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SYNTHESIS OF LYCOTETRAOSE

KEN'ICHI TAKEO*, TOSHIO NAKAJI, AND KAZUYUKI SHINMITSU
Department of Agricultural Chemistry, Kyoto Prefectural University, Shimogamo, Kyoto 606 (Japan)
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ABSTRACT

The title tetrasaccharide, namely, *O*-β-D-glucopyranosyl-(1→2)-*O*-[β-D-xylopyranosyl-(1→3)]-*O*-β-D-glucopyranosyl-(1→4)-D-galactose, has been synthesized by Koenigs–Knorr type of condensations in a stepwise manner by way of the preparation of the di- and tri-saccharide fragments, 4-*O*-β-D-glucopyranosyl-D-galactose (lycobiose) and *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-D-galactose (lycotriose I), using benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside as the starting glycosyl acceptor, and 2,3,4,6-tetra- and 2,4,6-tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl bromide and 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide as the glycosyl donors.

INTRODUCTION

A branched, reducing tetrasaccharide, *O*-β-D-glucopyranosyl-(1→2)-*O*-[β-D-xylopyranosyl-(1→3)]-*O*-β-D-glucopyranosyl-(1→4)-D-galactose (lycotetraose, **30**), is the carbohydrate moiety of such steroidal alkaloids from *Solanum* species as α-tomatine and demissine, from which it has been isolated after partial hydrolysis with acid, together with the component trisaccharide, *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-D-galactose (lycotriose I, **25**), as well as the two component disaccharides, 4-*O*-β-D-glucopyranosyl-D-galactose (lycobiose, **6**) and 2-*O*-β-D-glucopyranosyl-D-glucose (sophorose)[1,2]. The di- (**6**) and tri- (**25**) saccharide respectively form[2] the sugar portions of the closely related alkaloid glycosides, γ- and β_1-tomatine. Evidence has also been presented that the tetrasaccharide **30** occurs as the sugar moiety in F-gitonin[3], a saponin from the leaves of *Digitalis purpurea* L, and in the furostanol glycoside from the immature berries[4] of *Solanum nigrum* L, whereas the trisaccharide **25** constitutes the sugar portion of the furostanol glycosides from the seeds of *Lycoperisum esculentum* Miller[5] and from the stem parts of *Solanum lyratum* Thung[6].

We now report the synthesis of **6, 25,** and **30**. The disaccharide **6** had previously been synthesized as its methyl α-glycoside by condensation of methyl 2,3,6-

*To whom enquiries should be addressed.

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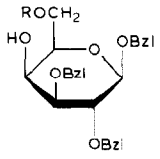
tri-*O*-benzoyl-α-D-galactopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**), followed by *O*-deacylation[7].

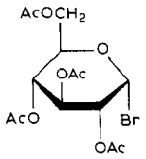
RESULTS AND DISCUSSION

Benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[8–10] (**2**), which corresponds to the reducing end of **30**, was used as the starting glycosyl acceptor. Compound **2** was recently prepared by three different methods[8–10] and obtained as a syrup. In our hands, however, compound **2**, prepared by regioselective benzylation of benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside[11] (**1**) by phase-transfer catalysis[9,12], was obtained in crystalline form.

Condensation of **2** with **3** in 1:1 benzene–nitromethane, in the presence of mercuric cyanide, gave a mixture shown by t.l.c. to contain a major product, accompanied by traces of marginally faster-moving, unreacted **2** that could not be removed by chromatography. When the mixture was *O*-deacetylated with sodium methoxide in methanol, benzyl 2,3,6-tri-*O*-benzyl-4-*O*-β-D-glucopyranosyl-β-D-galactopyranoside (**4**) crystallized directly from the products in 62% yield, and fractionation of the mother liquor on a column of silica gel afforded a further 27% yield of **4**. The ^{13}C-n.m.r. spectrum of **4** showed a signal for C-1′ at δ 104.73 with $^{1}J_{CH}$ 161.4 Hz, consistent[13] with the β configuration at C-1′. Catalytic hydrogenolysis of **4** in acetic acid in the presence of palladium-on-charcoal furnished **6**, whose physical constants were in good agreement with those given in the literature[1]. Acetylation of **6** with acetic anhydride and sodium acetate afforded β-lycobiose octaace-



1 R = H
2 R = Bzl
Bzl = $PhCH_2$



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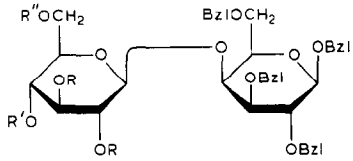
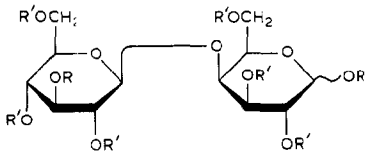
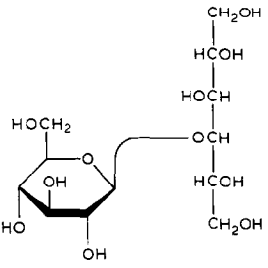


4 R = R′ = R″ = H
5 R = H, R^2, R^3 = PhCH



6 R = R′ = H
7 R = Ac (β anomer), R′ = Ac



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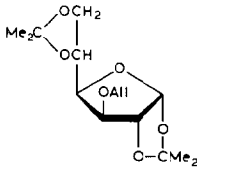
tate[1] **7**, whereas reduction of **6** with sodium borohydride produced 4-*O*-β-D-glucopyranosyl-D-galactitol[14] (lycobiitol, **8**). Treatment of **4** with α,α-dimethoxytoluene in acetonitrile, in the presence of *p*-toluenesulfonic acid, gave benzyl 2,3,6-tri-*O*-benzyl-4-*O*-(4,6-*O*-benzylidene-β-D-glucopyranosyl)-β-D-galactopyranoside (**5**).

In order to synthesize the tri- (**25**) and tetra- (**30**) saccharides, it was necessary to obtain a derivative of **5** having a temporary protecting-group at HO-3′, namely, benzyl 4-*O*-(3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**16**), and the synthesis of **16** was achieved by two different sequences of reactions. In the first route, *O*-deisopropylidenation of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[15] (**9**) by use of a cation-exchange resin[16] in water gave crystalline 3-*O*-allyl-β-D-glucopyranose[17] (**10**), to which the β configuration was assigned on the basis of noticeable, upward mutarotation ($[\alpha]_D$ +18.6 → +51.5°) in water. Ito *et al.*[17] had prepared **10** by hydrolysis of **9** in refluxing, dilute sulfuric acid, but did not report its optical rotation value. Acetylation of **10** with acetic anhydride and sodium acetate gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranose[18] (**11**) which, on treatment in dichloromethane at 0° with hydrogen bromide in acetic acid, afforded crystalline 2,4,6-tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl bromide (**12**). During the course of this work, a similar preparation of **12** was reported[18], but no physical data for **12**, obtained as a syrupy product, were given. Reaction of **2** with **12** in 1:1 benzene–nitromethane, in the presence of mercuric cyanide, and purification of the crude product by column chromatography, gave crystalline benzyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-allyl-β-D-glucopyranosyl)-β-D-galactopyranoside (**13**) in 87% yield. The β configuration at the nonreducing anomeric center was clear from the ^{1}H-n.m.r. signal for H-1′ at δ 4.43, with $J_{1',2'}$ 7.6 Hz, and the ^{13}C-n.m.r. signal for C-1′ at δ 101.42 with $^1J_{CH}$ 164.7 Hz.

Interestingly, the acetyl group on O-2′ in **13** resisted an attempt at conventional *O*-deacetylation. Treatment of **13** with a catalytic amount of sodium methoxide in methanol at room temperature led to exclusive formation of benzyl 4-*O*-(2-*O*-acetyl-3-*O*-allyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**14**); its structure was established by transformation with α,α-di-



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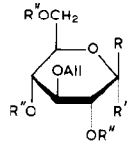
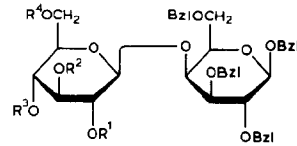
All = $H_2C{=}CH{-}CH_2$



10 R = OH, R′ = R″ = H
11 R = OAc, R′ = H, R″ = Ac
12 R = H, R′ = Br, R″ = Ac



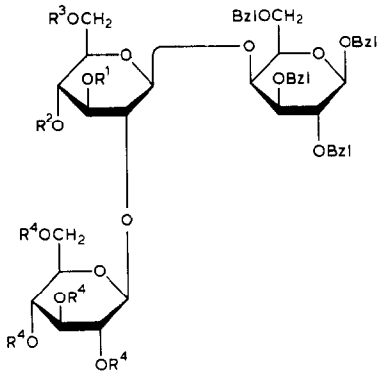
13 R^1 = R^3 = R^4 = Ac, R^2 = All
14 R^1 = Ac, R^2 = All, R^3 = R^4 = H
15 R^1 = R^3 = R^4 = H, R^2 = All
16 R^1 = H, R^2 = All, R^3, R^4 = PhCH
17 R^1 = Ac, R^2 = All, R^3, R^4 = PhCH
18 R^1 = All, R^2 = H, R^3, R^4 = PhCH

methoxytoluene and *p*-toluenesulfonic acid in acetonitrile into benzyl 4-*O*-(2-*O*-acetyl-3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**17**), identical to the compound described later.

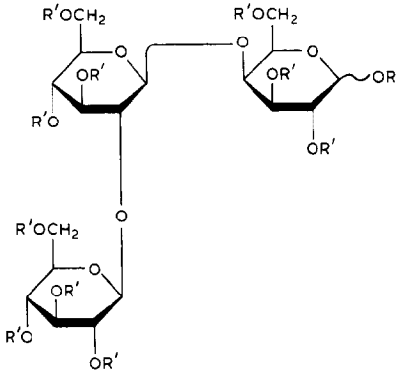
Heating of **13** or **14** in methanol under reflux, in the presence of sodium methoxide, readily removed the acetyl groups, to give crystalline benzyl 4-*O*-(3-*O*-allyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**15**), which was treated with α,α-dimethoxytoluene and *p*-toluenesulfonic acid in acetonitrile, to afford crystalline **16**. Acetylation of **16** produced **17**.

In a second route to **16**, regioselective allylation of the dibutylstannylene derivative of **5** in benzene with allyl bromide, in the presence of tetrabutylammonium bromide[10,19], gave, after column-chromatographic separation, the 2′- (**18**) and 3′-allyl (**16**) ethers in 34 and 54% yield, respectively. Compound **16** obtained by the two routes was identical in all respects.

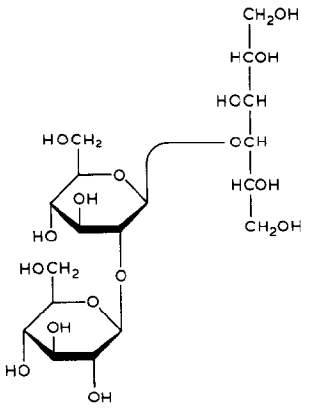
Coupling of **16** with **3** in toluene, in the presence of silver



19 R^1 = All, R^2, R^3 = PhCH, R^4 = Ac
20 R^1 = All, R^2, R^3 = PhCH, R^4 = H
21 R^1 = All, R^2 = R^3 = R^4 = H
22 R^1 = R^2 = R^3 = R^4 = H
23 R^1 = All, R^2 = R^3 = R^4 = Bzl
24 R^1 = H, R^2 = R^3 = R^4 = Bzl



25 R = R′ = H
26 R = Ac (β anomer), R′ = Ac



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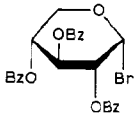
trifluoromethanesulfonate (triflate)[7,20], 2,4,6-trimethylpyridine[20], and molecular sieve, afforded, in 82% yield after column chromatography, the fully protected trisaccharide derivative **19**. The configuration at the newly introduced, interglycosidic linkage in **19** was supported by the ^{13}C-n.m.r. spectrum, which showed a signal for C-1″ at δ 99.40, with $^{1}J_{CH}$ 163.4 Hz, indicating[13] the β configuration at C-1″.

Successive removal of the protecting groups of **19** by a reaction sequence involving *O*-deacetylation of **19** (to give **20**), debenzylidenation of **20** with aqueous acetic acid (to give **21**), isomerization of the allyl group in **21** to a 1-propenyl group with tris(triphenylphosphine)rhodium(I) chloride[21,22], followed by hydrolysis of the resulting 1-propenyl group with dilute acid[23] (to give **22**), and catalytic hydrogenolysis of **22**, furnished **25**, which agreed in m.p. and specific rotation with the values given in the literature[1,2]. Acetylation of **25** with acetic anhydride and sodium acetate gave β-lycotriose I undecaacetate[1] **26**. Reduction of **25** with sodium borohydride provided *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-D-galactitol[2] (lycotriitol **I**, **27**); the optical rotation value agreed well with that described[2], but the m.p. was higher than that reported[2], suggesting that **27** crystallizes in two isomorphic forms.

Benzylation[24] of **21** with benzyl bromide and sodium hydride in *N,N*-dimethylformamide gave **23** in crystalline form. That isomerization of the allyl to 1-propanol group in **21** during the benzylation, such as observed[17] for the benzylation of allyl 3-*O*-allyl-D-glucopyranoside, had not taken place under the conditions[24] employed was indicated by the ^{13}C-n.m.r. spectrum, which clearly showed the presence of an allyl group and the absence of a 1-propenyl group in **23**. *O*-Deallylation of **23** with the rhodium complex, in the presence of 1,4-diazabicyclo[2.2.2]octane[22], followed by mild hydrolysis with acid, afforded the nona-*O*-benzyl trisaccharide derivative **24**, having HO-3′ free.

Glycosylation of **24** with 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide[25] (**28**) in nitromethane and toluene, in the presence of silver triflate, 2,4,6-trimethyl-



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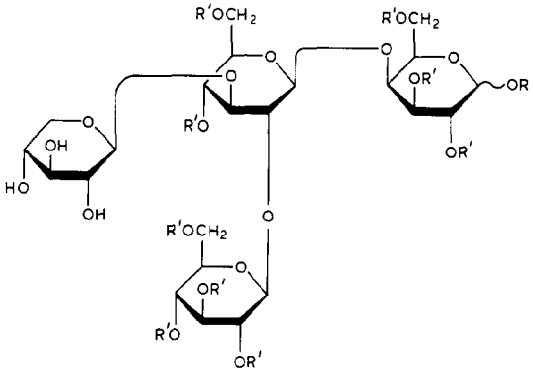

29 R = Bzl (β anomer), R′ = Bzl

30 R = R′ = H

pyridine, and molecular sieve, followed by *O*-debenzoylation to facilitate separation of the product, and column chromatography, gave benzyl *O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-(1→2)-*O*-[β-D-xylopyranosyl-(1→3)]-*O*-(4,6-di-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**29**) in 76% yield. In the ^{13}C-n.m.r. spectrum of **29**, the anomeric carbon atoms resonated at δ 103.92 ($^1J_{CH}$ 162.7 Hz), 103.10 ($^1J_{CH}$ 155.3 Hz), 100.47 ($^1J_{CH}$ 160.0 Hz), and 100.04 ($^1J_{CH}$ 155.3 Hz), which supported[13] the β configuration at each anomeric center in **29**. Catalytic hydrogenolysis of **29** furnished the title compound **30**, having physical constants in agreement with those reported[2] for this compound, isolated from the natural source.

EXPERIMENTAL

General methods. — Unless stated otherwise, the general experimental conditions were the same as those described previously[26]. N.m.r. spectra were recorded with a Jeol JNM-FX 200 spectrometer, both ^{1}H-n.m.r. (199.5 MHz) and ^{13}C-n.m.r. spectra (50.10 MHz) being obtained by use of the Fourier-transform (F.t.) mode. The values of δ_H and δ_C are expressed in p.p.m. downward from the internal standards, tetramethylsilane for solutions in chloroform-*d* and dimethyl sulfoxide-d_6, and sodium 4,4-dimethyl-4-silapentanoate-d_4 for solutions in deuterium oxide. The following solvent systems (v/v) were used for chromatography: (*1*) 4:1, (*2*) 2:1, and (*3*) 1:1 hexane–ethyl acetate, (*4*) 9:1 benzene–ethanol, (*5*) 1:1 benzene–ethyl acetate, (*6*) 4:1 chloroform–methanol, and (*7*) 8:1:1 1-butanol–pyridine–water.

*Benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside* (**2**). — A mixture of **1** (15.50 g, 34.4 mmol), tetrabutylammonium hydrogensulfate (4.67 g, 13.8 mmol), and benzyl bromide (13.9 mL, 120 mmol) in dichloromethane (570 mL) and 5% sodium hydroxide (100 mL) was stirred and boiled for 10 h under reflux. The mixture was cooled, and the two layers were separated. The organic layer was washed with water, dried, and evaporated to a syrup, which was fractionated on a column of silica gel. Elution with hexane removed the excess of benzyl bromide, and subsequent elution with solvent *1* gave **2** (15.05 g, 81%); m.p. 60–62° (from petroleum ether–diethyl ether), $[\alpha]_D^{24}$ −26.5° (*c* 1.5, chloroform); lit.[8] $[\alpha]_D$ −14°; $[\alpha]_D^{25}$ −27.8° (*c* 1.0, chloroform)[9]; $[\alpha]_D^{20}$ −15° (*c* 2.0, chloroform)[10].

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.70; H, 6.77.

*Benzyl 2,3,6-tri-*O*-benzyl-4-*O*-β-D-glucopyranosyl-β-D-galactopyranoside* (**4**). — A solution of **2** (8.04 g, 14.9 mmol) in 1:1 (v/v) benzene–nitromethane (320 mL) was boiled until ~80 mL of the solvent mixture had distilled off, and the mixture was then cooled to 45°. Mercuric cyanide (5.64 g, 22.3 mmol) and **3** (9.17 g, 22.3 mmol) were added, and the mixture was stirred for 17 h. The solution was evaporated to dryness, and the residue was dissolved in chloroform. The solution was washed successively with water, aqueous potassium bromide, and water, dried, and evaporated. A solution of the residual syrup in dry methanol (110 mL) was treated

with M sodium methoxide (7 mL). The solution was kept for 3 h at room temperature, made neutral with acetic acid, and evaporated. A solution of the residue in chloroform was washed with water, dried, and evaporated, giving a solid which was recrystallized twice from ethanol–hexane, to afford **4** (6.48 g, 62%); m.p. 113–114°, $[\alpha]_D^{24}$ −24.1° (*c* 1.2, chloroform); n.m.r. data (chloroform-*d*): δ_C 104.73 (C-1′, $^1J_{CH}$ 161.4 Hz) and 102.44 (C-1, $^1J_{CH}$ 159.9 Hz).

Anal. Calc. for $C_{40}H_{46}O_{11}$: C, 68.36; H, 6.60. Found: C, 68.24; H, 6.51.

The mother liquors were evaporated to a syrup that was fractionated on a column of silica gel with solvent *4*, to give an additional amount of **4** (2.70 g, 27%).

4-O-β-D-Glucopyranosyl-D-galactose (**6**). — A solution of **4** (1.98 g) in acetic acid (30 mL) was hydrogenolyzed in the presence of 10% palladium-on-charcoal (1.5 g) at atmospheric pressure for 1 day at room temperature. The catalyst was filtered off through a bed of Celite, and washed with hot water (50 mL). The filtrate and washings were combined, and evaporated to a syrup, which crystallized from aqueous methanol, to give **6** (0.86 g, 90%); m.p. 245–246° (dec.), $[\alpha]_D^{25}$ +65.7 → +41.1° (*c* 1.1, water); t.l.c. (2 ascents in solvent *7*): R_F 0.58; lit.[1] m.p. 246–247° (dec.) (from aqueous methanol), $[\alpha]_D^{20}$ +70 → +41.5° (*c* 1.0, water).

1,2,3,6-Tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-galactopyranose (**7**). — Compound **6** (0.32 g) was acetylated with acetic anhydride (5 mL) and sodium acetate (0.3 g) under reflux for 20 min. The mixture was cooled, and poured into ice–water, and the precipitate formed was filtered off, washed with water, and dried. Recrystallization from ethanol gave **7** (0.55 g, 87%); m.p. 177–178°, $[\alpha]_D^{26}$ +20.0° (*c* 1.6, chloroform); lit.[1] m.p. 165–166°, $[\alpha]_D^{20}$ +26.8° (*c* 1.064, ethanol); n.m.r. data (chloroform-*d*): δ_H 5.64 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.51 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1′), and 2.17–2.02 (24 H, 8 OAc); δ_C 101.23 (C-1′, $^1J_{CH}$ 162.7 Hz) and 91.86 (C-1, $^1J_{CH}$ 162.7 Hz).

4-O-β-D-Glucopyranosyl-D-galactitol (**8**). — Compound **6** (0.41 g) was reduced with sodium borohydride (40 mg) in water (15 mL) overnight at room temperature. The solution was treated with Amberlite IR-120 (H^+) ion-exchange resin to decompose the excess of hydride, the resin was filtered off and washed with methanol, and the filtrate and washings were combined and evaporated. Several additions and evaporations of methanol gave a solid, which was recrystallized from methanol, to afford **8** (0.34 g, 83%); m.p. 200–201°, $[\alpha]_D^{27}$ −13.9° (*c* 1.1, water); lit.[14] m.p. 204° (methanol), $[\alpha]_D$ −13° (*c* 1.1, water); n.m.r. data (dimethyl sulfoxide-d_6): δ_H 4.50 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′); δ_C 102.72 (C-1′, $^1J_{CH}$ 164.1 Hz).

Benzyl 2,3,6-tri-O-benzyl-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-β-D-galactopyranoside (**5**). — A mixture of **4** (6.11 g), α,α-dimethoxytoluene (2.5 g), and *p*-toluenesulfonic acid monohydrate (50 mg) in acetonitrile (60 mL) was stirred for 3 h at room temperature. The solution was made neutral with triethylamine, and evaporated to a syrup, which was purified by elution from a column of silica gel with solvent *3*, to give **5** as an amorphous powder (6.19 g, 90%); $[\alpha]_D^{27}$ −26.3° (*c* 2.0, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.55–7.23 (m, 25 H, arom. H), 5.48 (s, 1 H, benzylic H), and 2.91 (broad s, 2 H, disappeared on deuteration, OH-2′,3′).

Anal. Calc. for $C_{47}H_{50}O_{11}$: C, 71.36; H, 6.37. Found: C, 71.49; H, 6.48.

3-O-Allyl-β-D-glucopyranose (**10**). — A suspension of **9** (47.0 g) and Amberlite IR-120 (H^+) ion-exchange resin (90 g) in water (420 mL) was stirred for 7 h at 60°. The resin was filtered off, and washed with water. The filtrate and washings were combined and evaporated, to give a solid mass which, on recrystallization from ethanol–hexane, afforded **10** (30.1 g, 87%); m.p. 133.5–135°, $[\alpha]_D^{26}$ +18.6 → +51.5° (*c* 3.0, water); lit.[17] m.p. 126–128°.

1,2,4,6-Tetra-O-acetyl-3-O-allyl-β-D-glucopyranose (**11**). — Compound **10** (25.5 g) was acetylated with acetic anhydride (150 mL) and sodium acetate (25 g) under reflux for 25 min. Most of the solvent was evaporated, and the residue was poured into ice–water, and extracted with chloroform (3 × 100 mL). The extracts were combined, washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. Crystallization from ethanol gave **11** (37.9 g, 84%); m.p. 119–120°, $[\alpha]_D^{25}$ −1.5° (*c* 1.9, chloroform); lit.[18] m.p. 119–120° (from ethanol–hexane), $[\alpha]_D^{22}$ +4.7° (*c* 1.3, chloroform); n.m.r. data (chloroform-*d*): δ_H 6.13–5.53 (m, 1 H, -CH=), 5.67 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), and 2.09–2.07 (12 H, 4 OAc).

2,4,6-Tri-O-acetyl-3-O-allyl-α-D-glucopyranosyl bromide (**12**). — To a solution of **11** (10.2 g) in anhydrous dichloromethane (50 mL) at 0° was added a saturated solution of hydrogen bromide in acetic acid (50 mL) at 0°. The mixture was stirred for 30 min at 0°, diluted with dichloromethane, washed successively with iced water, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. Crystallization from petroleum ether–diethyl ether gave **12** (9.4 g, 88%); m.p. 69–70°, $[\alpha]_D^{26}$ +173.5° (*c* 1.7, chloroform); n.m.r. data (chloroform-*d*): δ_H 6.64 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 6.18–5.57 (m, 1 H, -CH=), and 2.13, 2.10, and 2.08 (s, each 3 H, 3 OAc).

Anal. Calc. for $C_{15}H_{21}BrO_8$: C, 44.03; H, 5.17. Found: C, 43.85; H, 5.28.

Benzyl 2,3,6-tri-O-benzyl-4-O-(2,4,6-tri-O-acetyl-3-O-allyl-β-D-glucopyranosyl)-β-D-galactopyranoside (**13**). — Treatment of **2** (7.95 g, 14.7 mmol) in 1:1 benzene–nitromethane (240 mL) with **12** (9.03 g, 22.1 mmol) and mercuric cyanide (5.57 g, 22.0 mmol) for 16 h at 45°, followed by processing as described for the preparation of **4**, gave a syrup, which was fractionated on a column of silica gel with solvent *2*, to afford **13** (11.12 g, 87%); m.p. 44–45° (petroleum ether–diethyl ether), $[\alpha]_D^{27}$ −23.4° (*c* 1.5, chloroform); n.m.r. data (chloroform-*d*): δ_H 5.83–5.72 (m, 1 H, -CH=), 5.23–5.11 (m, 2 H, $=CH_2$), 4.43 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), and 2.06, 2.01, and 1.92 (s, each 3 H, 3 OAc); δ_C 170.57, 169.27, and 169.13 (3 C=O), 134.54 and 116.82 (CH_2=CH), 102.67 (C-1, $^1J_{CH}$ 158.3 Hz), 101.42 (C-1', $^1J_{CH}$ 164.7 Hz), and 20.90, 20.81, and 20.68 (3 OAc).

Anal. Calc. for $C_{49}H_{56}O_{14}$: C, 67.73; H, 6.50. Found: C, 67.85; H, 6.66.

Benzyl 4-O-(2-O-acetyl-3-O-allyl-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-β-D-galactopyranoside (**14**). — A solution of **13** (4.45 g) in dry methanol (60 mL) was treated with methanolic M sodium methoxide (3 mL). The mixture was kept for 5 h at room temperature, made neutral with Amberlite IR-120 (H^+) ion-exchange

resin, the resin filtered off, and the filtrate evaporated. The resulting syrup was purified by elution from a column of silica gel with solvent *5*, to give **14** as an amorphous powder (3.70 g, 92%); $[\alpha]_D^{24}$ −24.7° (*c* 1.5, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.35–7.25 (m, 20 H, arom. H), 5.94–5.80 (m, 1 H, -CH=), 5.29–5.16 (m, 2 H, $=CH_2$), and 1.87 (s, 3 H, OAc); δ_C 169.27 (C=O), 134.72 and 116.75 (CH_2=CH), 102.42 (C-1), 101.88 (C-1′), and 20.69 (OAc).

Anal. Calc. for $C_{45}H_{52}O_{12}$: C, 68.86; H, 6.68. Found: C, 68.80; H, 6.54.

*Benzyl 4-O-(3-O-allyl-β-*D*-glucopyranosyl)-2,3,6-tri-O-benzyl-β-*D*-galactopyranoside* (**15**). — (*a*) A solution of **13** (5.42 g) in methanol (120 mL) was boiled with M sodium methoxide (10 mL) for 1 h under reflux. The solution was cooled, and processed as just described, to give **15** (4.31 g, 93%); m.p. 147–148° (ethanol), $[\alpha]_D^{26}$ −30.9° (*c* 2.0, chloroform); n.m.r. data (chloroform-*d*): δ_C 135.19 and 116.89 (CH_2=CH), 105.46 (C-1′), and 102.35 (C-1).

Anal. Calc. for $C_{43}H_{50}O_{11}$: C, 69.52; H, 6.78. Found: C, 69.40; H, 6.69.

(*b*) A solution of **14** (2.56 g) in methanol (30 mL) containing M sodium methoxide (3 mL) was boiled for 40 min under reflux, and processed as described in method *a*, to give **15** (2.20 g, 91%); m.p. and mixed m.p. 146–147°, $[\alpha]_D^{27}$ −30.2° (*c* 1.5, chloroform).

*Benzyl 4-O-(3-O-allyl-4,6-O-benzylidene-β-*D*-glucopyranosyl)-2,3,6-tri-O-benzyl-β-*D*-galactopyranoside* (**16**). — A mixture of **15** (5.20 g), α,α-dimethoxytoluene (2 g), and *p*-toluenesulfonic acid monohydrate (0.1 g) in acetonitrile (50 mL) was stirred for 2 h at room temperature. The acid was neutralized with Amberlite IR-400 (OH^-) ion-exchange resin, the resin filtered off, and the filtrate evaporated. The residue crystallized, and was recrystallized, from ethanol, to give **16** (5.12 g, 88%); m.p. 119–120°, $[\alpha]_D^{27}$ −22.7° (*c* 1.4, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.50–7.24 (m, 25 H, arom. H), 6.05–5.90 (m, 1 H, -CH=), 5.53 (s, 1 H, benzylic H), and 5.37–5.15 (m, 2 H, $=CH_2$); δ_C 135.23 and 116.53 (CH_2=CH), 106.21 (C-1′), 102.37 (C-1), and 101.08 (benzylic C).

Anal. Calc. for $C_{50}H_{54}O_{11}$: C, 72.27; H, 6.55. Found: C, 72.15; H, 6.60.

*Benzyl 4-O-(2-O-acetyl-3-O-allyl-4,6-O-benzylidene-β-*D*-glucopyranosyl)-2,3,6-tri-O-benzyl-β-*D*-galactopyranoside* (**17**). — (*a*) Treatment of **14** (0.46 g) with α,α-dimethoxytoluene (0.2 g) and *p*-toluenesulfonic acid monohydrate (50 mg) in acetonitrile (3 mL), as just described, and subsequent purification of the product by elution from a column of silica gel with solvent *2*, gave **17** as an amorphous solid (0.46 g, 90%); $[\alpha]_D^{20}$ −31.1° (*c* 1.8, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.49–7.18 (m, 25 H, arom. H), 5.81–5.70 (m, 1 H, -CH=), 5.52 (s, 1 H, benzylic H), and 1.91 (s, 3 H, OAc).

Anal. Calc. for $C_{52}H_{56}O_{12}$: C, 71.54; H, 6.47. Found: C, 71.64; H, 6.30.

(*b*) Compound **16** (0.37 g) was acetylated with 1:1 (v/v) acetic anhydride–pyridine (5 mL) overnight at room temperature. The mixture was evaporated, and coevaporated with toluene, to give a syrup which was eluted from a column of silica gel with solvent *2*, to afford **17** (0.36 g, 92%); $[\alpha]_D^{24}$ −32.3° (*c* 2.0, chloroform); the ^{1}H-n.m.r. spectrum was identical with that of the compound prepared by method *a*.

Regioselective allylation of **5**. — A mixture of **5** (4.26 g) and dibutyltin oxide (1.47 g) in benzene (150 mL) was boiled for 2 h under reflux, with azeotropic removal[19] of water. After ~30 min, the mixture became clear, and it was concentrated to ~100 mL. Tetrabutylammonium bromide (1.91 g) and allyl bromide (9.3 mL) were added, and the mixture was boiled for 20 h under reflux. The mixture was cooled, and evaporated to a syrup, which was dissolved in chloroform. The solution was washed with water, dried, and evaporated. The residue was fractionated on a pre-packed column of silica gel. Elution with solvent *1* gave **16** (2.42 g, 54%); m.p. and mixed m.p. 119–120°, $[\alpha]_D^{26}$ −23.1° (*c* 1.6, chloroform). Subsequent elution with solvent *2* afforded benzyl 4-*O*-(2-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**18**) as an amorphous powder (1.52 g, 34%); $[\alpha]_D^{25}$ −37.5° (*c* 1.8, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.60–7.17 (m, 30 H, arom. H), 6.22–5.68 (m, 1 H, -CH=), 5.45 (s, 1 H, benzylic H), and 3.02 (broad s, 1 H, disappeared on deuteration, OH-3′).

Anal. Calc. for $C_{50}H_{54}O_{11}$: C, 72.27; H, 6.55. Found: C, 72.41; H, 6.63.

Benzyl O-*(2,3,4,6-tetra*-O-*acetyl-β-*D-*glucopyranosyl)-(1→2)*-O-*(3*-O-*allyl-4,6*-O-*benzylidene-β-*D-*glucopyranosyl)-(1→4)-2,3,6-tri*-O-*benzyl-β-*D-*galactopyranoside* (**19**). — A mixture of **16** (6.15 g), silver triflate (4.19 g), 2,4,6-trimethylpyridine (2 mL), and molecular sieve 4A (10 g) in anhydrous toluene (60 mL) was stirred for 30 min at room temperature, with exclusion of moisture and light, and then cooled to −20°. A solution of **3** (6.09 g) in toluene (30 mL) was added dropwise during 30 min, with stirring. After being stirred for 1 h at −20°, the mixture was allowed to warm gradually to 0°, and the solids were removed by filtration, and washed with ether. The filtrate and washings were combined, washed successively with water, cold M hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The resulting syrup was fractionated on a column of silica gel with solvent *2*, to give **19** as an amorphous powder (7.05 g, 82%); $[\alpha]_D^{26}$ −31.7° (*c* 2.5, chloroform); n.m.r. data (chloroform-*d*): δ_H 7.48–7.24 (m, 25 H, arom. H), 6.04–5.88 (m, 1 H, -CH=), 5.50 (s, 1 H, benzylic H), 2.05 (s, 3 H, OAc), 1.96 (s, 6 H, 2 OAc), and 1.95 (s, 3 H, OAc); δ_C 170.17 (C=O), 169.97 (C=O), 168.90 (2 C=O), 135.02 and 116.84 (CH_2=CH), 102.66 (C-1, $^1J_{CH}$ 158.5 Hz), 100.98 (C-1 , $^1J_{CH}$ 164.8 Hz), 100.21 (benzylic C), 99.40 (C-1″, $^1J_{CH}$ 163.4 Hz), 20.69 (OAc), 20.40 (2 OAc), and 20.33 (OAc).

Anal. Calc. for $C_{64}H_{72}O_{20}$: C, 66.20; H, 6.25. Found: C, 66.03; H, 6.21.

Benzyl O-*β-*D-*glucopyranosyl-(1→2)*-O-*(3*-O-*allyl-β-*D-*glucopyranosyl)-2,3,6-tri*-O-*benzyl-β-*D-*galactopyranoside* (**21**). — Treatment of **19** (6.09 g) in methanol (80 mL) with M sodium methoxide (3 mL) for 3 h at room temperature, followed by processing as described for the preparation of **14**, gave benzyl *O*-β-D-glucopyranosyl-(1→2)-*O*-(3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**20**) as a syrup (4.95 g, 95%); $[\alpha]_D^{27}$ −43.9° (*c* 1.4, chloroform). A solution of **20** (4.56 g) in 60% acetic acid (70 mL) was stirred for 30 min at 90°, cooled, and evaporated, and the last trace of solvent was removed with the aid of repeated addition and evaporation of toluene. The residual syrup

was purified by passage through a column of silica gel with solvent *4*, to give **21** as an amorphous powder (3.83 g, 92%); $[\alpha]_D^{27}$ −25.6° (*c* 1.1, chloroform).

Anal. Calc. for $C_{49}H_{60}O_{16}$: C, 65.50; H, 6.68. Found: C, 65.69; H, 6.76.

O-β-D-*Glucopyranosyl-(1→2)*-O-β-D-*glucopyranosyl-(1→4)*-D-*galactose* (**25**). — A solution of **21** (1.51 g) in 7:3:1 (v/v/v) ethanol–toluene–water (50 mL) containing tris(triphenylphosphine)rhodium(I) chloride (0.25 g) was boiled for 20 h under reflux, cooled, and evaporated to dryness. The residue was dissolved in 9:1 (v/v) acetone–M hydrochloric acid (30 mL), and the mixture was boiled for 10 min under reflux, cooled, made neutral with aqueous sodium hydrogencarbonate, and evaporated to dryness. The residue was chromatographed on a column of silica gel with solvent *6*, to give benzyl *O*-β-D-glucopyranosyl-(1→2)-*O*-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**22**) as a syrup (1.19 g, 83%); $[\alpha]_D^{26}$ −10.4° (*c* 1.8, methanol). Hydrogenolysis of **22** (0.98 g) in acetic acid (15 mL) in the presence of 10% palladium-on-charcoal (0.8 g), followed by processing as described for the preparation of **6**, gave a solid which was recrystallized from aqueous methanol, to afford **25** (0.50 g, 88%); m.p. 248–249° (dec.), $[\alpha]_D^{26}$ +19.7 → +12.7° (*c* 1.4, water); t.l.c. (2 ascents in solvent *7*): R_F 0.48; lit. m.p. 260–261° (dec.) (from aqueous methanol), $[\alpha]_D^{20}$ +21 → +13.1° (*c* 1.4, water)[1]; m.p. 242–243° (from aqueous methanol); $[\alpha]_D^{25}$ +22 → +12.5° (*c* 1.0, water)[2].

O-*(2,3,4,6-Tetra*-O-*acetyl*-β-D-*glucopyranosyl)-(1→2)*-O-*(3,4,6-tri*-O-*acetyl*-β-D-*glucopyranosyl)-(1→4)-1,2,3,6-tetra*-O-*acetyl*-β-D-*galactopyranose* (**26**). — Acetylation of **25** (0.14 g) with acetic anhydride (3 mL) and sodium acetate (0.14 g), as described for the preparation of **7**, gave **26** (0.23 g, 85%); m.p. 120.5–122° (from diethyl ether–petroleum ether), $[\alpha]_D^{21}$ +17.9° (*c* 1.3, ethanol); lit.[1] m.p. ~120°, $[\alpha]_D^{20}$ +17.8° (*c* 1.04, ethanol); n.m.r. data (deuterium oxide): δ_H 5.59 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1), 4.61 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), and 2.13–1.99 (33 H, 11 OAc); δ_C 101.15 (C-1′, $^1J_{CH}$ 158.3 Hz), 101.00 (C-1″, $^1J_{CH}$ 161.2 Hz), and 92.21 (C-1, $^1J_{CH}$ 168.5 Hz).

O-β-D-*Glucopyranosyl-(1→2)*-O-β-D-*glucopyranosyl-(1→4)*-D-*galactitol* (**27**). — Reduction of **25** (0.19 g) with sodium borohydride (20 mg) in water (5 mL), as described for the preparation of **8**, gave **27** (0.15 g, 79%); m.p. 211–212° (from methanol), $[\alpha]_D^{25}$ −26.1° (*c* 1.3, water); lit.[2] m.p. 142° (from methanol), $[\alpha]_D^{24}$ −27° (*c* 0.5, water); n.m.r. data (deuterium oxide): δ_H 4.87 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′) and 4.68 (d, 1 H, $J_{1'',2''}$ 6.8 Hz, H-1″); δ_C 105.12 (C-1′, $^1J_{CH}$ 164.1 Hz) and 103.95 (C-1″, $^1J_{CH}$ 164.1 Hz).

Benzyl O-*(2,3,4,6-tetra*-O-*benzyl*-β-D-*glucopyranosyl)-(1→2)*-O-*(3*-O-*allyl-4,6-di*-O-*benzyl*-β-D-*glucopyranosyl)-(1→4)-2,3,6-tri*-O-*benzyl*-β-D-*galactopyranoside* (**23**). — A solution of **21** (2.02 g) in *N,N*-dimethylformamide (40 mL) was stirred for 1 h with sodium hydride (1.92 g; 50% in mineral oil) at room temperature. Benzyl bromide (4.73 mL) was added dropwise, and the mixture was stirred for 3 h at room temperature. Methanol was added, to decompose the excess of hydride, and most of the solvent was evaporated. A solution of the residue in chloroform was washed with water, dried, and evaporated, to give a syrup which

was fractionated on a column of silica gel with solvent *1*, affording **23** (3.23 g, 87%); m.p. 84–86° (from petroleum ether–diethyl ether), $[\alpha]_D^{26}$ +3.5° (*c* 1.1, chloroform); n.m.r. data (chloroform-*d*): δ_C 135.21 and 116.31 (CH_2=CH), 103.15 (C-1′ or -1″, $^1J_{CH}$ 153.7 Hz), 101.71 (C-1, $^1J_{CH}$ 163.6 Hz), and 101.08 (C-1′ or -1″, $^1J_{CH}$ 164.0 Hz).

Anal. Calc. for $C_{91}H_{96}O_{16}$: C, 75.63; H, 6.66. Found: C, 75.81; H, 6.52.

Benzyl O-*(2,3,4,6-tetra*-O-*benzyl-β*-D-*glucopyranosyl)-(1→2)*-O-*(4,6-di*-O-*benzyl-β*-D-*glucopyranosyl)-(1→4)-2,3,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**24**). — A mixture of **23** (2.57 g), tris(triphenylphosphine)rhodium(I) chloride (0.25 g), and 1,4-diazabicyclo[2.2.2]octane (1.5 g) in 8:3:1 (v/v/v) ethanol–toluene–water (90 mL) was boiled for 5 h under reflux. The mixture was cooled, evaporated to dryness, and extracted with chloroform. The extract was washed successively with water, cold M hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residue was dissolved in 9:1 acetone–M hydrochloric acid (50 mL). The solution was boiled for 15 min under reflux, cooled, made neutral with aqueous sodium hydrogencarbonate, evaporated, and the residue extracted with chloroform. The extract was washed with water, dried, and evaporated to a syrup which was chromatographed on a column of silica gel with solvent *1*, to give **24** as an amorphous powder (1.95 g, 78%); $[\alpha]_D^{27}$ +4.2° (*c* 0.9, chloroform).

Anal. Calc. for $C_{88}H_{92}O_{16}$: C, 75.19; H, 6.60. Found: C, 75.35; H, 6.77.

Benzyl O-*(2,3,4,6-tetra*-O-*benzyl-β*-D-*glucopyranosyl)-(1→2)*-O-[*β*-D-*xylopyranosyl-(1→3)*]-O-*(4,6-di*-O-*benzyl-β*-D-*glucopyranosyl)-(1→4)-2,3,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**29**). — To a stirred mixture, cooled to −30°, of **24** (1.58 g), silver triflate (0.69 g), 2,4,6-trimethylpyridine (0.28 mL), and molecular sieve 4A (5 g) in 1:1 (v/v) nitromethane–toluene (20 mL) was added dropwise a solution of **28** (1.18 g) in 1:1 nitromethane–toluene (10 mL). The mixture was stirred for 2 h at −20°, and allowed to warm to 0°. Processing of the mixture, as described for the preparation of **19**, gave a syrup. T.l.c. (solvent *2*) showed the presence of a major product that had a mobility similar to that of unreacted **24**. A solution of the syrup in methanol (20 mL) and dichloromethane (10 mL) was treated with M sodium methoxide (1 mL), and the mixture was kept overnight at room temperature, and processed as described previously. The residual syrup was fractionated on a column of silica gel with solvent *2*, to give **29** as an amorphous powder (1.31 g, 76%); $[\alpha]_D^{26}$ +3.9° (*c* 1.0, chloroform).

Anal. Calc. for $C_{93}H_{100}O_{20}$: C, 72.64; H, 6.55. Found: C, 72.86; H, 6.69.

O-*β*-D-*Glucopyranosyl-(1→2)*-O-[*β*-D-*xylopyranosyl-(1→3)*]-O-*β*-D-*glucopyranosyl-(1→4)*-D-*galactose* (**30**). — Hydrogenolysis of **29** (0.91 g), as described previously, gave a syrup which was purified by precipitation from water–ethanol, to afford **30** as an amorphous solid (0.31 g, 82%); m.p. 185–189° (dec.) after slight foaming at 177–180°, $[\alpha]_D^{26}$ +2.0° (*c* 1.2, water); lit.[2] m.p. ~188° after foaming at 180°, $[\alpha]_D^{22}$ +2° (*c* 0.5, water); t.l.c. (2 ascents in solvent *7*): R_F 0.36.

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