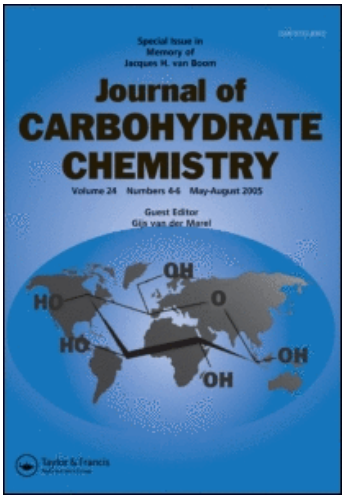

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ONE-POT SYNTHESIS OF TRI-ACETALATED ALDOHEXOSES WITH 1,1-DIALKOXYCYCLOHEXANE--p-TOLUENESULFONIC ACID*

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ABSTRACT

2-Deoxy-D-arabino-hexose (1), 2-acetamido-2-deoxy-D-glucose (2), and 2-deoxy-2-trifluoroacetamido-D-glucose (3) were each treated with 1,1-dimethoxycyclohexane or 1,1-dibenzyloxycyclohexane in 1,4-dioxane in the presence of p-toluenesulfonic acid. The major products were the 1,1-dimethyl or 1,1-dibenzyl acetals (4-9) of 3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-arabino-hexose, and of 2-(acylamino)-3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-glucose. The dibenzyl acetal derivatives were converted, by hydrogenolysis, into the corresponding, acyclic aldehydes (10-12) in good yields.

INTRODUCTION

In the previous papers,[1,2] we have shown that when the acetalation of some aldohexoses with 2,2-dimethoxypropane and p-toluene-

*The Behavior of Some Aldoses with Acetal Exchange Reagents, Part XII. For Part XI, see ref. 1.

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sulfonic acid was conducted in the absence of N,N-dimethylformamide or in 1,4-dioxane, acyclic, 1,1-dialkyl acetal derivatives were mainly produced. Hough et al.[3] and Ueno et al.[4] prepared, under similar conditions, some new tetra-acetal derivatives of naturally occurring disaccharides, and recently, this acetalation procedure has also been applied to a synthesis of benzylidene acetals.[5]

We now describe the one-pot tri-acetalation of 2-deoxy-D-arabino-hexose and 2-(acylamino)-2-deoxy-D-glucose with 1,1-dimethoxy or 1,1-dibenzyloxycyclohexane as a reagent for acetal exchange.

RESULTS AND DISCUSSION

Acetalation of 2-deoxy-D-arabino-hexose (1), 2-acetamido-2-deoxy-D-glucose (2), or 2-deoxy-2-trifluoroacetamido-D-glucose (3) with 1,1-dimethoxycyclohexane in dry 1,4-dioxane in the presence of p-toluenesulfonic acid was each conducted at 65-70° by the procedure employed for the reaction with 2,2-dimethoxypropane reagent.[1,2] The yields of the corresponding 3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-hexose dimethyl acetal derivatives, i. e., 4, 5 and 6 were, purified by chromatography, 71, 67 and 83%, respectively. All of the spectral features, particularly in the ^{1}H NMR, were quite similar to those of the corresponding 3,4:5,6-di-O-isopropylidene derivatives[1,2] to strongly suggest the structures 4, 5 and 6, respectively.

When treated with 1,1-dibenzyloxycyclohexane as just described, compounds 1-3 respectively gave the corresponding 3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-hexose dibenzyl acetal derivatives, 7 (64%), 8 (51%) and 9 (61.4%), which were then converted, by hydrogenolysis, into 3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-arabino-hexose (10), 2-acetamido-3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-glucose (11), and 3,4:5,6-di-O-cyclohexylidene-2-deoxy-2-trifluoroacetamido-aldehydo-D-glucose (12). Such suitably protected, acyclic sugar aldehydes might be potentially useful as

synthetic precursors — for example, in the extention reactions of carbon chain.

EXPERIMENTAL

General Methods. See ref. 1.

2-Deoxy-3,4:5,6-di-O-cyclohexylidene-aldehydo-D-arabino-hexose dimethyl acetal (4). A stirred suspension of 2-deoxy-D-arabino-hexose 1 (300 mg) in dry 1,4-dioxane (5 ml) was heated to 65°, and then p-toluenesulfonic acid monohydrate (75 mg) and 1,1-dimethoxy-cyclohexane (2 ml) were added; stirring was continued for 2 h at 65°. The mixture was cooled and freed of the acid by addition of sodium hydrogen carbonate. The suspension was filtered and washed with 1,4-dioxane and methanol. The filtrate and washings were combined, and evaporated to a syrup that was chromatographed on a column of silica gel with (a) chloroform, (b) 500:1 chloroform-methanol, and (c) 300:1 chloroform-methanol. Eluant c gave crystalline 4(71% yield), mp 32-35°C, $[\alpha]_D$ +20.1° (c 0.7, chloroform); IR (film): 1060 and 1110 cm^{-1} (ether), and no absorption band due to OH group was observed; ^1H NMR ($CDCl_3$): δ 1.2-1.7 (m, 20 H, $2C_6H_{10}$), 1.75 (m, 1 H, J_{gem} 14, $J_{1,2}$ 3.8, $J_{2,3}$ 9 Hz, H-2), 2.15 (m, 1 H, $J_{1,2'}$ 8, $J_{2',3}$ 3.2 Hz, H-2'), 3.35 (s, 6 H, 2MeO), 3.56 (m, 1 H, H-5), and 4.65 (dd, 1 H, $J_{1,2}$ 3.8, $J_{1,2'}$ 8 Hz, H-1); Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 65.14; H, 9.13.

2-Acetamido-3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-glucose dimethyl acetal (5). A suspension of 2 (1 g) in dry 1,4-dioxane (10 ml) was stirred at 65°, while 1,1-dimethoxycyclohexane (5 ml) and p-toluenesulfonic acid monohydrate (150 mg) were added. The mixture was stirred for 2 h at 65°, and worked up as described for 4. The title compound 5, purified by chromatography, was obtained as a syrup (67% yield), $[\alpha]_D$ +5.6° (c 0.7, chloroform); ^1H NMR ($CDCl_3$): δ 1.2-1.9 (m, 20 H, $2C_6H_{10}$), 2.0 (s, 3 H, AcN), 3.33 and 3.38 (2 s, 6 H, 2MeO), 3.6 (m, 1 H, H-5), and 5.82 (d,

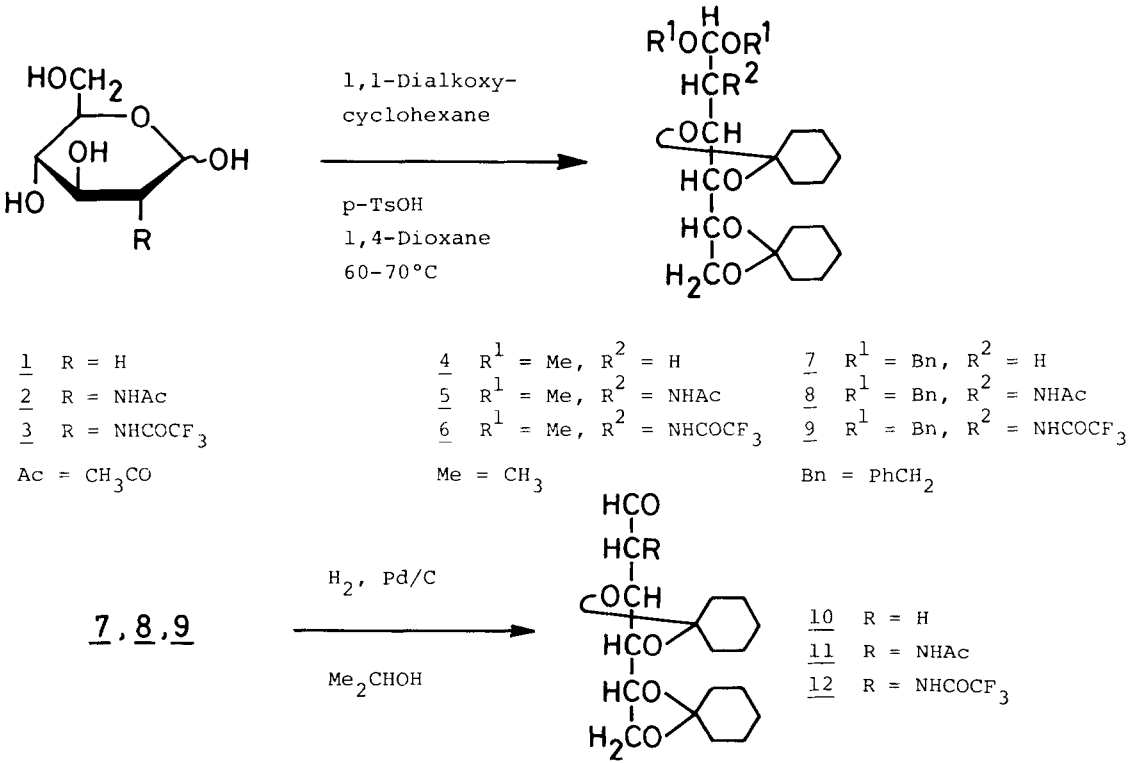

FIGURE 1

1 H, NH); Anal. Calcd for $C_{22}H_{37}NO_7$: C, 61.80; H, 8.72. Found: C, 62.09; H, 8.64.

3,4:5,6-Di-O-cyclohexylidene-2-deoxy-2-trifluoroacetamido-aldehydo-D-glucose dimethyl acetal (6). A suspension of 2-deoxy-2-trifluoroacetamido-D-glucose 3 (500 mg) in dry 1,4-dioxane (6 ml) was heated at 70°, and stirred while 1,1-dimethoxycyclohexane (6 ml) and p-toluenesulfonic acid monohydrate (70 mg) were added; stirring was continued for 1.5 h at 70°. The mixture was treated as just described, and the product purified by chromatography on a column of silica gel with 200:1 chloroform-methanol to give 6 (83% yield) as a syrup, $[\alpha]_D$ +0.31° (c 0.95, chloroform); IR (film): ν 3400 and 3300 (NH), 1730 and 1530 (amide), and 1050-1240 cm^{-1} (ether); ^1H NMR ($CDCl_3$): δ 1.2-1.9 (m, 20 H, $2C_6H_{10}$), 3.38 and 3.42 (2 s, 6 H, 2MeO), 3.58 (m, 1 H, H-5), 3.85-4.6 (m, 6 H, H-1~4, 6, 6'), and 6.7 (d, 1 H, NH); Anal. Calcd for $C_{22}H_{34}NO_7F_3$: C, 54.87; H, 7.12; N, 2.91. Found: C, 54.63; H, 6.95; N, 3.10.

3,4:5,6-Di-O-cyclohexylidene-2-deoxy-aldehydo-D-arabino-hexose dibenzyl acetal (7). Compound 1 (240 mg) was suspended in 1,1-dibenzyloxycyclohexane (5 ml) which was prepared, by acetal exchange reaction, from 1,1-dimethoxycyclohexane and benzyl alcohol according to the procedure used for 2,2-dibenzyloxypropane.[1] The suspension was stirred at ~70°, while p-toluenesulfonic acid monohydrate (50 mg) was added; stirring was continued for 1.5 h at ~70°. The product was roughly purified by chromatography on a column of silica gel with chloroform, and a syrup obtained was subjected to further purification by a preparative TLC (Merk Co.; 60 F_{254}) using 75:1 chloroform-methanol as an eluant. The title compound 7 (64% yield) was a syrup, $[\alpha]_D$ +14.2° (c 0.8, chloroform); IR (film): ν 3050, 3020, 735 and 700 (Ph), and 1000-1100 cm^{-1} (ether); ^1H NMR ($CDCl_3$): δ 1.2-2.0 (m, 20 H, $2C_6H_{10}$), 1.9-2.34 (m, 2 H, H-2,2'), 3.55 (m, 1 H, H-5), 3.8-4.2 (m, 4 H, H-3,4,6,6'), 4.45-4.85 (m, 4 H, $2PhCH_2$), 5.06 (dd, 1 H, $J_{1,2}$ 3.8, $J_{1,2'}$ 8 Hz, H-1), and 7.2-7.4 (m, 10 H, 2Ph); Anal. Calcd for $C_{32}H_{42}O_6$: C, 73.53; H, 8.10. Found: C, 73.34; H, 8.19.

2-Acetamido-3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-glucose dibenzyl acetal (8). A stirred suspension of 2 (470 mg) in 1,1-dibenzyloxycyclohexane (6 ml) was heated at ~70°, and then p-toluenesulfonic acid monohydrate (75 mg) was added. The mixture was stirred for 2 h at ~70°, and worked up. The product was purified by chromatography on a column of silica gel with (a) chloroform and (b) 200:1 chloroform-methanol. Eluant b gave crystalline 8 (51%) that was recrystallized from n-hexane, mp 70-71°C, $[\alpha]_D$ +12.5° (c 1, chloroform); IR (nujol): ν 3270 (NH), 1640 and 1560 (amide), 1050-1150 (ether), and 740 and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$): δ 1.1-1.8 (m, 20 H, $2C_6H_{10}$), 1.96 (s, 3 H, AcN), 3.65 (m, 1 H, H-5), 5.87 (d, 1 H, NH), and 7.28 and 7.29 (2 s, 10 H, 2Ph); Anal. Calcd for $C_{34}H_{45}NO_7$: C, 70.44; H, 7.82; N, 2.41. Found: C, 70.38; H, 7.66; N, 2.52.

3,4:5,6-Di-O-cyclohexylidene-2-deoxy-2-trifluoroacetamido-aldehydo-D-glucose dibenzyl acetal (9). Compound 3 (290 mg) was treated with 1,1-dibenzyloxycyclohexane (5 ml) in the presence of p-toluenesulfonic acid monohydrate (50 mg) as just described for 7. The crude product obtained by chromatography on a column of silica gel with chloroform, was purified by a preparative TLC (Merck Co.; 60 F_{254}) using 100:1 chloroform-methanol as an eluant to give a syrup of 9 (61.4%), $[\alpha]_D$ +6.6° (c 0.6, chloroform); IR (film): ν 3400 and 3300 (NH), 3100-3000, 735 and 695 (Ph), 1730 and 1530 (amide), and 1240-1050 cm^{-1} (ether); ^1H NMR ($CDCl_3$): δ 1.2-1.8 (m, 20 H, $2C_6H_{10}$), 3.57 (m, 1 H, H-5), 6.77 (d, 1 H, NH), and 7.28 and 7.31 (2 s, 10 H, 2Ph); Anal. Calcd for $C_{34}H_{42}NO_7F_3$: C, 64.44; H, 6.68; N, 2.21. Found: C, 64.17; H, 6.54; N, 2.13.

3,4:5,6-Di-O-cyclohexylidene-2-deoxy-aldehydo-D-arabino-hexose (10). To a stirred solution of 7 (160 mg) in 2-propanol (25 ml) was added 10% palladium-carbon catalyst (100 mg), and hydrogen was bubbled through for 3-4 h while the solution was stirred at 40°. The catalyst was filtered off, and washed with 2-propanol. The filtrate and washings were combined, and evaporated

to a residue which was chromatographed on a column of silica gel with 500:1 chloroform-methanol to give 10 (64% yield) as a syrup, $[\alpha]_D$ +20.2° (c 0.64, chloroform); IR (film): ν 2750 and 1738 cm^{-1} (CHO); ^1H NMR ($CDCl_3$): δ 1.1-1.8 (m, 20 H, $2C_6H_{10}$), 2.62 (m, 1 H, J_{gem} 16.3, $J_{1,2}$ 2.5, $J_{2,3}$ 7.8 Hz, H-2), 2.87 (m, 1 H, $J_{1,2'}$ 2, $J_{2',3}$ 4 Hz, H-2'), 3.55 (m, 1 H, H-5), 3.85-4.2 (m, 3 H, H-4,6,6'), 4.38 (m, 1 H, $J_{3,4}$ 7.8 Hz, H-3), and 9.8 (~t, 1 H, H-1); Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.32; H, 8.51.

2-Acetamido-3,4:5,6-di-O-cyclohexylidene-2-deoxy-aldehydo-D-glucose (11). Compound 8 (420 mg) was hydrogenolyzed in 2-propanol (50 ml) in the presence of 10% palladium-carbon catalyst (190 mg) as just described. The product was purified by chromatography on a column of silica gel with 200:1 chloroform-methanol to afford 11 (72.4% yield) as a syrup, $[\alpha]_D$ +15.8° (c 0.54, chloroform); IR (film): ν 3330 (NH), 1745 (CHO), 1670 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$): δ 1.2-2.0 (m, 20 H, $2C_6H_{10}$), 2.09 (s, 3 H, AcN), 3.7 (m, 1 H, H-5), 3.85-4.25 (m, 3 H, H-4,6,6'), 4.5 (dd, 1 H, $J_{2,3}$ 2, $J_{3,4}$ 8 Hz, H-3), 4.98 (dd, 1 H, $J_{1,2}$ 0, $J_{2,NH}$ 9 Hz, H-2), 6.32 (d, 1 H, NH), and 9.62 (s, 1 H, H-1); Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.26; H, 8.31; N, 3.76.

3,4:5,6-Di-O-cyclohexylidene-2-deoxy-2-trifluoroacetamido-aldehydo-D-glucose (12). Hydrogenolysis of 9 (180 mg) in 2-propanol (25 ml) in the presence of 10% palladium-carbon catalyst (100 mg) was achieved as described in the previous section. The product was purified by chromatography on a column of silica gel with 400:1 chloroform-methanol to give 12 (76% yield) as a syrup, $[\alpha]_D$ +8.5° (c 1, chloroform); IR (film): ν 3380 (NH), 1750-1680 (CO; CHO and amide), and 1530 (NH; amide); ^1H NMR ($CDCl_3$): δ 1.1-2.0 (m, 20 H, $2C_6H_{10}$), 3.65 (m, 1 H, H-5), 3.85-4.25 (m, 3 H, H-4,6,6'), 4.46 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 8 Hz, H-3), 5.05 (dd, 1 H, $J_{1,2}$ 0, $J_{2,NH}$ 9 Hz, H-2), and 9.75 (s, 1 H, H-1); Anal. Calcd for $C_{20}H_{28}NO_6F_3$: C, 55.16; H, 6.48; N, 3.22. Found: C, 54.78; H, 6.21; N, 3.45.

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