Synthetic Approach toward Antibiotic Tunicamycins. II.

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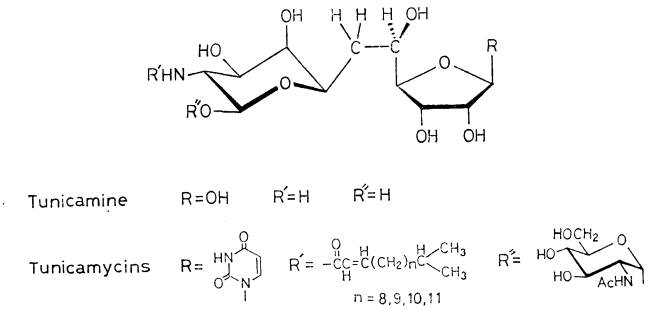
Some higher-carbon carbohydrates, dodecose derivatives, have been synthesized by means of the base-catalyzed addition of nitro sugar to sugar aldehyde. The addition reaction of 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-α-D-*galacto*-heptopyranose to 2,3:4,5-di-*O*-isopropylidene-D-arabinose yielded three isomeric dodecose derivatives, and their configurations have been studied. The nitro dodecose derivatives were converted into the corresponding hydroxy and acetoxy derivatives.

The higher-carbon carbohydrates, such as the undecose, decose, and octose derivatives, have been found in nucleoside antibiotics, such as tunicamycins,[1,2] anthelmycin[3,4] (hikizimycin), sinefungin,[5] ezomycin,[6] and mildiomycin.[7] The tunicamycins are produced by a strain of *Streptomyces* and exhibit broad-spectrum antitumor activities. They have a unique common structure consisting of uracil, fatty acid, and an undecose derivative named tunicamine, together with *N*-acetyl-D-glucosamine[2] (Scheme 1).



Scheme 1.

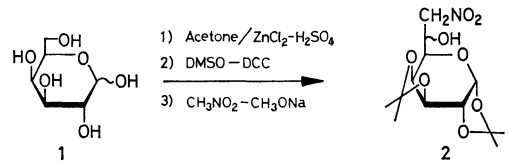
The occurrence of the higher-carbon carbohydrates in nature stimulated us to attempt to synthesize higher-carbon carbohydrates. In recent years the development of new methods of chain extension has been described in the literature.[8–14] In a previous paper of this series, we ourselves described the synthesis of 3,5-*O*-benzylidene-6,7-dideoxy-1,2:9,10:11,12-tri-*O*-isopropylidene-7-nitro-α-D-dodecofuranoses by the addition of the 7-nitro-α-D-glucofuranose derivative to 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**5**).[15] Now we wish to report, as a part of a synthetic study toward tunicamycins, the addition reaction of 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-α-D-*galacto*-heptopyranose (**3**) to **5**, in which three diastereoisomeric dodecose derivatives have been afforded. The conversion of the nitro group in these derivatives into an oxo or a hydroxyl group has been performed successfully.

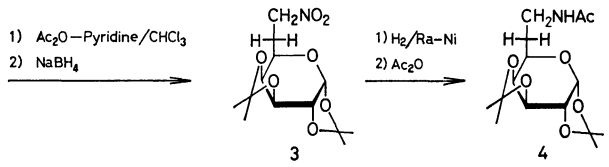
This reaction can be used as a general procedure for the conversion of a hindered nitro group of a sugar into an oxo or a hydroxyl group.

Results and Discussion

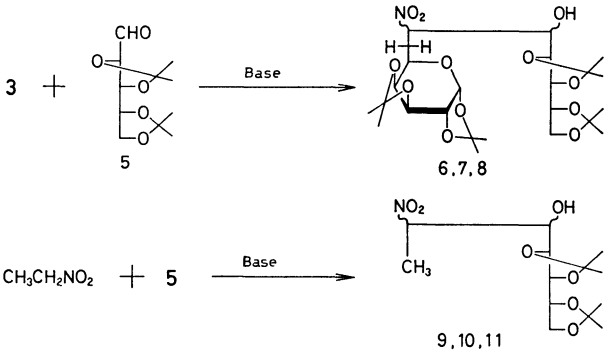
The oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose,[16] obtained from D-galactopyranose (**1**), by the method of Pfitzner-Moffatt oxidation[17,18] yielded the aldehyde derivative. A reaction of the intact aldehyde with nitromethane in methanol in the presence of sodium methoxide gave 7-deoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-DL-*glycero*-D-*galacto*-heptopyranose (**2**). The acetylation of **2** with acetic anhydride in chloroform–pyridine, followed by treatment with sodium borohydride, afforded 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-α-D-*galacto*-heptopyranose (**3**) in a 21% yield from **1**. The catalytic hydrogenation of **3** in methanol with Raney nickel and the subsequent acetylation of the reduction product with acetic anhydride in pyridine gave 7-acetamido-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranose (**4**) in a 56% yield.

When **3** was reacted with the arabinose derivative, **5**,[19] in the presence of a base catalyst, a mixture of three diastereomers of dodecose derivatives was obtained in a 65—67% yield after chromatography. These three isomeric dodecose derivatives, **6**, **7**, and **8**, were successfully isolated after repeated chromatographic fractionations. Their structures were establish-





Scheme 2.



Scheme 3.

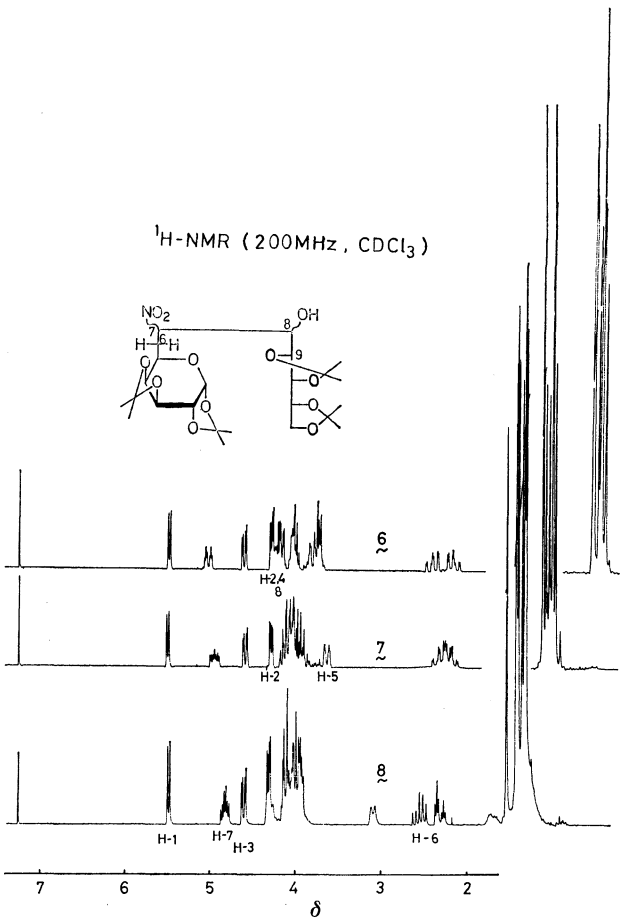


Fig. 1.

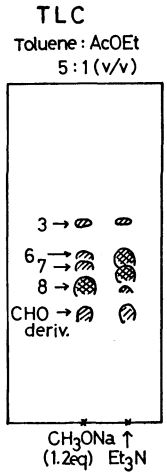
ed by means of the ^{1}H NMR, ^{13}C NMR, and IR spectra as 6,7-dideoxy-7-nitro-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-D-dodecopyranoses.

Concerning the stereochemistry of the two newly introduced chiral centers on the C-7 and C-8 positions of compounds **6**, **7**, and **8**, four diastereomers (**A**)—(**D**) are theoretically possible, as is shown in Scheme 5. Their relative configurations among the C-7, C-8, and C-9 positions of **A**—**D** are *erythro-threo*, *threo-erythro*, *erythro-erythro*, and *threo-threo* respectively. In this reaction, three isomers have been obtained, but the fourth one was scarcely produced at all. As **D**, *threo-threo*, seems to be most unstable; compared to the other three diastereomers, scarcely no **D** is produced. These configurations were determined primarily on the basis of the course of the nucleophilic addition of nitronate anion to the sugar aldehyde, and secondarily on the basis of the course of the protonation of the nitronate anion, according to thermodynamic and kinetic controls.[20,21] Also **C**, *erythro-erythro*, is thermodynamically the most stable among them.

In this reaction, the ratio of the formation of three isomeric dodecose derivatives, **6**, **7**, and **8**, was markedly influenced by the amounts and kinds of catalysts used, as is shown in Table 1, but was little affected by the reaction time. That is, in the presence of a 1.2 equiv. of sodium methoxide as a base catalyst, **8** became the major product. On the other hand, in the presence of triethylamine or a 0.2 equiv.

Table 1. Isomeric ratios of nitrododecoses obtained by condensation of **3** and **5** under various base catalysts

Base	Nitrododecoses 6	7	8
$(CH_3CH_2)_3N$	7—10	: 7—11	: 1
CH_3ONa (0.1 equiv.)	4—7	: 4—8	: 1
CH_3ONa (1.2 equiv.)	0.3—0.6	: 0.3	: 1
CH_3OLi (1.2 equiv.)	0.6—0.8	: 0.7—1	: 1
CH_3OK (1.2 equiv.)	1	: 2	: 1



The reaction mixture was developed on TLC (solvent system: toluene–ethyl acetate 3:1 (v/v)) and was charred with 10% sulfuric acid. Then the ratio of dodecose isomers was estimated by by chromatoscan methods (Shimadzu CS-910).

Table 2. ^{13}C-NMR chemical shifts[a] of **6**, **7**, **8**, and **3**

C-No.	6	7	8	3
1	96.4	96.3	96.4	96.2
2	70.6	70.5	70.4	70.4
3	71.2	71.0	70.9	70.9
4	73.1	72.8	72.6	72.5
5	63.9	63.9	64.8	64.1
6	27.0	31.5	30.8	28.0
7	85.6	88.0	86.2	71.8
8	73.7	70.8	69.6	
9	80.3	77.3	77.2	
10	81.6	77.1	77.0	
11	76.1	79.8	79.0	
12	67.9	68.0	67.7	

a) Ppm downfield from internal TMS in $CDCl_3$.

of sodium methoxide, **6** and **7** were formed more readily than **8**.

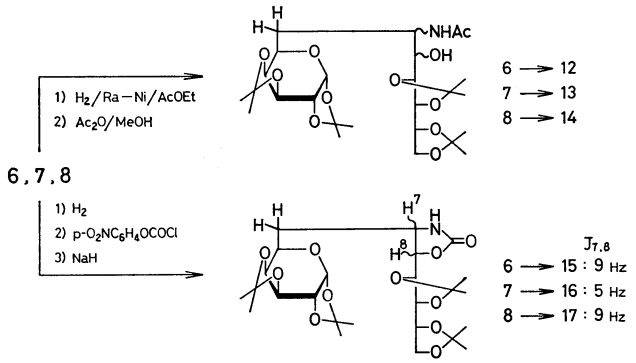
The epimerization of **7** and **8** in the presence of triethylamine occurred very slowly until the ratio of **7** and **8** reached to *ca.* 7:1, but under the same conditions the epimerization of **6** to another isomer was not observed. These results showed that the configurations of C-8 in **7** and **8** were the same but those of C-7 were different. Compounds **7** and **8** are assigned to be **B** or **C**, while **6** is designated as **A**, since scarcely no **D** is produced because of the instability.

In the ^{13}C NMR spectrum, the chemical shifts of 4 carbon signals, C-9, 10, 11, and 12, of **7** were similar to those of **8**, but they were different from those of **6** as is shown in Table 2. That is, the configurations on the C-8 of **7** and **8** seem to be same.

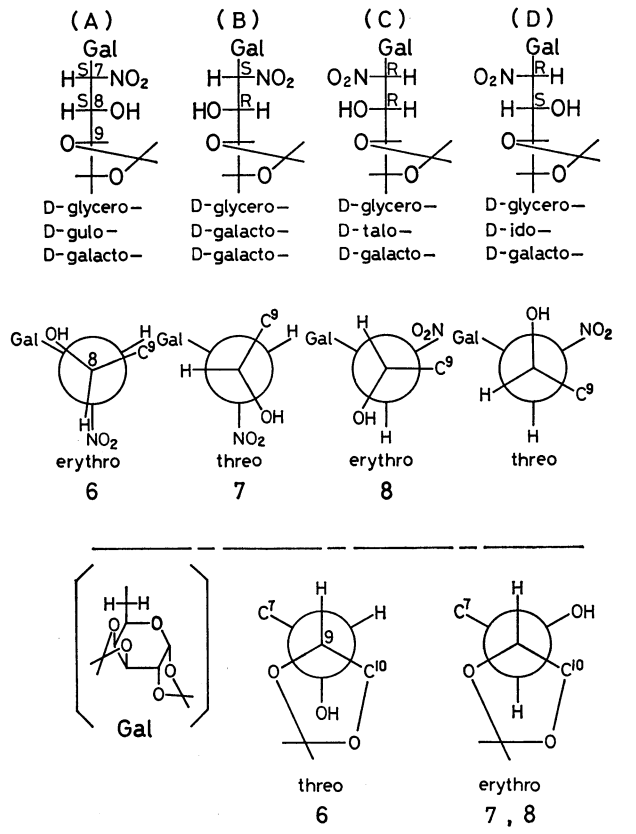
Then the configurations of the nitro dodecose derivatives were established by the conversion of the nitro groups to amino groups. The catalytic hydrogenation of each one of the nitro dodecose derivatives

in ethyl acetate in the presence of Raney nickel, followed by *N*-acetylation, afforded a corresponding acetamidodideoxy-dodecose, **12** from **6**, **13** from **7**, and **14** from **8**.

The catalytic hydrogenation of the nitro-dodecose isomers, followed by *N*-benzyloxycarbonylation and cyclic *N,O*-carbonylation, gave the corresponding 7,8-*N,O*-carbonyl derivatives; **15** from **6**, **16** from **7**, and **17** from **8**. The structures of **15**, **16**, and **17** were determined by means of ^{1}H NMR and IR spectroscopy as 7-amino-7,8-*N,O*-carbonyl-6,7-dideoxy-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-D-dodecopyranoses. The ^{1}H NMR spectra showed that the coupling constants of H-7 and H-8 of **15** and **17** were 9 Hz, while that of **16** was 5 Hz. These results suggested that the oxazolidinones of **15** and **17** had *vicinal cis* protons and that the 5 Hz coupling of **16** was due to the *trans* protons.[22,23]



Scheme 4.



Scheme 5.

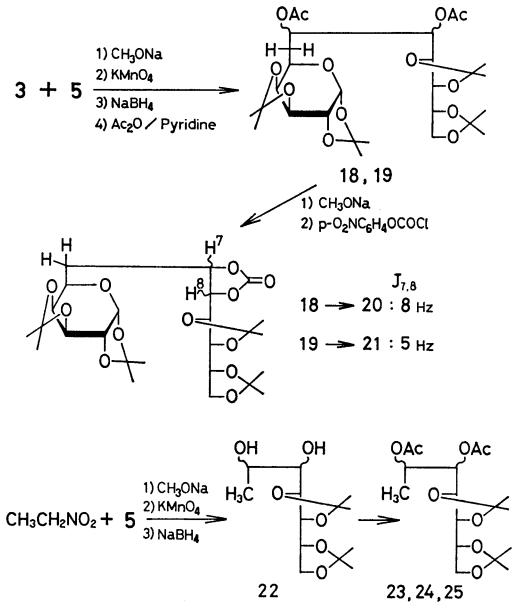
Considering the above-mentioned results, the configurations of **6**, **7**, and **8** were tentatively assigned as D-*glycero*-D-*gulo*-D-*galacto*-, **A**, D-*glycero*-D-*galacto*-D-*galacto*-, **B**, and D-*glycero*-D-*talo*-D-*galacto*-dodecose, **C**, respectively (Scheme 5).

The analogous addition reaction between the aldehyde **5** and nitroethane, instead of the D-galactose derivative, **3**, has been carried out as a simple model reaction. The reaction yielded a mixture of all theoretically predictable diastereomers in a 74% yield from **5**. Three of the four diastereomers (**9**, **10**, and **11**) have been isolated by column chromatography. Their structures have been identified as 1,2-dideoxy-4,5:6,7-di-*O*-isopropylidene-2-nitro-D-heptitols by means of ^{1}H NMR and IR spectroscopy. The ratio among the four isomers was not affected by the kind or amount of the catalyst in this model reaction.

The most notable difference between the two above-mentioned addition reactions between **5** and **3** and between **5** and nitroethane was the absence of one of the four diastereomers in the former reaction; this may be due to the existence of the bulky D-galactosyl group.

Then, the conversion of the nitro groups of **6**, **7**, and **8** into hydroxyl groups was attempted under mild conditions where the cleavage of a protective group does not occur. Since the Nef reaction[24,25] and the titanium trichloride method[26,27] are rather drastic, though these reactions have been used widely to convert a nitro group to an oxo group, an oxidative denitration with permanganate[28–31] has been employed in the present experiment.

The oxidation of the intact mixture of the nitro-dodecoses, **6**, **7**, and **8**, with potassium permanganate in water, followed by reduction with sodium borohydride and acetylation with acetic anhydride, afforded a mixture of three 7,8-di-*O*-acetyl derivatives, from which two diastereomers, **18** and **19**, were isolated by column chromatography. The ^{1}H NMR of **18** and **19** showed two acetyl metyl signals each at δ 2.07



Scheme 6.

and 2.11 for **18**, and at δ 2.04 and 2.16 for **19**.

The deacetylation of **18** and **19** in methanolic sodium methoxide, followed by the cyclic carbonylation of the *vicinal* hydroxyl groups on C-7 and C-8, gave the corresponding 7,8-*O*-carbonyl derivatives, **20** and **21** respectively. In the ^{1}H NMR spectra of **20** and **21**, H-7 was observed as a doublet at δ 4.82 with $J_{7,8}$= 8 Hz on **20** and as a double-doublet at δ 4.49 with $J_{7,8}$=5 Hz on **21**.

The analogous reaction processes were carried out with an addition compound between the aldehyde, **5**, and nitroethane. The reactions gave three of the four theoretically predictable diastereomers after column chromatography. Their structures were established by ^{1}H NMR as 1-deoxy-2,3-di-*O*-acetyl-4,5:6,7-di-*O*-isopropylidene-D-heptitols, **23**, **24**, and **25**.

It has been demonstrated by the present study that a higher-carbon carbohydrate, dodecose, is prepared by the base-catalyzed addition of a nitro sugar to a sugar aldehyde, and that a hindered nitro sugar is converted to the corresponding keto or hydroxy derivative.

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 (90 MHz) and a JEOL FX-200 (200 MHz) spectrometer. The chemical shifts are reported as δ values in parts per million, relative to tetramethylsilane as the internal standard. The TLC was performed on precoated silica gel 60 F-254 plaques (Merck, Darmstadt; Art. 5715, 0.25 mm thickness). The silica-gel column used for chromatography utilized Wako gel C-200 (Wako Pure Chemical Industries, Ltd.).

*7-Deoxy-1,2:3,4-di-O-isopropylidene-7-nitro-*DL*-glycero-*D*-galacto-heptopyranose (**2**) and 6,7-Dideoxy-7-nitro-1,2:3,4-di-O-isopropylidene-α-*D*-galacto-heptopyranose (**3**).* Nitromethane (228 ml) and 1 M† methanolic sodium methoxide (232 ml) were added to a solution of crude 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-dialdopyranose-(1,5)[16] in methanol (400 ml), obtained from D-galactose (**1**) (50.0 g), under ice cooling with agitation. After 1 h at the ambient temperature, the solution was neutralized with Amberlite IR-120B(H$^+$) resin, and the resin was filtered off. The filtrate was concentrated to give an oily residue which contained **2** as the main product. A part (1/20) of the residue was purified on a silica-gel column using 7:1 (v/v) toluene–ethyl acetate to give 1.52 g (34%) of a homogeneous oily product of **2**: $[\alpha]_D^{20}$ −51.4° (*c* 0.3, methanol); IR (neat): 3450 (OH), 1550, 1390, 1380 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 5.53 (1H, d, J=5 Hz, H-1), 1.37—1.53 (12H, isopropylidene CH_3). Found: C, 48.60; H, 6.59; N, 4.12%. Calcd for $C_{13}H_{21}NO_8$: C, 48.90; H, 6.63; N, 4.39%.

To a solution of the crude **2** in chloroform (500 ml), was added acetic anhydride (102 ml) and pyridine (68 ml) under ice cooling. After 6 h at the ambient temperature, the solution was washed with water, a saturated sodium hydrogencarbonate solution, and water, and concentrated under reduced pressure at 30 °C. To a solution of the residue in ethanol (600 ml), was added sodium borohydride (24 g) under ice cooling. After 1 h, the solution was neutralized with Amberlite IR-120B(H$^+$) resin, and the resin was filtered off. The filtrate was concentrated, and the residue was purified on a silica-gel column, using 30:1 (v/v) toluene–ethyl acetate, to give 17.0 g (21% yield from **1**) of **3** as a syrup: $[\alpha]_D^{18}$ −35.6° (*c* 3.4, chloroform); IR (neat) 1560, 1380 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 5.35 (1H, d, $J_{1,2}$= 5 Hz, H-1), 1.25—1.75 (12H, isopropylidene CH_3). Found: C, 51.66; H, 6.87; N, 4.54%. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62%.

*7-Acetamido-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-heptopyranose (**4**).* A solution of **3** (368 mg) in methanol (5 ml) was hydrogenated in the presence of Raney nickel in a hydrogen atmosphere (2.7 kg/cm^2) for 19 h. After the catalyst had then been filtered off, acetic anhydride (0.5 ml) was added to the filtrate. After 3 h, the product was purified on a silica-gel column, using 1:1 (v/v) chloroform–ethyl acetate as the eluent. Fractions corresponding to R_f 0.16 on the TLC in the same solvent were collected and concentrated. The residue was recrystallized from cyclohexane to give 214 mg (56%) of **4**: mp 98—99 °C; $[\alpha]_D^{23}$ −40° (*c* 1.5, methanol); ^{1}H NMR ($CDCl_3$) δ 5.50 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.53 (1H, dd, $J_{2,3}$=2 Hz, $J_{3,4}$=7.5 Hz, H-3), 4.26 (1H, dd, $J_{1,2}$=5 Hz, $J_{2,3}$=2 Hz, H-2), 4.07 (1H, dd, $J_{3,4}$=7.5 Hz, $J_{4,5}$=1.5 Hz, H-4), 3.80 (1H, dt, $J_{4,5}$=1.5 Hz, $J_{5,6}$=6 Hz, H-5), 3.37 (2H, q, J=6 Hz, H-7), 2.93 (3H, s, NHAc), 1.80 (2H, q, J=6 Hz, H-6), 1.50, 1.76, 1.66 (3H×2 and 6H, s×3, isopropylidene CH_3). Found: C, 56.84; H, 7.81; N, 4.36%. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44%.

*6,7-Dideoxy-7-nitro-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-*D*-dodecopyranoses (**6**, **7**, and **8**).* *a)*: 1 M Methanolic sodium methoxide (9 ml) was added to a solution of **3** (1.76 g) and **5** (2.01 g) in methanol (17 ml) at the ambient temperature. After 18 h, the solution was neutralized with Amberlite IR-120B(H$^+$) resin under ice cooling, and the resin was filtered off. The filtrate was concentrated, and the residue was chromatographed on a silica-gel column two times. (C-200, 90 g, 10:1 (v/v) toluene–ethyl acetate, wet column), (1:1 (wt/wt) C-200:C-300, 50 g, 6:1 (v/v) toluene–ethyl acetate, dry column). The fractions were combined and concentrated to give 183 mg (6%) of only **6**, 625 mg (20%) of a mixture of **6** and **7**, 443 mg (14%) of **7**, 500 mg (16%) of **7** and **8**, and 329 mg (11%) of only **8** (total yield 2.08 g (67%)); **6**; R_f=0.49 (3:1 (v/v) toluene–ethyl acetate); mp 161—162 °C; $[\alpha]_D^{23}$ −32° (*c* 0.5, methanol); IR ($CHCl_3$ solution) 3540, 3440 (OH), 1550, 1390, 1380 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 5.48 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.29 (1H, dd, $J_{2,3}$=2.5 Hz, H-2), 4.61 (1H, dd, $J_{3,4}$=8 Hz, H-3), 2.40 (1H, m, $J_{5,6}$=2 Hz, $J_{6,6}$=15 Hz, $J_{6,7}$=11.5 Hz, H-6), 2.16 (1H, m, $J_{5,6}$=11 Hz, $J_{6,6}$=15 Hz, $J_{6,7}$=2 Hz, H-6), 5.03 (1H, m, $J_{7,8}$= 3 Hz, H-7). Found: C, 54.27; H, 7.22; N, 2.43%. Calcd for $C_{24}H_{39}NO_{12}$: C, 54.03; H, 7.37; N, 2.63%.

7; R_f=0.45 (3:1 (v/v) toluene–ethyl acetate); mp 121—122 °C; $[\alpha]_D^{23}$ −30° (*c* 0.8, methanol); IR ($CHCl_3$ solution) 3510 (OH), 1555, 1390, 1380 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 5.49 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.28 (1H, dd, $J_{2,3}$=2.5 Hz, H-2), 4.58 (1H, dd, $J_{3,4}$=8 Hz, H-3), 2.24 (2H, m, H-6), 4.95 (1H, m, $J_{7,8}$=7 Hz, H-7). Found: C, 54.22; H, 7.26; N, 2.81%.

8; R_f=0.37 (3:1 (v/v) toluene–ethyl acetate); mp 125—127 °C; $[\alpha]_D^{23}$ −27° (*c* 1.0, methanol); IR ($CHCl_3$ solution) 3410 (OH), 1550, 1390, 1380 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 5.48 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.31 (1H, dd,

† 1 M=1 mol dm^{-3}.

$J_{2,3}$=2.5 Hz, H-2), 4.60 (1H, dd, $J_{3,4}$=8 Hz, H-3), 2.55 (1H, m, $J_{5,6}$=7 Hz, $J_{6,6}$=15 Hz, $J_{6,7}$=7.5 Hz, H-6), 2.30 (1H, m, $J_{5,6}$=4 Hz, $J_{6,6}$=15 Hz, $J_{6,7}$=4 Hz, H-6), 4.82 (1H, m, $J_{7,8}$=7 Hz, H-7). Found: C, 50.85; H, 7.37; N, 4.70%.

b): Triethylamine (0.75 ml) was added to a solution of **3** (426 mg) and **5** (393 mg) in methanol (7 ml) at the ambient temperature. After 4 days, the solution was concentrated at 30 °C under reduced pressure. The residue was chromatographed on a silica-gel column two times, (C-200, 50 g, 10:1 (v/v) toluene–ethyl acetate), (C-200, 20 g, 5:1 (v/v) toluene–ethyl acetate), to give 164 mg (22%) of only **6**, 62 mg (8%) of a mixture of **6** and **7**, 198 mg (26%) of **7**, 49 mg (7%) of **7** and **8**, and 17 mg (2%) of **8** (total yield, 490 mg (65%).

*1,2-Dideoxy-2-nitro-4,5:6,7-di-*O*-isopropylidene-*D*-heptitols (**9**, **10**, and **11**).* Triethylamine (0.67 ml) was added to a solution of **5** (895 mg) and nitroethane (1.68 ml) in methanol (9 ml). After 2 days, the reaction mixture was concentrated to dryness under reduced pressure at 30 °C. The oily residue was purified on a silica-gel column, using 10:1 (v/v) toluene–ethyl acetate (C-200, 33 g, C-300 10 g), to give a mixture of four isomers (800.3 mg, 69% from **5**) as crystals. The chromatography of the mixture was repeated several times to give homogeneous compounds of the three isomers, **9**, **10**, and **11**:**9**; R_f=0.42 (5:1 (v/v) toluene–ethyl acetate); mp 111—113 °C; $[\alpha]_D^{23}$ +8.55° (*c* 1.0, methanol); IR (CCl_4 solution) 3420 (OH), 1560, 1390, 1380 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 1.78 (3H, d, $J_{1,2}$=6.5 Hz, CH_3), 1.34—1.44 (12H, isopropylidene CH_3). Found: C, 51.36; H, 7.41; N, 4.65%. Calcd for $C_{11}H_{17}NO_7$: C, 51.13; H, 7.59; N, 4.59%.

10; R_f=0.36 (5:1 (v/v) toluene–ethyl acetate); mp 96—98 °C; $[\alpha]_D^{23}$ +31.0° (*c* 1.4, methanol); IR (CCl_4 solution) 3420 (OH), 1560, 1390, 1380 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 1.64 (3H, d, $J_{1,2}$=6.5 Hz, CH_3), 1.33—1.44 (12H, isopropylidene CH_3). Found: C, 51.36; H, 7.52; N, 4.64%.

11; R_f=0.31 (5:1 (v/v) toluene–ethyl acetate); mp 95—96 °C; $[\alpha]_D^{32}$ +12.7° (*c* 0.9, methanol); IR (CCl_4 solution) 3550 (OH), 1560, 1390, 1380 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 1.60 (3H, d, $J_{1,2}$=6.5 Hz, CH_3), 1.33—1.44 (12H, isopropylidene CH_3). Found: C, 50.85; H, 7.37; N, 4.70%.

*7-Acetamido-6,7-dideoxy-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-*D*-dodecopyranoses (**12**, **13**, and **14**).* One of three compounds, **10**, **11** and **12** (50 mg), was hydrogenated in ethyl acetate (6 ml) with a Raney nickel catalyst in a hydrogen atmosphere (2.7 kg/cm^2) for 18 h. The catalyst was then filtered off, and the filtrate was concentrated. The residue was acetylated with acetic anhydride (0.5 ml) in methanol (4 ml) for 4 h. The reaction mixture was then concentrated, and the residue was purified on a silica-gel column, using 1:3 (v/v) toluene–ethyl acetate, to give a 7-acetamido-dodecose derivative: **12**; 68% yield from **6**; R_f=0.12 (1:2 (v/v) toluene–ethyl acetate); mp 178—179 °C; $[\alpha]_D^{23}$ −13.5° (*c* 0.4, methanol); ^1H NMR ($CDCl_3$) δ 5.46 (1H, d, J=5 Hz, H-1), 1.93 (3H, s, NHAc). Found: C, 56.98; H, 7.77; N, 2.52%. Calcd for $C_{26}H_{43}NO_{11}$: C, 57.23; H, 7.94; N, 2.57%.

13; 61% yield from **7**; R_f=0.25 (1:2 (v/v) toluene–ethyl acetate); mp 162—163 °C; $[\alpha]_D^{23}$ −25° (*c* 0.35, methanol); ^1H NMR ($CDCl_3$) δ 5.50 (1H, d, J=5 Hz, H-1), 1.97 (3H, s, NHAc). Found: C, 57.22; H, 7.78; N, 2.56%.

14; 56% yield from **8**; R_f=0.15 (1:2 (v/v) toluene–ethyl acetate); mp 62—63.5 °C (amorphous solid); $[\alpha]_D^{23}$ −30° (*c* 0.7, methanol); ^1H NMR ($CDCl_3$) δ 5.43 (1H, d, J=5 Hz, H-1), 1.97 (3H, s, NHAc). Found: C, 57.31; H, 7.81; N, 2.41%.

*7-Amino-7,8-*N,O*-carbonyl-6,7-dideoxy-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-*D*-dodecopyranoses (**15**, **16**, and **17**).* A solution of a 7-nitro-dodecose, **6**, **7**, or **8** (40 mg), in ethyl acetate (5 ml) was hydrogenated analogously to the preparation of **12**, **13**, and **14**, and subsequently reacted with *p*-nitrophenoxycarbonyl chloride (56 mg) in pyridine (2 ml) for 1 d. The reaction mixture, diluted with ethyl acetate (20 ml), was then washed with water, saturated $NaHCO_3$, and water. The ethyl acetate solution was co-evaporated with toluene to give an oily residue, which was subsequently allowed to react with sodium hydride 60% in oil (5 mg) in dioxane (10 ml) to afford a carbamate derivative, **15**, **16**, or **17**, after short silica-gel column chromatography.

15; 59% yield from **7**; R_f=0.35 (1:1 (v/v) toluene–ethyl acetate); mp 48—49.5 °C (amorphous solid); IR ($CHCl_3$ solution) 3400 (NH), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.52 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.59 (1H, dd, $J_{2,3}$=2 Hz, $J_{3,4}$=6 Hz, H-3), 4.53 (1H, dd, $J_{7,8}$=9 Hz, $J_{8,9}$=7.5 Hz H-8), 4.31 (1H, dd, $J_{1,2}$=5 Hz, $J_{2,3}$=2 Hz, H-2). Found: C, 56.55; H, 7.37; N, 2.49%. Calcd for $C_{25}H_{38}NO_{11}$: C, 56.81; H, 7.25; N, 2.65%.

16; 41% yield from **8**; R_f=0.37 (1:1 (v/v) toluene–ethyl acetate); mp 67—69° (amorphous solid); IR ($CHCl_3$ solution) 3460 (NH), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.46 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.57 (1H, dd, $J_{2,3}$=2 Hz, $J_{3,4}$=5.5 Hz, H-3), 4.34 (1H, d, $J_{7,8}$=5 Hz, H-8), 4.28 (1H, dd, $J_{1,2}$=5 Hz, $J_{2,3}$=2 Hz, H-2). Found: C, 57.04; H, 7.39; N, 2.67%.

17; 37% yield from **9**; R_f=0.33 (1:1 (v/v) toluene–ethyl acetate); mp 196—197 °C (crystallized from ethyl acetate–hexane); IR (KBr) 3380 (NH), 1755 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.50 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.72 (1H, d, $J_{7,8}$= 9 Hz, H-8), 4.60 (1H, dd, $J_{2,3}$=2 Hz, $J_{3,4}$=7.5 Hz, H-3), 4.32 (1H, dd, $J_{1,2}$=5 Hz, $J_{2,3}$=2 Hz, H-2). Found: C, 56.50; H, 7.28; N, 2.59%.

*7,8-Di-*O*-acetyl-6-deoxy-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-*D*-dodecopyranoses (**18** and **19**).* To a solution of **3** (842 mg) and **5** (2.09 g) in methanol (30 ml) was added 1 M methanolic sodium methoxide (3 ml). After 18 h at the ambient temperature, the reaction mixture was poured into ice cold water (250 ml). To the solution was then added a solution of magnesium sulfate (722 mg) in water (18 ml); subsequently, a solution of potassium permanganate (553 mg) in water (430 ml) was stirred, drop by drop, into the mixture under ice cooling. After 1 h at the ambient temperature, acetic acid (1 ml) and chloroform (100 ml) were added to the reaction mixture and the inorganic precipitate was removed by filtration. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (100 ml×3). The organic layers were combined and concentrated. The residue was dissolved in ethanol (100 ml), and sodium borohydride (150 mg) was added to the solution under ice cooling. After 1 h, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (120 ml). The solution was washed with brine and water, and concentrated. The oily residue was purified on a silica-gel column, using 3:1 (v/v) toluene–ethyl acetate (C-200 50 g), and acetylated with pyridine (20 ml) and acetic anhydride (8 ml) for 2 d. The reaction mixture was then concentrated to dryness. The residue was purified on a silica-gel column, using 6:1 (v/v) toluene–ethyl acetate (C-200, 40 g), to give a mixture of isomers of diacetyl-dodecoses (492.4 mg, 30% from **3**). The mixture was chromatographed several times as has been described above to separate **18** and **19** as homogeneous compounds. However, another one, corresponding to R_f 0.51 on TLC using 3:1 (v/v) toluene–ethyl acetate, could not

be isolated.

18; R_f=0.52 (3:1 (v/v) toluene–ethyl acetate); mp 48—50 °C; $[\alpha]_D^{20}$ −24.0° (*c* 2.1, methanol); ^{1}H NMR ($CDCl_3$) δ 5.49 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.27 (1H, dd, $J_{2,3}$=2 Hz, H-2), 4.57 (1H, dd, $J_{2,3}$=8 Hz, H-3), 5.26 (1H, dd, $J_{7,8}$= 3.5 Hz, $J_{8,9}$=7 Hz, H-8), 2.11 (3H×2, s×2, Ac). Found: C, 57.30; H, 7.51%. Calcd for $C_{28}H_{44}O_{13}$; C, 57.13; H, 7.53%.

19; R_f=0.46 (3:1 (v/v) toluene–ethyl acetate); mp 98—99 °C; $[\alpha]_D^{20}$ −10.5° (*c* 0.8, methanol); ^{1}H NMR ($CDCl_3$) δ 5.51 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.28 (1H, dd, $J_{2,3}$=2 Hz, H-2), 4.57 (1H, dd, $J_{3,4}$=8 Hz, H-3), 5.25 (1H, dd, $J_{7,8}$= 4.5 Hz, $J_{8,9}$=2 Hz, H-8), 2.04, 2.16 (3H×2, s×2, Ac). Found: C, 56.90; H, 7.32%.

*7,8-O-Carbonyl-6-deoxy-1,2:3,4:9,10:11,12-O-isopropylidene-α-D-dodecopyranoses (**20** and **21**).* 1 M methanolic sodium methoxide (1 ml) was added to a solution of an acetyl derivative, **18** or **19** (40 mg), in methanol (5 ml). After 3 h at the ambient temperature the solution was neutralized with Amberlite IR-120B (H^+) resin; the resin was then filtrated off, and the filtrate was concentrated. The residue was reacted with *p*-nitrophenoxycarbonyl chloride (50 mg) in pyridine (3 ml) for 20 h at the ambient temperature. The reaction mixture, diluted with ethyl acetate (20 ml), was washed with water, brine, and water. The solution was then concentrated to give an oily residue, which was purified on a short silica-gel column to give **20** or **21** as a crystal, **20**; 63% from **18**; R_f=0.42 (3:1 (v/v) toluene–ethyl acetate); mp 136—137 °C; IR ($CHCl_3$ solution) 1800 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 5.51 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.33 (1H, dd, $J_{2,3}$=2 Hz, H-2), 4.64 (1H, dd, $J_{3,4}$=8 Hz, H-3), 4.94 (1H, m, $J_{7,8}$=8 Hz, H-7), 4.82 (1H, d, $J_{7,8}$=8 Hz, H-8). Found: C, 56.50; H, 7.05%. Calcd for $C_{25}H_{38}O_{12}$: C, 56.60; H, 7.22%.

21; 70% from **19**; R_f=0.44 (3:1 (v/v) toluene–ethyl acetate); mp 159.5—161 °C; IR ($CHCl_3$ solution) 1795 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 5.47 (1H, d, $J_{1,2}$=5 Hz, H-1), 4.30 (1H, dd, $J_{2,3}$=2 Hz, H-2), 4.62 (1H, dd, $J_{3,4}$=8 Hz, H-3), 4.88 (1H, m, $J_{7,8}$=5 Hz, H-7), 4.49 (1H, dd, $J_{7,8}$=5 Hz, H-8). Found: C, 56.43; H, 7.03%.

*1-Deoxy-4,5:6,7-di-O-isopropylidene-D-heptitol (**22**) and 2,3-Di-O-acetyl-1-deoxy-4,5:6,7-di-O-isopropylidene-D-heptitols (**23**, **24**, and **25**).* To a solution of **5** (3.30 g) and nitroethane (2.30 ml) in methanol (23 ml), was added 1 M methanolic sodium methoxide (14 ml) under ice cooling. After 3 h at the ambient temperature, the mixture was poured into ice cold water (400 ml) containing sodium hydroxide (6.4 g), and then we added to the solution a solution of magnesium sulfate (3.4 g) in water (70 ml). The mixture was subsequently cooled in an ice–water bath, and potassium permanganate (4.5 g) in water (250 ml) was slowly stirred in. After 2 h, acetic acid (4 ml) and chloroform (100 ml) were added to the mixture, and the inorganic precipitate was removed by filtration. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (250 ml×2). The organic phases were combined and concentrated. To a solution of the residue dissolved in ethanol (150 ml) was added sodium borohydride (1.04 g) under ice cooling. After 2 h, the mixture was evaporated. The residue was dissolved in chloroform (200 ml), and the solution was washed with brine and water, and concentrated. The oily residue was purified on a silica-gel column, using 7:1 (v/v) toluene–ethyl acetate (C-200, 100 g), to give a single isomer, **22**, R_f=0.2 (3:1 (v/v) toluene–ethyl acetate), of a diol derivative (476 mg) and a mixture of two other isomers (827 mg) which could not be separated. (Total yield, 1.3 g, 33.5% from **5**) **22**; recrystallization from cyclohexane–hexane; mp 91—92 °C; $[\alpha]_D^{25}$ +23.5° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, d, $J_{1,2}$=6 Hz, CH_3), 1.40, 1.50 (9H and 3H, s×2, isopropylidene CH_3). Found: C, 56.86; H, 8.30%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09%.

22 (123 mg) was acetylated with acetic anhydride (0.23 ml) and pyridine (0.77 ml) for 18 h. The reaction mixture, diluted with chloroform (30 ml), was then washed with water, a saturated sodium hydrogencarbonate solution, and water, and concentrated to give a syrupy residue. The residue was purified on a silica-gel column, using 7:1 (v/v) toluene–ethyl acetate (C-200, 4 g and C-300, 1 g), to give a homogeneous oily product, **23** (96 mg, 60%); R_f=0.34 (5:1 (v/v) toluene–ethyl acetate); $[\alpha]_D^{20}$ +11.0° (*c* 1.3, methanol); ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, $J_{1,2}$= 6 Hz, CH_3), 1.35—1.42 (12H, isopropylidene CH_3), 2.04, 2.16 (3H×2, s×2, Ac). Found: C, 56.54; H, 7.77%. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83%.

The mixture of the two isomers was acetylated analogously to the method described above to a mixture of the two isomers of **24** and **25** (872 mg, 80.5%). The mixture was chromatographed several times to give two homogeneous products, **24** and **25**; **24**; R_f=0.35 (5:1 (v/v) toluene–ethyl acetate); $[\alpha]_D^{25}$ +29.1° (*c* 0.6, methanol); ^{1}H NMR ($CDCl_3$); δ 1.30 (3H, d, $J_{1,2}$=6.5 Hz, CH_3), 2.00, 2.10 (3H×2, s×2, Ac). Found: C, 56.37; H, 7.64%. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83%.

25; R_f=0.31 (5:1 (v/v) toluene–ethyl acetate); $[\alpha]_D^{20}$ +27.5° (*c* 0.2, methanol); ^{1}H NMR ($CDCl_3$); δ 1.30 (3H, d, $J_{1,2}$=6.5 Hz, CH_3), 2.05, 2.10 (3H×2, s×2, Ac). Found: C, 57.06; H, 7.86%.

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