A Regioselective Reductive Ring Opening of 4,6-*O*-Prop-2-enylidene Acetals of Hexopyranosides

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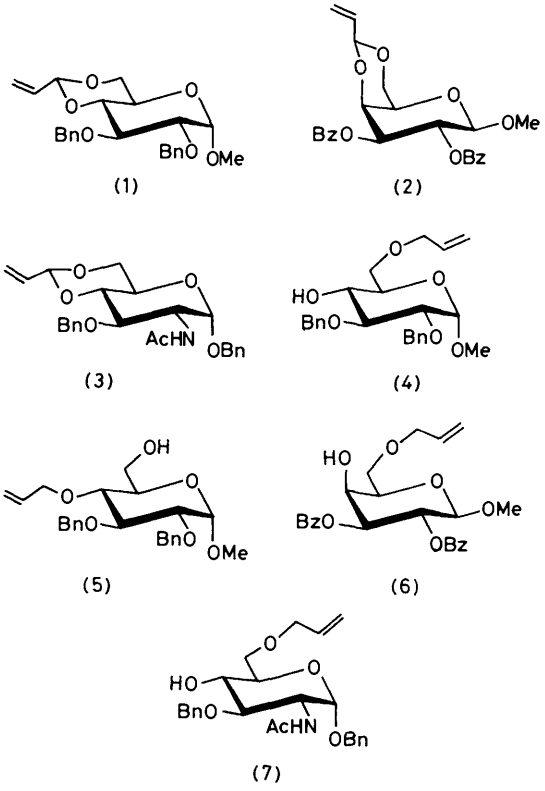
The 4,6-*O*-prop-2-enylidene acetals (1)—(3) on reductive cleavage with sodium cyanoborohydride–hydrogen chloride in tetrahydrofuran yield the 6-*O*-prop-2-enyl ethers (4), (6), and (7) in good yield. The reduction is thus compatible with the presence of glycosidic bonds, benzyl, benzoyl, and acetamido-groups and gives ready access to protected hexopyranosides with free 4-hydroxy-group.

REDUCTIVE cleavage of 4,6-*O*-benzylidene derivatives of hexopyranosides using lithium aluminium hydride–aluminium chloride [1-3] gives varying regioselectivity depending on the structure of the starting material. With hexopyranosides with bulky substituents (*e.g.* benzyl) in the 3-position,[3] however, the main product has a free 6-hydroxy group and a benzyl group at O-4. We have previously described reductive cleavages of 4,6-*O*-benzylidene acetals of hexopyranosides using sodium cyanoborohydride–hydrogen chloride.[4,5] The regioselectivity of this reduction is such that, in contradistinction to the results obtained with the lithium aluminium hydride–aluminium chloride reagent, the benzyl group in the main product is at O-6 and the 4-hydroxy-group is free. Furthermore, the reduction is compatible with the presence of ester and acetamido-groups at other positions in the hexopyranoside. Introduction of an *O*-allyl group instead of benzyl in the products should give increased flexibility in protective-group strategies and the reductive opening of 4,6-*O*-prop-2-enylidene acetals using the sodium cyanoborohydride–hydrogen chloride reagent was, therefore, investigated. Opening of these acetals with lithium aluminium hydride–aluminium chloride, which gives the alternative regioselectivity to that reported above, proceeds in low yield.[2,6,7]

The 4,6-*O*-prop-2-enylidene acetals (1)—(3) were selected as appropriate starting materials, comprising α-D- and β-D-configurations at C-1, a varying configuration at C-4, and the presence of varying protective groups at C-2 and C-3. The compounds (1)—(3) were prepared in good yields from the parent hexopyranosides by reaction with acrolein dimethyl acetal in *N*,*N*-dimethylformamide containing catalytic amounts of toluene-*p*-sulphonic acid, followed by benzylation or benzoylation of remaining free hydroxy-groups.

Reductions were carried out in tetrahydrofuran, containing an excess of sodium cyanoborohydride, by adding hydrogen chloride in diethyl ether until gas evolution ceased.[8] The reactions, at room temperature, were rapid, The acetal (1) afforded the allyl ether (4) in a 79% yield, in addition to the minor product (5) obtained in a 13% yield. The acetals (2) and (3) afforded (6) and (7) in yields of 86 and 74%, respectively.

The substitution patterns in the products (4)—(7) were demonstrated by the expected variations in the signals given by C-6 in the ^{13}C n.m.r. spectra. In the acetals (1)—(3) the δ values for C-6 are 62.2, 66.5, and 63.1, respectively. In the product (5), with a free 6-hydroxy-group, the δ value for C-6 is 61.9. In the other three products, (4), (6), and (7), the δ values are shifted downfield to 68—69 p.p.m. showing that O-6 is allylated.



Furthermore, in the ^1H n.m.r. spectrum in dimethyl sulphoxide,[9] the hydroxy-signal for the product (5) was a triplet, whereas those for the products (4), (6), and (7) were doublets.

The present method allows flexible protection group strategies in synthetic carbohydrate chemistry in that it gives ready access to partially protected derivatives with one free hydroxy-group and one *O*-allyl group together with benzyl, ester, or acetamido-groups.

EXPERIMENTAL

General Methods.—Melting points are corrected. Concentrations were performed under reduced pressure at a bath temperature <40 °C. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter; 99.55 MHz ^{1}H and 25.05 MHz ^{13}C n.m.r. spectra (in $CDCl_3$) were recorded in the Fourier-transform mode using a JEOL JNM FX instrument. Chemical shifts are given in p.p.m. downfield from tetramethylsilane. N.m.r. spectra, recorded for all new compounds, were invariably in accordance with postulated structures. Only ^{13}C n.m.r. spectra are given below. T.l.c. was performed using pre-coated silica gel plates (F_{254}, Merck) and the spots were detected by charring with 8% aqueous sulphuric acid. Column chromatography was performed in the flash mode [10] using silica gel (0.040—0.063 mm, Merck).

The quality of sodium cyanoborohydride varies. With poor qualities, higher amounts than those described below may have to be added. This is not critical for the outcome of the reactions.

Methyl 2,3-*Di*-O-*benzyl*-4,6-O-*prop*-2-*enylidene*-α-D-*glucopyranoside* (1).[2,6]—A solution of methyl α-D-glucopyranoside (1.0 g), acrolein dimethyl acetal (1.0 g), and a catalytic amount of toluene-*p*-sulphonic acid in *N*,*N*-dimethylformamide (3 ml) was allowed to stand at 50 °C overnight; it was then neutralized with triethylamine and concentrated. The residue was dissolved in dichloromethane and the solution was washed with water, dried (Na_2SO_4), filtered, and concentrated. The product was dissolved in *N*,*N*-dimethylformamide (5 ml) and added to a stirred suspension of sodium hydride (1.0 g) in *N*,*N*-dimethyl-formamide (4 ml). After 30 min at room temperature, benzyl bromide (3.4 g) was added and the mixture was stirred at room temperature for 2 h. Methanol was added and the mixture was diluted with toluene–diethyl ether (9 : 1), washed with water, dried (Na_2SO_4), filtered, and concentrated. Silica-gel column chromatography (toluene–ethyl acetate, 4 : 1) afforded compound (1) (1.50 g, 71%) as a syrup, $[\alpha]_D^{20}$ +17° (*c* 1.7, $CHCl_3$). A satisfactory elemental analysis could not be obtained for this compound. Its purity was, however, demonstrated by t.l.c. (toluene–ethyl acetate, 4 : 1), δ_C: 55.2, 62.2, 68.7, 73.7, 75.3, 78.5, 79.2, 81.8, 99.2, 100.4, 118.8, 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 133.7, 138.1, and 138.8 p.p.m.

Methyl 2,3-*Di*-O-*benzoyl*-4,6-O-*prop*-2-*enylidene*-β-D-*galacto-pyranoside* (2).—A solution of methyl β-D-galactopyranoside (1.0 g), acrolein dimethyl acetal (1.0 g), and a catalytic amount of toluene-*p*-sulphonic acid in *N*,*N*-dimethylformamide (3 ml) was allowed to stand at 50 °C overnight. Pyridine (2 ml) was added and the mixture was cooled. Benzoyl chloride (2 ml) in pyridine (2 ml) was added and the mixture was stirred at room temperature for 30 min. Ice was added and stirring was continued for another 10 min. The mixture was diluted with dichloromethane and washed with water, 2M-sulphuric acid, saturated aqueous sodium hydrogencarbonate, and water, and was then dried (Na_2SO_4), filtered, and concentrated. Silica-gel column chromatography (toluene–ethyl acetate 8 : 1) afforded compound (2) (1.5 g, 67%). An aliquot was crystallized from ethanol–water, m.p. 59—62 °C, $[\alpha]_D^{20}$ +88° (*c* 1.8, $CHCl_3$) (Found: C, 65.4; H, 5.6. $C_{24}H_{24}O_8$ requires C, 65.4; H, 5.49), δ_C 56.7, 66.5, 68.5, 69.1, 72.7, 73.2, 100.4, 102.1, 119.1, 128.3, 128.4, 129.2, 129.7, 129.9, 133.0, 133.3, 133.9, 165.3, and 166.1 p.p.m.

Benzyl 2-*Acetamido*-3-O-*benzyl*-2-*deoxy*-4,6-O-*prop*-2-*enylidene*-α-D-*glucopyranoside* (3).—A solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (1.0 g), acrolein dimethyl acetal (1.0 g), and a catalytic amount of toluene-*p*-sulphonic acid in *N*,*N*-dimethylformamide (5 ml) was allowed to stand at room temperature overnight. Powdered sodium hydroxide (0.5 g) and benzyl bromide (0.5 ml) were added and the mixture was stirred at room temperature overnight. It was then diluted with water (70 ml) and stirred for 10 min. Crystalline product was filtered off and recrystallized from ethanol to yield compound (3) (0.95 g, 65%), m.p. 213—215 °C, $[\alpha]_D^{20}$ +160° (*c* 1.7, $CHCl_3$) (Found: C, 68.2; H, 6.65; N, 3.15. $C_{25}H_{29}NO_6$ requires C, 68.3; H, 6.65; N, 3.19), δ_C 23.3, 52.5, 63.1, 68.6, 70.0, 72.2, 74.0, 76.2, 82.4, 97.7, 100.5, 118.9, 127.7, 127.8, 128.1, 128.2, 128.4, 128.6, 133.7, 137.0, 138.7, and 169.8 p.p.m.

Methyl 2,3-*Di*-O-*benzyl*-6-O-*prop*-2-*enyl*-α-D-*glucopyranoside* (4).—Diethyl ether saturated with hydrogen chloride was added at room temperature to a stirred mixture of compound (1) (1.0 g) and sodium cyanoborohydride (1.0 g) in tetrahydrofuran until the evolution of gas ceased. After a further 15 min, Dowex 50 (H^+) (*ca.* 2 g) was added to the mixture which was then stirred at room temperature for 30 min. The reaction mixture was filtered through Celite and the filtrate was diluted with dichloromethane. The solution was washed with water, saturated aqueous sodium hydrogencarbonate and water, and then dried (Na_2SO_4), filtered, concentrated, and evaporated three times with methanol. Silica-gel column chromatography (toluene–ethyl acetate, 2 : 1) afforded compound (4) (0.79 g, 79%), $[\alpha]_D^{20}$ +12° (*c* 0.95, $CHCl_3$) (Found: C, 69.3; H, 7.1. $C_{24}H_{30}O_6$ requires C, 69.5; H, 7.29), δ_C 55.2, 69.4, 69.9, 70.7, 72.5, 73.2, 75.4, 79.6, 81.5, 98.2, 117.2, 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 134.5, 138.1, and 138.9 p.p.m.

Further elution of the chromatographic column (same solvent) afforded methyl 2,3-*O*-benzyl-4-*O*-prop-2-enyl-α-D-glucopyranoside (5) [2,6] (0.1 g, 13%), m.p. 65—66 °C, $[\alpha]_D^{22}$ +35° (*c* 1.0, $CHCl_3$) (Found: C, 69.3; H, 7.25. $C_{24}H_{30}O_6$ requires C, 69.5; H, 7.29), δ_C 55.2, 61.9, 70.7, 73.4, 73.8, 75.7, 77.6, 79.9, 81.8, 98.3, 117.0, 127.6, 127.9, 128.0, 128.1, 128.4, 128.5, 134.8, 138.2, and 138.8 p.p.m.

Methyl 2,3-*Di*-O-*benzoyl*-6-O-*prop*-2-*enyl*-β-D-*galacto-pyranoside* (6).—Compound (2) (0.65 g) was reduced and the product was worked up as described for the preparation of compound (4) to yield, after silica-gel column chromatography (toluene–ethyl acetate, 5 : 1), compound (6) (0.56 g, 86%), which crystallized from ethyl acetate–hexane, m.p. 106—107 °C, $[\alpha]_D^{20}$ +70° (*c* 0.9, $CHCl_3$) (Found: C, 65.0; H, 6.05. $C_{24}H_{26}O_8$ requires C, 65.1; H, 5.92), δ_C 56.8, 68.1, 69.3, 69.7, 72.7, 73.5, 74.6, 102.4, 117.5, 128.3, 128.4, 129.9, 130.0, 133.1, 133.3, 134.3, 165.5, and 165.9 p.p.m.

Benzyl 2-*Acetamido*-3-O-*benzyl*-2-*deoxy*-6-O-*prop*-2-*enyl*-α-D-*glucopyranoside* (7).—Compound (3) (0.70 g) was reduced and the product was worked up as described for the preparation of compound (4) to yield, after silica-gel column chromatography (toluene–ethanol, 15 : 1), compound (7) (0.52 g, 74%), which crystallized from ethyl acetate–hexane, m.p. 124—125 °C, $[\alpha]_D^{20}$ +123° (*c* 2, $CHCl_3$) [lit.,[11] m.p. 124—125 °C, $[\alpha]_D$ +122° ($CHCl_3$)], δ_C 23.2, 52.0, 69.5, 70.1, 70.8, 72.0, 72.6, 73.8, 80.0, 97.2, 117.2, 127.7, 128.0, 128.5, 134.5, 137.3, 138.7, and 169.9 p.p.m.

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