Carbohydrate Research, 54 (1977) 217–230

C-GLYCOSYL COMPOUNDS STEREOSPECIFIC SYNTHESIS OF 2,5-ANHYDRO-D-ALLOSE DERIVATIVES *via* DIAZOTIZATION

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(Received April 12th, 1976, accepted for publication, after revision, October 25th, 1976)

ABSTRACT

A stereospecific synthesis of substituted derivatives of 2,5-anhydro-D allose *via* conformational control and diazotization is described Diazotization of the conformationally mobile methyl 2-amino-2-deoxy-α-D-altropyranoside (**7**) and its 3,4 6-tri-*O*-benzoyl derivative (**8**) led to a selectively disfavored, ring-contraction reaction, but, for the conformationally rigid 2-amino-1 6-anhydro-2-deoxy-3-*O*-*p*-tolylsulfonyl-β-D-altropyranose (**19**), the rearrangement was unequivocally channelled stereospecifically, and almost quantitatively to a 2,5-anhydro-D-alloseptanose derivative (**21**) Conformational assignments and rearrangement mechanisms are discussed *O*-Detosylation was achieved by photolysis The 1,3-dioxolane derivative used for the protection of the anomeric center was found very resistant toward acid hydrolysis, and disadvantageous in the regeneration of the free aldehyde group

INTRODUCTION

The resistance of *C*-nucleosides towards enzymic cleavage[1], presumably due to the greater stability of the *C*-glycosyl bond compared with the usual *N*-glycosyl bond, has made *C*-nucleosides interesting targets for chemical synthesis In the past few years, several routes having a potential for the elaboration of syntheses of *C*-nucleosides have been reported[2–6] Most of these syntheses involved intermolecular displacement or addition at the anomeric center As in many asymmetric syntheses, such condensations present the stereochemical problem of anomeric assignment[7]. On the other hand, synthesis of *C*-glycosyl compounds from non-sugar precursors is handicapped by racemic intermediates[7,8]

2,5-Anhydro sugar derivatives are of prime importance for the synthesis of *C*-nucleosides, especially when their mode of synthesis gives suitable control of the stereochemistry An ingenious synthesis of a *C*-nucleoside, with stereochemical control of a 2 5-anhydro sugar intermediate, has been achieved by an intramolecular

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displacement of a sulfonic ester group[8]. Deamination of certain 2-amino-2-deoxy-aldohexoses with nitrous acid constitutes the oldest route to 2,5-anhydro sugars[9], and the chemistry of the deamination has been extensively studied[10,11]. The rearrangement of carbonium ions formed through a diazonium intermediate is a complex process, and certain steps are still imperfectly understood. It is well known that a group, or atom, *trans* and antiparallel to the amino group readily attacks the cationic center by an "SN2-like", intramolecular displacement. Only recently has diazotization been employed in the synthesis of *C*-nucleosides[12]. The drawbacks of this mild reaction for general use in the synthesis of 2,5-anhydro sugars are the occurrence of side reactions leading to low yields, and ambiguity as to the stereochemistry of the products.

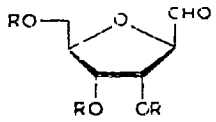
Initially, we sought to synthesize 2,5-anhydro-D-allose (**1**) from the reaction of methyl 2-amino-2-deoxy-α-D-altropyranoside (**7**) with nitrous acid, reasoning that the deamination mechanism would lead to ring contraction of the $^1C_4$(D) conformer and configurational inversion at C-2. However, the results indicated that the desired rearrangement is only a minor process, and that the major pathway involves the other conformer of **7**. We have investigated this reaction for free and substituted 2-amino-2-deoxy-D-altrose. To obviate conformational mobility in the diazotization of the aminopyranoside and to exert stereochemical control on the reaction, we stereospecifically synthesized a 2,5-anhydro-D-alloseptanose derivative (**21**) from 2-amino-1,6-anhydro-2-deoxy-3-*O*-*p*-tolylsulfonyl-β-D-altrose (**19**) in excellent yield.

RESULTS AND DISCUSSION

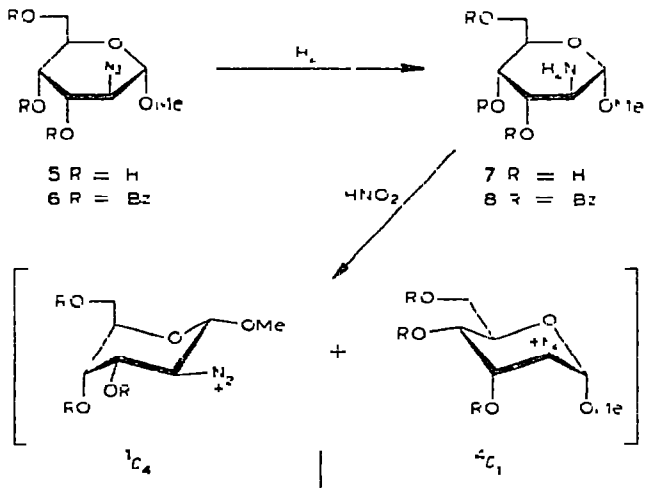
2-Amino-2-deoxy-D-altroses were prepared by catalytic hydrogenation of the corresponding azides. Methyl 2-azido-2-deoxy-α-D-altropyranoside (**5**) and its tri-*O*-benzoyl (**6**) and 3-*O*-*p*-tolylsulfonyl (**17**) derivatives were prepared from methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside according to described procedures[13]. 1,6-Anhydro-2-azido-2-deoxy-3-*O*-*p*-tolylsulfonyl-β-D-altropyranose (**18**) was prepared from **17** by *p*-toluenesulfonic acid-catalyzed cyclization[14].

The deamination of methyl 2-amino-2-deoxy-α-D-altroside (**7**) with sodium nitrite in acetic acid gave an intractable mixture. Acetylation of the lyophilized residue gave mixed esters which could not be resolved by chromatographic techniques. N.m.r.-spectral and microanalytical data indicated that the methoxyl group was essentially unchanged and that four acetyl substituents were present in the mixed esters. According to stereochemical studies on the deamination of aminocyclohexane[11], two plausible mechanisms for the deamination would be: (*i*) intramolecular displacement, through the $^1C_4$(D) conformer, *via* an equatorial attack of the diazonium ion by the ring-oxygen atom, inversion of configuration at C-2, and then attack by solvent on the resultant, C-1 carbonium ion, to yield ring-contracted product **9**, or (*ii*) solvolysis, SN2 displacement (axially) by solvent (inversion) through the $^4C_1$(D) conformer, or capture of solvent, after decomposition of the diazonium ion to the carbonium ion and nitrogen, to afford **12** (epimerization). Any

hydrolysis at the anomeric center from the former path to **1** would result in cyclization[9] to **15**, consequently, an acetal methine proton (instead of a free aldehyde proton) would be observed in the n m r. spectrum Only barely appreciable signals

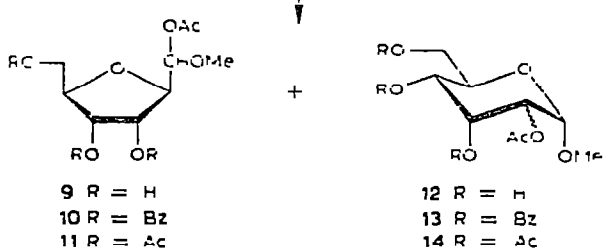


1 R = H
2 R = Bz
3 R = Ac
4 R = CH_2Ph



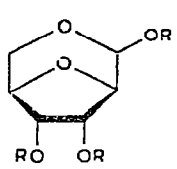
5 R = H
6 R = Bz

7 R = H
8 R = Bz



9 R = H
10 R = Bz
11 R = Ac

12 R = H
13 R = Bz
14 R = Ac



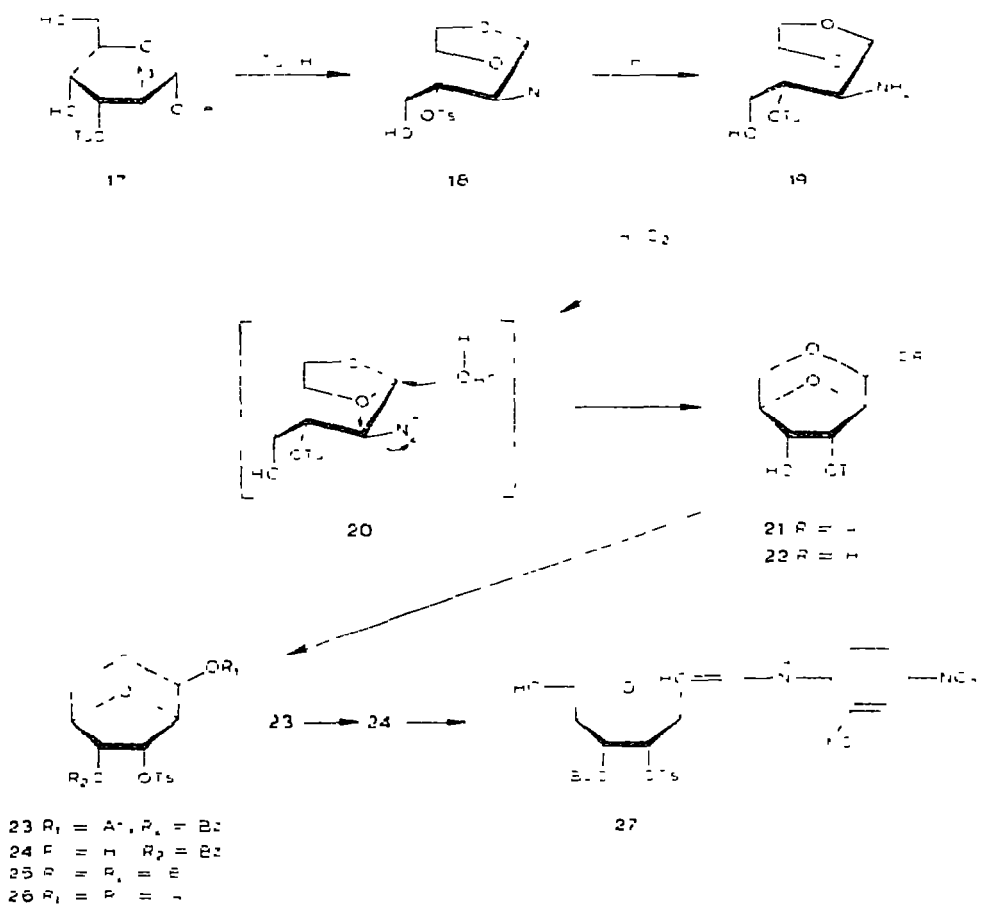
15 R = H
16 R = Ac

(around δ 6), attributable to the acetal[15] of either **11** or **16** (from acetylation of the diazotized **7**) were detected, suggesting the unfavorable, ring-contraction path.

The singlet at δ 2.1 in the n.m.r. spectrum of the processed organic extract from diazotization of methyl 2-amino-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-altropyranoside (**8**) verified the general participation of the solvent (acetic acid) in the reaction. A small doublet at δ 9.85, indicative of free aldehyde, and a small absorption around δ 6 for acetyl methyl acetal were ascribed to the ring-contracted derivative. The low conversion into 2,5-anhydro sugar from the conformationally mobile methyl 2-amino-2-deoxy-α-D-altroside (**7**) can be attributed to the thermodynamically less favorable $^1C_4$(D) conformer[16].

In contrast, diazotization of **19**, which has the $^1C_4$ conformation fixed by the 1,6-anhydro ring[17], gave ring-contracted 1-*O*-acetyl-2,5-anhydro-3-*O*-*p*-tolylsulfonyl-D-alloseptanose (**21**) as the only isolable product (in 90% yield) in high purity. Configurational assignment for **21** was based on n.m.r.-spectral and optical analyses. A dramatic change in the pattern of the sugar-ring protons in the n.m.r. spectra was observed on passing from the pyranoid to the furanoid form. The pair of doublets at δ 5.15 and 4.6 (collapsed from a broad triplet by D_2O), corresponding to H-3 and H-4, are in an AB system indicative of their relative, symmetrical, chemical environment. The values of $J_{3,4}$ (6.5 Hz) and $J_{2,3}$ or $J_{4,5}$ (~0 Hz) show vicinal coupling (comparable to the interaction of *cis*-methine protons and two bridgehead protons in norcamphorlike, fused, five-membered rings) consistent with their dihedral angles[18]. The nonequivalent C-6 protons at δ 3.5 for H-6a and 4.1 for H-6e show normal, geminal coupling ($J_{6a,6e}$ 12.5 Hz). With a "Newman" projection (**I**) similar to that used in Horton and Turner's analysis of tri-*O*-acetyl-β-D-ribopyranosyl bromide[19], small coupling-constants (<2 Hz) were observed, compatible with the dihedral angles between H-5 and two H-6 (or H-2 and H-1) of a distorted, chair conformation. The overlapping of H-2 and H-5 to a single band at δ 4.3 is attributable to their relatively symmetrical environment and small coupling with all vicinal protons. The shift of H-1 (indistinct doublet) at δ 5.2 for **19** to δ 5.75 for **21** suggested the change of the alkyl acetal to an acetoxyl group at the anomeric center. The small coupling ($J_{1,2}$ 0.5 Hz), indicative of an almost perpendicular dihedral angle of H-1 and H-2, therefore indicates that the acetoxyl group is disposed equatorially. The reversal of sign of the specific optical rotation (from −116.3° to +18.5°) suggested inversion of configuration, from Hudson's rule of isorotation[20]. Although **21** was not obtained in crystalline form, the crystalline 4-benzoate **23** and the (2,4-dinitrophenyl)hydrazone (**27**) of 2,5-anhydro-4-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-D-allose were prepared from **21**. In each case, the i.r., n.m.r., optical, and microanalytical data were consistent with the structures proposed. The cleavage of the acetyl group by mild, acid hydrolysis of **23** (to give **24**) regenerated the character of a reducing septanose, and shift of the H-1 signal from δ 5.75 to 4.9 also verified the assignment of the acetoxyl group at the anomeric center of **21**.

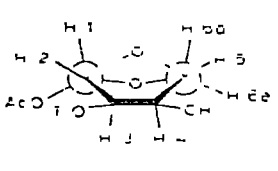
A speculation as to the unique, stereospecific, rearrangement reaction was the possibility that some relatively polar, diazotized by-product(s), such as **22**, would be



overlooked, because of aqueous washing in the isolation procedure To test for existence of any such by-product, all products from the lyophilized residue from the reaction of **19** were characterized Treatment of the residue with benzoyl chloride afforded benzoate **23** plus diacetate **26** (in the ratio of one to four), separable by preparative t l c , and no dibenzoate **25** was observed The preponderant **26** was unexpected, but the same results were obtained on repetition of the experiment The acetylation is presumably due to the activation of acetate (salt) residue to acetic benzoic anhydride which, in turn, reacts more accessibly at the (less hindered) acetyl moiety Replacement of benzoyl chloride by acetic anhydride in the esterification afforded crystalline **26** in 93% yield

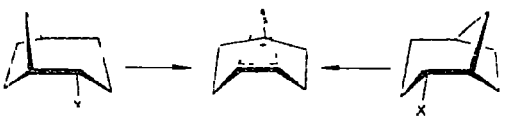
A precedent for the deamination of a conformationally locked 2-amino-2-deoxyhexopyranose has been demonstrated by Micheel *et al* [21], who obtained only a 37% yield of 2,6-anhydro-D-mannopyranose from 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose by diazotization The axial attack of the cationic center on the ring-oxygen atom of the septanose (intermediate **II**) would, conceivably, compete

with the neighboring, electron-rich group and solvated counter-ion or solvent[11]. The change of the amino group to the equatorial disposition in the amino-1,6-anhydride **19** eliminated those possible side-reactions The 1,6-anhydro ring not only locked it in the appropriate orientation but also permitted the ring-oxygen atom to be the unique nucleophile accessible to the back-side attack on the cationic center created at C-2 The inversion of configuration at the center was unequivocally established by the presence of the intact 1,6-anhydro bridge after the reaction. Thus, the stereochemical disposition of **19** confined the rearrangement mechanism of diazotization so as to give the 2,5-anhydro-D-alloseptanose derivative (**21**) stereospecifically. The stereochemical results from this investigation are in good agreement with the current theory[22] regarding the importance of conformational factors in the diazonium intermediate, consequently determining the outcome of the reaction



I

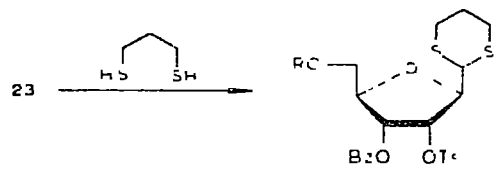
II



III

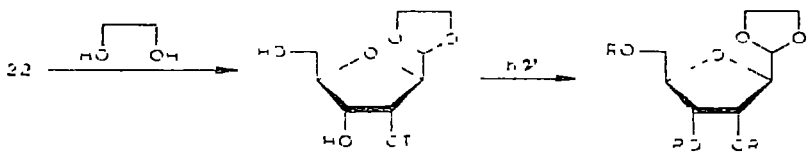
The solvolysis of endo-bicyclo[3.2.1]octan-2-yl (equatorial) *p*-toluenesulfonate[23] is the nearest analogy as regards structural geometry. However, the ion-pair return phenomena, and the symmetry properties of the nonclassical, ion intermediate **III**, result in racemization and isomerization, which are not possible in the diazotization of **19**. The reactive intermediate from **19** is more likely to be the diazonium (rather than the decomposed carbonium) ion Mechanistically, we could not distinguish whether the 1-acetoxyl group was formed by a simultaneous, SN2-like displacement, or solvent capture by the new cationic center shifted to the anomeric carbon atom, as the thermodynamically stable, equatorial, acetoxyl group resulted

Acid stability and general crystalline properties are advantages of most sulfonate derivatives[24], however, *O*-detosylation with retention of configuration is not always easy Prior to the removal of the sulfonic ester group on O-3, the labile, anomeric acetal group of **21** has to be protected. In a preliminary study treatment of **23** with 1,3-propanedithiol in benzene containing *p*-toluenesulfonic acid gave non-crystalline 1,3-dithiane **28** and its 6-*O*-acetyl derivative (**29**) in the ratio of one to three, the latter appears to result from intramolecular migration of the acetoxyl group from the anomeric carbon atom to C-6 Acetylation of the reaction mixture afforded **29** as the only product Crystalline 1,3-dioxolane derivative **30** was obtained as the only product from the acetalation of **22** with ethylene glycol. The conventional methods of *O*-detosylation, by sodium amalgam, Raney nickel[25], and sodium naphthalene[26], either failed, or no deprotected, free alcohol was detectable. Cleavage of the O–S bond of sulfonic ester **30** was readily achieved by photolysis at room



28 R = r
29 R = -

temperature in methanolic sodium methoxide[27]. The free alcohol, 2-β-D-ribofuranosyl-1,3-dioxolane (**31**), was purified by preparative t l c, and obtained as a colorless syrup in good yield (70%). The 2,3,5-tri-*O*-benzoyl (**32**) and -benzyl (**33**) derivatives were obtained as syrups from **31**. Their i r., n m r., optical, and microanalytical data were consistent with those expected for β-D-ribofuranosyl derivatives.



30

31 R = H
32 R = Bz
33 R = CH_2Ph

Regeneration of the free aldehyde from the 1,3-dioxolane derivatives (**32** and **33**) by treatment with 1 to 4 M hydrochloric acid in aqueous 1,4-dioxane or acetone failed, the starting material being recovered unchanged. More-drastic hydrolysis with *p*-toluenesulfonic acid in aqueous acetic acid at elevated temperature led to extensive decomposition of **32**. A free aldehyde, supposedly **4**, was obtained by hydrolysis of **33**, but the n m r. and microanalytical data indicated that this aldehyde was partially decomposed. The crude aldehyde reacted with (2,4-dinitrophenyl)hydrazine, but no crystalline hydrazone or *N*,*N*-diphenylimidazolidine derivative could be obtained. The 1,3-dioxolane derivatives proved very resistant towards acid hydrolysis as compared with diphenylimidazolidines[28].

EXPERIMENTAL

General — All melting points are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 237 spectrophotometer. N.m.r. spectra were recorded with a Varian T-60 or A-60 spectrometer, with tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin–Elmer 141 polarimeter (1-dm microtube), and are given to the nearest degree. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Analytical, thin-layer

chromatography (t.l.c.) was conducted on silica gel 254, and preparative, thick-layer chromatography on layers (2 × 200 × 200 mm) of silica gel (295 and 254). Aprotic organic extracts were routinely dried with anhydrous magnesium sulfate. Solvents were removed under diminished pressure in a rotary evaporator.

Methyl 2-azido-2-deoxy-β-D-altropyranoside (**5**). — A solution of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[13] (20 g) in 1,4-dioxane (300 ml) and dilute sulfuric acid (1.2%, 120 ml) was heated overnight at 55–60° with stirring. The solution was made neutral with barium carbonate, the suspension was filtered through a Celite pad, and the filtrate was evaporated to give a solid. Recrystallization from 95% ethanol, and washing with chloroform, gave 12.5 g (84%) of **5**. The analytical sample was recrystallized from methanol, to give colorless prisms, m.p. 138–139° (lit.[14] m.p. 140–141°), ν_{max}^{KBr} 2100 cm^{-1} (N_3).

Methyl 2-amino-2-deoxy-α-D-altropyranoside (**7**), *and its deamination with nitrous acid*. — The 2-azido-D-altroside (**5**) (1 g, 4.5 mmoles) in methanol (50 ml) was reduced with hydrogen under atmospheric pressure at room temperature in the presence of Adams' catalyst for 24 h. After removal of the catalyst and solvent, the resultant syrup showed a single spot (with a trace of impurities) ν_{max}^{film} 1600 cm^{-1} (NH_2), no absorption at 2100 cm^{-1}. A hygroscopic hydrochloride was obtained by passing gaseous hydrogen chloride into an ethanolic solution of the syrup, and washing the product with ether.

Sodium nitrite (0.5 g, 7.2 mmoles) in water (2.5 ml) was added dropwise to a solution of the 2-aminoaltroside hydrochloride (0.5 g, 2.1 mmoles) in aqueous acetic acid (90%, 30 ml). The solution was stirred under nitrogen and kept below 5° in an ice-bath until all gas evolution ceased (over 3 h). The mixture was then stirred for 1 h at room temperature, purged with nitrogen for 30 min, and evaporated to dryness. The residue was co-distilled with toluene to remove moisture, and acetylated with acetic anhydride (5 ml) in dry pyridine (20 ml) overnight at room temperature. The mixture was poured into ice–water, and extracted with chloroform. The extract was successively washed with 4M hydrochloric acid, water, saturated sodium hydrogencarbonate solution, and water, dried, and evaporated to a syrup that showed a major spot, with tailing, in t.l.c. The major component was isolated by preparative t.l.c., its n.m.r. spectrum indicated that it was a mixture of acetates (presumably, **11** and **14**), with acetyl (δ 2.1) and methoxyl (δ 3.5) protons in the ratio of 4 to 1.

Anal. Calc. for $C_{15}H_{22}O_{10}$ (both **11** and **14**): C, 49.72; H, 6.08; OCH_3, 8.56. Found: C, 49.89; H, 6.12; OCH_3, 9.09.

Methyl 2-amino-3,4,6-tri-O-benzoyl-2-deoxy-α-D-altropyranoside (**8**). — To an ice-cooled, stirred solution of the 2-azido-D-altroside **5** (1 g, 4.5 mmoles) in dry pyridine (20 ml) was added benzoyl chloride (2.5 ml, 19 mmoles), and the mixture was kept overnight at room temperature. The mixture was then poured into ice–water, and processed as in the foregoing acetylation. The benzoate **6** was obtained as a thick oil (2.4 g, 98%) which showed only one component in t.l.c., ν_{max}^{neat} 2100 (N_3) and 1720 cm^{-1} (benzoate), n.m.r. ($CDCl_3$): δ 3.5 (s, 3, OCH_3), 4.1 (q, 1, $J_{1,2}$ 3 Hz, $J_{2,3}$ 5 Hz, H-2), 4.85 (d, 1, H-1), and 7.2–8.2 (m, 15, Ar H).

Anal Calc for $C_{28}H_{25}N_3O_8$ C, 63 27, H, 4 74, N, 7 91 Found C, 63 14, H, 4 84; N, 7 71

The azide **6** (2 4 g, 4 5 mmoles) was reduced to amine **8** as described for **7** The crude amine hydrochloride was recrystallized from chloroform–ether to give a white, non-hygroscopic crystalline product (1 66 g, 70%) m p 205° (dec) ν_{max}^{KBr} 3000–2500 (br) and 1610 cm^{-1} (NH_3^+), n m r ($CDCl_3$) δ 5 4 (d 1, H-1) and 9 3 (br s, collapsed with D_2O, NH_3^+)

Anal Calc for $C_{28}H_{28}ClNO_8$ C, 62 05, H, 5 17, Cl, 6 54, N, 2 59 Found C, 61 88, H, 5 06, Cl, 6 64, N, 2 51

Reaction of **8** *with nitrous acid* — The amine hydrochloride **8** was deaminated with sodium nitrite as described for **7** The reaction mixture was lyophilized, and the residue partitioned between chloroform and water The organic extracts were combined, washed, and processed, to give a syrup which was found by t l c to be a mixture Its n m r spectrum ($CDCl_3$) showed a minor, aldehydic proton at δ 9 85

*1,6-Anhydro-2-azido-2-deoxy-3-*O*-p-tolylsulfonyl-β-*D*-altropyranose* (**18**) — Methyl 2-azido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-altropyranoside[13] (1 5 g, 4 mmoles) was stirred in benzene (150 ml) containing *p*-toluenesulfonic acid dihydrate (1 5 g, 6 9 mmoles) The mixture was then boiled for 5 h under reflux (Dean–Stark trap) and cooled, ice–water was added, and the organic layer was successively washed with aqueous sodium hydrogencarbonate and water, dried and evaporated to syrup which crystallized overnight Recrystallization from benzene–hexane afforded **18** as prisms (1 1 g, 81%), m p 81–82 (lit [14] m p 86–87°)

*2-Amino-1,6-anhydro-2-deoxy-3-*O*-p-tolylsulfonyl-β-*D*-altropyranose* (**19**) — The 1,6-anhydro-2-azido sugar (**18**) (3 41 g, 1 mmole) in ethyl acetate (100 ml) was reduced with hydrogen at atmospheric pressure with 5% Pd/C (1 5 g) as the catalyst The hydrogenation was conducted for over 24 h, until no azide absorption at 2100 cm^{-1} was observed in the i r spectrum of an aliquot of the reaction mixture All the solids were collected by filtration, and hot methanol was used to dissolving the amine The catalyst residue was repeatedly washed with hot methanol Cotton-like crystals were obtained on evaporation of the solvent, these were washed with ether, to give pure **19** (2 7 g, 84%), m.p 162–163 °, $[\alpha]_D^{25}$ −116 3° (*c* 1 % methanol), ν_{max}^{KBr} 3500, 3400, 1580 (NH_2), 3300 (br, OH), 1360, and 1200 cm^{-1} (sulfonyl) n m r (Me_2SO-d_6) δ 2 9 (q, 1, $J_{1,2}$ 1 5 Hz and $J_{2,3}$ 9 5 Hz, H-2), 3 6 (d, 2, *exo*- and *endo*-H-6), 3 7 (m, 1, H-4), 4 1 (q, 1, $J_{3,4}$ 4 Hz, H-3) 4 45 (q, 1, H-5), and 5 2 (d, 1, H-1), free amino protons were not resolved in the spectrum, and were probably hidden by other protons, three ammonium protons were observed (at δ 8 8) in the n m r spectrum of the hydrochloride formed by addition of hydrogen chloride

Anal Calc for $C_{13}H_{17}NO_6S$ C, 49 51 H, 5 44, N, 4 44, S, 10 17 Found C, 49 21, H, 5 20, N, 4.19, S, 9 95

*1-O-Acetyl-2,5-anhydro-3-*O*-p-tolylsulfonyl-*D*-alloseptanose* (**21**) — The amino sugar **19** (9 0 g, 29 mmoles) was treated with sodium nitrite (4 5 g, 65 mmoles) as already described The solvent was removed by lyophilization, the residue was dissolved in chloroform (200 ml), and the solution was successively washed with

aqueous sodium hydrogencarbonate (20 ml) and water (20 ml), dried, and evaporated to a colorless oil (9.2 g, 90%). T.l.c. showed that this product was essentially pure, only a trace of impurities being detected (at the origin). The crude product was pure enough for the next steps without further purification. The analytical sample was prepared by preparative t.l.c.; $[\alpha]_D^{27}$ +18.5° (*c* 1.0, chloroform); ν_{max}^{neat} 3500 (broad, OH), 1740 (acetyl), 1360, and 1180 cm^{-1} (sulfonyl). n.m.r. ($CDCl_3$): δ 2.15 (s, 3, acetyl), 3.2 (br d, 1, collapsed with D_2O, $J_{4,OH}$ 6 Hz, OH-4), 3.5 (d, 1, $J_{6e,6a}$ 12 Hz, H-6a), 4.1 (dd, 1, J 12 Hz and $J_{6e,5}$ 1.8 Hz, H-6e), 4.3 (s, 2, H-2,5), 4.6 (t, collapsed to d with D_2O, 1, J 6 Hz and $J_{3,4}$ 6.5 Hz, H-4), 5.15 (d, 1, H-3), and 5.7 (incomp. d, 1, $J_{1,2}$ 0.5 Hz, H-1).

Anal. Calc. for $C_{15}H_{18}O_8S$: C, 50.27; H, 5.06; S, 8.94. Found: C, 49.91; H, 5.08; S, 8.58.

1-O-Acetyl-2,5-anhydro-4-O-benzoyl-3-O-p-tolylsulfonyl-D-alloseptanose (**23**). — The 1,6-anhydro-D-allose **19** (1.5 g, 4.2 mmoles) was benzoylated with benzoyl chloride (3 ml, 21 mmoles) in dry pyridine, and processed as described for the other acetylations and benzoylations, to furnish a light-yellow oil. T.l.c. showed the product to be a single component; it crystallized after a few days at room temperature. Recrystallization from ethanol gave white crystals (1.7 g, 87%), m.p. 155–156°, $[\alpha]_D^{27}$ +85° (*c* 1.0, chloroform); ν_{max}^{KBr} 1740 (acetyl), 1720 (benzoyl), 1360, and 1180 cm^{-1} (sulfonyl). n.m.r. ($CDCl_3$): δ 5.3 (d, 1, $J_{3,4}$ 6.5 Hz, H-3), 5.6 (d, 1, H-4), 5.76 (s, 1, H-1), and 7.0–8.0 (m, 4 Ar H for tosyl, and 5 for benzoyl).

Anal. Calc. for $C_{22}H_{22}O_9S$: C, 57.13; H, 4.80; S, 6.96. Found: C, 56.96; H, 4.83; S, 6.80.

Very slow reaction of **23** with Fehling solution was observed, in comparison with the fast reaction of deacetylated **24** (from mild, acid hydrolysis of **23**).

Acylation of the reaction mixture from diazotized **19**. — *A. Benzoylation.* Compound **19** (1 g, 3.2 mmoles) was deaminated as described for **21**. After removal of solvent by lyophilization and co-distillation with toluene, the resultant semi-solid was suspended in ice-cooled, dry pyridine (20 ml), and benzoyl chloride (2 ml, 15 ml) was slowly added dropwise. The mixture was stirred overnight at room temperature, and then processed as before, giving a syrup that contained two components (t.l.c.). The components were separated by preparative t.l.c., and characterized as the benzoate **23** (0.25 g, 17%) and acetate **26** (0.9 g, 69%).

B. Acetylation. 1,4-Di-O-acetyl-2,5-anhydro-2-O-p-tolylsulfonyl-D-alloseptanose (**26**). — The residue from the diazotization of **19** (500 mg, 1.6 mmoles) was dried as previously described, and acetic anhydride (1 ml, 10 mmoles) was added to a suspension of the product in pyridine. The mixture was stirred overnight at room temperature, and processed as before. The chloroform extract contained only one component (t.l.c.). Crystallization of the syrup was achieved from benzene–hexane, with scratching or nucleating, to give white, crystalline **26** (600 mg, 93%), m.p. 124–125°, $[\alpha]_D^{25}$ +84.5° (*c* 1.0, chloroform), ν_{max}^{KBr} 1740 cm^{-1} (acetyl); n.m.r. ($CDCl_3$): δ 2.1 (s, 3, acetyl), 2.2 (s, 3, acetyl), 5.23 (d, 1, $J_{3,4}$ 6.5 Hz, H-3), 5.55 (d, 1, J 6.5 Hz, H-4), and 5.8 (s, 1, H-1).

Anal. Calc. for $C_{17}H_{20}O_9S$ C, 51.00, H, 5.03, S, 8.01 Found: C, 51.13; H, 4.98; S, 8.11

2,5-Anhydro-4-O-benzoyl-3-O-p-tolylsulfonyl-D-alloseptanose (**24**). — Compound **23** (1.5 g, 3.2 mmoles) was hydrolyzed with dilute sulfuric acid as described for the preparation of **5**. After filtration of barium sulfate, the filtrate was evaporated to a syrup which was partitioned between chloroform and water Evaporation of the chloroform extract gave amorphous material (1.2 g, 88%) ν_{max}^{neat} 3500 (br OH) and 1720 cm^{-1} (benzoyl), n.m.r. ($CDCl_3$) δ 3.75 (d, 1, *J*, 12 Hz, H-6a), 4.35 (s, 2, H-2,5), 4.1 (dd, 1, *J* 12 Hz and 1.5 Hz, H-6e), 4.9 (incomp. d, 1, $J_{1,2}$ 0.5 Hz, H-1), 5.35 (d, 1, *J* 6.5 Hz, H-3), and 5.65 (d, 1, *J* 6.5 Hz, H-4)

A solution of crude 2,5-anhydro-D-allose **24** (100 mg) in diglyme (0.5 ml) was mixed with (2,4-dinitrophenyl)hydrazine (5% in diglyme, 5 ml) and heated on a hot-water bath After being stirred for 10 min, the solution was diluted with water, to precipitate a brown oil which crystallized on rubbing The crude, brown solid was recrystallized from diglyme–50% ethanol, to give yellow hydrazone **27** (130 mg), m.p. 134–135°, $[\alpha]_D^{27}$ −77 (*c* 1.0, chloroform), ν_{max}^{KBr} 3500 (br, OH), 3200 (sharp, NH), 1710 (benzoyl), 1580 (C=N), 1500, and 1300 cm^{-1} (NO_2) n.m.r. (Me_2SO-d_6) σ 3.5–3.7 (m, 3, H-5 and two H-6), 4.3 (indistinct d, 1, H-1), 4.7 (t, 1, H-2), 5.05 (br t, 1, OH, collapsed with D_2O), 5.3–5.6 (m, 2, unresolved H-3,4), 7.0–9.0 (m, 4 Ar H for tosyl, 5 for benzoyl, and 3 for dinitrophenyl), and 11.2 (s, 1, collapsed with D_2O, NH)

Anal. Calc. for $C_{29}H_{24}O_{11}S$ C, 52.00, H, 4.02, N, 9.33, S, 5.34. Found C, 51.75, H, 3.82; N, 9.59; S, 5.60

1,3-Dithiane derivatives (**28** *and* **29**). — A solution of the 2,5-anhydro-D-allose **23** (500 mg, 1.1 mmoles), 1,3-propanedithiol (2 ml, 2 mmoles), and *p*-toluenesulfonic acid, dihydrate (100 mg, 0.45 mmole) in dry benzene (50 ml) was boiled for 8 h under reflux (Dean–Stark trap) After azetropic distillation, the solution was cooled, successively washed with water (twice), 10% sodium hydroxide, and water, dried, and evaporated to a yellowish oil which showed two spots in t.l.c. A portion (200 mg) of the syrup was fractionated by preparative t.l.c. to afford two components (**28** and **29**)

2-(3-O-Benzoyl-2-O-p-tolylsulfonyl-β-D-ribofuranosyl)-1,3-dithiane (**28**) — This compound had the lower mobility in t.l.c., yield 75 mg (23%), $[\alpha]_D^{27}$ −9.0° (*c* 0.9, chloroform); ν_{max}^{neat} 3500 (OH), 1720 (benzoyl), 1370, and 1180 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$) δ 2.0 (m, 2, CH_2), 2.8–3.0 (m, 4, S-CH_2), 3.85 (m, 2, H-5), 4.15 (d, 1, *J* 5 Hz, thioacetal H), 4.25 (m, 1, H-4), 4.5 (t, 1, H-1), and 5.2–5.35 (m, 2, H-2,3)

Anal. Calc. for $C_{23}H_{26}O_7S_3$ C, 54.09, H, 5.13, S, 18.84 Found C, 53.84; H, 5.20, S, 18.58.

2-(5-O-Acetyl-3-O-benzoyl-2-O-p-tolylsulfonyl-β-D-ribofuranosyl)-1,3-dithiane (**29**) — This compound was obtained in a yield of 210 mg (60%), $[\alpha]_D^{27}$ −13.3° (*c* 1.0, chloroform), ν_{max}^{neat} 1740 and 1720 cm^{-1} (acetyl and benzoyl) n.m.r. ($CDCl_3$) σ 2.0 (m, 2, CH_2), 2.1 (s, 3, acetyl), 2.7–3.0 (m, 4, S-CH_2), 4.0 (d, 1, *J* 4 Hz, thioacetal H), 4.4 (m, 3 unresolved H-4 and H-5), 4.6 (t, 1, H-1), and 5.3 (m, 2, H-2,3)

Anal. Calc. for $C_{25}H_{28}O_8S_3$: C, 54.33; H, 5.10; S, 17.40. Found: C, 53.98; H, 5.10; S, 17.28.

2-(2-O-p-Tolylsulfonyl-β-D-ribofuranosyl)-1,3-dioxolane (**30**) — A solution of the crude 2,5-anhydro-D-allose **21** (1 g, 2.8 mmoles) was hydrolyzed (as described in the preparation of **24**) to crude **22**. The hemiacetal **22** was unstable at room temperature and so it was prepared fresh before acetalation with ethylene glycol (10 ml) in dry benzene (80 ml) containing *p*-toluenesulfonic acid (100 mg) as the catalyst. The azeotropic distillation was conducted for over 4 h (until no more water could be distilled). The solution was cooled, and extracted with chloroform, and the extract was successively washed with 20-ml portions of water, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to a crystalline mass. Recrystallization from benzene gave colorless needles (600 mg, 52%), m.p. 115–116°, $[\alpha]_D^{27}$ −22.3° (*c* 1.0, chloroform), ν_{max}^{KBr} 3500 and 3400 cm^{-1} (OH). n.m.r. ($CDCl_3$): δ 2.5 (s, 3, Me of tosyl), 2.6–3.0 (br. m, 2, OH), 3.8 (m, 2, H-5), 3.9 (s, 4, ethylene), 4.0–4.4 (m, 2, unresolved H-1,3), 4.8–5.0 (m, 2, superimposed thioacetal H and H-2), and 7.3–8.0 (q, 4, tosyl Ar H).

Anal. Calc. for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.90. Found: C, 49.76; H, 5.49; S, 8.65.

Photolytic O-detosylation of **30** *to 2-β-D-ribofuranosyl-1,3-dioxolane* (**31**) — A methanolic solution (400 ml) of **30** (2 g, 5.5 mmoles) containing sodium methoxide (360 mg, 6.7 mmoles) was purged with argon for 3 min, and then irradiated with a 100-W, medium-pressure, mercury lamp in a water-cooled, quartz immersion-well (ACE Glassware) for 5 h at 30–35° while being flushed with a gentle, continuous bubbling of argon. After irradiation, the solution was light-yellow and contained a white precipitate, this was removed by filtration, the filtrate was mixed with absolute ethanol (100 ml), the mixture was filtered to remove more insoluble material, and the solid was washed with ethanol (25 ml). The filtrate and washing were combined, evaporated to dryness, and the residue triturated with benzene. The benzene was decanted, and the residual syrup was redissolved in the minimal volume of ethanol and chromatographed on preparative-t.l.c. plates which were developed with 4:1:1 1-butanol–methanol–water for 8 h. The plates were dried in air and **30** and the detosylated compound **30** (**31**) were located under short-wavelength, u.v. light. R_F 0.8 for **30** (dark blue) and 0.6 for **31** (faint green). Compound **31** was eluted with methanol, to give a light-yellow syrup (0.8 g, 70%), $[\alpha]_D^{27}$ +3.5° (*c* 1.0, methanol). ν_{max}^{neat} 3400 cm^{-1}. n.m.r. (Me_2SO-d_6) δ 3.0–4.0 (m, unresolved sugar-ring protons and free hydroxyls), 4.0 (s, 4, ethylene), and 4.85 (d, 1, *J* 3.5 Hz, acetal H).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.68; H, 6.87.

2-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,3-dioxolane (**32**) — Benzoylation of **31** was conducted as described for **6**, to give **32** as a colorless oil (almost quantitatively), $[\alpha]_D^{27}$ +35.9° (*c* 1.0 chloroform), ν_{max}^{neat} 1720, 1600, and 1450 cm^{-1} (benzoyl). n.m.r. ($CDCl_3$): δ 3.8–4.0 (m, 4, ethylene), 4.5–4.8 (m, 4, H-1,4,5), 5.2 (d, 1, *J* 2.5 Hz, acetal H), 5.7–6.0 (m, 2, H-2,3), and 7.2–8.2 (m, 15, Ar H).

Anal. Calc. for $C_{29}H_{26}O_8$: C, 67.17; H, 5.05. Found: C, 67.18; H, 5.14.

2-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)-1,3-dioxolane (**33**) — Sodium hydride (200 mg, in oil dispersion, washed with ether before use) was added to a solution of **31** (300 mg, 1 45 mmoles) in dry *N,N*-dimethylformide (10 ml), the suspension was stirred at room temperature for 30 min, cooled to 5° in an ice-bath, and α-bromotoluene (benzyl bromide) (1 ml, 6 mmoles) was added The mixture was stirred for two days; then, methanol (2 ml) was added to decompose the excess of benzyl bromide, and the solution was evaporated to dryness The residue was extracted with chloroform, and the extract was washed with water, dried, and evaporated Traces of solvent were removed under high vacuum, to afford an oil which was chromatographed on preparative-t l c plates, to give **33** (0 54 g, 77%): $[\alpha]_D^{27}$ +38 5° (*c* 1.0, chloroform), ν_{max}^{neat} 1600 (weak), 1495, and 1450 cm^{-1} (benzyl ether) n m r ($CDCl_3$) δ 3 6 (incomp d, 2, H-5), 3 85 (s, 4, ethylene), 4 0 (m, 2, H-1,4), 4 25 (m, 2, H-2,3) 4 6 (d, 6, benzylic CH_2) 4 95 (d, 1, *J* 3 5 Hz, acetal H), and 7 35 (s, 15, Ar H)

Anal Calc for $C_{29}H_{32}O_6$ C, 73 09, H, 6 77 Found C, 73 29, H, 6 90

Attempted regeneration of free aldehyde by acid hydrolysis — Treatment of **32** and **33** with 1 to 4M hydrochloric acid in aqueous 1,4-dioxane or acetone gave recovery of unchanged starting-materials only. A stirred solution of **33** (1 45 g, 3 mmoles) in 1 l acetic acid–water (30 ml) containing *p*-toluenesulfonic acid dihydrate (300 mg, 1 45 mmoles) was gently heated just below the boiling point for over 5 h (until t l c showed that most of the **33** had disappeared) The solution was evaporated to dryness, and the residue was extracted with benzene The extract was successively washed with aqueous sodium hydrogencarbonate and water, and evaporated to a syrup The main component was isolated by preparative t l c , ν_{max}^{neat} 1740 cm^{-1} (carbonyl), n m r ($CDCl_3$) δ 9 8 (incomp d, *J* 1 5 Hz, aldehydic proton)

ACKNOWLEDGMENT

The authors are grateful to Dr R S Tipson for his encouragement, and for his help in the preparation of the manuscript

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