



Article

C-Linked Glycomimetic Libraries Accessed by the Passerini Reaction

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Abstract: Carbohydrates and their conjugates are the most abundant natural products, with diverse and highly important biological roles. Synthetic glycoconjugates are versatile tools used to probe biological systems and interfere with them. In an endeavor to provide an efficient route to glycomimetics comprising structurally diverse carbohydrate units, we describe herein a robust, stereoselective, multicomponent approach. Isopropylidene-protected carbohydrate-derived aldehydes and ketones were utilized in the Passerini reaction, giving different glycosylated structures in high yields and diastereoselectivities up to 90:10 diastereomeric ratio (d.r). Access to highly valuable building blocks based on α -hydroxy C-glycosyl acids or more complex systems was elaborated by simple post-condensation methodologies.

Keywords: multicomponent reactions; carbohydrates; diastereoselective synthesis; glycosylation; C-glycosides

1. Introduction

Carbohydrates are a ubiquitous group of natural products that mediate numerous, highly diverse cellular events and, consequently, participate in development of various diseases. Synthetic carbohydrates and their derivatives are powerful tools in biology and medicinal chemistry with diverse applications ranging from diagnostics to vaccines and therapeutics [1–4]. Moreover, carbohydrates represent attractive chiral synthons susceptible to diverse modifications and transformations, a highly desirable feature in diversity-oriented synthesis [5] and in the synthesis of chiral catalyst systems [6] or of noncovalent systems built upon weak interactions [1]. Carbohydrates are still a relatively untapped pool of new therapeutics [7,8]; however, advances in the functional understanding of carbohydrate-involving biological processes enabled carbohydrates to take over a prominent role in drug design. A particular group of compounds, glycomimetics, has emerged in the response to the growing demand for highly specific structures aimed to probe biological processes or interfere with them [9]. Klebe and Diederich described structurally rigid and metabolically stable lin-benzoguanines functionalized with isopropylidene-protected carbohydrate moieties as superior ligands for tRNA-guanine transglycosylase, the enzyme associated with *Shigella flexneri*-caused infection [10]. According to the DrugBank [11], there are 14 approved drugs bearing the isopropylidene motif in their structure; however, such structures are generally neglected in drug development.

As a part of our ongoing project aimed to enrich the chemical space of natural product-like compounds, we have recently reported a strategy to access a library of densely functionalized glycomimetics. We utilized, for the first time, bis-isopropylidene-protected D-fructose-derived aldehyde **1** (Figure 1) in the Passerini reaction with various acids and isocyanides [12]. Although carbohydrate-derived aldehydes were reported to affect diastereoselectivity in multicomponent reactions (MCRs), observed stereoselectivity was highly influenced by

OH-protecting groups (acetyl or benzyl protecting groups were frequently used) and other components in MCRs [13]. Contrary to that, all reactions performed with bis-isopropylidene-protected aldehyde 1 yielded glycomimetics in high yields and diastereoselectivities up to diastereomeric ratio (d.r.) 94:6. Therefore, to validate the methodology, in this work, we expanded the pool of carbohydrate-derived carbonyl compounds to obtain Passerini products adorned with structurally different carbohydrate units. We were also intrigued by the possible role of the rigid isopropylidene protecting group(s) in the diastereoselective outcome of the reactions. Moreover, an important advantage of the selected carbohydrate derivatives is the fixed anomeric configuration, since the presence of multiple anomers often hampers the purification and characterization of carbohydrate-related compounds.

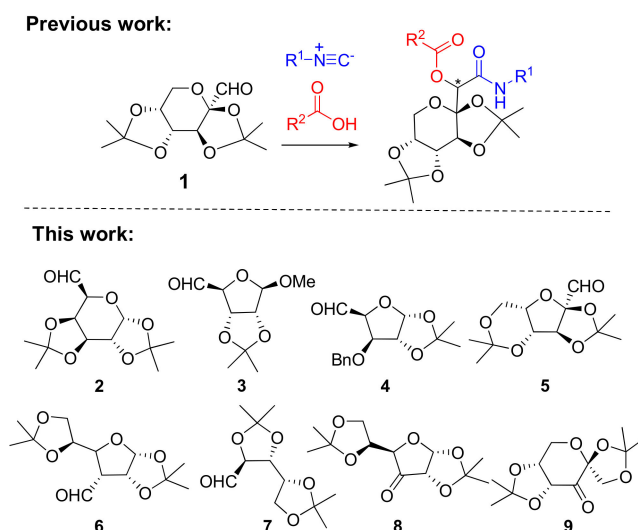


Figure 1. The selection of isopropylidene-protected aldehydes and ketones used as carbonyl components in the Passerini reaction.

We selected commercially available hexoses and pentoses in pyranose, furanose, or open chain forms, easily convertible into aldehyde or keto-derivatives by oxidation with Dess–Martin periodinane. Six aldehydes were utilized in this study (Figure 1): 1,2:3,4-di-*O*-isopropylidene- α -*D*-galactopyranose-derived aldehyde 2, methyl-2,3-*O*-isopropylidene- β -*D*-ribofuranoside-derived aldehyde 3, 3-*O*-benzyl-1,2-*O*-isopropylidene- α -*D*-xylofuranose-derived aldehyde 4, 2,3:4,6-di-*O*-isopropylidene- α -*L*-sorbofuranose-derived aldehyde 5, 1,2:5,6-di-*O*-isopropylidene- α -*D*-allofuranose-derived aldehyde 6, and 2,3:4,6-di-*O*-isopropylidene-*D*-arabinose-derived aldehyde 7. In addition, to complement our selection of carbohydrate-related carbonyl components, two ketones were envisaged: derivatives 8 and 9, obtained from 1,2:5,6-di-*O*-isopropylidene- α -*D*-glucofuranose and 1,2:4,5-di-*O*-isopropylidene- β -*D*-fructopyranose, respectively (Figure 1).

2. Results and Discussion

Our initial experiments were performed with aldehyde 2, and a collection of examples is listed in Figure 2. All reactions were performed in dichloromethane (DCM) at room temperature until the consumption of the aldehyde, typically 6–24 h. Passerini reactions with acetic acid and cyclohexyl isocyanide, *tert*-butyl isocyanide, or methyl isocyanoacetate furnished the desired Passerini products 2a–c in very good yields (~80%, Figure 2). The ratio of two diastereoisomers, determined by ¹H NMR spectroscopy of the reaction mixture, was 80:20 d.r. for compounds 2a and 2b and 70:30 d.r. for 2c. Next, we expanded the scope of the acid components by utilizing *N*-terminally protected amino acids. Gratifyingly, Boc-protected phenylalanine, leucine, and proline in the reaction with methyl isocyanoacetate produced depsitriptides 2d–f in very good yields (58–80%). In earlier work from our group, we successfully used α -hydrazino acids in the Passerini reaction to obtain hydrazino depsipeptides, a novel class of backbone-extended peptidomimetics [14]. Therefore, we performed

Passerini reactions with N^α -Cbz-, N^β -Boc-protected hydrazino acids related to phenylalanine, leucine, and proline and obtained the corresponding hydrazino depsitriptides in very good yields (53–74%). The ratio of two diastereoisomers, ~70:30 d.r. remained constant through all reactions performed with methyl isocyanoacetate, with the exception of **2f**, for which lower diastereoselectivity can be attributed to a somewhat problematic purification. We managed to isolate the major diastereoisomer of compound **2a** and prepared crystals suitable for X-ray analysis (Supplementary Materials). The configuration of the new stereocenter formed in the Passerini reaction was determined as *S*, as found for products obtained with fructose-derived aldehyde **1** [12].

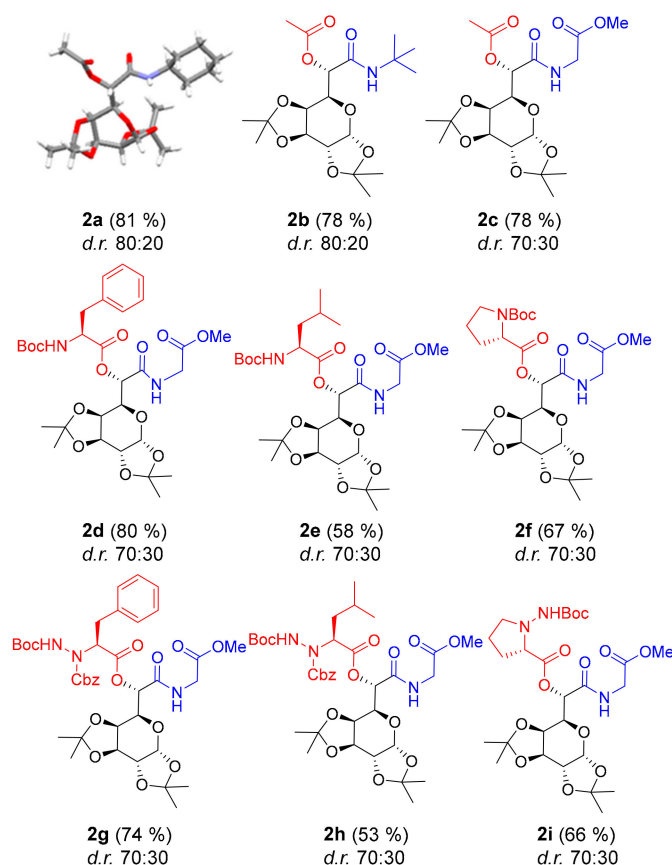


Figure 2. Passerini products obtained with aldehyde 2. Isolated yields are given in parentheses. Diastereomeric ratios (d.r.) were determined by ^1H NMR analysis of the reaction mixtures.

Encouraged by the highly consistent results obtained with aldehyde 2, we proceeded to examine the Passerini reaction with carbonyl compounds 3–9. In all further experiments, two groups of acid–isocyanide components were used: a “simple” acetic acid–cyclohexyl isocyanide combination and an “amino acid-derived” combination with Boc-protected phenylalanine as the acid component and methyl isocyanoacetate (glycine-derived isocyanide). Such selection enabled us to ascertain the influence of sugar-derived carbonyl compounds on the yield and diastereoselectivity of the reaction, as well as the contribution of other components. To our satisfaction, Passerini reactions performed with ribofuranoside-derived aldehyde 3 gave the products **3a** and **3d** in high yields, i.e., 82% and 78%, respectively (Figure 3). Unlike aldehyde 2, the ratio of two diastereoisomers was the same for the two combination of reactants, i.e., 77:23 d.r., determined by ^1H NMR spectroscopy of the reaction mixtures.

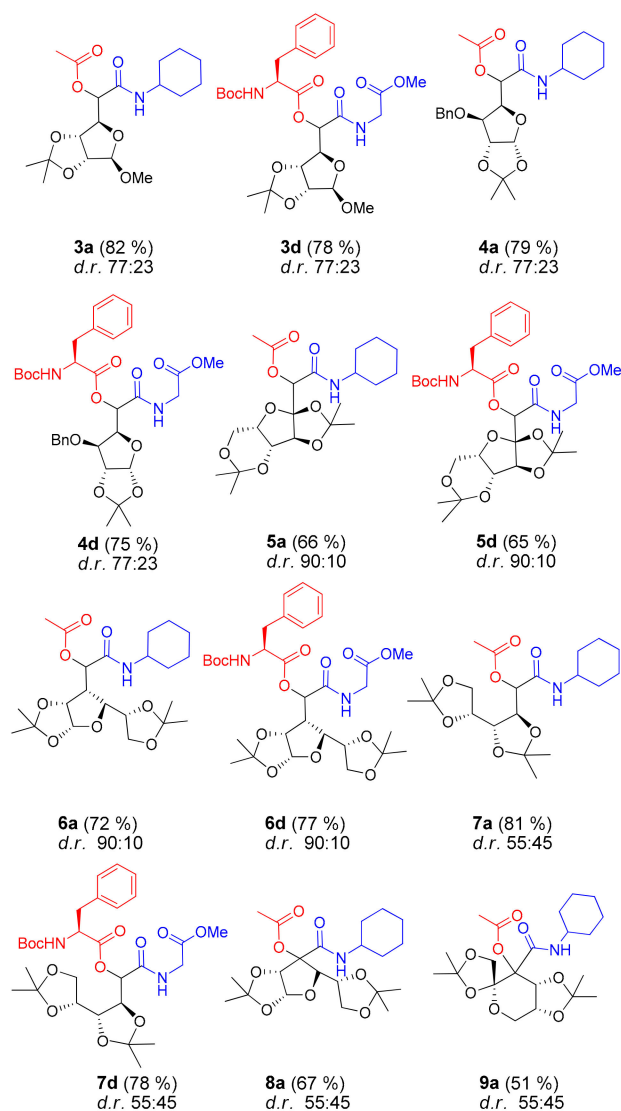


Figure 3. Passerini products obtained with aldehydes and ketones 3–9. Isolated yields are given in parentheses; d.r. was determined by ^1H NMR analysis of the reaction mixture.

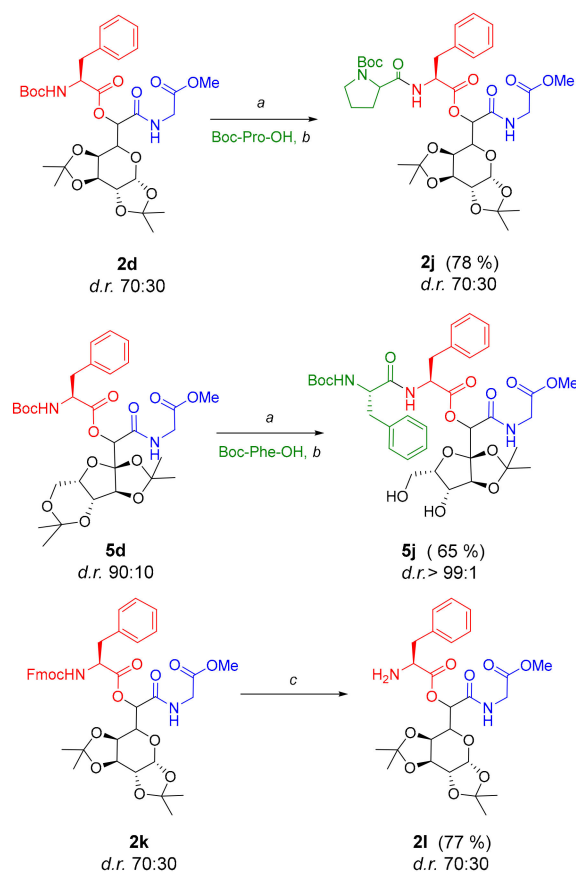
Comparable results were obtained with xylofuranose-derived aldehyde **4**, with high yields (79% for **4a** and 75% for **4d**) and moderate diastereoselectivity (77:23 d.r.). We then turned our attention to sorbofuranose-derived aldehyde **5**, which can be considered a furanose equivalent of the fructose-derived aldehyde **1**. The reaction turned out to be efficient with both groups of acid–isocyanide components, giving Passerini products **5a** and **5d** in satisfactory yields (~65%, Figure 3). More importantly, the reactions performed with aldehyde **5** were highly diastereoselective (90:10 d.r.), as previously observed with aldehyde **1** [12]. Further study was directed toward allofuranose-derived aldehyde **6**, with a carbonyl group attached to the C3 position of the furanose ring. We were pleased to find that reactions proceeded with very good yields, i.e., 72% for **6a** and 77% for **6d**, and again with high diastereoselectivity, i.e., 90:10 d.r. Riva et al. reported Lewis acid catalyzed Passerini reactions on chiral aldehydes derived from desymmetrized erythritol with diastereoselectivities up to 92:8 [15]. This report prompted us to examine aldehyde **7**, obtained by oxidation of 2,3:4,6-di-*O*-isopropylidene-*D*-arabinose, under our Passerini reaction conditions. The reactions proceeded smoothly, giving the products **7a** and **7d** in very good yields (~80%, Figure 3), but stereoselectivity was disappointing, corresponding to 55:45 d.r.. Riva et al. used 0.4 equiv. of Lewis acid (ZnBr_2) to improve the diastereoselectivity with erythritol-derived aldehydes; however, our attempts to affect stereoselectivity by adding a Lewis acid were unsuccessful. A possible explanation can be the presence of only one dioxolane ring in

erythritol-derived aldehydes, where chelation of the metal occurred by the carbonyl oxygen and one of the dioxolane oxygens [15], while bis isopropylidene-protected aldehyde **7** possesses multiple binding sites for the Lewis acid. Finally, to complete our pool of sugar-derived carbonyl compounds, Passerini reactions were performed with furanose ketone **8** and pyranose ketone **9**. Although ketones are generally less reactive in the Passerini reaction, products **8a** and **9a** were obtained in satisfactory yields (67% and 51%, respectively), while isolation and purification of products **8d** and **9d** were inefficient, so their data are not included in this paper. As with aldehyde **7**, there was virtually no stereoselectivity (55:45 d.r.).

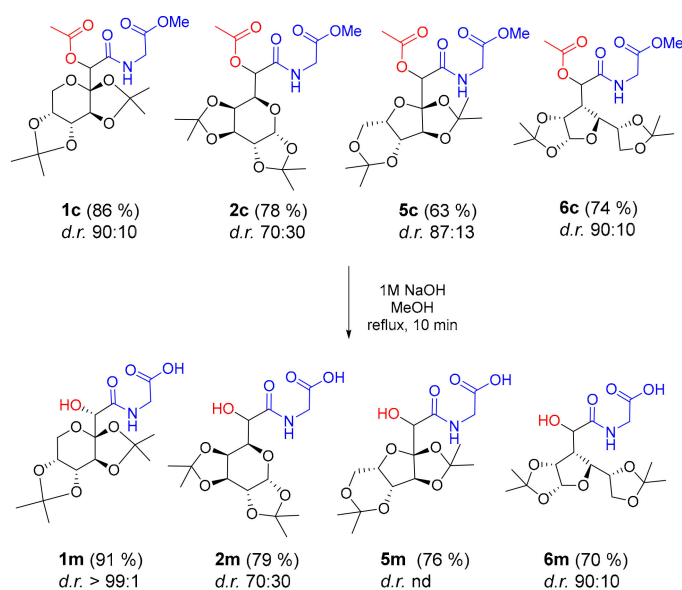
At this point, we were able to observe that bis-isopropylidene-protected compounds bearing an aldehyde group attached to the tetrasubstituted carbon atoms (**1** and **5**) are efficient chiral inductors, supplying Passerini products with 90:10 d.r. The same diastereoselectivity was observed with compound **6**, in which an aldehyde group is attached to the trisubstituted carbon atom (C3 position of the furanose ring). Other compounds with an aldehyde group attached to the trisubstituted carbon atom (**2**, **3**, and **4**) were less efficient chiral inductors, giving Passerini products with up to 77:23 d.r. A possible explanation can be the increased steric hindrance of aldehyde **6** compared with **2**, **3**, or **4**, where the aldehyde group is adjacent to the ring oxygen. Acyclic aldehyde **7** and ketones **8** and **9** gave practically racemic mixtures of Passerini products.

There are many examples of synthetic glycopeptide structures exploited for the generation of new biomaterials based on weak noncovalent interactions [1]. For example, sulfated glycopeptide supramolecular nanostructures were demonstrated to amplify the signaling of bone morphogenetic protein 2 and promote the regeneration of bone [16], while glycosaminoglycan-like nanofibers were found to mimic the bioactive functions of natural hyaluronic acid molecules [17]. Due to the fact that different supramolecular architectures can be accessed by varying peptide length and composition, we considered further functionalization of Passerini products, especially those derived from N-terminally protected amino acids. Although the presence of two different acid-labile groups, Boc and isopropylidene, seems an aggravating factor, we found a smooth deprotection/coupling approach and confirmed it on two examples presented in Scheme 1. The removal of the Boc group in product **2d** and the subsequent coupling with Boc-Pro-OH afforded the tetrapeptide **2j** in 78% yield. Following the same methodology, in situ deprotection of **5d** and coupling with Boc-Phe-OH gave the partially deprotected product **5j** in 65% yield. It seems that the six-membered dioxolane ring is more susceptible to acid cleavage under the applied conditions compared to the five-membered ring. Additionally, we prepared Passerini product **2k** (Scheme 1) comprising Fmoc-protected phenylalanine to confirm that selective Fmoc-deprotection in the presence of other base-labile groups is feasible with 20% piperidine in dimethylformamide (DMF) to yield 77% of the free amine **2l**.

The presence of a base-labile ester group in Passerini products can be of interest for another post-condensation modification, namely, the synthesis of highly valuable α -hydroxy amides or acids [18–20]. Therefore, we attempted the NaOH-mediated removal of acetyl groups in Passerini products **1c**, **2c**, **5c**, and **6c** (Scheme 2). All reactions worked efficiently affording the C-terminally protected dimers **1m**, **2m**, **5m**, and **6m**, comprising α -hydroxy C-glycosyl acid and glycine. Moreover, NMR analysis revealed the preservation of the chiral information derived from the diastereoselective Passerini reaction. C-glycosyl amino acids are widely exploited for the synthesis of glycomimetics, peptidomimetics, and foldamers [21]. The conformational bias imposed by the presence of a furanoid or pyranoid ring, adjustable hydrophilicity, and tunable properties in terms of substituents and stereochemistry are highly desirable features, making C-glycosyl amino acids and their derivatives versatile building blocks for multiple purposes.



Scheme 1. Post-condensation modification of selected Passerini products: *a* trifluoroacetic acid (TFA)/ dichloromethane (DCM) = 1:1, room temperature (RT), 2 min; *b* benzotriazol-1-yloxytris(dimethylamino)phosphonium (BOP, 1.5 eq), hydroxybenzotriazole (HOBT, 1.2 eq), *N*-methylmorpholine (NMM, 2 eq), dimethylformamide (DMF)/DCM = 1:1, RT, overnight; *c* 20% piperidine in DMF, RT, 15 min.



Scheme 2. Base-mediated deprotection of selected Passerini products; nd: not determined.

With a rich portfolio of different glycosylated structures in hands and an elaborated methodology to access more complex glycopeptide systems, we are currently focused toward building up multivalent glycosylated structures, exploring and understanding the functions of the obtained molecules. We are particularly interested in understanding how the selection of carbohydrate scaffolds as well as their number and distribution within the “carrier” molecule can help in solving highly challenging problems, like targeting carbohydrate–peptide or carbohydrate–carbohydrate interactions [22].

3. Materials and Methods

All experiments were monitored by analytical thin-layer chromatography (TLC) on Silica Gel 60 F254 plates (Merck; Darmstadt, Germany) after spraying with 10% H₂SO₄ and heating. Flash column chromatography was performed on silica gel (Merck, 40–63 μm particle size) by standard techniques, eluting with solvents as indicated. All NMR experiments were carried out by using a Bruker Avance 600 spectrometer (600.13 MHz, ¹H; 150.91 MHz, ¹³C). Samples in CDCl₃ solutions were recorded in 5 mm NMR tubes at 298 K. Chemical shifts in parts per million were referenced to tetramethylsilane (TMS) as internal standard. Spectra were assigned on the basis of 2D homonuclear (COSY) and heteronuclear (HMQC, HMBC) experiments. ¹H chemical shifts were assigned to the particular starting component, and the following abbreviations were used: cyclohexyl = CyHex; tetrabutyl = tBu; methyl cyanoacetate = Gly; fructopyranose-derived aldehyde **1** = Fru; galactose-derived aldehyde **2** = Gal; ribose-derived aldehyde **3** = Rib; xylose-derived aldehyde **4** = Xyl; sorbose-derived aldehyde **5** = Sor; allose-derived aldehyde **6** = Alo; arabinose-derived aldehyde **7** = Ara; glucofuranose-derived ketone **8** = GluF; fructopyranose-derived ketone **9** = FruP. High-resolution mass spectrometry (HRMS) was performed with a MALDI–TOF/TOF spectrometer in positive ionization mode. The calibration type was internal, with calibrants produced by matrix ionization dissolved in α-cyano-4-hydroxycinnamic acid matrix. Accurately measured spectra were internally calibrated, and elemental analysis was performed on Data Explorer v. 4.9 software with mass accuracy better than 5 ppm. NMR spectra of all compounds are given in Supplementary Materials.

DS1,2 refers to a product isolated as an inseparable mixture of two diastereoisomers, while DS1 and DS2 refer to isolated diastereoisomer 1 and diastereoisomer 2.

3.1. General Procedure for Passerini Reactions

To a glass vial containing 1 M solution of oxo-compound (0.1 mmol) in DCM under nitrogen were added acid (0.11 mmol) and the isocyanide component (0.11 mmol) dissolved in 100 μL DCM. With all reactants added, the reaction mixture was stirred at room temperature until the consumption of the aldehyde/ketone component, which typically required 6–24 h. The reactions were concentrated under reduced pressure, and the reaction mixtures were purified by flash column chromatography.

3.1.1. Methyl 2-(2-acetoxy-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4-b:4',5'-d]pyran-3a-yl)acetamido)acetate (**1c**)

Yield 86% (36 mg); colorless oil; R_f (DS1,2) = 0.47 (EtOAc/petroleum ether 2:1, *v/v*); d.r. 90:10. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. δ = 6.95 (s, 0.9H, NH), 6.91 (s, 0.1H, NH), 5.50 (s, 0.1H, H-1 Fru), 5.18 (s, 0.9H, H-1 Fru), 4.69 (d, *J* = 2.6 Hz, 0.1H, H-3 Fru), 4.58 (dd, *J* = 7.9, 2.8 Hz, 0.9H, H-4 Fru), 4.54 (dd, *J* = 8.0, 2.6 Hz, 0.1H, H-4 Fru), 4.36 (d, *J* = 2.8 Hz, 0.9H, H-3 Fru), 4.22 (dd, *J* = 7.9, 1.3 Hz, 0.9H, H-5 Fru), 4.17 (dd, *J* = 8.0, 1.6 Hz, 0.1H, H-5 Fru), 4.09 (dd, *J* = 18.5, 5.0 Hz, 1H, CH₂ Gly), 4.02 (dd, *J* = 18.5, 4.9 Hz, 1H, CH₂ Gly) 3.96 (dd, *J* = 18.5, 4.6 Hz, 0.1H, H-6 Fru), 3.92 (dd, *J* = 13.0, 1.9 Hz, 0.9H, H-6 Fru), 3.83 (d, *J* = 13.0 Hz, 1H, H-6 Fru), 3.73 (s, 0.3H, CH₃ Gly), 3.72 (s, 2.7H, CH₃ Gly), 2.19 (s, 0.3H, CH₃ Ac), 2.17 (s, 2.7H CH₃ Ac), 1.51 (s, 3H, CH₃ isop), 1.48 (s, 3H, CH₃ isop), 1.44 (s, 3H, CH₃ isop), 1.31 (s, 3H, CH₃ isop). ¹³C NMR (CDCl₃) δ = (170.2, 169.2, 165.7) (CO), (109.9, 109.6) (CH₃ isop), (102.1, 101.5) (C-2 Fru), (75.7, 73.8, 71.6, 70.8, 70.8, 70.4, 70.3) (C-1,3,4,5 Fru), (62.0, 61.8) (C-6 Fru), (52.6, 52.4) (CH₃ Gly), (41.6, 41.3) (CH₂ Gly), (26.7, 26.7, 26.2, 26.0, 25.5, 25.2, 24.3, 24.2)

(CH₃ isop), (21.1, 20.9) (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₈H₂₇NO₁₀Na [M + Na]⁺ 440.1533; found 440.1528.

3.1.2. 2-(Cyclohexylamino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4-b:4',5'-d]pyran-5-yl)ethyl acetate (**2a**)

Yield 81% (35 mg); white solid mp = 111–112 °C; R_f (DS1) = 0.52, R_f (DS2) = 0.47 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 80:20. ¹H NMR (CDCl₃) Chemical shifts are given for major isomer. δ = 6.18 (d, *J* = 7.9 Hz, 1H, NH), 5.49 (d, *J* = 4.8 Hz, 1H, H-1 Gal), 4.95 (d, *J* = 9.7 Hz, 1H, H-6 Gal), 4.60 (dd, *J* = 7.9, 2.6 Hz, 1H, H-3 Gal), 4.31 (dd, *J* = 4.8, 2.6 Hz, 1H, H-2 Gal), 4.28 (dd, *J* = 8.0, 1.8 Hz, 1H, H-4 Gal), 4.17 (dd, *J* = 9.7, 1.7 Hz, 1H, H-5 Gal), 3.84–3.70 (m, 1H, CH-1 CyHex), 2.13 (s, 3H, CH₃ Ac), 1.88 (m, 2H, CyHex), 1.67 (m, 2H, CyHex), 1.56 (m, 1H, CyHex), 1.50 (s, 3H, CH₃ isop), 1.41 (s, 3H, CH₃ isop), 1.36–1.32 (m, 2H, CyHex), 1.31 (s, 3H, CH₃ isop), 1.30 (s, 3H, CH₃ isop), 1.16 (d, *J* = 11.9 Hz, 3H, CyHex). ¹³C NMR (CDCl₃): δ = (169.9, 167.0) (CO), (109.8, 109.7) (C isop), 96.4 (C-1 Gal), (71.0, 70.7, 70.6, 70.6, 67.2) (C-2,3,4,5,6 Gal), 48.6 (CH CyHex), (33.04, 32.99) (CyHex), (26.29, 26.17) (CH₃ isop), 25.78 (CyHex), 25.23 (CH₃ isop), (24.95, 24.91) (CyHex), 24.63 (CH₃ isop), 20.95 (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₁H₃₃NO₈ [M + H]⁺ 428.2284; found 428.2291.

3.1.3. 2-(tert-Butylamino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4-b:4',5'-d]pyran-5-yl)ethyl acetate (**2b**)

Yield 78% (31 mg); colorless oil; R_f (DS1) = 0.58, R_f (DS2) = 0.60 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 80:20. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. δ = 6.19 (s, 0.8H, NH), 6.09 (s, 0.2H, NH), 5.49 (d, *J* = 4.8 Hz, 1H, H-1 Gal), 5.14 (d, *J* = 6.5 Hz, 0.2H, H-6 Gal), 4.87 (d, *J* = 9.8 Hz, 0.8H, H-6 Gal), 4.61–4.55 (m, 1H, H-3 Gal), 4.32–4.23 (m, 2H, H-2,4 Gal), 4.18 (d, *J* = 6.4 Hz, 0.2H, H-5 Gal), 4.11 (dd, *J* = 9.8, 1.4 Hz, 0.8H, H-5 Gal), 2.13 (s, 3H, CH₃ Ac), 1.49 (s, 3H, CH₃ isop), 1.40 (s, 3H, CH₃ isop), 1.36–1.25 (m, 15H, CH₃ isop, CH₃ tBu). ¹³C NMR (CDCl₃) δ = (170.5, 169.7, 167.2, 166.3) (CO), (109.8, 109.7, 109.7, 109.3) (C isop), (96.6, 96.4) (C-1 Gal), (73.9, 71.6, 71.1, 71.0, 70.9, 70.6, 70.6, 67.4, 67.4) (C-2,3,4,5,6 Gal), 51.7 (C tBu), (28.9, 28.7) (CH₃ tBu), (26.3, 26.2, 26.2, 26.1, 25.2, 24.6, 24.3) (CH₃ isop), (21.2, 20.9) (CH₃ OAc). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₉H₃₁NO₈ [M + H]⁺ 402.2128; found 402.2146.

3.1.4. Methyl 2-(2-acetoxy-2-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)acetamido)acetate (**2c**)

Yield 78% (32 mg); colorless oil; R_f (DS1, DS2) = 0.45 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. δ = 6.88 (s, 0.3H, NH), 6.79 (s, 0.7H, NH), 5.50 (d, *J* = 4.7 Hz, 1H, H-1 Gal), 5.37 (d, *J* = 6.8 Hz, 0.3H, H-6 Gal), 5.08 (d, *J* = 9.5 Hz, 0.7H, H-6 Gal), 4.61 (m, 1H, H-3 Gal), 4.41 (d, *J* = 8.0 Hz, 0.3H, H-4 Gal), 4.32–4.26 (m, 2H, H-4 Gal, H-2 Gal, H-5 Gal), 4.20 (dd, *J* = 16.5, 8.4 Hz, 1H, H-5 Gal, CH₂ Gly), 4.04 (m, 1.4H, CH₂ Gly), 3.91 (dd, *J* = 18.3, 4.3 Hz, 0.3H, CH₂ Gly), 3.72 (s, 3H, CH₃ Gly), 2.15 (s, 0.9H, CH₃ Ac), 2.12 (s, 2.1H, CH₃ Ac), 1.53 (s, 0.9H, CH₃ isop), 1.51 (s, 2.1H, CH₃ isop), 1.44 (s, 0.9H, CH₃ isop), 1.42 (s, 2.1H, CH₃ isop), 1.31 (s, 6H, CH₃ isop). ¹³C NMR (CDCl₃) δ = (170.5, 170.0, 169.9, 169.8, 168.3, 167.6) (CO), (110.0, 109.8, 109.6, 109.3) (C isop), (96.5, 96.4) (C-1 Gal), (72.9, 71.3, 71.1, 70.91, 70.8, 70.7, 70.7, 70.5, 67.2, 67.0) (C-2,3,4,5,6 Gal), (52.5, 52.5) (CH₃ Gly), (41.6, 41.4) (CH₂ Gly), (26.3, 26.2, 26.1, 26.1, 25.2, 25.2, 24.7, 24.4) (CH₃ isop), (21.1, 20.8) (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₈H₂₇NO₁₀ [M + H]⁺ 418.1713; found 418.1711.

3.1.5. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3] dioxolo)[4,5-b:4',5'-d] pyran-5-yl)ethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (**2d**)

Yield 80% (49 mg); colorless oil; R_f (DS1,2) = 0.47 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃) δ = 7.27–6.92 (m, 6H, Ph, NH), 5.50 (d, *J* = 5.0 Hz, 1.3H, H-1,6 Gal), 5.19 (d, *J* = 8.9 Hz, 0.7H, H-6 Gal), 4.97 (t, *J* = 8.0 Hz, 1H, NH), 4.67–4.45 (m, 2H, H-3 Gal, α-Phe), 4.30 (dd, *J* = 6.8, 4.4 Hz,

1.3H, H-2,4 Gal), 4.25–4.09 (m, 1.7H, H-5, H-4 Gal), 4.07–3.87 (m, 2H, CH₂ Gly), 3.72 (d, *J* = 4.6 Hz, 3H, CH₃ Gly), 3.22 (dd, *J* = 14.0, 6.2 Hz, 1H, β-Phe), 3.08 (dd, *J* = 14.8, 6.5 Hz, 1H, β-Phe), 1.54 (d, *J* = 3.8 Hz, 3H, CH₃ isop), 1.46 (s, 1H, CH₃ isop), 1.37 (bs, 11H, CH₃ Boc, CH₃ isop), 1.30 (dd, *J* = 8.0, 3.5 Hz, 6H, CH₃ isop). ¹³C NMR (CDCl₃) δ = (171.5, 170.8, 169.8, 169.8, 167.8, 167.3) (CO), (155.5, 155.4) (CO Boc), (136.5, 136.4) (C Ph), (129.8, 129.7, 128.7, 128.6, 127.1, 126.9) (CH Ph), (109.9, 109.8, 109.6, 109.3) (C isop), (96.4, 96.4) (C-1), (80.3, 80.1) (C Boc), (73.3, 71.6, 71.43, 71.03, 70.9, 70.6, 70.3) (C-2,3,4,6), (67.2, 67.0) (C-5 Gal), (54.9, 54.5) (α-Phe), 52.5 (CH₃Gly), (41.5, 41.3) (CH₂ Gly), (38.3, 37.5) (β-Phe), 28.5 (CH₃ Boc), (26.3, 26.2, 26.2, 26.0, 25.2, 24.5, 24.5) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₀H₄₂N₂O₁₂Na [M + Na]⁺ 645.2635; found 645.2615.

3.1.6. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3] dioxolo)[4,5-b:4',5'-d] pyran-5-yl)ethyl 2-((tert-butoxycarbonyl)amino)-4-methylpentanoate (**2e**)

Yield 58% (34 mg); colorless oil; R_f (DS1,2) = 0.55, (EtOAc/petroleum ether 1:1, *v/v*); *d.r.* 75:25. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. δ = 7.33 (s, 0.25H, NH), 6.93 (s, 0.75H, NH), 5.50 (0.25, H-6 Gal), 5.50 (d, *J* = 4.8 Hz, 0.75H, H-1 Gal), 5.44 (d, *J* = 4.8 Hz, 0.25H, H-1 Gal), 5.19 (d, *J* = 8.9 Hz, 0.75H, H-6 Gal), 4.90 (dd, *J* = 16.4, 7.7 Hz, 1H, NH Leu), 4.63–4.60 (m, 0.75H, H-3 Gal), 4.57 (dd, *J* = 7.9, 2.1 Hz, 0.25H, H-3 Gal), 4.50 (d, *J* = 7.6 Hz, 0.25H, α-Leu), 4.36 (m, 0.75H, α-Leu), 4.33–4.16 (m, 3H, H-2,4,5 Gal), 4.02 (ddd, *J* = 41.5, 18.2, 5.3 Hz, 2H, CH₂ Gly), 3.70 (d, *J* = 6.9 Hz, 3H, CH₃ Gly), 1.74 (s, 3H, β-Leu, γ-Leu), 1.51 (d, *J* = 7.5 Hz, 3H, CH₃ isop), 1.45–1.37 (m, 15H, CH₃ Boc, CH₃ isop), 1.31–1.27 (m, 3H, CH₃ isop), 0.94–0.91 (m, 6H, CH₃ Leu). ¹³C NMR (CDCl₃) δ = (172.8, 172.0, 169.9, 169.8, 167.8, 167.5) (CO), (156.0, 155.7) (CO Boc), (109.9, 109.6, 109.1) (C isop), 96.4 (C-1 Gal), (80.3, 80.0) (C Boc), (72.7, 71.6, 71.0, 71.0, 70.6, 70.4) (C-2,3,4,6 Gal), (67.4, 67.0) (C-5 Gal), (52.9, 52.4, 52.3) (CH₃ Gly, α-Leu), (41.8, 41.4, 41.3, 41.0) (CH₂ Gly, β-Leu), 29.9, (28.5, 28.5) (Boc), (26.3, 26.2, 26.1) (CH₃ isop), (25.3, 25.2) (γ-Leu), (24.9, 24.8, 24.6, 23.1, 23.0) (CH₃ isop), (22.3, 22.0) (δ-Leu). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₇H₄₄N₂O₁₂Na [M + Na]⁺ 611.2792; found 611.2805.

3.1.7. 1-tert-Butyl 2-((2-methoxy-2-oxoethyl) amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3] dioxolo)[4,5-b:4',5'-d] pyran-5-yl)ethyl)pyrrolidine-1,2-dicarboxylate (**2f**)

Yield 67% (40 mg); colorless oil; R_f (DS1,2) = 0.35, (EtOAc/petroleum ether 1:1, *v/v*); *d.r.* 55:45. ¹H NMR (CDCl₃) δ = 7.38 (dd, *J* = 19.5, 14.3 Hz, 0.45H, NH), 6.74 (t, *J* = 4.7 Hz, 0.55H, NH), 5.49 (d, *J* = 4.8 Hz, 1H, H-1 Gal), 5.28 (d, *J* = 8.0 Hz, 0.55H, H-6 Gal), 5.05 (d, *J* = 9.7 Hz, 0.45H, H-6 Gal), 4.60 (ddd, *J* = 25.8, 7.9, 2.3 Hz, 1H, H-3 Gal), 4.38–4.23 (m, 4H, H-2, H-4, H-5 Gal, CH₂ Gly), 4.10 (dd, *J* = 17.9, 6.0 Hz, 0.55H, CH₂ Gly), 4.02 (t, *J* = 5.7 Hz, 1H, α-Pro), 3.88 (dd, *J* = 17.9, 5.3 Hz, 0.45H, CH₂ Gly), 3.71 (s, 1.6H, CH₃ Gly), 3.68 (s, 1.4H, CH₃ Gly), 3.55–3.46 (m, 1H, δ-Pro), 3.42–3.30 (m, 1H, δ-Pro), 2.33–2.26 (m, 0.55H, β-Pro), 2.22–2.13 (m, 1.5H, β-Pro), 1.88 (ddd, *J* = 25.6, 11.5, 8.4 Hz, 2H, γ-Pro), 1.36 (ddd, *J* = 36.5, 29.4, 26.3 Hz, 21H, CH₃ Boc, CH₃ isop). ¹³C NMR (CDCl₃) δ = (171.8, 171.5, 169.9, 168.3, 167.8) (CO), (155.3, 154.1) (CO Boc), (109.8, 109.7, 109.6, 109.3) (C isop), (96.5, 96.4) (C-1 Gal), (80.2, 80.1) (C Boc), (71.9, 71.2, 70.9, 70.8, 70.7, 70.5, 70.4) (C-2,3,4,6 Gal), (67.1, 66.9) (C-5 Gal), (59.2, 58.9) (α-Pro), (52.4, 52.3) (CH₃ Gly), (47.0, 46.5) (δ-Pro), (41.5, 41.2) (CH₂ Gly), (30.9, 30.2) (β-Pro), (28.7, 28.5) (CH₃ Boc), (26.3, 26.2, 26.2, 25.2, 25.2, 24.7, 24.4) (CH₃ isop), (24.4, 23.4) (γ-Pro). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₆H₄₀N₂O₁₂ [M + H]⁺ 595.2479; found 595.2453.

3.1.8. 1-Benzyl 2-tert-butyl 1-(1-(2-((2-methoxy-2-oxoethyl) amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d] pyran-5-yl)ethoxy)-1-oxo-3-phenylpropan-2-yl) hydrazine-1,2-dicarboxylate (**2g**)

Yield 74% (57 mg); colorless oil; R_f (DS1,2) = 0.44 (EtOAc/petroleum ether 1:1, *v/v*); *d.r.* 70:30. ¹H NMR (CDCl₃) δ = 7.27 (d, *J* = 16.6 Hz, 11H, CH Ph, NH), 5.50 (d, *J* = 4.8 Hz, 1H, H-1 Gal), 5.25–5.16 (m, 4H, H-6 Gal, CH₂ Cbz, NH), 5.07 (m, 1H, α-hPhe), 4.55 (d, *J* = 10.2 Hz, 1H, H-3 Gal), 4.46 (dd, *J* = 8.0, 1.3 Hz, 1H, H-4 Gal), 4.30 (dd, *J* = 4.7, 2.5 Hz, 1H, H-2 Gal), 4.15–3.98 (m, 3H, H-5 Gal, CH₂ Gly), 3.72

(s, 1.8H, CH₃ Gly), 3.70 (s, 1.2H, CH₃ Gly), 3.31 (dd, *J* = 12.8, 6.8 Hz, 1H, β-hPhe), 3.24–3.07 (m, 1H, β-hPhe), 1.54–1.12 (m, 21H, CH₃ Boc, CH₃ isop). ¹³C NMR (CDCl₃) δ (169.8, 169.1, 168.5, 167.6) (CO), 155.3 (CO Boc), (137.9, 136.0) (C Ph), (129.6, 128.5, 128.4, 128.2, 127.9, 126.6) (CH Ph), (110.1, 109.8, 109.6, 109.6) (C isop), (96.4, 96.3) (C-1 Gal), (81.2, 81.2) (C Boc), (70.9, 70.8, 70.8, 70.4, 70.2) (H-2,3,4,6 Gal), (68.5, 68.3) (CH₂ Cbz), (67.7, 67.1) (C-5 Gal), (62.7, 62.2) (α-Phe), 52.5 (CH₃ Gly), (41.5, 41.2) (CH₂ Gly), (34.6, 34.3) (β-Phe), (28.3, 28.1) (CH₃ Boc), (26.2, 26.1, 26.0, 25.9, 25.1, 24.4, 24.4, 24.2) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₈H₄₉N₃O₁₂Na [M + Na]⁺ 794.3112; found 794.3111.

3.1.9. 1-Benzyl 2-tert-butyl 1-(1-(2-((2-methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethoxy)-4-methyl-1-oxopentane-2-yl)hydrazine-1,2-dicarboxylate (**2h**)

Yield 53% (39 mg); colorless oil; R_f (DS1,2) = 0.54 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃) δ = 7.31 (m, 5H, Ph Cbz), 6.91 (s, H, NH), 6.72 (s, H, NH), 5.49 (dd, *J* = 13.6, 4.7 Hz, 1H, H-1 Gal), 5.15 (ddd, *J* = 33.8, 24.8, 12.0 Hz, 4H, H-6 Gal, CH₂ Cbz, NH), 4.79 (t, *J* = 10.2 Hz, 1H, α-hLeu), 4.63–4.48 (m, 1H, H-3 Gal), 4.39–3.86 (m, 5H, H-2,4,5 Gal, CH₂ Gly), 3.72 (d, *J* = 3.1 Hz, 3H, CH₃ Gly), 1.94 (m, 1H, β-hLeu), 1.63 (m, 1H, β-hLeu), 1.56–1.19 (m, 21H, CH₃ Boc, CH₃ isop), 1.06–0.80 (m, 6H, δ-hLeu). ¹³C NMR (CDCl₃) δ = (169.8, 169.7, 167.7) (CO), (156.4, 155.1) (CO Boc), 136.1 (C Cbz), (128.8, 128.8, 128.3) (CH Cbz), (109.9, 109.86, 109.8, 109.8) (C isop), (96.4, 96.3) (C-1 Gal), (81.5, 81.4) (CO Boc), (74.4, 71.6, 71.4, 70.9, 70.6, 70.4, 70.2) (C-2,3,4,6), (68.8, 68.7) (CH₂ Cbz), (67.2, 67.1, 66.9) (C-5 Gal), (60.3, 59.3) (α-Leu), 52.5 (CH₃ Gly), (41.6, 39.9) (CH₂ Gly), (37.0, 36.8) (β-Leu), 28.4 (CH₃ Boc), (26.2, 26.2, 26.1, 26.0) (CH₃ isop), (25.2, 25.2) (γ-Leu), (24.5, 24.4, 24.3, 23.9, 23.5) (CH₃ isop), (21.7, 21.7) (δ-Leu). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₅H₅₁N₃O₁₄ [M + Na]⁺ 760.3269; found 760.3243.

3.1.10. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethyl 1-((tert-butoxycarbonyl)amino)pyrrolidine-2-carboxylate (**2i**)

Yield 66% (39 mg); colorless oil; R_f (DS1,2) = 0.38 (EtOAc/petroleum ether 2:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃) δ = 7.03 (s, 0.3H), 6.95 (s, 0.7H), 6.71 (d, *J* = 13.8 Hz, 1H), 5.52 (d, *J* = 4.8 Hz, 0.7H), 5.49 (d, *J* = 4.9 Hz, 0.3H), 5.37 (d, *J* = 8.0 Hz, 0.3H), 5.19 (d, *J* = 9.3 Hz, 0.7H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.47 (dd, *J* = 8.0, 1.7 Hz, 0.3H), 4.32 (dd, *J* = 4.9, 2.6 Hz, 0.7H), 4.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.21 (dd, *J* = 9.3, 1.8 Hz, 0.3H), 4.18–4.13 (m, 0.7H), 4.03 (dd, *J* = 7.4, 5.4 Hz, 2H), 3.92 (dd, *J* = 18.3, 4.8 Hz, 0.3H), 3.71 (s, 0.9H), 3.71 (s, 2.1H), 3.29 (td, *J* = 14.2, 7.6 Hz, 1H, δ-Pro), 3.13–3.06 (m, 1H, δ-Pro), 2.21 (dq, *J* = 16.4, 8.2 Hz, 1H, β-Pro), 2.13–2.03 (m, 1H, β-Pro), 1.93–1.84 (m, 2H, γ-Pro), 1.38 (m, 21H, CH₃ Boc, CH₃ isop). ¹³C NMR (CDCl₃) δ = (173.0, 172.0, 170.0, 169.9, 168.3, 167.1) (CO), (110.1, 110.0, 109.7, 109.3) (C isop), (96.5, 96.4) (C-1 Gal), (80.2, 80.0) (CO Boc), (72.8, 71.1, 70.9, 70.8, 70.7, 70.6, 70.4) (C-2,3,4,6 Gal), (67.5, 67.2) (C-5 Gal), (64.8, 64.0) (α-Pro), (53.4, 53.2) (δ-Pro), (52.5, 52.4) (CH₃ Gly), (41.5, 41.3) (CH₂ Gly), (28.6, 28.5) (CH₃ Boc), (27.9, 27.6) (β-Pro), (26.2, 26.2, 26.1, 25.2, 25.1, 24.6, 24.5) (CH₃ isop), (22.3, 22.2) (γ-Pro). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₆H₄₁N₃O₁₂Na [M + Na]⁺ 610.2588; found 610.2571.

3.1.11. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanoate (**2k**)

Yield 74% (55 mg); colorless oil; R_f (DS1,2) = 0.39, (EtOAc/petroleum ether 1:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃) δ = 7.73 (d, *J* = 7.5 Hz, 2H, Fmoc), 7.54–7.49 (m, 2H, Fmoc), 7.37 (t, *J* = 7.4 Hz, 2H, Fmoc), 7.30–7.19 (m, 7H, Ph), 6.96 (s, 0.3H, NH), 6.87 (s, 0.7H, NH), 5.52 (d, *J* = 4.7 Hz, 0.3H, H-1 Gal), 5.50 (d, *J* = 4.8 Hz, 0.7H, H-1 Gal), 5.44 (d, *J* = 7.6 Hz, 0.3H, H-6 Gal), 5.31 (d, *J* = 8.3 Hz, 0.7H, NH), 5.29–5.24 (m, 0.3H, NH), 5.17 (d, *J* = 9.2 Hz, 0.7H, H-6 Gal), 4.78–4.69 (m, 1H, α-Phe), 4.58 (ddd, *J* = 32.1, 7.8, 2.2 Hz, 1H, H-3 Gal), 4.38 (dt, *J* = 18.2, 9.1 Hz, 1H, CH₂ Fmoc), 4.30 (dd, *J* = 4.9, 2.6 Hz, 1H, H-2 Gal), 4.27–4.00 (m, 6H, CH₂ Gly, CH Fmoc, CH₂ Fmoc, H-5,4 Gal), 3.72 (s, 2.1H, CH₃ Gly), 3.68 (s, 0.9H, CH₃ Gly), 3.26 (dd, *J* = 14.0, 6.2 Hz, 1H, β-Phe), 3.13 (dd, *J* = 14.0, 6.4 Hz, 1H, β-Phe), 1.55–1.21 (m, 12H, CH₃

isop). ^{13}C NMR (CDCl_3) δ (171.1, 170.5, 169.8, 167.7) (CO Fmoc), (155.9, 155.8) (CO Fmoc), (144.0, 143.9, 141.5) (C Fmoc), (136.4, 136.1) (C Ph), (129.8, 129.8, 128.8, 128.6, 127.9, 127.2, 127.1) (CH Ph), (125.3, 125.3, 125.2) (CH Fmoc-Ph), (120.2, 120.1) (CH Fmoc-Ph), (110.0, 109.9, 109.6, 109.3) (C isop), (96.4, 96.4) (C-1 Gal), (73.5, 71.5, 71.3, 71.0, 70.9, 70.8, 70.5, 70.3) (C-2,3,4,6 Gal), 67.4 (C-5 Gal), 67.2 (CH_2 Fmoc), 67.0 (C-5 Gal), (55.1, 54.9) (α -Phe), (52.5, 52.4) (CH_3 Gly), (47.4, 47.3) (CH Fmoc), (41.5, 41.3) (CH_2 Gly), (38.3, 37.6) (β -Phe), (26.3, 26.2, 26.2, 26.0, 25.2, 24.5, 24.4) (CH_3 isop). HRMS (MALDI-TOF/TOF) m/z : calcd. for $\text{C}_{40}\text{H}_{44}\text{N}_2\text{O}_{12}$ $[\text{M} + \text{H}]^+$ 745.2972; found 745.2990.

3.1.12. 2-(Cyclohexylamino)-1-((3*R*,4*S*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-oxoethyl acetate (**3a**)

Yield 82% (30 mg); colorless oil; R_f = 0.63 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 77:23. ^1H NMR (CDCl_3) Chemical shifts are given for both isomers. δ = 5.97 (d, J = 7.5 Hz, 0.77H, NH), 5.90 (d, J = 7.7 Hz, 0.23H, NH), 5.11 (d, J = 7.6 Hz, 0.23H, H-5 Rib), 5.07 (d, J = 6.9 Hz, 0.77H, H-5 Rib), 4.95 (s, 0.23H, H-1 Rib), 4.94 (s, 0.77H, H-1 Rib), 4.87 (dd, J = 6.0, 1.4 Hz, 0.23H, H-2 Rib), 4.71 (dd, J = 6.2, 0.5 Hz, 0.77H, H-2 Rib), 4.60 (d, J = 6.9 Hz, 0.77H, H-4 Rib), 4.55 (d, J = 6.0 Hz, 0.77H, H-3 Rib), 4.53 (d, J = 6.0 Hz, 0.23H, H-3 Rib), 4.50 (dd, J = 7.6, 1.4 Hz, 0.23H, H-4 Rib), 3.79–3.72 (m, 1H, CH-1 CyHex), 3.32 (s, 2.3H, OCH₃), 3.28 (s, 0.7H, OCH₃), 2.15 (s, 0.7H, CH₃ Ac), 2.13 (s, 2.3H, CH₃ Ac), 1.89 (m, 2H, CyHex), 1.66 (m, 2H, CyHex), 1.58 (m, 1H, CyHex), 1.45 (s, 3H, CH₃ isop), 1.34 (m, 2H, CyHex), 1.29 (s, 2.3H, CH₃ isop), 1.28 (s, 0.7H, CH₃ isop), 1.16–1.14 (m, 3H, CyHex). ^{13}C NMR (CDCl_3) δ = (170.0, 166.1) (CO), 112.9 (C isop), (111.1, 110.3) (C-1 Rib), (86.2, 86.0) (C-4 Rib), (85.4, 85.3) (C-3 Rib), (81.7, 81.4) (C-2 Rib), (74.8, 73.6) (C-5 Rib), (56.2, 55.5) (OCH₃), 48.5 (CH CyHex), 48.35 (CH CyHex), (33.1, 33.1) (CyHex), (26.8, 26.7) (CH₃ isop), (25.7, 25.6, 25.3, 24.9, 24.9) (CyHex), (21.4, 21.1) (CH₃ Ac). HRMS (MALDI-TOF/TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{29}\text{NO}_7\text{Na}$ $[\text{M} + \text{Na}]^+$ 394.1842; found 394.1843.

3.1.13. 1-((3*R*,4*S*,6*R*,6*aR*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (**3d**)

Yield 78% (44 mg); colorless oil; R_f (DS1) = 0.53, (EtOAc/petroleum ether 1:1, *v/v*); d.r. 77:23. ^1H NMR (CDCl_3) δ = 7.36–7.08 (m, 5H, CH Ph), 7.15 (s, 1H, NH), 5.36 (d, J = 4.6 Hz, 1H, NH), 5.19 (d, J = 4.8 Hz, 0.23H, H-5 Rib), 5.04 (d, J = 7.6 Hz, 0.77H, H-5 Rib), 4.96 (s, 0.77H, H-1 Rib), 4.94 (s, 0.23H, H-1 Rib), 4.74–4.53 (m, 4H, H-2,3,4 Rib, α -Phe), 4.09 (d, J = 5.8 Hz, 0.23H, CH₂ Gly), 4.03 (d, J = 5.8 Hz, 0.77H, CH₂ Gly), 3.94 (d, J = 5.4 Hz, 0.77H, CH₂ Gly), 3.88 (d, J = 5.4 Hz, 0.23H, CH₂ Gly), 3.71 (d, J = 5.2 Hz, 3H, CH₃ Gly), 3.33–3.30 (m, 3.77H, CH₃ Rib, β -Phe), 2.98 (dd, J = 14.3, 8.8 Hz, 1.23H, β -Phe), 1.46 (s, 2.31H, CH₃ isop), 1.42 (s, 0.69H, CH₃ isop), 1.39 (s, 2.31H, Boc), 1.37 (s, 6.9H, Boc), 1.31 (s, 2.1H, CH₃ isop), 1.27 (s, 0.69H, CH₃ isop). ^{13}C NMR (CDCl_3) δ = (170.5, 169.6, 167.2) (CO), 156.2 (CO Boc), 136.4 (C Ph), (129.6, 129.3, 129.0, 128.9, 127.6, 127.3) (CH Ph), 112.8 (C isop), (111.9, 109.9) (C-1 Rib), (86.4, 86.2) (C-4 Rib), (85.7, 85.6) (C-3 Rib), (81.2, 81.0) (C-2 Rib), (80.9, 80.7) (C Boc), (75.0, 74.5) (C-5 Rib), (56.3, 55.9) (α -Phe), (55.3, 54.9) (CH₃ Rib), (52.5, 52.3) (CH₃ Gly), (41.2, 41.1) (CH₂ Gly), (37.6, 37.6) (β -Phe), (28.5, 28.4) (CH₃ Boc), (26.9, 26.7) (CH₃ isop), (25.7, 25.3) CH₃ isop). HRMS (MALDI-TOF/TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_{11}\text{Na}$ $[\text{M} + \text{Na}]^+$ 589.2373; found 589.2399.

3.1.14. 1-((3*R*,5*S*,6*S*,6*aR*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-(cyclohexylamino)-2-oxoethyl acetate (**4a**)

Yield 79% (36 mg); colorless oil; R_f (DS1) = 0.40, R_f (DS2) = 0.26 (EtOAc/petroleum ether 1:2, *v/v*); d.r. 77:23. ^1H NMR (CDCl_3) Chemical shifts are given for major isomer. δ = 7.41–7.14 (m, 5H, Ph), 6.01 (d, J = 7.9 Hz, 1H, NH), 5.92 (d, J = 3.7 Hz, 1H, H-1 Xyl), 5.11 (d, J = 9.2 Hz, 1H, H-5 Xyl), 4.62 (d, J = 11.6 Hz, 1H, CH₂a-Ph), 4.60 (d, J = 3.7 Hz, 1H, H-2 Xyl), 4.45–4.38 (m, 2H, H-4 Xyl, CH₂b-Ph), 3.99 (d, J = 3.1 Hz, 1H, H-3 Xyl), 3.79–3.70 (m, 1H, CH-1 CyHex), 1.98 (s, 3H, CH₃ Ac), 1.84 (m, 2H, CyHex), 1.63 (m, 2H), 1.55–1.50 (m, 1H, CyHex), 1.45 (s, 3H, CH₃ isop), 1.30 (bs, 5H, CH₃ isop, CyHex), 1.16–1.06 (m, 3H, CyHex). ^{13}C NMR (CDCl_3) δ (169.70, 166.78) (CO), 136.97 (C Ph), (128.84, 128.45, 128.35) (CH Ph), 112.61 (C isop), 105.65 (C-1 Xyl), (81.79, 81.30, 78.64, 72.47, 70.22) (C-2,3,4,5-Xyl, CH₂-Ph), 48.52 (CH

CyHex), (32.89, 32.83) (CyHex), (27.01, 26.58) (CH₃ isop), (25.73, 24.79, 24.75) (CyHex), 20.78 (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₄H₃₃NO₇ [M + H]⁺ 448.2335; found 448.2346.

3.1.15. 1-((3aR,5S,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-((2-methoxy-2-oxoethyl) amino)-2-oxoethyl 2-((tert-butoxycarbonyl) amino)-3-phenylpropanoate (**4d**)

Yield 75% (48 mg); colorless oil; R_f (DS1) = 0.52, (EtOAc/petroleum ether 1:1, *v/v*); d.r. 77:23. ¹H NMR (CDCl₃) δ = 7.42–7.11 (m, 10H, Bn, Ph), 6.86 (s, 1H, NH), 5.94 (d, *J* = 3.6 Hz, 1H, H-1 Xyl), 5.65 (d, *J* = 7.2 Hz, 0.23H, H-5 Xyl), 5.43 (d, *J* = 9.0 Hz, 0.77H, H-5 Xyl), 4.91 (m, 1H, α-Phe), 4.67–4.39 (m, 5.77H, H-2, H-4, H-3 Xyl, NH, CH₂ OBn), 4.24 (d, *J* = 3.9 Hz, 0.23H, H-3 Xyl), 4.02 (d, *J* = 5.3 Hz, 0.77H, CH₂ Gly), 3.99 (m, 0.77H, CH₂ Gly), 3.92 (d, *J* = 5.7 Hz, 0.46H, CH₂ Gly), 3.71 (s, 2.31H, CH₃ Gly), 3.69 (s, 0.69H, CH₃ Gly), 3.28 (dd, *J* = 14.1, 5.6 Hz, 0.77H, β-Phe), 3.12 (dd, *J* = 14.2, 5.3 Hz, 0.23H, β-Phe), 3.00 (dd, *J* = 14.1, 7.7 Hz, 0.77H, β-Phe), 2.88 (dd, *J* = 14.1, 8.3 Hz, 0.23H, β-Phe), 1.48 (s, 3H, CH₃ isop), 1.35 (s, 3H, CH₃ isop), 1.30 (s, 9H, CH₃ Boc). ¹³C NMR (CDCl₃) δ (171.0, 169.8, 167.7) (CO), 155.4 (CO Boc), (137.1, 136.5, 136.1) (C Ph), (129.7, 129.5, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 127.2, 127.0) (CH Ph), (112.8, 112.4) (C isop), (105.8, 105.2) (C-1 Xyl), (83.0, 83.0) (C-2 Xyl), (81.9, 81.4) (C-3 Xyl), (80.6, 80.0) (C Boc), (79.0, 78.5) (C-4 Xyl), (72.8, 72.6) (CH₂-OBn), (72.1, 70.0) (C-5 Xyl), (55.0, 54.3) (α-Phe), (52.5, 52.4) (CH₃ Gly), (41.5, 41.1) (CH₂ Gly), (37.9, 37.1) (β-Phe), 28.3 (CH₃ Boc), (28.35, 27.2, 27.0, 26.6, 26.5) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₃H₄₂N₂O₁₁Na [M + Na]⁺ 665.2686; found 665.2682.

3.1.16. 2-(Cyclohexylamino)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl acetate (**5a**)

Yield 66% (28 mg); colorless oil; R_f (DS1) = 0.50, R_f (DS2) = 0.40 (toluen/acetone 5:1, *v/v*); d.r. 90:10. ¹H NMR (CDCl₃) Chemical shifts are given for major isomer. δ = 6.30 (d, *J* = 7.6 Hz, 1H, NH), 5.26 (s, 1H, H-1 Sor), 4.41 (s, 1H, H-5 Sor), 4.31 (d, *J* = 2.2 Hz, 1H, H-4 Sor), 4.17 (d, *J* = 1.5 Hz, 1H, H-3 Sor), 4.07 (dd, *J* = 13.6, 2.2 Hz, 1H, H-6a Sor), 3.98 (d, *J* = 13.5 Hz, 1H, H-6b Sor), 3.85–3.75 (m, 1H, CH-1 CyHex), 2.17 (s, 3H, CH₃ Ac), 1.89 (m, 2H, CyHex), 1.63 (s, 3H, CyHex), 1.54 (m, 1H, CyHex), 1.46 (s, 3H, CH₃ isop), 1.41 (d, 6H, CH₃ isop), 1.38 (bs, 3H, CH₃ isop), 1.34 (m, 1H, CyHex), 1.24–1.17 (m, 3H, CyHex). ¹³C NMR (CDCl₃): δ = (169.6, 164.6) (CO), (113.8, 113.2) (C isop), 97.8 (C-2 Sor), 85.66 (C-5 Sor), 73.7 (C-3 Sor), 72.9 (C-4 Sor), 72.7 (C-1 Sor), 60.6 (C-6 Sor), 48.4 (CH CyHex), 32.9 (CyHex), (32.8, 29.2) (CyHex), (27.8, 26.5, 25.9) (CH₃ isop), (24.7, 24.7) (CyHex), 21.0 (CH₃ isop), 18.9 (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₁H₃₃NO₈ [M + H]⁺ 428.2284; found 428.2272.

3.1.17. Methyl 2-(2-acetoxy-2-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)acetamido)acetate (**5c**)

Yield 63% (26 mg); colorless oil; R_f (DS1) = 0.30, R_f (DS2) = 0.27 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 87:13. ¹H NMR (CDCl₃) δ = 7.10 (s, 0.87H, NH), 6.84 (s, 0.13H, NH), 5.68 (s, 0.13H, H-1 Sor), 5.39 (s, 0.87H, H-1 Sor), 4.87 (s, 0.13H, H-5 Sor), 4.41 (s, 0.87H, H-5 Sor), 4.33 (d, *J* = 1.7 Hz, 0.87H, H-4 Sor), 4.29 (d, *J* = 2.3 Hz, 0.13H, H-4 Sor), 4.23–3.96 (m, 5H, H-3,6 Sor, CH₂ Gly), 3.73 (d, *J* = 1.8 Hz, 3H, CH₃ Gly), 2.22 (s, 0.39H, CH₃ Ac), 2.18 (s, 2.61H, CH₃ Ac), 1.47–1.30 (m, 12H, CH₃ isop). ¹³C NMR (CDCl₃) δ (170.2, 169.4, 165.6) (CO), 114.0 (C isop), 112.9 (C isop), 97.8 (C-2 Sor), 85.6 (C-5 Sor), (74.5, 74.0, 73.5, 73.2, 72.8, 72.4) (C-1,3,4 Sor), 60.4 (C-6 Sor), 52.5 (CH₃ Gly), (41.7, 41.3) (CH₂ Gly), (29.1, 28.5, 27.9, 27.7, 26.4) (CH₃ isop), (19.2, 18.8) (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₈H₂₇NO₁₀ [M + H]⁺ 418.1713; found 418.1697.

3.1.18. 2-((2-Methoxy-2-oxoethyl) amino)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl 2-((tert-butoxycarbonyl) amino)-3-phenylpropanoate (**5d**)

Yield 65% (40 mg); colorless oil; R_f (DS1,2) = 0.34 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 90:10. ¹H NMR (CDCl₃) δ = 7.35–7.05 (m, 6H, CH Ph, NH), 5.50 (s, 1H, H-1 Sor), 4.94 (d, *J* = 8.4 Hz, 1H, NH Phe), 4.65 (dd, *J* = 12.9, 8.0 Hz, 1H, α-Phe), 4.42 (s, 1H, H-5 Sor), 4.36 (s, 1H, H-4 Sor), 4.25 (s, 1H, H-3 Sor),

4.17 (dd, $J = 18.5, 4.9$ Hz, 1H, CH₂ Gly), 4.14–4.10 (m, 2H, H-6 Sor), 4.07 (dd, $J = 18.5, 4.7$ Hz, 1H, CH₂ Gly), 3.76 (s, 3H, CH₃ Gly), 3.42 (dd, $J = 14.2, 4.7$ Hz, 1H, β -Phe), 3.06 (dd, $J = 14.2, 8.2$ Hz, 1H, β -Phe), (1.51, 1.44, 1.40, 1.36) (21H, CH₃ isop, CH₃ Boc). ¹³C NMR (CDCl₃) δ (170.8, 170.1, 165.3) (CO), 155.4 (CO Boc), 136.6 (C Ph), (129.8, 128.7, 126.9) (CH Ph), (114.1, 112.8) (C isop), 97.8 (C-2 Sor), 85.5 (C-5 Sor), 80.0 (C Boc), 74.2 (C-3 Sor), 72.7 (C-4 Sor), 60.5 (C-6 Sor), 54.6 (α -Phe), 52.5 (CH₃ Gly), 41.8 (CH₂ Gly), 38.4 (β -Phe), (29.1, 28.4, 27.7, 26.5) (CH₃ isop), 18.9 (CH₃ Boc). HRMS (MALDI-TOF/TOF) m/z : calcd. for C₃₀H₄₂NO₁₂Na [M + Na]⁺ 645.2635; found 645.2641.

3.1.19. 2-(Cyclohexylamino)-1-((3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-2-oxoethyl acetate (**6a**)

Yield 72% (32 mg); colorless oil; R_f (DS1, DS2) = 0.37, (EtOAc/petroleum ether 1:1, v/v); d.r. 90:10. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. $\delta = 6.04$ (d, $J = 7.9$ Hz, 1H, NH), 5.75 (d, $J = 3.6$ Hz, 0.9H, H-3' Alo), 5.73 (d, $J = 3.7$ Hz, 0.1H, H-3' Alo), 5.37 (d, $J = 6.4$ Hz, 0.1H, H-1 Alo), 5.21 (d, $J = 8.7$ Hz, 0.9H, H-1 Alo), 4.69–4.62 (m, 1H, H-2 Alo), 4.27–4.16 (m, 2H, H-4,5 Alo), 4.03 (dd, $J = 8.4, 6.5$ Hz, 1H, H-6 Alo), 3.95 (dd, $J = 8.4, 6.6$ Hz, 0.9H, H-6 Alo), 3.88 (dd, $J = 8.1, 5.4$ Hz, 0.1H, H-6 Alo), 3.76 (m, 1H, CH-1 CyHex), 2.51 (m, 0.1H, H-3 Alo), 2.40–2.28 (m, 0.9H, H-3 Alo), 2.11 (s, 2.7H, CH₃ Ac), 2.09 (s, 0.3H, CH₃ Ac), 1.86 (s, 2H, CyHex), 1.70–1.54 (m, 3H, CyHex), 1.50 (s, 3H, CH₃ isop), 1.40 (s, 3H, CH₃ isop), 1.38–1.33 (m, 2H, CyHex), 1.32 (s, 3H, CH₃ isop), 1.27 (s, 3H, CH₃ isop), 1.20–1.11 (m, 3H, CyHex). ¹³C NMR (CDCl₃) δ (170.2, 167.2) (CO), (112.7, 109.8) (C isop), (105.1, 104.6) (C-1 Alo), (81.6, 81.4, 80.3, 78.5, 76.9, 71.4, 71.3) (C-2,3',4,5), (66.9, 65.8) (C-6 Alo), (48.6) (C-3 Alo), (48.4, 48.3) (CH CyHex), 32.9 (CyHex), (27.0, 26.6, 26.5, 25.7) (CH₃ isop), (25.7, 24.8) (CyHex), 21.1 (CH₃ Ac). HRMS (MALDI-TOF/TOF) m/z : calcd. for C₂₂H₃₅NO₈Na [M + Na]⁺ 464.2260; found 464.2254.

3.1.20. Methyl 2-(2-acetoxy-2-((3aS,5S,6R,6aS)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)acetamido) acetate (**6c**)

Yield 74% (32 mg); colorless oil; R_f (DS1, DS2) = 0.38, (EtOAc/petroleum ether 1:1, v/v); d.r. 90:10. ¹H NMR (CDCl₃) Chemical shifts are given for both isomers. $\delta = 6.77$ (s, 0.9H, NH), 6.74 (s, 0.1H, NH), 5.76 (d, $J = 3.6$ Hz, 0.9H, H-3' Alo), 5.73 (d, $J = 3.7$ Hz, 0.1H, H-3' Alo), 5.48 (d, $J = 6.0$ Hz, 0.1H, H-1 Alo), 5.38 (d, $J = 8.2$ Hz, 0.9H, H-1 Alo), 4.82 (t, $J = 4.1$ Hz, 0.9H, H-2 Alo), 4.77 (t, $J = 4.1$ Hz, 0.1H, H-2 Alo), 4.26 (dd, $J = 9.7, 5.0$ Hz, 0.9H, H-4 Alo), 4.22–4.06 (m, 2.1H, H-4,5 Alo, CH₂ Gly), 4.05–4.00 (m, 1H, H-6 Alo), 3.94 (dd, $J = 8.2, 6.9$ Hz, 0.9H, H-6 Alo), 3.87 (dd, $J = 18.3, 4.4$ Hz, 1.1H, H-6 Alo, CH₂ Gly), 3.74 (s, 0.3H, CH₃ Gly), 3.72 (s, 2.7H, CH₃ Gly), 2.52–2.45 (m, 0.1H, H-3 Alo), 2.37–2.30 (m, 0.9H, H-3 Alo), 2.12 (s, 2.7H, CH₃ Ac), 2.10 (s, 0.3H, CH₃ Gly), 1.77 (s, 0.3H, CH₃ isop), 1.50 (s, 0.3H, CH₃ isop), 1.47 (s, 2.7H, CH₃ isop), 1.39 (s, 2.7H, CH₃ isop), 1.30 (s, 3H, CH₃ isop), 1.28 (s, 3H, CH₃ isop). ¹³C NMR (CDCl₃) δ (170.1, 170.0, 168.8) (CO), (112.7, 109.8) (C isop), (105.1, 104.6) (C-1 Alo), (81.3, 81.2, 79.9, 78.4, 77.3, 76.9, 71.0, 70.7) (C-2,3',4,5), (67.2, 66.0) (C-6 Alo), (52.7, 52.5) (CH₃ Gly), (48.8, 48.7, 48.3) (CH CyHex, C-3 Alo), (41.3, 41.2) (CH₂ Gly), (26.9, 26.8, 26.7, 26.5, 26.4, 25.6, 25.2) (CH₃ isop), (21.0, 20.9) (CH₃ Ac). HRMS (MALDI-TOF/TOF) m/z : calcd. for C₁₉H₂₉NO₁₀Na [M + Na]⁺ 454.1689; found 454.1696.

3.1.21. 1-((3aS,6aS)-5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (**6d**)

Yield 77% (49 mg); colorless oil; R_f (DS1,2) = 0.47 (EtOAc/petroleum ether 1:1, v/v); d.r. 90:10. ¹H NMR (CDCl₃) δ 7.33–7.16 (m, 5H, Ph), 6.92 (s, 1H, NH), 5.75 (d, $J = 3.7$ Hz, 1H, H-3' Alo), 5.49 (d, $J = 7.6$ Hz, 1H, H-1 Alo), 5.01 (d, $J = 7.4$ Hz, 1H, NH Phe), 4.78 (t, $J = 4.0$ Hz, 1H, α -Phe), 4.59 (dd, $J = 13.3, 6.7$ Hz, 1H, H-2 Alo), 4.31 (dd, $J = 9.7, 4.4$ Hz, 1H, H-5 Alo), 4.12 (ddd, $J = 22.6, 11.3, 5.5$ Hz, 2H, H-4 Alo, CH₂ Gly), 3.98 (d, $J = 6.5$ Hz, 2H, H-6 Alo), 3.86 (dd, $J = 18.0, 4.9$ Hz, 1H, CH₂ Gly), 3.72 (s, 3H, CH₃ Gly), 3.22 (dd, $J = 14.1, 5.7$ Hz, 1H, β -Phe), 3.07 (dd, $J = 14.0, 7.1$ Hz, 1H, β -Phe), 2.35 (ddd, $J = 9.9, 7.8, 4.6$ Hz, 1H, H-3 Alo), 1.57–1.28 (m, 21H, CH₃ Boc, CH₃ isop). ¹³C NMR (CDCl₃) δ (171.1, 169.9, 168.6) (CO), 155.7 (CO Boc), 136.2 (C Ph), (129.6, 128.8, 127.3) (CH Ph), (112.7, 110.0) (C isop),

104.6 (C-1 Alo), 81.3 (C-2 Alo), 80.5 (C Boc), 79.5 (C-4 Alo), 76.6 (C-5 Alo), 71.3 (C-3' Alo), 65.8 (C-6 Alo), 54.8 (α -Phe), 52.5 (CH₃ Gly), 48.2 (C-3 Alo), 41.3 (CH₂ Gly), 37.9 (β -Phe), 28.49 (CH₃ Boc), (26.86, 26.62, 26.39, 25.44) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₁H₄₄N₂O₁₂Na [M + Na]⁺ 659,2792; found 659,2790.

3.1.22. 2-(Cyclohexylamino)-2-oxo-1-((4R,4'R,5S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethyl acetate (**7a**)

Yield 81% (32 mg); colorless oil; R_f (DS1) = 0.50, R_f (DS2) = 0.48 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 55:45. ¹H NMR (CDCl₃) δ = 5.95 (d, *J* = 7.9 Hz, 0.55H, NH), 5.77 (d, *J* = 8.1 Hz, 0.45H, NH), 5.37 (d, *J* = 2.7 Hz, 0.55H, H-1 Ara), 5.28 (d, *J* = 2.3 Hz, 0.45H, H-1 Ara), 4.37 (dd, *J* = 7.5, 2.3 Hz, 0.45H, H-2 Ara), 4.32 (t, *J* = 7.8 Hz, 0.55H, H-3 Ara), 4.10 (dd, *J* = 8.0, 2.7 Hz, 0.55H, H-2 Ara), 4.08–3.99 (m, 2H, H-4, H-5 Ara), 3.94 (dd, *J* = 8.4, 4.9 Hz, 0.55H, H-5 Ara), 3.89 (m, 0.45H, H-5 Ara), 3.78–3.70 (m, 1.45H, H-3 Ara, CH-1 CyHex), 2.15 (s, 1.35H, CH₃ Ac), 2.14 (s, 1.65H, CH₃ Ac), 1.85 (m, 2H, CyHex), 1.64 (m, 2H, CyHex), 1.56 (m, 1H, CyHex), 1.45 (s, 2H, CH₃ isop), 1.36–1.26 (m, 12H, CH₃ isop, CyHex), 1.17–1.07 (m, 3H, CyHex). ¹³C NMR (CDCl₃) δ = (169.3, 169.13, 166.7, 165.9) (CO), (110.5, 110.2, 110.2, 110.1) (C isop), (80.1, 79.4) (C-2 Ara), (77.4, 77.2) (C-3 Ara), (77.1, 76.9) (C-4 Ara), (73.7, 72.7) (C-1 Ara), 67.4 (C-5 Ara), (48.4, 48.3) (CH CyHex), (33.2, 33.1, 33.1, 33.0) (CyHex), (27.4, 27.4, 27.0, 27.0, 26.7) (CH₃ isop), (25.7, 25.7) (CyHex), (25.6, 25.3) (CH₃ isop), (24.9, 24.8) (CyHex), (21.1, 21.0) (CH₃ Ac). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₀H₃₃NO₇Na [M + Na]⁺ 422.2155; found 422.2138.

3.1.23. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((4R,4'R,5S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (**7d**)

Yield 78% (46 mg); colorless oil; R_f (DS1) = 0.48 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 55:45. ¹H NMR (CDCl₃) δ 7.60 (m, 0.55H, NH), 7.36–7.25 (m, 5H, CH Ph), 7.11 (m, 0.45H, NH), 5.50 (d, *J* = 2.7 Hz, 0.55H, H-1 Ara), 5.44 (d, *J* = 1.6 Hz, 0.45H, H-1 Ara), 5.12 (d, *J* = 6.0 Hz, 0.45H, α -Phe), 4.97 (d, *J* = 7.1 Hz, 0.55H, α -Phe), 4.65–4.45 (m, 1.45H, H-2 Ara, NH), 4.29 (t, *J* = 7.4 Hz, 0.55H, H-3 Ara), 4.15–3.92 (m, 5.45H, H-2, H-3, H-4, H-5, CH₂ Gly), 3.81 (td, *J* = 7.9, 3.4 Hz, 0.55H, H-5 Ara), 3.73 (s, 1.65H, CH₃ Gly), 3.71 (s, 1.35H, CH₃ Gly), 3.21–3.05 (m, 2H, β -Phe), 1.47–1.27 (m, 21H, CH₃ Boc, CH₃ isop). ¹³C NMR (CDCl₃) δ (171.7, 170.6, 169.8, 169.6, 168.0, 167.0) (CO), 156.0 (CO Boc), (135.9, 135.5) (C Ph), (129.4, 129.3, 129.2, 129.0, 127.6, 127.4) (CH Ph), (110.5, 110.3, 110.0, 109.9) (C isop), (81.0, 80.8) (C Boc), (79.6, 79.2) (C-2 Ara), 77.1 (C-3 Ara), (76.8, 76.6) (C-4 Ara), (74.2, 72.9) (C-1 Ara), (67.47, 67.2) (C-5 Ara), (55.9, 54.8) (α -Phe), (52.4, 52.3) (CH₃ Gly), (41.3, 41.1) (CH₂ Gly), (37.8, 37.7) (β -Phe), (28.4, 28.4) (CH₃ Boc), (27.4, 27.4, 26.9, 26.9, 26.7, 26.6, 25.5, 25.1) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₉H₄₂N₂O₁₁Na [M + Na]⁺ 617.2686; found 617.2687.

3.1.24. (3aR,5S,6aR)-6-(Cyclohexylcarbamoyl)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate (**8a**)

Yield 67% (29 mg); colorless oil; R_f (DS1) = 0.70, R_f (DS2) = 0.50 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 55:45. ¹H NMR (CDCl₃) Major isomer: δ = 7.40 (d, *J* = 7.5 Hz, 1H, NH), 5.88 (d, *J* = 3.6 Hz, 1H, H-1 GlcF), 4.87 (d, *J* = 3.6 Hz, 1H, H-2, GlcF), 4.45 (t, *J* = 4.7 Hz, 1H, H-5, GlcF), 4.42 (d, *J* = 2.8 Hz, 1H, H-4 GlcF), 4.13 (dd, *J* = 8.4, 6.5 Hz, 1H, H-6a GlcF), 4.06 (dd, *J* = 8.4, 6.9 Hz, 1H, H-6b, GlcF), 3.80–3.73 (m, 1H, CH-1 CyHex), 2.09 (m, 3H, CH₃ Ac), 1.93–1.82 (m, 2H, CyHex), 1.67–1.60 (m, 2H, CyHex), 1.59 (m, 5H, CH₃ isop, CyHex), 1.41 (s, 3H, CH₃ isop), 1.36 (m, 4H, CH₃ isop, CyHex), 1.33 (s, 3H, CH₃ isop), 1.27–1.15 (m, 3H, CyHex). Minor isomer: δ = 6.17 (d, *J* = 8.1 Hz, 1H, NH), 5.85 (d, *J* = 3.8 Hz, 1H, H-1 GlcF), 5.33 (d, *J* = 3.8 Hz, 1H, H-2 GlcF), 4.10–4.06 (m, 1H, H-6a GlcF), 4.02 (d, *J* = 9.3 Hz, 1H, H-5 GlcF), 3.97–3.91 (m, 2H, H-4, H-6b GlcF), 3.83–3.77 (m, 1H, CH-1 CyHex), 2.11 (s, 3H, CH₃ Ac), 1.85 (ddd, *J* = 27.8, 12.4, 3.5 Hz, 2H, CyHex), 1.69–1.54 (m, 4H, CyHex), 1.50 (s, 3H, CH₃ isop), 1.46 (s, 3H, CH₃ isop), 1.41–1.33 (m, 1H, CyHex), 1.33 (s, 3H, CH₃ isop), 1.31 (s, 3H, CH₃ isop), 1.22–1.08 (m, 3H, CyHex). ¹³C NMR (CDCl₃) Major isomer: δ = (170.0, 163.9) (CO), (114.0, 108.7) (C isop), 105.4 (C-1 GlcF), 85.6 (C-3 GlcF), 82.8 (C-2 GlcF), 82.3 (C-4 GlcF), 73.5 (C-5 GlcF), 65.0 (C-6 GlcF), 48.4 (CH CyHex), (32.7, 32.7)

(CyHex), (27.0, 26.7, 26.5) (CH₃ isop), 25.8 (CyHex), 25.5 (CH₃ isop), (24.6, 24.5) (CyHex), 21.5 (CH₃ Ac). Minor isomer: δ = (169.0, 166.6) (CO), (112.8, 110.1) (C isop), 105.7 (C-1 GlcF), 85.3 (C-3 GlcF), 80.9 (C-2 GlcF), 80.4 (C-4 GlcF), 74.6 (C-5 GlcF), 68.4 (C-6 GlcF), 48.2 (CH CyHex), (33.1, 32.7) (CyHex), (27.1, 27.0, 26.8, 25.8) (CH₃ isop), (25.7, 24.7, 24.7) (CyHex), 21.0 (CH₃ Ac). HRMS (MALDI-TOF/TOF) m/z : calcd. for C₂₁H₃₃NO₈ [M + H]⁺ 428.2284; found 428.2302.

3.1.25. (3aR,4'R,7aR)-7-(Cyclohexylcarbamoyl)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl acetate (9a)

Yield 51% (22 mg); colorless oil; R_f (DS1) = 0.80, R_f (DS2) = 0.40 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 55:45. ¹H NMR (CDCl₃) Major isomer: δ = 5.99 (d, *J* = 7.7 Hz, 1H, NH), 5.30 (d, *J* = 7.0 Hz, 1H, H-4 FruP), 4.60 (dt, *J* = 7.3, 3.7 Hz, 1H, H-5 FruP), 4.57 (d, *J* = 9.6 Hz, 1H, H-1a FruP), 4.07 (m, 1H, H-1b FruP), 4.05 (m, 1H, H-6a FruP), 3.80–3.74 (m, 1H, CH-1 CyHex), 3.68 (dd, *J* = 12.8, 3.4 Hz, 1H, H-6b FruP), 2.11 (s, 3H, CH₃ Ac), 1.86 (t, *J* = 17.8 Hz, 2H, CyHex), 1.65–1.57 (m, 4H, CyHex), 1.47 (s, 6H, CH₃ isop), 1.46 (s, 3H, CH₃ isop), 1.38 (s, 1H, CyHex), 1.30 (s, 3H, CH₃ isop), 1.21–1.06 (m, 3H, CyHex). Minor isomer: δ = 6.66 (d, *J* = 7.3 Hz, 1H, NH), 5.08 (d, *J* = 7.2 Hz, 1H, H-4 FruP), 4.31 (d, *J* = 9.9 Hz, 1H, H-1a FruP), 4.30–4.24 (m, 1H, H-5 FruP), 4.20 (dd, *J* = 12.6, 3.3 Hz, 1H, H-6a FruP), 3.93 (d, *J* = 9.9 Hz, 1H, H-1b FruP), 3.79 (dd, *J* = 12.6, 0.9 Hz, 1H, H-6b FruP), 3.77–3.73 (m, 1H, CyHex CH-1), 2.12 (s, 3H, CH₃ Ac), 1.92 (dd, *J* = 33.6, 9.8 Hz, 2H, CyHex), 1.66 (m, 2H, CyHex), 1.58 (m, 2H, CyHex), 1.51 (s, 3H, CH₃ isop), 1.49 (s, 3H, CH₃ isop), 1.43 (s, 3H, CH₃ isop), 1.36 (s, 3H, CH₃ isop), 1.33 (m, 1H, CyHex), 1.23–1.12 (m, 3H, CyHex). ¹³C NMR (CDCl₃) Major isomer: δ = 168.8, 166.6 (CO), 110.6, 109.5 (C isop), 104.5 (C-2 FruP), 80.5 (C-3 FruP), 73.1 (C-4 FruP), 72.8 (C-5 FruP), 72.3 (C-1 FruP), 64.7 (C-6 FruP), 48.3 (CH-1 CyHex), 32.9, 32.7 (CyHex), 26.9, 26.6, 26.1, 25.8, 25.0, 24.7, 24.6 (CH₃ isop), 21.6 (CH₃ Ac). Minor isomer: δ = 169.3, 164.6 (CO), 111.6, 110.8 (C isop), 103.9 (C-2 FruP), 81.0 (C-3 FruP), 73.60 (C-1 FruP), 73.4 (C-4 FruP), 73.0 (C-5 FruP), 64.4 (C-6 FruP), 48.9 (CH-1 CyHex), 32.9, 32.7 (CyHex), 26.4, 26.3, 26.2 (CH₃ isop), 25.8 (CyHex), 25.3 (CH₃ isop), 24.9 (CyHex), 21.7 (CH₃ Ac). HRMS (MALDI-TOF/TOF) m/z : calcd. for C₂₁H₃₃NO₈Na [M + Na]⁺ 450.2104; found 450.2107.

3.2. Post-Condensation Modification of Selected Passerini Products

Boc deprotection and coupling of amino acid: Passerini product 2d (10 mg, 0.016 mmol) was dissolved in trifluoroacetic acid (TFA)/DCM (1:1, *v/v*, 100 μ L), the reaction was stirred at room temperature for 2 min, and the reaction mixture was evaporated with toluene. Boc-Pro-OH (4 mg, 0.018 mmol, 1.2 eq), benzotriazol-1-yloxytris(dimethylamino)phosphonium (BOP, 10 mg, 0.023 mmol, 1.5 eq), and hydroxybenzotriazole (HOBT, 3.5 mg, 0.023 mmol, 1.5 eq) were dissolved in 1 mL DCM/DMF (1:1), followed by the addition of the Boc-deprotected compound (8 mg, 0.015 mmol) and *N*-methylmorpholine (NMM, 2eq). The reaction mixture was stirred for 24 h. The product was purified by flash column chromatography (petrol ether/ethyl acetate, *v/v* = 1:6).

3.2.1. tert-Butyl 2-((1-(2-((2-methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo[4,5-b:4',5'-d]pyran-5-yl)ethoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl) pyrrolidine-1-carboxylate (2j)

Yield 78% (9 mg); colorless oil; R_f (DS1,2) = 0.55 (EtOAc/petroleum ether 6/1, *v/v*); d.r. 70:30. ¹H NMR (MeOD) δ = 7.36–7.18 (m, 5H, Ph), 5.52 (d, *J* = 4.9 Hz, 0.3H, H-1 Gal), 5.49 (d, *J* = 4.7 Hz, 0.7H, H-1 Gal), 5.44 (m, 0.3H, H-6 Gal), 5.13 (m, 0.7H, H-6 Gal), 4.84 (s, 1H, α -Phe), 4.66 (dd, *J* = 8.0, 2.3 Hz, 1H, H-3 Gal), 4.39 (ddd, *J* = 11.1, 4.7, 2.4 Hz, 1H, H-2 Gal), 4.28–4.18 (m, 2H, H-4,5 Gal), 4.15 (bs, 1H, α -Pro), 4.06–3.92 (m, 2H, CH₂ Gly), 3.74 (d, *J* = 2.7 Hz, 3H, CH₃ Gly), 3.44 (m, 1H, δ -Pro), 3.39–3.34 (m, 2H, δ -Pro, β -Phe), 3.01 (bs, 1H, β -Phe), 2.17 (m, 1H, β -Pro), 1.91 (m, 1H, β -Pro), 1.78 (m, 2H, γ -Pro), 1.55 (d, *J* = 11.6 Hz, 3H, CH₃ isop), 1.46 (d, *J* = 16.2 Hz, 6H, CH₃ isop), 1.37–1.24 (m, 12H, CH₃ isop, Boc). ¹³C NMR (MeOD) δ (170.0, 169.8, 169.3, 169.1, 168.5, 167.7, 167.4) (CO), 136.4 (C Ph), (128.4, 127.6, 125.9) (CH Ph), (108.9, 108.5, 108.3) (C isop), (95.9, 95.7) (C-1 Gal), (72.5, 71.1, 70.3, 70.3, 70.2, 70.0, 69.5, 67.2, 66.5) (C-2,3,4,5,6 Gal), 59.7 (α -Pro), (53.2, 52.9) (α -Phe), (50.7, 50.7) (CH₃ Gly), 45.9 (δ -Pro), (40.1,

39.9) (CH₂ Gly), (36.3, 36.0) (β-Phe), 30.3 (Boc), (26.7, 24.5, 24.4, 23.3) (CH₃ isop), (22.8, 22.5) (γ-Pro). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₅H₄₉N₃O₁₃Na [M + Na]⁺ 742.3163; found 742.3190.

Boc deprotection and coupling of amino acid: Passerini product **5d** (13 mg, 0.02 mmol) was dissolved in TFA/DCM (1:1, *v/v*, 100 μL), the reaction was stirred at room temperature for 2 min, and then the solvent was evaporated. Boc-Phe-OH (6.4 mg, 0.024 mmol, 1.2 eq), BOP (13 mg, 0.03 mmol, 1.5 eq), and HOBt (4.6 mg, 0.03 mmol, 1.5 eq) were dissolved in 1 mL DCM/DMF (1:1) followed by the addition of the Boc-protected compound and NMM (2 eq). The reaction mixture was stirred for 24 h, the solvent was evaporated, and the product was extracted with DCM. The product was purified by flash column chromatography (petrol ether/ethyl acetate, *v/v* = 1/1).

3.2.2. (S)-(S)-1-((3aR,5S,6R,6aS)-6-Hydroxy-5-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-3a-yl)-2-((2-methoxy-2-oxoethyl)amino)-2-oxoethyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-phenylpropanoate (**5j**)

Yield 65% (9.5 mg); colorless oil; R_f = 0.30 (EtOAc/petroleum ether 1/1, *v/v*). ¹H NMR (CDCl₃): δ = 7.68 (s, 1H, NH), 7.38–7.16 (m, 8H, CH Ph), 6.91 (dd, *J* = 6.4, 2.9 Hz, 2H, CH Ph), 6.00 (d, *J* = 5.4 Hz, 1H, NH Phe), 5.77 (s, 1H, H-1 Sor), 5.16 (d, *J* = 7.5 Hz, 1H, NH Phe), 4.93 (s, 1H, H-5 Sor), 4.60 (dt, *J* = 8.8, 5.3 Hz, 1H, α-Phe), 4.35–4.12 (m, 4H, α-Phe, CH₂ Gly, H-3,4 Sor), 3.91–3.78 (m, 3H, CH₂ Gly, H-6 Sor), 3.75 (s, 3H, CH₃ Gly), 3.14 (dd, *J* = 14.3, 5.1 Hz, 1H, β-Phe), 3.02 (d, *J* = 7.1 Hz, 2H, β-Phe), 2.94–2.81 (m, 1H, β-Phe), 1.91 (bs, 2H, OH), 1.49 (s, 3H, CH₃ isop), 1.34–1.23 (m, 12H, CH₃ isop, Boc). ¹³C NMR (CDCl₃): δ = (173.0, 170.0, 169.30, 168.3) (CO), (137.1, 135.2) (C Ph), (129.9, 129.2, 129.1, 129.1, 127.72, 127.5) (CH Ph), 112.7 (C isop), 112.0 (C-2 Sor), (88.0, 82.7, 80.6, 76.7, 75.2) (C-1,3,4,5 Sor), 61.2 (C-6 Sor), (55.9, 54.3) (α-Phe), 52.8 (CH₃ Gly), 41.1 (CH₂ Gly), (38.6, 36.9) (β-Phe), 28.5 (Boc), (27.4, 26.3) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₃₅H₄₉N₃O₁₃Na [M + Na]⁺ 742.3163; found 742.3190.

Fmoc deprotection: A solution of 20% piperidine in DMF (0.2 mL) was added to the Passerini product **2k** (20 mg, 0.03 mmol), the mixture was stirred at room temperature for 15 min, and then the solvent was evaporated. The product was purified by flash column chromatography (petrol ether/ethyl acetate, *v/v* = 1/1).

3.2.3. 2-((2-Methoxy-2-oxoethyl)amino)-2-oxo-1-((3aR,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethyl 2-amino-3-phenylpropanoate (**2l**)

Yield 77% (12 mg); colorless oil; R_f (DS1,2) = 0.40 (EtOAc/petroleum ether 1:1, *v/v*); d.r. 70:30. ¹H NMR (CDCl₃): δ = 7.25 (m, 5H, Ph), 5.45 (d, *J* = 4.9 Hz, 0.7H, H-1 Gal), 5.41 (d, *J* = 4.6 Hz, 0.3H, H-1 Gal), 4.91–4.84 (m, 0.7H, H-6 Gal), 4.75 (td, *J* = 8.3, 4.9 Hz, 0.3H, H-6 Gal), 4.62 (ddd, *J* = 14.4, 8.0, 2.5 Hz, 1H, H-3 Gal), 4.46 (dd, *J* = 8.0, 1.6 Hz, 0.3H, α-Phe), 4.40 (dd, *J* = 7.9, 1.7 Hz, 0.7H, α-Phe), 4.31 (dd, *J* = 4.9, 2.5 Hz, 1H, H-2 Gal), 4.28–3.87 (m, 4H, CH₂ Gly, H-5,4 Gal), 3.72 (m, 3H, CH₃ Gly), 3.29 (ddd, *J* = 37.2, 14.3, 5.2 Hz, 1H, β-Phe), 3.15–3.10 (m, 1H, β-Phe), 2.95 (s, 1H, NH), 2.88 (s, 1H, NH), 1.51–1.25 (m, 12H, CH₃ isop). ¹³C NMR (CDCl₃): δ 171.7, 170.4, 170.3, 170.1, 169.8, 169.5 (CO), 136.1, 135.8 (C Ph), 128.8, 128.8, 128.2, 126.5, 126.4 (CH isop), 109.7, 109.1, 109.1, 108.8 (CH₃ isop), 95.9, 95.4 (C-1 Gal), 73.5, 73.5, 70.3, 70.2, 70.2, 70.0, 69.8, 68.8, 67.8, 66.5 (C-2,3,4,5,6 Gal), 53.6, 53.2 (α-Phe), 51.7, 51.5 (CH₃ Gly), 40.7, 40.6 (CH₂ Gly), 36.9, 36.1 (β-Phe), 25.5, 25.4, 25.3, 25.2, 24.6, 24.3, 23.7, 23.3 (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₂₅H₃₄N₂O₁₀Na [M + Na]⁺ 545.2111; found 545.2109.

3.3. Base-Mediated Deprotection of Selected Passerini Products

General procedure: the Passerini product (0.035 mmol) was dissolved in MeOH (0.5 mL), and 1N NaOH (2 eq) was added. The reaction was stirred under reflux (10 min) or at room temperature (30 min), followed by TLC (EtOAc/EtOH/HOAc/H₂O 70:10:2:2, *v/v*). The solvent was evaporated, and the product was purified by flash column chromatography.

3.3.1. 2-((S)-2-Hydroxy-2-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)acetamido)acetic acid (**1m**)

Yield 91% (11.5 mg); colorless oil; $R_f = 0.74$ (EtOAc/EtOH/HOAc/H₂O 70:10:2:2, *v/v*). ¹H NMR (CDCl₃) $\delta = 7.36\text{--}7.29$ (m, 1H, NH), 5.52 (bs, 2H, OH), 4.66 (d, $J = 2.6$ Hz, 1H, H-3 Fru), 4.61 (dd, $J = 7.8, 2.6$ Hz, 1H, H-4 Fru), 4.22 (d, $J = 8.2$ Hz, 1H, H-5 Fru), 4.16–4.09 (m, 2H, H-1 Fru, CH₂ Gly), 3.99 (dd, $J = 18.1, 4.6$ Hz, 1H, CH₂ Gly), 3.90 (d, $J = 11.7$ Hz, 1H, H-6 Fru), 3.80 (d, $J = 12.9$ Hz, 1H, H-6 Fru), 1.47 (s, 3H, CH₃ isop), 1.46 (s, 3H, CH₃ isop), 1.38 (s, 3H, CH₃ isop), 1.33 (s, 3H, CH₃ isop). ¹³C NMR (CDCl₃) δ 171.3 (CO), 109.7, 109.4 (C isop), 103.5 (C-2 Fru), 71.6, 70.9, 70.5, 70.4 (C-1,3,4,5 Fru), 61.9 (C-6 Fru), 42.4 (CH₂ Gly), 26.6, 26.2, 25.7, 24.2 (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: Calcd. for C₁₅H₂₃NO₉Na [M + Na]⁺ 384.1271; found 384.1269.

3.3.2. 2-(2-Hydroxy-2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)acetamido)acetic acid (**2m**)

Yield 79% (10 mg); colorless oil; R_f (DS1,2) = 0.58 (EtOAc/EtOH/HOAc/H₂O 70:10:2:2, *v/v*); *d.r.* 70:30. ¹H NMR (CDCl₃) δ 7.44 (s, 1H, NH), 5.54 (dd, $J = 16.6, 4.7$ Hz, 1H, H-1 Gal), 5.13 (bs, 2H, OH), 4.61 (dt, $J = 8.0, 4.0$ Hz, 1H, H-3 Gal), 4.48 (d, $J = 8.1$ Hz, 1H, H-4 Gal), 4.38–4.23 (m, 2H, H-2,6 Gal), 4.12–3.96 (m, 3H, CH₂ Gly, H-5 Gal), 1.53–1.26 (m, 12H, CH₃ isop). ¹³C NMR (CDCl₃) δ 173.5, 171.8 (CO), 110.1, 109.8, 109.60, 109.6 (C isop), 96.6, 96.5 (C-1 Gal), 73.7, 72.9, 71.3, 71.2, 70.9, 70.8, 70.7, 70.4, 67.8, 66.7 (C-2,3,4,5,6), 41.78 (CH₂ Gly), 26.1, 26.1, 26.0, 25.2, 25.1, 24.4, 24.2 (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₅H₂₃NO₉Na [M + Na]⁺ 384.1271; found 384.1272.

3.3.3. 2-((S)-2-Hydroxy-2-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)acetamido)acetic acid (**5m**)

Yield 76% (9.6 mg); colorless oil; R_f (DS1,2) = 0.75 (EtOAc/EtOH/HOAc/H₂O 70:10:2:2, *v/v*); *d.r.* nd. ¹H NMR (CDCl₃) δ 7.35 (d, $J = 5.2$ Hz, 1H), 4.63 (s, 1H), 4.32 (d, $J = 8.0$ Hz, 2H), 4.16 (s, 1H), 4.13–3.98 (m, 4H), 1.40 (m, 12H). ¹³C NMR (CDCl₃) δ 171.1 (CO), 114.5, 113.7 (C isop), 97.9 (C-2 Sor), 85.3 (C-5), 73.7, 73.0, 70.8 (C-1,3,4), 60.5 (C-6), 42.5 (CH₂ Gly), 29.2, 27.7, 26.6, 18.8 (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₅H₂₃NO₉Na [M + Na]⁺ 384.1271; found 384.1281.

3.3.4. 2-(2-((3aS,5S,6R,6aS)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-2-hydroxyacetamido)acetic acid (**6m**)

Yield 70% (0.11 mmol, 29 mg); colorless oil; R_f (DS1,2) = 0.62 (EtOAc/EtOH/HOAc/H₂O 70:10:2:2, *v/v*); *d.r.* 90:10. ¹H NMR (CDCl₃): δ 7.44 (t, $J = 5.3$ Hz, 0.9H, NH), 7.35–7.31 (m, 0.1H, NH), 5.76 (d, $J = 3.4$ Hz, 0.1H, H-3 Alo), 5.74 (d, $J = 3.5$ Hz, 0.9H, H-3 Alo), 5.58 (s, 2H, OH), 4.86 (t, $J = 4.0$ Hz, 0.9H, H-2 Alo), 4.83 (t, $J = 4.0$ Hz, 0.1H, H-2 Alo), 4.63 (d, $J = 3.3$ Hz, 0.1H, H-4 Alo), 4.51 (d, $J = 7.0$ Hz, 0.9H, H-4 Alo), 4.28–4.22 (m, 0.1H, H-5 Alo), 4.20 (dd, $J = 9.5, 6.7$ Hz, 0.9H, H-5 Alo), 4.12–4.01 (m, 3H, H-1 Alo, H-6, CH₂ Gly), 4.00–3.90 (m, 2H, H-6 Alo, CH₂ Gly), 2.66 (dt, $J = 10.2, 3.8$ Hz, 0.1H, H-3 Alo), 2.28 (ddd, $J = 9.7, 7.1, 4.7$ Hz, 0.9H, H-3 Alo), 1.54 (s, 0.3H, CH₃ isop), 1.52 (s, 2.7H, CH₃ isop), 1.43 (s, 0.3H, CH₃ isop), 1.41 (s, 2.7H, CH₃ isop), 1.33 (s, 2.7H, CH₃ isop), 1.31 (s, 2.7H, CH₃ isop), 1.28 (s, 0.6H, CH₃ isop). ¹³C NMR (CDCl₃): δ 173.2 (CO), (112.7, 110.4) (C isop), 104.7 (C1 Alo), (82.9, 79.5, 77.0, 69.3) (C-2,4,5,3 Alo), 67.2 (C-6 Alo), 51.1 (CH₂ Gly), 47.6 (C-3 Alo), 41.6 (CH₂ Gly), (27.0, 26.5, 26.4, 25.5) (CH₃ isop). HRMS (MALDI-TOF/TOF) *m/z*: calcd. for C₁₆H₂₅NO₉Na [M + Na]⁺ 398.1427; found 398.1445

4. Conclusions

In summary, we systematically validated the reactivity of eight different isopropylidene-protected carbohydrate-derived aldehydes and ketones in the Passerini-type multicomponent reaction. Simple post-condensation modifications allowed to gain more complex structures or versatile building blocks to access new types of biomimetics. The here described methodology can be also applied to other classes of biomolecules, like lipids and peptides, and used as a platform for generating new nature-mimicking systems.

Supplementary Materials: Supplementary materials can be found at <http://www.mdpi.com/1422-0067/20/24/6236/s1>.

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Abbreviations

MCRs	multicomponent reactions
DCM	dichloromethane
NMR	nuclear magnetic resonance
DMF	dimethylformamide
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
HOBt	hydroxybenzotriazole
TFA	trifluoroacetic acid
NMM	N-methylmorpholine
RT	room temperature
MALDI TOF/TOF	matrix-assisted laser desorption/ionization with time-of-flight mass spectrometer

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