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1,2-MONO-, 1,2:3,5-DI-, AND 1,2:5,6-DI-*O*-ISOPROPYLIDENE-β-L-IDOFURANOSES; AN EXAMPLE OF 1,3-DIOXOLANE–1,3-DIOXANE ISOMERISATION

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ABSTRACT

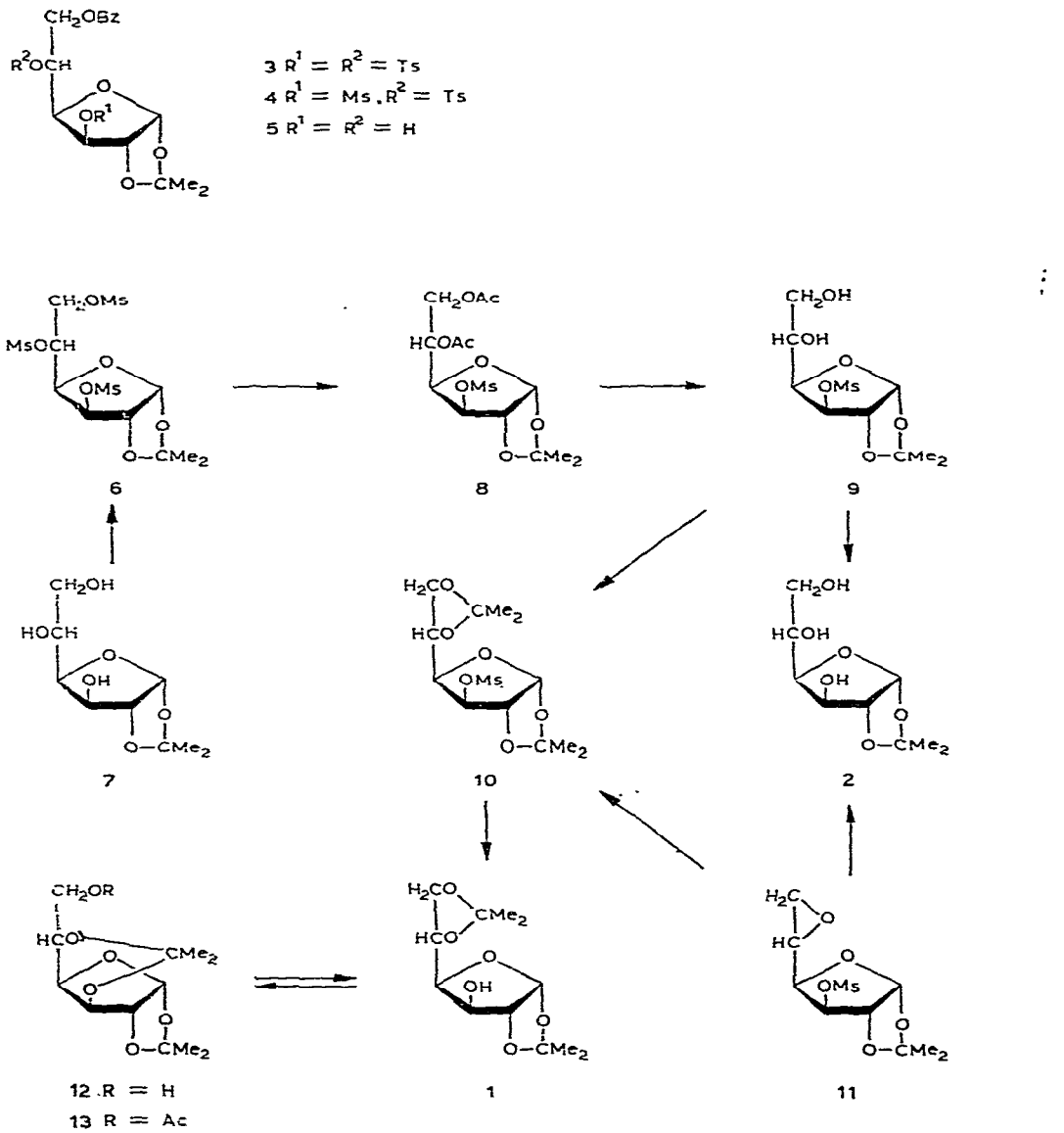
Simple preparative routes to 1,2-*O*-isopropylidene- and 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranoses are described. The 1,2:5,6-diacetal is the kinetic product of the reaction of 1,2-*O*-isopropylidene-β-L-idofuranose with acetone and 2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid but, during longer reaction times, isomerisation to 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranose occurs, resulting in an approximately equal mixture of the two diacetals.

INTRODUCTION

In connection with other work, an efficient synthesis of 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**1**) was required. This compound has previously been obtained from 1,2-*O*-isopropylidene-β-L-idofuranose (**2**) by the action of acetone in the presence of copper sulphate or zinc chloride and phosphoric acid[1,2]. Improved syntheses of **2** have been reported[3,4] using the 3,5-disulphonates **3** or **4** of 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) as starting materials. Inversion at C-5 of **3** or **4** was effected by displacement by acetate ions. The acyl and sulphonyl groups of the products of these reactions were cleaved by sodium in liquid ammonia to give **2**. We now report on a simplification of the above route and the results of a more detailed investigation of the isopropylidenation of the monoacetal **2**.

DISCUSSION

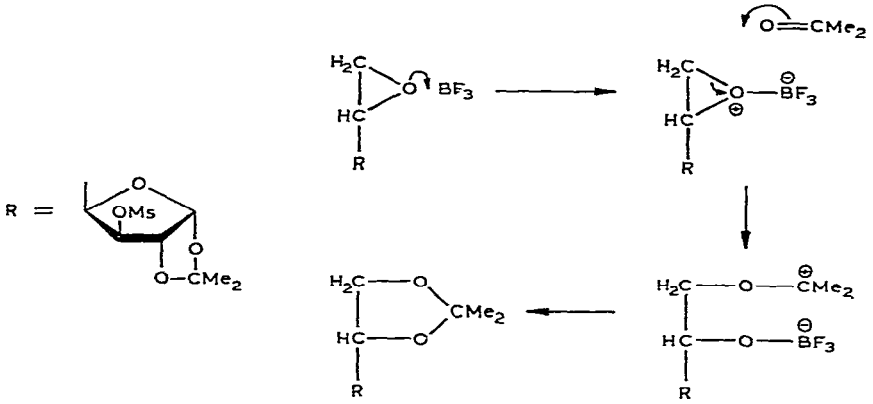
A more convenient starting-material for the displacement reaction is the trimesylate **6**, readily obtained[5] from 1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) in yields in excess of 90%. On heating **6** with the acetate form of an anion-exchange resin in acetic anhydride, the sulphonate groups at C-5 and C-6 were smoothly displaced to give the *ido*-diacetate **8**. Cold, methanolic sodium methoxide removed only the acetyl groups from **8** to give the known[2] mesylate **9**, which underwent isopropylidenation to give the known[2] diacetal **10**. The sulphonate group in **10** was smoothly cleaved with refluxing, methanolic sodium methoxide, to give **1** in an overall



yield of 58% from **7**. Refluxing, methanolic sodium methoxide also cleaved the sulphonate group as well as the acetyl groups of **8**, to give 1,2-*O*-isopropylidene-β-L-idofuranose (**2**) without the need for liquid ammonia as in the previous preparations[3,4].

The *ido*-acetal **2** could also be obtained directly from 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methanesulphonyl-β-L-idofuranose[6] (**11**) by the action of hot, aqueous sodium hydroxide, which not only opened the epoxide ring but also hydrolysed the sulphonate group. The epoxide **11** also reacted with acetone in the presence of boron trifluoride etherate to give the diacetalmesylate **10**. The reaction of an

epoxide with an aldehyde or a ketone in the presence of a Lewis acid catalyst to give an acetal has been known[7] for sometime, but this appears to be the first application in carbohydrate chemistry. The retention of the *ido* configuration in this reaction is in keeping with the accepted mechanism involving complexing of the oxirane oxygen followed by reaction of the carbonyl oxygen at the primary position in the oxirane (see Scheme 1). The reaction effectively provides a mild method of converting an epoxide into a vicinal diol. Though the yields in these two reactions were acceptable, the routes *via* the trimesylate **6** are to be preferred on grounds of practical convenience as well as overall yield.



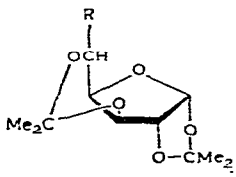
Scheme 1

In the syntheses[1,2] of **1** by isopropylidenation of 1,2-*O*-isopropylidene-β-L-idofuranose (**2**), the yields were only modest and this reaction has been re-investigated. The reaction of **2** with acetone in the presence of toluene-*p*-sulphonic acid was incomplete (t.l.c.), but was completed by adding 2,2-dimethoxypropane. Work-up after 30 min gave crystalline **1**, but in disappointing yield (43%). The remainder of the reaction product was a syrupy material whose ^{1}H-n.m.r. spectrum showed it to be a di-*O*-isopropylidene derivative, and the presence of the characteristic doublets for H-1 and H-2 indicated it to be an idofuranose derivative. That it was the isomeric 1,2:3,5-diacetal **12** was readily confirmed by the ^{13}C-n.m.r. data. The various types of isopropylidene acetals may be easily identified[8] by the ^{13}C-chemical shifts of the acetal carbon atoms and the associated methyl groups. The decoupled ^{13}C-n.m.r. spectrum of the syrupy diacetal showed signals at 111.8, 26.6, and 26.1 p.p.m., characteristic of a 5-membered acetal ring fused to a furanoid ring, and at 98.2, 29.2, and 19.2 p.p.m., characteristic of a 6-membered acetal ring. The 1,2:3,5-diacetal **12** gave a crystalline acetate **13**.

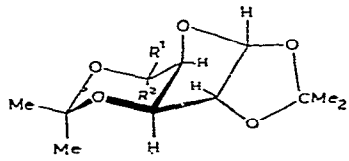
In acetalation reactions with hexoses, 2,2-dimethoxypropane generally reacts[9] first at the more accessible primary hydroxyl group at C-6. In agreement with this, when the reaction with **2** was stopped as soon as the starting material had disappeared (~2 min), the 1,2:5,6-diacetal **1** was the only detectable product and could be isolated

in yields of over 80%. Thus, **1** is the kinetic product of isopropylidenation in acetone–dimethoxypropane and, apparently, on longer reaction times, it is partly isomerised into the 1,2:3,5-diacetal **12**. When either **12** or **1** was left in acidified acetone–dimethoxypropane, isomerisation occurred and the final equilibrium mixture contained both diacetals in almost equal amounts; essentially similar results were obtained in acidified acetone.

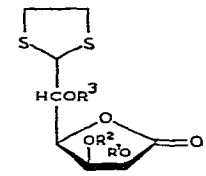
The 1,2:3,5-*ido*-diacetal **12** was remarkably stable to hydrolysis in 80% acetic acid. Compared to its 1,2:5,6-isomer **1** and the corresponding 1,2:3,5-*gluco*- and *xylo*-acetals **14** and **15**, the times for hydrolysis at room temperature to the related 1,2-monoacetals were 48, 12, 8, and 9 h, respectively. The diacetals **12** and **1** were not readily separated by column chromatography and advantage could be taken of the above result to obtain pure samples of **12** from such mixtures by preferential hydrolysis of **1**.



14 R = CH_2OH
15 R = H



16 R^1 = CH_2OH, R^2 = H
17 R^1 = H, R^2 = CH_2OH



18 R^1 = R^2 = R^3 = H
19 R^1 = H; R^2, R^3 = CMe_2
20 R^1, R^2 = CMe_2; R^3 = H

The equilibrium between **12** and **1** was at first surprising, since, although 6-membered isopropylidene acetals are known, it has generally been assumed that, where a choice exists, the 5-membered form is preferred[10]. In particular, the 1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose system can only be prepared when HO-6 is blocked[11]. Mills[12] pointed out that such *gluco*-diacetals must contain[11] an unfavourable *syn*-diaxial interaction whichever chair form the 3,5-acetal ring adopts. Buchanan and co-workers suggested[8] that the ring probably exists in a skew conformation, and that this is the reason why the ^{13}C-chemical shifts for the 3,5-acetal group of 6-*O*-benzoyl-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose lie outside the expected ranges. Inversion at C-5 leading to an *ido* configuration removes one of these *syn*-diaxial interactions (see structures **16** and **17**) and a 3,5-acetal is more readily formed, as shown by the much greater ease of formation of 6-deoxy-1,2:3,5-di-*O*-isopropylidene-6-nitro-β-L-idofuranose compared to that of the *gluco*-isomer[13]. The finding that the ^{13}C-chemical shifts for the *ido*-diacetal **12** lie in the expected ranges is further support for the explanation[8] of the anomalous shifts of the above benzoate.

The present, unexpected finding of a 6-membered isopropylidene acetal having a stability comparable to that of a 5-membered form is, in fact, the second such observation. The first, which is perhaps even more surprising, involves the *gulo*-lactone **18**, which was reported[14] to give the 3,5-acetal **19**, instead of the expected

2,3-acetal **20**, on treatment with acetone, dimethoxypropane, and sulphuric acid. It is noteworthy that the stereochemistry at C-3,4,5 is the same for the two 3,5-acetals **12** and **19**, and that a chair conformation without a serious *syn*-diaxial interaction is also possible for the *gulo*-acetal **19**.

EXPERIMENTAL

General methods. — N.m.r. spectra were recorded at 22.63 Hz (^{13}C) and 90 MHz (^{1}H) for deuteriochloroform solutions with tetramethylsilane as internal standard. Silica gel was used for t.l.c. (Gelman, I.T.L.C. Type SA) and column chromatography (Merck Kieselgel). G.l.c. was performed with a stainless-steel column (2 m × 2 mm i.d.) packed with 3% of Silar 5 CP on Gas Chrom Q; samples were run isothermally at 160° in nitrogen and detected by flame ionisation.

1,2-O-Isopropylidene-3,5,6-tri-O-methanesulphonyl-α-D-glucofuranose (**6**). — Methanesulphonyl chloride (14 mL) was slowly added to an ice-cooled, stirred solution of 1,2-*O*-isopropylidene-α-D-glucofuranose (**7**, 10.3 g) in pyridine (100 mL), and the mixture was left at 4° for 2 days. The mixture was liquefied by warming, poured into hot water, and stirred for 15 min. It was then cooled in ice-water, and the crystalline product was filtered-off and washed well with water. After drying to constant weight, **6** (19.1 g) was sufficiently pure for the next stage. It had m.p. 160–163°, $[\alpha]_D$ −21° (*c* 1.2, pyridine); lit.[5], m.p. 164°, $[\alpha]_D$ −24° (pyridine).

5,6-Di-O-acetyl-1,2-O-isopropylidene-3-O-methanesulphonyl-β-L-idofuranose (**8**). — The trimesylate (**6**, 7.0 g) was added to a suspension of Zerolit FF (IP) (AcO^-) resin (100–200 mesh; DVB 2–3%; 70 mL) in acetic anhydride (100 mL), and the mixture was boiled under reflux with stirring for 3 days. The resin was filtered-off and the filtrate was evaporated to dryness. The residue was partitioned between dichloromethane and aqueous sodium hydrogencarbonate. The organic extract was dried ($MgSO_4$) and evaporated, to give a syrupy residue which was decolourized by passage through a little silica gel in dichloromethane–ether (1:1). Crystallisation from ethanol gave **8** (4.75 g), m.p. 115–117°, $[\alpha]_D$ +28.5° (*c* 1.4, chloroform) (Found: C, 44.0; H, 5.8. $C_{14}H_{22}O_{10}S$ calc.: C, 44.2; H, 5.8%).

1,2-O-Isopropylidene-3-O-methanesulphonyl-β-L-idofuranose (**9**). — A solution of **8** (2.25 g) in methanol containing sodium methoxide [from sodium (50 mg)] was kept for 30 min at room temperature, neutralised (CO_2), and evaporated to dryness. A solution of the residue in water was extracted continuously with ethyl acetate, to give **9** (1.76 g) which, after recrystallisation from ethanol, had m.p. 123–123.5°, $[\alpha]_D$ −24° (*c* 1.2, methanol); lit.[2], m.p. 125–125.5°, $[\alpha]_D$ −22° (ethanol).

1,2:5,6-Di-O-isopropylidene-3-O-methanesulphonyl-β-L-idofuranose (**10**). — (*a*) *From the diacetate* **8**. Deacetylation of **8** (4.1 g), as in the previous experiment, gave a product that was stirred for 10 min with acetone (20 mL) and 2,2-dimethoxypropane (10 mL) containing toluene-*p*-sulphonic acid (0.2 g). The mixture was neutralised (Na_2CO_3) and evaporated, and the residue was partitioned between dichloromethane and water. The organic extract was dried ($MgSO_4$), filtered, and

evaporated, and the residue was crystallised from ethanol, to give **10** (3.4 g), m.p. 136–138°, $[\alpha]_D$ −31° (*c* 1.5, chloroform); lit.[2], m.p. 138.5–139.5°, $[\alpha]_D$ −27° (chloroform).

(*b*) *From 3,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methanesulphonyl-β-*L*-idofuranose* (**11**). Boron trifluoride etherate (0.05 mL) was added to a solution of **11** (0.47 g) in acetone (4.7 mL). After 6 h at room temperature, the reaction was stopped by addition of an excess of aqueous sodium carbonate, acetone was removed by evaporation, more water was added, and the mixture was extracted with dichloromethane, to give, after two recrystallisations from ethanol, **10** (0.43 g), m.p. 132–135°, mixture m.p. 134–137° with product in (*a*).

*1,2-*O*-Isopropylidene-β-*L*-idofuranose* (**2**). — (*a*) *From the diacetate* **8**. A solution of **8** (1.8 g) in methanol (16 mL) containing sodium methoxide [from sodium (0.5 g)] was heated under reflux for 5 h. After neutralisation (CO_2), ethyl acetate (50 mL) was added, the precipitated salts were filtered-off, and the filtrate was evaporated to dryness. A solution of the residue in ethyl acetate was then passed through a short column of silica gel to remove remaining salts. Evaporation of the eluate and crystallisation of the product from ether–light petroleum gave **2** (0.75 g), m.p. 111–113°, $[\alpha]_D$ −19° (*c* 1.2, methanol); lit.[3], m.p. 116–117°; lit.[4], m.p. 114–115°, $[\alpha]_D$ −28.7° (*c* 0.5, water).

(*b*) *From the epoxide* **11**. A suspension of **11** (1.3 g) in 2M sodium hydroxide (26 mL) was heated under reflux with stirring for 1 h. After neutralisation (CO_2) and evaporation to dryness, the residue was worked-up as in (*a*), to give **2** (0.55 g), m.p. 111–113°.

*1,2:5,6-Di-*O*-isopropylidene-β-*L*-idofuranose* (**1**). — A solution of the mesylate (3.7 g) in methanol (40 mL) containing sodium methoxide [from sodium (1.25 g)] was heated under reflux for 3 h. Aqueous sodium hydrogencarbonate (20 mL) was added and the methanol was evaporated. The remaining aqueous mixture was extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated, and the crude product was crystallised from ether–light petroleum, to give **1** (2.4 g), m.p. 150–152°, $[\alpha]_D$ −19° (*c* 1.3, chloroform); lit.[1], m.p. 153–154°, $[\alpha]_D$ −22° (*c* 0.6, water).

*The reaction of acetone and 2,2-dimethoxypropane with 1,2-*O*-isopropylidene-β-*L*-idofuranose* (**2**). — (*a*) *Short reaction time.* The monoacetal **2** (0.22 g) was dissolved in acetone (3.6 mL) and 2,2-dimethoxypropane (0.6 mL) containing toluene-*p*-sulphonic acid (45 mg). After 2 min at room temperature, the mixture was neutralised (Na_2CO_3) and evaporated to dryness. G.l.c. showed the product to consist of a single component. The crude product was partitioned between water and dichloromethane. Work-up as in the previous experiment gave **1** (0.19 g), m.p. 150–152°.

(*b*) *Longer reaction time.* The above reaction was repeated with twice the quantities, and continued for 30 min before neutralisation. The crude product was worked-up as before, to give **1** (0.23 g), m.p. 150–152°. Evaporation of the mother liquors gave a syrup (0.28 g) which was chromatographed on silica gel with ether–light petroleum (1:1), to give a main fraction (0.20 g) having the same t.l.c. mobility as

TABLE I

^{1}H- AND ^{13}C-N.M.R. SPECTRAL DATA

	^{1}H Chemical shifts[a]								
Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*CMe$_2$*	*Other signals*
8	5.96	4.88	5.06	4.40	5.38	4.50	4.06	1.52, 1.33	3.21 ($MeSO_2$); 2.13, 2.08 (MeCO)
1	5.91	4.48	←		3.7–4.55		→	1.48, 1.46 1.39, 1.31	4.20 (OH)
12	5.92	4.49	4.31	4.03	4.12	3.79[b]		1.51, 1.43 1.42, 1.34	2.65 (OH)
13	5.90	4.47	4.28	3.96	←	4.1–4.4	→	1.48, 1.43 1.40, 1.31	2.08 (MeCO)

	^{1}H-Coupling constants (Hz)						
Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
8	4.0	<0.5	3.0	8.0	3.0	6.5	12.0
1	3.5	<0.5					
12	3.5	<0.5	2.0	2.0	5.8		
13	3.5	<0.5	2.0	2.0			

	^{13}C-Chemical shifts[a]						
Compound	*C-1*	*C-2*	*C-3, C-4, C-5*	*C-6*	*CMe$_2$*	*CMe$_2$*	*COMe*
1	104.9	85.3	78.4, 76.2, 74.7	66.0	111.7 110.3	26.7, 25.9 25.9, 25.9	
21[c]	105.1	85.1	81.2, 74.7, 72.9	67.5	111.7 109.4	26.5, 26.5 25.9, 25.0	
12	105.3	83.9	73.9, 71.7, 69.1	62.9	111.8 98.6	29.2, 26.6 26.1, 19.2	
14[16]	106.4	84.0	75.0, 78.9, 72.5	63.4	112.2 100.9	27.1, 26.5 24.0, 24.0	
13	105.2	84.0	73.7, 71.1, 67.0	64.4	111.7 98.1	29.0, 26.6 26.1, 19.0	20.8

[a]In p.p.m. [b]Doublet (2H). [c]1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose[15].

1 and a small proportion of faster-running material (0.03 g). G.l.c. of the main fraction showed ~10% of **1** in addition to a major component, the 1,2:3,5-diacetal **12**, of slightly longer retention-time. The ^{1}H- and ^{13}C-n.m.r. spectra of this material are recorded in Table I.

6-O-Acetyl-1,2:3,5-di-O-isopropylidene-β-L-idofuranose (**13**). — The syrup (0.10 g) from the previous experiment was treated with acetic anhydride (0.5 mL) and pyridine (1 mL) overnight at room temperature. Work-up in the usual way and crystallisation from light petroleum gave **13** (0.08 g), m.p. 103–105°, $[\alpha]_D$ −1.5° (*c* 1.5, chloroform) (Found: C, 55.4; H, 7.45. $C_{14}H_{22}O_7$ calc.: C, 55.6; H, 7.3%); 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose[1] has m.p. 77–78°, $[\alpha]_D$ −12° (*c* 0.75, chloroform).

Isomerisation experiments. — Separate solutions of **1** and **12** (60 mg, each) in acetone (1.0 mL) and 2,2-dimethoxypropane (0.2 mL) containing toluene-*p*-sulphonic acid (12 mg) were left at room temperature. Samples were taken at 10 min, 24 h, and 72 h, neutralised (Na_2CO_3), and examined by g.l.c. The ratio of 1,2:3,5- to 1,2:5,6-diacetal present is shown below.

Starting diacetal	*10 min*	*24 h*	*72 h*
1,2:3,5-	85:15	48:52	48:52
1,2:5,6-	37:63	48:52	48:52

1,2:3,5-Di-O-isopropylidene-β-L-idofuranose (**12**). — (*a*) *From the acetate* **13**. Deacetylation of **13** (0.21 g) with methanolic sodium methoxide, in the usual way, gave **12** (0.18 g) as a syrup, $[\alpha]_D$ +11° (*c* 1.3, chloroform), which showed (g.l.c.) a single component.

(*b*) *From the 1,2:5,6-diacetal* **1**. A mixture of **1** (0.60 g), acetone (5 mL), and 2,2-dimethoxypropane (1 mL) containing toluene-*p*-sulphonic acid (60 mg) was kept for 6 h at room temperature, neutralised (Na_2CO_3), and worked-up as described above. Crystallisation of the product from ether–light petroleum gave **1** (0.17 g), m.p. and mixture m.p. 150–152°. The mother liquors were evaporated and the syrupy residue (0.47 g) was treated with 80% acetic acid (4.8 mL) for 12 h at room temperature. Water (50 mL) was added, the mixture was extracted with dichloromethane, and the extract was washed with aqueous sodium carbonate, dried ($MgSO_4$), and evaporated, to give the syrupy diacetal **12** (0.17 g), indistinguishable by g.l.c. from the sample obtained in (*a*). Acetylation in the usual way gave **13** (0.09 g), m.p. and mixture m.p. 103–105°.

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