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Syntheses of Some Derivatives of D-Glucuronic Acid*1

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The syntheses of some derivatives of D-glucuronic acid from D-glucofuranurono-6→3-lactone have been investigated. That is, 5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranurono-6→3-lactone (**2**) and 5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone (**3**) were prepared by heating 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranurono-6→3-lactone (**1**) with lithium bromide in dimethylformamide (DMF); methyl 5-*O*-(*p*-toluenesulfonyl)-β-D-glucofuranurono-6→3-lactone, 5-bromo-5-deoxy-α-L-idofuranurono-6→3-lactone, and 5-bromo-5-deoxy-β-D-glucofuranurono-6→3-lactone were prepared by heating **1**, **2**, and **3** respectively in methanol in the presence of strong acidic ion-exchange resins; 5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone (**7**) was prepared by the reaction of **2** with thiolacetic acid of benzylmercaptan in pyridine or by the reaction of **2** with triethyl phosphite; 5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hexodialdo-3,6-furanoid(6S)-1,4-furanose (**8**) was prepared by the reduction of **2** with lithium aluminum hydride; 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-*gluco*-hexodialdo-3,6-furanoid-1,4-furanose and 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose (**10**) were prepared by the reduction of **1** with lithium aluminum hydride, and 1,2;3,6-di-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose and 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose were prepared by the acetonation and the acetylation of **10** respectively.

D-Glucuronic acid is of considerable biological importance; moreover, it is easily obtained as a commercial sugar. Therefore, it seemed that it would be interesting to investigate the preparation of its deribatives. The present paper will report on the syntheses of compounds derived from 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranurono-6→3-lactone (**1**). When a solution of **1** and lithium bromide in dimethylformamide (DMF) was heated and the progress of the reaction was monitored by thin-layer chromatography in a solvent (ethyl acetate and petroleum ether, 1 : 4), it was found that the starting compound **1**, R_f 0.2, was initially transformed into a product **2** having R_f 0.5, and that then another product **3** with R_f 0.3 appeared. After the **1** was gone, fractional recrystallization gave **2** and **3** in 34 and 28% yields respectively. The compound **2** was identified as 5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranurono-6→3-lactone and **3**, as 5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone. The structures of **2** and **3** were established by elementary analyses and by studies of the NMR spectra. The coupling constants, $J_{4,5'}$ in **1** and **3** were 4.1 and 4.0 Hz respectively. The coupling constants of 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose and 3,6-anhydro-5-*O*-(*p*-toluenesulfonyl)-1,2-*O*-isopropylidene-α-D-glucofuranose have been reported to be 4.1 and 3.9 Hz[1] respectively. It seems reasonable to say that the structure of **3** is a D-*gluco*-form. In the case of **2**, however, the $J_{4,5}$ is about zero. As the conformation of the lactone ring in **2** is considered to be an envelope form (E_4), the structure of **2** must be L-*ido*-form. The compound **3** seems to be produced by the inversion of the initial product **2** by a displacement reaction with lithium bromide, as the tracing by TLC showed.

The treatment of **1**, **2**, and **3** in methanol with strong acidic ion-exchange resins[2,3] afforded methyl 5-*O*-(*p*-toluenesulfonyl)-β-D-glucofuranuronoside-6→3-lactone (**4**), methyl 5-bromo-5-deoxy-α-L-idofuranuronoside-6→3-lactone (**5**), and methyl 5-bromo-5-deoxy-β-D-glucofuranuronoside-6→3-lactone (**6**) respectively, all in good yields. The structures of **4**, **5**, and **6** were established by elementary analyses and/or by studies of the NMR spectra. The

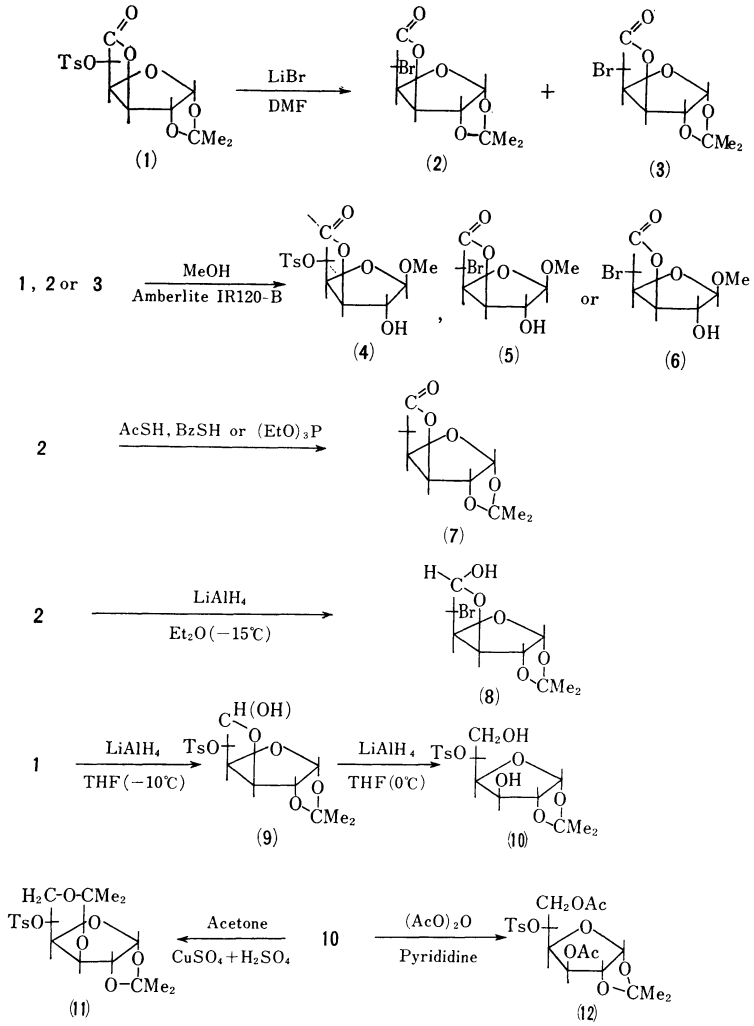
*1 This work was presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April 4, 1970.

1) R. J. Abraham, L. Hall, L. Hough and K. A. McLauchlan, *J. Chem. Soc.*, **1962**, 3702.
2) E. M. Osman, K. C. Hobbs and W. E. Walton, *J. Amer. Chem. Soc.*, **73**, 2726 (1951).
3) J. E. Cadotte, F. Smith and D. Spriestersbath, *ibid.*, **74**, 1501 (1952).

values of $J_{1,2}$ in **4** and **5** were near zero; therefore, the anomeric structures should be β-glucofuranoside and α-idofuranoside forms.[4] The structure of **6** also seems to be the same form, although the low solubility of **6** in chloroform-*d* did not give a clear NMR spectrum by which we could observed $J_{1,2}$.

The reaction of **2** in pyridine with thiolacetic acid or benzylmercaptan did not give the expected product having a carbon-sulfur bond at the C-5 position; instead, it gave 5-dioxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone (**7**)[5] with an uncertain mechanism. The reaction of **2** with triethyl phosphite also gave **7**, probably *via* the route of the Perkow reaction.[6]

The reduction of **2** in ether with lithium aluminum hydride (LAH) at −15°C gave 5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hexodialdo-3,6-furanoid(6S)-1,4-furanose (**8**) in a 20% yield. The structure of **8** was established by elementary analysis and by studies of the NMR and IR spectra. The IR spectrum of **8** showed the absorption of a hydroxy group at 3400 cm^{-1} in place of the absorption of a carbonyl group at 1780 cm^{-1} in **2**. In the NMR spectrum of **8**, the coupling constants, $J_{4,5}$ and $J_{5,6'}$ were about zero. These values probably show that the conformation of C-6 is S-form, because the conformation of the γ-lactone seems to be an envelope conformation (E_4).[1] The reduction of **1** in tetrahydrofuran (THF) with LAH at −10°C gave 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-*gluco*-hexodialdo-3,6-furanoid-1,4-furanose (**9**) in a 70% yield. The structure of **9** was established by elementary analysis and by studies of the NMR and IR spectra. The coupling constant, $J_{5,6'}$ was 3.0 Hz in its NMR spectrum. The conformation of C-6 remained uncertain. The



4) S. J. Angyal, *Angew. Chem.*, **81**, 179 (1969).

5) H. Paulsen and D. Stoy, *Chem. Ber.*, **99**, 908 (1966).

6) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, London and New York (1965), p. 153.

further reduction of **9** in THF with LAH at 0°C gave 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose (**10**) in a 48% yield based on **1**. The structure of **10** was established by elementary analysis and by a study of the NMR spectrum.

The acetonation and acetylation of **10** gave 1,2;3,6-di-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucose (**11**) and 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose (**12**) in a 33% and a quantitative yield respectively. The structures of these compounds were established by elementary analyses and by studies of the NMR spectra.

Considering that **12** was prepared in a 25% overall yield, and in only three steps, from D-glucuronolactone, the route through **12** from D-glucuronolactone seems to be an atractive one for the synthesis of 5-thio-D-glucopyranose.

Experimental

The infrared spectra were measured on a Hitachi-Perkin-Elmer 337 spectrophotometer. The nuclear magnetic resonance spectra were measured at 60 Mc on a Hitachi-Perkin-Elmer R-20 spectrometer, using tetramethylsilane as the internal reference. The thin-layer chromatograms were run on a silica-layer G[7] using various mixtures of ethyl acetate and petroleum ether, while sugars were detected by spraying the plates with a methanolic 20% sulfuric acid solution and then heating them. Periodic sampling and examination by thin-layer chromatography permitted the determination of the most suitable reaction conditions for the preparative runs.

Materials. The 1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranurono-6→3-lactone (**1**), mp 185—187°C, was prepared in an 89% yield by a modification of the method of Hall *et al.*,[8] while 1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone, mp 121.5—122.5°, was prepared in an 85% yield by the acetonation of D-glucuronolactone using the method of Schmidt.[9] The thiolacetic acid, bp 87—88°C and the benzylmercaptan, bp 111—112°C/54 mmHg were prepared by the method of Ellingboe[10] and by the method of Shishido *et al.*[11] respectively.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranurono-6→3-lactone (2) and 5-Bromo-5-deoxy-1,2-*O*-isopropylidene-α-d-glucofuranurono-6→3-lactone (3). A solution of 20 g of **1** and 5 g of lithium bromide in 50 m*l* of DMF was heated at 100°C for 8 hr. The solution was then concentrated *in vacuo*; the residue was dissolved in chloroform, washed with water, dried over sodium sulfate, and concentrated *in vacuo* to give a solid. After fractional recrystallization from ether and acetone, **2** was obtained in a 34% yield from the acetone solution and **3** was obtained in a 28% yield from the ether solution. The compound **2** had mp 146.5—147.0°C and $[\alpha]_D^{16}$ +35° (*c* 1.54, chloroform).

Found: C, 38.48; H, 3.90; Br, 27.8%. Calcd for $C_9H_{11}BrO_5$: C, 38.73; H, 3.97; Br, 27.7%. PMR (in carbon tetrachloride): τ 4.1 (one-proton doublet, $J_{1,2}$= 3.5 Hz, H_1), 5.0—5.3 (three-proton doublets, $J_{2,3}$=0.5, $J_{3,4}$=3.4 Hz, $H_{2,3,4}$), 5.9 (one-proton singlet, $J_{4,5}\fallingdotseq 0$, H_5), and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$]. The compound **3** had mp 135.0—137.5°C and $[\alpha]_D^{16}$ +68° (*c* 1.03, chloroform).

Found: C, 38.99; H, 4.06; Br, 26.9%. Calcd for $C_9H_{11}BrO_5$: C, 38.73; H, 3.96; Br, 27.7%. PMR (in carbon tetrachloride): τ 4.0 (one-proton doublet, $J_{1,2}$= 4.0 Hz, H_1), 5.1—5.0 (three-proton multiplets, $J_{2,3}\fallingdotseq 0$, $H_{2,3,4}$), 5.5 (one-proton doublet, $J_{4,5}$=4.0 Hz, H_5), and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$].

Methyl 5-*O*-(*p*-Toluenesulfonyl)-β-D-glucofuranuronoside-6→3-lactone (4). A solution of 2 g of **1** and 10 m*l* of methanol was refluxed with 3 g of acidic Amberlite IR-120B for 10 hr. The solution was then filtered, and the filtrate was concentrated *in vacuo* to give a sirup of **4** in an almost quantitative yield. The sirup was pure enough for the measurement of the NMR spectrum; $[\alpha]_D^{16}$ +21° (*c* 3.4, chloroform).*2 PMR (in chloroform-*d*): τ 2.1—2.7 (four-proton multiplets, $-C_6H_4-$), 4.8—5.3 (two-proton multiplets, $H_{4,5}$), 5.7 (one-proton singlet, $J_{1,2}\fallingdotseq 0$, H_1), 6.3—6.8 (two-proton multiplets, overlapping with $-OCH_3$, $H_{2,3}$), 6.8 (three-proton singlet, overlapping with $H_{2,3}$, $-OCH_3$), 6.9 (one-proton singlet, disappearing upon the addition of D_2O, –OH), and 7.6 (three-poroton singlet, Ar–CH_3).

Methyl 5-Bromo-5-deoxy-α-L-idofuranuronoside-6→3-lactone (5). A solution of 1 g of **2** in 5 m*l* of methanol was refluxed with 1.5 g of acidic Amberlite IR-120B for 3 hr. The solution was then concentrated *in vacuo* to give colorless needles (from ethyl acetate–petroleum ether) in a 90% yield; mp 116—117°C, $[\alpha]_D^{16}$ −87° (*c* 0.92, chloroform).

Found: C, 33.21; H, 3.66%. Clacd for $C_7H_9BrO_5$: C, 33.23; H, 3.58%. PMR (chloroform-*d*): τ 4.8—5.1 (three-proton multiplets, $H_{1,3,4}$), 5.5 (one-proton singlet, $J_{1,2}\fallingdotseq 0$, H_2), 5.7 (one-proton singlet, $J_{4,5}\fallingdotseq 0$, H_5), 6.8 (three-proton singlet, $-OCH_3$), and 7.0 (one-proton singlet, disappearing upon the addition of D_2O, –OH).

Methyl 5-Bromo-5-deoxy-β-D-glucofuranuronoside-6→3-lactone (6). The compound **3** was treated as has been described above. Recrystallization from ethyl acetate gave colorless needles in a 90% yield; mp 192—194°C, $[\alpha]_D^{16}$ −0.86° (*c* 1.2, methanol).

Found: C, 33.40; H, 3.60%. Calcd for $C_7H_9BrO_5$: C, 33.23; H, 3.58%.

5-Deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6→3-lactone (7). *a) The Reaction of* **2** *with Thiolactic Acid.* A solution of 1 g of **2** and 0.4 g of thiolacetic acid in 10 m*l* of pyridine was heated at 100°C for 3 hr under a nitrogen atmosphere; the solution was then concentrated *in vacuo*. The residue was extracted with chloroform; the solution was then washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give cololess needles (from petroleum ether)

7) Nakarai Chemicals, Ltd. Kyoto.

8) L. D. Hall, L. Hough and R. A. Pritchard, *J. Chem. Soc.*, **1961**, 1953.

9) O. T. Schmidt, "Methods in Carbohydrate Chemistry," Vol. II, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1963), p. 318.

10) E. K. Ellingboe, "Organic Syntheses," Coll. Vol. IV, p. 928 (1963).

11) K. Shishido, H. Nozaki and Y. Arido, "Yukikagobutsu Goseiho," ed. by the Society of Synthetic Organic Chemistry, Japan, Tokyo (1960), p. 11.

*2 Containing a small amount of an impurity.

in a 40% yield; mp 90—90.5°C, $[\alpha]_D^{16}$ +104° (*c* 0.89, chloroform).[5]

Found: C, 54.27; H, 6.15%. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04%. PMR (in chloroform-*d*): τ 4.1 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 4.9—5.3 (three-proton multiplets, $H_{2,3,4}$), 7.32 (one-proton singlet, $J_{4,5}\fallingdotseq 0$, H_5), 7.34 (one-proton doublet, $J_{4,5'}$=2.8 Hz, $H_{5'}$), and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$].

b) The Reaction of **2** *with Benzylmercaptan.* A solution of 1 g of **2** and 0.5 g of benzylmercaptan in 10 m*l* of pyridine was heated at 90°C for 6 hr under a nitrogen atmosphere, and then treated as has been described above to give **7** in a 30% yield.

c) The Reaction of **2** *with Triethyl Phosphite.* A solution of 1 g of **2** and 10 m*l* of triethyl phosphite was heated at 150°C for 3 hr and then treated as has been described above to give **7** in a 10% yield.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hexodialdo-3,6-furanoid(6S)-1,4-furanose (8). A solution of LAH in ether was added, drop by drop, into a solution of 1 g of **2** in 20 m*l* of ether at 15°C until the spot of **2** disappeared on TLC with a solvent (ethyl acetate–petroleum ether, 1 : 4; R_f=0.3); the excess of LAH was then destroyed water-containing ether; the solution was filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with hot ether, the ether solution was concentrated *in vacuo*, and the residue was recrystallized from petroleum ether to give **7** in a 20% yield; mp 75.0—76.0°C; $[\alpha]_D^{16}$ +1.9 (*c* 1.07, chloroform).

Found: C, 38.46; H, 4.79. Calcd for $C_9H_{13}BrO_5$: C, 38.45; H, 4.66%. PMR (in chloroform-*d*); τ 4.1 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 4.5 (one-proton doublet, $J_{6,OH}$=9.0 Hz, H_6), 5.1—5.4 (three-proton doublets, $J_{2,3}$=0.5, $J_{3,4}$=4.0 Hz, $H_{2,3,4}$), 5.9 (one-proton singlet, $J_{5,6}\fallingdotseq 0$, H_5), 6.8 (one-proton doublet, disappearing upon the addition of D_2O, C_6–OH), and 8.6, 8.7 [six-proton singlets, $C(CH_3)_2$].

1,2-*O*-Isopropropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-*gluco*-hexodialdo-3,6-furanoid-1,4-furanose (9). A solution of LAH in THF was added, drop by drop, into a solution of 2 g of **1** in 20 m*l* of THF at −10°C until the spot of **1** disappeared on TLC. The excess of LAH was destroyed with water-containing THF; the solution was then filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with hot ether; the ether solution was concentrated *in vacuo*, and the residue was recrystallized with ethyl acetate–petroleum ether to give **9** in a 70% yield; mp 141—143°C, $[\alpha]_D^{16}$ +54°(*c*1.5, chloroform).

Found: C, 51.47; H, 5.50%. Calcd for $C_{16}H_{20}O_8S$: C, 51.61; H, 5.41%. PMR (in chloroform-*d*): τ 2.1—2.7 (four-proton multiplets, $-C_6H_4-$), 4.1 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 4.6 (one-proton doublet, $J_{5,6}$=3.0 Hz, H_6), 5.1—5.5 (four-proton multiplets, $H_{2,3,5}$), 6.4 (one-proton broad, disappearing upon the addition of D_2O, C_6–OH), 7.5 (three-proton singlet, Ar–CH_3), and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$]. TLC: R_f 0.6 (ethyl acetate–petroleum ether, 1 : 1).

1,2-*O*-Isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose (10). To a solution of 0.2 g of LAH in 20 m*l* of THF, 5 g of **1** were added at −10°C under stirring; then a solution of LAH in ether was further added at 0°C untill the spots of **1** and **9** disappeared on TLC. The solution was then treated as has been described above. The recrystallization of the residue from ether gave **10** in a 48% yield; mp 124.0—125.5°C; $[\alpha]_D^{16}$ +11.6° (*c* 1.55, chloroform).

Found: C, 51.47; H, 6.04. Calcd for $C_{16}H_{22}O_8S$: C, 51.32; H, 5.92%. PMR (in chloroform-*d*): τ 2.1—2.7 (four-proton multiplets, $-C_6H_4-$), 4.1 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 5.1 (one-proton doublet of triplets, $J_{4,5}$=8.5, $J_{5,6}=J_{5,6'}$=3.5Hz, H_5), 5.5 (one-proton doublet, H_2), 5.6—5.9 (two-proton multiplets, $H_{3,4}$), 6.2 (two-proton triplet, $H_{6,6'}$), 6.6 (one-proton doublet, disappearing upon the addition of D_2O, $J_{3,OH}$= 4.5 Hz, C_3–OH), 7.4 (one-proton triplet, disappearing upon the addition of D_2O, $J_{6,OH}=J_{6'OH}$=6.0 Hz, C_6–OH), 7.7 (three-proton singlet, Ar–CH_3), and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$].

The acetonation of **10** by the usual method[9] gave 1,2; 3,6-di-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose (**11**) in a 33% yield; mp 133.0—133.5°C (from ethyl acetate–petroleum ether); $[\alpha]_D^{15}$ +25° (*c* 0.73, chloroform).

Found: C, 54.78; H, 6.44%. Calcd for $C_{19}H_{26}O_8S$: C, 55.06; H, 6.32%. PMR (in chloroform-*d*): τ 2.1—2.8 (four-proton multiplets, $-C_6H_4-$), 4.2 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 5.2—5.6 (two-proton multiplets, $H_{2,5}$), 5.8—6.1 (three-proton multiplets, $H_{3,4,6}$), 6.5 (one-proton quartet, $H_{6'}$), 7.6 (three-proton singlet, Ar–CH_3), 8.6—8.7 [twelve-proton singlets, $[C(CH_3)_2]_2$].

The acetylation of **10** by the usual method[12] gave 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-(*p*-toluene-sulfonyl)-α-D-glucofuranose (**12**) in a quantitative yield; mp 131.5—132.5°C (from methanol); $[\alpha]_D^{16}$ −15° (*c* 2.9, chloroform). Found: C, 52.12; H, 5.88%. Calcd for $C_{20}H_{26}O_{10}S$: C, 52.39; H, 5.72%. PMR (in chloroform-*d*): τ 2.2—2.7 (four-proton multiplets, $-C_6H_4-$), 4.1 (one-proton doublet, $J_{1,2}$=3.5 Hz, H_1), 4.7—5.0 (two-proton multiplets, $H_{3,5}$), 5.3—6.0 (four-proton multiplets, $H_{2,4,6,6'}$), 7.6 (three-proton singlet, Ar–CH_3), 7.9, 8.0 [six-proton singlets, $(OCOCH_3)_2$], and 8.5, 8.7 [six-proton singlets, $C(CH_3)_2$].

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12) M. L. Wolfrom and A. Thompson, "Methods in Carbohydrate Chemistry," Vol. II, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1963), p. 221.