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Note

# Benzylation of aldonolactones with benzyl trichloroacetimidate

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**Abstract**

A number of aldono-1,4-lactones have been converted to their perbenzylated derivatives by treatment with benzyl trichloroacetimidate. 2,3,6-Trideoxy-D-*erythro*-hexono-1,4-lactone could be benzylated in dichloromethane, but lactones containing two or more hydroxy-groups were insoluble and could therefore not be benzylated in this solvent. It has now been found that the benzylation can be performed in dioxane and, using this solvent, a number of perbenzylated lactones, including tetra-*O*-benzyl-D-galactono-1,4-lactone, were prepared in good yields. © 1997 Elsevier Science Ltd.

*Keywords:* Benzylated aldonolactones; Benzyl trichloroacetimidate

The benzyl group has been used extensively as a protecting group in carbohydrate chemistry [1]. Perbenzylated sugars have mostly been prepared by benzylation of glycosides with benzyl chloride or bromide in the presence of a strong base such as potassium hydroxide [2] or sodium hydride [3]. The resulting perbenzylated glycosides may be hydrolyzed with aqueous acid as described for the preparation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [2] or 2,3,5-tri-*O*-benzyl-D-arabinofuranose [4]. Aldonolactones cannot be benzylated in the presence of strong base since this would lead to isomerization and elimination reactions. Therefore, perbenzylated aldonolactones have been prepared by oxidation of benzylated hexoses or pentoses [4–6].

Benzyl trichloroacetamidate, readily obtained from trichloroacetonitrile and benzyl alcohol, has been used to prepare benzylated carbohydrate derivatives. The reaction is carried out under slightly acidic conditions in a nonpolar solvent such as tetra- or di-chloromethane and cyclohexane. Under these conditions, a number of monosaccharide derivatives having one or two hydroxy groups were benzylated in good yield [7], but compounds with more hydroxy groups did not react because they were not sufficiently soluble in the apolar solvents used. Using this procedure, 2,3,6-trideoxy-D-*erythro*-hexono-1,4-lactone **1a** has now been converted into the 5-*O*-benzyl derivative **1b** in good yield. Benzylation of 2-deoxy-D-*erythro*-pentono-1,4-lactone **2a** with benzyl trichloroacetimidate in dichloromethane gave only a low yield of the dibenzylated lactone **2b**. However, when dioxane was used as the solvent, **2b** was obtained in 74% yield. Similarly, 2,6-dideoxy-D-*arabino*-hexono-1,4-lactone (**3a**) was converted into the dibenzylated lactone (**3b**) in 69% yield. 3-Deoxy-D-*arabino*-hexono-1,4-lactone (**4a**), L-arabinono-1,4-lactone (**5a**), and D-ribono-1,4-lactone (**6a**), having three hydroxy groups, were also

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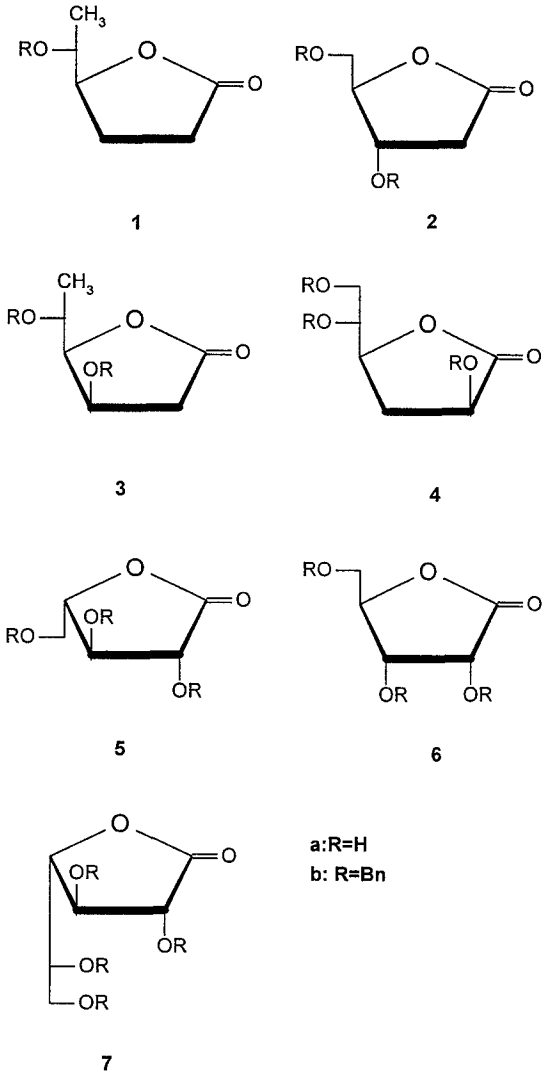
benzylated in dioxane and gave the corresponding benzylated lactones in 60–70% yields. Finally, D-galactono-1,4-lactone (**7a**) was converted into the fully benzylated derivative **7b** in 70% yield.




In order to achieve complete benzylation of the lactones, it was necessary to use 2–2.5 equiv of benzyl trichloroacetamide per hydroxy-group. After hydrolysis of the reaction mixture, large amounts of trichloroacetamide and other products were present [7]. Most of the trichloroacetamide could be removed by crystallization [8]. However, to obtain reasonably pure perbenzylated lactones it was usually necessary to carry out two chromatographic purifications. A third purification may be required to obtain an analytical sample. The crude benzylated 3-deoxy-lactone **4b** was boiled with aqueous sodium hydroxide in order to hydrolyze the trichloroacetamide. After this treatment, one chromatographic purification gave the pure product. This procedure can only be used with 3-deoxy or 2,3-deoxylactones; other lactones will undergo elimination or rearrangement on heating with strong bace.

## 1. Experimental

*General methods.*—Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. NMR spectra were recorded on Bruker AC-250 or AM-500 instruments using tetramethylsilane as internal reference. Microanalyses were performed by Leo Microanalytical Laboratory.

*5-O-Benzyl-2,3,6-trideoxy*-D-erythro-*hexono-1,4-lactone* (**1b**).—To a soln of 2,3,6-trideoxy-D-*erythro*-1,4-lactone [9] **1a** (3.30 g, 25.4 mmol), in a mixture of $CH_2Cl_2$ (15 mL) and cyclohexane (30 mL), was added benzyl trichloroacetimidate [7,10] (12.8 g, 53.8 mmol) and trifluoromethane-sulfonic acid ( ~ 0.1 mL, enough acid should be added to render the mixture acidic (pH $\cong$ 3) to wet indicator paper). The soln was kept overnight and then filtered. The filtrate was washed with aq $NaHCO_3$ and concd. The residue was boiled with 1 M NaOH (30 mL) for 0.5 h. The mixture was acidified with concd HCl and extracted with $CH_2Cl_2$ (3 × 25 mL), the extract was washed with water, dried and concd. The residue (7.9 g) was purified by column chromatography using diethylether–pentane (1:4) as eluant to give 4.0 g (72%) of **1b** as a syrup; $[\alpha]_D^{20}$ −23.3° (*c* 2.5, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.25–7.36 (m, 5 H, Ph), 4.69–4.49 (dd, 2 H, Ph$CH_2$), 4.39 (ddd, 1 H, $J_{4,5}$ 4.0 Hz, H-4), 3.78 (dq, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 2.55 (ddd, 1 H, $J_{2,2'}$ 17.0, $J_{2,3}$ 7.0 Hz, H-2), 2.42 (ddd, 1 H, $J_{2',3}$ 10.0, $J_{2',3'}$ 7.0 Hz, H-2'), 2.20 (m, 2 H, $J_{3,4}$ 6.0, $J_{3',4}$ 8.0 Hz, H-3, H-3'), 1.19 (d, 3 H, H-6); $^{13}C$ NMR: δ 177.5 (C-1), 138.0–126.4 (Ph), 82.3 (C-4), 75.0 (Ph$CH_2$), 71.2 (C-5), 27.9, 21.5 (C-2,3), 15.1 (C-6). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.54, H, 7.27.

*3,5-Di-O-benzyl-2-deoxy*-D-erythro-*pentono-1,4-lactone* (**2b**).—A soln of 2-deoxy-D-*erythro*-pentono-1,4-lactone **2a** [11] (1.83 g, 13.9 mmol) in dioxane (40 mL) was treated with benzyl trichloroacetimidate (14.7 g, 61 mmol) and trifluoromethanesulfonic acid (0.1 mL) as described above. The soln was then concd and the residue, in water (30 mL), was extracted with $CH_2Cl_2$ (3 × 30 mL). The extract was washed with water and concd. The residue was dissolved in $CH_2Cl_2$ (5 mL) and pentane (5 mL), and

the soln was kept at 0 °C to crystallize the trichloroacetamide. Filtration and concd of the filtrate gave a residue (9.8 g) which was chromatographed with $Et_2O$–pentane (1:3) as eluant. This gave 3.2 g (74%) of **2b**, sufficiently pure for further use. A sample was rechromatographed to give **2b** as a syrup; $[\alpha]_D^{20}$ +31.0° (*c* 2, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.46–7.32 (Ph), 4.70 (ddd, 1 H, $J_{4,5}$ 3.0, $J_{4,5'}$ 3.5 Hz, H-4), 4.64–4.55 (2 × d, 4 H, 2 $OCH_2$), 4.36 (dt, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 3.70 (dd, 1 H, $J_{5,5'}$ 11.0 Hz, H-5), 3.35 (dd, 1 H, H-5'), 2.93 (dd, 1 H, $J_{2,3}$ 7.0, $J_{2,2'}$ 18.0 Hz, H-2), 2.65 (dd, 1 H, $J_{2',3}$ 2.0 Hz, H-2'); $^{13}C$ NMR: δ 175.5 (C-1), 138.0–127.4 (Ph), 83.8 (C-4), 75.0 (C-3), 73.4, 70.9 (Ph*CH*$_2$), 69.3 (C-5), 35.5 (C-2). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.21; H, 6.59.

*3,5-Di-*O*-benzyl-2,6-dideoxy-*D-arabino-*hexono-1,4-lactone* (**3b**).—2,6-Dideoxy-D-*arabino*-hexono-1,4-lactone **3a** [12] (1.30 g, 8.9 mmol) in dioxane (30 mL) was treated with benzyl trichloroacetimidate (10.9 g, 45.3 mmol) and trifluoromethanesulfonic acid (0.1 mL) as described above. After crystallization of trichloroacetamide, the product (7.7 g) was purified by chromatography (1:3 $Et_2O$–pentane) giving 1.95 g (69%) of **3b**. The product was crystallized from ether-pentane and repeated crystallization gave material with mp 72–74 °C; $[\alpha]_D^{20}$ −56.3° (*c* 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.5–7.3 (Ph), 4.61, 4.44 (2 dd, 4 H, 2 Ph*CH*$_2$), 4.40 (dt, 1 H, $J_{3,4}$ 4.0 Hz, H-3), 4.24 (dd, 1 H, $J_{4,5}$ 8.5 Hz, H-4), 4.41 (dq, 1 H, $J_{5,6}$ 6.0 Hz, H-5), 2.72 (dd, 1 H, $J_{2,2'}$ 17.5, $J_{2,3}$ 1.0 Hz, H-2), 2.62 (dd, 1 H, $J_{2',3}$ 5 Hz, H-2'), 1.39 (d, 3 H, H-6); $^{13}C$ NMR: δ 175.0 (C-1), 138.3–127.3 (Ph), 85.5 (C-4), 74.3 (C-3), 71.2 (Ph*CH*$_2$), 70.7 (C-5), 35.8 (C-2), 16.9 (C-6). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.75; H, 6.81.

*2,5,6-Tri-*O*-benzyl-3-deoxy-*D-arabino-*hexono-1,4-lactone* (**4b**).—3-Deoxy-D-*arabino*-hexono-1,4-lactone **4a** [13] (2.0 g, 12.3 mmol), in dioxane (40 mL), was treated with benzyl trichloroacetimidate (18.6 g, 75.4 mmol) as described above. The crude product was boiled with 1 M NaOH (30 mL) for 30 min. The mixture was then acidified and extracted with $CH_2Cl_2$; the extract was washed with water, dried and evaporated. The residue (12.8 g) consisted of **4b** and *N*-benzyl-trichloroacetamide. It was purified by chromatography (1:2 ether–pentane) to give 3.4 g (64%) of **4b** as a syrup; $[\alpha]_D^{20}$ −34.2° (*c* 2, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.4–7.2 (Ph), 4.92, 4.74, 4.69, 4.64, 4.54, 4.50 (bd, 6 H, 3 Ph*CH*$_2$), 4.52 (m, 1 H, $J_{4,5}$ 5.0 Hz, H-4), 4.27 (dd, 1 H, $J_{2,3}$ 8.5, $J_{2,3'}$ 9.5 Hz, H-2), 3.85 (q, 1 H, $J_{5,6} = J_{5,6'} = 5.0$ Hz, H-5), 3.58 (dd, 2 H, H-6,6'), 2.46 (m, 1 H, $J_{3,3'}$ 12.5, $J_{3,4}$ 5.5 Hz, H-3), 2.31 (dt, 1 H, $J_{3',4}$ 9.5 Hz, H-3'); $^{13}C$ NMR: δ 174.4 (C-1), 136.6–127.4 (Ph), 77.2 (C-4), 75.8 (C-2), 73.2, 73.1, 72.9, 71.8 (3 Ph*CH*$_2$, C-5), 68.3 (C-6), 30.1 (C-3). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.79, H, 6.46.

*2, 3, 5 - Tri -* O *- benzyl -* L *- arabinono - 1, 4 - lactone* (**5b**).—It was prepared, as described above, from L-arabinono-1,4-lactone **5a** [13] (3.5 g, 23.6 mmol) in dioxane (235 mL) by treatment with benzyl trichloroacetimidate (14.9 g, 59 mmol) and trifluoromethanesulfonic acid. After crystallization of trichloroacetamide, the product was purified by chromatography (1:10 → 1:5 ether–pentane). This gave 7.3 g (74%) of **5b** as a syrup, which was crystallized from ether-pentane; mp 65–67 °C; $[\alpha]_D^{20}$ −5.9° (*c* 1, $CHCl_3$); reported [4,14] for the D-enantiomer mp 67.5–68.5°; $[\alpha]_D$ +6.6°; $^1H$ and $^{13}C$ NMR spectra were identical with those reported for the D-enantiomer [14]. Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.37; H, 6.20.

*2,3,5-Tri-*O*-benzyl-*D*-ribono-1,4-lactone* (**6b**).—It was prepared as described above from 1.0 g of D-ribono-1,4-lactone (**6a**). Chromatography (1:3 diethylether–pentane) gave 2.0 g (70%) of **6b** as a syrup; $[\alpha]_D^{20}$ +65.1° (*c* 1.5, $CHCl_3$). The product crystallized when seeded with material prepared according to Ref. [14]. Recrystallization from EtOH gave a product with mp 54–55 °C, lit. 54–55 °C [14]; $[\alpha]_D$ +74.1° (*c* 2, $CHCl_3$), lit. +74.8° [14].

*2,3,5,6-Tetra-*O*-benzyl-*D*-galactono-1,4-lactone* (**7b**).—It was prepared as described above from D-galactono-1,4-lactone **7a** (1.56 g, 8.8 mmol) in dioxane (100 mL) by reaction with benzyl trichloroacetimidate (21.2 g, 88 mmol) and trifluoromethanesulfonic acid (~ 0.1 mL). Purification by chromatography (10:1 → 5:1 ether–pentane) gave 3.44 g (73%) of **6b** as a syrup; $[\alpha]_D^{20}$ −16.8° (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, benzene-$d_6$): δ 7.0–7.4 (m, 20 H, Ph), 5.11 and 4.82 (2 d, 2 H, Ph*CH*$_2$), 4.49 and 4.28 (2 d, 2 H, Ph*CH*$_2$), 4.48 and 4.27 (2 d, 2 H, PhCH$_2$), 4.29 (br s, 2 H, Ph*CH*$_2$), 4.46 (t, 1 H, $J_{3,4}$ 7.3 Hz, H-3), 4.33 (dd, 1 H, $J_{4,5}$ 3.0 Hz, H-4), 3.69 (ddd, 1 H, $J_{5,6}$ and $J_{5,6'}$ 5.5 and 6.5 Hz, H-5), 3.62 (2 H, H-6,6'); $^{13}C$ NMR: δ 171.9 (C-1), 138–128 (Ph), 79.7 (C-2), 79.1 (C-4), 78.5 (C-3), 75.3 (C-5), 73.4, 72.9, 72.3, 72.1 (Ph*CH*$_2$), 69.3 (C-6), Signals were assigned by means of DEPT, COSY, and CH-correlated spectra. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.36; H, 6.38.

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