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Synthetic Approach toward Antibiotic Ezomycins. III. Synthesis of a Protected Derivative of the Octose Moiety

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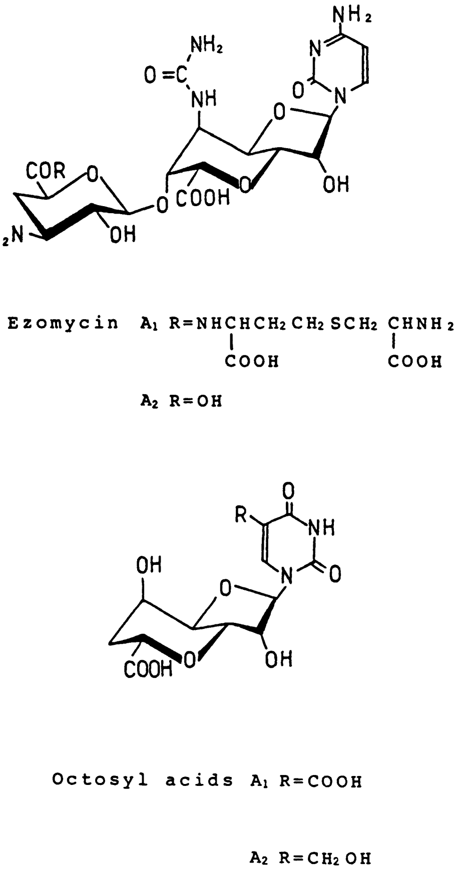
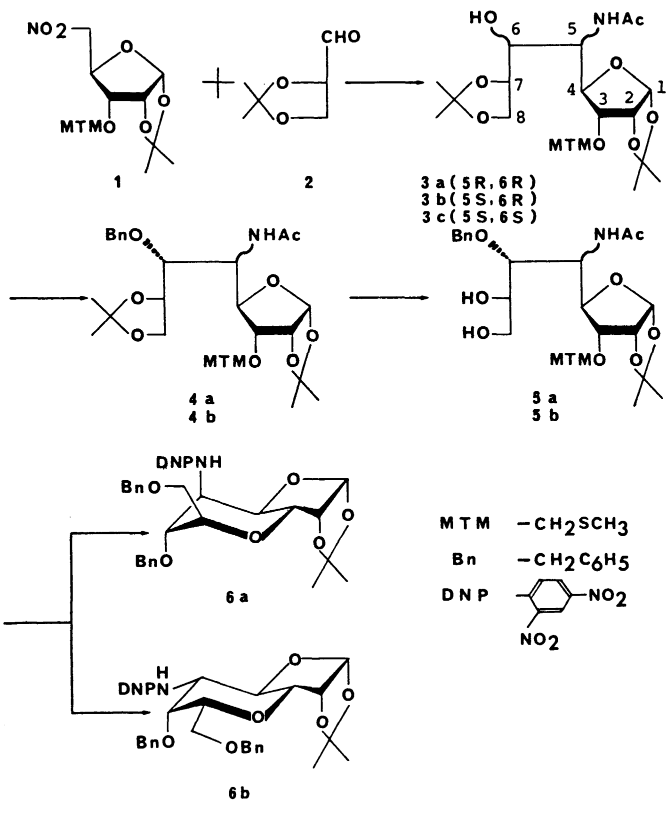
A protected derivative of the octose moiety of antibiotic ezomycins A_1 and A_2, 4-*N*-benzoyl-1-[methyl 3,7-anhydro-2-*O*-benzoyl-5-(3-*N*-benzoylureido)-6-*O*-benzyl-5-deoxy-*β*-D-*threo*-D-allooctofuranos-(1,4)-yluronate]-cytosine, has been synthesized from 5-acetamido-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyll-*β*-L-*erythro*-D-allooctofuranose-(1,4) by a series of reactions involving 23 steps.

Antibiotic ezomycins are produced by a fermentation of a very similar strain of Streptomyces Kitazawaensis.[1] They exhibit antimicrobial activity against limited species of phytopathogenic fungi, such as Sclerotinia and Botritis. Their structures were established by a degradation study and a spectroscopic analysis as shown in Scheme 1.[2–4] The unique bicyclic trans-fused 3,7-anhydrooctofuranose-(1,4) skeleton was also found in octosyl acids.[5] Several synthetic approaches toward 3,7-anhydrooctofuranose-(1,4) derivatives have been reported,[6–8] and total syntheses of octosyl acid A_1 were recently published by two groups.[9,10] However, so far any synthesis of the octose moiety of ezomycins has not appeared in the literature.

In the preceding papers,[11,12] a preliminary investigation on the synthesis of 5-acetamido-5-deoxy-octofuranose-(1,4) derivatives and their conversion into 3,7-anhydrides has been described. A potassium fluoride-catalyzed Henry reaction between 5-nitro-D-ribose derivative (**1**) and L-glyceraldehyde derivative (**2**) and a successive hydrogenation followed by *N*-acetylation afforded three diastereomeric isomers (**3a**, **3b** and **3c**). Also their absolute configurations of the newly introduced chiral centers on C-5 and C-6 have been established. The configurations of the major product **3a** were found to be identical with those of the octose moiety of ezomycins. Furthermore, from **3a** and **3b** 3,7-anhydride (**6a** and **6b**) could be successfully synthesized by a series of reactions involving ten and



Scheme 1.



Scheme 2.

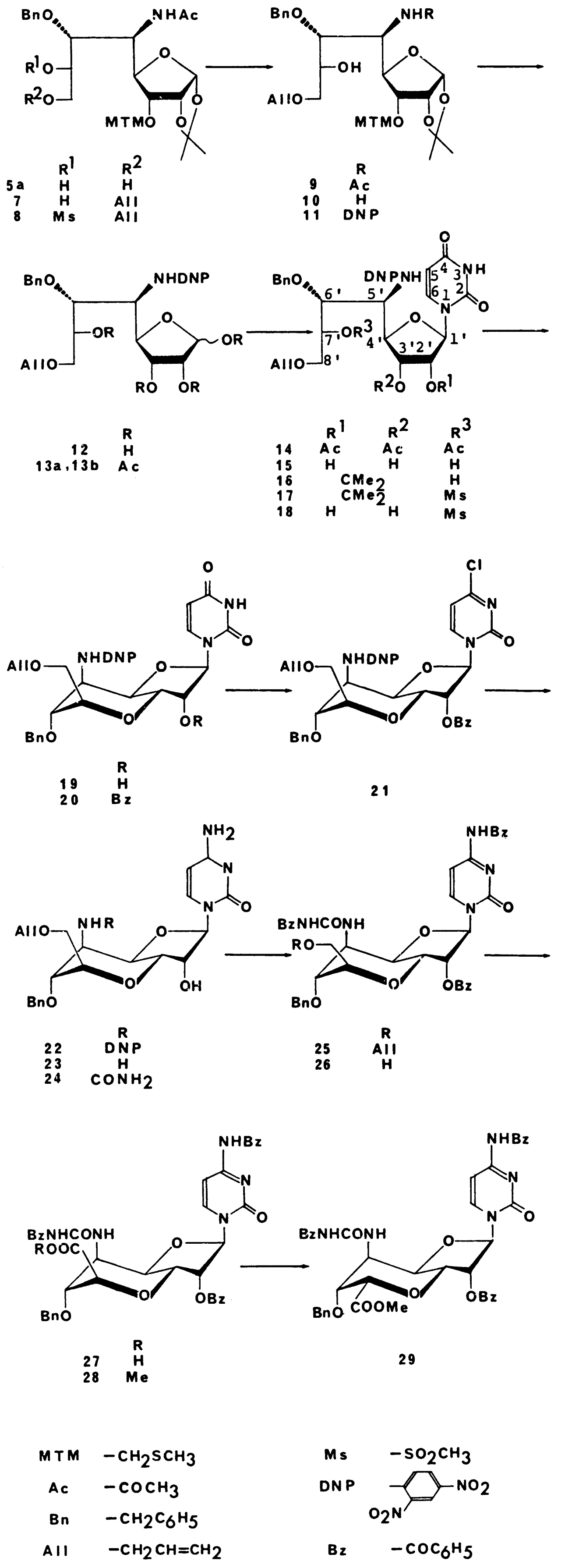
eight steps, respectively.

In the present paper, we wish to report a synthesis of the octose moiety of ezomycins A_1 and A_2 as a protected form.

Results

A preparation of **5a** was previously described.[11] *O*-Benzylation of an intact mixture (67% yield from **1**) of **3a** and **3b**, which could not be separated chromatographically, with benzyl bromide and sodium hydride in *N,N*-dimethylformamide (DMF) gave the corresponding benzyl ethers (**4a** and **4b**), which could be isolated readily in 49 and 30% yield, respectively. Selective removal of 7,8-*O*-isopropylidene group in **4a** with aqueous acetic acid afforded a diol (**5a**) in 91% yield.

Preferential protection of a primary alcoholic group of **5a** with allyl bromide and sodium hydride in tetrahydrofuran (THF) gave an allyl ether (**7**) in 65% yield. *O*-Mesylation of **7** with methanesulfonyl chloride in pyridine and successive treatment of the resultant mesylate (**8**) with sodium hydride in DMF followed by an acidic workup with silica gel afforded an epimer (**9**) at C-7 in a high yield. An alkaline hydrolysis of **9** with sodium hydroxide in aqueous 2-methoxyethanol and successive treatment of the free amine (**10**) with 2,4-dinitrofluorobenzene and triethylamine in THF gave a reprotected compound **11** in a high yield. Simultaneous removal of 1,2-*O*-isopropylidene and 3-*O*-methylthiomethyl groups of **11** with aqueous trifluoroacetic acid followed by a conventional *O*-acetylation produced an anomeric mixture of tetra-*O*-acetates (**13a** and **13b** 1/2.8) in 82% yield. A glycosidation of the intact mixture with bis(trimethylsilyl)uracil in the presence of trimethylsilyl trifluoromethanesulfonate in acetonitrile[13] afforded only the aimed β-glycoside (**14**) in a high yield. De-*O*-acetylation with methanolic sodium methoxide, *O*-isopropylidenation with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid in DMF, *O*-mesylation with methanesulfonyl chloride in pyridine and removal of isopropylidene group with aqueous trifluoroacetic acid were successively carried out to give a mesylate (**18**) in 82% yield from **14**. Treatment of **18** with sodium hydride in dimethyl sulfoxide (DMSO) afforded the desired 3,7-anhydride (**19**) in 87% yield. *O*-Benzoylation of **19** with benzoyl chloride in pyridine yielded a benzoate (**20**) almost quantitatively. Treatment of **20** with oxalyl dichloride in 1,2-dichloroethane containing a small amount of DMF and successive ammonolysis of the resultant chloropyrimidinone (**21**) with methanolic ammonia gave a cytosine derivative (**22**) in 80% yield. De-*N*-protection of **22** with Amberlite IRA-400 (OH^-) in a mixture of acetone, methanol and water[14] and successive *N*-carbamoylation of the resultant amine (**23**) with



Scheme 3.

sodium cyanate in aqueous acetic acid[15] afforded an ureido derivative (**24**) in 31% yield. Benzoylation of **24** with benzoyl chloride in pyridine gave a tribenzoyl compound **25** in 62% yield. Oxidative cleavage of allyl group of **25** with selenium dioxide in dioxane containing acetic acid[16] afforded a primary alcohol (**26**) in 73% yield. Oxidation of **26** with chromium trioxide in acetone containing sulfuric acid yielded an uronic acid (**27**), which was successively esterified with methanolic hydrogen chloride to give a methyl ester (**28**) in 47% yield. Treatment of **28** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF resulted in an epimerization at C-7′ as expected to afford an epimer (**29**) in 60% yield. It was confirmed by comparison with the ^{1}H NMR data of the derivatives from natural product that the uronate (**29**) had the identical configurations with those of the octose moiety of ezomycins.[2]

Experimental

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. IR spectra were recorded on a Hitachi 225 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or a JEOL FX-200 (200 MHz) spectrometer with a reference to tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi M-80A or a Hitachi M-80B spectrometer. Solutions were dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C. Column chromatography was performed using Merck Kieselgel 60 F$_{254}$ (Art. 7734) or Wakogel C-200. Preparative TLC was performed on glass plates coated with Merck Kieselgel 60 F$_{254}$ (Art. 5715).

5-Acetamido-8-*O*-allyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-*β*-L-*erythro*-D-allooctofuranose-(1,4) (7). To a solution of **5a** (2.80 g) in anhydrous THF (28 ml) were added allyl bromide (0.67 ml) and sodium hydride (60% dispersion in mineral oil, 475 mg) under ice cooling, and the mixture was allowed to stand for 40 h in the refrigerator. After addition of cold water (100 ml), the mixture was repeatedly extracted with dichloromethane. The combined extract was dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 1:2) to afford 1.96 g (64.5%) of **7** as crystals and 0.35 g (12.5%) of the starting material. Recrystallization from cyclohexane–toluene (2:1 v/v) yielded an analytical sample: Mp 130—131 °C; $[\alpha]_D^{27}$ +8.5° (*c* 1.09, $CHCl_3$); IR (KBr) 3240, 3080, 1635 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.36, 1.54 (3H×2, s×2, CMe$_2$), 1.99 (3H, s, NHAc), 2.18 (3H, s, SMe), 5.25 (2H, m, $OCH_2CH{=}C\underline{H}_2$), 5.81 (1H, d, *J*=5 Hz, H-1), 5.69—6.18 (2H, NH and $OCH_2C\underline{H}{=}CH_2$), 7.35 (5H, s, Ph).

Found: C, 58.77; H, 7.18; N, 2.71%. Calcd for $C_{25}H_{37}O_8NS$: C, 58.69; H, 7.29; N, 2.74%.

5-Acetamido-8-*O*-allyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-*α*-D-*threo*-D-allooctofuranose-(1,4) (9). To a solution of **7** (2.34 g) in dry pyridine (24 ml) was added methanesulfonyl chloride (1.06 ml) under ice cooling, and the mixture was allowed to stand for 14 h in the refrigerator. After addition of cold water (2 ml) the mixture was concentrated, and the residue was dissolved in ethyl acetate, and the solution was washed with aqueous sodium hydrogencarbonate and water successively, dried and concentrated to dryness. The residue was dissolved in anhydrous DMF (24 ml), and under ice cooling to the solution was added sodium hydride (732 mg). After 90 min at room temperature, the reaction mixture was partitioned between cold water and ethyl acetate. The organic layer was repeatedly washed with water, dried and concentrated to dryness. The residue was dissolved in a small amount of toluene, and a silica-gel column was charged with the solution. After 2 h, elution (toluene–ethyl acetate (v/v) 1:2) gave 2.28 g (97.2%) of **9** as crystals: Mp 91—92 °C; $[\alpha]_D^{25}$ +30.5° (*c* 1.11, $CHCl_3$); IR (KBr) 3410, 3290, 1655 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.34, 1.53 (3H×2, s×2, CMe$_2$), 1.93 (3H, s, NHAc), 2.19 (3H, s, SMe), 2.59 (1H, d, *J*=4 Hz, OH), 5.24 (2H, m, $OCH_2CH{=}C\underline{H}_2$), 5.67—6.13 (3H, H-1, NH and $OCH_2C\underline{H}{=}CH_2$), 7.35 (5H, s, Ph).

Found: C, 58.57; H, 7.13; N, 2.56%. Calcd for $C_{25}H_{37}O_8NS$: C, 58.69; H, 7.29; N, 2.74%.

8-*O*-Allyl-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-*α*-D-*threo*-D-allooctofuranose-(1,4) (11). A mixture of **9** (1.38 g), 2-methoxyethanol (19 ml), water (1 ml) and sodium hydroxide (1.6 g) was heated for 90 min under reflux. The mixture was partitioned between cold water and ethyl acetate. The organic layer was repeatedly washed with water, dried and concentrated to dryness. The residue was dissolved in THF (14 ml), and to the solution were added triethylamine (1.13 ml) and 2,4-dinitrofluorobenzene (1.0 g). After 90 min at room temperature, the reaction solution was diluted with ethyl acetate. The mixture was washed with water, dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 5:1) to give 1.64 g (95.9%) of **11** as amorphous solids: $[\alpha]_D^{24}$ +17.4° (*c* 1.70, $CHCl_3$); IR (KBr) 3430, 3330, 1525 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.34, 1.53 (3H×2, s×2, CMe$_2$), 2.09 (3H, s, SMe), 2.55 (1H, d, *J*=5 Hz, OH), 5.16 (2H, m, $OCH_2CH{=}C\underline{H}_2$), 5.75 (1H, d, *J*=5 Hz, H-1), 5.78 (1H, m, $OCH_2C\underline{H}{=}CH_2$), 7.16 (1H, d, *J*=10 Hz, H-6′), 7.32 (5H, s, Ph), 8.02 (1H, dd, *J*=3, 10 Hz, H-5′), 9.06—9.28 (2H, NH and H-3′).

Found: C, 54.78; H, 5.90; N, 6.30%. Calcd for $C_{29}H_{37}O_{11}N_3S$: C, 54.79; H, 5.87; N, 6.61%.

1,2,3,7-Tetra-*O*-acetyl-8-*O*-allyl-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-*β*(and *α*)-D-*threo*-D-allooctofuranose-(1,4) (13a and 13b). Compound **11** (2.25 g) was dissolved in 90% aqueous trifluoroacetic acid (45 ml), and the solution was allowed to stand for 75 min at room temperature. After coevaporation with toluene, the residue was dissolved in a mixture of dry pyridine (55 ml) and acetic anhydride (5.4 ml). After 1 h at room temperature, the mixture was coevaporated with toluene to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 5:1) to afford 0.54 g of **13a** and 1.50 g of **13b** (total 81.9%) as amorphous solids, respectively.

13a: $[\alpha]_D^{24}$ −137° (*c* 1.34, $CHCl_3$); IR (KBr) 3320, 1750, 1535 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.78, 1.93, 1.98, 2.09 (3H×4, s×4, OAc×4), 4.75 (1H, d, *J*=12 Hz, CH_2Ph), 4.92 (1H, d, *J*=12 Hz, CH_2Ph), 5.79 (1H, m, OCH_2-

C$\underline{\mathrm{H}}$=CH$_2$), 6.10 (1H, s, H-1), 7.09 (1H, d, J=10 Hz, H-6′), 7.38 (5H, s, Ph), 8.26 (1H, dd, J=3, 10 Hz, H-5′), 8.89—9.26 (2H, NH and H-3′).

Found: C, 54.56; H, 5.36; N, 5.77%. Calcd for $\mathrm{C_{32}H_{37}O_{15}N_3}$: C, 54.62; H, 5.30; N, 5.97%.

13b: $[\alpha]_{\mathrm{D}}^{24}$ −51.1° (c 1.00, CHCl$_3$); IR (KBr) 3330, 1750, 1515 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ=1.93, 1,97, 2.03, 2.09 (3H×4, s×4, OAc×4), 4.73 (1H, d, J=12 Hz, CH$_2$Ph), 4.89 (1H, d, J=12 Hz, CH$_2$Ph), 5.82 (1H, m, OCH$_2$-C$\underline{\mathrm{H}}$=CH$_2$), 6.32 (1H, d, J=4 Hz, H-1), 7.39 (5H, s, Ph), 8.27 (1H, dd, J=3, 9 Hz, H-5′), 9.01—9.27 (2H, NH and H-3′).

Found: C, 54.64; H, 5.29; N, 5.91%. Calcd for $\mathrm{C_{32}H_{37}O_{15}N_3}$: C, 54.62; H, 5.30; N, 5.97%.

1-[2,3,7-Tri-*O*-acetyl-8-*O*-allyl-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-*β*-D-*threo*-D-allooctofuranos-(1,4)-yl]uracil (14). A suspension of uracil (1.4 g) in 1,1,1,3,3,3-hexamethyldisilazane (14 ml) was heated for 90 min under reflux to become a clear solution, which was concentrated to give 2,4-*O*-bis(trimethylsilyl)uracil quantitatively as a syrup. Without any purification the product was dissolved in dry acetonitrile (5 ml) containing trimethylsilyl trifluoromethanesulfonate (1.04 ml), and the solution was added to a solution of an intact mixture of **13a** and **13b** (2.04 g) in dry acetonitrile (21 ml). The total mixture was heated for 45 min under reflux. The mixture was partitioned between aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was washed with water, dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 2:3) to give 2.01 g (91.8%) of **14** as amorphous solids: $[\alpha]_{\mathrm{D}}^{23}$ −235° (c 3.52, CHCl$_3$); IR (KBr) 3330, 1750, 1700, 1525 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ=1.86, 1.92, 2.07 (3H×3, s×3, OAc×3), 4.71 (1H, d, J=13 Hz, CH$_2$Ph), 4.92 (1H, d, J=13 Hz, CH$_2$Ph), 7.36 (5H, s, Ph), 8.29 (1H, dd, J=3, 9 Hz, H-5″), 8.99 (1H, d, J=9 Hz, N$\underline{\mathrm{H}}$DNP), 9.11 (1H, d, J=3 Hz, H-3″), 9.74 (1H, s, H-3).

Found: C, 53.88; H, 5.02; N, 9.14%. Calcd for $\mathrm{C_{34}H_{37}O_{15}N_5}$: C, 54.04; H, 4.93; N, 9.27%.

1-[8-*O*-Allyl-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-7-*O*-methylsulfonyl-*β*-D-*threo*-D-allooctofuranos-(1,4)-yl]uracil (18). A solution of **14** (1.08 g) in 0.1 M methanolic sodium methoxide (20 ml) was stirred for 3 h under ice cooling. The solution was neutralized with Amberlite IR-120 (H$^+$), and the resin was filtered off. The filtrate was concentrated to dryness, and the residue was dissolved in dry DMF (9 ml). To the solution were added 2,2-dimethoxypropane (3.5 ml) and p-toluenesulfonic acid monohydrate (55 mg), and the mixture was stirred for 10 h at room temperature. The reaction mixture was partitioned between aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was repeatedly washed with water, dried and concentrated to dryness. The residue was dissolved in dry pyridine (9 ml), and to the solution was added methanesulfonyl chloride (0.33 ml) under ice cooling. The mixture was stirred for 90 min at room temperature, and partitioned between aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was washed with water, dried and concentrated to dryness. The residue was dissolved in ice-cooled 90% aqueous trifluoroacetic acid (10 ml). After 3 h under ice cooling the solution was concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 1:3) to afford 824 mg (81.6% from **14**) of **18** as crystals: Mp 166—167 °C; $[\alpha]_{\mathrm{D}}^{24}$ −134° (c 3.16, CHCl$_3$); IR (KBr) 3280, 1675, 1515, 1175 cm^{-1}; ^{1}H NMR (90 MHz, CD$_3$COCD$_3$) δ=2.98 (3H, s, SO$_2$Me), 8.30 (1H, dd, J=3, 9 Hz, H-5″), 9.02 (1H, d, J=3 Hz, H-3″), 9.29 (1H, d, J=11 Hz, N$\underline{\mathrm{H}}$DNP), 10.20 (1H, bs, H-3).

Found: C, 49.36; H, 4.75; N, 9.94%. Calcd for $\mathrm{C_{29}H_{33}O_{14}N_5S}$: C, 49.22; H, 4.70; N, 9.90%.

1-[8-*O*-Allyl-3,7-anhydro-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-*α*-L-*erythro*-D-allooctofuranos-(1,4)-yl]uracil (19). To a solution of **18** (1.41 g) in anhydrous DMSO (14 ml) was added sodium hydride (0.40 g), and the mixture was stirred for 4 h at 30 °C. The reaction mixture was poured into cold water, and the mixture was extracted with ethyl acetate. The extract was dried and concentrated to dryness, and the residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 1:5) to give 1.06 g (86.9%) of **19** as amorphous solids: $[\alpha]_{\mathrm{D}}^{23}$ +206° (c 2.17, CHCl$_3$); IR (KBr) 3330, 1730, 1695, 1515 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ=5.59 (1H, s, H-1′), 6.33 (1H, d, J=10 Hz, H-6″), 7.18 (1H, d, J=8 Hz, H-6), 7.45 (5H, s, Ph), 7.94 (1H, dd, J=3, 9 Hz, H-5″), 8.74 (1H, d, J=5 Hz, N$\underline{\mathrm{H}}$DNP), 8.98 (1H, d, J=3 Hz, H-3″), 9.92 (1H, bs, H-3).

Found: C, 54.71; H, 4.76; N, 11.09%. Calcd for $\mathrm{C_{28}H_{29}O_{11}N_5}$: C, 54.99; H, 4.78; N, 11.45%.

1-[8-*O*-Allyl-3,7-anhydro-2-*O*-benzoyl-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-*α*-L-*erythro*-D-allooctofuranos-(1,4)-yl]uracil (20). To a solution of **19** (531 mg) in dry pyridine (5.3 ml) was added benzoyl chloride (0.18 ml), and the mixture was stirred for 1 h under ice cooling. After addition of water (1 ml) the mixture was concentrated. The residue was dissolved in ethyl acetate, and the solution was washed with aqueous sodium hydrogencarbonate and water successively, dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 2:1) to afford 610 mg (98.2%) of **20** as amorphous solids: $[\alpha]_{\mathrm{D}}^{22}$ +114° (c 1.20, CHCl$_3$); IR (KBr) 3330, 1720, 1520, 1515 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ=5.56 (1H, s, H-1′), 6.30 (1H, d, J=10 Hz, H-6″), 7.14 (1H, d, J=8 Hz, H-6), 7.46 (5H, s, CH$_2$Ph), 7.93 (1H, dd, J=2, 9 Hz, H-5″), 8,77 (1H, d, J=5 Hz, N$\underline{\mathrm{H}}$DNP), 8.99 (1H, d, J=2 Hz, H-3″), 9.34 (1H, bs, H-3); MS (FD) 716 (M+1).

1-[8-*O*-Allyl-3,7-anhydro-6-*O*-benzyl-5-deoxy-5-(2,4-dinitrophenylamino)-*α*-L-*erythro*-D-allooctofuranos-(1,4)-yl]cytosine (22). To a solution of **20** (463 mg) in dry 1,2-dichloroethane (25 ml) were added oxalyl dichloride (0.42 ml) and dry DMF (1 drop) under ice cooling, and the mixture was stirred for 36 h at room temperature. The mixture was poured into cold 1% aqueous sodium hydrogencarbonate, and the mixture was extracted with ethyl acetate. The extract was repeatedly washed with water, dried and concentrated to dryness. The residue was dissolved in saturated methanolic ammonia (60 ml), and the solution was allowed to stand for 5 d at ambient temperature. The reaction mixture was concentrated to dryness, and the residue was chromatographed on a silica-gel column (dichloromethane–methanol (v/v) 10:1) to afford 316 mg (80.0%) of **22** as amorphous solids: $[\alpha]_{\mathrm{D}}^{22}$ +173° (c 1.05, MeOH); IR (KBr) 3390, 1650 cm^{-1}; ^{1}H NMR (90 MHz, CD$_3$OD) δ=5.65 (1H, d, J=9 Hz, H-5), 5.70 (1H, s, H-1′), 6.84 (1H, d, J=11 Hz, H-6″), 7.40 (5H, s, Ph), 8.08 (1H, dd, J=2, 9 Hz, H-5″), 8.95 (1H, d, J=2 Hz, H-3″); MS (SIMS) 611 (M+1).

1-[8-*O*-Allyl-3,7-anhydro-6-*O*-benzyl-5-deoxy-5-ureido-α-L-*erythro*-D-allooctofuranos-(1,4)-yl]cytosine (24). A mixture of **22** (267 mg), Amberlite IRA-400 (OH^-) (ca. 3 ml), acetone (14 ml), methanol (7 ml) and water (7 ml) was heated for 3 h under reflux. After the resin was filtered off, the filtrate was concentrated to dryness. To a solution of the residue in 30% aqueous acetic acid (15 ml) was added sodium cyanate (270 mg), and the mixture was allowed to stand for 10 h at 50 °C. The reaction mixture was coevaporated with ethanol, and the residue was roughly chromatographed on a silica-gel column (dichloromethane–methanol (v/v) 5:1). Crystallization of the crude product from ethanol gave 66 mg (31%) of **24**: Mp 158—159 °C; $[\alpha]_D^{25}$ +21° (*c* 0.76, $CHCl_3$–MeOH (v/v) 1:1) IR (KBr) 3400, 1670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$–CD_3OD (v/v) 1:1) δ=5.30 (1H, s, H-1′), 5.84 (1H, d, *J*=8 Hz, H-5), 7.32 (5H, s, Ph), 7.51 (1H, d, *J*=8 Hz, H-6); MS (SIMS) 488 (M+1).

1-[8-*O*-Allyl-3,7-anhydro-2-*O*-benzoyl-5-(3-benzoylureido)-6-*O*-benzyl-5-deoxy-α-L-*erythro*-D-allooctofuranos-(1,4)-yl]-4-*N*-benzoylcytosine (25). To a solution of **24** (66 mg) in dry pyridine (2 ml) was added benzoyl chloride (145 mg) at −20 °C, and the mixture was stirred for 1 h under ice cooling. The reaction mixture was diluted with ethyl acetate, and the solution was washed with aqueous sodium hydrogencarbonate and water successively, dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 2:3) to afford 68 mg (62%) of **25** as crystals. Recrystallization from toluene yielded an analytical sample: mp 200—201 °C (decomp); $[\alpha]_D^{25}$ +42° (*c* 0.65, $CHCl_3$); IR (KBr) 3400, 3250, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.65 (1H, dd, *J*=6, 10 Hz, H-8′), 3.76 (1H, dd, *J*=5, 10 Hz, H-8′), 4.60 (1H, d, *J*=12 Hz, CH_2Ph), 4.74 (1H, d, *J*=12 Hz, CH_2Ph), 5.08—5.20 (3H, H-5′ and $OCH_2CH{=}\underline{CH_2}$), 5.77 (1H, d, *J*=6 Hz, H-2′), 5.80 (1H, m, $OCH_2CH{=}CH_2$), 6.18 (1H, s, H-1′), 7.30 (5H, s, $CH_2\underline{Ph}$).

Found: C, 66.05; H, 5.17; N, 8.60%. Calcd for $C_{44}H_{41}O_{10}N_5$: C, 66.07; H, 5.17; N, 8.76%.

1-[3,7-Anhydro-2-*O*-benzoyl-5-(3-benzoylureido)-6-*O*-benzyl-5-deoxy-α-L-*erythro*-D-allooctofuranos-(1,4)-yl]-4-*N*-benzoylcytosine (26). To a solution of **25** (45 mg) in anhydrous dioxane (4.5 ml) were added selenium dioxide (7.5 mg) and acetic acid (5 μl), and the mixture was vigorously stirred for 45 min under reflux. The reaction mixture was concentrated to dryness, and the residue was chromatographed on a silica-gel column (ethyl acetate) to give 31 mg (73%) of **26** as amorphous solids: $[\alpha]_D^{25}$ +32° (*c* 0.69, $CHCl_3$); IR (chloroform) 3270, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=4.41 (1H, dd, *J*=6, 10 Hz, H-3′), 4.55 (1H, d, *J*=12 Hz, CH_2Ph), 4.67 (1H, d, *J*=12 Hz, CH_2Ph), 4.92 (1H, m, H-5′), 5.95 (1H, d, *J*=6 Hz, H-2′), 6.10 (1H, s, H-1′), 7.25 (5H, s, Ph); MS (FD) 760 (M+1).

4-*N*-Benzoyl-1-[methyl 3,7-anhydro-2-*O*-benzoyl-5-(3-benzoylureido)-6-*O*-benzyl-5-deoxy-α-L-*erythro*-D-allooctofuranos-(1,4)-yluronate]cytosine (28). To a solution of **26** (31 mg) in acetone (4 ml) was added Jones' reagent (0.3 ml, a solution of chromic trioxide (2.67 g) in sulfuric acid (2.3 ml) diluted with water to a volume of 10 ml) under ice cooling, and the mixture was stirred for 1 h under ice cooling. After the reaction mixture was diluted with ethyl acetate the solution was repeatedly washed with water, dried and concentrated to dryness. The residue was dissolved in 5% methanolic hydrogen chloride, and the solution was refluxed for 1 h. The reaction solution was concentrated to dryness, and the residue was dissolved in pyridine (2 ml). To the solution was added benzoyl chloride (30 mg) under ice cooling, and the mixture was stirred for 15 min under ice cooling. The mixture was partitioned between aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was washed with water, dried and concentrated to dryness. The residue was chromatographed on a silica-gel column (toluene–ethyl acetate (v/v) 1:2) to give 16 mg (47%) of **28** of amorphous solids: $[\alpha]_D^{25}$ +27° (*c* 1.05, $CHCl_3$); IR (KBr) 3400, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.70 (3H, s, COOMe), 4.52 (1H, dd, *J*=5, 11 Hz, H-3′), 4.88 (1H, m, H-5′), 5.87 (1H, d, *J*=5 Hz, H-2′), 6.24 (1H, s, H-1′), 7.26 (5H, s, CH_2Ph); MS (FD) 788 (M+1).

4-*N*-Benzoyl-1-[methyl-3,7-anhydro-2-*O*-benzoyl-5-(3-*N*-benzoylureido)-6-*O*-benzyl-5-deoxy-β-D-*threo*-D-allooctofuranos-(1,4)-yluronate]cytosine (29). To a solution of **28** (11.3 mg) in dry DMF (0.5 ml) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (20 mg), and the mixture was stirred for 2 h at room temperature. After addition of acetic acid (20 mg) the mixture was diluted with ethyl acetate, and the solution was repeatedly washed with water, dried and concentrated to dryness. The residue was chromatographed on a silica-gel preparative plate (toluene–ethyl acetate (v/v) 2:3) to afford 6.8 mg (60%) of **29** as amorphous solids: $[\alpha]_D^{25}$ +5.2° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=3.55 (3H, s, COOMe), 4.33 (1H, dd, *J*=5.5, 11 Hz, H-3′), 4.42 (1H, dd, *J*=2.5, 5.5 Hz, H-6′), 4.61 (1H, d, *J*=2.5 Hz, H-7′), 4.62 (1H, d, *J*=12 Hz, CH_2Ph), 4.66 (1H, dd, *J*=4.5, 11 Hz, H-4′), 4.82 (1H, d, *J*=12 Hz, CH_2Ph), 4.90 (1H, m, H-5′), 5.81 (1H, d, *J*=5.5 Hz, H-2′), 5.95 (1H, s, H-1′), 7.32 (5H, s, CH_2Ph); MS (FD) 788 (M+1).

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