on a dry column chromatograph (1.5 × 36 cm) and developed as follows: toluene–ethyl acetate 200:10 mL, 100:10 mL. The appropriate fraction containing the R_f 0.58 and R_f 0.32 spots were pooled and evaporated. (Handling of these iodo compounds beyond this point must be carried out in very dimly lighted rooms, otherwise decomposition becomes pronounced.)

The pooled concentrated R_f 0.58 fractions left a syrup, which was dissolved in ethanol by warming. On cooling, needles of **18** separated, mp 101–103 °C.

Anal. Calcd for $C_{11}H_{16}I_2O_6$: C, 26.52; H, 3.24; I, 50.96. Found: C, 26.71; H, 3.39; I, 50.87.

The pooled concentrated R_f 0.32 fractions left a syrup which was dissolved in ethanol by warming. On cooling, platelets of **17** separated, mp 84–85 °C.

Anal. Calcd for $C_9H_{13}IO_5$: C, 32.92; H, 3.99; I, 38.68. Found: C, 33.12; H, 3.98; I, 38.26.

Reaction of 5 with base: 2.02, 50, 17, W, 4, X. Evaporation of the extract gave a crystalline solid, mp 71–78 °C. Recrystallization gave an analytical sample of **19**, mp 81–83 °C. Mass spectrum shows a strong (m/e $-OCH_3$) peak 223.

Anal. Calcd for $C_8H_{14}O_7S$: C, 37.79; H, 5.55. Found: C, 37.60; H, 5.65.

Methyl 2,3-Anhydro-4-*O*-benzoyl-6-*O*-mesyl-α-D-allopyranoside (19-Bz). Compound **19** (128 mg) was dissolved in pyridine (2 mL) and cooled to −20 °C, benzoyl chloride (0.1 mL) was added and the reaction mixture was stored for 18 h at −20 °C and 24 h at 5 °C. On the addition of water (3 mL), a solid separated and was removed by filtration. Recrystallization from ethanol (5 mL) gave the benzoate ester **19-Bz**, mp 157–158 °C. Mass spectrum shows a strong (m/e − OCH_3) peak 327.

Reaction of 19 with base: 0.141, 0, 25 (0.04 N), R, 18, DCC 1.5 × 17 cm ethyl acetate. Evaporation gave crystalline **13**, mp 106–108 °C.

Reaction of 6 with base: 4.2, 100, 40, W, 4-18, X or DCC. The ratio of **16**/**20** will depend on the length of heating and time of reaction. For example, 1 h of refluxing will yield only the dianhydrohexoside **16**. If the reaction is neutralized too quickly, small quantities of methyl 4,6-di-*O*-mesyl-α-D-glucopyranoside can be detected. A 4-h room-temperature reaction on evaporation gave a tacky solid, which was crystallized from ethanol (7 mL)–ether (7 mL) to give 1.23 g of product, mp 98–104 °C. A subsequent crystallization gave 1.12 g, mp 100–104 °C. TLC on this product (toluene–ethyl acetate 1:2 v/v) revealed a major spot R_f 0.38 (**20**) and minor spot R_f 0.14 (methyl 4,6-di-*O*-mesyl-α-D-glucopyranoside). Applying 218 mg to a dry column chromatograph (1.5 × 17 cm) and developing with toluene–ethyl acetate 1:2 v/v eluted the R_f 0.38 spot. Evaporation of the pooled fractions gave a syrup, which on standing crystallized: 155 mg, mp 114–115 °C.

Anal. Calcd for $C_8H_{14}O_7S$: C, 37.79; H, 5.55. Found: C, 37.61; H, 5.60.

Developing the column with ethyl acetate–methanol 15:1 v/v eluted 56 mg of R_f 0.14 spot.

Reaction of 20 with base: 0.20, 0, 25 (0.1 N), R, 5, DCC 1.5 × 15 cm, toluene–ethyl acetate 1:2 v/v. Evaporation gave crystalline **16**, mp 57–59 °C.

Acknowledgment. To Clara E. Johnson for microchemical analyses, Larry W. Tjarks for NMR data, and Dr. W. K. Rohwedder for mass spectral data.

Registry No. **1**, 22860-24-8; **2**, 70941-12-7; **3**, 14257-63-7; **4**, 29781-02-0; **5**, 70941-13-8; **6**, 22435-33-2; **7**, 70941-14-9; **8**, 70941-15-0; **8** (6-Ac), 70941-16-1; **8** (6-Bz), 70941-17-2; **9**, 70941-18-3; **9** (6-Bz), 70941-19-4; **11**, 10226-98-9; **12**, 70941-20-7; **12** (4-Ac), 70941-21-8; **13**, 13407-60-8; **14**, 29411-58-3; **15**, 70941-22-9; **16**, 70941-23-0; **17**, 70941-24-1; **18**, 70941-25-2; **19**, 70941-26-3; **19** (4-Bz), 70941-27-4; **20**, 70941-28-5; methyl 3-*O*-benzoyl-2,4,6-tri-*O*-mesyl-α-D-glucopyranoside, 61252-79-7; methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-mesyl-α-D-glucopyranoside, 28538-15-0; methyl 2-*O*-benzoyl-3-*O*-mesyl-α-D-glucopyranoside·pyridine, 70941-30-9; methyl 3,6-anhydro-α-D-galactopyranoside, 5540-31-8; methyl 4,6-di-*O*-mesyl-α-D-glucopyranoside, 70941-31-0.

Synthesis of Seven- and Eight-Carbon Sugar Derivatives from 2,3:5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone and Preparation of a New Anhydro Sugar[1]

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2,3:5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone (**1**) was condensed with ethyl bromoacetate in the presence of zinc to give the expected Reformatsky product, ethyl 2-deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosonate (**2**). Treatment of **2** with methanol and an acid ion-exchange resin afforded the completely blocked methyl α-glycoside **3**, the methyl 4,5-*O*-isopropylidene α-glycoside **4**, and a 3,8-anhydro sugar **5**. Proof of the structure of **5** was based upon NMR spectroscopy and periodate oxidation. The main product, **4**, was converted to the 7,8-di-*O*-benzoate **6** and 7,8-di-*O*-methanesulfonate **7**. Sodium iodide elimination of the latter yielded the 7,8-olefinic glycoside **8**. Glycoside **4** was reduced with calcium borohydride to give methyl 2-deoxy-4,5-*O*-isopropylidene-α-D-*gulo*-3-octulofuranoside (**9**). Treatment of **4** with sodium metaperiodate gave the 7-aldehydo derivative **10** which was reduced with Raney nickel to give the seven-carbon sugar. Tosylation of the primary hydroxyl group gave the 7-*O*-tosylate **12**.

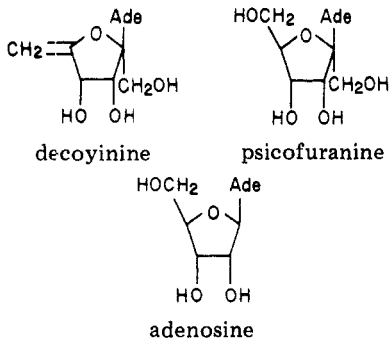
Decoyinine and psicofuranine are nucleoside antibiotics[2] differing from each other only in the unsaturation of the former at the terminal position (Chart I). Psicofuranine is closely related to adenosine except for a hydroxymethyl group that occupies the position on the anomeric carbon atom normally occupied by the hydrogen atom. The biochemical role of the hydroxymethyl group has not been elucidated. At the very minimum it can be presumed that it provides an additional site for hydrogen bonding to an enzyme. As part of a program of synthesis of decoyinine analogues and in order to explore the biological effect of a change in structure at the anomeric carbon atom, a route was sought to replace the hydroxymethyl group with a

(1) This work was supported by Grant No. CA 13802 from the National Cancer Institute, National Institutes of Health.

(2) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, 1970.

0022-3263/79/1944-3368$01.00/0

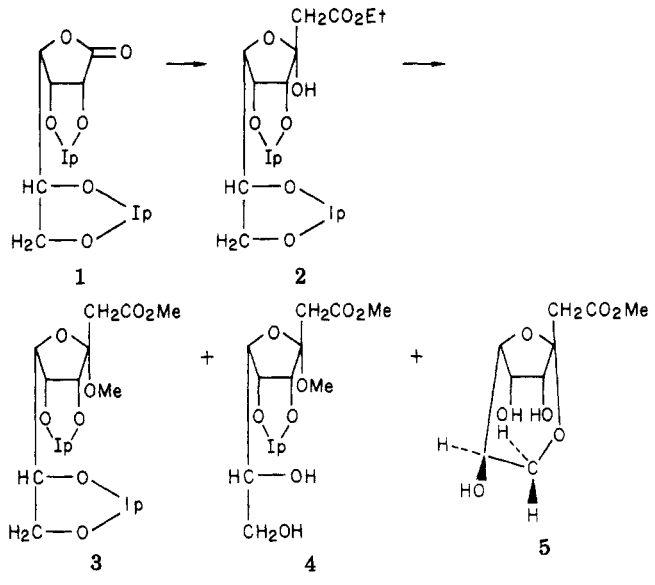
Chart I



1-hydroxyethyl group (CH_2CH_2OH). The preparation of a suitable sugar derivative was required as a precursor, and its synthesis is the subject of this paper.

The most direct means of inserting a two-carbon fragment on a sugar so as to create a 3-ketose having a furanose ring is simply to react a sugar 1,4-lactone with a suitable two-carbon fragment. The lactones are ideal starting materials because they have the desired five-membered ring, and many derivatives of the acetal and ketal type are known compounds. The blocking groups are excellent ones to use with most carbanionic reagents. The reaction of sugar lactones with carbanionic reagents has not been extensively studied.[3] Of the reactions available that would afford a product closest in structure to the desired one, the classical Reformatsky reaction seemed the most suitable. Zhdanov and co-workers[4] had already performed the condensation of ethyl bromoacetate with 2,3:5,6-di-O-cyclohexylidene-D-mannono-1,4-lactone in the presence of zinc and obtained ethyl 4,5:7,8-di-O-cyclohexylidene-2-deoxy-β-D-*manno*-3-octulofuranosonate. In our case, the ring hydroxyl groups had to have the D-*erythro* configuration. It was desirable that the product be of one configuration at the newly formed anomeric position at C-3. Therefore, as much steric bulk as possible had to be on one side of the lactone ring so that the nucleophile would attack from the opposite side. In looking ahead several steps to nucleoside synthesis, we found it desirable to insert a good leaving group prior to coupling of the base to the sugar.[5] Of the commercially available aldono-1,4-lactones, the most suitable one appeared to be D-gulono-1,4-lactone. The diisopropylidene derivative[6] is easily obtained, and both groups are on the same side of the ring. The isopropylidene group outside the furanose ring is usually much more labile to acid and can be selectively removed. Therefore, the use of hexono-1,4-lactones enables the formation of new derivatives of eight-carbon sugars and of seven-carbon sugars after cleavage of the terminal carbon with periodate or lead tetraacetate. This should make possible the synthesis of some very interesting seven-carbon and eight-carbon analogues of psicofuranine in the future. In contrast, D-ribono-1,4-lactone requires more extensive blocking procedures to completely protect the molecule, has the terminal hydroxymethyl group in a less desirable configuration, and would yield only seven-carbon ketose derivatives.

Scheme I[a]



[a] Ip = $(CH_3)_2C$.

Condensation of 2,3:5,6-di-O-isopropylidene-D-gulono-1,4-lactone (**1**) with ethyl bromoacetate in the presence of zinc dust (Reformatsky reaction) gave, after column chromatography, a 50% yield of the desired product, ethyl 2-deoxy-4,5:7,8-di-O-isopropylidene-α-D-*gulo*-3-octulofuranosonate (**2**), as a crystalline material (Scheme I). The NMR spectrum supported the assigned structure. The one-proton peak at δ 4.80 was exchangeable with D_2O and was assigned to the anomeric hydroxyl group. The α configuration of this group was assigned because the peak at δ 2.86, corresponding to the protons on C-2, was a singlet. Ulose sugars having a group of the type CH_2X will generally exhibit a singlet for the CH_2 group when it is on the side of the furanose ring opposite the ring hydroxyl groups; otherwise the peak appears as what is variably described as two doublets or a multiplet.[4,7,8] The singlet would be observed because the methylene protons are free to rotate and would appear equivalent. In contrast, the methylene group on the same side of the ring as the isopropylidene group would have a restricted rotation and would appear as two doublets or a more complex multiplet because the two protons would be in different environments.

Treatment of **2** with methanol in the presence of a strong acid ion-exchange resin afforded a mixture of three products which were separated by column chromatography on silica gel. The first substance eluted from the column was identified as methyl (methyl 2-deoxy-4,5:7,8-di-O-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate (**3**), the second as methyl (methyl 2-deoxy-4,5-O-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate (**4**), and the third as methyl 3,8-anhydro-2-deoxy-α-D-*gulo*-3-octulofuranosonate (**5**). Zhdanov and co-workers[4] had also reported some hydrolysis of the blocking group at the 7,8 position and attributed this to traces of water in the methanol. This is probably correct in part, but we tend to think that water trapped in the resin, despite several washings with methanol, was in large part responsible for this hydrolysis.[9]

(3) For some examples see: H. Ogura, H. Takahashi, and T. Itoh, *J. Org. Chem.*, **37**, 72 (1972); A. M. Sepulchre, A. Gateau-Olesker, G. Lucas, G. Vass, and S. D. Gero, *Tetrahedron Lett.*, 3945 (1972); H. Ogura and H. Takahashi, *Synth. Commun.*, **3**, 135 (1973); Yu. A. Zhdanov, G. V. Bogdanova, and O. Yu. Riabuchina, *Carbohydr. Res.*, **29**, 274 (1973); A. Kampf and E. Dimant, *ibid.*, **32**, 380 (1974); H. Ogura, K. Furuhata, H. Takahashi, and Y. Iitaka, *Chem. Pharm. Bull.*, **26**, 2782 (1978).

(4) Yu. A. Zhdanov, Yu. E. Alexeev, and Ch. A. Khourdanov, *Carbohydr. Res.*, **14**, 422 (1970); *Zh. Obshch. Khim.*, **42**, 2776 (1972).

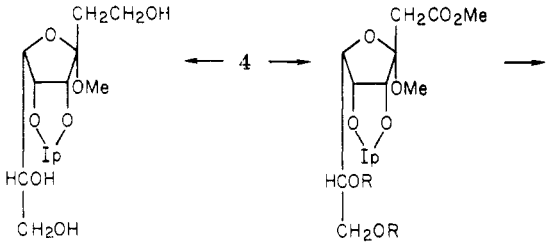
(5) Details concerning the reasons for this approach have been discussed: L. M. Lerner, *Carbohydr. Res.*, **53**, 177 (1977).

(6) L. M. Lerner, B. D. Kohn, and P. Kohn, *J. Org. Chem.*, **33**, 1780 (1968).

(7) R. S. Tipson and R. F. Brady, Jr., *Carbohydr. Res.*, **10**, 549 (1969).

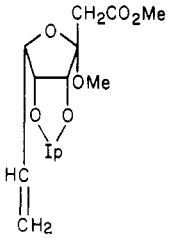
(8) S. J. Angyal, C. L. Bodkin, J. A. Mills, and P. M. Pojer, *Aust. J. Chem.*, **30**, 1259 (1977).

Scheme II



9

6, R = benzoyl
7, R = methanesulfonyl



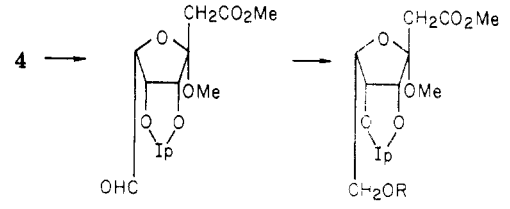
8

As it turned out, the results were serendipitous since the partially hydrolyzed product **4** was the substance needed in order to prepare the desired seven-carbon sugar, as described below. Compound **4** was obtained in 54% yield as crystals, whereas **3** and **5** were isolated in only 4.6 and 3.2%, respectively. At first **5** was believed to be the free, reducing, eight-carbon ketose, but its identity has been established as the anhydro sugar, as shown later on.

The NMR spectra of **3** and **4** confirmed their structures. The ethoxyl group at C-1 of **2** was exchanged for a methoxyl group and appeared as singlets at δ 3.70 in **3** and at δ 3.74 in **4**. The isopropylidene groups of **3** each appeared as a six-proton peak at δ 1.42 and 1.30, whereas the isopropylidene peak of **4** integrated for six protons and had one-proton hydroxyl peaks at δ 3.74 and 2.74 which were identified by exchange with D_2O. Degradation of **4** to the seven-carbon sugar, as described below, further established the position of the remaining isopropylidene group. The methyl glycoside peaks of **3** (δ 3.26) and **4** (δ 3.23) were typical singlets. The α configuration was concluded in both compounds because the methylene protons at C-2 again appeared as singlets, δ 3.03 in **3** and δ 3.01 in **4**. These assignments are in agreement with previous assignments of anomeric configuration of methyl glycosides of ketose sugars made from NMR data.[4,7,8] Zhdanov et al.[4] had reported that when the NMR spectra of their glycoside was obtained in benzene, the methyl ester peak was shifted dramatically, whereas the methyl glycoside peak was only slightly affected. When the spectrum of **4** was repeated in benzene there was also a large shift of the methoxyl ester peak from δ 3.74 in chloroform to δ 3.37 in benzene; the methyl glycoside peak moved only slightly. This behavior has been ascribed to the screening effect of the ketal blocking group on the glycoside methoxyl group which prevents the latter's interaction with benzene.[4] In contrast, the exposed ester interacts readily. This kind of data tends to support the assignment of the anomeric configuration of **4**.

It is interesting to note that the optical rotations of **2**, **3**, and **4** are negative values. Most α-D glycosides of aldoses and ketoses have positive optical rotations. However, according to Hudson's isorotation rules, the α-D anomer should only have the more positive value when compared to the β-D form. Therefore, without the availability of the other anomer, optical rotation data is not helpful. It is of interest that ethyl 4,5:7,8-di-*O*-cyclohexylidene-2-deoxy-β-D-*manno*-3-octulofuranosonate[4] and its methyl glycoside had positive rotations rather than negative values.

Scheme III



10

11, R = H
12, R = Ts

Benzoylation of **4** afforded the 7,8-di-*O*-benzoate **6** (Scheme II), a compound that will be utilized to prepare other eight-carbon ketose derivatives, including some new nucleosides. Treatment of **4** with methanesulfonyl chloride gave the 7,8-di-*O*-methanesulfonate **7**. This derivative will be useful for the conversion of furanose glycosides to terminal deoxy sugars,[10] the inversion of configuration at C-7,[11] or the preparation of unsaturated derivatives.[12] As an example of the latter, **7** was treated with sodium iodide in boiling 2-butanone to obtain the olefinic glycoside **8**. The NMR spectrum of **8** had an octet for H-7 centered at δ 6.06 and an AB pattern at δ 5.53 and 5.24 for the protons at C-8.

A major goal of this work was the reduction of C-1 to a hydroxymethyl group. Usually this can be accomplished by treatment of an ester with lithium aluminum hydride or a similar reducing agent.[13] However, treatment of **4** with lithium aluminum hydride failed to provide the desired product **9**, except possibly as one component of a very complex mixture of products. A similar result occurred with lithium triethylborohydride.[14] Recently, Daluge and Vince[15] experienced difficulty in the reduction of methyl *cis*-4-acetamidocyclopent-2-enecarboxylate to the corresponding alcohol with the usual reagents. They solved their problem with calcium borohydride and touted the advantages of this reagent. Treatment of **4** with calcium borohydride gave an 82% yield of crystalline methyl 2-deoxy-4,5-*O*-isopropylidene-α-D-*gulo*-3-octulofuranoside (**9**). The NMR spectrum showed that no carboxylate was present, and the singlet previously at δ 3.01 had been converted to a sextet at δ 2.23, indicative of coupling of the methylene protons at C-2 with the methylene protons at C-1. Moreover, a new methylene group (C-1) appeared buried in a complex multiplet at δ 3.93–3.73 that also contained the protons at C-6 and C-7. This procedure should find future use in the reduction of other related Reformatsky type products as well as the reduction of other carboxylates reported in this paper.

When the monoisopropylidene derivative **4** was treated with sodium metaperiodate, the 7-aldehydo derivative **10** was obtained (Scheme III). Reduction of the aldehyde with Raney nickel provided methyl (methyl 2-deoxy-4,5-*O*-isopropylidene-β-L-*lyxo*-3-heptulofuranosid)onate

(9) Recent experiments not related to the present study revealed that many more equilibrations with methanol are required to assure removal of most of the water.

(10) L. M. Lerner, *Carbohydr. Res.*, 36, 392 (1974).
(11) M. E. Evans and F. W. Parrish, *Carbohydr. Res.*, 28, 359 (1973); L. M. Lerner, *J. Org. Chem.*, 41, 306 (1976).
(12) L. M. Lerner, *Carbohydr. Res.*, 44, 13 (1975); *J. Org. Chem.*, 43, 2469 (1978).
(13) M. N. Rerick in "Reduction. Techniques and Applications in Organic Syntheis", R. L. Augustine, Ed., Marcel Dekker, New York, 1968, p 1.
(14) Marketed under the name Super Hydride by Aldrich Chemical Co., as a molar solution in tetrahydrofuran.
(15) S. Daluge and R. Vince, *J. Org. Chem.*, 43, 2311 (1978).

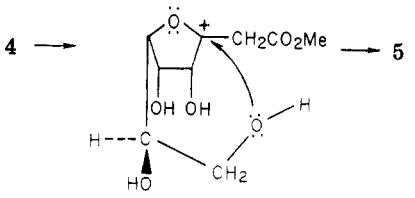
(11), which could not be induced to crystallize. The elemental analysis and NMR spectrum supported the identity of this compound. A crystalline derivative (12), which may be of value for the preparation of halo sugars and unsaturated enolic sugars, was prepared by treatment of 11 with *p*-toluenesulfonyl chloride. Most of these octulose and heptulose derivatives, whose syntheses are currently being scaled up, will be utilized for the synthesis of new nucleosides, and 12 should provide an excellent precursor to a decoyinine analogue.

When the anhydro sugar 5 was first isolated, it was thought to be the methyl glycofuranoside because of its failure to give a typical Benedict's test. However, the glycoside methoxyl group was not present in the NMR spectrum. Treatment of a sample of 4 with methanol in the presence of the acid ion-exchange resin for 40 h afforded a 99% yield of the same product (5). Treatment of 5 with acetic anhydride in pyridine gave a crystalline tri-O-acetate (13) as determined by elemental analysis and integration of the acetate methyl groups by NMR spectroscopy. Similarly, the tri-O-benzoate 14 was prepared, and it too integrated for three phenyl groups. Comparison of the NMR spectra of 5, 13, and 14 supports the assignment of the 3,8-anhydrofuranose ring to these compounds. The signals at H-4, H-5, and H-7 all appear at lower field in 13 than in 5, whereas those at H-6, H-8_{endo}, and H-8_{exo} remain in approximately the same position. A similar set of data for the comparison of 14 to 5 also showed that the same signals had moved to lower field. Therefore, since the two-proton signal for the methylene group at C-8 and the one-proton signal for C-6 did not move to lower field, the anhydro bond could not be in a 3,7 link. It was unlikely that 5 was in the pyranose form because the coupling constants $J_{4,5}$ and $J_{5,6}$ would be expected to be between 9.0 and 9.9 Hz,[16,17] whereas they are actually 7.2 and 5.2 Hz, respectively. The coupling constants for 13 ($J_{4,5}$ = 7.2 Hz, $J_{5,6}$ = 5.2 Hz, and $J_{6,7}$ = 4.2 Hz) are typical of the kinds of values[16] found for the corresponding positions in 1,6-anhydrofuranose triacetates when the furanose ring protons are cis oriented.[17,18] All of these values would be significantly lower if these protons were trans,[16] indicating that no change in configuration had occurred during the transformations.

Confirmatory evidence for the structure of 5 was sought by periodate oxidation. One mole of periodate was consumed in less than 5 min,[19] indicating that the ring had to be in the furanose form with cis hydroxyl groups at C-4 and C-5. Trans-oriented hydroxyl groups of 1,6-anhydrohexofuranoses are completely resistant to oxidation.[16]

The formation of the anhydro sugar 5 under the conditions described seemed rather strange, particularly since we have used these conditions before to remove isopropylidene groups from methyl glycosides. No clue to this behavior could be found in the literature. Most 1,6-anhydrohexofuranoses are formed as minor products after treatment of sugars or polysaccharides with hot aqueous acid. The preparation[18] of 1,6-anhydro-α-L-gulofuranose offered no clue since it was formed from the D-*manno* isomer by inversion of configuration at C-5. We decided to repeat the methanolysis on some derivatives of D-gulose previously prepared in this laboratory. Since 5 was synthesized from D-gulono-1,4-lactone, the structure from carbons 3 to 8 is identical with D-gulose. When 2,3:5,6-di-O-isopropylidene-D-gulofuranose[6] or methyl 2,3-O-isopropylidene-β-D-gulofuranoside[20] were heated in a mixture of methanol and the acidic ion-exchange resin under the exact same conditions as 4, the anomeric α,β mixtures of methyl gulofuranosides were obtained in quantitative yields. The NMR spectra had peaks at δ 3.56 and 3.46 in a ratio of 7:3 (β:α). Acetylation of these glycosidic mixtures gave the syrupy glycoside acetates for which the NMR spectra showed four acetyl methyl groups by integration. It can be concluded that the formation of the anhydro sugar is not inherent to the gulofuranoside structure. The methyl acetate group of 4 (carbons 1 and 2) should be highly electron-withdrawing and must play an important role. Since the methoxyl group at C-3 is on the same side of the furanose ring as the oxygen at C-8, the usual mechanism[16] showing the direct displacement of this group cannot be applicable. The mechanism must require the formation of a carbonium ion at C-3 due to activation by the methyl acetate group and stabilized by the ring oxygen (Scheme IV). The incoming oxygen on C-8 would then attack C-3 from the same side of the ring previously occupied by the methoxyl group, forming 5. The easy formation of the carbonium ion would explain why the molecule did not rearrange to form the pyranose ring.

Scheme IV



Experimental Section

General Methods. Elemental analyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. NMR spectra were obtained on a Varian T-60A spectrometer with Me_4Si as the internal reference, except for spectra recorded in D_2O where the ester methoxyl peak was used as reference. IR spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter and a Kofler micro hot stage was used to determine melting points as corrected values. TLC was performed on silica gel HF plates (E. Merck, Darmstadt) of 0.25-mm thickness prepared with Desaga equipment. Spots were developed by spraying the plates with a solution of 10% concentrated sulfuric acid in ethanol and heating in an oven at 140 °C. Preparative TLC was performed on silica gel GF plates, 1 mm in thickness and 20 cm × 20 cm in dimensions. Silica gel column chromatography was run with Baker No. 3404 silica gel, 40–140 mesh. Evaporation of solvents was performed with a rotary evaporator at a bath temperature of 40–50 °C. Moist organic solutions of compounds were dried over anhydrous magnesium sulfate or sodium sulfate. Dioxane was dried by distillation from sodium hydroxide pellets, and tetrahydrofuran was dried over molecular sieve 4A and distilled. Ethyl bromoacetate was purchased from Aldrich Chemical Co. and was used without any special purification. Unless otherwise stated, the petroleum ether used was the 60–110 °C fraction. All chloroform contained 0.75% ethanol.

Periodate consumption of compound 5 was determined by the procedure of Rammler and Rabinowitz.[21]

(16) M. Cerny and J. Stanek, Jr., *Adv. Carbohydr. Chem. Biochem.*, 34, 24 (1977).

(17) The *J* values reported in ref 16 are for the 1,6-anhydrohexofuranoses, where C-1 is the anomeric carbon rather than C-3 as in our case.

(18) Coupling constants reported for 2,3,5-tri-O-acetyl-1,6-anhydro-α-L-gulofuranose are $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 5.5 Hz, and $J_{4,5}$ = 3.5 Hz: K. Heyns, P. Köll, and H. Paulsen, *Chem. Ber.*, **104**, 830 (1971).

(19) If 5 was allowed to continue standing in an excess of periodate, it very slowly consumed an additional 0.45 mol of periodate over 68 h. A similar case of overoxidation of 2,7-anhydroheptulofuranose by lead tetraacetate has been reported: L. C. Stewart, E. Zissis, and N. K. Richtmyer, *J. Org. Chem.*, **28**, 1842 (1963).

(20) L. M. Lerner, *J. Org. Chem.*, **40**, 2400 (1975).

Ethyl 2-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosonate (2). A three-neck flask was dried in an oven and allowed to cool to room temperature while a stream of dry nitrogen was passed through. The flask was set up with an overhead stirrer (mercury seal), a condenser through which nitrogen was passed, and a side-arm addition funnel. The flask was charged with 2.7 g of activated zinc dust[22] and a solution containing 4 g (15.5 mmol) of 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone[6] and 7.2 g (43 mmol) of ethyl bromoacetate in 30 mL of dry dioxane was placed in the addition funnel. A few milliliters of this mixture was added to the zinc, and the reaction was initiated by addition of a crystal of iodine. The mixture was stirred and heated at 45–50 °C until it began to turn green. The rest of the solution was added dropwise from the funnel, and heating was continued for 3 h. The reaction mixture was cooled to room temperature and diluted with 40 mL of water, and the solvents were evaporated. The solid residue was triturated with a solution of 10% acetic acid in ethyl ether (5 × 30 mL), and the ether layer was separated from some residual water. The combined ether extracts were dried and evaporated to a syrup weighing 3.8 g. TLC with 9:1 chloroform–methanol as the solvent system revealed a major product with R_f 0.71 and three slower moving minor products. Chromatography on a column (52 × 1.8 cm) of silica gel with the same solvent system enabled the separation of the major component, 2.69 g (50% yield), as a syrup which crystallized from a mixture of chloroform and petroleum ether after storage in a freezer for 4 weeks: mp 39–40.5 °C; $[\alpha]^{22}D$ −12.7° (*c* 1.04, $CHCl_3$); NMR (chloroform-*d*) δ 4.80 (s, 1 H, OH), 4.74–4.50 (m, 4 H, H-4, H-5, and CH_2CH_3), 4.23 (m, 3 H, H-7, H-8a, H-8b), 3.70 (m, 1 H, H-6), 2.86 (s, 2 H, CH_2CO_2Et), 1.43 (s, 6 H, *gem*-dimethyl), 1.38–1.27 (m, 9 H, CH_2CH_3 and *gem*-dimethyl).

Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.76; H, 7.26.

Methanolysis of 2. Amberlite IR-120 (H^+ form) cation-exchange resin was equilibrated under methanol with occasional stirring. The methanol was decanted, the process repeated twice, and the resin freed of solvent on a glass filter funnel using suction. A mixture containing 5 g (14.4 mmol) of **2**, 4 g of the resin, and 100 mL of methanol was heated at 38–40 °C with stirring for 48 h. TLC, with 9:1 chloroform–methanol as the solvent system, revealed three products. The resin was removed by filtration, and the methanol was evaporated. The syrup was fractionated on a column (52 × 1.8 cm) of silica gel with 9:1 chloroform–methanol. The fractions having identical R_f values were combined, and the solvents were evaporated.

Methyl (Methyl 2-deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate (3). The first fraction from the above procedure gave a syrup (310 mg) that crystallized from chloroform–petroleum ether to yield 230 mg (4.6%) of product, mp 94–95 °C. Sublimation (90–95 °C, 1 mmHg) gave needles: mp 96–97 °C; $[\alpha]^{21}D$ −46.2° (*c* 0.75, $CHCl_3$); NMR (chloroform-*d*) δ 4.68 (d, 2 H, H-4, H-5), 4.26 (m, 4 H, H-6, H-7, H-8a, H-8b), 3.70 (s, 3 H, CO_2CH_3), 3.26 (s, 3 H, OCH_3), 3.03 (s, 2 H, $CH_2CO_2CH_3$), 1.42 and 1.30 (d, 6 H each, *gem*-dimethyl).

Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.65; H, 8.06.

Methyl (Methyl 2-deoxy-4,5-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate (4). The syrup (2.6 g) obtained from the second fraction was crystallized from a mixture of chloroform and petroleum ether (bp 30–65 °C) to afford fine needles weighing 2.4 g (54%): mp 97.5–98.5 °C; $[\alpha]^{22}D$ −66.5° (*c* 0.72, $CHCl_3$); NMR (chloroform-*d*) δ 4.74 (m, 2 H, H-4, H-5), 4.17–3.82 (m, 4 H, H-6, H-7, H-8a, H-8b), 3.74 (s, 4 H, CO_2CH_3 and OH), 3.23 (s, 3 H, OCH_3), 3.01 (s, 2 H, $CH_2CO_2CH_3$), 2.74 (br s, 1 H, OH), 1.47 and 1.34 (both s, 3 H, *gem*-dimethyl); (benzene-d_6)[23] δ 4.79 (d, 1 H, H-4), 4.45 (q, 1 H, H-5), 4.12 (m, 1 H, H-6), 3.84 (m, 3 H, H-7, H-8a, H-8b). 3.37 (s, 3 H, CO_2CH_3), 3.22 (br s, 1 H, OH), 3.14 (s, 3 H, OCH_3), 3.06 (s, 2 H, $CH_2CO_2CH_3$), 2.54 (br s, 1 H, OH), 1.30 and 1.05 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 51.31; H, 7.04.

(21) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, 4, 116 (1962).
(22) Zinc dust was activated according to the method described by K. Tsuda, E. Ohki, and S. Nogoe, *J. Org. Chem.*, 28, 783 (1963).
(23) This spectrum was obtained on a Varian XL-100-15 spectrometer.

Methyl 3,8-Anhydro-2-deoxy-α-D-*gulo*-3-octulofuranosonate (5). Route A. The third fraction from the column gave a syrup weighing 0.16 g (3.2 %) that was identified as **5** by further studies with **4** as described in the following section.

Route B. Glycoside **4** (0.25 g, 0.82 mmol) was dissolved in 10 mL of absolute methanol, 2 mL of Amberlite IR-120 (H^+ form) ion-exchange resin was added, and the mixture was heated under reflux and with stirring for 40 h. TLC (9:1 chloroform–methanol) revealed a singlet spot at R_f 0.17. The resin was removed by filtration, and the methanol was evaporated to give a light yellow syrup (**5**) weighing 0.19 g (99% yield): $[\alpha]^{22}D$ +6.4° (*c* 0.95, H_2O); NMR (D_2O) δ 4.70 (m, 1 H, H-6), 4.10 (d, 1 H, $J_{7,8exo}$ = 7.8 Hz, H-7), 3.80 (m, 2 H, H-4, H-5), 3.71 (d, 1 H, H-8_{endo}), 3.67 (s, 3 H, CO_2CH_3), 3.48 (q, 1 H, H-8_{exo}), 2.94 (s, 2 H, $CH_2CO_2CH_3$).

Methyl (Methyl 7,8-di-*O*-benzoyl-2-deoxy-4,5-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate (6). The glycoside **4** (0.5 g, 1.6 mmol) was dissolved in 3 mL of pyridine, and the solution was chilled to −10 °C. Benzoyl chloride (0.5 mL, 4.3 mmol) was added slowly, and the mixture was left for 18 h at room temperature. The mixture was poured over ice slush (50 g), and when the ice had melted the product was extracted into chloroform (3 × 20 mL). The chloroform layer was washed with saturated sodium bicarbonate solution (20 mL) and water (3 × 20 mL) and dried. Evaporation of the chloroform gave a residue that was heavily contaminated with benzoic anhydride. This product was treated with a mixture of pyridine (3 mL) and methanol (10 mL) at room temperature for 72 h. Evaporation and multiple coevaporations with methanol (10 × 10 mL) gave a syrup which was dissolved in 20 mL of chloroform, washed with sodium bicarbonate and water as before, and dried. Evaporation of the solvent resulted in a syrup weighing 0.81 g (96% yield). A 100-mg sample of this syrup was subjected to preparative TLC on four plates. The product **6** could be crystallized from ethanol in the freezer, but the crystals would melt upon filtration: $[\alpha]^{23}D$ −37.1° (*c* 0.53, $CHCl_3$); NMR (chloroform-*d*) δ 8.02 (m, 4 H, *m*-aromatic protons), 7.43 (m, 6 H, ortho and para aromatic protons), 5.80 (sextet, 1 H, $J_{7,8}$ = 4.5 Hz, H-7), 4.90 (m, 2 H, H-4, H-5), 4.77 (m, 2 H, H-8a, H-8b), 4.22 (q, 1 H, H-6), 3.66 (s, 3 H, CO_2CH_3), 3.22 (s, 3 H, OCH_3), 2.95 (s, 2 H, $CH_2CO_2CH_3$), 1.49 and 1.32 (both s, 3 H, *gem*-dimethyl).

Anal. Calcd for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 63.69; H, 5.76.

Methyl (Methyl 2-deoxy-4,5-*O*-isopropylidene-α-D-*gulo*-3-octulofuranosid)onate 7,8-Bis(*O*-methanesulfonate) (7). A solution containing 1.2 g (3.9 mmol) of **4** in 7 mL of dry pyridine was chilled in an ice bath while 1.4 mL of methanesulfonyl chloride was slowly added. The reaction mixture was stored in a refrigerator for 12 h. The excess reagent was decomposed with ice–water until a total of 50 mL had been added. The product settled out as a dark brown gum. The liquid was removed by decantation, the gum was triturated with ice-cold water, and the water was decanted. This procedure was repeated several times. The gum was dissolved in 25 mL of chloroform, washed with saturated sodium bicarbonate solution (25 mL) and water (3 × 25 mL), and dried. The solution was treated with Darco G-60 charcoal and filtered. Evaporation of the solvent gave a pale yellow syrup (1.69 g) that crystallized from methanol to yield 1.46 g (81%), mp 104–106 °C. Recrystallization from methanol raised the melting point slightly: mp 108.5–109.5 °C; $[\alpha]^{22}D$ −45.1° (*c* 1.02, $CHCl_3$); NMR (chloroform-*d*) δ 4.93 (m, 2 H, H-4, H-5), 4.83 (q, 1 H, H-7), 4.60 (d, 2 H, H-8a, H-8b), 4.13 (q, 1 H, H-6), 3.73 (s, 3 H, CO_2CH_3), 3.27 (s, 3 H, OCH_3), 3.16 and 3.13 (both s, 3 H each, SO_2CH_3), 2.96 (s, 2 H, $CH_2CO_2CH_3$), 1.50 and 1.36 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{15}H_{26}O_{12}S_2$: C, 38.96; H, 5.67; S, 13.86. Found: C, 39.05; H, 5.59; S, 13.83.

Methyl (Methyl 4,5-*O*-isopropylidene-2,7,8-trideoxy-β-L-*lyxo*-3-octulo-7-enofuranosid)onate (8). Dimesylate **7** (0.5 g, 1.1 mmol) was dissolved in 20 mL of 2-butanone, 1.8 g of sodium iodide was added, and the mixture was heated under reflux for 24 h. The mixture was cooled, the sodium mesylate was removed by filtration, and the ketone was evaporated. The residue was dissolved in 20 mL of chloroform, washed with water (20 mL), 10% aqueous sodium thiosulfate (20 mL), and water (3 × 20 mL), and dried. Evaporation afforded 0.28 g (95%) of a syrup that crystallized from chloroform–petroleum ether in the freezer;

however, the crystals melted at room temperature: $[\alpha]^{22}D$ -34.8° (c 2.08, $CHCl_3$); NMR (chloroform-d) δ 6.36–5.76 (octet centered at 6.06, 1 H, H-7), 5.53 and 5.24 (both t, 1 H each, H-8a, H-8b, $CH{=}CH_2$), 4.74 (m, 2 H, H-4, H-5), 4.25 (q, 1 H, H-6), 3.73 (s, 3 H, CO_2CH_3), 3.26 (s, 3 H, OCH_3), 3.01 (s, 2 H, $CH_2CO_2CH_3$), 1.49 and 1.35 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 56.97; H, 7.35.

Methyl 2-Deoxy-4,5-O-isopropylidene-α-D-*gulo*-3-octulofuranoside (9). A mixture containing 0.32 g (2.9 mmol) of $CaCl_2$ and 0.22 g (5.8 mmol) of sodium borohydride in tetrahydrofuran was stirred at room temperature for 1 h. To this mixture was added 0.25 g (0.82 mmol) of **4**, and the mixture was stirred at room temperature for 48 h. It was then chilled in an ice bath, and 7 mL of ice-cold water was added very slowly, dropwise (*effervescence*). Cold glacial acetic acid (2 mL) was added until the pH was adjusted to 2. The clear solution was stirred at room temperature for 1 h, evaporated, and coevaporated with methanol (2 × 10 mL) and then pyridine (2 × 10 mL) to give a white solid in a pale yellow syrup. Pyridine (10 mL) was added, and the insoluble material was removed by filtration. Methanol (10 mL) was added to the filtrate, and the solution was evaporated to dryness. TLC (10:1 chloroform–methanol) showed the presence of two products. Chromatography on silica gel (40 × 2.5 cm column) separated the two substances. The faster moving component was the starting material **4** (0.06 g), mp 97–98 °C. The second compound was the desired product **9** (0.14 g, 82% yield based upon utilized **4**), mp 132–133 °C. Recrystallization from ethanol raised the melting point slightly: mp 133–134 °C; $[\alpha]^{20}D$ -49.5° (c 0.95, H_2O); NMR (D_2O) δ 4.95 (q, 1 H each, H-4, H-5), 3.93–3.73 (complex m, 6 H, H-6, H-7, H-8a, H-8b, CH_2CH_2OH), 3.23 (s, 3 H, OCH_3), 2.23 (sextet, 2 H, CH_2CH_2OH), 1.50 and 1.36 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.89; H, 7.95.

Methyl (Methyl 7-aldehydo-2-deoxy-4,5-O-isopropylidene-β-L-*lyxo*-3-heptulofuranosid)onate (10). Glycoside **4** (0.35 g, 1.1 mmol) was dissolved in 10 mL of hot water, and the solution was cooled to room temperature. Sodium metaperiodate (0.42 g, 1.9 mmol) was added in small portions while the pH was adjusted between 6 and 7 with 0.1 N sodium hydroxide solution. After 1 h, 5 mL of water was added, and the product was extracted with chloroform (5 × 15 mL). The extracts were combined, the chloroform solution was washed with water (3 × 15 mL) and dried, and the chloroform was removed by evaporation to afford 0.21 g (67%) of a clear, colorless syrup: $[\alpha]^{22}D$ -38.1° (c 1.69, $CHCl_3$); NMR (chloroform-d) δ 9.64 (s, 1 H, CHO), 5.16–4.76 (m, 2 H, H-4, H-5), 4.2 (m, 1 H, H-6), 3.78 (s, 3 H, CO_2CH_3), 3.27 (s, 3H, OCH_3), 3.08 (s, 2 H, $CH_2CO_2CH_3$), 1.43 and 1.33 (both s, 3 H each, *gem*-dimethyl).

Methyl (Methyl 2-deoxy-4,5-O-isopropylidene-β-L-*lyxo*-3-heptulofuranosid)onate (11). To a stirred solution of aldehyde **10** (0.3 g) in 10 mL of absolute ethanol was added 1 g of Raney nickel (W 2), and the mixture was refluxed for 3 h. The mixture was filtered through a pad of Celite-545, and the filtrate was evaporated to a syrup (**11**) weighing 0.29 g (96% yield): $[\alpha]^{22}D$ -41.7° (c 0.98, $CHCl_3$); NMR (chloroform-d) δ 4.76 (m, 2 H, H-4, H-5), 4.21 (m, 1 H, H-6), 3.93 (br s, 2 H, H-7a, H-7b), 3.72 (s, 3 H, CO_2CH_3), 3.25 (s, 3 H, OCH_3), 3.00 (s, 2 H, $CH_2CO_2H_3$), 2.23 (m, 1 H, OH), 1.50 and 1.34 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.25; H, 7.23.

Methyl (Methyl 2-deoxy-4,5-O-isopropylidene-7-O-(p-toluenesulfonyl)-β-L-*lyxo*-3-heptulofuranosid)onate (12). To a solution containing 0.1 g of **11** in 2 mL of dry pyridine, chilled in an ice bath, was added 90 mg of *p*-toluenesulfonyl chloride in 2 mL of pyridine. The reaction mixture was kept at room temperature for 24 h, and then a few drops of ice-cold water was added. After a few minutes the reaction mixture was poured over ice slush. The crude product separated as a gum which became a powder by triturating the gum with a rod in the ice. The powder (0.147 g, 94%) was filtered and recrystallized from ethanol to yield **12**: mp 71–72 °C; $[\alpha]^{23}D$ -37.7° (c 1.05, $CHCl_3$); NMR (chloroform-d) δ 7.85 and 7.35 (both d, 2 H each, aromatic protons), 4.68 (m, 2 H, H-4, H-5), 4.33–4.06 (complex m, 3 H, H-6, H-7a, H-7b), 3.66 (s, 3 H, CO_2CH_3), 3.16 (s, 3 H, OCH_3), 2.88 (s, 2 H, $CH_2CO_2CH_3$), 2.46 (s, 3 H, tosyl CH_3), 1.36 and 1.28 (both s, 3 H each, *gem*-dimethyl).

Anal. Calcd for $C_{19}H_{26}O_9S$: C, 53.01; H, 6.09. Found: C, 53.08; H, 6.06.

Methyl 3,8-Anhydro-4,5,7-tri-O-acetyl-2-deoxy-α-D-*gulo*-3-octulofuranosonate (13). To a solution of compound **5** (0.15 g) in 4 mL of dry pyridine was added 1.5 mL of acetic anhydride, and the mixture was kept at room temperature for 24 h. The mixture was poured into ice, and when the ice had melted, the product was extracted with chloroform (3 × 15 mL), and the solution was washed with water (20 mL) and saturated sodium bicarbonate (20 mL) and water (3 × 20 mL). The solution was dried, and the solvent was evaporated to yield a syrup that crystallized from ethanol to give fine needles: 0.26 g (94% yield); mp 167.5–168.5 °C; $[\alpha]^{22}D$ +8.4° (c 0.99, $CHCl_3$); NMR (chloroform-d) δ 5.48 (d, 1 H, H-4), 5.42 (dd, 1 H, $J_{4,5}$ = 7.2 Hz, H-5), 5.36 (dd, 1 H, H-7), 4.64 (t, 1 H, $J_{5,6}$ = 5.2 Hz, $J_{6,7}$ = 4.2 Hz, H-6), 4.19 (d, 1 H, $J_{7,8}$ < 0.5 Hz, H-8_{endo}), 3.85 (dd, 1 H, $J_{7,8exo}$ = 4.8 Hz, $J_{8endo,8exo}$ = 7.8 Hz, H-8_{exo}), 3.74 (s, 3 H, CO_2CH_3), 2.82 (s, 2 H, $CH_2CO_2CH_3$), 2.14, 2.06, and 1.98 (all s, 3 H each, acetyl CH_3).

Anal. Calcd for $C_{15}H_{20}O_{10}$: C, 50.00; H, 5.59. Found: C, 49.99; H, 5.52.

Methyl 3,8-Anhydro-4,5,7-O-benzoyl-2-deoxy-α-D-*gulo*-3-octulofuranosonate (14). To a solution of **5** (0.2 g) in 5 mL of dry pyridine, chilled in an ice bath, was added 0.8 g of benzoyl chloride. After 24 h at room temperature, the reaction mixture was poured into ice (50 mL) containing 20 mL of saturated sodium bicarbonate solution. A gum settled out, which was dissolved in 15 mL of chloroform, washed with saturated sodium bicarbonate (20 mL) and water (3 × 25 mL), and dried. Evaporation afforded a syrup (0.7 g). TLC (9:1 chloroform–methanol) showed two products. The slower moving spot appeared to be benzoic anhydride since it did not char with the sulfuric acid spray. Preparative TLC yielded the product (0.38 g) which was crystallized from ethanol. Recrystallization from methanol gave the analytical sample: mp 212–214 °C; $[\alpha]^{23}D$ +118° (c 0.6, $CHCl_3$); NMR (chloroform-d) δ 8.00 (m, 6 H, *m*-benzoyl protons), 7.46 (m, 9 H, *o*- and *p*-benzoyl protons), 5.95 (m, 2 H, H-4, H-5), 5.01 (m, 1 H, H-7), 4.81 (m, 1 H, H-6), 4.39 (d, 1 H, $J_{7,8endo}$ < 0.5 Hz, H-8_{endo}), 4.01 (dd, 1 H, $J_{7,8exo}$ = 4.6 Hz, $J_{8endo,8exo}$ = 8.0 Hz, H-8_{exo}), 3.67 (s, 3 H, CO_2CH_3), 2.96 (s, 2 H, $CH_2CO_2CH_3$).

Anal. Calcd for $C_{30}H_{26}O_{10}$: C, 65.93; H, 4.80. Found: C, 65.67; H, 4.82.

Registry No. **1**, 67642-42-6; **2**, 71042-33-6; **3**, 71042-34-7; **4**, 71042-35-8; **5**, 71042-36-9; **6**, 71042-37-0; **7**, 71042-38-1; **8**, 71042-39-2; **9**, 71042-40-5; **10**, 71042-41-6; **11**, 71042-42-7; **12**, 71042-43-8; **13**, 71042-44-9; **14**, 71042-45-0.