30}O_4Si$	69.31	7.59		69.40	7.65	
5	78	0.65 *(C)*	glass			$C_{26}H_{32}N_2O_4Si \cdot 0.5\ H_2O$	65.93	7.02	5.91	65.95	6.95	5.83
6	67	0.23 *(C)*	glass			[b]						
8a	87	0.16 *(D)*	syrup		+35.3°, 0.68 (20)	$C_{22}H_{28}O_3Si$	71.70	7.66		71.67	7.69	
8b	67	0.19 *(D)*	syrup		+18.0°, 2.6 (23)	$C_{23}H_{30}O_3Si$	72.21	7.90		72.28	7.92	
8c	77	0.15 *(E)*	syrup		+23.3°, 0.57 (21)	$C_{24}H_{32}O_3Si$	72.68	8.13		72.75	8.15	
8d	76	0.22 *(E)*	syrup		+3.7°, 1.2 (22)	$C_{25}H_{34}O_3Si$	73.12	8.34		73.03	8.39	

9a	100	0.38 *(A)*	syrup		$C_{22}H_{30}O_3Si$	71.31	8.16		71.34	8.17	
9b	90	0.45 *(A)*	syrup		$C_{23}H_{32}O_3Si$	71.83	8.39		71.94	8.45	
9c	98	0.50 *(A)*	syrup		$C_{24}H_{34}O_3Si$	72.32	8.60		72.38	8.61	
9d	97	0.10 *(C)*	syrup		$C_{25}H_{36}O_3Si$	72.66	8.79		[c]	[c]	
10a	86	0.43 0.49 *(B)*	syrup		$C_{24}H_{32}O_4Si$	69.87	7.82		69.95	7.85	
10b	78	0.50 0.55 *(B)*	syrup		$C_{25}H_{34}O_4Si$	70.38	8.03		70.45	8.22	
10c	84	0.53 0.58 *(B)*	syrup		$C_{26}H_{36}O_4Si$	70.87	8.23		70.97	8.27	
10d	83	0.57 0.62 *(B)*	syrup		$C_{27}H_{38}O_4Si$	71.32	8.42		71.42	8.44	
11a[d]	91	0.15 *(A)*	cryst.	48–56	$C_{27}H_{34}N_2O_4Si \cdot 0.1\ CHCl_3$[e]	66.35	7.01	5.71	66.61	7.14	5.70
11b[f]	85	0.18 *(A)*	glass		$C_{28}H_{36}N_2O_4Si \cdot 0.15\ CHCl_3$[e]	66.22	7.14	5.49	66.24	7.29	5.46
11c[g]	88	0.18 *(A)*	glass		$C_{29}H_{38}N_2O_4Si \cdot 0.1\ CHCl_3$[e]	67.39	7.40	5.40	67.22	7.42	5.32
11d[h]	86	0.20 *(A)*	semi-solid		$C_{30}H_{40}N_2O_4Si \cdot 0.2\ H_2O$	68.72	7.77	5.34	68.77	7.84	5.15

TABLE III *(continued)*

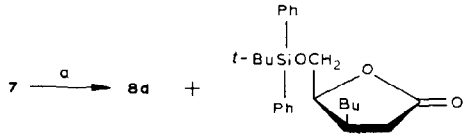
PHYSICOCHEMICAL DATA FOR COMPOUNDS **2–6** AND **8–13**

Compound	*Yield (%)*	R_F[a] *(Solvent)*	*Physical state*	*m.p. (°)*	$[\alpha]_D$, c *in CHCl₃ (temp.)*	*Formula*	*Elemental analysis*					
							Calculated			*Found*		
							C	*H*	*N*	*C*	*H*	*N*
12a[i]	95	0.13 *(F)*	cryst.	160–165		$C_{11}H_{16}N_2O_4$	54.99	6.71	11.66	54.87	6.73	11.61
12b[j]	86	0.29 *(F)*	cryst.	~21		$C_{12}H_{18}N_2O_4 \cdot 0.195\ CHCl_3$[c]	52.77	6.61	10.09	52.83	6.76	10.09
12c[k]	86	0.32 *(F)*	glass			$C_{13}H_{20}N_2O_4 \cdot 0.12\ CHCl_3$[c]	55.76	7.17	9.91	55.85	7.35	9.79
12d[l]	84	0.44 *(F)*	glass			$C_{14}H_{22}N_2O_4 \cdot 0.15\ H_2O$	58.99	7.89	9.83	59.21	8.17	9.45
13	15	0.19 (E)	glass		−2.6°, 1.52 (19)	$C_{25}H_{34}O_3Si \cdot 0.55\ H_2O$	71.40	8.41		71.22	8.62	

[a] *A*, 99:1 Chloroform–methanol; *B*, chloroform; *C*, 9:1 chloroform–methanol; *D*, 6:1 hexane–ethyl acetate; *E*, 9:1 hexane–ethyl acetate; *F*, 19:1 chloroform–methanol. [b] See ref. 23 for β anomer. [c] Unacceptable analysis. Compound **9d** was characterized as **10d**. [d] α:β ratio 1:1.5 [e] Chloroform was confirmed by ^{1}H-n.m.r. spectroscopy. [f] α:β ratio 1:1.9 [g] α:β ratio 1:1.5. [h] α:β ratio 1:1.7. [i] α:β ratio 1:1.15. [j] α:β ratio 1:1.2. [k] α:β ratio 1:1.79. [l] α:β ratio 1:1.7.

(67–87%) of the ethyl (**8b**), propyl (**8c**), and butyl (**8d**) adducts could be realized through use of the complex (see Table III and Method B, Experimental section). As with the lithium dimethylcuprate, the addition was found to be stereospecific from the α-face of the lactone, except in one experiment using the butyl reagent, where atmospheric moisture was suspected to have entered the system. In a confirming experiment, water was deliberately added to the reaction, giving rise to a substantial proportion (19%) of the *cis*-adduct, 3-*C*-butyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*threo*-pentono-1,4-lactone (**13**), in addition to the *trans*-adduct **8d**. The two compounds were easily distinguished by t.l.c., by optical rotation, and by ^{1}H-n.m.r. spectroscopy (see Tables II and III). That the compound indeed has structure **13** is supported by the ^{1}H-n.m.r. data that show for H-4 (sugar numbering) a chemical shift almost identical to that for **8d**, with large differences observed in most other sugars resonances, especially those of H-2a and H-2b. Had **13** been the product of C-4 racemization[20,21] of **7**, followed by the addition of organocuprate from the less-hindered side of the racemized lactone, the product (a *trans* adduct) would have been enantiomeric to **8d**. The diastereometric relationship between **8d** and **13** is well established by the spectroscopic and physicochemical data (see Tables II and III) cited.

Reduction of the lactones **8a–8d** proceeded as with **2**. Products **9a–9d** were



13

a, $PhSCu(RMgX)_n$

acetylated, and the acetates coupled with 2,4-di-*O*-(trimethylsilyl)thymine to give nucleosides **11a–11d** as anomeric mixtures. Deprotection afforded the free nucleosides **12a–12d**, which were obtained as mixtures of inseparable anomers. Examination of the mixtures by ^{1}H-n.m.r. spectroscopy (using the 5-CH_3 resonance, as for **5**) showed that the 3′-alkyl substituent influenced to some extent the direction of nucleoside coupling as α:β ratios of anomers of 1:1.6, 1:1.8, 1:1.7, and 1:1.7 were observed for **11a–11d**, respectively (compare, 1:1.2 for **5**). The anomeric ratios in the deprotected nucleosides **12a–12d** were, in general, slightly altered (α:β = 1:1.15, 1:1.3, 1:1.7, and 1:1.6 for **12a–12d**, respectively), due no doubt to partial separation of mixtures during column chromatography; however, neither a preparative nor an analytical separation of either the protected or free nucleosides could be achieved by h.p.l.c., operating either in the adsorption mode (on silica gel) or in the reverse-phase mode (on C-18).

Biological evaluation. — Compounds **12a–12d** were evaluated *in vitro* against herpes simplex viruses types 1 and 2 (HSV1 and HSV2) and the AIDS virus (HIV), and were found to be inactive. The ID_{50} values for the compounds were at least ten times

those of the active controls, which were acyclovir for HSV1 and HSV2, and AZT for HIV. Thus, the effect of the 3′-alkyl substituent is detrimental to the antiviral effect, possibly supporting a very recent hypothesis that the 3′-azido group might function as a mimic for the natural 3′-phosphate[22]. It is noteworthy that the β anomeric form of **6** [1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine, that is , 3′-deoxythymidine, has been determined, in at least one laboratory, to be active[23] against HIV.

EXPERIMENTAL

General procedures. — Melting points were determined on a Thomas–Hoover capillary melting-point apparatus equipped with a Cole–Parmer model 8520-50 Digi-Sense digital thermometer that was calibrated with known standards. Solutions were evaporated at aspirator vacuum at ~40°. Optical rotations at the sodium D-line were determined at the indicated temperatures, for solutions in chloroform in 1-dm cells, with a Perkin–Elmer model 241 spectropolarimeter. Thin-layer (t.l.c.) and column chromatography were carried out by using E. Merck silica gel products (aluminum-backed t.l.c. plates with a 0.2-mm coating, Cat. No. 5554) and bulk silica gel (230–400 mesh ASTM, Cat. No. 9385). T.l.c. visualization was achieved either by 245-nm u.v. light or by spray–heat development using anisaldehyde–sulfuric acid reagent[24]. ^{1}H-N.m.r. spectra at 200 MHz of ~0.1% solutions were recorded with a Nicolet NT-200 instrument. Chemical shifts are reported as δ values downfield from an internal standard of tetramethylsilane. High-performance liquid chromatography (h.p.l.c.) was conducted in an Altex–Beckman system with columns (4 x 30 cm) of Spherisorb C-18 reverse-phase media or Lichrosorb silica gel, both of 10 μm particle size. Chemicals were reagent grade and were used directly. Anhydrous solvents were prepared as follows: toluene, dried over calcium hydride and distilled from phosphorus pentaoxide; *N*,*N*-dimethylformamide, distilled *in vacuo* from calcium hydride; tetrahydrofuran, distilled from potassium-benzophenone ketyl; 1,2-dichloroethane, fractionally distilled from calcium hydride. Elemental analyses were performed by Atlantic Microlab, Inc. of Atlanta, GA.

*5-O-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-C-methyl-*D*-*erythro*-pentono-1,4-lactone* (**8a**). — *Method A. Addition of Me_2CuLi to 5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-*glycero*-pent-2-enono-1,4-lactone* (**7**). To a stirred suspension of copper(I) iodide (1.14 g, 6.0 mmol) in dry ether (10 mL), maintained at −25° under nitrogen, was added dropwise methyllithium (8.6 mL of a 1.4M solution in ether, 12.0 mmol), and the mixture was stirred for ~45 min at the same temperature. The mixture was cooled to −78°, and chlorotrimethylsilane (0.76 mL, 6 mmol) was added, followed by a solution of the butenolide[13] **7** (1.76 g, 5.0 mmol) in THF (10 mL). The mixture was held for 30 min at −78°, and then allowed to warm slowly to −10°, and monitored by t.l.c. After the butenolide was found to have reacted completely, the excess of reagent was decomposed by addition of saturated, aqueous ammonium chloride (60 mL), and the mixture was filtered. The filtrate was extracted with ether (3 x 50 mL), and the extracts were combined, dried (magnesium sulfate),

and evaporated to give a crude product which was purified by column chromatography on silica gel, using hexane–ethyl acetate as the eluant; the yield and physicochemical data are provided in Table III, and the ^{1}H-n.m.r. data in Table II.

*3-C-Alkyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-erythro-pentono-1,4 lactones* (**8b–8d**). — *Method B. Addition of PhSCu $(RMgX)_n$ to 5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-glycero-pent-2-enono-1,4-lactone* (**7**). To a slurry of phenylthiocopper (866 mg, 5 mmol)[19] in THF (20 mL) maintained at −40° under nitrogen was added dropwise the appropriate Grignard reagent (15 mmol) in THF. The mixture was allowed to warm slowly until a color change, indicating formation of the complex, was observed (~ −15°). The reaction was held at −15°, and a solution of butenolide[13] **7** (1.76 g, 5 mmol) in THF (20 mL) was added dropwise. The temperature was held between −15° and −10°, and the reaction monitored by t.l.c. until **7** had been entirely consumed (~30 min). The mixture was then added slowly to saturated, aqueous ammonium chloride (60 mL) with stirring. The cuprous thiophenoxide precipitate was filtered off, the filtrate was extracted with ether (3 x 50 mL), and the extracts were combined, dried (magnesium sulfate), and evaporated. The crude product was purified by column chromatography on silica gel and eluted with hexane–ethyl acetate; the yields and physicochemical data are provided in Table III, and the ^{1}H-n.m.r. data, in Table II.

*Preparation of 5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-glycero-pentono-1,4-lactone* (**2**). — To a solution of compound **1** (ref.9; 6.7 g, 57.7 mmol) in anhydrous DMF (50 mL) was added imidazole (5.9 g, 87.0 mmol), followed by *tert*-butylchlorodiphenylsilane (19.8 g, 72.2 mmol). The mixture was stirred for 1 h, at room temperature, methanol (50 mL) was added, the solvents were evaporated, and xylene (2 x 2 mL) was added to, and distilled from, the residue. A solution of the product in ether (250 mL) was washed with water (2 x 100 mL), dried (magnesium sulfate), and evaporated. The glassy product was triturated with hexane (4 x 100 mL) and the suspension filtered to give compound **2** (16.6 g, 81%) as a white solid. For physicochemical data, refer to Table III; for ^{1}H-n.m.r. data, see Table II.

*5-O-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-*D*-glycero-pentofuranose* (**3**) *and 3-C-alkyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-erythro-pentofuranoses* (**9a–9d**). — *General procedure.* To a solution of 4.0 mmol of lactone[11] **2**, or **8a–8d** (4.0 mmol), in toluene (30 mL), maintained under nitrogen at −70°, was added dropwise during 15 min a 1.0 M solution of diisobutylaluminum hydride in hexane (6 mL, 6 mmol). The mixture was stirred for 1.5 h at −70°; then methanol (200 mL) was added, and the mixture was stirred for 1 h at room temperature. The resulting white precipitate was filtered off and washed with methanol. The filtrates were combined and evaporated to give a syrup; this was purified by column chromatography, eluting successively with hexane and 99:1 chloroform–methanol to afford the product as a colorless syrup. For yields and physicochemical data, refer to Table III; for ^{1}H-n.m.r. data, see Table II.

*1-O-Acetyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,β-*D*-glycero-pentofuranose* (**4**) *and 1-O-acetyl-3-C-alkyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,*

β-D-erythro-*pentofuranoses* (**10a–10d**). — *General procedure.* To a solution of 3.5 mmol of **3** or **9a–9d** in 10 mL of dry pyridine was added 7 mmol of acetic anhydride (Fisher), and the mixture was stirred for 12–16 h at room temperature. The solvent was evaporated, and toluene (3 x 20 mL) was distilled from the mixture to remove traces of pyridine. The resulting syrup was dissolved in ether (200 mL), washed with water (2 x 100 mL), dried (magnesium sulfate), and evaporated. The resulting crude product was purified by column chromatography, eluting with 1:1 hexane–chloroform, to give the product as a colorless syrup. For yields of products and physicochemical data, see Table III; for ^{1}H-n.m.r. data, see Table II.

*1-[5-O-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-α,β-*D*-*glycero*-pentofuranosyl]-thymine* (**5**) *and 1-[3-C-alkyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α,β-*D*-*erythro*-pentofuranosyl]thymines* (**11a–11d**). — *General procedure.* To 2,4-di-*O*-(trimethylsilyl)thymine[25] (1.35 g, 5 mmol) in dry 1,2-dichloroethane (5 mL) was added the appropriate 1-*O*-acetyl sugar (**4** or **10a–10d**; 2.2 mmol) in dry 1,2-dichloroethane (5 mL), and then trimethylsilyl triflate (10.0 mL of a 507mM solution in 1,2-dichloroethane, 5.07 mmol). The mixture was stirred for 12–16 h at room temperature, diluted with 1,2-dichloroethane (150 mL), washed with water (2 x 100 mL), dried (magnesium sulfate), and evaporated to give a crude product which was purified by column chromatography, eluting with 99:1 chloroform–methanol. For yields of products and physicochemical data, see Table III; for ^{1}H-n.m.r. data, see Table I.

*1-(2,3-Dideoxy-α,β-*D*-glycero-pentofuranosyl)thymine* (**6**) *and 1-[3-C-alkyl-2,3-dideoxy-α,β-*D*-erythro-pentofuranosyl]thymines* (**12a–12d**). — *General procedure.* To a solution of the 5′-protected nucleosides **5** or **11a–11d** (1.2 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (2.8 mL of a 1.0M solution in THF, 2.8 mmol), and the mixture was stirred for 45 min at room temperature. The solvent was evaporated, and the product was purified by column chromatography, eluting with 9:1 chloroform–methanol for **6** and **12d**, and 19:1 chloroform–methanol for **12a–12c**. For yields of products and physicochemical data, see Table III; for ^{1}H-n.m.r. data, see Table I.

*3-C-Butyl-5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-*D*-threo-* (**13**) *and -*D*-erythro-* (**8d**) *pentono-1,4-lactone.* — To a slurry of phenylthiocopper (1.07 g, 6.20 mmol) in THF (30 mL) maintained at −40° under nitrogen atmosphere was added, during 20 min, butylmagnesium bromide (20.7 mL of a 0.90M solution in THF, 18.6 mmol). The mixture was then allowed to warm slowly to ~15°, at which temperature it had changed to a tan color, and a solution of **7** (2.17 g, 6.2 mmol) in 3.9:1 THF–H_2O (20 mL) was added during 10 min. The temperature of the mixture was maintained for 45 min between −10° and −15°. The reaction was quenched with saturated, aqueous ammonium chloride solution, and the resulting yellow solid was filtered off. The filtrate was extracted with ether (3 x 150 mL), and the extracts were combined, dried (magnesium sulfate), and evaporated. The resulting syrup was purified by column chromatography on silica gel, eluting with 9:1 hexane–ethyl acetate, to afford 1.9 g (76%) of **8d** and 0.48 g (19%) of **13**.

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