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TETRAHEDRON: *ASYMMETRY*

Syntheses of 5′-*O*-glycosylnucleosides

Z. J. Liu, M. Zhou, J. M. Min and L. H. Zhang *

School of Pharmaceutical Sciences, Beijing Medical University, Beijing, 100083, People's Republic of China

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Abstract

A general synthetic approach to 2,3-unsaturated glycosides connecting with nucleosides involving Ferrier rearrangements of glycals is discussed. The new compounds were identified by NMR and MS (HRFAB$^+$). The hydroxylation of the resulting 2,3-unsaturated glycosides was completed using OsO_4 to give 5′-*O*-glycosylnucleosides in good yield.

1. Introduction

It has been found that many natural antibiotics possessing significant antitumor and antiviral activities have the structure of a nucleoside connected to oligosaccharides.[1–3] Watanabe et al.[4] via the Koenigs–Knorr condensation, prepared 5′-*O*-glucuronides of 5-fluorouridine and 5-fluorocytidine, which were less toxic against several leukemic cell lines in tissue culture. Sugimura[5] reported the synthesis of disaccharide nucleosides as intermediates for amicetins by the reaction of glycopyranosyl fluoride with hexopyranosylnucleoside, but the yield was only 47%. It is of interest, therefore, to investigate the syntheses and biological activities of nucleoside analogues containing oligosaccharides.

Stimulated by the biological background, the *O*-glycosylation method is becoming more and more important. From a survey of the current advances in methodology glycosyl donors are roughly classified as follows, based on the type of anomeric functional group: glycosyl halide, thioglycoside, 1-*O*-acyl sugar, ortho ester, 1-*O*- and 1-*S*-carbonate, 4-pentenyl glycoside, 1,2-anhydro sugar, 1-hydroxyl sugar and glycal, etc.[6,7] An efficient approach for the synthesis of oligosaccharides was reported recently.[8,9]

Glycal, which is a very versatile synthetic intermediate, has proven to be useful in the syntheses of glycoconjugates. Reaction of glycal with nucleophilic agents mediated by Lewis acids yields 2,3-unsaturated glycosides which can be used as intermediates for a variety of reactions such as Sharpless *cis*-oxyamination, epoxidations or hydroxylations. Herdewjin et al.[10] reported the synthesis of nucleosides via Ferrier rearrangements. Recently, catalytic Ferrier rearrangements of unsaturated nucleosides were

* Corresponding author. E-mail: zdszlh@mail.bjmu.edu.cn

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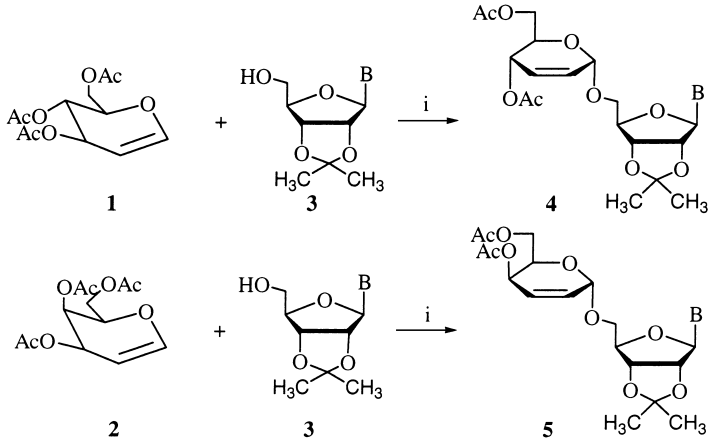
also reported,[11] however, the reaction has not been applied to the synthesis of nucleosides connected to saccharides. Here we wish to report a general synthetic approach to 2,3-unsaturated glycosides connected to nucleosides resulting from Ferrier rearrangements (Scheme 1).



Scheme 1. a: B=uracil-1-yl; b: B=hypoxanthin-9-yl; c: B=adenin-9-yl; i. $BF_3 \cdot Et_2O$/acteone

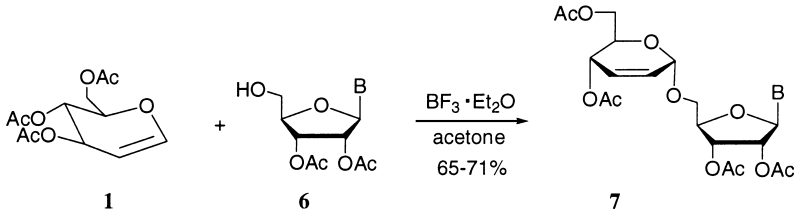
2. Results and discussion

Tri-*O*-acetyl-glucal **1** and tri-*O*-acetyl-galactal **2** were prepared from D-glucose and D-galactose, respectively, by the usual two-step process.[12] The preparation of 2′,3′-*O*-isopropylidene-D-ribonucleosides **3** followed the known reaction from D-nucleosides.[13] Compounds **4a–c** and **5a–c** were obtained in reasonable yield by the reaction of **1** and **2**, with **3** in the presence of boron trifluoride (Scheme 1). Many catalysts have been recommended for the Ferrier rearrangement, such as I_2,[14] $SnCl_4$,[15] $SbCl_5$, HCl, H_2SO_4, CCl_3CO_2H[16] and *p*-toluenesulfonic acid.[17] However, due to the instability of the glycosyl bond between the pentofuranose and the hexopyranose, protic acids cannot be used as catalysts. Investigating the reaction by using different Lewis acids as catalysts, it was found that I_2 and $BF_3 \cdot Et_2O$ can promote the reaction between the glycal and nucleosides with $BF_3 \cdot Et_2O$ being much better than I_2 (Table 1). It seems that the configurations of glycal, glucal and galactal, have no significant effect on the reaction. To deprotect under the basic conditions of the next synthesis, 2′,3′-di-*O*-acetyl-nucleoside was used instead of 2′,3′-*O*-isopropylidene-nucleoside in the Ferrier rearrangement and compounds **7a–b** were obtained (Scheme 2).

The Ferrier arrangement is believed to proceed via a delocalized cation formed by departure of the acyloxy moiety from a starting glycal followed by attack of a nucleophile, with the configuration of products being in favor of α-glycosides.[18,19] It has been reported that the α-anomer of the 2,3-unsaturated glycosides adopted the $^0H_5$ conformation and the β-anomer the $^5H_0$ conformation.[20] The two anomers

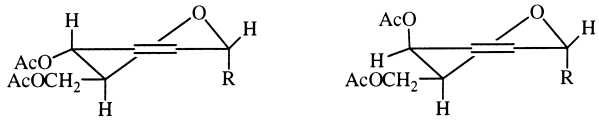
Table 1
Yields of the Ferrier reaction of **1** and **2** using different catalysts

	4a	**4b**	**4c**	**5a**	**5b**	**5c**
I_2	10%	10%	20%	25%	5%	10%
$BF_3 \cdot Et_2O$	85%	40%	56%	56%	30%	45%



1 **6** **7**

Scheme 2. a: B=N^6-acetyl-adenin-9-yl; b: B= hypoxanthin-9-yl

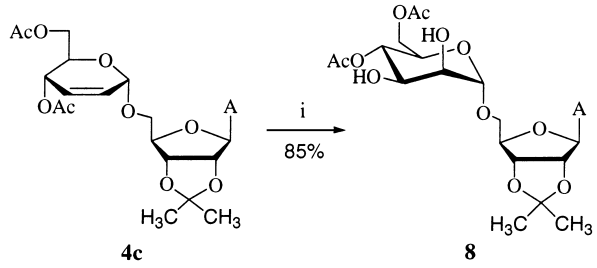


4a-4c, 7a-7b **5a-5c**

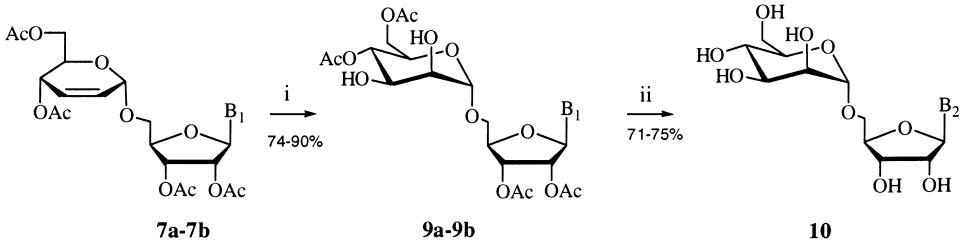
Figure 1.

could be identified by the value of $J_{4'',5''}$ in ^{1}H NMR spectrum. In our case, only one compound was obtained from each reaction of glycal with nucleosides in the presence of $BF_3 \cdot Et_2O$. The ^{1}H NMR of **4a**–**c** and **7a**–**b** showed that the $J_{4'',5''}$ (**4a**: 9.0 Hz; **4b**: 9.0 Hz; **4c**: 9.5 Hz; **7a**: 9.5 Hz; **7b**: 10.0 Hz) were in accord with a favorable α-anomer, in which 4″-H and 5″-H were at anti-quasi-axial positions. The coupling constants of 4″-H and 5″-H of **5a**–**c** (**5a**: 5.5 Hz; **5b**: 5.5 Hz; **5c**: 6.0 Hz), having quasi-axial acetoxy groups at 4″-C, were less than those of **4a**–**c** and **7a**–**b** (Fig. 1). Employing computer-aided molecular simulation, the configurations of compounds **4c** and **5c** were studied. It was found that the distances between 6″-H of the hexopyranose and 4′-H of the pentofuranose were 2.250 Å (**4c**) and 2.242 Å (**5c**), respectively, for the β-anomers and should give NOE signals in the ^{1}H NMR. The corresponding distances in the α-anomers were 7.043 Å (**4c**) and 7.127 Å (**5c**), and no NOE signal should be expected in the ^{1}H NMR. The ^{1}H NMR experiments identified compound **4c** and **5c** in favor of α-anomers.

The double bond in the 2,3-unsaturated glycosides can be dihydroxylated to give 5′-*O*-glycosylnucleosides. Different reagents were studied for this synthesis. Compound **4c** was reacted with potassium permanganate in acetone at 0°C to give the corresponding product but the yield was only 20%. By using OsO_4 as an oxidant, the hydroxylation of compound **4c** took place smoothly in the presence of water. The disaccharide nucleoside **8** was obtained in very good yield (85%) (Scheme 3). The configuration of the hydroxy groups in the disaccharide nucleosides was determined by ^{1}H NMR and ^{13}C NMR, and compared with the corresponding known sugar. It is well known that the hydroxylation of the double bond by OsO_4 gives the *cis*-dihydroxy compounds.[21] In the hydroxylation of **7a** and **7b**, there are two possibilities for the configuration of the hexose moiety in **9a** and **9b**, α-D-mannopyranose or α-D-allopyranose. From the point of view of stereochemistry, it seems that OsO_4 attacks the double bond away from the bulky groups, 1″-nucleoside and 4″-*O*-acetyl, to give mannopyranose. The hydroxylation of compounds **7a**–**b** with osmium tetroxide proceeded to give **9a** and **9b** in 74–90% yield. 5′-*O*-Glycosylnucleosides (**10a**–**b**) were obtained by deprotection of compounds **9a** and **9b** under 25% of ammonia water at 50°C in 70% yield (Scheme 4). The ^{13}C NMR showed that the hexose moiety in **10a** was in accord with α-D-mannopyranose[22] (Table 2). Compounds **10a** and **10b** were degraded by 1N HCl at 80°C for about 1 h. D-Mannose was detected in the hydrolysate by paper chromatography.



Scheme 3. i. $OsO_4/H_2O_2/THF/H_2O$



Scheme 4. i. $OsO_4/H_2O_2/THF/H_2O$; ii. $NH_3 \cdot H_2O$; B_1: a: N^6-acetyl-adenin-9-yl; b: hypoxanthin-9-yl; B_2: a: adenin-9-yl; b: hypoxanthin-9-yl

Table 2
^{13}C NMR data of the hexose moiety of **10a** compared with the known sugars (ppm)

position	1	2	3	4	5	6
α-D-mannopyranose	90.5	71.7	71.3	68.0	73.4	62.1
α-D-allopyranose	93.4	67.6	72.3	66.7	67.5	61.4
hexose moiety of **10a**	99.8	70.1	71.0	66.7	73.8	61.0

3. Conclusion

5′-*O*-Glycosylnucleosides were synthesized by the reaction of glycal with nucleoside via Ferrier rearrangement followed by hydroxylation using OsO_4. The reaction was stereoselective and the yield was reasonable. The configurations of the products were identified by NOE of ^1H NMR and ^{13}C NMR.

4. Experimental

4.1. General procedure

Acetone was dried and distilled prior to use. Thin-layer chromatography was performed by using silica gel GF-254 (Qing Dao Chemical Company, China) plates with detection by UV, or charring with 5% H_2SO_4 in ethanol. Column chromatography was performed on silica gel (200–300 mesh, purchased from Qing Dao Chemical Company, China). Paper chromatography was performed on No. 1 Whatman paper with *n*-butanol:HOAc:H_2O (4:1:2) as a mobile phase and developed in a solution of oxalic acid and aniline. NMR spectra were recorded on a Varian INOVA-500 or a Bruker DPX-400 instrument with TMS as an internal standard. Optical rotations were recorded on a Perkin–Elmer 243B polarimeter.

Zapspec and APEX II spectrometers were used for mass spectra. The software used for the computational optimizing molecular model was CS Chem 3D.

4.2. General procedure for 2′′,3′′-unsaturated glycosides containing nucleoside

Compounds **4a**–**c**, **5a**–**c** and **7a**–**b** were synthesized as follows: glycal (0.02 mmol) and **3** or **6** (0.02 mmol) were dissolved in acetone (ca. 4 ml) and boron trifluoride–ether (0.1 ml) was added. Stirring was continued at room temperature until TLC showed the glycal had disappeared. After cooling in ice and neutralization with saturated $NaHCO_3$, the solution was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, then purified with silica gel chromatography to give the products.

4.3. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-erythro-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylideneuridine **4a**

Yield: 85%, $[\alpha]_D^{25}$ +1.67 (c, 0.120, MeOH), ^{1}H NMR (DMSO-d_6), δ 11.40 (s, 1H, N-H), 7.69 (d, 1H, 6-H), 5.85 (m, 2H, 2′′,3′′-H), 5.81 (d, 1H, 1′-H, $J_{1',2'}$=1.5 Hz,), 5.62 (m, 1H, 5-H), 5.17 (d, 1H, 4′′-H, $J_{4'',5''}$=9 Hz), 5.09 (s, 1H, 1′′-H), 4.91 (dd, 1H, 2′-H, $J_{1',2'}$=1.5 Hz, $J_{2',3'}$=4 Hz), 4.77 (dd, 1H, 3′-H, $J_{3',4'}$=4 Hz), 4.26 (dd, 1H, 4′-H, $J_{3',4'}$=4 Hz), 4.11 and 4.10 (m, 2H, 6′′-H×2), 3.95 (m, 1H, 5′′-H), 3.80 (m, 1H, 5′-H), 3.72 (m, 1H, 5′-H), 2.00 (s, 3H, -OAc), 2.02 (s, 3H, -OAc), 2.04 (s, 3H, -OAc), 1.47 (s, 3H, -CH_3), 1.29 (s, 3H, -CH_3), HRFAB$^+$ ($C_{22}H_{28}O_{11}N_2$+H^+), calcd mass 497.1771, found mass 497.1773.

4.4. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-erythro-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylideneinosine **4b**

Yield: 40%, $[\alpha]_D^{25}$ −33.8 (c, 0.130, MeOH), ^{1}H NMR (DMSO-d_6), δ 12.44 (br, 1H, N-H), 8.20 (s, 1H, 8-H), 8.07 (d, 1H, 2-H, $J_{1,2}$=2 Hz), 6.12 (d, 1H, 1′-H, $J_{1',2'}$=2.5 Hz), 5.82 (m, 1H, 3′′-H), 5.66 (m, 1H, 2′′-H), 5.33 (m, 1H, 2′-H), 5.13 (d, 1H, 4′′-H, $J_{4'',5''}$=9 Hz), 5.04 (m, 1H, 1′′-H), 4.97 (m, 1H, 3′-H), 4.42 (m, 1H, 4′-H), 4.07 (m, 2H, 6′′-H×2), 3.90 (m, 1H, 5′′-H), 2.75 (m, 1H, 5′-H), 3.67 (m, 1H, 5′-H), 2.04 (s, 3H, -OAc), 2.00 (s, 3H, -OAc), 1.50 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3), HRFAB$^+$ ($C_{23}H_{28}O_{10}N_4$+H^+), calcd mass 521.1884, found mass 521.1884.

4.5. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-erythro-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylideneadenosine **4c**

Yield: 56%, $[\alpha]_D^{25}$ −26.7 (c, 0.105, MeOH), ^{1}H NMR (DMSO-d_6), δ 8.29 (s, 1H, 8-H), 8.18 (s, 1H, 2-H), 7.45 (br, 2H, -NH_2), 6.16 (d, 1H, 1′-H, $J_{1',2'}$=2.5 Hz), 5.83 (d, 1H, 3′′-H, $J_{2'',3''}$=10 Hz), 5.72 (m, 1H, 2′′-H), 5.43 (dd, 1H, 2′-H, $J_{1',2'}$=2.5 Hz, $J_{2',3'}$=6 Hz), 5.14 (d, 1H, 4′′-H, $J_{4'',5''}$=9.5 Hz), 5.02 (m, 2H, 1′′-H, 3′-H), 4.40 (m, 1H, 4′-H), 4.07 (m, 2H, 6′′-H×2), 3.91 (m, 1H, 5′′-H), 3.72 (m, 2H, 5′-H×2), 2.04 (s, 3H, -OAc), 1.99 (s, 3H, -OAc), 1.54 (s, 3H, -CH_3), 1.34 (s, 3H, -CH_3), HRFAB$^+$ ($C_{23}H_{29}O_9N_5$+H^+), calcd mass 520.2044, found mass 520.2045.

4.6. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-threo-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylidene-uridine ***5a***

Yield: 56%, $[\alpha]_D^{25}$ −152 (c, 0.075, MeOH), ^{1}H NMR (DMSO-d_6), δ 11.39 (s, 1H, N-H), 7.67 (d, 1H, 6-H), 6.03 (m, 2H 2′′,3′′-H), 5.81 (d, 1H, 1′-H, $J_{1',2'}$=2 Hz), 5.63 (m, 1H, 5-H), 5.10 (d, 1H, 1′′-H, $J_{1'',2''}$=3 Hz), 4.98 (dd, 1H, 4′′-H, $J_{4'',5''}$=5.5 Hz), 4.90 (m, 1H, 2′-H), 4.74 (m, 1H, 3′-H), 4.28 (m, 1H, 4′-H), 4.23 (m, 1H, 5′′-H), 4.10 (m, 2H, 6′′-H×2), 3.80 (m, 1H, 5′-H), 3.72 (m, 1H, 5′-H), 2.00 (m, 6H, -OAc×2), 1.46 (s, 3H, -CH_3), 1.30 (s, 3H, -CH_3), HRFAB$^+$ ($C_{22}H_{28}O_{11}N_2$+H^+), calcd mass 497.1771, found mass 497.1772.

4.7. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-threo-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylidene-inosine ***5b***

Yield: 30%, $[\alpha]_D^{25}$ −175.8 (c, 0.095, MeOH), ^{1}H NMR (DMSO-d_6), δ 12.46 (br, 1H, N-H), 8.20 (s, 1H, 8-H), 8.09 (d, 1H, 2-H, $J_{1,2}$=3.4 Hz), 6.12 (d, 1H, 1′-H, $J_{1',2'}$=2.44 Hz), 6.02 (m, 1H, 3′′-H), 5.80 (dd, 1H, 2′′-H, $J_{2'',3''}$=10.0 Hz), 5.34 (dd, 1H, 2′-H, $J_{1',2'}$=2.9 Hz), 5.07 (d, 1H, 1′′-H, $J_{1'',2''}$=2.8 Hz), 4.98 (dd, 1H, 4′′-H, $J_{4'',5''}$=5.5 Hz), 4.95 (m, 1H 3′-H), 4.45 (m, 1H, 4′-H), 4.22 (m, 1H, 5′′-H), 4.07 (m, 2H, 6′′-H×2), 3.78 (m, 1H, 5′-H), 3.68 (m, 1H, 5′-H), 1.99 (s, 3H, -OAc), 1.98 (s, 3H, -OAc), 1.52 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3), HRFAB$^+$ ($C_{23}H_{28}O_{10}N_4$+H^+), calcd mass 521.1884, found mass 521.1884.

4.8. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-threo-hex-2′′-enopyranosyl-(1→5)-2′,3′-O-isopropylidene-adenosine ***5c***

Yield: 45%, $[\alpha]_D^{25}$ −175.6 (c, 0.135, MeOH), ^{1}H NMR (DMSO-d_6), δ 8.28 (s, 1H, 8-H), 8.17 (s, 1H, 2-H), 7.45 (br, 2H, -NH_2), 6.15 (d, 1H, 1′-H, $J_{1',2'}$=2.5 Hz), 6.02 (dd, 1H, 3′′-H, $J_{2'',3''}$=10.0 Hz, $J_{3'',4''}$=5.5 Hz), 5.91 (dd, 1H, 2′′-H, $J_{1'',2''}$=2.5 Hz), 5.43 (dd, 1H, 2′-H, $J_{1',2'}$=2.50 Hz, $J_{2',3'}$=6 Hz), 5.07 (d, 1H, 1′′-H, $J_{1'',2''}$=2.5 Hz), 4.98 (m, 2H, 4′′-H, 3′-H), 4.42 (m, 1H, 4′-H), 4.22 (m, 1H, 5′′-H, $J_{4'',5''}$=6 Hz), 4.08 (m, 2H, 6′′-H×2), 3.72 (m, 2H, 5′-H×2), 2.01 (s, 3H, -OAc), 1.98 (s, 3H, -OAc), 1.53 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), HRFAB$^+$ ($C_{23}H_{29}O_9N_5$+H^+), calcd mass 520.2044, found mass 520.2043.

4.9. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-erythro-hex-2′′-enopyranosyl-(1→5)-2′,3′-di-O-acetyl-N^6-acetyladenosine ***7a***

Yield: 65%, $[\alpha]_D^{25}$ −16.8 (c, 0.125, MeOH), ^{1}H NMR (DMSO-d_6), δ 10.78 (s, 1H, NHAc), 8.68 (s, 1H, 8-H), 8.26 (s, 1H, 2-H), 6.33 (d, 1H, 1′-H, $J_{1',2'}$=5.5 Hz), 6.00 (m, 1H, 2′-H), 5.89 (m, 2H, 2′′-H, 3′′-H), 5.63 (m, 1H, 3′-H), 5.17 (d, 1H, 4′′-H, $J_{4'',5''}$=9.5 Hz), 5.14 (s, br, 1H, 1′′-H), 4.44 (m, 2H, 4′-H), 4.09 (m, 2H, 6′′-H×2), 3.98 (m, 1H, 5′′-H), 3.88 (m, 2H, 5′-H×2), 2.26 (s, 3H, -Ac), 2.14 (s, 3H, -Ac), 2.02 (s, 3H, -Ac). Anal. calcd for $C_{26}H_{31}O_{12}N_5$ (605.55): C, 51.57; H, 5.12; N, 11.57, found: C, 51.20; H, 4.79; N, 11.19.

4.10. 4′′,6′′-Di-O-acetyl-2′′,3′′-dideoxy-α-D-erythro-hex-2′′-enopyranosyl-(1→5)-2′,3′-di-O-acetyl-inosine ***7b***

Yield: 71%, $[\alpha]_D^{25}$ −23.8 (c, 0.130, MeOH), ^{1}H NMR (DMSO-d_6), δ 12.48 (s, 1H, N-H), 8.24 (s, 1H, 8-H), 8.08 (d, 1H, 2-H), 6.18 (d, 1H, 1′-H, $J_{1',2'}$=5.5 Hz), 5.86 (m, 3H, 3′′-H, 2′′-H, 2′-H), 5.54 (dd, 1H, 3′-H, $J_{3',4'}$=4 Hz, $J_{2',3'}$=5.5 Hz), 5.17 (dd, 1H, 4′′-H, $J_{4'',5''}$=10 Hz, $J_{3'',4''}$=1.5 Hz), 5.13 (s, br, 1H,

1′′-H), 4.40 (dd, 1H, 4′-H), 4.10 (m, 2H, 6′′-H×2), 3.96 (m, 1H, 5′′-H), 3.85 (m, 2H, 5′-H×2), 2.114 (s, 3H, -OAc), 2.04 (s, 3H, -OAc), 2.01 (s, 3H, -OAc), 1.99 (s, 3H, -OAc). Anal. calcd for $C_{24}H_{28}O_{12}N_4$ (564.50): C, 51.06; H, 5.00; N, 9.93, found: C, 50.83; H, 5.06; N, 9.59.

4.11. *General procedure for hydroxylation of 2′′,3′′-unsaturated glycosides containing nucleoside*

Reagents: (a) hydrogen peroxide reagent: 45 ml of 30% hydrogen peroxide was added to 200 ml of *t*-butyl alcohol; (b) osmium tetroxide reagent: 1.0 g of osmium tetroxide was dissolved in 200 ml of *t*-butyl alcohol.

Compound **4c**, **7a** or **7b** (0.25 mmol) was dissolved in 5 ml of tetrahydrofuran. Then, 1 ml of H_2O, 2 ml of hydrogen peroxide reagent and 12 ml of osmium tetroxide (0.24 mmol) reagent was added successively. Stirring continued until TLC showed that the reactant had disappeared. Then, 15 ml of saturated $NaHSO_3$ was added at 0°C for decomposition of the osmium complexes. After 30 min, the reaction mixture was filtered, neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was then dried over $MgSO_4$, and purified with silica gel chromatography.

4.12. *4′′,6′′-Di*-O-*acetyl-α*-D-*mannopyranosyl-(1→5)-2′,3′*-O-*isopropylideneadenosine* ***8***

Yield: 85%, $[\alpha]_D^{25}$ −0.9 (c, 0.115, MeOH), ^{1}H NMR (DMSO-d_6), δ 8.29 (s, 1H, 8-H), 8.17 (s, 1H, 2-H), 7.34 (s, 2H, -NH_2), 6.18 (d, 1H, 1′-H, $J_{1',2'}$=2 Hz), 5.43 (dd, 1H, 2′-H, $J_{2',3'}$=6 Hz), 5.16 (d, 1H,-OH), 5.04 (dd, 1H, 3′-H), 4.97 (d, 1H, -OH), 4.91 (t, 1H, 3′′-H), 4.68 (s, br, 1H, 1′′-H), 4.34 (m, 1H, 4′-H), 3.96 (dd, 1H, 5′′-H, $J_{4'',5''}$=5 Hz, $J_{5'',6''}$=12 Hz), 3.79 (dd, 1H, 6′′-H), 3.66 (m, 4H, 6′′-H, 2′′-H, 5′-H×2), 3.54 (m, 1H, 4′′-H), 2.00 (s, 3H, -OAc), 1.95 (s, 3H, -OAc), 1.55 (s, 3H, -OAc), 1.34 (s, 3H, -OAc), HRFAB$^+$ ($C_{23}H_{31}O_{11}N_5$+H^+), calcd mass 554.2093, found mass 554.2096.

4.13. *4′′,6′′-Di*-O-*acetyl-α*-D-*mannopyranosyl-(1→5)-2′,3′-di*-O-*acetyl-N*^{6}*-acetyladenosine* ***9a***

Yield: 90%, $[\alpha]_D^{25}$ −9.68 (c, 0.31, MeOH), ^{1}H NMR (DMSO-d_6), δ 10.79 (s, 1H, N-H), 8.69 (s, 1H, 8-H), 8.63 (s, 1H, 2-H), 6.32 (d, 1H, 1′-H, $J_{1',2'}$=5.76 Hz), 6.04 (t, 1H, 2′-H), 5.64 (dd, 1H, 3′-H), 5.20 (d, 1H, 2′′-OH), 5.04 (d, 1H, 3′′-OH), 4.95 (t, 1H, 4′′-H, $J_{3'',4''}$=9.6 Hz), 4.74 (s, br, 1H, 1′′-H), 4.39 (dd, 1H, 4′-H), 4.01 (m, 1H, 5′′-H), 4.01 (m, 1H, 6′′-H), 3.85 (m, 1H, 5′-H), 3.70 (m, 4H, 5′-H, 6′′-H, 2′′-H, 3′′-H), 2.26 (s, 3H, -OAc), 2.13 (s, 3H, -OAc), 2.01 (s, 3H, -OAc), 1.97 (s, 3H, -OAc), HRFAB$^+$ ($C_{26}H_{33}O_{14}N_5$+H^+), calcd mass 640.2096, found mass 640.2094.

4.14. *4′′,6′′-Di*-O-*acetyl-α*-D-*mannopyranosyl-(1→5)-2′,3′-di*-O-*acetylinosine* ***9b***

Yield: 74%, $[\alpha]_D^{25}$ −7.5 (c, 0.04, MeOH), ^{1}H NMR (DMSO-d_6), δ 12.50 (s, 1H, N-H), 8.25 (s, 1H, 8-H), 8.09 (d, 1H, 2-H), 6.18 (d, 1H, 1′-H), 5.88 (m, 1H, 2′-H), 5.54 (dd, 1H, 3′-H, $J_{2',3'}$=5.6 Hz), 5.22 (d, 1H, 2′′-OH), 5.04 (d, 1H, 3′′-OH), 4.94 (t, 1H, 4′′-H, $J_{3'',4''}$=9.6 Hz), 4.76 (s, br, 1H, 1′′-H), 4.36 (m, 1H, 4′-H), 4.02 (m, 1H, 5′′-H), 3.92 (m, 1H, 6′′-H), 3.75 (m, 1H, 5′-H), 3.69 (m, 4H, 5′-H, 6′′-H, 2′′-H, 3′′-H), 2.12 (s, 3H, -OAc), 2.03 (s, 3H, -OAc), 2.01 (s, 3H, -OAc), 1.98 (s, 3H, -OAc), HRFAB$^+$ ($C_{24}H_{30}N_4O_{14}$+H^+), calcd mass 599.1837, found mass 599.1845.

4.15. General procedure for deprotection

About 100 mg of compound **9a** or **9b** was suspended in 10 ml of 25% ammonia water in a sealed vessel. The solution was stirred for 24 h at 50°C, then concentrated to a syrup under reduced pressure at 50°C, and purified with Sephadex LH-20 chromatography (methanol as the mobile phase) to give the product **10a** or **10b**.

4.16. α-D-*Mannopyranosyl-(1→5)-adenosine* ***10a***

Yield: 71%, $[\alpha]_D^{25}$ −1.05 (c, 0.095, MeOH), ^{1}H NMR (DMSO-d_6), δ 8.26 (s, 1H, 8-H), 8.18 (s, 1H, 2-H), 7.31 (s, 2H, NH_2), 5.92 (d, 1H, 1′-H, $J_{1',2'}$=5.52 Hz), 5.55 (d, 1H, 2′-OH), 5.31 (d, 1H, 3′-OH), 4.82 (d, 1H, 2″-OH), 4.77 (d, 1H, 4″-OH), 4.66 (s, 1H, 1″-H), 4.56 (d, 1H, 3″-OH), 4.56 (dd, 1H, 2′-H, $J_{1',2'}$=5.52 Hz, $J_{2',3'}$=11.04 Hz), 4.50 (t, 1H, 6″-OH), 3′ (dd, 1H, 3′-H), 4.10 (m, 1H, 4′-H), 3.77 (dd, 1H, 5′-H, $J_{4',5'}$=11.16 Hz, $J_{5',5'}$=4.32 Hz), 3.63 (m, 3H, 2″-H, 5′-H, 6″-H), 3.46 (m, 3H, 3″-H, 6″-H, 4″-H), ^{13}C NMR (DMSO-d_6), δ 155.8 (6-C), 152.7 (2-C), 149.4 (4-C), 147.9 (5-C), 138.9 (8-C), 99.8 (1″-C), 87.1 (1′-C), 82.8 (4′-C), 73.8 (5″-C), 73.5 (2′-C), 71.0 (3″-C), 70.3 (3′-C), 70.1 (2″-C), 66.7 (4″-C), 66.3 (5′-C), 61.0 (6″-C), HRFAB$^+$ ($C_{16}H_{23}O_9N_5$+H^+), calcd mass 430.1568, found mass 430.1569. Anal. calcd for $C_{16}H_{23}O_9N_5$: C, 44.55; H, 5.84; N, 16.23, found: C, 44.14; H, 6.00; N, 15.86.

4.17. α-D-*Mannopyranosyl-(1→5)-inosine* ***10b***

Yield: 75%, $[\alpha]_D^{25}$ −4.3 (c, 0.18, MeOH), ^{1}H NMR (DMSO-d_6), δ 12.30 (br, 1H, N-H), 8.18 (s, 1H, 8-H), 8.08 (s, 1H, 2-H), 5.88 (d, 1-H, 1′-H, $J_{1',2'}$=5.8 Hz), 5.57 (d, 1H, 2′-OH), 5.34 (d, 1H, 3′-OH), 4.83 (d, 1H, 2″-OH), 4.80 (d, 1H, 4″-OH), 4.66 (s, 1H, 1″-H), 4.62 (d, 1H, 3″-OH), 4.51 (m, 2H, 6″-OH, 2′-H), 4.12 (m, 2H, 3′-H, 4′-H), 3.76 (dd, 1H, 5′-H), 3.65 (m, 2H, 2″-H, 6″-H), 3.48 (dd, 1H, 5′-H), 3.40 (m, 4H, 3″-H, 4″-H, 5″-H, 6″-H), HRFAB$^+$ ($C_{16}H_{22}O_{10}N_4$+H^+), calcd mass 431.1408, found mass 431.1406.

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