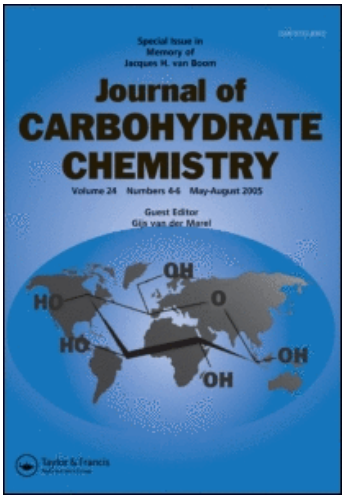

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THIOACETOLYSIS REACTIONS OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE DERIVATIVES

Lai-xi Wang, Nobuo Sakairi, and Hiroyoshi Kuzuhara*

RIKEN (The Institute of Physical and Chemical Research)
Wako-Shi, Saitama 351-01, Japan

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ABSTRACT

Thioacetolysis of per-O-benzylated and per-O-acetylated derivatives of 1,6-anhydro-β-D-glucopyranose (1 and 3) with acetyl sulfide using acidic catalysts gave α- and β-anomers of 1-S-acetyl-1-thio-D-glucopyranose, respectively. The formation of the β-anomer from 3 was in contrast to the predominance of the α-anomer as the product of the usual acetolysis of 3. Similar thioacetolysis of per-O-benzylated 1,6-anhydro-maltose (5) under optimized conditions resulted in opening of the 1,6-anhydro ring and simultaneous removal of the C-6' benzyl group without cleavage of the internal glycosidic linkage, giving the 6,6'-di-O-acetyl-1-S-acetyl-α-thio-maltose derivative (6) in moderate yield.

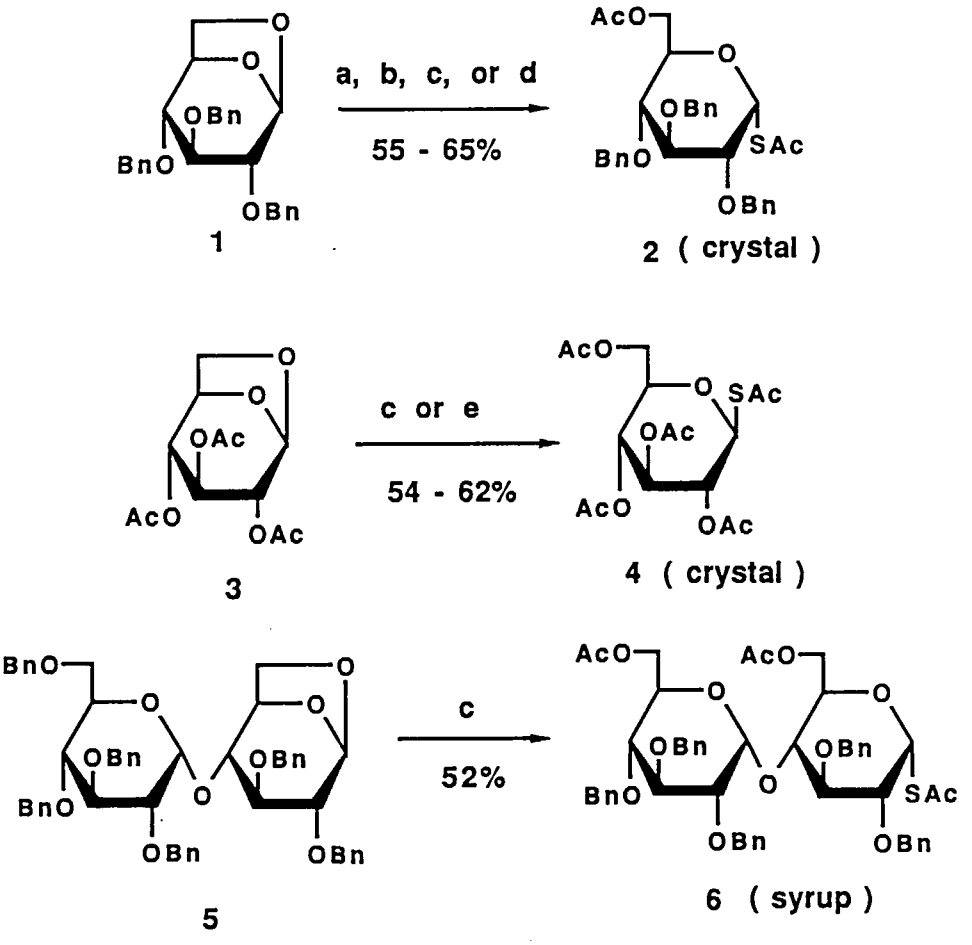
INTRODUCTION

1,6-Anhydro derivatives of D-glucopyranose and of di- and trisaccharides such as maltose, cellobiose and maltotriose, that are readily available from the parent mono- and oligosaccharides[1] have been used as versatile synthons for the syntheses of various bioactive compounds.[2] On the other hand, thioglycosides have attracted much attention, e.g. as enzyme substrates,[3] as potential enzyme inhibitors,[4] and as key intermediates for O-glycoside synthesis.[5] Very recently, we have developed a novel method for the direct conversion of 1,6-anhydro derivatives of D-glucopyranose, maltose and maltotriose into the

corresponding thioglycosides, and also showed a certain limitation of the method.[6] Here we wish to describe the thioacetolysis of 1,6-anhydro-β-D-glucopyranose derivatives, which led to the preparation of 1-S-acetyl-1-thio-D-glucopyranose and maltose derivatives (2, 4 and 6). These 1-S-acetyl-1-thio-D-glucopyranoses are usually prepared by nucleophilic substitution[7] of glycosyl halides or by the Lewis acid catalyzed reaction[8] of glycosyl acetate with thioacetic acid. As the S-alkylation of glycosyl thiols has been one of the most frequently used synthetic approaches towards thioglycosides,[9] the present thioacetolysis of 1,6-anhydrohexopyranoses is considered to constitute one of the useful routes that supplements the direct thioglycosidation reactions [6] currently employed in thioglycoside synthesis.

RESULTS AND DISCUSSION

Though it is well known that the 1,6-anhydro ring of hexopyranoses is susceptible to opening by acetolysis with acetic anhydride[10] under acid catalysis to give the corresponding glycosyl acetate, thioacetolysis of 1,6-anhydrohexopyranoses has not been reported as yet. When 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose (1) was treated with acetyl sulfide (Ac_2S)-concd sulfuric acid or with Ac_2S-thioacetic acid (AcSH)-concd sulfuric acid, 6-O-acetyl-1-S-acetyl-2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranose (2) was obtained in moderate yields with a trace of the β-anomer (α:β = 9:1). Replacing the sulfuric acid catalyst by boron trifluoride etherate ($BF_3 \cdot Et_2O$) or fused zinc chloride ($ZnCl_2$) gave almost the same results (see Experimental Section). In contrast to this, the treatment of 2,3,4-tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (3) with Ac_2S-$ZnCl_2$ or with Ac_2S-$BF_3 \cdot Et_2O$ resulted in production of 1-S-acetyl-1-thio-β-D-glucose predominantly (α:β = 1:9), and gave 2,3,4,6-tetra-O-acetyl-1-S-acetyl-1-thio-β-D-glucopyranose (4) as crystals in ca. 55% yield.[11] It is to be noted that compound 3 predominantly gives α-anomer (7) of peracetylated D-glucopyranose (α:β = 7:1) when treated with Ac_2O-$ZnCl_2$ or with Ac_2O-$BF_3 \cdot Et_2O$, as expected from many other reported results of ordinary acetolysis of peracetylated 1,6-anhydrohexopyranoses.[12] No detailed stereochemical study on the acetolysis of 1,6-anhydro sugars seems have been done, despite the wide

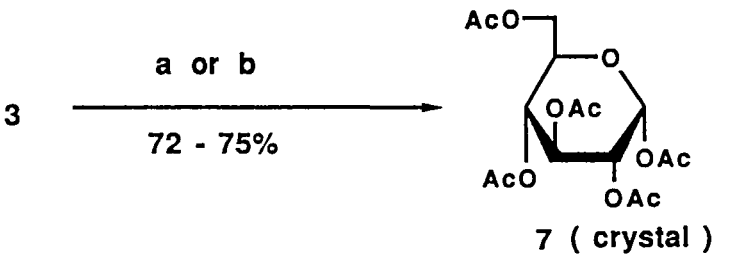


(a) Ac_2S / AcSH / concd H_2SO_4 (b) Ac_2S / concd H_2SO_4

(c) Ac_2S / $ZnCl_2$ (d) Ac_2S / $BF_3 \cdot Et_2O$

(e) Ac_2S / AcSH / $BF_3 \cdot Et_2O$

Scheme I

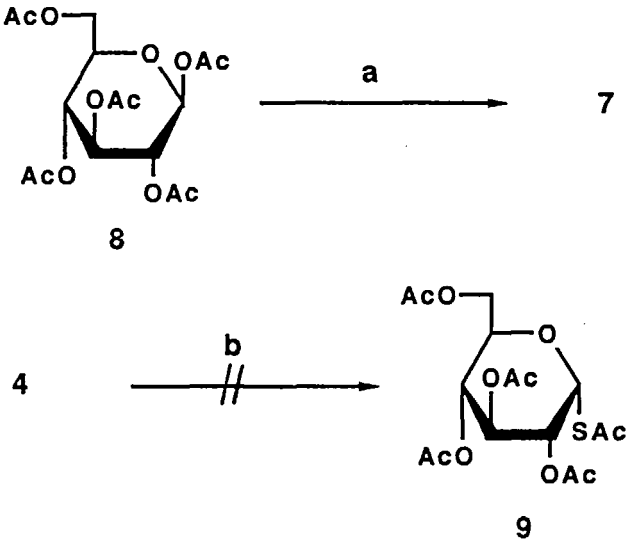


(a) Ac_2O / $ZnCl_2$ (b) Ac_2O / $BF_3 \cdot Et_2O$

Scheme II

use of this kind of reaction.[10] In the present case, the neighboring acetoxy group is probably taking part in this apparently reversed stereoselectivity. Supposedly, such participation of the neighboring groups may also be actually involved in ordinary acetolysis of peracetylated 1,6-anhydro-β-D-glucopyranose, producing β-glycosyl acetate as a labile intermediate which presumably isomerizes in situ to more stable α-anomer. Indeed, we found that the β-glycosyl acetate (8) was easily converted into its α-anomer (7) in the presence of Ac_2O-$ZnCl_2$, whereas the β-thioacetate (4) was not converted into its α-anomer (9) under similar conditions (Ac_2S-$ZnCl_2$) (Scheme III).[13]

Next, thioacetolysis with Ac_2S-$ZnCl_2$ was applied to a disaccharide derivative, 1,6-anhydro-2,3,2',3',4',6'-hexa-O-benzyl-β-maltose (5). Monitoring the reaction by TLC revealed the appearance of several spots at an early stage but gradual accumulation of one of the products. Usual work-up followed by flash column chromatography gave 6,6'-di-O-acetyl-1-S-acetyl-2,3,2',3',4'-penta-O-benzyl-1-thio-α-maltose (6) in 52% yield, showing that the internal glycosidic linkage could survive but the primary benzyloxy group was cleaved under these thioacetolysis conditions. Since employment of more drastic conditions led to the crucial decomposition of 5, the reaction conditions for such oligosaccharide substrates had to be made as mild as possible. The structure of 6 was elucidated mainly on the basis of its ^1H NMR spectrum



(a) Ac_2O / $ZnCl_2$ (b) Ac_2S / $ZnCl_2$

Scheme III

through decoupling techniques. In the spectrum of **6**, the signals due to two OAc groups appeared at δ 2.05 and δ 2.02 as a couple of singlets and the SAc signal at δ 2.44 as a singlet. The methylene protons at the 6' position appeared at δ 4,17-4.25, which were in the lower field region than those for the corresponding protons of **5** (δ 3.65-3.68), indicating that the 6'-hydroxy group was acetylated. The resonance of the C-1 proton at δ 6.18 with J = 5.2 Hz revealed that this compound had an α-acetylthio group at the anomeric center.[14]

These results, including the unexpected formation of the β-anomer **4**, suggest that the 1,6-anhydro derivatives of D-glucose and other hexopyranoses, *e.g.* galactose, are potentially able to produce either α- or β-anomers by thioacetolysis, depending on the mode of protection at the neighboring C-2 hydroxyl group. This kind of thioacetolysis

reaction would also be applicable to 1,6-anhydrooligosaccharides by careful choice of reaction conditions but some kinds of alkyloxy protecting groups may be cleaved simultaneously. However, this may in turn offer the possibility of establishing intentionally selective de-O-protection techniques.[15]

EXPERIMENTAL

GENERAL PROCEDURES. Melting points were determined with a Yamato micro melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter. IR spectra were recorded with Shimadzu IR-27 spectrophotometer, using KBr disks for solid samples and KRS (thallium bromide-iodide) for liquid samples. ^{1}H NMR spectra were recorded at 400 MHz with a JEOL JNM-GX 400 spectrometer, using tetramethylsilane as the internal standard for solutions in $CDCl_3$. Reactions were monitored by TLC on precoated plates of silica gel $60F_{254}$ (layer thickness, 0.25mm, E.Merck, Darmstadt, Germany), spots were visualized under UV light and/or by charring with a solution of MeOH - concd H_2SO_4 - p-anisaldehyde (85:10:5 v/v). Flash column chromatography was performed on silica gel 60 (230-400 mesh, E. Merck, Darmstadt, Germany). All extractions were concentrated below 45 °C under diminished pressure.

6-O-Acetyl-1-S-acetyl-2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranose (2). (a) with Ac_2S - AcSH / concd H_2SO_4. To a solution of 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose (1)[16] (0.216 g, 0.5 mmol) in Ac_2S (2 mL) and AcSH (2 mL) was added concd H_2SO_4 (0.1 mL). The resulting mixture was stirred at room temperature for 2.5 h, then poured into saturated $NaHCO_3$ solution, stirred at room temperature for 2 h, and extracted with EtOAc. The extract was washed with aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (toluene-EtOAc, 15:1) to give a white solid consisting of 2 and its β-anomer (1.80 g, 65%, α:β = 9:1); ^{1}H NMR δ ppm 6.18 (d, J = 5.4 Hz, 0.9 H, H-1α), 5.15 (d, J = 11 Hz, 0.1 H, H-1β). Recrystallization (EtOH) afforded 2 as white crystals (0.153 g, 55%): TLC R_f 0.52 (benzene-EtOAc, 9:1); mp 71.0-71.5 °C; $[\alpha]_D^{20}$ + 90.5° (c 0.7,

$CHCl_3$); IR ν_{max}^{film} 1730 cm^{-1} (OAc), 1690 cm^{-1} (SAc); ^1H NMR δ ppm 7.35-7.20 (m, 15 H, 3 C_6H_5), 6.18 (d, J = 5.4 Hz, 1H, H-1), 4.97, 4.84, 4.77, 4.66, 4.57, 4.53 (d each, J = 11 Hz, 1 H each, 3 CH_2Ph), 4.28 (dd, J = 3.9, 12 Hz, 1 H, H-6a), 4.18 (dd, J = 2.2, 12 Hz, 1 H, H-6b), 3.89 (dd, J = 5.2, 9.5 Hz, 1 H, H-2), 3.78 (m, 1 H, H-5), 3.59 (t, J = 9.2 Hz, 1 H, H-3), 3.51 (t, J = 9.5 Hz, 1 H, H-4), 2.42 (s, 3 H, $SCOCH_3$), 1.99 (s, 3 H, $OCOCH_3$).

Anal. Calcd for $C_{31}H_{34}O_7S$: C, 67.61; H, 6.22; S, 5.82. Found: C, 67.58; H, 6.22; S, 5.74.

(b) with Ac_2S–concd H_2SO_4. To a solution of **1** (0.216 g, 0.5mmol) in Ac_2S (3 mL) was added concd H_2SO_4 (0.1 mL), and the resulting mixture was stirred at room temperature for 2 h. Work-up as described in procedure (a) gave a white solid as an anomeric mixture (0.195 g, 71%, α:β = 9:1). Recrystallization (EtOH) afforded **2** as white crystals (0.165 g, 60%).

(c) with Ac_2S – $BF_3 \cdot Et_2O$. To a solution of **1** (0.216 g, 0.5 mmol) in Ac_2S (2 mL) was added $BF_3 \cdot Et_2O$ (20 μL) under argon atmosphere, and the resulting mixture was stirred at room temperature for 2 h. Work-up as described in procedure (a) afforded an anomeric mixture (0.21 g, 76%, α:β = 9:1). Recrystallization gave pure **2** (0.18 g, 65%).

(d) with Ac_2S – $ZnCl_2$. To a solution of **1** (0.216 g, 0.5 mmol) in Ac_2S (2 mL) was added fused $ZnCl_2$ (75 mg), and the resulting suspension was stirred at room temperature for 2.5 h. Work-up as described in procedure (a) gave an anomeric mixture (0.20 g, 72%, α:β = 9:1). Recrystallization gave pure **2** (0.175 g, 63%).

2,3,4,6-Tetra-O-acetyl-1-S-acetyl-1-thio-β-D-glucopyranose (4). (a) with Ac_2S – $ZnCl_2$. To a solution of 2,3,4-tri-O-acetyl-1,6-anhydro-β-D-glucose (**3**)[1a] (0.288 g, 1.0 mmol) in Ac_2S (2 mL) was added fused $ZnCl_2$ (80 mg), and the resulting suspension was stirred at room temperature for 15 h. The reaction mixture was then poured into aq. $NaHCO_3$ and stirred for 2 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine and H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (benzene-EtOAc, 4:1) to give a white solid consisting of **4** and its α-anomer (0.257 g, 63%, α:β = 1:9): ^1H NMR δ ppm 6.20 (d, J = 5.3 Hz, 0.1 H, H-1α), 5.25 (d, J = 11

Hz, 0.9 H, H-1β). Recrystallization of the anomeric mixture from EtOH afforded **4** as white crystals (0.22 g, 54%): TLC R_f 0.47 ($CHCl_3$-EtOH, 20:1) mp 118.5-119 °C; $[\alpha]_D^{20}$ + 11.2° (c 0.3, $CHCl_3$); lit.[8c] mp 114-115 °C; $[\alpha]_D^{25}$ + 11.0°($CHCl_3$); IR ν_{max}^{KBr} 1735 cm^{-1} (OAc), 1690 cm^{-1} (SAc); ^1H NMR δ ppm 5.25 (d, J = 10.5 Hz, 1 H, H-1), 5.26 (t, J = 9.3 Hz, 1 H, H-3), 5.14-5.08 (m, 2 H, H-2,4), 4.26 (dd, J = 4.4, 12.7 Hz, 1 H, H-6a), 4.09 (dd, J = 2.0, 12.7 Hz, 1 H, H-6b), 3.83 (ddd, J = 2.2, 4.4, 11.5 Hz, 1 H, H-5), 2.38 (s, 3 H, $SCOCH_3$), 2.07, 2.03, 2.02, 2.00 (s, 3 H each, 4 $OCOCH_3$). Further elution of the column afforded 1,2,3,4,6-penta-O-acetyl-D-glucopyranose as a white solid (60 mg, α:β = ca. 7:1).

(b) with Ac_2S - AcSH / BF_3·Et_2O. To a solution of **3** (0.288 g, 1.0 mmol) in Ac_2S - AcSH (1/1, v/v, 2 mL) was added BF_3·Et_2O (100 μL) under argon atmosphere, and the resulting mixture was stirred at room temperature for 12 h. Work-up as described above gave an anomeric mixture (0.31 g, 75%, α:β = 1:9). Recrystallization (EtOH) afforded pure **4** (0.252 g, 62%). 1,2,3,4,6-Penta-O-acetyl-D-glucopyranose (45 mg) was also isolated from the column as white crystals.

6,6'-Di-O-acetyl-2,3,2',3',4'-penta-O-benzyl-1-thio-α-maltose (6). To a solution of 1,6-anhydro-2,3,2',3',4',6'-hexa-O-benzyl-β-maltose (**5**)[17] (0.20 g, 0.23 mmol) in CH_2Cl_2 (2 mL) was added Ac_2S (2 mL) and fused $ZnCl_2$ (80 mg). The resulting mixture was stirred at room temperature and the reaction was monitored by TLC (benzene-EtOAc, 9:1). After stirring for 1.5 h, the reaction mixture was poured into aq. $NaHCO_3$ solution, stirred at room temperature for 2 h and extracted with EtOAc. The extract was washed with brine and H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (benzene-EtOAc, 9:1) to give **6** as a colorless syrup (0.115 g, 52%): TLC R_f 0.3 (benzene-EtOAc, 9:1); $[\alpha]_D^{20}$ + 91.6° (c 0.2, $CHCl_3$); IR ν_{max}^{film} 1735 cm^{-1} (OAc), 1690 cm^{-1} (SAc); ^1H NMR δ ppm 7.35-7.15 (m, 25 H, 5 C_6H_5), 6.18 (d, J = 5.2 Hz, 1 H, H-1), 5.47 (d, J = 3.9 Hz, 1 H, H-1'), 4.95-4.45 (m, 10 H, 5 CH_2Ph), 4.39 (dd, J = 2.0, 10 Hz, 1 H, H-6a), 4.26 (dd, J = 4.0, 10 Hz, 1 H, H-6b), 4.17-4.25 (m, 2 H, H-6'a,6'b), 3.95 (m, 1 H, H-3'), 3.92-3.85 (m, 3 H, H-2,3,5), 3.82 (m, 1 H, H-5'), 3.67 (t, J = 9.0 Hz, 1 H, H-4), 3.45 (m, 2 H, H-2',4'), 2.44 (s, 3 H, $SCOCH_3$), 2.05, 2.02 (s, 3 H each, 2 $OCOCH_3$).

Anal. Calcd for $C_{53}H_{58}O_{13}S$: C, 68.07; H, 6.25; S, 3.43. Found: C, 68.14; H, 6.28; S, 3.30.

Acetolysis of 3. (a) with Ac_2O–$ZnCl_2$. To a solution of **3** (0.288 g, 1 mmol) was added $ZnCl_2$ (80 mg) and the resulting mixture was stirred at room temperature for 12 h. Usual work-up gave a white solid (0.36 g) consisting mainly of **7** and its β-anomer (**8**) (**7**:**8** = ca. 7:1); ^1H NMR δ ppm 6.34 (d, J = 3.7 Hz, 7/8 H, H-1α), 5.73 (d, J = 8.3 Hz, 1/8 H, H-1β). Recrystallization from EtOH gave **7** as white crystals (0.293 g, 75%): mp 110-111 °C; $[\alpha]_D^{23}$ + 101.5° (c 1.0, $CHCl_3$); lit.[18] mp 112-113 °C; $[\alpha]_D^{20}$ +102° ($CHCl_3$).

(b) with Ac_2O–BF_3·Et_2O. To a solution of **3** (0.288 g, 1 mmol) was added BF_3·Et_2O (80 μL) and the resulting mixture was stirred at room temperature for 20 h, then the mixture was poured into aq. $NaHCO_3$. Usual work-up gave a white solid (0.34 g) consisting mainly of **7** and its β-anomer (α:β = 7:1). Recrystallization (EtOH) afforded pure **7** as white crystals (0.281 g, 72%).

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11. Compound 4 was accompanied with an unexpected side product, 1,2,3,4,6-penta-O-acetyl-D-glucopyranose (in 10% yield, α:β = ca. 7:1). The extra acetoxyl group attached to the anomeric carbon might come from acetic anhydride contaminating commercial acetyl sulfide, since the ^{1}H NMR spectrum of the commercial acetyl sulfide revealed the presence of 5% acetic anhydride.

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13. Treatment of the β-anomer (8) with Ac_2O-$ZnCl_2$ at room temperature for 5 h gave an anomeric mixture (7 and 8) with predominance of α-anomer (7:8 = 6:1). Similar conversion of peracetylated D-galactopyranose was also reported; see M. L. Wolfrom and A. Thompson, Methods Carbohydr. Chem., 2, 213 (1963). In contrast, the β-anomer (4) never underwent any change on treatment with Ac_2S-$ZnCl_2$ at room temperature for 10 h.

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