saturation time) can also be created by the user.

Transmitter power applied in the low-power mode is controlled by the transmitter attenuator on the spectrometer. The pulse power necessary to achieve saturation must be established empirically by systematically changing the dB attenuation and observing the effect on exchange spectra. A titration-like curve is obtained (Figure 11) which is used to determine the best attenuation for the experiment. Our experiments were conducted at 15 dB attenuation.

The experiment is initiated by the GS command. After entering the number of spectra to be collected (equal to the number of P4 values entered), a file name is chosen under which spectra will be collected and distinguished from each other by an arithmetically increasing numerical extension. It is also best to include several discarded scans (DG = 2) in the experiment to insure proper pulse sequencing.

It is important to achieve good digital resolution (computer points/hz) in ST spectra if intensities are to be used to evaluate rate constants. Spectra can be collected with fewer points to save disk space and zero-filled during data processing.

Registry No. D-Idose, 5978-95-0; α-D-idofuranose, 41847-67-0; β-D-idofuranose, 40461-75-4; α-D-idopyranose, 7282-82-8; β-D-idopyranose, 7283-02-5; 5-*O*-methyl-α-D-xylofuranose, 94707-49-0; 5-*O*-methyl-β-D-xylofuranose, 94707-50-3; D-[1-^{13}C]idose, 70849-26-2; D-glycero-D-[1-^{13}C]idoheptose, 102368-20-7.

Methyl 2,3-Dideoxy-3-nitro-D-*erythro*-pentofuranoside, Isomers and Derivatives

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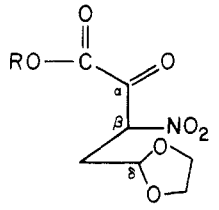
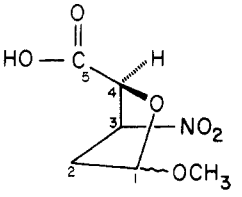
Practical syntheses are described for the versatile intermediates, methyl 2,3-dideoxy-3-nitro-D-*erythro*-pentofuranoside (**12**), the corresponding uronic acid (**2**), and some derivatives, starting from either D-glucose or D-xylose.

In previous studies[1,2] we had prepared the protected δ-aldehydo-α-keto-β-nitro ester **1** but found it to be too unstable for our projected synthetic purposes.[3,4] We have therefore selected structure **2** as a target molecule, which has the same carbon skeleton and basic functionality with the exception that the α-keto in **1** is present in reduced



1

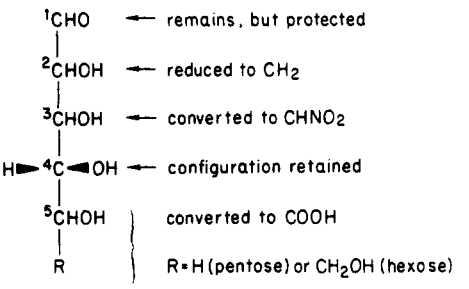


2

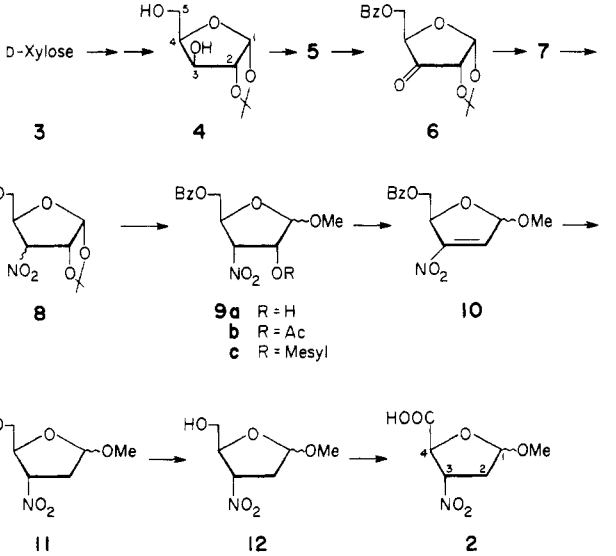
form as the ring oxygen in the furanose derivative **2**. The crucial stereochemistry from the standpoint of our projected synthesis is the configuration at C-4 as shown[5] in **2**, since all other chiral centers are to be elminated or modified in subsequent reactions. Thus, any pentose or hexose with the D configuration at C-4 which can undergo the indicated transformations shown in Scheme I could serve as a suitable starting point. Scheme II shows the strategy followed starting with D-xylose and Scheme III with D-glucose.

D-Xylose was an attractive starting material because intermediate **8** was already described.[6] By variations of

Scheme I



Scheme II

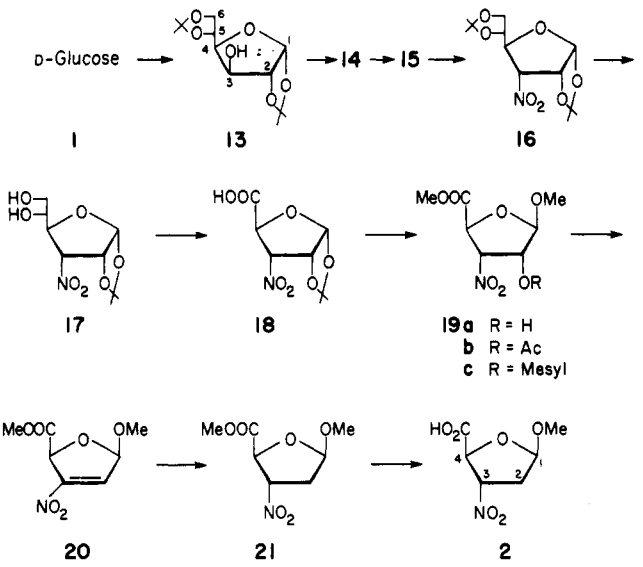


the methods reported,[6-15] as shown in Scheme II (**4** → **5** → **6** → **7** → **8**), the synthesis of **8** has been developed in

(1) Williams, T. M.; Crumbie, R. L.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 91.
(2) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040.
(3) Nachman, R. J. Ph.D. Thesis, Stanford University, 1981.
(4) Williams, T. M.; Mosher, H. S. *Tetrahedron Lett.* **1985**, *26*, 6269.
(5) The numbering system in **2** is chosen to correspond to the precursor carbohydrates.

0022-3263/86/1951-2702$01.50/0

Scheme III



an overall yield of 85% from the commercially available 1,2-*O*-isopropylidene-D-xylose (**4**). Protection of the primary hydroxyl group by benzoylation[7,8] gave intermediates which were easily handled because of enhanced solubility in organic solvents and which were convenient to follow because of the UV chromophore and aromatic ^{1}H NMR signals.

We obtained a 2:3 ratio of the epimeric nitro compounds **8a** and **8b** (D-xylo and D-ribo forms), while the literature reported[6] a 1:2 ratio. The xylo epimer could be obtained crystalline by chromatography. However, for synthetic purposes the mixture of isomers was carried forward without separation because the stereochemistry at C-3 is destroyed and reestablished in subsequent steps. Furthermore, methanolysis of **8** by 48-h reflux in the presence of strong acid resin removed the 1,2-isopropylidene group and gave the methyl glycoside of the 2-hydroxy compound **9a** as the β-anomer of the ribo form in near quantitative yield. With shorter reflux times, a mixture of epimers was obtained. The α- and β-anomers of **9a** were separated from this mixture and characterized; however, for synthetic purposes, the mixture could be carried through directly to **11**. The reductive elimination sequence **9a** → **10** → **11** was achieved by two procedures; in the *first*, nitro carbinol **9a** was treated with acetic anhydride and sodium acetate[16,17] to give a mixture of nitro olefin **10** and nitro acetate **9b**. Further treatment of this mixture with sodium borohydride[18,19] with heating in ethanol gave the saturated 2-deoxy-3-nitro compound **11** (61% crude yield) from which the β-anomer could be obtained pure by chromatography but only in about 30% yield from **9a**. The second and preferred method involved treatment of **9a** in chloroform containing triethylamine with methanesulfonyl chloride[20,21] at 20 °C. The crude olefin was treated directly with sodium borohydride (0 °C → 20 °C) to give crude **11**, which was chromatographed to give pure β-anomer (53% yield). The route via the mesylate (**19**) was also preferred in the glucose series (Scheme III, **19a** → **21**).

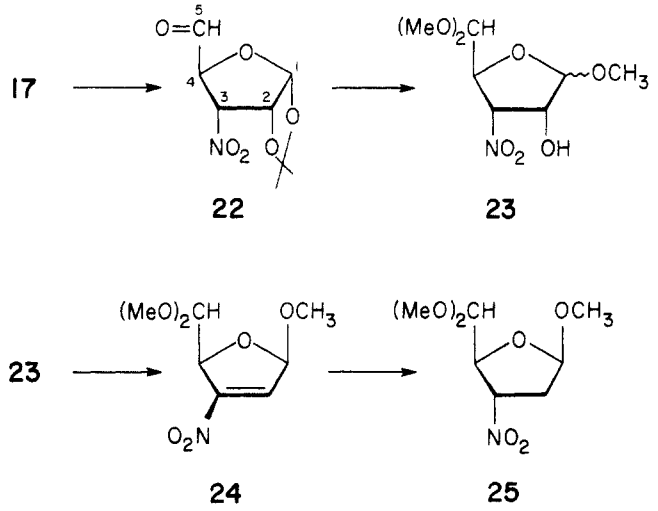
Debenzoylation of **11** to **12** was not feasible by acid hydrolysis since this leads to the unprotected pyranose form[4] of **12**. Debenzoylation was achieved initially by allowing **11** to stand with ammoniacal methanol for 90 h at room temperature.[22] Column chromatography was required to purify this product and the yield was only 57% (51% of the β-anomer and 6% of the α-anomer). Finally, methanolysis of **11** to **12** was worked out in near quantitative yield by using sodium methoxide in methanol followed by workup with ammonium chloride.[23] Conversion of carbinol **12** to acid **2** was best accomplished by the Sharpless variation[24] of ruthenium tetraoxide oxidation[11] (RuO_2, $NaIO_4$, CH_3CN solvent); pure **12** (β-anomer) was oxidized to give crystalline **2** (β-anomer) in 78% yield. In preparative experiments the methanolysis and oxidation steps (**11** → **12** → **2**) were combined. The five-step sequence from the known nitro compound **8** was carried through with isolation of intermediates **9a** and **11** to give **2** in a yield of 33% (29% yield in nine steps from the available 1,2-isopropylidene-D-xylose **4**).

An alternate pathway for the synthesis of the target compound **2**, starting from D-glucose, has been developed as shown in Scheme III. The procedure uses the same rationale as delineated in Scheme II and similar chemical manipulations but in a different sequence from that starting with D-xylose (Scheme II). The known starting diisopropylidene-3-nitro compound[6,25] **1b** is made in three steps from the commercially available diisopropylidene-D-glucose **13**. Ruthenium tetraoxide oxidation (Sharpless procedure[24]) of **13** gave the corresponding ketone **14** (77% yield), a method slightly preferred to the literature described pyridine chlorochromate[26] oxidation. This ketone **14** was converted via the oxime **15**, followed by oxidation[6,11,12] (CF_3CO_3H) to the crystalline nitro compound (overall yield of 60% from **13**). The product is almost entirely the allo isomer **16**, as reported previously.[6]

Selective hydrolysis of the 5,6-isopropylidene group of **16** gave the 5,6-diol **17**, which was oxidized (Sharpless procedure[24]) to nitro acid **18** (67% yield, two steps). Methanolysis of crude **18** (strong acid resin, 48-h reflux) gave the methyl ester, methyl glycoside **19a** (80% yield), which was entirely the β-anomer, as shown by the unique NMR coupling constants of the C-1 through C-5 protons.[27] Reductive elimination of the 2-hydroxy function of **19a** to **21** was achieved by two different procedures analogous to those outlined in the xylose series (Scheme II, **9** → **10** → **11**). In the glucose series we also preferred the procedure via the mesylate[18,20,21] (**19c** → **20** → **21**). In this series the intermediate nitro olefin **20** was isolated. For preparative purposes, however, it was directly reduced with sodium borohydride in watter and a minimum amount of methanol to give **21** (75% yield from **19a**). As in the conversion of **9** → **10** → **11** in the xylose series, this reaction sequence could be accomplished by treatment with acetic anhydride

(6) Takamoto, T.; Sudoh, R.; Nakagawa, T. *Tetrahedron Lett.* **1971**, 2053.
(7) Levene, P. A.; Raymond, A. L. *J. Biol. Chem.* **1933**, *102*, 317.
(8) Tong, G. L.; Lee, W. W.; Goodman, L. *J. Org. Chem.* **1967**, *32*, 1984.
(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
(10) Andersson, F.; Sanuelsson, B. *Carbohydr. Res.* **1984**, *129*, C1-C3.
(11) Tachimori, Y.; Sakakibara, T.; Sudoh, R. *Carbohydr. Res.* **1981**, *95*, 299.
(12) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 4557.
(13) Svanberg, D.; Sjöberg, K. *Chem. Ber.* **1923**, *56*, 863.
(14) Müller, H.; Reichstein, T. *Helv. Chim. Acta* **1938**, *21*, 251.
(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) Schmidt, E.; Rutz, G. *Chem. Ber.* **1928**, *61*, 2142.
(17) Baer, H. H.; Chiu, C.-H. *Can. J. Chem.* **1974**, *52*, 111.
(18) Melton, J.; McMurry, J. E. *J. Org. Chem.* **1975**, *40*, 2138.
(19) Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, 3219.
(20) Tachimori, Y.; Takamoto, T.; Sudoh, R. *Chem. Lett.* **1976**, 483.
(21) Baer, H. H.; Georges, F. Z. *J. Org. Chem.* **1976**, *41*, 3474.
(22) Chavis, C.; Dumont, F.; Wightman, R. H.; Ziegler, J. C.; Imbach, J. L. *J. Org. Chem.* **1982**, *47*, 202.
(23) Seela, F.; Winkler, H.-D. *J. Org. Chem.* **1982**, *47*, 226.
(24) Carlsen, P. H. J.; Katsuki, T.; Martin, V. X.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(25) Kovár, J.; Baer, H. H. *Can. J. Chem.* **1971**, *49*, 3203.
(26) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(27) Stevens, J. D.; Fletcher, H. G., Jr. *J. Org. Chem.* **1968**, *33*, 1799.

Scheme IV



and sodium acetate. However, this procedure gives a mixture of nitro olefin **20** (α and β forms) and acetate **19b**, which on treatment with sodium borohydride resulted in a less pure product **21** in poorer yield.

Methyl ester **21** was hydrolyzed to nitro acid **2** (71% yield), which crystallized on standing and which could be recrystallized from ether–cyclohexane. This recrystallization removes small amounts of the α-anomer to give methyl 2,3-dideoxy-3-nitro-β-D-*erythro*-pentofuranosiduronic acid (**2**), identical with that obtained from the sequence of Scheme II and that prepared by total synthesis from D-glyceraldehyde.[4] Scheme III was carried through in an overall yield of about 28% in six steps from the previously described nitro compound **16** (17% from the readily available diacetone glucose, **13**, in nine steps).

Under conditions of the Sharpless oxidation[24] ($RuCl_3$, $NaIO_4$, CCl_4, CH_3CN) of the 5,6-diol **17**, Scheme IV, after a short time (1 h) the aldehyde **22** was isolated instead of the acid **18**. This same aldehyde was formed by the action of periodate alone. Further treatment of aldehyde **22** by the Sharpless reagent gave acid **2**. Aldehyde **22**, upon treatment with methanol and strong acid resin, was converted into acetal **23** that gave nitro olefin **24** (85% yield) upon treatment with triethylamine and methanesulfonyl chloride. Reduction of the olefin ($NaBH_4$ in water–methanol) produced the saturated nitro acetal **25** (crude yield 80%).

Experimental Section

Melting points are uncorrected and were determined either in capillary on a "Meltemp" aluminum block or on a thin glass cover plate on a microscope hot stage. IR spectra were determined on a Perkin-elmer Model 237 B grating instrument, and major signals were recorded in cm^{-1}. Proton NMR spectra were determined on a Nicolet 300-MHz instrument in the FT mode. NMR spectra were taken in $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si) unless otherwise noted. Coupling constants are in hertz (Hz) and splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet, q, quartet; m, unresolved multiplet; dd, doublet of doublets; ddd, doublet of double doublets (eight signals; dq, doublet of quartets (eight signals); br, broad. Optical rotations were taken on a Rudolph Autopol III, which reads to 0.001°, with permanent-window cells, 1 dcm, thermostated at 20.0 °C. Reactions were followed routinely by using silica gel GF thin-layer chromatography (TLC) plates (250 μm, Analtech). Preparative TLC separations were accomplished on silica gel GF plates (1000 μm, Analtech). TLC plates were visualized either by spraying with 10% H_2SO_4 followed by heating to 150 °C or by dipping into a 7% solution of phosphomolybdic acid in ethanol followed by heating to 150 °C. Column chromatography refers to flash chromatography as described by Still, Kahn, and Mitra[15] and was performed on silica gel G (0.032–0.063 mm, ICN Nutritional Biochemicals).

1,2-*O*-Isopropylidene-5-α-D-xylofuranose Benzoate[6] (5). 1,2-*O*-Isopropylidene-α-D-xylose (Aldrich Chemical Company, 100 g) was benzoylated by the method of Levene and Raymond[7] and Tong, Lee, and Goodman[8] to give the monobenzoate **5** in near quantitative yield, which contained about 3% of the dibenzoate. The crude product solidified on standing and could be purified by crystallization from ether but was used as the crude product in the next step: NMR ($CDCl_3$), monobenzoate, δ 8.05 (2 H, d), 7.61 (1 H, t), 7.47 (2 H, t), 5.96 (1 H, d, J = 3.56), 4.82 (1 H, m), 4.61 (1 H, d, J = 3.56), 4.37 (2 H, m), 4.17 (1 H, d, J = 2.15), 3.30 (OH, br s), 1.51 (3 H, s), 1.33 (3 H, s).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pent-3-ulofuranose[8] (6). Benzoate **5** (65 g, 0.22 mol) in CH_2Cl_2 (660 mL) was oxidized by reflux (2 h) with pyridine dichromate (PDC, 50 g, 0.133 mol) and acetic anhydride (68 g, 0.66 mol). The reaction mixture was diluted with ether (350 mL) and filtered through a 35 × 100 cm column of silica gel. The column was eluted with ether (200 mL) and CH_2Cl_2 (2 × 150 mL), and the combined eluants were evaporated to give a greenish white solid (64 g, 99%): NMR ($CDCl_3$) δ 7.3–8.1 (5 H, m), 6.13 (1 H, d, J = 4.4), 4.3–4.8 (4 H, m), 1.50 (3 H, s), 1.42 (3 H, s); IR (neat) 1765 (ester CO), 1725 (ring CO) cm^{-1}. Oxidation by the Sharpless procedure[24] (H_2O, CCl_4, KIO_4 but not $NaIO_4$, RuO_2) gave a 55% yield of crystalline **6**, but this method was less convenient than the above PDC method. Oxidation by the method of Swern[9] (Me_2SO, CH_2Cl_2, $(CF_3CO)_2O$, −65 °C, 45 min) as described in ref 8 gave a near quantitative yield of crude **6** which did not solidify and was contaminated with a sulfur-containing impurity which could not be easily removed and which greatly hindered subsequent synthetic steps.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pent-3-ulofuranose Oxime[8] (7). We only obtained good yields (85%) of oxime **7** when the reaction was carried out at pH 4 in pyridine–acetic acid solution as described[11] for an analogous case. Ketose **6** (114 g) gave oxime **7** (102 g, 85% yield, mp 125–126 °C), which was crystallized from ethanol to give purified **7** (69 g, mp 132–136 °C). The NMR of this material indicated a 2:1 mixture of isomers, which we assume to be anti and syn forms: NMR ($CDCl_3$) major component, δ 8.2 (1 H, br, oxime OH), 7.96 (2 H, d), 7.44 (2 H, t), 7.60 (1 H, t), 6.07 (1 H, d, J = 4.32), 5.11 (1 H, d, J = 4.32), 5.39 (1 H, dd, J = 3.09, 2.33), 4.79 (1 H, dd, J = 3.09, 11.71), 4.61 (1 H, dd, J = 2.33, 11.71), 1.52 (3 H, s), 1.46 (3 H, s); minor component, δ 8.2 (1 H, br, oxime OH), 8.02 (2 H, d), 7.60 (1 H, t), 7.44 (2 H, t), 6.03 (1 H, d, J = 4.36), 5.12 (1 H, d, J = 4.36), 5.36 (1 H, dd, J = 2.73, 5.42), 4.68 (1 H, dd, J = 2.73, 12.08), 4.44 (1 H, dd, J = 5.42, 5.42), 1.55 (3 H, s), 1.45 (3 H, s). The NMR of the syrupy product (32 g) from the mother liquors was not much different from that of the above crystalline mixture; however, only crystalline material was used in the subsequent oxidation to nitro compound **8**.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-deoxy-3-nitro-D-ribofuranose and -xylofuranose (8). Crystalline oxime **7** was oxidized by the method of Emmons and Pagano[12] according to the procedure of Takamoto et al.[6] but with a significantly different ratio of reagents. Trifluoroacetic anhydride (82 mL) was added with stirring at 0 °C to a solution of 90% H_2O_2 (13 mL) in CH_3CN (100 mL). This solution was added with stirring and cooling to mixture of crystalline oxime **7** (35.9 g), Na_2HPO_4 (182 g), and urea (4.7 g) in CH_3CN (400 mL) over a 30-min period at a rate which maintained gentle reflux. The mixture was then refluxed for 2 h, cooled, diluted with water (800 mL), and extracted with CH_2Cl_2 (3 × 200 mL). The extracts were washed successively with $NaHCO_3$ (2 × 300 mL, 15% solution) and NaCl (300 mL saturated solution), dried ($MgSO_4$), and concentrated to give a clear yellow oil (37.1 g, 98%). NMR showed this to be a 3:2 mixture of the xylo and ribo isomers. These were not separated, but the NMR signals could be deconvoluted (Cosy4 program) with the following results: xylo isomer, NMR ($CDCl_3$): δ 8.1–7.3 (5 H, m, Ar H), 5.85 (1 H, d, J = 3.72), 5.03 (1 H, d, J = 3.72), 4.93 (1 H, ddd, J = 9.35, 3.18, 3.62), 4.80 (1 H, d, J = 9.35), 4.65 (1 H, dd, J = 3.18, 12.51), 4.54 (1 H, dd, J = 3.62, 12.51), 1.49 (3 H, s), 1.31 (3 H, s); ribo isomer, NMR ($CDCl_3$): δ 8.1–7.3 (5 H, m, Ar H), 6.11 (1 H, d, J = 3.71), 5.03 (1 H, dd, J = 3.71, 7.98), 4.79 (1 H, d, J

= 7.98), 4.76 (1 H, dd, J = 5.76, 5.67), 4.59 (1 H, dd, J = 5.76, 12.21), 4.45 (1 H, dd, J = 5.67, 12.21), 1.52 (3 H, s), 1.49 (3 H, s).

Methyl 5-*O*-Benzoyl-3-deoxy-3-nitro-α- and -β-D-ribofuranosides (9a). The mixture of isomers of 8 (33 g) was refluxed in anhydrous methanol (1750 mL) and strong acid resin (Dowex 50W-X8, 22 g, H^+ form) for 6.5 h. The reaction mixture was cooled, the resin removed by filtration, and the filtrate concentrated to a yellow oil (29.5 g, 97% crude yield). From the NMR this contained a small amount of starting material 8, methyl benzoate, and two product isomers. The crude product was chromatographed (4 × 100 cm silica gel column, $CHCl_3$) to give a mixture of diastereomers of 9 (90% yield), which can be used as such in the subsequent steps. Further chromatographic separation gave the major product, ribo-β-anomer **9a**: mp 102–104 °C; $[\alpha]^{20}_D$ −43.8° (c 1.0, CH_3OH); NMR ($CDCl_3$): δ 8.04 (2 H, d, *o*-Ar H), 7.59 (1 H, t, *p*-Ar H), 7.46 (2 H, t, *m*-Ar H), 5.29 (1 H, dd, J = 7.8, 4.0), 5.13 (1 H, ddd, J = 7.80, 4.21, 4.40), 4.95 (1 H, s), 4.66 (1 H, dd, J = 4.0, 5.5), 4.66 (1 H, dd, J = 4.2, 12.1), 4.55 (1 H, dd, J = 4.4, 12.1), 2.68 (1 H, J = 5.5, OH), 3.32 (3 H, s, OCH_3). Anal. Calcd for $C_{13}H_{15}NO_7$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.20 H, 5.15; N, 4.64.

Methyl 5-*O*-Benzoyl-2,3-dideoxy-3-nitro-β-D-*erythro*-pentofuranoside (11). Methanesulfonyl chloride (5.3 g) was added at 0 °C over 15 min to a solution of nitro carbinol **9a** (7.0 g chromatographed major isomer) in THF (180 mL). Without attempted isolation of the intermediate mesylate **9c**, the solution was immediately treated with Et_3N (7.2 mL) and stirred for 30 min while warming to 20 °C. Water (100 mL) was added and the mixture extracted with ether (3 × 50 mL). The organic layer was concentrated to 70 mL (but no further) and a solution of $NaBH_4$ (2 g) in absolute ethanol (80 mL) was added at 0 °C (20 min). The mixture was allowed to reach room temperature (30 min), diluted with water (50 mL), and acidified (8 mL, 3 N HCl), and most of the ether, ethanol, and THF were removed under vacuum. The aqueous residue was extracted with ether (4 × 70 mL), and the ether extracts were washed (150 mL saturated $NaHCO_3$, 150 mL saturated NaCl), dried ($MgSO_4$), and vacuum evaporated to give a yellowish oil (7 g). This crude product was chromatographed (4 × 50 cm silica gel column, hexane/EtOAc, 3:1) to give a colorless oil (3.5 g, 53%) which by NMR was pure **11** as the β-anomer: NMR ($CDCl_3$) δ 8.07 (2 H, d), 7.60 (1 H, t), 7.47 (2 H, t), 5.29 (1 H, d, J = 8), 5.25 (1 H, ddd, J = 5.4, 8.0, 1.0), 4.84 (1 H, m), 4.51 (2 H, d, J = 6.2), 2.88 (1 H, ddd, J = 8.0, 8.0, 13.8), 2.58 (1 H, ddd, J = 1.0, 13.8), 3.35 (3 H, s, OCH_3).

This same reductive elimination was also achieved by treating nitro carbinol **9a** (17.6 g of mixed isomers) with acetic anhydride (100 mL) and sodium acetate[16,17] (25 g) first at 0 °C and then by warming to 20 °C over 16 h. Workup by neutralization (400 mL, 5 N NaOH, 5 °C), extraction with ether, and successive washings of these extracts with saturated $NaHCO_3$, 3 N HCl, and saturated NaCl, followed by drying ($MgSO_4$) and vacuum concentration, gave a mixture of olefin **10** and acetate **9b**. This mixture in absolute ethanol (200 mL) was treated at 0 °C with $NaBH_4$ (3.1 g) and then warmed to 60 °C for 4 h. Workup gave crude **12** (10.1 g, 61%), from which one pure anomer of 11 could be obtained by chromatography (silica gel, hexane–ether, 3:1): NMR ($CDCl_3$) δ 8.05 (2 H, d, *o*-Ar H), 7.60 (1 H, t, *p*-Ar H), 7.45 (2 H, t, *m*-Ar H), 5.15 (1 H, d, J = 4.7), 5.05 (1 H, ddd, J = 2.3, 4.1, 9.5), 4.90 (1 H, m), 4.63 (1 H, dd, J = 4.1, 9.5), 4.58 (1 H, dd, J = 4.1, 9.5), 2.92 (1 H, dd, J = 2.3, 12.8), 2.49 (1 H, ddd, J = 4.7, 9.5, 12.8), 3.40 (3 H, s, OCH_3). This isomer differs from the one obtained by the mesylate route starting from **9a** (β-anomer) described above.

Methyl 2,3-Dideoxy-3-nitro-β-D-*erythro*-pentofuranoside (12) by Methanolysis of 11. Benzoate ester **11** (pure β anomer, 3.67 g) was treated at 20 °C for 1 h with a solution of anhydrous methanol (95 mL), to which had been added sodium metal (1.0 g). Ammonium chloride crystals (5 g) were added and the mixture was stirred (45 min), diluted with ether (150 mL), and filtered, and the filtrate was concentrated to give a light yellow oil (3.71 g) which by NMR was a 1:1 mixture of methyl benzoate and **12**. Chromatography on a silica gel column (2 × 20 cm, cyclohexane/EtOAc, 3:1) gave pure **12** (2.08 g, β-anomer, 90% yield): NMR ($CDCl_3$) δ 5.27 (H-1, dd, J = 5.8, 1.9), 5.22 (H-3, ddd, J = 8.2, 4.5, 3.2), 4.71 (H-4, ddd, J = 5.0, 2.8, 2.6), 3.83 (H-5_a, dd, J = 12.5, 2.6), 3.76 (H-5_b, dd, J = 2.8, 12.5), 3.45 (OCH_3, s), 2.97 (H-2_β, ddd, J = 3.3, 5.8, 14.8), 2.47 (H-2_α, ddd, J = 1.9, 8.2, 14.8); $[\alpha]^{20}_D$ −102° (c 1.2, CH_3OH). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.90. Found: C, 40.87; H, 6.25; N, 7.76.

By Ammonolysis of Mixture of α- and β-Anomers of 11. A solution of **11** (7.8-g mixture of anomers) in saturated ammoniacal methanol (100 mL) was stirred in a closed flask for 89 h at room temperature. The solvent and NH_3 were removed under vacuum and the residue was purified by silica gel, chromatography (solvent: $CHCl_3$/EtOAc 10:1) to give two major isomeric products. The first (300 mg) corresponded exactly with the above β-D-ribo isomer **12**; the second (2.0 g) was identical with the α-D-ribo isomer reported earlier.[4] NMR ($CDCl_3$) δ 5.14 (H-1, d, J = 4.9), 4.92, (H-3, ddd, J = 9.8, 4.8, 2.5), 4.71 (H-4, ddd, J = 4.9, 2.8, 2.5), 4.00 (H-5_a, m), 3.85 (H-5_b, m), 3.45 (OCH_3, s), 2.88 (H-2_β, ddd, J = 14.8, 2.6), 2.47 (H-2_α, ddd, J = 14.8, 9.8, 4.9), 1.82 (OH, dd, $J \simeq$ 10.5); $[\alpha]^{20}_D$ +140° (c 1.0, CH_3OH). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.90. Found: C, 40.50; H, 6.18; N, 7.90.

Methyl 2,3-Dideoxy-3-nitro-β-D-*erythro*-pentofuranosiduronic Acid (2). Sharpless Procedure.[24] Carbinol **12** (1.9 g, pure β-anomer) was mixed with H_2O (18 mL), CCl_4 (18 mL), CH_3CN (18 mL), and $NaIO_4$ (7.8 g); with vigorous stirring $RuCl_3 \cdot 3H_2O$ (148 mg) was added at a rate to maintain a yellow-colored reaction mixture. After 2 h the mixture was diluted with CH_2Cl_2 (200 mL), the water layer removed, and the combined organic layer was evaporated to dryness. The residue was taken up in ether (200 mL) and the RuO_2 removed by filtration through a Celite pad. The filtrate was treated with 60 mL of 10% $NaHSO_3$, and the product in the aqueous layer was recovered by acidifying, saturating with NaCl, and extracting with ether (5 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated to give yellow crystals of **2** (β-anomer, 1.6 g, 78%), which were recrystallized (ether–cyclohexane, 2:3), mp 72–77 °C; NMR ($CDCl_3$) δ 5.56 (H-3, ddd, $J_{3,2\beta}$ = 8.5, $J_{3,2\alpha}$ = 5.7, $J_{3,4}$ = 3.0), 5.32 (H-1, dd, $J_{1,2\alpha}$ = 5.1, $J_{1,2\beta}$ = 1.5), 5.24 (H-4, d, $J_{3,4}$ = 3.2), 3.45 (OCH_3, s), 2.79 (H-2_α, ddd, J_{AB} = 14.2, $J_{2\alpha,1}$ = 5.7, $J_{2\alpha,3}$ = 5.5), 2.58 (H-2_β, ddd, J_{AB} = 14.2, $J_{2\beta,3}$ = 8.5, $J_{2\beta,1}$ = 1.5); $[\alpha]^{20}_D$ −86° (c 1.3, CH_3OH). Anal. Calcd for $C_6H_9O_6N$: C, 37.70; H, 4.74; N, 7.33. Found: C, 37.95; H, 4.77; N, 6.50.

Oxidation of the pure α-anomer of carbinol **12** by the above procedure gave the α-anomer of carbinol **12** that was purified by preparative TLC ($CHCl_3$/HOAc, 10:1). This anomer did not crystallize: NMR ($CDCl_3$) δ 5.55 (H-1, d, $J_{1,2}$ = 3.0), 5.28 (H-4, $J_{3,4}$ = 4.7), 5.1 (H-3, ddd, $J_{2,3}$ = 7.23 and 1.57, $J_{3,4}$ = 3.0), 3.37 (3 H, s), 2.97 (H-2α, dd, $J_{2,2}$ = 15, $J_{2,3}$ = 7.2, $J_{2,1}$ = 4.7), 2.50 (H-2β, ddd, $J_{2,2}$ = 15, $J_{2,1}$ = 4.7, $J_{2,3}$ = 1.6).

1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-3-hexulofuranose (14).[6] Diacetone glucose[28] (**13**) (5.2 g) was oxidized by the use of pyridinium chlorochromate (PCC) to give **14** (3.85 g, 77%) as a light yellow gum, which crystallized. Diacetone glucose (**13**) (30 g) was also oxidized by the Sharpless procedure to give **14** (22.2 g, 77% yield) as a white semisolid product that is a mixture of ketone **14** and its hydrate.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-nitro-α-D-allofuranose (16).[6,25] Keto sugar **14** was converted to the oxime **15** (83% yield). The oxime **15** (10.0 g) was oxidized to the nitro compound by the method of Takamoto et al.[6,20] (CH_3CN, 315 mL; 90% H_2O_2, 11.5 g; $(CF_3CO)_2O$, 55 mL; Na_2HPO_4, 146 g; urea, 1 g) at 0–5 °C to give the nitro compound **16** (9.7 g, 95% yield) as a crystalline solid, mp 112–113 °C.

3-Deoxy-1,2-*O*-isopropylidene-3-nitro-D-allofuranose (17). The protected 3-nitro sugar **16** (8.0 g) was kept at 35–40 °C in acetic acid (200 mL, 60%) for 18 h.[2] Removal of the acetic acid/water under vacuum followed by azeotroping with CH_2Cl_2 until the smell of acetic acid was gone gave a gummy product **17** (6.9 g, 95%), which was used without further purification in the next step: NMR ($CDCl_3$) δ 5.91 (1 H, d, J = 3.28), 5.11–4.89 (3 H, m), 4.06–3.59 (3 H, m), 1.55 and 1.36 (6 H, 2 s).

3-Deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-ribofuranosuronic Acid (18). A yellow-green suspension was prepared from $NaIO_4$ (15 g), water (37 mL), CCl_4 (25 mL), and $KHCO_3$ (124 mg) to which RuO_2 (150 mg) was added.[24] Crude diol **17** (2.12 g) in CH_3CN (25 mL) was added slowly at 20 °C to

(28) Schmidt, O. T. *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol. 2, pp 318–325.

this suspension at a rate to maintain the yellow-green color. The reaction was stirred for 2 h after addition was complete. The reaction mixture was extracted with $CHCl_3$ and ether; the extracts were combined, dried ($MgSO_4$), and vacuum evaporated to give a dark gummy product (1.4 g, 71%) which was pure enough to carry through the next step. It could be purified by filtration of its ether solution through a Celite pad and recrystallizing from ether hexane; white crystals, mp 86–87 °C; IR (neat) 3400, 1725, 1560, 1380 cm^{-1}; NMR ($CDCl_3$) δ 6.04 (1 H, d, J = 5.1), 5.32 (1 H, d, J = 8.25), 5.1 (2 H, m), 1.57 (3 H, s), 1.38 (3 H, s). Anal. Calcd for $C_8H_{11}O_7N$: C, 41.20; H, 4.72; N, 6.00. Found: C, 41.25, H, 4.99; N, 5.91. Interruption of the oxidation after 1 h gave aldehyde **22** (mixed with its hydrate); NMR ($CDCl_3$) δ 9.82 (1 H, s), 5.94 (1 H, br d, $J_{1,2}$ = 3.5), 5.1–5.0 (2 H, m), 4.89 (1 H, dd, $J_{2,1}$ and $J_{2,3}$ = 5), 1.56 (3 H, s), 1.36 (3 H, s).

Methyl 3-Deoxy-3-nitro-β-D-ribofuranosiduronic Acid Methyl Ester (19a). Crude acid **18** (1.1 g) in CH_3OH (50 mL, almost black solution) was refluxed for 48 h with strong acid ion exchange resin (Dowex-50, H^+ form). The resin was removed by filtration and washed with CH_3OH and the filtrate and washings were evaporated (vacuum) to give crude **19a** (0.83 g, 80% dark green solid), which was decolorized by dissolving in ether, filtering through a Celite pad, and reevaporating: IR (neat) 3400, 1750, 1560 cm^{-1}; NMR ($CDCl_3$) δ 5.53 (1 H, dd, J = 5.82, 5.48), 5.40 (1 H, d, J = 5.06), 5.02 (1 H, s), 4.61 (1 H, d, J = 5.22), 3.89 (3 H, s), 3.40 (3 H, s). Under these conditions of extended reflux with acid catalyst, only β-anomer was detected; if the α-anomer is present, it is to the extent of less than 5%.

Methyl 2,3-Dideoxy-3-nitro-β-D-*erythro*-pentofuranosiduronic Acid Methyl Ester (21). To 2-hydroxy-3-nitro ester **19a** (378 mg, 1.7 mmol) in $CHCl_3$ (16 mL) and Et_3N (800 mg, 7.9 mmol) was added methanesulfonyl chloride (750 mg, 6.5 mmol) over 10–15 min at 20–30 °C. After stirring 1 h, water was adeed and vigorous stirring continued for 30 min. The $CHCl_3$ layer and CH_2Cl_2 extracts of the aqueous layer were washed (1% HCl, saturated $NaHCO_3$, saturated NaCl, 5 °C) and dried ($MgSO_4$), and the solvent was evaporated (ultimately to 1 mm torr for several h) to give gummy nitro olefin **20** (306 mg, 90%): IR (neat) 1760, 1565, 1540, 1375 cm^{-1}; NMR ($CDCl_3$) δ 6.98 (1 H, dd, J = 1.33, 1.53), 5.95 (1 H, t, J = 1.07, 1.16), 5.40 (1 H, t, J = 1.30, 1.43, 3.83 (3 H, s), 3.50 (3 H, s). This crude nitro olefin **20**, suspended in water (12 mL) and just enough CH_3OH added to dissolve it, was added to a solution of $NaBH_4$ (120 mg), in dilute NaOH (12 mL, 0.3%) at 0 °C. Enough methanol was again added to dissolve any precipitate. After 2 h, the mixture was acidified (6 N HCl to pH 2–3) and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated (ultimately to 1 mm torr for several h) to give the reductive elimination product **21** as a clear viscous oil (252 mg, 84%): IR (neat) 1745, 1565 cm^{-1}; NMR ($CDCl_3$) δ 5.60 (1 H, m), 5.26 (1 H, d, J = 5.2), 5.15 (1 H, d, J = 3.3), 3.83 (3 H, s), 3.38 (3 H, s), 2.79 (1 H, m), 2.52 (1 H, m).

Methyl 2,3-Dideoxy-3-nitro-β-D-*erythro*-pentofuranosiduronic Acid (2). Crude ester **21** (40 mg) was dissolved in ethanol (0.5 mL) and 10% NaOH (5 mL) at 20 °C and stirred (1 h). The mixture was acidified (6 N HCl at 0 °C to pH 2–3), saturated with NaCl, and extracted with CH_2Cl_2. The dried ($MgSO_4$) extracts were evaporated (ultimately to high vacuum for several hours) to give an oil (26.3 mg, 71%) which, in this form, gave IR and NMR spectra identical with those obtained for **2** prepared by the previously described route from D-xylose or from D-glyceraldehyde.[4]

Methyl 3-Deoxy-3-nitro-β-D-ribofuranosid(1,4)dialdose 5,5-Dimethyl Acetal (23). Aldehyde **22** (1.0 g) dissolved in absolute methanol (40 mL) was treated with Dowex 50W-8X resin, H^+ form (3 g), and the mixture refluxed for 42 h. Filtration and vacuum concentration gave the dimethyl acetal **23** as a gum (0.922 g, 92%): NMR ($CDCl_3$) δ 5.13 (1 H, t, J = 5.6 Hz), 4.96 (1 H, s), 4.88 (1 H, t, J = 6.33 Hz), 4.52 (1 H, d, J = 6.23 Hz), 4.33 (1 H, d, J = 6.36 Hz), 4.49 (3 H, s), 3.45 (3 H, s), 3.41 (3 H, s).

Methyl 2,3-Dideoxy-3-nitro-β-D-ribofuranosid(1,4)dialdose 5,5-Dimethyl Acetal (25). To alcohol **23** (0.508 g) dissolved in $CHCl_3$ (7 mL) containing triethylamine (1.0 g) was gradually added methanesulfonyl choride (0.95). After stirring (1 h, 20 °C), water (15 mL) was added and stirring continued (0.5 h). The $CHCl_3$ layer and CH_2Cl_2 extracts of the aqueous layer were washed (1% HCl, saturated $NaHCO_3$, saturated NaCl, 5 °C) and dried ($MgSO_4$) and the extracts concentrated (vacuum) to give crude olefin **24** as a brown gum (430 mg, 84%): NMR ($CDCl_3$) δ 6.78 (1 H, d, J = 0.8 Hz), 5.78 (1 H, d, J = 0.7 Hz), 5.12 (1 H, dd, J = 0.90, 4.41 Hz), 4.55 (1 H, dd, J = 0.70, 4.23 Hz), 3.53 (3 H, s), 3.48 (3 H, s), 3.44 (3 H, s).

A solution of $NaBH_4$ (210 mg in 15 mL of water to which was added 3 dropsof 1% NaOH) was added dropwise to nitro olefin **24** (429 mg) in CH_3OH (1 mL) and water (15 mL) at 0 °C. After 1 h the mixture was acidified (6 N HCl) to pH 2 and extracted with CH_2Cl_2 (2 × 75 mL). The extracts, on washing, drying, and evaporating, yielded an oil (321 mg, 74%) which was purified by flash chromatography (45 g silica gel; $CHCl_3/C_6H_{14}$, 3:1) to give an oil (129 mg): NMR ($CDCl_3$) δ 5.22 (1 H, dd, J = 2.0, 5.2 Hz), 5.12 (1 H, m), 4.60 (1 H, dd, J = 3.9, 7.0 Hz), 4.35 (1 H, d, J = 7.0 Hz), 3.44 (3 H, s), 3.43 (3 H, s), 3.39 (3 H, s), 2.75 (1 H, m), 2.48 (1 H, m). Anal. Calcd for $C_8H_{15}O_6N$: C, 43.43; H, 6.84; N, 6.33. Found: C, 43.45; H, 6.96; N, 6.33.

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Registry No. **2** (β-anomer), 102342-35-8; **2** (α-anomer), 102342-36-9; **4**, 20031-21-4; **5**, 6022-96-4; **6**, 6698-46-0; **7** (isomer 1), 102419-23-8; **7** (isomer 2), 102419-24-9; **8** (xylo isomer), 34304-34-2; **8** (ribo isomer), 34304-33-1; **9a** (β-anomer), 102342-27-8; **9a** (α-anomer), 102342-28-9; **9b**, 102342-31-4; **9c**, 102342-29-0; **10**, 102419-25-0; **11** (β-anomer), 102342-30-3; **11** (α-anomer), 102342-32-5; **12** (β-anomer), 102342-33-6; **12** (α-anomer), 102342-34-7; **13**, 582-52-5; **14**, 2847-00-9; **15**, 10578-95-7; **16**, 34304-35-3; **17**, 42776-36-3; **18**, 102342-37-0; **19a**, 102342-38-1; **20**, 102342-39-2; **21**, 102342-40-5; **22**, 102342-41-6; **23**, 102342-42-7; **24**, 102342-43-8; **25**, 102342-44-9.