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TOTAL SYNTHESIS OF TUNICAMYCIN*

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ABSTRACT

The first total synthesis of tunicamycin V, a major component of tunicamycin homologues, is described. Condensation of 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-propanoyl-α-D-glucopyranose with 1-[(11*R*)-2,3,5,8,9-penta-*O*-acetyl-10-(benzyloxycarbonyl)amino-11-chloro-6,10,11-trideoxy-α-L-*galacto*-D-*allo*-undecodialdo-1,4-furanose-11,7-pyranose-1-yl]uracil in the presence of silver salts gave the desired product. *O*-Deacylation of the product, followed by catalytic hydrogenolysis, *N*-acylation with (*E*)-13-methyl-2-tetradecenoic acid and successive hydrolysis, afforded tunicamycin V.

INTRODUCTION

The antibiotic tunicamycin has been isolated from the fermentation broth of *Streptomyces lysosuperficus* as a mixture of several homologues that differ from each other in their fatty acid residues[1]. The chemical structures of the antibiotics were determined by Ito *et al.*[2] in 1980 as shown in Scheme 1. Tunicamycins are composed of uracil, a fatty acid, and a carbohydrate comprised of 2-acetamido-2-deoxy-D-glucose and a C_{11}-dialdose named tunicamine[3].

The antibiotic tunicamycin exhibits wide biological properties such as antiviral and antimicrobial activity, G_1 arrest of cell culture, higher susceptibility of malignant cells than normal cells, alteration in translocation of intracellular materials, and modulation of cell differentiation. These activities are attributed to the inhibition by tunicamycin of the transfer of *N*-acetylglucosamine 1-phosphate from UDP-*N*-acetylglucosamine to dolichol monophosphate[4]. Almost all biological activities of tunicamycin have been determined with a mixture of the antibiotic homologues.

Recently, the tunicamycin mixture was separated by l.c. into sixteen homologues[5]. It has been shown that the biological activities of some separated components are slightly different[6].

*Part VIII of the series: Synthetic Approaches Toward Antibiotic Tunicamycins.

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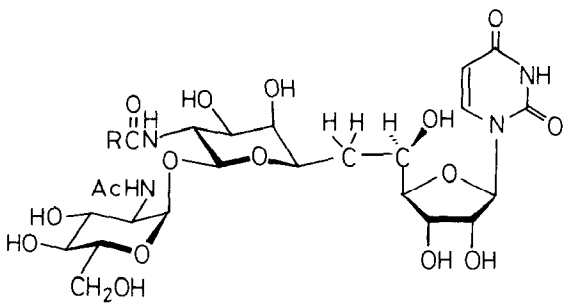


R		R	
I :	$(CH_3)_2CH(CH_2)_7CH{=}CH-$	VI :	$(CH_3)_2CH(CH_2)_{11}-$
II :	$(CH_3)_2CH(CH_2)_8CH{=}CH-$	VII :	$(CH_3)_2CH(CH_2)_{10}CH{=}CH-$
III :	$CH_3(CH_2)_{10}CH{=}CH-$	VIII :	$CH_3(CH_2)_{12}CH{=}CH-$
IV :	$CH_3(CH_2)_{11}CH{=}CH-$	IX :	$CH_3(CH_2)_{13}CH{=}CH-$
V :	$(CH_3)_2CH(CH_2)_9CH{=}CH-$	X :	$(CH_3)_2CH(CH_2)_{11}CH{=}CH-$

Tunicamycins

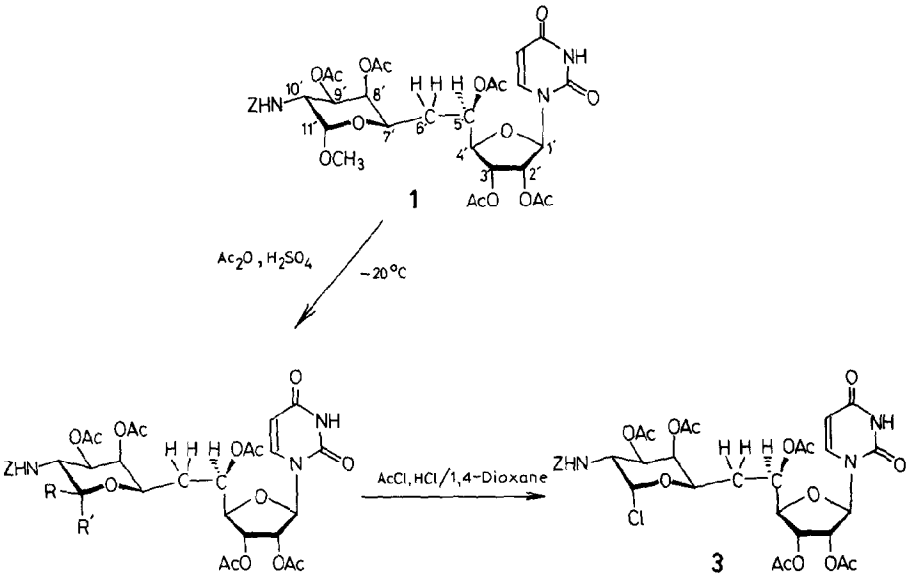
Scheme 1

Tunicamycin V, formerly designated tunicamycin A, is a major component of tunicamycins and consists of uracil, tunicamine, 2-acetamido-2-deoxy-D-glucose, and an (*E*)-13-methyl-2-tetradecenoic acid residue[1].

In a preceding paper[7], tunicaminyluracil was synthesized in protected form. As a continuation of this work, tunicamycin V has now been synthesized from the tunicaminyluracil derivative. The synthetic method described herein may be applied for other tunicamycin homologues and to the chemical modification of tunicamycin.

RESULTS AND DISCUSSION

Synthesis of 2-acetamido-2-deoxy-α-D-glucosyltunicaminyluracil derivative (**11**). — Acetolysis of the tunicaminyluracil derivative 1-[(11*S*)-2,3,5,8,9-penta-*O*-acetyl-10-(benzyloxycarbonyl)amino-6,10-dideoxy-11-*O*-methyl-α-L-*galacto*-D-*allo*-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil[7] (**1**) in acetic anhydride containing a small volume of conc. sulfuric acid for 1 h at −20° gave an anomeric mixture of the hexaacetates (**2a**:**2b**, 7:1) as an amorphous solid in 70% yield. Chlorination of **2** in a mixture of acetyl chloride and 1,4-dioxane saturated with dry hydrogen chloride for 14 h at room temperature afforded 1-[(11*R*)-2,3,5,8,9-penta-*O*-acetyl-10-(benzyloxycarbonyl)amino-11-chloro-6,10,11-trideoxy-α-L-*galacto*-D-*allo*-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil (**3**), m.p. 105° (dec.) in 74% yield (Scheme 2).



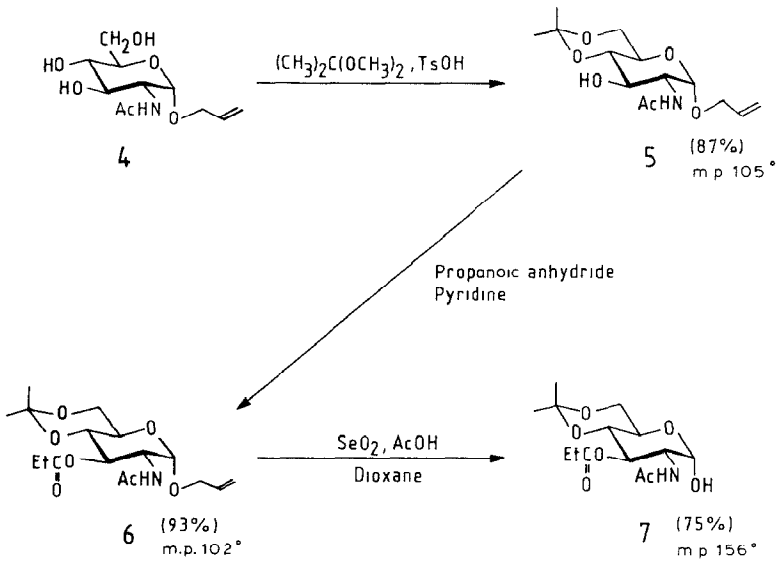
Scheme 2

The aglycon, 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-3-*O*-propanoyl-α-D-glucopyranose (**7**) was prepared as shown in Scheme 3. *O*-Isopropylidenation of allyl 2-acetamido-2-deoxy-α-D-glucopyranoside[8] (**4**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave the 4,6-*O*-isopropylidene derivative **5**, m.p. 105° in 87% yield. *O*-Acylation of **5** with propanoic anhydride in pyridine afforded the 3-propanoate (**6**), m.p. 102° in 93% yield. Oxidative cleavage of the 1-*O*-allyl group in **6** with selenium dioxide in 1,4-dioxane containing 1.5 mol eq. of acetic acid gave **7**, m.p. 156° in 72% yield. The ^{1}H-n.m.r. spectrum of **7** shows that the configuration at the anomeric position is α.

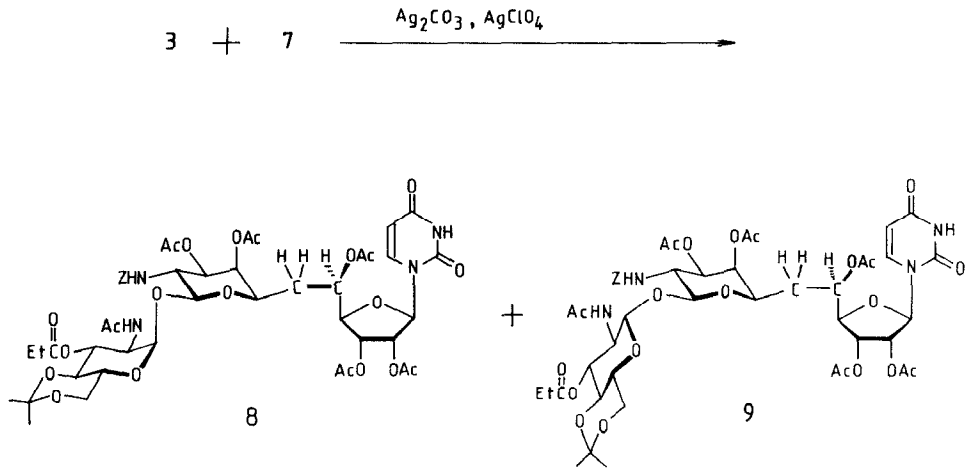
Condensation of the chloride **3** and the aglycon **7** in dichloromethane in the presence of silver carbonate and silver perchlorate under argon in the dark gave condensation products **8** and **9** in 18 and 15% yields, respectively (Scheme 4).

The ^{1}H-n.m.r. spectrum of **8** shows three doublets for anomeric protons at δ 4.65 (*J* 8.0 Hz), 5.01 (*J* 3.5 Hz), and 5.63 (*J* 4.0 Hz). The narrow, low-field doublet (δ 5.63) is attributable to the *N*-glycosylic anomeric proton (H-1′). A proton-decoupling study showed the doublet at δ 5.01 to be the anomeric-proton resonance of the 2-acetamido-2-deoxy-α-D-glucose residue (H-1″) and the wide doublet at δ 4.65 is the anomeric-proton resonance of a β-type (10′,11′ *trans*) glycoside.

The ^{1}H-n.m.r. spectrum of **9** is similar to that of **8** except for the doublets for the anomeric protons at δ 4.58 (*J* 8.0 Hz) and 4.82 (*J* 8.0 Hz). The two, rather wide, doublets arise from a β,β type glycoside. Therefore, **8** is the desired compound having a β,α type 11′,1″ glycosidic linkage.

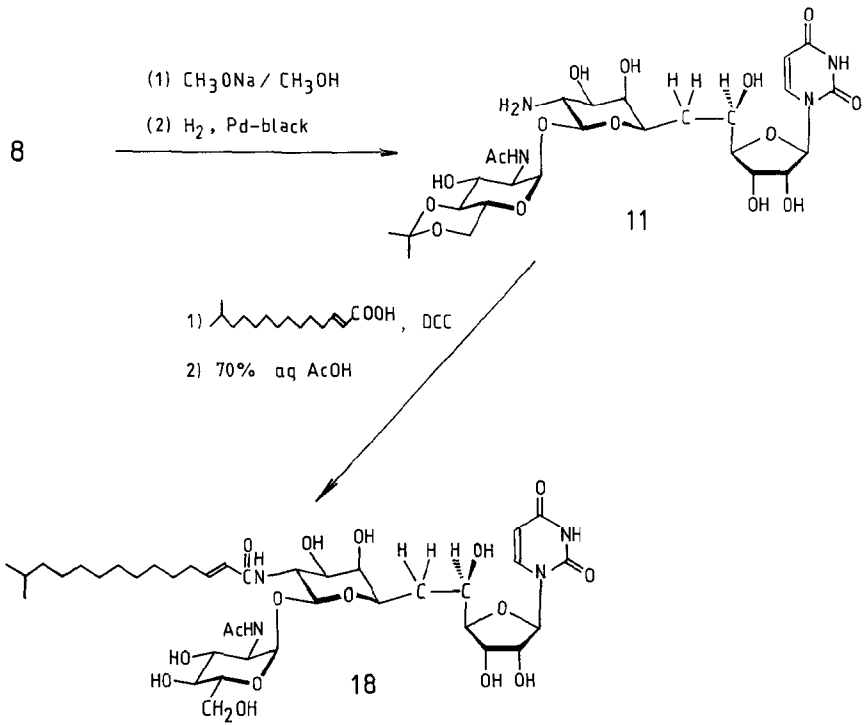


Scheme 3



Scheme 4

O-Deacylation of **8** in 0.1M methanolic sodium methoxide gave 1-[(11*S*)-11-*O*-(2-acetamido-2-dexoy-4,6-*O*-isopropylidene-α-D-glucopyranosyl)-10-(benzyloxycarbonyl)amino-6,10-dideoxy-α-L-*galacto*-D-*allo*-undecodialdo-1,4-furanose-11,7-pyranosy-1-yl]uracil (**10**) in 83% yield. Catalytic hydrogenolysis of **10** in methanol in the presence of palladium black under hydrogen (3.4 kg/cm^2) for 1.5 h afforded the 10′-amino derivative (**11**) (Scheme 5).

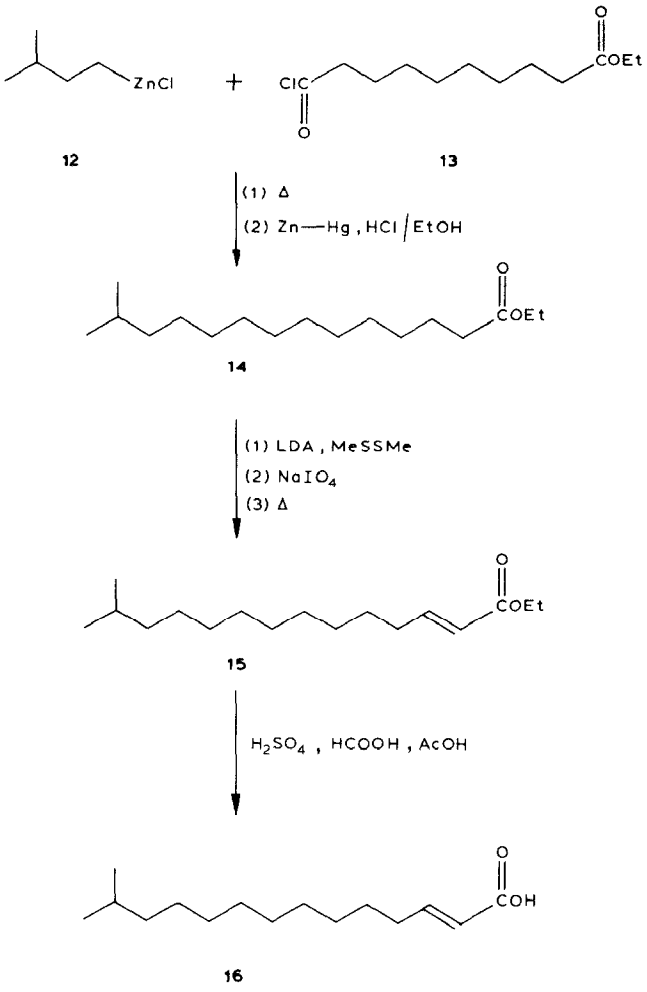


Scheme 5

Synthesis of (E)-*13-methyl-2-tetradecenoic acid* (**16**). — Addition of (2-methylbutyl)zinc chloride[9] (**12**) to ethyl 10-chloro-10-oxodecanoate[10] (**13**), followed by Clemmensen reduction of the resultant keto ester with amalgamated zinc and hydrogen chloride under reflux in ethanol gave ethyl 13-methyltetradecanoate (**14**) in 37% overall yield.

Dehydrogenation of **14** at the C-2 position was performed by a method described by Trost *et al.*[11] and ethyl (*E*)-13-methyl-2-tetradecenoate (**15**) was obtained in 76% yield. Hydrolysis of **15** in a mixture of acetic acid, formic acid, and a small volume of sulfuric acid at 90° afforded (*E*)-13-methyl-2-tetradecenoic acid (**16**) in 86% yield (Scheme 6).

Synthesis of tunicamycin V (**18**). — *N*-Acylation of **11** with **16** in the presence of *N,N'*-dicyclohexylcarbodiimide, followed by hydrolysis of the α-isopropylidene group in aqueous acetic acid afforded tunicamycin V (**18**), as shown in Scheme 5. Compound **18** was identical with an authentic sample in all respects. Compound **18** exhibited antiviral activity against Newcastle disease virus and inhibited glycoconjugate biosynthesis as well as the formation of lipid-linked intermediates *in vitro*[12].



Scheme 6

EXPERIMENTAL

General methods. — Solutions were evaporated under diminished pressure below 40°. Chromatography was performed on a column of silica gel (Wakogel C-200 and/or C-300, Wako Pure Chemical Co. Ltd.). T.l.c. was performed on Merck silica gel 60 F_{254} Art. 5715 and detection was effected with 10% sulfuric acid and u.v. absorption. Melting points are determined in capillary tubes, unless otherwise noted, and are uncorrected. Optical rotations were recorded with a Japan Spectroscopic DIP-4 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 spectrometer (90 MHz) or a JEOL FX-200 spectrometer (200 MHz), using tetramethylsilane as an internal standard. I.r. spectra were recorded with a Hitachi 225 spectrophotometer.

*1-[(11R)-2,3,5,8,9,11-Hexa-O-acetyl-10-(benzyloxycarbonyl)amino-6,10-dideoxy-α-*L-galacto-D-allo-*undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**2a**) *and its 11'S anomer* (**2b**). — Compound[7] **1** (42 mg) was dissolved in a mixture of acetic anhydride (5.0 mL) and sulfuric acid (0.25 mL) at −20° with stirring. After 1 h at −20°, the mixture was poured into ice-cold water (50 mL) and extracted with chloroform (40 mL). The organic layer was washed successively with saturated $NaHCO_3$ solution (2 × 20 mL) and water (30 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue on a column of silica gel (C-300, 13 g, 50:1 chloroform–ethanol) gave 27 mg of **2a** and 4 mg of **2b** (**2a**:**2b**, 7:1, total yield 70%). Compound **2a**: powder; R_F 0.31 on t.l.c. (20:1 chloroform–ethanol); m.p. 115–116° (hot stage), $[\alpha]_D^{21}$ +69° (*c* 0.4, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.88, 2.05, 2.07, 2.09, 2.12, 2.15 (6s, 18 H, OAc), 6.18 (d, 1 H, $J_{10',11'}$ 4.0 Hz, H-11'), 7.34 (s, 5 H, arom. H), and 9.75 (bs, 1 H, uracil NH).

Anal. Calc. for $C_{35}H_{41}N_3O_{18} \cdot H_2O$: C, 51.92; H, 5.35; N, 5.19. Found: C, 52.09; H, 5.10; N, 5.09.

Compound **2b**: powder; R_F 0.29 on t.l.c. (20:1 chloroform–ethanol); m.p. 111–117° (hot stage), $[\alpha]_D^{20}$ +22° (*c* 0.6, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.86, 1.94, 1.99, 2.03, 2.05, 2.13 (6s, 18 H, OAc), 7.30 (s, 5 H, arom. H), and 9.34 (bs, 1 H, uracil NH).

Anal. Found: C, 52.02; H, 5.10; N, 5.09.

*1-[(11R)-2,3,5,8,9,-Penta-O-acetyl-10-(benzyloxycarbonyl)amino-11-chloro-6,10,11-trideoxy-α-*L-galacto-D-allo-*undecodialdo-1,4-furanose-11,7-pyranos-1-yl]-uracil* (**3**). — To a stirred solution of **2** (1.08 g) in acetyl chloride (7 mL) was added a 29 wt% solution of hydrogen chloride in 1,4-dioxane (10 mL) under ice cooling. After stirring for 14 h at room temperature, chloroform (100 mL) was added and the mixture was washed successively with ice-cold water (50 mL), saturated $NaHCO_3$ solution (2 × 50 mL) and ice-cold water (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified on a column of silica gel (C-200, 30 g, ethyl acetate) to give 0.78 g (74%) of **3** as an amorphous powder, R_F 0.26 on t.l.c. (2:1 ethyl acetate–toluene); m.p. 97–105° (dec.), $[\alpha]_D^{19}$ +97.4° (*c* 0.6, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.92, 2.01, 2.07, 2.10, 2.17 (5s, 15 H, Ac), 6.26 (d, 1 H, $J_{10',11'}$ 5.0 Hz, H-11'), and 9.03 (s, 1 H, uracil NH): ν_{max}^{KBr} 3400 (NH) and 1740 cm^{-1} (C=O).

Anal. Calc. for $C_{33}H_{38}ClN_3O_{16}$: C, 51.60; H, 4.99; N, 5.47; Cl, 4.62. Found: C, 51.63; H, 5.09; N, 5.67; Cl, 4.85.

*Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-α-*D-*glucopyranoside* (**5**). — To a stirred suspension of allyl 2-acetamido-2-deoxy-α-D-glucopyranoside[8] (**4**) (1.6 g) in THF (10 mL) was added 2,2-dimethoxypropane (7.6 mL) and *p*-toluenesulfonic acid (120 mg) under ice-cooling. After 14 h at room temperature, the solution was made neutral with Amberlite IRA-400 (OH^-) resin and the resin was filtered off. The filtrate was evaporated and the residue chromatographed on a column of silica gel (C-200, 20 g, ethyl acetate) to give **5** (1.6 g, 87%) as an amorphous powder; R_F 0.52 on t.l.c. (3:1 ethyl acetate–toluene); m.p. 103–107°, $[\alpha]_D^{27}$ +78° (*c* 1.1, chloroform); $\nu_{max}^{CHCl_3}$ 3430 (NH and OH) and 1660 cm^{-1} (C=O).

Anal. Calc. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 56.08; H, 7.58; N, 4.52.

Allyl 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-O-propanoyl-α-D-glucopyranoside (**6**). — To a solution of **5** (910 mg) in pyridine (10 mL) was added propanoic anhydride (0.47 mL) and the solution was stirred for 14 h at room temperature. Chloroform was added and the mixture was successively washed with water (50 mL), saturated $NaHCO_3$ solution (50 mL), and brine (50 mL). The chloroform solution was dried over Na_2SO_4, evaporated, and the residue recrystallized from hexane to give 1.01 g (93%) of **6** as white crystals; R_F 0.40 on t.l.c. (2:1 ethyl acetate–toluene); m.p. 99–105°, $[\alpha]_D^{20}$ +85.1° (*c* 1.1, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.12 (t, 3 H, *J* 7.5 Hz, propanoyl CH_3), 1.38 and 1.48 (2s, 6 H, isopropylidene), 2.33 (q, 2 H, *J* 7.5 Hz, propanoyl CH_2), and 4.83 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); ν_{max}^{KBr} 3270 cm^{-1} (NH).

Anal. Calc. for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.32; H, 7.44; N, 4.05.

2-Acetamido-2-deoxy-4,6-O-isopropylidene-3-O-propanoyl-α-D-glucopyranose (**7**). — A suspension of a mixture of **6** (291 mg), selenium dioxide (99.4 mg) and acetic acid (0.07 mL) in 1,4-dioxane (4 mL) was heated under reflux for 45 min. The mixture was filtered and the insoluble material was washed with 1,4-dioxane (1 mL). Toluene (2 mL) was added to the filtrate and the mixture was evaporated. The resultant residue was purified on a column of silica gel (C-300, 5 g, ethyl acetate) to give 187 mg (72%) of **7** as an amorphous powder, R_F 0.10 on t.l.c. (2:1 ethyl acetate–toluene), m.p. 155–159°, ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.10 (t, 3 H, *J* 6.9 Hz, propanoyl CH_3), 1.35 and 1.45 (2s, 6 H, isopropylidene), 1.93 (s, 3 H, Ac), 2.33 (q, 2 H, *J* 6.9 Hz, propanoyl CH_2), 4.21 (dt, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.4 Hz, $J_{NH,2}$ 10.4 Hz, H-2), 5.19 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), and 6.20 (d, 1 H, $J_{NH,2}$ 10.4 Hz, NH).

Anal. Calc. for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.81; H, 7.06; N, 4.13.

1-[(11S)-11-O-(2-Acetamido-2-deoxy-4,6-O-isopropylidene-3-O-propanoyl-α-D-glucopyranosyl)-2,3,5,8,9-penta-O-acetyl-10-(benzyloxycarbonyl)amino-6,10-dideoxy-α-L-galacto-D-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil (**8**) *and 1-[(11S)-11-O-(2-acetamido-2-deoxy-4,6-O-isopropylidene-3-O-propanoyl-β-D-glucopyranosyl)-2,3,5,8,9-penta-O-acetyl-10-(benzyloxycarbonyl)amino-6,10-dideoxy-α-L-galacto-D-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**9**). — To a solution of **3** (217 mg) and **7** (180 mg) in dichloromethane (1 mL) were added molecular sieves 4A (300 mg), silver carbonate (38 mg), and silver perchlorate (33 mg) under an argon atmosphere in the dark at room temperature. After stirring for 1 h, chloroform (20 mL), saturated $NaHCO_3$ solution (20 mL), and brine (10 mL) were added and the mixture was filtered. Chloroform (20 mL) was added to the filtrate and the organic layer was dried over Na_2SO_4 and evaporated. A solution of the residue in dichloromethane (1 mL) and pyridine (1 mL) was acetylated with acetic anhydride (0.2 mL) for 14 h at room temperature. The

mixture was evaporated and the residue was purified on a column of silica gel (C-300, 20 g, ethyl acetate). Each fraction at R_F 0.30 and 0.16 on t.l.c. (ethyl acetate) was subjected to further column chromatography on silica gel (C-300, 20 g, 27:1 chloroform–ethanol) to give 54.2 mg (18%) of **8** and 44.5 mg (15%) of **9**, respectively. Compound **8**: powder; m.p. 149–151°, $[\alpha]_D^{21}$ +60.7° (*c* 0.54, chloroform); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 1.12 (t, 3 H, *J* 7.6 Hz, propanoyl), 1.44 and 1.49 (2s, 6 H, isopropylidene), 1.88, 1.89, 2.07, 2.09, 2.13, and 2.23 (6s, 18 H, Ac), 2.34 (q, 2 H, *J* 7.6 Hz, propanoyl), 4.65 (d, 1 H, $J_{10',11'}$ 8.0 Hz, H-1′), 5.01 (d, 1 H, $J_{1'',2''}$ 3.5 Hz, H-1″), 5.63 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1′), 5.72 (d, 1 H, $J_{5,6}$ 8.3 Hz, H-5), 6.20 (bd, 1 H, *J* 10.1 Hz, acetamido NH), 7.13 (d, 1 H, $J_{5,6}$ 8.3 Hz, H-6), 7.29 (s, 5 H, arom. H), and 9.45 (bs, 1 H, uracil NH); ν_{max}^{KBr} 3380 (NH), 1735 and 1690 cm^{-1} (C=O).

Anal. Calc. for $C_{47}H_{60}N_4O_{23} \cdot H_2O$: C, 52.91; H, 5.86; N, 5.25. Found: C, 52.82; H, 5.86; N, 5.25.

Compound **9**: powder; m.p. 146–148°, $[\alpha]_D^{27}$ −2.3° (*c* 1.1, chloroform: ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 1.15 (t, 3 H, *J* 7.3 Hz, propanoyl), 1.38 and 1.46 (2s, 6 H, isopropylidene), 1.86, 1.92, 2.12, 2.14, 2.17 (5s, 3 H × 2, 6 H, and 3 H × 2, Ac_6), 2.28 (q, 2 H, *J* 7.3 Hz, propanoyl), 4.58 (d, 1 H, *J* 8.8 Hz, H-11′), 4.82 (d, 1 H, *J* 8.8 Hz, H-1″), and 7.35 (s, 5 H, arom. H).

Anal. Calc. for $C_{47}H_{60}N_4O_{23}$: C, 53.81; H, 5.76; N, 5.34. Found: C, 53.52; H, 5.69; N, 5.23.

*1-[(11S)-11-*O*-(2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-α-*D*-glucopyranosyl)-10-(benzyloxycarbonyl)amino-6,10-dideoxy-α-*L*-*galacto*-*D*-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**10**). — A solution of **8** (54 mg) in 0.1M methanolic sodium methoxide (5 mL) was stirred for 2 h at room temperature. The solution was made neutral with Amberlite IR-120B (H^+) resin and the resin was filtered off. The filtrate was evaporated and the residue chromatographed on a column of silica gel (C-300, 5 g, 5:1 chloroform–methanol) to give 34 mg (83%) of **10** as a white powder; R_F 0.49 on t.l.c. (3:1 chloroform–methanol); m.p. 184–189°, $[\alpha]_D^{26}$ +52.6° (*c* 1.1, methanol); ^{1}H-n.m.r. (200 MHz, CD_3OD): δ 1.34 and 1.48 (2s, 6 H, isopropylidene), 1.88 (s, 3 H, Ac), 4.59 (d, 1 H, $J_{10',11'}$ 7.6 Hz, H-11′), 4.99 (d, 1 H, $J_{1'',2''}$ 3.2 Hz, H-1″), 5.72 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-5), 5.90 (d, 1 H, $J_{1',2'}$ 5.1 Hz, H-1′), 7.32 (s, 5 H, arom. H), and 7.81 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-6); ν_{max}^{KBr} 3400 (OH and NH) and 1680 cm^{-1} (C=O).

*1-[(11S)-11-*O*-(2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-α-*D*-glucopyranosyl)-10-amino-6,10-dideoxy-α-*L*-galacto-*D*-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**11**). — A solution of **10** (43 mg) in methanol (1 mL) was added to a suspension of activated Pd-black (~15 mg) in methanol (1 mL) and the suspension was shaken under a hydrogen atmosphere (3.4 kg/cm^2) for 1.5 h at room temperature. The catalyst was filtered off and washed with small volume of methanol. The filtrate and the washings were combined and the solution was used for the synthesis of **17**.

Ethyl 13-methyltetradecanoate (**14**). — To a solution of (2-methylbutyl)zinc

chloride[9] (**12**), prepared from 1-bromo-3-methylbutane (25 g) in ethyl ether (300 mL) was added dropwise an ethereal solution (50 mL) of 9-ethoxycarbonylnonanoyl chloride[10] (**13**) prepared from decandioyl chloride (25 g). After heating for 3 h under reflux, the mixture was diluted with ethyl ether (300 mL). The solution was washed with water three times, dried over Na_2SO_4, and evaporated to an oil (30 g). A mixture of the oil (5 g) and amalgamated zinc (100 g) in abs. ethanol (300 mL) was saturated with dry HCl and boiled under reflux for 24 h. The mixture was saturated with dry HCl again and boiled under reflux for additional 48 h. The mixture was filtered and the filtrate evaporated. Toluene (500 mL) was added to the residue and the solution was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a column of silica gel (1:1 C-200 and C-300, 250 g, 2:1 hexane–toluene) to give 2.1 g (37%) of **14** as an oil; R_F 0.2 on t.l.c. (2:1 hexane–toluene); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.86 (d, 6 H, J 6.3 Hz, terminal CH_3), 1.26 (m, 23 H, -$(CH_2)_{10}$- and ester CH_3), 2.26 (t, 2 H, J 7.2 Hz, H-2), and 4.10 (q, 2 H, J 7.2 Hz, ester CH_2).

Anal. Calc. for $C_{17}H_{34}O_2$: M = 270.2566. Found: *m/z* 270.2575 (M^+).

Ethyl (E)*-13-methyl-2-tetradecenoate* (**15**). — A solution of vacuum-dried **14** (630 mg, 2.33 mmol) in THF (5 mL) was added dropwise to a stirred solution of lithium diisopropylamide (2.8 mmol) in THF (7 mL) at −78° under argon. After stirring for 30 min at −78°, the solution was added to a solution of dimethyl disulfide (0.23 mL) in THF (4 mL) and allowed to warm to room temperature. To the mixture was added ethyl acetate (100 mL) and the organic layer was washed successively with 10% aqueous hydrochloric acid (80 mL), saturated $NaHCO_3$ solution (80 mL), and water (2 × 50 mL), dried over Na_2SO_4 and evaporated to give ethyl 13-methyl-2-(methylthio)tetradecanoate (717 mg) as a pale-yellow oil. The product was practically one spot on t.l.c. and was used in the next reaction without purification. To a solution of the sulfide (323 mg) in methanol (6 mL) was added a solution of sodium metaperiodate (240 mg) in water (1 mL), and the solution was stirred vigorously for 24 h at room temperature. The mixture was filtered and the insoluble material was washed with ethanol (10 mL). The filtrate and the washings were combined and evaporated. The residue was dissolved in toluene (7 mL) and heated for 14 h at 120°. The solution was concentrated and chromatographed on a column of silica gel (C-300, 30 g, 3:2 hexane–toluene) to give 216 mg (76%) of **15** as an oil; R_F 0.28 on t.l.c. (3:2 hexane–toluene); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.86 (d, 6 H, J 6 Hz, terminal CH_3), 4.15 (q, 2 H, J 6.9 Hz, ester CH_2), 5.78 (bd, 1 H, $J_{2,3}$ 15.6 Hz, H-2), and 6.94 (dt, 1 H, $J_{2,3}$ 15.6, $J_{3,4}$ 7.5 Hz, H-3); ν_{max}^{KBr} 1725 (C=O) and 1650 cm^{-1} (C=C).

Anal. Calc. for $C_{17}H_{32}O_2$: M = 268.2401. Found: *m/z* 268.2423 (M^+).

(E)*-13-Methyl-2-tetradecenoic acid* (**16**). — To a solution of **15** (146 mg) in acetic acid (3 mL) were added formic acid (3 mL) and sulfuric acid (0.05 mL) and the mixture was heated for 24 h at 90°. Formic acid (2 mL) was added and the mixture was heated for an additional 24 h. The mixture was poured into ice-cold water and the resulting precipitate was collected by filtration and washed with water

(3 × 2 mL). The precipitate was chromatographed on a column of silica gel (C-200, 5 g, 1:5 butanone–toluene) to give 112 mg (86%) of **16** as a white powder; R_F 0.49 on t.l.c. (10:1 chloroform–ethanol); m.p. 40°; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.85 (d, 6 H, J 6 Hz, terminal CH_3), 5.81 (bd, 1 H, $J_{2,3}$ 16 Hz, H-2), and 7.10 (dt, 1 H, $J_{2,3}$ 16, $J_{3,4}$ 7.5 Hz, H-3); ν_{max}^{KBr} 1685 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calc. for $C_{15}H_{28}O_2$: C, 74.95; H, 1.74. Found: C, 74.84; H, 11.52.

*1-[(11S)-11-*O*-(2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-α-*D*-glucopyranosyl)-6,10-dideoxy-10-*[(E)*-13methyl-2-tetradecenoyl]-amino-α-*L*-galacto-*D*-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**17**). — To a stirred solution of **16** (78 mg) in dichloromethane (1 mL) was added *N,N'*-dicyclohexylcarbodiimide (67 mg) at room temperature. After 1 h, the solution was added to the aforementioned methanolic solution of **11**, and the mixture was stirred for 24 h. The mixture was evaporated and the residue chromatographed on a column of silica gel (C-300, 5 g, 5:1 chloroform–methanol) to give 22 mg (45%) of **17** as a white powder; R_F 0.64 on t.l.c. (5:1 acetonitrile–water); m.p. 226–232° (dec.) (hot stage), $[\alpha]_D^{23}$ +58° (*c* 1.2, methanol); ^{1}H-n.m.r. (200 MHz, CD_3OD): δ 0.86 (d, 6 H, J 6.5 Hz, H-14‴ and H-15‴), 1.33 and 1.48 (2s, 6 H, isopropylidene), 1.89 (s, 3 H, Ac), 4.50 (d, 1 H, $J_{10',11'}$ 8.3 Hz, H-11′), and 4.92 (d, 1 H, $J_{1'',2''}$ 3.7 Hz, H-1″).

*1-[(11S)-11-*O*-(2-Acetamido-2-deoxy-α-*D*-glucopyranosyl)-6,10-dideoxy-10-[(E)-13-methyl-2-tetradecenoyl]amino-α-*L*-galacto-*D*-allo-undecodialdo-1,4-furanose-11,7-pyranos-1-yl]uracil* (**18**). — A solution of **17** (22 mg) in 70% aqueous acetic acid was stirred for 20 min at 40°. The solution was diluted with toluene (15 mL) and evaporated to give **18** as a white powder of (21 mg, 100%); R_F 0.49 on t.l.c. (5:1 acetonitrile–water); m.p. 242–244° (dec.) (hot stage), $[\alpha]_D^{20}$ +50° (*c* 0.2, methanol); ^{1}H-n.m.r. (200 MHz, CD_3OD): δ 0.86 (d, 6 H, J 6.5 Hz, H-14‴ and H-15‴), 1.93 (s, 3 H, Ac), 4.60 (d, 1 H, $J_{10',11'}$ 8.5 Hz, H-11′), 4.93 (d, 1 H, $J_{1'',2''}$ 3.4 Hz, H-1″), 5.74 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-5), 5.91 (d, 1 H, $J_{1',2'}$ 5.4 Hz, H-1′), 5.95 (d, 1 H, $J_{2''',3'''}$ 15.4 Hz, H-2‴), 6.79 (dt, 1 H, $J_{2''',3'''}$ 15.4, $J_{3''',4'''}$ 7.0 Hz, H-3‴), and 7.88 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-6); ^{13}C-n.m.r. [$(CD_3)_2S$=O]: δ 88.3, 98.7, and 100.9 (anomeric carbon atoms); ν_{max}^{KBr} 3410 (NH and OH) and 1670 cm^{-1} (C=O); *m/z* 831 (M + 1$^+$).

Anal. Calc. for $C_{38}H_{62}N_4O_{16} \cdot H_2O$: C, 53.76; H, 7.60; N, 6.60. Found: C, 53.50; H, 7.40; N, 6.32.

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