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2-DEOXY SUGARS

PART XIII. 1,3-DIDEOXY-D-*erythro*-HEXULOSE*

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ABSTRACT

The known 3,4,5-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentose (prepared in three steps from 2-deoxy-D-*erythro*-pentose) was oxidized to 3,4,5-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentonic acid, which was converted into the corresponding acid chloride. Treatment of the acid chloride with ethereal diazomethane afforded the diazomethyl ketone, which underwent reduction to give crystalline 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose, obtained alternatively, in 46% yield, by the action of diazomethane on 3,4,5-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentose. Mercaptalation of the benzoylated 1,3-dideoxy-D-*erythro*-hexulose with methanethiol yielded syrupy 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal which, on debenzoylation, gave 1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal (likewise a syrup), which was converted into crystalline 6-*O*-adamantoyl-1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal. Debenzoylation of 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose afforded 1,3-dideoxy-D-*erythro*-hexulose as an impure syrup.

INTRODUCTION

C'-Methyl branched-chain nucleosides are those in which a ring proton of the sugar residue has been replaced by a methyl group (the smallest possible alkyl substituent), which may serve as a metabolic impediment. For example, both 2'-methyladenosine[1] and 3'-methyladenosine[1] inhibit the growth of KB cells in culture and the incorporation of hypoxanthine-8-^{14}C into ribonucleic acid by Ehrlich ascites cells, and we have considered that the preparation of nucleosides in which the anomeric proton has been replaced by a methyl group might yield compounds having unexpected

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biological properties. Because direct replacement of the anomeric proton of a sugar (to include its glycosyl derivatives) is not possible, we sought to prepare a 1-deoxy-2-ketose, which would be capable of forming glycosyl derivatives having a methyl group attached to the anomeric center. This paper reports the synthesis of the heretofore unknown 1,3-dideoxy-D-*erythro*-hexulose and a crystalline derivative; nucleosides prepared from the new sugar could be considered as being those that contain a 2-deoxy-D-*erythro*-pentofuranose (2-deoxy-D-ribofuranose) residue in which the anomeric proton has been replaced by a methyl group.

DISCUSSION AND RESULTS

Wolfrom *et al.* have shown[2] that the diazomethane synthesis for lengthening the carbon chain of sugars may be employed in the preparation of 1-deoxy-2-ketoses; this suggested a convenient means for the synthesis of 1,3-dideoxy-D-*erythro*-hexulose (**9**). Our synthesis required, as the starting compound, 2-deoxy-D-*erythro*-pentose (**1**), and appears to be the first application of this particular variation of the diazomethane synthesis to 2-deoxy sugars, in which the product would be a 1,3-dideoxy-2-ketose.

2-Deoxy-D-*erythro*-pentose (**1**) was converted, in three steps, into the known 3,4,5-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentose (**2**) by a procedure described[3] by Zinner *et al.* Normally, the bromine-water oxidation of an aldose is performed with the unsubstituted sugar or its open-chain, acetylated derivative, either of which dissolves in the aqueous medium. The tribenzoate (**2**) is, however, insoluble in water, and an attempt was made to oxidize it in methanolic solution containing suspended calcium carbonate. A crystalline product was obtained which was not, however, the desired aldonic acid (**3**), but its methyl ester (**3a**), instead. A second attempt was made, in which the bromine was slowly added to a solution of **2** in methanol containing 10% of water (with suspended calcium carbonate); this also gave the methyl ester **3a**. To the best of our knowledge, the oxidation of an aldose, in one operation, to an aldonic ester has not been previously reported. When 10:1 water–tetrahydrofuran was substituted for methanol, the benzoylated aldose (**2**) was converted smoothly, and in high yield, into 3,4,5-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentonic acid (**3**).

On refluxing the acid (**3**) with pure thionyl chloride, the corresponding acid chloride (**4**) was obtained as crystalline material. Reaction of **4** with ethereal diazomethane yielded the diazomethyl ketone (**5**), likewise crystalline, which underwent reduction with hydriodic acid to give, in high yield, 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose (**6**) as a crystalline product.

A more direct route to compound **6** was investigated that involved treatment of the benzoylated aldose (**2**) with diazomethane. Although complicated by the formation of epoxides and homologous ketones, simple, aliphatic aldehydes yield methyl ketones when treated with diazomethane, and Wolfrom *et al.*[2] were successful in converting either D- or L-arabinose tetraacetate, by this method, into 1-deoxy-D- or L-fructose tetraacetate, respectively, in 62% yield. Treatment of **2** with an excess

of ethereal diazomethane, followed by evaporation of the solvent, gave a crystalline product that was identified as the desired benzoylated hexulose (**6**). Contrary to reports of other reactions with diazomethane, a vigorous evolution of nitrogen was not observed, and the best yields (*ca.* 50%) were obtained when freshly prepared diazomethane was used and when the reaction proceeded for no less than one, nor more than two, hours. The crystalline residue, obtained after evaporation of the ethereal diazomethane, had to be scrupulously free of residual diazomethane; otherwise, the colorless product became yellow after being kept overnight. Also, it was necessary to bring the product (**6**) to a high degree of purity without delay, because contaminating side-products of undetermined composition appear to catalyze the decomposition of the product. In several instances, the crude product (**6**) was recrystallized from 95% ethanol, and, from the mother liquors, there could be obtained no additional crystalline material, but only dark-yellow syrups that showed a powerful vesicant action.

A 100-MHz n.m.r. spectrum (see Fig. 1) of **6** in chloroform-*d*, with tetramethylsilane as the internal standard, showed a three-proton singlet for the C-1 methyl protons at τ 7.82; a two-proton doublet ($J_{3,4}$ 6 Hz) at τ 6.97 for the C-3 methylene protons; an asymmetric, two-proton, eight-line pattern centered at τ 5.31

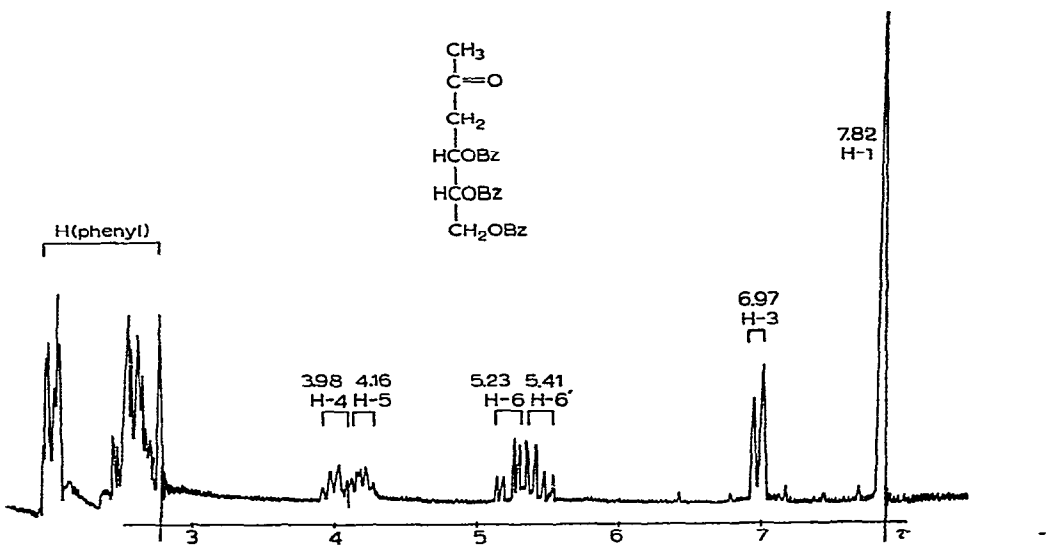

Fig. 1. 100-MHz n.m.r. spectrum of 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose (**6**).

for the two non-equivalent, C-6 methylene protons coupling with the C-5 methine proton ($J_{5,6'}$ 3.4 Hz, $J_{5,6}$ 6.3 Hz); and two overlapping, one-proton multiplets centered at τ 4.16 and τ 3.98 that were assigned to the C-5 and C-4 methine protons, respectively. The two complex multiplets at τ 2.66 and τ 2.10 represented the 15 phenyl protons. That these assignments were correct was proved by decoupling experiments: irradiation at τ 3.98 caused the C-3 methylene doublet to collapse to a singlet at

τ 6.97, whereas irradiation of the proton having the higher-field multiplet at τ 4.16 changed the C-6 methylene peaks from an eight-line pattern to an AB quartet. An AB analysis of this multiplet gave τ (H-6) 5.41 (A) and τ (H-6') 5.23 (B), ($|J_{6,6'}|$ 12.3 Hz). Furthermore, irradiation of the C-3 methylene protons resulted in the collapse of the C-4 methine multiplet to an asymmetric doublet at τ 3.98 ($J_{4,5}$ 6 Hz).

Debenzoylation of **6** with methanolic sodium methoxide gave 1,3-dideoxy-D-*erythro*-hexulose (**9**) as an impure syrup that resisted all efforts to secure it in crystalline form. It gave a positive iodoform test, and its infrared absorption spectrum was concordant with the structure assigned to **9**. Reaction of 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose (**6**) with methanethiol[4] resulted in a syrup that gave analytical results in excellent agreement with those calculated for 4,5,6-tri-*O*-benzoyl-1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal (**7**). Debenzoylation of **7** was effected with methanolic barium methoxide as described by Isbell[5] and modified by Levene and Tipson[6]; this resulted in 1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal (**8**), which could not be obtained in crystalline form. The infrared absorption spectrum of **8** had a striking similarity to that of the known 2-deoxy-D-*erythro*-pentose dimethyl dithioacetal[3].

Efforts were made to protect O-6 of the mercaptalated dideoxyketose (**8**) preferentially; this would not only ensure the formation of a furanoid ring on demercaptalation, but could also provide for a crystalline derivative of the ketose (**9**). One approach involved a low-temperature *p*-nitrobenzoylation, successfully applied to the preparation of 2-deoxy-5-*O*-*p*-nitrobenzoyl-D-*erythro*-pentose diisobutyl dithioacetal;[7] however, when we treated **8** in a similar manner, a complex mixture [including unreacted starting-material (**8**)] was obtained, as disclosed by thin-layer chromatography. Similar results were obtained when attempts were made to secure a 6-*p*-toluenesulfonate of **8**, and tritylation gave only a syrupy product.

As an alternative, we turned our attention to an adamantoyl derivative. The 1-adamantoyl group has recently been employed for the selective protection of primary hydroxyl groups of nucleosides[8], and, because of its bulk, the group is probably restricted by steric factors to attacking the usually more accessible, primary hydroxyl groups. An adamantoyl ester may be hydrolyzed with 0.25M base to regenerate the free primary hydroxyl group, thus serving as a base-sensitive counterpart to the acid-labile trityl group in syntheses involving carbohydrates and nucleosides. Accordingly, the mercaptalated ketose (**8**) was treated in pyridine at 0° with 1-adamantoyl chloride*, giving 6-*O*-(1-adamantoyl)-1,3-dideoxy-D-*erythro*-hexulose dimethyl dithioacetal (**10**) as a crystalline product.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage. Thin-layer chromatographic plates were prepared with Kiesel-Gel DF-5 (ultraviolet indicating), and

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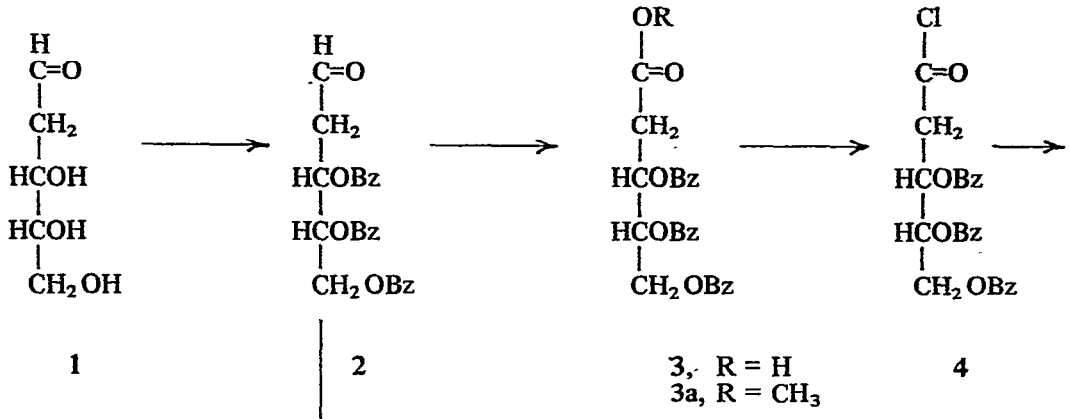

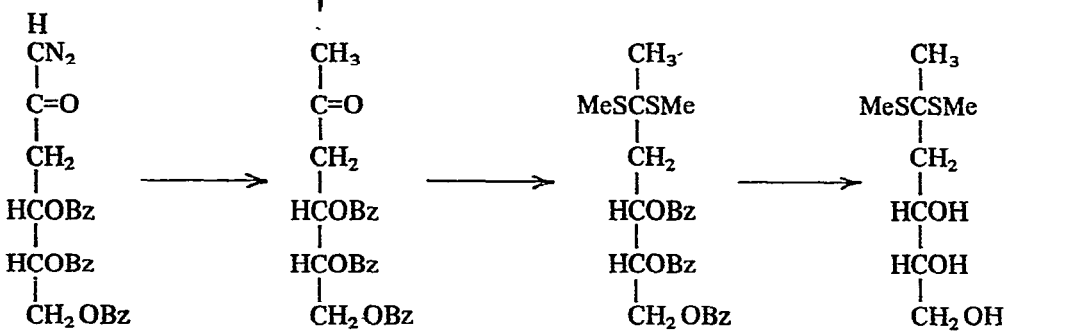

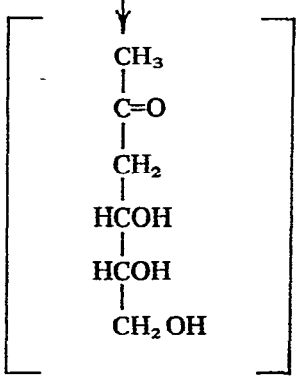

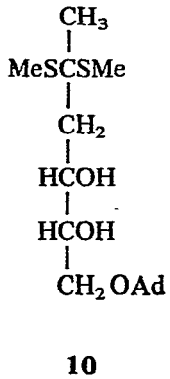

Bz = PhC(=O); Ad = 1-adamantoyl

detection of all derivatives was made with alkaline potassium permanganate spray reagent. To distinguish between the ketoses and their mercaptalated derivatives, (2,4-dinitrophenyl)hydrazine spray reagent was used.

Optical rotations were determined with a Rudolph Model 80 polarimeter, infrared spectra were recorded with a Perkin–Elmer Model 137B i.r. spectrophotometer, and n.m.r. spectra were recorded with Varian Models T-60 and HA-100 n.m.r. spectrometers, with tetramethylsilane (τ 10.00) as the internal standard.

3,4,5-Tri-O-benzoyl-2-deoxy-D-erythro-pentonic acid (**3**). — A solution of 1.0 g (2.24 mmoles) of[3] **2** in 10 ml of tetrahydrofuran was added, with magnetic stirring, to a solution of 5 g of sodium hydrogen carbonate and 1.0 ml of bromine in 100 ml of water and 10 ml of tetrahydrofuran. The solution was stirred overnight at room temperature, and then adjusted with 2M hydrochloric acid to pH 2.5 (pH test-paper). The white solid was filtered off, and recrystallized from 95% ethanol to yield 579 mg (56%) of **3** as fine, colorless needles, m.p. 145–155°. The mother liquors were concentrated, to yield an additional 391 mg of product, bringing the total yield to 94%. Recrystallization from 95% ethanol raised the melting point of the product to 152.5–155°, $[\alpha]_D^{24}$ +3.30° (*c* 1.0, dichloromethane); $\nu_{max}^{CHCl_3}$ 1725 (carboxylic acid carbonyl) and 1735 cm^{-1} (benzoic ester carbonyl).

Anal. Calc. for $C_{26}H_{22}O_8$: C, 67.53; H, 4.76. Found: C, 67.95; H, 5.16.

Methyl 3,4,5-tri-O-benzoyl-2-deoxy-D-erythro-pentonate (**3a**). — To 10 ml of methanol containing 200 μl of bromine and 2.83 g of calcium carbonate was added 250 mg (460 μmoles) of **2**. The suspension was stirred magnetically for 20 h at room temperature, and the white solid was filtered off (from filtrate *A*) and then suspended in 5 ml of water. To this suspension was added, dropwise, 2M hydrochloric acid to decompose the excess of calcium carbonate, and the residual white solid (insoluble in the acidified solution) was extracted into dichloromethane. The extract was evaporated under diminished pressure to a white solid that was recrystallized from ethanol–water to yield a colorless, crystalline product (**3a**), m.p. 110–113°. The methanol solution (*A*) was concentrated to yield additional product which, when recrystallized, gave a total yield of 130 mg (50%). Recrystallization raised the melting point to 112–113.5°, $[\alpha]_D^{20}$ +0.49° (*c* 1.07, chloroform); $\nu_{max}^{CHCl_3}$ 1725 (aldonic ester carbonyl) and 1735 cm^{-1} (benzoic ester carbonyl); 60-MHz n.m.r.: singlet at τ 6.37 (methoxyl protons).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.07; H, 5.04. Found: C, 67.99; H, 4.86.

3,4,5-Tri-O-benzoyl-2-deoxy-D-erythro-pentonyl chloride (**4**). — A solution of 1.50 g (3.42 mmoles) of **3** in 15 ml of *pure* thionyl chloride[9] was refluxed overnight, and concentrated to approximately half its volume under diminished pressure, and 5 ml of dry benzene was added. The solution was reconcentrated under diminished pressure, and this process was repeated three times. The resulting solid residue was dissolved in a large volume of warm cyclohexane, and the solution was concentrated to approximately half its volume under diminished pressure and kept overnight at room temperature. The product (**4**) crystallized in fine, colorless needles, weighing 1.152 g (74%) and having m.p. 118–121° and $[\alpha]_D^{24}$ +17.0° (*c* 0.83, dichloromethane).

Anal. Calc. for $C_{26}H_{21}ClO_7$: C, 65.00; H, 4.38; Cl, 7.29. Found: C, 65.18; H, 4.61; Cl, 6.87.

*4,5,6-Tri-O-benzoyl-1,3-dideoxy-1-diazo-*D-erythro-*hexulose* (**5**). — A solution of 810 mg (1.69 mmoles) of **4** in 75 ml of dry ether was slowly added to 50 ml of a magnetically stirred, freshly prepared solution of diazomethane in ether (containing approximately 30 mg of diazomethane per ml). The product began crystallizing within 5 min, and the suspension was stirred for 1 h at 0° and then refrigerated overnight. The product was filtered off, and dissolved in dry acetone; some acetone-insoluble, flocculent material was removed by filtration, and 2 ml of dry ether was added to the clear filtrate, followed by 2 ml of petroleum ether (b.p. 30–60°). The solution was refrigerated overnight, giving 565 mg of fine, pale-yellow granules. Concentration of the mother liquor, followed by the addition of a little ether, yielded an additional 170 mg, bringing the total yield of product (**5**) to 735 mg (95%), m.p. 137.5–144° (with darkening and decomposition), $[\alpha]_D^{24}$ −28.4° (*c* 1.0, dichloromethane).

*4,5,6-Tri-O-benzoyl-1,3-dideoxy-*D-erythro-*hexulose* (**6**). — (*a*) *From the diazomethyl ketone* (**5**). To a solution of 735 mg (1.51 mmoles) of **5** in 10 ml of chloroform was added 5 ml of 47% hydriodic acid[10], and the resulting solution was vigorously shaken for 5 min. It was washed successively with 3 ml of water, 3 ml of saturated, aqueous sodium thiosulfate (freshly prepared), and three 3-ml portions of water. The chloroform solution was dried with sodium sulfate, the suspension was filtered, and the filtrate was evaporated under diminished pressure to a yellow syrup that crystallized on trituration with ether. The crystals were dissolved in 95% ethanol, and the suspension was filtered through a bed of Celite to remove colloidal sulfur. The filtrate, on being cooled, yielded 581 mg (84%) of **6** as fine, colorless needles, m.p. 119.5–123°, $[\alpha]_D^{24}$ +21.8° (*c* 1.0, dichloromethane); $\nu_{max}^{CHCl_3}$ 1725 (C-2 carbonyl) and 1735 cm^{-1} (benzoic ester carbonyl); n.m.r. data: see discussion in text.

Anal. Calc. for $C_{27}H_{24}O_7$: C, 70.43; H, 5.24. Found: C, 70.53; H, 5.53.

(*b*) *From 3,4,5-tri-O-benzoyl-2-deoxy-*D-erythro-*pentose* (**2**). — To a solution of 92 mg (205 μmoles) of **2** in 2 ml of dry benzene, stirred magnetically (ice-bath), was added 5 ml of a solution of diazomethane in ether (containing approximately 30 mg of diazomethane per ml). The solution was kept for 2 h at 0°, and then evaporated under diminished pressure to a syrup, which was re-evaporated several times with dry ether to remove excess of diazomethane. The crude product, a white solid, was recrystallized from ether–pentane, to yield **6** as fine, colorless needles; yield 43 mg (46%), m.p. 119–123°, $[\alpha]_D^{24}$ +21.8° (*c* 1.0, dichloromethane).

*4,5,6-Tri-O-benzoyl-1,3-dideoxy-*D-erythro-*hexulose dimethyl dithioacetal* (**7**). — To 969 mg (2.11 mmoles) of **6** (cooled in an ice-salt bath to −18°) was added 40 ml of methanethiol, precooled to −18°. Hydrogen chloride was bubbled through the solution for 1 h, and the solution, saturated with hydrogen chloride, was kept for 2 h at −18°. The solution was allowed to warm slowly to room temperature to permit volatilization of the methanethiol, and the residue, a clear syrup, was repeatedly co-evaporated with dry ether to remove traces of methanethiol. The yield of syrup was 1.14 g (100%), $[\alpha]_D^{24}$ +17.5° (*c* 0.96, dichloromethane); C-2 carbonyl absorption

absent from i.r. spectrum; 100-MHz n.m.r.: singlet at τ 8.44 (C-1 methyl protons), singlets at τ 8.99 and τ 7.97 (3 protons each from C-2 methylthio groups), and a two-proton multiplet at τ 7.60 (C-3 methylene protons); R_F 0.55 [upper layer of 10:6:5:3 (v/v) ethyl acetate–methanol–water–heptane].

Anal. Calc. for $C_{29}H_{30}O_6S_2$: C, 64.68; H, 5.58; S, 11.90. Found: C, 64.64; H, 5.82; S, 12.65.

1,3-Dideoxy-D-erythro-*hexulose dimethyl dithioacetal* (**8**). — To a solution of 1.97 g (3.66 mmoles) of **7** in 50 ml of dry methanol, stirred in an ice-bath, was added 0.7 ml of 0.25M barium methoxide in methanol (immediately after the addition of barium methoxide, the odor of methyl benzoate was noted). The solution was kept for 20 min at 0° and for 24 h at room temperature. An excess of solid carbon dioxide was added to decompose the barium methoxide, and the mixture was briefly warmed. On cooling the mixture, barium carbonate was precipitated from the solution; the suspension was filtered, and the clear filtrate was evaporated under diminished pressure to a syrup. This was dissolved in absolute ethanol, and the solution was evaporated under diminished pressure to remove methyl benzoate and traces of water, giving the product (**8**) as a syrup; $[\alpha]_D^{24}$ −37.8° (*c* 7.4, chloroform); R_F 0.088 [10:1 (v/v) chloroform–methanol].

1,3-Dideoxy-D-erythro-*hexulose* (**9**). — To 176 mg (38 μmoles) of **6** suspended in 50 ml of dry methanol was added, with magnetic stirring, 10.2 mg of freshly cut sodium. Within 10 min, the suspended solid had dissolved, and the solution was kept for 20 h at room temperature. T.l.c. [10:1 (v/v) chloroform–methanol] indicated a major component, and a minor component of higher R_F value. The methanol solution was concentrated under diminished pressure to approximately one-third its volume, 1 g of mixed-bed ion-exchange resin [Fisher Rexyn-300 (H^+, OH^-)] was added to the solution, and the suspension was stirred for 0.5 h. The resin was filtered off, and the filtrate was evaporated under diminished pressure to a syrup. The syrup was dissolved in water, and the solution was washed once with ether, and evaporated to a clear syrup that weighed 35 mg. T.l.c. of the impure **9** disclosed a major component having R_F 0.805 [upper layer of 10:6:5:3 (v/v) ethyl acetate–methanol–water–2,2,4-trimethylpentane]; $\nu_{max}^{CHCl_3}$ 1725 cm^{-1} (C-2 carbonyl).

6-O-(*1-Adamantoyl*)-*1,3-dideoxy*-D-erythro-*hexulose dimethyl dithioacetal* (**10**). — To a solution of 256 mg (800 μmoles) of **8** in 5 ml of dry benzene (ice-bath), was added slowly, with magnetic stirring, a solution of 226 mg (1.14 mmoles) of 1-adamantoyl chloride in 2 ml of pyridine. The solution was kept for 4 days at 0°, the pyridinium chloride was filtered off, and the filtrate was washed with 5 ml of dilute, aqueous sodium hydrogen carbonate. To the mixture was added 5 ml of ethyl acetate, the mixture was shaken, and the aqueous phase was separated. The ethyl acetate solution was washed with 5 ml of water, dried with sodium sulfate, and evaporated to a syrup which began crystallizing after standing for one week at room temperature. The product (**10**) was recrystallized from 2:1 (v/v) ether–hexane to yield 26 mg (8.4%), m.p. 89–92°, $[\alpha]_D^{24}$ −26.5° (*c* 0.804, chloroform); $\nu_{max}^{CHCl_3}$ 1725 cm^{-1} (adamantoyl carbonyl); 100-MHz n.m.r.: singlet at τ 8.84 (C-1 methyl protons), a two-proton

multiplet at τ 7.99 (C-3 methylene protons), singlets at τ 7.98 and τ 7.92 (C-2 methylthio protons), and multiplets at τ 8.29 and τ 8.09 (adamantoyl protons); R_F 0.64 [10:1 (v/v) chloroform–methanol].

Anal. Calc. for $C_{19}H_{33}O_4S_2$: C, 58.61; H, 8.48; S, 16.45. Found: C, 58.61; H, 8.35; S, 16.0.

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