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"STANDARDIZED INTERMEDIATES" FOR OLIGOSACCHARIDE SYNTHESIS. A CONVENIENT PREPARATION OF PARTIALLY BENZYLATED DERIVATIVES OF ALLYL 2-ACETAMIDO-2-DEOXY-α-D-GALACTOPYRANOSIDE HAVING CHAIN EXTENSION AT POSITION 4

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ABSTRACT

Allyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5**) was prepared from the corresponding *gluco* compound, allyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**1**), by successive selective benzoylation at O-3 and O-6, *p*-bromobenzenesulfonylation, displacement with cesium benzoate, and *O*-debenzoylation. Allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**10**) was prepared from **5** *via* the 4,6-benzylidene acetal **6**, which was successive benzylated and subjected to mild acid hydrolysis to furnish the diol **8**. Selective benzylation of O-6 was then accomplished by the action of α-bromotoluene on the 4,6-*O*-dibutylstannylene derivative **9**.

INTRODUCTION

For work now in progress in this laboratory on chemical oligosaccharide synthesis from "standard building blocks", Nashed and Anderson[1] described the synthesis of a selectively benzylated glycoside of 2-acetamido-2-deoxy-D-galactose from the corresponding derivative of 2-acetamido-2-deoxy-D-glucose.

Nashed and Anderson[2,3] and David *et al.*[4] showed that acylation or alkylation of the cyclic 3,4-*O*-dibutylstannylene-D-galactopyranoside or 2,3-*O*-dibutylstannylene-D-mannopyranoside[5] occurs essentially exclusively at the equatorial oxygen atom. Recently, David *et al.*[6] showed that benzylation of the stannylene derivative of benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside gives regiospecifically the 6-benzyl ether in high yield.

In the present paper, we report an improved synthesis in few steps of allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**10**) from the allyl glycoside of 2-acetamido-2-deoxy-D-glucose. This objective was achieved by the

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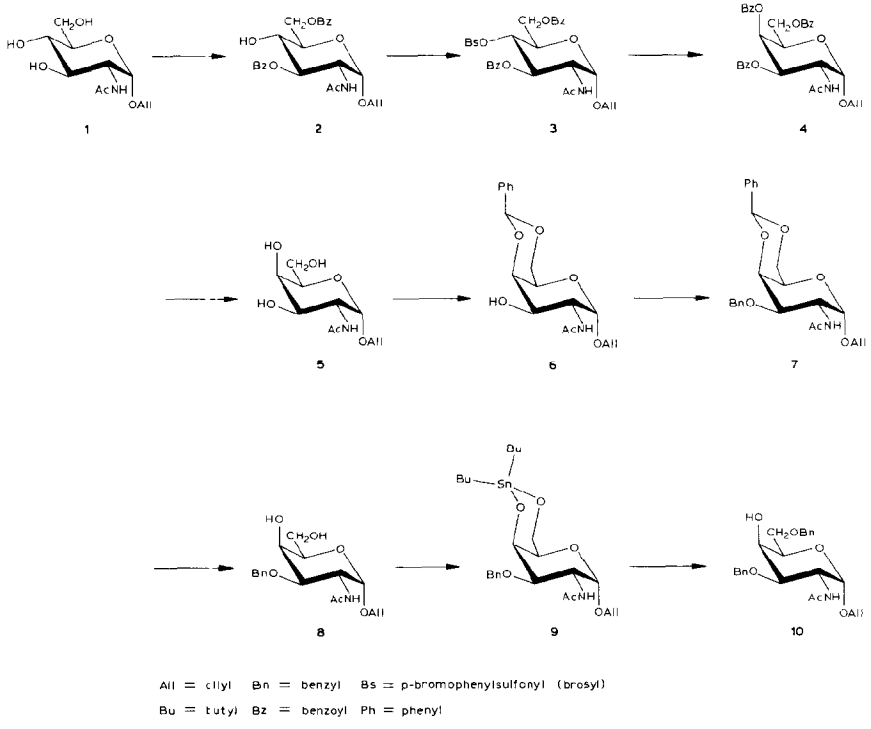
use of a modern method[6] for regiospecific benzylation at O-6 *via* the stannylene derivative in toluene.

RESULTS AND DISCUSSION

In previous work, Nashed[7] showed a ready conversion of allyl 2-acetamido-2-deoxy-β-D-glucopyranoside into allyl 2-acetamido-2-deoxy-β-D-galactopyranoside by partial benzoylation to the 3,6-di-benzoate, sulfonylation with *p*-bromobenzenesulfonyl chloride ("brosyl chloride") at O-4, and displacement of the brosylate group with sodium benzoate.

The same overall scheme was used in the present work. Low-temperature, partial benzoylation of **1** gave allyl 2-acetamido-3,6-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**2**) in good yield, after chromatographic separation from some accompanying 3,4,6-tribenzoate. Compound **2** was characterized from its ^{1}H-n.m.r. spectrum, which showed a doublet of doublets at δ 5.40 with spacings of 9.2 and 11.0 Hz, identifiable by decoupling experiments as the signal for H-3. Treatment with brosyl chloride in pyridine quantitatively converted it into allyl 2-acetamido-3,6-di-*O*-benzoyl-4-*O*-brosyl-2-deoxy-α-D-glucopyranoside (**3**). The 270-MHz n.m.r. spectrum of this compound showed a new signal shifted downfield as a triplet having a spacing of 9.6 Hz, identifiable by decoupling as the signal for H-4.



Displacement of brosylate from O-4 of the β anomer[7] with sodium benzoate required hexamethylphosphortriamide (HMPT) as a solvent, at high temperature. More recently, Nashed and Anderson[1] found that the displacement step could be conducted in *N,N*-dimethylformamide rather than in HMPT, when cesium benzoate was substituted for the (less soluble) sodium salt as the source of benzoate ion[8]. With this combination of leaving group and nucleophile, an excellent yield of the displacement product **4** was obtained. The characterization of compound **4** was based on its ^{1}H-n.m.r. spectrum, in which the signal for H-3 showed a large ($J_{2,3}$ 11.6 Hz) and a small ($J_{3,4}$ 3.3 Hz) spacing, and that for H-4 was the broadened doublet ($J_{3,4}$ 3.3 Hz) typical of the *galacto* configuration.

Zemplén *O*-debenzoylation of **4** afforded the previously unreported allyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5**) in 95% yield. Treatment of **5** with benzaldehyde and zinc chloride[9] furnished the crystalline allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (**6**) in excellent yield. Benzylation of **6** (benzyl bromide, barium oxide, barium hydroxide, *N,N*-dimethylformamide)[10] gave allyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (**7**) in high yield. Boiling with 50% ethanolic acetic acid for 30 min, and evaporation of toluene from the residual acid left **8** as a glassy residue whose ^{1}H-n.m.r. spectrum (at 90 MHz) showed no benzylidene group; it was used without further characterization for the next step.

Various reaction-conditions have been reported[11–13] for the selective, partial benzylation of HO-6 in 4,6-diol derivatives, but with only moderate yields and troublesome purification. Sinaÿ *et al.*[14] have reported a two-step procedure based on regiospecific tosylation of HO-6 followed by SN2 displacement with sodium benzylate in benzyl alcohol, but this reaction was not applicable in our case because of the difficulty of effecting displacement at C-6 in *galacto* compounds. However, regiospecific benzylation and allylation of various diols[6] *via* their stannylene derivative has been found quite attractive.

Treatment of allyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**8**) with dibutyltin oxide in boiling, dry toluene gave the 4,6-*O*-dibutylstannylene derivative (**9**). Subsequent treatment with benzyl bromide in the presence of tetrabutylammonium iodide furnished the crystalline allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**10**) in 75% yield. Characterization of compound **10** was based on the ^{1}H-n.m.r. spectrum (at 90 MHz) of its acetyl derivative, in which the signal for H-4 showed a broadened doublet ($J\sim4$ Hz) typical of H-4 of *galacto* derivatives. This proved that the parent alcohol **10** had a free hydroxyl group at C-4; conversely, a downfield shift of the signal of the H-6, H-6′ protons was not observed.

EXPERIMENTAL

Instrumental and chromatographic procedures. — These were described in a previous paper in this series[16]. ^{1}H-N.m.r. spectra were recorded with a Bruker

WH-270 or Varian E390 (90 MHz) spectrometer (specifically noted) and chemical shifts are expressed in p.p.m. downfield from tetramethylsilane used as the internal standard. Chromatography on silica gel was accomplished with mixtures of methanol and chloroform or acetone and chloroform. Elemental analyses were performed with a Perkin–Elmer 240 elemental analyzer, Microanalysis unit, Faculty of Science, Alexandria and by Galbraith Laboratories, Inc., Knoxville, TN, U.S.A.

*Allyl 2-acetamido-3,6-di-*O*-benzoyl-α-*D*-glucopyranoside* (**2**). — Allyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**1**) was prepared as described by Lee and Lee[15]; ^{1}H-n.m.r. [$(CD_3)_2SO$ + D_2O]: δ 5.97–5.75 (m, 1 H, =C*H*-), 5.29–5.14 (m, 2 H, CH_2=), 4.69 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.57–3.50 (3 m, total 8 H, -OCH_2CH= and C*H* of sugar), and 1.84 (s, 3 H, CH_3CO). A solution of compound **1** (4.5 g, 17.2 mmol) in anhydrous pyridine (50 mL) was cooled to −35° in Dry Ice bath, and benzoyl chloride (4.4 mL, 2.2 molar eq) was added dropwise. The solution was allowed to warm to 15° over a period of 4 h, when t.l.c. showed complete disappearance of the starting material. Methanol was added to decompose the excess of benzoyl chloride, and the mixture was evaporated to dryness under diminished pressure. The residue obtained was dissolved in chloroform, washed successively with 10% hydrochloric acid, 5% sodium hydrogencarbonate, and water, and then dried with anhydrous magnesium sulfate. After purification on a column of silica gel, the yield of **2** was 6.1 g (75%), $[\alpha]_D^{25}$ +114°, $[\alpha]_{436}^{25}$ +232° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **1** except for the appearance of δ 8.10–7.32 (m, 10 H, 2 Bz), 5.97 (d, 1 H, $J_{2,NH}$ 9.2 Hz, NH), 5.40 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 9.2 Hz, downshifted signal for H-3), and 3.69 (d, 1 H, D_2O-exchangeable, OH).

Anal. Calc. for $C_{25}H_{27}NO_8$ (469.50): C, 63.96; H, 5.80; N, 2.98. Found: C, 63.47; H, 5.54. N. 2.57.

*Allyl 2-acetamido-3,6-di-*O*-benzoyl-4-*O*-(p-bromophenylsulfonyl)-2-deoxy-α-*D*-glucopyranoside* (**3**). — Pure **2** (1 g, 2 mmol) was dissolved in dry pyridine (5 mL), the solution was cooled to 5°, and *p*-bromobenzenesulfonyl chloride (0.9 g, 3.5 mmol) was added portionwise with stirring during 15 min. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with chloroform, and then processed by conventional aqueous extraction. Evaporation of the solvents gave a crude residue that was purified on a column of silica gel to furnish 1.22 g (88%) of the title compound as an amorphous solid, $[\alpha]_D^{25}$ +35.3°, $[\alpha]_{436}^{25}$ +53.2° (*c* 0.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **2** except for the additional signal at δ 8.14–7.20 (BrC_6H_4), and δ 5.16 (downfield shift, t, *J* 9.6 Hz, H-4), and loss of the O*H* signal.

Anal. Calc. for $C_{31}H_{30}BrNO_{10}S$ (688.55): C, 54.08; G, 4.39; N, 2.03; S, 4.66. Found: C, 54.19; H, 4.10; N, 1.77; S, 4.34.

*Allyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-α-*D*-galactopyranoside* (**4**). — A solution of compound **3** (7 g, 10.2 mmol) in *N,N*-dimethylformamide (40 mL) was stirred with cesium benzoate (5.2 g, 20.4 mmol) overnight at 135°. The mixture was poured with stirring into ice–water, and the resultant solid precipitate was col-

lected on a filter and washed with water. Purification on a column of silica gel yielded 4.75 g (82%) of the pure title compound as a glassy foam; $[\alpha]_D^{25}$ +120°, $[\alpha]_{436}^{25}$ +248° (*c* 0.9, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **3** except for the replacement of the low-field quartet (BrC_6H_4) by a signal for Bz at slightly higher field, modification of the signal for H-4 (δ 5.88) to the form characteristic of galactopyranose derivatives (broadened d, $J_{3,4}$ 3.3 Hz), and 5.48 (dd, 1 H, $J_{1,2}$ 11.6, $J_{3,4}$ 3.3 Hz, H-3).

Anal. Calc. for $C_{32}H_{31}NO_9$ (573.60): C, 67.01; H, 5.45; N, 2.44. Found: C, 66.71; H, 5.46; N, 2.13.

*Allyl 2-acetamido-2-deoxy-α-*D*-galactopyranoside* (**5**). — Catalytic *O*-debenzoylation in methanolic sodium methoxide converted **4** quantitatively into **5**. After recrystallization from ethanol, the compound melted at 193–194°, $[\alpha]_D^{25}$ +213°, $[\alpha]_{436}^{25}$ +425° (*c* 0.35, water); ^{1}H-n.m.r. [$(CD_3)_2SO$ + D_2O]: δ 6.00–5.78 (m, 1 H, =C*H*-), 5.32–5.16 (m, 2 H, CH_2=), 4.64 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.58–3.48 (m, 8 H, -OCH_2-C= and C*H* of sugar), and 1.84 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{11}H_{19}NO_6$ (261.27): C, 50.57; H, 7.35; N, 5.36. Found: C, 50.57; H, 7.54; N, 5.24.

*Allyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-*D*-galactopyranoside* (**6**). — With stirring, fused zinc chloride (3 g) was quickly added to dry benzaldehyde (15 mL). After 30 min, compound **5** (3 g, 11.5 mmol) was quickly added and stirring was continued for 3 h. The syrupy mass obtained was poured into a 100-mL separatory funnel containing ice–water (30 mL) and petroleum ether (30 mL). The mixture was vigorously shaken, and washed successively with water and petroleum ether. The air-dried product obtained was recrystallized from ethanol to give 3.5 g (87%) of the title compound as needles, m.p. 223–225°, $[\alpha]_D^{25}$ +143° (*c* 0.84, ethanol); ^{1}H-n.m.r. [$(CD_3)_2SO$]: δ 7.79 (d, 1 H, $J_{N,H,2}$ 8.4 Hz, NH), 7.55–7.30 (m, 5 H, Ph-H), 6.00–5.78 (m, 1 H, -C*H*=), 5.60 (s, 1 H, PhC*H*), 5.40–5.11 (m, 2 H, -CH=CH_2), 4.82 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.75 (d, 1 H, *J* 7.6 Hz, D_2O-exchangeable, O*H*), 4.22–3.25 (m, 8 H, OCH_2CH=, and sugar C*H*), and 1.84 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{18}H_{23}NO_6$ (349.38): C, 61.88; H, 6.64; N, 4.01. Found: C, 61.85; H, 6.87; N, 4.15.

*Allyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-*D*-galactopyranoside* (**7**). — To a well-stirred solution of **6** (2 g, 5.7 mmol) in *N,N*-dimethylformamide (30 mL), barium oxide (6 g) and barium hydroxide octahydrate (2 g) were added. After 15 min, α-bromotoluene (4 mL) was added and stirring was continued for 18 h at room temperature. Chloroform was added and the mixture was filtered (the residue being washed thoroughly with more chloroform), and then processed by conventional aqueous extraction. Evaporation of the solvents gave a crude residue that crystallized from ethanol to give 2.1 g (83%) of the title compound as needles, m.p. 238–241°; ^{1}H-n.m.r. [$(CD_3)_2SO$] similar to that of **6** except for additional signals at δ 7.55–7.20 (m, 5 H, Ph-H), 4.60 (AB, 2 H, *J* 12.3 Hz, PhCH_2), and loss of O*H*.

Anal. Calc. for $C_{22}H_{29}NO_6 \cdot 0.5\ H_2O$ (448.52): C, 66.95; H, 6.74; N, 3.12. Found: C, 66.62; H, 6.76; N, 3.07.

Allyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-galactopyranoside (**10**). — Pure **7** (1.5 g, 3.4 mmol) was dissolved in 1:1 (v/v) acetic acid–ethanol (20 mL), the solution was heated at 70°, and the reaction was monitored by t.l.c. Heating was discontinued as soon as hydrolysis was complete (30 min), as prolongation of the reaction time was found to decrease the yield of product. The mixture was evaporated to dryness under diminished pressure, and then several portions of toluene were successively added and evaporated off to give residue of crude *allyl 2-acetamido-3-O-benzyl-2-deoxy-α-D-galactopyranoside* (**8**); ^{1}H-n.m.r. (at 90 MHz) [$(CD_3)_2SO + D_2O$] similar to that of **7** except for the disappearance of the benzylidene group signals.

The solid **8** was dissolved in dry toluene (25 mL) containing dibutyltin oxide (1.28 g, 1.5 molar eq.). The mixture was boiled under reflux for 20 h with azeotropic removal of water. The solution was evaporated to ~10 mL and then tetrabutylammonium iodide (1.26 g, 1 molar eq.) and benzyl bromide (0.8 mL, ~2 molar eq.) were added, and the mixture was stirred for 3 days at 70°. Evaporation to dryness gave a residue that was purified on a column of silica gel to yield 1.1 g (73%) of the title compound. After recrystallization from ethyl acetate–hexane, the compound had m.p. 120–122°; ^{1}H-n.m.r. at 90 MHz ($CDCl_3$) similar to that of **8** except for an additional signal at δ 7.55–7.20 (now 10 H, 2 Ph-H), and loss of O*H* signals.

Anal. Calc. for $C_{25}H_{31}NO_6$ (441.52): C, 68.01; H, 7.08; N, 3.17. Found: C, 67.89; H, 7.31; N, 3.06.

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