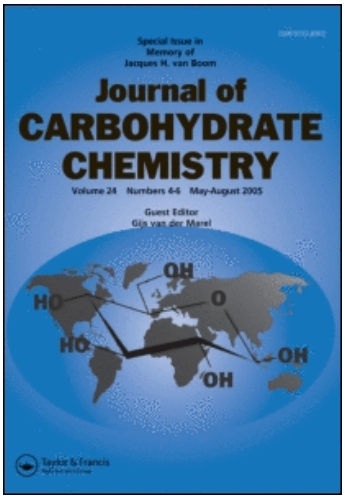

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A SIMPLE ROUTE TO β,β-TREHALOSE VIA TRICHLOROACETIMIDATES

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ABSTRACT

The reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl trichloroacetimidate in CH_2Cl_2 promoted by $BF_3;OEt_2$ gives β,β-octaacetyltrehalose in up to 58% isolated yield, which is readily deacetylated to β,β-trehalose. The corresponding 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate is configurationally stable and inert to coupling under mild conditions.

INTRODUCTION

The ready availability of α,α-trehalose from natural sources, and the interest in some of its biologically active derivatives has led to extensive development of its chemistry and the preparation of a range of derivatives.[1] By contrast, the anomer β,β-trehalose, which does not occur naturally, has not been studied to the same extent, and has not been readily obtainable in pure form. Conventional variants on the Koenigs-Knorr reaction[2] give low yields of β,β-trehalose derivatives and require tedious separations of the product from its stereoisomers. This makes the imidate coupling route,[3] whose most

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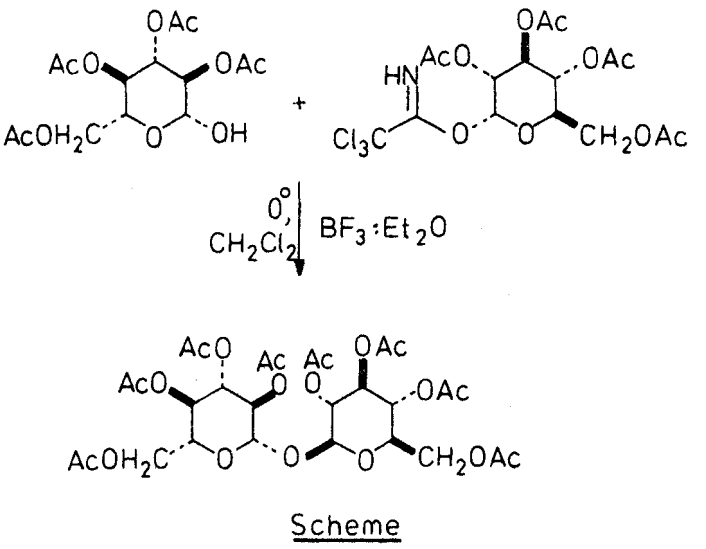

Scheme

effective practical variant is the β-specific acid-catalysed reaction of alcohols with α-anomeric trichloroacetimidates,[4] particularly attractive. We show that this can be applied to the synthesis of octaacetyl β,β-trehalose in up to 58% isolated yield, according to the Scheme.

RESULTS AND DISCUSSION

There have been few reports in the literature on the chemistry of the interesting disaccharide β,β-trehalose largely because the conventional syntheses use unpleasant reagents such as $Hg(CN)_2$ or require tedious chromatographic separations. Formation of glycosidic linkages by the trichloroacetimidate variant[3] of the imidate coupling reaction[4] has now been applied to β,β-trehalose synthesis. Reaction occurs under mild acid catalysis and the co-product is trichloroacetamide. This makes the method very suitable for large-scale preparative work, and base-catalysed methanolysis of the intermediate β,β-trehalose octaacetate[2] leads directly to the crystalline disaccharide. The ^1H NMR spectrum of product in D_2O shows a number of differences from that of the α,α-anomer which are tabulated below. Axial ring-protons at C2, C3 and C5 are more shielded by 0.23 to 0.36 ppm in the β,β-anomer.

TABLE Chemical shifts of trehalose protons in D_2O, relative to internal DSS. The spectra were recorded using a Bruker WH 300 machine operating at 24°C with a sweep width of 4KHz, pulse width 60° and 32K data points. Coupling constants, β,β anomer: $J_{1,2}$ = 7.5; $J_{2,3}$ = 9.2; $J_{3,4}$ = 8.9; $J_{4,5}$ = 9.5; $J_{5,6a}$ = 2.2; $J_{5,6b}$ = 5.6; $J_{6a,6b}$ = 12.4 Hz. We thank Dr. S.J. Kimber for these measurements.

Proton	H_1	H_2	H_3	H_4	H_5	H_{6a}	H_{6b}
ββ	4-74	3-35	3-45	3-29	3-40	3-85	3-67
αα	5-20	3-64	3-84	3-44	3-81	3-80	3-77

It was felt that the corresponding pentafluorophenylimidate would provide a useful alternative starting material since 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl trichloroacetimidate is a viscous oil and trace impurities were evident in the ^1H NMR spectrum. Replacement of CCl_3CN with C_6F_5CN in the imidate synthesis did indeed lead to a crystalline product but we were surprised to discover that this was the pure β-anomer. All attempts to equilibrate it with the (presumed more stable) α-anomer using KH in CH_2Cl_2, a silica gel, led to its quantitative recovery. An example of the "reverse anomeric effect" cannot be ruled out.[6]

EXPERIMENTAL

General Methods

^1H-Nuclear magnetic resonance spectra were obtained on a Bruker WH 300 (300.13 MHz) instrument. Chemical shifts (δ) are expressed in parts per million from tetramethylsilane. The mass spectrum was recorded on a V.G. Micromass spectrometer operating in electron impact mode. The infra-red spectrum was recorded on a Unicam SP 1000 spectrometer as a nujol mull. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Commercial solvents were distilled prior to use from an appropriate drying agent according to standard procedures. Dichloromethane was distilled from phosphorus pentoxide; diethyl ether was distilled from sodium wire employing sodium benzophenone ketyl as an indicator; methanol was distilled from magnesium turnings.

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl trichloroacetimidate. To a stirred, argon-blanketed solution of 2,3,4,6-tetra-O-acetyl-β-D-glucose[2] (1.50 g, 4.12 mmol) and distilled CCl_3CN 1.50 ml, 2.16 g., 15 mmol) in dry CH_2Cl_2(10 ml) at -78°, there was added a suspension of potassium hydride 0.20 g, 4.99 mmol) in dry CH_2Cl_2 (10 ml). The suspension was allowed to warm to ambient temperature over 0.5 h. The potassium salts then filtered off and the solution was passed through a short column of silica gel and concentrated in vacuo. 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl trichloroacetimidate was obtained as an oil (1.6 g, 76%). ^1H NMR [$CDCl_3$,300 MHz]: δ 8.7(brs,NH) 6.55(d,H_1,$J_{1,2}$ = 4 Hz) 5.55 t,H_3,$J_{2,3}$ = $J_{3,4}$ = 9.5 Hz) 5.2(t,H_4,$J_{4,5}$ = 9.5 Hz) 5.15(dd,H_2 $J_{1,2}$ = 4 Hz) 4.25(m,H_5,H_{6b}) 4.15(dd,H_{6a} $J_{6,6}$ = 12.5 Hz,$J_{5,6a}$ = 2.5 Hz) 2.0 - 2.15 (4 x S,$COCH_3$) p.p.m.

2,3,4,6-Tetra-O-acetyl β-D-glucopyranosyl pentafluorophenylimidate. An argon-blanketed solution of 2,3,4,6-tetra-O--acetyl-β-D-glucose (0.90 g, 2.47 mmol) and pentafluorobenzonitrile 0.80 ml, 1.22 g, 6.6 mmol) in dry CH_2Cl_2 (20 ml) at -78°, was added to dry potassium hydride (0.13 g, 3.24 mmol) also held at -78°. The mixture was stirred at -78° for 0.25 h and then warmed to ambient temperature over 0.5 h. The reaction mixture was passed through a short column of silica gel and concentrated in vacuo. Recrystallization of the resulting solid from CH_2Cl_2/Et_2O gave white crystals of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate (1.24 g, 93%) m.p. 139.5-42°. $[\alpha]_D^{20}$ = -13.7° (c,4.8,CH_2Cl_2). Found: C,47.13; H,3.76; $C_{21}H_{20}F_5NO_{10}$ requires: C,46.59; H,3.72%. M.S. m/z 539 (M^+-2, 67%) 331(M^+-C_6F_5CONH, 100%) 213 ($C_6F_5C^+(OH)NH_2$, 26%) ^1H NMR [$(CD_3)_2SO$,300 MHz] δ 5.7 (d,H_1,$J_{1,2}$ = 8 Hz) 5.45(t,H_3,$J_{2,3}$ = $J_{3,4}$ = 9.5 Hz) 5.13(dd,H_2) 5.03(t,H_4,$J_{4,5}$ = 10 Hz) 4.2(dd,H_{6a},$J_{6,6}$ = 12.5 Hz, $J_{6a,5}$ = 5 Hz) 4.1(brm,H_5) 4.02(dd,H_{6b},$J_{6b,5}$ = 2 Hz) 2.1 = 2.0 (4 x s, $COCH_3$)ppm. In $CDCl_3$ the ^1H NMR spectrum was highly second-order in the 5.2 ppm region IR (nujol) 1745(s) 1230(s) cm^{-1}.

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl 2',3',4',6'--tetra-O-acetyl-β-D-glucopyranoside; (β,β-trehalose octaacetate). To a mixture of 1.14 g (2.24 mmol) 2,3,4,6-tetra-O-acetyl-α-D--glucopyranosyl trichloroacetimidate and 0.816 g (2.24 mmol)

2,3,4,6-tetra-O-acetyl-β-D-glucose (freshly prepared) in CH_2Cl_2 (25 ml) at 0°, was added 0.6 ml (4.88 mmol) BF_3: Et_2O in CH_2Cl_2 (5 ml) with stirring. The solution stood for 16 h at room temperature, then saturated $NaHCO_3$ aq. (15 ml) was added and the separated organic phase washed with water (3 x 15 ml) and saturated NaCl solution, dried over Na_2SO_4, and then solvent removed in vacuo. Recrystallization from Et_2O/40-60 petrol gave 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl 2',3',4',6'--tetra-O-acetyl-β-D-glucopyranoside (0.666 g). Further product was obtained by flash chromatography (Et_2O/40-60 petrol, 9:1) and combined to give 0.869 g (55%) of white needles, m.p. 181.5 - 183°(lit.[2] 181.5 - 182.5°); $[\alpha]_D^{20}$ -15.5°(c5.4,$CHCl_3$), lit.[3] -17°($CHCl_3$); ^1H NMR [$CDCl_3$, 300 MHz] 5.2 (t,H_3,$J_{2,3} = J_{3,4}$ = 8.5 Hz) 5.15 (t,H_4,$J_{4,5}$ = 9 Hz) 5.0(t,H_2,$J_{1,2}$ = 8.5 Hz) 4.9(d,H_1,$J_{1,2}$ = 8 Hz) 4.25(dd,H_{6a}, $J_{5,6}$ = 4.5 Hz, $J_{6,6}$ = 12.5 Hz) 4.15(dd,H_{6b} $J_{5,6b}$ = 2.5 Hz) 3.75(ddd,H_5) 2.0 ▪ 2.25(4 x s, $COCH_3$) ppm.

A large scale preparation afforded 16.91 g (62%) of crude material which gave 15.82 g (58%) of pure material on recrystallization as before, without the requirement for chromatography.

β-D-Glucopyranosyl β-D-glucopyranoside (β,β-trehalose). Methanolic NaOMe (1.45 ml 0.1 M) was added to a solution of 2,3,4,6-tetra--O-acetyl-β-D-glucopyranosyl 2',3',4',6'-tetra-O-acetyl-β-D-glucopyranoside (2.24 g, 3.16 mmol) in hot MeOH. The solution was then refluxed for 0.25 h, solvent removed in vacuo and the solid was precipitated from MeOH/EtOH and dried in vacuo at 64° for 3 h and then 110° for 14 h. There was thus obtained β-D-glucopyranosyl β-D-glucopyranose as an off-white solid (1.05g, 97%) m.p. 129-34° (lit[3] 135-40°), $[\alpha]_D^{20}$ = -35.2°(c5.0,H_2O), lit -40°(H_2O). A single recrystallization from H_2O/Me_2CO gave colourless plates, m.p. 134-9°, $[\alpha]_D^{20}$ = -39°(7.4,H_2O); ^1H NMR [D_2O,300 MHz] recorded in Table.

Attempted epimerisation of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate

To a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate (0.63 g,1.17 mmol) in CH_2Cl_2(12 ml) was added distilled boron trifluoride etherate (0.15 ml,1.2 mmol).

The solution was stirred for 24 h at room temperature, then saturated aqueous $NaHCO_3$ (10 ml) was added and the separated organic phase washed with water (3 x 5 ml), dried (anhydrous magnesium sulphate) and the solvent was removed *in vacuo*. Examination of the residue (^{1}H-NMR) showed only the presence of unreacted starting material.

Attempted coupling of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate and methanol

To a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl pentafluorophenylimidate (0.15 g,0.28 mmol) and methanol (0.050 ml, 1.2 mmol) in CH_2Cl_2 (5 ml) was added distilled boron trifluoride etherate (0.040 ml, 0.32 mmol) at 0°. The solution was stirred for 16 h at room temperature and the solvent was then removed *in vacuo*. Examination of the residue (^{1}H-NMR) showed only the presence of unreacted starting material.

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