Calcd for C₁₄H₁₃NO₃: C, 69.12; H, 5.38. Found: C, 69.16; H, 5.37. 5,7-O-Benzylidene-2,6-anhydro-3,4-dideoxy-aldehydo-D-

arabino-hept-3-enose (15b). The nitrile 15a (0.30 g, 1.23 mmol) was dissolved in dry diethyl ether (50 mL) and cooled to 0 °C. To this was added diisobutylaluminium hydride (3 mL of a 25% solution in toluene), and the reaction mixture was stirred for 1 h. A saturated solution of ammonium chloride was then added, and the solution was filtered and dried. Evaporation of the solvent gave 15b (0.25 g, 85%) as a syrup which exhibited the following characteristics: TLC $R_f 0.63$ (D); $[\alpha]^{20}_{D} - 9.0^{\circ}$ (c 0.26, CHCl₃); ¹H NMR (200 MHz) & 3.78 (m, 2, H-6, H-6'), 4.2 (m, 1, H-5), 4.42 (m, 1, $J_{4,5} = 10.8$ Hz, H-4), 5.0 (m, 1, H-1), 5.6 (s, 1, PhCH), 5.75 $(m, 1, J_{2,3} = 10.0 \text{ Hz}, \text{H-3}), 6.20 (br d, 1, \text{H-2}).$ Anal. Calcd for C₁₄H₁₄O₄; C, 68.28; H, 5.73. Found: C, 68.34; H, 5.78.

5,7-O-Benzylidene-2,6-anhydro-3,4-dideoxy-aldehydo-Derythro-hept-2-enose (16). A solution of compound 15b (0.5 g, 2.0 mmol) in diethyl ether (50 mL) was evaporated in vacuo by using a rotary evaporator and a water bath ~ 50 °C. Gentle heating was continued until TLC (D) analysis of a sample of the residue showed that 15b had been transformed completely into a less polar product (0.43 g, 85%). For 16: mp 143-144 °C (recrystallized from ether-petroleum ether); TLC R_f 0.65 (D); $[\alpha]^{20}_{D}$ +47.0° (c 1.10, CHCl₃); ¹H NMR (60 MHz) δ 2.6 (m, 2, H-3, H-3'), 3.8-4.6 (m, 4, H-4, H-5, H-6, H-6'), 5.6 (s, 1, PhCH), 5.9 (br t, 1, $J_{2,3} = J_{2,3} = 4.0$ Hz, H-2), 7.4 (m, 5, C₆H₅), 9.2 (s, 1, CHO). Anal. Calcd for C14H14O4; C, 68.28; H, 5.73. Found: C, 68.38; H, 5.79.

5,7-O-Benzylidene-2,6-anhydro-3,4-dideoxy-D-arabinohept-3-enitol (12). (a) To a solution of the aldehyde 15b (0.10 g mmol) in dry THF (20 mL) was added lithium aluminium hydride (0.04 g), and the resulting solution was stirred for 0.5 h. The reaction mixutre was processed in the usual manner, and evaporation gave 12 as a syrup.

(b) A solution of glycal 1 (0.235 g, 1.0 mmol) in tetrahydrofuran (50 mL) was stirred at room temperature for 1 h with sodium hydride (0.03 g, 1.25 mmol). To this HMPA (3 mL) was added followed by n-Bu₃SnCH₂I²³ (0.430 g, 1.0 mmol), and the reaction mixture was stirred for an additional 6 h. Methanol was added, and the solution was evaporated to dryness. Column chromatography afforded the stannylmethyl ether 10: 80% yield; $R_f 0.72$ (B). The stannylmethyl ether 10 (0.27 g, 0.5 mmol) was dissolved in dry THF (50 mL) and cooled to -78 °C under argon. n-Butyllithium (1.5 mmol) was added, and after 0.5 h the reaction mixture was warmed to room temperature. The mixture was diluted with diethyl ether, washed with water, and dried over sodium sulfate. Evaporation of solvent gave a mixture of 11 and 12 (in 3:1 ratio) which was separated by column chromatography with 1:1 petroleum ether/ethyl acetate. Compound 12 showed following characteristics: $R_f 0.15$ (D); $[\alpha]^{20} - 7.6^{\circ}$ (c 1.2, CHCl₃); ¹H NMR (200 MHz) δ 3.45 (m, 2, H-1), 4.32 (m, 1, H-1'), 5.58 (s, 1, PhCH), 5.80 (m, 1, J_{2,3} = 10.2 Hz, H-3), 6.15 (m, 1, H-2). Anal. Calcd for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.53.

Registry No. 1, 5987-33-7; 2, 88180-31-8; 3, 88200-24-2; 4, 88180-32-9; 5, 72233-94-4; 6, 88243-83-8; 7, 72233-96-6; 8, 88180-33-0; 9a, 88180-35-2; 9b, 88180-34-1; 10, 72246-03-8; 11, 16697-45-3; 12, 72233-97-7; 13, 52485-06-0; 14, 83938-00-5; 14 (deacetyl), 88180-36-3; 15a, 88180-37-4; 15b, 88180-38-5; 16, 88180-39-6; ethyl vinyl ether, 109-92-2; diethylaluminum cyanide, 5804-85-3.

Stereocontrolled Routes to Functionalized C-Glycopyranosides¹

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4.6-O-Ethylidene-D-glucopyranose (1) reacts with an acid-washed, stabilized Wittig reagent to give the trans-oct-2-enoate 2 in excellent yield. Cyclization is effected by treatment with dilute base, and after 1 h, a 1:1 mixture of anomers exists which is the optimum concentration of the α -D form. Continuing base treatment for 5 h leads to the β -D anomer exclusively. α -D-C-Glycopyranosides can be obtained as predominant products by Lewis acid catalyzed condensation of acetylated glycals with siloxyalkenes, and anomerization to the β -D forms can be effected with potassium tert-butoxide. For a given pair of these anomers, ¹H or ¹³C NMR parameters can be used for assigning configuration α or β .

In the accompanying paper⁴ we describe some of our work on the development on stereocontrolled routes to functionalized C-glycopyranosides by means of [3,3] or [2,3] sigmatropic rearrangements. These processes ensured the stereochemistry of the product, and in many cases the yields were excellent. Nevertheless, in the hope of providing a greater range of products, other routes have been examined, and these are reported herein.

Chain Extension. The pioneering work of Zhdanov on application of the Wittig reaction for carbohydrate chain

extension⁵ paved the way for the development of routes to C-glycofuranosides from glycofuranoses.⁶ Having utilized this methodology for our work on nonactic acid, we were prompted to examine comparable routes to Cglycopyranosides. 4,6-O-Ethylidene-D-glucopyranose (1) was a readily accessible starting material,⁸ and its chain extension to the trans-octenoate 2 in 87% yield was achieved (see Scheme I). Premature in situ cyclization⁵ could be averted by subjecting the phosphorane to an acid wash prior to use (see Experimental Section). Following Zhdanov's lead,⁵ we cyclized 2 with base, the process being

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Scheme I





Figure 1. Reaction of the trans-octenoate 2 with 0.01 M sodium methoxide in methanol. The optical rotations were taken at the sodium D line.

monitored polarimetrically. With 0.01 molar equiv of base, the reaction occurred at a manageable rate, leading to the curve shown in Figure 1. The substance isolated after equilibrium had been established was shown by 220-MHz ¹H NMR to be a single anomer. On the other hand, if the reaction was quenched by acidification at maximum rotation (1 h) a 1:1 mixture (NMR estimation) of 3 and 4 was obtained.

The specific rotation of the anomer isolated at equilibrium was -32.7° , while that of the 1:1 mixture was $+5.9^{\circ}$. Assuming a two-component mixture, the optical rotation of the "other" anomer can be calculated to be +44.6°. On the basis of Hudson's rule of isorotation,⁹ which has been known to hold for some C-glycosides,¹⁰ the less dextrorotatory, thermodynamically preferred product should have the β -D anometric configuration 3. Chemical proof of configuration was considered necessary, and we sought to take advantage of the olefinic ester 5, whose synthesis was described in the accompanying paper.⁴ Thus, the pure anomer 3 was subjected to the Tipson-Cohen reductive elimination¹¹ whereby the olefinc ester 6 was obtained. The ¹³C NMR parameters of esters 5 and 6 were used for assinging the anomeric configurations in accordance with

the γ -effect rule of Stothers¹² which predicts that C-5 of ester 5 should be shielded relative to C-5 of 6. Gratifyingly, the observed values for 5 and 6 were 65.824 and 70.912 ppm, respectively. Hudson's rule therefore holds for the anomers 3 and 4.

The thermodynamic preference for the β anomer 3 undoubtedly reflects the tendency of the C-1-alkyl substituent to be equatorially oriented. The disfavored α anomer could conceivably be isolated by trapping as lactone 7. Imidazole is known to promote hydrolysis of esters, and hence the octenoate 2 was subjected to this reagent in water for 1.5 h at room temperature. In addition to esters 3 and 4, 7 was indeed formed, but unfortunately it was isolated in only 24% yield.

The formation of 3 gave us easy access to the pure β -D-C-glycopyranoside, but a ready route to the corresponding α -D system was still lacking. We sought to take advantage of the recent work of Mukaiyama, who has demonstrated the coupling of ketals or acetals with siloxvalkenes.¹³ Noyori has recently suggested that this process occurs via oxo-carbonium ion intermediates.¹⁴ Hex-2-enopyranosides such as 8 ought to be favorable substrates in view of the ease with which the alkoxyl group is lost to the Lewis acid, with the formation of ion 10^{15} (Scheme II). In fact, treatment of 8a with α -(trimethylsiloxy)styrene (9) and aluminum trichloride did give a mixture of C-glycosides 11 and 12, 21% yield. However, the major product (31%) showed the presence of ethoxyl in the ¹H NMR and a free hydroxyl group (IR) which could be acetylated. This information is consistent with 14a.

Obviously the cyclic and acyclic ions 10 and 13, respectively, were competing. Mukaiyama has reported the enhanced reactivity of isopropyl acetals toward siloxyalkenes.¹⁶ However, the isopropyl glycoside 8b fared equally badly, 14b being isolated in 30% yield along with 11 and 12.

In view of this failure, an even better leaving group was required at the anomeric center. The formation of Cglycofuranosides by reaction of siloxyalkenes with fura-

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Table I. Reaction of Tri-O-acetyl-D-glucal (15) with α -(Trimethylsiloxy)styrene (9)

entry	solvent	catalyst	temp, °C	time, h	12/11 ratio	% yield
1	CH,Cl,	BF ₃ ·Et ₂ O	-40-0	0.5	4:1	99
2	CH,Cl,	BF, Et, O	-78	2.5		1
3	CH,CI,	AlČl	-40-0	1	7:3	92
4	CH,CI,	CF ₂ SO ₂ -SiMe ₂ ²⁹	23	0.3	7:3	75
5	THF	BF , Et, O	-40 to $+23$	5		1
6	$\mathbf{T}\mathbf{H}\mathbf{F}$	AlĈI,	-40-0	18		
7	\mathbf{THF}		23	36	7:3	77
8	CH ₂ CN	BF ,Ĕt,O	-45-0	0.75		1
9	CH,CN	AlČl,	-45 to +10	1	4:1	97

nosyl acetates was reported by Hanessian and Pernet.^{10b} Indeed, the appropriate structure, pseudoglucal triacetate (16),¹⁷ reacted smoothly, giving no evidence of acyclic products. Isomers 11 and 12 were isolated in 22% and 38% yields, respectively.

These modest yields indicate that 16 is a plausible precursor; however, tri-O-acetyl-D-glucal (15) was a logical alternative, since ion 10 is easily generated therefrom as demonstrated in the Ferrier reaction.¹⁵ Furthermore, the overall routes to 11 and 12 would be shorter since, as indicated in Scheme II, triacetate 16 is (usually) prepared from $15.^{17}$ (While this phase of our work was in progress, the related studies of Grynkiewicz and BeMiller were published.)^{18,19}

Several variations in the reaction conditions were examined, and these are summarized in Table I. In general,

boron trifluoride etherate, the traditional reagent for the Ferrier reaction,^{15,20} gave excellent results with methylene chloride as the solvent. However, when THF was used, substantial amounts of starting material were recovered, presumably because of complex formation between the solvent and the Lewis acid.

In the hope of achieving greater stereoselectivity than the 4:1 shown in entry 1 of Table I, we noted that Schmidt and Rücker²¹ had recently shown that the use of acetonitrile as a solvent for glycosylation reactions had enhanced the formation of the α anomer, owing to the intermediacy of the isonitrilium ions (17, Scheme II), which adopts the β configuration as the consequence of the antianomeric effect. However, as is apparent from entries 8 and 9 in Table I, these hopes were not fulfilled in our case.

Structural Assignments. Before proceeding further, justification for assignment of structures 11 and 12 is warranted. The major and minor isomers have specific rotations of $+35.7^{\circ}$ and $+111.3^{\circ}$, respectively, and hence

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Routes to Functionalized C-Glycopyranosides

could have been assigned as the β -D and α -D configurations, respectively, in keeping with Hudson's rule⁹ which was found to hold for 3 and 4 (vide supra). However, in the ¹³C NMR spectrum, the C-5 resonance in the major isomer was 5 ppm further upfield than in the minor isomer, and these data suggested the reverse of the foregoing assignment. Thus, the minor, more dextrorotatory product is the β anomer 11, and the major, less dextrorotatory is 12, *disobeying* Hudson's rule.

Guided by the discoveries of Achmatowicz and Burkowski,²² we sought support for these revised assignments from the ¹H NMR spectra. The β anomer 11 is expected to be conformationally stable since all substituents are in the preferred equatorial orientations. However, in the case of the α anomer, some configurational mobility would be experienced,^{19,22} so that the observed value for $J_{6,7}$ will be ~9 Hz for the ⁴H₁ from 12 and 1.5 for the ¹H₄ from 12'. Accordingly, the observed values of $J_{6,7}$ were 3.5 Hz for 12 \approx 12' and 8.7 Hz for 11.

From the data for compounds described in this and the preceding paper, the structural assignments indicated in Chart I of the accompanying paper⁴ for a given anomeric pair appear to be general.

Anomerization Studies. The ratio of 11 and 12 found in the addition shown in Scheme II was found to be constant throughout the life of the reaction. Each anomer was recovered unchanged after being exposed separately to the reaction conditions, showing thereby that interconversion between anomers does not occur during the reaction. In other words, the observed ratio 4:1 for 11 and 12 is kinetic.

Weak bases could be used safely for deacetylation, since upon reacetylation, the pure anomeric diacetate, 11 or 12, was regenerated intact. However, with potassium *tert*butoxide in benzene, the α anomer, 12, was isomerized, giving a 2:1 mixture of 11 and 12 along with a number of uncharacterized degradation products. Clearly with these unsaturated *C*-glycosides, the β anomers 3 and 11 are thermodynamically preferred.

In view of the above encouraging results a number of other systems were studied, the results of which are shown in Scheme III. With triacetyl glucal and 1-(trimethylsiloxy)cyclohexene (18, entry 2), the product, 19, appeared by NMR to be a mixture of three isomers in a 95% total yield. No attempt was made to isolate or identify these; so the β/α ratio was not determined. Ferrier initially reported that triacetylgalactal displayed low reactivity in the Ferrier reaction;²⁰ however, as is evident from entry 3, the isomers 21 and 22 were isolated and 25% and 70% yields, respectively. The highly reactive glycal 23b gave interesting results. Only the α anomer 24 was isolated in approximately 90% yield. The assignment of stereochemistry to 24 is based on the similarity of the coupling constant $(J_{6.7} = 4 \text{ Hz})$ to that in 12 (3.5 Hz, vide supra). The alkylation of diacetylarabinal 25 was less satisfying since the product was a complex mixture, 26 being the only isolable substance in 12% yield. With the 2-acetoxyglycal 27 (entry 6) a complex mixture of substances was obtained which was not investigated. Addition of the sugar-derived siloxyalkene 28 to triacetylglucal (14) did not give the C-glycopyranoside 29 which was a reasonable expectation in view of the formation of 19 (entry 2).

In summary, we have shown in this paper that β -D-Cglycopyranosides, such as 3 and 11, bearing an active methylene group at C-1 are the thermodynamically preferred anomers. The latter, e.g., 4 and 12, which are formed under the kinetic conditions described herein or by the sigmatropic rearrangement procedures described in the accompanying paper,⁴ can be smoothly anomerized by treatment with potassium *tert*-butoxide.

Experimental Section

General Methods. For general experimental conditions see the accompanying paper.⁴

Methyl 2,3-Dideoxy-6,8-O-ethylidene-D-gluco-oct-2(E)enoate (4). (Carbomethoxymethylene)triphenylphosphorane (20 g, 60 mmol) was dissolved in acetonitrile (150 mL), and the resulting solution was stirred with Dowex 50W-X2 (acid form) for 10 min. The mixture was filtered and 4,6-O-ethylidene-Dglucopyranose (1; 10 g, 48 mmol) was added to the filtrate. The solution was refluxed with stirring for 60 h. The solvent was removed, yielding a brown syrup from which triphenylphosphine oxide was removed by crystallization from diethyl ether. Evaporation of the supernatant liquid left an oil (25 g) which yielded crystalline 2 from methylene chloride. The supernatant liquid was evaporated to dryness and the residue chromatographed by using solvent F. Unreacted ethylideneglucose (1.6 g) was recovered, and more 2 was obtained, bringing the total yield to 9.3 g (87% based on recovered starting material). Compound 2 showed the following characteristics: mp 132.5-133 °C; TLC R_f 0.25 (F); $[\alpha]_{D}^{20}$ -62.9° (c 1.44, MeOH); IR (neat) 3400 (OH), 1715 (C=O) cm⁻¹; ¹H NMR (80 MHz, D₂O) δ 1.40 (d, 3, J = 6 Hz, H₃CCH), 3.55 (m, 2, H-8 and H-8'), 3.80 (s, 3, H₃CO), 4.0 (m, 3, H-5, H-6 and H-7), 4.55 (m, 1, H-4), 4.8 (q, , H₃CCH), 6.18 (dd, 1, $J_{2,3} = 16$ Hz, $J_{2,4} = 1.5$ Hz, H-2), 7.02 (dd, 1, $J_{3,4} = 5.8$ Hz, H-3). Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.37; H, 6.91. Found: C, 50.35; H, 7.04.

Cyclization of 2. (a) To Completion: Methyl (4',6'-O-Ethylidene- β -D-glucopyranosyl)acetate (3). A solution of the α,β -unsaturated ester 2 (46 mg, 0.18 mmol) in methanolic potassium hydroxide (3 mL, 5 × 10⁻³ M) was placed in a polarimeter cell, and the optical rotation was recorded as a function of time over a 10-h period to give the plot shown in Figure 1. After neutralization with Dowex 50W-X2 (H⁺), the mixture was filtered and evaporated to dryness, yielding the title compound 3 as a pale yellow oil (44 mg, 96%). Purification was effected by PTLC (solvent, F). For 3: TLC R_1 0.35 (F); $[\alpha]^{20}$ -32.7° (c 0.58, CHCl₃); IR (neat) 1730 (C=O) cm⁻¹; ¹H NMR (220 MHz) 1.36 (d, 3, J =5 Hz, H₃CC), 2.50 (dd, 1, $J_{1,7} = 8.5$ Hz, $J_{7,7'} = 16$ Hz, H-7), 2.86 (dd, 1, $J_{1,7'} = 4.0$ Hz, H-7'), 3.2–3.7 (m, 7, H-2, H-3, H-4, H-5, H-6, 2 OH), 3.69 (s, 3, H₃CO), 3.79 (ddd, 1, $J_{1,2} = 3.5$ Hz, H-1), 4.12 (dd, 1, $J_{5,6'} = 9.5$ Hz, H-6'), 4.70 (q, 1, CH₃CH). Anal. Calcd for C₁₁H₁₈O₇: C, 50.35 H, 6.91. Found: C, 49.42; H, 6.51.

(b) To Maximum Rotation. Ester 2 was treated as described in part a, but as soon as the optical rotation had reached its maximum value (ca. 1 h), the reaction was quenched by the addition of Dowex 50W-X2 (H⁺). The mixture was filtered and evaporated to dryness, yielding a clear oil (46 mg) which was subjected to PTLC (F). Starting material (8 mg, 17%) was recovered. The product was obtained as a clear oil (37 mg, 80%) consisting of an inseparable mixture of 3 and 4. ¹H NMR (220 MHz) indicated that the anomers were present in equal amounts.

For the mixture: $[\alpha]^{20}_{D} + 5.9^{\circ}$ (c 0.54, CHCl₃).

Significant features of the ¹H NMR (220 MHz) spectrum attributable to 4: δ 2.67 (dd, 1, $J_{1,7} = 9.0$ Hz, $J_{7,7'} = 15.0$ Hz, H-7), 2.85 (partially obscured by H-7' of the β anomer, H-7'), 4.59 (ddd, 1, $J_{1,2} = 5.0$ Hz, $J_{1,7'} = 5.0$ Hz, H-1).

Methyl (2',3'-Dideoxy-4',6'-O-ethylidene- β -D-erythrohex-2'-enopyranosyl)acetate (6). The cyclized ester 3 (1.8 g, 6.9 mmol) was dissolved in dry pyridine (50 mL), the solution was cooled to 0 °C, and methanesulfonyl chloride (3 mL, 39 mmol) was added dropwise. After 2 h ice-cold water (10 mL) was added, and the reaction mixture was extracted with diethyl ether (300 mL) and processed in the usual way to yield a brown oil. Silica gel chromatography with solvent D yielded a yellow oil (1.8 g, 61%) which was consistent with the disulfonate [¹H NMR δ 3.20 (s, 3, CH₃SO₃), 3.27 (s, 3, CH₃SO₃)]. A portion of the oily compound (1.14 g, 2.7 mmol) was dissolved in dry dimethylformamide (10 mL), and sodium iodide (1.75 g, 11.7 mmol) and freshly prepared, dried zinc-copper couple (0.80 g, 12.2 mmol) were added.¹¹ The reaction mixture was refluxed with stirring for 1.25 h, after which

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^a All reactions were carried out in methylene chloride by using boron trifluoride etherate as a catalyst under the typical conditions described for 15 in the Experimental Section.

time it was poured into water and extracted repeatedly with diethyl ether. The ethereal extract was washed with water, dried, and evaporated, yielding a yellow oil (0.4 g) which was chromatographed with solvent D. Compound 6 was obtained as a clear oil (0.170 g, 27%) which upon further purification by TLC (solvent D) gave the following characteristics: TLC R_f 0.75 (D); $[\alpha]^{20}_{\rm D}$ +49.39° (c 1.37, CHCl₃); IR (neat) 1735 (C==O); cm⁻¹; ¹H NMR (220 MHz) δ 1.37 (d, 3, J = 5.25 Hz, CH₃CH), 2.52 and 2.56 (AB of ABX, 2, $J_{1,7} =$ 6.0 Hz, $J_{1,7} = 7$ Hz, $J_{7,7} = 15.5$ Hz, H-7, H-7′), 3.53 (m, 2, H-5, H-6), 3.72 (s, 3, CH₃O), 3.97 (m, 1, H-4), 4.15 (dd, 1, $J_{2,6} = 4$ Hz, $J_{6,6'} = 9.5$ Hz, H-6′), 4.73 (m, 1, H-1), 4.80 (q, 1, CH₃CH), 5.71 (ddd, 1, $J_{2,3} = 10.5$ Hz, $J_{1,3} = J_{3,4} = 2$ Hz, H-3), 5.94 (dm, 1, H-4); ¹³C NMR (25.2 MHz) δ 70.91 (C-5), 72.42 (C-1), 74.33 (C-4); MS, m/e 228 (M⁺). Anal. Calcd for C₁₁H₁₆O₆: C, 57.86; H, 7.06. Found: 58.32; H, 7.07.

(4',6'-O-Ethylidene- α -D-glucopyranosyl)acetic Acid 1',2'-Lactone (7). The α , β -unsaturated ester 2 (105 mg, 0.40 mmol) was dissolved in water (10 mL). Imidazole (75 mg, 1.1 mmol) was added to the solution. After 1.5 h at 23 °C TLC showed a optimum formation of a new product, R_f 0.48 (F). The reaction mixture was evaporated to dryness, and the residue was separated by PTLC (F). The more polar component (R_f 0.35; 35 mg, 33%) was a mixture of 3 and 4. Compound 7 was obtained as a white glassy material (25 mg, 24%) which, after further chromatography, exhibited the following: TLC R_f 0.48 (F); $[\alpha]^{20}_{\rm D}$ +25.3° (c 0.587, CHCl₃); IR 1795 (C==O) cm⁻¹; ¹H NMR (220 MHz) δ 1.36 (d, 3, J = 5 Hz, CH₃CH), 2.59 (dd, 1 $J_{1,7} = 7.5$ Hz, $J_{7,7'} = 18$ Hz, H-7), 2.81 (dd, 1, $J_{1,7'} = 10$ Hz, H-7'), 3.20 (br s, 1, OH), 3.35 (dd, 1, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 3.53 (m, 2, H-5, H-6), 3.91 (dd, 1, $J_{2,3} = 7.5$ Hz, H-3), 4.15 (dd, 1, $J_{5,6'} = 10$ Hz, $J_{6,6'} = 16$ Hz, H-6'), 4.53 (dd, 1, $J_{1,2} = 7.5$ Hz, H-3), 4.78 (q, 1, CH₃CH), 4.88 (ddd, 1, H-1). Anal. Calcd for C₁₀H₁₄O₆: C, 52.17; H, 6.13. Found: C, 51.92; H, 6.42.

Reaction of Alkyl 4,6-Di-O-acetyl-2,3-dideoxy- α -Derythro-hex-2-enopyranosides 8a,b, with α -(Trimethylsiloxy)styrene (9). Anhydrous aluminum chloride (150 mg, 1.1 mmol) was dissolved in dry methylene chloride (10 mL) under argon. The pyranoside 8a or 8b (170 mg, 0.66 mmol) was added with stirring, and the solution was cooled to -45 °C. α -(Trimethylsiloxy)styrene (9:²³ 0.20 mL, 1.2 mmol) was added, and after 0.75 h, during which time the reaction temperature had risen to 0 °C, the reaction mixture was poured into water (50 mL) and extracted with methylene chloride $(2 \times 50 \text{ mL})$. After the mixture was dried (Na_2SO_4) and the solvent evaporated, a yellow oil remained which was fractionated by column chromatography (C) to afford in the case of 8a unreacted 8a (97 mg, 57%) and products 11 + 12 (34 mg) and 14a (70 mg) in 21% and 31% yields, respectively, based on recovered starting material; in the case of 8b, the corresponding yields were as follows: unreacted 8b, 50%; 11 + 12, 17%; 14c, 30%. Acetylation of 14a in the usual manner afforded 14b which was obtained as an oil after purification by PTLC (B): TLC R_f 0.48 (C); IR (neat) 1745 (O-C=O), 1690 (PhC=O) cm⁻¹; ¹H NMR (80 MHz) δ 0.85–1.2 (m, 3, CH₃CH₂), 2.0 (m, 9, 3 OAc), 2.9-4.4 (m, 6, H-6, H-6', H-7, H-7', CH₃CH₂), 5.0-5.8 (m, 5, H-1, H-2, H-3, H-4, H-5), 7.5 (m, 3, meta and para Ph), 7.9 (m, 2, ortho Ph); MS, m/e 420 (M⁺).

Reaction of Tri-O-acetyl-D-glucal (15) with 1-(Trimethylsiloxy)alkenes. In a typical experiment, triacetylglucal 15 (203 mg, 0.75 mmol) and the siloxyalkene (1.1 mmol) were dissolved in dry methylene chloride (10 mL) under argon. The solution was cooled to -45 °C, boron trifluoride etherate (0.13 mL, 1.1 mmol) added, and the reaction mixture allowed to warm to 0 °C. The mixture was poured into water, extracted with methylene chloride, washed with water, dried (Na₂SO₄), and concentrated to a residue which was processed as indicated.

α-(4',6'-Di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)acetophenone (11) and α-(4',6'-Di-O-acetyl-2',3'dideoxy-β-D-erythro-hex-2'-enopyranosyl)acetophenone (12). The product from reaction of 15 (200 mg, 0.74 mmol) with α-(trimethylsiloxy)styrene (9) was separated by column chromatography (solvent C). The β anomer 11 was eluted first as a pale yellow oil (56 mg, 20%) and displayed the following characteristics: TLC R_f 0.47 (C); $[\alpha]^{23}_{D}$ +111.3° (c 0.574, CHCl₃); IR (CHCl₃) 1735 (O-C=O), 1685 (PhC=O) cm⁻¹; ¹H NMR (360 MHz) δ 2.06 (s, 3, OAc), 2.08 (s, 3, OAc), 3.08 (dd, 1, $J_{1,7}$ = 8 Hz, $J_{7,7'}$ = 16 Hz, H-7), 3.41 (dd, 1, $J_{1,7'}$ = 6.5 Hz, H-7'), 3.79 (ddd, 1, $J_{4,5}$ = 5 Hz, $J_{5,6'}$ = 2.8 Hz, H-5), 4.17 (dd, 1, $J_{6,6'}$ = 10.5 Hz, H-6), 4.18 (dd, 1, H-6'), 4.86 (m, 1, H-1), 5.29 (ddd, 1, $J_{2,4}$ = 1.4 Hz, $J_{3,4}$ = 1.4 Hz, H-4), 5.77 (ddd, 1, $J_{1,3}$ = 1.5 Hz, $J_{2,3}$ = 10.3 H-3), 5.99 (ddd, 1, $J_{1,2}$ = 1.1 Hz, H-2), 7.5 (t, 2, meta Ph), 7.6 (t, 1, para Ph), 7.95 (d, 2, ortho Ph); ¹³C NMR (25.2 MHz) δ 74.531 (C-5). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 64.64; H, 6.10.

The more polar α anomer 12, obtained as a pale yellow oil (223 mg, 79%), exhibited the following characteristics: TLC R_{f} 0.40 (C); $[\alpha]^{23}_{\text{D}} + 35.7^{\circ}$ (c 0.99, CHCl₃); IR (CHCl₃) 1738 (O—C=O), 1685 (PhC=O) cm⁻¹; ¹H NMR (360 MHz) δ 2.02 (s, 3, OAc), 2.08 (s, 3, OAc), 3.15 (dd, 1, $J_{1,7} = 7$ Hz, $J_{7,7'} = 16$ Hz, H-7), 3.48 (dd, 1, $J_{1,7'} = 7$ Hz, H-7'), 4.05 (ddd, 1, $J_{4,5} = J_{5,6} = 3.5$ Hz, $J_{5,6'} = 6.5$ Hz, H-5), 4.125 (dd, 1, $J_{6,6'} = 14$ Hz, H-6), 4.25 (dd, 1, H-6'), 4.95 (m, 1, H-1), 5.15 (m, 1, H-4), 5.86 (ddd, 1, $J_{1,3} = 1.8$ Hz, $J_{2,3} = 10$ Hz, $J_{3,4} = 2$ Hz, H-3), 6.08 (ddd, 1, $J_{1,2} = 2.3$ Hz, H-2), 7.5 (t, 2, meta Ph), 7.6 (t, 1, para Ph), 7.95 (d, 1, ortho Ph); ¹³C NMR (25.2 MHz) δ 68.295 (C-5). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 64.90; H, 6.30.

2-(4',6'-Di-O-acetyl-2',3'-dideoxy-D-erythro-hex-2'-enopyranosyl)cyclohexanones (19). The residue from reacting 14 (203 mg 0.75 mmol) with 1-(trimethylsiloxy)cyclohexene $(18)^{23}$ was an oil. Chromatographic separation (solvent C) of the carbohydrate components was incomplete. The total yield of the carbohydrate components 19, obtained as a clear oil, was 220 mg (95%).

The mixture displayed the following: TLC R_f 0.45 (C); IR (neat) 1735 (O--C=O), 1705 (cyclohexanone C=O) cm⁻¹; ¹H NMR (80 MHz) δ 1.4–2.2 (m, 6, H-8, H-8', H-9, H-9', H-10, H-10'), 2.1 (s, 6, 2 OAc), 2.4–2.7 (m, 3, H-7, H-11, H-11'), 4.0–4.3 (m, 3, H-5, H-6, H-6'), 4.7 (m, 1, H-1), 5.1 (m, 1, H-4), 5.7–6.2 (m, 2, H-1, H-3). Anal. Calcd for C₁₆H₂₂O₆: C, 61.92; H, 7.14. Found: C, 61.71; H, 7.33.

 α -(4',6'-Di-O-acetyl-2',3'-dideoxy- β -D-threo-hex-2'-enopyranosyl)acetophenone (20) and α -(4',6'-Di-O-acetyl-2',3'dideoxy- α -D-threo-hex-2'-enopyranosyl)acetophenone (21). The oily residue from reaction of triacetyl galactal, 20 with α - (trimethylsiloxy)styrene (9) was separated on a silica column (solvent C). Compound 21 was eluted first (44 mg, 25%) and had the following characteristics: TLC R_f 0.50 (C); $[\alpha]^{23}_D$ -32.5° (c 0.62, CHCl₃); IR (CHCl₃) 1735 (O—C=O), 1683 (PhC=O) cm⁻¹; ¹H NMR (80 MHz) δ 2.07 (s, 3, OAc), 2.10 (s, 3, OAc), 3.13 and 3.36 (AB of ABX, 2, $J_{1,7}$ = 7.5 Hz, $J_{1,7'}$ = 6.0 Hz, $J_{7,7'}$ = 17 Hz, H-7, H-7'), 3.95–4.3 (m, 3, H-5, H-6, H-6'), 4.85 (m, 1, $J_{1,2}$ and $J_{1,3} < 1$ Hz, H-1), 5.12 (ddd, 1, $J_{2,4} = J_{3,4} = 4.5$ Hz, $J_{4,5} = 2.25$ Hz, H-4), 5.95–6.4 (m, 2, H-2, H-3), 7.5 (m, 3, meta and para Ph), 7.95 (m, 2, ortho Ph). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 64.35; H, 6.08.

The other compound, **22**, was eluted next (141 mg, 70%) and had the following characteristics: TLC R_f 0.42 (C); $[\alpha]^{23}_D$ -194.2° (c 1.6, CHCl₃); IR (CHCl₃) 1735 (O—C=O), 1683 (PhC=O) cm⁻¹; ¹H NMR (80 MHz) δ 1.98 (s, 3, OAc), 2.08 (s, 3, OAc), 3.13 and 3.26 (AB of ABX, 2, $J_{1,7} = 6$ Hz, $J_{1,7'} = 7$ Hz, $J_{7,7'} = 16$ Hz, H-7, d-7'), 4.20 (br s, 3, H-5, H-6, H-6'), 5.06 (m, 2, H-1, H-4), 6.13 (m, 2, H-2, H-3), 7.50 (m, 3, meta and para Ph), 7.97 (m, 2, ortho Ph). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 64.88; H, 6.17.

α-(4'-O-Acetyl-2',3'-dideoxy-3'-C-methyl-α-D-erythrohex-2'-enopyranosyl)acetophenone (24). The enone 23a (150 mg, 0.39 mmol) was dissolved in dry tetrahydrofuran and treated successively with excess methyllithium at -78 °C and excess acetic anhydride at -45 °C.²⁴ After warming to 0 °C, the reaction mixture was poured into water and quickly extracted with methylene chloride. After being dried (Na₂SO₄) and concentrated, the mixture of diacetates, 23b, was redissolved in dry methylene chloride (10 mL) and 9²³ (0.10 mL, 0.60 mmol) added. The solution was cooled to -45 °C under argon, boron trifluoride etherate (0.10 mL, 0.81 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then poured into water and processed as previously described. Column chromatography (solvent D) on the residue yielded the title compound 24 as a colorless oil (90 mg, 76% from the enone): TLC $R_f 0.40$ (D); $[\alpha]^{20}_{D} -15^{\circ}$ (c 0.58, CHCl₃); IR (CHCl₃) 3530 (OH), 1735 (O-C=O), 1680 (PhC=O) cm⁻¹, ¹H NMR (80 MHz) δ 1.67 (br s, 3, CH₃), 2.10 (s, 3, OAc), 2.25 (br s, 1, OH), 3.17 and 3.38 (AB of ABX, 2, $J_{1,7} = 5.5$ Hz, $J_{1,7'} = 6.5$ Hz, $J_{7,7'} = 16$ Hz, H-7, H-7'), 3.67 (m, 2, H-6, H-6'), 3.85 (ddd, 1, $J_{4,5}$ = 4.0 Hz, $J_{5,6}$ $= J_{5,6'} = 4.5$ Hz, H-5), 4.90 (m, 1, H-1), 5.15 (br d, 1, H-4), 5.80 $(dq, 1, J_{1,2} = J_{CH_{3,2}} = 1.3 Hz, H-2), 7.5 (m, 3, meta and para Ph), 7.95 (m, 2, ortho Ph). Anal. Calcd for <math>C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.32; H, 6.74.

 α -(4'-O-Acetyl-2',3'-dideoxy- α -D-glycero-pent-2'-enopyranosyl)acetophenone (26). Di-O-acetyl-D-arabinal (25; 260 mg, 1.3 mmol) and 9 (0.40 mL, 2.2 mmol) were dissolved in dry methylene chloride (10 mL) under argon. The solution was cooled to -45 °C and boron trifluoride etherate (0.26 mL, 2.2 mmol) added. The reaction mixture was allowed to warm to 0 °C and then poured into water. The aqueous mixture was extracted with methylene chloride which was then washed, dried, and concentrated to a yellow oil, which showed at least eight components on TLC. The residue was separated by column chromatography (1:3 ethyl acetate/petroleum ether), whereby 26 was obtained as a pale yellow oil: 40 mg (12%); TLC $R_f 0.52$ (C); $[\alpha]^{22}_{D} + 152^{\circ}$ (c 2.30, CHCl₃); IR (neat) 1735 (O-C=O), 1686 (PhC=O) cm⁻¹; ¹H NMR (60 MHz) δ 2.1 (s, 3, OAc), 3.1 and 3.45 (AB of ABX, 2, $J_{1,6} = J_{1,6'} = 7$ Hz, $J_{6,6'} = 17$ Hz, H-6, H-6'), 3.6 (dd, 1, $J_{4,5} = 6.5$ Hz, $J_{5,5'} = 11.5$ Hz, H-5), 4.15 (dd, 1, $J_{4,5'} = 5$ Hz, H-5'), 4.85 (br dd, 1, H-1), 5.3 (m, 1, H-4), 6.0 (m, 2, H-2, H-3), 7.6 (m, 3, meta and para Ph), 8.05 (m, 2, ortho Ph). Anal. Calcd for C₁₅H₁₆O₄: C, 69.22; H, 6.20. Found: C, 69.50; H, 6.33.

Reaction of Tri-O-acetyl Pseudoglucal 16 with α -(Trimethylsiloxy)styrene (9). The triacetate 16^{17} (225 mg, 0.83 mmol) was dissolved in dry methylene chloride (10 mL), and anhydrous aluminum chloride (130 mg, 0.97 mmol) was added to the stirred solution. The mixture was sealed under argon and cooled to -45 °C, and 9²³ (0.20 mL, 1.2 mmol) was then added. After 1 h, during which time the temperature of the reaction mixture was allowed to warm to 0 °C, the reaction mixture was poured into water (50 mL) and extracted with methylene chloride (2 × 50 mL). After the extract was dried (Na₂SO₄), a yellow oil was recovered which was subjected to silica gel column chromatography with solvent C. Previously described 11 and 12 were obtained, 66 mg (22%) and 105 mg (38%), respectively.

Base-Catalyzed Isomerization of α -(4',6'-Di-O-acetyl-2',3'-dideoxy- α -D-*erythro*-hex-2'-enopyranosyl)acetophenone (12). The α -C-glycoside 12 (78 mg, 0.23 mmol) was dissolved in dry benzene (10 mL), potassium *tert*-butoxide (ca. 5 mg, 0.04 mmol) was added, and the solution was stirred at 23 °C for 6 h. TLC of the reaction mixture showed no decomposition and little, if any, change after the initial 4-h period. The reaction mixture was poured into water, and the aqueous phase was extracted with methylene chloride. The methylene chloride extract was washed (water), dried (Na₂SO₄), and concentrated to an oil (60 mg), which was separated by column chromatography (solvent C) to yield two homogeneous (TLC) fractions. The less polar fraction (R_f 0.47 (C); 25.5 mg, 33%) was found to be identical with the β -Cglycopyranoside 11. The other fraction (R_f 0.04 (C); 25 mg, 32%) was shown by ¹H NMR to consist of approximately equal amounts of starting material 12 and an isomeric compound (or compounds). This mixture could not be resolved by TLC.

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Synthesis of 3-Glycofuranosyl-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thiones: Thioguanosine-Type *C*-Nucleosides

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The first C-nucleosides of the thioguanosine type are the 3- β -D-ribofuranosyl, 3- β -D-arabinofuranosyl, and 3-(2-deoxy- β -D-erythro-pentofuranosyl) derivatives of 5-aminopyrazolo[4,3-d]pyrimidine-7-thione. Synthesis of these products employed C₆H₅CH₂SC(Cl)=NCOC₆H₅ as a new reagent for ring closure of the 3-glyco-furanosyl-4-aminopyrazole-5-carbothioamide precursors. The new ring closure requires fewer steps and minimizes side reactions encountered in previous guanosine ring closures. The amino thioamide precursors are prepared from pyrazole C-nucleosides available as in previous formycin syntheses.

The furanosides of thioguanine (1) make up a series of synthetic nucleosides (2) that have consistently shown



 $\underline{1}$, R = H $\underline{2}$, R = glycofuranosyl

 $\underline{2a}$, R = β -D-ribofuranosyl

- <u>2b</u>, R = 2-deoxy- β -D-<u>erythro</u>-pentofuranosyl
- 2c, R = 2-deoxy-a-D-erythro-pentofuranosyl



antitumor activity.¹⁻⁴ Almost invariably, however, 2 un-

dergo biological cleavage at the nucleoside bond and are to some extent produgs of 1. This produces thioguanine toxicity and cross-resistance in addition to the antitumor effects and frustrates the potential advantage of the nucleoside over 1. These specifically were limitations encountered in the clinical trial⁵ of thioguanosine⁶ (2a) and more recently⁷ of β -2'-deoxythioguanosine (2b)^{8,9} which was designed¹⁰ as a more proximate precursor of DNA incorporation in order to overcome these problems. The synthetic byproduct, α -2'-deoxythioguanosine (2c),⁸ was an unusual nucleoside not only because it was an active α anomer but also because it was resistant to nucleoside cleavage, permitting high doses to be used in animals and in clinical trials.¹¹ Because it appears that absence of cleavage could provide distinct advantages, the inherently noncleavable C-nucleosides are analogues of interest. Despite this, no C-nucleoside related to thioguanine has previously been synthesized. There are only a handful of examples, recently reported,^{12,13} that are related even to

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