Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

SYNTHESIS OF BRANCHED-CHAIN AMINO SUGARS *via* A SPIRO-EPOXIDE DERIVATIVE OF 2-AMINO-2-DEOXY-D-GLUCOSE

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(Received April 23rd, 1970; in revised form, May 27th, 1970)

ABSTRACT

Treatment of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (**1**) with dimethyloxosulfonium methylide gave methyl 3,3′-anhydro-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-(hydroxymethyl)-α-D-allopyranoside (**2**). Reduction of **2** with lithium borohydride afforded the known 3-*C*-methylallopyranose derivative (**3**). The epoxide ring was hydrolyzed with sodium acetate to give methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-(hydroxymethyl)-α-D-allopyranoside (**5**). This diol was oxidized with methyl sulfoxide containing phosphorus pentaoxide to the 3-*C*-formyl derivative **10**. Ring opening of **2** with sodium acetate in buffered *N*,*N*-dimethylformamide gave the 3-*C*-(acetoxymethyl)alloside (**6**), and opening with potassium phthalimide gave the 3-*C*-(phthalimidomethyl) derivative (**8**). The configuration of substituents at the branching point was indicated by n.m.r. spectra of *O*-acetyl derivatives.

INTRODUCTION

Several approaches are available for the synthesis of branched-chain sugar derivatives[1]. Branching has been introduced into suitably protected ketoses by application of the Wittig reaction with alkylidene phosphoranes[2], trimethyl phosphonoacetate[3,4], and dimethyl cyanomethylphosphonate[5]. Oxo-sugars have also been treated with Grignard reagents[6], or condensed with nitromethane[7,8], or nitroethane[9], to produce branched-chain derivatives. Formation of exocyclic epoxides[10–14] from ketoses, and subsequent opening of the epoxide ring, has afforded several sugars of this type.

In branched-chain amino sugars, the amino group may be situated at the branching point[9], it may occur in the branched-chain itself[7,8], or it may be introduced at a carbon atom that does not bear the branched side-chain[6]. Synthetic routes to the latter type of amino sugar have not been explored extensively, and examples are restricted to compounds that contain alkyl side-chains[6]. It therefore seemed of interest to examine possible syntheses of amino sugar bearing functionalized, branched chains. Functional groups in the side chain would facilitate the modification and elaboration of these chains into other interesting structures.

This report describes the synthesis of a spiro-epoxide derivative (**2**) of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose[15] (**1**), and opening of the oxirane ring by various nucleophiles, to give branched-chain amino sugars that lend themselves to further modification of the side chain.

DISCUSSION AND RESULTS

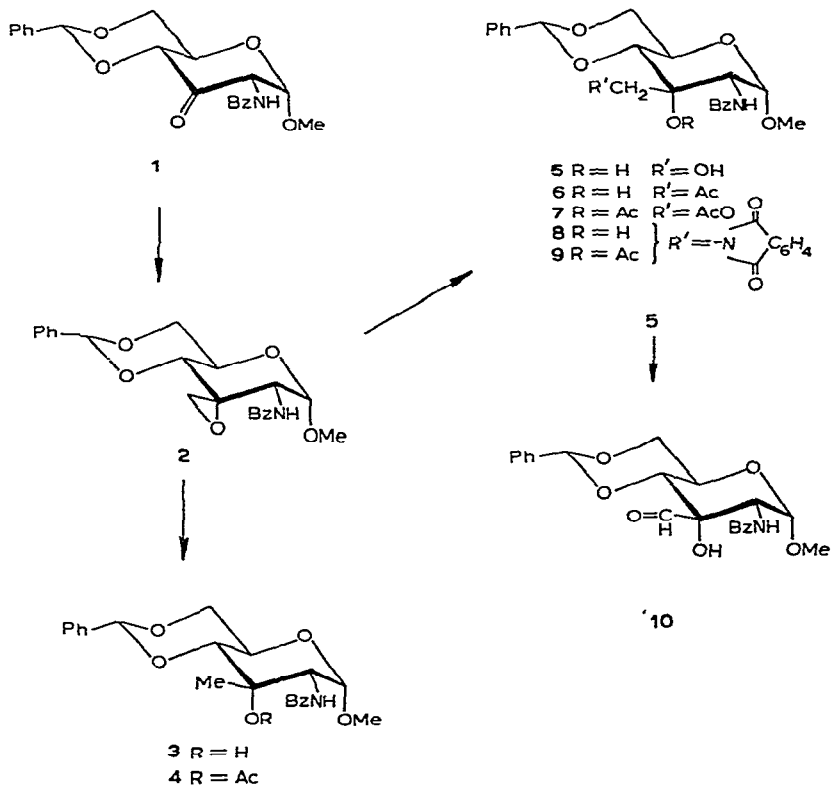
Large quantities of the 3-ketose[15] (**1**) could be prepared conveniently by the use of diphosphorus pentaoxide[16], instead of the *N,N'*-dicyclohexylcarbodiimide used in the original oxidation[15] of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside with methyl sulfoxide. The use of 0.6 mmoles of diphosphorus pentaoxide (as P_4O_{10}), and 30 ml of methyl sulfoxide per mmole of 3-hydroxy compound to be oxidized, was found to be optimal. Wittig reactions with **1** gave low or negligible yields of product, but the epoxidation route proved successful for the introduction of branched chains.

The reaction of glycopyranosiduloses with diazomethane frequently leads to a mixture of isomeric epoxides[10,11], and under appropriate conditions, may result in expansion of the pyranose ring[11,13]. Dimethyloxosulfonium methylide forms oxiranes from cyclohexanones almost exclusively by equatorial attack[17]; likewise, one spiro-epoxide is formed from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose, by equatorial attack[12] at C-3. Preferential equatorial attack by methyl Grignard reagent on methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (**1**) has been observed[6]; therefore, equatorial addition of dimethyloxosulfonium methylide[17] to **1** was expected. Treatment of **1** with the methylide in methyl sulfoxide afforded a spiro epoxide (**2**) in 64% yield. The n.m.r. spectrum of the product gave the expected proton count of 23. Two 1-proton doublets at τ 7.37 and 7.00 formed a typical AB system (J_{AB} 4.9 Hz), and were assigned to the protons of the epoxide ring. All other signals in the n.m.r. spectrum were in agreement with the structure shown.

Reduction of **2** with sodium borohydride in *N,N*-dimethylformamide–methanol gave methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-allopyranoside (**3**), which was acetylated with acetic anhydride containing *p*-toluenesulfonic acid to give **4**. Both products thus obtained were indistinguishable from **3** and **4** prepared by Baker and Buss[6]. The expected equatorial addition to the 3-keto group of **1** was therefore confirmed, and the configuration of the spiro epoxide at C-3 was established.

Most of the reactions for opening of epoxide rings[24,18–23] requiring acid conditions could not be applied with **2**, because of the sensitivity of the benzylidene acetal to acid. Thus, the boron trifluoride-catalyzed oxidation of a terminal epoxide with methyl sulfoxide to give an α-hydroxyaldehyde[19] could not be applied successfully with **2**; the reaction gave a complex mixture and no aldehydecarbonyl absorption in the infrared. Similarly, attempted reduction of the epoxide ring of **2** with diborane[20] in tetrahydrofuran, to obtain a 3-deoxy-3-*C*-(hydroxymethyl) derivative, gave a mixture of products. Attempted opening and rearrangement of the epoxide, with

lithium perchlorate[21], to give a 3-deoxy-3-*C*-formyl derivative, afforded only unchanged starting material.



Hydrolysis, and opening of the epoxide ring of **2** by nucleophiles, proceeded smoothly. Treatment of **2** with sodium acetate in hot *N,N*-dimethylformamide produced the diol (**5**) in 88% yield. The equatorial orientation of the 3-*C*-(hydroxymethyl) group thus formed can be inferred from the known configuration of the spiro epoxide **2**. Nucleophilic attack by hydroxide ion on epoxides has been shown to occur preferentially at the less-substituted carbon atom[10,12,14,23], and nucleophilic attack on the methylene carbon atom of the terminal epoxide **2** should therefore give an allopyranose derivative, in which the branched side-chain at C-3 is equatorial. Similarly, treatment of **2** with sodium acetate in *N,N*-dimethylformamide containing some acetic acid, gave an equatorial 3-*C*-(acetoxymethyl)allose derivative (**6**) in 77% yield, and treatment of **2** with potassium phthalimide gave the analogous 3-*C*-(phthalimidomethyl) derivative (**8**) in 50% yield.

The tertiary 3-hydroxyl groups of **6** and **8** were acetylated at room temperature in acetic anhydride, with *p*-toluenesulfonic acid as catalyst. Acetylation of **6** gave a diacetate (**7**), in 74% yield. The n.m.r. spectrum of **7** showed two sharp 3-proton singlets at τ 7.85 and 8.02, which were attributed to the methyl protons of the axial

acetoxy group and those of the side-chain acetyl group, respectively. This assignment seems acceptable, since the n.m.r. spectrum of the mono-acetoxy compound (**6**) showed a singlet at τ 7.99 due to the methyl protons of the acetyl group, and acetylation of the tertiary 3-hydroxyl group would be expected to affect the position of the signal for the side-chain acetyl group only slightly. Furthermore, a signal at τ 7.89 was found for the axially oriented, tertiary acetoxy group of the *C*-methyl derivative[6] (**4**). Acetylation of the phthalimidomethyl derivative (**8**) gave an acetate (**9**) in 83% yield. The n.m.r. spectrum of **9** had a 3-proton singlet at τ 7.76, due to the methyl protons of the acetoxy group. Axial acetoxy groups of pyranose acetates usually give methyl signals at τ values lower than 7.90, and equatorial acetoxy groups usually[23] generate methyl signals at τ values greater than 7.90. The signal positions of τ 7.85 and 7.76, found in the n.m.r. spectra of **7** and **9** respectively, therefore suggest that the tertiary acetoxy groups of these products should be axial.

Oxidation of the primary hydroxyl group of the diol (**5**), with methyl sulfoxide containing phosphorus pentaoxide, afforded the crystalline α-hydroxycarboxaldehyde (**10**) in 61% yield. The n.m.r. spectrum of **10** gave a proton count of 23, and showed signals in agreement with the assigned structure. The presence of the carboxaldehyde group in **10** was confirmed by the presence of a strong absorption peak at 1742 cm^{-1} in the i.r., and a 1-proton singlet at τ 0.42 in the n.m.r. spectrum. The aldehyde **10** should be useful for extension of the branched-chain at C-3 by chain-lengthening reactions.

EXPERIMENTAL

General. — Melting points were taken in capillary tubes in a Büchi silicone-bath apparatus, and are corrected. I.r. spectra were determined for KBr disks with a Perkin-Elmer 257 grating spectrophotometer. N.m.r. spectra were recorded in chloroform-*d* on a Varian A-60A spectrometer with tetramethylsilane as internal standard. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Thin-layer chromatograms were run on precoated silica gel F plates (Merck), and spots were detected by visual examination under 254 nm u.v. light. Anhydrous solvents were prepared by distillation from calcium hydride, and were stored over Linde 5A molecular sieves. Microanalyses were performed by Dr. Franz Pascher, Bonn, West Germany.

Methyl 3,3'-anhydro-2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(hydroxymethyl)-α-D-allopyranoside (**2**). — A solution of dimethyloxosulfonium methylide in methyl sulfoxide was prepared by the general method of Corey and Chaykovsky[17], from 5.03 g (110 mmoles) of sodium hydride (50% dispersion in mineral oil), 150 ml of anhydrous methyl sulfoxide, and 24.3 g (110 mmoles) of powdered trimethyloxosulfonium iodide. To the solution being stirred at 50° under nitrogen was added a solution of 35.3 g (92 mmoles) of compound[15] **1** in 500 ml of anhydrous methyl sulfoxide. Stirring was continued for 4 h at 50°, and the mixture was then kept overnight at ambient temperature. The solution was added to 2.5 l of ice–water, and the

mixture was extracted with dichloromethane (5 × 100 ml). The extract was washed with 200 ml of water, and the dried (magnesium sulfate) organic layer was evaporated to leave a solid. The product was recrystallized twice from acetone–water to give 23.4 g (64%) of colorless needles that showed one spot on t.l.c. (benzene–acetone, 9:1); m.p. 205–206°, $[\alpha]_D^{18}$ +118° (*c* 2.07, chloroform); n.m.r. data: τ 7.00 and 7.37 (two 1-proton doublets, epoxide -CH_AH_B-, $J_{A,B}$ 4.9 Hz), 6.03 (1-proton doublet, H-4, $J_{4,5}$ 8.8 Hz), 5.82 (1-proton sextet, H-5, $J_{5,4}$ 8.8 Hz, $J_{5,6ax}$ 9.0 Hz, $J_{5,6ep}$ 4.5 Hz) 6.21 (1-proton quartet, H-6 axial), 5.60 (1-proton quartet, H-6 equatorial, $J_{6ax,\,6eq}$ −9.0 Hz).

Anal. Calc. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.29; H, 5.73; N, 3.55.

Reduction of **2** *with sodium borohydride.* To a stirred solution of 400 mg (1.0 mmole) of **2** in a mixture of 5 ml of *N,N*-dimethylformamide and 25 ml of methanol was added 400 mg of sodium borohydride in 8 portions, at 30-min intervals. Stirring was continued for 12 h at ambient temperature. The solution was then concentrated *in vacuo* to *ca.* 7 ml, diluted with 75 ml of water, and the mixture extracted with chloroform (5 × 10 ml). The combined extracts were washed with water, and the dried (magnesium sulfate) organic layer was evaporated *in vacuo.* Crystallization of the residue from absolute ethanol–petroleum ether gave 370 mg of colorless crystals that showed one major spot and a minor contaminant on t.l.c (benzene–acetone, 9:1). Recrystallization from the same solvent pair gave 340 mg (85%) of colorless needles that moved as a single spot on co-chromatography with *methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-methyl-α-D-allopyranoside* (**3**). The product had m.p. 195–196° (lit.[6] m.p. 196–199°), and i.r. and n.m.r. spectra in full agreement with the published[6] data.

Acetylation of the product gave *methyl 3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-methyl-α-D-allopyranoside* (**4**). The product was indistinguishable from **4**, prepared by the procedure of Baker and Buss[6], by m.p., t.l.c., i.r., and n.m.r. spectra.

Methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(hydroxymethyl)-α-D-allopyranoside (**5**). — A stirred mixture of 3.5 g (8.8 mmoles) of **2** and 4.0 g (50 mmoles) of anhydrous sodium acetate in 25-ml of *N,N*-dimethylformamide was heated for 24 h at 80°. The mixture was cooled, poured into 200 ml of 3% aqueous acetic acid, and then extracted with three 25 ml portions of chloroform. The combined extracts were washed with water, and the dried (magnesium sulfate) organic layer was evaporated *in vacuo* to leave a colorless oil that crystallized from acetone–petroleum ether. Recrystallization from the same solvent pair gave 3.2 g (88%) of colorless crystals that moved as a single spot on t.l.c. (benzene–acetone, 9:1); m.p. 203–204°, $[\alpha]_D^{18}$ +13.7° (*c* 1.46, chloroform).

Anal. Calc. for $C_{22}H_{25}NO_7$: C, 63.61; H, 6.07; N, 3.37. Found: C, 63.67; H, 5.98; N, 3.40.

Methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(acetoxymethyl)-α-D-allopyranoside (**6**). — A mixture of 1.0 g (2.5 mmoles) of **2**, 1.64 g (20 mmoles) of anhy-

drous sodium acetate, and 0.30 g (5 mmoles) of glacial acetic acid in 10 ml of anhydrous *N,N*-dimethylformamide was heated for 12 h at 80°, with stirring. The cooled mixture was then diluted with 100 ml of water, and the white precipitate collected on a filter. Recrystallization of the dried residue from acetone–petroleum ether gave 875 mg (77%) of colorless crystals that moved as a single spot on t.l.c. (benzene–acetone, 9:1); m.p. 173–174°, $[\alpha]_D^{18}$ +76° (*c* 2.01, chloroform).

Anal. Calc. for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 63.00; H, 5.86; N, 3.02.

Methyl 3-C-(acetoxymethyl)-3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-α-D-allopyranoside (**7**). — A solution of 1.45 g (3.5 mmoles) of **5** in 20 ml of acetic anhydride, containing 0.67 g (3.5 mmoles) of *p*-toluenesulfonic acid, was stirred for 18 h at ambient temperature. The mixture was then poured into 400 ml of ice-cold, saturated, aqueous sodium hydrogen carbonate in a 1-liter beaker, stirred for 1 h, and extracted with chloroform (4 × 25 ml). The dried (magnesium sulfate) extract was evaporated *in vacuo*, and the remaining syrup was crystallized from aqueous ethanol. Recrystallization from acetone–petroleum ether gave 1.3 g (74%) of colorless needles that moved as a single spot on t.l.c.; m.p. 176–177°, $[\alpha]_D^{18}$ +8.0° (*c* 1.5, chloroform).

Anal. Calc. for $C_{26}H_{29}NO_9$: C, 62.52; H, 5.85; N, 2.80. Found: C, 62.32; H, 5.77; N, 2.85.

Methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(phthalimidomethyl)-α-D-allopyranoside (**8**). — A mixture of 2 g (5 mmoles) of **2** and 4 g (20 mmoles) of potassium phthalimide was stirred in 25 ml of *N,N*-dimethylformamide for 24 h at 80°. To the cooled mixture was added 0.6 g (10 mmoles) of glacial acetic acid, followed by 150 ml of ice–water. The solid precipitate was collected on a filter, and then crystallized from acetone–petroleum ether. Recrystallization from the same solvent pair gave 1.3 g (50%) of colorless crystals that showed one spot on t.l.c. (benzene–acetone, 9:1); m.p. 250–251°, $[\alpha]_D^{18}$ +28° (*c* 1.28, chloroform).

Anal. Calc. for $C_{30}H_{29}N_2O_8$: C, 66.05; H, 5.36; N, 5.13. Found: C, 65.68; H, 5.25; N, 5.12.

Methyl 3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(phthalimidomethyl)-α-D-allopyranoside (**9**). — Acetylation of 1.08 g (2 mmoles) of **8**, as described for **7**, by using 20 ml of acetic anhydride and 0.38 g (2 mmoles) of *p*-toluenesulfonic acid, followed by two recrystallizations of the product from acetone–petroleum ether, gave 0.97 g (83%) of colorless crystals that moved as one spot on t.l.c. (benzene–acetone, 9:1); m.p. 150–151°, $[\alpha]_D^{18}$ −143° (*c* 1.68, chloroform).

Anal. Calc. for $C_{32}H_{31}N_2O_9$: C, 65.41; H, 5.32; N, 4.77. Found: C, 65.62; H, 5.27; N, 4.66.

Methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-formyl-α-D-allopyranoside (**10**). — To a stirred solution of 426 mg (1.5 mmoles of P_4O_{10}) of diphosphorus pentaoxide in 10 ml of anhydrous methyl sulfoxide at room temperature, was added 830 mg (2 mmoles) of **5**. Stirring was continued for 60 h at ambient temperature. The mixture was then diluted with 20 ml of chloroform and poured into 100 ml

of cold, saturated, aqueous sodium hydrogen carbonate. The aqueous phase was extracted with chloroform (3 × 10 ml), and the combined extracts were washed successively with aqueous sodium hydrogen carbonate (100 ml), and twice with water. The dried (magnesium sulfate) organic layer was evaporated *in vacuo* at 30°, and the solid residue dissolved in hot acetone, treated with charcoal, and filtered. The filtrate was diluted with four volumes of hot petroleum ether. The crystals that formed on cooling were recrystallized from acetone–petroleum ether to give 500 mg (61%) of colorless crystals that showed one spot on t.l.c. (benzene–acetone, 9:1), with mobility between that of **5** and **2**. The product had m.p. 217–219°, and $[\alpha]_D^{18}$ +52° (*c* 1.85, chloroform).

Anal. Calc. for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found: C, 63.71; H, 5.65; N, 3.44.

ACKNOWLEDGMENT

The South African Council for Scientific and Industrial Research is thanked for the n.m.r. spectra.

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