Synthesis of α-*N*-Glycosides of 3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (KDN) Using Nucleobases and Their Photocycloaddition to 2,3-Dimethyl-2-butene

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α-*N*-Glycosides of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) having a nucleobase, such as uracil, thymine, 5-fluorouracil or cytosine, were synthesized. Their acetone-sensitized photocycloaddition to 2,3-dimethyl-2-butene under near-UV irradiation gave a pair of diastereomers having a cyclobutane ring. The absolute configuration of the bridgehead carbon atoms in the products was identified by measurement of specific rotation as well as ^{1}H-NMR spectral analysis.

Keywords photocycloaddition; 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN); *N*-glycosides; pyrimidine base; 2,3-dimethyl-2-butene

Since a method for the large-scale preparation of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) (**1**) has been established,[1,2] we attempted the synthesis of several *N*-glycosides of KDN in the hope of obtaining biologically active compounds.[3] Our recent work on the photochemistry of pyrimidine nucleosides revealed that two photo-adducts of the cyclobutane type were generated in UV-irradiated acetone solution containing uridine,[4,5] 2′-deoxyuridine,[6,7] or 2′-deoxycytidine[8] in the presence of 2,3-dimethyl-2-butene. Some of them showed remarkable differentiation-inducing and growth-inhibitory activities towards HL-60 cells.[9] Consequently, we anticipated that the cyclobutane-type photoproducts of the *N*-glycosides of KDN might also possesses biological activities.

In this paper, we wish to report the photocycloaddition of α-*N*-glycosides of KDN to 2,3-dimethyl-2-butene employing uracil, thymine, 5-fluoro-2′-deoxyuracil and cytosine derivatives. Analyses of the structures of the α-*N*-glycosides and elucidation of the absolute configuration of bridgehead carbon atoms of the photocycloaddition products are also described.

Results and Discussion

Preparation of α-*N*-Glycosides The α-*N*-glycosides **2** were prepared according to the previously reported method (Chart 1, Table I).[3] In the preparation of **2b** and **2d**, the β-anomer (**3**) was also isolated albeit in low yield, suggesting that the Williamson reaction partially proceeded *via* an *S*N1 mechanism. In each case, the 2,6-anhydro derivative (**4**) was formed in relatively high yield. The structures of **2a**, **2c** and **2d** were established unambiguously on the basis of elemental analysis and spectral properties. The anomeric configuration of **2a** was found to be α by X-ray diffraction analysis (Fig. 1). It was found that the glycosyl bond in the crystal takes the *ac* (high anti) conformation, which is typical of pyrimidine nucleosides, and that the KDN adopts the $^5C_2$ form. The anomeric configuration of **2c** and **2d** was deduced from a comparison of the ^{1}H-NMR spectral properties with those of **2a**. That is, the signals of H-3ax, H-3eq, H-4 and H-5 which appear at relatively high field for H-3ax and H-5,

TABLE I. Yields of *N*-Glycosides (**2**, **3**) and **4**

Aglycone	Yield (%)[a]		
	α-Anomer (**2**)	β-Anomer (**3**)	**4**
Uracil	20	0	31
Thymine	21	5	30
5-Fluorouracil	26	0	31
Cytosine	15	3	28

a) Isolated yields.

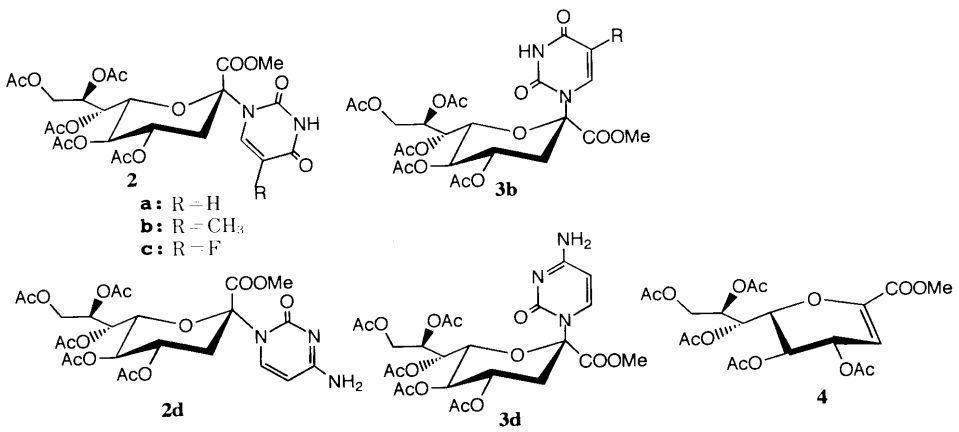

Chart 1

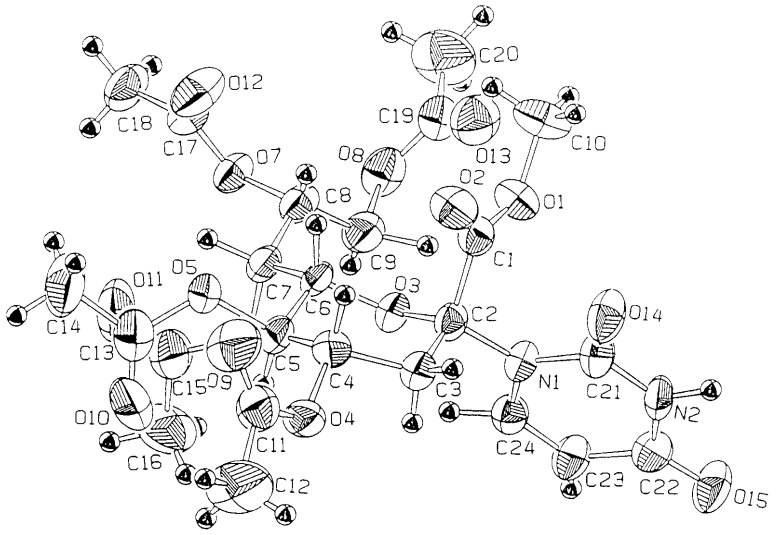

Fig. 1. Stereoscopic View of **2a**

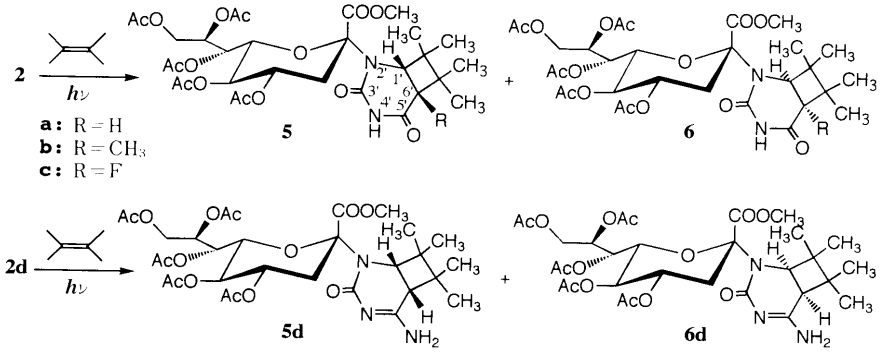

Chart 2

TABLE II. Summary of Chemical Shifts and Coupling Constants of α-*N*-Glycosides (**2**, **3**) in $CDCl_3$

N-Glycoside	Type	Chemical shift[a]				Coupling constants[b]	
		H-3ax	H-3eq	H-4	H-5	$J_{3eq,4}$	$J_{3ax,4}$
2a	α	1.89	3.33	5.58	4.92	5.4	10.2
2b	α	1.91	3.30	5.54	4.93	5.6	10.2
3b	β	2.21	3.16	5.08	5.07	3.2	11.5
2c	α	1.95	3.31	5.55	4.92	5.7	10.2
2d	α	1.72	3.40	5.62	4.86	5.4	12.9
3d	β	2.29	2.66	5.09	4.89	4.8	12.3

a) ppm from TMS. b) Hz.

and relatively low field for H-3eq and H-4, and the coupling constants (relatively small $J_{3ax,4}$ and relatively large $J_{3eq,4}$) in **2c**, **2d** showed a similar pattern to that of **2a**. These results are in accord with the previously reported anomeric configuration of **2b**.[3] In Table II, these values are summarized.

Photocycloaddition of 2 to 2,3-Dimethyl-2-butene Photocycloaddition of **2** to 2,3-dimethyl-2-butene was carried out in acetone as a triplet sensitizer. A high-pressure mercury lamp with a 2.0 mm Pyrex filter was the lamp of choice. This set-up allows lines longer than 304 nm of the arc to be absorbed, where only the α-*N*-glycosides used in this work absorb. A degassed solution of 2.0 mmol dm^{-3} of **2** containing 10.0 mmol dm^{-3} of 2,3-dimethyl-2-butene in acetone was irradiated until the starting α-*N*-glycoside was not detected on TLC. From each α-*N*-glycoside, except **2d**, two products were isolated by silica-gel chromatography. On the basis of elemental analysis, FAB-MS, UV and 400 MHz ^{1}H-NMR spectral properties, the products were unambiguously identified as the cyclobutane photoproducts (**5** and **6**) formed by linking α-*N*-glycosides to 2,3-dimethyl-2-butene across positions 5 and 6 of the pyrimidine ring (Chart 2). In the case of the reaction of **2d**, the ^{1}H-NMR spectrum of the reaction mixture showed the presence of two products inseparable even by chromatography. Therefore, the amino group at position 4 was acetylated with acetic anhydride in pyridine (**5e** and **6e**) to facilitate isolation and purification. The absolute configurations of C-1′ and C-6′ were determined from the specific rotation as follows. During the course of our study on KDN, it was found that KDN of furanose-type was formed in preference to the pyranose-type under conditions of low temperature and short reaction time.[2] Photocycloaddition of the α-*N*-glycoside with furanose-type KDN and thymine to 2,3-dimethyl-2-butene, which had been previously prepared, gave a photoadduct (**7**),[10] whose absolute configuration of the bridgehead carbon

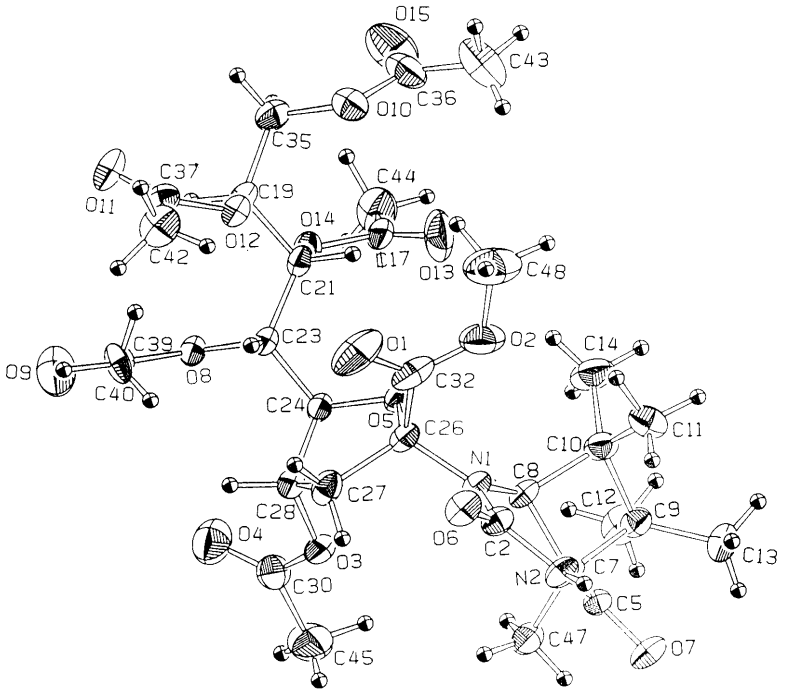

Fig. 2. Stereoscopic View of **7**

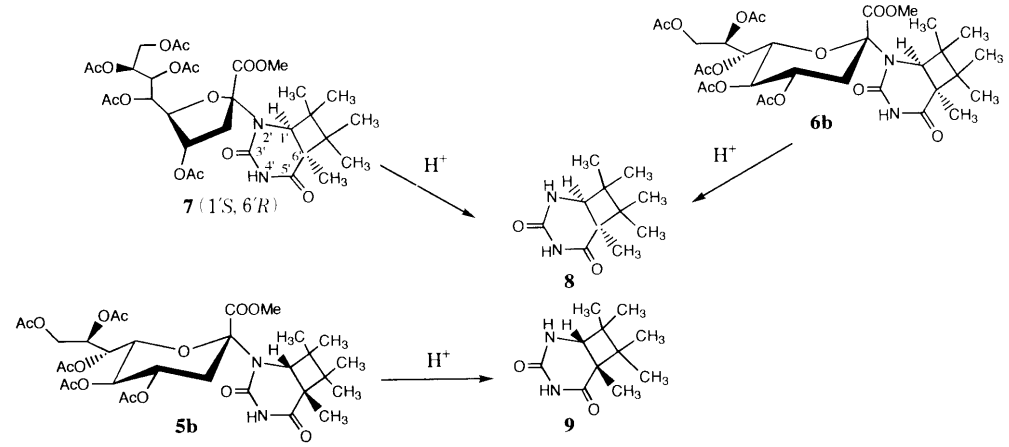

Chart 3

atoms was determined as (1′*S*,6′*R*) by X-ray diffraction analysis (Fig. 2). Hydrolysis of **7** gave **8**, whose specific rotation was compared with those of the hydrolysis products (a pair of enantiomers, Chart 3) derived from the two photoadducts (**5b** and **6b**). That is, specific rotation in methanol was 18.6° ($c=0.32$) for **8**, −20.0° ($c=0.08$) for the hydrolysis product from one of the two adducts (*Rf*: 0.60, eluent: $CHCl_3$–MeOH 6 : 1), and 18.7° ($c=0.14$) for the other (*Rf*: 0.50, eluent: $CHCl_3$–MeOH 6 : 1), respectively. Thus, it was revealed that the absolute configuration of the bridgehead carbon atoms of the latter is identical to that of the (1′*S*,6′*R*)-isomer, **8** (and **6b**). As a matter of course, the former was identified as the (1′*R*,6′*S*)-isomer **9** (and **5b**). The absolute configuration of the other photoproducts (**5a**, **5c**, **5d**, **6a**, **6c** and **6d**) was deduced on the basis of the ^{1}H-NMR chemical shifts of **5b** and **6b**. The assignment of the ^{1}H-NMR spectra of all eight photoproducts was achieved by comparison with that of **1** and by the application of double resonance techniques. That is, the (1′*R*,6′*S*)-isomer (**5**) is characterized by a downfield chemical shift by 0.3—0.5 ppm of the H-1′ signal (except for 6′-fluoro derivatives) and a downfield shift by about 0.4—0.7 ppm of that of H-3eq,

Table III. Summary of Chemical Shifts of **5**, **6** and **7** in $CDCl_3$

Photoproducts	Type	Chemical shift[a]	
		H-1′	H-3eq
5a	(1′*R*,6′*S*)	4.48	3.41
6a	(1′*S*,6′*R*)	4.18	2.76
5b	(1′*R*,6′*S*)	4.10	3.47
6b	(1′*S*,6′*R*)	3.61	2.82
5c	(1′*R*,6′*R*)	5.32	3.22
6c	(1′*S*,6′*S*)	5.30	2.80
5e	(1′*R*,6′*S*)	4.42	3.45
6e	(1′*S*,6′*R*)	4.10	2.76
7	(1′*S*,6′*R*)	3.62	2.30

a) ppm from TMS.

TABLE IV. Photocycloaddition of α-*N*-Glycosides (**2**) to 2,3-Dimethyl-2-butene

α-*N*-Glycoside	Irradiation time (h)	Yield (%)[a]		6/5
		5	6	
2a	1.0	25	50	2.0
2b	2.0	7	46	6.6
2c	1.0	27	54	2.0
2d	2.0	24	30	1.3

a) Isolated yields.

as compared to the (1′*S*,6′*R*)-isomer (**6**). These are diagnostic of the absolute configuration of positions 1′ and 6′. The results are given in Table III.

Yields of **5** and **6** are given in Table IV. In each case, slight stereoselectivity was observed. Variation in the ratio of **5** to **6** may be a reflection of the steric hindrance of the carboxyl group at position 1. That is, on the basis of the X-ray diffraction analysis, the dihedral angle of O3–C2–N1–C21 was found to be 160.1° (Fig. 1; the sign is positive since, when looking from C2 to N1, a clockwise motion of O3 would superimpose it on C2). In this conformer, attack of 2,3-dimethyl-2-butene from the appropriate direction to form **5** would be relatively hindered by the carboxyl group at position 1. Accordingly, the formation of **6** would be favored.

Experimental

Melting points were obtained on a Mitamura micro hot plate and are not corrected. ^{1}H-NMR spectra were taken with a Varian UNITY 400 spectrometer in chloroform-*d*, with tetramethylsilane (TMS) as an internal reference. Specific rotation was obtained on a JASCO JIP-4 digital polarimeter. UV spectra were obtained on a Hitachi UV-VIS 340 spectrophotometer. FAB-MS were taken on a JMS-DX 300 in an *m*-nitrobenzylamine (*m*-NBA) matrix. Column chromatography was done on silica gel (Merck Art 7734 Kieselgel 60). TLC was done on silica gel (Merck Art 11696 TLC-Kieselgel 60 HF). Microanalyses were done in the micro analytical laboratory of our school.

Materials Commercially available uracil, thymine, 5-fluorouracil, cytosine and 2,3-dimethyl-2-butene were used for photoreaction without purification.

Compounds **2** were prepared as described in a previous paper[3] (Chart 1). The yields are given in Table I.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**2a**): On recrystallization from dichloromethane-ether, colorless prisms were obtained. mp 203.5—204.5 °C. FAB-MS *m/z*: 587 ($M^+ + 1$) (*m*-NBA as a matrix). *Anal.* Calcd for $C_{24}H_{30}N_2O_{15}$: C, 49.14; H, 5.12; N, 4.78; Found: C, 49.15; H, 5.20; N, 4.69. UV (CH_3CN) nm (ε): 254 (20300), 204 (17200). IR (KBr): 1750, 1698, 1234 cm^{-1}. ^{1}H-NMR δ: 1.89 (1H, dd, *J*=13.8, 10.2 Hz, 3ax-H), 3.33 (1H, dd, *J*=13.8, 5.4 Hz, 3eq-H), 3.99 (1H, dd, *J*=10.8, 2.6 Hz, 6-H), 4.09 (1H, dd, *J*=12.6, 5.4 Hz, 9-H), 4.28 (1H, dd, *J*=12.6, 3.3 Hz, 9-H), 4.92 (1H, dd, *J*=9.4, 10.8 Hz, 5-H), 5.23 (1H, ddd, *J*=8.7, 5.4, 3.3 Hz, 8-H), 5.39 (1H, dd, *J*=8.7, 2.6 Hz, 7-H), 5.58 (1H, ddd, *J*=10.2, 5.4, 9.4 Hz, 4-H), 3.82 (3H, s, CO_2CH_3), 1.98, 2.03, 2.04, 2.09, 2.14 (each 3H, s, OAc), 5.82 (1H, dd, *J*=8.4, 2.1 Hz, 5′-H), 7.67 (1H, d, *J*=8.4 Hz, 6′-H), 8.94 (1H, br, NH).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-5-fluoro-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**2c**): On recrystallization from ether–hexane, colorless needles were obtained. mp 181—182 °C. FAB-MS *m/z*: 605 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{29}FN_2O_{15}$: C, 47.60; H, 4.96; F, 3.15; N, 4.63. Found: C, 47.46; H, 4.82; F, 3.15; N, 4.47. ^{1}H-NMR δ: 1.95 (1H, dd, *J*=13.8, 10.2 Hz, 3ax-H), 3.31 (1H, dd, *J*=13.8, 5.7 Hz, 3eq-H), 3.98 (1H, dd, *J*=10.8, 2.1 Hz, 6-H), 4.10 (1H, dd, *J*=12.3, 5.4 Hz, 9-H), 4.28 (1H, dd, *J*=12.3, 3.0 Hz, 9-H), 4.92 (1H, dd, *J*=10.2, 10.8 Hz, 5-H), 5.27 (1H, ddd, *J*=9.0, 5.4, 3.0 Hz, 8-H), 5.38 (1H, dd, *J*=9.0, 2.1 Hz, 7-H), 5.55 (1H, ddd, *J*=10.2, 5.7, 10.2 Hz, 4-H), 3.83 (3H, s, CO_2CH_3), 1.99, 2.00, 2.02, 2.04, 2.08 (each 3H, s, OAc), 7.79 (1H, s, 6′-H).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(4-amino-2(1*H*)-pyrimidin-1-yl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**2d**): On recrystallization from ethyl acetate, colorless needles were obtained. mp 124—126 °C. FAB-MS *m/z*: 586 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{31}N_3O_{14}$: C, 49.24; H, 5.32; N, 7.18. Found: C, 49.20; H, 5.48; N, 7.26. ^{1}H-NMR δ 1.72 (1H, dd, *J*=13.2, 12.9 Hz, 3ax-H), 3.40 (1H, dd, *J*=13.2, 5.4 Hz, 3eq-H), 3.94 (1H, dd, *J*=10.2, 2.1 Hz, 6-H), 4.08 (1H, dd, *J*=12.6, 4.8 Hz, 9-H), 4.29 (1H, dd, *J*=12.6, 2.4 Hz, 9-H), 4.86 (1H, dd, *J*=9.6, 10.2 Hz, 5-H), 5.22 (1H, ddd, *J*=8.4, 4.8, 2.4 Hz, 8-H), 5.40 (1H, dd, *J*=8.4, 2.1 Hz, 7-H), 5.62 (1H, ddd, *J*=12.9, 5.4, 9.6 Hz, 4-H), 3.81 (3H, s, CO_2CH_3), 1.96, 2.03, 2.04, 2.07, 2.14 (each 3H, s, OAc), 5.96 (1H, d, *J*=7.8 Hz, 5′-H), 7.70 (1H, d, *J*=7.8 Hz, 6′-H).

Methyl 4,5,7,8,9-Penta-*O*-acetyl 2,3-Dideoxy-2-(4-amino-2(1*H*)-pyrimidin-1-yl)-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (**3d**): On recrystallization from ethyl acetate–benzene, an amorphous powder was obtained. mp 82—84 °C. FAB-MS *m/z*: 586 ($M^+ + 1$). *Anal.* Calcd. for $C_{24}H_{31}N_3O_{14}$: C, 49.24; H, 5.32; N, 7.18. Found: C, 49.37; H, 5.45; N, 6.91. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (1H, dd, *J*=13.2, 12.3 Hz, 3ax-H), 2.26 (1H, dd, *J*=13.2, 5.4 Hz, 3eq-H), 4.11 (1H, dd, *J*=12.6, 2.1 Hz, 9-H), 4.24 (1H, dd, *J*=12.6, 1.7 Hz, 9-H), 5.01 (1H, br, *J*=10.8 Hz, 6-H), 5.09 (1H, ddd, *J*=12.3, 5.4, 9.3 Hz, 4-H), 5.30 (2H, m, NH_2), 5.35 (2H, m, 7-H, 8-H), 6.09 (1H, d, *J*=5.7 Hz, 5′-H) , 7.97 (1H, d, *J*=5.7 Hz, 6′-H), 3.63 (3H, s, CO_2CH_3), 2.01, 2.03, 2.06, 2.10, 2.13 (each 3H, s, OAc).

Photoreaction of 2a—d with 2,3-Dimethyl-2-butene by Acetone-Sensitized Excitation As a typical example, photochemical reaction of **2a** with 2,3-dimethyl-2-butene will be described. A solution of 586 mg (1.0 mmol) of **2a** and 421 mg (5.0 mmol, 5 eq) of 2,3-dimethyl-2-butene in acetone (500 ml) was irradiated for 1 h through a Pyrex filter (2.0 mm thickness). Before and during the irradiation, nitrogen gas was bubbled into the reaction system. The solvent was removed under reduced pressure to dryness and the residue was treated with hot hexane. A colorless amorphous residue obtained was chromatographed (silica gel, eluent: *n*-hexane–ether 8 : 2) to give 170 mg (25%) of **5a** and 350 mg (50%) of **6a** as a colorless oil. For the reactions of **2b** and **2c**, irradiation was done similarly. For the reaction of **2d**, acetic anhydride (130 mg) in 20 ml of pyridine was added to a mixture of **5d** and **6d** (120 mg) obtained from the reaction of **2d** (200 mg, 0.34 mmol) and 2,3-dimethyl-2-butene (143 mg, 1.7 mmol). The solution was stirred for 5 h at ambient temperature. The solvent was removed by evaporation under reduced pressure, followed by extraction of the residue with ethyl acetate and saturated sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and filtered. After evaporation of the solvent under reduced pressure, the residue was chromatographed (eluent: benzene–acetone 3 : 1) to give 38 mg (21%) of **5e** and 47 mg (27%) of **6e**.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*R*,6*S*)-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**5a**): On recrystallization from ether–hexane, an amorphous powder was obtained. mp 95—96 °C. FAB-MS *m/z*: 671 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{42}N_2O_{15}$: C, 53.73; H, 6.26; N, 4.17. Found: C, 53.99; H, 6.51; N, 4.07. ^{1}H-NMR δ: 1.80 (1H, dd, *J*=13.8, 13.8 Hz, 3ax-H), 3.41 (1H, dd, *J*=13.8, 5.4 Hz, 3eq-H), 3.93 (1H, dd, *J*=10.5, 2.4 Hz, 6-H), 4.02 (1H, dd, *J*=12.6, 5.1 Hz, 9-H), 4.31 (1H, dd, *J*=12.6, 2.7 Hz, 9-H), 4.87 (1H, dd, *J*=9.7, 10.5 Hz, 5-H), 5.31 (1H, ddd, *J*=9.3, 5.1, 2.7 Hz, 8-H), 5.38 (1H, dd, *J*=9.3, 2.4 Hz, 7-H), 5.61 (1H, ddd, *J*=13.8, 5.4, 9.7 Hz, 4-H), 3.79 (3H, s, CO_2CH_3), 4.48 (1H, d, *J*=10.21 Hz, 1′-H), 3.03 (1H, d, *J*=10.2 Hz, 6′-H), 1.99, 2.02, 2.03, 2.06, 2.09 (each 3H, s, OAc), 1.04, 1.05, 1.11, 1.29 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*S*,6*R*)-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**6a**): Recrystallized from dichloromethane–hexane, colorless needles. mp 189.5—191.5 °C. FAB-MS *m/z*: 671 ($M^+ + 1$). *Anal.* Calcd. for $C_{30}H_{42}N_2O_{15}$: C, 53.73; H, 6.26; N, 4.17. Found: C, 53.44; H, 6.32; N, 3.78. ^{1}H-NMR δ: 1.86 (1H, dd, *J*=13.2, 11.7 Hz, 3ax-H), 2.76 (1H, dd, *J*=13.2, 5.4 Hz, 3eq-H), 4.40 (1H, dd, *J*=10.8, 1.8 Hz, 6-H), 4.07 (1H, dd, *J*=12.3, 5.1 Hz, 9-H), 4.26 (1H, dd, *J*=12.3, 2.1 Hz, 9-H), 4.82 (1H, dd, *J*=9.6, 10.5 Hz, 5-H), 5.28 (1H, ddd, *J*=10.8, 5.1, 2.1 Hz, 8-H), 5.34 (1H, dd, *J*=10.8, 1.8 Hz, 7-H), 5.27 (1H, ddd, *J*=11.7, 5.4, 10.5 Hz, 4-H), 3.77 (3H, s, CO_2CH_3), 2.93 (1H, d, *J*=10.2 Hz, 6′-H), 4.18 (1H, d, *J*=10.2 Hz, 1′-H), 2.01, 2.00, 2.05, 2.07, 2.13 (each 3H, s, OAc), 1.03, 1.12, 1.15, 1.29 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*R*,6*S*)-6,7,7,8,8-

pentamethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**5b**): On recrystallization from acetone–hexane, colorless needles were obtained. mp 102—104 °C. FAB-MS *m/z*:685 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{44}N_2O_{15}$: C, 54.39; H, 6.43; N, 4.09. Found: C, 54.25; H, 6.61; N, 4.89. ^{1}H-NMR δ 1.74 (1H, dd, J=13.2, 12.6 Hz, 3ax-H), 3.47 (1H, dd, J=13.2, 5.7 Hz, 3eq-H), 3.95 (1H, dd, J=10.8, 2.4 Hz, 6-H), 3.99 (1H, dd, J=12.9, 5.1 Hz, 9-H), 4.29 (1H, dd, J=12.9, 2.5 Hz, 9-H), 4.88 (1H, dd, J=9.9, 10.8 Hz, 5-H), 5.30 (1H, ddd, J=9.3, 5.1, 2.5 Hz, 8-H), 5.38 (1H, dd, J=9.3, 2.4 Hz, 7-H), 5.64 (1H, ddd, J=12.6, 5.7, 9.9 Hz, 4-H), 3.81 (3H, s, CO_2CH_3), 4.10 (1H, s, 1′-H), 1.36 (3H, s, 6′-CH_3), 2.01, 2.02, 2.04, 2.06, 2.09 (each 3H, s, OAc), 1.02, 1.03, 1.07, 1.17 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*S*,6*R*)-6,7,7,8,8-pentamethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**6b**): On recrystallization from chloroform, colorless needles were obtained. mp 101—102 °C. FAB-MS *m/z*: 685 ($M^+ + 1$). *Anal.* Calcd, for $C_{31}H_{44}N_2O_{15}$: C, 54.39; H, 6.43; N, 4.09. Found: C, 54.64; H, 6.60; N, 3.85. ^{1}H-NMR δ: 1.75 (1H, dd, J=13.2, 11.2 Hz, 3ax-H), 2.82 (1H, dd, J=13.2, 5.4 Hz, 3eq-H), 4.28 (1H, dd, J=10.5, 1.8 Hz, 6-H), 4.25 (1H, dd, J=12.0, 2.3 Hz, 9-H), 4.34 (1H, dd, J=12.0, 5.2 Hz, 9-H), 4.82 (1H, dd, J=9.6, 10.5 Hz, 5-H), 5.26 (1H, ddd, J=10.2, 5.2, 2.3 Hz, 8-H), 5.30 (1H, dd, J=10.2, 1.8 Hz, 7-H), 5.36 (1H, ddd, J=11.2, 5.4, 9.6 Hz, 4-H), 3.83 (3H, s, CO_2CH_3), 3.61 (1H, s, 1′-H), 1.30 (3H, s, 6′-CH_3), 1.92, 2.01, 2.06, 2.10, 2.12 (each 3H, s, OAc), 1.02, 1.04, 1.08, 1.10 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*R*,6*R*)-6-fluoro-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**5c**): On recrystallization from acetone–benzene, colorless needles were obtained. mp 152—153 °C. FAB-MS *m/z*: 690 ($M^+ + 2$). *Anal.* Calcd for $C_{30}H_{41}FN_2O_{15}$: C, 52.33; H, 5.96; N, 4.07. Found: C, 52.25; H, 5.86; N, 4.12. ^{1}H-NMR δ; 1.95 (1H, dd, J=13.6, 12.4 Hz, 3ax-H), 3.22 (1H, dd, J=13.6, 5.6 Hz, 3eq-H), 3.93 (1H, dd, J=10.8, 2.1 Hz, 6-H), 4.02 (1H, dd, J=12.9, 6.8 Hz, 9-H), 4.30 (1H, dd, J=12.9, 2.6 Hz, 9-H), 4.92 (1H, dd, J=9.8, 10.8 Hz, 5-H), 5.30 (1H, ddd, J=9.6, 6.8, 2.6 Hz, 8-H), 5.36 (1H, dd, J=9.6, 2. 1 Hz, 7-H), 5.61 (1H, ddd, J=12.4, 5.6, 9.8 Hz, 4-H), 3.78 (3H, s, CO_2CH_3), 5.32 (1H, s, 1′-H), 2.00, 2.02, 2.04, 2.08, 2.11 (each 3H, s, OAc), 1.14, 1.15, 1.26, 1.33 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*S*,6*S*)-6-fluoro-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dioxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**6c**): On recrystallization from ether–hexane, colorless plates were obtained. mp 261—262 °C. FAB-MS *m/z*: 690 ($M^+ + 2$). *Anal.* Calcd, for $C_{30}H_{41}N_2O_{15}$: C, 52.33; H, 5.96; N, 4.07. Found: C, 52.09; H, 5.99; N, 3.889. ^{1}H-NMR δ: 1.76 (1H, dd, J=13.2, 11.2 Hz, 3ax-H), 2.80 (1H, dd, J=13.2, 5.7 Hz, 3eq-H), 4.03 (1H, dd, J=10.2, 1.7 Hz, 6-H), 4.12 (1H, dd, J=12.6, 2.4 Hz, 9-H), 4.31 (1H, dd, J=12.6, 6.9 Hz, 9-H), 4.82 (1H, dd, J=9.3, 10.2 Hz, 5-H), 5.31 (1H, ddd, J=9.0, 6.9, 2.4 Hz, 8-H), 5.37 (1H, dd, J=9.0, 1.7 Hz, 7-H), 5.46 (1H, ddd, J=11.2, 5.7, 9.3 Hz, 4-H), 3.80 (3H, s, CO_2CH_3), 5.30 (1H, s, 1′-H), 2.00, 2.02, 2.04, 2.05, 2.12 (each 3H, s, OAc). 1.18, 1.29, 1.33, 1.47 (each 3H, s, CH_3).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*R*,6*S*)-5-aminoacetyl-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3-oxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**5e**): On recrystallization from acetone–hexane, amorphous powder was obtained. mp 96—98 °C. FAB-MS *m/z*: 712 ($M^+ + 1$) *Anal.* Calcd for $C_{32}H_{45}N_3O_{15}$: C, 54.00; H, 6.33; N, 5.91. Found: C, 54.02; H, 6.45; N, 5.60. ^{1}H-NMR δ: 1.84 (1H, dd, J=13.8, 11.7 Hz, 3ax-H), 3.45 (1H, dd, J=13.8, 6.0 Hz, 3eq-H), 3.41 (1H, d, J=9.6 Hz, 6′-H), 3.89 (1H, dd, J=10.8, 2.4 Hz, 6-H), 4.03 (1H, dd, J=12.0, 4.8 Hz, 9-H), 4.30 (1H, dd, J=12.9, 2.4 Hz, 9-H), 4.42 (1H, d, J=9.6 Hz, 1′-H), 4.86 (1H, dd, J=9.6, 10.8 Hz, 5-H), 5.28 (1H, ddd, J=9.3, 4.8, 2.4 Hz, 8-H), 5.37 (1H, dd, J=9.3, 2.4 Hz, 7-H), 5.64 (1H, ddd, J=11.7, 6.0, 9.6 Hz, 4-H), 3.78 (3H, s, CO_2CH_3), 2.00, 2.02, 2.04, 2.07, 2.09 (each 3H, s, OAc), 1.02, 1.06, 1.14, 1.30 (each 3H, s, CH_3), 2.22 (3H, s, $NHCOCH_3$).

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-[(1*S*,6*R*)-5-aminoacetyl-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3-oxo-2-yl]-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**6e**): On recrystallization from chloroform–hexane, an amorphous powder was obtained. mp 109—110 °C. FAB-MS *m/z*: 712 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{45}N_3O_{15}$: C, 54.00; H, 6.33; N, 5.91. Found: C, 53.84; H, 6.47; N, 5.83. ^{1}H-NMR δ: 1.82 (1H, dd, J=13.2, 12.3 Hz, 3ax-H), 2.76 (1H, dd, J=13.2, 5.1 Hz, 3eq-H), 3.28 (1H, d, J=9.6 Hz, 6′-H), 4.35 (1H, dd, J=10.5, 1.8 Hz, 6-H), 4.08 (1H, dd, J=12.3, 4.2 Hz, 9-H), 4.10 (1H, d, J=9.6 Hz, 1′-H), 4.25 (1H, dd, J=12.3, 2.7 Hz, 9-H), 4.81 (1H, dd, J=9.3, 10.5 Hz, 5-H), 5.26 (1H, ddd, J=9.0, 4.2, 2.7 Hz, 8-H), 5.34 (1H, dd, J=9.0, 1.8 Hz, 7-H), 5.30 (1H, ddd, J=12.3, 5.1, 9.3 Hz, 4-H), 3.75 (3H, s, CO_2CH_3), 1.99, 2.02, 2.04, 2.06, 2.13 (each 3H, s, OAc), 1.00, 1.11, 1.13, 1.33 (each 3H, s, CH_3), 2.22 (3H, s, $NHCOCH_3$).

Hydrolysis of 7, 5b and 6b A solution of **7** (236 mg, 0.35 mmol) and 3 mol dm^{-3} of hydrochloric acid in 10 ml of methanol was refluxed for 6 h. After evaporation of methanol under reduced pressure, the residue was extracted with ethyl acetate (20 ml × 3). The combined organic phase was washed with water, dried over sodium sulfate and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by preparative TLC (eluent: $CHCl_3$–MeOH 6 : 1) to give 17 mg (32%) of **8** and 120 mg (51%) of **7** (unconverted). Hydrolysis of **5b** and **6b** was performed as described above. From 45 mg of **5b** and 45 mg of **6b**, 8 mg (54%) of **9** and 16 mg (51%) of **8** were formed, respectively.

(1*S*,6*R*)-6,7,7,8,8-Pentamethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (**8**): On recrystallization from chloroform, colorless prisms were obtained. mp 242—244 °C. FAB-MS *m/z*: 211 ($M^+ + 1$). ^{1}H-NMR δ 1.00, 1.00, 1.02, 1.08 (each 3H, s, CH_3), 1.36 (3H, S, 6-CH_3), 3.37 (1H, d, J=4.2 Hz, 1-H). $[\alpha]_D$: +18.750 (c=0.32, MeOH) when converted from **7**, +18.571 (c=0.14, MeOH) when converted from **6b**.

(1*R*,6*S*)-6,7,7,8,8-Pentamethyl-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (**9**): On recrystallization from chloroform, colorless needles were obtained. mp 230—232 °C. FAB-MS *m/z*: 211 ($M^+ + 1$) (*m*-NBA as a matrix). ^{1}H-NMR ($CDCl_3$) δ: 1.00, 1.00, 1.02, 1.08 (each 3H, s, CH_3), 1.36 (3H, s, 6-CH_3), 3.37 (1H, δ, J=4.2 Hz, 1-H), $[\alpha]_D$: −20.000 (c=0.08, MeOH).

X-Ray Crystallographic Analysis of 2a and 7 A crystal having approximate dimensions of 0.4 × 0.2 × 0.2 mm (**2a**) or 0.4 × 0.5 × 0.5 mm (**7**) was used for the analysis. The cell dimensions and diffraction intensities were measured on a Rigaku AFC-5R diffractometer using graphite-monochromated CuK_α radiation (λ=1.54178 Å) and a 12 kW rotating anode generator at 23 °C. Crystal data are as follows. **2a**: Empirical formula; $C_{24}H_{30}N_2O_{15}$. Crystal system; orthorhombic. Lattice parameters; a=16.636(1) Å, b=21.687(2) Å, c=7.935(2) Å, V=2862.07(4) Å^3. Space group; $p2_12_12$. Z value; 4. Density (calculated); 1.361 g cm^{-3}. **7**: Empirical formula; $C_{31}H_{44}N_2O_{15}$. Crystal system; orthorhombic. Lattice parameters; a=10.0433(9) Å, b=11.9745(8) Å, c=7.9668(5) Å, V=883.918(4) Å^3. Space group; P_1. Z value; 1. Density (calculated); 1.286 g cm^{-3}. The data were collected using the $\omega-2\theta$ scan technique in the range of $2\theta < 140.3°$. Scans of $(1.31+0.30\tan\theta)°$ at a speed of 16.0° min^{-1} for **2a** and $(1.63+0.30\tan\theta)°$ at a speed of 32.0° min^{-1} for **9** were made. In total, 3026 reflections for **2a** and 3444 reflections for **9** were collected and corrections were made for Lorentz and polarization factors but not for absorption. The structure was elucidated by a direct method using TEXSAN.[11] The non-hydrogen atoms were refined anisotropically by the full-matrix least-squares refinement. A difference Fourier synthesis was calculated and the positions of all hydrogen atoms were found. They were refined isotropically. The final R values were 5.3% for **2a** and 8.1% for **7**, where $R=\Sigma\|F_O|-|F_C\|/\Sigma|F_O|$. The final R_w values were 5.3% for **2a** and 8.8% for **7**, where $R_w=[(\Sigma w(|F_O|-|F_C|)^2/\Sigma wF_O^2)]^{1/2}$.

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