Carbohydrate Research, 62 (1978) 89–103

SYNTHESIS OF 5-DEOXY-D-*xylo*-HEXOSE AND 5-DEOXY-L-*arabino*-HEXOSE, AND THEIR CONVERSION INTO ADENINE NUCLEOSIDES*

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(Received March 24th, 1977; accepted for publication, May 20th, 1977)

ABSTRACT

Anti-Markovnikov hydration of the olefinic bond of 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hex-5-enofuranose (**4**) and methyl 5,6-dideoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hex-5-enofuranoside (**11**) by the addition of iodine trifluoroacetate, followed by hydrogenation in the presence of a Raney nickel catalyst in ethanol containing triethylamine, afforded 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranose (**6**) and methyl 5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hexofuranoside (**14**), respectively. 5-Deoxy-D-*xylo*-hexose and 5-deoxy-L-*arabino*-hexose were prepared from **6** and **14**, respectively, by photolytic *O*-detosylation and acid hydrolysis. Syntheses of 9-(5-deoxy-β-D-*xylo*-hexofuranosyl)-adenine and 9-(5-deoxy-α-L-*arabino*-hexofuranosyl)adenine are also described. Application of the sodium naphthalene procedure, for *O*-detosylation, to **11** is reported in connection with an alternative synthetic route to methyl 5-deoxy-α-L-*arabino*-hexofuranoside.

INTRODUCTION

An earlier publication[1] from this laboratory reported a synthesis of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**8**) by way of the addition of iodine trifluoroacetate (produced *in situ* by the reaction of silver trifluoroacetate and iodine) to 5,6-dideoxy-3-*O*-trifluoroacetyl-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**2**). In the present report, an improved method is described for the preparation of **8** and, hence, of 5-deoxy-D-*xylo*-hexose; also, the addition of iodine trifluoroacetate to methyl 5,6-dideoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hex-5-enofuranoside (**11**) has been studied, a reaction which has led to the synthesis of 5-deoxy-L-*arabino*-hexose (**17**). Syntheses of 9-adenyl nucleosides (**10** and **19**) of the two 5-deoxyhexoses are also described. The preparation of the nucleosides was prompted by the growing interest in the synthesis of 5′-*C*-substituted analogs of adenosine[2] and "homonucleosides" and their analogs[3–7] for their great utility in the elucidation of structure-

*For a preliminary report of part of this work, see ref. 1.

activity relationships in naturally occurring nucleosides and nucleotides, and for their potential as chemotherapeutic agents. For example, 9-(5-deoxy-β-D-*ribo*-hexofuranosyl)adenine has exhibited biological properties[8] of interest in cancer research. A synthesis of 9-(5-deoxy-β-D-*xylo*-hexofuranosyl)adenine (**10**) had actually been achieved in 1958 by Reist *et al.*[3]; however, in their work the nucleoside was believed to be a derivative of 6-deoxy-L-idose (see below). Lerner[6] obtained 9-(5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosyl)adenine in very low yield by application of the hydroboration–oxidation procedure to 9-(5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranosyl)adenine.

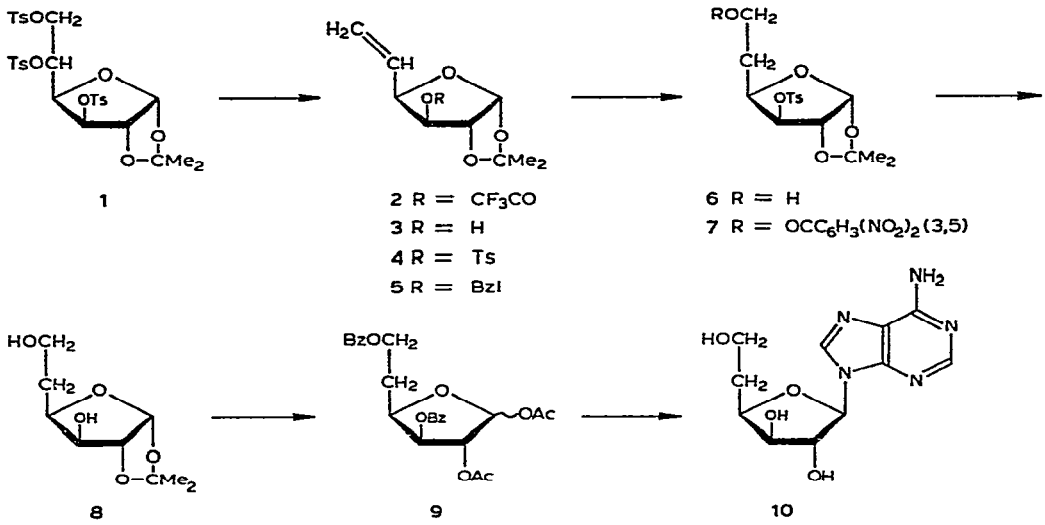
RESULTS AND DISCUSSION

In the earlier work[1], it was found that the major product, formed on treatment of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**3**) with silver trifluoroacetate and iodine in acetonitrile, was a mixture of epimers, namely, 3,6-anhydro-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose and the β-L-*ido* isomer. The formation of a 3,6-anhydro derivative could be obviated by the use of the 3-trifluoroacetate (**2**). It has now been shown that the 3-*O*-*p*-tolylsulfonyl derivative **4** is a convenient, alternative intermediate for the synthesis of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**8**). One particular virtue of using this intermediate is its ease of preparation. Thus, treatment of 1,2-*O*-isopropylidene-3,5,6-tri-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**1**), prepared in high yield by the method of Shyluk *et al.*[9], with sodium iodide in 2-butanone for 24 h at reflux temperature resulted in an almost quantitative conversion into 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hex-5-enofuranose (**4**), which was obtained in the form of "gram-size" crystals.* In contrast, the production in high yield of the precursor **3** of the 3-*O*-trifluoroacetyl derivative **2**, by way of the reaction of 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with sodium iodide is frequently hampered by the difficulty which may be encountered in the preparation of the 5,6-di-*p*-toluenesulfonate in high yield.

Treatment of **4** with silver trifluoroacetate and iodine in diethyl ether**, followed by hydrogenation of the resultant syrup over a Raney nickel catalyst in ethanol containing triethylamine, and then fractionation of the product on silica gel, afforded in 65% yield syrupy 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranose (**6**), which could be readily converted into its highly crystalline 3,5-dinitrobenzoate **7** for characterization. Irradiation[12,13] of the syrupy *p*-toluenesulfonate **6** with a 450-watt mercury-arc lamp in conjunction with a Vycor filter, in

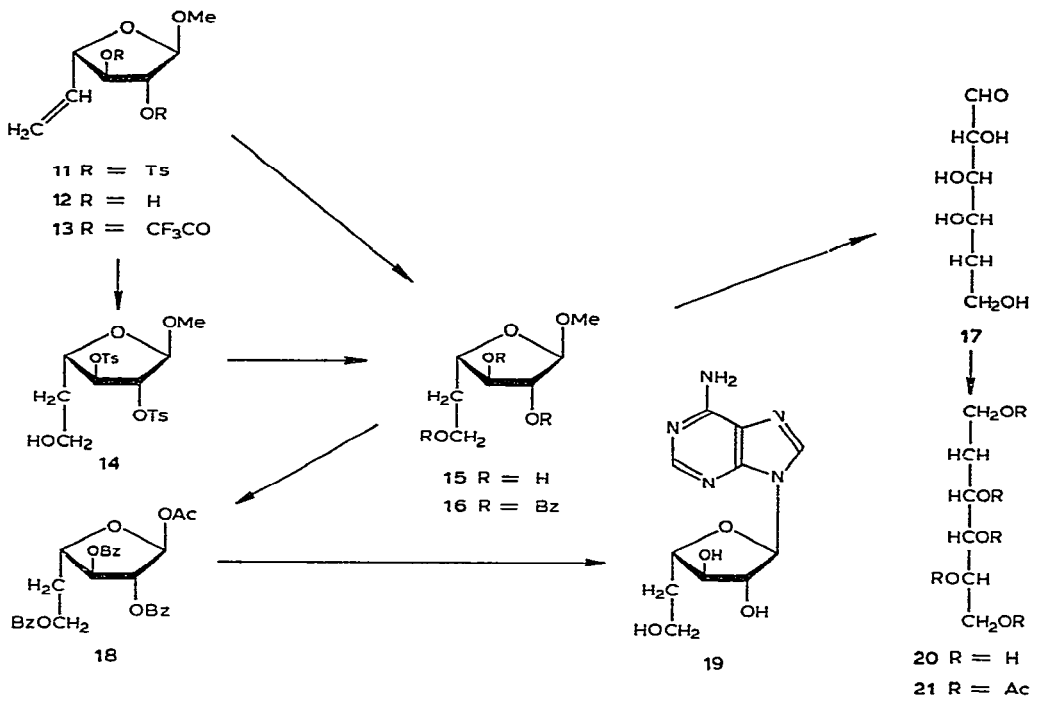
*The isolation of the 3-*O*-*p*-tolylsulfonyl derivative **4** in crystalline form in 62% yield has been described previously by Whiteley[10]; also, Jones and Thompson[11] reported the formation of a syrupy, unsaturated *p*-tolylsulfonyl derivative when **1** was heated in the presence of sodium iodide.

**In the earlier study[1], acetonitrile was employed for the *in situ* generation of iodine trifluoroacetate. However, the use of diethyl ether greatly facilitates the isolation of the product. Acetonitrile is recommended when the solubility of the starting olefin in diethyl ether is low.



methanol in the presence of 1.2 equiv. of sodium methoxide at room temperature, gave compound[1,14] **8** in crystalline form in 50% yield (based on the olefin **4**); compound **8** could be readily converted into the free sugar 5-deoxy-D-*xylo*-hexose by acid-catalyzed hydrolysis. The overall yield of **8**, based on 1,2-*O*-isopropylidene-α-D-glucofuranose, was 35%. The facile, photochemically induced desulfonylation is another reason for the attractiveness of the 3-*O*-*p*-tolylsulfonyl derivative **4** as an intermediate for the synthesis of **8**. Recently, a new method for reductive desulfonylation of carbohydrate *p*-toluenesulfonates, namely, with sodium naphthalene, was reported[15] from this laboratory; this method should also be effective with the *p*-toluenesulfonate **6**. It is noteworthy that, under the conditions employed in the present work, the preferred reaction of iodine trifluoroacetate with **4** was addition to the carbon–carbon double bond; it is known[16] that the positive iodine generated by the reaction of iodine and silver trifluoroacetate is reactive in electrophilic aromatic substitution.

The reaction of iodine trifluoroacetate with methyl 5,6-dideoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hex-5-enofuranoside[17,18] (**11**) has also been investigated. In one experiment, the reaction was performed in acetonitrile for 25 min at room temperature, and the resultant syrup was then treated with ethanol–triethylamine to remove *O*-trifluoroacetyl groups. The major component (t.l.c.) of the mixture of products was isolated by column chromatography in 57% yield, and was identified as an approximately 1:1 mixture of epimers, namely, methyl 5-deoxy-5-iodo-2,3-di-*O*-*p*-tolylsulfonyl-β-D-galactofuranoside and the α-L-*altro* isomer; the n.m.r. spectrum of this component in chloroform-*d* showed the presence of two signals of approximately equal intensities at τ 6.71 and 6.75 attributable to methoxyl groups. Hydrogenation over freshly prepared W-4 Raney nickel catalyst afforded methyl 5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hexofuranoside (**14**) in 90% yield; the i.r. spectrum of this product showed hydroxyl-group absorption, and the substitution



of C-5 was indicated by the observation in the n.m.r. spectrum of a 2-proton multiplet centered at τ 8.19. The preparation of the 5-deoxy derivative **14** by way of the addition of iodine trifluoroacetate to the olefin **11** represents an overall anti-Markovnikov hydration of **11**, an attempt to achieve this result by the hydroboration–oxidation procedure led to an intractable, black material, presumably because of the lability to base of the *trans*-vicinal *p*-toluenesulfonates. Recently Czernecki *et al.*[19] have reported the preparation of a mixture of 5-deoxy- and 6-deoxy-hexose derivatives by hydration of **5** employing the mercuric trifluoroacetate addition procedure.

Prior to the present work, syntheses of only two 5-deoxyaldohexoses had been reported, namely 5-deoxy-D-*xylo*-hexose[1,14] and 5-deoxy-D-*ribo*-hexose[4,20]. Compound **14** was converted, therefore, into the free sugar 5-deoxy-L-*arabino*-hexose (**17**). Not surprisingly, attempts to remove the *O*-*p*-tolylsulfonyl groups in **14**, to obtain methyl 5-deoxy-α-L-*arabino*-hexofuranoside (**15**), by irradiation with u.v. light in methanol in the presence of the strong base sodium methoxide, were not successful. The desired desulfonylation could be achieved by substituting triethylamine for sodium methoxide. A disadvantage of this modification was the concomitant formation of by-products arising from the photolysis of triethylamine[21]; however, **15** could be readily separated by chromatography on silica gel. Thus, the triol **15** was obtained in 63% yield, when a 1-g sample of **14** in methanol containing 2 ml of triethylamine was irradiated at room temperature for 90 min. Unfortunately, attempts to prepare **13** on a larger scale, by increasing the concentrations of **14** and triethylamine, required longer reaction times for the complete consumption of starting material and resulted

in a drastic diminution of the yield of **15**. Treatment of **15** with benzoyl chloride–pyridine afforded in high yield methyl 2,3,6-tri-*O*-benzoyl-5-deoxy-α-L-*arabino*-hexofuranoside (**16**); the small coupling constants $J_{1,2}$ and $J_{2,3}$ observed in the n.m.r. spectrum of **16** were consistent[22] with the assigned structure, and thus corroborated the observation that the removal of the *O*-*p*-tolylsulfonyl groups had occurred without inversion.

Acid-catalyzed hydrolysis of the glycoside **15** gave the new sugar **17** as a syrup. The n.m.r. spectrum of this sugar in deuterium oxide showed a very sharp triplet (spacings 6.5 Hz) for the terminal methylene protons and a pattern of signals for the protons at C-5 similar to that observed for the corresponding protons in the spectra of the furanoid derivatives **14** and **15**; only one signal attributable to a proton at the anomeric center was observed, namely, a doublet ($J_{1,2}$ 3.0 Hz) at τ 4.74. The n.m.r. spectral data suggest that **17** exists in aqueous solution essentially in the α-L-furanose form; a 5-deoxyaldohexose cannot, of course, form a pyranoid ring. The i.r. spectrum (film) of **17** did not show any absorption attributable to a carbonyl group, and it was in fact very similar to the spectrum of the furanoside **15**. Reduction of **17** with sodium borohydride afforded 2-deoxy-L-*lyxo*-hexitol (**20**) which, after purification by way of its pentaacetate **21**, was obtained in crystalline form. The specific rotation (−10.3° in methanol) of the sample of **20** agrees with the value reported[23] for the D-enantiomer (+12° in methanol), but the melting point (89–90°) was considerably lower (112–113°, ref. 23); however, the structural assignment was confirmed by a comparison of the electrophoretic mobilities of **20** in tungstate and molybdate solutions with those of the four 2-deoxyhexitols reported by Angus *et al.*[24] (see Table I).

An alternative method for the conversion of the olefin **11** into **15** has also been developed in the present work, namely, one involving desulfonylation of **11** rather than of the hydration product **14**. Ball *et al.*[17] have described the reductive desulfonylation of **11**, on a 1-g scale, by the use of sodium amalgam in aqueous ethanol, to afford crystalline methyl 5,6-dideoxy-α-L-*arabino*-hex-5-enofuranoside (**12**); in the present work, an application of this procedure to 5 g of **11** required a

TABLE I

ELECTROPHORETIC MOBILITIES OF 2-DEOXYHEXITOLS[a]

2-Deoxyhexitol	$M_{glucitol}$ (*W*)	$M_{glucitol}$ (*Mo*)	*References*
D-*arabino*	1.00	1.0	23
D-*ribo*	0.17–0.57	0.13–0.57	23
L-*xylo*	1.09	1.07	23
D-*lyxo*	0.42–0.61	0.8	23
20	0.3 –0.6	0 8	This work

[a]Relative to D-glucitol in tungstate [$M_{glucitol}$ (W)] and molybdate [$M_{glucitol}$ (Mo)] solutions. See Experimental section for details of paper electrophoresis.

longer reaction time and resulted in a lower yield of the diol. However, the use of the sodium naphthalene anion radical in tetrahydrofuran solution[15] was found to be an effective, rapid method for removal of the *O*-*p*-tolylsulfonyl groups of **11**. Treatment of the resultant **12** with trifluoroacetic anhydride–sodium trifluoroacetate afforded methyl 5,6-dideoxy-2,3-di-*O*-trifluoroacetyl-α-L-*arabino*-hex-5-enofuranoside (**13**) as an oil which could be purified by distillation. The reaction of **13** with silver trifluoroacetate and iodine in diethyl ether then gave an adduct which, on hydrogenation over a W-4 Raney nickel catalyst in ethanol containing triethylamine, afforded **15** in a 50% yield (based on methyl 5,6-dideoxy-α-L-*arabino*-hex-5-enofuranoside). The glycoside **15** could be obtained in an overall yield of ~75% (based on the starting olefin **11**), if purification of the intermediates **12** and **13** was omitted.

Treatment of diol **8** with benzoyl chloride and pyridine afforded, as a syrup, 3,6-di-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose, which, without further purification, on acetolysis and column chromatography gave an anomeric mixture of 1,2-di-*O*-acetyl-3,6-di-*O*-benzoyl-5-deoxy-D-*xylo*-hexofuranoses (**9**) in 50% yield. Condensation of **9** with 6-benzamido-9-chloromercuripurine in 1,2-dichloroethane by the titanium tetrachloride method[6,25] gave a blocked nucleoside; deacylation by heating under reflux in methanol containing sodium methoxide and purification of the resultant product by way of the picrate salt[25] afforded **10** as a white crystalline solid in 25% yield. The β-D configuration was assigned to **10** on the basis of its n.m.r. spectral data in methyl sulfoxide-d_6 (after four treatments with D_2O); the characteristic H-1′ chemical shift[5] (τ 4.10) and $J_{1',2'}$ (1.2 Hz)[27] were in agreement with the vicinal *trans* disposition of H-1′ and H-2′ in **10**. The other physical constants (see Experimental) of **10** were consistent with those initially reported by Reist *et al.*[3] for the supposed 6-deoxy-L-idofuranose derivative; however, this compound was later claimed by Ryan *et al.*[4] to be the nucleoside **10**.

Acetolysis (acetic acid–sulfuric acid–acetic anhydride at 0° for ~5 min) of crude **16** obtained by benzoylation of **15**, afforded 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-5-deoxy-α-L-*arabino*-hexofuranose (**18**) as the only major component, as shown by a single acetoxyl peak and one singlet due to the anomeric proton at τ 7.87 and 3.53, respectively, in the n.m.r. spectrum of the product. No evidence was obtained for a possible rearrangement involving C-2 and C-3 during the acetolysis reaction; epimerisations at C-2 have been observed[28] with sugar derivatives in which the groups at C-2 and C-3 have a *cis* relationship. Crude acetate **18**, on condensation with 6-benzamido-9-chloromercuripurine in the same fashion as just described for acetates **9**, and purification of the deacylated material by the picrate method afforded 9-(5-deoxy-α-L-*arabino*-hexofuranosyl)adenine (**19**) (25% yield from **15**) as a chromatographically homogeneous syrup, which eventually crystallized. An absorption maximum at 260 μm in the u.v. spectrum indicated[29] that the carbohydrate moiety was attached to N-9 of the purine ring. The α-L configuration of **19** was readily established as in **10** by the observation, in its n.m.r. spectrum in methyl sulfoxide-d_6 (after deuteration) at 50°, of a doublet due to the anomeric proton (H-1′) at τ 4.10 ($J_{1',2'}$ 4.2 Hz).

EXPERIMENTAL

Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer model 141 automatic polarimeter at 26 ± 3°. I.r. spectra were recorded with a Unicam SP 1000 spectrophotometer. The n.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard, unless otherwise stated. T.l.c. was performed with Silica Gel G containing 1–3% of indicator Lumilux Green ZS (Brinkmann Instruments Ltd., Rexdale, Ontario) as the adsorbent in the following solvent systems (v/v): (*A*) 2:3 petroleum ether (b.p. 60–80°)–ethyl acetate; (*B*) 3:3; (*C*) 3:1; and (*D*) ethyl acetate. The developed plates were air dried and the detection of components consisted of three stages: irradiation with a short-wavelength u.v. lamp (UVS-54) to detect benzoates, tosylates, and purines; spraying with dilute, aqueous permanganate to test for isolated double bonds; and finally spraying with a solution of 1% cerium sulfate and 1.5% molybdic acid in 10% sulfuric acid and heating the plates at ~150°. Paper chromatography was performed on Whatman No. 1 paper by the descending method, using aqueous 5% disodium hydrogenphosphate (*E*), water-saturated butanol (*F*), or 3:1:1 (v/v) butanol–ethanol–water (*G*) as eluants. Detection was by a short-wavelength u.v. lamp for nucleosides, and aniline hydrogenphthalate[30] for free sugars. The terms R_{Ade}, R_{Rha}, and R_{Ara} refer to mobilities relative to adenine, rhamnose, and arabinose, respectively. Electrophoresis was performed on sheets (12 × 40 cm) of Whatman 3MM filter paper, with a high-voltage, zone-electrophoretic apparatus (enclosed-strip type) that was capable of delivering up to 2600 V at 100 mA. Spots of compounds were deposited on the paper mid-way between the electrodes before spraying the paper with buffer. The electrolytes consisted of 2% aqueous sodium molybdate or sodium tungstate solutions (25 gm of the dihydrate/1200 ml of water), adjusted to pH 5.0 with concentrated sulfuric acid. Electrophoretograms were run in the constant-current mode[31] at 92 ± 2 mA for 30 min. Under these conditions, an initial gradient of 60 V/cm decreased to 30V/cm for tungstate and 20 V/cm for molybdate. Compounds were detected by spraying with acetone–silver nitrate, then ethanolic sodium hydroxide, and fixing in a bath of thiosulfate[32]. Mobilities are expressed relative to D-glucitol ($M_{glucitol}$ 1); D-glucose was used as a standard marker for correction of electroosmosis ($M_{glucitol}$ 0). Migration rates in molybdate and tungstate are expressed as $M_{glucitol}$(Mo) and $M_{glucitol}$(W) values[24], respectively. Ultraviolet irradiations were achieved with a 450-W Hanovia high-pressure, mercury-arc lamp (cat. No. 679A-36) contained in a water-cooled, quartz immersion-well; a Vycor 7010 filter-sleeve was employed. The whole assembly was mounted in a borosilicate-glass reaction vessel.

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-p-tolylsulfonyl-α-*D*-xylo-hex-5-enofuranose* (**4**). — 1,2-*O*-Isopropylidene-3,5,6-tri-*O*-*p*-tolylsulfonyl-α-D-glucofuranose [**1**, 250 g, 300 mmol, R_F (C) 0.16], prepared by the method of Shyluk *et al.*[9], and sodium iodide (100 g) were heated under reflux in 2-butanone (4.0 l) for 4 h. The mixture was filtered, sodium iodide (80 g) was added to the filtrate, and heating under reflux

was continued. After 20 h, the reaction solution was evaporated to complete dryness under reduced pressure. A solution of the residue in chloroform was washed with aqueous sodium thiosulfate, dried (magnesium sulfate), and decolorized (Norit); removal of the solvent gave a crude syrup (105 g). Crystallization of this syrup in 1:1 (v/v) ether–petroleum ether was induced by a seed crystal, and afforded three crops of **4** (95.1 g, 93%), m.p. 66.5–66.8°, $[\alpha]_D^{26}$ −50° (*c* 1.10, chloroform); lit.[10] m.p. 65–66.5°, $[\alpha]_D$ −51.5° (*c* 7.6, chloroform); R_F 0.45 (*C*); ν_{max}^{film} 1655 (C=C), 1600, 1500 (OTs), and 1380 cm^{-1} (CMe_2); n.m.r.: τ 2.12–2.72 (H, aromatic H), 4.03 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.06–4.96 (3 H, H-5 and H-6,6'), 5.19–5.40 (3 H, H-2, H-3, and H-4), 7.58 (s, 3 H, aromatic Me), 8.52 and 8.72 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{16}H_{20}SO_6$: C, 56.7; H, 5.9; S, 9.4. Found: C, 56.7; H, 6.0; S, 9.3.

*5-Deoxy-1,2-*O*-isopropylidene-3-*O*-p-tolylsulfonyl-α-*D*-xylo-hexofuranose* (**6**). — Olefin **4** (6.8 g, 20 mmol) and silver trifluoroacetate (4.9 g, 1.1 equiv.) in dry ether were added to a solution of iodine (5.62 g, 1.1 equiv.) in dry ether (125 ml), with the exclusion of light and maintenance of vigorous stirring. After 10 min, the filtrate was washed with aqueous sodium thiosulfate, saturated sodium chloride solution, and dried (magnesium sulfate). Removal of solvent afforded a colorless syrup that was immediately dissolved in ethanol containing triethylamine (5 ml) and hydrogenated over W-4 Raney nickel. T.l.c. (solvent A) revealed that the reaction was complete within 8 h. Removal of the catalyst and solvent gave a syrup that, on dissolution in hot ether, precipitated triethylammonium iodide. The crude syrup (6.65 g), obtained after filtration and solvent removal, contained five minor components (t.l.c., solvent B). The major component was isolated by column chromatography with 1:1 (v/v) carbon tetrachloride–ethyl acetate as eluent to yield syrupy **6** (4.59 g, 65%), $[\alpha]_D^{26}$ −7° (*c* 3.6, chloroform); R_F 0.50 (solvent A); ν_{max}^{film} 3540, 3460, (OH), 1600, 1500 (OTs), 1450 (CH_2), 1380, and 1360 cm^{-1} (CMe_2); n.m.r.: τ 2.09–2.68 (4 H, aromatic H), 4.10 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.22 (d, 1 H, $J_{3,4}$ 3.0 Hz, $J_{2,3}$ < 0.5 Hz, H-3), 5.36 (d, 1 H, H-2), 5.45–5.74 (m, 1 H, H-4), 6.26–6.46 (2 H, H-6,6'), 6.98 (s, 1 H, OH), 7.56 (s, 3 H, aromatic Me), 8.05–8.39 (m, 2 H, H-5,5'), 8.57 and 8.75 (2s, 6 H, CMe_2).

Acylation of alcohol **6** [1.25 g, 3.5 mmol, R_F 0.10 (solvent B)] with 3,5-dinitrobenzoyl chloride (1.0 g, 1.2 equiv.) in pyridine (10 ml) at room temperature gave crystalline 5-deoxy-6-*O*-(3,5-dinitrobenzoyl)-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-*D*-*xylo*-hexofuranose (**7**) (1.27 g, 63%), m.p. 155–157°, $[\alpha]_D^{26}$ +5° (*c* 5.6, chloroform); R_F 0.43 (solvent B); ν_{max}^{Nujol} 1738 (C=O), 1633 (aromatic C=C), 1550 (C-NO_2), 1600, and 1498 cm^{-1} (OTs); n.m.r.: τ 0.85, 0.93 (3 protons, AB_2 pattern, $J_{A,B}$ 2.1 Hz, aromatic H of dinitrobenzoyl ring), 2.10–2.70 (4 H, aromatic H), 4.12 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.21 (d, 1 H, $J_{2,3}$ < 0.5 Hz, $J_{3,4}$ 3.0 Hz, H-3), 5.38–5.56 (4 H, H-2, H 4, and H-6,6'), 7.53 (s, 3 H, aromatic Me), 7.79–8.15 (m, 2 H, H-5,5'), 8.55 and 8.74 (2 s, 6 H, CMe_2)

Anal. Calc. for $C_{23}H_{24}N_2O_{12}S$: C, 50.0; H, 4.4; N, 5.1; S, 5.8. Found: C, 50.8; H, 4.6; N, 5.1; S, 5.7.

*5-Deoxy-1,2-O-isopropylidene-α-*D-xylo-*hexofuranose* (**8**). — When a solution of crude mono-*p*-toluenesulfonate **6** (7.2 g) in methanol (300 ml), containing 2M sodium methoxide (8 ml), was irradiated for 8 h at ~7° with u.v. light by use of a Vycor filter, the starting material was fully consumed. After treatment with charcoal, the filtrate was evaporated to dryness. The residue (6.9 g) was extracted with boiling ethyl acetate (2 × 25 ml) and the yellow salts were removed by filtration. Column chromatography of the resultant dark-yellow syrup (5.6 g) on silica gel with ethyl acetate as eluent afforded diol **8** (2.08 g, 50% based on pure **4**.) After crystallization from ether–petroleum ether (b.p. 60–80°), the compound had m.p. 93–94.5° and $[\alpha]_D^{26}$ −10.5° (*c* 1.7, chloroform). These physical constants are in agreement with those reported by other workers[33,34]; the n.m.r. spectrum was identical with that published by Wolfrom *et al.*[33].

*Methyl 5-deoxy-2,3-di-*O-p-*tolylsulfonyl-α-*L-arabino-*hexofuranoside* (**14**). — Olefin **11** (1.02 g, 2.19 mmol) and silver trifluoroacetate (580 mg, 1.2 equiv.) in dry acetonitrile (15 ml) were added, in one portion, to a stirred solution of iodine (669 mg, 1.2 equiv.) in dry acetonitrile (20 ml) and then the flask was covered with aluminium foil. After 5 min, the reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was extracted with carbon tetrachloride, and the extract was washed with aqeous sodium thiosulfate solution, dried (magnesium sulfate) in the presence of decolorizing carbon, and filtered through Celite. The clear, colorless filtrate was concentrated to a syrup. T.l.c. (solvent B) showed that all of the starting olefin (R_F 0.67) had been consumed and revealed the presence of a new component (R_F 0.52–0.75). A solution of this syrup in ethanol containing W-4 Raney nickel catalyst and triethylamine was subjected to a hydrogen pressure of 2.7 atm for 2 h. The catalyst was removed by filtration, and then extracted with boiling ethanol. The combined filtrate and extract were concentrated to a residue, which was extracted with ether. The ether was evaporated and the residue (1.23 g) was chromatographed on silica gel, with 2:1 (v/v) carbon tetrachloride–ethyl acetate as eluent, to yield **14** (457 mg, 43%). After recrystallization from chloroform–petroleum ether (b.p. 60–80°), the compound had m.p. 84–85°, $[\alpha]_D^{26}$ −57° (*c* 1.6, chloroform); R_F 0.33 (solvent B); ν_{max}^{film} 3580, 3420 (OH), 1600, 1498, 1375, 1195, 1180 (OTs), and 1455 cm^{-1} (CH_2); n.m.r.: τ 2.10–2.70 (8 H, aromatic H), 5.19–5.42 (m, 3 H, H-1, H-2, and H-3), 5.64–5.93 (m, 1 H, H-4), 6.32 (t, 2 H, H-6,6'), 6.78 (s, 3 H, OMe), 7.55 (s, 6 H, aromatic Me), 7.65 (s, 1 H, OH), and 8.02–8.40 (m, 2 H, H-5,5').

Anal. Calc. for $C_{21}H_{26}O_4S_2$: C, 51.9; H, 5.4; S, 13.2. Found: C, 52.0; H, 5.3; S, 13.0.

*Methyl 5-deoxy-α-*L-arabino-*hexofuranoside* (**15**). — Di-*p*-toluenesulfonate **14** (three separate samples: 1.01, 0.51, and 1.51 g) was dissolved in methanol (300 ml, each run) containing triethylamine (1.0, 0.6, and 1.0 ml, respectively) and irradiated with u.v. light by use of a Vycor filter for 2.0, 1.5, and 2.0 h, respectively. Concentration of each reaction mixture to dryness afforded a tan syrup (1.56, 0.86, and 1.56 g, respectively). The three runs were combined and chromatographed on silica gel with 1:1 (v/v) acetone–ethyl acetate as the eluent. Collection and concentration of the

major fraction having R_F 0.5 (eluting solvent) [R_F (**14**) 1] afforded a light-tan solid (616 mg, 63%), which resisted recrystallization and had m.p. 75–77.5°, $[\alpha]_D^{26}$ −137° (*c* 1.1, methanol); ν_{max}^{film} 3400 cm^{-1} (OH); n.m.r. (D_2O): τ 5.10 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 5.76–6.50 (5 H, H-2, H-3, H-4, H-6,6′), 6.63 (s, 3 H, OMe), and 7.94–8.27 (m, 2 H, H-5,5′).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.2; H, 7.9. Found: C, 46.9; H, 7.7.

*Methyl 2,3,6-tri-*O*-benzoyl-5-deoxy-α-*L-arabino-*hexofuranoside* (**16**). — To a solution of **15** (274 mg, 1.5 mmol) in dry pyridine (2 ml) was added, dropwise, freshly distilled benzoyl chloride (0.75 ml, 4 equiv.) at ~0° (ice bath). Isolation of the product according to the published procedure of Fletcher[35] afforded a clear syrup (767 mg). Chromatography on silica gel with initially benzene (250 ml), and finally one bed volume of ethyl acetate as eluents afforded pure **16** as a colorless oil (597 mg, 79%), $[\alpha]_D^{26}$ +26° (*c* 1.5, chloroform)*; R_F 0.72 (solvent C); ν_{max}^{film} 1740, 1730, 1715 (C=O), 1600, 1585, 1455 (aromatic ester), and 1470 cm^{-1} (CH_2); n.m.r.: τ 1.85–2.75 (2 m, 15 H, aromatic H), 4.40–4.49 (2 H, $J_{1,2} < 0.5$, $J_{2,3}$ 1.6 Hz, $J_{3,4}$ 6.2 Hz, H-2 and H-3), 4.84 (s, 1 H, H-1), 5.25–5.60 (3 H, H-4, H-6,6′), 6.57 (s, 3 H, OMe), and 7.40–7.80 (m, 2 H, H-5,5′).

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.6; H, 5.3. Found: C, 68.3, H, 5.7.

*5-Deoxy-*L*-arabino-hexose* (**17**). — Methyl glycoside **15** (281 mg, 1.58 mmol) was hydrolyzed with Rexyn 101 (H^+) cation-exchange resin in water (25 ml) for 65 min at 95°. The hot solution was treated with decolorizing charcoal and filtered hot through Celite. To avoid possible polymerization[35], the filtrate was freeze-dried to give the free sugar **17** as a syrup (221 mg, 86%), R_F 0.3–0.4 (1:1, v/v, acetone–ethyl acetate); $[\alpha]_D^{26}$ −18° (*c* 1.05, water); R_{Rha} 1.17 and R_{Ara} 2.05 (solvent G); no absorption attributable to C=O in the i.r. spectrum; n.m.r. (D_2O): τ 4.74 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1 of α-L anomer; no other anomers detected with 5% noise background), 5.70–6.40 (3 H, H-2, H-3, and H-4), 6.27 (t, 2 H, H-6,6′), and 7.92–8.29 (m, 2 H, H-5,5′).

*2-Deoxy-*L*-lyxo-hexitol* (**20**) *and 1,3,4,5,6-penta-*O*-acetyl-*L*-lyxo-hexitol* (**21**). — A solution of **15** (718 mg, 4.04 mmol) in water (9 ml) was heated on a steam bath, in the presence of a strong cation-exchange resin (1 g), for 2 h with intermittent stirring. The mixture was cooled, filtered, and the resin thoroughly washed. The combined aqueous filtrates were treated overnight with sodium borohydride (0.2 g). Usual processing of the reaction mixture afforded **20** (500 mg, 70%) as a syrup. Acetylation with 1:1 (v/v) pyridine–acetic anhydride (10 ml) gave the pentaacetate **21** (613 mg, 54%), b.p. 98–103°/0.05 torr; $[\alpha]_D^{26}$ −42° (*c* 1.5, methanol); R_F 0.4 (solvent B); ν_{max}^{film} 1750 (C=O), 1380 (CH_3-CO), 1230 (acetate), 1440 (C-CH_2), and 1070–1050 cm^{-1} (CH_2-O and CH-O); n.m.r.: τ 4.54–5.10 (3 H, H-3, H-4, and H-5), 5.59–6.12

*Although this rotational change is very large relative to that of the free glycoside **15**, it is comparable in magnitude to that of the corresponding lower homolog, methyl 2,3,5-tri-*O*-benzyl-α-D-arabinoside, $[\alpha]_D$ −19.5° (chloroform), as reported by Fletcher[35].

(4 H, H-1,1′ and H-6,6′), and 7.85–8.30 (17 H, H-2,2′, 5 CH_3's as singlets at τ 7.88, 7.94, and 7.97 in the ratio 1:1:3).

Anal. Calc. for $C_{16}H_{24}O_{10}$: C, 51.1; H, 6.4. Found: C, 50.9; H, 6.4.

O-Deacetylation of **21** (445 mg, 1.18 mmol) in methanol containing a catalytic amount of sodium methoxide gave **20** (169 mg, 86%) as a syrup that spontaneously crystallized. Recrystallization from methanol afforded **20**, m.p. 89–90°, $[\alpha]_D^{26}$ −10.3° (*c* 1.5, methanol); ν_{max}^{film} 3480–3340 (OH), 2950 (C-H), 1430 (C-CH_2), and 1080–1050 cm^{-1} (CH_2-OH and CH-OH); electrophoretic data: $M_{glucitol}$(Mo) 0.8, $M_{glucitol}$(W) 0.3–0.6 (for comparison with other 2-deoxyhexitols, see Table I); lit.[23,24] (for D isomer): m.p. 112–113° (methanol), $[\alpha]_D$ +12° (*c* 1.7, methanol); $M_{glucitol}$(Mo) 0.80 and $M_{glucitol}$ 0.42–0.61.

*O-Detosylation of methyl 5,6-dideoxy-2,3-di-*O-p-*tolylsulfonyl-α-*L-arabino-*hex-5-enofuranoside* (**11**) *with sodium naphthalene.* — A solution of olefin **11** (2.91 g, 6.2 mmol) in a minimum volume of dry tetrahydrofuran was added rapidly to a stirred, standardized[15], stock solution of sodium naphthalene (15 ml, 0.35 mol) (diluted with tetrahydrofuran), under nitrogen in a Dry Ice–acetone bath. At the completion of the reaction (10 min, t.l.c.), the reaction mixture was quenched with a few drops of water, and then neutralized with a strong-acid, ion-exchange resin at room temperature. The solids were removed by filtration, the filtrate was evaporated, and the residue was partitioned between chloroform and water. The chloroform solution was washed once with water, dried (magnesium sulfate), and then evaporated to give a crude syrup (1.2 g). Upon column chromatography on silica gel with ethyl acetate as the eluent, methyl 5,6-dideoxy-α-L-*arabino*-hex-5-enofuranoside (**12**, 713 mg, 72%) was obtained as an orange syrup that crystallized, m.p. 57–59° (distilled at 80–90°/0.1 torr), $[\alpha]_D^{26}$ −93° (*c* 1.56, ethanol); lit.[12] m.p. 60°, $[\alpha]_D$ −110° (no solvent reported); R_F 0.12 (solvent B) and 0.50 (solvent D); ν_{max}^{film} 3450 (OH) and 1650 cm^{-1} (C=C); n.m.r.: τ 3.70–4.90 (3 H, CH=CH_2), 5.15 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 5.1–6.4 (4 H, H-2, H-3, 2 OH), and 6.61 (s, 3 H, OMe).

*Methyl 5,6-dideoxy-2,3-di-*O-*trifluoroacetyl-α-*L-arabino-*hex-5-enofuranoside* (**13**). — Compound **12** (453 mg, 2.83 mmol) was disolved in ice-cold trifluoroacetic anhydride (10 ml), and a catalytic amount of sodium trifluoroacetate (100 mg) was added. After 5 min, the reaction mixture was diluted with carbon tetrachloride (50 ml) and the solvent was removed under reduced pressure. The residue was extracted with carbon tetrachloride (3 × 20 ml), filtered hot, and concentrated to give the bis(trifluoroacetate) **13** as an odorless oil (936 mg, 93%), b.p. 37–43°/0.015 torr; $[\alpha]_D^{26}$ −93° (*c* 3.9, carbon tetrachloride); $\nu_{max}^{CCl_4}$ 1800 cm^{-1} (CF_3C=O), no absorption attributable to OH; n.m.r.: 3.98 (1 H, $J_{4,5}$ 7.0, $J_{5,6}$ 18.0 Hz, $J_{5,6'}$ 11.0 Hz, H-5), 4.48 (1 H, $J_{6,6'}$ 0.9 Hz, H-6), 4.92 (1 H, H-6′), 4.67 (1 H, $J_{1,2} < 0.5$, $J_{2,3}$ 2.8 Hz, H-2), 4.90 (1 H, $J_{3,4}$ 6.5 Hz, H-3), 4.93 (1 H, H-1), 5.60 (1 H, H-4), and 6.55 (s, 3 H, OMe).

Anal. Calc. for $C_{11}H_{10}F_6O_6$: C, 37.5; H, 2.9; F, 32.4. Found: C, 37.7; H, 3.0; F, 32.5.

Hydration of **13** *by way of iodine–trifluoroacetate addition reaction.* — Compound

13 (671 mg, 1.9 mmol) and silver trifluoroacetate (508 mg, 1.2 equiv.) in dry acetonitrile (15 ml) were added, in one portion, to a stirred solution of iodine (579 mg, 1.2 equiv.) in dry acetonitrile (25 ml), and then the flask was covered with aluminium foil. After 5 min of reaction time, isolation of the product in the usual fashion afforded a colorless liquid (960 mg, 87%), which upon hydrogenation in ethanol containing W-4 Raney nickel catalyst and triethylamine gave **15** (205 mg, 60%) as the sole carbohydrate component. The glycoside **15** was obtained in an overall yield of 75% (based on olefin **11**), when purification of the intermediates **12** and **13** was omitted.

*1,2,-Di-*O*-acetyl-3,6-di-*O*-benzoyl-5-deoxy-*D-xylo*-hexofuranoside* (**9**). — Benzoylation of **8** (3.2 g, 1.57 mmol) was accomplished by treatment with benzoyl chloride (5.5 ml) in pyridine (13 ml) for 15 min; isolation of the product in the usual fashion afforded the dibenzoate as a crude, yellow syrup (4.9 g). Acetolysis of this material in 100:20:1 (v/v) acetic acid–acetic anhydride–98% sulfuric acid (60.5 ml) was effected in 60 min. After neutralization of the acid with sodium acetate, the reaction mixture was partitioned between water and chloroform. The chloroform solution was successively treated with aqueous sodium hydrogencarbonate and water. Drying (sodium sulfate) and evaporation of solvent afforded a crude anomeric mixture of 1,2-di-*O*-acetyl-3,6-di-*O*-benzoyl-5-deoxy-D-*xylo*-hexofuranose (**9**) (2.5 g, 40%), which was used without further purification in the nucleoside coupling reaction.

*9-(5-Deoxy-β-*D-xylo-*hexofuranosyl)adenine* (**10**). — From the reaction mixture, consisting of crude **9** (2.5 g, 5.5 mmol), Celite (5 g), 6-benzamido-9-chloromercuripurine (3.3 g, 1.25 equiv.), and dry 1,2-dichloroethane (300 ml), was distilled 50 ml of the solvent to exclude moisture. Titanium tetrachloride (0.9 ml, 1.25 equiv.) in dry 1,2-dichloroethane (50 ml) was added, dropwise, to the vigorously stirred mixture, under reflux. T.l.c. (solvent D) after 7 h revealed the presence of a major new component having R_F 0.6 (R_F of **9**, 0.96). Saturated aqueous sodium hydrogencarbonate (100 ml) was added, and the reaction mixture was filtered. The residue obtained on drying (sodium sulfate) and evaporation of the organic layer was dissolved in chloroform, and the solution was washed with 30% aqueous potassium iodide, dried (sodium sulfate), decolorized (by passing through a short silica gel column), and concentrated to a syrup. The crude, syrupy nucleoside (2.8 g) was deacylated by heating under reflux in methanol (50 ml) containing M sodium methoxide in methanol (7 ml) for 2.5 h, and then immediately treated with picric acid; this procedure yielded a yellow precipitate of the picrate salt (1.03 g), which on recrystallization from water (50 ml) gave yellow needles (850 mg, 30% from **9**), m.p. 202–216° (dec.).

Anal. Calc. for $C_{17}H_{18}N_8O_{11}$: C, 40.0; H, 3.5; N, 22.0. Found: C, 40.3; H, 3.5; N, 22.5.

The free nucleoside **10** was regenerated from the picrate salt by stirring the yellow needles in water (30 ml) containing Dowex 1-X8 (CO_3^{2-}) anion-exchange resin for 1 h. The solvent was evaporated and the white solid residue (397 mg), on recrystallization from ethanol (50 ml), afforded pure **10** (380 mg, 25%) as a white powder, m.p. 227–230°, $[\alpha]_D^{26}$ −40.5° (*c* 1.16, water); R_{Ade} 1.43 (solvent E), R_{Ade} 0.78

(solvent F); {lit.[3] m.p. 196–198°, $[\alpha]_D$ −36.9° (*c* 0.4, water); R_{Ade} 1.44 (solvent E), R_{Ade} 0.76 (solvent F)}; λ_{max}^{MeOH} 260 nm (ε 15 300); ν_{max}^{KBr} 3380–3160 (OH, NH) 1680, 1615, 1575, 1485 (purine ring), 1112, 1088, 1060, 1040, and 1015 cm^{-1} (C–O); n.m.r. (methyl sulfoxide-d_6, at 50°): τ 1.74 (s, 1 H, H-2), 1.82 (s, 1 H, H-8), 2.73 (unexchanged NH), 4.10 (d, 1 H, $J_{1',2'}$ 1.2 Hz, H-1'), 4.2 (unexchanged OH or HOD), 5.62 (1 H, $J_{2',3'}$ 0.9 Hz, H-2'), 5.64 (1 H, $J_{3',4'}$ 3.1 Hz, $J_{4',5'}$ 6.7 Hz, H-4'), 6.00 (1 H, H-3'), 6.40 (t, 2 H, spacings 6.5 Hz, H-6',6''), and 8.07 (m, 2 H, H-5',5'').

Anal. Calc. for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.4; N, 24.9. Found: C, 47.4; H, 5.8; N, 24.9.

*1-O-Acetyl-2,3,6-tri-O-benzoyl-5-deoxy-α-*L-arabino-*hexofuranoside* (**18**). — To a solution of **16** (4.29 g, 8.45 mmol) in acetic acid (9 ml) and acetic anhydride (3.5 g, 4 equiv.) was added, dropwise, sulfuric acid (98%, 0.50 ml) at ~0° (ice bath). On completion of the reaction (5 min, t.l.c.), the strong acid was neutralized with sodium acetate, and the reaction mixture was evaporated under high vacuum. The residue was partitioned between chloroform and water; the organic layer was washed with aqueous sodium hydrogencarbonate and water, and dried (magnesium sulfate). Removal of the solvent afforded **18** as a crude syrup (3.5 g), R_F 0.34 (benzene) [R_F (**16**) 0.50 (benzene)]; ν_{max}^{film} 1760 (acetate), 1750, 1730, 1720 (C=O), 1600 and 1585 (benzoate); n.m.r.: τ 1.80–2.80 (15 H, aromatic H's), 3.53 (s, 1 H, $J_{1,2} < 0.5$ Hz, H-1), 4.20–4.60 (m, 2 H, H-2 and H-3), 5.25–5.60 (3 H, H-4 and H-6,6'), and 7.30–8.00 (m, 5 H, for H-5,5' with an overlapping singlet at τ 7.87 due to -OCOCH_3). This material, without further purification, was used for the nucleoside-coupling reaction.

*9-(5-Deoxy-α-*L-arabino-*hexofuranosyl)adenine* (**19**). — From a mixture of crude acetate **18** (3.5 g, 6.7 mmol), Celite (5 g), 6-benzamido-9-chloromercuripurine (4.0 g, 1.25 equiv.), and 1,2-dichloroethane (300 ml), was distilled 100 ml of the solvent to exclude moisture from the reaction mixture. Titanium tetrachloride (1.1 ml) in dry 1,2-dichloroethane (35 ml) was added, dropwise, over a 45-min period; vigorous stirring and refluxing were maintained for 12 h. Isolation of the product (4.25 g), in the same fashion as described for **10**, and deacylation in methanol (50 ml) containing sodium methoxide (5 ml, 1.5M in MeOH) by heating under reflux for 3 h afforded free crude nucleoside **19** (1.2 g). The picrate salt of **19** was prepared as a yellow solid (1.49 g) by adding picric acid (in 20 ml MeOH) to a boiling solution of **19** (1.2 g) in methanol (40 ml). Recrystallization from water (50 ml) yielded fine, yellow needles (1.2 g, 28% based on **15**), m.p. 209–217° (dec.).

Treatment of the picrate salt (1.18 g) with Dowex 1-X8 (CO_3^{2-}) anion-exchange resin in water (40 ml), afforded chromatographically pure nucleoside **19** as a syrup, which eventually crystallized (587 mg, 25% based on **15**), m.p. 133–135° (ethanol), $[\alpha]_D^{26}$ −90° (*c* 0.62, methanol); R_{Ade} 1.59 (solvent E). R_{Ade} 0.72 (solvent F); λ_{max}^{MeOH} 260 nm (ε 14 500); ν_{max}^{KBr} 3470–3040 (OH, NH), 1670, 1610, 1580, 1485 (purine ring), 1055 and 1015 cm^{-1} (C–O); n.m.r. (methyl sulfoxide-d_6 at 50°): τ 1.68 (s, 1 H, H-2), 1.80 (s, 1 H, H-8), 2.65 (unexchanged NH), 4.10 (d, 1 H, $J_{1',2'}$ 4.2 Hz, H-1'), 4.67 (unexchanged OH or HOD), 5.34 (1 H, $J_{2',3'}$ 5.0 Hz, H-2'), 5.72 (1 H, $J_{3',4'}$ 6.0 Hz,

$J_{4',5'}$ 5.6 Hz, $J_{4',5''}$ 7.0 Hz, H-4'), 6.13 (1 H, H-3'), 6.47 (t, 2 H, spacings 6.5 Hz, H-6',6''), and 8.20 (m, 2 H, H-5',5'').

Anal. Calc. for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.4; N, 24.9. Found: C, 46.9; H, 5.3; N, 24.8.

ACKNOWLEDGMENT

The authors are grateful to the National Research Council of Canada for financial support of this work.

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