Synthetic Approach toward Antibiotic Tunicamycins. 3. Methyl 3,4,7,8-Tetra-*O*-acetyl-10-*O*-benzyl-2-benzyloxycarbonylamino-2,6-dideoxy-11,12-*O*-isopropylidene-β-L-dodecodialdo-(12*R*)-furanose-(12,9)-pyranosides-(1,5)

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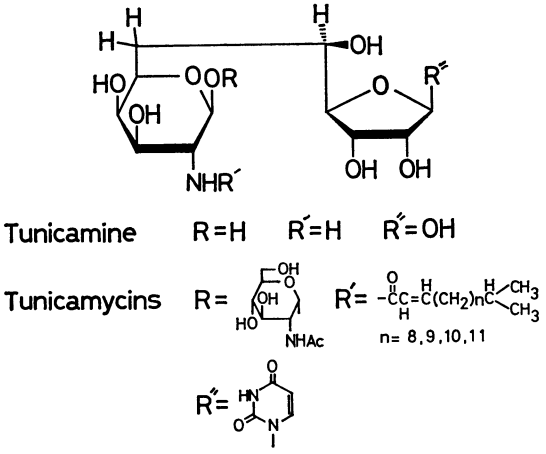
Higher carbon carbohydrates, dodecose derivatives have been synthesized by the base-catalyzed addition of nitro sugar to sugar aldehyde. The addition reaction of methyl 2-benzyloxycarbonylamino-2,6,7-trideoxy-3,4-*O*-isopropylidene-7-nitro-α-D-*galacto*-heptopyranoside to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribodialdofuranose-(1,4) yielded nitro-dodecose derivatives. The nitro-dodecose derivatives were then converted into the corresponding hydroxy and acetoxy derivatives.

The nucleoside antibiotic tunicamycins are found in a fermentation broth of a strain of *streptomyces* and exhibit a broad spectrum of antitumor activity.[1] Their structures were established by Ito *et al.* in 1980 by chemical degradation.[2] The structures of tunicamycins consist of uracil, a novel higher-carbon carbohydrate named tunicamine, fatty acid, and *N*-acetyl-D-glucosamine. The tunicamine is an undecose derivative which, in turn, is bound to uracil to form tunicaminyl uracil. Analogous higher-carbon carbohydrates have been found in other nucleoside antibiotics, such as anthelmycin (hikizimysin),[3] sinefungin,[4] ezomycin,[5] and mildiomycin.[6]

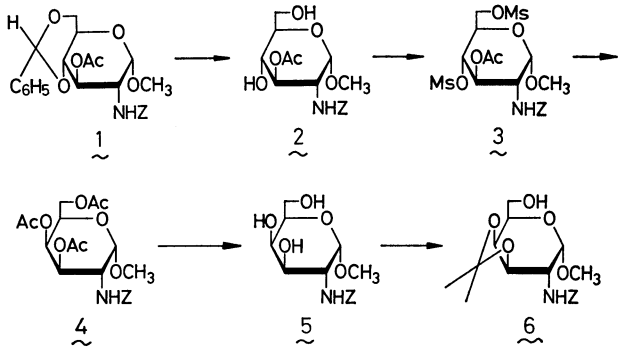


Scheme 1.

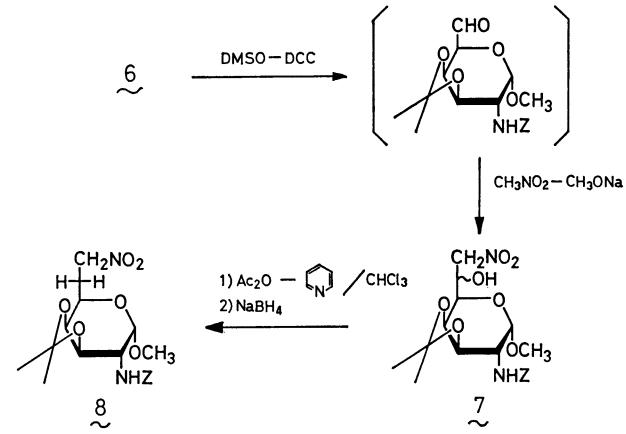
In preceding papers,[7] the base-catalyzed addition of nitro sugar to sugar aldehyde has been developed as a generally applicable method for the synthesis of higher-carbon complex carbohydrates. For a synthetic approach to tunicamine in the present study, the base-catalyzed addition of methyl 2-benzyloxycarbonylamino-2,6,7-trideoxy-3,4-*O*-isopropylidene-7-nitro-α-D-*galacto*-heptopyranoside (**8**) to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribodialdofuranose-(1,4) (**9**) has been investigated. Then the nitro-dodecose derivatives were converted into the corresponding hydroxy and acetoxy derivatives to afford the four theoretically possible diastereoisomers of dodecose derivatives.

Results and Discussion

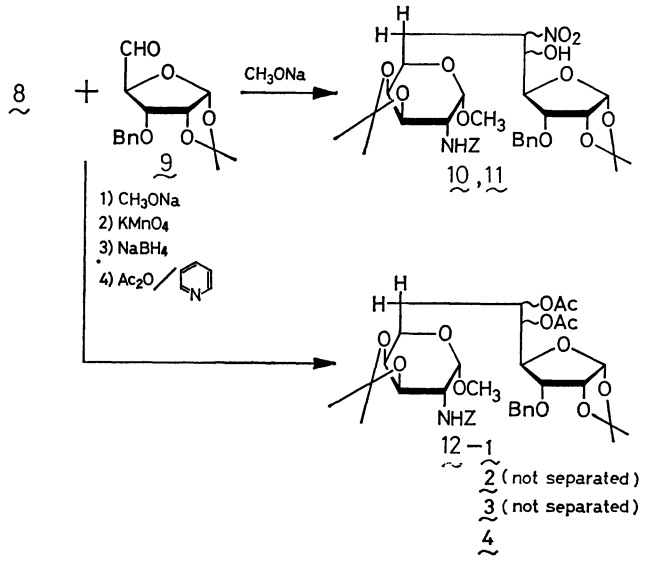
The hydrolysis of methyl 3-*O*-acetyl-2-benzyloxycarbonylamino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**1**)[8] in warm aqueous acetic acid gave the hydrolyzate (**2**). The mesylation of **2** with an excess amount of mesyl chloride in pyridine afforded the dimesylate (**3**). The displacement of the mesyloxy groups of **3** by acetate ions occurred with an epimerization of the configuration on C-4, giving the methyl α-D-galactoside derivative (**4**) in a yield of 59%. The deacetylation of **4** in methanolic ammonia, followed by acetonation, gave the 3,4-*O*-isopropylidene derivative (**6**) in 53% yield. The oxidation of the hydroxyl group on C-6 of **6** by the Pfitzner-Moffatt oxidation method,[9] followed by addition with nitromethane in the presence of sodium methoxide, afforded a mixture of two diastereoisomers of 7-nitroheptopyranosides (**7**) in 46% yield. The dehydroxylation of the hydroxyl group on C-6 of **7** with acetic anhydride and pyridine in chloroform, followed by



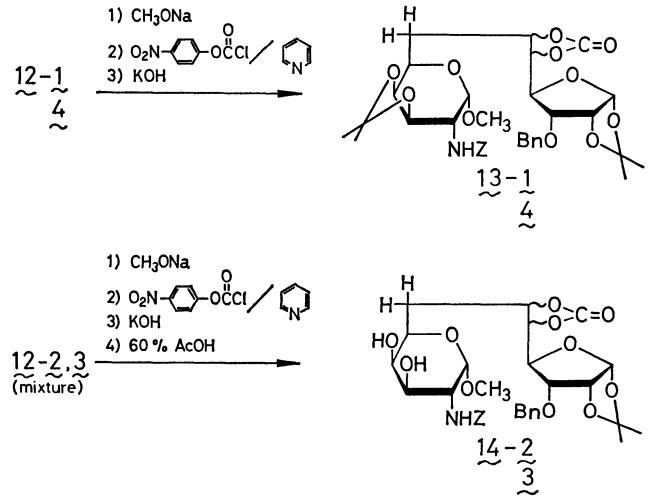
Scheme 2.



Scheme 3.



Scheme 4.

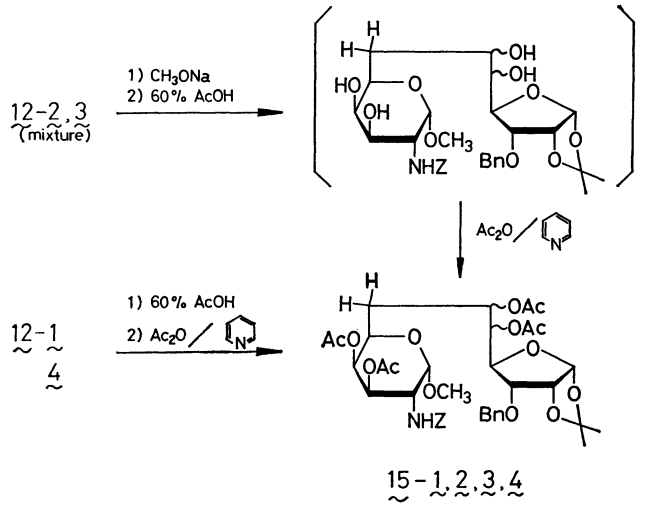


Scheme 5.

the hydrogenation of a double bond between C-6 and C-7 with sodium borohydride, afforded the 6-deoxy derivatives (**8**) in 78% yield.

On the other hand, 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribodialdofuranose-(1,4) (**9**) was prepared by the periodate oxidation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose.[10]

When the nitro-heptoside, **8**, reacted with the ribo-dialdofuranose-(1,4) derivative, **9**, in the presence of sodium methoxide, a mixture of diastereomers was obtained in a yield of 92%. The TLC and ^{1}H NMR of the intact mixture revealed the presence of the four theoretically possible diastereoisomeric nitro-dodecose derivatives, from which only two compounds (**10**) and (**11**) were obtained in homogeneous states by repeated chromatographic fractionations. The structures of **10** and **11** were established, by means of their ^{1}H NMR and IR spectra, as methyl 10-*O*-benzyl-2-benzyloxycarbonylamino-2,6,7-trideoxy-3,4: 11,12-di-*O*-isopropylidene-7-nitro-β-L-dodecodialdo-(12*R*)-furanose-(12,9)-pyranosides-(1,5), but the absolute configurations on C-7 and C-8 have not yet been established.



Scheme 6.

On the other hand, the oxidation of the intact mixture of the nitro-dodecoses with potassium permanganate[11] in water, followed by reduction with sodium borohydride and conventional acetylation, afforded a mixture of 7,8-di-*O*-acetyl derivatives in 43% yield. Chromatographic fractionations of the mixture gave two compound (**12-1** and **12-4**) as homogeneous products and the rest as a mixture of (**12-2**) and (**12-3**). The deacetylation of **12-1**, followed by carbonylation, gave a cyclic 7,8-*O*-carbonyl derivative (**13-1**) in 52% yield. By analogous reactions, the diastereomer (**13-4**) was obtained from **12-4**. The mixture of **12-2** and **12-3**, by analogous reactions plus mild hydrolysis in aqueous acetic acid, yielded two compounds (**14-2** and **14-3**), which were subsequently succesfully separated by column chromatography. The coupling constant of $J_{7,8}$ in the ^{1}H NMR spectrum of **14-2** was 8.0 Hz, suggesting the existence of vicinal cis protons on C-7 and 8.[12] That of **13-4** was 5.0 Hz, which showed trans protons on C-7 and 8. Those of **13-1** and **14-3** were 7.3 Hz and 6.4 Hz; their configurations have not yet been designated.

Finally, an intact mixture of **12-1** **12-2**, **12-3**, and **12-4** was hydrolyzed in 58% aqueous acetic acid at 40 °C for 1.5 h. The 3,4-*O*-isopropylidene group was selectively hydrolyzed under those conditions without a cleavage of the 11,12-*O*-isopropylidene group (another *O*-isopropylidene group on C-11 and 12). The product was acetylated to give four tetra-*O*-acetyl derivatives (**15-1**, **15-2**, **15-3**, and **15-4**), which were subsequently isolated by means of column chromatography. These compounds are important intermediates for further studies of the synthesis of tunicamine; that is, the selective removal of the 11,12-*O*-isopropylidene group, followed by oxidation (the cleavage of the C–C bond between C-11 and 12 by periodate oxidation) with sodium metaperiodate and deacylation, may provide undecose derivatives. However, it is still unknown which intermediate has the same configurations on C-7 and 8 as those of tunicamine.

Experimental

General Methods. The melting points were taken in capillary tubes in a liquid bath and are uncorrected. The solutions were concentrated under reduced pressure below 50 °C. The IR spectra were measured with a Hitachi 225 spectrophotometer and are expressed in reciprocal centimeters. The ^{1}H NMR spectra were obtained on a Varian EM-390 apparatus (90 MHz) and are reported as δ values in parts per million relative to tetramethylsilane as an internal standard. The TLC was performed on precoated silica-gel 60 F-254 (Merck, Darmstadt; Art. 5715; 0.25-mm thickness). The silica-gel columns used for chromatography utilized Wako gel C-200 or C-300 (Wako Pure Chemical Industries, Ltd.).

Methyl-3-O-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (2). A stirred solution of methyl 3-*O*-acetyl-2-benzyloxycarbonylamino-4,6,-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**1**)[8] (76.7 g) in 70% aqueous acetic acid (1000 ml) was heated at 60—70 °C for 1 h. The solution was then concentrated to dryness. The residue was purified on a silica-gel column [C-300, 250 g, toluene–ethyl acetate 8:1—1:1 (v/v)] to give 58.2 g (94%) of **2**; R_f 0.39 [benzene–ethanol 5:1 (v/v)], $[\alpha]_D^{21}$ +75.5° (*c* 1.0, chloroform), ^{1}H NMR ($CDCl_3$) δ 1.93 (3H, s, Ac), 3.36 (3H, s, OCH_3), 7.27 (5H, s, C_6H_5). Found: C, 55.28; H, 6.32; N, 3.62%. Calcd for $C_{17}H_{23}NO_8$: C, 55.28; H, 6.28; N, N, 3.79%.

Methyl 3-O-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-di-O-methylsulfonyl-α-D-glucopyranoside (3). To a solution of **2** (58.2 g) in pyridine (450 ml) was added methanesulfonyl chloride (29.3 ml) under ice cooling. After 18 h in a refrigerator, the reaction mixture was poured into ice and water (8 l), and then extracted with chloroform (500 ml). The chloroform layer was washed with water, a $NaHSO_4$ solution, water, a saturated $NaHCO_3$ solution, and water, and then concentrated to give an oily crude residue (76.5 g) which showed a single spot on TLC in 5:1 (v/v) benzene–ethyl acetate. A part (869.8 mg) of the crude residue was purified on a silica-gel column [C-300, 73 g, 3:1 (v/v) benzene–ethyl acetate] to give **3** (836.4 mg) as a homogeneous syrup in 89% yield from **2**. **3**; R_f 0.53 [5:1 (v/v) benzene–ethanol], $[\alpha]_D^{21}$ +77.3° (*c* 1.1, chloroform), ^{1}H NMR ($CDCl_3$) δ 1.91 (3H, s, Ac), 3.01, 3.05 (3H×2, s×2, CH_3SO_3), 3.39 (3H, s, OCH_3), 7.27 (5H, s, C_6H_5). Found: C, 43.39; H, 5.21; N, 2.48; S, 12.06%. Calcd for $C_{19}H_{27}NS_2O_{12}$: C, 43.42; H, 5.18; N, 2.67; S, 12.20%.

Methyl 3,4,6-Tri-O-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-galactopyranoside (4). To a stirred solution of **3** (4.64 g) in acetic acid (35 ml) was added water (1.8 ml) and sodium acetate (29.3 g). After 24 h at 130—135 °C, acetic anhydride (25 ml) was added to the reaction mixture. After 2 h at 130 °C, the mixture was cooled to room temperature. The reaction mixture was then poured into a mixture of ice (500 g), chloroform (300 ml), and sodium carbonate (60 g). The chloroform layer was separated, washed with a saturated $NaHCO_3$ solution and water, and concentrated. The residue was purified on a silica-gel column [C-200, 25 g, 5:1 (v/v) toluene–ethyl acetate] to give oily **4** (2.69 g, 59% yield); R_f 0.28 [3:1 (v/v) toluene–ethyl acetate], $[\alpha]_D^{21}$ +86.6° (*c* 1.1, chloroform), IR ($CHCl_3$ solution) 3435 (NH), 1740 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ 1.86, 2.01, 2.12 (3H×3, s×3, Ac), 3.36 (3H, s, OCH_3), 7.26 (5H, s, C_6H_5). Found: C, 55.71; H, 5.81; N, 2.85%. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.87; H, 5.81; N, 3.10%.

Methyl 2-Benzyloxycarbonylamino-2-deoxy-α-D-galactopyranoside (5). A solution of **4** (26.8 g) in methanolic ammonia (11%) was left to settle in a refrigerator for 18 h. The reaction mixture was then concentrated, and the residue was recrystallized from water to give 11.4 g (58.8%) of **5**; R_f 0.22 [5:1 (v/v) benzene–ethanol]; mp 197—197.5 °C, $[\alpha]_D^{20}$ +131° (*c* 0.5, methanol), ^{1}H NMR (CD_3OD) δ 7.37 (5H, s, C_6H_5), 3.30 (3H, s, OCH_3). Found: C, 55.17; H, 6.43; N, 4.18%. Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28%.

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside (6). To a suspension of **5** (5.01 g) in acetone (80 ml) was added acetone (200 ml) containing concentrated sulfuric acid (0.1 ml). After 2.5 h at the ambient temperature, the reaction mixture was neutralized with Amberlite IRA-400(OH^-) resin; the resin was then filtered off. The filtrate was concentrated, and toluene (100 ml) was added to the residue. The insoluble matter was removed by filtration, and the filtrate was concentrated to *ca.* 30 ml, and then left for 1 d. The precipitate was collected to give 2.13 g (38.2%) of **6** as crystals. The filtrate was repeatedly worked-up as has been described above to give 0.81 g (14.6%) of **6**. Total yield, 2.94 g (53%). **6**; R_f 0.53 [5:1 (v/v) benzene–ethanol], mp 105—105.5 °C, $[\alpha]_D^{23}$ +131° (*c* 1.0, methanol), ^{1}H NMR ($CDCl_3$) δ 3.32 (3H, s, OCH_3), 1.57, 1.32 (3H×2, s×2, isopropylidene). Found: C, 59.03; H, 6.85; N, 3.74%. Calcd for $C_{18}H_{25}NO_7$: C, 58.85; H, 6.86; N, 3.80%.

*Methyl 2-Benzyloxycarbonylamino-2,7-dideoxy-3,4-O-isopropylidene-7-nitro-*DL-glycero-D-galacto-*heptopyranoside (7).* To a stirred solution of **6** (4.07 g) in benzene (8 ml) and dimethyl sulfoxide (26 ml) were added pyridine (0.2 ml), phosphoric acid (0.1 ml), and dicyclohexylcarbodiimide (7.2 g) under ice cooling. After stirring for 4 h at the ambient temperature, a suspension of oxalic acid (5 g) in methanol (5 ml) was added to the solution. After 1 h, the mixture was extracted with ethyl acetate (150 ml). The ethyl acetate layer was washed with a $NaHCO_3$ solution and water dried over Na_2SO_4 and concentrated. To a solution of the residue in methanol (35 ml) was added nitromethane (8.55 ml) and 1 M methanolic sodium methoxide (9.54 ml). After 1 h at the ambient temperature, the solution was neutralized with Amberlite IR-120B(H^+) resin and concentrated. The residue was chromatographed on a silica-gel column [C-200, 2:1 (v/v) chloroform–ethyl acetate]. The product was then recrystallized from toluene to give 2.18 g (46%) of **7**; mp 115—117 °C, $[\alpha]_D^{23}$ +96.8° (*c* 1.0, methonol), IR (KBr) 3510 (OH), 3360 (NH), 1698 (C=O), 1555, 1530, 1390 cm^{-1} (NO_2), ^{1}H NMR ($CDCl_3$) δ 1.34, 1.56 (3H×2, s×2, isopropylidene), 3.29 (3H, s, OCH_3), 7.26 (5H, s, C_6H_5). Found: C, 53.70; H, 6.16; N, 6.56%. Calcd for $C_{19}H_{26}N_2O_9$: C, 53.52; H, 6.15; N, 6.57%.

*Methyl 2-Benzyloxycarbonylamino-2,6,7-trideoxy-3,4-O-isopropylidene-7-nitro-α-D-*galacto-*heptopyranoside (8).* To a solution of **7** (2.1 g) in chloroform (50 ml) were added acetic anhydride (2.8 ml) and pyridine (1.6 ml) under ice cooling. After 22 h at the ambient temperature, the reaction mixture was washed with water, a saturated $NaHCO_3$ solution, and water, then chloroform layer was concentrated. The residue was dissolved in ethanol (50 ml) and toluene (20 ml), and to the solution was added a suspension of sodium borohydride (0.56 g) in ethanol (30 ml). After 1 h at the ambient temperature, the reaction mixture was neutralized with Amberlite IR-120B(H^+) resin; the resin was then filtered off. The filtrate was concentrated, and the residue was recrystallized from ethanol to give 1.58 g (77.8%) of **8**; R_f 0.44 [3:1 (v/v) toluene–ethyl acetate], $[\alpha]_D^{19}$ +140.6° (*c* 0.5, chloroform), IR (KBr) 1690 (C=O), 1550, 1386, 1375

cm^{-1} (NO_2), ^1H NMR ($CDCl_3$) δ 1.27, 1.52 (3H×2, s×2, isopropylidene), 3.32 (3H, s, OCH_3), 7.18 (5H, s, C_6H_5). Found: C, 55.74; H, 6.42; N, 6.66%. Calcd for $C_{19}H_{26}N_2O_8$: C, 55.60; H, 6.38; N, 6.83%.

*Methyl 10-O-Benzyl-2-benzyloxycarbonylamino-2,6,7-trideoxy-3,4:11,12-di-O-isopropyridene-7-nitro-β-L-dodecodialdo-(12R)-furanose-(12,9)-pyranosides-(1,5) (**10** and **11**).* To a solution of **9** (300 mg) in ethanol (15 ml) were added **8** (305.4 mg) and 1 M methanolic sodium methoxide (0.74 ml) under ice cooling. After 18 h at the ambient temperature, the reaction mixture was neutralized with Amberlite IR-120B (H^+) resin; the resin was then filtered off. The filtrate was concentrated, and the residue was purified on a silica-gel column [C-300:C-200 1:5, 30 g, 7:1 (v/v) toluene–ethyl methyl ketone] to give a mixture of nitrododecose derivatives; 437.2 mg (92.3% yield from **8**). The mixture was repeatedly chromatographed analogously to the method described above to afford two homogenous nitrododecose isomers, **10** and **11**. However, the other two isomers could not separated. **10**; syrup, R_f 0.58 [1:1 (v/v) toluene–ethyl acetate], $[\alpha]_D^{19}$ +107° (*c* 1.0, chloroform), IR (chloroform solution) 3570 (OH), 3430 (NH), 1720 (C=O), 1567, 1386 cm^{-1} (NO_2), ^1H NMR ($CDCl_3$) δ 7.25, 7.23 (5H×2, s×2, C_6H_5), 5.64 (1H, d, $J_{11,12}$=3 Hz, H-12), 3.23 (3H, s, OCH_3), 1.56, 1.38, 1.36, 1.23 (3H×4, s×4, isopropylidene). Found: C, 59.05; H, 6.37; N, 4.14%. Calcd for $C_{34}H_{44}N_2O_{13}$: C, 59.29; H, 6.44; N, 4.07%.

11; Mp 182—183.5 °C, R_f 0.37 [1:1 (v/v) toluene–ethyl acetate], $[\alpha]_D^{19}$ +111° (*c* 0.4, chloroform), IR (chloroform solution) 3530 (OH), 3435 (NH), 1740 (C=O), 1550, 1385 cm^{-1} (NO_2), ^1H NMR ($CDCl_3$) δ 7.25 (10H, s, C_6H_5×2), 5.62 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 3.26 (3H, s, OCH_3), 1.53, 1.33, 1.29 (6H and 3H×2, s×3, isopropylidene). Found: C, 59.50; H, 6.47; N, 4.25%.

*Methyl 7,8-Di-O-acetyl-10-O-benzyl-2-benzyloxycarbonylamino-2,6-dideoxy-3,4:11,12-di-O-isopropylidene-β-L-dodecodialdo-(12R)-furanose-(12,9)-pyranosides-(1,5) (**12-1**, **12-2**, **12-3**, and **12-4**).* 1 M methanolic sodium methoxide (2.2 ml) was added to a solution of **8** (900 mg) and **9**, obtained from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose (672 mg), in methanol (30 ml). After 18 h at the ambient temperature, methanol (45 ml) was added to the reaction mixture, which was then poured into ice-cold water (300 ml). To the solution was added a solution of magnesium sulfate (450 mg) in water (50 ml); subsequently, a solution of potassium permanganate (630 mg) in water (120 ml) was added, drop by drop, to the stirred mixture under ice cooling. After 1 h at the ambient temperature, acetic acid (2.7 ml) and chloroform (150 ml) were added to the solution and inorganic precipitates were removed by filtration. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (50 ml×4). The organic layers were combined and concentrated. The residue was dissolved in ethanol (80 ml), and sodium borohydride (460 mg) was added to the solution under ice cooling. After 2 h at the ambient temperature, the mixture was concentrated. Water (30 ml) was added to the residue, and the mixture was extracted with ethyl acetate (45 ml×2). The organic solution was concentrated. The oily residue was acetylated by acetic anhydride (4.5 ml) in pyridine (35 ml) for 18 h. The reaction mixture was concentrated, and the residue was purified on a silica-gel column (C-200, 65 g), using 4:1 (v/v) toluene–ethyl acetate, to give 185.8 mg of a mixture of **12-1**, **12-2**, and **12-3** 128.1 mg of a mixture of **12-2** and **12-3**, 48 mg of a mixture of **12-2**, **12-3**, and **12-4**, and 389 mg of only **12-4** as crystals. Total yield, 650.9 mg (43.1% from **8**).

The mixture of **12-1**, **12-2**, and **12-3**, (185.8 mg) obtained above, was chromatographed again on a silica-gel column [C-200, 18 g, 4:1 (v/v) toluene–ethyl acetate] to give 28.1 mg of only **12-1**, 75.6 mg of a mixture of **12-1**, **12-2**, and **12-3**, and 56.7 mg of a mixture of **12-2** and **12-3**. Total yield, 160.4 mg (86.3% recovery). However **12-2** and **12-3** could not be separated, as their R_f values on TLC were the same in several solvent systems.

12-1: R_f 0.61 [1:1 (v/v) toluene–ethyl acetate], mp 78—81 °C, $[\alpha]_D^{19}$ +104° (*c* 0.3, chloroform), ^1H NMR ($CDCl_3$) δ 7.25 (10H, s, C_6H_5×2), 5.65 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 3.20 (3H, s, OCH_3), 1.97, 1.91 (3H×2, s×2, Ac), 1.55, 1.33 (6H×2, s×2, isopropylidene), IR (KBr) 1735 cm^{-1} (C=O). Found: C, 61.22; H, 6.77; N, 1.70%. Calcd for $C_{38}H_{49}NO_{14}$: C, 61.36; H, 6.64; N, 1.88%.

12-2 and **12-3**: R_f 0.55 [1:1 (v/v) toluene–ethyl acetate].

12-4: R_f 0.44 [1:1 (v/v) toluene–ethyl acetate], mp 192—193 °C, $[\alpha]_D^{21}$ +123° (*c* 1.0, chloroform), ^1H NMR ($CDCl_3$) δ 7.33 (10H, s, C_6H_5×2), 5.70 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 3.25 (3H, s, OCH_3), 2.05 (6H, s, Ac×2), 1.58 1.57, 1.35, 1.31 (3H×4, s×4, isopropylidene), IR (KBr) 1740, 1690 cm^{-1} (C=O). Found: C, 61.23; H, 6.69; N, 2.06%.

*Methyl 10-O-Benzyl-2-benzyloxycarbonylamino-7,8-O-carbonyl-2,6-dideoxy-3,4:11,12-di-O-isopropylidene-β-L-dodecodialdo-(12R)-furanose-(12,9)-pyranosides-(1,5) (**13-1** and **13-4**).* To a solution of **12-1** or **12-4** (20 mg) in methanol (10 ml) was added 1 M methanolic sodium methoxide (0.2 ml). After 3 h at the ambient temperature, toluene (30 ml) was added to the reaction mixture, which was then concentrated to *ca.* 20 ml. To the solution were added water (10 ml) and ethyl acetate (30 ml). The organic layer was separated, dried, and concentrated. The residue was reacted with *p*-nitrophenoxycarbonyl chloride (30 mg) in pyridine (2 ml) and tetrahydrofuran (0.5 ml). After 18 h at the ambient temperature, water (20 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (30 ml). The ethyl acetate layer was washed with a saturated $NaHCO_3$ solution and water, and then concentrated. The residue was purified on a silica-gel column (C-200, 2 g), using 1:1 (v/v) toluene–ethyl acetate, to give **13-1** or **13-4**.

13-1: Yield, 52%, R_f 0.67 [1:1 (v/v) toluene–ethyl acetate], mp 179.5—180 °C, IR (KBr) 1808 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 7.34 (10H, s, C_6H_5×2), 5.72 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 5.08 (1H, m, $J_{7,8}$=7.3 Hz, H-7), 3.35 (3H, s, OCH_3), 1.60, 1.57, 1.27, 1.28 (3H×4, s×4, isopropylidene). Found: C, 61.04; H, 6.33; N, 1.83%. Calcd for $C_{35}H_{43}NO_{13}$: C, 61.31, H, 6.32, N, 2.04%.

13-4: Yield, 48%, R_f 0.69 [1:1 (v/v) toluene–ethyl acetate], mp 87.5—88.5 °C (amorphous solid), IR (KBr) 1805 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 7.35, 7.34 (5H×2, s×2, C_6H_5), 5.73 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 4.94 (1H, m, $J_{7,8}$=5.0 Hz, H-7), 3.34 (3H, s, OCH_3), 1.62, 1.60, 1.36, 1.34 (3H×4, s×4, isopropylidene). Found: C, 61.48; H, 6.49; N, 2.06%.

*Methyl 10-O-Benzyl-2-benzyloxycarbonylamino-7,8-O-carbonyl-2,6-dideoxy-11,12-O-isopropylidene-β-L-dodecodialdo-(12R)-furanose-(12,9)-pyranosides-(1,5) (**14-2** and **14-3**).* A mixture of **12-2** and **12-3** (110.8 mg) was hydrolyzed in 0.1 M methanolic sodium methoxide (17.9 ml) for 1 h at the ambient temperature. The reaction mixture was then neutralized with Amberlite IR-120B (H^+) resin and the resin was filtered off. The fitrate was subsequently concentrated. To a solution of the residue in pyridine (6 ml) was added *p*-nitrophenoxycarbonyl chloride (300 mg).

After 18 h, the reaction mixture was extracted with chloroform, and the chloroform layer was washed with saturated $NaHCO_3$ solution and water. The solution was concentrated to give an oily residue, which contained *p*-nitrophenoxycarbonyl derivatives. The residue was treated with methanol (4 ml) containing potassium hydroxide (9.4 mg) at the ambient temperature for 3 h, then the reaction mixture was concentrated. To the residue was added water, which was then extracted with ethyl acetate (20 ml×3). The ethyl acetate layers were combined and concentrated. The oily product, without purification, was treated with 60% acetic acid at 40 °C for 3 h. The reaction mixture was concentrated, and the residue was purified on a silica-gel column [C-300, 5 g, 2:1 (v/v) toluene–ethyl methyl ketone] to give **14-2** and **3**, each as a homogenous amorphous solid.

14-2: Mp 96—98 °C, R_f 0.52 [1:1 (v/v) toluene–ethyl methyl ketone], IR (KBr) 1805, 1705 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 7.35 (10H, s, $C_6H_5\times2$), 5.73 (1H, d, $J_{11,12}$= 3.8 Hz, H-12), 4.94 (1H, m, $J_{7,8}$=8.0 Hz, H-7), 3.33 (3H, s, OCH_3), 2.33 (2H, m, H-6) 1.55, 1.35 (3H×2, s×2, isopropylidene). Found: C, 59.30; H, 6.25; N, 2.36%. Calcd for $C_{33}H_{39}NO_{13}$: C, 59.53; H, 6.09; N, 2.17%.

14-3: Mp 81—84 °C, R_f 0.45 [1:1 (v/v) toluene--ethyl methyl ketone], IR (KBr) 1805, 1705 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 7.35 (10H, s, $C_6H_5\times2$), 5.73 (1H, d, $J_{11,12}$= 3.8 Hz, H-12), 4.82 (1H, m, $J_{7,8}$=6.4 Hz, H-7), 3.34 (3H, s, OCH_3), 1.59, 1.36 (3H×2, s×2, isopropylidene). Found: C, 59.53; H, 6.19; N, 2.16%.

*Methyl 3,4,7,8-Tetra-*O*-acetyl-10-*O*-benzyl-2-benzyloxycarbonylamino-2,6-dideoxy-11,12-*O*-isopropylidene-β-*L*-dodecodialdo-(12*R*)-furanose-(12,9)-pyranoside-(1,5) (**15**).* *a) **15-1** and **15-4**:* Compound **12-1** or **12-4** (200 mg) was treated with acetic acid (70 ml) and water (50 ml) at 40 °C for 1.5 h. The reaction mixture was concentrated to dryness. The residue was purified on a silica-gel column [C-200, 20 g, 1:1 (v/v) toluene–ethyl acetate] to afforded a diol derivative. The diol derivative was reacted with acetic anhydride (0.7 ml) in pyridine (10 ml) for 2 d. The reaction mixture was co-evaporated with toluene, and the residue was extracted with chloroform. The chloroform layer was washed with water, a saturated $NaHCO_3$ solution, and water, dried and cocentrated. The residue was purified on silica-gel column [C-200, 15 g, 2:1 (v/v) toluene–ethyl acetate] to give **15-1** or **4**.

15-1: Yield, 70%, R_f 0.62 [1:1 (v/v) toluene–ethyl acetate] mp 84—86 °C, $[\alpha]_D^{23}$ +98.4° (*c* 0.5, chloroform), ^1H NMR ($CDCl_3$) δ 7.20 (10H, s, $C_6H_5\times2$), 5.57 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 3.18 (3H, s, OCH_3), 2.07, 1.95, 1.86, 1.78 (3H×4, s×4, Ac), 1.52, 1.30 (3H×2, s×2, isopropylidene). Found: C, 59.20; H, 6.29; N, 1.87%. Calcd for $C_{39}H_{49}NO_{16}$: C, 59.46; H, 6.27; N, 1.78%.

15-4: Yield, 80%, R_f 0.49 [1:1 (v/v) toluene–ethyl acetate] mp 130.5—131.5 °C, $[\alpha]_D^{28}$ +125.4° (*c* 0.5, chloroform), ^1H NMR ($CDCl_3$) δ 7.22 (10H, s, $C_6H_5\times2$), 5.53 (1H, d, $J_{11,12}$=3.5 Hz H-12), 3.23 (3H, s, OCH_3), 2.08, 1.96, 1.94, 1.82 (3H×4, s×4, Ac), 1.49, 1.28 (3H×2, s×2, isopropylidene). Found: C, 59.65; H, 6.37; N, 1.79%.

*b) **15-2** and **15-3**:* A mixture of **12-2** and **12-3** (128.1 mg) was hydrolyzed in 0.1 M methanolic sodium methoxide (20 ml) for 3 h. To the reaction mixture was added toluene (30 ml), which was subsequently concentrated to *ca.* 20 ml. To the solution was added water (10 ml) and ethyl acetate (20 ml). The organic layer was separated and cocentrated. The residue was treated with 60% acetic acid (10 ml) at 40 °C for 2 h. The reaction mixture was co-evaporated with toluene, and the residue was purified on a silica-gel column [C-200, 20 g, 30:1 (v/v) chloroform–methanol] to give the tetrahydroxy derivative, 13.4 mg (10.3%) with an R_f value of 0.30 [10:1 (v/v) chloroform–methanol], 14.9 mg (12.4%) with an R_f value of 0.32 in the same solvent system, and 39.1 mg of a mixture of them. Total yield, 67.4 mg (55%). Each tetrahydroxy derivative obtained above was reacted with acetic anhydride (0.3 ml) in pyridine (2 ml) for 18 h. The reaction mixture was then co-evaporated with toluene, and the residue was purified on a silica-gel column [C-200, 4 g, 3:1 (v/v) toluene–ethyl acetate] to give 14.3 mg (76%) of **15-2** and 13.7 mg (81%) of **15-3**.

15-2: R_f 0.52 [1:1 (v/v) toluene–ethyl acetate], mp 77—78 °C $[\alpha]_D^{28}$ +102.4° (*c* 0.5, chloroform), ^1H NMR ($CDCl_3$) δ 7.24 (10H, s, $C_6H_5\times2$), 5.50 (1H, d, $J_{11,12}$=3.5 Hz, H-12), 3.33 (3H, s, OCH_3), 2.04, 1.97, 1.87, 1.83 (3H×4, s×4, Ac), 1.62, 1.30 (3H×2, s×2, isopropylidene). Found: C, 59.24; H, 6.26; N, 1.76%. Calcd for $C_{39}H_{49}NO_{16}$: C, 59.46; H, 6.27; N, 1.78%.

15-3: R_f 0.54 [1:1 (v/v) toluene–ethyl acetate], mp 81.5—83.5 °C, $[\alpha]_D^{23}$ +101° (*c* 0.5, chloroform), ^1H NMR ($CDCl_3$) δ 7.20 (10H, s, $C_6H_5\times2$), 5.55 (1H, d, $J_{11,12}$= 3.5 Hz, H-12), 3.25 (3H, s, OCH_3), 1.97, 2.10, 1.83 (6H and 3H×2, s×3, Ac), 1.53, 1.30 (3H×2, s×2, isopropylidene). Found: C, 59.44; H, 6.33; N, 1.84%.

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