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Note

O-(3-Butenyl), a stable blocking group removable by ozonolysis

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Among the many blocking groups used in carbohydrate chemistry, only a few can be removed under very mild and neutral conditions, while resisting the reagents generally applied in chemical reactions. We demonstrate here the utility of the *O*-(3-butenyl) group for differential protection in carbohydrates.

The 3-butenyl group is readily attached to the anomeric oxygen atom of any reducing mono- or oligo-saccharide, using either the Koenigs–Knorr or Fischer type of reaction, with 3-buten-1-ol as the aglyconic alcohol. When 3-butenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside [1] (**1**) in dichloromethane was treated with ozone under standard ozonolysis conditions at −75°, β-elimination of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose from the resulting *O*-glycosylated 3-hydroxypropanal occurred spontaneously when the reaction mixture was allowed to reach room temperature. The glucose tetraacetate was recovered quantitatively on evaporating the solvent and the acrolein (bp 52.5°) formed.

The α anomer (**2**) of compound **1** was obtained from 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose and 3-buten-1-ol under catalysis [2] by tin(IV) chloride. Unlike the β anomer, **2** on ozonolysis afforded the intermediate aldehyde, 3-oxopropyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside, without spontaneous β-elimination. Mild treatment of the aldehyde with potassium carbonate in dry acetone afforded 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose. Apparently the higher polarity of the anomeric C–O bond [3] makes 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose a better leaving group than the α anomer.

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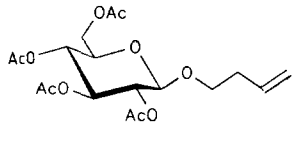

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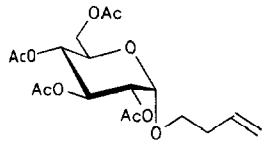

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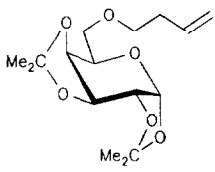

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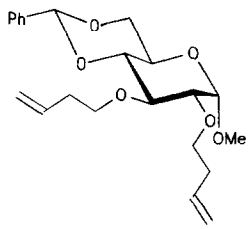

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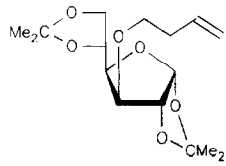

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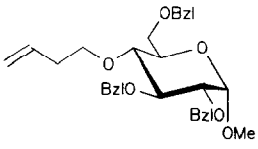

6

Attempts to introduce the 3-butenyl group elsewhere than into the anomeric position by alkylation with 1-bromo-3-butene failed, apparently because under all conditions tried, elimination to yield the volatile butadiene was faster than alkylation of a hydroxy group. This problem could, however, be overcome by using 1,4-diiodobutane in excess as the alkylating agent. The reaction was performed with several standard monosaccharide derivatives, such as 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside, under two sets of standardised conditions. In all cases *O*-alkylation was fast and led initially to the 4-iodobutyl ethers, as demonstrated by TLC and detection of the strongly UV-absorbing iodides. Subsequently elimination took place, giving the respective stable 3-butenyl ethers. Ozonolysis of the 3-butenyl ethers at low temperatures yielded the intermediate aldehydes (3-oxopropyl ethers), which were not isolated.

Warming up the mixture did not result in the spontaneous β-elimination observed with 3-butenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**1**). The reason is as for the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose derivative (**2**). The increased

TABLE I

Yield data for the *O*-butenylation and subsequent *O*-debutenylation of several standard sugar derivatives

Butenylated compound	Isolated yield (%)	Isolated yield of *O*-debutenylated product (%)
1	60	100
2	55	70
3	45	65
4	55	75
5	66	77
6	97	51

stability may be ascribed to the lower polarity of an α-disposed alkoxy group or an ordinary alkoxy group in comparison with the β-anomeric alkoxy group. However, the addition of potassium carbonate in acetone led to removal of the 3-oxopropyl groups as acrolein (see Table I). These are conditions under which *O*-acetyl and other protective groups are not affected. Allyloxy groups can also be removed by a procedure involving ozonolysis [4], but only after isomerisation. Final saponification of the immediate ozonolysis product, a formate ester, needs basic conditions, which also affect other acyl blocking groups.

EXPERIMENTAL

General methods.—All reactions were monitored by TLC on Silica Gel 60 F_{254} (Merck), and column chromatography was performed on Silica 32-63, 60 A (ICN). Optical rotations were determined with a Schmidt & Haensch Polartronic I polarimeter. ^{1}H-NMR spectra (250 MHz) were recorded with a Bruker WM 250 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Melting points are uncorrected. Ozonolyses were carried out with a Fischer ozone generator 500 M.

*2,3,4,6-Tetra-*O*-acetyl-β-*D*-glucopyranose from its 3-butenyl glycoside.*—Ozone (30 L/h O_2, 10 mmol O_3/h) was bubbled through a solution of 3-butenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside [1] (**1**) (100 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at −78°. After the blue colour of the solution persisted for 10 min, the excess O_3 was removed with a stream of O_2. Methyl sulfide (2 mL) was added, and the mixture was allowed to attain room temperature then concentrated. The product (86 mg, 100%) crystallised spontaneously. It was identical by mp, chromatographic behavior, and ^{1}H-NMR data with an authentic sample [5].

*3-Butenyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranoside* (**2**).—To a solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (2 g, 5.1 mmol) in dry CH_2Cl_2 (100 mL) was added $SnCl_4$ (0.78 mL, 6.6 mmol). The mixture was stirred for 15 min at room temperature, 3-buten-1-ol (0.48 g, 6.6 mmol) was added, and stirring was continued overnight. To the mixture water (50 mL) was added, and after 15 min

the solution was extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were made neutral with satd aq $NaHCO_3$ (50 mL), washed with water (50 mL), dried (Na_2SO_4), and concentrated. Column chromatography (1:3 EtOAc–cyclohexane) of the residue gave **2** (1.1 g, 55%), isolated as a colourless syrup, $[\alpha]_D^{23}$ +97° (*c* 1.17, $CHCl_3$); R_F 0.47 (1:1 EtOAc–cyclohexane); ^{1}H-NMR ($CDCl_3$): δ 5.82 (ddt, 1 H, $J_{2',3'}$ 6.75, $J_{3',4'a}$ 10.5, $J_{3',4'b}$ 17.25 Hz, H-3'), 5.49 (dd, 1 H, $J_{3,4}$ 0.9 Hz, H-3), 5.10 (d, 1 H, $J_{1,2}$ 3.75 Hz, H-1), 5.08 (m, 3 H, H-4, H-4'), 4.85 (dd, 1 H, $J_{2,3}$ 10.5 Hz, H-2), 4.28 (dd, 1 H, $J_{5,6a}$ 4.35, $J_{6a,6b}$ 12 Hz, H-6a), 4.09 (dd, 1 H, $J_{5,6b}$ 2.4 Hz, H-6b), 4.04 (m, 1 H, H-5), 3.74 (dt, 1 H, $J_{1'a,2'}$ 6.25, $J_{1'a,1'b}$ 10.35 Hz, H-1'a), 3.53 (dt, 1 H, $J_{1'b,2'}$ 6.25 Hz, H-1'b), 2.38 (ddt, 2 H, $J_{2'a,2'b}$ 13.5 Hz, H-2'), and 2.07 (m, 12 H, OAc).

Anal. Calcd for $C_{18}H_{26}O_{10}$: C, 53.76; H, 6.47. Found: C, 53.65; H, 6.57.

*2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranose from* **2**.—A solution of **2** (68 mg, 0.17 mmol) in CH_2Cl_2 was treated as described for the β anomer. After evaporating the solvent the residue was redissolved in dry acetone (10 mL), and powdered K_2CO_3 (200 mg) was added. When the reaction was complete (4 h, R_F 0.19 in 1:1 EtOAc–cyclohexane), the suspension was filtered. The filtrate was concentrated and purified by column chromatography (1:1 EtOAc–cyclohexane) to give the title compound (41 mg, 70%) as colourless crystals whose analytical data corresponded with the literature [5].

*6-*O*-(3-Butenyl)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**3**).—To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [6] (1 g, 3.8 mmol) in dry Me_2SO (20 mL) was added powdered NaOH (5 g). After 1 h diiodobutane (2.9 g, 16 mmol) was added to the vigorously stirred and cooled (0°) suspension. The mixture was stirred at room temperature for 4 h, poured into ice–water, and extracted with ether (4 × 50 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:10 EtOAc–cyclohexane) of the residue gave **3** (500 mg, 45%) as a colourless syrup, $[\alpha]_D^{23}$ −61° (*c* 1.13, $CHCl_3$); R_F 0.41 (1:3 EtOAc–cyclohexane); ^{1}H-NMR ($CDCl_3$): δ 5.83 (ddt, 1 H, $J_{2',3'}$ 6.9, $J_{3',4'a}$ 10.5, $J_{3',4'b}$ 17.2 Hz, H-3'), 5.55 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 5.08 (m, 2 H, H-4'), 4.62 (dd, 1 H, $J_{2,3}$ 2.7, $J_{3,4}$ 7.97 Hz, H-3), 4.29 (dd, 1 H, H-2), 4.25 (dd, 1 H, $J_{4,5}$ 1.65 Hz, H-4), 3.98 (m, 1 H, H-5), 3.62 (m, 4 H, H-1', H-6), 2.37 (ddt, 2 H, $J_{1',2'}$ 13.5 Hz, H-2'), 1.53 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), and 1.32 (d, 6 H, 2 CH_3).

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.18; H, 8.28. Found: C, 60.18; H, 8.09.

*1,2:3,4-Di-*O*-isopropylidene-α-*D*-galactopyranose from* **3**.—A solution of **3** (64 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was treated as described for compound **2**. When the reaction was complete (12 h, R_F 0.19 in 1:2 EtOAc–cyclohexane), the suspension was filtered. The filtrate was concentrated and purified by column chromatography (1:2 EtOAc–cyclohexane) to give the title compound (34 mg, 65%) as a colourless syrup, identical with the product [6] used for *O*-butenylation.

*Methyl 4,6-*O*-benzylidene-2,3-di-*O*-(3-butenyl)-α-*D*-glucopyranoside* (**4**).—To a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside [7] (4 g, 14 mmol) in dry

Me_2SO (40 mL) was added powdered NaOH (30 g). After 1 h diiodobutane (22 g, 70 mmol) was added and the mixture treated as described above. Column chromatography (1:5 EtOAc–cyclohexane) yielded **4** (3 g, 55%) as colourless needles, mp 79° (MeOH) $[\alpha]_D^{23}$ +43° (*c* 1, $CHCl_3$); R_F 0.42 (1:3 EtOAc–cyclohexane); ^{1}H-NMR ($CDCl_3$): δ 7.43 (m, 5 H, ArH), 5.83 (m, 2 H, H-3′, 3″), 5.56 (s, 1 H, PhC*H*), 5.07 (m, 4 H, H-4′, 4″), 4.82 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.29 (dd, 1 H, $J_{3,4}$ 3.75 Hz, H-3), 3.78 (m, 7 H, H-1′, 1″,5,6), 3.52 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 3.44 (s, 3 H, CH_3), 3.38 (dd, 1 H, $J_{2,3}$ 9.15 Hz, H-2), and 2.37 (m, 4 H, H-2′,2″).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.72; H, 7.69. Found: C, 67,75; H, 7.46.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside from **4**.—A solution of **4** (67 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) was treated as described for compound **2**. Column chromatography (3:1 EtOAc–cyclohexane) gave the title compound as colourless crystals (34 mg, 75%) identical with the product [7–9] used for *O*-butenylation.

3-O-(3-Butenyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**5**).—To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose [10] (500 mg, 1.92 mmol) in DMF (100 mL) was added NaH (0.75 g, 9.62 mmol). The cooled suspension (0°) was stirred for 1 h and then diiodobutane (1.3 mL, 9.62 mmol) was added dropwise. Stirring was continued overnight after which MeOH (25 mL) was added and the mixture was evaporated to dryness. A solution of the residue dissolved in $CHCl_3$ (50 mL) was washed with ice–water (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:2 ether–*n*-hexane) of the residue followed by distillation (160–165°, 100 Pa) yielded **5** (398 mg, 66%) as a liquid, $[\alpha]_D^{23}$ −31° (*c* 0.76, $CHCl_3$); R_F 0.39 (1:5 EtOAc–cyclohexane); ^{1}H-NMR ($CDCl_3$): δ 5.88 (d, 1 H, $J_{1,2}$ 3.75 Hz, H-1), 5.82 (ddt, 1 H, $J_{2',3'}$ 6.75, $J_{3',4'a}$ 10.5, $J_{3',4'b}$ 17.25 Hz, H-3′), 5.09 (m, 2 H, H-4′), 4.54 (d, 1 H, H-2), 4.31 (dt, 1 H, $J_{4,5}$ 7.5 Hz, H-5), 4.13 (dd, 1 H, $J_{3,3}$ Hz, H-4), 4.08 (dd, 1 H, $J_{5,6a}$ 6, $J_{6a,6b}$ 8.25 Hz, H-6a), 3.98 (dd, 1 H, $J_{5,6b}$ 6 Hz, H-6b), 3.88 (d, 1 H, H-3), 3.63 (m, 2 H, H-1′), 2.32 (ddt, 2 H, $J_{2'a,2'b}$ 13.5, $J_{1',2'}$ 6.25 Hz, H-2′), 1.51 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), and 1.34 (d, 6 H, 2 CH_3).

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.16; H, 8.28. Found: C, 61.29; H, 8.26.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose from **5**.—A solution of **5** (69 mg, 0.22 mmol) in CH_2Cl_2 (20 mL) was treated as described for compound **2**. After Me_2S (2 mL) was added the reaction mixture had to be left at room temperature overnight for complete reduction of the ozonide. β-Elimination was carried out under the same conditions as described for ozonolysed **2**. The title compound was purified by column chromatography (1:2 EtOAc–cyclohexane) to yield 45 mg (77%). The title compound was identical with the product [10] used for *O*-butenylation.

Methyl 2,3,6-tri-O-benzyl-4-O-(3-butenyl)-α-D-glucopyranoside (**6**).—To a solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside [11] (340 mg, 0.7 mmol) in dry Me_2SO (15 mL) was added powdered NaOH (5 g). After 1 h diiodobutane (2.3 g, 7.3 mmol) was added and the mixture was treated as described for compound **3**. Column chromatography (1:8 EtOAc–cyclohexane) yielded **6** (368 mg, 97%) as a

slightly yellow syrup, $[\alpha]_D^{23}$ +25° (*c* 1.05, $CHCl_3$); R_F 0.47 (1:2 EtOAc–cyclohexane); ^{1}H-NMR ($CDCl_3$): δ 7.32 (m, 15 H, ArH), 5.69 (ddt, 1 H, $J_{2',3'}$ 6.75, $J_{3',4'a}$ 10.5, $J_{3',4'b}$ 17.25 Hz, H-3'), 5.08 (m, 2 H, H-4'), 4.98–4.43 (m, 6 H, CH_2Ph), 4.61 (d, 1 H, $J_{1,2}$ 3.75 Hz, H-1), 3.89 (d, 1 H, $J_{3,4}$ 7.5, $J_{4,5}$ 9.75 Hz, H-4), 3.82 (dt, 1 H, $J_{1'a,2'}$ 6.25, $J_{1'a,1'b}$ 10.35 Hz, H-1'a), 3.62 (m, 4 H, H-5, H-1'), 3.5 (dd, 1 H, $J_{2,3}$ 9.75 Hz, H-2), 3.46 (dd, 1 H, $J_{3,4}$ 7.5 Hz, H-3), 3.4 (s, 3 H, CH_3), and 2.38 (ddt, 2 H, $J_{2'a,2'b}$ 13.5 Hz, H-2').

Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.16; H, 7.33. Found: C, 74.09; H, 7.31.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside from **6**.—A solution of **6** (71 mg, 0.14 mmol) in MeOH (20 mL) was treated as described for compound **2**. When the reaction was complete (12 h, R_F 0.37 in 1:2 EtOAc–cyclohexane), the suspension was filtered, concentrated, and purified by column chromatography (1:5 EtOAc–cyclohexane) to give the title compound (32 mg, 51%) as a colourless syrup, identical with the product [11] used for *O*-butenylation.

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