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NUCLEOSIDES LXXXIII. SYNTHETIC STUDIES ON NUCLEOSIDE ANTIBIOTICS. 11. SYNTHESIS OF METHYL 4-AMINO-3,4-DIDEOXY-β-D-*ribo*-HEXOPYRANOSIDE AND -HEXOPYRANOSIDURONIC ACID (DERIVATIVES RELATED TO THE CARBOHYDRATE MOIETY OF GOUGEROTIN)*

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ABSTRACT

Methyl 4-amino-3,4-dideoxy-β-D-*ribo*-hexopyranoside (**17**) and its uronic acid (**19**) were synthesized *via* a series of reactions starting from 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose. A method suitable for the large scale preparation of 3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**2**) was devised.

INTRODUCTION

Recently, we reported[1] the total synthesis of the nucleoside antibiotic, Gougerotin, from D-galactose. We have also prepared analogs of this antibiotic bearing modifications in the 5′-position or in the peptidyl moiety[2], or in both. As an extension of these studies[2] we undertook the synthesis of a 3′-deoxy analog of Gougerotin in order to evaluate the importance, if any, of the 3′-hydroxyl function in the biological activity of this antibiotic. To our best knowledge, neither 4-amino-3,4-dideoxyhexoses nor 4-amino-3,4-dideoxyhexuronic acids have been reported. In this report, we describe the synthesis of methyl β-D-pyranosides of 4-amino-3,4-dideoxy-*ribo*-hexose (**17**) and its uronic acid derivative (**19**). In a later paper we will report on the synthesis of Gougerotin analogs involving these sugars.

RESULTS AND DISCUSSION

The starting material in this series of reactions (see Flow Chart) was the tetraacetate of 3-deoxy-β-D-*xylo*-hexopyranose (**5**) whose synthesis from **1** has been reported[3]. This reported procedure from **1** to **2**, however, was not suitable for large-scale reactions. We found that treatment of **1** with finely pulverized potassium hydroxide in refluxing toluene afforded the 3,4-unsaturated sugar derivative (**2**) in

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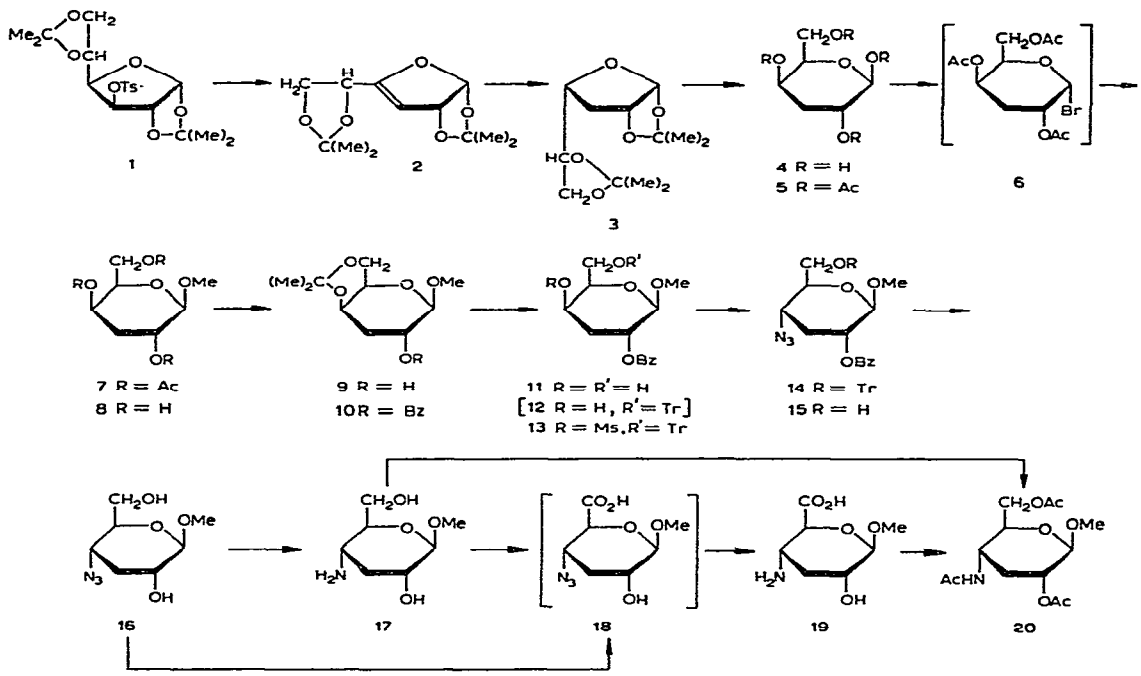

consistently high yields (~80%). The conversion of **2** to **5** was accomplished by the reported procedure[3]. Treatment of **5** with ~30% hydrogen bromide–acetic acid mixture gave the syrupy bromo derivative (**6**), to which was tentatively assigned the α-D configuration on the basis of the anomeric effect[4]. Application of the Koenigs–Knorr reaction to **6** by treatment with silver carbonate in methanol afforded the crystalline methyl glycoside (**7**) in 60% overall yield from **5**. The n.m.r. spectrum of **7** was consistent with a 3-deoxy-*xylo*-hexoside derivative [3 acetyl signals at δ 2.04 (6 H) and 2.10 (3 H); methyl signal for glycoside at δ 3.51; anomeric signal at δ 4.41 ($J_{1,2} \cong 8.0$ Hz indicative of the β-D configuration); a broad multiplet for H-2 centered at δ 4.90; and a narrow multiplet for H-4 centered at δ 5.09].

After deacetylation of **7**, the product (**8**) was condensed with acetone to give **9**, which was benzoylated to give **10**. Removal of the isopropylidene group gave **11**. Tritylation afforded **12** which, without isolation, was mesylated to give **13**. Reaction of **13** with sodium azide in hexamethylphosphoric triamide[5] yielded the dideoxy-*ribo*-hexose derivative (**14**) which was detritylated to **15**, giving by saponification **16**. Catalytic reduction of the 4-azido group of **16** in the presence of 10% palladium-on-carbon afforded crystalline methyl 4-amino-3,4-dideoxy-β-D-*ribo*-hexopyranoside (**17**). The yield in each step from compounds **8** to **17** was at least 80% and, with the exceptions of compounds **12** and **16**, all intermediates were isolated in crystalline form. The triacetyl derivative of **17** exhibited an n.m.r. spectrum consistent with structure **20**: *N*-acetyl signal at δ 1.96 (3 H); *O*-acetyl signal at δ 2.08 (6 H), glycoside methyl signal at δ 3.49 (3 H), and the anomeric signal at δ 4.38 ($J_{1,2} \cong 8.0$ Hz).

Oxidation of **15** with potassium permanganate in a mixture of acetic acid and acetone[5], followed by esterification of the product with diazomethane gave the methyl uronate which was saponified to the uronic acid (**18**). Compound **18** was not isolated, but the azide group of **18** was reduced directly with palladium-on-carbon to give methyl 4-amino-3,4-dideoxy-β-D-*ribo*-hexopyranosiduronic acid (**19**) as colorless crystals.

The uronic acid (**19**) was also obtained by catalytic oxidation of **16** with platinum and oxygen[6] at 80° followed by reduction of the azide group.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover capillary apparatus and are corrected. N.m.r. spectra were obtained on a Varian A-60 spectrometer. I.r. spectra were recorded on a Perkin–Elmer model 137B spectrometer. Optical rotations were determined on a Keston polarimeter attachment to a Beckman DU spectrophotometer set at 589 nm. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

*3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-α-*D*-erythro-hex-3-enofuranose* (**2**). — A mixture of 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose (**1**, 300 g) and finely pulverized anhydrous potassium hydroxide (126 g) in toluene (1.5 l) was heated at reflux for 45 min under vigorous mechanical stirring. After cooling, water (1.5 l) was added to the mixture. The toluene layer was separated, washed with water (5 × 500 ml), dried over sodium sulfate, and evaporated to a pale yellow syrup (120 g) which solidified. This solid was sufficiently pure to be directly converted into **5** according to the known procedure.

*2,4,6-Tri-*O*-acetyl-3-deoxy-α-*D*-xylo-hexopyranosyl bromide* (**6**). — Compound **5** (51 g) was dissolved in 30% acetic acid (47 ml) and the mixture was kept for 2 h at room temperature, then diluted with dichloromethane (250 ml) and an ice–water mixture (1 liter). The organic layer was washed with water, dried over sodium sulfate, and evaporated to a syrup. Several additions of toluene to the residual syrup, followed by evaporation gave a thick syrup (55.0 g) which was not purified further, but used directly in the next step.

*Methyl 2,4,6-tri-*O*-acetyl-3-deoxy-β-*D*-xylo-hexopyranoside* (**7**). — To a solution of compound **6** (55 g) in absolute methanol (750 ml) was added finely pulverized silver carbonate (60 g), and the mixture was stirred overnight at room temperature. The solid was filtered off and washed with methanol. The combined filtrate and washings were evaporated to give a syrup (44 g). A small amount of the syrup was crystallized from ether–petroleum ether, m.p. 124–126°, $[\alpha]_D^{27}$ −22° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 50.98; H, 6.71.

*Methyl 3-deoxy-β-*D*-xylo-hexopyranoside* (**8**). — To a solution of **7** (40 g) in methanol (250 ml), M sodium methoxide in methanol (5 ml) was added, and the mixture was stirred overnight at room temperature. The solution was neutralized with

ion-exchange resin Amberlite IRC-50 (H^+, 10 ml) and the suspension filtered. The filtrate was evaporated to dryness, and the residue was crystallized from ethanol to give **8** (16 g, 80%), m.p. 175–177°, $[\alpha]_D^{27}$ −69° (*c* 1, water).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.20; H, 7.70.

*Methyl 3-deoxy-4,6-*O*-isopropylidene-β-*D*-*xylo*-hexopyranoside* (**9**). — A mixture of **8** (8 g), *p*-toluenesulfonic acid monohydrate (1.0 g), and 2,2-dimethoxypropane (30 ml) in acetone (150 ml) was shaken for 4 h at room temperature, and then neutralized with sodium hydrogen carbonate powder (3.0 g). After filtration of the insoluble salts, the filtrate was evaporated to dryness. The residue was dissolved in ether (50 ml), and **9** crystallized as colorless needles (9.0 g, 92%), m.p. 111–113°, $[\alpha]_D^{27}$ −84° (*c* 1, methanol).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.94; H, 8.33.

*Methyl 2-*O*-benzoyl-3-deoxy-4,6-*O*-isopropylidene-β-*D*-xylo-hexopyranoside* (**10**). — To a solution of **9** (6.5 g) in pyridine was added benzoyl chloride (4.1 ml), and the mixture was kept overnight at room temperature. An ice–water mixture (350 ml) was added and the precipitate was crystallized from ethanol–water to give **10** (6.5 g, 68%), m.p. 95–96°, $[\alpha]_D^{27}$ −59° (*c* 1, methanol).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.29; H, 6.90.

*Methyl 2-*O*-benzoyl-3-deoxy-β-*D*-xylo-hexopyranoside* (**11**). — Compound **10** (4.5 g) was dissolved in 88% formic acid (20 ml). After 1 h, the solution was diluted with water (25 ml) and the mixture was evaporated to dryness. The residue was recrystallized from water to give 3.2 g (82%) of **11**, m.p. 161–163°, $[\alpha]_D^{27}$ −60° (*c* 1, methanol).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.73; H, 6.52.

*Methyl 2-*O*-benzoyl-3-deoxy-4-*O*-mesyl-6-*O*-trityl-β-*D*-xylo-hexopyranoside* (**13**). — A mixture of **11** (3.2 g) and chlorotriphenylmethane (3.6 g) in pyridine (25 ml) was kept for 4 h at 80°, then cooled at 0°. Methanesulfonyl chloride (1.1 ml) was added, and the mixture was kept for 18 h at 0° and then poured into an ice–water mixture. The precipitate was dissolved in dichloromethane, reprecipitated with ether, and finally crystallized from ethanol as plates (6.4 g), m.p. 182–186°, $[\alpha]_D^{27}$ −59° (*c* 1, chloroform).

Anal. Calc. for $C_{34}H_{35}O_8S$: C, 67.64; H, 5.84; S, 5.13. Found: C, 67.61; H, 5.74; S, 5.44.

*Methyl 4-azido-2-*O*-benzoyl-3,4-dideoxy-6-*O*-trityl-β-*D*-ribo-hexopyranoside* (**14**) — A mixture of **13** (5.3 g) and sodium azide (2.0 g) in hexamethylphosphoric triamide (25 ml) was heated with stirring for 6 h at 80° and poured into an ice–water mixture (200 ml) with stirring. The precipitate was filtered off and crystallized from ether to give **14** (4.5 g), m.p. 121–124°, $[\alpha]_D^{27}$ +8° (*c* 1, methanol).

Anal. Calc. for $C_{33}H_{32}N_3O_5$: C, 71.98; H, 5.86; N, 7.63. Found: C, 72.09; H, 5.78; N, 7.47.

*Methyl 4-azido-2-*O*-benzoyl-3,4-dideoxy-β-*D*-ribo-hexopyranoside* (**15**). — Compound **14** (4.2 g) was dissolved in a mixture of acetic acid (12 ml) and water (3 ml), and the solution was kept overnight at room temperature. The solution was evapo-

rated to dryness and the residue was crystallized from ethanol–water to give **15** (2.3 g), m.p. 86–88°, $[\alpha]_D^{27}$ +14° (*c* 1, methanol).

Anal. Calc. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.61; H, 5.58; N, 13.54.

*Methyl 4-azido-3,4-dideoxy-β-*D-ribo-*hexopyranoside* (**16**). — To a solution of compound **15** (1.5 g) in methanol (20 ml) was added M sodium methoxide in methanol (0.8 ml), and the mixture was stirred for 3 h at room temperature. Amberlite IRC 50 resin (H^+, 7 ml) was added to neutralize the solution. The resin was filtered off and washed with a small amount of methanol. The combined filtrate and washings were evaporated to a syrup that was dissolved in water (20 ml), and the solution was extracted with ether (2 × 20 ml). The aqueous solution was evaporated to give **16** (0.9 g) as a syrup that was not further purified but used directly in the next step.

*Methyl 4-amino-3,4-dideoxy-β-*D-ribo-*hexopyranoside* (**17**). — Compound **16** (168 mg) was dissolved in water (10 ml) and hydrogenated in the presence of 10% palladium-on-carbon (40 mg) for 20 min with an initial hydrogen pressure at 23×10^3 kg m^{-2}. After removal of the catalyst by filtration, the filtrate was evaporated to dryness to a solid that, after several co-evaporations with ethanol, was crystallized from ethanol–ethyl acetate to yield **17** as colorless platelets (136 mg), m.p. 59–61°, $[\alpha]_D^{27}$ −45° (*c* 0.6, water).

Anal. Calc. for $C_7H_{15}NO_4 \cdot 0.5H_2O$: C, 45.15; H, 8.53; N, 7.52. Found: C, 45.13; H, 8.76; N, 7.34.

*Methyl 4-amino-3,4-dideoxy-β-*D-ribo-*hexopyranosiduronic acid* (**19**). — *A. From* **15**. Compound **15** (1.2 g) was dissolved in 1:1 acetic acid–acetone (40 ml), and powdered potassium permanganate (1.0 g) was added with stirring over a period of 10 min. After stirring of the mixture for 1 h at room temperature, additional potassium permanganate (1.0 g) was added, followed by another charge (0.4 g) after 1.5 h. The mixture was stirred overnight at room temperature and the excess permanganate was decomposed with sulfur dioxide. The resultant gel was evaporated to a volume of ~10 ml to which was added water (100 ml). The aqueous suspension was extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with water (4 × 100 ml), dried (magnesium sulfate), and evaporated to a clear syrup (1.0 g) that was dissolved in methanol (20 ml), cooled, and treated with an excess of diazomethane. The solution was evaporated to dryness and chromatographed on silica gel G (50 g) with 9:1 benzene–ethyl acetate as the eluent. Chromatographically homogeneous methyl ester was obtained as a clear syrup (0.55 g), $[\alpha]_D^{27}$ +8.8° (*c* 1.0, chloroform); λ_{max}^{film} 4.7 (N_3), 5.75 (ester carbonyl), and 7.9 μm (ester C–O–C).

This syrup (0.5 g) was dissolved in methanol (15 ml) and M sodium methoxide in methanol (0.4 ml) was added. The mixture was stirred overnight at room temperature, and the methanol was evaporated. The residue was partitioned between water (2 ml) and ether (2 ml). To the aqueous layer was added M sodium hydroxide (2 ml), and the mixture was stirred for 2 h. Dowex 50 W (H^+, 2 ml) resin was added, filtered off from the acidic solution, and washed with water (3 × 3 ml). The combined filtrate and washings were shaken in a hydrogen atmosphere in the presence of 10%

palladium-on-carbon (90 mg) for 2 h. After removal of the catalyst by filtration, the solution was evaporated to a crystalline residue that was recrystallized from water–ethanol to give 84 mg of **19** as the hemihydrate; it slowly decomposes above 250°, $[\alpha]_D^{27} -84°$ (*c* 1.0, water).

Anal. Calc. for $C_7H_{13}NO_5 \cdot 0.5H_2O$: C, 42.00; H, 7.05; N, 7.00. Found: C, 41.69; H, 7.19; N, 6.89.

B. From **16**. To a solution of **16** (150 mg) in water (50 ml) was added platinum catalyst (150 mg) prepared according to the procedure of Heyns and Beck[7], and the pH was brought to 8 by addition of a saturated sodium hydrogen carbonate solution. The mixture was heated in a water bath to 80–85°, and oxygen was blown into the mixture with vigorous mechanical vibration by a Vibro-Mischer vibrator. During the course of oxidation, the pH of the mixture was kept at 7–8 by occasional addition of saturated sodium hydrogen carbonate solution. After 8 h, the catalyst was removed by filtration and the filtrate was treated with Amberlite IR 120 (H^+, ~5 ml) resin to remove sodium ions. The resin was filtered off and the filtrate was shaken in a hydrogen atmosphere in the presence of 10% palladium-on-carbon for 20 min with the initial hydrogen pressure at 23×10^3 kg m^{-2}. The catalyst was removed by filtration and washed with water. The combined filtrate and washings were evaporated to dryness, and the residue was crystallized from water–ethanol to give **19** (50 mg), no m.p. below 250°, $[\alpha]_D^{27} -84°$ (*c* 1.0, water). The i.r. spectrum of this compound was identical with that of **19** prepared from compound **16** *via* permanganate oxidation.

Methyl 4-acetamido-2,6-di-O-*acetyl-3,4-dideoxy-β*-D-ribo-*hexopyranoside* (**20**). — A mixture of **17** (80 mg) and acetic anhydride (0.5 ml) in pyridine (2 ml) was kept overnight at room temperature. The mixture was evaporated to dryness and several additions of methanol to the residue, followed by evaporation, removed the remaining acetic acid and acetic anhydride. The residue was crystallized from ethanol to give 90 mg of **20**, m.p. 189–190°, $[\alpha]_D^{27} -5°$ (*c* 0.7, chloroform).

Anal. Calc. for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.30; H, 7.03; N, 4.57.

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