Carbohydrate Research 343 (2008) 2887–2893

Contents lists available at ScienceDirect

Carbohydrate Research

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

Synthesis of iminoalditol and *N*-alkyl iminoalditol derivatives of ribopyranosides

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ARTICLE INFO

Article history:
Received 17 June 2008
Received in revised form 24 July 2008
Accepted 3 August 2008
Available online 9 August 2008

Dedicated to Professor Yongzheng Hui on the occasion of his 70th birthday

Keywords:
Aza-C-glycoside
Iminoalditols
N-Alkylation
Amidation
Michael addition

ABSTRACT

Iminoalditol analogs of ribopyranosides were prepared by reduction of a vinylogous urethane intermediate formed from methyl 2-*C*-(5-*O*-methanesulfonyl-β-D-ribofuranosyl)acetate (**1**) by treatment with sodium azide in DMF at reflux. The N-alkylated analogs were synthesized either by N-alkylation of the corresponding parent iminoalditol or, more efficiently, from the product of the reaction of **1** with various alkylamines. The latter process involves an S_N2 substitution at C-5 by the amine followed by an intramolecular hetero-Michael reaction under basic conditions. The 'aglycon' of the iminoalditol was also modified through amidation and esterification.

1. Introduction

N-Alkylation of iminoalditols often results in better inhibitory specificity against glycan-processing enzymes and improves bioavailability.[1] For example, *N*-hydroxyethyl 1-deoxynojirimycin (Miglitol),[1b] and *N*-butyl 1-deoxynojirimycin (Miglustat)[1a] have been used as therapeutics for the treatment of type II diabetes and type I Gaucher disease, respectively. It has been suggested that even better inhibition selectivity of iminoalditols could be achieved by introducing additional interaction between the 'aglycon' and the enzyme.[2] By careful selection of the N-alkyl group and aglycon, one might be able to tune the inhibitory activity of an iminoalditol and its intracellular bioavailability.

One of the synthetic methods to iminoalditols uses 2-*C*-(azidoglycosyl)acetates as intermediates, from which reduction of the azido group to an amine is followed by an intramolecular hetero-Michael addition leading to the product.[3] The resultant iminoalditols can be further N-alkylated. However, this protocol may not work well when intramolecular amidation between the amino group and acetate ester takes place. In this paper, we describe an alternative method to iminoalditols via a vinylogous urethane intermediate, and also report an efficient synthesis of N-alkylated iminoalditols by treatment of methyl 2-*C*-(5-*O*-methanesulfonyl-β-D-ribofuranosyl)acetate with amines, which involves an S_N2 substitution of 5-*O*-methanesulfonyl group by an amine followed by an intramolecular hetero-Michael addition.

2. Results and discussion

The key intermediate methyl 2-*C*-(5-*O*-methanesulfonyl-β-D-ribofuranosyl)acetate (**1**) was prepared from readily available 2,3-*O*-isopropylidene ribofuranose[4] by a Wittig reaction[5] followed by 5-*O*-mesylation.[6] We treated **1** with sodium azide at 80 °C to introduce a 5-azido group to obtain **2** in 86% yield. The product was further converted by hydrogenation to amine **3** in 92% yield (see Scheme 1). However, subsequent treatment with base produced desired iminoalditol **4** in only 35% yield. The reaction produced, as the major product, tricyclic lactam **5** in 63% yield, which was not observed in the previous study.[5] Apparently, because of the cis relationship between the groups at C1 and C4 in **1**, the spatial proximity between ester and 5-amino groups favors the amidation leading to **5**. In contrast, the less favored β-elimination and intramolecular Michael addition thereafter produced iminoalditol **4**.

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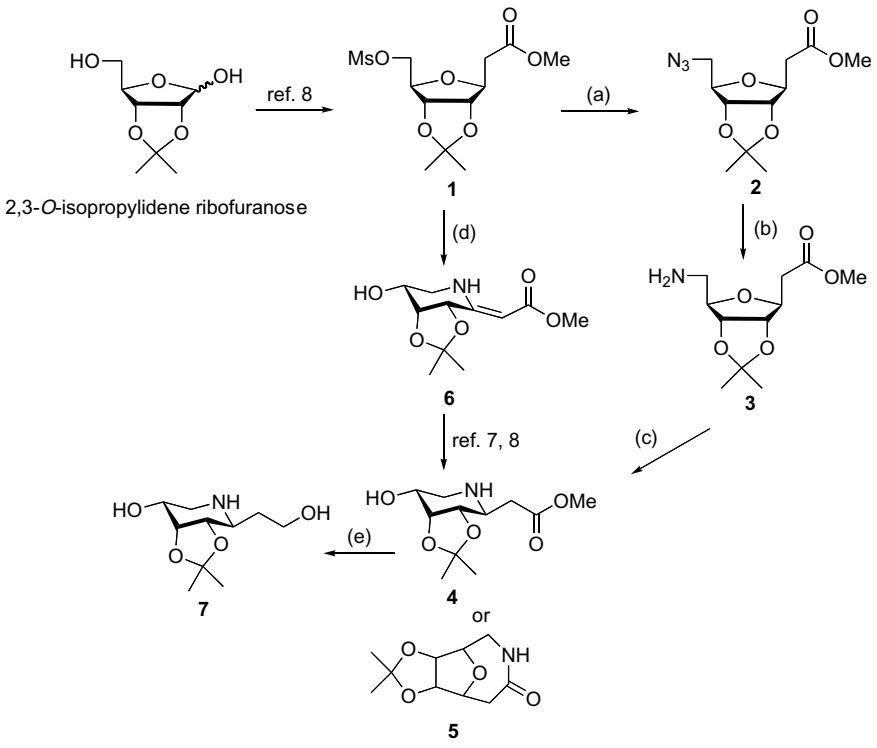
doi:10.1016/j.carres.2008.08.005

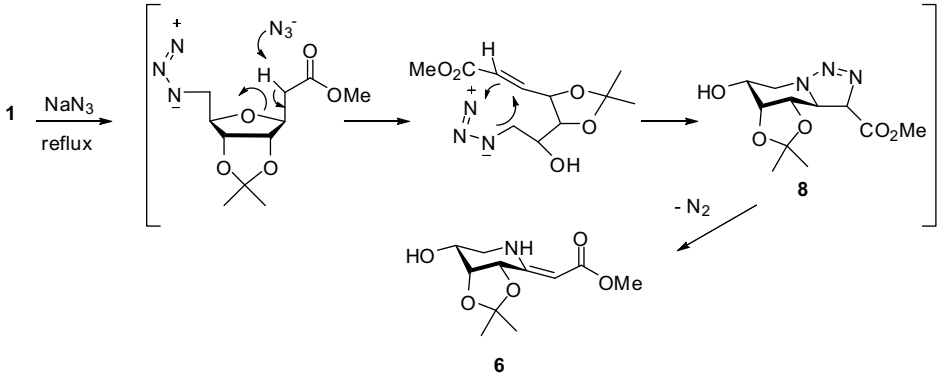


Scheme 1. Reagents and conditions: (a) NaN_3, DMF, 80 °C, 86%; (b) H_2/Pd/C, MeOH, 92%; (c) NaOMe, MeOH, 35% for **4**, 63% for **5**; (d) NaN_3, DMF, reflux, 71%; (e) DIBALH, CH_2Cl_2, 85%.

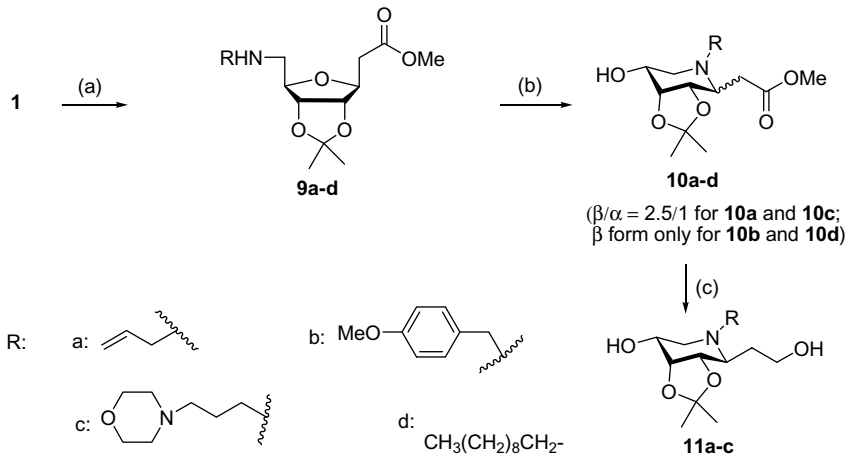
In a parallel experiment, we treated **1** with sodium azide in DMF, which resulted in the isolation of vinylogous urethane **6** as major product (71%) and azidoester **2** as minor product (10%) (Scheme 1). The vinylogous urethane is produced following a mechanism illustrated in Scheme 2. Initial sodium azide substitution at C-5 was followed by an intramolecular 1,3-dipolar cycloaddition of the azido group to an α,β-unsaturated ester, which led to formation of a triazoline intermediate (**8**). Extrusion of nitrogen gas and hydrogen atom migration in **8** afforded **6**. This mechanism is very similar to those described in literature.[7,8] It is noteworthy that triazoline was isolated in a similar reaction between azido group and an unsaturated ester as only major product.[9] Reduction of the double bond of **6** gave iminoalditol **4** in 80% yield. Thus, this method allows us to circumvent an undesired intramolecular amidation and to use compound **1** as a substrate for the synthesis of iminoalditol analogs or ribopyranosides. DIBALH reduction of the ester was able to convert **4** to alcohol **7** in 85% yield.

We reasoned that the intramolecular amidation from **3** to **5** might be suppressed if a secondary amine is used as the nucleophile. This may allow β-elimination to compete more favorably with amidation and consequently facilitate the hetero-Michael addition. An additional advantage of this approach is the spontaneous formation of N-alkylated iminoalditol. As expected, treatment of **1** with varies alkyl amines in the presence of triethylamine afforded 5-*N*-alkyl-derivatives **9a–d** in 72–84% yield (Scheme 3). Upon further treatment with stronger base, these compounds gave the respective N-alkylated iminoalditol (**10a–d**) in moderate yield. Compounds **10b** and **10d** were obtained as a single β-anomer, while **10a** and **10c** were obtained as a mixture of two isomers in a ratio of ~1:2.5 (a:b) according to NMR analysis. Reduction of **10a–c** with DIBALH or $LiAlH_4$ afforded alcohols **11a–c** in 47–87% yield.

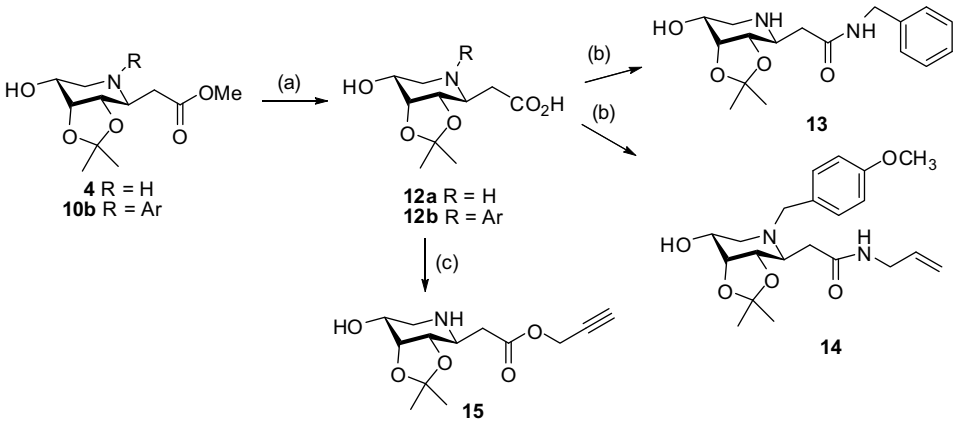
We also attempted to introduce different 'aglycons' to the iminoalditols through modification of the ester. Thus, treatment of **4**



Scheme 2.



Scheme 3. Reagents and conditions: (a) RNH_2, Et_3N, CH_3CN, 72–84%; (b) NaOMe, MeOH, 37–59%; (c) DIBALH, CH_2Cl_2 or $LiAlH_4$, THF, 47–87%.



Scheme 4. Reagents and conditions: (a) NaOH, dioxane; (b) amines, Et_3N, DEPC, DMF; (c) propagyl alcohol, DCC, DMAP, CH_2Cl_2.

and **10b** with aqueous sodium hydroxide converted these esters to acids **12a** and **12b**, which were then coupled with amines using diethyl cyanophosphonate (DEPC) in DMF to give iminoalditol amides **13** and **14**, in 83% and 62% yield, respectively (Scheme 4).

In addition to amidation, we also prepared the alkynyl ester **15** in 66% yield from **12a** and propargyl alcohol using *N*,*N*-dicyclohexyl-carbodiimide (DCC) and catalytic amount of 4-dimethyl aminopyridine (DMAP). Compound **15** as a substrate was tested for Click reaction[10] using a copper (I) catalyst in ethanol under refluxing conditions, which produced triazole **16** in 47% yield (Scheme 5).

In summary, we report here an alternative method for the preparation of iminoalditols via a vinylogous urethane intermediate. In addition, a new efficient procedure to *N*-alkyl iminoalditols from 2-*C*-(5-*O*-methanesulfonyl-β-D-ribofuranosyl)acetate and amines, as well as further derivatization was also described. This work may provide an easy access to a large number of iminoalditol analogs.

3. Experimental

3.1. General methods

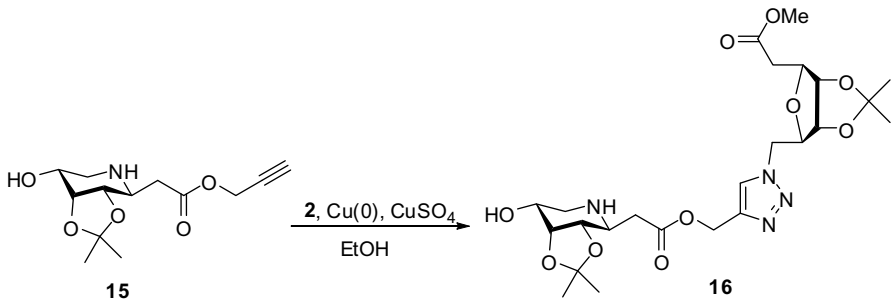
All reagents were obtained from commercial suppliers and were used without further purification. CH_2Cl_2 was distilled over CaH_2. MeOH was distilled over magnesium and iodine. Analytical thin-layer chromatography was performed using Silica Gel 60 F254 plates (Merck). The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Chemical shifts are given in ppm with residual $CHCl_3$, CHD_2OD, or D_2O as reference. Mass spectra were recorded under fast atom bombardment (FAB) conditions.

3.2. Methyl 2-C-(5-azido-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl)acetate (2)

A mixture of **1** (2.39 g, 7.37 mmol) and NaN_3 (1.44 g, 22.1 mmol) in DMF (60 mL) was stirred overnight at 80 °C. Upon cooling to room temperature the reaction mixture was diluted by the addition of Et_2O (40 mL) and the solution was washed with water and brine. Purification by chromatography (hexanes–EtOAc 9:1) gave **2** (1.72 g, 86%) as a yellow oil. ^1H NMR ($CDCl_3$) δ: 4.52–4.49 (m, 2H, H-2, H-3), 4.23–4.21 (m, 1H, H-1), 4.01 (q, 1H, H-4), 3.64 (s, 3H, CO_2Me), 3.48 (dd, J = 13.2, 3.9 Hz, 1H, H-5a), 3.27 (dd, J = 13.0, 4.5 Hz, 1H, H-5b), 2.64–2.59 (m, 2H, H-1′a, H-1′b), 1.51 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.7 (C=O), 114.9 (C-*i*Pr), 84.1 (C-3), 83.0 (C-2), 82.0 (C-4), 80.8 (C-1), 52.2 (C-5), 51.8 (CO_2Me), 37.9 (C-1′), 27.3 ($C(CH_3)_2$), 25.4 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{11}H_{17}N_3O_5$ $[M+H]^+$, 271.1168, found 271.1168.

3.3. Methyl 2-C-(5-amino-5-deoxy-2,3-di-O-isopropylidene-β-D-ribofuranosyl)acetate (3)

A mixture of **2** (1.72 g, 6.34 mmol) and 10% Pd–C (0.17 g) in MeOH (20 mL) was stirred under H_2 atmosphere (balloon pressure) for 40 min when the starting material was completely consumed.



Scheme 5.

The reaction mixture was filtered and the filtrate was concentrated. Purification by chromatography (CH_2Cl_2–MeOH 10:1) gave **3** (1.43 g, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.52–4.43 (m, 2H, H-2, H-3), 4.23–4.18 (m, 1H, H-1), 3.88 (q, 1H, H-4), 3.66 (s, 3H, CO_2Me), 2.91–2.73 (m, 2H, H-5a, H-5b), 2.64–2.52 (m, 2H, H-1′a, H-1′b), 1.50 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.9 (C=O), 114.7 (C-*i*Pr), 85.5 (C-3), 84.2 (C-2), 82.4 (C-4), 80.3 (C-1), 51.8 (C-5), 44.0 (CO_2Me), 38.1 (C-1′), 27.4 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{11}H_{20}NO_5$ $[M+H]^+$, 246.1341, found 246.1343.

3.4. Methyl 2-C-(5-amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetate (4)

A solution of **3** (1.43 g, 5.96 mmol) in 2% NaOMe–MeOH (10 mL) was stirred overnight and then neutralized by the addition of Dowex 50WX8(H^+) resin. The filtrate was concentrated to a residue. Purification by chromatography (hexanes–EtOAc 12:1) gave **4** (0.51 g, 35%) as a yellow oil and tricyclic lactam **5** (0.80 g, 63%) as a yellow oil. For **4**: ^{1}H NMR ($CDCl_3$) δ: 4.75 (dd, J = 6.0, 3.9 Hz, 1H, H-3), 4.59 (dd, J = 7.2, 1.2 Hz, 1H, H-2), 4.39–4.33 (m, 1H, H-4), 4.16 (t, J = 10.8 Hz, 1H, H-1), 3.66 (s, 3H, CO_2Me), 3.37 (dd, J = 12.9, 6.6 Hz, 1H, H-1′a), 3.22 (dd, J = 12.9, 4.8 Hz, 1H, H-1′b), 2.72 (dd, J = 6.9, 3.3 Hz, 2H, H-5a, H-5b), 1.44 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 171.3 (C=O), 113.0 (C-*i*Pr), 83.2 (C-2), 82.7 (C-1), 81.2 (C-3), 77.3 (C-4), 51.8 (CO_2Me), 51.5 (C-1′), 34.2 (C-5), 26.2 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{11}H_{19}NO_5$ $[M+H]^+$, 246.1341, found 246.1339.

For **5**: ^{1}H NMR ($CDCl_3$) δ: 6.43 (br d, J = 5.7 Hz, NH), 4.78 (d, J = 5.7 Hz, 1H, H-3), 4.63 (d, J = 5.7 Hz, 1H, H-2), 4.34 (d, J = 3.9 Hz, 1H, H-4), 4.26 (q, 1H, H-1), 3.54 (d, J = 15.0 Hz, 1H, H-5a′), 3.17–3.08 (m, 1H, H-5b′), 2.82 (dd, J = 16.5, 2.4 Hz, 1H, CH_2CO), 2.69–2.61 (m, 1H, CH_2CO), 1.46 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 176.0 (C=O), 112.0 (C-*i*Pr), 83.9 (C-2), 82.9 (C-3), 82.4 (C-4), 79.2 (C-1), 46.3 (C-5), 43.7 (C-1′), 26.0 ($C(CH_3)_2$), 24.3 ($C(CH_3)_2$). FABMS Calcd for $C_{10}H_{15}NO_4$ [M], *m/z* 213.1001, found 213.1005.

3.5. Methyl 2-C-(5-amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosylidene)-acetate (6)

A mixture of **1** (0.12 g, 0.369 mmol) and NaN_3 (72.1 mg, 1.11 mmol) in DMF (20 mL) was heated at reflux for 3 h. Upon cooling to room temperature, the reaction mixture was diluted by the addition of Et_2O (20 mL), and the solution was washed with water and brine. Purification by chromatography (hexanes–EtOAc 2:1) gave **6** (64 mg, 71%) as a white solid; mp: 135 °C; ^{1}H NMR ($CDCl_3$) δ: 8.26 (s, 1H, NH), 4.74 (s, 1H, H-1′), 4.57 (d, J = 13.2 Hz, 1H, H-2), 4.48–4.44 (m, 1H, H-3), 3.75–3.67 (m, 1H, H-4), 3.60 (s, 3H, CO_2Me), 3.27–3.14 (m, 2H, H-5a, 5b), 2.52 (d, J = 8.4 Hz, 1H, OH), 1.50 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.7 (C=O), 155.6 (C-1), 110.4 (C-*i*Pr), 84.5 (C-1′), 75.0 (C-2), 73.2 (C-3), 67.0 (C-4), 50.4 (CO_2Me), 41.6 (C-5), 26.0 ($C(CH_3)_2$), 24.2 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{11}H_{17}NO_5$ [M], 243.1107, found 243.1110.

3.6. 2-C-(5-Amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)ethanol (7)

To a solution of **4** (0.2 g, 0.815 mmol) in dry CH_2Cl_2 was added 1 M solution of DIBALH (2.45 mL, 3 equiv) at 0 °C. The reaction mixture was stirred at the temperature for 1.5 h. MeOH (0.2 mL) was added and the temperature was raised to room temperature. Saturated NaCl (0.41 mL), Et_2O (10.2 mL), and $MgSO_4$ (1.07 g) were added subsequently. The mixture was stirred for 1 h and then filtered through Celite. The solvent was removed and the crude was purified by chromatography (hexanes–EtOAc 1:1) to give **7** (0.15 g, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.69–4.66 (m, 1H, H-2), 4.60–4.57 (m, 1H, H-3), 4.21–4.09 (m, 2H, H-4, H-1), 3.78–3.75 (m, 2H, H-2′a, H-2′b), 3.39 (dd, J = 16.8, 9.9 Hz, 1H, H-5a), 3.20 (dd, J = 12.9, 4.8 Hz, 1H, H-5b), 2.13 (br s, 1H, OH), 2.05–1.85 (m, 2H, H-1′a, H-1′b), 1.46 (s, 3H, $C(CH_3)_2$), 1.30 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 112.8 (C-*i*Pr), 83.2 (C-3), 82.9 (C-4), 82.0 (C-2), 79.7 (C-1), 60.3 (C-2′), 51.3 (C-5), 31.7 (C-1′), 26.3 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{10}H_{19}NO_4$ [M], 217.1314, found 217.1323.

3.7. Methyl 2-C-(5-allylamino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl)acetate (9a)

To a solution of **1** (3.89 g, 11.99 mmol) and triethylamine (10 mL, 71.95 mmol) in dry CH_3CN (40 mL) was added allylamine (1.34 mL, 17.98 mmol), and the mixture was heated at reflux for 48 h. After cooling, the solvent was removed and the crude was purified by chromatography (hexanes–EtOAc 1:2) to give **9a** (2.78 g, 81%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 5.91–5.78 (m, 1H, =CH), 5.12 (dd, J = 17.1, 1.5 Hz, 2H, $=CH_2$), 4.57–4.54 (m, 1H, H-3), 4.48–4.44 (m, 1H, H-2), 4.21 (q, J = 4.8 Hz, 1H, H-1), 4.01 (q, J = 6.0 Hz, 1H, H-4), 3.68 (s, 3H, CO_2Me), 3.24 (d, J = 6.0 Hz, 2H, $CH_2CH=$), 2.87–2.52 (m, 4H, H-5a, H-5b, H-1′a, H-1′b), 1.50 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.9 (C=O), 136.4 (=CH), 116.3 ($=CH_2$), 114.7 (C-*i*Pr), 84.2 (C-4), 83.5 (C-2), 82.9 (C-3), 80.5 (C-1), 52.3 ($CH_2CH=CH_2$), 51.8 (CO_2Me), 50.7 (C-5), 38.2 (C-1′), 27.4 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{14}H_{23}NO_5$ [M], 285.1576, found 285.1580.

3.8. Methyl 2-C-[5-deoxy-2,3-di-*O*-isopropylidene-5-(4-methoxybenzylamino)-β-D-ribofuranosyl]acetate (9b)

To a solution of **1** (0.1 g, 0.31 mmol) and triethylamine (0.042 mL, 0.31 mmol) in dry CH_3CN (5 mL) was added 4-methoxy-

benzylamine (0.06 mL, 0.46 mmol), and the mixture was heated at reflux for 48 h. After cooling, the solvent was removed and the crude was purified by column chromatography (hexanes–EtOAc 1:1) which afforded **9b** (0.092 g, 84%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J = 8.7 Hz, 2H, Ph), 6.83 (d, J = 8.7 Hz, 2H, Ph), 4.55 (dd, J = 6.9, 4.5 Hz, 1H, H-3), 4.44 (dd, J = 6.9, 4.8 Hz, 1H, H-2), 4.23–4.17 (m, 1H, H-1), 4.03–3.99 (m, 1H, H-4), 3.83 (s, 3H, OMe), 3.77 (d, J = 2.7 Hz, 2H, $PhCH_2$), 3.65 (s, 3H, CO_2Me), 2.85–2.50 (m, 4H, H-5a, H-5b, H-1′a, H-1′b), 1.46 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.8 (C=O), 158.6 (2Ph), 132.2 (Ph) , 129.3 (2Ph), 114.6 (C-*i*Pr), 113.7 (2Ph), 84.2 (C-2), 83.6 (C-4), 82.9 (C-3), 80.4 (C-1), 55.2 (OMe), 53.2 ($PhCH_2$), 51.8 (CO_2Me), 50.6 (C-5), 38.1 (C-1′), 27.4 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{19}H_{27}NO_6$ [M], 365.1838, found 365.1836.

3.9. Methyl 2-C-(5-deoxy-2,3-di-*O*-isopropylidene-5-morpholinopropylamino-β-D-ribofuranosyl)acetate (9c)

To a solution of **1** (4.34 g, 13.37 mmol) and triethylamine (5.65 mL, 3 equiv) in dry CH_3CN (40 mL) was added *N*-(3-aminopropyl)morpholine (2.5 mL, 1.2 equiv), and the mixture was heated at reflux for 48 h. After cooling, the solvent was removed and the crude was purified by column chromatography (EtOAc–MeOH 6:1) to give **9c** (3.58 g, 72%) as a light yellow syrup. ^{1}H NMR ($CDCl_3$) δ: 4.46–4.40 (m, 2H, H-2, H-3), 4.22–4.09 (m, 1H, H-4), 4.01–3.93 (m, 1H, H-1), 3.80–3.54 (m, 7H, 2H-10a, 2H-10b, CO_2Me), 2.80–2.75 (m, 2H, H-6a, H-6b), 2.66–2.51 (m, 4H, H-5a, H-5b, H-8a, H-8b), 2.36–2.28 (m, 6H, 2H-9a, 2H-9b, H-1′a, H-1′b), 1.62–1.58 (m, 2H, H-7a, H-7b), 1.45 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.6 (C=O), 114.6 (C-*i*Pr), 84.0 (C-3), 83.3 (C-2), 82.8 (C-1), 80.3 (C-4), 66.7 (2C-10), 57.1 (C-1′), 53.6 (2C-9), 51.6 (CO_2Me), 51.4 (C-6), 48.4 (C-5), 38.0 (C-8), 26.17 (C-7), 27.2 ($C(CH_3)_2$), 25.4 ($C(CH_3)_2$). FABMS *m/z* calcd for $C_{18}H_{32}N_2O_6$ [M] 372.2260, found 372.2253.

3.10. Methyl 2-C-(5-decylamino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl)acetate (9d)

To a solution of **1** (0.54 g, 1.66 mmol) and triethylamine (0.7 mL, 3 equiv) in dry CH_3CN (10 mL) was added decyl amine (0.40 g, 1.5 equiv), and the mixture was heated at reflux for 24 h. After cooling, the solvent was removed and the crude was purified by column chromatography (CH_2Cl_2–MeOH 30:1) to give **9d** (0.50 g, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.48–4.36 (m, 2H, H-2, H-3), 4.13 (dd, J = 6.9, 4.8 Hz, 1H, H-1), 3.94 (td, J = 6.6, 4.2 Hz, 1H, H-4), 3.60 (s, 3H, CO_2Me), 2.78–2.45 (m, 6H, H-1′a, H-1′b, H-5a, H-5b H-6a, H-6b), 1.43 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 1.22–1.15 (m, 16H), 0.78 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.68 (C=O), 114.46 (C-*i*Pr), 84.05, 83.43, 82.83, 80.27, 51.59 (CO_2Me), 51.54, 49.93, 38.03, 31.71, 29.77, 29.42, 29.39 (2C), 29.14, 27.21, 27.12, 25.36 ($C(CH_3)_2$), 22.48 ($C(CH_3)_2$), 13.92. FABMS *m/z* Calcd for $C_{21}H_{40}NO_5$ $[M+H]^+$, 386.2906, found 386.2901.

3.11. Methyl 2-C-(5-allylamino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetate (10a)

A solution of **9a** (2.78 g, 9.74 mmol) in 2% NaOMe–MeOH (20 mL) was stirred overnight and then neutralized by the addition of Dowex 50WX8(H^+) resin. The filtrate was concentrated to a residue. Purification by chromatography (hexane–EtOAc 10:1) gave **10a–β** (0.96 g, 35%) as a light yellow syrup and **10a–α** (0.41 g, 15%) as a light yellow syrup. For **10a–β**: ^{1}H NMR ($CDCl_3$) δ: 5.85–5.71 (m, 1H, =CH), 5.16 (dd, J = 10.5, 6.3 Hz, 2H, $=CH_2$), 4.26 (dd, J = 6.0, 3.9 Hz, 1H, H-2), 3.98 (dd, J = 5.4, 5.1 Hz, 1H, H-3), 3.65 (s, 4H, H-4, CO_2Me), 3.24 (dd, J = 14.1, 4.6 Hz, 1H, CH_2CH=), 3.13–3.07 (m, 1H, H-1), 3.02 (d, J = 7.8 Hz, 1H, CH_2CH=), 2.98–2.91 (m, 1H, H-5a), 2.71 (d, J = 6.6 Hz, 2H, H-1′a, H-1′b), 2.28 (d, J = 12.3 Hz, 1H, H-5b), 1.54 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 172.4 (C=O), 133.8 (=CH), 118.6 (=$CHCH_2$), 108.9 (C-*i*Pr), 74.3 (C-2), 74.1 (C-3), 65.0 (C-4), 56.2 (=$CHCH_2$), 56.1 (C-1), 53.2 (C-5), 51.7 (CO_2Me), 34.6 (C-1′), 25.7 ($C(CH_3)_2$), 25.3 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{14}H_{23}NO_5$ [M], 285.1576, found 285.1583.

For **10a–α**: ^{1}H NMR ($CDCl_3$) δ: 5.82–5.68 (m, 1H, =CH), 5.15 (dd, J = 17.7, 9.0 Hz, 2H, $=CH_2$), 4.32 (dd, J = 4.5, 4.5 Hz, 1H, H-3), 4.00 (dd, J = 7.8, 5.1 Hz, 1H, H-2), 3.88 (br t, J = 5.1 Hz, 1H, H-4), 3.66 (s, 3H, CO_2Me), 3.25 (dd, J = 13.9, 5.3 Hz, 1H, CH_2CH=CH_2), 2.96–2.80 (m, 2H, CH_2CH=CH_2, H-1), 2.53 (dt, J = 10.5, 4.5 Hz, 2H, H-1′), 2.29 (t, J = 10.8 Hz, 2H, H-5a, H-5b), 1.50 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 172.3 (C=O), 134.5 (=CH), 119.0 (=$CHCH_2$), 109.4 (C-*i*Pr), 77.4 (C-2), 74.6 (C-3), 66.1 (C-4), 59.4 (C-1), 55.9 (CH_2CH=), 53.0 (C-1′), 51.8 (CO_2Me), 35.6 (C-5), 27.7 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{14}H_{23}NO_5$ [M], 285.1576, found 285.1583.

3.12. Methyl 2-C-[5-deoxy-2,3-di-*O*-isopropylidene-5-(4-methoxybenzylamino)-β-D-ribopyranosyl]acetate (10b)

The same procedures as described above were used to obtain **10b** (37%) as a semi-solid. ^{1}H NMR ($CDCl_3$) δ: 7.03 (d, J = 8.4 Hz, 2H, Ph), 6.68 (d, J = 8.7 Hz, 2H, Ph), 4.22 (dd, J = 4.5, 4.5 Hz, 1H, H-2), 3.95 (dd, J = 7.8, 5.1 Hz, 1H, H-3), 3.70 (d, J = 12.6 Hz, 2H, H-1, $PhCH_2$), 3.66 (s, 3H, OMe), 3.55 (s, 3H, CO_2Me), 3.02 (d, J = 12.6 Hz, 1H, $PhCH_2$), 2.80–2.72 (m, 1H, H-4), 2.62–2.43 (m, 3H, H-5a, H-1′a, H-1′b), 2.08–2.01 (m, 1H, H-5b), 1.36 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 172.4 (C=O), 158.7 (Ph), 130.6 (Ph), 129.8 (2Ph), 113.7 (2Ph), 109.4 (C-*i*Pr), 77.3 (C-3), 74.6 (C-2), 66.0 (C-1), 60.1 (C-4), 56.3 ($PhCH_2$), 55.2 (OMe), 52.4 (C-5), 51.8 (CO_2Me), 35.8 (C-1′), 27.7 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{19}H_{27}NO_6$ [M], 365.1838, found 365.1843.

3.13. Methyl 2-C-(5-deoxy-2,3-di-O-isopropylidene-5-morpholinopropylamino-β-D-ribopyranosyl)acetate (10c)

The same procedures as described above were used to obtain **10c–β** (42%) as a light yellow syrup and **10c–α** (17%) as a yellow syrup. For **10c–β**: ^{1}H NMR ($CDCl_3$) δ: 4.32 (dd, J = 4.8 Hz, 4.5 Hz, 1H, H-3), 3.95 (dd, J = 7.5, 5.1 Hz, 1H, H-2), 3.93–3.85 (m, 1H, H-4), 3.71 (t, J = 4.5 Hz, 4H, 2H-10a, 2H-10b), 3.68 (s, 3H, CO_2Me), 3.16 (br s, OH), 2.93–2.83 (m, 3H, H-1, H-6), 2.75–2.23 (m, 10H, H-1′a, H-1′b, H-5a, H-5b, H-8a, H-8b, 2H-9a, 2H-9b), 1.68–1.55 (m, 2H, H-7a, H-7b), 1.52 (s, 3H, $C(CH_3)_2$), 1.47 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 172.34 (C=O), 109.38 (C-*i*Pr), 77.35 (C-2), 74.39 (C-3), 66.68 (2C-10), 65.99 (C-4), 59.25 (C-1), 56.40 (C-5), 53.51 (2C-9), 52.51 (C-6), 51.78 (CO_2Me), 50.30 (C-8), 35.62 (C-1′), 27.56 ($C(CH_3)_2$), 26.15 (C-7), 23.02 ($C(CH_3)_2$). FABMS *m/z* calcd for $C_{18}H_{32}N_2O_6$ [M], 372.2260, found 372.2258.

For **10c–α**: ^{1}H NMR ($CDCl_3$) δ: 5.47 (br s, s, OH), 4.73–4.68 (d, J = 6.0 Hz, 1H, H-3), 4.51–4.48 (d, J = 6.0 Hz, 1H, H-2), 4.26–4.19 (m, 2H, H-1, H-4), 3.67–3.65 (m, 7H, 2H-10a, 2H-10b, CO_2Me), 2.82–2.64 (m, 6H, H-1′a, H-1′b, H-5a, H-5b, H-6a, H-6b), 2.42–2.37 (m, 6H, H-8a, H-8b, 2H-9a, 2H-9b), 1.75–1.63 (m, 2H, H-7a, H-7b), 1.43 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 171.4 (C=O), 112.8 (C-*i*Pr), 83.6 (C-2), 81.8 (C-1), 80.9 (C-3), 76.0 (C-4), 66.7 (2C-10), 57.4 (C-8), 53.5 (2C-9), 51.7 (CO_2Me), 48.3 (C-6), 48.2 (C-1′), 33.8 (C-5), 26.1 ($C(CH_3)_2$), 25.0 (C-7), 24.9 ($C(CH_3)_2$). FABMS *m/z* calcd for $C_{18}H_{32}N_2O_6$ [M], 372.2260, found 372.2262.

3.14. Methyl 2-C-(5-decylamino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetate (10d)

The same procedures as described above were used to obtain **10d** (40%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.31 (dd, J = 4.5, 4.5 Hz, 1H), 4.05–4.00 (m, 1H), 3.95 (br, OH, 1H), 3.65 (s, 3H), 3.00–2.85 (m, 2H), 2.61–2.37 (m, 6H), 1.50 (s, 3H), 1.33 (s, 3H), 1.30–1.10 (m, 16H), 0.84 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 172.21, 109.55, 77.17, 74.28, 59.20, 52.83, 52.32, 51.85, 35.38, 31.84, 29.55, 29.51 (2C), 29.40, 29.26, 27.53, 27.17, 26.11, 25.64, 22.64, 14.08. FABMS m/z Calcd for $C_{21}H_{40}NO_5$ $[M+H]^+$, 386.2906, found 386.2901.

3.15. 2-C-(5-Allylamino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)ethanol (11a)

To a solution of **10a** (0.84 g, 2.94 mmol) in dry CH_2Cl_2 was added 1 M solution of DIBALH (8.83 mL, 3 equiv) at 0 °C. The reaction mixture was stirred at the temperature for 1.5 h. MeOH (0.86 mL) was added at 0 °C and was raised to room temperature. Saturated NaCl (1.72 mL), Et_2O (43.0 mL), and $MgSO_4$ (4.5 g) were added, and the mixture was stirred for 1 h and then filtered through a Celite pad. The solvent was removed and the crude mixture was purified by column chromatography (hexanes–EtOAc) to give **11a** (0.66 g, 87%) as a yellow oil. For **11a–β**: ^{1}H NMR ($CDCl_3$) δ: 5.83–5.73 (m, 1H, =CH), 5.15 (dd, J = 17.7, 9.3 Hz, 2H, $=CHCH_2$), 4.20 (dd, J = 6.0, 3.3 Hz, 1H, H-2), 3.96 (dd, J = 5.7, 4.8 Hz, 1H, H-3), 3.79–3.67 (m, 3H, H-4, CH_2OH), 3.32 (dd, J = 14.3, 5.2 Hz, 1H, $=CHCH_2$), 3.08–2.91 (m, 2H, $=CHCH_2$, H-5a′), 2.73–2.68 (m, 1H, H-1), 2.24 (d, J = 1.5 Hz, 1H, H-5b′), 1.98–1.91 (m, 2H, H-1′a, H-1′b), 1.52 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 133.5 (=CH), 118.6 ($=CH_2$), 108.9 (C-*i*Pr), 74.4 (C-3), 74.3 (C-2), 64.9 (C-4), 59.3 (C-2′), 56.7 (C-1), 55.7 ($CH_2CH=$), 53.4 (C-5), 32.0 (C-1′), 25.7 ($C(CH_3)_2$), 25.3 ($C(CH_3)_2$). FABMS m/z Calcd for $C_{13}H_{23}NO_4$ [M], 257.1627, found 257.1630.

For **11a–α**: ^{1}H NMR ($CDCl_3$) δ: 5.82–5.68 (m, 1H, =CH), 5.12 (dd, J = 18.9, 8.4 Hz, 2H, $=CH_2$), 4.26 (dd, J = 4.5, 4.2 Hz, 1H, H-3), 3.97 (dd, J = 10.2, 4.8 Hz, 1H, H-2), 3.87–3.83 (m, 1H, H-4), 3.66 (t, J = 6.0 Hz, 2H, H-2′a, H-2′b), 3.25 (dd, J = 13.9, 6.2 Hz, 1H, $=CHCH_2$), 2.99 (dd, J = 13.5, 7.2 Hz, 1H, $=CHCH_2$), 2.76 (dd, J = 11.4, 4.8 Hz, 1H, H-5a′), 2.56–2.50 (m, 1H, H-1), 2.31 (t, J = 11.1 Hz, 1H, H-5b′), 1.83–1.72 (m, 1H, H-1′a), 1.66–1.56 (m, 1H, H-1′b), 1.41 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 133.8 (=CH), 118.2 ($=CH_2$), 108.9 (C-*i*Pr), 76.9 (C-2), 74.4 (C-3), 65.0 (C-4), 59.9 (C-2′), 59.4 (C-1), 55.8 ($CH_2CH=$), 51.9 (C-5), 32.0 (C-1′), 27.4 ($C(CH_3)_2$), 25.6 ($C(CH_3)_2$). FABMS m/z Calcd for $C_{13}H_{23}NO_4$ [M], 257.1627, found 257.1622.

3.16. 2-C-(5-Deoxy-2,3-di-*O*-isopropylidene-5-(4-methoxybenzyl)-β-D-ribopyranosyl)ethanol (11b)

To a solution of LAH (62.6 mg, 1.65 mmol) in dry THF (4 mL) under N_2 at 0 °C was added **10b** (0.1 g, 0.27 mmol). The solution was stirred for 2 h, and then acidified with 30% H_2SO_4. The precipitate was filtered through a Celite pad and the filtrate was extracted with CH_2Cl_2. Purification by column chromatography (EtOAc–hexanes–CH_2Cl_2 4:1:2) afforded **11b** (52 mg, 57%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.16 (d, J = 8.4 Hz, 2H, Ph), 6.83 (d, J = 8.4 Hz, 2H, Ph), 4.38 (dd, J = 5.1, 4.8 Hz, 1H, H-2), 4.20 (dd, J = 6.3, 6.0 Hz, 1H, H-3), 3.96 (d, J = 12.9 Hz, 1H, $PhCH_2$), 3.87–3.79 (m, 6H, OMe, H-2′a, H-2′b, H-4), 3.41 (d, J = 12.6 Hz, 1H, $PhCH_2$), 2.84–2.73 (m, 2H, H-1, H-5a), 2.58 (t, J = 5.4 Hz, 1H, H-5b), 2.17–2.13 (m, 2H, H-1′a, H-1′b), 1.40 (s, $C(CH_3)_2$), 1.26 (s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 158.9 (Ph), 130.3 (2Ph), 113.9 (3Ph), 109.3 (C-*i*Pr), 77.3 (C-3), 74.1 (C-2), 65.4 (C-4), 60.8 (C-2′), 60.3 (C-1), 57.5 ($PhCH_2$), 55.3 (OMe), 51.2 (C-5), 32.6 (C-1′), 27.5 ($C(CH_3)_2$), 25.7 ($C(CH_3)_2$). FABMS: m/z Calcd for $C_{18}H_{28}NO_5$ $[M+H]^+$, 338.1967, found 338.1962.

3.17. 2-C-(5-Deoxy-2,3-di-*O*-isopropylidene-5-morpholinopropylamino-β-D-ribopyranosyl)ethanol (11c)

To a solution of **10c** (0.25 g, 0.67 mmol) in dry CH_2Cl_2 (5 mL) was added a 1 M solution of DIBALH (2.0 mL, 3 equiv) at 0 °C. Same workup as above and purification by column chromatography (EtOAc–MeOH 6:1) gave **11c** (0.11 g, 47%) as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ: 4.32 (dd, J = 5.1, 4.8 Hz, 1H, H-3), 4.04 (dd, J = 6.0, 6.0 Hz, 1H, H-2), 3.94–3.86 (m, 1H, H-4), 3.75–3.70 (m, 2H, H-2′a, H-2′b), 3.65 (t, J = 4.8 Hz, 4H, 2H-10a, 2H-10b), 2.85 (br, s, OH), 2.80 (dd, J = 11.1, 4.5 Hz, 1H, H-5a), 2.74–2.65 (m, 2H, H-1, H-1′a), 2.59–2.50 (m, 1H, H-1′b), 2.44–2.22 (m, 7H, H-5b, H-6a, H-6b, 2H-9a, 2H-9b), 1.73–1.62 (m, 4H, H-7a, H-7b, H-8a, H-8b), 1.47 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 109.1 (C-*i*Pr), 77.2 (C-2), 74.1 (C-3), 66.7 (2C-10), 65.3 (C-4), 60.2 (C-2′), 59.8 (C-1), 56.3 (C-6), 53.6 (2C-9), 51.7 (C-5), 51.3 (C-1′), 32.7 (C-8), 27.4 ($C(CH_3)_2$), 25.6 ($C(CH_3)_2$), 23.0 (C-7). FABMS m/z Calcd for $C_{17}H_{33}N_2O_5$ $[M+H]^+$, 345.2389, found 345.2394.

3.18. 2-C-(5-Amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetic acid (12a)

A mixture of **4** (0.23 g, 0.938 mmol) and aq NaOH (0.76 mL of a 1 M solution) in dioxane (2 mL) was stirred for 4 h. The solution was acidified to pH 2 with 1 M HCl and extracted thoroughly with EtOAc (6 × 5 mL). The combined organic phase was dried ($MgSO_4$), concentrated, and purified by column chromatography (hexane/EtOAc, 1:2) to give **12a** (0.16 g, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.77 (dd, J = 6.0, 4.2 Hz, 1H, H-3), 4.62 (dd, J = 6.0, 1.5 Hz, 1H, H-2), 4.40–4.34 (m, 1H, H-4), 4.18 (t, J = 5.1 Hz, 1H, H-1), 3.40 (dd, J = 12.9, 6.0 Hz, 1H, H-1′a), 3.28 (dd, J = 12.9, 4.8 Hz, 1H, H-1′b), 2.77 (dd, J = 6.6, 5.7 Hz, 2H, H-5a, H-5b), 1.46 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 176.4 (C=O), 113.1 (C-*i*Pr), 83.1 (C-2), 82.5 (C-1), 81.1 (C-3), 77.1 (C-4), 51.6 (C-1′), 34.2 (C-5), 26.1 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$). FABMS m/z Calcd for $C_{10}H_{18}NO_5$ $[M+H]^+$, 232.1185, found 232.1184.

3.19. 2-C-[5-Deoxy-2,3-di-*O*-isopropylidene-5-(4-methoxybenzylamino)-β-D-ribopyranosyl]acetic acid (12b)

A mixture of **10b** (0.8 g, 2.19 mmol) and aq NaOH (1 M, 2.66 mL) in dioxane (8 mL) was stirred for 12 h. The solution was acidified to pH 2 with 1 M HCl and extracted thoroughly with EtOAc (6 × 5 mL). Purification by column chromatography afforded **12b** (0.63 g, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.22 (d, J = 8.4 Hz, 2H, Ph), 6.83 (d, J = 8.7 Hz, 2H, Ph), 4.33 (dd, J = 5.4, 4.5 Hz, 1H, H-3), 4.18–4.04 (m, 3H, H-2, H-4, $PhCH_2$), 3.75 (s, 3H, OMe), 3.66 (d, J = 12.9 Hz, 1H, $PhCH_2$), 3.11 (dd, J = 11.7, 5.4 Hz, 1H, H-1), 2.84–2.56 (m, 4H, H-5a, H-5b, H-1′a, H-1′b), 1.47 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 173.7 (C=O), 159.7 (Ph), 131.2 (2Ph), 125.6 (Ph), 114.3 (2Ph), 110.2 (C-*i*Pr), 75.6 (C-2), 73.4 (C-3), 64.1 (C-4), 58.4 (C-1), 57.8 ($PhCH_2$), 55.3 (OMe), 48.4 (C-5), 33.6 (C-1′), 27.3 ($C(CH_3)_2$), 25.4 ($C(CH_3)_2$), FABMS m/z Calcd for $C_{18}H_{26}NO_6$ $[M+H]^+$, 352.1760, found 352.1757.

3.20. *N*-Benzyl 2-C-(5-amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetamide (13)

To a stirred solution of benzylamine (0.048 mL) and acid **12a** (0.102 g, 0.441 mmol) in DMF (73 mL), DEPC (0.1 mL, 1.5 equiv) and Et_3N (0.18 mL, 3 equiv) were added at 0 °C under an argon

atmosphere. The solution was warmed to room temperature and stirred for 24 h. The mixture was partitioned in EtOAc–H_2O (1:1), and the organic layer was washed with brine. The aqueous phase was extracted with EtOAc (2 × 10 mL). The organic layers were combined, dried, and concentrated. Purification by chromatography (hexanes–EtOAc 1:1) gave **13** (0.117 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.19 (m, 5H, Ph), 4.66 (dd, J = 6.0, 3.9 Hz, 1H, H-3), 4.54 (d, J = 6.0 Hz, 1H, H-2), 4.48–4.30 (m, 2H, $PhCH_2$), 4.37–4.30 (m, 1H, H-4), 4.14 (t, J = 5.8 Hz, 1H, H-1), 3.34 (dd, J = 12.9, 6.9 Hz, 1H, H-1′a), 3.17 (dd, J = 12.7, 4.9 Hz, 1H, H-1′b), 2.60 (d, J = 6.3 Hz, 2H, H-5a, H-5b), 1.42 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.1 (C═O), 138.2 (Ph), 128.5 (2Ph), 127.5 (2Ph), 127.3 (Ph), 112.8 (C-*i*PrC-*i*Pr), 83.0 (C-2), 82.9 (C-1), 81.4 (C-3), 77.8 (C-4), 51.2 (C-1′), 43.4 ($PhCH_2$), 36.8 (C-5), 26.2 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$). FABMS *m/z* $[M+H]^+$: Calcd for $C_{17}H_{25}N_2O_4$, 321.1814, found 321.1807.

3.21. *N*-Allyl 2-C-[5-deoxy-2,3-di-*O*-isopropylidene-5-(4-methoxybenzylamino)-β-D-ribopyranosyl acetamide (14)

To a solution of **12b** (0.1 g, 0.28 mmol) in DMF were added allylamine (0.02 mL, 1 mmol), DEPC (0.065 mL), and TEA (0.11 mL) at 0 °C under N_2. The solution was warmed to room temperature and stirred for 24 h. Same workup as above and purification by column chromatography (hexanes–EtOAc 1:1) afforded **14** (0.068 g, 62%) as a colorless syrup. ^{1}H NMR ($CDCl_3$) δ: 7.12 (d, J = 8.4 Hz, 2H, Ph), 6.82 (d, J = 8.4 Hz, 2H, Ph) 5.89–5.76 (m, 1H, CH═), 5.23–5.07 (m, 2H, CH_2═), 4.38 (dd, J = 4.8, 4.5 Hz, 1H, H-3), 4.12–4.00 (m, 1H, H-2), 3.94–3.83 (m, 4H, CH_2CH═, H-4, $PhCH_2$), 3.81 (s, 3H, OMe), 3.22 (d, J = 12.9 Hz, 1H, $PhCH_2$), 2.82–2.71 (m, 3H, H-1′a, H-5a, H-1), 2.56 (dd, J = 17.7, 6.0 Hz, 1H, H-1′), 2.22 (t, J = 11.0 Hz, 1H, H-5b), 1.48 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.4 (C═O), 158.0 (Ph), 134.2 (CH═), 130.1 (2Ph), 129.3 (Ph), 116.6 (CH_2═), 113.9 (2Ph), 109.8 (C-*i*Pr), 77.2 (C-2), 74.5 (C-3), 65.6 (C-4), 60.2 (C-1), 56.0 ($PhCH_2$), 55.3 (OMe), 51.7 (C-5), 41.8 (═$CHCH_2$), 35.6 (C-1′), 27.9 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$). FABMS *m/z* Calcd for $C_{21}H_{31}N_2O_5$ $[M+H]^+$, 391.2233, found 391.2243.

3.22. Propargyl 2-C-(5-amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribopyranosyl)acetate (15)

To a stirred solution of acid **12a** (0.279 g, 1.20 mmol) in dry CH_2Cl_2 (20 mL), DMAP (0.147 g, 1.20 mmol), DCC (0.746 g, 3.61 mmol), and propargyl alcohol (0.091 mL, 1.56 mmol) were added. The reaction mixture was then stirred overnight at room temperature. The reaction mixture was filtered and the filtrate washed with 1 M HCl, water, aq $NaHCO_3$, and brine, dried and concentrated. Purification by chromatography (hexanes–EtOAc 6:1) afforded **15** (0.213 g, 66%) as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ: 4.78 (dd, J = 6.0, 3.9 Hz, 1H, H-3), 4.69 (dd, J = 2.4, 1.8 Hz, 2H, OCH_2C≡), 4.61 (dd, J = 6.0, 1.2 Hz, 1H, H-2), 4.43–4.37 (m, 1H, H-4), 4.18 (td, J = 4.8, 1.2 Hz, 1H, H-1), 3.40 (dd, J = 12.9, 6.3 Hz, 1H, H-1′a), 3.26 (dd, J = 13.0, 4.8 Hz, 1H, H-1′b), 2.79 (dd, J = 6.7, 3.0 Hz, 2H, H-5a, H-5b), 2.46 (t, J = 2.4 Hz, 1H, C≡CH), 1.46 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.1(C═O), 113.1 (C-*i*Pr), 83.2 (C-2), 82.6 (C-1), 81.2 (C-3), 77.2 (C-4), 75.0 (Cq, CH_2C≡CH), 52.1 (CH_2, OCH_2C≡), 51.6 (C-1′), 34.3 (C-5), 26.2 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$).

3.23. 1,2,3-Triazole-linked aza-*C*-glycoside (16)

To a solution of **15** (0.213 g, 0.79 mmol) and **2** (0.236 g, 0.87 mmol) in ethanol (10 mL) were added copper turnings (21.3 mg) and a copper sulfate solution (0.414 mL, 1 M). The mixture was heated at reflux for 12 h when the reaction was complete (monitored by TLC). The reaction mixture was filtered through Celite, and the filtrate was concentrated. Purification by column chromatography (hexanes–EtOAc, 1:3) afforded **16** (0.20 g, 47%) as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ: 7.67 (s, 1H, ArH), 5.27 (d, J = 12.9 Hz, 1H, $ArCH_2$), 5.21 (d, J = 12.6 Hz, 1H, $ArCH_2$), 4.76 (td, J = 6.0, 4.2 Hz, 1H, H-3), 4.63–4.49 (m, 4H, H-2, H-4, H-5′a, H-5′b), 4.42–4.36 (m, 1H, H-1), 4.29–4.13 (m, 4H, H-1′, H-2′, H-3′, H-4′), 3.69 (s, 3H, CO_2Me), 3.39 (dd, J = 12.9, 6.6 Hz, 1H, CH_2CO_2), 3.24 (dd, J = 12.9, 4.8 Hz, 1H, CH_2CO_2), 2.75 (dd, J = 6.7, 2.7 Hz, 2H, H-5a, H-5b), 2.62 (dd, J = 15.9, 4.5 Hz, 1H, CH_2CO_2), 2.45 (dd, J = 15.9, 6.6 Hz, 1H, CH_2CO_2), 1.49 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.7 (C═O), 170.6 (C═O), 142.6 (Ar), 125.4 (C-ArH), 115.3 (C-*i*Pr), 113.1 (C-*i*Pr), 83.8, 83.2, 82.7, 82.1, 81.5, 81.2 (C-2, C-4, C-1′, C-2′, C-3′, C-4′), 80.8 (C-3), 77.2 (C-1), 57.8 ($ArCH_2$), 51.9 (CO_2Me) , 51.7 (CH_2CO_2), 51.5 (C-5′), 37.8 (CH_2CO_2), 34.5 (C-5), 27.4 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$).

Acknowledgment

This work was supported by the National Science Council of Taiwan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.08.005.

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