Synthesis of 3,6-Dideoxy-D-*erythro*-hexos-4-ulose (3,6-Dideoxy-4-keto-D-glucose)[1]

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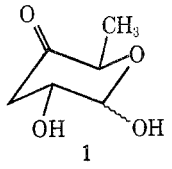
The synthesis of 3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranoside (**14**) starting from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (**2**) and from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside (**16**) is described. An attempt to prepare **14** by the direct isopropylidation of the known 3,6-dideoxy-D-*xylo*-hexose (**29**) was unsuccessful as the major product formed in this reaction was a furanose derivative, **30**. Oxidation of **14** with ruthenium tetroxide in carbon tetrachloride gave the keto sugar derivative **32** which was hydrolyzed with Dowex-50 (H^+) to give 3,6-dideoxy-D-*erythro*-hexos-4-ulose (3,6-dideoxy-4-keto-D-glucose, **1**), an important intermediate in the biosynthesis of several biologically important 3,6-dideoxy hexoses. The identification of the natural product with the synthetic material **1** has already been recorded.

Elucidation of the biochemical pathways for the formation of the biologically important 3,6-dideoxy hexoses, which contribute to the serological specificity of many immunologically active lipopolysaccharides,[2] has been the subject of several investigations.[1,3,4] Abequose, paratose, and ascarylose were shown to originate from cytidine 5′-diphosphate-6-deoxy-4-keto-D-glucose which in turn was formed from cytidine 5′-diphosphate-D-glucose. It was established recently that 3,6-dideoxy-D-*erythro*-hexos-4-ulose (**1**) as its cytidine diphosphate nucleotide conjugate is the intermediate between cytidine 5′-diphosphate-6-deoxy-4-keto-D-glucose and the 3,6-dideoxy hexoses in *Pasteurella pseudotuberculosis* type V strain VO.[1,7] The biological importance of this keto sugar **1** has been increased by the finding that its L isomer (3,6-dideoxy-L-*erythro*-hexos-4-ulose) occurs in nature as part of the antibiotic cinerubine B.[8] In this paper we describe the total synthesis of the free keto sugar **1**. The preparation of the α-methyl glycoside of **1** by another route was recently reported by Paulsen and co-workers.[9]



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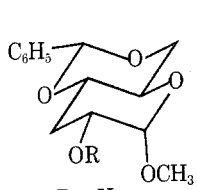
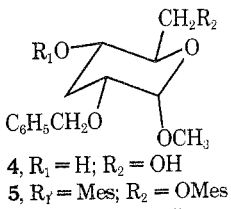
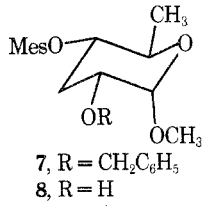
Methyl 3-deoxy-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranoside[10,11] (**2**) was prepared according to the method of Hedgley et al.[11] Conversion of **2** to the benzyl ether **3** followed by removal of the benzylidene protection by acid hydrolysis provided methyl 2-*O*-benzyl-3-deoxy-α-D-ribohexopyranoside (**4**). Treatment of **4** with excess of methanesulfonyl chloride in pyridine gave the dimesylate **5**. Selective displacement of the primary methanesulfonate group to obtain the 6-iodo derivative **6** was achieved by the treatment of **5** with 1.1 equiv of potassium iodide in refluxing 2-butanone for 90 hr. Hydrogenation of **6** in the presence of triethylamine and 10% Pd/C using ethanol as solvent provided the 3,6-dideoxy sugar derivative, **7**.



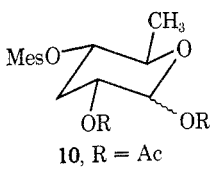
2, R = H
3, R = $CH_2C_6H_5$



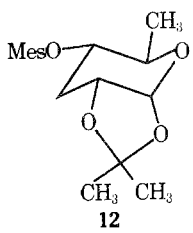
4, R_1 = H; R_2 = OH
5, R_1 = Mes; R_2 = OMes
6, R_1 = Mes; R_2 = I



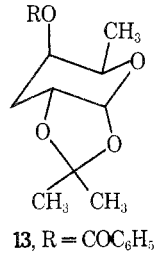
7, R = $CH_2C_6H_5$
8, R = H
9, R = Ac



10, R = Ac
11, R = H



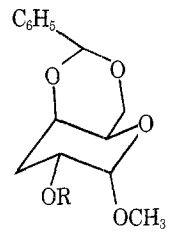
12

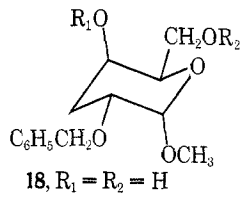


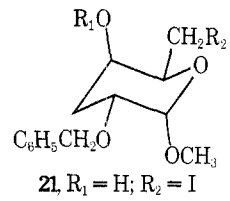
13, R = COC_6H_5
14, R = H
15, R = Tos

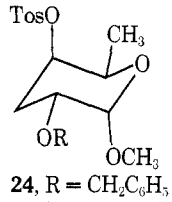
As a keto sugar is usually very sensitive toward acids, it was necessary to change the protection of the hydroxyl group at position 1 from the methyl glycoside (which requires very strong acid conditions for hydrolysis) to a group that can be easily converted to the free sugar after a carbonyl function is introduced in the molecule. An isopropylidene derivative was considered appropriate as it would protect both the 1 and 2 hydroxyl groups and can be hydrolyzed under very mild acid conditions. To this end, compound **7** was debenzylated by hydrogenation in the presence of 10% Pd/C and hydrogen chloride as catalysts to give methyl 3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (**8**). Although acid hydrolysis of this methyl glycoside **8** would be expected to provide the free sugar **11** easily, in practice this reaction was not clean and the product **11** was obtained only in a low yield. The free sugar **9** was, therefore, prepared by the following method. Acetylation of **8** with acetic anhydride in pyridine to give **9** and subsequent treatment of **9** with acetic acid and acetic anhydride in the presence of sulfuric acid provided 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-D-*ribo*-hexopyranose (**10**) as a mixture of anomers from which the pure α isomer (**10a**) was obtained by fractional crystallization. Saponification of the mixture of diacetates **10** with sodium methoxide in methanol gave the free sugar **11** as a gum. Conversion of **11** to the isopropylidene derivative **12** was accomplished by the treatment of **11** with 2,2-diethoxypropane in acetone in the presence of *p*-toluenesulfonic acid as a catalyst. An attempt at the direct oxidation of **12** to the ketone **32** using dimethyl sulfoxide[12] in collidine was not successful owing to a competing elimination reaction of the sulfonyloxy group and difficulty in the separation of the product from dimethyl sulfoxide. Mesylate **12** was therefore converted to the easily oxidizable alcohol, **14**, by the treatment of **12** with sodium benzoate in dimethylformamide to give **13** and subsequent deacylation with sodium methoxide in methanol.

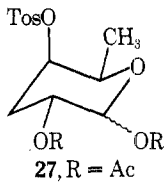
Compound **14** was also obtained by a series of reactions starting from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside[13,14] (**16**). Treatment of **16** with benzyl chlo-

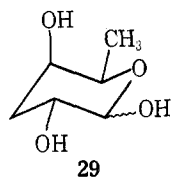

16, R = H
17, R = $CH_2C_6H_5$


18, $R_1 = R_2 = H$
19, $R_1 = R_2$ = Mes
20, $R_1 = H$; R_2 = Tos


21, $R_1 = H$; $R_2 = I$
22, $R_1 = R_2 = H$
23, R_1 = Ac; $R_2 = H$


24, R = $CH_2C_6H_5$
25, R = H
26, R = Ac


27, R = Ac
28, R = H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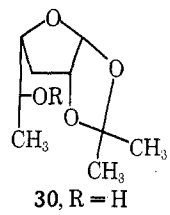
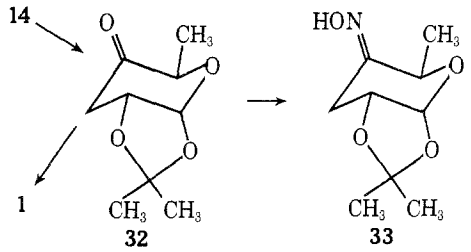

30, R = H
31, R = Mes

ride in the presence of sodium hydroxide to give **17** followed by hydrolysis of the benzylidene group gave the diol **18** which was characterized as the crystalline dimesylate **19.** Selective esterification of the primary hydroxyl group of **18** with *p*-toluenesulfonyl chloride in a mixture of pyridine and chloroform at low temperature yielded the 6-tosylate **20.** Displacement of the sulfonyloxy group with iodide anion to give **21** and subsequent reduction of the 6-iodo derivative by hydrogenation in the presence of 10% Pd/C and triethylamine provided the 3,6-dideoxy sugar derivative **22** as an oil which was characterized as the crystalline acetate **23.** In order to protect the 4-OH group in **22** it was treated with *p*-toluenesulfonyl chloride in pyridine. The tosylate **24** thus obtained was debenzylated by catalytic hydrogenation to give **25,** which was characterized as the acetate **26.** Acetolysis of **25** with acetic acid and acetic anhydride in the presence of sulfuric acid provided the 1,2-diacetate **27** as a mixture of anomers. The free sugar **28** was obtained as a viscous syrup by saponification of **27** with barium methoxide in methanol. Treatment of **28** with 2,2-diethoxypropane in acetone in the presence of *p*-toluenesulfonic acid gave the isopropylidene derivative, **15.** Removal of the sulfonyloxy group from **15** to obtain **14** was accomplished by the treatment of **15** with sodium naphthalenide reagent in tetrahydrofuran.[15]

An attempt to prepare **14** by direct isopropylidation of the free sugar, 3,6-dideoxy-D-*xylo*-hexose[16,17] (**29**), was unsuccessful. The major product obtained was the furanose derivative[18] **30,** with less than 10% of the required material, **14.** The structure of **30** was established by the preparation of its crystalline mesylate **31** having the same characteristics as reported by Antonakis.[19]

Oxidation of **14** with ruthenium tetroxide[20,21] in carbon tetrachloride provided the ketone **32** in excellent yield. Compound **32** was also characterized as its crystalline oxime, **33.** Hydrolysis of **32** to the keto free sugar **1** was accomplished by stirring **32** with Dowex-50 (H^+) in water at room temperature. Free sugar **1** was characterized by converting it back to the isopropylidene derivative, **32,** followed by preparation of **33.** The identification of the natural product isolated from *Pasteurella pseudotuberculosis* type V strain VO with the synthetic material, **1,** has already been described.[1]


32 33

Experimental Section

Melting points were determined on either a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC), both analytical and preparative, was performed on glass plates coated with silica gel G from Brinkmann Instruments or Quantagram precoated plates containing fluorescent indicator. Compounds were detected by absorbance at 256 nm using an ultraviolet source when applicable and/or by spraying with 50% sulfuric acid followed by baking at 120°. Gas chromatographic analyses were conducted on a F & M Model 810 instrument equipped with dual flame ionization detectors. A 10 ft × 0.25 in. 3% ethylene glycol succinate on Chromosorb W column was used. NMR spectra were taken on a Varian A-60, T-60, or T-60A spectrometer using tetramethylsilane as an internal standard. The infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Specific rotations were measured using a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (3). A mixture of 50 g (0.19 mol) of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside[10,11] (**2**) in 2.0 l. of toluene and 80 g (2.0 mol) of powdered potassium hydroxide was stirred and heated under reflux using a Dean-Stark trap for 1 hr. Benzyl chloride (200 ml, 1.8 mol) was added dropwise over a period of 3 hr and the mixture was heated under reflux for an additional 12 hr. Water was added and excess benzyl chloride was removed by steam distillation under reduced pressure. When all the volatile materials were removed, the mixture was cooled, and the crystalline material formed was filtered, washed with water, and dried. It was dissolved in 95% ethanol, decolorized using Norit, and recrystallized to give 62.0 g (92%) of **3,** mp 103–104°, $[\alpha]^{24}D$ +23.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.87; H, 6.89

Methyl 2-*O*-Benzyl-3-deoxy-α-D-*ribo*-hexopyranoside (4). A solution of 50 g (0.14 mol) of **3** in 980 ml of 95% ethanol and 12.5 ml of concentrated HCl in 196 ml of water was stirred and heated under reflux for 1 hr. The ethanol was removed under vacuum and the residue was diluted with 1300 ml of water. The acid was neutralized by stirring with solid $NaHCO_3$ and the mixture was steam distilled under reduced pressure to remove the benzaldehyde. The mixture was extracted with 6 × 250 ml of $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from benzene to give 34.5 g (88%) of **4,** mp 105–106°, $[\alpha]^{25}D$ +67.4° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.60, H, 7.69.

Methyl 2-*O*-Benzyl-3-deoxy-4,6-di-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (5). A solution of 47.0 g (175 mmol) of **4** in 260 ml of pyridine was cooled in an ice bath and 30 ml (0.39 mol) of methanesulfonyl chloride was added dropwise with stirring over a period of 1 hr. The mixture was allowed to warm up to room temperature and stirring was continued overnight. The mixture was poured onto ice water, and the solid formed was filtered, washed with water, dried, and recrystallized from methanol to give 67.6 g (91%) of **5,** mp 78–79°, $[\alpha]^{27}D$ +60.7° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_9S_2$: C, 45.27; H, 5.69; S, 15.10. Found: C, 45.45; H, 5.65; S, 14.85.

Methyl 2-*O*-Benzyl-3,6-dideoxy-6-iodo-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (6). A solution of 25 g (59 mmol) of **5** and 10.6 g (65.3 mmol) of potassium iodide in 800 ml of 2-butanone was heated under reflux for 5 days. The mixture was cooled and the precipitated sodium mesylate removed by filtration. The filtrate was evaporated to dryness, and the residue was

dissolved in $CHCl_3$, washed with $NaHCO_3$ solution followed by 20% aqueous sodium thiosulfate solution and water, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from absolute ethanol to give 22.6 g (84%) of **6**, mp 86–87°, $[\alpha]^{25}D$ +71.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{21}IO_6S$: C, 39.48; H, 4.63; I, 27.81; S, 7.02. Found: C, 39.61; H, 4.62; I, 27.59; S, 7.07.

Methyl 2-*O*-Benzyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (7). A solution of 50.0 g (0.11 mol) of **6** in 1 l. of ethanol and 51.4 ml of triethylamine was mixed with 5.0 g of 10% Pd/C and hydrogenated under atmospheric pressure until hydrogen uptake was complete. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in $CHCl_3$, washed successively with 1.0 *N* HCl, 10% $KHCO_3$ solution, 20% $Na_2S_2O_3$ solution, and water, dried (Na_2SO_4), and evaporated to dryness. The solid residue was recrystallized from CH_2Cl_2–hexane to give 34.1 g (94%) of **7**, mp 95–96°, $[\alpha]^{25}D$ +70.9° (*c* 0.9 $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; S, 9.70. Found: C, 54.32; H, 6.84; S, 9.46.

Methyl 3,6-Dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (8). A solution of 25.0 g (75.7 mmol) of **7** in 125 ml of tetrahydrofuran and 225 ml of ethanol containing 1.0 g of 10% Pd/C and 25 drops of concentrated HCl was hydrogenated under atmospheric pressure until there was no more hydrogen uptake. The catalyst was filtered off, the filtrate was neutralized with Dowex-1 (OH^-), and the solution was evaporated to dryness. The residue was recrystallized from methylene chloride–ether–pentane to give 16.8 g (93%) of **8**, mp 88–89° $[\alpha]^{27}D$ +162.3° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_8H_{16}O_6S$: C, 39.99; H, 6.71; S, 13.34. Found: C, 40.26; H, 6.68; S, 13.10.

Methyl 2-*O*-Acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (9). A solution of 10 g (41.6 mmol) of **8** in 100 ml of pyridine and 15 ml of acetic anhydride was stirred at room temperature overnight. The mixture was poured onto ice water and extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with cold 3 *N* HCl followed by 10% $KHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The oily residue was crystallized from ether–hexane to give 10.9 g (92%) of **9**, mp 68–69°, $[\alpha]^{27}D$ + 127.7° (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_7S$: C, 42.54; H, 6.43; S, 11.36. Found: C, 42.50; H, 6.14; S, 11.14.

1,2-Di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranose (10a). A solution of 10.0 g (35.4 mmol) of **9** in 200 ml of acetic acid and 50 ml of acetic anhydride was mixed with 40 drops of a cold solution of 1:1 H_2SO_4 and acetic anhydride. After the solution was stirred overnight at room temperature, it was poured onto crushed ice with stirring. When all the ice was melted, the solid formed was filtered, washed with cold water, and dried. The filtrate was extracted with $CHCl_3$, washed with 20% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The residue was combined with the air-dried solid to give 10.64 g (96%) of 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-D-*ribo*-hexopyranose (**10**) as a mixture of α and β anomers. Several recrystallizations of this material from methylene chloride–hexane provided pure **10a**, mp 159–160°, $[\alpha]^{25}D$ +98.8° (*c* 0.85, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_8S$: C, 42.57; H, 5.85; S, 10.33. Found: C, 42.47; H, 5.82; S, 10.40.

3,6-Dideoxy-1,2-*O*-isopropylidene-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranose (12). A solution of 5.44 g (17.5 mmol) of **10** in 500 ml of methanol was cooled in an ice bath, 200 ml of 0.1 *N* sodium methoxide in methanol was added, and the mixture was stirred at 0° for 45 min. As a TLC analysis indicated that the deacetylation was complete, the reaction mixture was carefully neutralized with Dowex-50 (H^+). After removal of the Dowex by filtration, the filtrate was evaporated to dryness to give 4.24 g of 3,6-dideoxy-4-*O*-methylsulfonyl-D-ribohexose (**11**) as a white gum. This material was treated with 500 ml of anhydrous acetone, 50 g of freshly distilled 2,2-diethoxypropane, and 250 mg of anhydrous *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 24 hr. The reaction mixture was neutralized by stirring with solid $NaHCO_3$ and filtered and the filtrate was concentrated under vacuum to give 4.64 g of a yellow oil. Column chromatography of this material over alumina using benzene–chloroform (1:1) and $CHCl_3$ as eluents gave 3.6 g of a light yellow oil which crystallized from ether–hexane to give 2.77 g of **12**, mp 59–60°, $[\alpha]^{25}D$ +32.1° (*c* 1.0, $CHCl_3$). Preparative TLC of the mother liquors provided an additional 113 mg for a total yield of 60% for the two steps starting from **10**.

Anal. Calcd for $C_{10}H_{18}O_6S$: C, 45.10; H, 6.81; S, 12.04. Found: C, 45.00; H, 6.56; S, 11.82.

4-*O*-Benzoyl-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (13). A mixture of 500 mg (1.9 mmol) of **12** in 50 ml of DMF and 810 mg (5.6 mmol) of sodium benzoate was heated at 130–135° with stirring for 24 hr. The solvent was removed under vacuum and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by preparative TLC (ether–hexane, 1:1 system) and the product crystallized from pentane to give 220 mg (40%) of **13**, mp 76–77°, $[\alpha]^{24}D$ −28.7° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.88; H, 7.09.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside (17). Compound **16** (67.0 g, 0.25 mol) was benzylated as described for the preparation of **3** to give 71.4 g (80%) of **17**, mp 73–74°, $[\alpha]^{24}D$ +43.6° (*c* 0.9, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.56; H, 6.64.

Methyl 2-*O*-Benzyl-3-deoxy-α-D-*xylo*-hexopyranoside (19). A solution of 48.7 g (0.14 mol) of **17** in 955 ml of 95% ethanol and 191 ml of water containing 12.2 ml of concentrated HCl was stirred and heated under reflux for 1 hr. The ethanol was evaporated in vacuo, 1270 ml of water was added, and the benzaldehyde formed was removed by steam distillation under reduced pressure. The residue was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness to give 38.7 g (65%) of **18** which failed to crystallize. It was therefore characterized as its dimesylate as follows. Treatment of 500 mg (1.87 mmol) of **18** with excess of methanesulfonyl chloride in pyridine followed by the usual work-up and recrystallization from 95% ethanol gave 530 mg (67%) of methyl 2-*O*-benzyl-3-deoxy-4,6-di-*O*-methylsulfonyl-α-D-*xylo*-hexopyranoside (**19**), mp 97–98°, $[\alpha]^{25}D$ +32.8° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_9S_2$: C, 45.27; H, 5.70; S, 15.11. Found: C, 45.13; H, 5.80; S, 14.92.

Methyl 2-*O*-Benzyl-3-deoxy-6-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (20). A solution of 38.7 g (0.14 mol) of **18** in 240 ml of pyridine was cooled to 0° and mixed with 28.7 g (0.15 mol) of *p*-toluenesulfonyl chloride in 120 ml of $CHCl_3$, also cooled to 0°. The mixture was kept at 5° for 3 days, when an additional 2.6 g of *p*-toluenesulfonyl chloride was added and the mixture was kept at 5° for 2 more days. After the standard work-up, a yellow syrup was obtained which was crystallized from methylene chloride–ether–hexane to give 34.0 g (59% for two steps) of **20**, mp 108–109°, $[\alpha]^{25}D$ +45.4° (*c* 0.9, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_7S$: C, 59.70; H, 6.20; S, 7.59. Found: C, 59.43; H, 6.14; S, 7.38.

Methyl 2-*O*-Benzyl-3,6-dideoxy-6-iodo-α-D-*xylo*-hexopyranoside (21). A solution of 35.3 g (83.7 mmol) of **20** in 1 l. of 2-butanone and 17.7 g (118 mmol) of NaI was stirred and heated under reflux for 4 days. The sodium tosylate formed was filtered and the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with 20% sodium thiosulfate solution followed by water, dried (Na_2SO_4), and concentrated under vacuum. The yellow syrup obtained crystallized on standing and was recrystallized from methylene chloride–hexane to give 28.5 g (90%) of **21**, mp 90–91°, $[\alpha]^{25}D$ +83.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{19}IO_4$: C, 44.46; H, 5.06; I, 33.55. Found: C, 44.59; H, 5.12; I, 33.71.

Methyl 2-*O*-Benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (22). A solution of 27.7 g (73.3 mmol) of **21** in 750 ml of methanol and 12 ml of triethylamine was hydrogenolyzed in the presence of 5.0 g of 10% Pd/C. When the hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed successively with 3 *N* H_2SO_4, $NaHCO_3$ solution, 20% sodium thiosulfate, and water, dried (Na_2SO_4), and concentrated in vacuo to give 18.4 g (99.6%) of **22** which failed to crystallize. It was therefore characterized as its 4-acetyl derivative by treating 200 mg (0.8 mmol) of **22** with excess of acetic anhydride in pyridine. The standard work-up provided 221 mg of a colorless gum which was purified by preparative TLC (ether–benzene, 1:1 system) and subsequently crystallized from pentane to give 108 mg (46%) of methyl 4-*O*-acetyl-2-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (**23**), mp 36–37°, $[\alpha]^{23}D$ +33.5° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.45; H, 7.41.

Methyl 2-*O*-Benzyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-

***xylo*-hexopyranoside (24).** A solution of 18.4 g (73 mmol) of **22** in 100 ml of pyridine was treated with 17.0 g (89.2 mmol) of *p*-toluenesulfonyl chloride at room temperature for 3 days. As a TLC analysis indicated that the reaction was complete, the mixture was poured into ice water, and the crystals formed were collected, washed with water, and dried to give 25.7 g (86%) of **24.** A small portion was recrystallized from methylene chloride–hexane for analysis, mp 105–106°, $[\alpha]^{25}D$ +28.8° (*c* 1.6, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_6S$: C, 62.05; H, 6.45; S, 7.89. Found: C, 61.96; H, 6.36; S, 7.70.

Methyl 2-*O*-Acetyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (26). A solution of 25.4 g (62.6 mmol) of **24** in 150 ml of THF and 360 ml of 95% ethanol was mixed with 45 drops of concentrated HCl and 3.0 g of 10% Pd/C and hydrogenated at atmospheric pressure. When a TLC analysis showed that the debenzylation was complete, the catalyst was filtered and the filtrate concentrated under vacuum. The residue was dissolved in $CHCl_3$, washed with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to dryness to give 19.7 g (99.6%) of methyl 3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (**25**) as a glassy material which did not crystallize. This substance (900 mg, 2.85 mmol) was acetylated with acetic anhydride in pyridine and the mixture poured onto ice–water. The crystals were collected and recrystallized from CH_2Cl_2–ether–pentane to give 0.9 g (89%) of **26,** mp 92–93°.

Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.94. Found: C, 53.69; H, 6.31; S, 8.81.

3,6-Dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexose (28). A solution of 19.2 g (60.8 mmol) of **25** in 225 ml of acetic acid and 60 ml of acetic anhydride was mixed with a solution of 3.75 ml of concentrated H_2SO_4 in 37.5 ml of acetic acid. The mixture was stirred at room temperature for 24 hr, poured onto crushed ice, extracted with $CHCl_3$, washed with water and $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to give 23.0 g (98.1%) of 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-D-*xylo*-hexopyranose (**27**) as a colorless, partially gummy and partially crystalline material, a mixture of α and β anomers. This substance (23.0 g) was dissolved in 200 ml of CH_3OH and treated with 5 ml of a 1.5 *N* barium methoxide solution in methanol. When a TLC analysis indicated the absence of starting material, the solution was neutralized with Dowex-50 X 2 (H^+), and after filtration of the Dowex, the filtrate was evaporated to dryness to give 17.5 g (97.2%) of the free sugar **28** as a colorless, viscous syrup.

3,6-Dideoxy-1,2-*O*-isopropylidene-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranose (15). A mixture of 17.5 g (58 mmol) of **28,** 700 ml of acetone, 100 ml of freshly distilled 2,2-diethoxypropane, and 500 mg of anhydrous *p*-toluenesulfonic acid was stirred at room temperature for 3 hr. As a TLC analysis showed only a trace of the starting material left, the acid was neutralized by stirring with solid $NaHCO_3$, the inorganic materials were filtered off, and the filtrate was evaporated to dryness to yield a dark brown oil. Column chromatography over 400 g of silica gel using hexane–ether (19:1) as eluent provided 9.886 g (50%) of **15,** homogeneous by TLC, $[\alpha]^{26}D$ +2.2° (*c* 0.9, $CHCl_3$).

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (14). A. By the Detosylation of 15. A solution of 9.0 g (26.3 mmol) of **15** in 250 ml of THF was treated with a solution of sodium naphthalenide[15] (prepared from 3.45 g of Na and 20.0 g of naphthalene) in THF under a nitrogen atmosphere until the green color of the reagent remained. The excess reagent was decomposed by the addition of water, and the solvents were evaporated in vacuo. A TLC analysis showed seven spots for the product with 14 as the major component. A rapid column chromatography to remove the naphthalene followed by a careful column chromatography over 100 g of silica gel with ether–hexane (1:3) as eluent gave 1.65 g (33.4%) of an oil which was crystallized from ether–pentane to give 1.30 g (26.3%) of **14,** mp 49–50°, $[\alpha]^{27}D$ −47.3° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.70; H, 8.57.

B. By the Debenzoylation of 13. A solution of 320 mg (1.1 mmol) of **13** in 15 ml of methanol and 15 ml of 0.1 *N* sodium methoxide in methanol was stirred at room temperature overnight. Solid $NaHCO_3$ was added to neutralize the base and after filtration of the inorganic materials, the solution was evaporated to dryness. The residue was extracted with hexane to remove any methyl benzoate and the remainder recrystallized from benzene–pentane to give 185 mg (88%) of **14,** mp 49–50°. A mixture melting point with the analyzed sample from A was unchanged.

Condensation of 3,6-Dideoxy-D-*xylo*-hexose (29) with Acetone. A solution of 1.0 g (6.76 mmol) of **29** in 50 ml of dry acetone and 50 mg of *p*-toluenesulfonic acid was stirred at room temperature for 21 hr. As TLC analyses indicated no further reaction, the mixture was neutralized by stirring with $BaCO_3$. The inorganic materials were removed by filtration, the filtrate was evaporated to dryness, and the residue was dissolved in $CHCl_3$ and washed with water to remove the unreacted starting material, **29** (recovered 305 mg, 30.5%). The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated in vacuo to give 870 mg of a yellow oil. Separation by preparative TLC using 3-pentanone–2,4-dimethyl-3-pentanone–ligroin (6:3:1) as solvent gave 92 mg (7%) of **14** and 435 mg (35%) of 3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose[18] (**30**), each fraction containing a small percentage of the other. Preparative gas chromatography (F&M Model 775 instrument, 8 ft × 2.5 in. 3% ethylene glycol succinate column) of the major fraction followed by recrystallization from ether–pentane provided pure **30,** mp 47–48°, $[\alpha]^{25}D$ −35.0° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.31; H, 8.62.

Treatment of 80 mg (0.42 mmol) of **30** with methanesulfonyl chloride in pyridine followed by the standard work-up gave 75 mg (67%) of 3,6-dideoxy-1,2-*O*-isopropylidene-5-*O*-methylsulfonyl-α-D-*xylo*-hexofuranose[19] (**31**), mp 104–105°, $[\alpha]^{25}D$ −88° (*c* 0.5, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_6S$: C, 45.10, H, 6.81; S, 12.04. Found: C, 45.10; H, 6.90; S, 12.10.

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexos-4-ulose (32). A solution of 452 mg (2.4 mmol) of **15** in 20 ml of CCl_4 was stirred at 0° and a solution of ruthenium tetroxide[12,21] in CCl_4 was added dropwise until the yellow color of RuO_4 remained. A GC analysis indicated that the oxidation was complete. The excess RuO_4 was destroyed by adding a few drops of 2-propanol, the precipitated RuO_2 was removed by filtration, the solvent was evaporated at reduced pressure, and the residue was distilled in vacuo to give 364 mg (82%) of **32** as a colorless liquid, bp 47–49° (0.3 mm Hg), $[\alpha]^{27}D$ +166.3° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.76; H, 7.60.

Oxidation of 266 mg (1.0 mmol) of the mesylate **12** in 7 ml of Me_2SO and 0.13 ml of dry collidine at 125° for 20 hr showed that a significant amount of the ketone **32** was formed by a GC analysis. The mixture was poured onto ice and extracted with $CHCl_3$ to give 486 mg of a dark yellow oil containing Me_2SO, ketone **32,** and a by-product, probably an unsaturated compound formed by the elimination of mesylate. However, neither distillation nor preparative TLC was effective in separating **32** from Me_2SO and therefore this method was abandoned.

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexos-4-ulose Oxime (33). A mixture of 50 mg (0.27 mmol) of **32** in 2.5 ml of ethanol and 2.5 ml of pyridine and 200 mg (2.9 mmol) of hydroxylamine hydrochloride was heated on a steam bath overnight. The solvents were removed under reduced pressure, and the residue was dissolved in water and extracted thoroughly with ether. The ether solution was dried (Na_2SO_4) and evaporated to dryness and the residue was recrystallized from hexane to give 32 mg (60%) of **33,** mp 132–134°, $[\alpha]^{27}D$ +159.3° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.75; H, 7.51; N, 6.80.

3,6-Dideoxy-D-*erythro*-hexos-4-ulose (3,6-Dideoxy-4-keto-D-glucose 1). A solution of 95 mg (0.5 mmol) of **32** in 10 ml of water was stirred with 1.0 g of prewashed Dowex-50 X 2 (H^+) (100–200 mesh) at room temperature for 24 hr. A TLC analysis (solvent EtOAc) showed that the hydrolysis was complete. The Dowex was removed by filtration and the solution lyophilized at 0.02 mm Hg to give 75.4 mg (95%) of **1** as a white gum. An NMR in Me_2SO-d_6–D_2O showed two anomeric protons at τ 4.85 ($J_{1,2}$ = 7 Hz) and 5.15 ($J_{1,2}$ = 3 Hz) in a 1:1 ratio indicating that the free sugar was a 50:50 mixture of β and α anomers. The other peaks in the NMR spectrum were consistent with the structure.

A mixture of 75.4 mg (0.48 mmol) of **1,** 10 ml of dry acetone, 1 ml of 2,2-diethoxypropane, and 5 mg of *p*-toluenesulfonic acid was stirred at room temperature for 2 hr. A TLC analysis (solvent EtOAc) showed that the free sugar was converted to the isopropylidene derivative, **32.** The acid was neutralized with solid $NaHCO_3$ and filtered, and the filtrate was evaporated, the residue was extracted with ether, and the ether was removed in vacuo to give 107 mg of **32,** over 90% pure by GC. A portion (50 mg) of this material was converted to the crystalline oxime as described earlier to give

27 mg (50%) of **33**, mp 132–133°. A mixture melting point of the two samples of **33** was unchanged.

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Registry No.—**1**, 56783-59-6; **2**, 40773-64-6; **3**, 50272-14-5; **4**, 50272-15-6; **5**, 50272-16-7; **6**, 50272-17-8; **7**, 50272-18-9; **8**, 50272-19-0; **9**, 50421-06-2; **10a**, 50272-20-3; **10** isomer A, 56783-60-9; **12**, 50272-21-4; **13**, 50272-22-5; **14**, 50272-23-6; **15**, 56783-61-0; **16**, 20196-81-0; **17**, 56783-62-1; **18**, 56783-63-2; **19**, 56783-64-3; **20**, 56783-65-4; **21**, 56783-66-5; **22**, 56783-67-6; **23**, 56783-68-7; **24**, 56783-69-8; **25**, 56783-70-1; **26**, 56783-71-2; **28**, 56783-72-3; **29**, 56816-60-5; **30**, 22395-75-1; **31**, 56783-73-4; **32**, 50272-24-7; **33**, 50272-13-4; benzyl chloride, 100-44-7; methanesulfonyl chloride, 124-63-0; *p*-toluenesulfonyl chloride, 98-59-9; acetone, 67-64-1.

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Imidazo[1,2-*c*]pyrimidine Nucleosides. Synthesis of N-Bridgehead Inosine Monophosphate and Guanosine Monophosphate Analogues Related to 3-Deazapurines[1]

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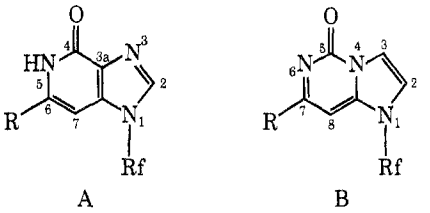
The first chemical syntheses of imidazo[1,2-*c*]pyrimidine nucleosides are described. Cyclization of 4-amino-6-chloro-2-pyrimidinol (**2**) with bromoacetaldehyde diethyl acetal gave 7-chloroimidazo[1,2-*c*]pyrimidin-5-one (**3**). Direct glycosylation of the trimethylsilyl derivative of **3** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile gave an anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**12**) which on deacetylation and separation of anomers furnished 7-chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**) and its α anomer (**11**). However, the glycosylation of Me_3Si-**3** with tetra-*O*-acetyl-β-D-ribofuranose in dichloroethane containing stannic chloride, followed by aminolysis, gave only the β anomer **10**. Catalytic dehalogenation of **10** and **11** furnished the 3-deazainosine analogue, 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**15**), and its α anomer (**17**), respectively. Amination of **10** gave 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**13**), an analogue of 3-deazaguanosine possessing a bridgehead nitrogen atom. Phosphorylation of **15**, **17**, and **13** gave 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-monophosphate (**16**), the IMP analogue, its α anomer (**18**), and 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-monophosphate (**14**), the GMP analogue, respectively. The assignment of site of ribosylation has been determined unequivocally by using ^{13}C NMR spectroscopy and the anomeric configurations have been established by using ^1H NMR of the 2′,3′-*O*-isopropylidene derivatives of **10** and **11**.

It is well established that alterations of either the furanose or the base moiety of naturally occurring purine nucleosides may produce analogues that exert interesting biological effects.[2] The role of the various nitrogen atoms of purine nucleosides as binding sites for important enzymes in biological systems has become the subject of considerable interest.[3] The isolation of a number of antibiotics of the deazapurine series (e.g., viomycin,[4] tubercidin,[5] toyocamycin[6]) which are isomeric or isosteric with purine are of particular interest because of their structural uniqueness and their biological properties.[6b,7] Since the majority of purine-type ribosides exist in the anti conformation (some exist in the syn conformation in the solid state[8]), 3-deazapurine nucleosides deserve special attention because N_3 of purine nucleosides is presumed to be involved in stabilizing the syn conformation through intramolecular hydrogen bonding [5′-OH···N_3H].[9] The syntheses of several 3-deazapurine nucleosides[10] and nucleotides[10f,g,11] (A) have been



Rf = -β-D-ribofuranosyl

reported. Some of these 3-deazapurine derivatives have demonstrated significant antibacterial,[12] anticancer,[10b,e] and antiviral[10g] activity. The imidazo[1,2-*c*]pyrimidine ring system (B), which has not been explored appreciably, may be regarded as 3-deazapurine with a bridgehead nitrogen atom in which N_3 and C_{3a} are interchanged. The nucleoside analogues of imidazo[1,2-*c*]pyrimidine have the potential, therefore, either to emulate or to antagonize the functions of the naturally occurring nucleosides and nucleotides.