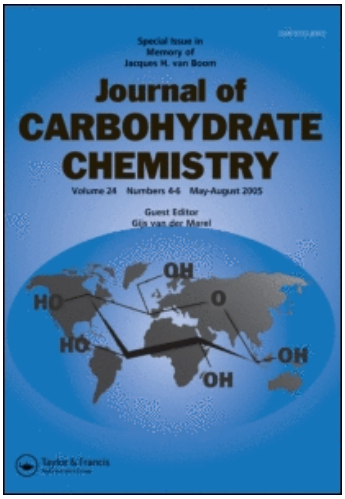

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REDUCTIVE RING OPENINGS OF CARBOHYDRATE BENZYLIDENE ACETALS USING BORANE-TRIMETHYLAMINE AND ALUMINIUM CHLORIDE. REGIOSELECTIVITY AND SOLVENT DEPENDANCE

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ABSTRACT

Regioselective reductive ring openings of 4,6-O-benzylidene acetals of hexopyranosides are described using borane trimethylamine-aluminium chloride. Using toluene as solvent, 4-O-benzyl ethers with the 6-OH free are obtained. Using tetrahydrofuran as solvent, 6-O-benzyl ethers with the 4-OH free are obtained.

INTRODUCTION

The regioselectivity in reductive ring openings of the dioxane rings of 4,6-O-benzylidene acetals of hexopyranosides varies with the reagent. We have previously shown that treatment of 4,6-O-benzylidene hexopyranosides with sodium cyanoborohydride and hydrogen chloride gives 6-O-benzyl ethers with the 4-OH unsubstituted.[1] The corresponding reductions with lithium aluminium hydride and aluminium chloride on the other hand tend to give the opposite regioselectivity, particularly if the hexopyranoside has a bulky group in the 3-position.[2-5] This is useful in protective group strategies. We now report the corresponding reductions using borane trimethylamine-aluminium chloride. The regioselectivity in the ring openings is strongly solvent dependant.

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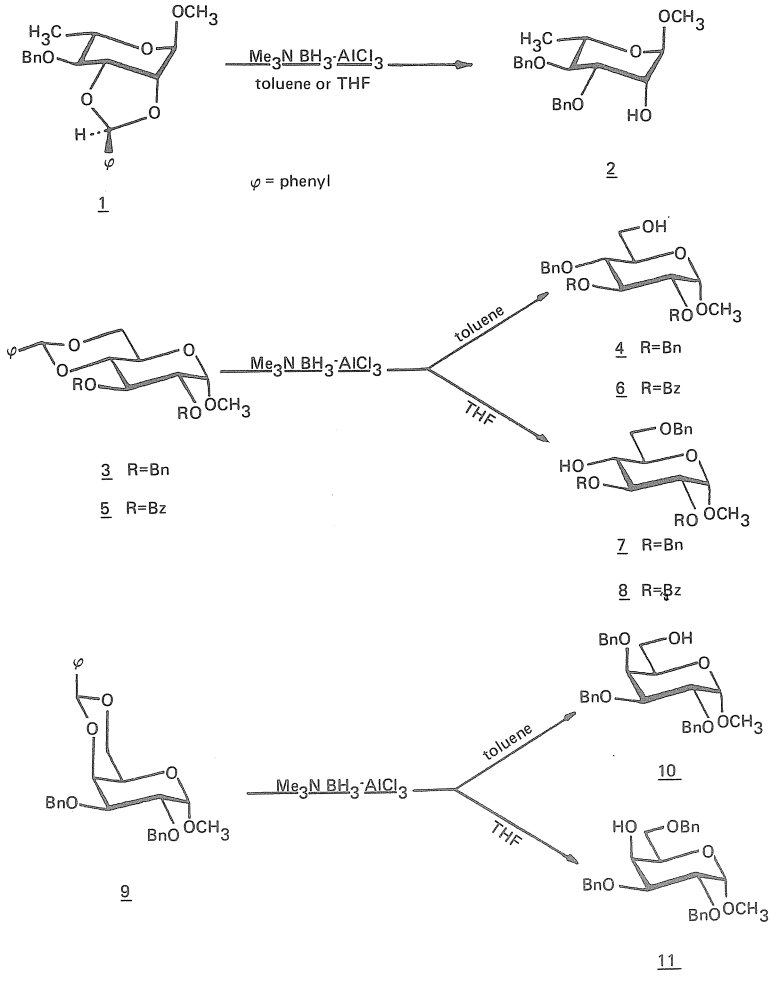

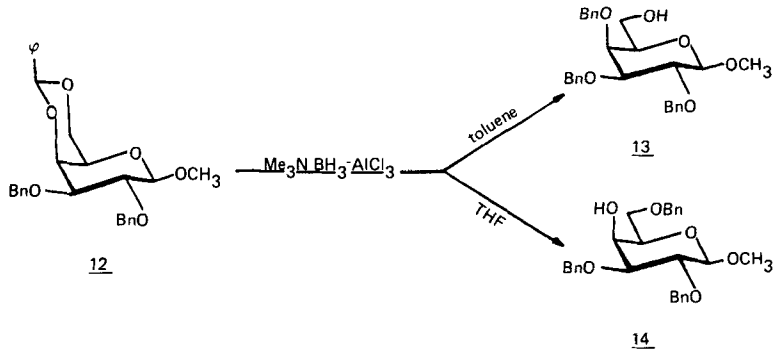

12 13 14

RESULTS AND DISCUSSION

Previous reductive ring openings of dioxolane benzylidene acetals of hexopyranosides using sodium cyanoborohydride and hydrogen chloride[1] have given the same regioselectivities as those observed for lithium aluminium hydride-aluminium chloride.[2-5] In the present work, reductive ring openings of the rhamnoside 1 using borane trimethylamine[6]-aluminium chloride gave the same 3-O-benzyl ether 2 as that previously obtained,[1-5] and the stereochemical outcome was the same irrespective of whether toluene or tetrahydrofuran was used as solvent.

In the reductive ring openings of the dioxane benzylidene acetals 3, 5, 9 and 12, the regioselectivities, however, were different for the two solvents. Thus, the use of toluene gave the 4-O-benzyl ethers 4, 6, 10 and 13 in addition to degradation products. The use of tetrahydrofuran, gave the 6-O-benzyl ethers 7, 8, 11 and 14 in good yields. The regioselectivities in these reductions were high. The yields obtained using toluene as solvent were generally moderate, but TLC examination of the initial reaction mixtures did not reveal the presence of appreciable quantities of the isomeric products.

Although an explanation of the observed results would require more detailed mechanistic studies, the difference in the regioselectivity observed in the two solvents most probably is a result of the stronger solvation of the Lewis acid or of cationic intermediates in tetrahydrofuran than in toluene.

The possibilities for controlling the regioselectivity of these reactions and the compatability of the reagents with the presence of ester groups (benzoyl) at other positions in the pyranose rings should prove useful in protecting group schemes in synthetic carbohydrate chemistry.

EXPERIMENTAL

General methods. General methods were the same as those published previously.[7] Tetrahydrofuran was distilled from lithium aluminium hydride. Toluene was dried over sodium wire. ^{1}H and ^{13}C NMR spectra recorded for all products were invariably in accordance with the postulated structures.

Methyl 3,4-di-O-benzyl-α-L-rhamnopyranoside (2).[8] Method A: A mixture of methyl 4-O-benzyl-2,3-O-(S)-benzylidene-α-L-rhamnopyranoside[8] (1) (450 mg), borane trimethylamine (450 mg, 6 equiv.) and 4Å molecular sieves in tetrahydrofuran (20 ml) was stirred at room temperature for 30 min. Aluminium chloride (800 mg, 6 equiv.) was added. When TLC (toluene-ethyl acetate 2:1) indicated complete reaction (several h), the mixture was filtered and the filtrate was treated with Dowex 50 (H^+) resin, filtered, and concentrated. The residue was co-concentrated three times with methanol, and the product was subjected to silica gel column chromatography (toluene-ethyl acetate 4:1) to yield (2) (381 mg, 85%), $[\alpha]_D$ -46^o (c, 1.37, $CHCl_3$), (Lit.[8] $[\alpha]_D$ -46^o, $CHCl_3$). Method B: Compound 1 (375 mg) was treated as described above, but using toluene instead of tetrahydrofuran as the solvent. Product 2 was obtained (117 mg, 31%), $[\alpha]_D$ -46^o (c, 1.78, $CHCl_3$). (Lit.[8] $[\alpha]_D$ -46^o, $CHCl_3$).

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside[4] (4). Aluminium chloride (500 mg, 4 equiv.) was added with stirring at room temperature to methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside[9] (3) (450 mg), borane trimethylamine (280 mg, 4 equiv.) and 4Å molecular sieves in toluene (20 ml). When TLC (toluene-ethyl acetate 1:1) indicated complete reaction (about 5-10 min), the reaction mixture was worked up as described above for the preparation of 2 and the product 4 (225 mg, 50%) was obtained after purification by silica gel column chromatography (toluene-ethyl acetate 4:1), $[\alpha]_D$ $+20^o$ (c, 1.25), $CHCl_3$). (Lit.[4] $[\alpha]_D$ $+20^o$, $CHCl_3$).

Methyl 2,3-di-O-benzoyl-4-O-benzyl-α-D-glucopyranoside (6). Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside[10] (5) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in toluene as described above for the preparation of 4. Work-up and purification by silica gel column chromatography (toluene-ethyl acetate 4:1) yielded 6 (200 mg, 40 %), which crystallised from diethyl ether-light petroleum, m.p. 117-118 °C, $[\alpha]_D$ $+132^o$ (c, 1.49, $CHCl_3$). ^{13}C NMR data ($CDCl_3$, from internal TMS): δ 55.3, 61.4, 71.0, 72.5, 72.7, 74.8, 75.7, 97.1, 127.9, 128.1, 128.4, 129.1, 129.6,

129.8, 129.9, 133.1, 133.3, 137.5, 165.7, 166.0.

Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.3; H, 5.73. Found: C, 67.8; H, 5.71.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside[11-13] (7). Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside[9] (3) (500 mg), was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in tetrahydrofuran as described above for the preparation of 2. The product 7 (356 mg, 71%) was obtained after purification by silica gel column chromatography (toluene-ethyl acetate 5:1), $[\alpha]_D$ +9° (c, 1.22, $CHCl_3$). (Lit.[11-13] $[\alpha]_D$ +11°, +11°, +13°, $CHCl_3$).

Methyl 2,3-di-O-benzoyl-6-O-benzyl-α-D-glucopyranoside[13] (8). Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside[10] (5) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in tetrahydrofuran as described above for the preparation of 2. Work-up and purification by silica gel column chromatography (toluene-ethyl acetate 8:1) yielded 8 (368 mg, 74%), $[\alpha]_D$ +123° (c, 1.03, $CHCl_3$). (Lit.[13] $[\alpha]_D$ +113°, $CHCl_3$).

Methyl 2,3,4-tri-O-benzyl-α-D-galactopyranoside[14] (10). Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside[15] (9) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in toluene as described above for the preparation of 4. Work-up and purification by silica gel column chromatography (toluene-ethyl acetate 4:1) yielded 10 (272 mg, 54%), which crystallised from diethyl ether-light petroleum, m.p. 70 °C, $[\alpha]_D$ +4° (c, 1.38, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 55.3, 62.3, 70.5, 73.6, 74.5, 75.2, 76.6, 79.1, 98.9, 127.6, 127.7, 127.9, 128.1, 128.5, 138.3, 138.5, 138.8. The same compound, with the same physical constants was obtained by the treatment of 9 with lithium aluminium hydride and aluminium chloride. The optical rotation does not agree with that published (Lit.[14] $[\alpha]_D$ +59° ($CHCl_3$).

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.4; H, 6.94. Found: C, 72.4; H 6.99.

Methyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside[4,16] (11). Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside[15] (9) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in tetrahydrofuran as described above for the preparation of 2. Work-up and purification by silica gel column chromatography (toluene-ethyl acetate 4:1) yielded 13 (309 mg, 62%), $[\alpha]_D$ +37° (c, 1.0, $CHCl_3$). (Lit.[4,16] $[\alpha]_D$ +35°, +40°, $CHCl_3$).

Methyl 2,3,4-tri-O-benzyl-β-D-galactopyranoside[1,17] (13). Methyl 2,3-di-

-O-benzyl-4,6-di-O-benzylidene-β-D-galactopyranoside[19] (12) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in toluene as described above for the preparation of 4. Work-up and purification by silica gel column chromatography (chloroform-acetone 24:1) yielded 13, (110 mg, 22%), m.p. 103-104 °C, $[\alpha]_D$ -24° (c, 0.88, $CHCl_3$). (Lit.[1,17] m.p. 103-104 °C, 103-105 °C, $[\alpha]_D$ -22°, -23°, $CHCl_3$).

Methyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside[1,18] (14). Methyl 2,3-di--O-benzyl-4,6-O-benzylidene-β-D-galactopyranoside[19] (12) (500 mg) was treated with borane trimethylamine, aluminium chloride and 4Å molecular sieves in tetrahydrofuran as described above for the preparation of 2. Work-up and purification by silica gel column chromatography (toluene-ethyl acetate 2:1) yielded 13 (428 mg, 86%), $[\alpha]_D$ +4° (c, 1.03, $CHCl_3$). (Lit.[4,12] $[\alpha]_D$ +3°, $CHCl_3$).

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