Carbohydrate Research 372 (2013) 15–22

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

A convenient synthesis of N-linked diglycose derivatives based on one-pot tandem Staudinger/aza-Wittig/reduction and biological evaluation

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ARTICLE INFO

Article history:
Received 13 November 2012
Received in revised form 5 February 2013
Accepted 13 February 2013
Available online 24 February 2013

Keywords:
N-linked diglycoses
Staudinger/aza-Wittig/reduction
One pot reaction
Glycosidase inhibition
Antitumor

ABSTRACT

A series of novel N-linked diglycose derivatives **9** and **10** were conveniently and directly synthesized based on the key step of one-pot tandem Staudinger/aza-Wittig/reduction reaction from the azido sugar and sugar-derived aldehyde followed by deprotection. The biological activities against glycosidases (α-amylase, α-glucosidase, and β-glucosidase) and HIV-RT and antitumor activity of these compounds were preliminarily evaluated.

1. Introduction

Diglycose derivatives (Neodisacharides) are hydrolytically stable glycomimics in which the two sugars were linked through the nonanomeric center. Since Pérez et al. isolated a hypoglycemic active compound which was originally assigned as a 6,6′-ether linked diallose and named Coyolosa (Fig. 1)[1] from Mexican traditional medicine[2] of the thorny palm *Acrocomia mexicana* in 1997, although this assigned structure was later certified to be incorrect according to the reported NMR data and structure activity studies of synthetic compounds,[3,4] increasing interest has been evoked in the synthesis of diglycose derivatives for developing novel potential glycosidase inhibition agents, and a variety of diglycose derivatives linked with ether,[3–7] thioether,[8–10] amine[11–14] and selenoether[15–17] have been recently discovered and synthesized. It is well known that the nitrogen-containing glycoside derivatives such as iminosugars, alkoids and amine-linked pseudo saccharide analogs (for instance Validoxylamine series) exhibit effective glycosidase inhibitory activity due to the strong interaction between the amine group in the molecule and the enzyme.[18–21] These promising bioactivities have attracted considerable attention to the design and synthesis of novel amine-linked diglycose derivatives for developing potential glycosidase inhibition agents. Some synthetic strategies have been exploited by using, for instance, epoxide opening,[22] reductive amination,[12,13] and Mitsunobu coupling reaction.[23] However, the development of a more convenient and efficient synthesis of the amine-linked diglycose derivatives for the molecular diversity and their biological activity investigation still remains a challenge.

Aza-Wittig reaction, as one of the powerful tools for constructing C=N (or C–N) bonds, has been widely used in the synthesis of nitrogenous compounds because of its mild reaction conditions and high yields, and the convenient generation of the intermediate of phosphinimines from the corresponding azido compounds by the Staudinger reaction.[24,25] And this methodology has also been successfully applied in the synthesis of glycoside derivatives, such as mono- and disaccharide glycosyl carbodiimides,[26–28] five to higher-membered aza-sugar derivatives,[29–31] N-glycoside neoglycotrimers[32] and sugar-aza-crown ethers.[33] More recently, we have developed a convenient and effective method for synthesizing thiazolidin-4-one and thiazinan-4-one derivatives containing glycoside moieties[34–37] using the one pot tandem Staudinger/aza-Wittig reaction strategy which generated the key intermediate imine-linked diglycoside from the azido sugar and sugar-derived aldehyde as shown in Scheme 1 route a. As the extensive application of this strategy of Staudinger/aza-Wittig/reduction tandem reaction, and in view of the promising bioactivity of nitrogen-containing glycoside derivatives, we would like to report a convenient

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http://dx.doi.org/10.1016/j.carres.2013.02.002

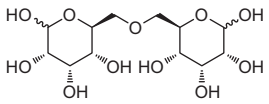


Figure 1. The originally reported structure of Coyolosa.

and direct synthesis of the amine-linked diglycose derivatives **9** and **10** from azido sugars **1a**–**1c** and sugar-derived aldehydes **3a**–**3c**, as shown in Scheme 1 route b (see Scheme 2).

2. Results and discussion

2.1. The synthesis of amine-linked diglycose derivatives

Azido sugar derivatives (**1a**,[38] **1b**,[39] **1c**[40]) and sugar-derived aldehydes (**3a**,[41] **3b**,[42] **3c**[43]) were synthesized from the corresponding sugars according to the literatures.

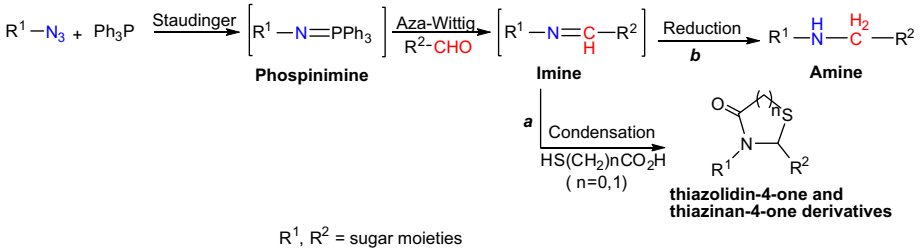
The one pot tandem Staudinger/aza-Wittig/reduction reaction was explored with azido sugar derivative (**1a**) and sugar-derived aldehyde (**3a**) under the conditions in three steps as shown in Scheme 2 and Table 1. Based on the previous studies[34,35,37] the reactions in the first two steps were first carried out at room temperature, followed by the reduction of C=N with $NaBH_4$, but instead of the desired product (**6aa**), the acetamido derivative (**8**) was obtained (entry 1), which possibly comes from the migration of the Ac group from 3-O to the newly generated NH; when the reduction took place in 0 °C, a small amount of the eliminated product (**7**) was also obtained because of the deacetoxyation (entry 2). Both the side reactions may result from the weak basic feature of $NaBH_4$. To reduce the acetyl migration and the elimination in the reduction step, the slightly acidic reagents of $NaBH_4$–AcOH and $NaBH_3CN$–AcOH were examined, respectively (entries 3 and 4). As a result, $NaBH_3CN$–AcOH provided the desired product (**6aa**) in a reasonable yield at lower reaction temperature (entry 5).

In order to improve the yield, the first two step reactions were performed in higher temperature, but the eliminated product (**7**) was increased without the total yield improvement with the temperature going up (entries 6 and 7). Considering the successful applications of microwave assisted organic synthesis in sugar chemistry,[44–46] we tried the second step with the microwave assisted method. As shown in Table 1, under microwave irradiation the reaction afforded only **7** at 80 °C (entry 8), which indicated that the microwave irradiation benefited the formation of the eliminated product **5**. In order to examine the microwave effect, the microwave irradiated reaction was performed at 25 °C,[47] the desired product (**6aa**) and a certain amount of the eliminated product **7** were produced (entry 9), although the reaction at 25 °C afforded the sole product (**6aa**) in non-microwave condition. In addition, the imine **4aa** was also unstable and eliminated AcOH to form the eliminated intermediate **5** completely at 80 °C, which could be clearly observed in the experiment of entry10: under the conditions of microwave irradiation (MW) at 25 °C for 20 min, the reaction showed that by TLC checking **4aa** accompanied with **5** was formed, followed by MW at 80 °C for 5 min, **4aa** disappeared and was transformed into the eliminated intermediate **5**. The above results showed that the sugar-derived aldehyde (**3a**) and the intermediate imine **4aa** were more unstable in microwave irradiation than in the normal conditions and easily generated the eliminated α,β-unsaturated imine **5**. Thus, the novel amine-linked diglycose derivatives were conveniently synthesized in the following procedure (Table 1, entry 5): the mixture of azido sugar derivative **1a** (1 mmol) and triphenylphosphine (Ph_3P, 1.2 mmol) in THF was stirred 0.5 h at room temperature under N_2 atmosphere; the sugar-derived aldehyde **3a** (1.0 mmol) was added, and stirred for another 2 h. Then the reaction mixture was cooled to 0 °C, the mixture of glacial acetic acid (2.0 mmol) and $NaBH_3CN$ (2.0 mmol) was added, and stirred for 0.5 h at 0 °C to complete the reaction. Saturated aqueous solution of ammonium chloride was added to quench the reaction, after work up and chromatographic purification, the protected amine-linked diglycose **6aa** was afforded in a yield of 51%. With the same procedure, the compounds **6ab**–**6cc** were synthesized in good yields of 46–53% from the corresponding azido sugar derivative (**1a**–**1c**) and sugar-derived aldehyde (**3a**–**3c**), respectively (Table 2 and Scheme 3).

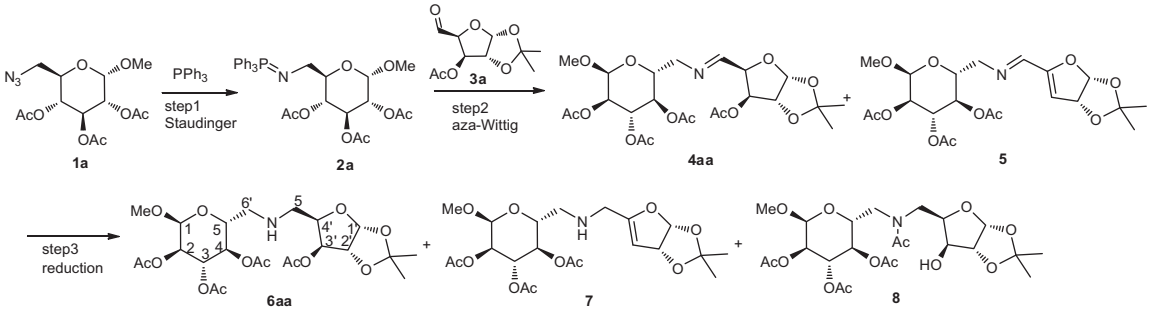
Subsequently, the deacetylation of the intermediates **6** was carried out in a methanolic solution of sodium methoxide at room temperature. However, it was found that some of the deproteced products were unstable, and an unseparated and unidentifiable mixture without the main component was obtained in each case of **6aa**, **6ab**, **6ba** and **6bb**. Only in the cases of **6ac**, **6ca**, **6cb**, and **6cc**, the deprotected diglycose products **9ac**, **9ca**, **9cb**, and **9cc** were obtained in 43–67% yields by deacetylation and followed by removing the isopropylidene under the treatment with 60% AcOH aqueous solution at 45 °C (Table 2). Furthermore, the amines **9ac**, **9ca**, **9cb**, and **9cc** were also found to be not so stable at the ambient conditions for a long time storage.[48] Accordingly, we envisaged to introduce an acetyl to the amino group to stabilize the product by forming the amide derivative. Thus, **6aa**–**6cc** was firstly treated with AcCl to form the corresponding amide-linked diglycose intermediates, followed by removing the *O*-acetyl and isopropylidene protective groups to afford the corresponding amide-linked diglycose derivatives **10aa**–**10cc** in good yields of 54–79%, respectively, (Scheme 3 and Table 2).

2.2. Biological activities

The inhibitions against HIV-1 reverse transcriptase (HIV-RT) and glycosidases, and the antitumor activity of some of compounds **9** and **10** were preliminarily evaluated. The cytotoxicity of the compounds **9** and **10** against HeLa cell lines and human lung adenocarcinoma epithelial cell line (A-549) was examined by the modified Mosmann's protocol.[49] As shown in Table 3, compounds **9cb**, **10ab** and **10bb** exhibited good cytotoxicity to A-549 with the IC_{50} values of 23.32, 27.89 and 24.77 μM, respectively, similar to that of the positive control Cisplatin, and most compounds have



Scheme 1. Diagram of one-pot synthesis of amine-linked diglycose derivatives by tandem Staudinger/aza-Wittig /reduction.



Scheme 2. Synthesis of compound **6aa** by one-pot tandem Staudinger/aza-Wittig reaction/reduction of **1a** with **3a**.

Table 1
Conditional optimization of the one-pot Staudinger/aza-Wittig/reduction of the azido sugar derivative **1a** with the sugar-derived aldehyde **3a**

Entry	Condition of step 2[a]		Condition of step 3		Yield (%)		
	Aldehyde (**3a**) (equiv)	Temperature and time[b]	Reduction reagent (equiv)	Temperature and time	**6aa**	**7**	**8**
1	1.0	rt, 2 h	$NaBH_4$ (3.0)	rt, 5 min	0	16	38
2	1.0	rt, 2 h	$NaBH_4$ (2.0)	0 °C, 5 min	0	0	50
3	1.0	rt, 2 h	$NaBH_3CN$ (2.0)	0 °C, 30 min	47	0	3
4	1.0	rt, 2 h	$NaBH_4$–AcOH (2.0)	0 °C, 5 min	35	0	10
5	**1.0**	**rt, 2 h**	**$NaBH_3CN$–AcOH (2.0)**	**0 °C, 30 min**	**51**	**0**	**0**
6	1.0	40 °C, 1.2 h	$NaBH_3CN$–AcOH (2.0)	0 °C, 30 min	45	4	0
7	1.0	50 °C, 1 h	$NaBH_3CN$–AcOH (2.0)	0 °C, 30 min	25	28	0
8	1.0	MW, 80 °C, 5 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 30 min	0	60	0
9	1.0	MW, 25 °C, 20 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 30 min	30	20	0
10	1.0	MW, 25 °C, 20 min then 80 °C, 5 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 30 min	0	50	0

[a] Condition of step 1: **1a**, THF, Ph_3P (1.2 equiv), rt 0.5 h, then step 2.
[b] Reaction completion time (checked by TLC).

Table 2
The yields of compounds **6**, **9** and **10**

Compounds **6**, **9** and **10**	Azido sugar **1**	Aldehyde **3**	Yields of **6**	Yields of **9**	Yields of **10**
aa	**a**	**a**	51	—[a]	79[d]
ab	**a**	**b**	51	—[a]	57[d]
ac	**a**	**c**	53	43[b]	61[d]
ba	**b**	**a**	47	—[a]	70[d]
bb	**b**	**b**	52	—[a]	63[d]
ca	**c**	**a**	50	65[c]	61[e]
cb	**c**	**b**	49	65[c]	70[e]
cc	**c**	**c**	46	67[c]	54[e]

[a] Not obtained.
[b] Condition: NaOMe (1 equiv), MeOH, rt.
[c] Condition: NaOMe (1 equiv), MeOH, rt, then 60% AcOH, 45 °C.
[d] Condition: (i) AcCl, Et_3N (5 equiv), CH_2Cl_2; (ii) NaOMe (1 equiv), MeOH, rt.
[e] Condition: (i) AcCl, Et_3N (5 equiv), CH_2Cl_2; (ii) NaOMe (1 equiv), MeOH, rt then 60% AcOH.

selectivity to A-549 than HeLa. The glycosidase inhibitory activities of compounds **9** and **10** were determined with hydrolytic reactions of α-amylase, α-glucosidase, and β-glucosidase using acarbose as a control, respectively; and the HIV-RT inhibitory activities of the compounds were measured using colorimetric reverse transcriptase assay by comparison with AZT.[50] However, the compounds have not shown obvious activities with both of them.

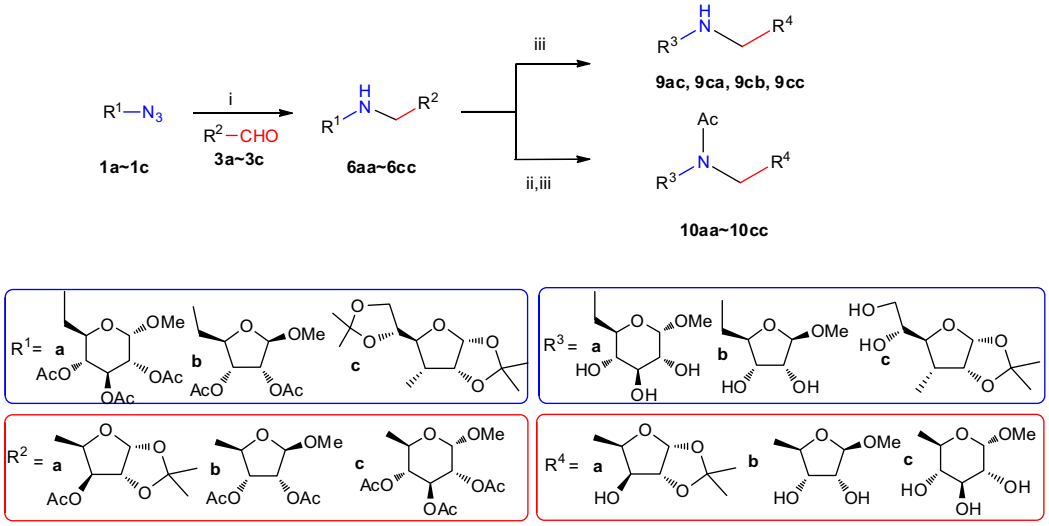
In summary, we have synthesized a series of primary-primary and primary-secondary N-linked diglycose derivatives conveniently by one-pot tandem Staudinger/aza-Wittig/reduction process from azido sugar derivatives and sugar-derived aldehydes at room temperature followed by deprotection, providing a convenient and direct method for constructing such amine-linked diglycose derivatives in good yields under very mild conditions. The biological activities of compounds **9** and **10** for glycosidases inhibition, antitumor, and antiviral against HIV-RT were preliminarily evaluated. The further study of the synthesis and biological activities of such N-linked diglycose derivatives using this methodology is underway.

3. Experimental

3.1. General methods

Melting points were measured on an SGW®X-4 micro melting point apparatus and are uncorrected. Optical rotations were determined on an SGW®-1 automatic polarimeter. ^1H NMR, ^{13}C NMR spectra were measured on a RT-NMR Bruker AVANCE 400 (400 MHz) and Bruker AVANCE 600 (600 MHz) spectrometer using tetramethylsilane (Me_4Si) as the internal standard. High-resolution mass spectra (HRMS) were carried out on a FTICR-MS (Ionspec 7.0T) mass spectrometer in the electrospray-ionization (ESI) mode. The microwave assisted reactions were performed on a DISCOVER S-Class Auto Focused Microwave Synthesis System (CEM Corporation, USA), the microwave reactions at 25 °C were performed using this microwave reactor equipped with a fiber-optic probe for direct monitoring of the internal reaction temperature in a 10 mL sealed reaction vessel, the reaction vessel is cooled from the outside by compressed air (0.3–0.5 MPa) (air compressor WSC 21070A, Shanghai Wispump Ind. Co., Ltd) which was precooled to ca. 0 °C by passing through a coil immersed in a cooling bath (cooling liquid circulating pump, −20 to −15 °C, DLSB-10/20, Zheng Zhou Great Wall Scientific Industrial and Trade Co. Ltd) before reaching the reaction vessel while being irradiated by microwaves.

The optical densities for examining the inhibitory activities against glycosidase and HIV-RT and anti-tumor activity were measured on a TU-1901 UV–vis spectrophotometer and a Bio-Rad Model 3550 microplate spectrophotometer, respectively.



Scheme 3. Synthesis of compounds **9** and **10** by one-pot tandem Staudinger/aza-Wittig /reduction of azido sugar derivative **1** with the sugar-derived aldehyde **3** followed by deprotection. Reagents and conditions: (i) Ph_3P (1.2 equiv), THF, rt, 0.5 h, then R_2-CHO (**3a**–**3c**) (1 equiv), rt, 2 h, and then $NaBH_3CN$–AcOH (2 equiv), 0 °C, 0.5 h; (ii) AcCl (5 equiv), Et_3N (5 equiv), CH_2Cl_2, 0 °C; (iii) NaOMe (1 equiv), MeOH, rt, then 60% AcOH, 45 °C.

Table 3
Antitumor activities

Compounds		9ac	9cb	9cc	10aa	10ab	10ac	10bb	10bb	Cisplatin
IC_{50} (μM)	HeLa	148.52 ± 3.69	116.01 ± 4.34	161.51 ± 3.39	346.99 ± 2.88	222.65 ± 3.43	133.89 ± 1.39	118.78 ± 3.46	44.10 ± 0.82	20.01 ± 1.36
	A-549	129.71 ± 7.12	**23.32 ± 1.16**	43.81 ± 2.15	204.85 ± 3.89	**27.89 ± 1.23**	60.23 ± 1.19	128.4 ± 47.28	**24.77 ± 0.63**	19.41 ± 5.67

Thin-layer chromatography (TLC) was performed on precoated plates (Qingdao GF_{254}) with detection by UV light or with phosphomolybdic acid in EtOH/H_2O followed by heating. Column chromatography was performed using a SiO_2 (Qingdao 300–400 mesh).

3.2. General procedure for the synthesis of compounds 6

Azido sugar derivative **1** (1.0 mmol) was dissolved in 2 mL anhydrous THF. Ph_3P (1.2 mmol) was then added to the solution with stirring under nitrogen atmosphere, the mixture was stirred at room temperature for 0.5 h and the sugar-derived aldehyde **3** (1 mmol) was added to the solution, stirred for another 2.0 h at rt. Then, it was cooled to 0 °C, a mixture of $NaBH_3CN$ (126 mg, 2 mmol) and AcOH (115 μL, 2.0 mmol) was added. After continuously stirring for 0.5 h at 0 °C, the reaction was quenched with the addition of saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$ and evaporated, and the residue was purified by a column chromatography using petroleum ether/ethyl acetate (v/v = 1:1) as the eluent to obtain the product **6aa**–**6cc**.

3.2.1. *N*-(Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(1,2-*O*-isopropylidene-3-*O*-acetyl-5-dexoy-α-D-xylos-5-yl) amine (6aa)

Colorless oil; $[\alpha]_D^{20}$ +31.6° (*c* 0.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) *δ*: 1.30 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.90 (td, 1H, *J* = 2.4 Hz, *J* = 12.0 Hz, CH_2), 2.96–3.04 (m, 2H, CH_2, CH), 3.25 (dd, 1H, *J* = 10.2 Hz, *J* = 13.2 Hz, CH_2), 3.32 (dd, 1H, *J* = 8.4 Hz, *J* = 14.4 Hz, CH_2), 3.48 (s, 3H, OCH_3), 4.16 (td, 1H, *J* = 2.4 Hz, *J* = 5.4 Hz, CH), 4.37 (td, 1H, *J* = 2.4 Hz, *J* = 5.4 Hz, CH), 4.57 (dd, 1H, *J* = 4.2 Hz, *J* = 10.2 Hz, CH), 4.87 (t, 1H, *J* = 9.6 Hz, CH, H-4), 4.97 (d, 1H, *J* = 4.2 Hz, CH), 5.20 (s, 1H, CH, H-1), 5.50 (t, 1H, *J* = 10.2 Hz, CH, H-3), 5.93 (d, 1H, *J* = 3.6 Hz, CH, H-1′); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 20.58, 20.62, 20.67, 20.70, 26.36, 26.75 (CH_3), 43.64 (CH_2), 54.21 (OCH_3), 56.74 (CH), 64.32 (CH_2), 69.16 (CH), 70.43 (CH), 70.85 (CH), 73.01 (CH), 76.34 (CH), 83.65 (CH), 97.26 (C-1), 104.54 (C-1′), 112.90 (C), 169.53, 169.73, 170.07, 170.24 (O═C). HRMS (ESI): Calcd $C_{25}H_{37}NO_{14}$ for ($M+H^+$): 575.7156. Found: 575.7141.

3.2.2. *N*-(Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(1,2-*O*-isopropylidene-3,5-dideoxy-3-enyl-α-xylos-5-yl) amine (7)

Colorless oil; $[\alpha]_D^{22}$ +72.6° (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.43 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.70–2.73 (m, 2H, H-6), 3.33 (s, 2H, H-5′), 3.40 (s, 3H, OCH_3), 3.87–3.92 (m, 1H, H-5), 4.85 (dd, 1H, *J* = 3.6 Hz, *J* = 10.2 Hz, H-2), 4.91 (d, 1H, *J* = 3.6 Hz, H-1), 4.97 (t, 1H, *J* = 19.4 Hz, H-4), 5.09 (s, 1H, H-3′), 5.27–5.29 (m, 1H, H-2′), 5.47 (t, 1H, *J* = 19.5 Hz, H-3), 6.05 (d, 1H, *J* = 5.2 Hz, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*:21.08 (CH_3), 21.29 (CH_3), 21.65 (CH_3), 28.20 (CH_3), 28.55 (CH_3), 47.05 (C-5′), 49.77 (C-6), 55.77 (OCH_3), 68.85 (C-5), 70.53 (C-3), 70.72 (C-4), 71.43 (C-2), 84.03 (C-2′), 96.95 (C-1), 98.99 (C-3′), 106.56 (C-1′), 112.40, 160.73 (C-4′), 170.23, 170.45, 170.57 (O═C). HRMS (ESI): Calcd $C_{21}H_{31}NO_{11}$ for ($M+H^+$): 473.6020. Found: 473.6031.

3.2.3. *N*-(Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(1,2-*O*-isopropylidene-5-dexoy-α-D-xylos-5-yl) acetamide (8)

Colorless oil; $[\alpha]_D^{20}$ +38.6° (*c* 0.1, MeOH); ^1H NMR (600 MHz, $CDCl_3$) *δ*:1.30 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.07 (s, 6H, CH_3), 2.13 (s, 3H, CH_3), 3.35 (s, 3H, OCH_3), 3.44–3.48 (m, 2H, H-6), 3.91 (s, 1H, H-4), 3.95–3.97 (m, 1H, H-5), 4.09–4.16 (m, 2H, H-5′), 4.58 (d, 1H, *J* = 3.5 Hz, H-2), 4.80–4.86 (m, 2H, H-1, H-4), 4.92 (d, *J* = 3.6 Hz, 1H, H-3′), 5.03 (s, 1H, H-2′), 5.44 (t, 1H,

J = 19.4 Hz, H-3), 5.88 (d, 1H, J = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.60, 20.63, 21.47, 25.94, 26.84 (CH_3), 45.41 (CH_2), 51.28 (OCH_3), 55.99 (CH), 69.65 (CH_2), 69.89 (CH), 70.56 (CH), 70.63 (CH), 73.66 (CH), 78.44 (CH), 84.83 (CH), 96.72 (C-1), 104.58 (C-1′), 111.51 (C), 169.79, 169.94, 170.05, 172.77 (O═C). HRMS (ESI): Calcd $C_{25}H_{37}NO_{14}$ for ($M+H^+$): 575.7156. Found: 575.7143.

3.2.4. *N*-(Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(methyl 2,3-di-*O*-acetyl-5-dexoy-β-D-ribofuranosid-5-yl) amine (6ab)

Colorless oil; $[\alpha]_D^{22}$ +67.6° (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98–2.06 (m, 15H, CH_3), 2.91–3.22 (m, 4H, H-6), 3.45 (s, 6H, OCH_3), 3.52–4.01 (m, 8H, CH, CH_2), 4.11–4.14 (m, 1H, CH), 4.51–4.53 (m, 1H, CH), 4.79–4.99 (m, 5H, CH), 5.27 (s, 1H, CH), 5.51–5.52 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.86 (CH_3), 53.53 (CH_2), 56.36 (CH_2), 57.04, 59.33 (OCH_3), 69.59 (CH), 70.24 (CH), 70.91 (CH), 71.30 (CH), 74.60 (CH), 75.20 (CH), 76.25 (CH), 97.75 (C-1), 107.53 (C-1′), 169.80, 169.92, 170.29, 170.58, 170.66 (O═C). HRMS (ESI): Calcd $C_{25}H_{37}NO_{15}$ for ($M+H^+$): 591.7150. Found: 591.7136.

3.2.5. *N,N*-Bis(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl) amine (6ac)

Colorless oil; $[\alpha]_D^{22}$ +45.8° (c 0.1, $CHCl_3$,); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.09 (s, 9H, CH_3), 2.86 (t, 1H, J = 15.0 Hz, CH_2), 3.02 (t, 1H, J = 17.4 Hz, CH_2), 3.10 (t, 1H, J = 17.4 Hz, CH_2), 3.24 (dd, 1H, J = 21.6 Hz, J = 13.2 Hz, CH_2), 3.47 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 4.14 (t, 1H, J = 15.6 Hz, CH), 4.46 (td, 1H, J = 2.4 Hz, J = 15.0 Hz, CH), 4.74–4.91 (m, 4H, CH), 4.95 (d, J = 5.4 Hz, 1H, H-1′), 5.02 (d, 1H, J = 5.4 Hz, H-1), 5.50–5.53 (td, 2H, J = 2.4 Hz, J = 8.4 Hz, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.64, 20.67 (CH_3), 52.75, 55.01 (C-6), 56.44, 56.88 (OCH_3), 64.26 (C-4), 69.01, 69.10 (C-2), 69.88, 70.50 (C-5), 70.76 (C-3), 97.04, 97.21 (C-1), 169.69, 169.84, 170.06, 170.26 (O═C). HRMS (ESI): Calcd $C_{28}H_{41}NO_{17}$ for ($M+H^+$): 663.7964. Found: 663.7954.

3.2.6. *N*-(Methyl 2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosid-5-yl)-*N*-(1,2-*O*-isopropylidene-3-*O*-acetyl-5-dexoy-α-D-xylos-5-yl) amine (6ba)

Colorless oil; $[\alpha]_D^{20}$ −24.8° (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.04–3.13 (m, 3H, CH_2), 3.37–3.39 (m, 1H, CH_2), 3.43 (s, 3H, OCH_3), 4.58 (d, 1H, J = 3.6 Hz, CH), 4.62–4.65 (m, 2H, CH), 4.92 (s, 1H, H-1′), 5.17 (t, 1H, J = 5.4 Hz, CH), 5.22 (m, 1H, CH), 5.24 (d, 1H, J = 4.8 Hz, CH, H-1′), 5.93 (d, 1H, J = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.46, 20.54, 20.61, 26.07, 26.74 (CH_3), 53.47 (CH_2), 56.27 (OCH_3), 56.75 (CH), 72.67 (CH_2), 72.97 (CH), 74.57 (CH), 75.59 (CH), 76.56 (CH), 83.52 (CH), 104.54 (C-1′), 106.70 (C-1),112.90 (C), 169.53, 169.73, 170.07, 170.24 (O═C). HRMS (ESI): Calcd $C_{22}H_{33}NO_{12}$ for ($M+H^+$): 503.6342. Found: 503.6357.

3.2.7. *N,N*-Bis(methyl 2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosid-5-yl) amine (6bb)

Colorless oil; $[\alpha]_D^{20}$ −11.3° (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.95–2.97 (m, 1H, H-5), 3.21–3.28 (m, 3H, H-5, H-5′), 3.43 (s, 3H, OMe), 3.45 (s, 3H, OMe), 4.63–4.65 (m, 2H, H-4, H-4′), 4.95 (s, 2H, H-1, H-1′), 5.18–5.22 (m, 2H, H-3, H-3′), 5.30 (d, 2H, J = 4.8 Hz, J = 15.2 Hz, CH, H-2′, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.81, 21.33 (CH_3), 55.30, 55.88 (C-5), 59.78, 60.70 (OCH_3), 73.30, 73.57 (C-3), 75.17 (C-4), 75.32, 76.21 (C-2), 107.17, 107.36 (C-1), 169.68, 169.99, 170.38, 170.41 (O═C). HRMS (ESI): Calcd $C_{22}H_{33}NO_{13}$ for ($M+H^+$): 519.6336. Found: 519.6341.

3.2.8. *N*-(1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(1,2-*O*-isopropy-lidene-3-*O*-acetyl-5-deoxy-α-D-xylos-5-yl) amine (6ca)

Colorless oil; $[\alpha]_D^{20}$ +69.0° (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 6H, CH_3), 2.26 (s, 3H, CH_3), 2.78 (dd, 1H, J = 3.6 Hz, J = 12.6 Hz, CH_2), 3.00 (dd, 1H, J = 7.2 Hz, J = 12.6 Hz, CH_2), 3.05 (dd, 1H, J = 4.2 Hz, J = 10.2 Hz, CH_2), 3.77 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, CH_2), 3.96 (t, 1H, J = 7.2 Hz, CH), 4.18 (t, 1H, J = 7.2 Hz, CH), 4.33–4.38 (m, 2H, CH), 4.51 (d, 1H, J = 3.6 Hz, CH), 4.65 (t, 1H, J = 4.2 Hz, CH), 5.22 (d, 1H, J = 3.0 Hz, CH), 5.81 (d, 1H, J = 3.6 Hz, H-1′), 5.92 (d, 1H, J = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.77, 25.25, 26.29, 26.48, 26.64, 26.75 (CH_3), 48.66 (CH_2), 60.13 (OCH_3), 62.19 (CH), 64.89 (CH_2), 75.52 (CH), 76.72 (CH), 78.24 (CH), 78.99 (CH), 79.33 (CH), 83.48 (CH), 99.79 (C-1), 103.77 (C-1′), 109.46, 111.97, 112.03 (C), 169.81 (O═C). HRMS (ESI): Calcd $C_{22}H_{35}NO_{10}$ for ($M+H^+$): 473.6512. Found: 473.6522.

3.2.9. *N*-(1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosid-5-yl) amine (6cb)

Colorless oil; $[\alpha]_D^{20}$ +20.5° (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.51 (s, 6H, CH_3), 2.58 (dd, 1H, J = 7.2 Hz, J = 11.4 Hz, CH_2), 2.96 (dd, 1H, J = 8.4 Hz, J = 11.4 Hz, CH_2), 3.10 (dd, 1H, J = 4.8 Hz, J = 9.6 Hz, CH_2), 3.38 (s, 3H, OCH_3), 3.80 (dd, 1H, J = 3.0 Hz, J = 9.6 Hz, CH_2), 3.99 (t, 1H, J = 7.8 Hz, CH), 4.23–4.26 (m, 2H, CH), 4.40 (td, 1H, J = 3.0 Hz, J = 7.2 Hz, CH), 4.58 (d, 1H, J = 6.0 Hz, CH), 4.63 (t, 1H, J = 4.2 Hz, CH), 4.65 (d, 1H, J = 6.0 Hz, CH), 4.97 (s, 1H, H-1), 5.81 (d, 1H, J = 3.6 Hz, H-1′);^{13}C NMR (150 MHz, $CDCl_3$) δ:25.06 (CH_3), 25.37 (CH_3), 26.27 (CH_3), 26.49 (CH_3), 26.50 (CH_3), 26.75 (CH_3), 51.84 (CH_2), 55.21 (OCH_3), 61.73 (CH), 65.06 (CH_2), 75.74 (CH), 77.94 (CH), 78.96 (CH), 82.68 (CH), 85.33 (CH), 86.83 (CH), 104.33 (C-1), 109.55 (C), 109.66 (C-1′), 111.97, 112.33 (C), 169.81 (O═C). HRMS (ESI): Calcd $C_{22}H_{35}NO_{11}$ for ($M+H^+$): 489.6506. Found: 489.6522.

3.2.10. *N*-(1,2:5,6-Di-*O*-isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl) amine (6cc)

Colorless oil; $[\alpha]_D^{20}$ +67.2° (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.65 (dd, 1H, J = 2.4 Hz, J = 12.6 Hz, CH_2), 2.90 (dd, 1H, J = 7.8 Hz, J = 12.6 Hz, CH_2), 3.06 (dd, 1H, J = 4.8 Hz, J = 9.0 Hz, CH_2), 3.41 (s, 3H, OCH_3), 3.75–3.78 (dd, 1H, J = 3.0 Hz, J = 9.0 Hz, CH_2), 3.86 (td, 1H, J = 2.4 Hz, J = 10.2 Hz, CH), 3.40 (t, 1H, J = 7.8 Hz, CH), 4.16 (t, 1H, J = 7.8 Hz, CH), 4.35 (td, 1H, J = 3.6 Hz, J = 7.2 Hz, CH), 4.61 (t, 1H, J = 4.2 Hz, CH), 4.86 (dd, 1H, J = 4.2 Hz, J = 10.8 Hz, CH), 4.93 (d, 1H, J = 3.6 Hz, H-1′), 4.99 (t, 1H, J = 9.6 Hz, CH), 5.47 (t, 1H, J = 9.6 Hz, CH), 5.79 (d, 1H, J = 4.2 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.66, 20.66, 20.66, 25.34, 26.20, 26.49, 26.68 (CH_3), 48.65 (CH_2), 55.15 (OCH_3), 62.56 (CH), 65.19 (CH_2), 69.24 (CH), 70.19 (CH), 70.36 (CH), 71.06 (CH), 75.78 (CH), 78.05 (CH), 79.22 (CH), 96.47 (C-1), 104.32 (C-1′), 109.54 (C), 112.09 (C), 169.77, 170.07, 170.18 (O═C). HRMS (ESI): Calcd $C_{25}H_{39}NO_{13}$ for ($M+H^+$): 561.7320. Found: 561.7334.

3.3. General procedure for the synthesis of compounds 9

Compound **6** was dissolved in dry methanol, sodium methoxide (1.0 equiv) was added, then the reaction mixture was stirred at room temperature till the completion of reaction. Ion exchange resin was added to adjust the pH of the solution to 7. The resin was

filtered off and methanol was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using acetoacetate/methanol (v/v = 10:1) as the eluent to obtain a colorless oil product. The product was dissolved in 60% AcOH and the reaction mixture was stirred at 45 °C, until the reaction completed (checked by TLC). The solvent was evaporated under reduced pressure and residue was purified by flash column chromatography (ethyl acetate/methanol (v/v = 8:1)) to afford the compound **9**.

3.3.1. *N,N*-Bis(methyl 6-deoxy-α-D-glucopyranosid-6-yl) amine (9ac)

White solid; $[\alpha]_D^{21}$ +86.7° (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 2.97–3.43 (m, 8H, CH_2, CH), 3.48 (s, 6H, OCH_3), 3.62 (t, *J* = 3.6 Hz, 2H, CH), 3.96–3.97 (m, 1H, CH), 4.10–4.11 (m, 1H, CH), 4.67 (d, *J* = 3.6 Hz, 1H, H-1), 4.72 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ: 48.46, 52.54 (CH_2), 55.46, 55.51 (OCH_3), 71.71 (CH), 72.12 (CH), 73.43 (CH), 73.62, 73.62 (CH), 73.76 (CH), 74.57 (CH), 75.07 (CH), 101.11 (C-1), 101.14 (C-1′). HRMS (ESI): Calcd $C_{14}H_{27}NO_{10}$ for ($M+H^+$): 369.4520. Found: 369.4527.

3.3.2. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylos-5-yl) amine (9ca)

Colorless oil; $[\alpha]_D^{22}$ +89.2° (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD); δ: 1.31 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.92–2.95 (m, 2H, CH_2), 3.11–3.14 (m, 1H, CH_2), 3.25–3.27 (m, 1H, CH), 3.69–3.71 (m, 2H, CH_2), 3.82 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, CH_2), 3.90 (d, 1H, *J* = 3.6 Hz, CH), 4.11–4.13 (m, 1H, CH), 4.21 (d, 1H, *J* = 4.2 Hz, CH_2), 4.48 (d, 1H, *J* = 3.6 Hz, CH), 4.81 (t, 1H, *J* = 4.2 Hz, CH), 5.83 (d, 1H, *J* = 3.6 Hz, H-1), 5.90 (d, 1H, *J* = 3.6 Hz, H-1′); ^{13}C NMR (150 MHz, CD_3OD) δ: 25.34, 25.39, 25.65, 25.77 (CH_3), 45.99 (CH_2), 63.27 (CH_2), 65.27 (CH), 75.72 (CH), 76.36 (CH), 78.36 (CH), 79.19 (CH), 79.25 (CH), 85.52 (CH), 104.75 (C-1), 104.85 (C-1′), 111.25 (C), 112.11 (C). HRMS (ESI): Calcd $C_{17}H_{29}NO_9$ for ($M+H^+$): 391.5194. Found: 391.5175.

3.3.3. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 5-deoxy-β-D-ribofuranosid-5-yl) amine (9cb)

White solid; $[\alpha]_D^{22}$ −16.8° (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.36 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.84–2.87 (m, 2H, CH_2), 3.27–3.29 (m, 2H, CH_2), 3.71 (d, 1H, *J* = 3.6 Hz, CH), 3.81 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, CH), 3.90 (d, *J* = 4.2 Hz, 1H, CH), 3.91–3.93 (m, 1H, CH); 3.96–4.02 (m, 2H, CH), 4.77 (s, 1H, H-1′), 4.83 (t, 1H, *J* = 4.2 Hz, CH), 5.83 (d, 1H, *J* = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD) δ: 25.29, 25.54 (CH_3), 51.96 (CH_2), 53.79 (OCH_3), 59.30 (CH), 62.93 (CH_2), 70.70 (CH), 73.48 (CH), 74.83 (CH), 77.15 (CH), 81.38 (CH), 81.97 (CH), 104.77 (C-1), 108.53 (C-1′), 111.88 (C). HRMS (ESI): Calcd $C_{15}H_{27}NO_9$ for ($M+H^+$): 365.4696. Found: 365.4686.

3.3.4. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 6-deoxy-α-D-glucopyranosid-6-yl) amine (9cc)

White solid; $[\alpha]_D^{22}$ +86.7° (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.37 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.94 (dd, 1H, *J* = 9.0 Hz, *J* = 12.0 Hz, CH_2), 3.02 (dd, 1H, *J* = 3.0 Hz, *J* = 12.0 Hz, CH_2), 3.14 (t, 1H, *J* = 9.6 Hz, CH), 3.30 (dd, 1H, *J* = 4.2 Hz, *J* = 9.6 Hz, CH_2), 3.32 (m, 1H, CH_2), 3.39 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, CH_2), 3.41 (s, 3H, OCH_3), 3.59 (d, 1H, *J* = 9.0 Hz, CH), 3.63 (dd, 1H, *J* = 2.4 Hz, *J* = 9.0 Hz, CH), 3.68 (dd, 1H, *J* = 3.6 Hz, *J* = 6.0 Hz, CH), 3.81 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, CH), 3.90 (q, 1H, *J* = 3.0 Hz, CH), 4.67 (d, 1H, *J* = 3.6 Hz, H-1′), 4.78 (t, 1H, *J* = 3.6 Hz, CH), 5.81 (d, 1H, *J* = 4.2 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD) δ:25.25, 25.50 (CH_3), 48.48 (CH_2), 54.35 (OCH_3), 59.76 (CH), 62.91 (CH_2), 70.48 (CH), 70.78 (CH), 72.18 (CH), 72.57 (CH), 73.55 (CH), 77.27 (CH), 82.13 (CH), 99.87 (C-1), 104.709 (C-1′), 112.08 (C). HRMS (ESI): Calcd $C_{16}H_{29}NO_{10}$ for ($M+H^+$): 395.5018. Found: 395.5007.

3.4. General procedure for the synthesis of compounds 10aa–10bb

The compounds **6aa**–**6bb** were dissolved in dry CH_2Cl_2 under an ice-water bath, Et_3N (5.0 equiv) and AcCl (5.0 equiv) were added, the reaction mixture was stirred at 0 °C till the completion of reaction (checked by TLC). Excess reagent was decomposed with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with ethyl acetate three times. The combined extracts were washed with water, brine, dried over $MgSO_4$ and evaporated, and the resulting product was dissolved in dry methanol, sodium methoxide (1.0 equiv) was added, then the reaction mixture was stirred at room temperature, ion exchange resin was added to adjust the pH of the solution to 7 after the completion of reaction (checked by TLC). The resin was filtered off and methanol was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/methanol (v/v = 10:1)) to afford the compounds **10aa**–**10bb**.

3.4.1. *N*-(Methyl 6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylos-5-yl) acetamide (10aa)

Colorless oil; $[\alpha]_D^{22}$ +37.1° (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.24 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.07 (t, 1H, *J* = 9.6 Hz, CH_2), 3.31 (s, 3H, OCH_3), 3.37 (dd, 1H, *J* = 4.2 Hz, *J* = 9.6 Hz, CH_2), 3.48 (dd, 1H, *J* = 4.2 Hz, *J* = 9.6 Hz, CH_2), 3.27(m, 1H, CH), 3.55 (t, 1H, *J* = 9.6 Hz, CH_2), 3.69 (d, 1H, *J* =9.6 Hz, CH), 3.74 (m, 1H, CH), 3.97 (m, 2H, CH), 4.25 (m, 1H, CH), 4.44 (t, 1H, *J* = 3.6 Hz, CH), 4.63 (t, 1H, *J* = 3.6 Hz, CH), 5. 83 (d, 1H, *J* = 3.6 Hz, H-1′);^{13}C NMR (150 MHz, CD_3OD) δ: 20.44, 24.95, 25.63 (CH_3), 46.34, 51.29 (CH_2), 54.36 (OCH_3), 71.69 (CH), 71.99 (CH), 72.16 (CH), 73.61 (CH), 74.30 (CH), 78.72 (CH), 85.17 (CH), 99.73 (C-1′), 104.75 (C-1), 173.50 (O═C). HRMS (ESI): Calcd $C_{17}H_{29}NO_{10}$ for ($M+H^+$): 407.5188. Found: 407.5176.

3.4.2. *N*-(Methyl 6-deoxy-α-D-glucopyranosid-6-yl)-*N*-(methyl 5-deoxy-β-D-ribofuranosid-5-yl) acetamide (10ab)

White solid; $[\alpha]_D^{22}$ −13.8° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 2.20 (s, 3H, CH_3), 3.05–3.14 (m, 1H, CH_2), 3.35 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.41–3.43 (m, 1H, CH_2), 3.52–4.01 (m, 8H, CH, CH_2), 4.11–4.14 (m, 1H, CH), 4.66 (d, *J* = 3.6 Hz, 1H, H-1), 4.74 (s, 1H, H-1′); ^{13}C NMR (100 MHz, CD_3OD) δ: 21.90 (CH_3), 51.60, 52.08 (CH_2), 55.57, 55.76 (OCH_3), 72.69 (CH), 73.45 (CH), 73.63 (CH), 74.70 (CH), 75.07 (CH), 76.14 (CH), 81.97 (CH), 101.11 (C-1), 109.99 (C-1′), 174.42 (O═C). HRMS (ESI): Calcd $C_{15}H_{27}NO_{10}$ for ($M+H^+$): 381.4690. Found: 381.4679.

3.4.3. *N,N*-Bis(methyl 6-deoxy-α-D-glucopyranosid-6-yl) acetamide (10ac)

White solid; $[\alpha]_D^{22}$ +63.2° (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD), δ: 2.22 (s, 3H, CH_3), 3.05–3.15 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.41–3.44 (m, 2H, H-6, CH_2), 3.58–3.79 (m, 6H, CH, CH_2), 3.84–3.87 (m, 1H, CH), 3.97–4.01 (m, 1H, CH), 4.66 (d, 1H, *J* = 3.6 Hz, H-1′), 4.69 (d, 1H, *J* = 3.6 Hz, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ: 21.83 (CH_3), 48.46, 52.54 (CH_2), 55.46, 55.51 (OCH_3), 71.71 (CH), 72.12 (CH), 73.43 (CH), 73.62, 73.62 (CH), 73.76 (CH), 74.57 (CH), 75.07 (CH), 101.11 (C-1), 101.14 (C-1′), 174.99 (O═C). HRMS (ESI): Calcd $C_{16}H_{29}NO_{11}$ for ($M+H^+$): 411.5012. Found: 411.5021.

3.4.4. *N*-(Methyl 5-deoxy-β-D-ribofuranosid-5-yl)-*N*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylos-5-yl) acetamide (10ba)

Colorless oil; $[\alpha]_D^{22}$ −16.8° (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.20 (s, 3H, CH_3),

3.39 (s 3H CH_3), 3.52 (dd, 1H, J = 9.0 Hz, J = 15.6 Hz, CH_2), 3.57 (dd, 1H, J = 7.2 Hz, J = 14.4 Hz, CH_2), 3.84–3.87 (m, 1H, CH), 3.88–4.11 (m, 5H, CH, CH_2), 4.31–4.33 (m, 1H, CH), 4.49 (d, 1H, J = 3.6 Hz, CH), 4.78 (s, 1H, H-1′), 5.89 (d, 1H, J = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD) δ: 20.40, 24.96, 25.62 (CH_3), 45.72 (CH_2), 53.45 (OCH_3), 54.61 (CH), 72.75 (CH_2), 74.29 (CH), 74.29 (CH), 78.82 (CH), 81.41 (CH), 85.16 (CH), 104.78 (C-1′), 108.98 (C-1), 111.28 (C), 173.00 (O═C). HRMS (ESI): Calcd $C_{16}H_{27}NO_9$ for ($M+H^+$): 377.4866. Found: 377.4881.

3.4.5. *N,N*-Bis(methyl 5-deoxy-β-D-ribofuranosid-5-yl) acetamide (10bb)

White solid; $[\alpha]_D^{22}$ +22.8° (c 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 2.20 (s, 3H, CH_3), 3.45 (s, 6H, OCH_3), 3.49 (dd, 1H, J = 12.0 Hz, J = 21.0 Hz, CH_2), 3.63 (dd, 1H, J = 12.6 Hz, J = 23.4 Hz, CH_2), 3.88 (m, 3H, CH, CH_2), 3.93–4.01 (m, 3H, CH), 4.09–4.17 (m, 2 H, CH), 4.75 (s, 1H, H-1), 4.77 (s, 1H, H-1′);^{13}C NMR (100 MHz, CD_3OD) δ: 21.90 (CH_3), 51.63 (C-5), 54.67 (C-5), 55.95, 56.15 (OCH_3), 74.04 (CH), 74.72 (CH), 75.79 (CH), 76.23 (CH), 81.90 (CH), 82.51 (CH), 110.14, 110.44 (C-1), 173.91 (O═C). HRMS (ESI): Calcd $C_{14}H_{25}NO_9$ for ($M+H^+$): 351.4368. Found: 351.4371.

3.5. General procedure for the synthesis of compounds 10ca–10cc

The compounds **6ca**–**6cc** were dissolved in dry CH_2Cl_2, Et_3N (5.0 equiv) and AcCl (5.0 equiv) were added, the reaction mixture was stirred at 0 °C till the completion of reaction (checked by TLC). Excess reagent was decomposed with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$ and evaporated, and the residue was dissolved in dry methanol, sodium methoxide (1.0 equiv) was added, then the reaction mixture was stirred at room temperature; Ion exchange resin was added to adjust the pH of the solution to 7 after the completion of reaction (checked by TLC). The resin was filtered off and methanol was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/methanol (v/v = 10:1)) to afford a colorless oil compound, then dissolved in 60% AcOH, the mixture was stirred at 45 °C, till the completion of reaction (checked by TLC), The solvent was evaporated under reduced pressure to afford a crude product then purified by silic gel flash column chromatography (ethyl acetate/methanol (v/v = 8:1)) to afford compounds **10ca**–**10cc**.

3.5.1. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylos-5-yl) acetamide (10ca)

Colorless oil; $[\alpha]_D^{22}$+50.4° (c 0.5, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.33 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 3.55–3.59 (m, 1H, CH_2), 3.74 (m, 1H, CH_2), 3.85 (m, 1H, CH_2), 3.93 (dd, J = 3.0 Hz, J = 15.6 Hz, 1H, CH_2), 4.09 (dd, 1H, J = 2.4 Hz, J = 9.6 Hz, CH), 4.39 (m, 1H, CH), 4.45 (dd, 1H, J = 5.4 Hz, J = 9.0 Hz, CH), 4.48 (m, 2H, CH), 4.56 (dd, J = 5.4 Hz, J = 9.0 Hz, 1H, CH), 4.78 (t, 1H, J = 4.8 Hz, CH), 5.83 (d, 1H, J = 3.6 Hz, H-1), 5.92 (d, 1H, J = 3.6 Hz, H-1′); ^{13}C NMR (150 MHz, CD_3OD) δ: 21.36, 25.07, 25.71 (CH_3), 51.97 (CH_2), 55.13 (OCH_3), 60.14 (CH), 62.67 (CH_2), 73.23 (CH), 73.59 (CH), 74.76 (CH), 79.83 (CH), 80.86 (CH), 81.82 (CH), 103.92 (C-1), 108.90 (C-1′), 112.73 (C). HRMS (ESI): Calcd $C_{17}H_{29}NO_{10}$ for ($M+H^+$): 407.5188. Found: 407.5175.

3.5.2. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 5-deoxy-β-D-ribofuranosid-5-yl) acetamide (10cb)

White solid; $[\alpha]_D^{22}$ +51.4° (c 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.33 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.43 (s, 3H, OCH_3), 3.57 (m, 1H, CH_2), 3.70 (m, 2H, CH_2), 3.79 (q, 1H, J = 5.4 Hz, CH), 3.90 (m, 2H, CH, CH_2), 3.95 (m, 1H, CH), 4.20 (m, 1H, CH), 4.45 (dd, 1H, J = 4.2 Hz, J = 8.4 Hz, CH), 4.66 (dd, 1H, J = 5.4 Hz, J = 10.2 Hz, CH), 4.75 (t, 1H, J = 4.2 Hz, CH), 4.80 (s, 1H, CH, H-1′), 5.80 (d, 1H, J = 3.0 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD) δ: 21.27, 25.26, 25.73 (CH_3), 48.88 (CH_2), 54.75 (OCH_3), 60.13 (CH), 62.91 (CH_2), 70.85 (CH), 72.11 (CH), 72.80 (CH), 73.39 (CH), 73.68 (CH), 79.01 (CH), 99.79 (C-1), 103.77 (C-1′), 112.65 (C), 170.18 (O═C). HRMS (ESI): Calcd $C_{18}H_{31}NO_{11}$ for ($M+H^+$): 437.5510. Found: 437.5523.

3.5.3. *N*-(1,2-*O*-Isopropylidene-3-deoxy-α-D-allos-3-yl)-*N*-(methyl 6-deoxy-α-D-glucopyranosid-6-yl) acetamide (10cc)

White solid; $[\alpha]_D^{23}$ +70.0° (c 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ: 1.31 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.10 (t, 1H, J = 8.4 Hz, CH_2), 3.37 (s, 3H, OCH_3), 3.38 (m, 2H, CH_2), 3.51 (m, 4H, CH, CH_2), 3.64 (m, 2H, CH), 4.28 (t, 1H, J = 9.0 Hz, CH), 4.54 (m, 1H, CH), 4.67 (dd, 1H, J = 3.6 Hz, J = 10.8 Hz, CH), 4.79 (t, 1H, J = 4.2 Hz, CH), 5.77 (d, 1H, J = 4.2 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD) δ: 21.33, 25.04, 25.18, 25.66, 25.69 (CH_3), 46.10 (CH_2), 60.14 (OCH_3), 62.84 (CH), 74.08 (CH_2), 74.72 (CH), 76.47 (CH), 79.15 (CH), 80.78 (CH), 85.17 (CH), 104.40 (C-1), 104.49 (C-1′), 173.57 (O═C). HRMS (ESI): Calcd $C_{19}H_{31}NO_{10}$ for ($M+H^+$): 433.5686. Found: 433.5671.

3.6. Biological activity assays

3.6.1. Inhibition of glycosidases

The inhibitory activity of the synthesized compounds against α-amylase, α-glucosidase and β-glucosidase: α-glucosidase (yeast) and β-glucosidase (almonds) were obtained from Fluka; α-amylase (*Bacillaceae*, 4000 U/mg) from Sanland-chen International Inc, Xiamen, China. Two substrates, *p*-nitrophenyl α-glucopyranoside (PNPG) and (−)-D-salicin, were purchased from Sigma Chemical Co. All other commercial reagents were used as received. Each enzyme assay was measured as follows.

The α-amylase assay was performed using 1% starch as substrate in phosphate buffer, pH 6.0, at 50 °C. The enzyme solution (0.1 mL, 5 mg of solid enzyme in 50 mL of pH 6.0 phosphate buffer), 0.1 mL of inhibitor (1 mg/mL) and 1 mL of buffer were incubated for 10 min, and then 1 mL of substrate was added. After 10 min, 2 mL of 3,5-dinitrosalicylic acid was added, and then the reaction was heated in boiling water for 5 min. The solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis spectrophotometer at 540 nm using distilled deionized water as a blank control and acarbose as a positive control.

The β-glucosidase assay was performed using (−)-D-salicin (2 mg/mL) as the substrate in phosphate buffer, pH 4.8, at 35 °C. The enzyme solution (0.1 mL, 10 mg of solid enzyme in 10 mL of pH 4.8 acetate buffer), 0.1 mL of inhibitor (1 mg/mL), and 0.9 mL of buffer were incubated for 10 min, and then 0.8 mL of substrate was added. After 10 min, 2 mL of 3,5-dinitrosalicylic acid was added, and then the reaction mixture was heated in boiling water for 5 min. The solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis spectrophotometer at 540 nm using distilled deionized water as a blank control.

The a-glucosidase assay was performed using PNPG (1 mg/mL) as substrates in phosphate buffer, pH 6.8, at 37 °C. The enzyme solution (0.1 mL, 10 mg of solid enzyme in 10 mL of pH 6.8 phosphate buffer), 0.1 mL of inhibitor (1 mg/mL), 1.9 mL of buffer, and 0.05 mL glutathione (reduced, 1 mg/mL) were incubated for 10 min, and then 0.15 mL of substrate was added. The reaction was quenched with 10 mL of sodium carbonate (0.1 mol/L) after 10 min, and the solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis

spectrophotometer at 400 nm using distilled deionized water as a blank control.

3.6.2. In vitro colorimetric reverse transcriptase assay

HIV-RT inhibition assay was performed by using a colorimetric reverse transcriptase assay (Roche), and the procedure for assaying reverse transcriptase (RT) inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of a template/primer complex, 2′-deoxy-nucleotide-5′-triphosphates (dNTPs) and reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors. After 1 h of incubation at 37 °C the reaction mixture was transferred to a streptavidine-coated microtitre plate (MTP). The biotin labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and antidigoxigenin–peroxidase (DIG–POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template were bound to anti-DIG–POD antibody. The unbound anti-DIG–POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalysed by a peroxide enzyme. The absorbance of the sample was determined at OD (optical density) 405 nm using a microtiter plate ELISA reader. The resulting color intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparing to a sample that does not contain an inhibitor. The percentage inhibition was calculated by the formula as given below: $\%\text{Inhibition} = 100 - [(OD_{405\ nm\ with\ inhibitor}/OD_{405\ nm\ without\ inhibitor}) \times 100]$.

3.6.3. Antitumor activity

The cytotoxicity of the compounds against HeLa cell lines (human cervical cancer cells) and human lung adenocarcinoma epithelial cell line (A-549) was examined by the modified Mosmann's protocol as follows: Briefly, cells (10^4 cells per well) were plated in 96-well culture plates and cultured overnight at 37 °C in a 5% CO_2 humidified incubator. Compounds were added to the wells at final concentrations of 1, 10 and 100 μmol/L. Control wells were prepared by the addition of DMEM. Wells containing DMEM without cells were used as blanks. The plates were incubated at 37 °C in a 5% CO_2 incubator for 48 h. Upon completion of the incubation, stock MTT dye solution (10 μL, 5 mg/mL) was added to each well. After 4 h of incubation, the supernatant was removed and dimethyl sulfoxide (DMSO) (100 μL) was added to dissolve the MTT. The optical density of each well was measured on a microplate spectrophotometer at a wavelength of 570 nm. The cytotoxicity effect was calculated according to the formula: $(OD_{control} - OD_{treated})/OD_{control} \times 100\%$.

Acknowledgments

The financial supports from the 973 Program (2010CB534913), the National Natural Science Foundation of China (20972039, 21172051), the Natural Science Foundations of the Department of Education of Hebei (12966417D, Y2011119, and ZH2011110), the Natural Science Foundations of Hebei University (2009-175) and open research fund of the State Key Laboratory of Natural and Biomimetic Drugs, Peking University (20080205) are gratefully acknowledged.

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