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Note

Standardized intermediates for oligosaccharide synthesis. A convenient preparation of partially protected derivatives of allyl *O*-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside suitable for chain extension at position O-4′

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During studies related to the chemistry of complex glycosphingolipids containing the sequence *O*-β-D-galactopyranosyl-(1 → 4)-D-glucose[1–3], we had undertaken the synthesis of partially protected derivatives of allyl β-D-lactoside in which the OH-4′ is free and, therefore, ready for chain extension at this position. Generally, an isopropylidene acetal[4–7] of unambiguous structure was readily converted into a lactoside with free OH-3 and OH-4 of the D-galactopyranose unit. In 1974, Wagner et al.[8] introduced the use of dibutylstannylene derivatives for the selective activation of a vicinal diol in nucleosides, and this approach has been successfully applied to carbohydrate derivatives[9]. We now describe the regioselective acylation and alkylation of the equatorial hydroxyl group in a vicinal equatorial–axial pair in lactoside derivatives, to give the disaccharide acceptors (**9**, **11**, **13**, and **16**).

Catalytic deacetylation of allyl hepta-*O*-acetyl-β-lactoside[10] (**1**) afforded allyl β-lactoside[11] (**2**), which was treated with 2,2-dimethoxypropane in the presence of camphorsulfonic acid[7] to give allyl *O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1 → 4)-D-glucopyranoside (**3**). Benzoylation of **3** gave the penta-*O*-benzoyl derivative **4**, which on treatment with 80% acetic acid afforded allyl *O*-(2,6-di-*O*-benzoyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**8**).

Treatment of **8** with dibutyltin oxide in boiling methanol[11–13] gave the unstable 3′,4′-*O*-dibutylstannylene derivative **7**, which was immediately treated with benzoyl chloride and triethylamine in 1,4-dioxane[12] at ambient temperature to give **9**

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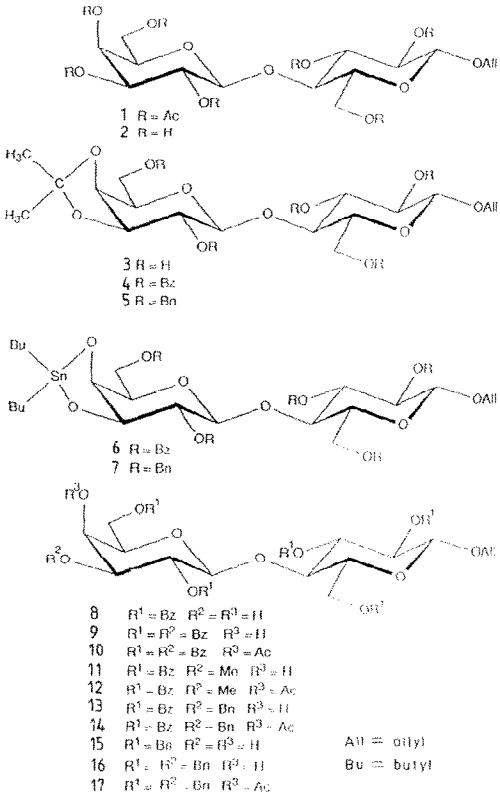

(78%). The characterization of compound **9** was based on its ^{1}H NMR spectrum, in which the signal for H-3′ was shifted down to δ 5.30–5.00. No 4′-*O*-benzoyl isomer could be detected (TLC).

For the synthesis of the 3′-*O*-methyl derivative **11**, compound **6** was treated with methyl iodide in *N*,*N*-dimethylformamide to give **11** (80%). Characterization of **11** was based on the ^{1}H NMR spectrum of its acetyl derivative **12**, which showed an additional, low-field broad doublet (δ 5.34) due to H-4′, now downfield relative to its position in **11**.

Benzylation of **7** with benzyl bromide in *N*,*N*-dimethylformamide was more difficult than expected, and gave the 3′-*O*-benzyl derivative **13** in only 60% yield. The ^{1}H NMR spectrum of the acetyl derivative **14** of **13** showed an additional, low-field broad doublet (δ 5.38) due to H-4′.

Benzylation of **3** gave the penta-*O*-benzyl derivative **5**, which on treatment with 80% acetic acid afforded allyl *O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**15**). Regioselective benzylation of **15** via its dibutylstannylene derivative **7** furnished the 3′-*O*-benzyl derivative **16** (80%). In

the ^{1}H NMR spectrum of its acetyl derivative **17**, H-4′ appeared as a broad doublet ($J_{3',4'}$, 3.1 Hz) at δ 5.66.

Dibutyltin oxide-mediated activation[11–13] of hydroxyl groups in carbohydrates has become a powerful tool in the preparation of selectivety protected saccharides. However, compatibility of this activation technique, especially the subsequent alkylation and acylation, with respect to other protective groups, has not been very well investigated. Our results show that the alkylation or acylation was more efficient in the case of compound **7** than for the corresponding benzoyl derivative **9**.

EXPERIMENTAL

General methods.—Melting points were measured with a Gallen-Kamp melting point apparatus and are uncorrected. Optical rotations were determined at 22°C with a Perkin–Elmer Model 241 polarimeter. ^{1}H NMR spectra were recorded at Glycomed, Inc. with a Varian Gemini 300-MHz spectrometer at ambient temperature, and ^{13}C NMR spectra with a Varian Gemini 300-MHz instrument operating at 75.50 MHz. Chemical shifts are referenced to Me_4Si as the internal standard. Liquid, secondary-ion mass spectrometry was performed on a Finnigan Mat TSQ-70, triple-stage quadrupole mass spectrometer equipped with an Antek Cs ion gun. 3-Nitrobenzyl alcohol (3-NBA) (Aldrich) was employed as the sample matrix. Separations were accomplished by open-column chromatography on Silica Gel 60 (70–230 mesh, Merck). TLC was performed on silica gel plates (250 μm, Merck). The following solvent combinations (v/v) were utilized for thin layer and column chromatography: (*A*) 29:1 $CHCl_3$–acetone and (*B*) 20:1 $CHCl_3$–MeOH. Elemental analyses were performed at the University of Hamburg, Germany.

Allyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1 → 4)-β-D-glucopyranoside (**1**).—2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-α-lactosyl bromide[13] (10 g, 14.3 mmol) was added to a stirred suspension of Ag_2O (4.0 g), Drierite (4.0 g), and allyl alcohol (28.0 mL) in 1:1 (v/v) C_6H_6–Et_2O (60 mL). The mixture was stirred for 20 h, then filtered (Celite), washed with Et_2O, and concentrated to dryness to give a crude syrup. Chromatography on a column of silica gel (solvent *A*) furnished **1** (6.8 g, 70%) as an amorphous solid; $[\alpha]_D$ − 14.3° (*c* 0.4, $CHCl_3$), lit.[11] $[\alpha]_D$ −11.7°; ^{1}H NMR ($CDCl_3$): δ 5.92–5.77 (m, 1 H, =CH–), 5.36 (d, 1 H, $J_{3',4'}$, 3.4 Hz, H-4′), 5.30–5.17 (m, 3 H, CH_2= and H-3), 5.12 (t, 1 H, $J \sim 8$ Hz, H-2), 5.00–4.90 (m, 2 H, H-3′,2′), 4.54 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.50 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.36–3.56 (m, $-OCH_2CH$=, CH, and CH_2 of sugar), 2.18–1.95 (5s, 21 H, 7 CH_3CO); negative-ion LSIMS: *m/z* 677.6 $(M - H^+)^-$, and 829.7 $(M - 3\text{-NBA})^-$.

Allyl O-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (**2**).—Compound **1** (6.0 g, 8.87 mmol) was dissolved in anhyd MeOH (200 mL) and NaOMe–MeOH (5 mL, 0.5 M) was added. The mixture was stirred at room temperature for ~2 h and then de-ionized with Rexyn 101 (H^+) resin, and the solvent was evaporated to dryness. Crystallization, and recrystallization, of the residue from MeOH furnished

2 (3.2 g, 94%) as needles; mp 172–174°C, lit.[11] 168–170°C; $[\alpha]_D$ −5.4°, $[\alpha]_{436}$ −12.5° (*c* 0.97, H_2O), lit.[11] $[\alpha]_D$ +2.1°; ^1H NMR (D_2O) δ 6.00–5.80 (m, 1 H, =CH–), 5.28–5.13 (m, 2 H, CH_2=), 4.41 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.32 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.30–4.07 (dq, 2 H, OCH_2CH=), and 4.00–3.25 (m, 12 H, CH, and CH_2 of sugar); negative-ion LSIMS: *m/z* 381.4$(M - H^+)^-$.

Allyl O-(3,4-O-isopropylidene-β-D-galactopyranosyl)-(1 → 4)-β-D-glucopyranoside (**3**).—To a solution of **2** (5 g, 13.08 mmol) in 2,2-dimethoxypropane (300 mL) was added dry camphorsulfonic acid (150 mg, 0.65 mmol). The mixture was stirred for 48 h at room temperature, triethylamine (0.90 mL, 6.5 mmol) was then added, and the mixture was stirred for 15 min. The mixture was concentrated to dryness and coevaporated with toluene to remove traces of triethylamine. A solution of the crude product in 10:1 MeOH–H_2O (300 mL) was boiled under reflux for 3 h. The solvents were evaporated and the residue was purified by flash chromatography (solvent *B*) to give **3** (4.9 g, 88%); mp 184–186°C (acetone–MeOH), lit.[11] mp 185–186°C; $[\alpha]_D$ +10.7° (c 1.1, H_2O), lit.[11] $[\alpha]_D$ +11.8°; ^1H NMR ($CDCl_3$) similar to that of **2** except for additional signals at δ 1.55–1.34 (2s, 6 H, CCH_3).

Allyl O-(2,6-di-O-benzoyl-β-D-galactopyranoside)-(1 → 4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (**8**).—To compound **3** (2.4 g, 5.67 mmol) in pyridine (15 mL), was added benzoyl chloride (5 mL) and the solution was kept overnight at room temperature. The crude product (**4**) was isolated by extraction with CH_2Cl_2. Compound **4** was dissolved in 80% AcOH (25 mL), and heated for 1 h at 100°C. The mixture was concentrated to dryness under diminished pressure, and then coevaporated with toluene. Crystallization of the residue from EtOAc–hexane gave **8** (2.9 g, 56%) as fine needles; mp 215–217°C; $[\alpha]_D$ +75.2°, $[\alpha]_{436}$ +167° (*c* 0.42, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.07–7.15 (m, 25 H, 5 Ph), 5.72 (2t, 2 H, *J* 9.2 Hz, H-3, 2), 5.77–5.62 (m, 1 H, =CH–), 5.41 (t, 1 H, *J* 9.3 Hz, H-2'), 5.16–4.98 (m, 2 H, CH_2=), 4.75 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.71 (d, 1 H , $J_{1,2}$ 8.7 Hz, H-1), 4.72–4.28 (m, 2 H, OCH_2CH=), 4.26–3.95 (m, 4 H, 2 CH_2), 3.85–3.75 (m, 1 H, H-5), 3.42–3.17 (m, 3 H, CH of sugar), 2.90–2.80 (bs, 1 H, D_2O-exchangeable, OH), and 1.65–1.50 (bs, 1 H, D_2O-exchangeable, OH); positive ion LSIMS: *m/z* 903.0 $(M + H^+)$, negative-ion LSIMS: 900.7 $(M - H^+)^-$, and 1055.3 $(M - 3\text{-NBA})^-$. Anal. Calcd for $C_{50}H_{46}O_{16}$ (902.91): C, 66.51; H, 5.14. Found: C, 66.32; H, 5.21.

Allyl O-(2,3,6-tri-O-benzoyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (**9**).—A stirred mixture of **8** (1.5 g, 1.7 mmol) and dibutyltin oxide (0.5 g, 1.2 equiv) in MeOH (50 mL) was heated for 1 h under reflux. The MeOH was evaporated off and the residual solid was dried under vacuum for 1 h. This product was dissolved in 1,4-dioxane (50 mL), and then triethylamine (1.3 mL, 9.5 mmol) and benzoyl chloride (1.1 mL, 9.5 mmol) were added, and the mixture was stirred for 1 h at room temperature. At this point, TLC showed no starting material and only one major product-spot. Water was added, the product was extracted with CH_2Cl_2, and the combined extract washed with 5% HCl, water, 5% $NaHCO_3$, and water, respectively, and dried (Na_2SO_4). Evaporation of the solution left a crude syrup, which was purified by chromatography on silica gel (solvent

A) to give **9** (1.2 g, 72%); $[\alpha]_D$ +47°, $[\alpha]_{436}$ +101° (*c* 2.03, CH_2Cl_2); ^1H NMR ($CDCl_3$) similar to that of **8** except for the increase of the aromatic protons at δ 8.15–7.10 to 30 H, the downfield shift of H-3′ to δ 5.30–5.00 (dd, 1 H, overlapped with the CH_2= signal), and only one OH signal at δ 3.20–3.00; positive ion LSIMS: *m/z* 1007.3 $(M + H^+)$, negative-ion LSMIS: 1005.3 $(M - H^+)^-$, 1159.3 (M + 3-NBA)$^-$. Anal. Calcd for $C_{57}H_{50}O_{17}$ (1007.01): C, 67.98; H, 5.00. Found: C, 68.03; H, 5.10.

An additional, downshifted broad doublet signal for sugar CH was clearly visible in the NMR spectrum of the acylated product (**10**) at δ 5.49 (bd, 1 H, $J_{3',4'}$ 3.4 Hz, H-4′) and 5.25 (dd, 1 H, $J_{2',3'}$, 10.3, $J_{3',4'}$, 3.4 Hz, H-3′).

Allyl O-(2,6-di-O-benzoyl-3-O-methyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzoyl)-β-D-glucopyranoside (**11**).—The dibutylstannylene derivative (**6**) from 0.60 g (0.67 mmol) of **8** was dissolved in *N*,*N*-dimethylformamide (5 mL) and MeI (0.5 mL, 8.1 mmol) was added. The solution was heated for 0.5 h at 60°C, at which time TLC showed the disappearance of the starting material and formation of one major product. Solvent was removed by evaporation under diminished pressure, and the product was extracted with CH_2Cl_2. The organic layer was washed with 10% $Na_2S_2O_3$, water and dried. After evaporation of the CH_2Cl_2, the residue was chromatographed on silica gel (solvent *A*) to give **11** (0.5 g, 82%); $[\alpha]_D$ +41.2°, $[\alpha]_{436}$ +88.5° (*c* 1.58, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 8.15–7.20 (m, 25 H, 5 Ph), 5.82–5.64 (m, 2 H, =CH– and H-3), 5.46 (t, 1 H, *J* 8.0 Hz, H-2), 5.38 (t, 1 H, *J* 8.5 Hz, H-2′), 5.22–5.02 (m, 2 H, CH_2=), 4.72 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.60 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1′), 4.78–3.32 (m, 13 H, OCH_2CH= and CH), 3.30 (s, 3 H, CH_3), and 2.65 (bs, 1 H, D_2O-exchangeable, OH); positive-ion LSIMS: m/z 917.1 $(M + H^+)$, negative ion LSIMS: 1068.8 (M + 3-NBA)$^-$. Anal. Calcd for $C_{51}H_{48}O_{16}$ (916.93): C, 66.80; H, 5.28. Found: C, 66.68; H, 5.22.

Acetylation of **11** with Ac_2O in pyridine gave allyl O-(4-*O*-acetyl-2,6-di-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (**12**), ^1H NMR ($CDCl_3$) similar to that of **11** except the signal downshifted to δ 5.34 (d, 1 H, $J_{3',4'}$ ~ 3.3 Hz, *H*-4′), 2.10 (s, 3 H, CH_3CO), and the absence of OH signal.

Allyl O-(2,6-di-O-benzoyl-3-O-benzyl-β-D-galactopyranosyl)-(1 → 4)-β-D-glucopyranoside (**13**).—The dibutylstannylene derivative (**6**) from 1.09 g (1.1 mmol) of **8** was dissolved in *N*,*N*-dimethylformamide (10 mL) and benzyl bromide (0.5 mL, 4.2 mmol) was added. The solution was heated for 1 h at 100°C, then the solvent was removed by evaporation under diminished pressure, and the product was extracted with CH_2Cl_2. After evaporation of the CH_2Cl_2, the residue was chromatographed on silica gel (solvent *A*) to give **13** (0.7 g, 641%); $[\alpha]_D$ +45°, $[\alpha]_{436}$ +98° (*c* 3.15, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 8.12–7.10 (m, 30 H, 6 Ph), 5.80–5.64 (m, 2 H, =CH– and H-3), 5.48–5.38 (2t, 2 H, H-2, 2′), 5.19–5.03 (m, 2H, CH_2=), 4.74–4.64 (bd, 2H, $PhCH_2$), and 1.90 (bd, 1 H, D_2O-exchangeable, OH). positive-ion LSIMS: m/z 993.2$(M + H^+)$, negative-ion LSIMS: 991.6 $(M - H^+)^-$,

and 1145.8 (M + 3-NBA)$^-$. *Anal.* Calcd for $C_{57}H_{52}O_{16}$ (993.03): C, 68.94; H, 5.28. Found: C, 68.70; H, 5.34.

Acetylation of **13** with Ac_2O in pyridine gave allyl *O*-(4-*O*-acetyl-2,6-di-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**14**); ^{1}H NMR ($CDCl_3$) similar to that of **1** except downfield shift of H-4 to δ 5.38 (d, 1 H, $J_{3',4'}$ 3.4 Hz), an additional signal at δ 2.05 (s, 3 H, CH_3CO), and no OH signal.

Allyl O-(2,6-di-O-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**15**).—To a solution of **3** (2 g, 4.74 mmol) in *N*,*N*-dimethylformamide (40 mL) was added NaH (1.2 g, 60% dispersion in oil) and benzyl bromide (4 mL), and the mixture was stirred for 4 h at room temperature. The excess NaH was decomposed by the addition of MeOH, then conventional isolation was carried out by CH_2Cl_2 extraction to give crude **5**. This was heated with 80% AcOH (similar to the preparation of **8** from **3**) to give **15** (2.8g, 74.3%); $[\alpha]_D$ +15.4°, $[\alpha]_{436}$ +33° (*c* 1.14, CH_2Cl_2), lit.[11] $[\alpha]_D$ +18.0°; ^{1}H NMR ($CDCl_3$): δ 7.45–7.15 (m, 25 H, 5 Ph), 6.04–5.85 (m, 1 H, =CH–), 5.38–5.18 (m, 2 H, CH_2=), 5.03–3.23 (m, 27 H, OCH, CH=, PhCH_2, and sugar CH), and 2.72–2.35 (bs, 1 H, D_2O-exchangeable, OH). positive-ion LSIMS: *m/z* 833.2 (M + H$^+$), 855.3 (M + Na$^+$); negative-ion LSIMS: 831.3 (M – H$^+$)$^-$. Anal. Calcd for $C_{50}H_{56}O_{11}$ (832.99): C, 72.09; H, 6.78. Found: C, 72.15; H, 6.91.

Allyl O-(2,3,6-tri-O-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**16**).—A solution of **15** (0.85 g, 1.0 mmol) in MeOH (50 mL) was heated for 1 h under reflux with dibutyltin oxide (0.3 g, 1.2 mmol). MeOH was evaporated and the residual syrup was dried under vacuum. To a solution of the syrup in *N*,*N*-dimethylformamide (20 mL) was added benzyl bromide (0.5 mL) and the mixture was heated for 1 h at 100°C. Most of the solvent was removed, and the product was extracted with CH_2Cl_2. After evaporation of the CH_2Cl_2, the residue was chromatographed on silica gel to give **16** (0.76 g, 81%); $[\alpha]_D$ +14°, $[\alpha]_{436}$ +30° (*c* 4.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) similar to that of **15** except for additional signals at δ 7.45–7.15 (C_6H_5), and 4.82–4.25 (PhCH_2); positive-ion LSIMS: *m/z* 923.2 (M + H$^+$), 945.3 (M + Na$^+$); negative-ion LSIMS: 921.4 (M – H$^+$)$^-$, 1075.8 (M + 3-NBA)$^-$. Anal. Calcd for $C_{57}H_{62}O_{11}$ (923.12): C, 74.16; H, 6.77. Found: C, 74.24; H, 6.83.

Acetylation of **16** with Ac_2O in pyridine afforded allyl *O*-(4-*O*-acetyl-2,3,6-tri-*O*-benzyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**17**), ^{1}H NMR ($CDCl_3$) similar to that of **16** except for the signal downshifted at δ 5.66 (d, 1 H, $J_{3',4'}$ 3.1 Hz, H-4'), 2.15 (s, 3 H, CH_3CO), and the absence of OH signal.

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