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Synthesis of N-substituted iminosugars from 2′-carbonyl-*C*-glycofuranosides

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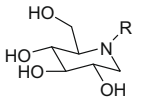
ABSTRACT

Under basic conditions 2′-carbonyl 5-N-substituted-*C*-glycofuranosides undergo a tandem β-elimination and intramolecular hetero-Michael addition to form N-substituted iminosugar derivatives in good to excellent yields.

1. Introduction

Iminosugars are a family of polyhydroxylated heterocycles carrying nitrogen at the position of the endocyclic oxygen atom.[1] These compounds represent one of the most interesting classes of glycomimetics.[2,3] The scope of the biological activities of iminosugars, initially known as potent glycosidase inhibitors, has considerably widened in recent years, as they have been found to be inhibitors of glycosyl transferases, glycogen phosphorylase, nucleoside-processing enzymes, metalloproteinases[4] and potential therapeutic candidates for the treatment of diabetes, cancer, viral infection and other diseases.[2,5–7] The deoxynojirimycin (DNJ) (1) (Fig. 1) family comprises potent inhibitors of the α-glucosidase mediated by iminosugars, especially N-alkylated piperidinols. For example, N-alkylated piperidinols were shown to exhibit potent antiviral activities and to have a protective effect in patients with Gaucher's disease, an inherited lysosomal disorder. These compounds are therefore of growing interest as new therapeutic leads, and two simple iminosugar derivatives have already been approved for therapeutic purposes: GlysetTM (*N*-hydroxyethyl-1-deoxynojirimycin, **2**) for the treatment of complications associated with type II diabetes,[8,9] and ZavescaTM (*N*-butyl-1-deoxynojirimycin, **3**) for the treatment of Gaucher disease.[10] The initial results were fairly promising as patients have shown clear improvement in organ volume as well as in haematological variables, which necessitated further exploration and investigation of N-alkylated iminosugars.[11–13] Considering the high potential of iminosugars as carbohydrate mimics, the design of a general and efficient approach to synthesize N-alkylated iminosugars appears to be an important issue yet to be solved. Recently, many such methods attempting to synthesize N-substituted iminosugars have emerged,[14–20] which may lead to superior inhibitors when the anomeric carbon in the piperidine rings is substituted.[21,22] In view of the high therapeutic and industrial potential of N-alkylated iminosugars, and as a part of our continuing interest in their synthesis,[23–28] we hereby report a practical approach for the synthesis of hitherto unknown N-substituted iminosugars.

Previously, we had found that 1-*C*-(2′-oxoalkyl)-glycosides form acyclic α,β-conjugates following base-mediated beta elimination,[23,24] which enabled an intramolecular addition of an amino group to form an iminosugar moiety.[25–28] Thus, we hypothesized that 1-*C*-(2′-oxoalkyl)-glycosides with an N-substituted amino group could also undergo a similar intramolecular Michael addition to produce N-substituted iminosugars. Additionally, iminosugars with different N-substituted amino groups could be further prepared for various iminosugar library constructions.



1 R = H (DNJ)
2 R = $(CH_2)_2OH$ Miglitol (Glyset)
3 R = Bu (Zavesca)

Figure 1.

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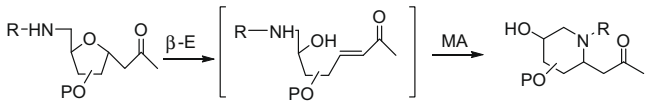


Scheme 1.

In this study, we report our results concerning the synthesis of N-substituted iminosugars and their analogues. The approach is outlined in Scheme 1. The strategy requires a tandem ring-opening β-elimination, which produces an acyclic α,β-conjugated ketone as a Michael acceptor, and an intramolecular hetero-Michael addition to form an N-substituted iminosugar intermediate under basic conditions.

2. Results and discussion

The synthesis of N-substituted iminosugars **8** employed the introduction of 5-substituted amino and 1-*C*-2′-oxoalkyl groups (Scheme 2). Starting from D-ribose, 5-azido-C-glycoside **2** was conveniently prepared using our previously reported methods.[23] Reduction of the 5-azido group in compound **2** with triphenylphosphine successfully produced the corresponding 5-amino-C-glycoside **3** in 78% yield. Subsequent treatment of **3** with various aldehydes and $NaBH_4$ generated the corresponding 5-N-substituted *C*-glycofuranosides **4 (a–i)** (Table 1). In addition, 5-N-substituted *C*-glycofuranosides **4 (a–c)** can also be neatly synthesized by the nucleophilic substitution of mesylate **1**[29–32] using propylamine (**a**), butylamine (**b**) and hexylamine (**c**). Protection of the amino function as tertbutyloxycarbamate (Boc) afforded **5 (a–i)** in quantitative yield.

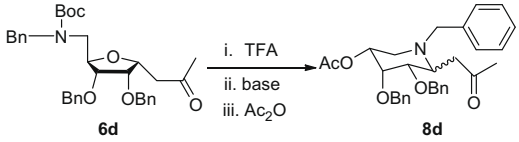
Subsequently the 1-*C*-allyl group was oxidized into glycoside (**6a–i**) with $Hg(OAc)_2$ and Jones reagent.[29–32] As expected, deprotection of the amine (giving **7**), followed by a base-mediated Michael addition, produced a pair of stereoisomers of 2′-ketonyl iminosugar. Then the 4-OH was protected by Ac_2O/Py to afford **8** (see Table 1). The configurations at C-1 were assigned by NMR and NOE analyses.

In order to investigate the influence of base to product stereoselectivity, we used 1-*C*-[5-(*N*-benzyl, *N*-boc)amino-2,3-di-*O*-benzyl-5-deoxy-α-D-ribofuranosyl]propan-2-one (**6d**) as the substrate (Scheme 3). After examining various base/solvent combinations, the ratio of α- and β-N-substituted iminosugar (**8d**) was summarized (see Table 2).

Table 1
Synthesis of compound **6** and compound **8**

Entry	R^1	Compound **6**	Yield[a] (%)	Compound **8**	Yield[b] (%)	Ratio **8α/8β**
1	C_3H_7	**6a**	78	**8a**	53	4:6
2	C_4H_9	**6b**	81	**8b**	55	3:7
3	C_6H_{13}	**6c**	75	**8c**	51	4:6
4	Bn	**6d**	55	**8d**	52	1:1
5	*p*-CH_3Bn	**6e**	52	**8e**	56	1:1
6	*p*-NO_2Bn	**6f**	50	**8f**	50	4:6
7	*p*-Cl–Bn	**6g**	58	**8g**	58	3:7
8	*o*-Cl–Bn	**6h**	50	**8h**	50	4:6
9	Thiophen-2-ylmethyl	**6i**	53	**8i**	51	1:1

[a] Isolated yield, **6a–c** over three steps from compound **1**, **6d–i** over three steps from compound **3**.
[b] Isolated yield, over three steps.



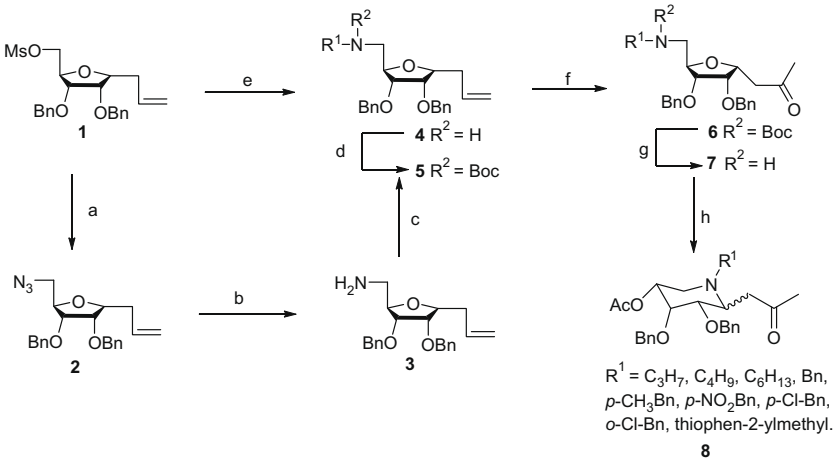
Scheme 3. Synthesis of 1-*C*-(4-*O*-acetyl-2,3-di-*O*-benzyl-5-benzylamino-5-deoxy-D-ribopyranosyl) propan-2-one.

Table 2
Synthesis of 1-*C*-(4-*O*-acetyl-2,3-di-*O*-benzyl-5-benzylamino-5-deoxy-D-ribopyranosyl)propan-2-one.

Entry	base/solvent	Ratio (α/β)	Product (%)[a]
1	$NaHCO_3$/MeOH	1:1	52
2	K_2CO_3/MeOH	4:6	72
3	Na_2CO_3/MeOH	4:6	55
4	K_2CO_3/MeCN	4:6	58
5	TEA/MeOH	4:6	56
6	NaOH/MeOH	3:7	66
7	KOH/MeOH	3:7	52
8	NaOMe/MeOH	3:7	80

[a] Isolated yield.

In conclusion, we have developed an efficient method for the synthesis of N-substituted iminosugars from 2′-carbonyl 5-N-substituted-*C*-glycofuranosides, which undergo a tandem β-elimination and intramolecular hetero-Michael addition.



Scheme 2. Synthesis of 1-*N*-alkyl iminosugars. Reagents and conditions: (a) NaN_3, DMF, 80 °C, 85%; (b) PPh_3/THF, rt, 78%; (c) RCHO, MeOH, 50 °C, 75–85%; then $NaBH_4$; (d) Et_3N, Boc_2O, rt, quant.; (e) RNH_2, 80 °C, 75–95%; (f) $Hg(OAc)_2$, Jones reagent, 85%; (g) TFA, CH_2Cl_2, 0 °C; (h) (1) $NaHCO_3$, MeOH, rt; (2) Ac_2O, Py, rt, 50–58% (from compounds **6**).

3. Experimental

3.1. General methods

All reagents were obtained from commercial suppliers and were used without further purification. CH_2Cl_2 was distilled over CaH_2. MeOH was distilled over magnesium and iodine. Reactions were monitored by thin-layer chromatography (TLC) using commercial silica gel HSGF254 plates. TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a 5% sulfuric acid in ethanol (v/v). Product purification by gravity column chromatography was performed using commercial silica gel HG/T2354-92 (200–300 mesh). ^{1}H NMR and ^{13}C NMR (600 and 150 MHz, respectively) spectra were recorded in $CDCl_3$, and TMS was used as an internal standard. HRESIMS spectra were recorded on a Bio-TOF Q instrument. Optical rotations were acquired on a Perkin–Elmer 341 digital polarimeter.

3.2. General procedure for the preparation of compounds 6a–c

Compound **1** (50.0 mg, 1.0 equiv) and RNH_2 (5.0 equiv) (R = C_3H_7, C_4H_9 and C_6H_{13}) were dissolved in DMF (1 mL). Then the reaction mixture was stirred at 80 °C, until the reaction was shown by TLC to be completed. The reaction was then quenched by the addition of water, and the aqueous solution was extracted three times with EtOAc. The combined organic solution was washed with water, satd $NaHCO_3$ and brine, then dried over $MgSO_4$ and concentrated. The residue was dissolved in 2 mL of CH_2Cl_2. Addition of triethylamine (50.0 equiv) was followed by addition of di-*tert*-butyldicarbonate (3.0 equiv). The reaction mixture was stirred for 16 h. All reagents and solvents were removed under reduced pressure to afford crude product. The crude product and $Hg(OAc)_2$ (30 mg) were dissolved in 2 mL of 4:1 acetone–water. The solution was cooled to 0 °C. Fresh Jones' reagent (0.6 mL, 5 mmol) was added dropwise. The reaction mixture was stirred until the reaction was deemed completed by TLC analysis. The reaction mixture was poured into water (15 mL) and extracted by CH_2Cl_2, and then organic phase was washed with water and brine. Purification by column chromatography (4:1 petroleum–EtOAc) gave **6a–c** as syrups.

3.2.1. 1-*C*-[2,3-Di-*O*-benzyl-5-deoxy-5-(*N*-propyl, *N*-boc)amino-α-D-ribofuranosyl]propan-2-one (6a)

Yield: 78% (over three steps). $[\alpha]_D^{25}$ 10.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 10H, Ph), 4.70 (m, 1H, H-4), 4.61–4.42 (m, 4H, PhCH_2), 4.17 (m, 1H, H-1), 4.08 (dd, 1H, *J* = 4.6, 4.5 Hz, H-2), 3.90 (m, 1H, H-3), 3.48–3.09 (m, 4H, H-5a, H-5b, N–CH_2), 2.86–2.80 (m, 2H, H-1′a, H-1′b), 2.07 (s, 3H, COCH_3), 1.54–1.48 (m, 2H, CH_2), 1.43 [s, 9H, C(CH_3)$_3$], 0.83 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 207.5 (C=O), 156.0 (–O–C=O), 138.1 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 81.2 (C-2), 79.7 (C-3), 79.3 (C-4), 78.1(C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (PhCH_2), 72.8 (PhCH_2), 49.7 (C-6), 48.6 (C-5), 44.1 (C-1′), 30.7 (COCH_3), 28.4 [C(CH_3)$_3$], 21.5 (CH_2), 11.2 (CH_3). HRESIMS: calcd for $C_{30}H_{41}NNaO_6$ $[M+Na]^+$: 534.2826; found: 534.2829.

3.2.2. 1-*C*-[2,3-Di-*O*-benzyl-5-(*N*-butyl, *N*-boc)amino-5-deoxy-α-D-ribofuranosyl]propan-2-one (6b)

Yield: 81% (over three steps). $[\alpha]_D^{25}$ 9.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 10H, Ar), 4.70 (m, 1H, H-4), 4.61–4.37 (m, 4H, PhCH_2), 4.16 (m, 1H, H-1), 4.08 (dd, 1H, *J* = 4.7, 4.4 Hz, H-2), 3.91 (m, 1H, H-3), 3.48–3.09 (m, 4H, H-5a, H-5b, N–CH_2), 2.87–2.78 (m, 2H, H-1′a, H-1′b), 2.07 (s, 3H, COCH_3), 1.43 [s, 9H, C(CH_3)$_3$], 1.28–1.22 (m, 4H, CH_2CH_2), 0.88 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 207.4 (C=O), 156.0 (–O–C=O), 138.1 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 81.2 (C-2), 79.7 (C-3), 79.3 (C-4), 78.1(C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (PhCH_2), 72.8 (PhCH_2), 48.6 (C-6), 47.7 (C-5), 44.1 (C-1′), 30.7 (COCH_3), 30.3 ($CH_3CH_2CH_2$), 28.4 [C(CH_3)$_3$], 19.9 (CH_3CH_2), 13.8 (CH_3). HRESIMS: calcd for $C_{31}H_{43}NNaO_6$ $[M+Na]^+$: 548.2983, found: 548.2971.

3.2.3. 1-*C*-[2,3-Di-*O*-benzyl-5-deoxy-5-(*N*-hexyl, *N*-boc)amino-α-D-ribofuranosyl]propan-2-one (6c)

Yield: 75% (over three steps). $[\alpha]_D^{25}$ 8.7 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 10H, Ph), 4.70 (m, 1H, H-4), 4.61–4.36 (m, 4H, PhCH_2), 4.16 (m, 1H, H-1), 4.08 (dd, 1H, *J* = 4.6, 4.3 Hz, H-2), 3.92 (m, 1H, H-3), 3.47–3.09 (m, 4H, H-5a, H-5b, N–CH_2), 2.86–2.77 (m, 2H, H-1′a, H-1′b), 2.07 (s, 3H, COCH_3), 1.43 [s, 9H, C(CH_3)$_3$], 1.29–1.22 [m, 8H, (CH_2)$_4$], 0.88 (t, 3H, *J* = 6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 207.4 (C=O), 156.0 (–O–C=O), 138.1 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 81.2 (C-2), 79.7 (C-3), 79.3 (C-4), 78.1 (C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (PhCH_2), 72.8 (PhCH_2), 48.8 (C-6), 48.0 (C-5), 44.1 (C-1′), 31.5, 30.7 (COCH_3), 28.4 [C(CH_3)$_3$], 28.1, 26.5, 22.6, 13.9 (CH_3). HRESIMS: calcd for $C_{33}H_{47}NO_6$ $[M+H]^+$: 553.3483, found: 553.3472.

3.3. General procedure for the preparation of compound 6d–i

$MgSO_4$ (anhyd, 400 mg) was added to a solution of amine **3** (50 mg, 0.125 mmol, 1.0 equiv) and aldehyde (1.1 equiv) in 2 mL of MeOH. The reaction mixture was sealed and stirred at ambient temperature for 16 h. Filtration through Celite and solvent elution (2 mL, MeOH) left a clear yellow solution that was treated with $NaBH_4$ (19 mg, 2.0 equiv) at 0 °C. After 3 h, the reaction was quenched with 3 mL of acetone and 3 mL of water and then extracted with 15 mL of EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residual oil was dissolved in 2 mL CH_2Cl_2. Addition of triethylamine (50.0 equiv) was followed by the addition of di-*tert*-butyldicarbonate (3.0 equiv). The reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure to afford the crude product. The crude product and $Hg(OAc)_2$ (30 mg) were dissolved in 2 mL 4:1 acetone–water. The solution was cooled to 0 °C. Fresh Jones' reagent (0.6 mL, 5 mmol) was added dropwise. The reaction mixture was stirred until the reaction was shown by TLC to be completed. The reaction mixture was poured into water (15 mL) and was extracted by CH_2Cl_2. The organic phase was washed with water and brine. Purification by column chromatography (4:1petroleum–EtOAc) gave **6** as a syrup.

3.3.1. 1-*C*-[2,3-Di-*O*-benzyl-5-(*N*-benzyl, *N*-boc)amino-5-deoxy-α-D-ribofuranosyl]propan-2-one (6d)

Yield: 55% (over three steps). $[\alpha]_D^{25}$ 13.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 15H, Ar), 4.72 (m, 1H, H-4), 4.60–4.34 (m, 6H, ArCH_2), 4.22 (d, 1H, *J* = 4.1 Hz, H-1), 4.05 (d, 1H, *J* = 4.3 Hz, H-2), 3.80 (m, 1H, H-3), 3.50–2.787 (m, 4H, H-5a, H-5b, N–CH_2), 2.07 (s, 3H, COCH_3), 1.43 [s, 9H, C(CH_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.4 (C=O), 156.0 (–O–C=O), 138.5 (Ar), 138.2 (Ar), 138.0 (Ar), 137.7 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.2 (Ar), 81.4 (C-2), 79.9 (C-3), 79.5 (C-4), 77.9 (C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (PhCH_2), 72.9 (PhCH_2), 51.3 (PhCH_2–N), 48.6 (C-6), 48.1 (C-5), 44.0 (C-1′), 30.7 (COCH_3), 28.4 [C(CH_3)$_3$]. HRESIMS: calcd for $C_{34}H_{41}NNaO_6$ $[M+Na]^+$: 582.2826, found: 582.2824.

3.3.2. 1-*C*-[2,3-Di-*O*-benzyl-5-deoxy-5-(*N*-*p*-methylbenzyl, *N*-boc)amino-α-D-ribofuranosyl]propan-2-one (6e)

Yield: 52% (over three steps). $[\alpha]_D^{25}$ 13.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.28 (m, 10H, Ar), 7.10–7.08 (m, 4H, Ar), 4.71 (m, 1H, H-4), 4.59–4.34 (m, 6H, ArCH_2), 4.22 (br s, 1H, H-1), 4.05 (d, 1H, *J* = 4.3 Hz, H-2), 3.85 (m, 1H, H-3), 3.47–2.77 (m, 4H, H-5a, H-5b, N–CH_2), 2.31 (s, 3H, *p*-CH_3–Ph), 2.07 (s, 3H, COCH_3), 1.43 [s, 9H, C(CH_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.4 (C=O), 156.0 (–O–C=O),

138.2 (Ar), 136.6 (Ar), 135.3 (Ar), 129.1 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 81.4 (C-2), 79.9 (C-3), 79.6 (C-4), 78.0 (C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (Ph*C*H_2), 72.8 (Ph*C*H_2), 50.9 (*p*-CH_3–Ph*C*H_2), 48.4 (C-6), 47.8 (C-5), 44.0 (C-1′), 30.7 (CO*C*H_3), 28.4 [C(*C*H_3)$_3$], 21.0 (*p*-*C*H_3–Ph). HRESIMS: calcd for $C_{35}H_{43}NNaO_6$ $[M+Na]^+$: 596.2983, found: 596.2966.

3.3.3. 1-*C*-[2,3-Di-*O*-benzyl-5-deoxy-5-(*N*-*p*-nitrobenzyl, *N*-boc)amino-α-D-ribofuranosyl]propan-2-one (6f)

Yield: 50% (over three steps). $[\alpha]_D^{25}$ 16.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 8.1 Hz, Ar), 7.35–7.28 (m, 12H, Ar), 4.76 (m, 1H, H-4), 4.64–4.34 (m, 6H, ArCH_2), 4.20 (m, 1H, H-1), 4.05 (d, 1H, *J* = 4.3 Hz, H-2), 3.81 (m, 1H, H-3), 3.59–2.76 (m, 4H, H-5a, H-5b, N–*C*H_2), 2.07 (s, 3H, CO*C*H_3), 1.43 [s, 9H, C(*C*H_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.0 (C=O), 155.6 (–O–C=O), 147.1 (Ar), 138.1(Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.5 (Ar), 123.6 (Ar), 81.7 (C-2), 80.5 (C-3), 79.3 (C-4), 77.6 (C-1), 75.6 [*C*(CH_3)$_3$], 73.6 (Ph*C*H_2), 73.0 (Ph*C*H_2), 51.2 (*p*-NO_2–Ph*C*H_2), 50.3 (C-6), 48.9 (C-5), 43.8 (C-1′), 30.7 (CO*C*H_3), 28.3 [C(*C*H_3)$_3$]. HRESIMS: calcd for $C_{34}H_{40}N_2NaO_8$ $[M+Na]^+$: 627.2677, found: 627.2649.

3.3.4. 1-*C*-[2,3-Di-*O*-benzyl-5-(*N*-*p*-chlorobenzyl, *N*-boc)amino-5-deoxy-α-D-ribofuranosyl]propan-2-one (6g)

Yield: 58% (over three steps). $[\alpha]_D^{25}$ 12.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.27 (m, 12H, Ar), 7.15–7.12 (m, 2H, Ar), 4.73 (m, 1H, H-4), 4.61–4.30 (m, 6H, ArCH_2), 4.19 (d, 1H, *J* = 4.3 Hz, H-1), 4.05 (d, 1H, *J* = 4.3 Hz, H-2), 3.85 (m, 1H, H-3), 3.50–2.77 (m, 4H, H-5a, H-5b, N–*C*H_2), 2.07 (s, 3H, CO*C*H_3), 1.43 [s, 9H, C(*C*H_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 155.8 (–O–C=O), 138.1(Ar), 137.9 (Ar), 137.6 (Ar), 137.1 (Ar), 136.8 (Ar), 132.7 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 81.5 (C-2), 80.1 (C-3), 79.4 (C-4), 77.8 (C-1), 75.5 [*C*(CH_3)$_3$], 73.5 (Ph*C*H_2), 72.9 (Ph*C*H_2), 50.8 (*p*-Cl–Ph*C*H_2), 49.8 (C-6), 48.9 (C-5), 43.9 (C-1′), 30.7 (CO*C*H_3), 29.6, 28.3 [C(*C*H_3)$_3$]. HRESIMS: calcd for $C_{34}H_{40}ClNNaO_6$ $[M+Na]^+$: 616.2436, found: 616.2410.

3.3.5. 1-*C*-[2,3-Di-*O*-benzyl-5-(*N*-*o*-chlorobenzyl, *N*-boc)amino-5-deoxy-α-D-ribofuranosyl]propan-2-one (6h)

Yield: 50% (over three steps). $[\alpha]_D^{25}$ 19.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.28 (m, 11H, Ar), 7.21–7.16 (m, 3H, Ar), 4.72 (m, 1H, H-4), 4.63–4.36 (m, 6H, ArCH_2), 4.22 (br s, 1H, H-1), 4.08 (d, 1H, *J* = 4.3 Hz, H-2), 3.86 (m, 1H, H-3), 3.57–2.76 (m, 4H, H-5a, H-5b, N–*C*H_2), 2.06 (s, 3H, CO*C*H_3), 1.43 [s, 9H, C(*C*H_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.0 (C=O), 156.0 (–O–C=O), 138.2 (Ar), 138.0 (Ar), 137.7 (Ar), 136.0 (Ar), 133.3 (Ar), 132.8 (Ar), 129.4 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 126.7 (Ar), 81.5 (C-2), 80.1 (C-3), 79.2 (C-4), 77.8 (C-1), 75.6 (*C*(CH_3)$_3$), 73.5 (Ph*C*H_2), 72.9 (Ph*C*H_2), 49.2 (*p*-Cl–Ph*C*H_2), 48.7 (C-6), 48.3 (C-5), 44.0 (C-1′), 30.7 (CO*C*H_3), 28.2[C(*C*H_3)$_3$]. HRESIMS: calcd for $C_{34}H_{40}ClNNaO_6$ $[M+Na]^+$: 616.2436, found: 616.2455.

3.3.6. 1-*C*-[2,3-Di-*O*-benzyl-5-deoxy-5-[*N*-(thiophen-2-ylmethyl), *N*-boc]amino-α-D-ribofuranosyl]propan-2-one (6i)

Yield: 53% (over three steps). $[\alpha]_D^{25}$ 14.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–7.28 (m, 10H, Ph), 7.19 (m, 1H, thiophen), 6.90 (d, 2H, *J* = 4.2 Hz, thiophen), 4.76 (m, 1H, H-4), 4.71–4.49 (m, 4H, Ph*C*H_2), 4.46–4.40 (m, 2H, thiophen-*C*H_2), 4.21 (d, 1H, *J* = 4.8 Hz, H-1), 4.05(d, 1H, *J* = 4.3 Hz, H-2), 3.86 (m, 1H, H-3), 3.48–2.78 (m, 4H, H-5a, H-5b, N–*C*H_2), 2.08 (s, 3H, CO*C*H_3), 1.49 [s, 9H, C(*C*H_3)$_3$]; ^{13}C NMR ($CDCl_3$): δ 207.3 (C=O), 155.4 (-O-C=O), 141.1 (thiophen C-1), 138.2 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 126.3 (thiophen), 125.0 (thiophen), 81.3 (C-2), 80.3 (C-3), 79.7 (C-4), 77.9 (C-1), 75.5 [*C*(CH_3)$_3$], 73.4 (Ph*C*H_2), 72.9 (Ph*C*H_2), 47.5 (C-6), 46.3 (C-5), 44.0 (C-1′), 30.7 (CO*C*H_3), 28.4 [C(*C*H_3)$_3$]. HRESIMS: calcd for $C_{32}H_{39}NNaO_6S$ $[M+Na]^+$: 588.2390, found: 588.2391.

3.4. General procedure for the preparation of compounds 8a–i

Compound **6** (100 mg) was dissolved in 5 mL of CH_2Cl_2. The solution was cooled to 0 °C. Trifluoroacetic acid (1 mL, 13.5 mmol) was added slowly. After 1 h the solution was co-distilled with toluene (2 × 5 mL), and the crude product was then generally used directly in the next step. The crude product was then dissolved in MeOH (2 mL), followed by the addition of $NaHCO_3$ (50 mg). After 8 h, the reaction mixture was concentrated by rotary evaporation; then it was poured into water (10 mL) and was extracted by CH_2Cl_2. The organic phase was washed with water and brine, dried with $MgSO_4$ and concentrated. The crude syrup was dissolved in 0.25 mL of pyridine, and 0.3 mL of Ac_2O was added. The solution was stirred at room temperature. After 20 h, the reaction mixture was poured into water (5 mL) and extracted by CH_2Cl_2. The organic phase was washed with satd $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated. The residual oil was purified by silica gel chromatography (3:1–1:1 petroleum–EtOAc) to afford products **8a–i**.

3.4.1. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-deoxy-5-propylamino-D-ribopyranosyl)propan-2-one (8a)

Yield: 53% (over three steps).

(**8a**–**α**) $[\alpha]_D^{25}$ 36.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.39–7.25 (m, 10H, Ph), 4.78–4.76 (m, 2H, H-4, Ph*C*H_2), 4.69 (d, 1H, *J* = 11.9 Hz, Ph*C*H_2), 4.57 (d, 1H, *J* = 11.8 Hz, Ph*C*H_2), 4.46 (d, 1H, *J* = 11.8 Hz, Ph*C*H_2), 4.11 (br s, 1H, H-3), 3.83 (m, 1H, H-1), 3.61 (m, 1H, H-2), 3.15 (dd, 1H, $J_{5a,5b}$ = 16.4, $J_{5a,4}$ = 5.5 Hz, H-5a), 2.73 (dd, 1H, *J* = 11.2, 11.1 Hz, N–*C*H_2CH$_2$CH$_3$), 2.61–2.55 (m, 2H, H-5b, N–*C*H_2CH$_2$CH$_3$), 2.42 (m, 1H, H-1′a), 2.35 (m, 1H, H-1′b), 2.08 (s, 3H, COCH_3), 1.98 (s, 3H, OCO*C*H_3), 1.45–1.42 (m, 2H, N–CH$_2$*C*H_2CH$_3$), 0.83 (t, 3H, *J* = 7.3 Hz, N–CH$_2$CH$_2$*C*H_3); ^{13}C NMR ($CDCl_3$): δ 209.3 (C=O), 170.2 (–O–C=O), 139.0 (Ar), 138.2 (Ar), 128.3 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 76.6 (C-2), 76.5 (C-3), 74.7 (C-4), 71.2 (Ph*C*H_2), 70.0 (Ph*C*H_2), 56.0 (N–*C*H_2CH$_2$CH$_3$), 55.2 (C-5), 44.3 (C-1), 37.4 (C-1′), 31.1 (CO*C*H_3), 21.0 (OCO*C*H_3, N–CH$_2$*C*H_2CH$_3$), 11.6 (N–CH$_2$CH$_2$*C*H_3). HRESIMS: calcd for $C_{27}H_{36}NO_5$ $[M+H]^+$: 454.2588, found: 454.2567.

(**8a**–**β**) $[\alpha]_D^{25}$ 10.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.25 (m, 10H, Ph), 4.84 (m, 1H, H-4), 4.76 (d, 1H, *J* = 12.2 Hz, Ph*C*H_2), 4.64 (d, 1H, *J* = 12.1 Hz, Ph*C*H_2), 4.59 (d, 1H, *J* = 11.5 Hz, Ph*C*H_2), 4.39 (d, 1H, *J* = 11.5 Hz, Ph*C*H_2), 4.17 (br s, 1H, H-3), 3.38 (m, 1H, H-1), 3.29 (d, 1H, *J* = 9.5 Hz, H-2), 2.83–2.76 (m, 2H, N–*C*H_2CH$_2$CH$_3$, H-5a), 2.66 (dd, 1H, $J_{5a,5b}$ = 16.1, $J_{5a,4}$ = 5.6 Hz, H-5b), 2.55–2.46 (m, 2H, N–*C*H_2CH$_2$CH$_3$, H-1′a), 2.33 (m, 1H, H-1′b), 2.09 (s, 3H, COCH_3), 2.00 (s, 3H, OCO*C*H_3), 1.44–1.42 (m, 2H, N–CH$_2$*C*H_2CH$_3$), 0.82 (t, 3H, *J* = 7.1 Hz, N–CH$_2$CH$_2$*C*H_3); ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 170.3 (–O–C=O), 138.9 (Ar), 137.6 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 79.8 (C-2), 74.0 (C-3), 72.9 (C-4), 71.3 (Ph*C*H_2), 70.1 (Ph*C*H_2), 55.8 (N–*C*H_2CH$_2$CH$_3$), 53.9 (C-5), 48.7 (C-1), 45.4 (C-1′), 30.0 (CO*C*H_3), 21.0 (OCO*C*H_3), 19.5 (N–CH$_2$*C*H_2CH$_3$), 11.6 (N–CH$_2$CH$_2$*C*H_3). HRESIMS: calcd for $C_{27}H_{36}NO_5$ $[M+H]^+$: 454.2588, found: 454.2553.

3.4.2. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-butylamino-5-deoxy-D-ribopyranosyl)propan-2-one (8b)

Yield: 55% (over three steps).

(**8b**–**α**) $[\alpha]_D^{25}$ 47.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.27 (m, 10H, Ph), 4.79–4.76 (m, 2H, H-4, Ph*C*H_2), 4.70 (d, 1H, *J* = 12.6 Hz, Ph*C*H_2), 4.57 (d, 1H, *J* = 11.7 Hz, Ph*C*H_2), 4.46 (d, 1H, *J* = 11.7 Hz, Ph*C*H_2), 4.11 (br s, 1H, H-3), 3.83 (d, 1H, *J* = 4.4 Hz, H-1), 3.60 (m, 1H, H-2), 3.16 (dd, 1H, $J_{5a,5b}$ = 16.3, $J_{5a,4}$ = 5.6 Hz, H-5a), 2.73 (t, 1H, *J* = 11.1 Hz, N–*C*H_2CH$_2$C$_2$HCH$_3$), 2.61–2.56 (m, 2H, H-5b, N–*C*H_2CH$_2$CH$_2$CH$_3$), 2.45 (m, 1H, H-1′a), 2.36 (m, 1H, H-1′b), 2.08 (s, 3H, COCH_3), 2.00 (s, 3H, OCO*C*H_3), 1.42–1.39 (m, 2H,

N–$CH_2CH_2CH_2CH_3$), 1.30–1.21 (m, 2H, N–$CH_2CH_2CH_2CH_3$), 0.88 (t, 3H, J = 7.2 Hz, N–$CH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 209.3 (C=O), 170.2 (–O–C=O), 139.0 (Ar), 138.2 (Ar), 128.4 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 76.6 (C-2), 76.4 (C-3), 74.7 (C-4), 71.2 (PhCH_2), 70.0 (PhCH_2), 55.3 (N–$CH_2CH_2CH_2CH_3$), 53.8 (C-5), 44.3 (C-1), 37.4 (C-1′), 31.1 ($COCH_3$), 30.0 (N–$CH_2CH_2CH_2CH_3$), 21.0 ($OCOCH_3$), 20.3 (N–$CH_2CH_2CH_2CH_3$), 13.9 (N–$CH_2CH_2CH_2CH_3$). HRESIMS: calcd for $C_{28}H_{38}NO_5$ $[M+H]^+$: 468.2744, found: 468.2754.

(**8b**–**β**) $[\alpha]_D^{25}$ 6.4 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.24 (m, 10H, Ph), 4.81 (m, 1H, H-4), 4.76 (d, 1H, J = 12.1 Hz, PhCH_2), 4.65 (d, 1H, J = 12.1 Hz, PhCH_2), 4.58 (d, 1H, J = 11.5 Hz, PhCH_2), 4.38 (d, 1H, J = 11.6 Hz, PhCH_2), 4.17 (br s, 1H, H-3), 3.38 (m, 1H, H-1), 3.30 (d, 1H, J = 8.0 Hz, H-2), 2.80–2.78 (m, 2H, N–$CH_2CH_2C_2HCH_3$, H-5a), 2.65 (dd, 1H, $J_{5a,5b}$ = 16.3, $J_{4,5b}$ = 5.2 Hz, H-5b), 2.57–2.53 (m, 2H, N–$CH_2CH_2C_2HCH_3$, H-1′a), 2.36 (m, 1H, H-1′b), 2.09 (s, 3H, $COCH_3$), 2.01 (s, 3H, $OCOCH_3$), 1.42–1.39 (m, 2H, N–$CH_2CH_2CH_2CH_3$), 1.26–1.24 (m, 2H, N–$CH_2CH_2CH_2CH_3$), 0.88 (t, 3H, J = 7.1 Hz, N–$CH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 170.2 (–O–C=O), 138.9 (Ar), 137.6 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 79.8 (C-2), 74.0 (C-3), 72.9 (C-4), 71.3 (PhCH_2), 70.1 (PhCH_2), 55.8 (N–$CH_2CH_2CH_2CH_3$), 53.9 (C-5), 48.7 (C-1), 45.3 (C-1′), 30.0 ($COCH_3$), 21.0 ($OCOCH_3$), 20.4 (N–$CH_2CH_2CH_2CH_3$), 19.7 (N–$CH_2CH_2CH_2CH_3$), 13.9 (N–$CH_2CH_2CH_2CH_3$). HRESIMS: calcd for $C_{28}H_{38}NO_5$ $[M+H]^+$: 468.2744, found: 468.2735.

3.4.3. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-deoxy-5-hexylamino-D-ribopyranosyl)propan-2-one (8c)

Yield: 51% (over three steps).

(**8c**–**α**) $[\alpha]_D^{25}$ 50.0 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.25 (m, 10H, Ph), 4.78–4.75 (m, 2H, H-4, PhCH_2), 4.69 (d, 1H, J = 12.1 Hz, PhCH_2), 4.57 (d, 1H, J = 11.6 Hz, PhCH_2), 4.46 (d, 1H, J = 11.8 Hz, PhCH_2), 4.11 (br s, 1H, H-3), 3.83 (d, 1H, J = 4.8 Hz, H-1), 3.60 (m, 1H, H-2), 3.15 (dd, 1H, $J_{5a,5b}$ = 16.3, $J_{5a,4}$ = 5.5 Hz, H-5a), 2.73 [dd, 1H, J = 11.2, 11.0 Hz, N–$CH_2(CH_2)_4CH_3$], 2.61–2.57 [m, 2H, H-5b, N–$CH_2(CH_2)_4CH_3$], 2.45 (m, 1H, H-1′a), 2.35 (m, 1H, H-1′b), 2.08 (s, 3H, $COCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.47–1.41 [m, 2H, N–$CH_2CH_2(CH_2)_3CH_3$], 1.28–1.24 [m, 6H, N–$CH_2CH_2(CH_2)_3CH_3$], 0.87 [t, 3H, J = 6.9 Hz, N–$CH_2(CH_2)_4CH_3$]; ^{13}C ($CDCl_3$): δ 209.3 (C=O), 170.2 (–O–C=O), 139.0 (Ar), 138.2 (Ar), 128.3 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 76.6 (C-2), 76.5 (C-3), 74.7 (C-4), 71.2 (PhCH_2), 70.1 (PhCH_2), 55.2 [N–$CH_2(CH_2)_4CH_3$], 54.1 (C-5), 44.3 (C-1), 37.4 (C-1′), 31.6 [N–$CH_2(CH_2)_2CH_2CH_2CH_3$], 31.1 ($COCH_3$), 27.8, 26.8 [N–$CH_2CH_2CH_2(CH_2)_2CH_3$], 22.6, 21.0 ($OCOCH_3$), 20.3, 14.0 [N–$CH_2(CH_2)_4CH_3$]. HRESIMS: calcd for $C_{30}H_{41}NaNO_5$ $[M+Na]^+$: 518.2933, found: 518.2931.

(**8c**–**β**) $[\alpha]_D^{25}$ 11.4 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.24 (m, 10H, Ph), 4.80 (m, 1H, H-4), 4.76 (d, 1H, J = 12.2 Hz, PhCH_2), 4.65 (d, 1H, J = 12.2 Hz, PhCH_2), 4.58 (d, 1H, J = 11.4 Hz, PhCH_2), 4.38 (d, 1H, J = 11.5 Hz, PhCH_2), 4.17 (br s, 1H, H-3), 3.37 (m, 1H, H-1), 3.29 (d, 1H, J = 9.1 Hz, H-2), 2.82–2.78 [m, 2H, N–$CH_2(CH_2)_4CH_3$, H-5a], 2.65 (dd, 1H, $J_{5a,5b}$ = 16.2, $J_{4,5b}$ = 5.2 Hz, H-5b), 2.54–2.51 (m, 2H, N–$CH_2CH_2CH_3$, H-1′a), 2.35 (m, 1H, H-1′b), 2.09 (s, 3H, $COCH_3$), 2.01 (s, 3H, $OCOCH_3$), 1.42–1.39 [m, 2H, N–$CH_2CH_2(CH_2)_3CH_3$], 1.29–1.18 [m, 6H, N–$CH_2CH_2(CH_2)_3CH_3$], 0.86 (t, 3H, J = 6.9 Hz, N–$CH_2(CH_2)_4CH_3$); ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 170.3 (–O–C=O), 138.9 (Ar), 137.6 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 79.9 (C-2), 74.0 (C-3), 72.9 (C-4), 71.3 (PhCH_2), 70.1 (PhCH_2), 55.8 [N–$CH_2(CH_2)_4CH_3$], 52.2 (C-5), 48.8 (C-1), 45.3 (C-1′), 31.7 [N–$CH_2(CH_2)_2CH_2CH_2CH_3$], 30.0 ($COCH_3$), 27.0, 26.3, 22.5, 21.0 ($OCOCH_3$), 14.0 [N–$CH_2(CH_2)_4CH_3$]. HRESIMS: calcd for $C_{30}H_{41}NaNO_5$ $[M+Na]^+$: 518.2933, found: 518.2911.

3.4.4. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-benzylamino-5-deoxy-D-ribopyranosyl)propan-2-one (8d)

Yield: 52% (over three steps).

(**8d**–**α**) $[\alpha]_D^{25}$ 63.0 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.39–7.21 (m, 15H, Ar), 4.78 (d, 1H, J = 11.9 Hz, PhCH_2), 4.74 (m, 1H, H-4), 4.68 (d, 1H, J = 11.9 Hz, PhCH_2), 4.56 (d, 1H, J = 11.7 Hz, PhCH_2), 4.48 (d, 1H, J = 11.9 Hz, PhCH_2), 4.16 (br s, 1H, H-3), 3.95 (m, 1H, H-1), 3.79 (d, 1H, J = 13.5 Hz, N–CH_2–Ph), 3.70 (dd, 1H, $J_{2,3}$ = 5.3, $J_{1,2}$ = 2.6 Hz, H-2), 3.45 (d, 1H, J = 13.5 Hz, N–CH_2–Ph), 3.22 (dd, 1H, $J_{5a,5b}$ = 16.5, $J_{4,5a}$ = 5.3 Hz, H-5a), 2.78–2.71 (m, 2H, H-1′a, H-5b), 2.46 (dd, 1H, $J_{1'a,1'b}$ = 11.3, $J_{1'b,1}$ = 5.3 Hz, H-1′b), 2.08 (s, 3H, $COCH_3$), 1.93 (s, 3H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$): δ 209.1 (C=O), 170.2 (–O–C=O), 138.8 (Ar), 138.2 (Ar), 128.4 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.1 (Ar), 76.7 (C-2), 76.2 (C-3), 74.8 (C-4), 71.2 (PhCH_2), 69.9 (PhCH_2), 58.6 (N–CH_2–Ph), 55.9 (C-5), 43.1(C-1), 38.0 (C-1′), 30.9 ($COCH_3$), 21.0 ($OCOCH_3$). HRESIMS: calcd for $C_{31}H_{36}NO_5$ $[M+H]^+$: 502.2588, found: 502.2586.

(**8d**–**β**) $[\alpha]_D^{25}$ 22.0 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.21 (m, 15H, Ar), 4.80 (m, 1H, H-4), 4.77 (d, 1H, J = 12.1 Hz, PhCH_2), 4.65 (d, 1H, J = 8.2 Hz, PhCH_2), 4.63 (d, 1H, J = 7.4 Hz, PhCH_2), 4.42 (d, 1H, J = 11.6 Hz, PhCH_2), 4.21 (br s, 1H, H-3), 3.80 (d, 1H, J = 13.5 Hz, N–CH_2–Ph), 3.48 (m, 1H, H-1), 3.40 (d, 1H, J = 8.8 Hz, H-2), 3.32 (d, 1H, J = 13.5 Hz, N–CH_2–Ph), 2.83 (dd, 1H, $J_{5a,5b}$ = 16.4, $J_{4,5a}$ = 3.9 Hz, H-5a), 2.71 (dd, 1H, J = 11.1, 11.0 Hz, H-5b), 2.63–2.58 (m, 2H, H-1′), 2.06 (s, 3H, $COCH_3$), 1.93 (s, 3H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 170.2 (-O-C=O), 139.1 (Ar), 138.9 (Ar), 137.6 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 127.8 (Ar), 127.6 (Ar), 127.4 (Ar), 127.0 (Ar), 79.5 (C-2), 74.1 (C-3), 72.9 (C-4), 71.3 (PhCH_2), 69.8 (PhCH_2), 56.7 (N–CH_2–Ph), 56.3 (C-5), 48.9 (C-1), 45.3 (C-1′), 30.1 ($COCH_3$), 21.0 ($OCOCH_3$). HRESIMS: calcd for $C_{31}H_{36}NO_5$ $[M+H]^+$: 502.2588, found: 502.2568.

3.4.5. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-deoxy-5-*p*-methylbenzylamino-D-ribopyranosyl)propan-2-one (8e)

Yield: 56% (over three steps).

(**8e**–**α**) $[\alpha]_D^{25}$ 63 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.24 (m, 10H, Ar), 7.13 (d, 2H, J = 7.4 Hz, p-CH_3–Ph), 7.09 (d, 2H, J = 7.6 Hz, p-CH_3–Ph), 4.77 (d, 1H, J = 11.8 Hz, PhCH_2), 4.74 (m, 1H, H-4), 4.67 (d, 1H, J = 11.8 Hz, PhCH_2), 4.57 (d, 1H, J = 11.6 Hz, PhCH_2), 4.47 (d, 1H, J = 11.6 Hz, PhCH_2), 4.15 (br s, 1H, H-3), 3.94 (d, 1H, J = 5.0 Hz, H-1), 3.74 (d, 1H, J = 13.4 Hz, N–CH_2–Ar), 3.69 (m, 1H, H-2), 3.40 (d, 1H, J = 13.4 Hz, N-CH_2-Ar), 3.21 (dd, 1H, $J_{5a,5b}$ = 16.7, $J_{4,5a}$ = 5.22 Hz, H-5a), 2.74–2.70 (m, 2H, H-1′), 2.46 (dd, 1H, J = 11.0, 4.3 Hz, H-5b), 2.32 (s, 3H, p-CH_3–Ph), 2.09 (s, 3H, $COCH_3$), 1.93 (s, 3H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$): δ 209.1 (C=O), 170.1 (–O–C=O), 138.9 (Ar), 138.2 (Ar), 136.7 (Ar), 135.7 (Ar), 129.0 (Ar), 128.4 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 76.3 (C-2, C-3), 74.7 (C-4), 71.2 (PhCH_2), 69.9 (PhCH_2), 58.3 (N-CH_2-Ar), 55.9 (C-5), 43.0 (C-1), 37.9 (C-1′), 30.9 ($COCH_3$), 21.1 ($OCOCH_3$), 21.0 (p-CH_3–Ph). HRESIMS: calcd for $C_{32}H_{38}NO_5$ $[M+H]^+$: 516.2744, found: 516.2735.

(**8e**-**β**) $[\alpha]_D^{25}$ 4.2 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.22 (m, 10H, Ar), 7.15–7.08 (m, 4H, Ar), 4.78 ((m, 1H, H-4), 4.77 (d, 1H, J = 11.9 Hz, PhCH_2), 4.64 (d, 1H, J = 11.8 Hz, PhCH_2), 4.62 (d, 1H, J = 11.8 Hz, PhCH_2), 4.43 (d, 1H, J = 11.8 Hz, PhCH_2), 4.21 (br s, 1H, H-3), 3.76 (d, 1H, J = 12.7 Hz, N-CH_2-Ar), 3.46 (br s, 1H, H-1), 3.40 (d, 1H, J = 8.6 Hz, H-2), 3.28 (d, 1H, J = 13.3 Hz, N-CH_2-Ar), 2.83 (dd, 1H, J = 16.5, 3.9 Hz, H-5a), 2.69 (dd, 1H, J = 11.2, 11.1 Hz, H-5b), 2.64–2.58 (m, 2H, H-1′), 2.31 (s, 3H, p-CH_3–Ph), 2.07 (s, 3H, $OCOCH_3$), 1.93 (s, 3H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$): δ 207.2 (C=O), 170.2 (–O–C=O), 138.9 (Ar), 137.6 (Ar), 136.6 (Ar), 135.9 (Ar), 129.0 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.6 (Ar), 127.4 (Ar), 79.5 (C-2), 74.0 (C-3), 72.9 (C-4), 71.3 (PhCH_2), 69.8 (PhCH_2), 56.7 (N-CH_2-Ar), 56.3 (C-5), 48.8 (C-1), 45.3 (C-1′), 30.1 ($COCH_3$), 21.0 ($OCOCH_3$). HRESIMS: calcd for $C_{32}H_{38}NO_5$ $[M+H]^+$: 516.2744, found: 516.2725.

3.4.6. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-deoxy-5-*p*-nitrobenzylamino-D-ribopyranosyl)propan-2-one (8f)

Yield: 50% (over three steps).

(**8f**–**α**) $[\alpha]_D^{25}$ 45.7 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 8.5 Hz, Ar), 7.42 (d, 2H, *J* = 7.7 Hz, Ar), 7.37–7.28 (m, 10H, Ar), 4.80–4.75 (m, 2H, PhCH_2, H-4), 4.70 (d, 1H, *J* = 11.9 Hz, PhCH_2), 4.55 (d, 1H, *J* = 11.6 Hz, PhCH_2), 4.48 (d, 1H, *J* = 11.6 Hz, PhCH_2), 4.15 (br s, 1H, H-3), 3.90 (m, 1H, H-1), 3.87 (d, 1H, *J* = 13.8 Hz, N-CH_2-Ar), 3.70 (m, 1H, H-2), 3.55 (d, 1H, *J* = 14.2 Hz, N-CH_2-Ar), 3.25 (dd, 1H, $J_{5a,5b}$ = 17.1, $J_{5a,4}$ = 4.6 Hz, H-5a), 2.79 (dd, 1H, *J* = 11.2, 10.3 Hz, H-1′a), 2.73 (dd, 1H, $J_{5a,5b}$ = 17.3, $J_{4,5b}$ = 5.0 Hz, H-5b), 2.41 (d, 1H, *J* = 7.7 Hz, H-1′b), 2.12 (s, 3H, COCH_3), 1.96 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 208.7 (C=O), 170.1 (–O–C=O), 147.3 (Ar), 138.7 (Ar), 137.9 (Ar), 128.8 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 123.6 (Ar), 76.4 (C-2), 76.0 (C-3), 74.8 (C-4), 71.2 (PhCH_2), 69.8 (PhCH_2), 57.8 (N-CH_2-Ar), 55.5 (C-5), 43.5 (C-1), 37.9 (C-1′), 30.9 (COCH_3), 20.9 (OCOCH_3). HRESIMS: calcd for $C_{31}H_{34}N_2NaO_7$ $[M+Na]^+$: 569.2258, found: 569.2270.

(**8f**–**β**) $[\alpha]_D^{25}$ 11.5 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.14 (d, 2H, *J* = 8.7 Hz, Ar), 7.43 (d, 2H, *J* = 8.1 Hz, Ar), 7.37–7.26 (m, 10H, Ph), 4.81 (d, 1H, *J* = 9.5 Hz, H-4), 4.77 (d, 1H, *J* = 12.0 Hz, PhCH_2), 4.67 (d, 1H, *J* = 11.9 Hz, PhCH_2), 4.63 (d, 1H, *J* = 11.5 Hz, PhCH_2), 4.42 (d, 1H, *J* = 11.4 Hz, PhCH_2), 4.22 (br s, 1H, H-3), 3.86 (d, 1H, *J* = 14.8 Hz, N-CH_2-Ar), 3.53 (br s, 1H, H-1), 3.46 (d, 1H, *J* = 14.8 Hz, N-CH_2-Ar), 3.40 (d, 1H, *J* = 9.1 Hz, H-2), 2.86 (dd, 1H, $J_{5a,5b}$ = 16.8, $J_{5a,4}$ = 3.8 Hz, H-5a), 2.77 (dd, 1H, *J* = 11.2, 10.8 Hz, H-5b), 2.64–2.59 (m, 2H, H-1′), 2.06 (s, 3H, COCH_3), 1.95 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 207.0 (C=O), 170.2 (–O–C=O), 147.2 (Ar), 138.7 (Ar), 137.5 (Ar), 128.8 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 79.9 (C-2), 74.1 (C-3), 72.8 (C-4), 71.4 (PhCH_2), 69.5 (PhCH_2), 56.1 (N–CH_2–Ph), 55.8 (C-5), 49.1 (C-1), 45.1 (C-1′), 30.1 (COCH_3), 20.9 (OCOCH_3). HRESIMS: calcd for $C_{31}H_{34}N_2NaO_7$ $[M+Na]^+$: 569.2258, found: 569.2256.

3.4.7. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-*p*-chlorobenzylamino-5-deoxy-D-ribopyranosyl)propan-2-one (8g)

Yield: 58% (over three steps).

(**8g**–**α**) $[\alpha]_D^{25}$ 60.3 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36–7.26 (m, 12H, Ar), 7.18 (d, 2H, *J* = 7.8 Hz, Ar), 4.78 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.73 (m, 1H, H-4), 4.68 (d, 1H, *J* = 12.0 Hz, PhCH_2), 4.55 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.47 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.15 (br s, 1H, H-3), 3.92 (m, 1H, H-1), 3.74 (d, 1H, *J* = 13.9 Hz, N-CH_2-Ar), 3.67 (d, 1H, *J* = 2.2 Hz, H-2), 3.41 (d, 1H, *J* = 13.6 Hz, N-CH_2-Ar), 3.22 (dd, 1H, $J_{5a,5b}$ = 16.8, $J_{5a,4}$ = 4.8 Hz, H-5a), 2.74–2.69 (m, 2H, H-1′), 2.42 (dd, 1H, $J_{5a,5b}$ = 10.8, $J_{4,5b}$ = 4.2 Hz, H-5b), 2.09 (s, 3H, COCH_3), 1.95 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 209.0 (C=O), 170.1 (–O–C=O), 138.9 (Ar), 138.0 (Ar), 137.3 (Ar), 132.8 (Ar), 129.7 (Ar), 128.4 (Ar), 128.2 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 76.6 (C-2), 76.2 (C-3), 74.8 (C-4), 71.2 (PhCH_2), 69.9 (PhCH_2), 57.8 (N-CH_2-Ar), 55.7 (C-5), 43.1 (C-1), 38.0 (C-1′), 30.9 (COCH_3), 21.0 (OCOCH_3). HRESIMS: calcd for $C_{31}H_{35}ClNO_5$ $[M+H]^+$: 536.2198, found: 536.2186.

(**8g**–**β**) $[\alpha]_D^{25}$ 11.4 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36–7.24 (m, 12H, Ar), 7.18 (d, 2H, *J* = 7.2 Hz, Ar), 4.79–4.75 (m, 2H, H-4, PhCH_2), 4.65 (d, 1H, *J* = 11.6 Hz, PhCH_2), 4.63 (d, 1H, *J* = 11.2 Hz, PhCH_2), 4.41 (d, 1H, *J* = 11.5 Hz, PhCH_2), 4.20 (br s, 1H, H-3), 3.74 (d, 1H, *J* = 13.7 Hz, N-CH_2-Ar), 3.48 (m, 1H, H-1), 3.38 (d, 1H, *J* = 7.7 Hz, H-2), 3.30 (d, 1H, *J* = 13.7 Hz, N-CH_2-Ar), 2.83 (dd, 1H, $J_{5a,5b}$ = 16.6, $J_{4,5a}$ = 1.1 Hz, H-5a), 2.70 (dd, 1H, *J* = 11.2, 11.1 Hz, H-1′a), 2.59–2.52 (m, 2H, H-1′b, H-5b), 2.06 (s, 3H, COCH_3), 1.94 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 207.1 (C=O), 170.2 (–O–C=O), 138.8 (Ar), 137.5 (Ar), 132.7 (Ar), 129.7 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 79.3 (C-2), 74.0 (C-3), 72.8 (C-4), 71.3 (PhCH_2), 69.7 (PhCH_2), 56.1 (N-CH_2-Ar), 55.8 (C-5), 48.8 (C-1), 45.2 (C-1′), 30.1 (COCH_3), 21.0 (OCOCH_3). HRESIMS: calcd for $C_{31}H_{35}ClNO_5$ $[M+H]^+$: 536.2198, found: 536.2189.

3.4.8. 1-*C*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-5-*o*-chlorobenzylamino-5-deoxy-D-ribopyranosyl)propan-2-one (8h)

Yield: 50% (over three steps).

(**8h**–**α**) $[\alpha]_D^{25}$ 68.2 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37–7.26 (m, 12H, Ar), 7.22 (m, 1H, Ar), 7.16 (m, 1H, Ar), 4.78 (d, 1H, *J* = 12.0 Hz, PhCH_2), 4.76 (m, 1H, H-4), 4.69 (d, 1H, *J* = 11.9 Hz, PhCH_2), 4.57 (d, 1H, *J* = 11.7 Hz, PhCH_2), 4.48 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.16 (br s, 1H, H-3), 3.95 (m, 1H, H-1), 3.77 (d, 1H, *J* = 14.5 Hz, N-CH_2-Ar), 3.70 (br s, 1H, H-2), 3.66 (d, 1H, *J* = 14.5 Hz, N-CH_2-Ar), 3.26 (dd, 1H, $J_{5a,5b}$ = 16.5, $J_{4,5a}$ = 5.5 Hz, H-5a), 2.84 (dd, 1H, *J* = 11.2, 11.2 Hz, H-1′a), 2.74 (dd, 1H, $J_{5a,5b}$ = 16.5, $J_{4,5b}$ = 5.9 Hz, H-5b), 2.48 (dd, 1H, $J_{H\text{-}1'a,H\text{-}1'b}$ = 11.3, $J_{H\text{-}1,H\text{-}1'b}$ = 4.7 Hz, H-1′b), 2.10 (s, 3H, COCH_3), 1.95 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 208.9 (C=O), 170.1 (–O–C=O), 138.9 (Ar), 138.1 (Ar), 136.1 (Ar), 134.1 (Ar), 130.1 (Ar), 129.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 126.7 (Ar), 76.6 (C-2), 76.2 (C-3), 74.8 (C-4), 71.2 (PhCH_2), 69.9 (PhCH_2), 55.9 (N-CH_2-Ar), 55.3 (C-5), 43.5 (C-1), 38.1 (C-1′), 31.0 (COCH_3), 21.0 (OCOCH_3). HRESIMS: calcd for $C_{31}H_{34}ClNNaO_5$ $[M+Na]^+$: 558.2018, found: 558.2008.

(**8h**–**β**) $[\alpha]_D^{25}$ 11.1 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35–7.29 (m, 12H, Ar), 7.20 (m, 1H, Ar), 7.15 (m, 1H, Ar), 4.83 (m, 1H, H-4), 4.77 (d, 1H, *J* = 12.1 Hz, PhCH_2), 4.65 (d, 1H, *J* = 11.5 Hz, PhCH_2), 4.63 (d, 1H, *J* = 11.4 Hz, PhCH_2), 4.42 (d, 1H, *J* = 11.5 Hz, PhCH_2), 4.21 (br s, 1H, H-3), 3.84 (d, 1H, *J* = 14.8 Hz, N-CH_2-Ar), 3.55 (m, 1H, H-2), 3.53 (d, 1H, *J* = 14.5 Hz, N-CH_2-Ar), 3.42 (m, 1H, H-1), 2.84 (dd, 1H, *J* = 10.9, 10.7 Hz, H-1′a), 2.77 (dd, 1H, $J_{5b,5a}$ = 16.7, $J_{4,5a}$ = 4.9 Hz, H-5a), 2.64 (dd, 1H, $J_{5a,5b}$ = 16.6, $J_{4,5b}$ = 5.8 Hz, H-5b), 2.60 (dd, 1H, $J_{1',1'}$ = 11.0, $J_{1,1'}$ = 4.5 Hz, H-1′b), 2.04 (s, 3H, COCH_3), 1.95 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 207.0 (C=O), 170.2 (–O–C=O), 138.8 (Ar), 137.6 (Ar), 136.4 (Ar), 133.8 (Ar), 130.3 (Ar), 129.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.6 (Ar), 127.4 (Ar), 126.7 (Ar), 79.6 (C-2), 74.0 (C-3), 72.9 (C-4), 71.4 (PhCH_2), 69.7 (PhCH_2), 56.4 (N–CH_2–Ph), 53.6 (C-5), 49.2 (C-1), 45.0 (C-1′), 30.1(COCH_3), 21.0(OCOCH_3). HRESIMS: calcd for $C_{31}H_{34}ClNNaO_5$ $[M+Na]^+$: 558.2018, found: 558.2010.

3.4.9. 1-*C*-[4-*O*-Acetyl-2,3-di-*O*-benzyl-5-deoxy-5-(thiophen-2-ylmethyl)amino-D-ribopyranosyl]propan-2-one (8i)

Yield: 51% (over three steps).

(**8i**–**α**) $[\alpha]_D^{25}$ 66.1 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36–7.27 (m, 10H, Ar), 7.20 (d, 1H, *J* = 4.7 Hz, thiophen), 6.91 (s, 1H, thiophen), 6.84 (s, 1H, thiophen), 4.79–4.76 (m, 2H, PhCH_2, H-4), 4.67 (d, 1H, *J* = 11.7 Hz, PhCH_2), 4.56 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.48 (d, 1H, *J* = 11.7 Hz, PhCH_2), 4.14 (br s, 1H, H-3), 3.97 (m, 1H, H-1), 3.94 (d, 1H, *J* = 14.3 Hz, N-CH_2-thiophen), 3.71 (d, 2H, H-2, N-CH_2-thiophen), 3.22 (dd, 1H, $J_{5b,5a}$ = 16.6, $J_{4,5a}$ = 4.9 Hz, H-5a), 2.76 (dd, 1H, *J* = 10.9, 10.8 Hz, H-1′a), 2.67 (dd, 1H, $J_{5a,5b}$ = 16.2, $J_{4,5b}$ = 5.5 Hz, H-5b). 2.60 (d, 1H, *J* = 6.8 Hz, H-1′b), 2.08 (s, 3H, COCH_3), 1.96 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 208.9 (C=O), 170.1 (–O–C=O), 143.3 (thiophen), 138.9 (Ar), 138.1 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 126.4 (Ar), 125.2 (Ar), 124.9 (Ar), 76.2 (C-2, C-3), 74.7 (C-4), 71.3 (PhCH_2), 69.9 (PhCH_2), 55.5 (N-CH_2-thiophen), 53.4 (C-5), 43.3 (C-1), 38.0 (C-1′), 30.9 (COCH_3), 21.0 (OCOCH_3). HRESIMS: calcd for $C_{29}H_{33}NNaO_5S$ $[M+Na]^+$: 530.1972, found: 530.1950.

(**8i**–**β**) $[\alpha]_D^{25}$ 11.5 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.27 (m, 10H, Ar), 7.20 (d, 1H, *J* = 9.5 Hz, thiophen), 6.90 (m, 1H, thiophen), 6.84 (s, 1H, thiophen), 4.80 (d, 1H, *J* = 8.6 Hz, H-4), 4.75 (d, 1H, *J* = 12.0 Hz, PhCH_2), 4.66–4.60 (m, 2H, PhCH_2), 4.41 (d, 1H, *J* = 11.5 Hz, PhCH_2), 4.21 (br s, 1H, H-3), 3.92 (d, 1H, *J* = 14.4 Hz, N-CH_2-thiophen), 3.69 (d, 1H, *J* = 14.6 Hz, N-CH_2-thiophen), 3.47

(m, 1H, H-1), 3.36 (d, 1H, J = 8.3 Hz, H-2), 2.82–2.78 (m, 2H, H-5a, H-1′a), 2.74 (dd, 1H, $J_{5a,5b}$ = 10.8, $J_{4,5b}$ = 4.7 Hz, H-5b), 2.65 (m, 1H, H-1′b), 2.08 (s, 3H, COCH_3), 1.93 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$): δ 207.0 (C═O), 170.2 (–O–C═O), 142.6 (thiophen), 138.8 (Ar), 137.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 79.7 (C-2), 74.0 (C-3), 72.8 (C-4), 71.4 (PhCH_2), 69.9 (PhCH_2), 55.7 (N-CH_2-thiophen), 55.0 (C-5), 49.0 (C-1), 45.3 (C-1′), 30.7 (COCH_3), 21.0 (OCOCH_3). HRESIMS: calcd for $C_{29}H_{33}NNaO_5S$ $[M+Na]^+$: 530.1972, found: 530.1962.

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