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# Amino Acid Derivatives, IV [1]: Synthesis and Antiviral Evaluation of New α-Amino Acid Esters Bearing Methyl β-D-Ribofuranoside Side Chain

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**Summary.** Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside was synthesized and oxidized with $HIO_4$ to afford the corresponding carboxylic acid. The latter was coupled with the appropriate acylated amino acids in the presence of HO*Bt* and *DDC* as coupling reagents to give the corresponding amides. The methyl acetate derivative was hydrolyzed with 2 *N* KOH/*Me*OH to the corresponding carboxylic acid, which was coupled with L-glycine methyl ester to furnish the amide. Deprotection was carried out with 70% *Ac*OH at reflux temperature. The prepared glycopeptides were tested for antiviral activity against *Herpes Simplex* virus type-1 (*HS*V-1) and hepatitis-A virus (HAV). The plaque reduction infectivity assay was used to determine virus count reduction as a result of treatment with tested compounds.

**Keywords.** Carbohydrates; Glycopeptides; α-Amino acids; 1-Hydroxybenzotriazole; *N*,*N*′-Dicyclohexylcarbodiimide.

## Introduction

Among the great variety of functions assumed by carbohydrates in biological systems, the role of the carbohydrate domain of glycoproteins in molecular recognition has been a focus of particular attention for many scientific disciplines [2]. Glycoproteins play an important role in biological processes, such as tumor metastasis [3] and immunogenic recognition [4]. As promising building blocks for the artificial glycopeptides, *C*-glycosyl amino acids are of particular interest due to their stability toward chemical and enzymatic degradation [5]. α-*C*-Glycosylglycine and its methylene chain tethered derivatives (Fig. 1, **I**) have been synthesized from glycosyl halides [6], glycols [7], allyl-*C*-glycosides [8], sugar nitrones [9], and sugar δ-lactones [10]. While the methodology of the C–C bond formation reactions and stereochemistry of the observed products with respect to the configuration of the anomeric center and/or the α-carbon of the amino acid moiety have been extensively studied for these synthetic *C*-glycosyl amino acids, only a small number of them have been utilized for *C*-glycosylpeptide synthesis [11]. Our interest in the synthesis of such compounds was to shed some light on their antiviral properties as a part of our program aimed at the development of new α-amino acid derivatives as antiviral agents [12].

## Results and Discussion

### *Synthesis*

A solution of dry D-ribose in acetone/2,2-dimethoxypropane/methanol saturated with HCl afforded after stirring methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside [13]. Oxidation of the primary hydroxyl group in this compound using $HIO_4$ gave methyl 2,3-*O*-isopropylidene-β-D-ribo-1,4-furanosyl carboxylic acid (**1**) [14]. A suitable coupling method [15] was employed for the formation of peptides by reaction of the carboxylic acid group with an acylated amino

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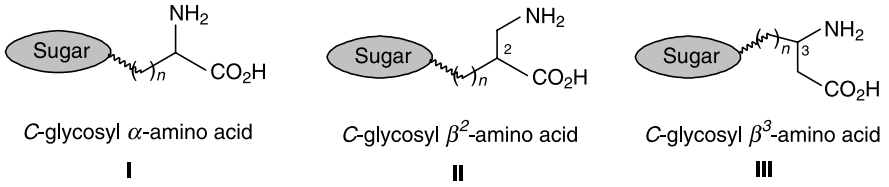
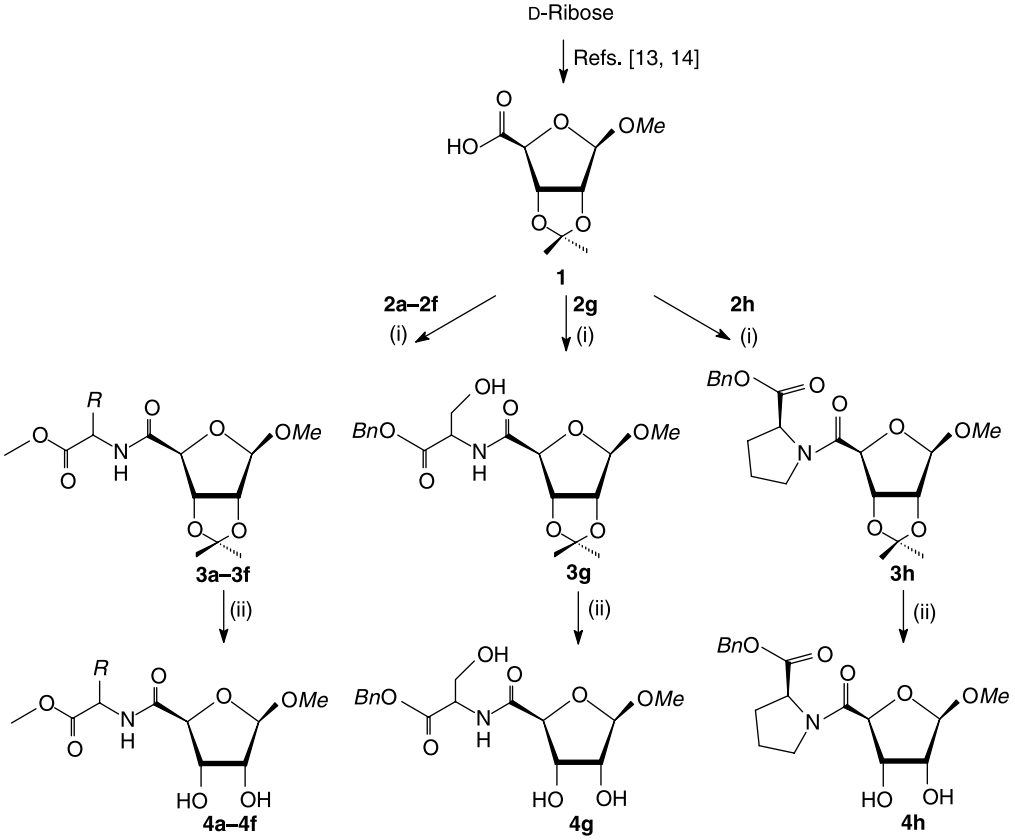



**Fig. 1.** Structures of *C*-glycosyl amino acids

acid using 1-hydroxybenzotriazole (HO*Bt*) [16], and *N,N′*-dicyclohexylcarbodiimide (*DCC*) [17] as coupling reagents. HO*Bt* is currently the most frequently used activating agent for the carboxyl group of amino acids. The procedure is fast and suppresses racemization, especially in the presence of *DCC* [12, 18].

Amides **3a**–**3h** were prepared by coupling of **1** with the appropriate acylated amino acids **2a**–**2h** in the presence of HO*Bt* and *DCC* to yield **3a**–**3h** in 55–74% yields after chromatography.

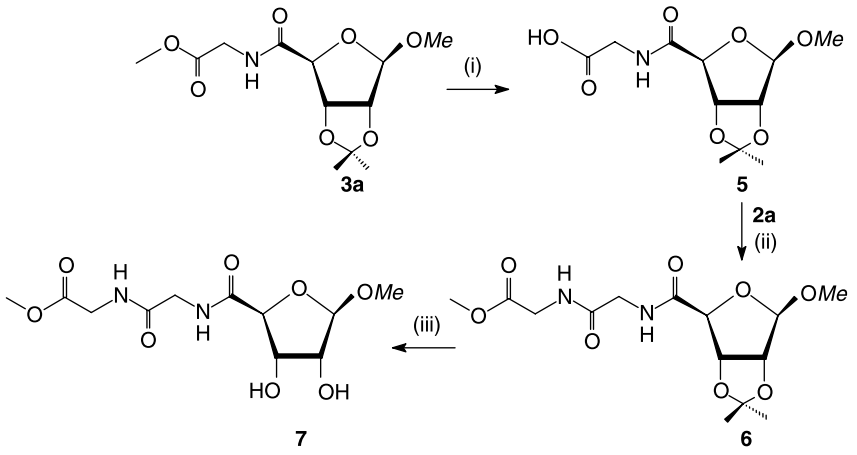
The structures of the newly synthesized compounds **3a**–**3h** were determined from their $^{1}H$, $^{13}C$ NMR,




| 2–4 | *R* | Amino Acid |
|---|---|---|
| **a** | H | L-Glycine |
| **b** | *Me* | L-Alanine |
| **c** | *Ph* | L-Phenylglycine |
| **d** | $CH_2CH_2SMe$ | L-Methionine |
| **e** | $CH_2CH(Me)_2$ | L-Leucine |
| **f** | $CH(Me)_2$ | L-Valine |

(i) *DCC*/HO*Bt*/*Me*CN; (ii) 70% *Ac*OH/reflux

**Scheme 1**




(i) KOH/*Me*OH; (ii) *DCC*/HO*Bt*/*Me*CN; (iii) 70% *Ac*OH/reflux

**Scheme 2**

and mass spectra. The $^1$H NMR spectra showed a singlet at $\delta = 3.22$–$3.43$ for the O*Me*, while the isopropylidene group appeared as two singlets at the region $\delta = 1.13$–$1.26$ and 1.29–1.43 ppm. The singlet at $\delta = 4.90$–$5.10$ corresponds to H-1 of the sugar moiety. The protons of the amino acid residues were fully assigned. $^{13}$C NMR of the amides (Experimental), showed similar pattern of methyl ribofuranoside carbons resonances, meanwhile compound **3d** was selected for this study. The anomeric carbon atom (C-1) was resonated at $\delta = 86.4$ ppm, two methoxy groups resonated at $\delta = 52.4$ and 56.4 ppm, two carbonyl groups at higher field ($\delta = 169.6$ and 171.8 ppm), while the S*Me* group appeared at lower field $\delta = 15.2$ ppm.

Deprotection of compounds **3a**–**3h** was carried out by using 70% *Ac*OH at reflux temperature. The crude products were purified by silica gel column affording **4a**–**4h** in 80–85%. The structures of the deprotected derivatives were confirmed by their $^1$H, $^{13}$C NMR, and mass spectra, which showed the disappearance of the isopropylidene group in all cases (Scheme 1).

Furthermore, we selected the amide **3a** as precursor for the synthesis of a new derivative to examine its antiviral activity in comparison with **4a**–**4h**. The methyl acetate derivative **3a** was hydrolyzed in 78% yield to the corresponding carboxylic acid **5** using 2 *N* KOH in methanol. The acid derivative **5** was coupled with L-glycine acetate (**2a**) by applying the method used previously in the presence of HO*Bt* and *DCC* as coupling reagents to afford **6** in 66% yield. Deprotection of **7** was carried out using 70% *Ac*OH at reflux for 2 h. The crude product was purified by silica gel column to afford **7** in 84% yield.

### *Testing*

The plaque infectivity assay [19] was carried out to test the prepared compounds for antiviral activity. The test was performed to include three possibilities for antiviral activity, virucidal effect, virus adsorption, and effect on virus replication for both HAV-27 and *HS*V-1.

For the antiviral activity against HAV-27 it was noticed that, at both concentrations 10 and 20 $\mu$g/10$^5$ cells, compounds **4c**–**4e**, **4h**, and **7** revealed the highest antiviral activity in this series of compounds and compounds **4g** revealed high activity at 10 $\mu$g/10$^5$ cells using amantadine (C$^*$) as a control. Compound **4b** showed moderate activity, while at concentration of 20 $\mu$g/10$^5$ cells, compounds **4a** and **4f** revealed little antiviral activity.

For the antiviral activity against *Herpes Simplex* virus-1 (*HS*V-1) the results revealed that compounds **4d**–**4f** showed the highest effect on *HS*V-1 at concentration 10 $\mu$g/10$^5$ cells, while compounds **4a**–**4c**, **4g**, **4h**, and **7** showed moderate activity.

## Conclusions

Some of *C*-glycosyl amino acid esters were prepared and tested for antiviral activity against Hepatitis-A virus (HAV, MBB-cell culture adapted strain) and *Herpes Simplex* virus type-1 (*HS*V-1).

## Experimental

Melting points were determined using a *Kofler* block instrument. TLC was performed on plastic plates Silica Gel 60 $F_{254}$ (E. Merck, layer thickness 0.2 mm). The detection was achieved by treatment with a solution of 15% $H_2SO_4$ in methanol, and heating at 150°C. NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for $^1$H NMR and 62.9 MHz for $^{13}$C NMR with *TMS* as an internal standard. MALDI-MS were measured with a KRATOS Analytical Compact, using 2,5-dihydroxybenzoic acid (*DHB*) as matrix. The $(M + Na)^+$ and $(M + K)^+$ ions were peak matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. The microanalyses were performed at the microanalytical unit, Universität Konstanz, Germany, and were found to agree favourably with the calculated values. Viral screening against HAV and *HS*V was conducted at the Environmental Virology Lab., Department of Water Pollution Research, National Research Centre, Cairo, Egypt.

*General Procedure for Preparation of Methyl 2,3-O-isopropyliden-β-D-ribofuranoside Bearing Amino Acid Esters **3a–3h***

A solution of **2a**–**2h** (5 mmol) in 20 $cm^3$ *Me*CN was cooled to −5°C. 1.10 g **1** (5 mmol), 0.70 g HO*Bt* (5 mmol), and 1.03 g *DCC* (5 mmol) were added successively. The reaction mixture was stirred at 0–5°C for 2 h, then at room temperature for 16 h. Dicyclohexylurea (*DCU*) was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 30 $cm^3$ ethyl acetate and extracted successively with 10 $cm^3$ brine, 10 $cm^3$ 5% $NaHCO_3$ solution, 10 $cm^3$ 1 *N* HCl, followed by 10 $cm^3$ brine, and finally with 10 $cm^3$ $H_2O$. The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography using 3% *Me*OH in $CH_2Cl_2$.

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-aminoacetate* (**3a**, $C_{12}H_{19}NO_7$)

Colorless oil (1.05 g, 73%); $R_f = 0.26$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.23$, 1.39 (2s, $2CH_3$), 3.31, 3.58 (2s, $2OCH_3$), 3.90 (dd, $J = 5.4$, 10.5 Hz, $CH_2$), 4.36 (d, $J = 6.0$ Hz, H-3), 4.43 (d, $J = 6.0$ Hz, H-2), 4.90 (d, $J = 6.5$ Hz, H-4), 4.99 (s, H-1) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 25.2$, 26.7 ($2CH_3$), 41.3 ($CH_2$), 52.5, 56.6 ($2OCH_3$), 82.6 (C-4), 84.7 (C-3), 86.4 (C-2), 86.6 (C-1), 112.8 ($CMe_2$), 170.2, 170.7 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 312 [$(M + Na)^+$, 19], 328 [$(M + K)^+$, 37].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-aminopropanoate* (**3b**, $C_{13}H_{21}NO_7$)

White powder (0.91 g, 74%); $R_f = 0.43$ (petroleum ether/ethylacetate, 2/1); mp 46–48°C; $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.14$ (s, $CH_3$), 1.24 (d, $J = 7.2$ Hz, $CH_3$), 1.30 (s, $CH_3$), 3.31, 3.58 (2s, $2OCH_3$), 4.37 (d, $J = 5.9$ Hz, H-3), 4.40 (m, CH), 4.44 (d, $J = 5.9$ Hz, H-2), 4.91 (d, $J = 6.5$ Hz, H-4), 4.96 (s, H-1), 7.05 (d, $J = 7.5$ Hz, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 18.1$ ($CH_3$), 24.7, 25.9 ($2CH_3$), 47.7 (CH), 52.2, 56.2 ($2OCH_3$), 82.2 (C-4), 84.4 (C-3), 86.0 (C-2), 86.1 (C-1), 112.4 ($CMe_2$), 169.4, 172.8 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 342 [$(M + K)^+$, 56].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-2-phenylacetate* (**3c**, $C_{18}H_{23}NO_7$)

White powder (1.30 g, 72%); $R_f = 0.53$ (petroleum ether/ethylacetate, 2/1); mp 83–85°C; $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.22$, 1.38 (2s, $2CH_3$), 3.41, 3.61 (2s, $2OCH_3$), 4.53 (d, $J = 6.0$ Hz, H-3), 4.55 (d, $J = 6.0$ Hz, H-2), 4.99 (d, $J = 6.5$ Hz, H-4), 5.03 (s, H-1), 5.45 (d, $J = 7.2$ Hz, CH), 7.26 (m, Ph-H), 7.68 (d, $J = 7.3$ Hz, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 24.9$, 26.4 ($2CH_3$), 34.8 (CH), 52.6, 56.2 ($2OCH_3$), 82.6 (C-4), 84.5 (C-3), 86.6 (C-2), 86.7 (C-1), 112.6 ($CMe_2$), 127.1, 128.5, 128.9, 136.1 (Ph-C), 169.6, 170.8 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 388 [$(M + Na)^+$, 78], 404 [$(M + K)^+$, 45].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-4-methylthiobutanoate* (**3d**, $C_{15}H_{25}NO_7S$)

Colorless oil (1.3 g, 72%); $R_f = 0.40$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.23$, 1.39 (2s, $2CH_3$), 1.88 (m, $CH_2$), 2.51 (s, $SCH_3$), 2.40 (m, $CH_2$), 3.41, 3.67 (2s, $2OCH_3$), 4.45 (d, $J = 5.9$ Hz, H-3), 4.54 (d, $J = 5.9$ Hz, H-2), 4.58 (m, CH), 4.87 (m, H-4), 5.00 (s, H-1), 7.15 (d, $J = 7.9$ Hz, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 15.2$ ($SCH_3$), 24.8 ($CH_2$), 26.3, 29.3 ($2CH_3$), 31.8 ($CH_2$), 51.2 (CH), 52.4, 56.4 ($2OCH_3$), 82.6 (C-4), 84.3 (C-3), 86.3 (C-2), 86.4 (C-1), 112.6 ($CMe_2$), 169.6, 171.8 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 386 [$(M + Na)^+$, 78], 402 [$(M + K)^+$, 34].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-4-methylpentanoate* (**3e**, $C_{16}H_{27}NO_7$)

Colorless oil (1.2 g, 69%); $R_f = 0.66$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 0.89$ (m, $2CH_3$), 1.26, 1.43 (2s, $2CH_3$), 1.54 (m, CH, $CH_2$), 3.42, 3.68 (2s, $2OCH_3$), 4.12 (m, CH), 4.48 (d, $J = 6.0$ Hz, H-3), 4.58 (d, $J = 6.0$ Hz, H-2), 5.01 (d, $J = 6.5$Hz, H-4), 5.10 (s, H-1), 6.94 (d, $J = 8.5$ Hz, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.9$, 22.6 ($2CH_3$), 24.5, 24.8 ($2CH_3$), 26.3 ($CH_2$), 34.8, 41.8 (2CH), 50.4, 56.3 ($2OCH_3$), 82.6 (C-4), 84.4 (C-3), 86.4 (C-2), 86.5 (C-1), 112.6 ($CMe_2$), 169.6, 172.8 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 368 [$(M + Na)^+$, 88].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-3-methylbutanoate* (**3f**, $C_{15}H_{25}NO_7$)

Colorless oil (1.4 g, 67%); $R_f = 0.63$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 0.80$ (d, $2CH_3$), 1.22, 1.39 (2s, $2CH_3$), 2.08 (m, CH), 3.43, 3.65 (2s, $2OCH_3$), 4.47 (m, CH, H-3), 4.55 (d, $J = 5.9$ Hz, H-2), 4.92 (m, H-4), 5.03 (s, H-1), 7.11 (br, s, NH) ppm; $^{13}$C NMR ($CDCl_3$,

62.5 MHz): $\delta = 17.4$, 18.5 ($2CH_3$), 25.2, 26.3 ($2CH_3$), 31.3, 34.7 (2CH), 51.8, 56.7 ($2OCH_3$), 83.0 (C-4), 84.4 (C-3), 86.7 (C-2), 86.8 (C-1), 112.6 (*CMe*$_2$), 169.6, 171.6 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 354 [$(M + Na)^+$, 66], 370 [$(M + K)^+$, 75].

*Benzyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-3-hydroxypropanoate* (**3g**, $C_{19}H_{25}NO_8$)
Colorless oil (0.26 g, 65%); $R_f = 0.17$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.23$, 1.39 (2s, $2CH_3$), 3.31 (s, $OCH_3$), 3.82 (dd, $J = 3.3$, 11.2 Hz, C*H*$_2$OH), 3.92 (dd, $J = 7.8$, 11.2 Hz, C*H*$_2$OH), 4.20 (br, s, OH), 4.46 (d, $J = 6.0$ Hz, H-3), 4.57 (m, CH, H-2), 5.00 (d, $J = 6.5$ Hz, H-4), 5.06 (s, H-1), 5.12 (m, C*H*$_2$Ph), 7.26 (m, Ph-H), 7.46 (d, $J = 7.7$ Hz, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 24.8$, 26.3 ($2CH_3$), 34.8 ($CH_2$), 54.6 (CH), 56.3 ($OCH_3$), 67.3 ($CH_2$), 82.3 (C-4), 84.3 (C-3), 86.1 (C-2), 86.8 (C-1), 112.6 (*CMe*$_2$), 127.9, 128.3, 128.5, 128.6, 135.1 (Ph-C), 169.8, 170.4 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 434 [$(M + K)^+$, 70].

*Benzyl 1-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosyl carbonyl)-amino-2-pyrrolidinecarboxylate* (**3h**, $C_{21}H_{27}NO_7$)
Colorless oil (1.10 g, 55%); $R_f = 0.17$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.25$, 1.43 (2s, $2CH_3$), 1.90 (m, $2CH_2$), 3.22 (s, $OCH_3$), 3.61–3.90 (m, $CH_2$), 4.42 (m, CH), 4.55 (d, $J = 5.9$ Hz, H-3), 4.70 (d, $J = 5.9$ Hz, H-2), 4.93 (m, H-4), 5.10 (s, H-1), 5.15 (m, C*H*$_2$Ph), 7.28 (m, Ph-H) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 24.3$, 24.6 ($2CH_3$), 26.1, 28.6, 46.7 ($CH_2$), 54.8 (CH), 55.4 ($CH_2$), 58.8 ($OCH_3$), 66.4 ($CH_2$), 80.6 (C-4), 83.3 (C-3), 83.4 (C-2), 109.6 (C-1), 111.8 (*CMe*$_2$), 127.7, 127.9,128.0, 128.2, 135.3 (Ph-C), 168.2, 171.5 (2C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 444 [$(M + K)^+$, 76].

*General Procedure for Preparation of Methyl β-D-Ribofuranoside Bearing Amino Acid Esters **4a–4h***
Compounds **3a–3h** (3 mmol) were dissolved in 5 cm$^3$ 70% *Ac*OH and heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was coevaporated two times with 3 cm$^3$ $H_2O$ and two times with 3 cm$^3$ ethanol. The residual oil was purified by silica gel column chromatography using 10% *Me*OH in $CHCl_3$ to give **4a–4h** in 75–80% yields.

*Methyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-aminoacetate* (**4a**, $C_9H_{15}NO_7$)
White foam (0.60 g, 80%); $R_f = 0.20$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 3.41$, 3.68 (2s, $2OCH_3$), 3.94 (dd, $J = 5.4$, 10.5 Hz, $CH_2$), 4.16 (m, H-3), 4.33 (m, H-2), 4.66 (m, H-4), 4.90 (br, s, 2OH), 5.01 (s, H-1) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 272 [$(M + Na)^+$, 55], 288 [$(M + K)^+$, 25].

*Methyl 2-(methyl β-D-ribofuranosyl carbonyl)-aminopropanoate* (**4b**, $C_{10}H_{17}NO_7$)
White foam (0.64 g, 81%); $R_f = 0.33$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.22$ (d, $J = 7.2$ Hz, $CH_3$), 3.41, 3.66 (2s, $2OCH_3$), 4.17–4.26 (m, CH, H-3), 4.34 (m, H-2), 4.70 (m, H-4), 4.90 (s, H-1), 7.00 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 286 [$(M + Na)^+$, 35], 302 [$(M + K)^+$, 19].

*Methyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-2-phenylacetate* (**4c**, $C_{15}H_{19}NO_7$)
White foam (0.78 g, 80%); $R_f = 0.42$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): 3.42, 3.71 (2s, $2OCH_3$), 4.23 (d, $J = 6.0$ Hz, H-3), 4.40 (d, $J = 6.0$ Hz, H-2), 4.59 (d, $J = 6.5$ Hz, H-4), 4.95 (br, s, 2OH), 5.01 (s, H-1), 5.45 (d, $J = 7.2$ Hz, CH), 7.26 (m, Ph-H), 7.60 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 348 [$(M + Na)^+$, 75], 364 [$(M + K)^+$, 28].

*Methyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-4-methylthiobutanoate* (**4d**, $C_{12}H_{21}NO_7S$)
White foam (0.79 g, 82%); $R_f = 0.32$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.90$–2.22 (m, $CH_2$), 2.46–2.57 (m, $SCH_3$, $CH_2$), 3.41, 3.65 (2s, $2OCH_3$), 4.15 (m, H-3), 4.34 (m, H-2), 4.60 (br, s, 2OH), 4.70–4.80 (m, CH, H-4), 5.02 (s, H-1), 7.10 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 346 [$(M + Na)^+$, 80], 362 [$(M + K)^+$, 41].

*Methyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-4-methylpentanoate* (**4e**, $C_{13}H_{23}NO_7$)
White foam (0.77 g, 84%); $R_f = 0.45$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 0.87$ (m, $2CH_3$), 1.45–1.70 (m, CH, $CH_2$), 3.42, 3.63 (2s, $2OCH_3$), 4.00 (m, CH), 4.18 (d, $J = 6.0$ Hz, H-3), 4.38 (d, $J = 6.0$ Hz, H-2), 4.88 (br, s, 2OH), 5.01 (m, H-4), 5.08 (s, H-1), 6.99 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 328 [$(M + Na)^+$, 65], 344 [$(M + K)^+$, 15].

*Methyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-3-methylbutanoate* (**4f**, $C_{12}H_{21}NO_7$)
White foam (0.72 g, 83%); $R_f = 0.47$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 0.79$ (d, $2CH_3$), 2.18 (m, CH), 3.43, 3.69 (2s, $2OCH_3$), 4.17–4.38 (m, CH, H-2, H-3), 4.90 (m, H-4), 4.97 (br, s, 2OH), 5.06 (s, H-1), 7.05 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 314 [$(M + Na)^+$, 77], 330 [$(M + K)^+$, 35].

*Benzyl 2-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-3-hydroxypropanoate* (**4g**, $C_{16}H_{21}NO_8$)
White powder (0.87 g, 82%); mp 109–110°C; $R_f = 0.13$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 3.39$–3.51 (m, $OCH_3$, C*H*$_2$OH), 4.25–4.59 (m, H-2, H-3, CH, OH), 4.89 (br, s, 2OH), 4.95 (m, H-4), 5.09 (s, H-1), 5.14 (m, C*H*$_2$Ph), 7.33 (m, Ph-H), 7.31 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 378 [$(M + Na)^+$, 66], 394 [$(M + K)^+$, 29].

*Benzyl 1-(methyl β-D-ribo-1,4-furanosyl carbonyl)-amino-2-pyrrolidinecarboxylate* (**4h**, $C_{18}H_{23}NO_7$)
White powder (0.93 g, 85%); mp 123–125°C; $R_f = 0.15$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz):

$\delta = 1.70$–$2.03$ (m, $2CH_2$), 3.42–3.58 (m, $OCH_3$, $CH_2$), 4.20–4.45 (m, H-2, H-3, CH), 4.80 (br, s, 2OH), 4.98 (m, H-4), 5.07 (s, H-1), 5.17 (m, $CH_2Ph$), 7.34 (m, Ph-H) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 388 [$(M + Na)^+$, 74], 404 [$(M + K)^+$, 45].

*2-(Methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosylcarbonyl)-aminoacetic acid* (**5**, $C_{11}H_{17}NO_7$)

A mixture of 0.54 g **3a** (1.87 mmol), 10 $cm^3$ *Me*OH, and 5 $cm^3$ 2 *N* KOH was stirred for 3 h. The reaction mixture was acidified with HCl and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethylacetate, 2/1) to give a white foam (0.40 g, 78%); $R_f = 0.21$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.18$, 1.24 (2s, $2CH_3$), 3.31 (s, $OCH_3$), 3.82 (m, $CH_2$), 4.32 (d, $J = 6.2$ Hz, H-3), 4.48 (s, H-4), 5.14 (s, H-1), 5.25 (d, $J = 6.2$ Hz, H-2) 11.32 (br, s, OH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 25.2$, 26.8 ($2CH_3$), 38.2 ($CH_2$), 52.2 ($OCH_3$), 83.0 (C-4), 84.3 (C-3), 86.8 (C-2), 87.1 (C-1), 112.6 ($CMe_2$), 175.6 (C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 314 [$(M + K)^+$, 66].

*Methyl 2-(methyl 2,3-O-isopropyliden-β-D-ribo-1,4-furanosylcarbonyl)-(aminoacetyl)aminoacetate* (**6**, $C_{14}H_{22}N_2O_8$)

A solution of 0.63 g **2a** (5 mmol) in 20 $cm^3$ *Me*CN was cooled to – 5°C. 1.10 g **1** (5 mmol), 0.70 g HO*Bt* (5 mmol), and 1.03 g *DCC* (5 mmol) were added successively. The reaction mixture was stirred at 0–5°C for 2 h, and at room temperature for 16 h. Dicyclohexylurea (*DCU*) was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 30 $cm^3$ ethyl acetate and extracted successively with 10 $cm^3$ brine, 10 $cm^3$ 5% $NaHCO_3$ solution, 10 $cm^3$ 1 *N* HCl, followed by 10 $cm^3$ brine, and finally with 10 $cm^3$ $H_2O$. The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography using 3% *Me*OH in $CH_2Cl_2$ to give a colorless oil (0.50 g, 66%); $R_f = 0.30$ (petroleum ether/ethylacetate, 2/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 1.15$, 1.34 (2s, $2CH_3$), 3.40, 3.63 (2s, $2OCH_3$), 3.94 (m, $2CH_2$), 4.45 (d, $J = 6.2$ Hz, H-3), 4.51 (d, $J = 6.2$ Hz, H-2), 4.93 (m, H-4), 5.04 (s, H-1), 7.10 (br, s, NH), 7.25 (br, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, 62.5 MHz): $\delta = 25.0$, 26.5 ($2CH_3$), 41.1, 42.6 ($2CH_2$), 52.3, 56.5 ($2OCH_3$), 82.5 (C-4), 84.4 (C-3), 86.2 (C-2), 86.4 (C-1), 112.7 ($CMe_2$), 169.9, 170.1, 170.8 (3C=O) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 369 [$(M + Na)^+$, 22], 385 [$(M + K)^+$, 45].

*Methyl 2-(methyl β-D-ribo-1,4-furanosylcarbonyl)-(aminoacetyl)aminoacetate* (**7**, $C_{11}H_{18}N_2O_8$)

Compound **6** (2 mmol, 0.69 g) was dissolved in 3 $cm^3$ 70% *Ac*OH and heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was coevaporated two times with 2 $cm^3$ $H_2O$ and two times with 2 $cm^3$ ethanol. The residual oil was purified by silica gel column chromatography using 10% *Me*OH in $CHCl_3$ to give 0.51 g **7** as white foam in 84% yield. $R_f = 0.28$ (petroleum ether/ethylacetate, 1/1); $^1$H NMR ($CDCl_3$, 250 MHz): $\delta = 3.41$, 3.67 (2s, $2OCH_3$), 3.74–3.86 (m, $2CH_2$), 4.15 (m, H-3), 4.32 (m, H-2), 4.82 (br, s, 2OH), 4.98 (m, H-4), 5.08 (s, H-1), 7.00 (br, s, NH), 7.29 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: DHB): $m/z$ (%) = 329 [$(M + Na)^+$, 65], 345 [$(M + K)^+$, 15].

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