

On the Reaction of 4,6-*O*-Benzylidene-2-deoxy pyranosides with Sodium Cyanoborohydride: Formation of 1,5-Anhydroalditols†

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Some methyl 4,6-*O*-benzylidene-2-deoxy pyranosides were submitted to the action of sodium cyanoborohydride in acidic medium. Regiospecific cleavage of the benzylidene ring was observed, giving the expected 6-*O*-benzyl derivative. Depending upon the substitution at C-2 reductive cleavage of the aglycone was observed as a side-reaction or as a main reaction. This could provide a new entry to 1,5-anhydroalditols branched at C-2.

In connection with a synthetic project, we were interested in the reductive cleavage of the 4,6-*O*-benzylidene protecting group¹ of a 2-deoxy-2-*C*-branched-chain sugar, which would give the corresponding 6-*O*-benzyl derivative and a free hydroxy group at C-4. As known from the literature, sodium cyanoborohydride and dry hydrochloric acid² could be used to solve this problem. Indeed, excellent results in the highly regioselective reductive cleavage of benzylidene acetals in good yields have been reported by several authors.³

We report here some results in the application of this reaction to several 2-deoxysugars, which lead to extensive formation of 1,5-anhydroalditols. Very recently Csuk *et al.*⁴ reported the synthesis and the structure of such a derivative obtained from the reaction of methyl 4,6-*O*-benzylidene- α -D-erythro-hex-2-enopyranoside with sodium cyanoborohydride-hydrochloric acid. Such aglycone cleavage also occurs on using other reducing reagents such as triethylsilane and trifluoroacetic acid or boron trifluoride⁵ as the catalyst. Zinc borohydride and chlorotrimethylsilane have been recently used for acetal cleavage.⁶

Results and Discussion

Our investigation began with the fully protected derivative (1) which was of interest in our planned synthesis. When treated with excess of sodium cyanoborohydride and dry hydrochloric acid as previously reported,³ two products were formed which were identified as (9) and (10). At that time such an over-reduction of 2-deoxysugar derivatives with sodium cyanoborohydride had never been reported. It was then concluded that the 2-deoxy structure of the substrate was responsible for the observed reaction; thus the 4,6-*O*-benzylidene ring opening of some 2-deoxy-2-*C*-alkylsugars has been examined. Such compounds are now readily available using our recently described methodology.⁷

The derivatives (1)–(8), some of them protected at C-3, were prepared and submitted to the action of 10 mol equiv. of sodium cyanoborohydride in dry tetrahydrofuran (THF) in the presence of 4 Å molecular sieves. A saturated solution of dry hydrochloric acid in diethyl ether was added dropwise until no starting material remained (t.l.c.). The results are summarized in the Table. All the substrates we studied gave regioselective benzylidene ring opening giving the 6-*O*-benzyl derivatives (Scheme 1). As seen from the Table (entries 5, 7, 8), compounds (5), (7), and (8) were exclusively transformed into 1,5-

anhydroalditols (15), (18), and (19) respectively, whereas compound (2) (entry 2) gave no 1,5-anhydroalditol but only compound (11). Other substrates gave mixtures of 1,5-anhydroalditols and methyl glycosides. It is noteworthy that this reaction is dependent upon the pH. Indeed, the use of a strong organic acid such as trifluoromethane sulphonic (triflic) acid instead of hydrochloric acid (entry 9) dramatically increases the formation of the 1,5-anhydroalditol (10).

Initially it was thought that formation of 1,5-anhydroalditol (C) proceeded through methyl glycoside reduction of (B) owing to the large excess of the reducing reagent used. Nevertheless the use of lesser amounts of sodium cyanoborohydride gave always a mixture of products (B) and (C) together with unchanged (A). Moreover when 1,5-anhydroalditols (C) were formed exclusively, no intermediate methyl glycoside (B) was detected by t.l.c., suggesting that the reduction of the aglycone is easier when the benzylidene ring is absent. This could be explained by the conformational bias of compounds (A), which impedes the formation of an oxocarbenium ion, a possible intermediate, subsequently reduced with sodium cyanoborohydride. The presence of electron-donating groups at C-2 will favour this process. Nevertheless the steric hindrance at C-2 on the α -face will reduce the accessibility of the aglycone oxygen toward protonation. Thus aglycone cleavage is observed mainly when (A) is unsubstituted or when the substituent is *trans* to the aglycone.

In summary, the reduction of 4,6-*O*-benzylidene acetals of 2-deoxy- and 2-deoxy-2-*C*-alkyl-sugars with sodium cyanoborohydride in the presence of hydrochloric acid proceeds well with complete regioselectivity, giving the corresponding 6-*O*-benzyl ether. Concomitant reduction of the aglycone is observed with unsubstituted or monosubstituted 2-*C*-alkyl derivatives. The use of triflic acid favours that reduction and could provide a new access to 1,5-anhydroalditols.

Experimental

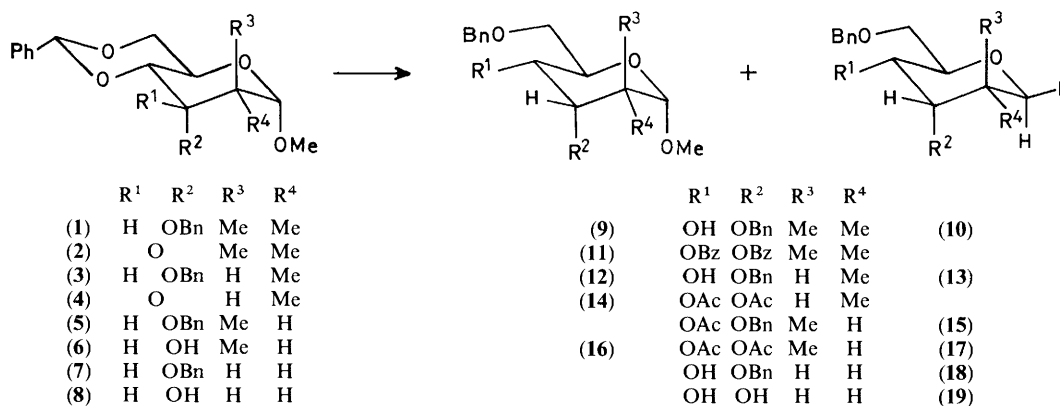
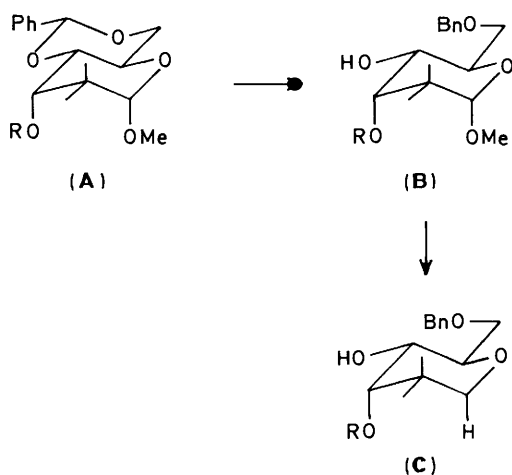
M.p.s were determined on a Kofler block and are uncorrected. Specific rotations were determined with a Perkin-Elmer 141 polarimeter, and i.r. spectra were recorded with a Perkin-Elmer 580B spectrometer. ¹H N.m.r. were recorded with a Bruker AM 400 spectrometer. Preparative chromatography was performed on silica gel Merck (60–230 mesh) with the solvent system ethyl acetate–hexane as specified (abbreviated A:H). Analytical t.l.c. was performed on precoated Merck plates and the plates were visualized under u.v. light and sprayed with 50% sulphuric acid in methanol and heated with an i.r. lamp. Solvents were removed under reduced pressure. Microanalyses were performed at the Service Central de Microanalyses du

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Table. Sodium cyanoborohydride reduction of some 4,6-*O*-benzylidene acetals

Entry	Substrate	Glycoside	Yield (%) ^c	1,5-Anhydroalditol	Yield (%) ^c	Ratio ^d
1	(1)	(9)	52	(10)	34	3:2
2	(2)	(11) ^a	87			<i>e</i>
3	(3)	(12)	7	(13)	50	1:9
4	(4)	(14) ^b	76			<i>e</i>
5	(5)			(15) ^b	75	<i>e</i>
6	(6)	(16) ^b	34	(17) ^b	18	3:2
7	(7)			(18)	62	<i>e</i>
8	(8)			(19)	51	<i>e</i>
9	(1) ^f			(10)	82	<i>e</i>

^a Isolated after benzylation. ^b Isolated after acetylation. ^c Isolated pure products. ^d Average of several runs, determined on pure isolated products. ^e Only one product was isolated. ^f Triflic acid (1 mol equiv.) used instead of hydrochloric acid.

**Scheme 1.** Reagents and conditions: NaBH₃CN, HCl in Et₂O-THF, 0 °C—room temperature**Scheme 2.**

CNRS, Vernaison (France). Starting compounds (1)—(4) were prepared according to ref. 7, compound (6) according to ref. 8, and compound (8) according to ref. 9. Benzylation was performed by standard literature procedures.

General Procedures.—*Reduction with sodium cyanoborohydride.* To a solution of the acetal (1 mmol) in dry THF (10 ml) were added sodium cyanoborohydride (630 mg, 10 mmol) and powdered 4Å molecular sieves (100 mg). To the vigorously

stirred suspension at 0 °C was then added dropwise a saturated ethereal solution of hydrogen chloride (*ca.* 0.5M solution obtained by extraction of 12M HCl with ether and drying over magnesium sulphate) until no starting material remained (t.l.c.) (*ca.* 20 ml were needed and were added within 1 h). In the case of entry 9, a solution of triflic acid (1 mmol) in ether (10 ml) was added. The mixture was then diluted with dichloromethane (100 ml) and filtered through a sintered glass filter. The filtrate was washed successively with 3% aqueous ammonia and water and dried (MgSO₄). Separation and/or purification by column chromatography gave the products. If derivatization were needed to improve separation, the crude mixture was treated as follows.

Acylation of the hydroxy groups. The above residue was dissolved in dry pyridine (10 ml) at 0 °C and a two-fold excess of acetic anhydride or benzoyl chloride was added. After being stirred at room temperature overnight, the mixture was evaporated and the crude residue was dissolved in dichloromethane (100 ml). The organic layer was washed successively with dil. hydrochloric acid, water, dil. aqueous sodium hydroxide, and water. After drying (MgSO₄) and evaporation of the solvent, the residue was purified by chromatography on a silica gel column. The following compounds were thus prepared.

Methyl 3,6-di-O-benzyl-2-deoxy-2,2-di-C-methyl-α-D-ribohexopyranoside (9): obtained as a gum (200 mg, 52%); *R*_F 0.27 (A:H, 1:2); [*α*]_D +68.8° (*c* 0.3 in CHCl₃) (Found: C, 71.3; H, 7.65. C₂₃H₃₀O₅ requires C, 71.48; H, 7.82%); δ 1.06 (3 H, s, Me), 1.12 (3 H, s, Me), 2.0 (1 H, m, OH), 3.35 (3 H, s, OMe), 3.45 (1 H, m, 3-H), 3.70–3.76 (2 H, m, 6-H₂), 3.86 (2 H, m, 4- and 5-H), 4.54 (1 H, d, *J* 11.5 Hz, CHHPh), 4.57 (1 H, d, *J* 11.5 Hz, CHHPh), 4.62 (1 H, d, *J* 11.5 Hz, CHHPh), 4.85 (1 H, d, *J* 11.5 Hz, CHHPh), and 7.32 (10 H, m, Ph).

1,5-Anhydro-3,6-di-O-benzyl-2-deoxy-2,2-di-C-methyl-D-ribo-hexitol (**10**): (121 mg, 34%) [entry 9, 290 mg (82%); R_F 0.34 (A:H, 1:2); $[\alpha]_D + 4.2^\circ$ (c 0.1 in CHCl_3) (Found: C, 73.85; H, 7.7. $\text{C}_{22}\text{H}_{28}\text{O}_4$ requires C, 74.13; H, 7.92%); δ 0.99 (3 H, s, Me), 1.07 (3 H, s, Me), 2.10 (1 H, OH), 3.27 (1 H, dd, $J_{1,3}$ 1, $J_{1,1'}$ 10 Hz, 1-H), 3.42 (1 H, dd, $J_{3,4}$ 3.5 Hz, 3-H), 3.53 (1 H, ddd, $J_{5,6}$ 2.5, $J_{5,6'}$ 6 Hz, 5-H), 3.58 (1 H, d, 1-H), 3.62 (1 H, dd, $J_{6,6'}$ 10 Hz, 6-H), 3.75 (1 H, dd, 6'-H), 3.76 (1 H, dd, $J_{4,5}$ 9.5 Hz, 4-H), 4.60 (1 H, dd, J 11.5 Hz, *CHHPh*), 4.65 (1 H, d, *CHHPh*), 4.75 (1 H, d, J 11.5 Hz, *CHHPh*), 4.78 (1 H, d, *CHHPh*), and 7.2–7.3 (10 H, m, Ph).

Methyl 3,4-di-O-benzoyl-6-O-benzyl-2,2-di-C-methyl-2-deoxy- α -D-ribo-hexopyranoside (**11**): (438 mg, 87%); R_F 0.48 (A:H, 1:4); $[\alpha]_D + 11.7^\circ$ (c 0.5 in CHCl_3) (Found: C, 71.2; H, 6.5. $\text{C}_{30}\text{H}_{32}\text{O}_7$ requires C, 71.41; H, 6.39%); δ 1.04 (3 H, s, Me), 1.33 (3 H, s, Me), 3.52 (3 H, s, OMe), 3.64 (2 H, m, 6-H₂), 4.40 (1 H, s, 1-H), 4.44 (1 H, m, $J_{4,5}$ 10, $J_{5,6} = J_{5,6'} = 3.5$ Hz, 5-H), 4.47 (1 H, d, $J = 12$ Hz, *CHHPh*), 4.62 (1 H, d, *CHHPh*), 5.50 (1 H, d, $J_{3,4}$ 3 Hz, 3-H), 5.58 (1 H, dd, 4-H), and 7.3–8.0 (15 H, m, Ph).

Methyl 3,6-di-O-benzyl-2-deoxy-2-C-methyl- α -D-allopyranoside (**12**): (26 mg, 7%); R_F 0.43 (A:H, 2:3); $[\alpha]_D + 64.7^\circ$ (c 0.2 in CHCl_3) (Found: C, 71.3; H, 7.5. $\text{C}_{22}\text{H}_{28}\text{O}_5$ requires C, 70.95; H, 7.58%); δ 1.09 (3 H, d, J 7 Hz, Me), 1.6 (1 H, m, OH), 1.99 (1 H, m, $J_{1,2}$ 4, $J_{2,3}$ 3.5 Hz, 2-H), 3.38 (3 H, s, OMe), 3.65 (1 H, m, 4-H), 3.72 (2 H, m, 6-H₂), 3.75 (1 H, t, $J_{3,4}$ 3.5 Hz, 3-H), 3.89 (1 H, m, 5-H), 4.51 (1 H, d, 1-H), 4.60 (3 H, m, CH_2Ph), 4.85 (1 H, d, J 12 Hz, *CHHPh*), and 7.37 (10 H, m, Ph).

1,5-Anhydro-3,6-di-O-benzyl-2-deoxy-2-C-methyl-D-alloitol (**13**): (170 mg, 50%); m.p. 104–106 °C; R_F 0.48 (A:H, 2:3); $[\alpha]_D + 32^\circ$ (c 0.3 in CHCl_3) (Found: C, 73.6; H, 7.7. $\text{C}_{21}\text{H}_{26}\text{O}_4$ requires C, 73.66; H, 7.61%); δ 0.96 (3 H, d, J 7 Hz, Me), 1.80 (1 H, m, OH), 1.97 (1 H, m, $J_{1,2}$ 9 Hz, 2-H), 3.47 (1 H, dd, $J_{1,1'}$ 13 Hz, 1-H), 3.6–3.7 (5 H, m, 1', 4-, and 5-H and 6-H₂), 3.77 (1 H, t, $J_{2,3} = J_{3,4} = 3$ Hz, 3-H), 4.57 (2 H, s, CH_2Ph), 4.67 (1 H, d, J 11.5 Hz, *CHHPh*), 4.77 (1 H, d, *CHHPh*), and 7.35 (10 H, m, Ph).

Methyl 3,4-di-O-acetyl-6-O-benzyl-2-deoxy-2-C-methyl- α -D-allopyranoside (**14**): (278 mg, 76%); R_F 0.53 (A:H, 2:3); $[\alpha]_D + 147.0^\circ$ (c 0.6 in CHCl_3) (Found: C, 62.0; H, 7.2. $\text{C}_{19}\text{H}_{26}\text{O}_7$ requires C, 62.28; H, 7.15%); δ 0.91 (3 H, dd, J 7 Hz, Me), 1.84 (3 H, s, OAc), 2.09 (3 H, s, OAc), 2.15 (1 H, m, 2-H), 3.53 (1 H, dd, $J_{5,6}$ 4, $J_{6,6'}$ 10.5 Hz, 6-H), 3.58 (1 H, dd, $J_{5,6'}$ 2 Hz, 6'-H), 4.11 (1 H, m, 5-H), 4.43 (1 H, d, J 12 Hz, *CHHPh*), 4.56 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), 4.68 (1 H, d, *CHHPh*), 5.01 (1 H, dd, $J_{3,4}$ 3, $J_{4,5}$ 10 Hz, 4-H), 5.37 (1 H, t, $J_{2,3}$ 3 Hz, 3-H), and 7.3 (5 H, m, Ph).

4-O-Acetyl-1,5-anhydro-3,6-di-O-benzyl-2-deoxy-2-C-methyl-D-altritol (**15**): (288 mg, 75%); R_F 0.42 (A:H, 1:4); $[\alpha]_D + 60.1^\circ$ (c 0.3 in CHCl_3) (Found: C, 71.8; H, 7.15. $\text{C}_{23}\text{H}_{28}\text{O}_5$ requires C, 71.85; H, 7.34%); δ 1.12 (3 H, d, J 7 Hz, Me), 1.93 (3 H, s, OAc), 2.05 (1 H, m, 2-H), 3.50 (1 H, m, 1-H), 3.55 (2 H, m, 6-H₂), 3.70 (1 H, t, $J_{2,3}$ 4, $J_{3,4}$ 3 Hz, 3-H), 3.95 (1 H, dd, $J_{1,1'}$ 11, $J_{1,2}$ 3 Hz, 1'-H), 4.01 (1 H, m, 5-H), 4.49 (1 H, d, J 11.5 Hz, *CHHPh*), 4.54 (2 H, s, CH_2Ph), 4.60 (1 H, d, *CHHPh*), 5.10 (1 H, dd, $J_{4,5}$ 8.5 Hz, 4-H), and 7.35 (10 H, m, Ph).

Methyl 3,4-di-O-acetyl-6-O-benzyl-2-deoxy-2-C-methyl- α -D-allopyranoside (**16**): (124 mg, 34%); R_F 0.31 (A:H, 1:4); $[\alpha]_D + 174.5^\circ$ (c 0.4 in CHCl_3) (Found: C, 61.9; H, 7.25. $\text{C}_{19}\text{H}_{26}\text{O}_7$

requires C, 62.28; H, 7.15%); δ 1.12 (3 H, d, J 7 Hz, Me), 1.93 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.17 (1 H, m, 2-H), 3.38 (3 H, s, OMe), 3.59 (2 H, m, 6-H₂), 4.2 (1 H, ddd, $J_{4,5}$ 8.5, $J_{5,6} = J_{5,6'} = 4$ Hz, 5-H), 4.47 (1 H, d, $J_{1,2}$ 2 Hz, 1-H), 4.50 (1 H, d, J 12 Hz, *CHHPh*), 4.64 (1 H, d, J 12 Hz, *CHHPh*), 5.08 (1 H, dd, $J_{3,4}$ 3.5, $J_{2,3}$ 5 Hz, 3-H), 5.18 (1 H, dd, 4-H), and 7.25 (5 H, m, Ph).

3,4-Di-O-acetyl-1,5-anhydro-6-O-benzyl-2-deoxy-2-C-methyl-D-altritol (**17**): (60 mg, 18%); R_F 0.4 (A:H, 1:4); $[\alpha]_D + 23.4^\circ$ (c 0.7 in CHCl_3) (Found: C, 64.3; H, 7.3. $\text{C}_{18}\text{H}_{24}\text{O}_6$ requires C, 64.27; H, 7.19%); δ 1.17 (3 H, d, J 7 Hz, Me), 1.91 (3 H, s, OAc), 1.92 (1 H, m, 2-H), 2.09 (3 H, s, OAc), 3.53 (2 H, m, 6-H₂), 3.6 (1 H, dd, $J_{1,2}$ 2, $J_{1,1'}$ 11 Hz, 1-H), 3.9 (1 H, dd, $J_{1,2}$ 3 Hz, 1'-H), 4.48 (1 H, d, J 12 Hz, *CHHPh*), 4.62 (1 H, d, *CHHPh*), 5.1 (1 H, dd, $J_{3,4}$ 3, $J_{4,5}$ 9 Hz, 4-H), 5.19 (1 H, dd, $J_{2,3}$ 3 Hz, 3-H), and 7.2 (5 H, m, Ph).

1,5-Anhydro-3,6-di-O-benzyl-2-deoxy-D-ribo-hexitol (**18**): (121 mg, 51%); R_F 0.44 (A); $[\alpha]_D + 71.1^\circ$ (c 0.3 in CHCl_3) (Found: C, 72.85; H, 7.4. $\text{C}_{20}\text{H}_{24}\text{O}_4$ requires C, 73.15; H, 7.37%); δ 1.75 (1 H, dddd, $J_{2,2'}$ 15, $J_{2,3}$ 2, $J_{1,2}$ 6.5, $J_{1,2}$ 10 Hz, 2-H), 1.99 (1 H, dddd, $J_{2,3} = J_{2,1'}$ = 1.5, $J_{1,2}$ 4 Hz, 2'-H), 2.50 (1 H, d, J 10 Hz, OH), 3.54 (1 H, ddd, $J_{5,6}$ 3, $J_{4,5} = J_{5,6'} = 10$ Hz, 5-H), 3.60–3.80 (5 H, m, 1-H₂, 4-H, and 6-H₂), 3.92 (1 H, m, 3-H), 4.47 (1 H, d, J 11.5 Hz, *CHHPh*), 4.58 (2 H, s, CH_2Ph), 4.69 (1 H, d, *CHHPh*), and 7.33 (10 H, m, Ph).

1,5-Anhydro-6-O-benzyl-2-deoxy-D-ribo-hexitol (**19**): (203 mg, 62%); R_F 0.45 (A:H, 2:3); $[\alpha]_D + 8.7^\circ$ (c 0.5 in CHCl_3) (Found: C, 65.45; H, 7.8. $\text{C}_{13}\text{H}_{18}\text{O}_4$ requires C, 65.53; H, 7.61%); δ 1.84 (2 H, m, 2-H₂), 3.45 (2 H, m, OH), 3.50–3.80 (6 H, m, 1-H₂, 4- and 5-H, and 6-H₂), 4.09 (1 H, m, 3-H), 4.55 (1 H, d, J 11.5 Hz, *CHHPh*), 4.60 (1 H, d, *CHHPh*), and 7.35 (10 H, m, Ph).

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