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SPECIFIC SYNTHESIS AND STEREOCHEMICAL ASSIGNMENT OF THE DIASTEREOMERIC 3,5-*O*-BENZYLIDENE-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE ISOMERS

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ABSTRACT

Pyridinium tosylate-catalyzed acetal exchange between benzaldehyde dimethyl acetal and 6-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-α-D-glucofuranose was investigated as an alternative to the original procedure of Brigl and Grüner (condensation of a D-glucose triol with benzaldehyde under zinc halide catalysis) for synthesis of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose. The two routes afford opposite benzylidene diastereoisomers: the traditional procedure leads to the thermodynamically favored isomer (phenyl and C-6 *trans*), whereas the new sequence gives the *cis* compound. The orientations and conformations of these isomers were determined after conversion into the corresponding 6-iodides **5** and **7**. X-Ray crystallography revealed that the 1,3-dioxane ring of the *trans* isomer **7** exists in the expected chair, "O-inside" conformation. In contrast, a combination of n.m.r. spectroscopy and molecular-mechanics calculations demonstrated that the same ring of *cis* diastereomer **5** does not adopt the alternative chair, "H-inside" conformation; instead, it exists in a specific twist form.

INTRODUCTION

In connection with a program directed toward the synthesis of a series of 6-substituted D-glucose analogs, we required a reliable source of the protected D-glucose derivative, 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose. We found the traditional, zinc halide-catalyzed acetalation[1] of the D-glucose acetal **1** to be capricious, and for this reason, we explored an alternative sequence. 1,2-*O*-Isopropylidene-α-D-glucofuranose[2] is silylated selectively on the primary hydroxyl group by using *tert*-butylchlorodiphenylsilane[3] to give the ether **2**. This compound undergoes transacetalation with benzaldehyde dimethyl acetal under pyridinium *p*-toluenesulfonate catalysis at 40°, and the resulting acetal (**3**) is deprotected with tetrabutylammonium fluoride, to afford **4** in 75% overall yield from acetal **1**.

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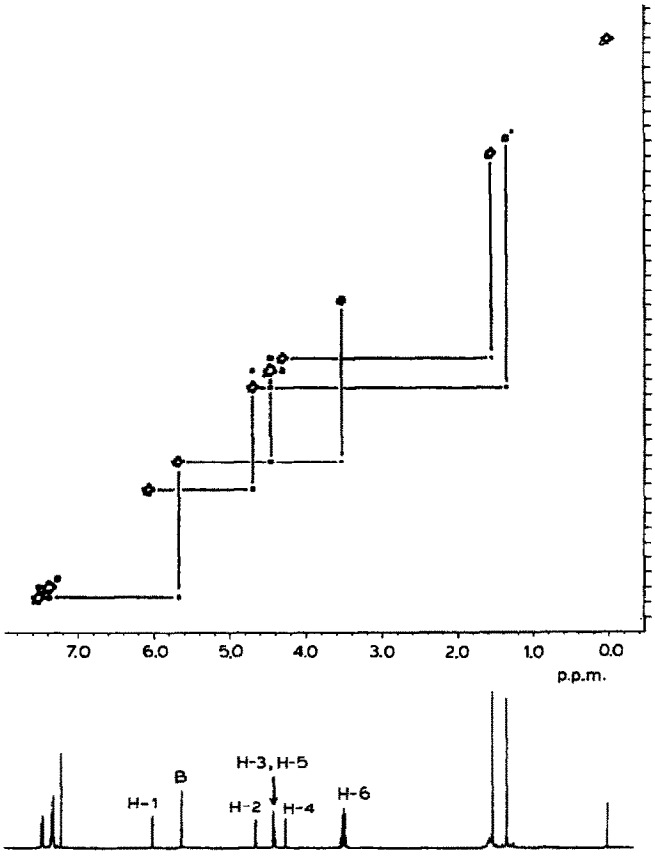


Fig. 1. NOESY spectrum of acetal **7**.

Although this route involves additional protection–deprotection steps, the higher yield and reproducibility commend it over the conventional, Lewis acid-catalyzed condensation for synthesis of the title compound (**4**).

The product of the sequence just described, namely acetal **4**, differs from that (**6**) formed by the traditional route. From the ^{1}H-n.m.r. spectral characteristics of the two compounds, it is clear that they are stereoisomers. To elucidate their configurations, the acetals were each converted with iodine and triphenylphosphine into the iodides (**5** and **7**), and the configurations of the benzylic carbon atoms were unambiguously assigned by 2-dimensional, NOESY n.m.r. spectroscopy. For iodide **7**, which arises from isomer **6**, nuclear Overhauser interaction is seen between the benzylic and the C-6 methylene hydrogen atoms (see Fig. 1). Thus, in isomer **7**, and hence, in **6**, the phenyl group and C-6 are *trans* with respect to the 1,3-dioxane ring. For the other diastereomer, **5**, a correlation is seen between the benzylic and the C-5 methine hydrogen atoms that is consistent with the alternative arrangement, in which the phenyl group and C-6 are *cis* (see Fig. 2). Treatment of

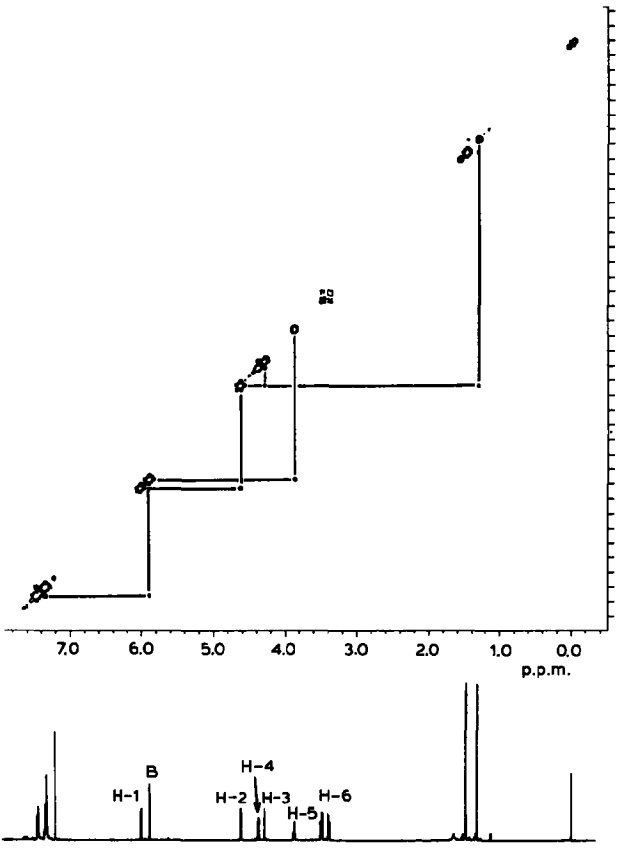
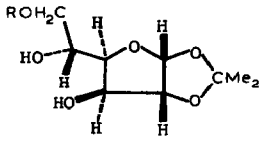


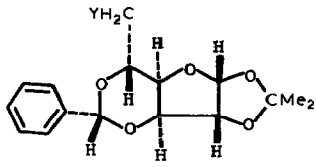
Fig. 2. NOESY spectrum of acetal **5**.

iodide **5** with a catalytic amount of aluminium chloride in ether at room temperature results in its isomerization to the other diastereomer (**7**), confirming that the latter ring-system is, indeed, the thermodynamically more stable one. Similar equilibration of the alcohols **4** and **6** leads to a complex mixture of structural isomers, as well as stereoisomers.

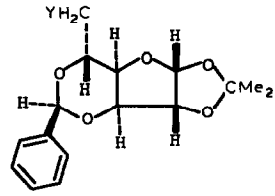
Although the orientation of the benzylidene group in **6** itself had not been assigned previously, that of the closely related dibenzylidene acetal **8** had been reported[4] by Coxon. A key finding in his investigation was that the tricyclic skeleton adopts a conformation in which the hydroxymethyl group is axial with respect to the 1,3-dioxane ring. This orientation is presumably favored because it allows O-4 to occupy the axial, "O-inside" position on the 1,3-dioxane ring[5]. Coxon found[6] the same conformational preference for both orthoformate isomers **9** and **10**, and similar behavior has been noted for related xylose and sorbose acetals[7]. Isomer **4** and its derivatives thus appear to constitute one of the few examples of D-glucose 3,5-acetals in which the alternative, "H-inside" orientation has been found[5].



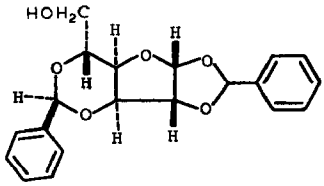
1 R = H
2 R = $SiPh_2(CMe_3)$



3 Y = $OSiPh_2(CMe_3)$
4 Y = OH
5 Y = I



6 Y = OH
7 Y = I



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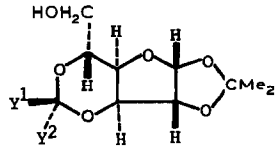
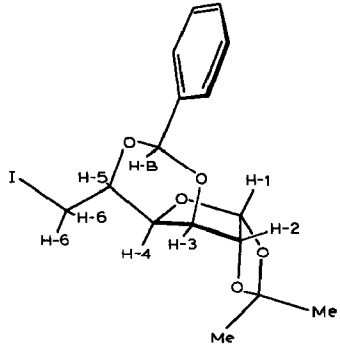


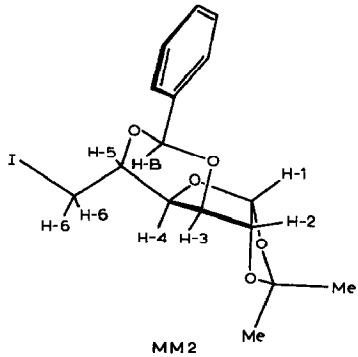
9 Y^1 = OMe, Y^2 = H
10 Y^1 = H, Y^2 = OMe

TABLE I

CONFORMATIONS OF ACETAL 7



X-Ray



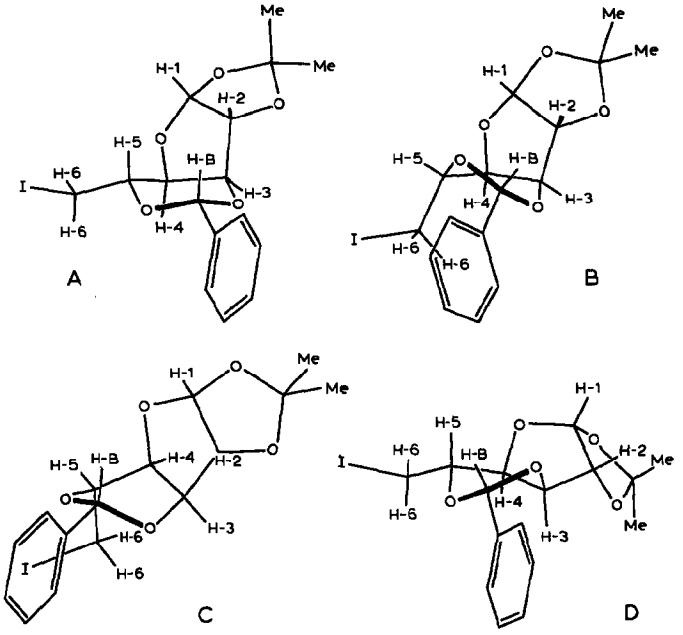
MM2

Atoms	*X-Ray*	*MM2*	*n.O.e. observed*
	Hydrogen–hydrogen distances (Å)		
H-B–H-3	2.5	2.4	+
H-B–H-6	2.2, 3.6	2.2, 3.7	+
H-1–H-5	4.1	4.6	–
H-1–H-2	2.4	2.4	+
H-2–H-3	2.5	2.8	+
H-3–H-4	2.4	2.5	(+)[a]
H-4–H-5	2.3	2.6	(+)[a]
H-3–H-6	2.5, 3.3	2.7, 3.7	–
	Dihedral angles (°)		J *(Hz) observed for* 7
H-1–H-2	26	9	3.65
H-2–H-3	76	87	<0.5
H-3–H-4	40	46	2.1
H-4–H-5	78	77	1.4

[a]Resonances for H-3 and H-5 superimposed; n.O.e. seen between H-4 and (H-3,H-5).

TABLE II

CONFORMATIONS OF ACETAL **5**



Atoms	*Conformation*				*n.O.e. observed*
	A	*B*	*C*[a]	*D*	
	Hydrogen–hydrogen distances (Å)				
H-B–H-1	3.9	3.6	2.8	5.2	–
H-B–H-2	2.2	2.2	2.8	4.5	–
H-B–H-5	2.3	4.0	3.4	2.5	+
H-1–H-5	2.6	3.0	4.6	4.1	–
H-1–H-2	2.4	2.4	2.4	2.4	+
H-2–H-3	3.1	3.0	2.9	2.8	+
H-3–H-4	2.4	2.4	2.4	2.4	+
H-4–H-5	3.1	2.7	2.6	3.1	–
H-3–H-6	4.8, 4.9	4.4, 3.8	3.4, 2.7	4.7, 4.1	–
	Dihedral angles (°)				*J (Hz) for* **5**
H-1–H-2	6	17	1	3	3.7
H-2–H-3	150	127	102	95	<0.5
H-3–H-4	38	24	30	36	3.6
H-4–H-5	166	93	68	149	4.8
	ΔH_f^0 (calc.; kcal/mol)				
	−164.7	−159.6	−164.4	−167.3	

[a]For conformation **C**, rotation of the iodine atom under the 1,3-dioxane ring is predicted to lead to stabilization by 2.1 kcal/mol. However, there are no differences between this conformer and the one depicted with respect to the distances and dihedral angles listed in Table II, except for those involving the hydrogen atoms on C-6.

The assigned orientation and chair conformation of iodide **7** are consistent with both the vicinal coupling constants and NOESY n.m.r. data; single crystal X-ray crystallography confirmed the structural assignment[8]; Table I lists the experimentally determined inter-hydrogen atom distances and dihedral angles, as well as those predicted by the molecular mechanics method of Allinger[9]. The two conformations differ with respect to the orientation of the phenyl ring relative to the benzylic carbon, as well as in the conformation of the dioxolane-furanose part of the fused ring system. The n.m.r. data, in particular the coupling constants $J_{1,2}$ and $J_{2,3}$, suggest that the solution structure is more closely approximated by that predicted from the MM2 calculations than it is by the one observed in the crystal.

The corresponding n.m.r. data for the *cis* isomer **5** are not compatible with a chair conformation of the 1,3-dioxane ring. To elucidate the actual conformation that this isomer adopts, the "H-inside" chair and three different boat conformations of **5** were minimized according to molecular mechanics calculations*. The results are displayed in Table II, along with the calculated (gas phase) heats of formation and selected hydrogen–hydrogen dihedral angles and internuclear distances. Both the coupling constants observed and the NOESY correlations observed for isomer **5** allow its unambiguous assignment as twist-boat conformation **D**. Only for this conformer are both the absent and the observed n.O.e. correlations explained, as well as the magnitude of the coupling constants. In **D**, both C-2 and C-6 of the D-glucose skeleton occupy quasi-equatorial positions, and O-4 is able to adopt a quasi-axial one. Thus, both unfavorable steric and electronic effects appear to be minimized. Interestingly, conformation **D** is predicted by the molecular-mechanics calculations to have the lowest energy-content, as well.

EXPERIMENTAL

General. — Dichloromethane (CH_2Cl_2) was dried by distillation from CaH_2, and toluene was dried by distillation from sodium metal. *N,N*-Dimethylformamide (DMF) was dried over $MgSO_4$, distilled under diminished pressure, and stored over 4A molecular sieves. Benzaldehyde dimethyl acetal was distilled prior to use. Column chromatography was performed according to the method of Still *et al.*[10] by using Silica Gel 60 (230–400 mesh, ASTM) from EM Reagents. Unless otherwise indicated, reaction workups culminated in washing the organic phase with brine, drying it over Na_2SO_4, and removing the solvent under diminished pressure in a rotary evaporator. N.m.r. spectra were recorded for solutions in $CDCl_3$; ^{1}H-n.m.r. data are presented as chemical shifts relative to internal tetramethylsilane. The 2-D NOESY spectra were obtained with a Bruker 500-MHz instrument.

6-O-(tert-Butyldiphenylsilyl)-1,2-O-isopropylidene-α-D-glucofuranose (**2**). — To a stirred solution of 1,2-*O*-isopropylidene-α-D-glucofuranose[2] (**1**; 9.70 g, 44.0 mmol) and imidazole (6.60 g, 97.0 mmol) in dry DMF (40 mL) under N_2 was added

*Crystals of **5** suitable for X-ray diffraction were not obtained.

tert-butylchlorodiphenylsilane (12.6 mL, 48.4 mmol) dropwise during 10 min at 21°. The mixture was stirred for 2 h at room temperature and then partitioned between 1:1 toluene–CH_2Cl_2 (250 mL) and satd. $NaHCO_3$ (200 mL). The aqueous layer was extracted with 1:1 toluene–CH_2Cl_2 (100 mL) and the organic layers were combined, and worked up, to give 26.3 g of the silyl ether **2** as a viscous oil. This compound was used in the next step without purification.

An analytical sample was prepared by chromatography (3:7 EtOAc–hexane); $\nu_{max}^{CCl_4}$ 3580, 3480 (br), 3090, 3075, 2970, 2940, 2905, 2870, 1475, 1468, 1433, 1388, 1376, 1254, 1223, 1171, 1115, 1110, 1080, 1036, 1023, 991, 892, 863, 829, and 708 cm^{-1}; ^{1}H-n.m.r.: δ 7.69–7.65 (m, 4 H), 7.49–7.37 (m, 6 H), 5.96 (d, 1 H, *J* 3.7 Hz), 4.54 (d, 1 H, *J* 3.7 Hz), 4.39 (d, 1 H, *J* 2.3 Hz), 4.15 (d, 1 H, *J* 2.3 Hz), 4.15 (dd, 1 H, *J* 5.1, 3.6 Hz), 3.90 (dd, 1 H, *J* 10.5, 3.6 Hz), 3.80 (dd, 1 H, *J* 10.5, 5.1 Hz), 3.24 (s, 1 H), 2.82 (s, 1 H), 1.47 (s, 3 H), 1.32 (s, 3 H), and 1.07 (s, 9 H); ^{13}C-n.m.r.: δ 135.50, 132.63, 129.91, 127.87, 111.56, 104.88, 85.07, 79.33, 75.70, 70.55, 64.85, 26.78, 26.20, and 19.24; $[\alpha]_D^{24}$ −18.7° (*c* 0.8, $CHCl_3$); f.a.b.-m.s. *m/z* = 459 (MH^+).

Anal. Calc. for $C_{25}H_{34}O_6Si$: C, 65.47; H, 7.47. Found: C, 65.50; H, 7.49.

*3,5-*O-(R)-*Benzylidene-6-*O-(tert-*butyldiphenylsilyl)-1,2-*O-*isopropylidene-α-*D-*glucofuranose* (**3**). — A solution of silyl ether **2** (≤44 mmol), freshly distilled benzaldehyde dimethyl acetal (66.0 mL, 440 mmol), and pyridinium *p*-toluenesulfonate (15.5 g, 61.6 mmol) in CH_2Cl_2 (250 mL) was stirred for 2 h at 40° under nitrogen. The mixture was washed with satd. $NaHCO_3$ (200 mL), and worked up in the usual manner. The excess of benzaldehyde dimethyl acetal was removed by distillation at 133 Pa in a Kugelrohr oven, to afford 25.4 g of the acetal **3** as a thick, colorless oil, which was used directly in the next step.

An analytical sample was obtained by chromatography (1:19 EtOAc–hexane): $\nu_{max}^{CCl_4}$ 3085, 3060, 3005, 2975, 2940, 2900, 2870, 1480, 1470, 1463, 1436, 1392, 1381, 1370, 1363, 1336, 1315, 1293, 1220, 1171, 1138, 1119, 1090, 1033, and 706 cm^{-1}; ^{1}H-n.m.r.: δ 7.74–7.67 (m, 5 H), 7.49–7.31 (m, 10 H), 6.05 (d, 1 H, *J* 3.8 Hz), 5.89 (s, 1 H), 4.66 (d, 1 H, *J* 3.8 Hz), 4.65 (t, 1 H, *J* 3.3 Hz), 4.38 (d, 1 H, *J* 3.3 Hz), 4.14 (dt, 1 H, *J* 4.5, 3.3 Hz), 3.91 (d, 2 H, *J* 4.5 Hz), 1.51 (s, 3 H), and 1.34 (s, 3 H), and 1.07 (s, 9 H); ^{13}C-n.m.r.: δ 138.47, 135.59, 135.55, 133.16, 133.09, 129.68, 128.91, 128.23, 127.66, 126.18, 111.97, 105.31, 96.15, 84.57, 76.37, 76.21, 75.41, 64.64, 26.71, 26.34, and 19.27; $[\alpha]_D^{24}$ +36.8° (*c* 1.05, $CHCl_3$); e.i.-m.s. *m/z* = 546 (M^+) and 163 (100%).

Anal. Calc. for $C_{32}H_{38}O_6Si$: C, 70.30; H, 7.00. Found: C, 70.40; H, 7.11.

*3,5-*O-(R)-*Benzylidene-1,2-*O-*isopropylidene-α-*D-*glucofuranose* (**4**). — The crude **3** (≤44 mmol) was treated with 0.5M tetrabutylammonium fluoride (176 mL, 88 mmol) under nitrogen for 10 min at 21°. The orange solution resulting was diluted with brine (200 mL), extracted with three 150-mL portions of CH_2Cl_2, and the extracts combined, dried, and evaporated under diminished pressure; a mixture of the crude product with ethyl acetate was filtered through a 200-mL plug of silica gel. The crude product was purified by chromatography (1:5 EtOAc–hexane), to afford 10.2 g (33.1 mmol, 75% overall yield from **1**) of the acetal **4** as a colorless

oil, and 0.86 g (6% of the isomer **6** as a white solid, m.p. 145–147.5° (lit.[1] 149°). For isomer **4**: $\nu_{max}^{CCl_4}$ 3610, 3500 (br), 3050, 3000, 2940, 2905, 1460, 1389, 1379, 1350, 1312, 1292, 1220, 1170, 1142, 1085, 1027, 895, 873, 730, and 705 cm^{-1}; ^{1}H-n.m.r. δ 7.49–7.36 (m, 5 H), 6.04 (d, 1 H, *J* 3.8 Hz), 5.93 (s, 1 H), 4.68 (d, 1 H, *J* 3.8 Hz), 4.49 (t, 1 H, *J* 3.5 Hz), 4.36 (d, 1 H, *J* 3.5 Hz), 4.09 (ddd, 1 H, *J* 3.2, 3.5, 5.5 Hz), 3.97 (ddd, 1 H, *J* 3.2, 6.6, 12.2 Hz), 3.81 (ddd, 1 H, *J* 5.5, 6.6, 12.2 Hz), 1.98 (t, 1 H, *J* 6.6 Hz), 1.50 (s, 3 H), and 1.33 (s, 3 H); ^{13}C-n.m.r.: δ 137.99, 129.05, 128.28, 126.03, 112.07, 105.34, 96.35, 84.38, 76.92, 76.38, 75.35, 63.57, 26.75, and 26.18; $[\alpha]_D^{24}$ +67.0° (*c* 0.7, $CHCl_3$); e.i.-m.s. *m/z* = 308 (M^+), and 105 (100%).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.40; H, 6.62.

3,5-O-(S)-Benzylidene-6-deoxy-6-iodo-1,2-O-isopropylidene-α-D-glucofuranose (**5**). — To a solution of alcohol **4** (4.80 g, 15.6 mmol) in toluene (100 mL), was added triphenylphosphine (5.71 g, 21.8 mmol), iodine (4.75 g, 18.9 mmol), and imidazole (2.12 g, 31.1 mmol), and the mixture was heated at reflux under N_2 for 15 min. The solution was cooled, stirred with satd. $NaHCO_3$ (100 mL) for 20 min at 21°, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed with two 125-mL portions of 10% $Na_2S_2O_3$, and worked up, and the crude product was purified by chromatography (1:15 EtOAc–hexane), to afford 4.95 g (11.8 mmol, 76% yield) of the iodide **5** as a white solid. Recrystallization from diisopropyl ether gave 4.62 g (11.1 mmol, 71%) of colorless crystals, m.p. 72–74°; ν_{max}^{KBr} 3018, 2985, 2940, 2900, 1498, 1455, 1430, 1383, 1374, 1345, 1330, 1310, 1273, 1233, 1212, 1163, 1135, 1107, 1085, 1070, 1030, 1002, 943, 895, 880, 860, 850, 806, 767, 730, and 700 cm^{-1}; ^{1}H-n.m.r.: δ 7.51–7.49 (m, 2 H), 7.41–7.35 (m, 3 H), 6.04 (d, 1 H, *J* 3.7 Hz), 5.93 (s, 1 H), 4.66 (d, 1 H, *J* 3.7 Hz), 4.41 (dd, 1 H, *J* 4.8, 3.6 Hz), 4.32 (d, 1 H, *J* 3.6 Hz), 3.90 (ddd, 1 H, *J* 5.9, 4.8, 4.7 Hz), 3.52 (dd, 1 H, *J* 10.75, 4.7 Hz), 3.41 (dd, 1 H, *J* 10.75, 5.9 Hz), 1.50 (s, 3 H), and 1.32 (s, 3 H); ^{13}C-n.m.r.: δ 137.74, 129.08, 128.33, 126.18, 112.35, 105.73, 97.00, 84.00, 80.76, 74.94, 74.84, 26.97, 26.37, and 6.28; $[\alpha]_D^{24}$ +64.0° (*c* 1, $CHCl_3$); e.i.-m.s. *m/z* 418 (M^+) and 105 (100%).

Anal. Calc. for $C_{16}H_{19}IO_5$: C, 45.95; H, 4.58; I, 30.34. Found: C, 46.12; H, 4.67; I, 30.17.

3,5-O-(R)-Benzylidene-6-deoxy-6-iodo-1,2-O-isopropylidene-α-D-glucofuranose (**7**). — This isomer was prepared from the known alcohol[1] **6** by the procedure described for diastereomer **5**. Purification by chromatography (1:3 EtOAc–hexane; 81% yield) and recrystallization from methanol (76% overall yield) gave iodide **7** as colorless needles; m.p. 140–141°; ν_{max}^{KBr} 3070, 3060, 3017, 2970, 2930, 2905, 2880, 1460, 1441, 1392, 1273, 1221, 1180, 1128, 1090, 1030, 1015, 990, 892, 878, 810, 762, and 708 cm^{-1}; ^{1}H-n.m.r.: δ 7.51 (m, 2 H), 7.40–7.34 (m, 3 H), 6.05 (d, 1 H, *J* 3.65 Hz), 5.67 (s, 1 H), 4.68 (d, 1 H, *J* 3.65 Hz), 4.45 (d, 1 H, *J* 2.1 Hz), 4.44 (t, 1 H, J_{obs} 7.7 Hz), 4.28 (dd, 1 H, *J* 2.1, 1.4 Hz), 3.54 (dd, 1 H, *J* 10.65, 7.9 Hz), 3.50 (dd, 1 H, *J* 10.65, 7.7 Hz), 1.54 (s, 3 H), and 1.35 (s, 3 H); ^{13}C-n.m.r.: δ 137.02, 129.17, 128.26, 126.11, 112.12, 105.18, 92.73, 83.49, 76.82, 73.50, 73.47, 26.77, 26.22, and 1.63; $[\alpha]_D^{22}$ +28.9° (*c* 0.5, $CHCl_3$); e.i.-m.s. *m/z* 418 (M^+) and 113 (100%).

Anal. Calc. for $C_{16}H_{19}IO_5$: C, 45.95; H, 4.58; I, 30.34. Found: C, 45.98; H, 4.64; I, 30.44.

ACKNOWLEDGMENTS

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