Carbohydrate Research, 108 (1982) 97–101
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

A NOVEL, REDUCTIVE RING-OPENING OF CARBOHYDRATE BENZYLIDENE ACETALS*

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(Received February 1st, 1982; accepted for publication, March 1st, 1982)

ABSTRACT

Further examples are given of a facile, highly regioselective, reductive opening of benzylidene acetals of hexopyranosides using sodium cyanoborohydride–hydrogen chloride. For 4,6-benzylidene acetals, the benzyl group in the product is at O-6 and HO-4 is free. For dioxolane benzylidene acetals, the direction of reductive opening of the five-membered ring depends on the stereochemistry at the asymmetric, benzylidene acetal carbon.

INTRODUCTION

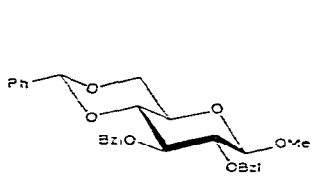
The reductive opening of benzylidene acetals using lithium aluminium hydride–aluminium chloride has been described[1–3]. For 4,6-benzylidene acetals carrying such bulky substituents as benzyl groups at O-3, the regioselectivity of the opening of the dioxane ring usually is such that the benzyl group in the product is situated at O-4 and HO-6 is unsubstituted[3]. For dioxolanes, the direction of the reductive opening depends on the steric disposition of the phenyl group (*exo* or *endo*) on the chiral, benzylidene acetal carbon.

Horne and Jordan have reported on the reduction of acetals with sodium cyanoborohydride–hydrogen chloride (gas)–methanol, to give methyl ethers[4]. Our preliminary experiments[5] applying this reaction in an inert solvent to 4,6-benzylidene acetals of hexopyranosides produced benzyl ethers with a stereoselectivity opposite to that generally observed for the lithium aluminium hydride–aluminium chloride reagent, in that the products had the benzyl group at O-6 and HO-4 was free. Furthermore, the reaction was compatible with the presence of benzoyl and acetamido groups in the hexopyranoside starting-materials[5]. We now report further examples of sodium cyanoborohydride–hydrogen chloride reductions of benzylidene derivatives of hexopyranosides, including the opening of dioxolane rings.

*Part II. For Part I, see ref. 5.

RESULTS AND DISCUSSION

Reduction of compounds **1**, **3**, **5**, **7**, **8**, and **11** yielded the products **2**, **4**, **6**, **9**, **10**, and **12**, respectively, in the yields indicated below the formulae. The regioselectivity of the reductions of **1**, **3**, and **5** is the same as that previously reported[5], in that the benzyl group produced is at O-6 in **2**, **4**, and **6**, while HO-4 is unsubstituted.



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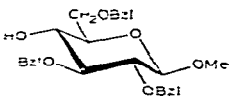

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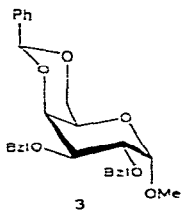

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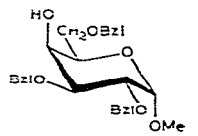
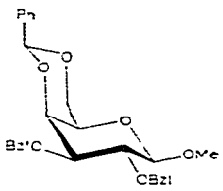


4 (93%)



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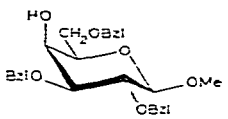
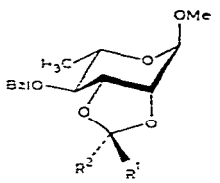
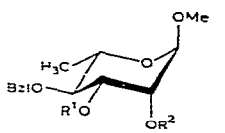


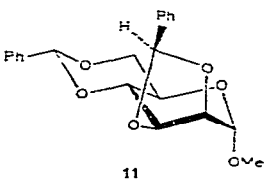
6 (81%)



7 R^1 = Ph, R^2 = H
8 R^1 = H, R^2 = Ph



9 R^1 = Bzl, R^2 = H (95%)
10 R^1 = H, R^2 = Bzl (88%)



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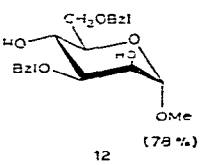
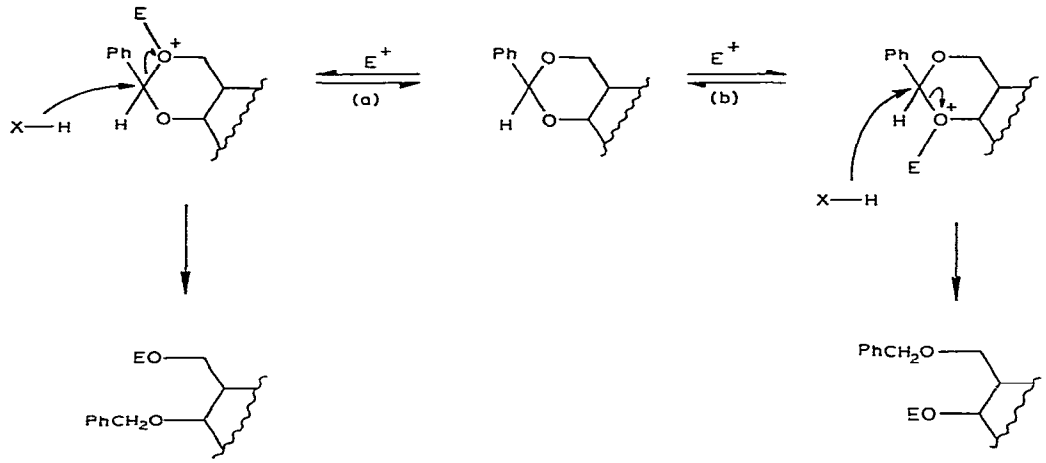


12 (78%)

A possible mechanism for the reductive opening of a benzylidene dioxane ring containing one primary and two secondary carbon atoms with a hydride and an acid may be formulated as follows.

The greater steric demand of a Lewis acid, as compared to a proton, may direct the reductive opening using the lithium aluminium hydride–aluminium chloride to take path (a), particularly if the O-4 substituent is bulky. In sodium cyanoborohydride–hydrogen chloride reductions, however, the steric requirement of the electrophile is much smaller and, presumably, the direction of the equilibrium is governed chiefly by the relative acidities of O-4 and O-6, giving preponderance of path (b).

The difference between the regioselectivities in the opening of 4,6-benzylidene acetals using the two methods therefore may be explained by steric factors. For the



opening of benzylidene dioxolane rings, there is no such obvious difference for the two reagents. Indeed, the stereoselectivity observed in the present work for the opening of the dioxolane rings in compounds **7**, **8**, and **11** is the same as that previously observed for the lithium aluminium hydride–aluminium chloride reagent.

The yields obtained in the sodium cyanoborohydride–hydrogen chloride reductions of benzylidene acetals are generally high. The compatibility with the presence of benzoyl and acetamido groups[5], the high regioselectivity, and the easy handling of the reagents involved should make this reaction generally useful in protective-group strategies in synthetic carbohydrate chemistry.

EXPERIMENTAL

General methods. — General methods were the same as those previously reported[7].

General procedure. — *Methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside* (**2**). Hydrogen chloride in diethyl ether was added at room temperature to methyl 2,3-di-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranoside[8] (**1**, 1.00 g) and sodium cyanoborohydride (1.70 g) in tetrahydrofuran (distilled from lithium aluminium hydride, 30 mL) containing 3 Å molecular sieves until the evolution of gas ceased. T.l.c. [light petroleum (b.p. 40–60°)–ethyl acetate, 5:1] after 5 min indicated complete reaction. The mixture was diluted with dichloromethane (50 mL) and water, filtered, and extracted with water and then with saturated, aqueous sodium hydrogencarbonate. The organic layer was dried (Na_2SO_4) and concentrated. The resulting syrup was applied to a column of silica gel which was eluted with light petroleum (b.p. 40–60°)–ethyl acetate (2:1), to yield the title compound (0.87 g, 87%), m.p. 64–65°, $[\alpha]_D^{22}$ −17° (*c* 1, chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$, internal tetramethylsilane): δ 57.1, 70.0, 71.3, 73.6, 74.1, 74.6, 75.1, 81.7, 83.9, 104.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.35, 128.4, 137.8, 138.4, and 138.5.

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.4; H, 6.94. Found: C, 72.3; H, 6.92.

A minor component was also isolated: methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (0.09 g, 9%), m.p. 89–90°, $[\alpha]_D^{22}$ +13° (*c* 1, chloroform); lit.[9] m.p. 90–91°, $[\alpha]_D$ +10° (chloroform).

Methyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside[10] (**4**). — Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside[11] (**3**, 1.00 g) was converted into **4** (0.93 g, 93%), $[\alpha]_D^{22}$ +35° (*c* 1, chloroform); lit.[10] $[\alpha]_D$ +40° (chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$): δ 55.0, 70.2, 70.6, 72.9, 73.3, 75.2, 79.6, 81.4, 98.0, 127.4, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 138.1, 138.15, and 138.9.

Methyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside[12] (**6**). — Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[13] (**5**, 1.0 g) was converted into **6** (0.81 g, 81%), $[\alpha]_D^{22}$ +3° (*c* 1.2, chloroform); lit.[12] $[\alpha]_D^{22}$ +3° (chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$): δ 56.9, 66.8, 69.2, 72.3, 73.2, 73.7, 75.1, 79.0, 80.6, 104.7, 127.5, 127.7, 127.8, 128.0, 128.3, 128.4, 137.9, 138.0, and 138.7.

A minor component was also isolated: methyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (0.07 g, 7%), m.p. 103–104°, $[\alpha]_D^{22}$ −23° (*c* 1.1, chloroform); lit.[14] m.p. 103–105°, $[\alpha]_D^{22}$ −22° (chloroform).

Methyl 3,4-di-O-benzyl-α-L-rhamnopyranoside[6] (**9**). — Methyl 4-*O*-benzyl-2,3-*O*-(*S*)-benzylidene-α-L-rhamnopyranoside[6] (**7**, 0.40 g) was converted into **9** (0.38 g, 95%), $[\alpha]_D^{22}$ −45° (*c* 1.2, chloroform); lit.[6] $[\alpha]_D$ −46° (chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$): δ 17.9, 54.6, 67.2, 68.3, 71.8, 75.1, 79.9, 100.1, 127.5, 127.7, 127.9, 128.0, 128.1, 128.2, 128.35, 138.0, and 138.4.

Methyl 2,4-di-O-benzyl-α-L-rhamnopyranoside[9] (**10**). — Methyl 4-*O*-benzyl-2,3-*O*-(*R*)-benzylidene-α-L-rhamnopyranoside[6] (**8**, 0.50 g) was converted into **10** (0.44 g, 88%), $[\alpha]_D^{22}$ −16° (*c* 1.2, chloroform); lit.[9] $[\alpha]_D$ −18° (chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$): δ 18.0, 54.4, 67.1, 71.6, 72.8, 74.6, 78.7, 82.0, 98.1, 127.3, 127.7, 128.1, 128.3, 138.0, and 138.7.

Methyl 3,6-di-O-benzyl-α-D-mannopyranoside[15] (**12**). — Methyl 2,3-(*R*):4,6-(*R*)-di-*O*-benzylidene-α-D-mannopyranoside[16] (**11**, 0.75 g) was converted into **12**, as described for the preparation of **2**, except that the solvent for column chromatography was light petroleum (b.p. 40–60°)–ethyl acetate (1:1). Compound **12** (0.59 g, 78%) had $[\alpha]_D^{22}$ +25° (*c* 1.3, chloroform); lit.[16] $[\alpha]_D$ +20° (*c* 0.6, chloroform); ^{13}C-n.m.r. data (25 MHz, $CDCl_3$): δ 54.7, 67.2, 67.7, 70.1, 71.0, 71.7, 73.4, 79.5, 100.6, 127.4, 127.5, 127.8, 128.2, 128.4, 128.5, 128.9, 138.0, and 138.1.

ACKNOWLEDGMENTS

We thank Professor Bengt Lindberg for his interest, and the Swedish Natural Research Council and the Swedish Board for Technical Development for financial support.

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