crop. The crude product was dissolved in dichloromethane and washed with water; moisture was removed with magnesium sulfate, and the solution was concentrated *in vacuo* to a dry solid. Recrystallization from methanol gave long needles of XVII: 3.5 g. (41%), m.p. 184–185°, $[\alpha]^{20}D$ +72° (*c* 0.538, chloroform). Further recrystallization failed to change these constants. A second crop (1.0 g.), m.p. 180–182°, raised the total yield to 53%. In anhydrous pyridine (*c* 1.47) the pure compound mutarotated $[\alpha]^{20}D$ +125 → +116° in 10 days.

Anal. Calcd. for $C_{29}H_{32}NO_6$ (491.59): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.73; H, 6.54; N, 2.89.

2-Acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranose (XVIII).—A solution of XVII (1.0 g.) in dry pyridine (10 ml.) was treated with 0.5 ml. of benzoyl chloride and left at 24° for 24 hr. On pouring into ice–water (100 ml.) and stirring, the reaction mixture gave a solid precipitate as a fine powder, 1.3 g. Recrystallization from ethanol afforded XVIII as a voluminous crystalline mass: 0.75 g. (62%), m.p. 148–149°, $[\alpha]^{20}D$ +2.5° (*c* 0.325, chloroform). Thin layer chromatography on silica gel G, using benzene–methanol (7:1), showed the material to be homogeneous and further recrystallization failed to change its physical constants.

Anal. Calcd. for $C_{36}H_{37}NO_7$ (595.70): C, 72.58; H, 6.26; N, 2.35. Found: C, 72.62; H, 6.52; N, 2.26.

The n.m.r. spectrum of the product showed a doublet for the C-1 proton with a spacing of 8 c.p.s. centered at δ 6.06, indicating that this is the β anomer. A doublet at δ 5.9 with a spacing of 9 c.p.s. was removed on shaking the $CDCl_3$ solution of the substance with a drop of D_2O, identifying the peaks in question as arising from the amide proton.

Thin layer chromatography of the mother liquor from the first crystallization of XVIII revealed a second component, moving slightly slower than XVIII, presumably the α anomer.

2-Acetamido-1-*O*-benzoyl-2-deoxy-β-D-galactopyranose (XIX).—Hydrogenation of XVIII (380 mg.) in methanol and in the presence of washed, freshly prepared palladium black (from 120 mg. of palladium chloride) gave, after removal of the catalyst and solvent, needles which were recrystallized from methanol: 180 mg. (88%), m.p. 203–205°, $[\alpha]^{20}D$ −5.2° (*c* 0.38, methanol). Further recrystallization from methanol failed to change these values.

Anal. Calcd. for $C_{15}H_{19}NO_7$ (325.33): C, 55.38; H, 5.89; N, 4.31. Found: C, 55.63; H, 6.17; N, 4.14.

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Syntheses with Partially Benzylated Sugars. V.[1] Substitution at Carbon 4 in an Aldose. The Synthesis of 4-*O*-Methyl-β-D-arabinopyranose

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The readily accessible 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I) was converted successively to 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose diethyl dithioacetal (III) and 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose dibenzyl acetal (VI). Replacement of the benzoyl group in the latter compound by methyl, followed by hydrogenolysis of the five benzyl groups, afforded crystalline 4-*O*-methyl-β-D-arabinopyranose (IX). This synthesis may be regarded as illustrating a possibly general technique whereby C-4 or C-5 in an aldose may be selectively substituted.

The synthesis of aldose derivatives with substituents at C-4 or C-5, the carbon atoms normally participating in hemiacetal ring formation, involves special problems which have been met with many ingenious solutions, each solution, in general, being unique for a specific aldose. The present paper describes a synthetic pathway for the preparation of 4-*O*-substituted derivatives of an aldose, a pathway which is not dependent upon the stereochemistry of the aldose.

The hydroxyl groups of aldopyranosides and aldofuranosides may readily be masked as benzyl ethers; subsequent removal of the aglycon by hydrolysis yields aldoses which are fully benzylated save at C-1 and at the other carbon atom involved in the hemiacetal ring (C-5 or C-4). A number of such aldose ethers have been reported in recent years.[1-7] The conversion of compounds of this class to acyclic derivatives, their dithioacetals, for instance, should unmask for selective substitution the carbon atom originally involved in the hemiacetal ring.[8] Having developed a simple synthesis of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I)[3,5] and being in need of 4-*O*-methyl-D-arabinopyranose (IX), we have investigated this synthetic approach (see Scheme I).

Treatment of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I) with ethanethiol and hydrogen chloride afforded an amorphous diethyl dithioacetal (II) which was conveniently isolated as its crystalline 4-*O*-benzoyl derivative (III). The dithioacetal II was further characterized through its 4-*O*-*p*-toluoyl and 4-*O*-*p*-chlorobenzoyl derivatives (IV and V); efforts to obtain a tosyl derivative were unsuccessful, owing, perhaps, to steric hindrance. Attempts to methylate either II or III (under conditions which would eliminate the benzoyl group) gave highly heterogeneous, amorphous mixtures and it seems probable that methylation was accompanied by

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(8) Alternative methods for the unmasking of C-4 or C-5 in partially benzylated aldoses may be envisaged. B. P. Vaterlaus, J. Kiss, and H. Spiegelberg [*Helv. Chim. Acta*, **47**, 381 (1964)], for instance, oxidized 3,5,6-tri-*O*-benzyl-2-*O*-methyl-D-glucofuranose to the corresponding D-glucono γ-lactone and then made the methyl ester as well as the N-methylamide of 2-*O*-methyl-3,5,6-tri-*O*-benzyl-D-gluconic acid, acyclic derivatives which were mesylated at C-4 in the course of an extremely ingenious synthesis of 3-*O*-carbamoylnoviose. Fortunately this synthesis did not involve subsequent reduction of C-1 to the aldehyde stage, since such reductions are difficult to carry out in high yield; the dithioacetal approach adopted here appears to be the method of choice when a substituted aldose is to be regenerated.

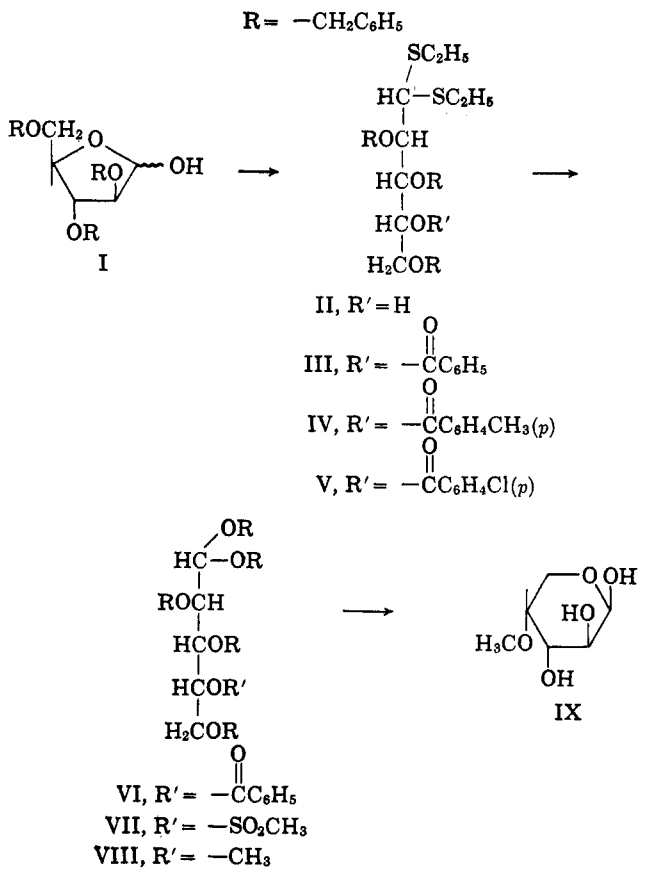
TABLE I

4-*O*-METHYLARABINOSE AND DERIVATIVES

Compd.	D enantiomorph[a] M.p., °C.	D enantiomorph[a] $[\alpha]^{20}D$, deg.	L enantiomorph[b] M.p., °C.	L enantiomorph[b] $[\alpha]^{27}D$, deg.
4-*O*-Methylarabinose	109–110	−135 (H_2O)	...	+132 ± 2 (H_2O)
4-*O*-Methyl-*erythro*-pentose phenylosazone	172–173		176–177.5	
Methyl 4-*O*-methyl-β-arabinopyranoside	113–114	−241 (MeOH)	112–114	+213 ± 2 (MeOH)

[a] Present work. [b] See ref. 10.

SCHEME I



alkylation of the bivalent sulfur atoms. To avoid this difficulty, the ethylthio groups in III were replaced by benzyloxy groups, giving crystalline 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose dibenzyl acetal (VI) in good yield. The corresponding 4-*O*-methylsulfonyl derivative (VII) was prepared in chromatographically homogeneous form but proved to be amorphous.

Direct methylation of VI, using barium oxide and methyl iodide in dimethylformamide[9] replaced the benzoyl group with a methyl group; attempts to crystallize the product (VIII) were unsuccessful and the five benzyl groups were removed directly by catalytic hydrogenolysis. Thus obtained, the 4-*O*-methyl-D-arabinopyranose crystallized in a form which showed dextromutarotation and is, therefore, the β anomer IX.

Several years ago Siddiqui and Bishop[10] methylated a mixture of methyl 2,3-di-*O*-benzyl-L-arabinopyranosides and -L-arabinofuranosides; successive hydrogenolysis and hydrolysis afforded them a mixture of 4- and 5-*O*-methyl-L-arabinoses from which the former was isolated as a sirup by chromatography. As may be seen in Table I, the equilibrium rotation of the 4-*O*-methyl-L-arabinose prepared by Siddiqui and Bishop[10] is numerically very close to that found for IX. Likewise, the melting points of the phenylosazones of the two enantiomorphs are in fair agreement. A sample of IX was converted to methyl 4-*O*-methyl-β-D-arabinopyranoside. As shown in Table I, the melting point of this glycoside corresponded quite closely with that of its enantiomorph; however, the specific rotations for the two enantiomorphs differed significantly. Inasmuch as the infrared spectrum of the L enantiomorph, kindly provided by Dr. Bishop, proved to be indistinguishable from that of IX, we are at a loss to account for this discrepancy in rotations.

In passing, it may be noted that 4-*O*-methyl-D-arabinopyranose is significantly volatile, being distillable at 90° (bath) and 5×10^{-4} mm.

Experimental[11]

4-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose Diethyl Dithioacetal (III).—A mixture of 200 g. of ethanethiol and 20 g. of anhydrous magnesium sulfate was cooled to 0° and saturated with hydrogen chloride. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose[3,5] (20 g.) was added and the mixture was stirred at 0°. After 15 min. and again after 30 min. the reaction mixture was resaturated with hydrogen chloride. The course of the reaction was monitored by thin layer chromatography, using 1:4 ether–benzene. In the initial phases of the reaction, three components were detectable; when only one component was detectable (typically after *ca.* 0.45 hr.), the reaction mixture was filtered through a thin layer of Darco X and the residue was washed with 200 ml. of benzene. The combined filtrate and washings were concentrated *in vacuo* (30° bath) to a heavy sirup (24.6 g.) which was dissolved in 100 ml. of pyridine. Benzoyl chloride (6 ml.) was added and the reaction mixture was left at room temperature overnight. A small amount of water was added; the mixture was left at room temperature for 0.5 hr. and then poured into 400 ml. of ice–water. The sirup thus precipitated was seeded[12] and left at 0° for *ca.* 3 hr. After washing and drying, the fine powder (28.2 g., 94%) was dissolved in 1 ml. of isopropyl ether/g. of compound, and the solution was filtered through Darco X. The solution was diluted with 40 ml. of absolute ethanol, chilled in ice, and seeded to yield 21.6 g., m.p. 49–50°, $[\alpha]^{20}D$ +16° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{37}H_{42}O_5S_2$ (630.88): C, 70.44; H, 6.71; S, 10.16. Found: C, 70.47; H, 6.98; S, 9.94.

2,3,5-Tri-*O*-benzyl-4-*O*-*p*-toluoyl-D-arabinose Diethyl Dithioacetal (IV).—Crude 2,3,5-tri-*O*-benzyl-D-arabinose diethyl dithioacetal (216 mg.), prepared as described above, was acylated with *p*-toluoyl chloride in pyridine solution in conventional fashion. Crystallized from ethanol, the ester (80 mg., 30%) melted at 38–39° and showed $[\alpha]^{20}D$ +14.4 ± 1° (*c* 1.1, $CHCl_3$).

Anal. Calcd. for $C_{38}H_{44}O_5S_2$ (644.85): C, 70.77; H, 6.88; S, 9.94. Found: C, 70.66; H, 6.92; S, 9.79.

2,3,5-Tri-*O*-benzyl-4-*O*-*p*-chlorobenzoyl-D-arabinose Diethyl Dithioacetal (V).—Crude 2,3,5-tri-*O*-benzyl-D-arabinose diethyl dithioacetal (216 mg.) was acylated with *p*-chlorobenzoyl chloride in the usual fashion to give, from ethanol, 90 mg. (33%)

(9) R. Kuhn and H. Trischmann [*Ber.*, **96**, 284 (1963)] used a mixture of barium oxide, barium hydroxide octahydrate, methyl iodide, and dimethylformamide for methylation. In the present case better results were obtained when the barium hydroxide octahydrate was omitted.

(10) I. R. Siddiqui and C. T. Bishop, *Can. J. Chem.*, **40**, 223 (1962).

(11) Melting points are corrected. Thin layer chromatography was conducted on standard microscope slides using silica gel G (E. Merck A.-G., Darmstadt), components being visualized by brief heating at *ca.* 100° after spraying with 5% sulfuric acid.

(12) Seeds were initially obtained from an ethanolic solution of a purified sample of the amorphous material.

of product, m.p. 42–44°. Recrystallized from the same solvent, the material had m.p. 42–43° and showed $[\alpha]^{20}D$ +17.0 ± 1° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{37}H_{41}ClO_5S_2$ (665.28): C, 66.79; H, 6.21; Cl, 5.33; S, 9.64. Found: C, 67.03; H, 6.30; Cl, 5.24; S, 9.76.

4-O-Benzoyl-2,3,5-tri-O-benzyl-D-arabinose Dibenzyl Acetal (VI).—4-O-Benzoyl-2,3,5-tri-O-benzyl-D-arabinose diethyl dithioacetal (21.0 g.) and 21 g. of Drierite were added to 210 ml. of benzyl alcohol freshly fractionated *in vacuo* under nitrogen. Cadmium carbonate (25.2 g.) and mercuric chloride (25.2 g.) were then added and the reaction mixture was stirred at room temperature for 1 hr. at the end of which time it had solidified. After 2 hr., dichloromethane (200 ml.) was added, and the solution was filtered through Darco X and concentrated, finally at 1 mm. and 85° (bath). Dichloromethane (175 ml.) was again added and the solution was filtered and reconcentrated to a sirup. Dissolved in 8 vol. of absolute alcohol and cooled to −5°, the product crystallized as needles, 19.2 g. (80%), m.p. 48–49°. Recrystallized from an ether–absolute ethanol mixture (1:10 v./v.) at −5°, the pure product melted at 48–49° and showed $[\alpha]^{20}D$ +4° (*c* 1.06, $CHCl_3$).

Anal. Calcd. for $C_{47}H_{46}O_7$ (722.84): C, 78.09; H, 6.41. Found: C, 77.96; H, 6.40.

2,3,5-Tri-O-benzyl-4-O-methylsulfonyl-D-arabinose Dibenzyl Acetal (VII).—4-O-Benzoyl-2,3,5-tri-O-benzyl-D-arabinose dibenzyl acetal 1.0 g. was debenzoylated with a catalytic quantity of barium methoxide in methanol; the methanol was removed *in vacuo* and the sirupy residue, dissolved in anhydrous pyridine, was treated with 0.2 ml. of methanesulfonyl chloride. After standing overnight at room temperature, the reaction mixture was worked up in the usual fashion to yield a sirup (0.71 g., 74%); thin layer chromatography of a sample using ether–benzene (1:4), showed the product to be homogeneous. The sirup showed $[\alpha]^{20}D$ +7.6° (*c* 1.0, $CHCl_3$); attempts to crystallize the product were unsuccessful.

Anal. Calcd. for $C_{41}H_{44}O_8S$ (696.87): C, 70.66; H, 6.36; S, 4.60. Found: C, 70.62; H, 6.23; S, 4.71.

4-O-Methyl-β-D-arabinopyranose (IX).—4-O-Benzoyl-2,3,5-tri-O-benzyl-D-arabinose dibenzyl acetal (15 g.), powdered Drierite (75 g.), freshly powdered barium oxide (150 g.), dimethylformamide (150 ml., freshly distilled from barium oxide), and methyl iodide (150 ml.) were stirred together under a reflux condenser at 56–58° (bath) for 16 hr. Dichloromethane (250 ml.) was added to the cooled reaction mixture and the solids were removed by filtration on a bed of Filter-Cel, the mass being washed with 250 ml. of dichloromethane. Concentration of the combined filtrate and washings *in vacuo* afforded a sirup which was dissolved in 200 ml. of dichloromethane. The solution was extracted with 700 ml. of water to give an emulsion which was broken by filtration through Filter-Cel; after separation, the organic layer was washed with water (four 300-ml. portions), no emulsion being encountered. After drying with sodium sulfate, the solution was filtered through Darco X and concentrated *in vacuo* to a sirup which was essentially homogeneous as shown by thin layer chromatography using ether–benzene (1:4). However, the infrared absorption spectrum of the sirup revealed the presence of a trace of dimethylformamide, an impurity which appears to nullify the catalytic activity of palladium. Water (15 ml.) was added to the sirup and then removed *in vacuo*, the sirup finally being held at 0.5 mm., giving 13.5 g. The infrared spectrum of the product then showed no absorption at 3650–3590 (OH) or at *ca.* 1667 $cm.^{-1}$ (DMF).

The sirupy 2,3,5-tri-O-benzyl-4-O-methyl-D-arabinose dibenzyl acetal was dissolved in 100 ml. of methanol and the solution was filtered through Darco X. Palladium chloride (0.75 g.) was added and the mixture was shaken with hydrogen at room temperature until the absorption of the gas had ceased (162 min.). The catalyst was removed by filtration, the solution was concentrated *in vacuo* to a sirup[13] which was dissolved in 45 ml. of 0.5 *N* hydrochloric acid, and the resulting solution was filtered through a bed of Darco X. After boiling under reflux for 1.5 hr., the solution contained only 4-O-methyl-D-arabinose as shown by thin layer chromatography using alcohol. The straw-colored solution was filtered through a layer of Darco X and then passed through a column of Duolite A-4 (2.4 × 20 cm.). Concentration *in vacuo* afforded a clear, colorless sirup (3.7 g.) which was dissolved at room temperature in 10 ml. of 2-propanol and the solution was seeded. After standing at −5° for 5 days, the crystals were removed by filtration, 1.90 g., m.p. 109–110°. On concentration *in vacuo* the mother liquor yielded a second crop (0.29 g., m.p. 108–109°), raising the total yield to 2.19 g. (64% based on VI). Recrystallized from either acetone or 2-propanol, the 4-O-methyl-β-D-arabinopyranose was obtained as clear prisms, m.p. 109–110°, $[\alpha]^{20}D$ −201° (extrapolated) → −135° (50 min., final, *c* 1.0, water). Siddiqui and Bishop[10] reported $[\alpha]^{27}D$ +132 ± 2° (H_2O) for amorphous 4-O-methyl-L-arabinopyranose. The substance may be distilled at 90° (bath) and 5 × 10^{-4} mm.

Anal. Calcd. for $C_6H_{12}O_5$ (164.17): C, 43.90; H, 7.37; CH_3O, 18.91. Found: C, 43.60; H, 7.57; CH_3O, 18.94.

A sample of the 4-O-methyl-D-arabinopyranose was converted into **4-O-methyl-D-*erythro*-pentose phenylosazone**, m.p. 172–173°; Siddiqui and Bishop[10] reported m.p. 175–177.5° for the enantiomorph of this substance.

Methyl 4-O-Methyl-β-D-arabinopyranoside.—4-O-Methyl-D-arabinopyranose (200 mg.) was dissolved in 15 ml. of methanol containing 4% of hydrogen chloride and the solution was boiled under reflux for 15 hr. Acid was removed with Amberlite IR-45 and the colorless solution was concentrated *in vacuo* to a sirup which was crystallized from ethyl acetate; 80 mg. (37%), m.p. 109–110°. Recrystallized from the same solvent, the methyl 4-O-methyl-β-D-arabinopyranoside (40 mg.) had m.p. 113–114° and $[\alpha]^{20}D$ −241° (*c* 0.87, methanol). Siddiqui and Bishop[10] reported m.p. 112–114° and $[\alpha]^{28}D$ +213 ± 2° (*c* 0.93, methanol) for methyl 4-O-methyl-β-L-arabinopyranoside. The infrared absorption spectrum of a sample of the L enantiomorph was identical with that of the D enantiomorph.

Acknowledgment.—We wish to thank Dr. C. T. Bishop for his kindness in providing us with samples of 4-O-methyl-L-arabinopyranose derivatives. We are also indebted to Dr. William C. Alford and his associates of the Section on Microanalytical Services and Instrumentation of this laboratory for microanalyses.

(13) This sirup contained the anomeric methyl 4-O-methyl-D-arabinosides, formed through the action of the methanol on the 4-O-methyl-D-arabinose in the presence of hydrogen chloride arising from the reduction of the palladium chloride. Avoidance of the formation of these glycosides through the use of washed palladium black proved impracticable inasmuch as hydrogenolysis often progressed at a very slow rate in the absence of acid.