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Note

A highly diastereoselective, practical synthesis of allyl, propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-gluco, β-D-galactopyranosides and allyl, propargyl heptaacetyl-β-D-lactosides

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Abstract

Commercially available β-D-glucopyranose pentaacetate, β-D-galactopyranose pentaacetate and β-D-lactose heptaacetate were reacted with propargyl alcohol in the presence of BF_3–Et_2O catalyst to obtain in high yield and selectivity, the corresponding propargyl derivatives, respectively. These were hydrogenated by use of Lindlar catalyst to give the corresponding allyl β-D-glycopyranosides in quantitative yield.

Keywords: Allyl β-D-glycopyranosides; Propargyl β-D-glycopyranosides; Allyl and propargyl β-D-lactosides; Lindlar catalyst

Allyl glycopyranoside derivatives find extensive application in oligosaccharide synthesis because the anomeric O-allyl group can be deprotected [1] by a choice of various reagents at any length of the growing saccharide chain [2] to obtain the reducing sugar. This can be used for further derivatisation with proteins to obtain glycoconjugates, for example, for serodiagnosis of antibodies [3]. The anomeric O-allyl group has also been modified to prepare glycoconjugates with a spacer arm [4]. Hydrosilylated polymers of allyl glycosides with commercial utility have also been reported [5]. The presence of the neighbouring chiral saccharide has aided the asymmetric functionalisation of the O-allyl group to obtain enantiomerically pure compounds for use in organic synthesis [6].

Allyl glycopyranoside derivatives **1a** and **2a** have earlier been prepared starting from the reaction of either unprotected sugars [7–13] or tetra-acetyl glycosyl bromide [14–18] or β-D-glycopyranose pentaacetate [19–22] with allyl alcohol in the presence of a suitable catalyst. Reaction of D-Glc with allyl alcohol as a solvent and dry HCl (gas) has been reported to result in the formation of an anomeric mixture of allyl α/β-D-Glc*p* in 40% yield [7,8,23]. Use of acidic ion-exchange resin (Dowex 50 X-8) instead of HCl (gas) has been reported to

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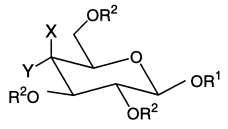
form allyl α-D-glucopyranoside in 41% yield [9,10] and a similar reaction of D-Gal gave allyl α-D-Gal*p* in a poor yield of 26% [10]. Use of BF_3-Et_2O as a catalyst at reflux has been reported to result in the formation of allyl α/β-D-Glc*p* in 8:1 ratio [12]. Reaction of D-Glc with allyl bromide and DMPU [11] has been reported to give allyl α/β-D-Glc*p* in 65% yield in 1:4.5 ratio. Reaction of tetraacetyl Glc*p* bromide and allyl alcohol by use of transition metal catalysts such as Ag_2CO_3 [14,16], HgO–$HgBr_2$ [15,17], $Hg(CN)_2$ [10] and ZnO-$ZnCO_3$ [18] has been carried out and reported to result in the formation of allyl 2,3,4,6-tetra-O-acetyl-β-D-Glc*p* (**1a**) in yields ranging from 40–60%. Commercially available, stable β-D-Glc*p* (**1b**) and β-D-Gal*p* pentaacetate (**2b**) have been reported to react with allyl alcohol (3–5 mole equivalents) in the presence of Lewis acid catalysts such as $SnCl_4$ [19], BF_3–Et_2O (2–10 mole equivalents) [20,22] and catalytic *p*-toluenesulfonic acid [21] to form **1a** and **2a** as anomeric mixture in yields ranging from 46–73%. Formation of allyl 3,4,6-tri-O-acetyl-β-D-Glc*p* [22] under similar conditions by use of BF_3–Et_2O has also been reported. In general these reactions required use of a large excess of allyl alcohol (many a times as a solvent) and BF_3–Et_2O; they invariably lead to the formation of anomeric mixtures in inconsistent yields. In our own experience reactions using **1b**–**3b** are very much dependent upon time, temperature and concentration of the substrate and we could not easily optimise these conditions to obtain any one single anomer of **1a**–**3a** and it always required column chromatography to purify them.



1 R^2 = Ac, X = H, Y = OAc
2 R^2 = Ac, X = OAc, Y = H
3 R^2 = Ac, X = H,
Y = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)

a) R^1 = CH_2-CH=CH_2
b) R^1 = Ac
c) R^1 = CH_2-C≡CH

We have now developed a simple procedure to prepare large quantities of anomerically pure **1a**,**2a** and allyl heptaacetyl β-D-lactose **3a** and to transform them into novel glycosyl donors possessing "acetal ester" leaving groups [24] and also for studies related to development of mild deprotection procedures [25]. The strategy involved preparation of the propargyl glycosides **1c**–**3c** first and then partial hydrogenation with the Lindlar catalyst to obtain **1a**—**3a**, respectively. Thus, β-D-glucopyranose pentaacetate **1b** [26] was reacted with propargyl alcohol (1.2 mole equivalent) in dry dichloromethane at room temperature containing BF_3–Et_2O (1.5 mole equivalent) for 2 h to obtain **1c** as a crystalline solid in very high yield (92.3%). Formation of the undesired *a*-anomer was not observed by TLC and ^{1}H NMR. **1c** was characterised from the appearance of the anomeric proton at δ 4.66 as a doublet ($J_{1,2}$ = 9.1 Hz) and the acetylenic proton at δ 2.45 as a triplet ($J_{1,3}$ = 2.3 Hz). Likewise, β-D-galactopyranose pentaacetate **2b** [26] and β-D-lactose heptaacetate **3b** were reacted with propargyl alcohol and BF_3–Et_2O for 2 h at room temperature to obtain their corresponding propargyl glycosides **2c** and **3c** in high yields (92–95%) pure enough for further reactions. **1c** and **3c** have also been recrystallised from dichloromethane-hexane to obtain crystalline **1c** (m.p. 114–115 °C) [27], **2c** (55–57 °C) and **3c** (m.p. 74–76 °C). While optimising the reaction conditions it was found that use of 2 mole equivalents of BF_3–Et_2O did not have any adverse effect on the diastereoselectivity, except that yields were lowered by 11–16% for **1c**–**3c**. Complete conversion of the substrates **1b**–**3b** was observed after 1.5 h and formation of products **1c**–**3c** at 6 h, 12 h and 16 h intervals of time indicated that after 16 h yields lowered by 2–3% and no anomerisation of the products **1c**–**3c** was observed unlike **1a**–**3a**. A temperature range of 20–35 °C did not have any adverse effect on yield and diastereoselectivity. Propargyl glycosides **1c**–**3c** were hydrogenated at atmospheric pressure by use of the Lindlar catalyst [28] for 3–4 h to obtain their corresponding allyl glycosides **1a**–**3a**, respectively, in almost quantitative yield. **1a** and **2a** [12,19] have been characterised by comparison of their physical data ($[\alpha]_D$, m.p. ^{1}H NMR) with that reported in literature. **3a** was characterised by analogy to **1a** and **2a** from the appearance of the H-2 proton at δ 6.0–5.7 as a multiplet.

1. Experimental

General methods.—^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with tetramethylsilane as internal standard

for solutions in deuteriochloroform. ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz) spectrometer with $CDCl_3$ as internal standard (δ c 77.0) for solutions in deuteriochloroform. Optical rotations were measured with a JASCO DIP-370 instrument, and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined by using a Fischer-John's melting point apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 1310 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo.

2-Propynyl 2,3,4,6-tetra-O-*acetyl*-β-D-*glucopyranoside* (**1c**).—To a solution of β-D-glucopyranose pentaacetate (**1b**) (10 g, 25.6 mmol) in dichloromethane (200 mL) was added freshly distilled propargyl alcohol (1.8 mL, 30.7 mmol) and BF_3–Et_2O (4.8 mL, 38.4 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction anhydrous K_2CO_3 (4.8 g) was added and stirring was continued for a further 30 min. and the reaction mixture was filtered and washed with dichloromethane.The filtrate was washed with water (2×150 mL), the aqueous phase was separated and extracted with dichloromethane (2×50 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated to yield a solid which was crystallised (dichloromethane-hexane) to obtain the title compound **1c** (9.10 g, 92%) as a crystalline solid. m.p. 114–115 °C, lit. 114–116 °C [27], $[\alpha]_D$−39 (*c* 1.0, $CHCl_3$), lit. −37.4 [27]; IR (KBr): ν 3260 (≡C–H), 2128 (C≡C), and 1744 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 5.32–4.9 (m, 3 H, H-2,3,4), 4.66 (d, 1 H, $J_{1,2}$ 9.1 Hz, H-1), 4.39 (d, 2 H, $J_{1,3}$ 2.3 Hz, H-1), 4.5–4.05 (m, 4 H, H-1,6), 3.80–3.6 (m, 1 H, H-5), 2.45 (t, 1 H, H-3), 2.12, 2.09, 2.06, and 2.03 (4s, 12 H, OCOC*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.0, 2×169.3 (O*C*OCH$_3$), 98.1 (C-1), 78.1, 75.5, 72.7, 71.9, 70.9, 68.3 (C-2, -3, -4, -5, -2, -3), 61.7 (C-6), 55.8 (C-1), 2×20.5, 2×20.4 (OCO*C*H$_3$). Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.77; H, 5.62.

2-Propynyl 2,3,4,6-tetra-O-*acetyl*-β-D-*galactopyranoside* (**2c**).—Reaction of **2b** (15 g, 38.4 mmol) with propargyl alcohol (2.72 mL, 46.1 mmol) and BF_3–Et_2O (7.2 mL, 57.6 mmol) in dichloromethane (300 mL) as described for **1c** gave **2c** (14.06 g, 95%) as a syrup which solidified on standing m.p. 55–57 °C, $[\alpha]_D$ −23 (*c* 1.0, $CHCl_3$); IR (KBr): ν 3267 (≡C-H), 2096 (C≡C), and 1744 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 5.37 (d, 1 H, $J_{3,4}$ 3 Hz, H-4), 5.16 (dd, 1 H, $J_{1,2}$ 7.6 Hz, $J_{2,3}$ 9 Hz, H-2), 5.03 (dd, 1 H, H-3), 4.72 (d, 1 H, H-1), 4.39 (d, 2 H, $J_{1,3}$ 2.0 Hz, H-1), 4.25–4.5 (m, 2 H, H-6), 3.85–4.0 (m, 1 H, H-5), 2.45 (t, 1 H, H-3), 2.17, 2.09, 2.07, and 2.01 (4 s, 12 H, OCOC*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 170.1, 170.0, 169.8, 169.3 (O*C*OCH$_3$), 98.5 (C-1), 70.8, 75.2, 2×70.7, 68.3, 66.9 (C-2,−3,−4,−5,−2,−3), 61.0 (C-6), 55.7 (C-1), 20.5, 2×20.4, 20.3 (OCO*C*H$_3$). Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.78; H, 5.65.

2-Propynyl 4-O-*[2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl]-2,3,6-tri*-O-*acetyl*-β-D-*galactopyranoside* (**3c**).—Reaction of **3b** (15 g, 2.21 mmol) with propargyl alcohol (1.56 mL, 2.65 mmol) and BF_3–Et_2O (4.17 mL, 3.31 mmol) in dichloromethane (300 mL) as described for **1c** gave **3c** (13.93 g, 93.5%) as a crystalline solid. m.p. 74–76 °C, $[\alpha]_D$ −12.8 (*c* 1.0, $CHCl_3$); IR (KBr): ν 3274 (≡C–H), 2118 (C≡C) and 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 5.4–4.8 (m, 5 H, H-2;,2,3,3,4), 4.72, 4.50 (2d, 2 H, $J_{1,2}/J_{1,2}$ 8, 8.2 Hz, H-1,1), 4.45–4.55 merged (m, 1 H, H-4), 4.4–4.24 (d, 2 H, $J_{1,3}$ 2.1 Hz, H-1), 4.2–3.55 (m, 6 H, H-5,5,6,6), 2.44 (t, 1 H, H-3), 2.19, 2.14, 2×2.09, 2×2.06, 1.98 (5 s, 21 H, OCOC*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 2×170.2, 2×170.0, 2×169.6, 169.0 (O*C*OCH$_3$), 100.6, 97.8 (C-1,−1), 78.0, 75.9, 75.4, 2×72.6, 71.2, 70.8, 70.6, 69.0, 66.5 (C-2,-2,-3,-3,-4,-4,-5,-5,-2,-3), 61.7, 60.7 (C-6,−6OCO*C*H$_3$). Anal. Calcd for $C_{29}H_{38}O_{18}$: C, 51.63; H, 5.68. Found: C, 51.52; H, 5.51.

2-Propenyl 2,3,4,6-tetra-O-*acetyl*-β-D-*glucopyranoside* (**1a**).—**1c** (5 g, 12.9 mmol) was dissolved in methanol (100 mL), and 5% Pd–$CaCO_3$ (250 mg) followed by quinoline (2.5 mL) were added and the contents were stirred at room temperature for 8 h under hydrogen atmosphere. When TLC indicated the formation of a faster moving spot and disappearence of starting material, the reaction mixture was filtered and concentrated to a residue, diluted with dichloromethane (50 mL) washed with chilled 2% aqueous hydrochloric acid (2×50 mL) and water. The organic phase was separated, dried (Na_2SO_4), concentrated to yield the title compound **1a** (4.9 g, 98%) as a solid. m.p. 86–88 °C, lit. 89–90 °C [12], $[\alpha]_D$ −11 (*c* 1.0, $CHCl_3$), lit. −11.7 (*c* 1.0, $CHCl_3$) [12].

2-Propenyl 2,3,4,6-tetra-O-*acetyl*-β-D-*galactopyranoside* (**2a**).—**2c** (6.4 g, 16.5 mmol) was hydrogenated in presence of 5% Pd–$CaCO_3$ (320 mg) and quinoline (3.2 mL) as described for **1a** to obtain **2a** (6.35 g, 98.8%) as a syrup. $[\alpha]_D$ −8 (*c* 1.0, $CHCl_3$).

2-Propenyl 4 - O - [2,3,4,6 - tetra - O - acetyl - β-D-glucopyranosyl] - 2,3,6 - tri - O - acetyl - β - D-galactopyranoside (**3a**).—**3c** (5 g, 0.74 mmol) was hydrogenated in presence of 5% Pd-$CaC0_3$ (250 mg) and quinoline (2.5 mL) as described for **1a** to obtain **3a** (4.93 g, 98.4%) as a crystalline solid. m.p. 66–68 °C, $[\alpha]_D$ −10 (*c* 1.0, $CHCl_3$); IR (KBr): ν 1752 (C=O) and 1664 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 6–5.7 (m, 1 H, H-2), 5.4–4.8 (m, 8 H, H-2,2,3,3,3,4,4), 4.6–4.4 (m, 4 H, H-1,1,1), 4.4–3.5 (m, 6 H, H-5,5,6,6), 2.18, 2.14, 2×2.08, 2×2.04, 1.98 (5 s, 21 H, OCOCH_3). Anal. Calcd for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.34; H,5.82.

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