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SYNTHESES RELATED TO THE 3,7-ANHYDRO-OCTOSE IN THE EZOMYCINS AND THE OCTOSYL ACIDS

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ABSTRACT

Two 3,7-anhydro-octoses, namely, methyl 3,7-anhydro-5,6,8-trideoxy-β-D-*allo*-octofuranoside and methyl 3,7-anhydro-5,6,8-trideoxy-α-L-*talo*-octofuranoside, have been synthesized. The synthetic sequence includes the preparation of an octose from D-ribose by way of a Wittig reaction and the elaboration of the bicyclic-ring system by intramolecular cyclization.

INTRODUCTION

The synthesis of higher-carbon sugars[1] has been one of the challenging problems in carbohydrate chemistry. Starting from a pentose or hexose, these syntheses require the creation of C–C bonds together with control of the absolute stereochemistry at each carbon center. Complex higher-carbon sugars are found as components of many important antibiotics, for example, lincomycin[2], celesticetin[3], apramycin[4], oxyapramycin[5], the ezomycins[6], mildiomycin[7], tunicamycin[8], and hikizimycin[9]. The biological activities and unique structures of these antibiotics have inspired several synthetic studies. Syntheses of lincomycin[10] and syntheses related to the octodiose in apramycin[11] have been accomplished in this laboratory. Secrist and Wu[12] have described a synthetic study related to hikizimycin.

Recently, we reported[13] the synthesis of a 3′,7′-anhydro-octuronic acid nucleoside that is the structural backbone of the antifungal ezomycins[14] and the octosyl acids[15] obtained from two different strains of *Streptomyces*. The carbohydrate moiety, a 3,7-anhydro-octuronic acid in ezomycins A_1 (**1**), A_2 (**2**), B_1, B_2, C_1, and C_2[6] and in octosyl acids A (**3**) and B (**4**)[15], is the first octose derivative containing a rigid bicyclic system in which a furanoid ring is *trans*-fused to a pyranoid ring. Although the octosyl acids show no biological activity, the adenine analog (**5**) of the octosyl acids, readily obtained from **3** by transglycosylation[16,17], is an inhibitor of cyclic-AMP phosphodiesterases from various animal tissues[17]. Various studies related to

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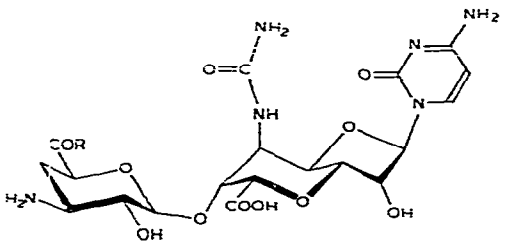
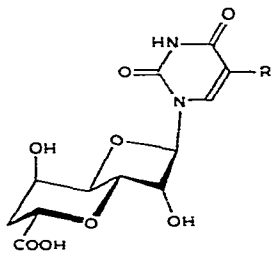
the ezomycins and the octosyl acids have been reported: a biosynthesis of octosyl acid A[18], a synthesis of an octose derivative related to the octosyl acids[19], and a ^{13}C-n.m.r. spectroscopic study of the ezomycins[20].



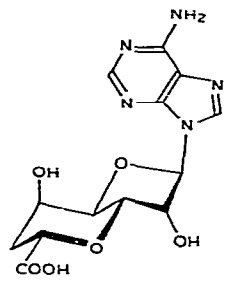
1 R = NHCHCH$_2$CH$_2$SCH$_2$CHNH$_2$ (COOH, COOH)

2 R = OH



3 R = COOH

4 R = CH$_2$OH



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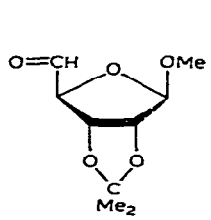
Our synthesis of the 3′,7′-anhydro-octuronic acid nucleoside[13] started from uridine. We now describe an approach to the synthesis of 3′,7′-anhydro-octose nucleosides starting from D-ribose, which was thought might be more advantageous. Thus, once the bicyclic-ring system has been prepared, it can be coupled to a variety of bases to afford bicyclic-octose nucleosides. Moreover, the reactions with ribosides should be less complicated than those with nucleosides.

RESULTS AND DISCUSSION

Methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**6**) was prepared[21] by oxidation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, which was obtained from D-ribose by a one-step process[22]. Treatment of **6** with the Wittig reagent acetylmethylenetriphenylphosphorane (**7**) afforded, after chromatography, methyl (*E*)-5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-oct-5-eno-1,4-furanosid-7-ulose (**8**) in 82% yield. The u.v. and i.r. spectra (λ_{max} 229 nm, ν_{max} 1670 cm^{-1}) indicated that compound **8** possesses an α,β-unsaturated ketone system. The ^{1}H-n.m.r. spectrum of **8** showed a large *trans*-ethylenic coupling ($J_{5,6}$ 16 Hz). Reduction of **8** with sodium borohydride in ethanol gave a chromatographically homogeneous mixture of methyl (*E*)-5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*allo*- and α-L-*talo*-oct-5-enofuranoside (**9**) in 95% yield, but the ^{13}C-n.m.r. spectrum indicated that ~99% of the saturated alcohol **10** was present. The H-8 signal of the ^{1}H-n.m.r. spectrum of **9** was complicated, because of the presence of **10**. It was not necessary to purify **9**, because the impurity **10** was the desired product in the next step. The reduction of the carbon–carbon double-bond in conjugated ketones and aldehydes by borohydride is known in a number of cases[23].



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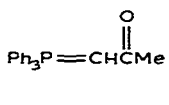

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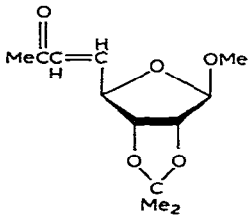

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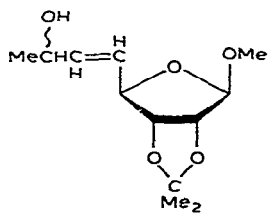
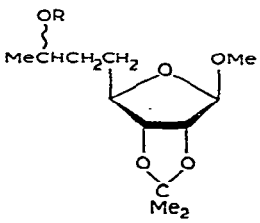
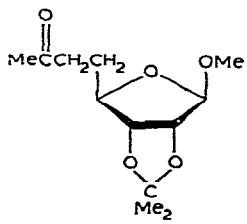


9

Hydrogenation of the allylic alcohol **9** over 10% palladium-on-charcoal afforded 82% of methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-octofuranoside (**10**) and 10% of methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-octo-1,4-furanosid-7-ulose (**11**). The structural assignment of **11** was confirmed by its conversion into **10**, using sodium borohydride. The saturated ketone **11** was the only product (100%) when **9** was stirred with 10% palladium-on-charcoal under nitrogen instead of hydrogen. The conversion of a secondary allylic alcohol into a saturated ketone during its hydrogenation using a heterogeneous catalyst has been reported[24]. One possible mechanism for the formation of the saturated ketone **11** involves a double-bond migration by way of a π-allyl complex followed by tautomerization.



10 R = H
12 R = Ts



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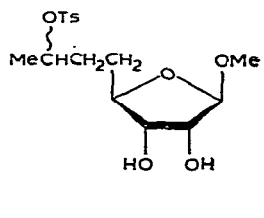
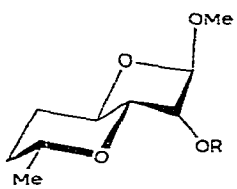


13

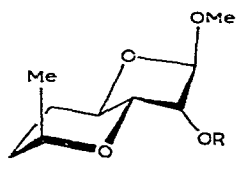
Treatment of **10** with *p*-toluenesulfonyl chloride in pyridine at 0° afforded methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-7-*O*-*p*-tolylsulfonyl-β-D-*allo*- and -α-L-*talo*-octofuranoside (**12**) in 88% yield. Deisopropylidenation of **12** was accomplished by using 90% formic acid below 10°. After chromatography, methyl 5,6,8-trideoxy-7-*O*-*p*-tolylsulfonyl-β-D-*allo*- and -α-L-*talo*-octofuranoside (**13**) was obtained in 23% yield.

The next step involves generation of the alkoxide ion at C-3 of **13** followed by intramolecular displacement of the *p*-tolylsulfonyloxy group at C-7. Although an alkoxide ion at C-2 of **13** can also be formed, a molecular model indicated that this ion cannot displace the *p*-tolylsulfonyloxy group at C-7 of the same molecule to form the 2,7-anhydride. It is therefore not necessary to protect HO-2 of **13**. Cyclization was accomplished by treatment of **13** with sodium hydride, in 1,2-dimethoxyethane or *N*,*N*-dimethylformamide, at room temperature. The mixture of two epimeric,

bicyclic octoses could be resolved by chromatography on silica gel, to afford crystalline methyl 3,7-anhydro-5,6,8-trideoxy-β-D-*allo*-octofuranoside (**14**) (28%) and syrupy methyl 3,7-anhydro-5,6,8-trideoxy-α-L-*talo*-octofuranoside (**15**) (24%). The structural assignment of the bicyclic octoses **14** and **15** was based on spectroscopic data and elemental analyses, and the characterization of their derivatives. Both compounds showed negative bromine and permanganate tests. Their ^{1}H- and ^{13}C-n.m.r. spectra showed all the expected resonances. The ^{1}H-n.m.r. spectra of the acetylated compounds **16** and **17** indicated that each was a monoacetate. The stereochemistry at C-7 of **14** and **15** was assigned on the basis of chemical-shift data. Thus, the H-8 signal of **14** (δ 1.25), bearing an equatorial methyl group, appears at higher field than that (δ 1.31) of **15**, bearing an axial methyl group. The C-8 resonance of **14** (δ 20.8) appears at lower field than that of **15** (δ 17.0). It is well established that the protons of an axial methyl group in cyclohexanone systems[25], 1,3-dioxane[26], and 1,3,5-trioxane[27] resonate at lower field than those of an equatorial group. On the other hand, the carbon of an axial methyl group in cyclohexane[28] and 1,3-dioxane[29] resonates at higher field than that of an equatorial group.



14 R = H
16 R = Ac



15 R = H
17 R = Ac

Acetolysis (acetic anhydride–acetic acid–sulfuric acid, 0°) of **14** or **15** gave a complex mixture of products, presumably attributable to the susceptibility of the 3,7-anhydro-octose system to acid. The instability of the bicyclic-octose system under acidic conditions has been observed in the degradation studies of the ezomycins[6] and the octosyl acids[15], and in the synthetic studies related to the octosyl acids[19].

EXPERIMENTAL

General. — Evaporations were performed under reduced pressure at ⩽40° (bath). Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter at 23 ±3°. I.r. spectra were recorded with a Perkin–Elmer 180 or 598 spectrophotometer. U.v. spectra were measured with a Unicam SP 800B or Perkin–Elmer 552 spectrophotometer. The ^{1}H-n.m.r. spectra ($CDCl_3$, internal Me_4Si) were recorded with a Varian EM-360 or Bruker HX-60 spectrometer. The ^{13}C-n.m.r. spectra ($CDCl_3$, internal Me_4Si) were recorded with a Bruker HX-60 spectrometer equipped with a FT60M Fourier transform accessory at 15.09 MHz. T.l.c. was performed on pre-coated glass plates (silica gel 60 F-254, 0.25-mm thickness; Merck),

with detection by irradiation of the plates with u.v. light or by heating the plates at 150° after they had been sprayed with 10% aqueous sulfuric acid containing 1% of cerium sulfate and 1.5% of molybdic acid. Column chromatography was performed on Brinkmann silica gel 60 (70–230 mesh, Merck). Merck, pre-coated, glass plates (silica gel F-254; 20 × 20 cm, 2-mm thickness) were used for preparative t.l.c. The following solvent systems were employed: toluene–ethyl acetate: *A*, 2:1; *B*, 3:1; and *C*, 9:1; and toluene–acetone: *D*, 2:1; *E*, 3:1; and *F*, 4:1.

Methyl (E)-*5,6,8-trideoxy-2,3*-O-*isopropylidene-β*-D-ribo-*oct-5-eno-1,4-furanosid-7-ulose* (**8**). — A solution of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[21] (**6**; 613 mg, 3.0 mmol) and acetylmethylenetriphenylphosphorane[30] (**7**; 1.26 g, 3.9 mmol) in toluene (50 ml) was stirred at room temperature overnight and then warmed at 60° for 2 h. T.l.c. (solvent *A*) indicated that **6** and **8** had almost the same R_F value (0.53), but that **8** could be detected on the t.l.c. plate by u.v. irradiation. The reaction mixture was concentrated and the resulting white solid was fractionated on a column of silica gel (solvent *C*), to afford **8** as a colorless syrup (602 mg, 82%), $[\alpha]_D$ +51° (*c* 0.16, chloroform); ν_{max}^{film} 1690, 1670, and 1620 cm^{-1}; λ_{max} (EtOH) 229 nm (*c* 13500); ^{1}H-n.m.r.: δ 1.33 and 1.50 (2 s, 6 H, CMe_2), 2.25 (s, 3 H, 3 H-8), 3.38 (s, 3 H, OMe), 4.38–4.73 (m, 3 H, H-2,3,4), 4.98 (s, 1 H, H-1), 6.14 (d, 1 H, $J_{5,6}$ 16.0 Hz, H-6), and 6.70 (dd, 1 H, $J_{4,5}$ 6.0 Hz, H-5).

Methyl (E)-*5,6,8-trideoxy-2,3*-O-*isopropylidene-β*-D-allo- *and* -α-L-talo-*oct-5-enofuranoside* (**9**). — To a stirred solution of **8** (580 mg, 2.4 mmol) in ethanol (12 ml) was added sodium borohydride (110 mg, 2.9 mmol). T.l.c. (solvent *A*) showed that, after 5 min, the reaction mixture contained only one component (R_F 0.24) but no starting material. The mixture was neutralized with M hydrochloric acid and evaporated to dryness. The solid residue was extracted with ethyl acetate, and the extracts were passed through a small amount of silica gel and evaporated, to give **9** as a chromatographically homogeneous syrup (556 mg, 95%). An analytical sample was obtained by preparative t.l.c. (solvent *A*); ν_{max}^{film} 3410 cm^{-1}; ^{1}H-n.m.r.: δ 1.24 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.31 and 1.48 (2 s, 6 H, CMe_2), 2.34 (bs, 1 H, OH, exchangeable in D_2O), 3.32 (s, 3 H, OMe), 4.04–4.61 (4 H, H-2,3,4,7), 4.90 (s, 1 H, H-1), and 5.66 (m, 2 H, H-5,6); ^{13}C-n.m.r.: δ 23.2 (C-8), 25.0 and 26.5 (CMe_2), 54.5 (OMe), 67.6 (C-7), 84.6 (C-3), 85.4 (C-4), 87.3 (C-2), 109.2 (C-1), 112.3 (O–CMe_2–O), 128.6 (C-6), and 137.5 (C-5).

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.18; H, 8.84.

Catalytic hydrogenation of **9**. — A sample (550 mg) of the foregoing product in ethanol (80 ml) was subjected to a hydrogen pressure (1 atm) over 10% palladium-on-charcoal. The reaction was complete within 30 min. The catalyst was removed by filtration through Celite, and evaporation of the solvent gave a colorless syrup which was fractionated on a column of silica gel (solvent *B*), to give methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-octofuranoside (**10**) as a colorless syrup (455 mg, 82%), R_F 0.24 (solvent *A*); ν_{max}^{film} 3430 cm^{-1}; ^{1}H-n.m.r.: δ 1.21 (d, 3 H, $J_{7,8}$ 6.0 Hz, H-8), 1.33 and 1.50 (2 s, 6 H, CMe_2), 1.56–1.71 (m, 4 H, 2 H-5, 2 H-6), 3.38 (s, 3 H, OMe), 3.64–4.78 (4 H, H-2,3,4,7), 4.93 (s, 1 H, H-1); ^{13}C-n.m.r.: δ 23.5

(C-8), 25.0 and 26.5 (CMe_2), 31.2 (C-5), 35.8 (C-6), 54.9 (OMe), 67.1 (C-7), 84.1 (C-3), 85.4 (C-2), 87.2 (C-4), 109.4 (C-1), and 112.1 (O–CMe_2–O).

Anal. Calc. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.01; H, 9.28.

Methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-octo-1,4-furanosid-7-ulose (**11**) was isolated as a colorless syrup (55 mg, 10%), R_F 0.46 (solvent *A*), $[\alpha]_D$ −33° (*c* 0.07, chloroform); ν_{max}^{film} 1715 cm^{-1}; ^{1}H-n.m.r.: δ 1.32 and 1.47 (2 s, 6 H, CMe_2), 1.59–2.08 (m, 2 H, 2 H-5), 2.16 (s, 3 H, 3 H-8), 2.57 (t, 2 H, $J_{5,6}$ 6.5 Hz, 2 H-6), 3.33 (s, 3 H, OMe), 3.83–4.60 (m, 3 H, H-2,3,4), and 4.88 (s, 1 H, H-1).

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.07; H, 8.52.

Treatment of **9** *with 10% palladium-on-charcoal.* — A solution of **9** (13 mg, 0.053 mmol) in ethanol was vigorously stirred overnight in the presence of 10% palladium-on-charcoal (0.39 mg) under nitrogen. T.l.c. indicated the formation of only one product, R_F 0.46 (solvent *A*). Evaporation of the solvent gave **11** as a colorless syrup (12.9 mg).

*Methyl 5,6,8-trideoxy-2,3-*O*-isopropylidene-7-*O*-p-tolylsulfonyl-β-*D*-allo- and -α-*L*-talo-octofuranoside* (**12**). — To a solution of **10** (450 mg, 1.8 mmol) in pyridine (4 ml) was added, at 0°, *p*-toluenesulfonyl chloride (366 mg, 1.9 mmol). The mixture was kept at 0° overnight, to give only one product, R_F 0.64 (solvent *A*). The mixture was poured into vigorously stirred ice–water (40 ml) and extracted with dichloromethane. The extract was washed successively with cold 0.5M sulfuric acid, saturated, aqueous sodium hydrogen carbonate, and cold water, dried ($MgSO_4$), and evaporated, to afford **12** as a chromatographically homogeneous syrup (644 mg, 88%). An analytical sample was obtained by preparative t.l.c. (solvent *A*); ν_{max}^{film} 1600, 1360, and 1180 cm^{-1}; ^{1}H-n.m.r.: δ 1.27 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.29 and 1.47 (2 s, 6 H, CMe_2), 1.48–1.77 (m, 4 H, 2 H-5, 2 H-6), 2.44 (s, 3 H, Ph*Me*), 3.21 (s, 3 H, OMe), 3.86–4.78 (4 H, H-2,3,4,7), 4.86 (s, 1 H, H-1), and 7.24–7.85 (4 H, aromatic).

*Methyl 5,6,8-trideoxy-7-*O*-p-tolylsulfonyl-β-*D*-allo- and -α-*L*-talo-octofuranoside* (**13**). — A solution of **12** (620 mg, 1.5 mmol) in cold 90% formic acid (5 ml) was kept at 0° overnight, diluted with cold water (15 ml), and concentrated below 30°. Addition of more water and evaporation were repeated several times, to afford a pale-yellow syrup which was fractionated on a column of silica gel (solvent *E*) to give **13** as a colorless syrup (128 mg, 23%), R_F 0.34 (solvent *D*); ν_{max}^{film} 3430, 1600, 1360, and 1180 cm^{-1}; ^{1}H-n.m.r.: δ 1.24 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.57–1.75 (m, 4 H, 2 H-5, 2 H-6), 2.44 (s, 3 H, Ph*Me*), 3.30 (s, 3 H, OMe), 3.65–4.28 (4 H, H-2,3,4,7), 4.74 (s, 1 H, H-1), and 7.22–7.83 (4 H, aromatic).

Cyclization of **13**. — A solution of **13** (125 mg, 0.35 mmol) in *N*,*N*-dimethylformamide (6 ml) was vigorously stirred with sodium hydride (33 mg, 1.39 mmol; 50% oil dispersion) at room temperature for 3 h. T.l.c. (solvent *D*) then showed the absence of **13**. The mixture was poured into ice–water (60 ml) with stirring, and extracted exhaustively with dichloromethane. The combined extracts were washed with cold water, dried ($MgSO_4$), and concentrated to a syrup. Column chromatography (solvent *F*) gave crystalline methyl 3,7-anhydro-5,6,8-trideoxy-β-D-*allo*-octofuranoside (**14**; 18.3 mg, 28%). Recrystallization from petroleum ether afforded

14, m.p. 82–84°, $[\alpha]_D$ −61° (*c* 0.02, chloroform), R_F 0.50 (solvent *D*); ν_{max}^{KBr} 3420 cm^{-1}; ^{1}H-n.m.r.: δ 1.25 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.58–2.58 (m, 4 H, 2 H-5, 2 H-6), 3.41 (s, 3 H, OMe), 3.17–4.12 (4 H, H-2,3,4,7), and 4.82 (s, 1 H, H-1); ^{13}C-n.m.r.: δ 20.8 (C-8), 29.5 (C-6), 31.7 (C-5), 55.6 (OMe), 72.1, 73.2, 77.2 and 82.1 (C-4, C-7, C-2, C-3), and 111.2 (C-1).

Anal. Calc. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.40; H, 8.79.

Methyl 3,7-anhydro-5,6,8-trideoxy-α-L-*talo*-octofuranoside (**15**) was isolated as a colorless syrup (15.7 mg, 24%), $[\alpha]_D$ −57° (*c* 0.02, chloroform), R_F 0.46 (solvent *D*); ν_{max}^{film} 3420 cm^{-1}; ^{1}H-n.m.r.: δ 1.31 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.48–2.35 (m, 4 H, 2 H-5, 2 H-6), 3.41 (s, 3 H, OMe), 3.23–4.31 (4 H, H-2,3,4,7), and 4.82 (s, 1 H, H-1); ^{13}C-n.m.r.: δ 17.0 (C-8), 25.4 (C-5), 27.8 (C-6), 55.6 (OMe), 71.1, 73.0, 74.6, 75.1 (C-7, C-4, C-2, C-3), and 110.8 (C-1).

Acetylation of **14** with acetic anhydride–pyridine (1 : 1) afforded methyl 2-*O*-acetyl-3,7-anhydro-5,6,8-trideoxy-β-D-*allo*-octofuranoside (**16**), R_F 0.67 (solvent *F*); ^{1}H-n.m.r.: δ 1.25 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.57–2.49 (m, 4 H, 2 H-5, 2 H-6), 2.13 (s, 3 H, OAc), 3.41 (s, 3 H, OMe), 3.26–3.69 (3 H, H-3,4,7), 4.78 (s, 1 H, H-1), and 5.03 (d, 1 H, $J_{2,3}$ 4.0 Hz, H-2).

Acetylation of **15** gave methyl 2-*O*-acetyl-3,7-anhydro-5,6,8-trideoxy-α-L-*talo*-octofuranoside (**17**), R_F 0.63 (solvent *F*); ^{1}H-n.m.r.: δ 1.31 (d, 3 H, $J_{7,8}$ 6.0 Hz, 3 H-8), 1.50–2.32 (m, 4 H, 2 H-5, 2 H-6), 2.13 (s, 3 H, OAc), 3.41 (s, 3 H, OMe), 3.31–3.79 (3 H, H-3,4,7), 4.78 (s, 1 H, H-1), and 5.14 (d, 1 H, $J_{2,3}$ 4.0 Hz, H-2).

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