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Stereoselective synthesis of novel *C*-azanucleoside analogues by microwave-assisted nucleophilic addition of sugar-derived cyclic nitrones

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ABSTRACT

A series of *C*-azanucleoside analogues were synthesized by microwave-assisted nucleophilic addition of electron-rich hetero-aromatics to sugar-derived cyclic nitrones, and followed by reduction and deprotection. The nucleophilic addition afforded the 2′,3′-trans isomer as the dominant by the favorite *exo* attack and showed high stereoselectivity in polar solvent.

1. Introduction

C-Azanucleosides, a class of nucleoside analogues with the C–C connection through the anomeric carbon of azasugars and heterocyclic base moieties,[1] have shown very important biological activities, such as inhibitions against nucleoside hydrolase[2] and RTA (ricin toxin A),[3] antiproliferative[4] and anti-HIV[5] activities, and so on. The promising potential of *C*-azanucleosides as drug candidates has attracted great attention to synthesize novel *C*-azanucleosides and analogues for investigating their biological activities,[6] and various synthetic methods have been exploited to develop convenient and practical preparations of such compounds, for instance, the glycosylation of azasugar to silylated bases (e.g., uracil, thymine, cytosine),[7] nucleophilic addition of organometallic compounds to iminium derivatives[8,9] or nitrones,[10] addition of organolithium to 2-hydroxytetrahydrofuran followed by oxidation and aminocyclization,[11] Heck arylation of endocyclic enecarbamates with aryldiazonium tetrafluoroborates,[12] etc. Among them, the nucleophilic addition of nitrone is the most convenient way because of its good stability and reactivity, and easy preparation of nitrone. Structurally, the imino carbon in the nitrone system is electrophilic enough to react with various electron-rich hetero-aromatics,[13] which has been successfully used to synthesize heterocyclic derivatives[14] and nitrogenous carbohydrate derivatives.[15]

Recently, Yu[16] et al. also reported that the nucleophilic reaction of sugar-derived nitrones with electron-rich hetero-aromatics was carried out effectively and stereoselectively under the catalysis of hydrochloric acid and afforded *C*-azanucleoside analogues in excellent yields, providing a very convenient access to the *C*-azanucleoside analogues. However, the reaction was usually carried out under acid catalysis for improving the reactivity, and such reaction condition was not suitable to the cases where the reactants or the products were sensitive to acid, such as *N*-azanucleoside derivatives.[17] From this point of view and in order to expand the utilization of the nucleophilic reaction of nitrone to the synthesis of azanucleoside analogues, we would like to report, herein, the reaction of sugar-derived nitrones with the electron-riched pyrrole and indole without acidic catalysis assisted by microwave irradiation which, followed by reductive cleavage of N–O bond and deprotection, afforded a series of novel *C*-azanucleoside analogues, providing an alternative method to synthesize such compounds.

2. Results and discussion

The sugar-derived nitrones (**1**) and (**2**) were readily prepared from D-mannose and D-arabinose following the reported procedures,[18–20] respectively. Considering the great achievements of microwave-assisted organic synthesis[21] and based on our preliminary study,[17] the microwave-assisted nucleophilic addition was performed with the nitrone (**1**) and pyrrole in sealed vial, which afforded the diastereomeric mixture of **3a** and **4a** (Scheme 1). As shown in Table 1, in polar solvents (EtOH, THF, and MeCN) the

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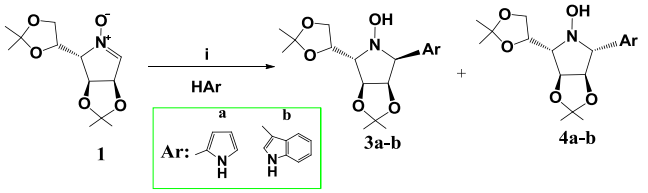
Table 1
The nucleophilic addition of sugar nitrone (**1**) and pyrrole[a]

Entry	Solvent	Temp/°C	Time/min	Yield/% of **3a**+**4a** (ratio[b]/**3a**/**4a**)
1	EtOH	100	10	10 (1: >100)
2	THF	100	10	9 (only **4a**)
3	MeCN	100	10	15 (1:98)
4	Toluene	100	10	23 (1:1.6)
5	EtOH	120	10	11[c,d] (1:98)
6	THF	120	10	14[c,d] (1:>100)
7	MeCN	120	10	12[c] (1:95)
8	Toluene	120	10	30 (1:1.5)
9	Toluene	140	10	50 (1:1.8)
10	Toluene	160	10	72 (1:2)
11	Toluene	180	10	—[d]

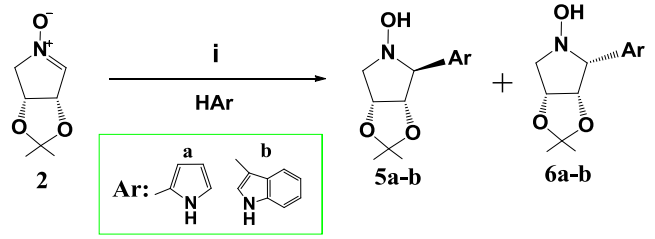
[a] Note: the reaction was performed with pyrrole (3 equiv) and nitrone **1** (1 mmol) in 5 mL of solvent.
[b] Determined by ^{1}H NMR.
[c] Pyrrole was found to be decomposed.
[d] Nitrone **1** was found to be decomposed.



Scheme 1. Synthesis of compounds **3a**,**b** and **4a**,**b** from nitrone **1**. Reagents and conditions: (i) HAr, Toluene, MW, 160 °C, 10 min, in sealed vial.

reaction exhibited an excellent stereoselectivity (entries 1–3 and 5–7) and although decomposition was observed at around 160 °C. However, in nonpolar solvent of toluene the reaction would take place smoothly with the yield of 72% at 160 °C even though its stereoselectivity was not satisfactory (entry 10). Thus, the reactions in polar solvents showed a much higher stereoselectivity than in nonpolar solvent. And in both cases, it was found that the isomer **4a** was the dominant product.

Following the same procedure as described in Table 1 entry 10, the reaction of nitrone **1** with indole was carried out and afforded the mixture of **3b** and **4b** in 40% yield with the diastereomeric ratio of 1:16 (**3b**/**4b**). Similarly, the nucleophilic additions of nitrone **2** with pyrrole and indole were performed in toluene under the microwave radiation at 160 °C for 10 min, and afforded the corresponding two diastereomers **5a** and **6a**, **6b** and **6b** in yields of 70% and 30% with good stereoselectivity (dr=1.5:1 and 3:1), respectively, as shown in Scheme 2 and Table 2.



Scheme 2. Synthesis of compounds **5a**,**b** and **6a**,**b** from nitrone **2**. Reagents and conditions: (i) HAr, toluene, MW, 160 °C, 10 min, in sealed vial.

The structures of **3a**,**b**, **4a**,**b**, **5a**,**b**, and **6a**,**b** were confirmed by the ^{1}H NMR, ^{13}C NMR, H,H-COSY, and HRMS. Their configurations were tentatively determined based on the NOE correlations between H-2′ and H-5′ as shown in Fig. 1 exemplified with compounds **3a** and **4a**. Furthermore, the H-2′ with the 2′,3′-*cis* forms in **6a** (3.60 ppm) and **6b** (3.79 ppm) appeared in higher field than

Table 2
The yield of the addition products **3a**,**b**, **4a**,**b**, **5a**,**b**, and **6a**,**b**[a]

Nitrones	(ArH)	Products and yields[b]/%			
1	Pyrrole	**3a**	24.0	**4a**	48.0
1	Indole	**3b**	2.4	**4b**	37.6
2	Pyrrole	**5a**	42.0	**6a**	28.0
2	Indole	**5b**	22.5[c]	**6b**	7.5[c]

[a] Note: hetero-aromatics (3 mmol), nitrone (**2**) (1 mmol), toluene (5 mL).
[b] Isolated yields.
[c] Determined by ^{1}H NMR.

those in the 2′,3′-*trans* isomers **5a** (4.30 ppm) and **5b** (4.03 ppm), respectively, which coincided with the literature data.[22]

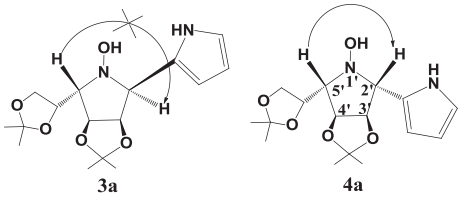


Fig. 1. NOE correlations between H-2′ and H-5′ in **3a** and **4a**.

For the reaction stereoselectivity, in all cases the stereochemistry of C-2′ was mainly depended upon the orientation of C-3′ and the 2′,3′-*trans* products were afforded as the dominant. The Felkin–Anh transition-state model for the nucleophilic addition of cyclo nitrone could rationally explain the 2′,3′-*trans* stereoselectivity by the favorite *exo* attack (Fig. 2).[23] Furthermore, in polar solvents the solvation would be beneficial to stabilizing the transition-state and the *exo* attack, which would induce much higher stereoselectivity than in nonpolar solvent.

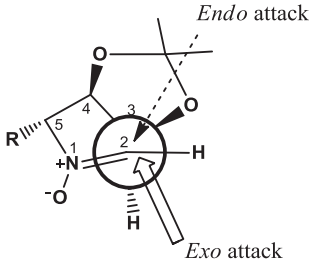
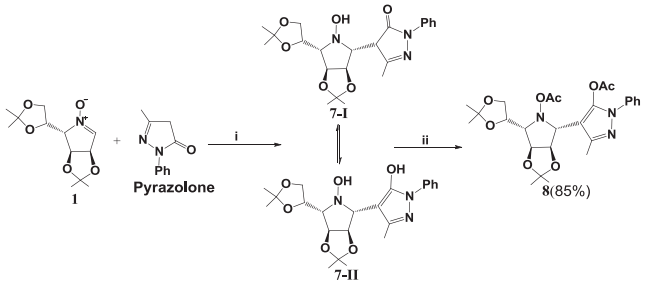


Fig. 2. Predictive Felkin-Anh transition-state model for nucleophilic addition of cyclo nitrone.

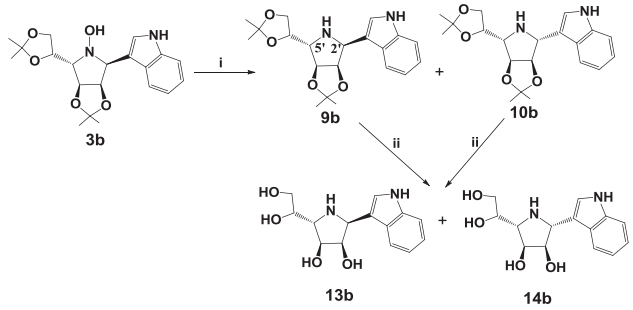
In addition, the steric hindrance of the nucleophilic heterocycles and the structure of the nitrone also had significant effect on the stereoselective discrepancy. As shown in Table 2, the addition reaction of the bulky heterocyclic indole and the 5′-substituent nitrone (**1**) gave higher stereoselectivity than others. The stereospecifically nucleophilic addition of the more bulky nucleophilic 1-phenyl-3-methyl-5-pyrazolone and nitrone (**1**) provided further supporting information as shown in Scheme 3. Thus, under the



Scheme 3. Synthesis of compound (**8**) from nitrone (**1**). Reagents and conditions: (i) Toluene, MW, 160 °C, 5 min in sealed tube; (ii) pyridine, Ac_2O, ice-bath.

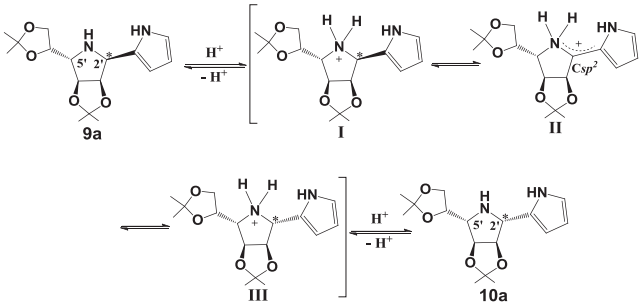
same conditions, the reaction completed within 5 min and afforded the sole 2′,3′-*trans* isomer (**8**) in yield of 85% after in situ acetyl protection with acetic anhydride, in order to fix the pyrazolone tautomeric structures [such as (**7-I**) and (**7-II**)].

The reduction and deprotection of the addition products were studied for synthesizing the target *C*-azanucleoside analogue with **3b** as shown in Scheme 4. In the first step (Scheme 4, step (i)), the hydroxylamine (**3b**) was reduced by Zn/AcOH/MeOH to afford the corresponding pyrrolidine derivative **9b** and its isomer **10b**, indicating that partial epimerization at C-2′ occurred during the reaction. In the following deprotection of the acetonide group of **9b** by the treatment of 2 N HCl/dioxane, accompanied with the partial epimerization at C-2′, the target *C*-azanucleoside analogues **13b** and its isomer **14b** were obtained in the yield of 75% with the ratio of 2.5:1 (Scheme 4, step (ii)). Similarly, in the cases of **4b**, **3a**, and **4a**, the C-2′ epimerization at C-2′ were observed in the above two steps, and the corresponding intermediates **9b** and **10b**, **9a** and **10a**, and the target *C*-azanucleoside analogues **13a**, **14a**, **13b**, and **14b** were obtained by column chromatography, respectively (see Table 3).



Scheme 4. Synthesis of the *C*-azanucleoside analogues **13b** and **14b** from **3b**. Reagents and conditions: (i) Zn (20 equiv), MeOH/AcOH (1:1), 60 °C, 3 h; (ii) 2 N HCl/dioxane, 50 °C, 0.5 h.

To confirm the epimerization, the isomerizations of **9a** in AcOH/MeOH and 2 N HCl/dioxane solutions were examined, respectively, and in each case the isomerization from **9a** to **10a** was observed in a few minutes. Probably such an epimerization took place in the process as shown in Scheme 5. Structurally, the C-2′ in the pyrrolidine derivatives **9a** and **10a** was in the double α-position to the aromatic ring and to the N-1′ of the pyrrolidine, which made the H-2′ highly active. Furthermore, in acidic condition the formation of an aminium by the N-1′ protonation resulted in a more active the H-2′, which easily forms the conjugated system of N-1′···C-2′···pyrrole(**II**), leading to the epimerization at C-2′ between **9a** and **10a** as shown in Scheme 5. The similar epimerization has been reported in other work.[24]



Scheme 5. The isomerization between **9a** and **10a** based on the epimerization of C-2′.

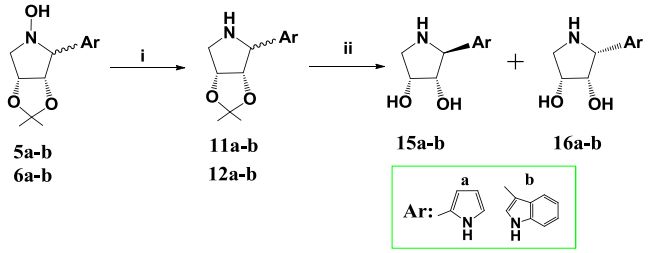
Considering the epimerization in the following acidic reactions, and because of the difficult separation of the diastereomers,[25] the mixtures of **5a** and **6a**, **6b**, and **6b** were directly used in reduction, which provided the corresponding mixtures of **11a** and **12a**, **11b** and **12b**, respectively, and followed by deprotection to afford the

Table 3
The synthesis of the *C*-azanucleoside analogues **13a**,**b**, **14a**,**b**, **15a**,**b**, **16a**,**b**

Entry	Addition product	Reductive product yield[a] (ratio)	*C*-Azanucleoside analogues	
1	**3a**(2′β) **4a**(2′α)	**9a**(2′β), **10a**(2′α) 71% (2.0:1.0) from **3a** 73% (1.0:2.2) from **4a**	**13a**(2′β) 45.9% from **9a** 24.7% from **10a**	**14a**(2′α) 24.1% from **9a** 49.3% from **10a**
2	**3b**(2′β) **4b**(2′α)	**9b**(2′β), **10b**(2′α) 65% (1.6:1.0) from **3b** 69%(1.0:1.5) from **4b**	**13b**(2′β) 53.6% from **9b** 22.1% from **10b**	**14b**(2′α) 21.4% from **9b** 50.9% from **10b**
3	**5a**(2′β) **6a**(2′α)	**11a**(2′β), **12a**(2′α) 70% (2.0:1.0)[b]	**15a**(2′β) 43.1%	**16a**(2′α) 26.9%
4	**5b**(2′β) **6b**(2′α)	**11b**(2′β), **12b**(2′α) 66% (3.2:1.0)[b]	**15b**(2′β) 57.6%	**16b**(2′α) 27.4%

[a] Isolated yield.
[b] The ratio of the diastereomers was determined by ^{1}H NMR.

target products **15a** and **16a**, **15b** and **16b**, respectively (Scheme 6). The results are summarized in Table 3.



Scheme 6. Synthesis of the *C*-azanucleoside analogues **15** and **16** from **5** and **6**. Reagents and conditions: (i) Zn (20 equiv), MeOH/AcOH (1:1), 60 °C, 3 h; (ii) 2 N HCl/dioxane, 50 °C, 0.5 h.

In conclusion, we have synthesized a series of novel *C*-azanucleoside analogues by stereoselectively nucleophilic addition of nitrones to electron-rich heterocyclic pyrrole and indole assisted with microwave radiation under neutral condition, and followed by reduction and deprotection. The nucleophilic addition afforded the 2′,3′-trans isomer as the dominant by the favorite *exo* attack in polar solvent. The epimerization of C-2′ in the *C*-azanucleoside derivatives was observed in acidic solution. Further experiments for the synthesis of other series of new *C*-azanucleoside analogues and biological evaluations on antiviral and antitumor activities are under way in this laboratory.

3. Experimental

3.1. General methods

Melting points were measured on an SGW® X-4 micro melting point apparatus and were uncorrected. Optical rotations were determined on an SGW®-1 automatic polarimeter. NMR experiments were recorded on an RT-NMR Bruker AVANCE 400 (400 MHz); chemical shifts are given in parts per million, using tetramethylsilane (Me_4Si) as an internal standard. Assignments were confirmed by homonuclear 2D COSY, NOESY, and heteronuclear multiple bond correlation (2D-HMBC) spectra. Mass Spectra (MS) and High Resolution Mass Spectra (HRMS) were carried out on an FTICR-MS (Ionspec 7.0 T) mass spectrometer with electrospray ionization (ESI). Microwave-assisted reaction was performed on a DISCOVER S-Class Auto Focused Microwave Synthesis System (CEM Corporation, USA). TLC was performed on silica gel plates (Qingdao GF_{254}) under UV (254 nm) light or with phosphomolybdic reagent. Flash chromatography was performed using 200–300 mesh silica gel. Solvents were dried and distilled immediately prior to use.

3.2. Experimental procedures

*3.2.1. Synthesis of the sugar-derived nitrones (**1**) and (**2**).* Nitrones **1** and **2** were synthesized following the reported methods[18–20] from D-mannose and D-arabinose, respectively.

Compound **1**: White solid, mp 88–90 °C, $[\alpha]_D^{20.1}$ +19.23 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) 1.27 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 3.99 (t, *J*=7.59 Hz, 1H), 4.11 (s, 1H), 4.37 (t, *J*=7.59 Hz, 1H), 4.44 (dt, *J*=6.55 , 1.98 Hz, 1H), 4.71 (d, *J*=5.82 Hz, 1H), 5.16 (d, *J*=5.68 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.55, 26.29, 27.66, 65.17, 74.49, 78.31, 78.86, 79.51, 110.09, 112.00, 134.20; ESIMS: 280 $[M+Na]^+$.

Compound **2**: White solid, mp 109–110 °C, $[\alpha]_D^{25}$ −25.9 (*c* 0.55, CH_2Cl_2); [lit.[18] mp 110–112 °C, $[\alpha]_D^{26}$ −26.3 (*c* 0.50, CH_2Cl_2)]. The ^1H NMR spectral data are identical with those in the reported literature.[18]

3.2.2. General procedure for the microwave-assisted nucleophilic addition of nitrones with electron-rich hetero-aromatics. A solution of 257 mg (1 mmol) of nitrone **1** and 201 mg (3 mmol) of pyrrole in toluene (5 mL) was irradiated with microwave at 160 °C in sealed vial for 10 min. The reaction mixture was cooled to room temperature, concentrated, and then submitted to silica gel column chromatography (cyclohexane/ethyl acetate) to obtain the mixture of **3a** and **4a** (233 mg, 72.0%). The isomeric ratio was determined according to the ^1H NMR spectra.

Following the procedure, the reactions of nitrone **1** to indole, nitrone **2** to pyrrole and to indole were carried out and gave the corresponding adducts **3b** and **4b**, and the mixture of **5a** and **6a**, **5b** and **6b**, respectively. Small amount of the mixtures of **5a** and **6a**, **5b** and **6b** were separated by repeated column chromatography for structural determination. The results are shown in Table 2.

Compound **3a**: White solid, mp 99–102 °C, $[\alpha]_D^{25.5}$ +97.50 (*c* 3.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.32 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.61 (s, 3H), 3.47 (d, *J*=3.24 Hz, 1H), 3.75 (t, *J*=7.98 Hz, 1H), 3.99 (dd, *J*=6.6 , 7.3 Hz, 1H), 4.28 (m, 1H), 4.36 (d, *J*=4.32 Hz, 1H), 4.72 (d, *J*=6.28 Hz, 1H), 4.79 (dd, *J*=4.44 , 6.12 Hz, 1H), 6.16 (m, 1H), 6.18 (d, *J*=1.40 Hz, 1H), 6.32 (s, 1H), 6.83 (d, *J*=1.52 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.47, 25.78, 26.62, 26.86, 66.97, 67.18, 73.39, 75.85, 82.59, 83.05, 107.85, 109.63, 110.10, 112.62, 118.93, 125.92; HRMS (ESI): calcd for $C_{16}H_{24}N_2NaO_5$ ($[M+Na]^+$): 347.1583, found: 347.1568.

Compound **4a**: Colorless oil, $[\alpha]_D^{24.5}$ +5.44 (*c* 3.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.32 (s, 3H), 1.37 (s, 3H), 1.49 (s, 3H), 1.56 (s, 3H), 3.22 (t, *J*=6.8 Hz, 1H), 3.95 (dd, *J*=5.7 , 8.6 Hz, 1H), 4.08 (m, 2H), 4.30 (m, 2H), 4.52 (br s, 1H), 6.17 (d, *J*=2.49 Hz, 1H), 6.21 (s, 1H), 6.49 (br s, 1H), 6.71 (s, 1H), 8.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.51, 25.72, 27.00, 27.61, 66.67, 71.09, 74.98, 76.88, 78.14, 80.91, 107.14, 108.87, 110.43, 114.66, 118.23, 129.00; HRMS (ESI): calcd for $C_{16}H_{24}N_2NaO_5$ ($[M+Na]^+$): 347.1583, found: 347.1546.

Compound **3b**: White solid, mp 108–112 °C, $[\alpha]_D^{24.6}$ +24.560 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 0.64 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.14 (d, *J*=11.74 Hz, 1H), 3.21 (dd, *J*=1.48 , 5.55 Hz, 1H), 3.72 (dd, *J*=3.70 , 12.29 Hz, 1H), 3.92 (d, *J*=10.36 Hz, 1H), 4.00 (d, *J*=12.30 Hz, 1H), 4.28 (d, *J*=5.74 Hz, 1H), 4.90 (t, *J*=5.92 Hz, 1H), 5.00 (t, *J*=5.92 Hz, 1H), 7.02–7.39 (m, 4H), 7.72 (d, *J*=7.76 Hz, 1H), 8.10 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) 37.34, 39.07, 39.63, 41.81, 78.56, 81.41, 83.97, 89.55, 92.23, 95.57, 118.31, 125.87, 128.16, 128.38, 134.30, 134.76, 136.79, 138.17, 141.18, 151.44; HRMS (ESI): calcd for $C_{20}H_{26}N_2NaO_5$ ($[M+Na]^+$): 397.1739, found: 397.1731.

Compound **4b**: Colorless oil, $[\alpha]_D^{25.0}$ −36.97 (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.28 (s, 3H), 1.39 (s, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 3.31 (t, *J*=5.44 Hz, 1H), 4.07 (dd, *J*=5.44 , 8.64 Hz, 1H), 4.12 (m, 1H), 4.24 (d, *J*=6.2 Hz, 1H), 4.47 (m, 2H), 4.64 (t, *J*=6.64 Hz, 1H), 5.21 (s, 1H), 7.08–7.35 (m, 4H), 7.76 (d, *J*=7.88 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.55, 25.61, 26.95, 27.75, 66.62, 71.87, 74.39, 76.66, 81.25, 110.31, 111.76, 114.14, 119.98, 120.48, 122.69, 123.69, 126.50, 137.30; HRMS (ESI): calcd for $C_{20}H_{26}N_2NaO_5$ ($[M+Na]^+$): 397.1739, found: 397.1735.

Compound **5a**: Colorless oil, $[\alpha]_D^{25.0}$ −30.51 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.35 (s, 3H), 1.55 (s, 3H), 3.22 (d, *J*=10.7 Hz, 1H), 3.32 (s, 1H), 4.29 (d, *J*=3.13 Hz, 1H), 4.79 (s, 1H), 4.87 (s, 1H), 6.10 (s, 1H), 6.16 (m, 1H), 6.78 (s, 1H), 8.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.74, 27.10, 61.70, 77.88, 82.67, 107.56, 108.59, 113.12, 118.59, 127.23; HRMS (ESI): calcd for $C_{11}H_{16}N_2NaO_3$ ($[M+Na]^+$): 247.1058, found: 247.1063.

Compound **6a**: Colorless oil, $[\alpha]_D^{24.1}$ −154.17 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.30 (s, 3H), 1.56 (s, 3H), 2.73 (dd, *J*=4.4, 10.8 Hz, 1H), 3.50 (d, *J*=11.2 Hz, 1H), 3.60 (s, 1H), 4.69 (t, *J*=4.0 Hz, 2H), 6.14 (dd, *J*=2.7 , 5.6 Hz, 1H), 6.21 (s, 1H), 6.77 (s, 1H), 8.94 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.36, 26.32, 27.33, 62.13, 69.00, 75.78, 79.54, 107.99, 110.11, 110.99, 119.148, 126.33; HRMS (ESI): calcd for $C_{11}H_{16}N_2NaO_3$ ($[M+Na]^+$): 247.1058, found: 247.1054.

Compound **5b**: Colorless oil, $[\alpha]_D^{18.3}$ +35.396 (*c* 1.0, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6) 1.24 (s, 3H), 1.49 (s, 3H), 2.88 (m, 1H), 3.52 (s, 1H), 4.03 (s, 1H), 4.70 (m, 2H), 6.92–7.80 (m, 5H), 10.97 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) 25.83, 28.02, 63.75, 71.03, 76.38, 83.67, 112.17, 113.33, 119.17, 120.39, 121.78, 124.74, 127.76, 137.34; HRMS (ESI): calcd for $C_{15}H_{18}N_2NaO_3$ ($[M+Na]^+$): 297.1215, found: 297.1228.

Compound **6b**: Colorless oil, $[\alpha]_D^{20.0}$ −38.733 (*c* 0.5, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6) 1.15 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.65 (m, 1H), 3.30 (s, 1H), 3.79 (s, 1H), 4.70 (m, 2H), 6.92–7.8 (m, 5H), 10.88 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) 25.47, 26.78, 63.41, 69.44, 79.47, 84.56, 110.08, 111.93, 118.86, 121.36, 125.42, 127.89, 137.00; HRMS (ESI): calcd for $C_{15}H_{18}N_2NaO_3$ ($[M+Na]^+$): 297.1215, found: 297.1218.

*3.2.3. Synthesis of compound **8**.* A solution of 257 mg (1 mmol) of nitrone **1** and 520 mg (3 mmol) of pyrazolone in toluene (5 mL) was reacted at 160 °C under microwave irradiation in sealed vial for 5 min. The reaction mixture was cooled to room temperature and concentrated in vacuo to remove toluene. To the mixture pyridine (2 mL) and acetic anhydride (1 mL) were added under ice-bath cooling and stirred for 0.5 h, then the reaction mixture was extracted with EtOAc and concentrated. The residue was submitted to silica gel column chromatography (cyclohexane/ethyl acetate) to afford the product **8** (438 mg, 85%).

Compound **8**: Amorphous solid, $[\alpha]_D^{24.9}$ +15.78 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.32 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.60 (s, 3H), 1.91 (s, 3H), 2.26 (s, 3H), 2.40 (s, 3H), 3.42 (t, *J*=5.32 Hz, 1H), 4.00 (dd, *J*=5.45 , 8.98 Hz, 1H), 4.15 (d, *J*=6.28 Hz, 1H), 4.18 (dd, *J*=7.18 , 8.93 Hz, 1H), 4.33 (q, *J*=6.44 Hz, 1H), 4.46 (dd, *J*=5.22, 6.95 Hz, 1H), 4.60 (t, *J*=6.68 Hz, 1H), 7.28–7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.93, 19.60, 20.85, 25.03, 25.62, 26.91, 27.78, 66.44, 68.10, 74.13, 75.19, 76.59, 80.00, 104.82, 110.12, 114.26, 123.30, 127.65, 129.50, 138.26, 142.44, 148.67, 167.88, 169.47; HRMS (ESI): calcd for $C_{26}H_{33}N_3NaO_8$ ($[M+Na]^+$): 538.2165, found: 538.2172.

*3.2.4. General procedure for the reduction of the addition products of **9a**,**b**, **10a**,**b**, **11a**,**b**, **12a**,**b**.* A mixture of 324 mg (1 mmol) of compound **3a** and 1.28 g (20 mmol) of zinc powder in MeOH/AcOH (10 mL) was vigorously stirred for 3 h at 60 °C under nitrogen atmosphere. The reaction mixture was neutralized with solid $NaHCO_3$, followed by filtration, concentration, and silica gel column chromatography (petroleum ether/ethyl acetate/acetic acid) to give the corresponding product **9a** and its epimer **10a** (219 mg, 71.0%). The isomeric ratio was determined by ^1H NMR. Following the procedure, compounds **9b** and **10b** were obtained from the pure compounds **3b** or **4b** in good yields, respectively.

Similarly, the mixtures of the adducts **5a** and **6a**, **5b** and **6b** were directed treated with zinc powder in MeOH/AcOH, the corresponding reductive products **11a** and **12a**, **11b** and **12b** were afforded as the mixtures, respectively. The isomeric ratio was determined by ^1H NMR. Small amount of the sample was separated by repeated column chromatography for structural characterization. The results are shown in Table 3.

Compound **9a**: White solid, mp 140–141 °C, $[\alpha]_D^{29.1}$ −14.29 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.31 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 2.29 (br s, 1H), 3.26 (dd, *J*=3.89 , 7.96 Hz, 1H), 3.77 (t, *J*=7.85 Hz, 1H), 3.85 (q, *J*=6.79 Hz, 1H), 4.03 (dd, *J*=6.21 , 7.92 Hz, 1H), 4.31 (dd, *J*=3.89 , 6.42 Hz, 1H), 4.36 (d, *J*=3.27 Hz, 1H), 4.65 (dd, *J*=3.41 , 6.47 Hz, 1H), 6.09 (s, 1H), 6.16 (q, *J*=2.80 Hz, 1H), 6.70 (d, *J*=2.41 Hz, 1H), 8.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.37, 25.65, 27.19, 27.54, 62.18, 67.16, 67.74, 82.79, 86.95, 105.00, 109.18, 109.82, 113.84, 117.25, 131.68; HRMS (ESI): calcd for $C_{16}H_{25}N_2O_4$ ($[M+H]^+$): 309.1814, found: 309.1820.

Compound **10a**: Colorless oil, $[\alpha]_D^{29.5}$ +36.17 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.33 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.58 (s, 3H), 2.40 (br s, 1H), 3.20 (d, *J*=6.40 Hz, 1H), 3.86 (dd, *J*=6.50, 7.80 Hz, 1H), 4.08 (dd, *J*=7.90 , 6.40 Hz, 1H), 4.14 (q, *J*=6.40 Hz, 1H), 4.44 (d, *J*=3.80 Hz, 1H), 4.54 (d, *J*=5.59 Hz, 1H), 4.73 (dd, *J*=4.00, 5.48 Hz, 1H), 6.14 (d, *J*=2.26 Hz, 2H), 6.77 (d, *J*=2.04 Hz, 1H), 8.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.73, 25.86, 26.83, 26.97, 58.63, 65.89, 67.34, 76.07, 83.31, 84.03, 108.16, 110.08, 112.14, 118.33, 128.56; HRMS (ESI): calcd for $C_{16}H_{25}N_2O_4$ ($[M+H]^+$): 309.1814, found: 309.1808.

Compound **9b**: Colorless oil, $[\alpha]_D^{29.8}$ −32.44 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.27 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.61 (s, 3H), 3.33 (t, *J*=5.72 Hz, 1H), 3.95 (t, *J*=7.04 Hz, 1H), 4.14 (dd, *J*=6.92, 8.14 Hz, 1H), 4.30 (q, *J*=6.53 Hz, 1H), 4.87 (m, 2H), 4.70 (dd, *J*=5.15 , 7.12 Hz, 1H), 7.10–7.35 (m, 4H), 7.79 (d, *J*=7.83 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.73, 25.82, 27.11, 27.91, 62.20, 66.83, 66.99, 77.86, 82.56, 86.68, 109.83, 111.66, 114.77, 116.70, 119.96, 120.15, 121.91, 122.68, 126.43, 137.23; HRMS (ESI): calcd for $C_{20}H_{27}N_2O_4$ ($[M+H]^+$): 359.1971, found: 359.1578.

Compound **10b**: Colorless oil, $[\alpha]_D^{29.8}$ +14.51 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.33 (s, 3H), 1.39 (s, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 3.29 (d, *J*=5.68 Hz, 1H), 3.97 (t, *J*=7.60 Hz, 1H), 4.11 (dd, *J*=6.28, 7.84 Hz, 1H), 4.27 (q, *J*=6.24 Hz, 1H), 4.71 (m, 2H), 4.88 (dd, *J*=4.04, 5.32 Hz, 1H), 7.09–7.34 (m, 4H), 7.70 (d, *J*=7.72 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.74, 25.93, 26.78, 27.09, 58.99, 65.85, 67.38, 76.81, 83.40, 84.93, 109.91, 111.54, 111.99, 112.97, 119.66, 119.90, 122.40, 123.59, 136.39; HRMS (ESI): calcd for $C_{20}H_{27}N_2O_4$ ($[M+H]^+$): 359.1971, found: 359.1565.

Compound **11a**: Colorless oil, $[\alpha]_D^{23.7}$ −58.90 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.36, 1.50 (s, 3H), 2.54 (dd, *J*=4.1 , 10.9 Hz, 1H), 3.00 (d, *J*=13.5 Hz, 1H), 3.88 (s, 1H), 4.38 (s, 1H), 4.69 (t, *J*=5.0 Hz, 1H), 4.97 (d, *J*=5.4 Hz, 1H), 6.02 (s, 1H), 6.15 (m, 1H), 6.72 (s, 1H), 9.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.30, 26.57, 52.80, 62.84, 82.52, 86.25, 105.71, 109.08, 111.05, 117.34, 129.40; HRMS (ESI): calcd for $C_{11}H_{17}N_2O_2$ ($[M+H]^+$): 209.1290, found: 208.1297.

Compound **12a**: Colorless oil, $[\alpha]_D^{24.7}$ −58.43 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.35 (s, 3H), 1.56 (s, 3H), 2.78 (d, *J*=12.8 Hz, 1H), 3.10 (d, *J*=13.1 Hz, 1H), 3.93 (s, 1H), 4.77 (d, *J*=1.52 Hz, 2H), 5.62 (br s, 1H), 6.15 (d, *J*=2.8 Hz, 1H), 6.28 (s, 1H), 6.78 (d, *J*=1.4 Hz, 1H), 9.44 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.14, 26.36, 52.53, 60.35, 81.54, 82.38, 108.46, 109.30, 111.29, 118.58, 137.15; HRMS (ESI): calcd for $C_{11}H_{17}N_2O_2$ ($[M+H]^+$): 209.1290, found: 209.1286.

Compound **11b**: Colorless oil, $[\alpha]_D^{24.5}$ +34.67 (*c* 1.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.37 (s, 3H), 1.59 (s, 3H), 3.11–3.21 (m, 2H), 4.71 (s, 1H), 4.74 (t, *J*=4.45 Hz, 1H), 4.99 (d, *J*=5.49 Hz, 1H), 7.03–7.74 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.67, 25.81, 50.00, 59.07, 78.29, 82.06, 111.57, 113.57, 119.92, 120.20, 122.65, 122.81, 127.28, 136.64; HRMS (ESI): calcd for $C_{15}H_{19}N_2O_2$ ($[M+H]^+$): 259.1446, found: 259.1451.

Compound **12b**: Colorless oil, $[\alpha]_D^{25.6}$ −26.83 (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 1.28 (s, 3H), 1.55 (s, 3H), 3.14 (d, *J*=13.04 Hz, 1H), 3.25 (d, *J*=13.04 Hz, 1H), 4.62 (s, 1H), 4.78 (s, 2H), 7.09–7.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.00, 25.96, 50.78, 59.30, 79.30, 80.44, 111.82, 112.00, 118.83, 120.15, 122.45, 126.36, 126.94, 136.17; HRMS (ESI): calcd for $C_{15}H_{19}N_2O_2$ ($[M+H]^+$): 259.1446, found: 259.1444.

*3.2.5. General procedure for the synthesis of the target C-azanucleoside analogues **13a**,**b**, **14a**,**b**, **15a**,**b**, **16a**,**b**.* A solution of 358 mg reduction product **9b** (1 mmol) in 10 mL of 2 N HCl/dioxane was stirred at 60 °C for 0.5 h. The reaction mixture was neutralized with solid $NaHCO_3$, followed by filtration, concentration, and silica gel column chromatography (ethyl acetate/methanol) to give the final deprotected products **13b** (148.9 mg, 53.6%) and **14b** (59.6 mg, 21.4%). Following the procedure, compounds **13a** and **14a** were obtained from the pure compounds **3a** or **4a** in good yields, respectively.

Following the same procedure, the deprotection of the mixtures of **11a** and **12a**, **11b** and **12b** were performed and the corresponding

target products **15a**, **16a**, **15b**, and **16b** were obtained, respectively. The results are listed in Table 3.

Compound **13a**: Pale yellow oil, $[\alpha]_D^{28.5}$ +15.01 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.47 (dd, *J*=3.47 , 4.8 Hz, 1H), 3.58 (m, 2H), 3.86 (q, *J*=3.44 Hz, 1H), 4.18–4.24 (m, 2H), 4.41 (d, *J*=6.32 Hz, 1H), 6.06 (t, *J*=2.90 Hz, 1H), 6.20 (t, *J*=2.2 Hz, 1H), 6.74 (dd, *J*=1.44, 2.61 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) 60.42, 64.25, 65.33, 69.55, 72.71, 75.15, 107.56, 108.38, 119.06, 126.00; HRMS (ESI): calcd for $C_{10}H_{17}N_2O_4$ ($[M+H]^+$): 229.1188, found: 229.1164.

Compound **14a**: Pale yellow oil, $[\alpha]_D^{28.1}$ −20.33 (*c* 0.63, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.56 (d, *J*=2.73 Hz, 1H), 3.60 (m, 2H), 3.88 (m, 1H), 4.19 (t, *J*=2.68 Hz, 1H), 4.34 (dd, *J*=3.40 , 8.7 Hz, 1H), 4.59 (d, *J*=2.28 Hz, 1H), 6.06 (t, *J*=3.23 Hz, 1H), 6.32 (dd, *J*=1.34 , 3.34 Hz, 1H), 6.80 (dd, *J*=1.46 , 2.58 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) 58.77, 62.71, 64.12, 68.52, 73.11, 73.73, 107.92, 111.30, 120.04, 121.43; HRMS (ESI): calcd for $C_{10}H_{17}N_2O_4$ ($[M+H]^+$): 229.1188, found: 229.1178.

Compound **13b**: Pale yellow oil, $[\alpha]_D^{25.5}$ +6.76 (*c* 2.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.74 (d, *J*=4.72 Hz, 2H), 3.85 (dd, *J*=4.52, 2.30 Hz, 1H), 4.08 (dd, *J*=4.56 , 7.53 Hz, 1H), 4.46 (t, *J*=4.65 Hz, 1H), 4.67 (dd, *J*=4.74 , 7.03 Hz, 2H), 7.11–7.80 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) 58.62, 63.40, 65.43, 68.82, 71.77, 73.17, 106.20, 112.60, 118.32, 120.51, 122.97, 125.99, 136.62; HRMS (ESI): calcd for $C_{14}H_{19}N_2O_4$ ($[M+H]^+$): 279.1345, found: 279.1351.

Compound **14b**: Pale yellow oil, $[\alpha]_D^{25.0}$ −10.32 (*c* 2.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.70 (m, 3H), 4.02 (m, 1H), 4.26 (t, *J*=3.23 Hz, 1H), 4.55 (dd, *J*=3.60 , 8.56 Hz, 1H), 4.62 (s, 2H), 4.98 (d, *J*=2.16 Hz, 1H), 7.10–7.77 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) 58.20, 63.28, 64.27, 70.53, 73.56, 74.56, 111.53, 118.27, 119.31, 121.78, 125.23, 127.12, 136.72; HRMS (ESI): calcd for $C_{14}H_{19}N_2O_4$ ($[M+H]^+$): 279.1345, found: 279.1339.

Compound **15a**: Pale yellow oil, $[\alpha]_D^{25.0}$ +14.91 (*c* 4.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.30 (t, *J*=12.62 Hz, 1H), 3.58 (dd, *J*=12.61, 4.10 Hz, 1H), 4.36 (m, 1H), 4.56 (dd, *J*=3.90 , 9.35 Hz), 4.64 (d, *J*=9.36 Hz, 1H), 6.13 (m, 1H), 6.34 (m, 1H), 6.86 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) 49.53, 57.96, 69.88, 75.12, 108.55, 109.24, 120.14, 123. 48; HRMS (ESI): calcd for $C_8H_{13}N_2O_2$ ($[M+H]^+$): 169.0977, found: 169.0982.

Compound **16a**: Pale yellow oil, $[\alpha]_D^{23.3}$ −21.69 (*c* 1.6, MeOH); ^{1}H NMR (400 MHz, CD_3OD) 3.15 (m, 1H), 3.53 (m, 1H), 4.26 (t, *J*=3.4 Hz, 1H), 4.55 (m, 1H), 4.73 (d, *J*=3.11 Hz, 1H), 6.09 (m, 1H), 6.34 (m, 1H), 6.86 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) 58.70, 71.06, 72.41, 107.95, 111.26, 120.24, 121.33; HRMS (ESI): calcd for $C_8H_{13}N_2O_2$ ($[M+H]^+$): 169.0977, found: 169.0978.

Compound **15b**: Pale yellow oil, $[\alpha]_D^{25.2}$ +3.39 (*c* 2.5, MeOH); ^{1}H NMR (400 MHz, D_2O) 3.23 (dd, *J*=7.59 , 12.09 Hz, 1H), 3.63 (dd, *J*=8.28 , 12.03 Hz, 1H), 4.34 (t, *J*=3.29 Hz, 1H), 4.64 (m, 1H), 4.97 (d, *J*=2.78 Hz, 1H), 7.14–7.66 (m, 5H); ^{13}C NMR (100 MHz, D_2O) 48.13, 58.92, 71.22, 72.19, 105.43, 112.91, 118.89, 120.85, 123.27, 126.76, 127.05, 136.44; HRMS (ESI): calcd for $C_{12}H_{15}N_2O_2$ ($[M+H]^+$): 219.1133, found: 219.1142.

Compound **16b**: Pale yellow oil, $[\alpha]_D^{25.5}$ −10.37 (*c* 2.0, MeOH); ^{1}H NMR (400 MHz, D_2O) 3.40 (d, *J*=13.27 Hz, 1H), 3.66 (dd, *J*=4.09, 13.29 Hz, 1H), 4.49 (t, *J*=3.62 Hz, 1H), 4.77 (dd, *J*=3.84 , 9.89 Hz, 1H), 4.93 (d, *J*=9.92 Hz, 1H), 7.15–7.67 (m, 5H); ^{13}C NMR (100 MHz, D_2O) 49.92, 56.87, 70.06, 74.50, 106.53, 113.05, 118.69, 120.93, 123.42, 126.38, 126.65, 137.20; HRMS (ESI): calcd for $C_{12}H_{15}N_2O_2$ ($[M+H]^+$): 219.1133, found: 219.1137.

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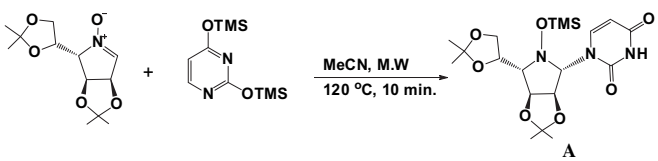
17. In order to synthesize azanucleoside analog, we had explored the nucleophilic addition of the sugar-derived nitrone (**1**) with trimethylsilylated uracil under microwave irradiation without using acid catalyst. A solution of 257 mg (1 mmol) of nitrone 1 and the trimethylsilylated uracil (3 mmol) obtained in situ by the reaction of uracil and BSA in MeCN at 50 °C [Ref: Bookser, B.C.; Raffale, N.B. *J. Org. Chem.*, **2007**, *72*, 173–179.] was irradiated with microwave at 120 °C in sealed vial for 10 min in MeCN. The reaction mixture was cooled to room temperature, concentrated and then submitted to silica gel column chromatography (cyclohexane/ethyl acetate) to get the stereospecific 1,2-*trans* addition product **A** (53 mg, 12%, shown in the following scheme). The product (**A**) was found to be very sensitive to acid due to the *N,N′*-acetal structure for the anomeric carbon, and was partially decomposed during the purification by silica gel column chromatography, which made the yield very low. It should be mentioned that the reaction did not take place with normal heating even at refluxing temperature.



A

Compound **A**: white solid, mp 210 °C (dec); $[\alpha]_D^{24.9}$ +45.52 (*c* 1.5 $CHCl_3$); ^{1}HNMR (400 MHz, DMSO-d_6) 0.014 (s, 9H), 1.24 (s, 3H), 1.30 (s, 3H), 1.38 (s, 3H), 1.49 (s, 3H), 3.12 (t, *J*=5.88 Hz, 1H), 3.93 (dd, *J*=5.68, 8.52 Hz, 1H), 4.05 (m, 1H), 4.22 (m, 1H), 4.43 (t, *J*=5.96 Hz, 1H), 4.57 (s, 1H), 5.44 (s, 1H), 5.78 (d, *J*=7.72 Hz, 1H), 7.75 (d, *J*=8.04 Hz, 1H), 11.43 (s, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) 0.66, 14.95, 21.61, 25.75, 25.91, 27.34, 27.80, 60.60, 65.90, 74.01, 75.52, 75.87, 79.25, 103.42, 109.79, 113.93, 142.88, 151.73, 163.73; HRMS (ESI): calcd for $C_{19}H_{31}N_3NaO_7Si$ ($[M+Na]^+$): 464.2914, found: 464.2922.

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25. The diastereomeric mixtures **5a** and **6a**, **6b** and **6b** and the corresponding reductive mixtures **11a** and **12a**, **11b** and **12b** could be separated by repeated column chromatography, respectively.