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Synthesis of Glycomimetics by Diastereoselective Passerini reaction

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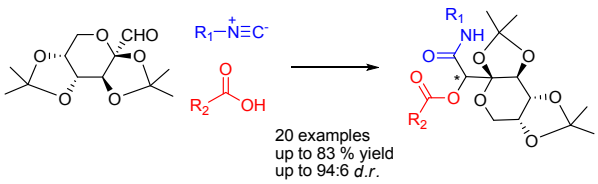


ABSTRACT: We describe the utilization of bis-isopropylidene-protected D-fructose-derived aldehyde in the Passerini reaction with various acids and isocyanides. A library of densely functionalised glycomimetics bearing up to 3 carbohydrate units was obtained in high yields and diastereoselectivities. The configuration of newly formed stereocenter was determined and the diastereoselectivity rationalized by DFT calculations.

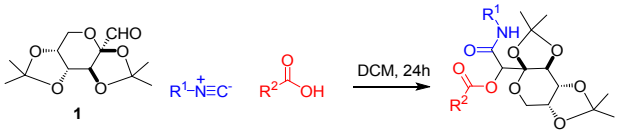
Introduction

Carbohydrates are the most abundant class of natural products with a distinctive role in different biological processes, like protein folding, cell-cell communication and immune response.[1] In addition, synthetic carbohydrate-based compounds found wide application in chemical biology and medicinal chemistry as diagnostics, therapeutics and vaccines,[2] drug delivery systems,[3,4] and molecular receptors.[4,5] Carbohydrates are highly valuable molecular scaffolds; their intrinsic stereochemical diversity and polyfunctionality makes them ideal for the generation of structurally diverse compound collections. However, there is still a limited number of carbohydrate-based drugs on the market, owing to the poor pharmacodynamic and pharmacokinetic properties of natural carbohydrates.[6] An attractive way to overcome these drawbacks is through design of glycomimetics, molecules that emulate bioactive function of carbohydrates but with improved drug-like properties.[7]

Multicomponent reactions (MCRs) offer an attractive one-pot strategy for generating a library of highly functionalized and complex compounds like glycomimetics.[8] A large number of MCRs comprising carbohydrates were developed,[9] providing access to structurally diverse glycoconjugates.[10] The formation of new stereocentre is inherent to many MCRs, and the utility of MCR strategy for drug discovery depends on the ability to deliver structurally complex but stereochemically defined compounds. Carbohydrate-derived aldehydes were reported to affect the diastereoselectivity in MCRs, due to the proximity to the newly formed stereocentre. However, the observed stereoselectivity depends on the position of aldehyde group, OH-protecting groups, and other components in MCRs.[11] To our surprise, sugar-derived aldehydes are neglected in isocyanide-based MCRs (e.g., Passerini, Ugi reaction), otherwise recognized as highly versatile tools in drug discovery.[12] Acetyl- and benzyl-protected galactose- and fucose-derived aldehydes were used in the synthesis of focused library of sialyl Lewis x glycomimetics, and observed diastereoselectivities ranged from 4:1 to 1:1.[13] In our search for carbohydrate building blocks suitable for utilization in MCRs, we opted for bis-isopropylidene-protected D-fructose-derived aldehyde **1** (Scheme 1), structurally analogous to the anticonvulsant drug topiramate, a rare example of central nervous system-active carbohydrates.[14] We anticipated that such bis-isopropylidene-protected aldehyde could serve as an efficient chiral inductor in MCRs. Thus, we report herein the Passerini reaction of easy accessible aldehyde **1**[15] with various acids and

isocyanides, where complex structures are obtained in very good yields and a highly stereocontrolled manner (Scheme 1).

Scheme 1 Passerini reaction with D-fructose-derived aldehyde 1.



Results and discussion

A first set of Passerini reactions was performed with two commercially available isocyanides, cyclohexyl- and 1,1,3,3-tetramethylbutyl isocyanide, and four different carboxylic acids. Along with simple acetic and benzoic acid, we utilized Boc-protected phenylalanine as a carboxylic component, because Passerini products comprising amino acids can be easily modified in post-condensation reactions.[16] Multivalent carbohydrate derivatives are promising mimics of ligands that recognize and bind to carbohydrate receptors placed on the cell surface,[1] so we opted for per-*O*-acetylated glucuronic acid to access carbohydrate-rich Passerini products. Reactions performed with selected isocyanides and carboxylic acids in dichloromethane at room temperature furnished Passerini products **2**-**9** in 68-83 % yield (Figure 1). We were pleased to find that even structurally complex bivalent derivatives **5** and **9**, bearing glucuronic acid part, are obtained in a very good yield in a single step. The most interesting observation is high stereoselectivity of the performed reactions. The ratio of two diastereoisomers, determined by NMR spectroscopy is ~ 9:1 *d.r.*, and the major isomer of all Passerini products with the exception of **5** and **9**, was isolated in a pure form. Compounds **5** and **9** were isolated as a mixture of four diastereoisomers, arising from the newly formed stereocentre and glucuronic acid component, present as a 15:85 mixture of α and β-pyranose forms.

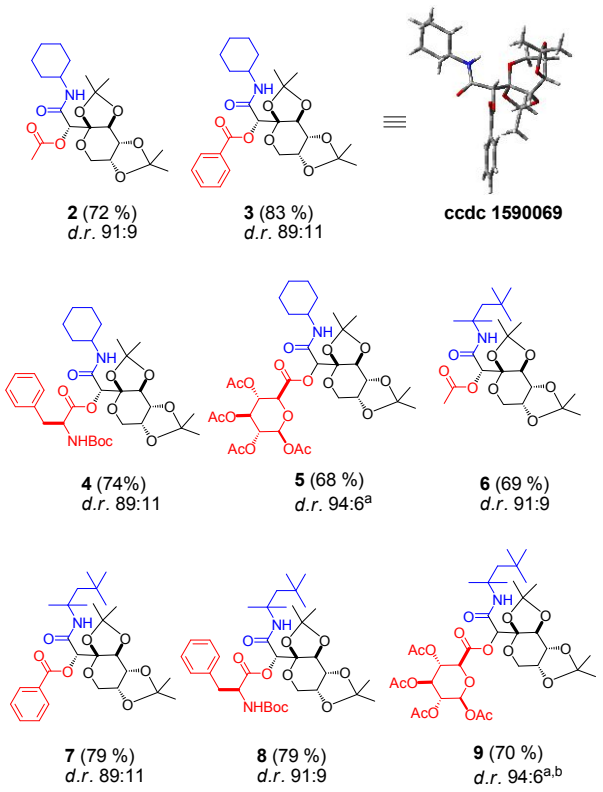


Figure 1. Passerini products obtained with sugar aldehyde 1 (isolated yields are given in parentheses). *d.r.* was determined by ^{1}H NMR analysis of reaction mixture (for compounds 2-4 and 6-8, or based on ratio of isolated diastereoisomers. [a]Ratio of α and β isomers (glucuronic acid) is 15:85. [b]Approximate *d.r.* due to poor peak resolving.

Encouraged by these results, we decided to explore the scope of the reaction by introducing sugar-derived isocyanides. Sugar isocyanides have been sporadically used in MCRs,[17,18] owing to challenging synthetic procedure, but also observed low stability of primarily 1-isocyano carbohydrate derivatives. Recently, anomeric per-*O*-acetylated glycosyl and arabinosyl isocyanides were prepared by an elegant Leuckart–Wallach approach and tested in different MCRs, however, substrate scope of these reaction has not been explored.[18] Since anomeric carbohydrate isocyanides are generally poor nucleophiles due to the proximal electronegative O-atom, we also consider 2-isocyano and 6-isocyanoglycosyl derivatives as potentially more reactive sugar building blocks. Passerini reactions performed with 1-isocyano glucose derivative gave di- and trivalent products **10-13** (Figure 2) in very good yields (57-80 %). Although purification and NMR

assignment of compounds comprising multiple carbohydrate units can be difficult and incomplete, Passerini products **10-12** were isolated as single diastereoisomers, while densely functionalised product **13** was isolated as a mixture of four diastereisomers. Next set of reactions was carried out with 2-isocyano glucose derivative and the corresponding Passerini products **14-17** were isolated again in very good yields (61-80 %, Figure 2) as a mixture of four diastereisomers. Inspection of the ^{1}H-NMR spectra of product **14** revealed nicely resolved signals of all four isomers that allowed determination of ratio of two isomers (9:1, *d.r.*). Finally, reactions performed with 6-isocyano glucose derivative under the same reaction conditions furnished Passerini products **18-21** in 66-76 % yield. Since 1-OBn-Ac$_3$-D-Glc unit is present in β-anomeric configuration, compounds **18-20** are isolated as inseparable mixtures of two isomers with *d.r.* > 9:1, while Passerini product **21** bearing three carbohydrate units is isolated as a mixture of four isomers.

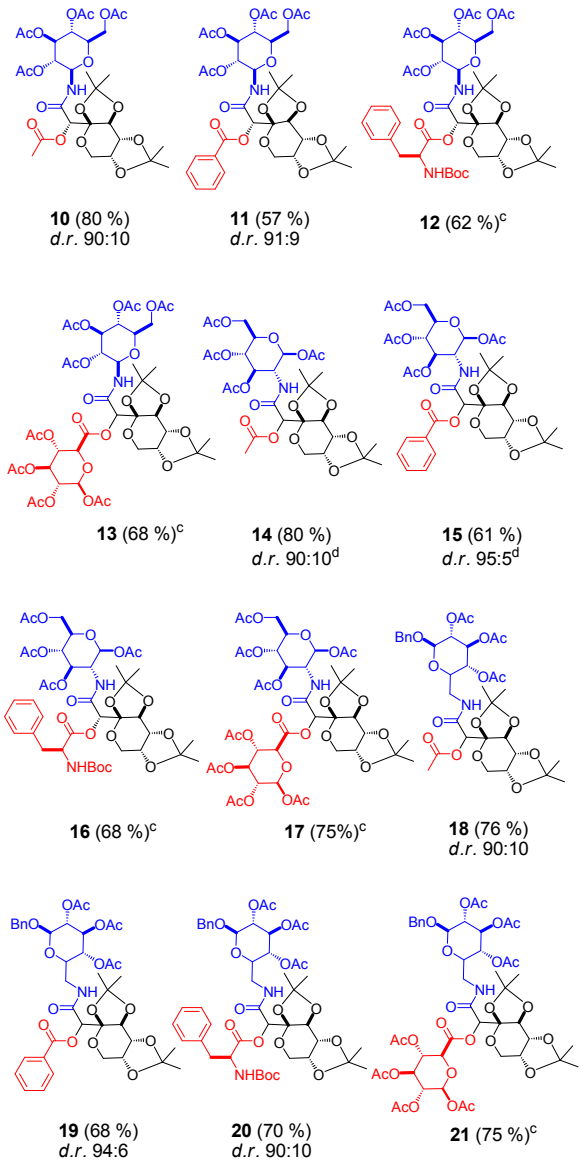
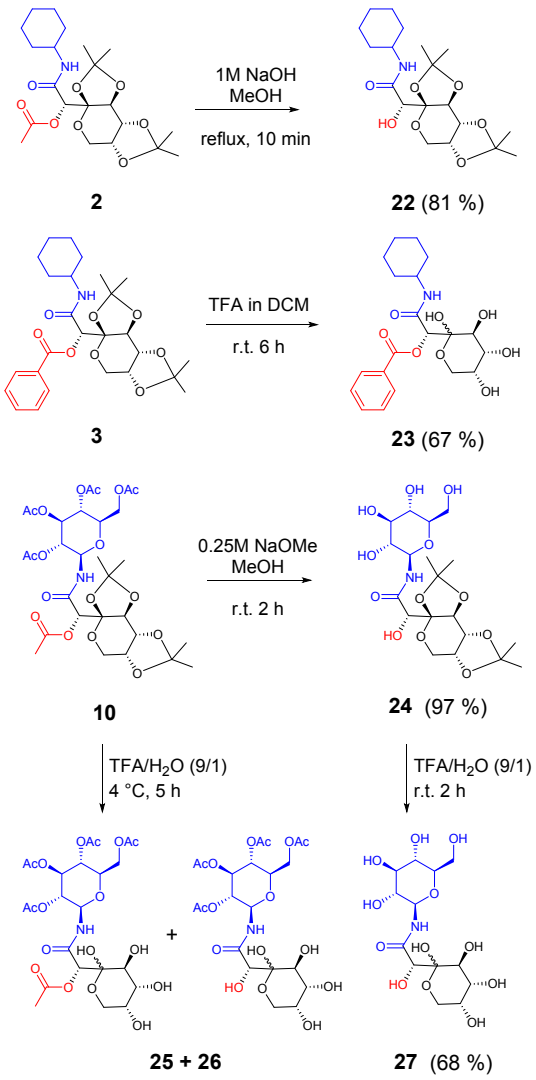


Figure 2. Passerini products obtained with sugar aldehyde 1 and sugar isocyanides (isolated yields are given in parentheses). *d.r.* was determined based on ratio of isolated diastereoisomers. [a]Ratio of α and β isomers (glucuronic acid) is 15:85. [b]Approximate *d.r.* due to poor peak resolving. [c]*d.r.* cannot be determined due to peak overlapping. [d]Ratio of α and β isomers for 2-NC-Ac$_4$-D-Glc is 60:40.

Having the general scope of the diastereoselective Passerini reaction on fructose-derived aldehyde **1** in hands, we applied acid- and base-mediated deprotection schemes on selected mono- and

bivalent Passerini products. Treatment of the Passerini product **2** (single diastereoisomer) with NaOH gave α-hydroxy amide derivative **22** in 81 % yield (Scheme 2). α-Hydroxy amides and their derivatives are recognized as privileged structures in medicinal chemistry and pharmaceutical industry, and are widely used as chiral ligands in the asymmetric synthesis.[19] ^{1}H NMR spectrum of α-hydroxy amide **22** (Supporting Information) revealed that the chiral information derived from diastereoselective Passerini reaction is preserved, so this chiral synthon is of high value for further modifications. Acid-based cleavage of isopropylidene groups was performed with TFA in DCM at room temperature and the Passerini product **23** was obtained in 67 % as a mixture of anomeric forms. Deprotection of bivalent Passerini products was expected to be more challenging owing to the presence of different carbohydrate units and protecting groups. Deacetylation of the Passerini product **10** afforded α-hydroxy amide derivative **24** in excellent yield (97 %, Scheme 2), with preservation of chiral information (Supporting Information). Treatment of compound **10** with TFA/H_2O (9/1) resulted in removal of isopropylidene groups, while NMR spectrum and mass spectra point toward presence of two compounds; a fructose moiety deprotected derivative **25** and the corresponding α-hydroxy amide **26**, but full assignment is hampered by the presence of multiple anomeric forms. Fully deprotected compound **27** was obtained by acid treatment of deacetylated compound **24** in 68 % yield, again as a mixture of anomers. It is also worth noting that *O*-deacetylation of per-acetylated carbohydrates can be performed enzymatically. Dunne and Palomo reported recently a mild and efficient strategy for deprotection of per-acetylated carbohydrates by the using commercially available lipase A from *Aspergillus niger*.[20] A high selectivity to the *O*-deacetylation instead of the *N*-deacetylation was observed, whereas isolated yields were > 99 % for α-glycopyranosides and 75–80 % for β-glycopyranosides. Therefore, a combination of chemical and enzymatic deprotection is available to access partially of fully deprotected carbohydrate-derived Passerini products.

Scheme 2. Deprotection schemes for the selected Passerini products.



To ascertain the stereochemistry of the newly created stereocentre, NOE contacts observed in 2D NOESY NMR experiments were compared to calculated interatomic distances in optimized structures of four different Passerini products (**2**, **4**, **6**, and **8**). The observed NOE contacts between hydrogen atom of the new stereocentre and other hydrogen atoms are likely to be observed in both diastereoisomers (as shown for compound **6** in Supporting Information), since calculated interatomic distances show similar values for both optimized diastereoisomers. However, according to calculated total energy the *S* configuration is more stable compared to the *R* configuration, which points towards the *S* configuration of the product (Supporting

Information). The *S* configuration of the new chiral centre was unambiguously determined by single-crystal x-ray diffraction analysis of product **3**.

In order to elucidate the observed stereoselectivity of Passerini reactions performed with sugar aldehyde **1**, we conducted density functional theory (DFT) calculations at the SMD/M062X/6-311++G(2d,p)//M062X/6-31G(d) level of theory[21] employing dichloromethane as a solvent starting from two different configurations leading to the final product **2** with *S* configuration (**path-a**) and *R* configuration (**path-b**), respectively, following the mechanistic pathway proposed recently by Ramozzi and Morokuma.[22,23] Figure 3a shows calculated free energy profiles for the reaction. The first step, e. g. complexation of cyclohexane isocyanide with sugar aldehyde **1** and two acetic acid molecules, results in two pre-complexes of different stabilities – for the **path-a**, the pre-complex is by 2.9 kcal mol^{-1} more stable than the pre-complex which serves as a starting point for the **path-b**. The remaining reaction profiles for both reaction paths have similar energetics (with free energy differences up to 10 kJ mol^{-1}), except for the transition state $\mathbf{TS_3}$, which is by ca. 10 kJ mol^{-1} more stable in the **path-a** *vs* **path-b**, and the intermediate $\mathbf{INT_5}$ which is by ca. 13 kJ mol^{-1} more stable in the **path-b** *vs* **path-a** (Figure 3a). Based on the presented energy profile, we identified the rearrangement of imidate-acid cluster ($\mathbf{INT_3}$) to dioxolane-acid cluster ($\mathbf{INT_4}$) *via* the transition state $\mathbf{TS_3}$ as the rate-determining step of the reaction with the free energy barrier of 82.3 kJ mol^{-1}, in accordance to previous studies of the mechanism of Passerini reaction.[24,25] In addition, the free energy difference is observed in the final product with the *S* configuration (**path-a)**, which is by ca. 6.5 kJ mol^{-1} more stable than the final product with the *R* configuration (**path-b**). We should also mention here that we tried to elucidate the mechanism with only one carboxylic acid instead of two as presented here (Figure 3). However, these attempts were not successful since we were not able to obtain the transition state **TS3** with reasonable energetics, similar to Ramozzi and Morokuma .[22]

There is also one important mechanistic step discriminating these two pathways – namely, in the **path-b**, the intermediate $\mathbf{INT_5}$ is directly converted into the final product *via* transition state $\mathbf{TS_4}$ in contrast to the **path-a** where additional intermediates $\mathbf{INT_6}$ and $\mathbf{INT_7}$ are located. In this reaction step in **path-a**, the proton transfer from *O*-atom to *N*-atom occurs *via* transition state $\mathbf{TS_4}$ resulting in an additional intermediate $\mathbf{INT_6}$ where proton is located on the imine nitrogen atom. A subsequent conformational change results in the intermediate $\mathbf{INT_7}$ which finally converts to the

final product with the *S* configuration *via* the barrier-less transition state **TS$_5$** (Figure 3c).[23] However, regardless of the mechanistic details of each of the reaction paths, the strong stabilization of the **TS$_3$** in the **path-a** *vs* **path-b,** is the main factor explaining the diastereoselectivity of the Passerini reaction and the formation of the product with *S* configuration. Figure 3c and 3d show the proposed mechanistic pathway for the Passerini reaction leading to *S* and *R* products.

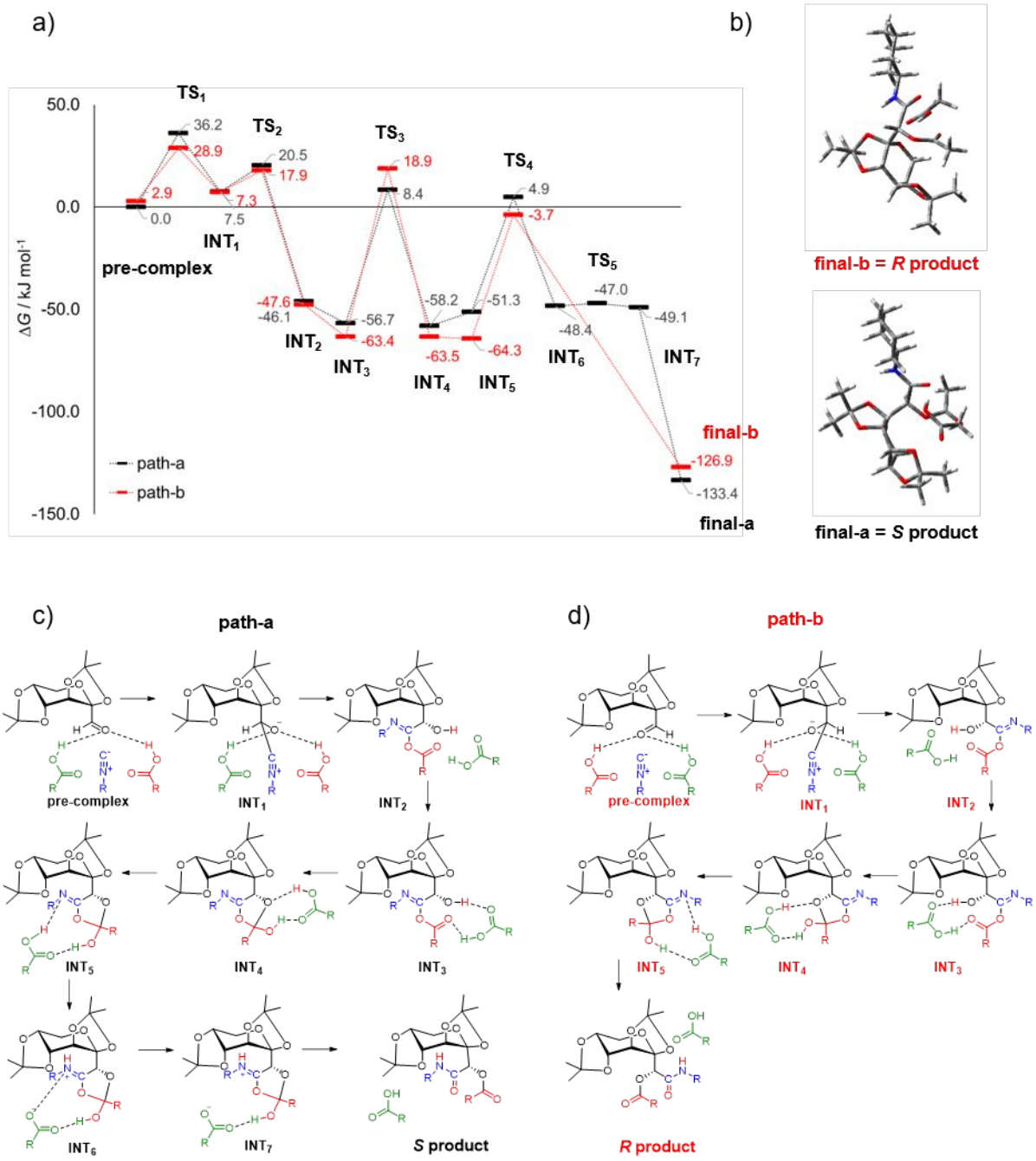
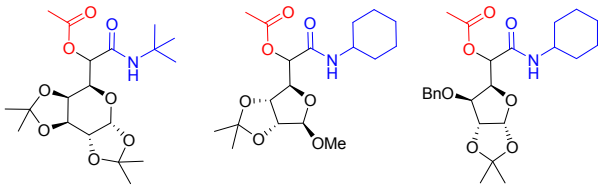


Figure 3. (a) Free energy profiles calculated at the SMD/M062X/6-311++G(2d,p)//M062X/6-31G(d) level of theory for two different starting configurations leading to final products with *S* configuration (path-a) and *R* configuration (path-b). (b) Optimized geometries of final products obtained at SMD/M062X/6-31G(d) level of theory. Qualitative indication of noncovalent van der Waals interactions is shown with red arrows. (c) Proposed mechanistic pathway for the formation of *S* product in the Passerini reaction. (d) Proposed mechanistic pathway for the formation of *R* product in the Passerini reaction.

To further explore the utility of here described multicomponent procedure, we performed Passerini reactions by using D-galactose-, D-ribose and D-xylose derived aldehydes, with acetic acid and either *tert*-butyl or cyclohexyl isocyanide. Reactions were conducted under the same reaction conditions as described previously, in dichloromethane at room temperature, and the corresponding Passerini products **28-30** were obtained in high yields (Figure 4), thus proving that approach can be easily expanded to different sugar-derived aldehydes.



28 (78 %) **29** (82 %) **30** (79 %)

Figure 4. Passerini product obtained with D-galactose, D-ribose and D-xylose-derived aldehydes.

Recently, Riva et al. reported Passerini reactions on acyclic isopropylidene protected aldehyde, where 0.4 equiv of Lewis acid ($ZnBr_2$) was required to improve diastereoselectivities up to 92:8.[26] Authors presumed that chelation of the metal by the carbonyl oxygen and one of the dioxolane oxygens accounts for the observed relative configuration of the main product. To reveal the role of the isopropylidene group in diastereoselectivity of MCRs, we are currently focused on the utilization of other carbohydrate-derived carbonyl compounds, and these results will be published in due course.

Conclusions

In conclusion, we developed a multicomponent approach to densely functionalised glycomimetics in a high diastereoselective manner. The approach is based on the Passerini reaction of bis isopropylidene-protected D-fructose-derived aldehyde with various acids and isocyanides and the observed diastereoselectivity was rationalized by DFT calculations.

Experimental section

General methods

All experiments were monitored by analytical thin layer chromatography (TLC) on Silica Gel 60 F254 plates (Merck; Darmstadt, Germany) after spraying with 10 % H_2SO_4 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 Bruker Avance 600 spectrometer (600.13 MHz, ^{1}H; 150.91 MHz, ^{13}C). Samples in $CDCl_3$ solutions were recorded in 5 mm NMR tubes at 298 K. Chemical shifts in parts per million were referenced to TMS as internal standard. Spectra were assigned based on 2D homonuclear (COSY, NOESY) and heteronuclear (HMQC, HMBC) experiments. ^{13}C (APT) spectra were recorded with broadband proton decoupling (WALTZ) using a broadband-observed probe (BBO; BB, ^{1}H; inner coil tuned for ^{13}C) with a built-in z-gradient coil. Typically, spectra at a spectral width of 35 kHz and a digital resolution of 2.1 Hz per point were measured with 10,000 scans using a standard pulse sequence (jmod) from the Bruker TopSpin library. All ^{1}H and 2D NMR spectra were recorded using a triple resonance inverse detection probe (TBI; ^{1}H, ^{13}C,BB; inner coil tuned for ^{1}H) with a built-in z-gradient coil. ^{1}H spectra at a spectral width of 6,600 Hz and a digital resolution of 0.4 Hz per point were measured with 128 scans. Standard gradient enhanced pulse programs supplied in the Bruker TopSpin library were used for HMQC (hmqcgpqf) and HMBC (hmbcgplpndqf) spectra. In the ^{1}H observation dimension (F2), 2 K data points were acquired at a spectral width of 6,600 Hz. In the indirect carbon dimension (F1), 256 data points (HMQC) or 512 data points (HMBC) at a spectral width of 35 kHz were used. GARP decoupling was employed for ^{13}C during proton detection in HMQC. 16 (HMQC) or 32 (HMBC) transients were recorded per evolution time increment. COSY (cosygpqf) and NOESY (noesyph) were applied using 2 K data points in F2 dimension and 256 (COSY) or 512 (NOESY) increments in F1 dimension at a spectral with of 6,600 Hz. 8 (COSY) or 16 (NOESY) transients were recorded per evolution time increment. NOESY mixing times where 600 ms. All experimental data were zero-filled to double the number of experimental points and then baseline-corrected using automatic baseline correction. The software TopSpin (Bruker BioSpin) version 2.1 was used for all acquisition and processing. Since Passerini products are three-component coupling products, ^{1}H chemical shifts are assigned to the particular starting component, and the following abbreviations are used: cyclohexyl = CyHex; tetramethylbutyl = tMeBu; fructose

derived aldehyde **1** = Fru; glucuronic acid = GlaA; 1-, 2-, and 6-isocyano glucose derivatives = Glc1NC, Glc2NC, and Glc6NC, respectively. High resolution mass spectrometry (HRMS) was performed on a MALDI-TOF/TOF spectrometer in positive ionization mode. 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.

Synthesis of sugar isocyanides

Per-*O*-acetylated 1-isocyano-glucose derivative (1-NC-Ac_4-D-Glc) was prepared by the Leuckart–Wallach approach.[18]

Per-*O*-acetylated 2-isocyano-glucose derivative (2-NC-Ac_4-D-Glc) was prepared by the modified approach described in the literature (Scheme S1 in the Supporting Information):[27]

Glucosamine hydrochloride (432 mg, 2 mmol) was dissolved in 8 mL of saturated $NaHCO_3$ solution, and methylformate (1.23 mL) was added and mixed at room temperature. Methylformate was added twice more, after 16 h and after 24 h (total volume was 4.23 mL). After 48 h, the reaction mixture was evaporated and dried for several hours in a desiccator. To the residue 5 mL of pyridine/Ac_2O 1:1, v/v mixture was added and stirred overnight at room temperature. The solvent was evaporated with addition of toluene and the residue was dried over H_2SO_4. To the residue, DCM (4.6 mL), Et_3N (820 μL) and $POCl_3$ (224 μL) were added. The reaction was stirred at room temperature for 1 h, and then Na_2CO_3 (400 mg) dissolved in water (1.6 mL) was added. The reaction mixture was stirred for 1 h at room temperature. DCM and water were added and extracted. The organic layers were collected and dried over K_2CO_3 filtered and evaporated. The residue was purified on silica gel column in a solvent system toluene/EtOAc 1:1, v/v. The product was obtained in 40 % yield. Spectral data are consistent with those published in Ref 27.

1-OBz-6-NC-Ac_3-D-Glc was prepared by the Leuckart–Wallach approach[18] starting from 1-O-Bn-6-NH_2-Glc (obtained by standard carbohydrate chemistry, as depicted at Scheme S2 in the Supporting Information).

1-O-Bn-6-NH_2-Glc (400 mg, 1.488 mmol) was dissolved in a saturated solution of $NaHCO_3$ (12 mL) and methylformate (12 mL, 194.4 mmol) was added and stirred overnight at room temperature. During this time methylformate was added twice (2×1 mL). After 48 h, the reaction

mixture was evaporated and purified by flash chromatography in a solvent system: EtOAc/EtOH/AcOH/H_2O 70:15:15:15. To the residue a mixture of pyridine/acetic anhydride 1:1, v/v (12 mL) was added and stirred at room temperature for 5 h. The solvent was evaporated with addition of toluene and the residue was purified by flash chromatography on silica gel column in a solvent system: EtOAc/AcOH/H_2O 70:1:1, v/v. A product of 1-O-Bn-6-NCO-Ac_3-Glc (70 %) was obtained and dried for 24 h in a desiccator.

1-O-Bn-6-NCO-Ac_3-Glc (370 mg, 0.87 mmol) was dissolved in DCM (2.4 mL), and Et_3N (472 µL) and $POCl_3$ (128 µL) were added. The reaction was stirred at room temperature for 1h, followed by the addition of Na_2CO_3 (232 mg) dissolved in water (0.920 mL). The reaction mixture was stirred for further 1 h at room temperature. DCM and water were added and extracted. The organic layers were collected and dried over K_2CO_3, filtered and evaporated. The residue was purified on silica gel column in a solvent system toluene/EtOAc 1:1, v/v. The product was obtained in 67 %.

^{1}H NMR ($CDCl_3$): δ 7.38–7.26 (m, 5H, CH-benzyl), 5.16 (t, J = 9.5 Hz, 1H, H-3), 5.04 (dd, J = 9.5, 8.0 Hz, 1H, H-2), 4.92 (d, J = 7.8 Hz, 1H, H-6a), 4.90 (d, J = 10.0 Hz, 1H, H-4), 4.66 (d, J = 12.3 Hz, 1H, H-5), 4.56 (d, J = 7.9 Hz, 1H, H-1β), 3.70–3.65 (m, 1H, H-6b), 3.55 (d, J = 5.4 Hz, 2H, CH_2-benzyl), 2.10 – 1.86 (m, 9H, CH_3-acetyl). ^{13}C NMR ($CDCl_3$): δ 170.33, 169.8, 169.4, 159.7, 136.5, 128.8, 128.4, 128.2, 99.2, 72.5, 71.7, 71.4, 71.0, 70.3, 43.3, 20.8, 20.8. (ESI+): *m/z* = 406,4. HRMS (MALDI-TOF/TOF) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{24}NO_8$ 406.1509; found 406.1507.

General procedure for Passerini reactions

To a glass vial containing 1 M solution of aldehyde **1** (0.1 mmol) in DCM under nitrogen were added acid (0.1 mmol) and the isocyanide component (0.1 mmol) dissolved in 100 µL DCM. With all reactants added, the solution was allowed to stir for 8-24 h. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

(S)-2-(cyclohexylamino)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)ethyl acetate (2)

Yield 72 % (31 mg); colorless oil; R_f = 0.39 (toluene/acetone 5:1, v/v).^{1}H NMR ($CDCl_3$): δ 6.25 (d, J = 7.5 Hz, 1H, NH), 5.05 (s, 1H, H1 Fru), 4.58 (dd, J = 7.9, 2.6 Hz, 1H, H4 Fru), 4.38 (d, J =

2.6 Hz, 1H, H3 Fru), 4.22 (d, *J* = 7.8 Hz, 1H, H 5 Fru), 3.92 (dd, *J* = 12.9 Hz, 1.4 Hz, 1H, H6 Fru), 3.78 (d, *J* = 12.9 Hz, 1H, H6' Fru), 3.75 (m, 1H, CyHex), 2.17 (s, 3H, CH_3 Ac), 1.87 (m, 2H, CyHex), 1.63 (m, 3H, CyHex), 1.53 (m, 1H, CyHex), 1.50 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.32 (m, 4H, CH_3, CyHex), 1.16 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$): δ 169.4, 164.5, 109.7, 109.5, 102.3, 73.9, 70.8, 70.3, 61.8, 48.5, 32.9, 32.9, 26.7, 26.3, 25.8, 25.5, 24.8, 24.8, 24.2, 21.0. MS (ESI+): *m/z* = 428.3. HRMS (MALDI-TOF/TOF) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{33}NO_8$ 428.2284; found 428.2278. HPLC analysis: *n*-hexane/*i*-PrOH = 80/20, υ = 0.5 mLmin^{-1}, λ = 215 nm, t =17.4 min (95 %). $[\alpha]_D^{20}$ = -14 ($CHCl_3$, c=0.5).

(S)-2-(cyclohexylamino)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)ethyl benzoate (3)

Yield 83 % (41 mg); white solid; R_f = 0.58 (toluene/acetone 5:1, v/v); m.p. 123-124 °C. ^{1}H NMR ($CDCl_3$): *δ* 8.08 (dd, *J* = 8.2, 1.1 Hz, 2H, Ph), 7.54 (dd, *J* = 10.6, 4.2 Hz, 1H, Ph), 7.42 (t, *J* = 7.8 Hz, 2H, Ph), 6.39 (d, *J* = 7.8 Hz, 1H, NH), 5.43 (s, 1H, H1 Fru), 4.59 (dd, *J* = 7.9 Hz, 2.7 Hz, 1H, H4 Fru), 4.47 (d, *J* = 2.8 Hz, 1H, H3 Fru), 4.24 (d, *J* = 8.0 Hz, 1H, H5 Fru), 3.99 (dd, *J* = 13.0, Hz, 1.7 Hz, 1H, H6 Fru), 3.84 (d, *J* = 13.0 Hz, 1H, H6' Fru), 3.82–3.76 (m, 1H, CyHex), 1.89 (s, 2H, CyHex), 1.63 (m, 2H, CyHex), 1.60 (s, 1H, CyHex), 1.55 (m, 1H, CyHex), 1.54 (s, 3H, CH_3), 1.53 (s, 6H, CH_3), 1.32 (s, 4H, CH_3, CyHex), 1.19 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$): δ 165.6, 164.6, 133.4, 130.2, 129.9, 128.6, 109.9, 102.4, 74.2, 70.8, 70.2, 61.9, 48.6, 33.00, 26.8, 26.3, 26.0, 25.8, 24.8, 24.2. MS (ESI+): *m/z* = 490.3. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{26}H_{35}NO_8Na$ 512.2260; found 512.2242.HPLC analysis: *n*-hexane/i-PrOH = 80/20, υ = 0.5 mLmin^{-1}, λ = 215 nm, t = 24.4 min (99 %). $[\alpha]_D^{20}$ = -12 ($CHCl_3$, c=0.5). Crystals suitable for x-ray analysis were obtained by slow evaporation from *n*-hexane/*i*-PrOH (9/1. v/v) solution.

(S)-((S)-2-(cyclohexylamino)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)ethyl) 2-(tert-butoxycarbonylamino)-3-phenylpropanoate (4)

Yield 79 % (50 mg); colorless oil; R_f = 0.52 (toluene/acetone 5:1, v/v). ^{1}H NMR ($CDCl_3$): *δ* 7.27-7.25 (m, 2H, Ph), 7.21-7.18 (m, 3H, Ph), 6.39 (d, *J* = 7.8 Hz, 1H, NH), 5.14 (s, 1H, H1 Fru), 4.90 (d, *J* = 8.4 Hz, 1H, NH Phe), 4.61 (dd, *J* = 8.3 Hz, 3.5 Hz, 1H, α Phe), 4.58 (dd, *J* = 7.8 Hz, 2.5 Hz, 1H, H4 Fru), 4.36 (d, *J* = 2.4 Hz, 1H, H3 Fru), 4.22 (d, *J* = 7.8 Hz, 1H, H5 Fru), 3.93 (d, *J* =

12.9 Hz, 1H, H6 Fru), 3.79 (m, 2H, H6' Fru, CyHex), 3.40 (dd, *J* = 14.3 Hz, 4.5 Hz, 1H, β Phe), 3.02 (dd, *J* = 14.2 Hz, 8.5 Hz, 1H, β' Phe), 1.89 (d, *J* = 11.6 Hz, 2H, CyHex), 1.67-1.54 (m, 2H, CyHex), 1.50 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.43 (s, 2H, CyHex), 1.34 (s, 9H, CH_3 Boc), 1.32 (s, 3H, CH_3), 1.28 (br s, 1H, CyHex), 1.18 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$): δ 170.9, 164.2, 155.4, 136.6, 129.7, 128.7, 127.0, 109.9, 109.5, 102.1, 80.1, 74.2, 70.8, 70.7, 70.2, 62.0, 54.6, 48.6, 38.5, 33.0, 28.4, 26.7, 26.3, 25.8, 25.6, 24.9, 24.8, 24.3. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{33}H_{48}N_2O_{10}Na$ 655.3207; found 655.3203. HPLC analysis: *n*-hexane/*i*-PrOH = 80/20, υ = 0.5 mLmin^{-1}, λ = 215 nm, t = 29.8 min (95 %). $[\alpha]_D^{20}$ = -10 ($CHCl_3$, c= 0.5).

(3R,4S,5S,6S)-6-((2-(cyclohexylamino)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)ethoxy)carbonyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (5)

Yield 68 % (49 mg); colorless oil; R_f= 0.38 (toluene/acetone 5:1, v/v); *α:β*= 15:85.Chemical shifts are given for major isomer. ^{1}H NMR ($CDCl_3$): δ 6.37 (d, *J* = 3.6 Hz, H1α GlcA), 6.31 (d, *J* = 7.8 Hz, β NH), 6.22 (d, *J* = 8.0 Hz, α NH), 5.79 (d, *J* = 7.5 Hz, H1β GlcA), 5.45 (t, *J* = 9.5 Hz, H4α GlcA), 5.40 (t, *J* = 9.5 Hz, H4β GlcA), 5.25 (t, *J* = 9.1 Hz, H3 GlcA), 5.11 (d, *J* = 7.8 Hz, H2 GlcA), 5.09 (s, H1 Fru), 4.58 (dd, *J* = 7.9 Hz, 2.7 Hz, H4 Fru), 4.39 (d, *J* = 9.8 Hz, H5 GlcA), 4.37 (d, *J* = 2.8 Hz, H3 Fru), 4.21 (d, *J* = 7.8 Hz, H5 Fru), 3.92 (d, *J* = 12.9 Hz, H6 Fru), 3.77 (d, *J* = 13.0 Hz, H6' Fru), 3.72 (m, H1 CyHex), 2.07-1.99 (s, CH_3-Ac), 1.83 (m, CyHex), 1.61 (m, CyHex), 1.48 (s, 3H, CH_3), 1.45 (s, CH_3), 1.41 (s, CH_3), 1.31 (s, CH_3), 1.29-1.16 (m, CyHex). ^{13}C NMR ($CDCl_3$): δ 170.3, 169.6, 169.4, 168.7, 165.2, 163.3, 110.1, 109.5, 102.0, 91.8, 88.9, 74.8, 73.1, 72.5, 70.8, 70.7, 70.5, 70.2, 70.2, 68.5, 62.0, 48.5, 32.8, 26.7, 26.3, 25.8, 25.4, 24.8, 24.7, 24.3, 20.9, 20.9, 20.8, 20.8. MS (ESI+): *m/z* = 730.3. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{33}H_{47}NO_{17}$ 752.2742; found 752.2743.HPLC analysis: (*n*-hexane/i-PrOH = 50/50, υ = 0.5 mLmin^{-1}, λ = 215 nm, t = 20.7 min (95 %).

(S)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-(2,4,4-trimethylpentan-2-ylamino)ethyl acetate (6)

Yield 69 % (32 mg); colorless oil; R_f= 0.69 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 6.36 (s, 1H, NH), 5.01 (s, 1H, H1 Fru), 4.58 (dd, *J* = 7.9 Hz, 2.7 Hz, 1H, H4 Fru), 4.32 (d, *J* = 2.7 Hz, 1H, H3 Fru), 4.22 (d, *J* = 7.0 Hz, 1H, H5 Fru), 3.92 (dd, *J* = 12.9 Hz, 1.6 Hz, 1H, H6 Fru), 3.77

(d, *J* = 12.9 Hz, 1H, H6' Fru), 2.17 (s, 3H, CH_3), 1.68 (d, *J* = 15.0 Hz, 1H, H2 tMeBu), 1.60 (d, *J* = 15.0 Hz, 1H, H2' tMeBu), 1.50 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.40 (s, 3H, CH_3 tMeBu), 1.38 (s, 3H, CH_3 tMeBu), 1.32 (s, 3H, CH_3), 0.98 (s, 9H, H4, H3',H3' CH_3 tMeBu). ^{13}C NMR ($CDCl_3$): δ 169.2, 164.0, 109.7, 109.6, 102.4, 74.0, 70.9, 70.9, 70.3, 61.8, 55.5, 53.1, 31.8, 29.2, 29.0, 26.7, 26.2, 25.6, 24.4, 21.0. HRMS (MALDI-TOF/TOF) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{39}NO_8$ 458.2754; found 458.2761. HPLC analysis: *n*-hexane/i-PrOH = 80/20, υ = 0.5 mLmin^{-1}, λ = 215nm, t = 16.4 min (96 %). $[\alpha]_D^{20}$ = -10 ($CHCl_3$, c= 0.5).

(S)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-(2,4,4-trimethylpentan-2-ylamino)ethyl benzoate (7)

Yield 79 % (41 mg); colorless oil; R_f = 0.77 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 8.11-8.07 (m, 2H, Ph), 7.54 (t, *J* = 7.4 Hz, 1H, Ph), 7.41 (t, *J* = 7.8 Hz, 2H, Ph), 6.49 (s, 1H, NH), 5.39 (s, 1H, H1 Fru), 4.58 (dd, *J* = 7.9 Hz, 2.8 Hz, 1H, H4 Fru), 4.41 (d, *J* = 2.8 Hz, 1H, H3 Fru), 4.24 (d, *J* = 7.9 Hz, 1H, H5 Fru), 3.99 (dd, *J* = 12.9 Hz, 1.6 Hz, 1H, H6 Fru), 3.82 (d, *J* = 12.9 Hz, 1H, H6' Fru), 1.70 (d, *J* = 14.9 Hz, 1H, H2 tMeBu), 1.60 (d, *J* = 15.0 Hz, 1H, H2' tMeBu), 1.54 (s, 3H, CH_3), 1.53 (s, 6H, CH_3), 1.41 (s, 3H, CH_3 tMeBu), 1.39 (s, 3H, CH_3 tMeBu), 1.32 (s, 3H, CH_3), 0.99 (s, 9H, H4, H3',H3' CH_3 tMeBu). ^{13}C NMR ($CDCl_3$): δ 165.4, 164.1, 133.4, 130.3, 130.0, 128.6, 109.9, 109.7, 102.4, 74.3, 70.9, 70.9, 70.2, 61.9, 55.5, 53.0, 31. 8, 31.7, 29.2, 29.1, 26.8, 26.2, 26.1, 24.3. MS (ESI+): *m/z* = 520.3. HRMS (MALDI-TOF/TOF) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{41}NO_8$ 520.2910; found 520.2936. HPLC analysis: *n*-hexane/i-PrOH = 80/20, υ = 0.5 mLmin^{-1}, λ = 215nm, t = 20.9 min 96 %. $[\alpha]_D^{20}$ = -12 ($CHCl_3$, c=0.5).

(S)-((S)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-(2,4,4-trimethylpentan-2-ylamino)ethyl) 2-(tert-butoxycarbonylamino)-3-phenylpropanoate (8)

Yield 79 % (52 mg); colorless oil; R_f = 0.83 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 7.31-7.17 (m, 5H, Ph), 6.35 (s, 1H, NH), 5.06 (s, 1H, H1 Fru), 4.90 (d, *J* = 8.4 Hz, 1H, NH Phe), 4.61 (d, *J* = 5.3 Hz, 1H, Hα Phe), 4.57 (dd, *J* = 7.8 Hz, 2.7 Hz, 1H, H4 Fru), 4.29 (d, *J* = 2.8 Hz, 1H, H3 Fru), 4.21 (d, *J* = 7.7 Hz, 1H, H5 Fru), 3.93 (d, *J* = 12.9 Hz, 1H, H6 Fru), 3.76 (d, *J* = 12.9 Hz, 1H, H6' Fru), 3.37 (dd, *J* = 14.1 Hz, 4.9 Hz, 1H, β Phe), 3.07 (dd, *J* = 14.2 Hz, 7.6 Hz, 1H, β'

Phe), 1.74 (d, *J* = 14.9 Hz, 1H, H2 tMeBu), 1.59 (d, *J* = 15.0 Hz, 1H, H2' tMeBu), 1.50 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.42 (s, 3H, CH_3 tMeBu), 1.39 (s, 3H, CH_3 tMeBu), 1.35 (s, 9H, CH_3 Boc), 1.32 (s, 3H, CH_3), 0.99 (s, 9H, H4, H3', H3' CH_3 tMeBu). ^{13}C NMR ($CDCl_3$): δ 170.7, 163.6, 155.3, 136.5, 130.0, 129.5, 128.6, 127.0, 109.9, 109.5, 102.1, 80.0, 74.3, 70.9, 70.7, 70.2, 62.0, 55.6, 54.5, 52.9, 52.4, 38.3, 31.8, 31.8, 29.1, 29.1, 28.5, 26.7, 26.3, 25.6, 24.3. MS (ESI+): *m/z* = 663.4. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{35}H_{54}N_2O_{10}Na$ 685.3676; found 685.3656. $[\alpha]_D^{20}$ = -5 ($CHCl_3$, c=0.5).

(3R,4S,5S,6S)-6-((2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-(2,4,4-trimethylpentan-2-ylamino)ethoxy)carbonyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (9)

Yield 70 % (53 mg); colorless oil; R_f = 0.60 (ethyl acetate/toluene 1:1, v/v); α:β = 15:85. Chemical shifts are given for major isomer. ^{1}H NMR ($CDCl_3$): δ 6.35 (br s, NH), 5.78-5.74 (m, H1 GlcA), 5.42 (t, *J* = 9.4 Hz, H4 GlcA), 5.28-5.22 (m, H3 GlcA), 5.12–5.10 (m, H2 GlcA), 5.00 (br s, 1H, H1 Fru), 4.57 (dd, *J* = 7.8, 2.8 Hz, H4 Fru), 4.36 (d, *J* = 9.7 Hz, H5 GlcA), 4.31 (d, *J* = 2.7 Hz, H3 Fru), 4.20 (d, *J* = 7.8 Hz, H5 Fru), 3.91 (dd, *J* = 12.8, 1.4 Hz, H6 Fru), 3.76-3.72 (m, H6 Fru, H1 CyHex), 2.06–1.99 (m, CH_3-Ac), 1.67 (d, *J* = 14.9 Hz, H2 tMeBu), 1.58 (d, *J* = 14.2 Hz, H2' tMeBu), 1.48 (s, CH_3), 1.44 (s, CH_3), 1.41 (s, CH_3), 1.35 (m, CH_3), 1.34 (s, CH_3), 1.31 (s, CH_3), 0.96 (s, H4, H3',H3' CH_3 tMeBu). ^{13}C NMR ($CDCl_3$): δ 170.3, 169.5, 169.4, 168.7, 165.0, 162.7, 110.1, 109.6, 102.0, 91.8, 89.1, 75.0, 73.2, 72.6, 72.1, 70.8, 70.8, 70.4, 70.2, 69.1, 68.5, 61.9, 55.5, 53.2, 52.8, 31.7, 29.0, 29.0, 26.7, 26.2, 25.5, 24.3, 20.9, 20.8, 20.7. MS (ESI+): *m/z* = 782.4. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{35}H_{53}NO_{17}Na$ 782.3211; found 782.3192.

(2R,3R,4S,5R,6R)-2-((S)-2-acetoxy-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (10)

Yield 80 % (54 mg); colorless oil; R_f = 0.50 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 6.94 (d, *J* = 9.4 Hz, 1H, NH), 5.27-5.20 (m, 2H, H1 Glc1NC, H3 Glc1NC), 5.07 (t, 1H, H4 Glc1NC), 5.02 (s, 1H, H1 Fru), 4.97 (t, 1H, H2 Glc1NC), 4.58 (dd, *J* = 7.9, 2.8 Hz, 1H, H4 Fru), 4.33 (dd, *J* = 12.4, 4.4 Hz, 1H, H6 Glc1NC), 4.30 (d, *J* = 2.8 Hz, 1H, H3 Fru)), 4.24 – 4.21 (m, 1H, H5 Fru), 4.04 (dd, *J* = 12.4, 2.2 Hz, 1H, H6 Glc1NC), 3.88 (dd, *J* = 12.9, 1.7 Hz, 1H, H6 Fru), 3.83

(d, *J* = 12.8 Hz, 1H, H6 Fru), 3.75 (ddd, *J* = 10.1, 4.3, 2.2 Hz, 1H, H5 Glc1NC), 2.16, 2.07, 2.02, 2.00, 1.97 (m, 15H, CH_3), 1.53, 1.50, 1.44, 1.32 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.8, 170.1, 169.8, 169.1, 166.3, 110.2, 109.7, 101.8, 78.6, 74.1, 73.9, 73.1, 70.8, 70.7, 70.4, 70.2, 68.7, 61.9, 61.9, 26.7, 26.1, 25.4, 24.4, 20.9, 20.9, 20.8, 20.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{29}H_{41}NO_{17}Na$ 698.2272; found 698.2289.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((S)-2-(benzoyloxy)-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (11)

Yield 57 % (42 mg); colorless oil; R_f = 0.62 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 2H, Ph), 7.57 (t, *J* = 7.5 Hz, 1H, Ph), 7.44 (t, *J* = 7.8 Hz, 2H, Ph), 7.20 (d, *J* = 9.2 Hz, 1H, NH), 5.42 (s, 1H, H1 Fru), 5.26 (m, 2H, H1 Glc1NC, H3 Glc1NC), 5.08 (t, *J* = 9.7 Hz, 1H, H4 Glc1NC), 5.01 (t, *J* = 9.6 Hz, 1H, H2 Glc1NC), 4.59 (dd, *J* = 7.8 Hz, 2.7 Hz, 1H, H4 Fru), 4.41 (d, *J* = 2.8 Hz, 1H, H3 Fru), 4.31 (dd, *J* = 12.4 Hz, 4.2 Hz, 1H, H6 Glc1NC), 4.25 (d, *J* = 7.8 Hz, 1H, H5 Fru), 4.03 (dd, *J* = 12.4 Hz, 1.7 Hz, 1H, H6' Glc1NC), 3.94 (d, *J* = 11.6 Hz, 1H, H6 Fru), 3.88 (d, *J* = 13 Hz, 1H, H6' Fru), 3.74 (dd, *J* = 10.0 Hz, 1.9 Hz, 1H, H5 Glc1NC), 2.08, 2.05, 2.00, 1.99, 1.60, 1.54, 1.51, 1.32 (s, 24H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.9, 170.9, 170.2, 169.8, 166.4, 165.4, 133.8, 130.2, 129.3, 128.7, 110.3, 109.7, 101.8, 78.7, 77.4, 77.2, 77.0, 74.0, 73.9, 73.0, 70.8, 70.7, 70.3, 70.1, 68.5, 62.0, 61.9, 26.8, 26.1, 25.9, 24.3, 21.0, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: $[M+K]^+$ Calcd. for $C_{34}H_{43}NO_{17}K$ 776.2168; found 776.2135.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((S)-2-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoyloxy)-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (12)

Yield 62 % (55 mg); colorless oil; R_f = 0.52 (ethyl acetate/toluene 1:1, v/v). ^{1}H NMR ($CDCl_3$): δ 7.28 (t, *J* = 7.3 Hz, 2H, Ph), 7.22 (m, 1H, Ph), 7.18 (d, *J* = 7.2 Hz, 2H, Ph), 7.02 (d, *J* = 9.4 Hz, 1H, NH), 5.28-5.22 (m, 2H, H1 Glc1NC, H3 Glc1NC), 5.09 (s, 1H, H1 Fru), 5.08 (m, 1H, H4 Glc1NC), 4.99-4.96 (m, 2H, NH Phe, H2 Glc1NC), 4.58 (m, 2H, α Phe, H4 Fru), 4.34 (dd, *J* = 12.5 Hz, 4.3 Hz, 1H, H6 Glc1NC),4.29 (d, *J* = 2.5 Hz, 1H, H3 Fru), 4.22 (d, *J* = 7.8 Hz, 1H, H5 Fru), 4.01 (d, *J* = 12.3 Hz, 1H, H6 Glc1NC), 3.86 (dd, *J* = 12.6 Hz, 2H, H6' Fru), 3.76 (m, 1H, H5 Glc1NC), 3.32

(dd, *J* = 14.1 Hz, 4.9 Hz, 1H, β Phe), 2.98 (dd, *J* = 14.1 Hz, 8.2 Hz, 1H, β' Phe), 2.02, 2.01, 2.00, 1.98 (s, 12H, CH_3), 1.54, 1.51, 1.44, 1.36, 1.33 (s, 21H, CH_3, Boc). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.7, 170.2, 169.8, 165.985, 155.3, 136.3, 129.7, 128.8, 127.1, 110.4, 109.7, 101.5, 80.2, 78.5, 77.4, 77.2, 77.0, 74.2, 74.0, 73.0, 70.8, 70.5, 70.4, 70.1, 68.6, 62.1, 61.9, 54.5, 38.4, 28.4, 26.7, 26.1, 25.5, 24.4, 20.9, 20.8, 20.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+K]^+$ calcd. for $C_{41}H_{56}N_2O_{19}K$ 919.3114; found 919.3116.

(3R,4S,5S,6S)-6-((2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-ylamino)ethoxy)carbonyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (13)

Yield 68 % (67 mg); colorless oil; R_f = 0.37 (ethyl acetate/toluene 1:1, v/v); α:β 15:85; *d.r.* cannot be determined due to peak overlap. Chemical shifts are given for major isomer. ^{1}H NMR ($CDCl_3$): δ 7.34 (d, *J* = 8.9 Hz, α NH), 7.06 (d, *J* = 9.2 Hz, β NH), 6.37 (d, *J* = 3.5 Hz, H1α GlcA), 5.77 (d, *J* = 7.5 Hz, H1β GlcA), 5.35 (t, *J* = 9.5 Hz, 1H, H4 GlcA), 5.15 (m, 1H, H1 Glc1NC), 5.11 (m, 1H, H3 Glc1NC), 5.06 (m, 1H, H4 Glc1NC), 5.06-5.00 (m, 2H, H1 Fru, H3 GlcA), 4.94 (t, 1H, *J* = 9.5 Hz, H2 Glc1NC), 4.58 (dd, *J* = 7.7, 2.6 Hz, 1H, H4 Fru), 4.36 (d, *J* = 9.7 Hz, 1H, H5 GlcA), 4.32 (d, *J* = 4.2 Hz, 1H, H6 Glc1NC), 4.30 (d, *J* = 2.7 Hz, 1H, H3 Fru), 4.22 (d, J = 7.7 Hz, 1H, H5 Fru), 4.04 (dd, J = 12.4, 1.8 Hz, 1H, H6 Glc1NC), 3.87 (m, 2H, H6 Fru), 3.74 (dd, *J* = 8.1, 1.9 Hz, 1H, H5 Glc1NC), 2.08-1.97 (m, 21H, CH_3), 1.61-1.31 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.9, 170.7, 170.2, 170.1, 169.8, 169.5, 169.4, 168.8, 165.2, 165.0, 110.5, 109.7, 101.4, 91.7, 78.6, 74.6, 73.9, 72.9, 72.5, 70.7, 70.6, 70.4, 70.2, 70.0, 68.6, 68.5, 62.0, 61.9, 26.7, 26.1, 25.4, 24.4, 20.9, 20.9, 20.9, 20.8, 20.8, 20.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{41}H_{55}NO_{26}Na$ 1000.2910; found 1000.2930.

(3R,4R,5S,6R)-3-(2-acetoxy-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,4,5-triyl triacetate (14)

Yield 60 % (41mg); colorless oil; R_f = 0.33 (ethyl acetate/ petrol ether 1:1, v/v); α:β 60:40; approx (peak overlap) *d.r.* 90:10. Chemical shifts are given for α and β isomer. ^{1}H NMR ($CDCl_3$): δ 6.32

(d, *J* = 9.2 Hz, 0.6H, α NH), 6.14 (d, J = 3.6 Hz, 0.6H, H1α Glc2NC), 6.06 (d, *J* = 9.2 Hz, 0.4H, β NH), 5.65 (d, *J* = 8.8 Hz, 0.4H, H1β Glc2NC), 5.28-5.23 (m, 0.6H, H3α Glc2NC), 5.14-5.08 (m, 1.4H, H3β Glc2NC, H4α,β Glc2NC), 4.99 (s, 0.6H, H1α Fru), 4.90 (s, 0.4H, H1β Fru), 4.58-4.56 (m, 1H, H4α,β Fru), 4.49-4.45 (m, 0.6H, H2α Glc2NC), 4.37-4.35 (m, 0.4H, H2β Glc2NC), 4.30 (d, 0.4H, *J* = 2.7 Hz, H3β Fru), 4.26 (d, 0.6H, *J* = 2.6 Hz, H3α Fru), 4.23-4.20 (m, 2.4H, H5β Fru, H6 Glc2NC), 4.11 (dd, *J* = 12.5 Hz, 1.9 Hz, 0.4H, H6β Fru), 4.04 (dd, 0.6H, *J* = 12.5 Hz, 2.1 Hz, H6α Fru), 3.98 (m, 0.6H, H5α Fru), 3.84-3.80 (dd, *J* = 13.0 Hz, 1.4 Hz, 0.6H, H6'α Fru), 3.80-7.76 (m, 1.4H, H6'β Fru, H5α,β Glc2NC), 2.15-1.99 (m, 15H, CH_3), 1.58-1.31 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): *δ* 171.2, 170.9, 169.4, 169.1, 169.1, 168.4, 165.7, 165.6, 110.0, 109.9, 109.7, 109.7, 101.9, 101.9, 92.7, 90.8, 77.4, 77.2, 77.0, 74.0, 73.7, 73.4, 72.0, 70.8, 70.8, 70.6, 70.5, 70.2, 70.2, 69. 9, 68.2, 68.1, 61.9, 61.9, 61.7, 52.4, 50.6, 26.8, 26.7, 26.3, 25.5, 24.4, 24.3, 21.0, 20.9, 20.9, 20.8, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{29}H_{41}NO_{17}Na$ 698.2272; found 698.2278.

(3R,4R,5S,6R)-6-(acetoxymethyl)-3-(2-(benzoyloxy)-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)tetrahydro-2H-pyran-2,4,5-triyl triacetate (15)

Yield 61 % (45 mg); colorless oil; R_f = 0.43 (ethyl acetate/ petrol ether 1:1, v/v); *α:β* 60:40; approx (peak overlap) *dr* 95:5. Chemical shifts are given for α and β isomer. ^1H NMR ($CDCl_3$): *δ* 8.07-8.03 (m, 2H, Ph), 7.58-7.55 (m, 1H, Ph), 7.42-7.45 (m, 2H, Ph), 6.56 (d, *J* = 9.1 Hz, 0.6H, α NH), 6.30 (d, *J* = 9.7 Hz, 0.4H, β NH), 6.19 (d, *J* = 3.6 Hz, 0.6H, H1α Glc2NC), 5.68 (d, *J* = 8.8 Hz, 0.4H, H1β Glc2NC), 5.43 (s, 0.6H, H1α Fru), 5.28 (s, 0.4H, H1β Fru), 5.30-5.27 (m, 0.6H, H3α Glc2NC), 5.16-5.07 (m, 1.4H, H3β Glc2NC, H4α,β Glc2NC), 4.58 (dd, *J* = 7.8 Hz, 3.0 Hz, 1H, H4α,β Fru), 4.49-4.44 (m, 0.6H, H2α Glc2NC), 4.40 (d, *J* = 2.7 Hz, 0.4H, H3β Fru), 4.37 (m, 0.4H, H2β Glc2NC), 4.33 (d, *J* = 2.7 Hz, 0.6H, H3α Fru), 4.23 (m, 2.6H, H5α Fru, H6 Glc2NC), 4.11 (dd, *J* = 12.5 Hz, 2.0 Hz, 0.4H, H6β Fru), 4.04 (dd, *J* = 12.4 Hz, 2.0 Hz, 0.6H, H6α Fru), 3.98 (m, 1H, H5β Fru), 3.89 (m, 1H, H6α,β Fru), 3.86-3.81 (m, 1H, H5α,β Glc2NC), 2.16-1.88 (m, 12H, CH_3), 1.58-1.31 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): *δ* 171.1, 170.9, 170.7, 169.8, 169.5, 169.4, 168.4, 165.9, 165.7, 165.3, 165.2, 133.7, 133.6, 130.2, 130.1, 128.7, 110.2, 110.0, 109.8,

109.7, 101.9, 101.9, 92.8, 90.7, 74.2, 73.8, 73.3, 71.9, 70.8, 70.8, 70.7, 70.4, 70.1, 70.1, 69.9, 68.3, 68.2, 62.0, 61.9, 61.7, 52.5, 50.8, 26.9, 26.8, 26.2, 26.0, 24.4, 24.2, 20.9, 20.9, 20.9, 20.9, 20.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+K]^+$ calcd. for $C_{34}H_{43}NO_{17}K$ 776.2168; found 776.2145.

(3R,4R,5S,6R)-6-(acetoxymethyl)-3-((R)-2-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoyloxy)-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)acetamido)tetrahydro-2H-pyran-2,4,5-triyl triacetate (16)

Yield 68 % (60 mg); colorless oil; R_f = 0.46 (ethyl acetate/toluene 1:1, v/v); $\alpha:\beta$ = 80:20. ^{1}H NMR ($CDCl_3$): δ 7.38-7.08 (m, 5H, Ph), 6.55 (d, J = 9.1 Hz, 0.8H, α NH), 6.45 (d, J = 9.3 Hz, 0.2H, β NH), 6.17 (d, J = 3.6 Hz, 0.8H, H1α Glc2NC), 5.67 (d, J = 8.8 Hz, 0.2H, H1-β Glc2NC), 5.28 (m, 1H, H3α,β Glc2NC), 5.14 (m, 0.8H, H4α Glc2NC), 5.11 (s, 0.8H, H1α Fru), 5.08 (m, 0.2H, H4β Glc2NC), 4.99 (s, 0.2H, H1β Fru), 4.89 (d, J = 8.6 Hz, 0.8H, α NH Phe), 4.83 (d, J = 7.8 Hz 0.2H, β NH Phe), 4.63-4.85 (m, 1H, α H Phe), 4.56 (dd, J = 7.8, 2.8 Hz, 1H, H4α,β Fru), 4.53-4.49 (m, 1.2H, H3β Glc2NC, H4α,β Glc2NC), 4.39 (dd, J = 19.9, 9.5 Hz, 0.2H, H2β Glc2NC), 4.30 (d, J = 2.4 Hz, 0.8H, H3β Fru), 4.23 (m, 2.8H, H5β Fru, H6 Glc2NC), 4.11 (dd, J = 12.5 Hz, 0.2H, H6β Fru), 4.04 (dd, J = 12.4, 2.1 Hz, 0.8H, H6α Fru), 4.01-3.98 (m, 0.2H, H5β Fru), 3.87-3.85 (dd,J = 13.0, 1.5Hz, 0.8H, H6α Fru), 3.82-3.85 (m, 1.2H, H6β Fru, H5α,β Glc2NC), 3.38 (dd, J = 14.2, 4.4Hz, 0.8H, Hβ Phe), 3.33 (dd, J = 14.1 Hz, 0.2H, Hβ Phe). 3.06 (dd. J = 13.7, 7.8 Hz, 0.2H, Hβ' Phe), 2.99 (dd, J = 14.2, 8.5 Hz, 0.8H, Hβ' Phe), 2.14-2,00 (m, 12H, Ac), 1.63-1.30 (m, 24H, CH_3-isop, CH_3 Boc). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.9, 170.8, 169.4, 168.6, 165.4, 155.3, 136.4, 129.8, 129.7, 128.8, 128.7, 127.1, 110.3, 110.0, 109.5, 101.8, 92.7, 90.8, 80.2, 77.4, 77.2, 77.0, 74.1, 73.4, 70.8, 70.7, 70.5, 70.4, 70.1, 70.0, 68.1, 62.1, 61.8, 54.4, 50.6, 38.2, 28.5, 28.4, 26.7, 26.7, 26.3, 25.5, 25.5, 24.3, 21.1, 21.0, 20.9, 20.8, 20.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{41}H_{56}N_2O_{19}Na$ 903.3375; found 903.3346.

(3R,4S,5S,6S)-6-((2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-((3R,4R,5S,6R)-2,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-3-ylamino)ethoxy)carbonyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (17)

Yield 75 % (73 mg); colorless oil; R_f = 0.37 (ethyl acetate/toluene 1:1, v/v); $\alpha:\beta$ 80:20. Chemical shifts are given for the major isomer. ^{1}H NMR ($CDCl_3$): δ 6.50 (d, J = 9.1Hz, α NH), 6.11 (d, J = 3.5 Hz, H1α Glc2NC), 5.78 (d, J = 7.5 Hz, H1β GlcA), 5.38 (t, J = 9.4 Hz, H4β GlcA), 5.27-5.23 (m, H3 GlcA, H3 Glc2NC), 5.12-5.09 (m, H2 GlcA, H4 Glc2NC), 5.02 (s, H1 Fru), 4.92 (s, H1 Fru), 4.57 (dd, J = 7.8 Hz, 2.6 Hz, H4 Fru), 4.46-4.42 (m, H2 Glc2NC), 4.38 (dd, J = 9.7, 4.2 Hz, H5 GlcA), 4.31-4.28 (d, J = 2.6 Hz, H3 Fru), 4.20 (m, H5 Fru), 4.09 (d, J = 12.2 Hz, H6 Glc2NC,), 4.03 (dd, J = 12.5, 2.1 Hz, H6 Glc2NC), 3.96 (m, H6 Fru), 3.87-3.74 (m, H5 Glc2NC, H6 Fru), 2.12-1.97 (m, CH_3), 1.61-1.30 (m, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.9, 170.3, 169.7, 169.4, 169.4, 168.8, 168.5, 165.1, 164.4, 110.4, 109.7, 101.6, 91.8, 90.8, 74.0, 72.9, 72.4, 70.7, 70.7, 70.5, 70.3, 70.0, 69.9, 68.3, 68.0, 62.0, 61.8, 52.4, 50.5, 26.8, 26.2, 25.4, 24.3, 21.0, 20.9, 20.8, 20.8, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: $[M+K]^+$ calcd. for $C_{41}H_{55}NO_{26}K$ 1016.2649; found 1016.2605.

(3R,4S,5R,6R)-2-((2-acetoxy-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)acetamido)methyl)-6-(benzyloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**18**)

Yield 66 % (48 mg); colorless oil; R_f = 0.34 (ethyl acetate/toluene 1:1, v/v); *d.r.* 90:10. Chemical shifts are given for major isomer. ^{1}H NMR ($CDCl_3$): δ 7.34-7.26 (m, 5H, Bn), 6.98 (br t, 1H, NH), 5.16 (s, 1H, H1 Fru), 5.10 (t, J = 9.5 Hz, 1H, H3 Glc6NC), 4.98-4.95 (m, 2H, H2 Glc6NC, H6 Glc6NC), 4.86 (d, J = 12.2 Hz, 1H, H4 Glc6NC), 4.60-4.58 (m, 2H, H5 Glc6NC, H4 Fru), 4.52 (d, J = 8.1 Hz, 1H, H1β Glc6NC), 4.42 (d, J = 2.7 Hz, 1H, H3 Fru), 4.23 (d, J = 7.9 Hz, 1H, H5 Fru), 3.97 (dd, J = 13.0 Hz, 1.7 Hz, 1H, H6 Fru), 3.81 (d, J = 13.0 Hz, 1H, H6' Fru), 3.60-3.57 (m, 2H, H6 Glc6NC, CH_2 Bn), 3.45-3.41 (m, 1H, CH_2 Bn), 2.19 (s, 3H, CH_3), 1.99-1-94 (m, 9H, CH_3), 1.57-1.31 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.4, 169.6, 169.4, 165.7, 136.9, 128.7, 128.3, 128.0, 110.1, 109.4, 102.4, 99.3, 77.4, 77.2, 77.0, 73.9, 73.2, 72.6, 71.4, 71.0, 70.8, 70.6, 70.3, 69.7, 61.8, 39.5, 26.6, 26.3, 25.4, 24.3, 21.0, 20.9, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{34}H_{45}NO_{16}Na$ 746.2636; found 746.2655.

(3R,4S,5R,6R)-2-((2-(benzoyloxy)-2-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)acetamido)methyl)-6-(benzyloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**19**)

Yield 68 % (54 mg); colorless oil; R_f = 0.51 (ethyl acetate/toluene 1:1, v/v); *d.r.* 94:6. Chemical shifts are given for the major isomer. ^{1}H NMR ($CDCl_3$): δ 8.09 (dd, J = 7.4 Hz, 2H, Ph), 7.56 (m, 1H, Ph), 7.43 (t, *J* = 7.7 Hz, 2H, Ph), 7.35-7.28 (m, 5H, Bn), 7.12 (br t, 1H, NH), 5.53 (s, 1H, H1 Fru), 5.10 (t, *J* = 9.5 Hz, 1H, H3 Glc6NC), 4.99 (m, 2H, H2 Glc6NC, H6 Glc6NC), 4.88 (d, *J* = 12.2 Hz, 1H, H4 Glc6NC), 4.62-4.58 (m, 2H, H5 Glc, H4 Fru), 4.54-4.51 (m, 2H, H1β Glc6NC, H3 Fru), 4.25 (d, *J* = 7.7 Hz, 1H, H5 Fru), 4.03 (dd, *J* = 13.0 Hz, 1.7 Hz, 1H, H6 Fru), 3.85 (d, *J* = 13.0 Hz, 1H, H6' Fru), 3.62-3.58 (m, 2H, H6 Glc6NC, CH_2 Bn), 3.51-3.46 (m, 1H, CH_2 Bn), 1.97-1-94 (m, 9H, CH_3), 1.62-1.30 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.5, 169.6, 169.6, 165.8, 165.6, 136.9, 133.5, 130.2, 129.8, 128.7, 128.7, 128.3, 128.0, 110.2, 109.5, 102.5, 99.3, 77.4, 77.2, 77.0, 74.2, 73.2, 72.6, 71.4, 70.9, 70.8, 70.6, 70.2, 69.7, 61.9, 39.5, 26.7, 26.3, 25.8, 24.2, 20.9. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{39}H_{47}NO_{16}Na$ 808.2793; found 808.2789.

(3R,4S,5R,6R)-2-((7R)-7-benzyl-11,11-dimethyl-3,6,9-trioxo-4-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-5,10-dioxa-2,8-diazadodecyl)-6-(benzyloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (20)

Yield 70 % (65 mg); colorless oil; R_f = 0.58 (ethyl acetate/toluene 1:1, v/v); *d.r.* 90:10. Chemical shifts are given for the major isomer. ^{1}H NMR ($CDCl_3$): δ 7.23-7.21 (m, 10H, Bn, Ph), 7.11 (m, 1H, NH), 5.23 (s, 1H, H1 Fru), 5.10 (t, *J* = 9.5 Hz, 1H, H3 Glc6NC), 5.01-4.96 (m, 2H, H2 Glc6NC, H6 Glc6NC), 4.93 (d, *J* = 8.4 Hz, 1H, NH Phe), 4.85 (d, *J* = 12.2 Hz, 1H, H4 Glc6NC), 4.65-4.57 (m, 3H, α Phe, H5 Glc, H4 Fru), 4.50 (d, *J* = 8.0 Hz, 1H, H1β Glc6NC), 4.40 (d, *J* = 2.5 Hz, 1H, H3 Fru), 4.22 (d, *J* = 7.5 Hz, 1H, H5 Fru), 3.89 (d, *J* = 11.9 Hz, 1H, H6 Fru), 3.81 (d, *J* = 13.0 Hz, 1H, H6' Fru), 3.60-3.51 (m, 3H, H6 Glc6NC, CH_2 Bn), 3.41 (dd, J = 14.2 Hz, 4.7 Hz, 1H, β Phe), 3.03 (dd, *J* = 14.2 Hz, 8.2 Hz, 1H, β' Phe), 1.97-1-94 (m, 9H, CH_3), 1.58-1.30 (m, 21H, CH_3 Boc). ^{13}C NMR ($CDCl_3$): δ 170.9, 170.5, 169.6, 169.5, 165.4, 155.3, 136.9, 136.7, 129.8, 128.7, 128.7, 128.3, 128.0, 127.0, 110.3, 109.4, 102.3, 99.3, 80.1, 77.4, 77.2, 77.0, 74.1, 73.2, 72.7, 71.3, 70.9, 70.8, 70.5, 70.1, 69.6, 62.0, 54.7, 39.6, 38.5, 28.4, 26.6, 26.3, 25.4, 24.3, 20.9, 20.9. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{46}H_{60}N_2O_{18}Na$ 951.3739; found 951.3741.

(3R,4S,5S,6S)-6-((2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl)-2-(((3R,4S,5R,6S)-3,4,5-triacetoxy-6-

(benzoyloxy)tetrahydro-2H-pyran-2-yl)methylamino)ethoxy)carbonyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (21)

Yield 75 % (76 mg); colorless oil; R_f = 0.37 (ethyl acetate/toluene 1:1, v/v). 4 isomers. Chemical shifts are given for the major isomer. ^{1}H NMR ($CDCl_3$): δ 7.35-7.25 (m, Bn), 7.00 (t, J = 5.9 Hz, NH), 5.80 (d, J = 7.7 Hz, H1β GlcA), 5.40 (t, J = 9.5 Hz, H4 GlcA), 5.26 (t, J = 9.1 Hz, H3 GlcA), 5.18-5.08 (m, H1 Fru, H2 GlcA, H3 Glc6NC), 4.98-4.92 (m, H2, H6 Glc6NC), 4.85 (d, J = 12.2 Hz, H4 Glc6NC), 4.60-4.56 (m, H4 Fru, H6 Glc6NC), 4.52 (d, J = 8.0 Hz, H1β Glc6NC), 4.41 (dd, J = 6.2, 3.4 Hz, H3 Fru, H5 GlcA), 4.21 (d, J = 7.8 Hz, H5 Fru), 3.97 (dd, J = 13.0, 1.6 Hz, H6 Fru), 3.80 (d, J = 13.0 Hz, H6 Fru), 3.56 (m, H6 Glc6NC, CH_2 Bn), 3.41 (m, CH_2 Bn), 2.08-1.94 (m, CH_3), 1.56-1.30 (m, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.5, 170.2, 169.6, 169.5, 169.4, 168.9, 165.5, 164.5, 136.9, 128.7, 128.3, 127.9, 110.4, 109.4, 102.1, 99.4, 91.8, 74.8, 73.2, 73.1, 72.6, 72.5, 71.3, 71., 70.8, 70.5, 70.4, 70.1, 69.8, 68.6, 62.0, 39.6, 26.6, 26.3, 25.3, 24.3, 20.9, 20.9, 20.8, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{46}H_{59}NO_{25}Na$ 1048.3274; found 1048.3307.

Deprotection of selected Passerini products

Synthesis of (S)-*N*-cyclohexyl-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)acetamide (22)

Passerini product **2** (15 mg; 0.035 mmol) was dissolved in MeOH and 1M NaOH (70 μL) was added. Reaction was stirred under reflux and followed by TLC (petrol ether/ethyl acetate 1:1, v/v). After 10 min, solvent was evaporated and the product purified by flash column chromatography (petrol/ethyl acetate 1:1, v/v). Yield 81 % (11 mg); colorless oil; R_f = 0.7 (petrol/ethyl acetate 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, J = 7.5 Hz, 1H, NH), 4.68 (d, J = 2.7 Hz, 1H, H3 Fru), 4.61 (dd, J = 7.9, 2.7 Hz, 1H, H4 Fru), 4.31 (s, 1H, OH), 4.22 (dd, J = 7.9, 1.2 Hz, 1H, H5 Fru), 3.97 (s, 1H, H1 Fru), 3.93 (dd, J = 12.9, 1.8 Hz, 1H, H6 Fru), 3.83 – 3.78 (m, 1H, CyHex), 3.76 (d, J = 13.0 Hz, 1H, H6 Fru), 1.92 – 1.85 (m, 2H, CyHex), 1.69 – 1.53 (m, 4H, CyHex), 1.46 (d, J = 4.7 Hz, 6H, CH_3), 1.38 (s, 3H, CH_3), 1.33 (s, 4H, CyHex, CH_3), 1.24 – 1.15 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$) δ 169.4, 109.4, 109.2, 103.7, 71.1, 71.0, 70.5, 61.9, 49.1, 33.0, 32.8, 26.6, 26.3, 25.8, 25.7, 24.8, 24.7, 24.2. HRMS (MALDI-TOF/TOF) *m/z*: $[M+H]^+$calcd. for $C_{19}H_{31}NO_7$ 386. 2179; found 386.2174.

Synthesis of (S)-2-(cyclohexylamino)-2-oxo-1-((3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)ethyl benzoate (23)

Compound **3** (20 mg, 0.04 mmol) was dissolved in mixture of DCM and TFA (200 µL, 1:1, v/v), and stirred at room temperature for 6 h. Product was precipitated with cold di-isopropyl ether. Yield 67 % (11 mg); colorless oil; ^{13}C NMR (151 MHz, DMSO) δ 209.1, 169.8, 166.9, 133.7, 129.6, 129.0, 128.7, 127.1, 96.3, 82.6, 77.8, 75.4, 75.3, 72.7, 72.5, 72.3, 70.8, 69.7, 68.7, 66.3, 62.4, 62.2, 60.2, 48.0, 47.5, 40.0, 39.9, 35.3, 34.2, 32.0, 31.9, 31.7, 25.0, 24.7, 24.5, 22.7. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$calcd. for $C_{20}H_{27}NO_8Na$ 432.1634; found 432.1637.

Synthesis of (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)-N-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)acetamide (24)

To the stirred solution of compound **10** (20.8 mg, 0.03 mmol) in MeOH (600 mL) sodium metoxide (25.5 mL, 0.25 M) was added. After stirring for 2 h at room temperature the reaction was quenched by addition of IR-120 resin (H^+). The insoluble materials were filtrated off and the filtrate was concentrated. The residue was passed through a short column of silica gel to afford compound **24**. Yield 97 % (13 mg); white solid; m.p. = 145-146° C; R_f = 0.28 (EtOAc/EtOH/AcOH/H_2O 70:5:2:2, v/v). ^{1}H NMR (600 MHz, DMSO) δ 7.64 (d, *J* = 8.9 Hz, 1H, NH), 4.70 (t, *J* = 8.9 Hz, 1H, H-1 Glc), 4.60 (dd, *J* = 7.9, 2.5 Hz, 1H, H-3 Fru), 4.50 (d, *J* = 2.5 Hz, 1H, H-4 Fru), 4.23 (t, *J* = 8.7 Hz, 1H, H-5 Fru), 3.93 (s, 1H, H-1 Fru), 3.74 (m, 1H, H-6 Fru), 3.63 (m, 2H, H-6 Fru, Glc), 3.46 (m, 1H, H-6 Glc), 3.19 (m, 1H, H-3 Glc), 3.10 (m, 3H, H-5, H-4, H-2 Glc), 1.44 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO) δ 170.2, 108.4, 108.2, 103.1, 80.0, 78.8, 77.2, 72.6, 72.0, 70.0, 69.8, 69.7, 69.5, 60.8, 60.7, 26.3, 25.8, 25.4, 24.0. HRMS (MALDI-TOF/TOF) *m/z*: $[M+Na]^+$calcd. for $C_{19}H_{31}NO_{12}Na$ 488.1744; found 488.1748.

Synthesis of (2R,3R,4S,5R,6R)-2-((S)-2-acetoxy-2-((3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)acetamido)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (25) and (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((S)-2-hydroxy-2-((3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)acetamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (26)

Compound **10** (18.3 mg, 0.027 mmol) was dissolved in mixture TFA and H_2O (9:1, v/v) and stirred for 5h at room temperature. The reaction was monitored by TLC in EtOAc/EtOH/AcOHH_2O 70:5:2:2. The products were precipitated with cold diisopropylether and centrifuged. The precipitate was dried, dissolved in water and passed through C-18 silica gel Bond Elute patron to give inseparable mixture of compounds **25** and **26** (5 mg) as a mixture of anomers. ^{13}C NMR (151 MHz, DMSO) δ 196.2, 169.9, 169.4, 169.2, 169.0, 168.97, 168.2, 104.7, 102.1, 101.4, 96.3, 93.7, 91.2, 89.0, 87.9, 84.1, 82.1, 79.8, 77.0, 76.6, 76.1, 75.5, 72.9, 72.7, 72.6, 72.4, 72.2, 71.1, 70.8, 70.6, 70.4, 69.3, 68.8, 68.5, 67.8, 66.2, 62.7, 62.3, 62.1, 61.8, 40.0, 39.9, 39.9, 39.8, 39.8, 39.7, 39.5, 39.4, 39.2, 39.1, 35.6, 34.6, 20.5, 20.3, 20.2, 15.6.

Synthesis of (S)-2-hydroxy-2-((3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)-N-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)acetamide (27)

Compound **24** (32 mg, 0.688 mmol) was dissolved in mixture TFA and H_2O (9:1, v/v) and stirred for 2h at room temperature. The reaction was monitored by TLC in EtOAc/EtOH/AcOH/H_2O 7:2:2:2. The products were precipitated with cold diisopropylether, centrifuged, and dried, to give compound **27** as TFA salt. Yield 68 % (23 mg); white solid; m.p. = 152-155° C; R_f = 0.35 (EtOAc/EtOH/AcOH/H_2O 7:2:2:2, v/v). ^{13}C NMR (151 MHz, DMSO) δ 175.09, 173.73, 171.73, 170.65, 152.96, 118.01, 102.43, 101.52, 100.06, 96.87, 92.19, 81.83, 81.78, 81.65, 81.34, 79.72, 79.36, 79.25, 79.21, 78.85, 78.76, 78.72, 77.18, 77.15, 77.07, 77.02, 76.75, 76.70, 76.17, 75.11, 74.83, 74.64, 74.47, 73.25, 73.07, 72.53, 72.50, 72.36, 72.18, 71.91, 70.90, 70.61, 70.32, 69.91, 69.79, 69.71, 69.65, 69.45, 69.12, 68.01, 67.12, 63.47, 63.41, 62.81, 62.70, 61.22, 60.93, 60.81, 60.48.

Synthesis of 2-(*tert*-butylamino)-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 acetate (28)

To a glass vial containing 1 M solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexadialdo-1,5-pyranose (0.1 mmol) in DCM under nitrogen were added acetic acid (0.1 mmol) and *tert*-butyl isocyanide (0.1 mmol) dissolved in 100 μL DCM. With all reactants added, the solution was allowed to stir for 8 h. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

Yield 78 % (31 mg); colorless oil; R_f = 0.60 (EtOAc/PE 1:1, v/v); *d.r.* 80:20. Chemical shifts are given for both isomers. ^{1}H NMR ($CDCl_3$) 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, CH_3), 1.49 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.36 – 1.25 (m, 15H, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.5, 169.7, 167.2, 166.3, 109.8, 109.7, 109.7, 109.3, 96.6, 96.4, 73.9, 71.6, 71.1, 71.0, 70.9, 70.6, 70.6, 67.4, 67.4, 51.7, 28.9, 28.7, 26.3, 26.2, 26.2, 26.1, 25.2, 24.6, 24.3, 21.2, 20.9. HRMS (MALDI-TOF/TOF) *m/z*: calcd. for $C_{19}H_{31}NO_8$ $[M+H]^+$ 402.2128; found 402.2146.

Synthesis of 2-(cyclohexylamino)-1-((3aR,4S,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-oxoethyl acetate (29)

To a glass vial containing 1 M solution of methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdofuranoside (0.1 mmol) in DCM under nitrogen were added acetic acid (0.1 mmol) and cyclohexyl isocyanide (0.1 mmol) dissolved in 100 µL DCM. With all reactants added, the solution was allowed to stir for 8 h. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

Yield 82 % (30 mg); colorless oil; R_f = 0.63 (EtOAc/PE 1:1, v/v); *d.r.* 77:23. Chemical shifts are given for both isomers. ^{1}H NMR ($CDCl_3$): 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, OCH_3), 3.28 (s, 0.7H, OCH_3), 2.15 (s, 0.7H, CH_3), 2.13 (s, 2.3H, CH_3), 1.89 (m, 2H, CyHex), 1.66 (m, 2H, CyHex), 1.58 (m, 1H, CyHex), 1.45 (s, 3H, CH_3), 1.34 (m, 2H, CyHex), 1.29 (s, 2.3H, CH_3), 1.28 (s, 0.7H, CH_3), 1.16 – 1.14 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$) δ 170.0, 166.1, 112.9, 111.1, 110.3, 86.2, 86.0, 85.4, 85.3, 81.7, 81.4, 74.8, 73.6, 56.2, 55.5, 48.5, 48.35, 33.1, 33.1, 26.8, 26.7, 25.7, 25.6, 25.3, 24.9, 24.9, 21.4, 21.1. HRMS (MALDI-TOF/TOF) *m/z*: calcd. for $C_{18}H_{29}NO_7Na$ $[M+Na]^+$ 394.1842; found 394.1843.

Synthesis of 1-((3aR,5S,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(cyclohexylamino)-2-oxoethyl acetate (30)

To a glass vial containing 1 M solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose (0.1 mmol) in DCM under nitrogen were added acetic acid (0.1 mmol) and cyclohexyl isocyanide (0.1 mmol) dissolved in 100 μL DCM. With all reactants added, the solution was allowed to stir for 8 h. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

Yield 79 % (36 mg); colorless oil; R_f = 0.35, (EtOAc/PE 1:2, v/v); *d.r.* 77:23. Chemical shifts are given for major isomers. ^{1}H NMR ($CDCl_3$): 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, CH_{2a}-Ph), 4.60 (d, *J* = 3.7 Hz, 1H, H-2 Xyl), 4.45 – 4.38 (m, 2H, H-4 Xyl, CH_{2b}-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, CH_3), 1.84 (m, 2H, CyHex), 1.63 (m, 2H), 1.55 – 1.50 (m, 1H, CyHex), 1.45 (s, 3H, CH_3), 1.30 (bs, 5H, CH_3 isop, CyHex), 1.16 – 1.06 (m, 3H, CyHex). ^{13}C NMR ($CDCl_3$) δ 169.7, 166.8, 137.0, 128.8, 128.4, 128.4, 112.6, 105.6, 81.8, 81.3, 78.6, 72.5, 70.2, 48.5, 32.9, 32.8, 27.0, 26.6, 25.7, 24.8, 24.7, 20.8. HRMS (MALDI-TOF/TOF) *m/z*: calcd. for $C_{24}H_{33}NO_7$ $[M+H]^+$ 448.2335; found 448.2346.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR and HRMS spectra, 2D NMR experiments, x-ray structure, computational details (PDF).

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Notes

The authors declare no competing financial interest.

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