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Note

A convenient synthesis of laminarabiose and some of its glycosides

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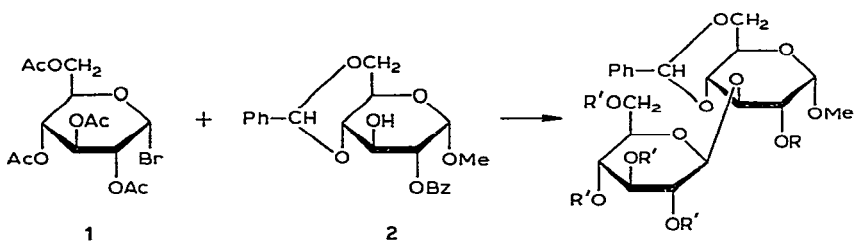
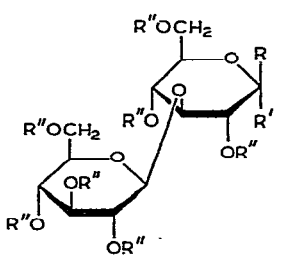
Further extension of our study of the chemical modifications[1] and the selective acylations[2] of oligosaccharides required the preparation of substantial quantities of laminarabiose (3-*O*-β-D-glucopyranosyl-D-glucopyranose) (**5**) and some of its β-glycosides such as methyl[3] (**12**) and benzyl β-laminarabioside (**14**). Compound **5** has been obtained on partial acid hydrolysis of laminaran[4] and pachyman[5], but the isolation required a tedious chromatographic separation. The chemical synthesis of **5** by the Koenigs–Knorr condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) with 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose[3,6] or benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside[7], followed by removal of the protecting groups, has been reported, but the reactions always resulted in extensive acetal migration[3,6,7],



1 2

3 R = Bz, R′ = Ac
4 R = R′ = H



5 R, R′ = H, OH, R″ = H
6 R = R″ = H, R′ = OMe
7 R = H, R′ = OMe, R″ = Ac
8 R = H, R′ = OAc, R″ = Ac
9 R = OAc, R′ = H, R″ = Ac
10 R = H, R′ = Br, R″ = Ac
11 R = OMe, R′ = H, R″ = Ac
12 R = OMe, R′ = R″ = H
13 R = OBzl, R′ = H, R″ = Ac
14 R = OBzl, R′ = R″ = H
15 R = OPh, R′ = H, R″ = Ac
16 R = OPh, R′ = R″ = H

leading to a low yield of **5**. A synthesis based on a modified orthoester method, and giving **5** in 23% yield, has been devised[8]; the procedure is, however, rather laborious and time consuming for a large-scale preparation of **5**. Recently, silver trifluoromethanesulfonate (triflate) has been reported to be an efficient catalyst for the synthesis of several 1,2-*trans*-linked disaccharide derivatives, in conjunction with 1,1,3,3-tetramethylurea as a proton acceptor[9]. Using this combination of catalyst and acid acceptor, we were able to develop a convenient synthetic method of **5** and its glycosides, such as methyl α-laminarabioside[10] (**6**), and methyl (**12**), benzyl (**14**), and phenyl β-laminarabioside (**16**), by condensation of **1** with readily available methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside[11-13] (**2**).

Reaction of **2** with 1.3 mol. equiv. of **1** in the presence of silver triflate and 1,1,3,3-tetramethylurea in dichloromethane under rigorously anhydrous conditions for 6 h at room temperature gave a mixture from which methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**3**) was directly isolated in crystalline form in 62% yield. *O*-Deacylation of **3** with methanolic sodium methoxide gave crystalline methyl 4,6-*O*-benzylidene-3-*O*-β-D-glucopyranosyl-β-D-glucopyranoside (**4**), which on treatment with aqueous acetic acid afforded the known compound[10] **6**, thus confirming the structure of **3**. The overall yield of **6** *via* **3** and **4** was 52% yield based on **2**. Acetylation of **6** gave crystalline methyl α-laminarabioside heptaacetate[10,14] (**7**). In a parallel experiment, an attempt to condense **1** with 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose under conditions similar to those described for **2** gave a mixture of at least seven products (t.l.c.), which were not separated on a column of silica gel. Furthermore, attempts to condense **1** with **2** under the classical Koenigs–Knorr conditions[15] using silver carbonate or silver oxide as the acid acceptors were unsuccessful; no formation of **3** was observed (t.l.c.).

Preliminary experiments of the acetolysis of **7** showed that the conditions employed previously for the acetolysis of a sophorose derivative[16] could be applied to the acetolysis of the derivative of **5**, without anomerization[17] and cleavage of the interglycosidic linkage. Treatment of **7** with 2% sulfuric acid in acetic anhydride for 4 h at room temperature gave, in 91% yield, α-laminarabiose octaacetate[3] (**8**) having physical constants in good agreement with those given in the literature[3]. Although Bächli and Percival[3] reported that their sample of **8** was slightly contaminated with β-laminarabiose octaacetate (**9**), as judged from the value of the optical rotation, the n.m.r. spectrum (chloroform-*d*) of **8** described here clearly indicates the absence of an H-1 resonance due to the β anomer **9**. The overall yield of **8** *via* **4**, **6**, and **7** from **3** was 71%. Subsequently, it was found that **8** could be prepared more conveniently from **3** without the isolation of **4**, **6**, and **7**. Thus, sequential treatment of **3** with methanolic sodium methoxide, aqueous acetic acid, acetic anhydride–pyridine, and 2% sulfuric acid in acetic anhydride afforded **8** in 86% yield. *O*-Deacetylation of **8** gave, in 91% yield, crystalline **5**, which on acetylation produced the β-octaacetate[3] (**9**). In a simplified approach to **5**, successive acetolysis of **3** under the same conditions as described for **7** and *O*-deacylation of the product

gave crystalline **5** in 65% yield; the overall yield (based on **2**) of **5** *via* **3** was 40%. Since **2** is readily prepared[12,13] from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in high yield (78–86%), and no chromatographic purification is needed in the just described reaction sequence **1** + **2**→**3**→**5**, this relatively simple, two-step procedure appears to be practical for the preparation of substantial amounts of **5**.

The α-octaacetate **8** was converted, in 91% yield, into crystalline 2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosyl bromide[3] (**10**) with hydrogen bromide in acetic acid. Methanolysis of **10** in the presence of mercuric cyanide in benzene gave methyl β-laminarabioside heptaacetate[3] (**11**) which on *O*-deacetylation furnished **12**. Condensation of **10** with benzyl alcohol in the presence of mercuric cyanide produced crystalline benzyl β-laminarabioside heptaacetate (**13**). This was *O*-deacetylated to give crystalline **14**, which is a useful starting material for the chemical modification of **5**. Treatment[18,19] of **10** with phenol and potassium hydroxide in 50% aqueous acetone afforded crystalline phenyl β-laminarabioside heptaacetate (**15**), which was *O*-deacetylated to give **16** in crystalline form. The n.m.r. spectra of **14** and **16** in deuterium oxide showed the H-1 resonances at δ 4.71 as a doublet with *J* 7.5 Hz and δ 5.15 as a doublet with *J* 7.5 Hz, respectively, consistent with the β configuration at C-1. The availability of the α-bromide **10** (49% yield based on **2**), without resort to column chromatography, by the reaction sequence **1** + **2**→**3**→**8**→**10** will make a number of hitherto unavailable β-glycosides of **5** accessible, as shown by the preparation of **14** and **16**.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto hot-stage microscope and are uncorrected. Optical rotations were measured with an Ohyo Denki automatic polarimeter, Model MP-1T. N.m.r. spectra were recorded with a Varian A-60 spectrometer, tetramethylsilane (in chloroform-*d* and dimethyl sulfoxide-d_6) and 2,2-dimethyl-2-silapentane-5-sulfonate (in deuterium oxide) being the internal standards. T.l.c. was performed on Silica gel No 7731 (Merck) with 4:1 (v/v) benzene–ethyl acetate as a developer, detection being effected by spraying the plates with 5% sulfuric acid in ethanol, followed by heating. Dichloromethane and 1,1,3,3-tetramethylurea were dried with calcium hydride and purified by distillation prior to use. Compounds **1** and **2**, and silver triflate, were dried for 20 h in a high vacuum before use. Unless otherwise stated, solutions were evaporated at a bath temperature below 40° under reduced pressure.

*Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside* (**3**). — A solution of **1** (13.8 g, 33.6 mmol) in dichloromethane (30 mL) was added dropwise over a period of 30 min at room temperature, with rigorous exclusion of moisture and light, to a stirred solution of **2** (10 g, 25.9 mmol), silver triflate (9.6 g, 37.4 mmol), and 1,1,3,3-tetramethylurea (11.2 mL, 93.4 mmol) in dichloromethane (120 mL). The mixture was stirred for 6 h at room temperature, after which t.l.c. indicated the absence of **1**. The mixture was then

filtered through a Celite pad and the solid was washed with dichloromethane. The combined filtrates were washed successively with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and evaporated to a syrup, which was crystallized from ethanol and recrystallized from ethanol–chloroform to give **3** (11.5 g, 62%), m.p. 185–186°, $[\alpha]_D^{20}$ +35.3° (*c* 1.7, chloroform); t.l.c.: R_F 0.47; n.m.r. (chloroform-*d*): δ 8.22–7.25 (m, 10 H, 2 Ph), 5.60 (s, 1 H, benzylic H), 3.38 (s, 3 H, OMe), 1.97, 1.95, 1.88, and 1.57 (s, 12 H, 4 OAc).

Anal. Calc. for $C_{35}H_{40}O_{16}$: C, 58.66; H, 5.63. Found: C, 58.78; H, 5.60.

*Methyl 4,6-*O*-benzylidene-3-*O*-β-*D*-glucopyranosyl-α-*D*-glucopyranoside* (**4**). — A solution of **3** (8 g) in dry methanol (80 mL) was treated with methanolic M sodium methoxide (1 mL), and the solution was kept for 1 h at room temperature. The mixture was diluted with water, neutralized with Amberlite IR-120 (H^+) cation-exchange resin, filtered, and evaporated to give a white solid, which on recrystallization from ethanol gave **4** (4.66 g, 94%), m.p. 245–246.5°, $[\alpha]_D^{20}$ +34.2° (*c* 0.7, methanol); n.m.r. (dimethyl sulfoxide-d_6): δ 7.57–7.25 (m, 5 H, Ph), 5.60 (s, 1 H, benzylic H), 4.72 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), and 3.33 (s, 3 H, OMe).

Anal. Calc. for $C_{20}H_{28}O_{11}$: C, 54.05; H, 6.35. Found: C, 54.21; H, 6.40.

*Methyl 3-*O*-β-*D*-glucopyranosyl-α-*D*-glucopyranoside* (**6**). — A solution of **4** (4.5 g) in 60% acetic acid (60 mL) was heated for 20 min at 100°. The solvents were evaporated and the last traces of volatile compounds were removed by repeated codistillation with toluene. Crystallization of the residue from ethanol–ether gave **6** (3.25 g, 90%), m.p. 180–182°, $[\alpha]_D^{20}$ +85.6° (*c* 1.5, water); lit.[10] m.p.: 177–179° (ethanol–ether), $[\alpha]_D$ +85° (*c* 1.37, water).

*Methyl 2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-glucopyranoside* (**7**). — Conventional acetylation of **6** (3 g) with 1:1 (v/v) acetic anhydride–pyridine (30 mL) overnight at room temperature and isolation in the usual way gave **7** (5.1 g, 93%), m.p. 192–193° (ethanol), $[\alpha]_D^{20}$ +37.7° (*c* 1.5, chloroform); lit.[14] m.p. 193–194°, $[\alpha]_D^{23}$ +38.0° (*c* 2.5, chloroform).

*1,2,4,6-Tetra-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-α-*D*-glucopyranose* (**8**). — *From* **7**. To a solution of **7** (2 g) in acetic anhydride (2.5 mL), cooled in an ice-bath, was slowly added 4% (v/v) sulfuric acid in acetic anhydride (2.5 mL). When the solution was complete, the mixture was stirred for 4 h at room temperature, poured into ice–water containing sodium hydrogencarbonate, and the product extracted with chloroform (4 × 20 mL). The extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and concentrated to give a crystalline mass, which on recrystallization from ethanol afforded **8** (1.91 g, 91%), m.p. 77–78°, $[\alpha]_D^{20}$ +20.5° (*c* 2.1, chloroform); n.m.r. (chloroform-*d*): δ 6.26 (s, 1 H, $J_{1,2}$ 3.5 Hz, H-1); lit.[3] m.p. 77–78° (ethanol), $[\alpha]_D^{17}$ +20° (*c* 3.6, chloroform).

From **3**. Sequential treatment of **3** (10 g) with M sodium methoxide (2 mL) in methanol (100 mL), 60% acetic acid (80 mL), 1:1 (v/v) acetic anhydride–pyridine (50 mL), 2% sulfuric acid in acetic anhydride (40 mL), as described earlier, gave **8** (8.14 g, 86%), m.p. and mixed m.p. 77–78°, $[\alpha]_D^{20}$ +20.5° (*c* 2.0, chloroform).

3-O-β-D-*Glucopyranosyl-*D*-glucopyranose* (**5**). — *From* **8**. *O*-Deacetylation of **8**

(3 g), as described for the preparation of **4**, gave **5** (1.38 g, 91%), m.p. 202–204° (aqueous methanol), $[\alpha]_D^{20}$ +14.8° (10 min)→+18.5° (24 h, constant, *c* 2.0, water); lit.[3] m.p. 204–206° (ethanol), $[\alpha]_D^{16}$ +24.9 (20 min)→+18.6° (9 h, constant, *c* 2.5, water); lit.[8] m.p. 196–198° (aqueous methanol), $[\alpha]_D$ +15° (10 min)→+18.5° (24 h, *c* 3.0, water).

From **3**. A solution of **3** (10 g) in acetic anhydride (20 mL) was treated, as described for **7**, with 4% sulfuric acid in acetic anhydride (20 mL) for 4 h at room temperature. The mixture was poured onto a mixture of ice and solid sodium hydrogencarbonate, and the product extracted with chloroform (4 × 80 mL). The combined extracts were washed with water (4 × 60 mL), dried ($MgSO_4$), and concentrated to a syrup, which was further dried by repeated codistillation of water with added absolute ethanol. The dried syrup was dissolved in methanol (100 mL), M sodium methoxide (2 mL) was added, and the solution was stirred for 1 h at room temperature. The solution was diluted with methanol and passed through columns of Amberlite IR-120 (H^+) and IR-45 (OH^-) ion-exchange resins. The resins were washed with 1:1 (v/v) methanol–water, and the combined eluate and washings were evaporated to a syrup. The syrup was dissolved in water (150 mL) and extracted with chloroform (3 × 40 mL). The combined chloroform extracts were washed with water, and the combined aqueous solutions evaporated to give a colorless syrup, which was crystallized and recrystallized from aqueous methanol to give **5** (3.12 g, 65%), m.p. and mixed m.p. 202–204°, $[\alpha]_D^{20}$ +15.5° (10 min)→+18.6° (24 h, *c* 2.3, water).

1,2,4,6-Tetra-O-*acetyl-3*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (**9**). — Compound **5** (2 g) was heated for 1.5 h on a boiling-water bath with sodium acetate (1 g) in acetic anhydride (12 mL). The precipitate, which separated on addition of ice–water, was filtered off, washed with water, dried, and crystallized from ethanol to give **9** (2.54 g, 64%), m.p. 161–162°, $[\alpha]_D^{20}$ −27.6° (*c* 1.2, chloroform); n.m.r. (chloroform-*d*): δ 5.63 (s, 1 H, $J_{1,2}$ 8.5 Hz, H-1); lit.[3] m.p. 160–161°, $[\alpha]_D^{18}$ −28.8° (*c* 2.5, chloroform).

2,3,4-Tri-O-*acetyl-3*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-α-D-*glucopyranosyl bromide* (**10**). — To a chilled solution of **8** (6 g) in acetic acid (18 mL) was added a saturated (at 0°) solution of hydrogen bromide in acetic acid (18 mL). The mixture was stirred for 2 h at room temperature, and then diluted with dichloromethane. The solution was washed successively with iced water, aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and evaporated to give a crystalline mass which on recrystallization from ethyl acetate–petroleum ether afforded **10** (5.62 g, 91%), m.p. 189–190°, $[\alpha]_D^{20}$ +86.5° (*c* 2.8, chloroform); lit.[3] m.p. 180.5–181.5° (chloroform–ether–petroleum ether), $[\alpha]_D^{18}$ +85° (*c* 3.0, chloroform).

Methyl 2,4,6-tri-O-*acetyl-3*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*β*-D-*glucopyranoside* (**11**). — Compound **10** (1.5 g) was dissolved in a mixture of anhydrous methanol (3 mL) and dry benzene (20 mL) containing mercuric cyanide (750 mg). The mixture was stirred for 3 h at room temperature and concentrated to a syrup, which was dissolved in chloroform. The solution was washed with water, dried

(Na_2SO_4), and evaporated. Crystallization of the residue from ethanol gave **11** (1.24 g, 89%), m.p. 164–165° and 179–181°, $[\alpha]_D^{20}$ −46.0° (*c* 1.2, chloroform); lit.[3] m.p. 164–165° and 179–180° (ethanol), $[\alpha]_D^{16}$ −45° (*c* 1.7, chloroform).

Methyl 3-O-β-D-glucopyranosyl-β-D-glucopyranoside (**12**). — *O*-Deacetylation of **11** (1.1 g), as described for the preparation of **4**, gave **12** (554 mg, 92%), m.p. 164–165° (ethanol–ether), $[\alpha]_D^{20}$ −28.8° (*c* 1.8, water); lit.[3] m.p. 165–166° (ethanol–ether), $[\alpha]_D^{19}$ −28° (*c* 2.5, water).

Benzyl 2,4,6-tri-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**13**). — Compound **10** (1.3 g) was dissolved in dry benzyl alcohol (16 mL) containing mercuric cyanide (1.1 g), and the mixture was stirred for 1.5 h at 80°. Most of the benzyl alcohol was removed *in vacuo* at 90° by repeated codistillation with water, and the residue was dissolved in chloroform. The solution was processed as described for **11**, and the resulting solid was recrystallized from ethanol to give **13** (2.7 g, 87%), m.p. 184–185°, $[\alpha]_D^{20}$ −53.8° (*c* 1.0, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.62; H, 5.76.

Benzyl 3-O-β-D-glucopyranosyl-β-D-glucopyranoside (**14**). — *O*-Deacetylation of **13** (2.5 g), as described earlier, gave **14** (1.3 g, 87%), m.p. 123–124°, (methanol–ether), $[\alpha]_D^{20}$ −49.6° (*c* 1.0, water).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.52. Found: C, 52.65; H, 6.69.

Phenyl 2,4,6-tri-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**15**). — A solution of phenol (800 mg) and potassium hydroxide (470 mg) in water (10 mL) was mixed with a solution of **10** (1.6 g) in acetone (10 mL), and the mixture was stirred for 6 h at room temperature. After evaporation of the solvent, a solution of the residue in benzene was washed successively with 2M sodium hydroxide and water, dried (Na_2SO_4), and evaporated to a syrup, which crystallized from ether–petroleum ether to give **15** (910 mg, 56%), m.p. 160–161°, $[\alpha]_D^{20}$ −41.5° (*c* 1.2, chloroform).

Anal. Calc. for $C_{32}H_{40}O_{18}$: C, 53.93; H, 5.66; Found: C, 54.02; H, 5.77.

Phenyl 3-O-β-D-glucopyranosyl-β-D-glucopyranoside (**16**). — *O*-Deacetylation of **14** (727 mg), as described earlier, gave **16** (363 mg, 85%), m.p. 129–131° (ethanol–ether), $[\alpha]_D^{20}$ −49.9° (*c* 0.7, water).

Anal. Calc. for $C_{18}H_{26}O_{11}$: C, 51.67; H, 6.26. Found: C, 51.52; H, 6.31.

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