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CONVERSION OF ALLYL 2-ACETAMIDO-2-DEOXY-β-D-GLUCOPYRANOSIDE INTO 2-METHYL-(3,4,6-TRI-*O*-BENZOYL-1,2-DIDEOXY-α-D-GALACTOPYRANO)-[2′,1′ 4,5]-2-OXAZOLINE

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ABSTRACT

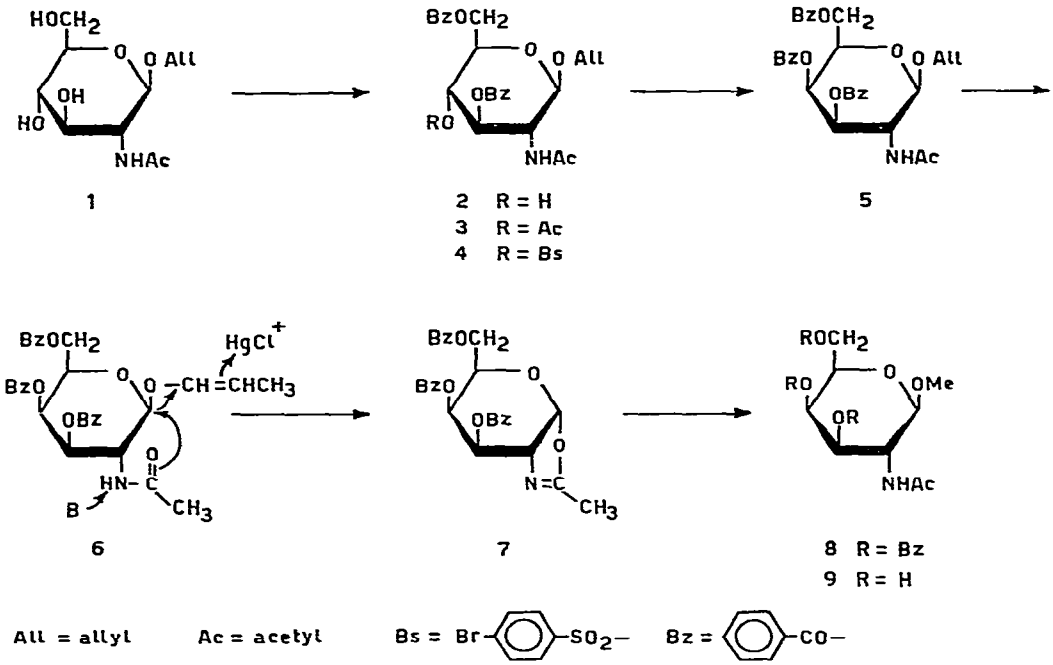
2-Methyl-(3,4,6-tri-*O*-benzoyl-1,2-dideoxy-α-D-galactopyrano)-[2′,1′ 4,5]-2-oxazoline (**7**) was prepared from 1-propenyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (**6**) The latter was prepared from allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**1**) through selective benzoylation at O-3 and O-6, conversion into the 4-*p*-bromobenzenesulfonate **4**, inversion of configuration at C-4 to afford allyl 2-acetamido-3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**5**), and subsequent isomerization with palladium–charcoal to give **6**

INTRODUCTION

Sugar oxazoline derivatives have proved useful for the synthesis of oligosaccharides containing 2-acetamido-2-deoxy sugars[1] Recently, Anderson's group[2] described a new method for the direct synthesis of 2-methyl-1,2-dideoxy-α-D-glucopyrano-[2′,1′ 4,5]-2-oxazolines from the corresponding allyl β-glycosides The validity of this synthesis as a route to oxazoline derivatives of other amino sugars, particularly 2-acetamido-2-deoxy-D-galactose ("*N*-acetyl-D-galactosamine"), is studied in the present work To accomplish the objective of the study it was necessary firstly to make a substituted allyl β-glycoside (**5**) of *N*-acetyl-D-galactosamine, and then to undertake the conversion of **5** into the galacto-oxazoline **7** Galactosaminide **5** was prepared from allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**1**) by epimerization of the latter at C-4

RESULTS AND DISCUSSION

It was reported by Williams and Richardson[3], and confirmed in other laboratories[3], that the partial benzoylation of hexopyranosides at low temperature yields, primarily, products unsubstituted at position 4 Thus, the partial benzoylation of the glucosaminide **1** would be expected to give the 3,6-dibenzoate **2**, which could be sulfonylated on OH-4 Epimerization would then be accomplished by displacement



of the 4-sulfonate group with benzoate ion Indeed, the transformation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside to the corresponding galactosaminide by this route has been described by Horner *et al*[4]

The benzoylation[5] of allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**1**) with *ca* two equivalents of benzoyl chloride in pyridine at —40° gave a single dibenzoate as the major product This product, isolated by fractional crystallization in 72% yield, was shown to be the desired 3,6-di-*O*-benzoyl compound **2** by p m r -spectroscopic analysis. The low-field portion of the spectrum included a 1-proton multiplet (dd, δ 5 43) attributable to a sugar-ring proton deshielded by a geminal acyloxy group. Only one such signal was found in the region below δ 5 0, and, on the basis of decoupling experiments (see Experimental), it was assigned to H-3 The signal for H-4 was found at δ ~3 8, indicating that O-4 was not acylated Therefore, the second benzoyl group must be at position 6 In corroboration of these arguments, the spectrum of the acetyl derivative (**3**) of **2** showed an additional low-field multiplet (t, δ 5.37) due to the proton on C-4, now downshifted by the conversion of OH-4 into an acetoxy group

Inversion of configuration at C-4 in 4-sulfonates of α-D-glucopyranosides, presumably through an SN2 displacement-reaction, was found largely dependent on the nature of the leaving group and on the solvent used In synthetic work in the carbohydrate field, the 4-methanesulfonate[6-9] and 4-(*p*-toluenesulfonate)[10] were examined, in different solvents, as potential leaving-groups, but the desired product was not always obtained in satisfactory yield Anderson *et al.*[11] and Perlin *et al*[12] established optimal conditions for such nucleophilic displacements by use of the *p*-

bromobenzenesulfonate leaving-group and hexamethylphosphoric triamide or *N,N*-dimethylformamide as the solvent In the present work, the foregoing conditions were adopted for the conversion of **4** into **5** Thus, treatment of **2** with *p*-bromobenzenesulfonyl chloride gave the crystalline allyl 2-acetamido-3,6-di-*O*-benzoyl-4-*O*-(*p*-bromobenzenesulfonyl)-2-deoxy-β-D-glucopyranoside (**4**) in ~84% yield, which afforded allyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (**5**) in ~78% yield upon treatment with sodium benzoate in hexamethylphosphoric triamide at 140°

The ^{1}H-n m r spectrum of **5** exhibited a doublet at δ 5 78 ($J_{3,4}$ 3 7 Hz) that was not detected in the spectrum of the precursor **4** This signal may be attributed to H-4; the magnitude of $J_{4,5}$ ($\leq$1 Hz) is consistent with the assigned structure

Isomerization[13] of the allyl ether group to the 1-propenyl ether may be accomplished conventionally with potassium *tert*-butoxide if the protecting groups are alkali-stable However, this reagent was inapplicable in the present work, as it would also saponify the benzoate groups Scheffold *et al*[14] found that 10% palladium–activated charcoal is a particularly effective catalyst for isomerization of allyl ethers The latter reagent was thus used for isomerization of **5** to 1-propenyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (**6**)

Treatment of **6** with mercuric chloride and mercuric oxide gave 2-methyl-(3,4,6-tri-*O*-benzoyl-1,2-dideoxy-α-D-galactopyrano)-[2′,1′ 4,5]-2-oxazoline (**7**) in ~86% yield Its ^{1}H-n m r spectrum indicated a marked deviation from the $^4C_1$(D) conformation of the parent galactoside Particularly diagnostic for the oxazoline structure[2] are the chemical shift (δ 6 09) and coupling constant ($J_{1,2}$ 7 3 Hz) of H-1, and the signal (δ 2 11) for the protons of the 2-methyl group The latter appears as a doublet because of long-range coupling (J 1 7 Hz) to H-2 of the sugar.

The glycosylating capability of the oxazoline **7** was examined by boiling it with methyl alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid Methyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (**8**) was obtained in ~89% yield Compound **8** was conventionally *O*-debenzoylated with sodium methoxide to give methyl 2-acetamido-2-deoxy-β-D-galactopyranoside (**9**). Assignment of the β-D configuration to **9** is based on the correspondence of its optical rotation and melting point with the values reported[15], and on the ^{1}H-n m r spectrum, which showed only one anomeric-proton signal, a doublet at δ 4 18 having a large spacing ($J_{1,2}$ 8 5 Hz)

EXPERIMENTAL

General methods — T l c plates were prepared from silica gel G (Merck), and column chromatography was performed on silica gel (Merck) The following solvent combinations (v/v) were utilized for thin-layer and column chromatography *A*, 19 1 chloroform–methanol, *B*, 17 3 chloroform–acetone, *C*, 9 1 chloroform–methanol, and *D*, 4 1 chloroform–methanol Evaporations were conducted under diminished pressure Melting points were determined in Pyrex-glass capillaries immersed in a heated oil-bath equipped with a calibrated thermometer Proton magnetic resonance

spectra, determined at 270 MHz with a Bruker WH-270 instrument, were provided by the Department of Biochemistry, University of Wisconsin, Madison, Wisconsin, U S A Spectra are referenced to tetramethylsilane, as the internal standard Optical rotations were recorded with a Perkin–Elmer Model 141 polarimeter Elemental analyses were performed by Micro-Tech Laboratories Inc , Skokie, Illinois, U S A

Allyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**2**). — Compound **1** was prepared by de-*O*-acetylation of its 3,4,6-triacetate, made as described by Lee and Lee[5] from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[16]; ^{1}H-n m r. at 270 MHz (Me_2SO-d_6 + 2 drops of D_2O) δ 7 85 (d, 1, $J_{2\,NH}$ 9 5 Hz, N*H*), 5 92–5 77 (m, 1, -C*H*=), 5 27–5.10 (m, 2, CH_2=), 4 31 (d, 1, $J_{1,2}$ 8 5 Hz, H-1), 4 26–3 94 (m, 2, -CH_2-O-), 3 54–3 07 (m, 6, ring protons), and 1.85 (s, 3, NCOCH_3) Compound **1** (3 0 g, 11 5 mmol) in anhydrous pyridine (40 ml) was treated at —40° with benzoyl chloride (2 8 ml, 24 mmol) dropwise during 0.5 h, with the exclusion of moisture The bath temperature was kept for an additional 2 h below —30°, and was then allowed to increase slowly to room temperature After this period, t l c (solvent *A*) showed a single, major product and three minor components, only one of which (tribenzoate) moved faster than the major component, the slowest-moving component was chromatographically indistinguishable from the starting material Most of the pyridine was evaporated off (<40°), and the residue was dissolved in chloroform, washed successively with 2M hydrochloric acid, water M sodium hydrogencarbonate, and water, dried (sodium sulfate), and then evaporated The resultant syrup was crystallized and recrystallized from ethyl acetate–Skellysolve B, giving 3 9 g (72%) of **2**, m p 197 5–198 5°, $[\alpha]_D^{25}$ +4 6°, $[\alpha]_{436}^{25}$ +19 8° (*c* 0 5, chloroform), ^{1}H-n.m.r ($CDCl_3$) δ 8 03–7 34 (m, 10, 2 PhCO), 5 88 (d, 1, D_2O-exchangeable, $J_{2\,NH}$ 8 1 Hz, N*H*), 5 43 (dd, 1, $J_{2\,3}$ 10 7 Hz and $J_{3\,4}$ 8 5 Hz, H-3), and 3 81 (d, 1, D_2O-exchangeable, O*H*) On irradiation of N*H*, the pattern of the multiplet at δ ~4 was changed (H-2), then on irradiation of H-2, N*H* collapsed to s, H-1 collapsed to s, and H-3 collapsed to d ($J_{3\,4}$ 8 46 Hz, H-1) On irradiation at H-3, the patterns at δ ~4 and 3 8 were changed (*H*-2 and *H*-4, respectively) Finally, on irradiation of *H*-4, H-3 collapsed to d ($J_{2\,3}$ 10 3 Hz) and O*H* collapsed to s

Anal Calc for $C_{25}H_{27}NO_8$ (469.47)· C, 63 95, H, 5 80, N, 2 98 Found C, 63 96, H, 5 89, N, 2 78.

Allyl 2-acetamido-3,6-di-O-benzoyl-4-O-(p-bromobenzenesulfonyl)-2-deoxy-β-D-glucopyranoside (**4**) — *p*-Bromobenzenesulfonyl chloride (0 45 g, 1 75 mmol) was added to a solution of **2** (0 5 g, 1 mmol) in pyridine (3 ml) at 45°, and the mixture was stirred for 24 h, whereupon t l c (solvent *B*) showed that the reaction was almost complete Water was introduced dropwise with cooling, followed by ice-water, and the resultant, solid precipitate was collected, and washed successively with water, 2M hydrochloric acid, water, M sodium hydrogen carbonate, and water The dried product was crystallized from ethyl acetate–Skellysolve B, and recrystallized from methanol to afford long needles of **4** (0 58 g, 84%), m p 173–175°, $[\alpha]_D^{25}$ —30 9°,

$[\alpha]_{436}^{25}$ −73 1° (*c* 0 83, chloroform), ^{1}H-n m r ($CDCl_3$) δ 8 00 (q, 4, BrC_6H_4-), 5 65 (dd, 1, $J_{2\ 3}$ 9 2 and $J_{3,4}$ 10 7 Hz, H-3), and 5 11 (t, 1, *J* 9 6 Hz, H-4)

Anal Calc for $C_{31}H_{30}BrNO_{10}S$ (688 54) C, 54 07, H, 4 39, N, 2 03, S, 4 66 Found C, 53 75, H, 4 36, N, 2 07, S, 4 72

*Allyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-*D*-galactopyranoside* (**5**) — A solution of compound **4** (0 5 g) in hexamethylphosphoric triamide (5 ml) was stirred with a suspension of sodium benzoate (0 5 g) for 24 h at 140–145° (bath temp) At this time, t l c (solvent *A*) showed that the reaction was almost complete The mixture was cooled, and poured with stirring into ice–water, and the resultant solid precipitate was washed several times with water Chromatography of the dried product on silica gel (solvent *A*) afforded **5** as an amorphous solid (0 34 g, 77 8%), $[\alpha]_D^{25}$ +28.1°, $[\alpha]_{436}^{25}$ +70 2° (*c* 0 9, chloroform), ^{1}H-n m r ($CDCl_3$) δ 5 78 (doublet of wide lines, 1, $J_{3\ 4}$ 3 3 Hz, H-4), and 5 40 (dd, 1, $J_{2\ 3}$ 11 0 and $J_{3,4}$ 3 3 Hz, H-3)

Anal Calc for $C_{32}H_{31}NO_9$ (573 58) C, 67 00, H, 5 45, N, 2 44 Found C, 66 56, H, 5.50, N, 2 18

*1-Propenyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-*D*-galactopyranoside* (**6**) — To a solution of **5** (0 4 g, 0 7 mmol) in methanol (7 2 ml) and water (0 8 ml) was added 10% palladium–activated charcoal (0 15 g) The resulting suspension was boiled for 8 h under reflux with stirring T l c (solvent *C*) (after hydrolysis with mercuric chloride)[17], then showed that isomerization was complete The residue obtained by removal of the catalyst and evaporation of the solvents was chromatographed on a column of silica gel (solvent *C*), to afford **6** as a glassy foam (0 31 g, 77%), $[\alpha]_D^{25}$ +37 1°, $[\alpha]_{436}^{25}$ +86 4° (*c* 0 7, chloroform), ^{1}H-n m r ($CDCl_3$) δ 6 28 (dd, 1, *J* 1 5 and 5 9 Hz, -OC*H*=), 5 95 (d, 1, $J_{3\ 4}$ 2 9 Hz, H-4), 5 79 (dd, 1, $J_{2,3}$ 11 0 and $J_{3\ 4}$ 2 9 Hz, H-3), and 1 64 (dd, 3, *J* 1 5 and 6 3 Hz, CH_3-CH=)

Anal Calc for $C_{32}H_{31}NO_9$ (573 58) N, 2 44 Found N, 2 40

*2-Methyl-(3,4,6-tri-*O*-benzoyl-1,2-dideoxy-α-*D*-galactopyrano)-[2′,1′ 4,5]-2-oxazoline* (**7**) — To a solution of **6** (0 25 g, 0 44 mmol) in dry acetonitrile (3 ml) were added mercuric chloride (0 17 g, 0 63 mmol) and mercuric oxide (0 09 g, 0 42 mmol) The resulting suspension was boiled for 15 min under reflux with stirring, at which time t l c (solvent *C*) showed that the reaction was complete The mixture was then filtered through Celite, washed with acetonitrile, and the combined filtrates were evaporated The syrupy residue was taken up in dichloromethane, the solution was washed twice with saturated, aqueous potassium iodide and twice with water, dried (magnesium sulfate), and evaporated Chromatography of the residue on silica gel (solvent *C*) gave 0 19 g (85%) of syrupy 7, $[\alpha]_D^{25}$ +21 2°, $[\alpha]_{436}^{25}$ +37 2° (*c* 0 9, chloroform), ^{1}H-n m r ($CDCl_3$) δ 6 09 (d, 1, $J_{1,2}$ 7 3 Hz, H-1), 5 90 (t, 1, $J_{3,4} = J_{4\ 5}$ = 3 2 Hz, H-4), 5 52 dd, 1, $J_{2\ 3}$ 6 and $J_{3,4}$ 3 2 Hz, H-3), and 2 11 (d, 3, J_{2,CH_3} 1 7 Hz, oxazoline-CH_3)

*Methyl 2-acetamido-2-deoxy-β-*D*-galactopyranoside* (**9**) — A solution of the oxazoline **7** (0 2 g) in abs methanol (3 ml) containing *p*-toluenesulfonic acid (~5 mg) was boiled for 1 5 h under reflux The light-brown solution was cooled, the acid

was neutralized with a drop of pyridine, and the solvent was evaporated off The residue was chromatographed on silica gel with solvent *A* as eluant to afford 0 18 g (88%) of methyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-*β*-D-galactopyranoside (**8**) as a glassy foam; $[\alpha]_D^{25}$ +23 6°, $[\alpha]_{436}^{25}$ +52 9° (*c* 0.8, chloroform); ^{1}H-n m r. ($CDCl_3$)· δ 5.90 (d, 1, $J_{3\,4}$ 3.4 Hz, H-4), 5 65 (dd, 1, $J_{3,4}$ 3 4 and $J_{2,3}$ 11.6 Hz, H-3), 4.78 (d, 1, $J_{1,2}$ 8 5 Hz, H-1), 3 59 (s, 3, OCH_3), and 1.89 (s, 3, $NCOCH_3$) To compound **8** (0.12 g) in abs methanol (15 ml) was added 0 1M sodium methoxide in methanol (3 ml), and the solution was boiled under reflux The debenzoylation was monitored by t l c (solvent *D*), which indicated disappearance of the starting material after 0 5 h Sodium ions were removed with Rexyn-101 (H^+) ion-exchange resin. the solution was evaporated, and the residue was crystallized and recrystallized from methanol–ether, to give the title compound (**9**) as needles, m p 192–195°, $[\alpha]_D^{23}$ −11 2°, $[\alpha]_{436}^{23}$ −20 8°, (*c* 0 5, methanol), (lit [15] m.p 191–193°, $[\alpha]_D^{23}$ −12 ± 1° in methanol), ^{1}H-n m r (Me_2SO-d_6 + 2 drops of D_2O) δ 4 18 (d, 1, $J_{1,2}$ 8 5 Hz, H-1), 3 33 (s, 3, OCH_3), and 1 85 (s, 3, $NCOCH_3$), the signal at δ 8 0–7 4 (15H of 3PhCO) was now absent, and the sugar-ring protons were shifted upfield

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