

## BF<sub>3</sub> – Etherate Induced Formation of 2,2,2-Trichloroethyl Glycopyranosides. Selective Visualization of Carbohydrate Derivatives on TLC Plates

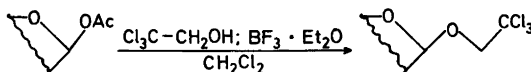
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Per-*O*-acetylated trichloroethyl glycopyranosides have been prepared in 59–89 % isolated yield by reaction of the corresponding per-*O*-acetylated sugar with 2,2,2-trichloroethanol and boron-tri-

fluoride etherate in dichloromethane. <sup>1</sup>H and <sup>13</sup>C NMR data are given. A simple method for selective visualization of carbohydrate derivatives on TLC plates is also reported.

Table 1. Yields and product data in the reaction.



Starting sugar (anomeric configuration)	Product Yield <sup>a</sup> (%)	Reaction temp./°C	M.p./°C Lit.	$[\alpha]_D^{25}$ (temp./°C) Lit.
Pentaacetyl- $\beta$ -D-glucopyranose	1 $\beta$ { 70 <sup>b,d</sup>	0	143–144(143–144 <sup>14</sup> ) 99–100 (99–100 <sup>14</sup> )	–26.4(28) +134 (20) +136 (23) <sup>14</sup>
	1 $\alpha$ { 0.5 <sup>b,e,f</sup>			
	1 $\beta$ 89 <sup>c,d</sup>			
Pentaacetyl- $\beta$ -D-galactopyranose	2 $\beta$ 56 <sup>d,b</sup>	0 25	109–111 139–140	–22.2 (28) +127.8 (28)
	2 $\beta$ { 70 <sup>c,d</sup>			
	2 $\alpha$ { 11 <sup>c,e,f</sup>			
Pentaacetyl- $\beta$ -D-mannopyranose	3 $\alpha$ 59 <sup>c,d</sup>	0	118–119	+51 (30)
Methyl tetraacetyl- $\beta$ -D-glucuronate	4 $\beta$ 85 <sup>b,d</sup>	25	160–161.5(160–161) <sup>4</sup>	–38 (20)
Tetraacetyl- $\beta$ -D-xylopyranose	5 $\beta$ 74 <sup>b,d</sup>	–10 25	155–157 117–120	–64.5 (20) +130.3 (20)
	5 $\beta$ { 37 <sup>c,d</sup>			
	5 $\alpha$ { 42 <sup>c,e,f</sup>			
Tetraacetyl-D-fucopyranose	6 $\beta$ { 16 <sup>b,d,g</sup>	–10 25	127–128	–157 (20)
	6 $\alpha$ { 51 <sup>b,e,g</sup>			
	6 $\beta$ { 11 <sup>c,d,f</sup> 6 $\alpha$ { 53 <sup>c,e</sup>			

<sup>a</sup>Not optimized; only isolated by spontaneous crystallization of crude reaction mixture. <sup>b</sup>By method A (see Experimental). <sup>c</sup>By method B (see Experimental). <sup>d</sup>1,2-*trans* Glycoside. <sup>e</sup>1,2-*cis* Glycoside. <sup>f</sup>Isolated by preparative chromatography of the mother liquor. <sup>g</sup>By analytical HPLC.

Table 2. <sup>1</sup>H NMR chemical shifts and coupling constants for per-*O*-acetylated 2,2,2-trichloroethyl glycopyranosides.

Compound	Chemical shift <sup>a</sup> (coupling constant <sup>b</sup> )									
	H1	H2	H3	H4	H5 <sub>ax</sub>	H5 <sub>eq</sub>	H6	H6'	Cl <sub>3</sub> C-CH <sub>2</sub>	CH <sub>3</sub> -C(=O)-
1β (gluco)	4.82 ( <i>J</i> <sub>1,2</sub> 7.3)	5.22- - - - - (- - - - - m - - - - -)	- - - - -	5.03 (- - - - -)	3.72 ( <i>J</i> <sub>5,6</sub> 4.3)	- - - - -	4.12 ( <i>J</i> <sub>AB</sub> 12.3)	4.24	4.36, 4.11 ( <i>J</i> <sub>AB</sub> 12.2)	2.06, 2.02 1.99, 1.98
1α (gluco)	5.43 ( <i>J</i> <sub>1,2</sub> 3.8)	4.89 ( <i>J</i> <sub>2,3</sub> 10.3)	5.56 ( <i>J</i> <sub>3,4</sub> 10.3)	5.09 ( <i>J</i> <sub>4,5</sub> 10.3)	4.27 (m)	- - - - -	4.10- - - - - (- - - - - m - - -)	4.30	4.24, 4.14 ( <i>J</i> <sub>AB</sub> 11.8)	2.10, 2.07 2.04, 2.03
2β (galacto)	4.82 ( <i>J</i> <sub>1,2</sub> 7.9)	5.33 ( <i>J</i> <sub>2,3</sub> 10.3)	5.05 ( <i>J</i> <sub>3,4</sub> 3.1)	5.42 ( <i>J</i> <sub>4,5</sub> <1)	3.95 ( <i>J</i> <sub>5,6</sub> 6.2)	- - - - -	4.25 ( <i>J</i> <sub>AB</sub> 12.0)	4.33	4.41, 4.17 ( <i>J</i> <sub>AB</sub> 12.0)	2.17, 2.08 2.07, 2.00
2α (galacto)	5.46 ( <i>J</i> <sub>1,2</sub> 3.8)	5.17 ( <i>J</i> <sub>2,3</sub> 10.8)	5.53- - - - - (- - - - - m - - -)	5.30 (- - - - -)	4.33 ( <i>J</i> <sub>4,5</sub> 6.8)	- - - - -	- - - 4.12 - - - (- - - <i>J</i> <sub>5,6</sub> 6.8 - -)	4.12	4.23, 4.13 ( <i>J</i> <sub>AB</sub> 11.8)	2.15, 2.08 2.06, 2.01
3α (manno)	5.10	5.55- - - - - (- - - - - m - - - - -)	- - - - -	5.25 (- - - - -)	4.35- - - - - (- - - - - m - - - - -)	- - - - -	- - - - -	3.95	4.21, 4.11 ( <i>J</i> <sub>AB</sub> 11.6)	2.12, 2.05 2.00, 1.95
4β (glucuro- rono)	4.91 ( <i>J</i> <sub>1,2</sub> 7.4)	5.40- - - - - (- - - - - m - - - - -)	- - - - -	5.10 (- - - - -)	4.08 ( <i>J</i> <sub>4,5</sub> 9.3)	3.77(-COOCH <sub>3</sub> )	- - - - -	- - - - -	4.44, 4.16 ( <i>J</i> <sub>AB</sub> 12.0)	2.06, 2.04 2.04
5β (xylo)	4.86 ( <i>J</i> <sub>1,2</sub> 6.1)	5.03 ( <i>J</i> <sub>2,3</sub> 7.9)	5.17 ( <i>J</i> <sub>3,4</sub> 7.9)	4.94 ( <i>J</i> <sub>4,5<sub>eq</sub></sub> 4.8)	3.45 ( <i>J</i> <sub>4,5<sub>ax</sub></sub> 7.9)	4.20 ( <i>J</i> <sub>ax,eq</sub> 12.1)	- - - - -	- - - - -	4.34, 4.11 ( <i>J</i> <sub>AB</sub> 11.8)	2.07, 2.06 2.05
5α (xylo)	5.37 ( <i>J</i> <sub>1,2</sub> 3.6)	4.83 ( <i>J</i> <sub>2,3</sub> 10.0)	5.56 ( <i>J</i> <sub>3,4</sub> 10.0)	5.00 ( <i>J</i> <sub>4,5<sub>eq</sub></sub> 6.4)	3.71 ( <i>J</i> <sub>4,5<sub>ax</sub></sub> 10.8)	3.86 ( <i>J</i> <sub>ax,eq</sub> 10.8)	- - - - -	- - - - -	4.25, 4.10 ( <i>J</i> <sub>AB</sub> 11.8)	2.07, 2.05 2.04
6α (fuco)	5.42 ( <i>J</i> <sub>1,2</sub> 3.4)	5.14 ( <i>J</i> <sub>2,3</sub> 10.3)	5.50- - - - - (- - - - - m - - -)	5.35 (- - - - -)	4.25 (m)	- - - - -	1.18 ( <i>J</i> <sub>5,6</sub> 6.5)	- - - - -	4.27, 4.14 ( <i>J</i> <sub>AB</sub> 11.7)	2.19, 2.09 2.02

<sup>a</sup> δ ppm, ca. 0.03 M in CDCl<sub>3</sub>, internal TMS. <sup>b</sup> Observed spacing only; Hz; m = multiplet.

Since the report <sup>1</sup> on tin(IV) chloride-induced formation of methyl and phenyl glucosides directly from pentaacetyl-β-D-glucopyranose, several papers have appeared on the use of this Lewis acid <sup>2-5</sup> (as well as iron(III) chloride <sup>6</sup> and *p*-toluenesulfonic acid <sup>7</sup>) for glycoside formation. Boron trifluoride etherate, however, has been utilized in but a few cases. Thus, with trimethyl orthoformate, containing a small amount of methanol, methyl glycosides were obtained in moderate yields directly from the unprotected sugar.<sup>8</sup> A similar report<sup>9</sup> has appeared on the use of allyl alcohol (as solvent and reagent) for the formation of allyl glycosides. Recently, BF<sub>3</sub>-etherate was used in the preparation of a variety of thioglycosides.<sup>10</sup>

We now report our own work on glycoside formation using BF<sub>3</sub>-etherate in the condensation of per-*O*-acetylated pyranosides with 2,2,2-trichloroethanol. This Lewis acid has the advantage of not giving rise to acetohalogeno sugars (as is the case with tin(IV) chloride<sup>1</sup>). Lemieux *et al.*<sup>11</sup> showed a few years ago that 2,2,2-trichloroethanol can be used for protection of the anomeric centre against

standard reaction conditions in carbohydrate chemistry. The aglycon can then be selectively removed (*e.g.* by zinc in acetic acid) in the presence of standard protecting groups. However, no experimental details were given for the synthesis of these compounds.

Our preferred method consists in stirring the appropriate sugar acetate with 2,2,2-trichloroethanol in dichloromethane in the presence of BF<sub>3</sub>-etherate. By using trichloroethanol as solvent, the yield of glycoside could be increased in some cases, but it is more costly than dichloromethane, and harder to remove during work-up.

Stereoselectivity for formation of 1,2-*trans* glycosides was generally high, and could be increased by lowering the temperature of the reaction. The fucose derivative, however, consistently gave a mixture of 1,2-*cis* and -*trans* glycosides (Table 1).

Treatment of pure 2,2,2-trichloroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside with BF<sub>3</sub>-etherate in dichloromethane for 2 h at room temperature did not lead to any anomerization unless a trace of the trichloroethanol was present.

Pure 1,2-*trans* acetates reacted more quickly and

Table 3. <sup>13</sup>C NMR chemical shifts and C–H coupling constants for per-*O*-acetylated 2,2,2-trichloroethyl glycopyranosides.

Compound	Chemical shift <sup>a</sup> (coupling constant <sup>b</sup> )									
	C1	C2	C3	C4	C5	C6	C7	C8	CH <sub>3</sub>	CO
1β (gluco)	101.3 (165)	70.8* (154)	72.1* (150)	68.1* (153)	72.2* (150)	61.6 (152)	80.4 (153)	96.1	20.6, 20.7 (130)	170.6, 170.2 169.3, 169.2
1α (gluco)	96.5 (176)	68.3* (148)	70.5* (148)	68.3* (148)	69.7* (148)	61.6 (148)	79.6 (155)	95.9	20.6 (131)	170.4, 170.2, 169.9, 169.4
2β (galacto)	101.9 (170)	68.4* (170)	70.4* (170)	66.9* (170)	71.1* (170)	61.2	80.4 (156)	96.2	20.6 (131)	170.0 169.3
2α (galacto)	97.0 (175)	67.7* (154)	67.3* (150)	67.2* (150)	67.7* (154)	61.6 (150)	79.5 (154)	96.0	20.7 (130)	170.6, 170.3, 170.1, 170.0
3α (manno)	98.1 (175)	68.7* (144)	69.1* (144)	66.0* (143)	69.6* (144)	62.3 (148)	79.4 (153)	95.6	20.7 (130.6)	170.4, 169.6
4β (glucurono)	101.2 (165)	72.6* (148)	71.5* (152)	70.6* (154)	69.2* (157)	166.8	80.5 (153)	96.0	20.6, 20.4 (130) (130) 53.0 (148)	170.0 169.3
5β (xylo)	100.6 (165)	70.2* (165)	69.7* (165)	68.4* (165)	61.8* (151)		80.0 (152)	96.1	20.7 (130)	169.7 169.1
5α (xylo)	96.7 (178)	70.7* (178)	69.2* (178)	69.2* (178)	59.1 (155)		79.5 (152)	96.2	20.6 (129)	170.2 169.8
6α (fuco)	97.0 (173)	67.8* (151)	67.8* (151)	65.4* (144)	70.8* (151)	15.9 (128)	79.6 (152)	96.3	20.7 (131)	170.5, 169.9

<sup>a</sup> δ ppm, CDCl<sub>3</sub>, TMS. <sup>b</sup> Hz. \* Assignment may be interchanged.

cleanly than the corresponding *cis*-isomers to give higher yields. This calls for efficient methods for preparing the former.

With special reference to the glycosidation reaction described here, we also report a simple technique for *selective* visualization (on TLC) of some generally used carbohydrate acetates. This procedure is especially valuable in cases where the developed spots are partly overlapping.

After development of the TLC-plate (SiO<sub>2</sub>), it is dried and heated (without spraying) at 160 °C for 10 min. This results in brown spots for certain categories of compounds. Thus, compounds capable of rapid 1,2-acetoxonium ion formation (*e.g.* carbohydrate per-*O*-acetates, 1,2-*O*-orthoester acetates, thio-orthoester acetates,<sup>12,13</sup> thioglycoside acetates) all gave strong, brown spots after heating. Per-*O*-acetylated *O*-glycosides and 1,2-acetals did not develop any colour. After heating, the visualized spots were recorded and the TLC-plate could then be sprayed with, *e.g.*, sulfuric acid for visualization of the rest of the material.

## EXPERIMENTAL

Melting points are uncorrected. NMR spectra were run in CDCl<sub>3</sub> (Me<sub>4</sub>Si) on a Varian XL 200 instrument.

*General procedure for the preparation of per-O-acetylated 2,2,2-trichloroethyl glycosides. Method A.* The appropriate per-*O*-acetylated sugar (10 mmol) was dissolved in dichloromethane (20 ml) and cooled (when appropriate). 2,2,2-Trichloroethanol (12 mmol) was added, followed by boron trifluoride etherate (50 mmol; drop-wise). The reaction mixture was stirred until the reaction was complete (TLC; usually 4–6 h) and then poured into ice water. The aqueous phase was extracted with methylene chloride and the organic extracts were washed with saturated sodium hydrogen carbonate solution and water. Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation gave a syrupy residue which was triturated with ether–light petroleum to give a pure, crystalline anomer (except for compound 2 which crystallized as a mixture of anomers in the reaction run at 25 °C).

*Method B.* The appropriate per-*O*-acetylated sugar (10 mmol) was dissolved in 2,2,2-tri-

chloroethanol (15 ml) and cooled in an ice bath. Boron trifluoride etherate (12 mmol) was added and the reaction was followed by TLC and worked-up as described above.

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