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Note

Synthesis of a disaccharide oxazoline: 2-methyl-[4,6-di-*O*-acetyl-1,2-dideoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galacto-pyranosyl)-α-D-glucopyrano][2′,1′:4,5]-2-oxazoline*

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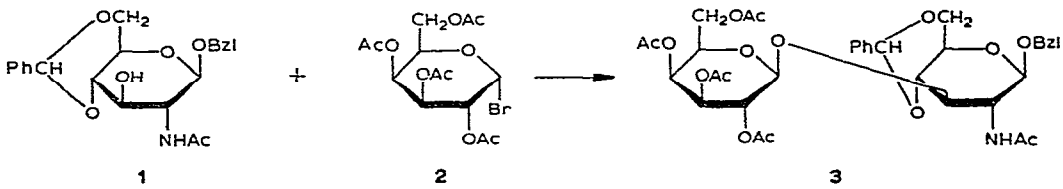
Glycosylation with 2-methylglyco[2′,1′:4,5]-2-oxazolines is an efficient procedure for the synthesis of 1,2-*trans*-2-acetamido-2-deoxy-D-glycosides[2–4], and oxazolines derived from a few disaccharides, such as 2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose[5], 2-acetamido-3-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose[3], and 2-acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-D-glucose[6], have been obtained in good yields and used with success for the preparation of glycosides[6] or trisaccharides[2,3].

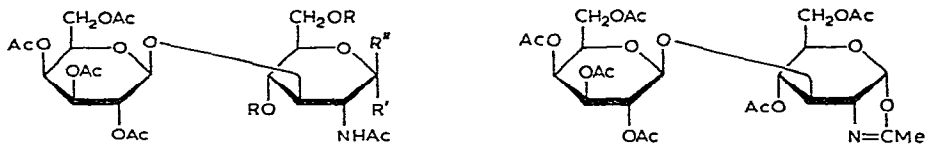
We now report the synthesis of a new disaccharide oxazoline, 2-methyl-[4,6-di-*O*-acetyl-1,2-dideoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyrano][2′,1′:4,5]-2-oxazoline (**10**), a compound that may prove to be useful for the synthesis of several oligosaccharides found in human milk[7] or blood-group substances[8].

Condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[9] (**2**) with benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[10] (**1**) in nitromethane–benzene in the presence of mercuric cyanide gave the crystalline disaccharide **3** in 78% yield; the isomeric benzyl α-D disaccharide had been obtained by Flowers and Jeanloz[11] in 53% yield. Hydrolysis of the benzylidene group of **3** gave the crystalline diol **4** in 64% yield. Conventional acetylation of **4** afforded crystalline **5** in nearly quantitative yield. Catalytic hydrogenation of **5** with 10% palladium-on-charcoal in aqueous ethanol gave an amorphous mixture of **6** and its α-D anomer, due to mutarotation in the solvent used for the reaction. Acetylation with acetic anhydride in pyridine at room temperature afforded a mixture of α and β acetates, **7** and **8** (ratio 2:1), which could be fractionated by chromatography. The anomeric configuration of these peracetylated disaccharides was readily determined from the observed $J_{1,2}$ values[12] and from the optical rotation. The α acetate **7** was obtained crystalline in 57% yield whereas the β acetate **8** was amorphous (27%).

*Studies in oligosaccharide chemistry, Part VI. For Part V, see Ref. 1.



1 2 3



4 R = H, R′ = H, R″ = OBzl
5 R = Ac, R′ = H, R″ = OBzl
6 R = Ac, R′ = H, R″ = OH
7 R = Ac, R′ = OAc, R″ = H
8 R = Ac, R′ = H, R″ = OAc
9 R = Ac, R′ = Cl, R″ = H

10

Ballou *et al.*[13] showed that the reduction of an acetylated benzyl glycoside with palladium and hydrogen in a neutral, inert solvent (ethyl ether) leads to a compound having an anomeric configuration that is identical with that of the starting benzyl glycoside. Hydrogenation of the benzyl β-D-glycoside **5** with 10% palladium-on-charcoal in absolute 1,4-dioxane gave amorphous **6** that had a rotation smaller than that of the compound obtained by hydrogenation in aqueous ethanol. This compound was immediately acetylated with pyridine–acetic anhydride overnight at 0° to afford the nearly pure β acetate **8** in a quantitative yield from **5**.

The crystalline α-chloride **9** was obtained in 68% yield when the α acetate **7** (or the β acetate **8**, or a mixture of **7** and **8**) was treated with acetyl chloride saturated with dry hydrogen chloride according to the procedure described by Zurabyan *et al.*[14]. The chloride **9** was converted directly into the oxazoline **10** by chloride-ion catalysis in the presence of sodium hydrogencarbonate[15]. Column chromatography on silica gel gave the pure oxazoline **10** in 60% yield as a syrup. However, the best method for preparing **10** was by action of anhydrous ferric chloride on the β acetate **8** in dichloromethane, according to the procedure described by Matta and Bahl[16]. Thus, **10** was obtained nearly pure without chromatography in 91% yield. The glycosylating capability of the oxazoline **10** was tested by treatment with benzyl alcohol in the presence of *p*-toluenesulfonic acid at room temperature, to give a benzyl β-D-glycoside identical to **5** in 38% yield.

EXPERIMENTAL

General methods. — See Part V. (Ref. 1).

Benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**3**). — A solution of benzyl 2-acetamido-4,6-

O-benzylidene-2-deoxy-β-D-glucopyranoside (**1**, 3.6 g, 9 mmol) in 14:11 (v/v) benzene–nitromethane (500 ml) was boiled until 100 ml of the solvent had distilled. The temperature of the solution was adjusted to 60°; mercuric cyanide (2.0 g, 7.9 mmol) was added and a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**2**, 3.7 g, 9 mmol) in 1:1 (v/v) benzene–nitromethane (40 ml) was added dropwise with stirring over a period of 4 h under nitrogen. The solution was stirred at 60° under nitrogen for a further 24 h. Mercuric cyanide (1.0 g, 4 mmol) and a solution of **2** (1.8 g, 4.4 mmol) in 1:1 (v/v) benzene–nitromethane (20 ml) were added, and the solution was stirred for an additional 24 h. T.l.c. in 7:7:1 (v/v) benzene–ether–methanol showed complete disappearance of **1**. The reaction mixture was cooled in ice–water and washed with ice-cold saturated aqueous sodium hydrogencarbonate (100 ml), then twice with ice-cold saturated aqueous sodium chloride (100 ml), and finally dried (sodium sulfate). Evaporation of the solvents yielded a foam that crystallized on trituration with dry ether (6.5 g, 99%). Recrystallization from acetone–ether gave pure **3** (5.1 g, 78%), m.p. 135–136°, $[\alpha]_D^{20}$ −30.5° (*c* 0.94, chloroform); i.r. data: ν_{max}^{KBr} 3300 (NH), 3080, 3060 and 3025 (Ph), 1740 (OAc), 1660 (Amide I), 1540 (Amide II), 1225 (OAc), 750, and 700 cm^{-1} (Ph); n.m.r. data: δ 7.47–7.33 (m, 10 H, 2 Ph), 5.85 (d, 1 H, NH), 5.54 (s, 1 H, PhCH), 2.11 (s, 3 H, NAc), and 1.96–1.92 (12 H, 4 OAc).

Anal. Calc. for $C_{36}H_{43}NO_{15}$: C, 59.25; H, 5.94; N, 1.92; O, 32.89. Found: C, 58.84; H, 5.93; N, 1.96; O, 32.98.

Benzyl 2-acetamido-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**4**). — To a solution of **3** (10 g, 13.7 mmol) in glacial acetic acid (36 ml) at 100°, hot water (24 ml) was added. The mixture was kept at 100° for 15 min. T.l.c. in 9:1 (v/v) chloroform–ethanol showed complete hydrolysis. The solution was cooled and evaporated; the residue, after being dried by repeated azeotropic distillation with toluene, crystallized from ethanol (5.6 g, 64%). An analytical sample was obtained by chromatography on silica gel with 9:1 (v/v) chloroform–ethanol, m.p. 176–177°, $[\alpha]_D^{20}$ −14° (*c* 3.39, chloroform); i.r. data: ν_{max}^{KBr} 3460 (OH), 3290 (NH), 3080, 3060, and 3020 (Ph), 1740 (OAc), 1655 (Amide I), 1545 (Amide II), 1220 (OAc), 740, and 700 cm^{-1} (Ph).

Anal. Calc. for $C_{29}H_{39}NO_{15}$: C, 54.28; H, 6.13; N, 2.18; O, 37.41. Found: C, 54.26; H, 6.09; N, 2.36; O, 37.40.

Benzyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**5**). — A solution of **4** (4.8 g, 7.5 mmol) in pyridine (15 ml) was treated with acetic anhydride (15 ml) overnight at room temperature. Evaporation and codistillation with toluene gave a residue that crystallized from acetone–ether (5.05 g, 93%), m.p. 150–151°, $[\alpha]_D^{20}$ −26° (*c* 2.01, chloroform); i.r. data: ν_{max}^{KBr} 3260 (NH), 3080, 3060, and 3020 (Ph), 1740 (OAc), 1650 (Amide I), 1555 (Amide II), 1220 (OAc), 740, and 700 cm^{-1} (Ph); n.m.r. data: δ 7.30 (5 H, Ph), 5.85 (d, 1 H, NH), and 2.14–1.89 (21 H, NAc and 6 OAc).

Anal. Calc. for $C_{33}H_{43}NO_{17}$: C, 54.62; H, 5.97; N, 1.93; O, 37.48. Found: C, 54.42; H, 5.71; N, 2.03; O, 37.38.

2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyl)-D-glucopyranose (**6**). — (*a*). A solution of **5** (1 g, 1.4 mmol) in 90% ethanol (50 ml) was hydrogenated catalytically with 10% palladium-on-charcoal (0.5 g) overnight, at room temperature and atmospheric pressure. The catalyst was removed and the filtrate evaporated to a foamy residue (0.86 g, 98%). An analytical sample was obtained by chromatography on silica gel with 9:1 (v/v) chloroform–ethanol, $[\alpha]_D^{20}$ +6→+9° (*c* 1.93, ethanol–water, 9:1, v/v); i.r. data: ν_{max}^{KBr}: 3440–3360 (OH and NH), 1730 (OAc), 1655 (Amide I), 1530 (Amide II), and 1225 cm^{-1} (OAc); n.m.r. data: δ 6.31 (d, 1 H, NH) and 2.18–1.90 (21 H, NAc and 6 OAc).

Anal. Calc. for $C_{26}H_{37}NO_{17}$: C, 49.13; H, 5.87; N, 2.20; O, 42.80. Found: C, 49.00; H, 5.76; N, 2.19; O, 42.82.

Crude compound **6** (3 g, 4.7 mmol) was acetylated with acetic anhydride (6 ml) in pyridine (6 ml) overnight at room temperature. The solution was evaporated to dryness. The residue crystallized from ethanol to give the pure α-D anomer **7** (1.45 g, 45%), m.p. 111–112°, $[\alpha]_D^{20}$ +25° (*c* 2.13, chloroform): n.m.r. data: δ 6.06 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.61 (d, 1 H, NH), and 2.19–1.94 (24 H, NAc and 7 OAc).

Anal. Calc. for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07; O, 42.50. Found: C, 49.38; H, 5.59; N, 1.94; O, 42.61.

The mother liquor was fractionated by column chromatography on silica gel (200 g) with 93:7 (v/v) chloroform–ethanol, 12-ml fractions being collected. Fractions 25–35 contained the pure β-D anomer **8** (0.875 g, 27%), which could not be crystallized, $[\alpha]_D^{20}$ −2° (*c* 4.16, chloroform); n.m.r. data: δ 6.21 (d, 1 H, NH), 5.83 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), and 2.13–1.93 (24 H, NAc and 7 OAc).

Anal. Calc. for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07; O, 42.50. Found: C, 49.44; H, 5.78; N, 1.85; O, 42.42.

Fractions 36–45 contained a mixture of **7** and **8** (0.350 g, 11%). Fractions 46–49 gave more crystalline α-D anomer **7** (0.385 g, 12%).

(*b*). A solution of **5** (1 g, 1.4 mmol) in dry 1,4-dioxane (50 ml) was hydrogenated catalytically with 10% palladium-on-charcoal (1 g) for 40 h, at room temperature and atmospheric pressure. The catalyst was removed and the filtrate evaporated to an amorphous residue (0.88 g, 100%), which was chromatographically identical to **6** (t.l.c. in 9:1, v/v, chloroform–ethanol), $[\alpha]_D^{20}$ +1° (*c* 1.27, chloroform); upon addition of a trace of hydrochloric acid, the rotation changed within 24 h to +11°.

Compound **6** (1 g, 1.6 mmol), obtained by hydrogenation of **5** in 1,4-dioxane, was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) overnight at 0°. Evaporation of the solution gave almost pure β-D anomer **8** (1.1 g, 100%); t.l.c. in 9:1 (v/v) chloroform–ethanol showed the product to be slightly contaminated with a trace of α-D anomer **7**.

2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyl)-α-D-glucopyranosyl chloride (**9**). — A solution of **7** (2.24 g, 3.3 mmol) in acetyl chloride (23 ml) was saturated at −20° with dry hydrogen chloride. After being kept at room temperature for 48 h, the solution was evaporated. The dry residue was

crystallized from dichloromethane–ether (1.47 g, 68%), m.p. 130–131°, $[\alpha]_D^{20}$ +44° (*c* 0.94, chloroform); i.r. data: ν_{max}^{KBr} 3360 (NH), 1745 (OAc), 1675 (Amide I), 1530 (Amide II), 1230 (OAc), and 770 cm^{-1} (CCl); n.m.r. data: δ 6.10 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.80 (d, 1 H, NH), and 2.14–1.97 (21 H, NAc and 6 OAc).

Anal. Calc. for $C_{26}H_{36}ClNO_{16}$: C, 47.75; H, 5.55; N, 2.14; O, 39.14. Found: C, 47.82; H, 5.45; N, 2.32; O, 39.15.

The same compound was obtained in identical yield when the β-D anomer **8** or a mixture of the α-D and β-D anomers (**7** and **8**) were used as starting materials.

2-Methyl-[4,6-di-O-acetyl-1,2-dideoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyl)-α-D-glucopyrano][2′,1′:4,5]-2-oxazoline (**10**). — (*a*). A solution of tetraethylammonium chloride (0.185 g, 1.1 mmol) in dry acetonitrile (8 ml) was boiled until 5 ml of the solvent had distilled. To the cooled solution were added sodium hydrogencarbonate (0.185 g, 2.2 mmol) and a solution of chloride **9** (0.640 g, 0.98 mmol) in dry acetonitrile (1 ml). The reaction mixture was stirred for 20 min at 60°, after which time t.l.c. in 7:7:1 (v/v) benzene–ether–methanol showed the starting material to have reacted. The solvent was removed and the residue dissolved in dichloromethane (12 ml). The solution was washed three times with water (6 ml), dried (sodium sulfate), and evaporated to give a foam (0.500 g, 83%). The oxazoline **10** was contaminated by the product of hydrolysis **6** and was purified by column chromatography on silica gel with 10:10:1 (v/v) chloroform–ether–methanol to give a syrup (0.360 g, 60%), $[\alpha]_D^{20}$ +5° (*c* 2.955, chloroform); i.r. data: ν_{max}^{KBr} 1740 (OAc), 1667 (C=N), and 1225 cm^{-1} (OAc); the NH and Amide II bands were absent.

Anal. Calc. for $C_{26}H_{35}NO_{16}$: C, 50.56; H, 5.71; N, 2.27. Found: C, 50.68; H, 5.89; N, 2.23.

(*b*). A solution of **8** (0.700 g, 1 mmol) in dichloromethane (20 ml) containing anhydrous ferric chloride (0.400 g, 2.5 mmol) was stirred at room temperature under anhydrous conditions. After 4 h, t.l.c. in 9:1 (v/v) chloroform–ethanol showed complete disappearance of the starting material. The reaction mixture was diluted with dichloromethane (35 ml), washed four times with water (20 ml), and dried (sodium sulfate). Evaporation gave a syrup (0.580 g, 91%) that contained the oxazoline **10** slightly contaminated by the product of hydrolysis **6**, as shown by t.l.c. in 10:10:1 (v/v) chloroform–ether–methanol. This compound was identical in every respect to the product obtained from the chloride **9**.

A solution of the oxazoline **10** (0.390 g, 0.6 mmol) in dry benzyl alcohol (1.6 ml) containing *p*-toluenesulfonic acid monohydrate (6 mg) was stirred at room temperature under anhydrous conditions. After 48 h, t.l.c. in 7:7:2 (v/v) benzene–ether–methanol showed the formation of the expected compound **5**, but also the presence of unreacted oxazoline. Benzyl alcohol (2.4 ml) and *p*-toluenesulfonic acid monohydrate (4 mg) were added, and the reaction mixture was stirred for a further 24 h, after which time the oxazoline had completely disappeared. After addition of pyridine (0.2 ml), the solution was evaporated and the residue was chromatographed on silica gel in 5:5:1 (v/v) chloroform–ether–methanol. The first-eluted fractions contained benzyl alcohol, and then **5** was eluted and crystallized from acetone–ether

(0.175 g, 38%), m.p. 150–152°, $[\alpha]_D^{20}$ −28° (*c* 1.74, chloroform). The fractions eluted last from the column contained the product of hydrolysis **6**.

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