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ACETONATION OF D-RIBOSE AND D-ARABINOSE WITH ALKYL ISOPROPENYL ETHERS*†

JACQUES GELAS AND DEREK HORTON

Ensemble Scientifique des Cézeaux, Université de Clermont-Ferrand, 63170 Aubière (France), and Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U. S. A.)

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ABSTRACT

D-Ribose (**1**) in *N,N*-dimethylformamide containing a trace of *p*-toluenesulfonic acid is acetonated under kinetic control by ethyl (or methyl) isopropenyl ether (**2**) to give mainly 3,4-*O*-isopropylidene-β-D-ribopyranose (**3**), together with lesser proportions of 2,3-*O*-isopropylidene-D-ribofuranose (**4**), its 5-(2-alkoxy-2-propyl) ether (**5** or **5a**), and 1,5:2,3-di-*O*-isopropylidene-β-D-ribofuranose (**6**). Similar treatment of D-arabinose (**10**) gives mostly 3,4-*O*-isopropylidene-β-D-arabinopyranose (**11**) together with a minor proportion of 1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranose (**12**). The structures of the monoacetals **3** and **11** were confirmed by an acetylation–deacetonation–acetylation sequence.

INTRODUCTION

The previous paper in this series[2] described the use of ethyl isopropenyl ether for the acetonation of sugars. It was shown that the reagent operates under kinetic control, with favored initial attack at primary hydroxyl groups of the sugar in its original tautomeric form. Thus, D-glucose is converted in high (95%) yield into its 4,6-isopropylidene acetal.

In related studies, Hasegawa and Fletcher[3], extending earlier work by Evans *et al.*[4], examined the acetonation of sugars with 2,2-dimethoxypropane; their results indicate that the products arising from use of this reagent may also be attributed, at least in part, to reaction under kinetic control. In general, however, acetonation reactions of sugars have been performed with acetone–mineral acid[5], usually with copper(II) sulfate present, under which conditions the thermodynamic product or products prevail[6]. Use of acetone–copper(II) sulfate alone has permitted isolation of products of kinetic control, but yields are generally modest or low[7].

In this report, the acetonation of D-ribose and D-arabinose with ethyl (and methyl) isopropenyl ether is described. As these sugars favor the pyranose form in

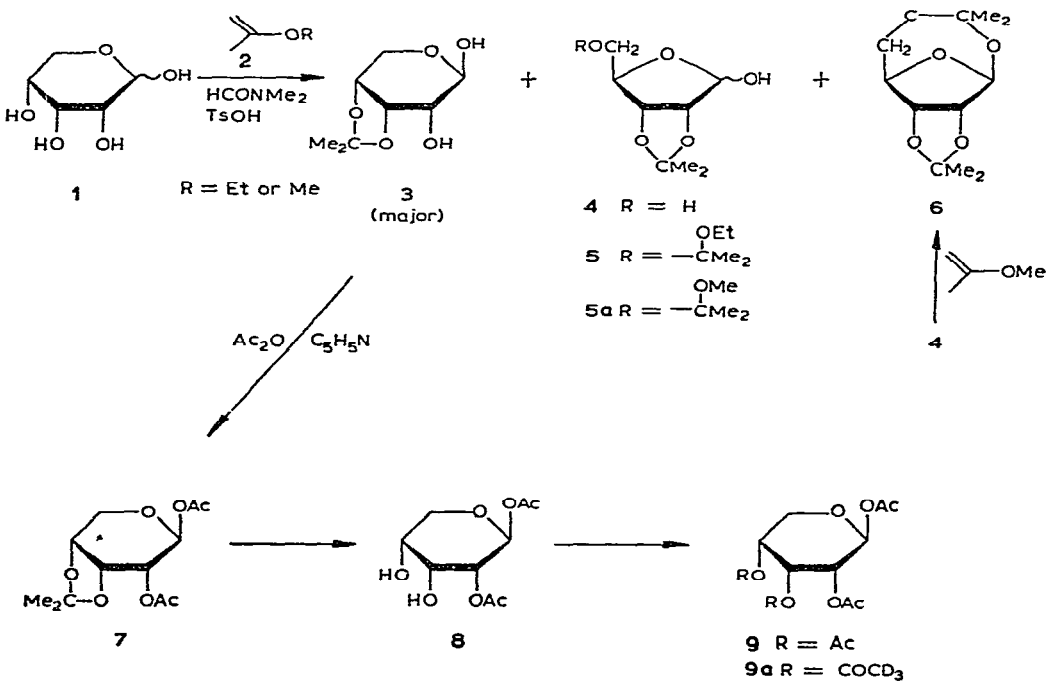
*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.
†For a preliminary report, see Ref. 1.

aqueous solution (almost exclusively for D-arabinose, and ~80% for D-ribose[8]), it was considered that the acetonation reagent would be largely constrained to initiate attack at a secondary hydroxyl group because a primary hydroxyl group would not be available from the pyranose form without prior tautomerization to the furanose, a process expected to be slower than the acetonation reaction.

DISCUSSION

Conventional acetonation of D-ribose with acetone–sulfuric acid leads[9] mainly (50–60%) to 2,3-*O*-isopropylidene-D-ribofuranose, together with a small proportion of its 1,5-anhydride and traces of a dimeric anhydride[10–12]; also formed in low yield are 1,2-*O*-isopropylidene-α-D-ribofuranose and a product formulated as 1,2:3,4-di-*O*-isopropylidene-α-D-ribopyranose[13]. The use of enol ethers for the acetonation of D-ribose appears not to have been described, although ethyl isopropenyl ether has been used[14] for the 2,3-acetonation of a ribonucleoside.

As in the previous study[2], the standard conditions used for acetonation with ethyl isopropenyl ether (**2**) employed a twofold molar excess of the reagent plus the aldose (1 molar equivalent), in *N*,*N*-dimethylformamide to permit a homogeneous reaction-medium, and with a catalytic amount of *p*-toluenesulfonic acid present. Scrupulously anhydrous conditions were essential for maximal yields. The reactions were conducted at ~5° and were interrupted when t.l.c. monitoring indicated that the starting aldose had all reacted.



Acetonation of D-ribose (**1**) by **2** under these conditions gave a principal product, isolated crystalline in 40–50% yield, that was identified as 3,4-*O*-isopropylidene-β-D-ribopyranose (**3**), together with two additional products that migrated faster on t.l.c. One of these, produced in 20% yield, was isolated as a syrup and identified as the known[11] 2,3-*O*-isopropylidene-D-ribofuranose (**4**). The fastest-migrating product, formed in ~7% yield and obtained crystalline, was shown to be 1,5:2,3-di-*O*-isopropylidene-β-D-ribofuranose (**6**). Accompanying **6** and difficultly separable from it by t.l.c. was a small proportion of an unstable, syrupy product considered to be the 5-(2-ethoxy-2-propyl) ether (**5**) of **4**.

The major product **3** {m.p. 115–117°, $[\alpha]_D$ −85° (water)} showed negligible mutarotation, and its elemental analysis and n.m.r. spectrum (Table I) indicated that it was a monoisopropylidene acetal of D-ribose. The monomeric nature of **3** was confirmed by its mass spectrum (Table II), which showed a strong highest-mass peak at *m/e* 175 ($M^{\ddagger} - \cdot CH_3$). The n.m.r. spectrum in methyl sulfoxide-d_6 showed two low-field doublets for hydroxyl groups, and for the anomeric proton a four-line pattern was observed that collapsed to a wide (7.0 Hz) doublet when deuterium oxide was added, with concomitant disappearance of the hydroxyl-proton signals. These observations indicate that both hydroxyl groups are secondary and that the anomeric hydroxyl group is unsubstituted. As chemical transformations established unequivocally that **3** had a pyranoid ring, the most probable structure was either a 3,4- or 2,3-isopropylidene acetal; the 1,2-acetal could be excluded because the anomeric position is free.

Acetylation of **3** with acetic anhydride–pyridine, conditions that are not expected to lead to tautomeric modification of sugars, gave a diacetate identified as 1,2-di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-ribopyranose (**7**). The n.m.r. spectrum of **7** resembled that of the precursor **3** except for the presence of two acetyl-group singlets and the absence of hydroxyl-group signals; the H-1 and H-2 signals were shifted strongly downfield. This evidence indicates that the two free hydroxyl groups in the precursor were at C-1 and C-2. The ring size of **7** was confirmed by deacetonation with aqueous acid to give the 3,4-diol **8**, followed by acetylation, which afforded β-D-ribopyranose tetraacetate (**9**) in near-quantitative yield. Use of acetic anhydride-d_6 for the acylation step afforded the 3,4-bis(trideuterioacetyl) analogue (**9a**), which differed from **9** only by its lack of two of the acetate-group resonances observed[15] for **9**.

This evidence establishes conclusively that **3** is 3,4-*O*-isopropylidene-β-D-ribopyranose, and the n.m.r.-spectral data (Table I) for **3** and **7** indicate that both favor the $^4C_1$(D) conformation, although there may be some distortion from the ideal chair form and possibly a minor contribution from the $^1C_4$(D) form in equilibrium. The n.m.r. spectrum of 1,2-di-*O*-acetyl-β-D-ribopyranose (**8**) in acetone-d_6 shows the H-1 and H-2 resonances as the lowest-field methine signals, at δ 6.00 and 4.81, respectively, thus resembling compound **7**; in contrast, the tetraacetate **9** showed all methine resonances at low field (δ 5.96, 5.00, 5.46, and 5.14 for H-1,2,3, and 4, respectively). The $J_{1,2}$ couplings observed for **8** (7.6 Hz in methyl sulfoxide-d_6,

TABLE I

P.M.R.-SPECTRAL DATA FOR THE ISOPROPYLIDENE ACETALS OF D-RIBOSE AND D-ARABINOSE

Solvent	*Compd.*	*Chemical shifts*[a] (δ)											
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*CMe_2*		*OH-1*	*OH-2*	*OMe*	*OAc*
Me_2SO-d_6	3	4.71dd[b]	4.22m[c]	4.37dd	3.33m	3.68dd	3.28dd	1.40s	1.28s	6.26d	5.08d		
Me_2SO-d_6	5a	5.20d[d]	4.45d	4.65dd	4.03m	←3.33m→		1.37s(3)	1.27s(6)	5.40d		3.12s	
								1.23s(3)					
CCl_4	6	5.20s	← 4.58s →		4.32m	3.95dd	3.58dd	1.46s(3)	1.38s(6)				
								1.25s(3)					
C_6D_6	6	5.61s	4.71d	4.45d	4.23m	3.55dd	3.13dd	1.43s(3)	1.38s(3)				
								1.35s(3)	1.17s(3)				
$(CD_3)_2CO$	7	6.06d	5.12dd	4.65dd	4.46 2t	3.97dd	3.61dd	1.46s	1.30s				2.07s 2.00s
$CDCl_3$	7	6.13d	5.09dd	4.65dd	4.37 2t	←3.75m→		1.53s	1.33s				2.17s 2.07s
Me_2SO-d_6	11	4.93m[e]	←4.40–3.20m→					1.40s	1.27s	6.26d	4.87d		
										6.55d	5.07d		
$CDCl_3$	13[f]	5.67d	5.17dd	←4.48–3.92m→				1.57s	1.37s				2.10s(6)
$(CD_3)_2CO$	13	5.61d	5.10dd	←4.50–3.60m→				1.48s	1.31s				2.04s 2.01s
C_6D_6	13	5.83d	5.50dd	←4.13–3.33m→				1.53s	1.20s				1.72s 1.67s

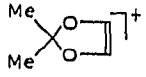
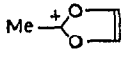
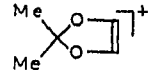
First-order couplings (Hz)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
3	7.0	3.0	7.0	2.8	2.8	12.8
7	7.0	2.6	7.4	1.7	1.2	12.8
5a	<0.5	6.0	~0.8			
6	0	5.8	0	~2	~1	12.8
11	3.4					
13	7.0	6.4				

[a]Multiplicities of the signals given by s (singlet), d (doublet), t (triplet), m (multiplet). [b]Gave a doublet after addition of D_2O to the solution, with concurrent disappearance of the OH signals; $^3J_{OH\text{-}1,1}$ 5.8 Hz, $^3J_{OH\text{-}2,2}$ 6.2 Hz. [c]Gave a doublet of doublets after addition of D_2O. [d]Gave a singlet after addition of D_2O to the solution, with concurrent disappearance of the OH-1 signal; $^3J_{OH\text{-}1,1}$ 4.5 Hz. [e]Gave a doublet after addition of D_2O to the solution, with concurrent disappearance of the OH signals; $^3J_{OH\text{-}1,1}$ 6.4 and 4.8 Hz; $^3J_{OH\text{-}2,2}$ 4.4 and 4.8 Hz. [f]Spectra recorded with an anomeric mixture (~10% of the β anomer) showed for H-1β: δ 6.12, $J_{1,2}$ 3.3 [$(CD_3)_2CO$] and δ 6.18, $J_{1,2}$ 3.4 ($CDCl_3$).

TABLE II

MASS-SPECTRAL DATA FOR THE ISOPROPYLIDENE ACETALS OF D-RIBOSE AND D-ARABINOSE[a]

m/e	3	11	*Assignment*	*m obs*	m/e	7	13	*Assignment*	*m obs*	m/e	5a	6	*Assignment*	*m obs*
190	not obs.		M^+		274	not obs.		M^+		262	not obs.		M^+ (5a)	
175	29	35	$M^+ - Me\cdot$		259	10	12	$M^+ - Me\cdot$		230	0.5	16.5	M^+ (6) and M^+ (5a) − MeOH	
173	0.8	1	$M^+ - \dot{O}H$		215	1.5	2.4	$M^+ - AcO\cdot$		247	1.2		M^+ (5a) − Me·	
159	8	5	$M^+ - \dot{C}H_2OH$		214	1	1.3	$M^+ - AcOH$		215	5	17	M^+ (6) − Me·	
157	1	1.2	$(M^+ - Me\cdot) - H_2O$	*140.8	199	0.9	3.5	$(M^+ - Me\cdot) - AcOH$	*152.9	231	0.6		M^+ (5a) − MeO·	
132	2.5	2	$M^+ - Me_2CO$		172	6.5	2.7	$(M^+ - AcOH) - CH_2CO$	*138.2	189	0.3		M^+ (5a) − $Me_2\dot{C}OMe$	
131	14	9.5	$M^+ - Me_2\dot{C}OH$		157	8	11	$(M^+ - AcO\cdot) - Me_2CO$	*114.7	184	0.1	2	*m/e* 230 − MeOMe	*147.3
115	3.8	5	$(M^+ - Me\cdot) - AcOH$	*75.5	156	1.2	1.5	$(M^+ - AcOH) - CH_2CO$ / *m/e* 199 − MeĊO		172	0.3	1.1	*m/e* 215 − MeĊO	
101	3	5	*m/e* 159 − Me_2CO	*64.1	141	0.9	2	*m/e* 157 − O·		159	0.9		*m/e* 189 − CH_2O	
100	3	3			139	6	7.5	*m/e* 199 − AcOH	*97.0	157	3.8	18	*m/e* 215 − Me_2CO	*114.6
97	3.5	4.5	*m/e* 115 − H_2O	*81.8	114	5.4	2.3	*m/e* 172 − Me_2CO	*75.5	114	2.4	24	*m/e* 157 − MeĊO	
85	9.5	12			97	18	20	*m/e* 157 − AcOH / *m/e* 156 − AcO·	*60.0 *60.2	101	2.6	9		
73	45	55			85	6	5.5	*m/e* 114 − CHO	*63.3	100	3	19		
69	22	30			81	3	5.5	*m/e* 141 − AcOH / *m/e* 97 − O·	*46.5 *67.6	97	3	4	*m/e* 157 − AcOH	
53	100	92	$Me_2\dot{C}OH^+$		73	2.5	1.6			85	5.5	23	*m/e* 100 − Me·	*72.2
43	90	100	$Me\dot{C}O^+$		69	4.5	5			73	100	6	$Me_2\dot{C}OMe^+$	
					59	10	8	$Me_2\dot{C}OH^+$		69	9	97		
					43	100	100	$Me\dot{C}O^+$		59	25	55		
										43	55	100	$Me\dot{C}O^+$	

[a] *m/e* values are recorded only for major fragments. The intensities are expressed as percentage of the base peak. Assignments are tentative.

6.0 Hz in acetone-d_6) indicate that it favors the $^4C_1$(D) conformation more strongly than does **9** ($J_{1,2}$ 4.8 Hz in acetone-d_6).

Very recently, Morgenlie[7] has reported the acetonation of D-ribose with acetone–copper(II) sulfate and the isolation in 17% yield of a product identified as **3** by periodate degradation; the m.p. and specific rotation reported are in good agreement with those determined here for **3**.

The syrupy acetonation product of intermediate mobility in t.l.c. was readily identified as the known[11] acetal **4** by direct comparison with an authentic sample[16].

The diacetal **6** gave an acceptable microanalysis and its mass spectrum showed strong peaks both for the molecular ion and for ($M^+ - \cdot CH_3$) (Table II). The n.m.r. spectrum in benzene-d_6 (Table I) was completely first-order and in accord with the structure assigned; in carbon tetrachloride, the H-2 and H-3 signals coincided. Although **6** was isolated in only low yield by the acetonation of **1** by **2**, it could be obtained in 86% yield by treating 2,3-*O*-isopropylidene-D-ribofuranose (**4**, prepared in high yield from **1** by conventional acetonation) with methyl isopropenyl ether (**2**, R = Me). The ready conversion of **4** into **6**, together with the spectral data, prove the structure of **6**.

Compound **6** has a seven-membered ring fused to a rigid system of two five-membered rings; the H-1–H-2 and H-3–H-4 dihedral angles are ~90°, as shown by the absence of coupling between these pairs of protons, and the relatively high $J_{2,3}$ value (5.8 Hz) indicates an acute H-2–H-3 dihedral angle. The small $J_{4,5}$ and $J_{4,5'}$ values indicate that, viewing along C-4–C-5, H-4 lies between H-5 and H-5'.

Hughes and Speakman[13] acetonated D-ribose with acetone–sulfuric acid and obtained a product (in 3% yield) having m.p. 68–69° and $[\alpha]_D^{20}$ −51° in chloroform, which they considered to be 1,2:3,4-di-*O*-isopropylidene-α-D-ribopyranose; a possible formulation as **6** was rejected. No n.m.r.-spectral data were given for the product. In view of the similarity of the constants recorded by Hughes and Speakman[13] with those recorded here for **6**, together the observed levorotation that accords with the β-D anomeric configuration, and the limited evidence advanced in support of the α-pyranose formulation, it is possible that their product was, in fact, compound **6**.

The ready conversion of compound **4** into the diacetal **6** by action of **2** suggests that **2** may be a generally useful reagent for preparing strained isopropylidene acetals that are inaccessible by acetonation under thermodynamic control. It may be noted that benzaldehyde reacts with **4** in the presence of zinc chloride to give the 1,5-benzylidene acetal[12]; the benzylidene group appears to be more readily incorporated into a 7-membered ring than is the isopropylidene group.

Compound **6** evidently arises from **4** by initial attack of the alkyl isopropenyl ether (**2**) at O-6, with subsequent reaction through attack by O-1 of the β-D anomeric form. If the cyclization step does not take place, the reaction should give the 5-(2-alkoxy-2-propyl) ether of **4**. An unstable product accompanying **6**, and having slightly lower t.l.c. mobility than it, was observed in the acetonation of **1** with ethyl isopropenyl ether. This product was suspected to be the 5-(2-ethoxy-2-propyl) ether **5**, but it was not sufficiently stable for detailed characterization. However, when the

acetonation was performed with methyl isopropenyl ether, the corresponding 5-(2-methoxy-2-propyl) ether (**5a**) of **4** could be isolated, and examined by n.m.r. and mass spectrometry. Its mass spectrum (Table II) showed a peak at *m/e* 247 ($M^{+} - \cdot CH_3$), and its n.m.r. spectrum (Table I) indicated the presence of a free hydroxyl group at the anomeric position, four *C*-methyl groups, and a methoxyl group; the chemical shifts and spin couplings observed for protons on the sugar chain were very close to those observed for **4** in the same solvent (methyl sulfoxide-d_6). Both compounds appeared to be mainly in the β-anomeric form, and showed $J_{1,2}$ and $J_{3,4}$ couplings of <1 Hz and $J_{2,3}$ couplings of 6 Hz; this greater magnitude of $J_{2,3}$ in comparison with that for **6** presumably reflects lower torsional strain along C-2–C-3 in the structures **4** and **5a**, which lack the 1,5-bridge present in **6**.

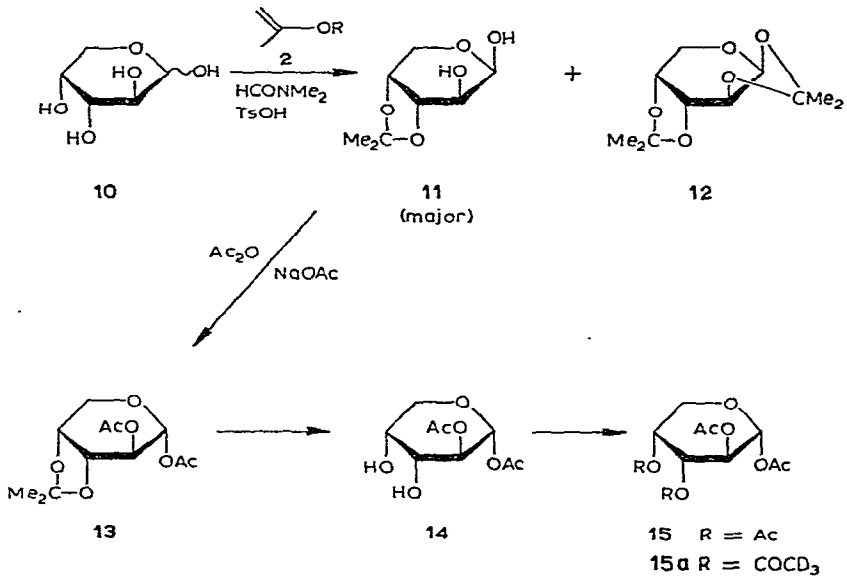
Apart from the somewhat enhanced stability of the methoxy derivative **5a** in comparison with its ethoxy analogue **5**, no significant difference was noted in the relative yields of the acetonation products when methyl isopropenyl ether was used instead of ethyl isopropenyl ether.

The diacetal **6**, and the per(trimethylsilylated) derivatives of the monoacetals **3** and **4** and of the starting aldose **1**, could be effectively resolved by gas–liquid chromatography; the unstable 5-(2-alkoxy-2-propyl) ethers (**5** and **5a**) decomposed under these conditions. By g.l.c. monitoring, it was established that at least 2 moles of ether **2** per mole of aldose (**1**) were required to ensure reaction of all of the aldose.

Conventional acetonation of D(or L)-arabinose appears to lead exclusively to pyranose derivatives[17]; the diacetal of Fischer[5] is the 1,2:3,4-substituted pyranose. A monoacetal was obtained in low yield by Ohle and Berend[18] by treating L-arabinose with acetone–copper(II) sulfate, and the analogous D compound was prepared, also in low yield, by Jones *et al.*[19], who showed that it was most probably the 3,4-substituted derivative; an indirect synthesis of 3,4-*O*-isopropylidene-D-arabinopyranose has been reported by Ballou[20]. 1,2-*O*-Isopropylidene-α-L-arabinofuranose has been described, but it was prepared indirectly from 5-*O*-*p*-tolylsulfonyl-L-arabinose[21].

Acetonation of D-arabinose (**10**) with ethyl (or methyl) isopropenyl ether by the procedure used with D-ribose (**1**) led to 3,4-*O*-isopropylidene-β-D-arabinopyranose (**11**), which could be isolated crystalline in 60–70% yield without chromatographic resolution of the product mixture, in admixture with 1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranose (**12**), obtained crystalline in 11% yield after chromatography. Other, minor products were observed, but were not characterized. The diacetal **12** had physical data in full accord with literature values[16,19,22].

A detailed proof of structure for the monoacetal **11** was performed in view of the limited data and structural evidence in the literature[19]. The n.m.r. spectrum (Table I) of **11** in methyl sulfoxide-d_6 indicated the presence of one isopropylidene and two $\rangle$CHOH groups, one of these being at the anomeric position. The crystalline material was exclusively the β-D anomer, as shown by the n.m.r. spectrum shortly after dissolution. The observed downward mutarotation in water also showed that the anomeric position was free.



Acetylation of **11** with hot acetic anhydride–sodium acetate, conditions that permit anomerization, gave 1,2-di-*O*-acetyl-3,4-*O*-isopropylidene-α-D-arabino-pyranose (**13**), which was isolated crystalline in 80% yield; a small proportion of β anomer was also formed. The n.m.r. spectrum of **13** (Table I) showed two signals at lowest field, the H-1 doublet and a doublet of doublets for H-2; other resonances were considerably further upfield. This evidence indicates that the two acetoxyl groups in **13** were at C-1 and C-2. A strong peak for $(M^{+} - \cdot CH_3)$ at *m/e* 259 in the mass spectrum (Table II) further supported the proposed structure.

Deacetonation of **13** with aqueous acetic acid gave 1,2-di-*O*-acetyl-α-D-arabino-pyranose (**14**), which was acetylated with acetic anhydride to give α-D-arabino-pyranose tetraacetate[15] (**15**). This sequence establishes the presence of the pyranoid ring in the precursor diol **11** and its diacetate **13**. Acetylation of **14** with acetic anhydride-d_6 gave the 3,4-bis(trideuterioacetate) **15a**, whose n.m.r. spectrum was the same as that of the all-protiated analogue[15] **15** except for the absence of two of the four acetate-group signals.

The $J_{1,2}$ spin couplings for the diacetate **13**, the diol **14**, and the tetraacetate **15**, all in acetone-d_6, were 7.0, 6.6, and 6.8 Hz, respectively, indicating that all three compounds favor the $^1C_4$(D) conformation as the principal conformer, but with an appreciable contribution[15] from the $^4C_1$ conformation. The similarity of the chemical shifts for H-1 and H-2 in **13**, **14**, and **15** is noteworthy; in acetone-d_6 these are δ 5.61, 5.59, and 5.73, respectively, for H-1, and 5.10, 5.12, and 5.28 for H-2.

For the acetonation of **10** by **2**, the molar ratio of 1:2 was optimal for maximal yield of the monoacetal **11**. Use of a large excess of **2** gave almost entirely the diacetal **12**, but this product is readily accessible by the conventional route.

The applications described here of **2** as an acetonation reagent afford, in

particular, convenient high-yielding routes to the 3,4-*O*-isopropylidenepentopyranoses **3** and **11**.

EXPERIMENTAL

General methods. — Evaporations were effected *in vacuo* below 40°. Melting points were determined with a Büchi SMP 20K apparatus and are uncorrected. T.l.c. was performed on 0.25-mm layers of Silica Gel 60 on 5-cm precoated plates (Merck); for detection, plates were sprayed with 30% aqueous sulfuric acid and heated. Plates of 20-cm length were used for recording R_F values. Column chromatography was conducted with Silica Gel 60 (70–230 mesh ASTM, Merck). Chromatographic solvents were distilled with use of a 130-cm static column; petroleum ether was the fraction having b.p. 35–65°. Pyridine and *N*,*N*-dimethylformamide were dried, and distilled under diminished pressure. I.r. spectra were recorded with a Beckman IR-8 spectrophotometer. Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter with use of 1-dm tubes. Gas–liquid chromatography was performed on a Hewlett–Packard Model 5720A apparatus equipped with a flame-ionization detector maintained at 250°; nitrogen was used as the carrier gas, at a flow-rate of 30 ml.min^{-1}. The glass column (3 mm × 2 m) was packed with 5% of OV-1 (Hewlett–Packard); the extremity was also packed and fitted into the injector (maintained at 205°) to permit direct injection onto the column. Per(trimethylsilylation) was typically effected by heating 10 mg of compound with 1 ml of *N*-trimethylsilylimidazole in pyridine (Tri-Sil Z, Pierce Chemicals) with shaking in a closed vial for a few min at 50–70°. N.m.r. spectra were recorded at 60 MHz with a Varian T-60 spectrometer with tetramethylsilane as the internal standard and source of a lock signal. Chemical shifts are given in δ (p.p.m.) and the recorded couplings are first-order spacings. Mass spectra were recorded with an AEI-MS9 spectrometer at an ionizing potential of 70 eV and an accelerating potential of 8 kV; a direct-insertion probe was employed. Elemental analyses were performed by the Service Central de Microanalyse (CNRS, Paris). X-Ray powder diffraction data give interplanar spacings in Å for CuKα radiation (camera diameter 114.59 mm). Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest).

Acetonation of D-*ribose* (**1**). — (*a*) *With ethyl isopropenyl ether* (**2**, *R* = *Et*). To a solution of D-ribose (**1**; 7.5 g, 50 mmol), in dry *N*,*N*-dimethylformamide (30 ml) containing 1 g of Drierite and maintained below 5° with an ice bath, ethyl isopropenyl ether (**2**; 8.6 g, 100 mmol) and *p*-toluenesulfonic acid (~20 mg) were added. The mixture was stirred magnetically at 0–5° until monitoring by t.l.c. indicated that all starting material had disappeared (~4 h), whereupon anhydrous sodium carbonate (~5 g) was added and the cold mixture was stirred vigorously for one h more. The mixture was filtered, poured into ice–water (50 ml), and extracted with dichloromethane (3 × 30 ml), and the combined organic extracts were washed with water (3 × 20 ml). The aqueous phase and the combined aqueous extracts were freeze-dried

to yield an amorphous solid (6.3 g). Evaporation of the dried (sodium sulfate) dichloromethane extract gave a solid residue (3.5 g). T.l.c. (ethyl acetate) of the latter residue indicated at least three components (**6**, **4**, and **3**, in decreasing order of mobility), and two of them (**4** and **3**) also constituted the compounds present in the fraction from the aqueous extract. Column chromatography (ethyl acetate, 100 g of silica gel) of the product from the dichloromethane extract gave **6** (0.7 g) that was slightly contaminated (t.l.c.) by a second component, followed by **4** (0.9 g) and **3** (0.6 g), both pure compounds by t.l.c. A similar separation (ethyl acetate, 150 g of silica gel) performed on the water-soluble fraction gave pure **4** (1.0 g) and **3** (3.5 g). The total yield of **3**, obtained as a solid, was 4.1 g (43%). In subsequent experiments, **3** was obtained directly by evaporating the neutralized reaction-mixture to remove *N*,*N*-dimethylformamide, extracting the residue with ethyl acetate, adding ether to the extract, and nucleating with **3**; yields of **3** were in the range 40–50%.

3,4-*O*-Isopropylidene-β-D-ribopyranose (**3**) obtained by this procedure had m.p. 115–117° (from ethyl acetate), $[\alpha]_D^{20}$ −85° (initial) → −82° (final, 24 h; *c* 1.1, water); lit.[7] m.p. 119–120° $[\alpha]_D^{27}$ −85° in water; R_F 0.34 (ethyl acetate); λ_{max}^{KBr} 2.98 (OH), 7.28 (CMe_2), 9.5–10 μm (COCOC); for n.m.r. and mass-spectral data, see Tables I and II; X-ray powder diffraction data: 8.54 m, 7.49 vs (1,1), 6.12 vs (2), 5.62 m, 5.21 s (3,3), 4.88 s (3,3), 4.64 w, 4.37 vs (1,1), 4.02 w, 3.78 m, 3.67 s, 3.50 m, 3.27 w, 3.18 s, 3.01 m, 2.77 m, 2.72 s, 2.58 m, 2.52 m, 2.42 m, 2.35 w, 2.21 s, 2.13 m, 2.07 m, 1.96 w, 1.88 m, 1.83 m.

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.37; O, 42.10. Found: C, 50.30; H, 7.23; O, 41.97.

2,3-*O*-Isopropylidene-D-ribofuranose (**4**) was obtained as a syrup; $[\alpha]_D^{20}$ −19° (final; *c* 1.1, water), −42° (*c* 1.0, acetone) (lit.[11] −27° in water; the value depends on the relative proportions of α and β anomers); R_F 0.57 (ethyl acetate). The i.r. and n.m.r. spectra of the product were identical with those of this known product prepared by the conventional procedure[11] from D-ribose and acetone in the presence of copper-(II) sulfate and sulfuric acid, and the product gave an acceptable elemental analysis. The mass spectrum was in accord with that reported[16].

1,5:2,3-Di-*O*-isopropylidene-β-D-ribofuranose (**6**), as obtained by column chromatography (R_F 0.79, ethyl acetate), contained a minor, slower-migrating contaminant (presumed to be compound **5**) as revealed by t.l.c. with 1:1 ethyl acetate–petroleum ether. A pure sample of **6** was obtained by rechromatography on a column containing 30 g of silica gel that was eluted with 1:1 ethyl acetate–petroleum ether. The minor product (**5**) appeared very unstable and was not isolated pure (but see following experiment). Pure diacetal **6** was obtained as a hygroscopic powder or as needles by slow evaporation in a dry atmosphere of a solution in ethyl acetate; m.p. 73–74°, $[\alpha]_D^{20}$ −42.5° (*c* 1.2, chloroform); R_F 0.79 (ethyl acetate), 0.73 (1:1 ethyl acetate–petroleum ether); λ_{max}^{KBr} 7.26, 7.36 (CMe_2), 8–10 μm (COCOC), no OH absorption; for n.m.r. and mass-spectral data, see Tables I and II; X-ray powder diffraction data (poor definition): 7.30 vs (1,1), 6.50 s, 4.82 vs (1,1), 4.40, 4.08, 3.62, 3.44, 2.93, 2.69, 1.95.

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83; O, 34.78. Found: C, 57.38; H, 7.97; O, 34.74.

A high-yielding procedure for obtaining this compound is described elsewhere in this paper.

(*b*) *Acetonation with methyl isopropenyl ether* (**2**, *R* = *Me*). The procedure used was identical to that described in (*a*). The products obtained were qualitatively and quantitatively identical to those described in (*a*), except that the side-product (**5a**) accompanying compound **6** contained a methoxyl group instead of the ethoxyl group present in **5**. The side-product (**5a**) was isolated in this instance.

2,3-*O*-Isopropylidene-5-*O*-(2-methoxy-2-propyl)-D-ribofuranose (**5a**) was obtained as an unstable syrup, $[\alpha]_D^{20}$ −21° (*c* 1.3, chloroform), R_F 0.56 (1:1 ethyl acetate–petroleum ether); λ_{max}^{film} 2.94 (OH), 7.26 (CMe_2), 8–10 μm (COCOC); for n.m.r. and mass-spectral data, see Tables I and II.

*High-yielding synthesis of 1,5:2,3-di-*O*-isopropylidene-β-*D*-ribofuranose* (**6**). — A solution of 2,3-*O*-isopropylidene-D-ribofuranose (**4**, 2.5 g) in anhydrous ether (5 ml) containing a small crystal of *p*-toluenesulfonic acid was maintained at ~0°. Methyl isopropenyl ether (**2**, R = Me; 1.42 g, 1.5 molar equivs.) was added slowly with stirring. After 5 h at ~0°, all of the starting material had disappeared. Anhydrous sodium carbonate (1 g) was added and the mixture was stirred for 15 min. Filtration and evaporation gave **6** containing two minor contaminants. Column chromatography (silica gel, 50 g, eluted with 1:1 ethyl acetate–petroleum ether) gave pure **6** (2.6 g, 86%), identical (by m.p., t.l.c., and i.r. and n.m.r. spectra) with compound **6** isolated in the preceding experiment.

G.l.c. analysis of the acetonation of D-*ribose* (**1**). — Samples of D-ribose (**1**) and the isopropylidene acetals **3** and **4** were trimethylsilylated, and analyzed by g.l.c. (column temperature 140°). The diacetal **6** was analyzed directly at the same temperature. Trimethylsilylation followed by g.l.c. of the methoxyl derivative **5a** indicated a mixture of products; evidently this unstable compound decomposed either during the derivatization step or during the g.l.c. analysis. Retention times (T_R) of the products are given relative to per(trimethylsilylated) **4** and also (in parentheses) as absolute retention times in seconds: **1** (α anomer) 2.10 (2370), **1** (β anomer) 2.22 (2500); **3** 0.91 (1025); **4** 1.00 (1125); **6** 0.47 (525).

The foregoing samples were used as standards to examine the influence of the ratio of D-ribose to methyl isopropenyl ether on the product distribution in the acetonation reaction. Three experiments were performed with 1 g of D-ribose and, respectively, 1, 1.5, and 2 times the stoichiometric amount of ether **2** (R = Me). G.l.c. of a per(trimethylsilylated) aliquot of the crude product indicated that the monoacetals **3** and **4** were formed in the same ratio in all three experiments. The proportion of diacetal **6** increased with increase in the proportion of enol ether. A ratio of at least 2 moles of enol ether per mole of D-ribose was required for total disappearance of the starting sugar.

*1,2-Di-*O*-acetyl-3,4-*O*-isopropylidene-β-*D*-ribopyranose* (**7**). — A solution of acetic anhydride (4.1 g, 40 mmol) in anhydrous pyridine (10 ml) was slowly added at

0° to a stirred solution of **3** (1.90 g, 10 mmol) in pyridine (5 ml). The mixture was stirred overnight at ~25° and then poured onto ice. The product was extracted with dichloromethane, and the dried (sodium sulfate) extract was evaporated to give **7** as a syrup (2.4 g, 90%), $[\alpha]_D^{20}$ −133° (*c* 1.1 chloroform); R_F 0.57 (1:1 ethyl acetate–petroleum ether); λ_{max}^{film} 5.70 broad (C=O), 7.30 (CMe_2), 8.5–10 μm (COCOC), no OH absorption. For n.m.r. and mass spectra, see Tables I and II.

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.57; O, 40.87. Found: C, 52.62; H, 6.62; O, 41.02.

The product could not be induced to crystallize, even after column chromatography (1:1 ethyl acetate–petroleum ether; recovery 2.0 g).

Deacetonation of **7** *and acetylation to give β-*D*-ribopyranose tetraacetate* (**9**) *and its 3,4-bis(trideuterioacetyl) analogue* (**9a**). — A solution of **7** (1.37 g, 5 mmol) in 3:1 acetic acid–water (30 ml) was heated for 1 h at 70°; t.l.c. then indicated disappearance of **7** and formation of a single component **8** having R_F 0.11 (1:1 ethyl acetate–petroleum ether). The solution was freeze-dried to afford amorphous 1,2-di-*O*-acetyl-β-D-ribopyranose (**8**; 1.1 g, 90%).

(*a*) A solution of acetic anhydride (5 ml) in pyridine (5 ml) was slowly added at 0° to a stirred solution of **8** (0.70 g) in pyridine (5 ml). After 5 h at ~25°, the solution was processed, as already described for isolation of **7**, to give **9** (0.85 g, 90%), m.p. 107–110°. Recrystallization from ethanol gave pure β-D-ribopyranose tetraacetate (**9**), m.p. 109–110°, $[\alpha]_D^{20}$ −57° (*c* 1.0, chloroform); lit.[23] m.p. 110°, $[\alpha]_D^{20}$ −55.4° in methanol[24]; R_F 0.51 (1:1 ethyl acetate–petroleum ether); λ_{max}^{KBr} 5.75 μm broad (C=O), no OH absorption. The n.m.r. spectra of the product in acetone-d_6, benzene-d_6, and chloroform-*d* were in complete accord with published data[15] for **9**.

(*b*) The procedure (*a*) just described was repeated on 0.40 g of **8**, but with use of acetic anhydride-d_6. All data recorded for the product (**9a**) were identical with those given for **9** except for the n.m.r. spectra, which showed signals for only two of the four acetyl groups; in acetone-d_6, these were the lowest-field one (δ 2.12) and the second-to-highest one (δ 2.05).

Acetonation of D-*arabinose* (**10**) *with alkyl isopropenyl ethers* (**2**). — The procedure already described for use with D-ribose was followed. D-Arabinose (**10**; 7.5 g, 50 mmol) in dry *N*,*N*-dimethylformamide (150 ml; the slightly turbid mixture became clear after 1 min of reaction) and 100 mmol of alkyl isopropenyl ether (**2**, R = Me, 7.2 g; or **2**, R = Et, 8.6 g) were brought into reaction as before, for a period of 3–4 h. From the dichloromethane extract there was obtained 3.1 g of solid residue, and the freeze-dried aqueous phase gave 6.1 g of a solid. The former showed about six components by t.l.c.; three of them were major and could be separated by column chromatography (100 g of silica gel, ethyl acetate) to give **11** (1.2 g), **12** (1.0 g), and an unidentified product (0.3 g) having R_F 0.80 (ethyl acetate).

T.l.c. of the freeze-dried solid showed essentially one component, the monoacetal **11**, and only minor proportions of faster- and slower-migrating components; it could be used directly for preparations requiring **11**. Column chromatography (silica gel, 150 g; 4:1 ethyl acetate–methanol) gave pure **11**; yield 4.8 g (63% total

yield of **11**). In a direct procedure most convenient if preparation of **11** was the main objective, the original, neutralized reaction mixture was evaporated directly *in vacuo* and the resultant syrup dissolved in ethyl acetate. Addition of ether and a crystal nucleus afforded solid **11** in 60–70% yield.

3,4-*O*-Isopropylidene-β-D-arabinopyranose (**11**) thus obtained had m.p. 75–76°. Slow evaporation of a solution in 1:1 ethyl acetate–methanol gave white crystals, m.p. 82–84°, $[\alpha]_D^{20}$ −156° (initial, extrapolated) → −128° (10–12 min) → −111° (final, 24 h; *c* 1.1, water) (lit. m.p. 76–77°, $[\alpha]_D^{19}$ +128.8° in water for the L enantiomorph[18]; m.p. 78°, $[\alpha]_D$ −111° in water[19]; m.p.[20] 82–85°); R_F 0.45 (ethyl acetate); λ_{max}^{KBr} ~3 (broad, OH), 7.30 (CMe_2), 8.5–10 μm (COCOC); for n.m.r. and mass spectra, see Tables I and II; X-ray powder diffraction data: 8.79 vs (1,1), 5.62 m, 5.46 s (2), 5.03 s (2,2), 4.66 vs (1,1), 4.37 m, 4.15 s (3), 3.93 w, 3.54 s, 3.48 m, 2.89 s, 2.63 m, 1.96 w.

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.37; O, 42.10. Found: C, 50.25; H, 7.50; O, 42.00. The sample used (m.p. 84–88°) had been crystallized from ethyl acetate–methanol and dried at 70° and 0.01 torr. Samples of **11** obtained by freeze-drying from water contained 0.5 to 1 mole per mole of water of crystallization.

1,2:3,4-Di-*O*-isopropylidene-β-D-arabinopyranose (**12**) obtained from the acetonation reaction had m.p. 41–42°, $[\alpha]_D^{20}$ −5° (*c* 1.0, water); lit.[19] m.p. 40–41°, $[\alpha]_D^{19}$ −4° in water; R_F 0.89 (ethyl acetate), 0.76 (1:1 ethyl acetate–petroleum ether); λ_{max}^{film} 7.26 (CMe_2), 8–10 μm (COCOC), no OH absorption. The n.m.r. spectrum was in full accord with literature data[22].

G.l.c. analysis of the acetonation of D-*arabinose* (**10**). — Analysis of per(trimethylsilylated) D-arabinose showed (column temperature 140°) a major peak (T_R 33 min) and a minor one (T_R 38 min), together with two very minor peaks emerging between the principal components. Retention times are given relative to 1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranose (**12**) and (in sec, in parentheses) as absolute times for the per(trimethylsilylated) products: **10** 3.41 (1980) and 3.93 (2280); **11** (α anomer) 1.83 (1065), (β anomer) 1.88 (1080); **12** 1.00 (580).

A freeze-dried and subsequently vacuum-dried and per(trimethylsilylated) sample of **11** showed a major peak (T_R 1.88) for the β anomer together with 10–15% of a faster-migrating peak (T_R 1.83) for the α anomer. Acetonation reactions were conducted with 1 g of D-arabinose and, respectively, 1, 1.5, and 2.0 molar equivalents of the ether **2**. Per(trimethylsilylation) of aliquots of the final, neutral mixture in each instance showed that **11** was the principal product, giving the α and β anomers in a ratio of ~2:3 (column temperature 130° for 30 min and then with programming to 250°). Optimal yields of **11** were evident when 2 moles of **2** was used. Use of a large excess of **2** gave the diacetal **12** essentially exclusively.

1,2-Di-O-acetyl-3,4-O-isopropylidene-α-D-arabinopyranose (**13**). — A stirred mixture of compound **12** (1.90 g, 10 mmol), acetic anhydride (5.1 g, 50 mmol), and sodium acetate (8.2 g, 100 mmol) was heated for 1 h at 100°. The cooled mixture was poured onto ice and the product extracted with dichloromethane. The dried (sodium sulfate) extract was evaporated and the crystalline residue recrystallized from ethanol

to give **13** (2.2 g, 80%). The n.m.r. spectrum of the product showed the presence of a small proportion of the β anomer. Slow evaporation from 1:1 ethyl acetate–petroleum ether gave the pure α anomer as long, white needles, m.p. 118–119°, $[\alpha]_D^{20}$ −49° (*c* 1.0, chloroform); R_F 0.65 (1:1 ethyl acetate–petroleum ether); λ_{max}^{KBr} 5.7 (broad, C=O), 8.5–10 μm (COCOC), no OH absorption; for n.m.r. and mass-spectral data, see Tables I and II; X-ray powder diffraction data: 9.50 s (3), 8.66 w, 7.40 s (4), 6.18 w, 5.17 m, 4.87 vs (2), 4.47 m, 4.22 vs (1), 3.72 w, 3.49 m, 3.27 w, 3.10 w, 2.94 w, 2.68 m.

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.57; O, 40.87. Found: C, 52.48; H, 6.33; O, 40.88.

Deacetonation of **13** *and acetylation to give* α-D-*arabinopyranose tetraacetate* (**15**) *and its 3,4-bis(trideuterioacetyl) analogue* (**15a**). — The deacetonation was performed exactly as described for the D-*ribo* derivative **7** with a sample of **13** (5 mmol) that contained about 10% of the β anomer. The syrupy diol **14** thus obtained (1.05 g, 90%) was homogeneous by t.l.c. (R_F 0.08, 1:1 ethyl acetate–petroleum ether). This product (0.70 g) was treated with acetic anhydride, and a further 0.35 g was treated with acetic anhydride-d_6, by the procedure described in the D-*ribo* series. The former experiment gave 0.80 g (85%) of **15** as a syrup, homogeneous by t.l.c. (R_F 0.55, 1:1 ethyl acetate–petroleum ether), $[\alpha]_D^{20}$ −55° (*c* 1.1, chloroform); the n.m.r. spectrum showed that the product contained about 10% of the β anomer; $\lambda_{max}^{CHCl_3}$ 5.75 μm (C=O), no OH absorption.

The syrup eventually crystallized, and recrystallization from methanol–petroleum ether afforded pure **15**, m.p. 95–97°, $[\alpha]_D^{20}$ −43° (*c* 1.0, chloroform); lit.[15] m.p. 96–97°, $[\alpha]_D^{20}$ −43.8° in chloroform. The chemical shifts and coupling constants observed in the n.m.r. spectrum of the product are in full accord with those reported[15] for α-D-arabinopyranose tetraacetate.

For the 3,4-bis(trideuterioacetate) **15a**, all of the data (yield, R_F, m.p., $[\alpha]_D$, i.r. spectrum) were essentially identical to those recorded for **15**, but the n.m.r. spectrum showed signals for only two acetate groups. Of the four distinct acetate-group signals observed[15] for **15** in acetone-d_6, only the inner two peaks of the pattern (at δ 2.02 and 2.07) were observed for **15a**.

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