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STEREOCHEMICAL CONTROL AS A FUNCTION OF PROTECTING-GROUP PARTICIPATION IN 2-DEOXY-D-*ERYTHRO*-PENTOFURANOSYL NUCLEOSIDES*

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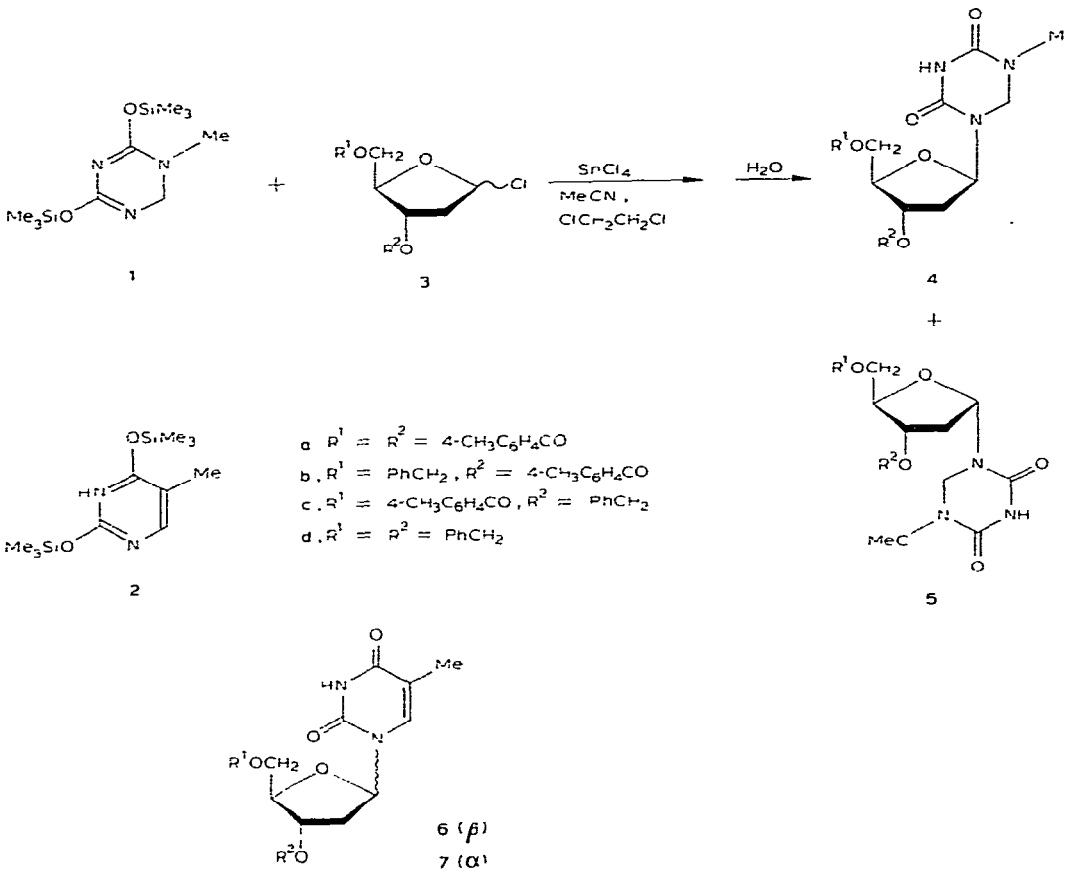
ABSTRACT

Possible features controlling the anomeric ratios in the synthesis of the antiviral antibiotic dihydro-5-azathymidine have been examined. Replacement of the 3- and 5-(4-methylbenzoyl) protecting groups in 2-deoxy-D-*erythro*-pentofuranosyl chloride by benzyl groups led to changes in anomeric ratios in stannic chloride-mediated condensations with both 5-methyl-2,4-bis(trimethylsilyl)triazine and 2,4-bis(trimethylsilyl)thymine. Analysis of the results suggested that steric elements, and more importantly, participating factors, of both the 3- and 5-protecting groups affect the anomeric ratios.

INTRODUCTION

As introduced in preceding work[1,2], the anomeric ratio of the antiviral antibiotic dihydro-5-azathymidine (**4**) obtained *via* Lewis acid-mediated condensation of the silylated triazine **1** with the 2-deoxy-D-*erythro*-pentofuranosyl chloride **3**, varies as a function of temperature and solvent. The question of anomeric control through directing effects of neighboring groups has been answered in the case of ribofuranosyl and glucopyranosyl nucleosides[3–5], wherein the adjacent 2′-*O*-acyl group participates through a 5-membered acyloxonium ion[6]. The situation with the 2′-deoxy-D-*erythro*-pentofuranosyl nucleosides is not so clear. Stereochemical results have been explained by various mechanisms ranging[7] from SN2 to SN1 mechanisms[8], with steric or participating effects of protecting groups[9] depending on the reaction conditions and reagents. To investigate the effects of protecting groups in Lewis acid-mediated 2-deoxy-D-*erythro*-pentosylations, we have independently substituted the 5- and 3-protecting groups with a non-participating, but sterically proximate group on the 2-deoxy-D-*erythro*-pentofuranoside. Specifically, this was accomplished by examining the effects, on the anomeric ratio, of substituting benzyl for 4-methylbenzoyl in the stannic chloride-mediated condensation with the triazine derivative **1** and thymine derivative **2**.

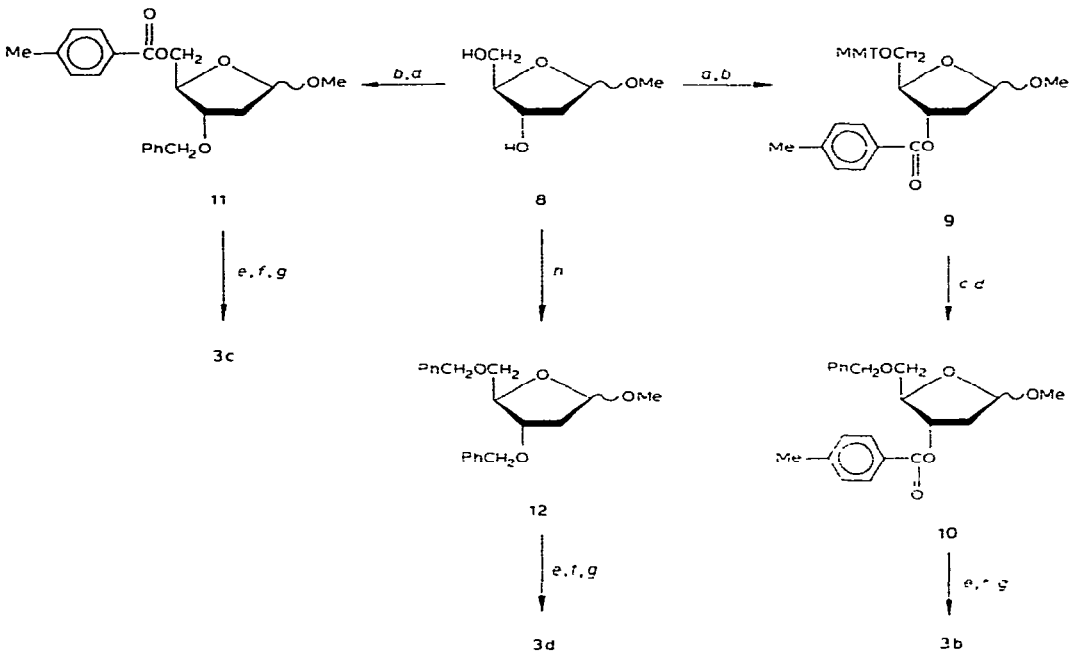
*Investigations of the Mechanism of Nucleosides Synthesis, Part II. For Part I, see ref. 2a.



RESULTS AND DISCUSSION

Examination of the concept of protecting-group participation in 2-deoxy-D-*erythro*-pentosylations required preparation of the appropriate glycosides. These were available from a common starting material, methyl 2-deoxy-D-*erythro*-pentofuranoside (**8**). The preparation of **3a** was previously described[1,10]. The preparation of **3b–d** is depicted in Scheme I. Protection of the 5-hydroxyl group of **8** with (4-methoxy phenyl)diphenylmethyl (MMT), followed by toluoylation of the 3-hydroxyl group afforded **9** in 20% yield. The use of the MMT group was necessitated by the premature hydrolysis of the aglycon during deprotection of the corresponding trityl analog with acetic acid. We found that the MMT group could be selectively cleaved by trifluoroacetic acid (2 equiv.) in chloroform at room temperature during 15 min (71% isolated yield). Alkylation with benzyl bromide employing silver(I) oxide afforded the 5-*O*-benzyl glycoside **10** in 43% yield.

As standard procedures for either the direct conversion of the 1-methoxyl into the 1-chloro group, or methoxyl into acetoxyl into chloro, resulted in substantial decomposition of substrate, a three-step procedure was employed. Brief exposure to



a, $MeOC_6H_4CPh_2Cl$, C_5H_5N, r.t. ; *b*, $4\text{-}CH_3C_6H_4COCl$, C_5H_5N, r.t. ; *c*, CF_3CO_2H, $CHCl_3$; *d*, $PhCH_2Br$, Ag_2O, Et-iso-Pr_2N, PhMe, 50° ; *e*, 80% AcOH, Δ, 20 min, *f*, Ac_2O, C_5H_5N, r.t. ; *g*, HCl, Et_2O, 0°-r.t. ; *h*, NaH, $PhCH_2Br$, $HCONMe_2$, 50°

Scheme 1

aqueous acetic acid followed by acylation with acetic anhydride gave the 1-acetate. Subsequent treatment with hydrogen chloride in ether afforded the furanosyl chloride **3b** in 55% overall yield. The preparation of **3c** involved similar chemistry with two fewer steps, and proceeded in 10% overall yield. Direct benzylation of **8** to give **12** (ref. 10b) was best accomplished with sodium hydride–*N*,*N*-dimethylformamide (45%). The sequential hydrolysis, acylation, and chlorination procedure afforded the last-required halide **3d**. Most of these reaction yields were not optimized.

Identical conditions were employed in investigating the condensation of **1** and **2** with **3a–d**. As the variously protected glycosyl chlorides reacted at different rates, and maximized nucleoside yield was not the goal of this investigation, the reactions were terminated after 2 h. Proof of structure for the triazine nucleosides **4a** and **5a** was accomplished by comparison with authentic material[1], and **4b,c** and **5b,c** by correlating their ^{1}H-n.m.r. spectra, optical rotation, and relative t.l.c. mobilities with data for **4a** and **5a**. Hydrogenation of **4d** and **5d** afforded nucleosides that were compared directly with authentic material. To confirm the regio- and stereo-chemical integrity of the thymidine series, the protected nucleosides **6a** and **7a** were compared with authentic samples[1] and **6b,c** and **7b,c** were hydrogenated over 5% palladium-on-carbon followed by deprotection with sodium methoxide–methanol to the known

TABLE I

COMPARATIVE DATA FOR GLYCOSYLATION REACTIONS

Reactants	*Products*	R^1	R^2	$\alpha:\beta$	*Yield (%)*	*Pathways*
1 + **3a**	**4a**, **5a**	4-$CH_3C_6H_4CO$	4-$CH_3C_6H_4CO$	4:1	50	$k_2 - k_3 > k_1 + k_4$
1 + **3b**	**4b**, **5b**	$PhCH_2$	4-$CH_3C_6H_4CO$	1:1	20	$k_3 \approx k_1 + k_4$
1 + **3c**	**5c**	4-$CH_3C_6H_4CO$	$PhCH_2$	α	11	$k_2 + k_3 \gg k_4$
1 + **3d**	**4d**, **5d**	$PhCH_2$	$PhCH_2$	1:1	14	$k_3 \approx k_4$
2 + **3a**	**6a**, **7a**	4-$CH_3C_6H_4CO$	4-$CH_3C_6H_4CO$	1:3	65	$k_1 + k_4 > k_2 + k_3$
2 + **3b**	**6b**, **7b**	$PhCH_2$	4-$CH_3C_6H_4CO$	1:2.5	15	$k_1 + k_4 > k_3$
2 + **3c**	**7c**	4-$CH_3C_6H_4CO$	$PhCH_2$	α	4	$k_2 + k_3 \gg k_4$
2 + **3d**	**6d**, **7d**	$PhCH_2$	$PhCH_2$	3:2	30	$k_3 > k_1$

α- and β-thymidine. Likewise, hydrogenolysis of **6d** and **7d** afforded α- and β-thymidine, comparable to authentic samples. The isomers of the protected nucleosides were in all cases isolated by p.l.c. on silica gel and anomeric assignments determined by the characteristic ^{1}H-n.m.r. resonances of H-1 (β.t;α.dd) and 5-CH_3 (α ~0.3 p.p.m. downfield from β)[1-10].

The results of these studies are presented in Table I. The anomeric ratios were determined by ^{1}H-n.m.r. spectroscopy at the protected nucleosides stage, and yields were determined after chromatography. A control experiment with **4a**,**b** demonstrated no anomeric interconversion at the nucleosides stage under the reaction conditions.

Several general trends are immediately evident from the data. Substitution of the similarly-sized, but non-participating benzyl for the participating 4-methylbenzoyl group has a striking effect at the 3-position (**3c**). This is particularly apparent on the anomeric ratio, but is also evident in the yield of nucleoside obtained. Secondly, the anomeric ratios are a function of the heterocycle involved and may result from a difference in reactivity and/or stability of the heterocycle–stannic chloride complex[2a]. The thymine–stannic chloride complex reacts substantially faster than the triazine–stannic chloride complex.

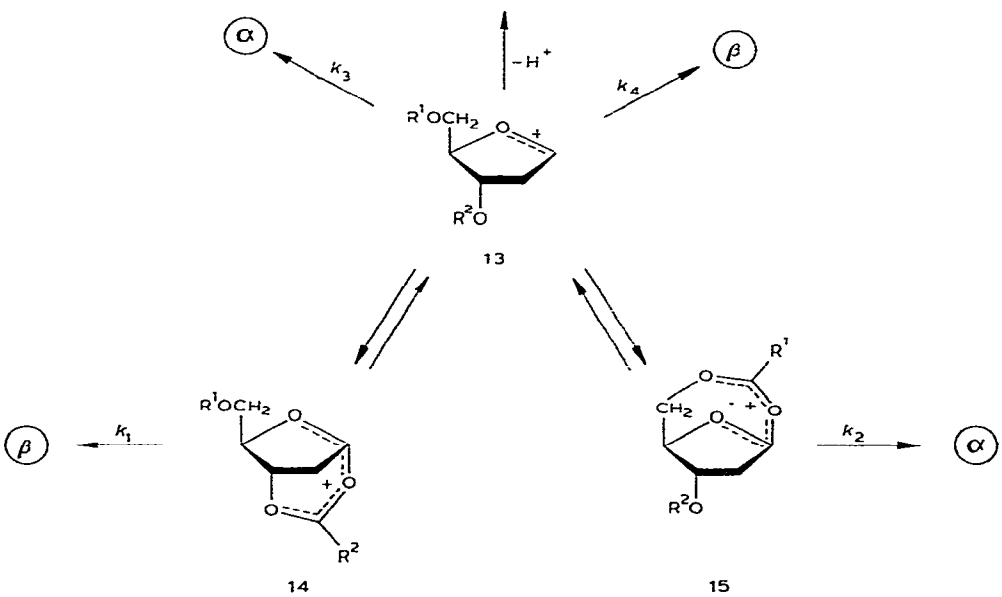
As regards participation *versus* steric effects of the protecting groups, it is apparent that removing the possibility of 5- and 3-participation (**3d**) has a moderate effect on both **1** and **2**. With triazine **1**, there was a four-fold enhancement for the β anomer relative to the ditoluoyl derivative **3a**, and a similar, but opposite effect was observed with **2**. Removing the possibility of 5-participation only, as in **3b** (namely, ion **15**), should favor β-coordination of the Sn complexes of **1** and **2** and thus lower the $\alpha:\beta$ ratio with both **1** and **2** to the exclusion of any β-nucleoside.

Šorm and co-workers[9] have examined the reaction of **3a** and the corresponding 3,5-di-*O*-(4-chlorobenzoyl)- and -(4-nitrobenzoyl)-2-deoxy-D-*erythro*-pentofuranosyl chlorides with 2,4-dimethoxy-5-methylpyrimidine in acetonitrile (Hilbert–Johnson reaction), and found only modest effects on the anomeric ratio ($\alpha:\beta$ of 5.7 (4-CH_3),

3.6 (4-Cl), and 3.8 (4-NO_2); with Hg(II) catalysis 0.9 (4-CH_3) and 2.1 (4-NO_2). For comparison, they also reported that alkylation of 2,4-dimethoxypyridine with **3d** gave of protected nucleosides in 1 : 1 anomeric ratio[10a]. It should be noted that, in all of these instances, the 3- and 5-positions always had the same protecting group. As the yield of β-anomer was enhanced when the (non-participating) benzyl group replaced the (participating) benzoate, and only minor changes were noted when different substituted benzoates were examined, it was concluded by Šorm and co-workers[9,10] that (*i*) both the 3- and 5-positions have a steric component in their effects on anomeric ratios, and (*ii*) that the steric effect is more pronounced than the participation effect.

The Lewis acid-catalyzed condensations described in this work, which allow **14** and **15** to function independently by virtue of their differential substitution, suggest conclusions that both complement and diverge from prior interpretations. We do, in fact, demonstrate steric components contributing to the anomeric ratio, but our results support the phenomenon of participation predominating over steric effects. For the triazine **1**, the following characterization of effects are found: 5-participation > 5-steric and 3-steric plus participation; for the thymine derivative **2**: 3-participation ≥ 5-participation > 3- and 5-steric.

These pathways are depicted in Scheme 2. Assuming initial ionization of **3a–d**, in the presence of the stannic chloride complexes of **1** and **2**, to **13**, (ref. 7), the α and β anomers could be derived *via* acyloxonium ions **14** and **15** when participation is possible through pathways k_1 and k_2, or by direct interception (pathways k_3 and k_4) when participation is precluded. The conclusions, then, are that for **1**, $k_2 > k_1, k_3, k_4$, and for **2** $k_1 \geqslant k_2 \gg k_3 > k_4$.



Scheme 2

One rationalization of the differences in anomeric ratios obtained with **1** and **2** may be offered within the context of differing reactivities of these bases or their respective tin complexes*. The enhancement for the β nucleoside from **3a,b** observed with the thymine-derivative **2** relative to the triazine derivative could result from k_1 predominating over the rate of the intramolecular conversion into **14** with the more reactive base, **2**. In the reaction with the less-reactive triazine (**1**), neither k_1 nor k_2 compete favorably with the rates of formation of ions **14** and **15**, respectively, thereby diminishing the relative importance of k_1 as a contribution to the β-nucleoside. This justification presupposes that the equilibrium between **13** and ions **14–15** favors **14** relative to **15**.

Although these results must be understood within the context of both substantially decreased yields with some of the glycosyl chlorides and the experimental difference between **1** and **2**, the general trends are consistent with the conclusions of participating factors predominating over steric factors as elements of anomeric control. The apparent unimportance of steric effects is further supported by other work involving the Hilbert–Johnson condensations of benzylated arabinosyl halides to produce a predominance of β-nucleoside either by direct alkylation[1–13,14,15] or with Lewis acid[5,16,17]. The existence of an intermediate such as **14** is, therefore, implicated with a definition of anchimeric assistance–stabilization, and the importance of the previously proposed intermediate **15** is further underlined with tangential steric effects apparent at both the 3- and 5-positions. Presumably, even lower $\alpha:\beta$ ratios could be realized with a more aggressive participating group at O-3 and a non-participating, sterically small group at O-5.

EXPERIMENTAL

General methods. — The solvents employed were reagent grade. Acetonitrile was distilled from calcium hydride under nitrogen and stored over 4-Å molecular sieves. 1,2-Dichloroethane was stored over 4-Å molecular sieves.

^{1}H-N.m.r. spectra were recorded on either Varian A-60-A, FT-80, or XL-100 spectrometers in $CDCl_3$ with internal Me_4Si, unless otherwise noted. Mass spectra were obtained with a CEC 21-110 spectrometer and optical rotations with a Perkin–Elmer 241 polarimeter.

*Methyl 2-deoxy-5-*O*-(4-methoxyphenyl)diphenyl-*D*-methyl-*erythro*-pento-*D*-furanoside.* — To 13.0 g (87 mmol) of methyl 2-deoxy-D-*erythro*-pentofuranoside[18] in 500 mL of pyridine was added 25.0 g (81 mmol) of chloro(4-methoxyphenyl)diphenylmethane. After stirring for 18 h at room temperature, the mixture was quenched with ice–water and then evaporated to a gum. Chromatography on silica gel (500 g) with 15% ethyl acetate–hexane as eluent gave 7.9 g (22%) of an oil; ^{1}H-n.m.r. δ 7.55–7.11, 6.83 (m, 14 H), 5.13 (m, 1 H), 4.33–4.05 (m, 3 H), 3.73 and 3.36 (s, 6 H), 3.16 (m, 2 H), and 2.12 (m, 2 H).

*The authors acknowledged the constructive suggestions of a referee on this point.

*Methyl 2-deoxy-3-*O*-(4-methylbenzoyl)-5-*O*-(4-methoxyphenyl)diphenylmethyl-*D*-erythro-pentofuranoside* (**9**). — In 100 mL of pyridine at 15° was added 7.9 g (18.8 mmol) of the preceding compound, followed by 2.89 g (18.8 mmol) of 4-methoxybenzoyl chloride. After stirring for 18 h at room temperature, the reaction was quenched with ice–water and the mixture evaporated. The residue was taken up in chloroform and the solution washed successively with 0.1M hydrochloric acid, saturated sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated to afford 8.5 g (84%) of **9** suitable for the next step: ^{1}H-n.m.r. 7.96, 7.63–7.1, 6.81 (m, 18 H), 5.13 (m, 2 H), 4.35 (q, 1 H), 3.71, 3.38 (s, 6 H), 3.31 (m, 2 H), 2.36 (s, 3 H), and 2.63–2.13 (m, 2 H).

*Methyl 2-deoxy-3-*O*-(4-methylbenzoyl)-*D*-erythro-pentofuranoside*. — To 200 mL of chloroform was added 7.1 g (13.2 mmol) of **9** followed by 2.7 mL of trifluoroacetic acid. The reaction was quenched after 15 min with 50 mL of saturated sodium hydrogencarbonate. The chloroform layer was separated, dried, and evaporated to a white foam. The material was chromatographed on silica gel (500 g) with a 20–40% ethyl acetate–hexane gradient, to afford 2.5 g of product (71%): ^{1}H-n.m.r. δ 7.96 and 7.23 (d, 4 H), 5.45–5.03 (m, 2 H), 4.27 (m, 1 H), 3.85 (m, 2 H), 3.38 (s, 3 H), 2.40 (s, 3 H), and 2.53–2.16 (m, 2 H).

*Methyl 5-*O*-benzyl-2-deoxy-3-*O*-(4-methylbenzoyl)-*D*-erythro-pentofuranoside* (**10**). — A solution of 25 mL of toluene, 2.50 g (9.3 mmol) of the preceding glycoside, 2.0 g of silver(I) oxide, 6.1 mL of benzyl bromide, and 0.64 mL of diisopropylethylamine was stirred for 18 h at 50° under nitrogen. Subsequent addition of 1.0 g of silver(I) oxide and 0.6 mL of amine, and continued heating for an additional 24 h, completed the reaction. The cooled mixture was filtered and the filtrate evaporated to a residue that was chromatographed on silica gel (300 g) with 15% ethyl acetate–hexane to give 1.42 g (42%) of **10**: ^{1}H-n.m.r. 7.91 and 7.18 (d, 4 H), 7.28 (s, 5 H), and 4.55 (s, 2 H); remainder as in **9**.

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.78. Found: C, 70.66; H, 6.70.

*1-*O*-Acetyl-5-*O*-benzyl-2-deoxy-3-*O*-(4-methylbenzoyl)-*D*-erythro-pentofuranose*. — Compound **10** (1.42 g, 4 mmol) was boiled in 80% aqueous acetic acid under reflux for 20 min (t.l.c., R_F 0.2 in 25% ethyl acetate–hexane, indicated hydrolysis to be complete). The solution was evaporated and the residue chromatographed on silica gel (20% ethyl acetate–hexane) to afford 850 mg (63%) of an oil; ^{1}H-n.m.r. analogous to that of **10** except that OCH_3 (s, δ 3.38) was replaced by OH (δ 4.5). The product was heated under nitrogen for 1 h at 50° in 20 mL of acetic anhydride and a catalytic amount of pyridine. Removal of the acetic anhydride *in vacuo* followed by azeotropic treatment with toluene and then 95% ethanol (both *in vacuo*) afforded 835 mg (90%) of an oily, anomeric mixture; ^{1}H-n.m.r. 7.95 and 7.25 (m, 4 H), 7.28 (s, 5 H), 6.43 (m, 1 H), 5.5 (m, 1 H), 4.45 (m, 1 H), 4.53 and 4.51 (5, 2 H), 3.66 (m, 2 H), 2.83–2.25 (m, 5 H, H_2 and CH_3Ph), and 2.00 and 1.91 (s, 3 H).

Anal. Calc. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.96; H, 6.18.

*Methyl 2-deoxy-5-*O*-(4-methylbenzoyl)-*D*-erythro-pentofuranoside*. — To a solution of 8.5 g (57 mmol) of methyl 2-deoxy-*D*-*erythro*-pentofuranoside in pyridine

(75 mL) at 5° under nitrogen was added 8.6 g (56 mmol) of 4-methylbenzoyl chloride dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h. To the re-cooled (5°) solution was added ice–water (10 mL) slowly and then the solution was evaporated. The residue was distributed between chloroform and water. The separated organic layer was washed with saturated sodium hydrogen carbonate followed by water, and dried. Chromatography of the residue on silica gel (600 g) with 25% ethyl acetate–hexane as eluent (which removed the diester, 950 mg) followed by 10% methanol–chloroform gave 7.8 g (51%) of the title product; ^{1}H-n.m.r. δ 7.95 and 7.23 (m, 4 H), 5.1 (m, 1 H), 4.7–4.0 (m, 5 H), 3.41 and 3.33 (s, 3 H, 11/9), 2.4 (s, 3 H), and 2.4–2.0 (m, 2 H).

Methyl 3-O-benzyl-2-deoxy-5-O-(4-methylbenzoyl)-D-erythro-*pentofuranoside* (**11**). — The foregoing glycoside (7.8 g, 29 mmol) was dissolved in toluene (80 mL) and treated with 6.24 (27 mmol) of silver oxide, 2.0 mL of ethyldiisopropylamine, and 19 mL of α-bromotoluene. The mixture was stirred under nitrogen for 36 h at 50°, filtered, and the filtrate evaporated to an oil. Chromatography on a dry-packed column of silica gel (300 g), eluting first with 10% ethyl acetate–hexane followed by 35% afforded 4.7 g (45%) of the desired product: ^{1}H-n.m.r. δ 7.94 and 7.19 (d, 4 H), 7.26 (s, 5 H), 5.09 (q, 1 H), 4.46 (s, 2 H), 4.66–4.11 (m, 5 H), 3.26 (s, 3 H), 2.35 (s, 3 H), and 2.35–2.0 (m, 2 H).

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.78. Found: C, 70.52; H, 6.98.

3-O-Benzyl-2-deoxy-5-O-(4-methylbenzoyl)-D-erythro-*pentofuranose*. — Followed the procedure detailed for **10**, 4.2 g of **11** yielded 1.72 g (43%) of the desired product, ^{1}H-n.m.r. similar to that of **11** except for the absence of the OCH_3 singlet at δ 3.26 and shifting of the H-1 signal to δ 5.6 (m).

Anal. Calc. for $C_{20}H_{22}O_5$: C, 70.15; H, 6.40. Found: C, 69.52; H, 5.76.

1-O-Acetyl-3-O-benzyl-2-deoxy-5-O-(4-methylbenzoyl)-D-erythro-*pentofuranose*. — Following the procedure detailed for **10**, 1.72 g of 3-*O*-benzyl-2-deoxy-5-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranose yielded 2.07 g (100%) of product; ^{1}H-n.m.r. similar to that of **10** with anomeric shift to δ 6.41 (m, 1 H) and Ac singlet at δ 2.03.

Anal. Calc. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.14, H, 6.28.

Methyl 3,5-di-O-benzyl-2-deoxy-erythro-*pentofuranoside*[9b] (**12**). — To 125 mL of *N,N*-dimethylformamide under nitrogen was added 7.16 g (149 mmol) of sodium hydride–oil dispersion (washed 3 times with ether), with subsequent dropwise addition of 11.0 g (74 mmol) of methyl 2-deoxy-D-*erythro*-pentofuranoside in 25 mL of *N,N*-dimethylformamide. After stirring for 60 min at room temperature and 120 min at 50°, the solution was cooled to room temperature and 13.0 mL of α-bromotoluene was added dropwise during 30 min and the mixture stirred to 18 h. The solution was brought to pH 7 with 3M hydrochloric acid and then evaporated to a solid. The residue was taken up in chloroform, washed successively with water and saturated aqueous sodium hydrogencarbonate, dried (sodium sulfate), and evaporated. Chromatography of the residue on silica gel (250 g) with 15% ethyl acetate–hexane afforded 11.0 g of product (45%); ^{1}H-n.m.r. δ 7.28 (s, 10 H), 5.04 (q, 0.5 H, α-anomeric H), 4.81

(t, 0.5 H, β-anomeric H), 4.54 and 4.54 and 4.51 (s, 4 H), 4.35–3.46 (m, 4 H), 3.80 and 3.38 (s, 3 H), and 2.31–1.86 (m, 2 H).

Anal. Calc. for $C_{20}H_{24}O_4$: C, 73.16; H, 7.37. Found: C, 72.94; H, 7.38.

*2-Deoxy-3,5-di-*O*-benzyl-*D-erythro-*pentofuranose.* — Following the procedure detailed for **10**, 1.40 g of **12** yielded 1.30 g (97%) of product (chromatography omitted: compound stored at −20° to prevent decomposition): ^{1}H-n.m.r. similar to that of **12** except for absence of the OCH_3 singlet at δ 3.80 (3.38) and the H-1 signal shifted to δ 5.54 (m).

Anal. Calc. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.54; H, 7.00.

*1-*O*-Acetyl-3,5-di-*O*-benzyl-2-deoxy-*D-erythro-*pentofuranose.* — Following the procedure detailed for **10**, 1.30 g of the foregoing furanose yielded 1.40 g (95%) of product (not very stable, even at −20° for storage: usually employed directly in the next step); ^{1}H-n.m.r.: δ 7.33 (s, 10 H), 6.39 (t, 1 H), 4.58 and 4.53 (s, 4 H), 4.45–4.03 (m, 2 H), 3.57 (m, 2 H), 2.36–2.20 (m, 2 H), and 2.05 and 1.95 (s, 3 H).

General condensation procedure[1].—Preparation of the bis(trimethylsilyl)-thymine or -dihydro-5-azathymine involved boiling a solution of 10 mL of hexamethyldisilizane under nitrogen containing 1.0 mmol of pyrimidine or triazine and several mg of ammonium sulfate for 18 h. This solution was then evaporated *in vacuo* under anhydrous conditions to a white solid (stored under high vacuum until ready to use). Preparation of the glycosyl chloride involved dissolution of 0.50 mmol of the protected 1-*O*-acetyl-D-glycofuranose in anhydrous ether (10 mL) under nitrogen and boiling hydrogen chloride into the cooled solution (5° for **3a**, **3b**, and **3c**, and −40° for **3d**) for 2 min, followed by stirring for 30 min. T.l.c. indicated product at R_F ~0.3 with starting material R_F ~0.15; 25% ethyl acetate–hexane). Evaporation of the solvent under diminished pressure afforded the product, which was employed directly. In a control reaction ^{1}H-n.m.r. revealed disappearance of the Ac singlet (δ ~2.0) and shift of H-1 to δ ~6.5.

The bis(trimethylsilyl)-pyrimidine or -triazine was dissolved in 10 mL of dry acetonitrile under nitrogen, the stirred solution was cooled to −30°, and 65 μL (0.60 mmol) of stannic chloride was added. After 3 min, the glycosyl halide in 2 mL of dry 1,2-dichloroethane was injected into the solution. The cooling bath was removed and the mixture stirred for an additional 120 min. The reaction was quenched with 10 mL of saturated aqueous sodium hydrogencarbonate and then extracted with chloroform (25 mL). The separated organic layer was washed with water, dried, evaporated, and the residue chromatographed on columns of E. Merck silica gel, with low-pressure solvent eluent.

*1-[3-*O*-Benzyl-2-deoxy-5-*O*-(4-methylbenzoyl-α-*D-erythro-*pentofuranosyl]-5,6-dihydro-5-*N*-methyl-s-triazine-2,4-(3H)-dione* (**5c**). Chromatography with 33% acetone–cyclohexane afforded 38 mg (11.5%) of product; $[\alpha]_D^{25}$ +9.2° (*c* 3.80, chloroform); ^{1}H-n.m.r.: δ 7.90 and 7.24 (d, 4 H), 7.68 (s, NH), 7.32 (s, 5 H), 6.34 (q, 1 H, $J_{1\alpha,2\alpha}$ 8 H, $J_{1\alpha,2\beta}$ 3 Hz), 4.70–4.08 (m, 8 H), 2.80 (s, NCH_3), 2.41 (3 H, s), and 2.9–1.8 (m, 2 H).

*1-[5-*O*-Benzyl-3-*O*-(4-methylbenzoyl)-2-deoxy-α,β-*D-erythro-*pentofuranosyl]-*

*5,6-dihydro-5-*N*-methyl-*s*-triazine-2,4-(3*H*)-dione* (**4b**, **5b**). — Chromatography as before afforded 22 mg (10%) of the faster-eluting β-nucleoside and 23 mg (10%) of the slower-eluting α-nucleoside. For the β anomer: $[\alpha]_D^{25}$ +34.4° (*c* 2.18, chloroform); ^{1}H-n.m.r.: δ 7.94 and 7.28 (d, 4 H), 7.4–7.1 (br. s, NH), 7.34 (s, 5 H), 6.36 (t, 1 H, *J* 7 Hz), 5.55 (m, 1 H), 4.6–4.20 (m, 5 H), 3.84 (s, 2 H), 2.58 (s, NCH_3), 2.41 (s, 3 H), and 2.4–2.2 (m, 2 H); m.s.: calc. for $C_{17}H_{29}N_3O_6$ ($PhCH_2$): 362.1352. Found: 362.1343.

Anal. Calc. for $C_{24}H_{27}N_3O_6$: C, 63.56; H, 6.00; N, 9.26. Found: C, 64.06; H, 6.22; N, 8.87.

For the α anomer: $[\alpha]_D^{25}$ +6.9° (*c* 2.31, chloroform): ^{1}H-n.m.r. 7.84 and 7.20 (d, 4 H), 7.32 (s, 5 H), 7.4 (br. s, NH), 6.36 (q, 1 H, $J_{1',2'}$ 3.5, $J_{1',2}$ 8 Hz), 5.44 (d, 1 H), 4.7–4.4 (m, 5 H), 3.65 (m, 2 H), 2.84 (s, 3 H), 24.0 (s, 3 H) and 2.9–1.81 (m, 2 H).

*1-(3,5-Di-*O*-benzyl-2-deoxy-α,β-*D*-*erythro*-pentofuranosyl)-5,6-dihydro-5-*N*-methyl-*s*-triazine-2,4-(3*H*)-dione* (**4d**, **5d**). — Chromatography with 30% acetone–cyclohexane afforded 29 mg (14%) of a 1:1 α,β mixture (inseparable), as determined by ^{1}H-n.m.r. δ 7.43 (s, NH), 7.34 (s, 10 H), 6.32–6.16 (m, 1 H, H-1′α,β), 4.54 (br. s, 6 H), 4.45–3.95 (m, 2 H), 3.65 (m, 1 H, β-H-5′), 3.43 (d, 1 H, α-H-5′), 2.76 (s, 1.5 H, α-NCH_3), 2.60 (s, 1.5 H, β-NCH_3), and 2.3–1.9 (m, 2 H).

Hydrogenation of **4d**, **5d** *to 1-(2-deoxy-α,β-*D*-erythro-pentofuranosyl)-5,6-dihydro-5-*N*-methyl-*s*-triazine-2,4-(3*H*)-dione.* — To 29 mg (0.07 mmol) of **4d**, **5d** in a pressure-hydrogenation vessel were added 3 mL of methanol and 35 mg of 10% palladium-on-carbon. The mixture was shaken under hydrogen at 38 lb.in^{-2} for 30 h, and then filtered and the filtrate evaporated *in vacuo* to a white solid. T.l.c. (two solvent systems) and ^{1}H-n.m.r. spectroscopy of the material indicated a 1:1 α,β ratio of anomers, identical to that of a standard mixture prepared from authentic materials[1].

*1-[5-*O*-Benzyl-2-deoxy-3-*O*-(4-methylbenzoyl)-α,β-*D*-erythro-pentofuranosyl]thymine* (**6b**, **7b**). — Chromatography employing 1.5% 2-propanol–chloroform afforded 35 mg (15%) of a 1:2 (α:β) mixture of nucleosides; ^{1}H-n.m.r. δ 7.90 (d, 2 H), 7.75–7.5 (m, 1 H, H-6), 7.45–7.06 (m, 7 H), 6.6–6.2 (m, 1 H), 5.52 (m, 1 H), 4.42 (m, 2 H), 3.9–3.55 (m, 2 H), 2.40 (s, 3 H), 1.86 (s, 1 H, 5-Hα), and 1.60 (s, 2 H, 5-Hβ).

*1-[3-*O*-Benzyl-2-deoxy-5-*O*-(4-methylbenzoyl)-α-*D*-erythro-pentofuranosyl]thymine* (**7c**). — Chromatography employing 30% acetone–cyclohexane gave 8 mg (3%) of product: $[\alpha]_D^{25}$ +57° (*c* 1.56, chloroform): ^{1}H-n.m.r. δ 7.83 (d, 2 H), 7.53 (s, 1 H), 7.3–7.0 (m, 7 H), 6.85 (q, 1 H, $J_{1\beta,2\beta}$ 3, $J_{1\beta,2\alpha}$ 6.5 Hz), 4.8–4.1 (m, 6 H), 2.45 (s, 3 H), 2.8–2.25 (m, 2 H), 1.75 (d, 3 H, *J* 2 Hz).

*1-(2-Deoxy-α-*D*-erythro-pentofuranosyl)thymine.* — To 8 mg of **7c** in a pressure-hydrogenation vessel were added 5 mg of 10% palladium-on-carbon and 4 mL of 95% ethanol. The mixture was shaken for 18 h at 30 lb.in^{-2} of hydrogen, filtered, and evaporated to a glass that was taken up in methanol (2 mL) and treated with 15 μL of 25% sodium methoxide–methanol. After stirring for 18 h, the solution was made neutral with Dry Ice and then evaporated to a solid that was triturated with

chloroform (4 × 5 mL). The remaining solid was identical with authentic material[1], as determined by t.l.c. and by n.m.r. spectroscopy (significant resonances, D_2O) δ 7.64 (1 H), 6.15 (q, J 3.8 Hz), and 1.87 (d, 3 H, J 2 Hz).

*1-(3,5-Di-O-benzyl-2-deoxy-α,β-*D-erythro-*pentofuranosyl)thymine* (**6d**, **7d**). — Chromatography employing 5% 2-propanol–chloroform afforded 62 mg (29%) of a 3:2 (α,β) mixture of nucleosides; ^{1}H-n.m.r.: δ 9.72 (s, NH), 7.56 (m, 1 H), 7.26 (s, 10 H), 6.47–6.32 (m, 1 H, H-1α,β), 4.56 (s, 4 H), 4.76–4.0 (m, 2 H), 3.57 (m, 2 H), 2.8–2.1 (m, 2 H), 1.78 (s, 1.8 H, H-5α), and 1.62 (s, 1.2 H, H-5β).

α,β-Thymidine. — To 62 mg of **6d**,**7d** in a hydrogenation pressure-vessel was added 7 mL of 95% ethanol and 150 mg of 10% palladium-on-carbon. This mixture was shaken for 36 h under 40 lb.in.$^{-2}$ and then filtered and the filtrate evaporated. The residue was identical by t.l.c. (two solvent systems) and ^{1}H-n.m.r. spectrum to a standard sample of authentic α,β-thymidine.

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