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Multicomponent approach to homo- and hetero-multivalent glycomimetics bearing rare monosaccharides

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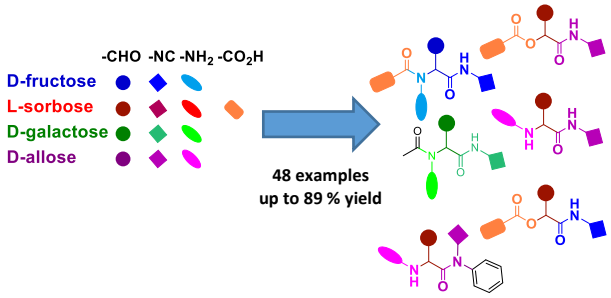


Abstract

We applied a multicomponent approach to access a library of densely functionalized homo- and hetero-multivalent glycomimetics comprising aldehyde, amine and isocyanide components related to isopropylidene-protected D-fructose, L-sorbose, D-galactose and D-allose. Passerini products were obtained in very good yields (up to 78 %) and high diastereoselectivities (up to 98:2). Three types of products were obtained by the Ugi reaction; along with the “classical” four-component product - α-acylaminoamides, a three-component α-aminoamides and a four-component α-aminoacylamides were isolated. Presence of multiple pathways is rationalized by the structure of imidate intermediate, mainly influenced by the amine component.

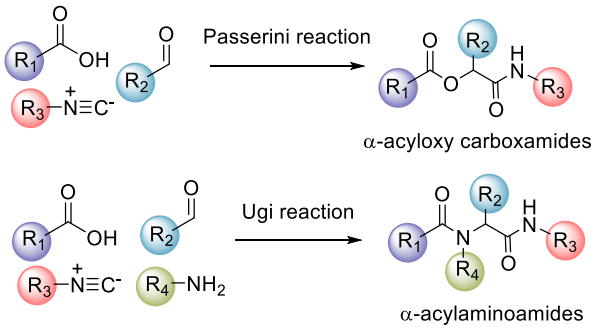
Introduction

Carbohydrates are ubiquitous group of natural compounds, and essential components of life we know.[1] Assembled at the surface of all living cells, carbohydrates mobilize binding and recognition events and play a key role in organism development, immunological responses and disease progression. In addition, glycosylation is the most prominent, and the most diverse post-translational modification that governs protein's life and function.[2] The advances in carbohydrate synthesis, and analysis[3] have led to the impactful discoveries that widen our understanding of carbohydrate-participating events at the molecular level and enabled creation of therapeutics that control human health and disease.[4] Some of the most successful examples include antiviral compounds zanamivir (Relenza)[5] and oseltamivir (Tamiflu),[6] type II diabetes mellitus drugs miglitol (Glyset) and acarbose (Precose, Glucobay),[7] STARFISH, a Shiga-like toxin inhibitor,[8] and recently carbohydrate-based vaccines.[4b] A basic principle underlying carbohydrate-protein interactions is their multivalency, which results in stronger and/or more specific binding of carbohydrate ligands to their cognate receptors.[9] Development of multivalent glycomimetics relies on the utilization of nanoparticles, polymers or dendrimers as scaffolds, providing multiple anchoring points for carbohydrate molecules.[10] While homo-multivalent glycomimetics carry several copies of identical sugar motifs, hetero-multivalent glycomimetics display structurally different saccharide motifs in a highly controlled manner.[11] Since biological systems are inherently heterogeneous, it has been presumed that hetero-multivalent glycomimetics are invaluable tools to determine contribution of not just valences and density, but also synergistic or antagonistic effects to molecular recognition events.

From a synthetic point of view, access to hetero-multivalent glycomimetics presents a daunting challenge, and various methods of solution[12] and solid-phase synthesis,[13] as well as dynamic combinatorial chemistry (DCC),[14] copper(I)-catalysed alkyne-azide cycloaddition (CuAAC),[15] combinatorial strategies,[16] and others were exploited.[11] Multicomponent reactions (MCRs) offer an attractive one-pot strategy for generating a library of highly functionalized and complex compounds like glycomimetics.[17] A large number of MCRs comprising carbohydrates were developed, providing access to structurally diverse glycoconjugates. Of particular interest are isocyanide-based MCRs (e.g., Passerini, Ugi reaction, Scheme 1), widely exploited for the generation of drug-like molecules.[18] Acetyl- and benzyl-protected galactose- and fucose-derived aldehydes were used in the synthesis of focused library of monovalent sialyl Lewis x glycomimetics.[19] Lockhoff used per-*O*-benzylated carbohydrate building blocks for the synthesis of glycoconjugate library,[20] while Westermann and Dőrner utilized the Ugi reaction for the

synthesis of multivalent aminoglycoside mimics aimed to bind to RNA targets.[21] Main advantages of MCRs for the synthesis of multivalent glycomimetics are their convergent nature, high atom economy, and control over structural identity of products, while β-elimination of carbohydrate-derived aldehydes, observed as a side-reaction in MCRs, and partial *N*-acetylation of the amine components when *O*-acetylated components are used,[19] present main drawbacks of the multicomponent methodology.

Scheme 1. Formation of Passerini and Ugi products.



In our previous work, we utilised isopropylidene-protected fructose-derived aldehyde as a carbonyl component to gain Passerini products in high yields and diastereoselectivities up to 92:8 *d.r.* without any detected side-reactions.[22] Moreover, isopropylidene protecting groups lock anomeric configuration thus facilitating purification and characterization of products, and can be smoothly removed under acidic conditions. In an endeavour to provide a multicomponent route to homo- and hetero-multivalent glycomimetics, herein we expend the pool of isopropylidene-protected carbohydrate-derived building blocks. A simple one-pot procedure comprising carbonyl components, amines, isocyanides and a carboxylic acid related to four different carbohydrates afforded highly functionalized Passerini and Ugi products with up to four carbohydrate units. Having reliable access to a library of compounds adorned with different, including uncommon carbohydrates represents an attractive alternative to the traditional approach relying solely on utilization of saccharides found in protein glycans. It has been shown that “non-self” sugars can break immune tolerance and might provide a means to create successful non-self antigens.[23] Therefore, in this work we selected carbohydrate scaffolds less frequently utilised in glycomimetic synthesis. Along with D-fructose and D-galactose, we opted for L-sorbose, known as a starting material in the synthesis of vitamin C, and D-allose, a rare monosaccharide found in nature with numerous reports claiming its protective effects against various disease states.[24] D-allose has

been found to inhibit the proliferation and metastasis of various cancer cells. Studies revealed that mechanism of D-allose activity is probably related to up-regulation of thioredoxin-interacting protein (TXNIP) which, in turn prohibit cancer cells from absorbing glucose, as a major energy source. Moreover, RbsB ribose binding protein from *Escherichia coli* and PA1946 protein from *Pseudomonas aeruginosa* were shown to bind specifically D-ribose and D-allose, with affinities in the lower micromolar range.[25] L-sorbose participates in carbohydrate-specific regulation of gene expression in bacteria, particularly lactic acid bacteria.[26] Recent study found that L-sorbose and xylitol promote the growth and metabolic activity of specific butyrate-producing bacteria in human colon and are therefore likely to have prebiotic benefits.[27]

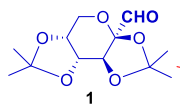
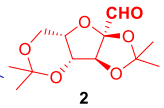
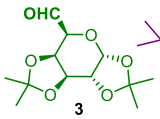
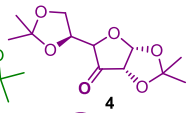
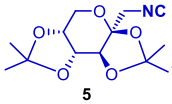
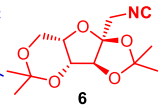
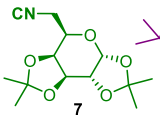
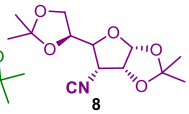
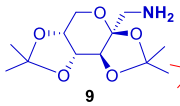
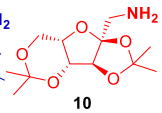
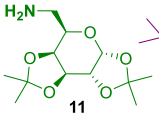
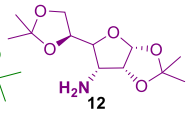
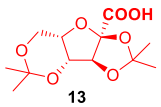
Results and Discussion

Bis-isopropylidene-protected β-D-fructopyranose (Fru), α-L-sorbofuranose (Sor), α-D-galactopyranose (Gal) and α-D-glucofuranose (Glc) were used as starting compounds for the synthesis of building blocks to be used in MCRs. Details are given in the Experimental section, but briefly, aldehydes **1**-**3** and ketone **4** (Table 1) were obtained in excellent yields (70-98 %) by oxidation with Dess−Martin periodinane. A two-step approach from amine component was used to obtain sugar isocyanides **5-8** in 30-40 % yield, while amines **9**-**12** were gained by reduction of corresponding azides in 37-69 % yield over three steps. Bis-isopropyldine protected L-gulonic acid **13** was used as carboxylic acid component. Aromatic amino acids are markedly preferred in carbohydrate-binding sites, and there is a growing body of evidence showing that presence of hydrophobic amino acids can improve interactions of glycomimetics with carbohydrate-binding proteins.[28] Therefore, we included phenylalanine and tyrosine-related carboxylic and amine components in MCRs (Table 1).

All Passerini reactions were performed with equimolar amounts of an aldehyde, an isocyanide and a carboxylic acid (0.1 mmol) in 100 μL methanol in closed vials at room temperature for 24 h. Higher temperature (up to 50 ºC), and longer reaction time (up to 48h) led to lower reaction yield. First set of reactions were performed with bis-isopropylidene protected fructose-related aldehyde **1**, isocyanide **5** and different carboxylic acids; acetic and benzoic acid and Boc-protected phenylalanine. The corresponding Passerini products **14**-**16** were isolated in 74-78 % yield (Figure 1). The formation of new stereocenter is inherent to the Passerini reaction, therefore access to stereochemically defined compounds is of utmost importance for any strategy aimed to deliver libraries of chiral, structurally diverse compounds. ^{1}H NMR spectrum of the compound **14** revealed presence of two diastereoisomers in the ratio 88:12 *d.r.* (Supporting

Information). Increasing the complexity of products hampers determination of diastereoselectivity from ^{1}H NMR spectra, however, two diastereoisomers were separated by column chromatography in most cases, and *d.r.* was determined as the ratio of isolated products. As seen at the Figure 1, presence of benzoic acid in the product **15** instead of acetic acid did not disturb stereochemical outcome of the reaction. Absolute configuration of the major isomer was unequivocally determined by the x-ray crystallographic analysis. The configuration of new stereocentre was confirmed to be *S*, and by analogy *S* configuration was assigned to all major isomers of the Passerini products comprising aldehyde **1**. Decreased stereoselectivity of the Passerini reaction observed with Boc-Phe-OH as carboxylic acid can be attributed to the purification procedure, where due to the partial overlapping with reactants or degradation byproducts, major diastereoisomer we isolated in lower yield. Finally, the Passerini reaction performed with L-gulonic acid **13** furnished trivalent Passerini product **17** in moderate yield (39 %, Figure 1) as a single diastereoisomer.

Table 1. Scope of carbonyl, isocyanide, amine and acid components used in the Passerini and Ugi reactions

Fructose	Sorbose	Galactose	Allose
 1 R_1-CHO	 2 R_2-CHO	 3 R_3-CHO	 4 $R_4C=O$
 5 R_1-CH_2NC	 6 R_2-CH_2NC	 7 R_3-CH_2NC	 8 R_4-NC
 9 $R_1-CH_2NH_2$	 10 $R_2-CH_2NH_2$	 11 $R_3-CH_2NH_2$	 12 R_4-NH_2
 13 R_2-COOH			

Other **carboxylic acid** components: acetil acid, benzoic acid, Boc-Phe-OH, Boc-Tyr(Boc)-OH

Other **amine** components: benzyl amine, H-Phe-OMe, H-Tyr-OBn

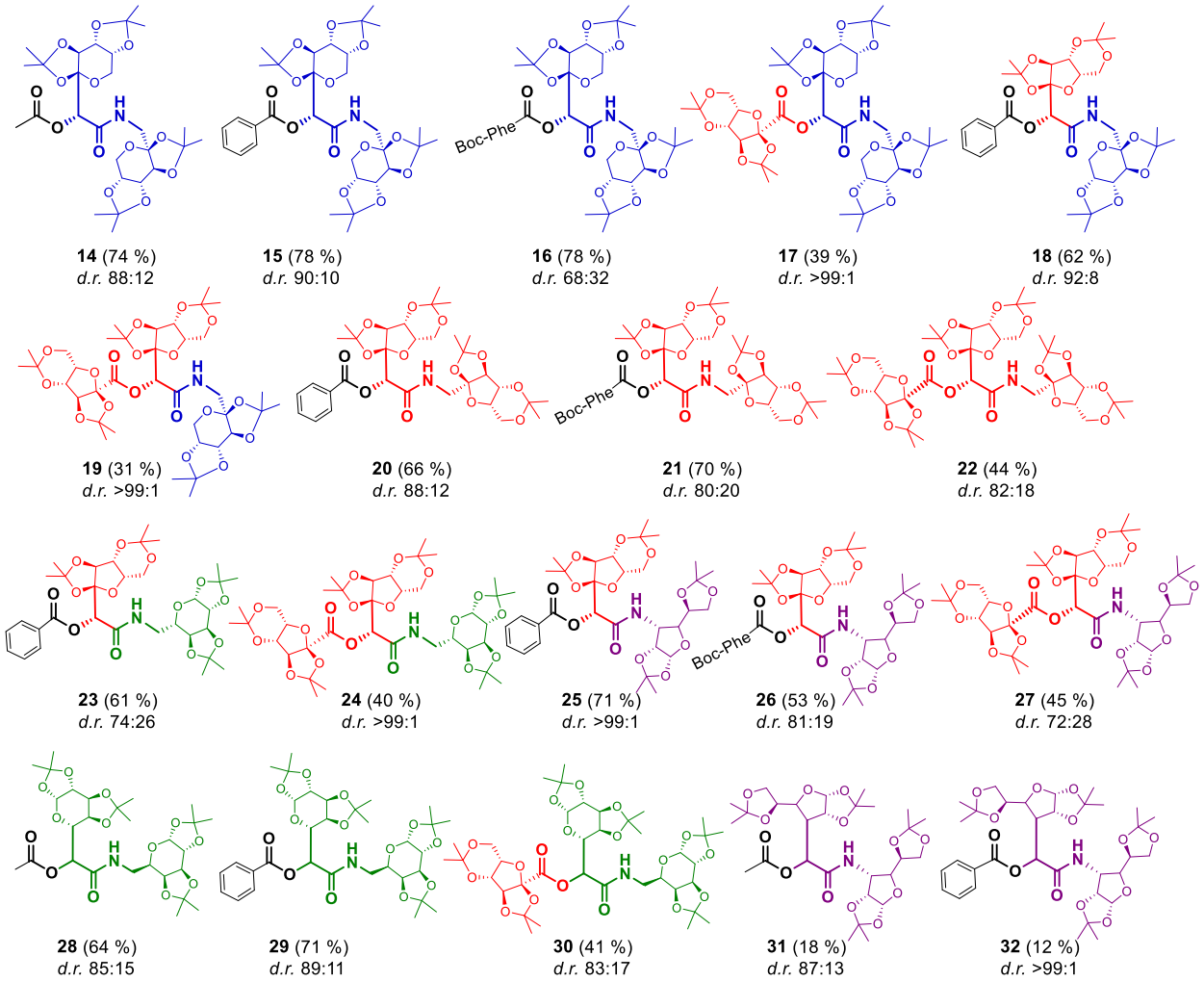


Figure 1. Products isolated from the Passerini reactions comprising selected carbohydrate derivatives from Table 1. *d.r.* was determined from the ratio of isolated products, while for compounds **14**, **15**, **27**, **28**, and **31** it was determined from ^{1}H NMR spectrum of product isolated as a mixture of diastereoisomers.

Next, we prepared two hetero-multivalent Passerini products utilizing sorbose-related aldehyde **2** and fructose-related isocyanide **5**. Bivalent product **18** was obtained in 62 % yield, while trivalent product **19** comprising L-gulonic acid was isolated in somewhat lower yield (31 %). To our delight, both products were isolated as single isomers, as detected by the NMR spectroscopy, while x-ray analysis of product **18** confirmed *S* configuration of the newly formed chiral centre. We further used sorbose-derived aldehyde **2** in reaction with isocyanides **6**-**8** and products **20**-**27** were gained in 40-70 % yield, and with very good diastereoselectivity (Figure 1). In this series, x-ray analysis of the major isomer of compound **23** and a single isomer of compound **25** confirmed *S* configuration of the chiral center. Galactose-derived aldehyde **3** was reacted with

the homologous isocyanide **7** and the corresponding products **28**-**30** were isolated in good yields (41-71 %) with diastereomeric ratio ~ 85:15. (Figure 1). Finally, we performed two reactions in the allose series; ketone **4** and isocyanide **8** in the reaction with acetic and benzoic acid afforded products **31** and **32**, respectively, in low yield but high diastereoselectivity (Figure 1).

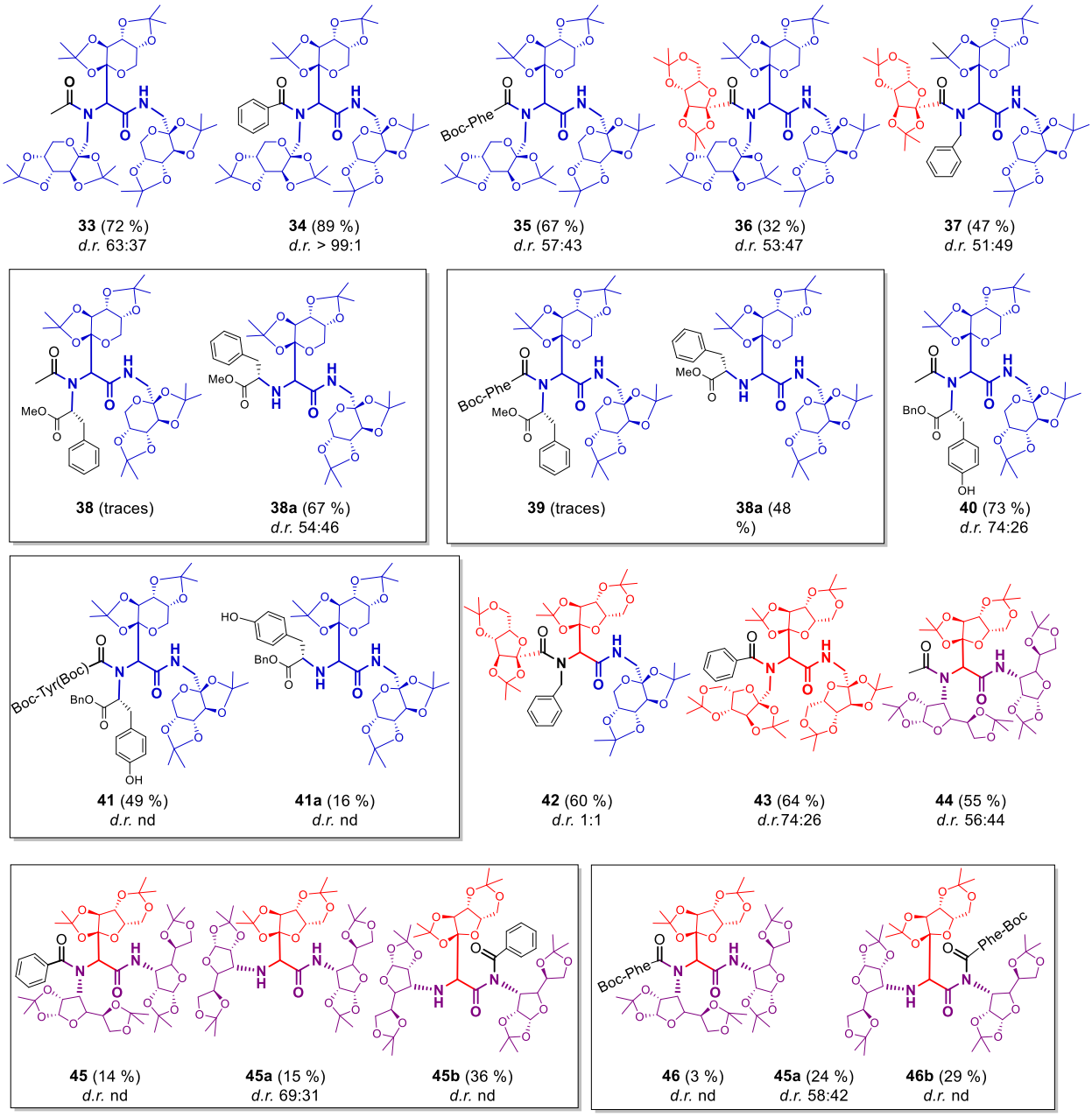
Stereocontrol of MCRs, despite many efforts, remains an open issue. Stereoselective outcome of the Passerini reaction is influenced primarily by the aldehyde component,[17b] however, when carbohydrate-derived components are used, the nature of OH protecting groups and other components in the reaction are not neglected. All Passerini reactions performed in this study with isopropylidene-protected components proceeded with high diastereoselectivity, and the individual isomers were successfully isolated in pure forms. Single crystal x-ray analysis of five Passerini products (**15**, **18**, **20**, **23** and **25**) revealed *S* configuration of the newly formed stereocentre in predominant diastereoisomer. Such stereoselective outcome can be rationalized by the mechanistic pathway for the Passerini reaction proposed by Ramozzi and Morokumaled[29] and also observed in our previous work.[22] The first step, complexation of an aldehyde, an isocyanide and two acid molecules results in two pre-complexes (a starting points leading to two diastereisomers) of different stabilities. Moreover, the rearrangement of imidate-acid cluster to dioxolane-acid cluster is the rate-determining step of the reaction, and the main factor explaining the diastereoselectivity of the Passerini reaction. We observed that the corresponding transition state leading to the *S* diastereoisomer is by ca. 10 kJ mol^{-1} more stable that the transition state leading to the *R* diastereoisomer. Presence of components bearing bulky isopropylidene groups increases the crowd close to the reaction centre, and could be responsible for the observed predominance of one diastereoisomer.

In order to increase molecular complexity and diversity of glycomimetics, we applied the four-component Ugi reaction approach to access homo- and hetero-multivalent α-acylaminoamides (Figure 2). Reactions were performed with equimolar amounts of all components (0.1 mmol) in 100 μL methanol in closed vials at room temperature for 24 h. An aldehyde and an amine component were allowed to react for 60 min, followed by the addition of acid and isocyanide component. First batch of reactions was performed with D-fructose series of compounds; aldehyde **1**, isocyanide **5** and amine **9**. Reactions performed with acetic and benzoic acid gave homo-trivalent Ugi products **33** and **34** in very good yield (72 and 89 %, respectively) but different diastereoselectivity. While product **33** was isolated as 63:37 *d.r.* mixture, a single diastereoisomer was isolated for product **34**. When Boc-Phe-OH was used as acid component, Ugi product **35** was isolated in 67 % yield and the ratio of diastereoisomers, determined from isolated products was 57:43 *d.r*. Product comprising D-gulonic acid (**36**, Figure 2) was isolated in moderate yield

(32 %) with 53:47 *d.r.* Comparable result was obtained with benzyl amine, and product **37** was isolated in 47 % yield. Further reactions were performed with amino acid components to gain hybrid amino acid-carbohydrate structures. In the reaction with H-Phe-OMe as amine component and acetic acid, expected Ugi product **38** was identified only in traces (based on mass spectrometry analysis). Instead, a three-component Ugi product **38a** was isolated in 67 % yield (Figure 2). In the reaction with Boc-Phe-OH as acid component and H-Phe-OMe as amine component, expected Ugi product **39** was again present in traces, while a three-component Ugi product **38a** was isolated in 48 % yield. Contrary to that, in the reaction with H-Tyr-OBn as amine component and acetic acid, Ugi product **40** was isolated in 73 % yield. When reaction was performed with Boc_2-Tyr-OH and H-Tyr-OBn, a four-component Ugi product **41** was isolated as a main product (49 %) with concomitant isolation of the three-component Ugi product **41a** (16 %, Figure 2). Next set of reaction was performed with sorbose-derived aldehyde **2**. Ugi product **42** comprising fructose derived isocyanide **5**, benzylamine and L-gulonic acid **13** was isolated in very good yield (60 %, Figure 2) as racemic mixture of two diastereoisomers. When benzoic acid was used with three sorbose-derived components, Ugi product **43** was also isolated in good yield (64 %) as inseparable mixture of diastereoisomers with 74:26 *d.r.* as determined by the ^{1}H NMR analysis. Next, we combined aldehyde **2** with sterically hindered allose-related isocyanide **8**, amine **12** (Table 1), and various acid components. While reaction conducted with acetic acid furnished Ugi product **44** in fair yield (55 %, Figure 2), when benzoic acid was used, reaction mixture indicated formation of multiple products. In addition to four-component Ugi product **45** isolated in 16 % and a three-component-Ugi product **45a** isolated in 15 % yield, Ugi product **45b** was isolated as the main product (36 % yield, Figure 2) and its structure was unambitiously confirmed by a single crystal x-ray analysis (Figure 3). Similar results were obtained with Boc-Phe-OH as acid component; four-component Ugi product **46** was isolated in 3 % yield, three-component-Ugi product **46a** was isolated in 24 % yield, and Ugi product **46b** was isolated in 29 % yield. Finally, when gulonic acid was introduced, main product isolated from the reaction mixture was a three-component Ugi product **45a** (43 %), with 17 % of a four-component Ugi product **47**. Replacement of amine **12** with sterically less hindered benzylamine afforded four-component Ugi product **48** in fair yield (50 %, 60:40 *d.r.*), without observed formation of other Ugi products.

Finally, a set of reactions was performed with galactose-derived components. Ugi product **49** comprising acetic acid was isolated in good yield (78 %) and diastereoselectivity 77:23 *d.r.* while those comprising benzoic acid was isolated in excellent yield (**50**, 83 %, 63:37 *d.r.*). Influence of amino acids as amine components was tested again with phenylalanine and tyrosine-related derivatives. Reaction performed with H-Phe-OMe and acetic acid furnished three-component Ugi

product **51a** in 50 % yield, while corresponding four-component product **51** was not detected in the reaction. When acetic acid was replaced with Boc-Phe-OH, four-component Ugi product **52** was isolated in low yield (14 %), while major product, a three-component Ugi product **51a** was isolated in 50 % yield. Contrary to that, the Ugi reaction performed with H-Tyr-OBn and acetic acid provided expected four-component product **53** as a main product (63 % yiled) a three-component Ugi product **53a** in 18 % yield. The Ugi reaction performed with Boc_2-Tyr-OH as acid component afforded single product **54** in 78 % yield.



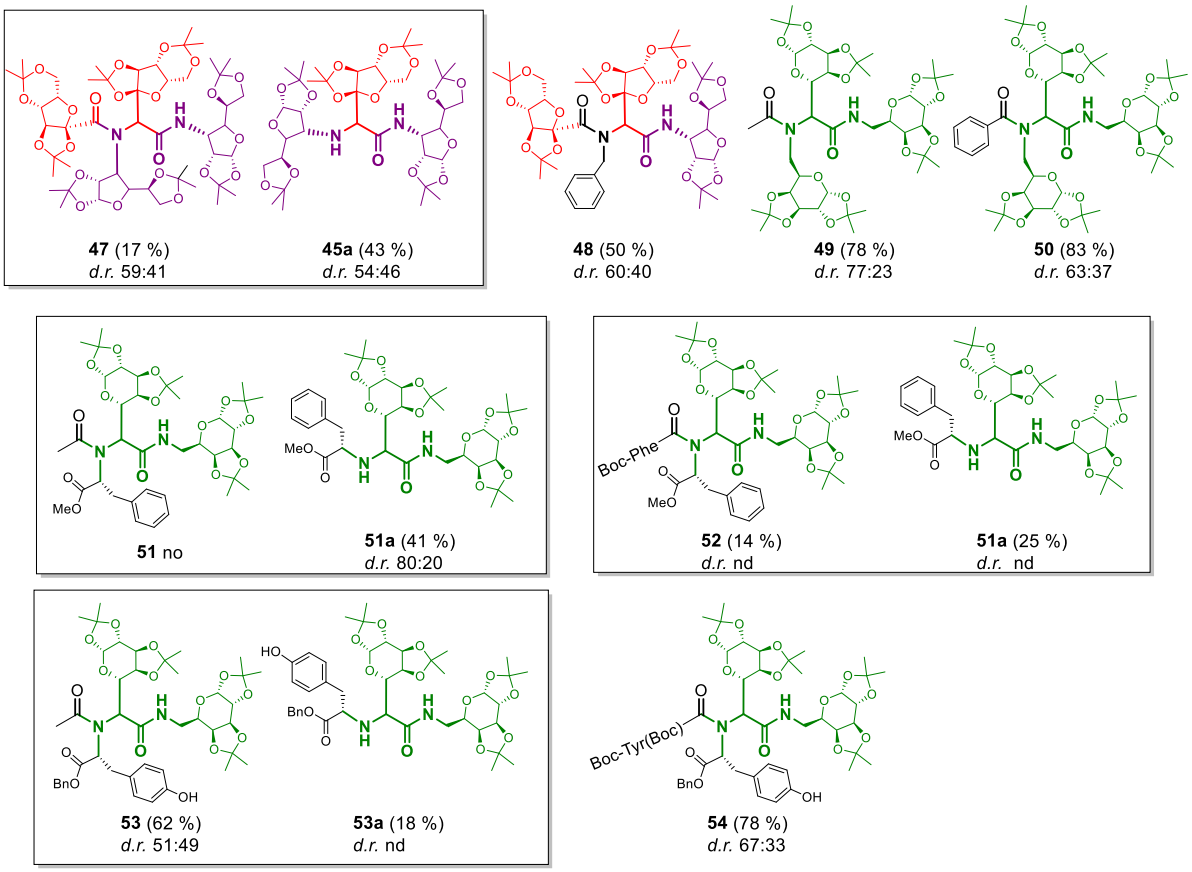


Figure 2. Products isolated from the Ugi reactions comprising selected carbohydrate derivatives from Table 1**.** *d.r.* was determined from the ratio of isolated products, and for compounds **43, 49** and **51a** it was determined from the ^{1}H NMR spectrum of the product isolated as a mixture of two diastereoisomers. Products obtained from the same reaction mixture, but through different pathways are placed in rectangles (see text).

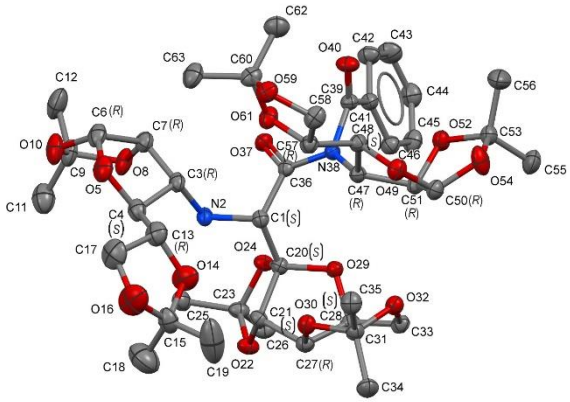
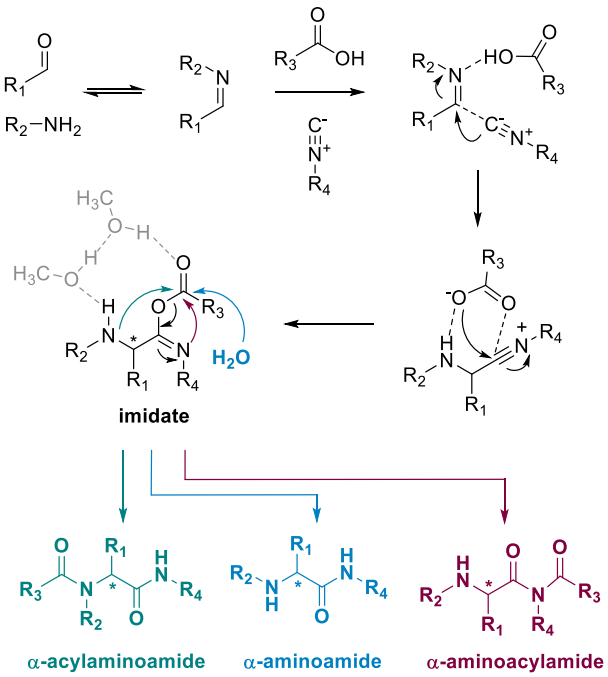


Figure 3. Molecular structure of **45b** with atom numbering and absolute configurations of chiral C atoms. Thermal ellipsoids are represented at the 30% probability level. Hydrogen atoms and a water molecule localized within the structure are omitted for clarity.

Analysis of obtained results in the Ugi product series revealed that multiple reaction paths must be envisioned. The general mechanism of the reaction, proposed by Ugi[30] involves *in situ* formation of an imine from the carbonyl compound and the primary amine in the first step, protonation of an imine followed by α-addition of the isocyanide and subsequent Mumm rearrangement to furnish substituted α-amino acid derivatives (Scheme 2). Many efforts has been devoted to elucidate each reaction step, role of the solvent, and possibility to control the stereochemical outcome of the reaction. A thorough theoretical study of the reaction, performed by Chéron et al. showed that the imine formed in the first reaction step is not activated by proton transfer, but through a hydrogen-bonded complex with the acidic substrate (Scheme 2).[31] The isocyanide addition is the rate-determining step and the non-reversibility of the nitrilium formation indicates that it should be possible to control the stereochemistry of the reaction. It was shown previously for the Passerini reaction that an extra carboxylic acid molecule is required, as a fourth partner, to allow the Mumm rearrangement of the imidate intermediate to proceed. Similar approach was applied in a study of Chéron et al. However, for the Ugi reaction, proton transfer might be mediated by the solvent or by the acid (Scheme 2). In both cases, the Mumm rearrangement of the imidate cluster leading to the four-component Ugi product, α-acylaminoamide, was found to proceed through very low barriers.

Scheme 2. Mechanism of the Ugi reaction; different paths for the imidate intermediate.



Next possible reaction path includes participation of water released during the imine formation in the first reaction step. Water, but also polar protic solvents, like methanol, can be responsible for a competitive reaction - addition to the imidate intermediate with concomitant acid elimination, giving a three-component Ugi product, α-aminoamides (Scheme 2). This pathway was exploited in the design of first catalytic three-component Ugi reaction.[32] Insight into our results of the Ugi reaction revealed a prevalence of the three-component Ugi pathway over a four-component one in some cases, particularly when phenylalanine was used as amine component (products **38**/**38a**, **39**/**38a**, **51**/**51a** and **52**/**51a**, Figure 2). In these examples, fructose or galactose components were used as an aldehyde and an isocyanide components, while two carboxylic acids were tested, acetic acid and Boc-Phe-OH with the same reaction outcome. It was therefore intriguing when we realised that replacement of phenylalanine-related amine component with tyrosine-related one, led to the opposite result. So, reactions performed with fructose or galactose aldehyde and isocyanide components along with acetic acid or tyrosine-related acid (Boc_2-Tyr-OH) furnished "classical" four-component Ugi products as the only or main products (**40**, **41**/**41a**, **53/53a**, **54**, Figure 2). Possible explanation can be sought in the structure of imidate-methanol cluster. Calculations performed by Chéron et al. showed that solvation of imidate by a methanol dimer is more favourable that with only one, or more than two methanol molecules. However, presence of protected ester group when an amino acid is used as an amine component might be responsible for the formation of more flexible, energetically less favourable imidate cluster with longer methanol bridges. Another possibility is that imidate cluster comprising amino acid-related amine component undergo conformational changes that induce formation of alternative hydrogen bonds between imidate and methanol molecule(s). In our previous work on the Passerini reaction comprising hydrazino acids, we observed the disparity in reaction yields of products obtained by different hydrazino acid derivatives.[33] This disparity was rationalised by the DFT calculations showing that alternative hydrogen bonds stabilize thermodynamically very stable non-productive conformations of imidate clusters which hamper the rearrangement into final products. Similar scenario is also possible here; occurrence of stable non-productive form of imidate cluster opens possibility for another nucleophile (water or methanol) to take part in the reaction leading to another type of the Ugi product. Presence of OH group in the tyrosine side-chain, which can participate in the formation of hydrogen bond networks, and possibly stabilise imidate cluster, might be responsible for the observed difference between phenylalanine and tyrosine-type of the Ugi products.

To determine the potential role of the solvent in predominance of one pathway over the other, we performed the Ugi reaction comprising galactose-related aldehyde **3** and isocyanide **7** with

phenylalanine-related amine and acid components and results are presented in Table 2. When reaction was performed with molecular sieves, we noticed change in the ratio of **52**:**51a** from 1:2 in the standard reaction conditions to 2:3. This outcome is consistent with the removal of water released during an imine formation by molecular sieves, but it also points that as expected, methanol can attack the imidate intermediate. Reaction performed in the absence of acid component yielded a three-component product **51a** in 58 %. Therefore, presence of acid in not necessary for the activation of imine and the formation of imidate intermediate (Scheme 2), instead solvent in acidic enough the imine activation. Reactions performed in more acidic trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) did not improve reaction yield, and the ratio of two products remained **52:51a** = 1:2, as with methanol as a solvent (Table 2).

Table 2. Influence of solvent on the distribution of four-component (**52**) and three-component (**51a**) Ugi products.[a]

Solvent	**Reactants**				**Product (%)**[b]	
	RCHO	RNH_2	RNC	RCOOH	**52**	**51a**
MeOH	**3**	H-Phe-OMe	**7**	Boc-Phe-OH	14	25
MeOH/ mol. sieves	**3**	H-Phe-OMe	**7**	Boc-Phe-OH	23	30
MeOH	**3**	H-Phe-OMe	**7**	-	-	58
TFE	**3**	H-Phe-OMe	**7**	Boc-Phe-OH	15	29
HFIP	**3**	H-Phe-OMe	**7**	Boc-Phe-OH	9	17

[a] Reaction conditions: 0.1 mmol of all components in 100 μL solvent, room temperature, 24h. [b] Isolated yields.

Finally, inspection of the Ugi products presented at Figure 2, points toward occurrence of third pathway, particularly when sorbose-related aldehyde **2** was utilized with allose-related isocyanide **8** and amine **12**. In the reaction performed with benzoic acid, a “classical” four-component Ugi product **45** was isolated in low yield (14 %), along with a three-component Ugi product **45a** (15 %). Surprisingly, main product isolated from the reaction was product **45b** (36 %, Figure 2). When reaction was performed with Boc-Phe-OH as acid component, only 3 % of the expected four-component Ugi product **46** was isolated, while three-component Ugi product **45a**

was isolated in 24 %, and product **46b** was isolated in 29 % yield (Figure 2). Formation of products **45b** and **46b**, α-aminoamides, can be rationalized by 1,3 (*O-N*) acyl transfer (Scheme 2), otherwise typical for the Ugi reactions comprising secondary amines.[34] When secondary amines are utilized in the Ugi reaction, imidate intermediate formed in the course of the reaction is tertiary, and can no longer be acylated. If an imine formation is slow, or the reaction is performed with an excess of amine component, secondary amine can intercept the imidate intermediate. Alternatively, polar solvent, like methanol can do the same, leading to a three-component Ugi product of type **45a**.[34] However, in the absence of nucleophilic groups (equimolar amounts of components or reaction performed in nonpolar solvent), the isocyanide nitrogen atom is responsible for the 1,3(*O-N*) acyl transfer of the imidate intermediate and the formation of α-aminoamides (Scheme 2). The fact that we isolated α-aminoamides from the Ugi reaction performed with primary amine and in methanol as a solvent, prompted us to take a closer look at components involved in the reaction. Along with aldehyde **2**, allose-related amine and isocyanide participated, both with their functional groups attached to the secondary carbon atom, and contrary to all other amines and isocyanides in our selection of building blocks. We can speculate that the increased steric hindrance around amine nitrogen impeded acyl transfer; instead, acyl transfer is initiated by an isocyanide nitrogen or methanol. Replacement of amine **12** with simple benzyl amine thus furnished "classical" Ugi product **48** in 50 % yield (Figure 2).

Mass spectrometry can be used as an elegant method for the fast identification and discrimination between α-acylaminoamides (**45**, **46**) and α-aminoacylamides (**45b**, **46b**), since both structures have identical molecular masses. Inspired by a work of de Angelis et al.[35] we undertook a closer insight into the fragmentation pattern of the molecular $[M+H]^+$ ions of Ugi products **45** and **45b**, looking for the fragment ions characteristic for two compounds. The MS/MS spectrum of the molecular $[M+H]^+$ ion *m/z* 891 of compound **45** is shown at Figure 4. A highly abundant fragment ion *m/z* 834 corresponds to the loss of one isopropylidene group (58 Da), while low abundant ion *m/z* 632 is a b-type fragment ion and corresponds to the formation of oxazolone structure (Figure 4a). Further elimination of one isopropylidene group from *m/z* 632 gave rise to high intensity fragment ion *m/z* 574. Contrary to that, the MS/MS spectrum of the molecular $[M+H]^+$ ion *m/z* 891 of the compound **45b** is characterized by a rich fragmentation, resulting mainly from the multiple elimination of isopropylidene protecting groups. However, fragment ion *m/z* 500 is a-type fragment ion and corresponds to the iminium ion presented at Figure 4b. The same fragments were also found in products **46** and **46b** (Supporting Information file). Oxazolone- and iminium-type ions can thus, be used for the fast screening of reaction mixtures and identification of two reaction pathways. This was confirmed by the MS analysis of a

number of Ugi reactions; oxazolone fragment ions were found in all Ugi reactions giving “classical” four-component product, while imonium fragment ions were found only in two examples presented at Figure 2, where three parallel reaction pathways occurred.

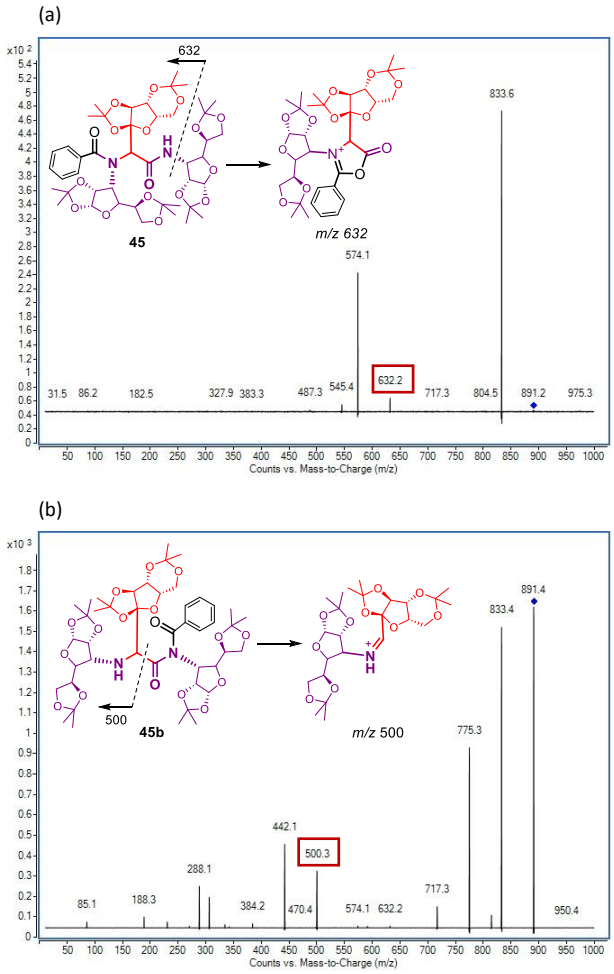


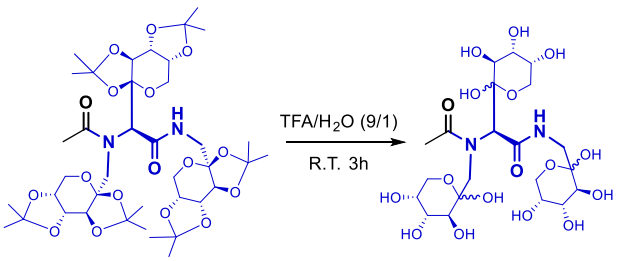
Figure 4. (a) The MS/MS spectrum of the molecular $[M+H]^+$ ion *m/z* 891 of Ugi product **45** and the rationale for the formation of the fragment ion *m/z* 632. (b) The MS/MS spectrum of the molecular $[M+H]^+$ ion *m/z* 891 of Ugi product **45b** and the rationale for the formation of the fragment ion *m/z* 500.

Many efforts have been devoted to the improvement of generally poor diastereoselectivity of the Ugi reaction. It is nowadays well-documented that utilization of chiral isocyanides, carbonyl components and carboxylic acids has little effect on diastereoselectivity, while some chiral induction has been reported only with chiral amines or chiral cyclic imines.[36] Contrary to that, in our work we did not observe any substantial influence of the chiral amine on the diastereoselective outcome of the Ugi reaction (Figure 2, compounds **36** and **37**, **47** and **48**). However, structure of

an amine component in great deal determined the fate of the imidate intermediate. In addition to the disparity in the ratio of four- and three-component Ugi products observed with phenylalanine- and tyrosine-derived amine components, another intriguing finding arose from reactions performed with allose-related amine **12**. When simple, acetic acid was used in the reaction with sorbose-related aldehyde **2** and allose-related isocyanide **8**, the four-component Ugi compound **44** was isolated as the only product. However, utilization of sterically more demanding carboxylic acids with amine **12** changed the course of the reaction. In addition to the four-component products (**45**, **46** and **47**), three-component products (**45a**, **46a** and **47a**) appeared along with α-aminoamides **45b**, **46b** (Figure 2). It should be emphasized that such alternative pathways were not observed with amines **9**, **10** and **11**. So, structure of imidate intermediate in terms of its bulky groups arrangement, can favor internal or external nucleophile attack or discriminate between two potential nucleophile sites within the molecule.

Final step prior to probing the biological potential of glycomimetics is removal of protecting isopropylidene groups. Access to deprotected glycomimetics was varified on Ugi product **33**. Treatment of compound **33** with TFA/H_2O (9/1) at room temeprature resulted in removal of isopropylidene groups after 3 hours, and derivative **55** was obtained in 89 % as a mixute of multiple anomeric forms (Scheme 3).

Scheme 3. Deprotection of Ugi product **33**.



33 **55** (89 %)

Conclusions

We applied a multicomponent strategy to afford a library of homo- and hetero-multivalent Passerini and Ugi products utilizing isopropylidene-protected D-fructose-, L-sorbose-, D-

galactose-, and D-allose-related building blocks. Passerini products were isolated in good yields and very good to excellent diastereoselectivities, with *S* diastereoisomer being the predominant one, as determined by the single crystal x-ray analysis. Three types of products were obtained by the Ugi reaction; along with the "classical" four-component product, α-acylaminoamides, a three-component α-aminoamides and a four-component α-aminoacylamides were isolated in some cases. Presence of multiple pathways is rationalized by the structure of imidate intermediate, mainly influenced by the amine component. Our library of homo- and hetero-multivalent glycomimetics thus consists of Passerini and three types of Ugi products bearing isopropylidene-protected uncommon carbohydrates that can be deprotected in a single step under acidic conditions. Binding of glycomimetic ligands to carbohydrate-binding proteins is a combination of different interactions, including hydrogen bonding, metal-chelation, ionic and hydrophobic interactions, and they are influenced by valency, topology and density of carbohydrates' distribution.[9] Our next step is therefore, to probe the interaction of selected glacomimetics bearing non-self carbohydrates with lectins and to elucidate the role of different factors on the binding.

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. An oil bath was used for reactions requiring heating. 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) and heteronuclear (HMQC, HMBC) experiments. ^{1}H chemical shifts are assigned to the particular starting component, and the following abbreviations are used: Fru = fructose; Sor = sorbose; Gal = galactose, All = allose, ald = aldehyde, isoc = isocyanide. 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 **1** is described in Ref. 37, while compound **13** is commertially available. When two diastereoisomers were separated, they were marked as DS1 and DS2.

Synthesis (3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carbaldehyde (2)[38]

2,3,4,6-di-*O*-isopropylidene-α-L-sorbofuranose (1-OH-isop-Sor, 130 mg, 0.50 mmol) was dissolved in anhydrous DCM (3 mL) and Dess Martin's (DMP) reagent (254.45 mg, 0.6 mmol) was added. The reaction mixture was stirred for 1 h at room temperature under nitrogen. The reaction was terminated by the addition of 720 mg of $Na_2S_2O_3$/4.2 mL of water and 4.2 mL of a saturated aq. $NaHCO_3$. This mixture was stirred for another 10 min and then extracted with 3x8 mL EtOAc and washed with 1x8 mL saturated aq. NaCl. The organic layer was dried over anhydrous $MgSO_4$. The product was purified by flash chromatography on silica gel column in a solvent system: PE:EtOAc 1:2. Yield: 70 % (90 mg); R_f = 0.56 (toluene:EtOAc 1:2, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.65 CHO (s, 1H), 4.53 H-3 (s, 1H), 4.34 H-4 (dd, *J*=3.1, 2.5, 1H), 4.21 H-5 (dd, *J*=3.9, 1.9, 1H), 4.10 H-6 (dd, *J*=4.9, 2.0, 2H), 1.52 CH_3 isop, (s, 3H), 1.42 CH_3 isop, (s, 3H), 1.37 CH_3 isop, (s, 3H), 1.32 CH_3 isop, (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 194.6 CO, 114.54 Cq isop, C-2, 97.8 Cq isop, 86.73 C-3, 74.1 C-5, 72.7 C-4, 60.2 C-6, 29.1 CH_3 isop, 27.1 CH_3 isop, 26.1 CH_3 isop, 18.9 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{19}O_6$ 259.1182; Found 259.1180.

Scale-up: for 1 mmol (260 mg) 1-OH-isop-Sor 76 % (196 mg) of **2** was obtained; for 1.5 mmol (390 mg) 1-OH-isop-Sor 69 % (267 mg) of **2** was obtained.

Synthesis of (3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-carbaldehyde (3)[39]

1,2:34-di-*O*-isopropylidene-α-D-galactopyranose (520 mg, 2 mmol) was dissolved in anhydous DCM (12 mL), and Dess Martin's reagent (DMP, 1040 mg, 2.4 mmol) was added. The reaction mixture was stirred for 1 h at room temperature under nitrogen. The reaction was terminated by addition of 2.88 g $Na_2S_2O_3$ / 16.8 mL water and 16.8 mL saturated $NaHCO_3$ solution. This mixture was stirred for another 10 min and then extracted with 3x32 mL EtOAc and washed with 1x32 mL saturated aq. NaCl. The organic layer was dried over anhydrous $MgSO_4$. The product was purified by flash chromatography on silica gel column in a solvent system: toluene:EtOAc 3:2. Yield: 98 % (505 mg); R_f = 0.6 (toluene:EtOAc 3:2, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.62 (H-6, s, 1H), 5.67 (H-1, d, *J* = 4.9 Hz, 1H), 4.65 (H-3, dd, *J* = 7.8, 2.5 Hz, 1H), 4.60 (H-4, dd, *J* = 7.8, 2.2 Hz, 1H), 4.38 (H-2, dd, *J* = 4.9, 2.5 Hz, 1H), 4.19 (H-5, d, *J* = 2.2 Hz, 1H), 1.51 (CH_3, s, 4H), 1.44 (CH_3, s, 4H), 1.35 (CH_3, s, 4H), 1.32 (CH_3, s, 4H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 200.3 C-6, 110.3 Cq-

isop, 109.3 Cq-isop, 96.5 C-1, 73.4 C-5, 71.9 C-4, 70.7 C-2, 70.6 C-5, 26.2 CH_3-isop, 26.0 CH_3-isop, 25.0 CH_3-isop, 24.4 CH_3-isop.

Scale up: from 5.76 mmol (1.5 g) of 1,2:34-di-*O*-isopropylidene-α-D-galactopyranose, 86 % (1.28 g) of **3** was obtained.

Synthesis of (3aR,5R,6aS)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(5H)-one (4)[40]

1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (260 mg, 1 mmol) was dissolved in 6 mL of dry DCM and DMP reagent (508.9 mg, 1.2 mmol) was added. The reaction was stirred for 1 h at room temperature under nitrogen. After that $Na_2S_2O_3$ (1.44 g, 5.8 mmol) / 8.4 mL water and 8.4 mL saturated aq. $NaHCO_3$ were added. This mixture was stirred for another 10 min, and then extracted with 3x16 mL EtOAc and washed with 1x16 mL saturated aq. NaCl. The organic layer was dried over anhydrous $MgSO_4$. The product was purified by flash chromatography on silica gel column in a solvent system: PE:EtOAc 1:1. Yiel: 89 % (230 mg); R_f = 0.56 (PE:EtOAc 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 H-1 (d, *J* = 4.5 Hz, 1H), 4.36 H-2 (m, 1H), 4.33 H-5, H-4 (m, 2H), 4.00 H-6 (m, 2H), 1.43 CH_3 isop (s 3H), 1.41 CH_3 isop (s, 3H), 1.31 CH_3 isop (s, 6H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 209.0 C-3, 114.5 Cq isop, 110.6 Cq isop, 103.3 C-1, 79.2 C-5, 77.4 C-2, 76.6 C-4, 64.5 C-6, 27.8 CH_3 isop, 27.4 CH_3 isop, 26.2 CH_3 isop, 25.5 CH_3 isop.

Synthesis of (3aS,5aR,8aR,8bS)-3a-(isocyanomethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (5)

((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methanamine (1-NH_2-isop-Fru) (45 mg, 0.17 mmol) was dissolved in saturated aq. $NaHCO_3$ (1.36 mL), methyl formate (1.36 mL, 22.1 mmol) was added and the mixture was stirred for 24 h at room temperature with the addition of methyl formate (2x1 mL). The reaction was monitored by TLC in a solvent system: EtOAc : HOAc : H_2O 70:2:2. Purification on silica gel column in this system yielded 64 % (31 mg) of the formamide derivative (N-(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)formamide, R_f = 0.18 (ETOAc:HOAc:H_2O 70:2:2).

In the second reaction step, formamide derivative (31 mg, 0.108 mmol) was dissolved in DCM (600 µL), and Et_3N (58.5 µL) and $POCl_3$ (15.8 µL) were added. The reaction was stirred at room temperature for 1h after which Na_2CO_3 (28.7 mg) dissolved in water (0.114 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 a silica gel column in a solvent system: toluene:EtOAc 1:1. Yield: 63 % (18 mg); yield over two steps 40 %; R_f = 0.76 (toluene:EtOAc 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.63 H-4 (dd, *J*=7.9, 2.7, 1H), 4.36 H-3 (d, *J*=2.7, 1H), 4.22 H-5 (dd, *J*=7.9, 1.3, 1H), 3.90 H-6a (dd, *J*=13.0, 1.9, 1H), 3.78 – 3.71 H-6b, H-1 (m, 2H), 3.63 H-1 (d, *J*=15.2, 1H), 1.55 CH_3 isop (s, 3H), 1.49 CH_3 isop (s, 3H), 1.45 CH_3 isop (s, 3H), 1.33 CH_3 isop (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 159.3 NC, 109.7 Cq isop, 109.5 Cq isop, 100.4 C-2, 70.8 C-5, 70.5 C-3, 70.2 C-4, 62.2 C-6, 47.4 C-1, 26.9 CH_3 isop, 26.1 CH_3 isop, 25.8 CH_3 isop., 24.2 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{20}NO_5$ 270.1341; Found 270.1347.

Scale up: from 1 mmol (259 mg) 1-NH_2-isop-Fru, 48 % (129 mg) of **5** was obtained over two reaction steps; from 1.8 mmol (466 mg) 1-NH_2-isop-Fru, 55 % (266 mg) of **5** was obtained over two reaction steps.

Synthesis of (3aS,3bR,7aS,8aS)-8a-(isocyanomethyl)-2,2,5,5-tetramethyltetrahydro-7H-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine (6)

I step

DCC (176.8 mg, 0.852 mmol, 1.3 eq) was dissolved in dry DCM (10 mL) at 0 ° C followed by slow addition of HCOOH (32.3 µL, 0.852 mmol, 1.3 eq). A white suspension was stirred for 10 min. To this reaction mixture was added ((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methanamine (172 mg, 0.66 mmol), DMAP (16.2 mg, 0.132 mmol, 0.2 eq.) and Et_3N (146.2 µL, 1.05 mmol, 1.6 eq) and mixed at 0 °C another 30 min and overnight at room temperature. At the end of the reaction, the precipitate of the urea was filtered off and the filtrate was evaporated. The residue was purified by flash liquid chromatography in a solvent system: EtOAc:HOAc:H_2O 70:2:2 to obtain formamide derivative N-(((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)formamide in 58 % (111 mg) (R_f = 0.69).

In the second reaction step, formamide derivative (111 mg, 0.386 mmol) was dissolved in DCM (2 mL), Et_3N (205.2 µL) and $POCl_3$ (54.6 µL). The reaction was stirred at room temperature for 80 min after which Na_2CO_3 (98.4 mg) dissolved in water (394.8 µL) 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 a silica gel column in a solvent system: PE:EtOAc 2:1. Yield: 69 % (72 mg); yield 40 % over two steps; R_f = 0.48 (PE:EtOAc 2:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.48 H-3 (s, 1H), 4.35 H-4 (d, *J*=2.2, 1H), 4.13 H-5 (dd, *J*=3.5, 2.1, 1H), 4.03 H-6 (dd, *J*=13.7, 2.2, 1H), 3.96 H-6 (d, *J*=13.7,

1H), 3.88 H-1 (s, 1H), 3.78 H-1 (d, *J*=15.3, 1H), 1.51 CH_3 isop (s, 3H), 1.47 CH_3 isop (s, 3H), 1.41 CH_3 isop (s, 3H), 1.36 CH_3 isop (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 157.8 NC, 113.6 Cq isop, 111.7 C-2, 97.7 Cq isop, 84.3, 73.5 C-4, 72.8 C-5, 60.3 C-6, 45.5 C-1, 29.1 CH_3 isop, 27.8 CH_3 isop, 26.6 CH_3 isop, 18.7 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{20}NO_5$ 270.1341; Found 270.1338.

Synthesis of (3aR,5R,5aS,8aS,8bR)-5-(isocyanomethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (7)

1,2,3,4-di-*O*-isopropylidene-6-deoxy-6-amino-α-D-galactopyranose (6-NH_2-isop-Gal) (140 mg, 0.54 mmol) was dissolved in saturated in saturated $NaHCO_3$ solution and methyl formate (4.46 mL) was added. The reaction was stirred at room temperature with the addition of 2x 4.46 mL methylformate overnight. Solvent was evaporated and the residue purified on a silica gel column in a solvent system: EtOAc:HOAc:H_2O 70:2:2 to give 32 % of formamide derivative N-(((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)formamide (R_f = 0.62).

Alternativelly, formamide derivative can be obtained following tje procedure: DCC (370 mg, 2.989 mmol, 1.3 eq) was dissolved in anhydrous DCM (10 mL) at 0 °C and CHOOH (112.8 µL, 2.989 mmol, 1.3 eq) was slowly added. A white suspension was stirred for 10 min. To this reaction mixture 6-NH_2-iprop-Gal (595 mg, 2.32 mmol), DMAP (56.4 mg, 0.46 mmol, 0.2 equiv) and Et_3N (509 µL, 3.67 mmol, 1.6 eq) were added, and stired overnight at room temperature. The precipitate of the urea was filtered off and the filtrate was evaporated. The residue was purified by flash liquid chromatography in a solvent system of EtOAc:HOAc:H_2O 70:2:2. to afford 69 % of formamide product.

In the second reaction step, formamide derivative (436 mg, 1.519 mmol) was dissolved in DCM (4.15 mL), Et_3N (820 µL) and $POCl_3$ (222.6 µL) were added. The reaction was stirred at room temperature for 1h after which Na_2CO_3 (401 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 a silica gel column in a solvent system: PE:EtOAc 2:1. Yield: 44 % (180 mg); yield 30 % over two steps; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.49 H-1 (d, *J* = 5.0 Hz, 1H), 4.64 H-3 (dd, *J* = 7.8, 2.5 Hz, 1H), 4.32 H-2 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.28 H-4 (dd, *J* = 7.8, 1.9 Hz, 1H), 3.99 H-5 (td, *J* = 6.9, 1.7 Hz, 1H), 3.62 H-6 (dd, *J* = 14.7, 7.0 Hz, 1H), 3.55 H-6 (dd, *J* = 14.7, 6.8 Hz, 1H), 1.53 CH_3-isop (d, *J* = 1.0 Hz, 3H), 1.42 CH_3-isop (s, 3H), 1.33 CH_3-isop (s, 3H), 1.32

CH_3-isop (s, 3H).^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 158.3 NC, 110.1 Cq-isop (1,2), 109.3 Cq-isop (3,4), 96.5 C-1, 70.8 C-3, 70.6 C-2, 70.4 C-4, 66.4 C-5, 41.8 C-6, 26.3 CH_3-isop, 26.1 CH_3-isop, 25.1 CH_3-isop, 24.6 CH_3-isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{20}NO_5$ 270.1341; Found 270.1350.

Scale up: from 1 mmol (259 mg) 6-NH_2-isop-Gal, 68 % (183 mg) of **7** was obtained over two reaction steps; from 2.2 mmol (570 mg) 6-NH_2-isop-Gal, 55 % (326 mg) of **7** was obtained over two reaction steps.

Synthesis of (3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-isocyano-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (8)

DCC (106 mg, 0.518 mmol) was dissolved in anhydrous DCM (3 mL) at 0 °C followed by a slow addition of CHOOH (19.6 µL, 0.518 mmol). A white suspension was stirred for 10 min. To this reaction mixture amine derivative (3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-amine (104 mg, 0.4 mmol), DMAP (9.8 mg, 0.08 mmol) and Et_3N (88.58 µL; 0.638 mmol) were added and the reaction was stirred 2.5 h at room temperature. The formed precipitate of the urea was filtered off, and the filtrate was evaporated. The residue was purified by liquid flash chromatography in EtOAc:HOAc:H_2O 70:2:2 solvent system to give 91 % of formamide derivative N-((3aR,5S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)formamide.

In the second reaction step, formamide derivative (105 mg, 0.365 mmol) was dissolved in DCM (1 mL), and Et_3N (106.8 µL) and $POCl_3$ (53.2 µL) were added. The reaction was stirred at room temperature for 1h, and than Na_2CO_3 (96.2 mg) dissolved in water (0.384 mL) was added. The reaction mixture was stirred for 1 h at room temperature. After extraction, the organic layers were collected, dried over K_2CO_3, and evaporated. The residue was purified on silica gel column in a solvent system: PE:EtOAc 2:1. Yield: 37 % (36 mg); yield 33 % ovet two steps; R_f = 0.63 (PE:EtOAc 2:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 H-1 (d, *J* = 3.7 Hz, 1H), 4.70 H-2 (dd, *J* = 4.6, 4.1 Hz, 1H), 4.25 H-5 (dd, *J* = 11.7, 5.5 Hz, 1H), 4.11 H-4, H-6 (m, 2H), 4.00 H-6 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.85 H-3 (dd, *J* = 8.9, 5.1 Hz, 1H), 1.57 CH_3 isop (d, *J* = 19.8 Hz, 3H), 1.44 CH_3 isop (d, *J* = 48.5 Hz, 3H), 1.36 CH_3 isop (s, 6H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 161.8 NC, 113.8 Cq isop, 110.6 Cq isop, 104.4 C-1, 79.6 C-4, 78.9 C-2, 75.6 C-5, 66.3 C-6, 55.3 C-3, 2696 CH_3 isop, 26.8 CH_3 isop, 26.7 CH_3 isop, 25.3 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{20}NO_5$ 270.1341; Found 270.1346.

Synthesis of ((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methanamine (9)

A solution of trifluoromethanesulfonyl anhydride (314 µL, 1.89 mmol) in anhydrous DCM (3.5 mL) was added dropwise at -20 °C under argon to a solution of 2,3,4,5-di-*O*-isopropylidene β-D-fructopyranose (325.08 mg, 1.26 mmol) in anhydrous DCM (14 mL) and pyridine (273 µL). The reaction mixture was stirred at -20 °C. for 1 h. The mixture was then diluted with DCM (10 mL) and extracted with water (15 mL). The organic layer was washed with saturated $KHSO_4$ solution (15 mL), saturated aq. $NaHCO_3$ (10 mL) and saturated aq. NaCl, and dried over Na_2SO_4, filtered and evaporated. The triflate derivative was used in synthesis without further purification.

Sodium azide (333 mg, 5.1 mmol) was added to a solution of the triflate derivative (322 mg, 1.25 mmol) in anhydrous DMF (18.2 mL). The reaction mixture was stirred at 80 °C. for 1 h and evaporated. The residue was dissolved in EtOAc (50 mL). The organic layer was washed with water (20 mL) and saturated aq. NaCl (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified on silica gel column in solvent system: toluene:EtOAc 2:1 to give azide derivative (3aS,5aR,8aR,8bS)-3a-(azidomethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran in 87 % yield.

Azide derivative (313 mg, 1.098 mmol) was dissolved in dry DCM (8 mL) and dry EtOH (39 mL) and $NaBH_4$ (82.8 mg) and catalytic amount of $NiCl_2 \cdot 6H_2O$ was added. After 1 hour at room temperature, the reaction mixture was evaporated and purified on silica gel column in a solvent system: EtOAc:EtOH:HOAc:H_2O 70:15:15:15. Yield: 98 % (279 mg); yield 57 % over three steps. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 4.55 H-3 (dd, *J*=8.0, 2.5, 1H), 4.32 H-4 (d, *J*=2.5, 1H), 4.21 H-5 (dd, *J*=8.0, 1.1, 1H), 1.44 CH_3 isop (s, 3H), 1.35 CH_3 isop (s, 3H), 1.34 CH_3 isop (s, 3H), 1.28 CH_3 isop (s, 3H). ^{13}C NMR{1H} (151 MHz, DMSO) δ = 107.9 Cq isop, 107.2 Cq- isop, 103.5 C-2, 70.2 C-3, 70.1 C-4, 69.5 C-5, 60.3 C-6, 47.6 C-1 26.3 CH_3 isop, 25.6 CH_3 isop , 25.5 CH_3 isop, 23.9 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{22}NO_5$ 260.1498; Found 260.1502. Scale up: from 2 mmol (520 mg) 1-OH-isop-Fru, 42 % (217 mg) of **9** was obtained over three reaction steps.

Synthesis of ((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methanamine (10)[41]

A solution of trifluoromethanesulfonyl anhydride (497 µL) in anhydrous DCM (5.5 mL) was added dropwise at -20 °C.under nitrogen to a solution of 2,3,4,6-di-*O*-isopropylidene sorbofuranose (520 mg, 2 mmol) in anhydrous DCM (22 mL) and pyridine (432 µL). The reaction mixture was stirred at -20 °C. for 2 h. The mixture was then diluted with DCM (20 mL) and extracted with water (24 mL). The organic layer was washed with saturated $KHSO_4$ solution (24 mL), saturated aq. $NaHCO_3$ (16 mL) and saturated aq.NaCl (16 mL), dried over Na_2SO_4, filtered and evaporated.

The triflate derivative (88 %) was used in synthesis without further purification. Sodium azide (460 mg, 7.1 mmol) was added to a solution of the triflate derivative (695 mg, 1.77 mmol) in anhydrous DMF (24 mL). The reaction mixture was stirred at 80 ˚C for 1 h. After evaporation the residue was dissolved in EtOAc (80 mL). The organic layer was washed with water (36 mL) and saturated aq. NaCl (36 mL), dried over Na_2SO_4 and evaporated. The residue was purified on silica gel column in PE:EtOAc 3:1. to give azide derivative (3aS,3bR,7aS,8aS)-8a-(azidomethyl)-2,2,5,5-tetramethyltetrahydro-7H-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine in 81 % yield R_f = 0.41 (PE:EtOAc 3:1, v/v).

Azide derivative (407 mg, 1.428 mmol) was dissolved in dry DCM (21 mL) and dry EtOH (102 mL) and $NaBH_4$ (107.9 mg, 2.856 mmol) and catalytic amount of $NiCl_2 \cdot 6H_2O$ was added. After 1 hour at room temperature, the reaction mixture was evaporated and purified on silica gel column in a solvent system of EtOAc:EtOH:HOAc:H_2O 7:1:1:1. Yield: 98 % (358 mg); yield 69 % over 3 steps; R_f = 0.43 (EtOAc:EtOH:HOAc:H_2O 7:1:1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ = 4.41 H-3 (s, 1H), 4.29 H-4 (d, *J*=2.2, 1H), 4.06 – 3.96 H-6, H-5 (m, 3H), 3.81 H-6 (d, *J*=13.3, 1H), 2.83 H-1 (q, *J*=13.7, 2H), 1.39 CH_3 isop (t, *J*=4.8, 6H), 1.31 CH_3 isop (s, 3H), 1.23 CH_3 isop. (d, *J*=4.1, 3H). ^{13}C NMR{1H} (151 MHz, DMSO) δ = 115.2 Cq isop., 110.7 C-2, 96.6 Cq isop, 84.2, 83.8 C-3, 72.7 C-4, 72.7, 71.5 C-5, 71.4, 59.6 C-6, 45.6 C-1, 28.9 CH_3 isop, 27.4 CH_3 isop, 27.3 CH_3 isop, 18.7 CH_3 isop. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{22}NO_5$ 260.1498; Found 260.1505.

Synthesis of ((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methanamine (11)[42]

1,2;3,4-di-*O*-isopropylidene-α-galactopyranose (260 mg, 1.00 mmol) was dissolved in dry DCM (11 mL) under nitrogen at -20 °C with pyridine (216 µL) and then trifluoromethanesulfonic acid anhydride (248.8 µL) dissolved in dry DCM (2.7 mL) were added slowly in 20 min time period. After 1 h of stirring the reaction was washed with 15 mL water, 15 mL $KHSO_4$ (10 %), 10 mL saturated aq. $NaHCO_3$ and 10 mL saturated aq. NaCl. Product (83 %) was dried and used in the next step.

The triflate derivative (328 mg, 0.83 mmol) was dissolved in dry DMF (11.6 mL), NaN_3 (216 mg, 33.2 mmol) was added and reaction mixture stirred for 1 h at 80 °C. DMF was evaporated, the residue was dissolved in EtOAc (40 mL) and extracted with 18 mL water, and 18 mL saturated aq. NaCl. The organic layer was dried over Na_2SO_4.Crude product was purified by flash chromatography on silica gel column in solvent system: toluene:EtOAc (2:1) to afford 78 % of azide derivative 1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-azido-α-D-galactopyranose Rf = 0.7 (toluene:EtOAc 2:1, v/v).

Azide derivative (185 mg, 0.64 mmol) was dissolved in dry DCM (9.48 mL) and dry EtOH (45.9 mL), $NaBH_4$ (48.4 mg) and a catalytic amount of $NiCl_2x6H_2O$ were added. After 1 hour at room temperature, the reaction mixture was evaporated and purified on silica gel column in a system: EtOAcEtOH:HOAc:H_2O 7:1:1:1. Yield: 89 % (148 mg); yield 57 % over three steps; R_f = 0.5 (EtOAc:EtOH:HOAc:H_2O 7:1:1:1, v/v). ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.47 H-1 (d, J = 5.0 Hz, 1H), 4.61H-3 (dd, J = 7.9, 2.3 Hz, 1H), 4.36 H-2 (dd, J = 5.0, 2.4 Hz, 1H), 4.24 H-4 (dd, J = 8.0, 1.3 Hz, 1H), 3.81 H-5 (d, J = 4.4 Hz, 1H), 2.81 H-6 (ddd, J = 21.1, 12.8, 6.2 Hz, 1H), 1.89 NH_2 (s, 2H), 1.49 CH_3-isop (m, 3H), 1.32 CH_3-isop (m, 9H). ^{13}C NMR{1H} (151 MHz, DMSO-d_6) δ 108.4 Cq-isop, 108.0 Cq-isop, 95.5 C-1, 70.4 C-4, 69.9 C-3, 69.7 C-2, 66.4 C-5, 40.2 C-6, 25.9 CH_3-isop, 25.8 CH_3-isop, 24.8 CH_3-isop, 24.2 CH_3-isop.

Scale up: from 2.5 mmol (650 mg) 6-OH-isop-Gal, 63 % (408 mg) of **11** was obtained over three steps; from 3.5 mmol (910 mg) 6-OH-isop-Gal, 59 % (535 mg) of **11** was obtained over three steps; from 6.4 mmol (1664 mg) 6-OH-isop-Gal, 45 % (746 mg) of **11** was obtained over three steps.

Synthesis of (3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-amine (12)[43]

1,2;5,6-di-O-isopropylidene-α-D-Glucofuranose (520 mg, 2.00 mmol) was dissolved in dry DCM (22 mL) under nitrogen at -20 °C and then pyridine (432 µL) anhydride of trifluoromethanesulfonic acid (497 µL) dissolved in dry DCM (5.5 mL) were added slowly over 20 min. After 1 h of stirring the reaction mixture was rinsed with 24 mL water, 24 mL $KHSO_4$ (10 %), 16 mL sat. solution of $NaHCO_3$ and 16 mL sat. solution of NaCl. Solvent was evaporated and the residue (94 %) dried and used in the next reaction step. R_f = 0.74 (toluene:EtOAc 2:1, v/v).

The triflate derivative (740 mg, 1.88 mmol) was dissolved in dry DMF (21 mL) and NaN_3 (530 mg, 66 mmol) was added and stirred for 1 h at 80 °C. DMF was evaporated, the residue was dissolved in EtOAc (80 mL) and extracted with 36 mL water, 36 mL sat. solution of NaCl. The organic layer was dried over Na_2SO_4, evaporated and the residue purified by flash chromatography on silica gel column in a solvent system: PE:EtOAc 3:1 to give 40 % of azide derivative.

Azide derivative (220 mg, 0.77 mmol) was dissolved in dry DCM (6.8 mL) and dry EtOH (34.5 mL), $NaBH_4$ (54 mg) and a catalytic amount of $NiCl_2x6H_2O$ were added. Reaction was stirred at room temperature for 2h. Solvent was evaporated and the residue purified on silica gel column in a system: EtOAc:EtOH:HOAc:H_2O 7:1:1:1. Yield: 97 % (194 mg); 37 % over 3 steps; R_f = 0.46 (EtOAc:EtOH:HOAc:H_2O 7:1:1:1, v/v) . ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 H-1 (d, *J* = 3.7 Hz, 1H), 4.53 H-2 (m, 1H), 4.09 H-5; H-6 (ddd, *J* = 14.8, 10.3, 6.3 Hz, 2H), 3.99 H-6 (dd, *J* = 8.4, 5.6 Hz,

1H), 3.60 H-4 (dd, *J* = 9.0, 6.4 Hz, 6H), 3.12 H-3 (dd, *J* = 9.0, 4.8 Hz, 1H), 1.52 CH_3 isop (s, 3H), 1.42 CH_3 isop (s, 3H), 1.34 CH_3 isop (s, 3H), 1.32 CH_3 isop (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 112.4 Cq isop, 109.9 Cq isop, 10448 C-1, 81.7 C-4, 81.4 C-2, 77.3 C-5, 67.4 C-6, 58.4 C-3, 26.9 CH_3 isop, 26.8 CH_3 isop, 26.5 CH_3 isop, 25.4 CH_3 isop.

General procedure for Passerini reactions: To a glass vial containing an aldehyde (0.1 mmol) in anhydrous MeOH (100 µL) were added acid component (0.1 mmol, 1 eq.) and an isocyanide component (0.1 mmol, 1 eq.). With all reactants added, the solution was allowed to stir for 24 h in closed vial at room temperature. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl acetate (14): Yield 74 % (43 mg); mp = 94-100 °C; R_f = 0.26 (PE:EtOAc 1:1, v/v), R_f = 0.55 (PE:EtOAc 1:2, v/v); *d.r.* 88:12 (determined from the ^{1}H NMR spectrum); $[\alpha]_D^{22}$ + 1 (c 1, $CHCl_3$). Chemical shifts are given for the major diastereoisomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.67 NH isoc (d, *J* = 8.9, 2.8 Hz, 1H), 5.06 H-1 ald (s, 1H), 4.58 H-4 ald (m, 1H), 4.57 H-4 isoc (m, 1H), 4.40 H-3 isoc (d, *J* = 2.7 Hz, 1H), 4.22 H-5 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.19 H-5 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.17 H-3 ald (d, *J* = 2.8 Hz, 1H), 4.12 H-1 isoc (dd, *J* = 14.2, 9.1 Hz, 1H), 3.90 H-6 isoc (m, 2H), 3.79 H-6 ald (d, *J* = 13.0 Hz, 1H), 3.71 H-6 ald (d, *J* = 12.9 Hz, 1H), 3.16 H-1 isoc (dd, *J* = 14.2, 3.3 Hz, 1H), 2.18 CH_3-ac. (s, 3H), 1.51 CH_3-isop. (s, 3H), 1.50 CH_3-isop (s, 3H) 1.48 CH_3-isop (s, 3H), 1.44 CH_3-isop (s, 3H), 1.43 CH_3-isop (s, 3H), 1.39 CH_3-isop (s, 3H), 1.31 CH_3-isop (s, 3H), 1.31 CH_3-isop (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$): δ 169.5 CO-ac, 165.6 CO-amid, 109.9 Cq-isop 109.5 Cq-isop, 109.4 Cq-isop, 108.9 Cq-isop, 102.8 C-2 isoc, 102.2 C-2 ald, 74.1 C-1 ald, 71.1, 71.0 C-3 ald, isoc, 70.8, 70.7 C-4 ald, isoc, 70.5, 70.3 C-5 ald, isoc, 62.0, 61.8 C-6 ald, isoc, 44.5 C-1 isoc, [26.9, 26.7, 26.2, 25.7, 25.5, 24.4, 24.2] CH_3-isop, 21.05 CH_3-ac. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{42}NO_{13}$ 588.2656; Found 588.2655.

(*S*)-2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl benzoate (15): Yield 78 % (51 mg); white solid; mp = 125-132 °C; R_f = 0.25 (PE:EtOAc 2:1, v/v); $[\alpha]_D^{22}$ + 10 (*c* 1, $CHCl_3$); *d.r.* 90:10 (determined from the ^{1}H NMR spectrum); Chemical shifts are given for the major

diastereoisomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.15-8.04 (m, 2H, benzoic acid), 7.55 (t, *J* = 7.4 Hz, 1H, benzoic acid), 7.42 (t, *J* = 7.8 Hz, 2H, benzoic acid), 6.78 (dd, *J* = 8.5, 3.1 Hz, 1H, NH), 5.84 (s, 1H, H-1, Fru-ald), 5.03 (d, *J* = 2.8 Hz, 1H, H-3 Fru-ald), 4.56 (ddd, *J* = 23.8, 7.9, 2.7 Hz, 2H, H-4 Fru-ald, isoc), 4.22-4.14 (m, 2H, H-5 Fru-ald, isoc), 4.11 (t, *J* = 3.8 Hz, 1H, H-3 Fru-isoc), 4.03 (dd, *J* = 14.1, 8.7 Hz, 1H, H-1 Fru-isoc), 3.84 (ddd, *J* = 22.1, 13.0, 1.9 Hz, 2H, H-6 Fru), 3.69 (d, *J* = 13.0 Hz, 2H, H-6 Fru), 3.25 (dd, *J* = 14.1, 3.5 Hz, 1H, H-1 Fru-isoc), 1.52 (dd, *J* = 20.4, 10.7 Hz, 9H, Fru-CH_3), 1.41 (m, 3H, Fru-CH_3), 1.38 (s, 3H, Fru-CH_3), 1.33 (s, 3H, Fru-CH_3), 1.31 (s, 3H, Fru-CH_3), 1.28 CH_3-isop (s, 3H, Fru-CH_3). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 166.9), 165.3, 133.5, 130.5, 129.9, 128.6, 109.5, 109.5, 109.4, 108.7, 102.3 C-2, 102.0 C-2, 76.5, 71.4, 71.1, 71.0, 70.7, 70.4, 70.3, 62.1, 61.8, 45.1, 26.9, 26.6, 26.2, 25.9, 25.5, 24.3, 24.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{43}NO_{13}Na$ 672.2632; Found 672.2612.

2-oxo-1-((3aR,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (16): Yield 78 % (62 mg); DS1: Yield 25 % (20 mg); R_f = 0.43 (PE:EtOAc 1.5:1, v/v). DS2: Yield 53 %; mp = 147-149 °C, R_f = 0.3 (PE:EtOAc 1.5:1, v/v); $[\alpha]_D^{22}$ - 2 (*c* 1, $CHCl_3$).. Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 Phe (m, 2H), 7.21 Phe (m, 2H), 6.72 NH (m, 1H), 5.14 H-1 ald (s, 1H), 4.91 NH Phe (d, *J* = 8.5 Hz, 1H), 4.63 Phe-α (m, 1H), 4.58 H-4 ald, isoc (m, 2H), 4.39 H-3 ald (d, *J* = 2.7 Hz, 1H), 4.21 H-5 ald, isoc (dd, *J* = 7.7, 1.2 Hz, 2H), 4.16 H-3 isoc (d, *J* = 2.8 Hz, 1H), 4.13 H-1 isoc.(m, 1H), 3.91 H-6 (ddd, *J* = 20.0, 13.0, 1.7 Hz, 2H), 3.79 H-6 (d, *J* = 13.0 Hz, 1H), 3.72 H-6 (d, *J* = 12.8 Hz, 1H), 3.37 Phe-β (dd, *J* = 14.2, 5.2 Hz, 1H), 3.20 H-1 isoc. (dd, *J* = 14.2, 3.1 Hz, 1H), 3.12 Phe-β (dd, *J* = 14.1, 7.1 Hz, 1H), [1.56 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.45 (s, 2H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36 (s, 6H), 1.34 (s, 3H), 1.31 (s, 3H)] CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 170.7 CO, 165.1 CO, 136.4 Phe-γ, 130.1 Phe-ζ, 128.6 Phe-δ, 127.0 Phe-ε, 110.0 Cq-isop, 109.5 Cq-isop, 109.4 Cq-isop, 108.9 Cq-isop, 102.67 C-2, 102.06 C-2, 74.2 C-1 ald, [71.2, 70.8, 70.6, 70.5, 70.2] C-3, C-4, C-5, 61.9 C-6 ald, isoc, 54.4 Phe-α, 44.7 C-1 isoc, 38.1 Phe β, [28.5, 26.9, 26.7, 26.2, 25.8, 25.6, 24.5, 24.2] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{39}H_{56}N2O_{15}Na$ 815.3578; Found 815.3557.

(3aS,3bR,7aS,8aR)-2-oxo-1-((3a*R*,5a*R*,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3a*S*,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl 2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-

carboxylate (17): Yield = 39 % (31 mg); mp = 141-142 °C, R_f = 0.64 (PE:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ - 11.8 (c 0.846, $CHCl_3$).. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 NH (dd, *J* = 8.9, 2.8 Hz, 1H), 5.25 H-1 ald. (s, 1H), 4.93 H-3 GulA (s, 1H), 4.55 H-4 (m, 3H), 4.30 H-3 (d, *J* = 2.3 Hz, 1H), 4.19 (m, 3H), 4.15 (d, *J* = 1.4 Hz, 1H), 4.05 H-1 isoc (m, 3H), 3.90 (ddd, *J* = 22.7, 12.9, 1.9 Hz, 2H), 3.74 (dd, *J* = 41.1, 12.9 Hz, 2H), 3.21 H-1 isoc (dd, *J* = 14.2, 3.1 Hz, 1H), [1.58 (s, *J* = 12.3 Hz, 3H), 1.55 (s, 3H), 1.50 (d, *J* = 1.7 Hz, 6H), 1.48 (s, 3H), 1.47 (s, 3H), 1.45 (d, *J* = 4.7 Hz, 6H), 1.40 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H)]CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.4 CO, 165.0 CO, 114.5 C-2 GulA, 110.4 Cq-isop, 109.5 Cq-isop, 109.47 Cq-isop, 108.9 Cq-isop, 102.7 C-2 ald, 102.3 C-2 isoc, 97.7 Cq-isop GulA, 88.0 C-3 GulA, 74.4 C-1 ald, [74.1, 73.0, 71.2, 71.17, 71.0, 70.6, 70.5, 70.2] C-3, C-4, C-5, 62.1 C-6 ald, 62.0 C-6 isoc, 60.2 C-6 GulA, 44.9 C-1 isoc, [28.7, 27.2, 26.9, 26.8, 26.2, 26.0, 25.9, 25.8, 24.5, 24.3, 19.0] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{37}H_{55}NO_{18}Na$ 824.3317; Found 824.3322.

2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl benzoate (18): Yield 62 % (40 mg). DS1: Yield 5 % (3 mg); R_f = 0.6 (toluene:EtOAc 1:2). DS2: *S* configuration, Yield 57 % (37 mg); mp = 191-197 °C; R_f = 0.57 (toluene:EtOAc 1:2); $[\alpha]_D^{22}$ + 28 (c 1, $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 benz-γ (dd, *J* = 8.2, 1.1 Hz, 2H), 7.55 benz-ε (dd, *J* = 10.6, 4.3 Hz, 1H), 7.42 benz-δ (t, *J* = 7.8 Hz, 2H), 6.85 NH (dd, *J* = 9.3, 2.9 Hz, 1H), 5.61 H-1 ald (s, 1H), 4.57 H-5 isoc (dd, *J* = 7.8, 2.8 Hz, 1H), 4.51 H-3 ald (s, 1H), 4.33 H-5 ald (d, *J* = 2.0 Hz, 1H), 4.23 H-1 isoc, H-3 isoc, H-4 ald (m, 3H), 4.19 H-4 isoc (dd, *J* = 7.8, 1.2 Hz, 1H), 4.07 H-6 ald (m, 2H), 3.90 H-6 isoc (dd, *J* = 12.9, 1.8 Hz, 1H), 3.71 H-6 isoc (d, *J* = 12.9 Hz, 1H), 3.19 H-1 isoc (dd, *J* = 14.3, 3.3 Hz, 1H), [1.53 (s, 3H), 1.51 (d, *J* = 2.9 Hz, 6H), 1.49 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H)] CH_3-isop.^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.6 CO (amide), 165.4 CO (ester), 133.5 benz-ε, 130.3 benz-γ, 129.86 benz-β, 128.60 benz-δ, 114.03Cq-isop, 113.47 C-2 ald, 109.44 Cq-isop, 109.1 Cq-isop., 102.8 C-2 isoc, 97.8 Cq-isop, 85.4 C-3 ald, 74.0 C-4 ald, 73.0 C-4 isoc, 72.7 C-1 ald, 71.1 C-4 isoc, 70.9 C-5 ald, 70.45 C-5 isoc, 61.91 C-6 isoc, 60.41 C-6 ald, 44.13 C-1 isoc, 29.1 CH_3-isop, 27.8 CH_3-isop, 27.0 CH_3-isop., 26.9 CH_3-isop, 26.1 CH_3-isop, 25.9 CH_3-isop, 24.2 CH_3-isop, 18.8 CH_3-isop. HRMS (ESI_TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{44}NO_{13}$ 650.2813; Found 650.2789.

(3aS,3bR,7aS,8aR)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-

tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl 2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylate (19): Yield 31 % (25 mg), mp = 143-145 °C, R_f = 0.39 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ -2.2 (*c* 0.9, $CHCl_3$).^{1}H NMR (600 MHz, $CDCl_3$) δ 6.75 NH (d, *J* = 8.0 Hz, 1H), 5.42 H-1 ald (s, 1H), 4.94 H-3 ald* (s, 1H), 4.59 H-3 GulA* (s, 1H), 4.56 (d, *J* = 7.7 Hz, 1H), 4.31 (s, 1H), 4.27 (s, 1H), 4.18 (m, 5H), 4.13 H-1 isoc (m, 1H), 4.04 H-6 ald, GulA (s, 2H), 4.01 H-6 ald, GulA (d, *J* = 13.2 Hz, 2H), 3.88 H-6 isoc (d, *J* = 12.9 Hz, 1H), 3.70 H-6 isoc (d, *J* = 12.9 Hz, 1H), 3.20 H-1 isoc (d, *J* = 11.9 Hz, 1H), 1.70-1.30 CH_3-isop. (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.3 CO, 164.7 CO, 114.5 C-2 GulA, 114.1 Cq-isop., 113.4 C-2 ald, 110.6 Cq-isop., 109.5 Cq-isop, 109.0 Cq-isop, 102.8 C-2 isop, 97.7 Cq-isop, 97.7 Cq-isop, 88.0 C-3 ald, 85.4 C-3 GulA, 74.2, 74.1, 73.5 C-1 ald, [72.9, 72.6, 71.2, 71.1, 70.6] C-3, C-4, C-5, 62.0 C-6 isoc, 60.4 C-6 ald, 60.2 C-6 GulA, 44.5 C-1 isoc, 29.0 CH_3-isop, 28.7 CH_3-isop, 27.9 CH_3-isop, 27.3 CH_3-isop, 26.9 CH_3-isop, 26.8 CH_3-isop, 26.2 CH_3-isop, 26.2 CH_3-isop, 25.9 CH_3-isop, 24.4 CH_3-isop, 19.0 CH_3-isop., 18.9 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{37}H_{55}NO_{18}Na$ 824.3317; Found 824.3303.**2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)amino)ethyl benzoate (20):** Yield 66 % (43 mg). DS1: Yield 8 % (5 mg), R_f = 0.48 (PE:EtOAc 1:1, v/v). DS2: *S* configuration; Yield 58 % (38 mg), mp = 205-206 ºC; R_f = 0.3 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 25 (*c* 1 $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 benz. (d, *J* = 8.3 Hz, 2H), 7.55 benz. (t, *J* = 7.5 Hz, 1H), 7.42 benz. (t, *J* = 7.8 Hz, 2H), 6.79 NH (d, *J* = 6.2 Hz, 1H), 5.63 H-1 ald. (s, 1H), 4.53 H-3 (s, 1H), 4.39 H- 3 (s, 1H), 4.34 – 4.32 H-1 isoc., H-5 (m, 1H), 4.27 H-4 (m, 1H), 4.24 H-4 (m, 1H), 4.12 – 3.94 H-6, H-5 (m, 1H), 3.35 H-1 isoc. (dd, *J* = 14.4, 3.4 Hz, 1H), 1.57-1.34 (24H) CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.4 CO, 165.3 CO, 133.4 benz., 130.3 benz., 130.0 benz, 128.6 benz, 114.3 C-2 isoc., 114.0 Cq-isop., 113.6 C-2 ald, 112.6 Cq isop, 97.8 Cq-isop., 97.7 Cq-isop, 85.6 C-3, 84.6 C-3, 74.1 C-4, 73.5 C-4, 73.1 C-1 ald, 72.9 C-5, 72.8 C-5, 60.6 C-6, 60.5 C-6, 42.2 C-1 isoc. (29.1, 29.1, 28.0, 27.9, 27.2, 27.1, 18.9, 18.8) CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{43}NO_{13}Na$ 672.2632; Found 672.2648.

2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)amino)ethyl (tert-butoxycarbonyl)phenylalaninate (21): Yield 70 %. DS1: Yield

15 % (12 mg), R_f = 0.47 (PE:EtOAc 1:1, v/v). DS2: Yield 58 % (46 mg), mp = 115-117 ºC; R_f = 0.28 (PE: EtOAc 1:1, v/v), $[\alpha]_D^{22}$ +5 (*c* 1, $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 Phe (m, 4H), 7.20 Phe (m, 1H), 6.64 NH (d, *J* = 9.6, 3.3 Hz, 1H), 5.26 H-1 ald (s, 1H), 4.90 NH-Phe (d, *J* = 8.7 Hz, 1H), 4.61 Phe-α (m, 1H), 4.42 H-3 ald (s, 1H), 4.41 H-1 isoc (m, 1H), 4.31 H-3 isoc, H-4 isoc, ald (m, 3H), 4.22 H-5 (m, 1H), 4.10 H-5 (m, 1H), 4.04 (m, 4H), 3.34 Phe-β, H-1 isoc (m, 2H), 3.17 Phe-β (m, 1H), 1.49-1.28 CH_3- isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 170.7 CO, 164.7 CO, 136.0 Phe-γ, 130.2 Phe-ζ, 128.5 Phe-δ, 126.9 Phe-ε, 114.2 C-2 ald, 114.0 C-2 isoc, 112.7 Cq-isop, 112.5 Cq-isop, 97.6 Cq-isop, 97.5 Cq-isop, 85.2 C-3 ald, 84.2 C-3 isoc, 80.0 Cq-isop, 73.9 C-5 ald, 73.1 C-4 ald, 73.0 C-4 ald, 72.6 C-1 ald, 72.5 C-5 ald, 60.4 C-6 ald, 60.2 C-6 isoc, 54.0 Phe-α, 41.7 C-1 isoc, 37.9 Phe-β, 29.2 CH_3-isop, 29.1 CH_3-isop, 28.4 CH_3-Boc, 27.9 CH_3-isop, 27.6 CH_3-isop, 27.0 CH_3-isop, 26.4 CH_3-isop, 18.73 CH_3-isop, 18.7 CH_3-isop. HRMS: HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{56}N_2O_{15}Na$ 815.3578; Found 815.3550.

2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)amino)ethyl (3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylate (22): Yield 44 % (55 mg). DS1: Yield 8 % (6 mg), R_f = 0.38 (PE:EtOAc 1:1.5, v/v). DS2: Yield 36 % (29 mg); R_f = 0.26 (PE:EtOAc 1:1.5, v/v); $[\alpha]_D^{22}$ 0 (*c* 0.51, $CHCl_3$).. Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 NH (dd, *J* = 9.2, 3.3 Hz, 1H), 5.44 H-1 ald (s, 1H), 4.94 H-3 GulA (s, 1H), 4.59 H-3 ald (s, 1H), 4.37 H-3 isoc (s, 1H), 4.37 H-4 GulA (d, *J* = 2.3 Hz, 1H), 4.27 H-1 isoc, H-4 ald, H-4 isoc (m, 1H), 4.19 H-5 GulA (d, *J* = 1.9 Hz, 1H), 4.16 H-5 ald (d, *J* = 1.9 Hz, 1H), 4.03H- isoc, H-6 ald, H-6 isoc, H-6 GulA (m, 7H), 3.36 H-1 isoc (dd, J = 14.4, 3.4Hz, 1H), 1.56 – 1.19 CH_3-isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.2 CO, 164.4 CO, 114.5 Cq-isop, 114.3 C-2 isoc, 114.1 Cq-isop, 113.3 C-2 ald, 110.5 C-2 GulA, 97.7 Cq-isop, 97.62 Cq-isop, 97.6 Cq-isop, 87.8 C-3 GulA, 85.4 C-3 ald, 84.5 C-3 isoc, 74.14 C-5 GulA, 74.06 C-5 ald, 73.4 C-4 GulA, 73.3 C-1 ald, 72.9 C-4 ald, 72.7 C-5 isoc, 72.5 C-4 isoc, 60.6 C-6, 60.4 C-6, 60.2 C-6, 42.1 C-1 isoc, 29.12 CH_3-isop, 29.05 CH_3-isop, 28.7 CH_3-isop, 28.0 CH_3-isop, 27.9 CH_3-isop, 27.2 CH_3-isop, 26.8 CH_3-isop, 26.1 CH_3-isop. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. for $C_{37}H_{55}NO_{18}$ 801.3419; Found 801.3403.

2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-

tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl benzoate (23): Yield 61 % (40 mg). DS1: Yield 16 % (10 mg); R_f = 0.65 (toluen:EtOAc 1:2, v/v). DS2: *S* configuration; Yield 45 % (30 mg); mp = 176-178 °C; R_f = 0.63 (toluene:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ - 12 (*c* 0.5, $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 benz-γ (m, 1H), 7.54 NH(t, *J* = 7.4 Hz, 1H), 7.41 benz-ε (t, *J* = 7.8 Hz, 1H), 6.98 benz-δ (dd, *J* = 6.4, 4.6 Hz, 1H), 5.66 H-1 ald (s, 1H), 5.48 H-1 isoc (d, *J* = 4.9 Hz, 1H), 4.55 H-3 isoc (dd, *J* = 7.9, 2.3 Hz, 1H), 4.51 H-3 ald (s, 1H), 4.33 H-4 ald (d, *J* = 2.1 Hz, 1H), 4.27 H-2 isoc (dd, *J* = 4.9, 2.4 Hz, 1H), 4.23 H-5 ald (d, *J* = 1.6 Hz, 1H), 4.20 H-4 isoc (dd, *J* = 7.9, 1.7 Hz, 1H), 4.07 H-6 ald (dt, *J* = 13.4, 7.9 Hz, 1H), 3.94 H-5 isoc (ddd, *J* = 8.5, 4.5, 1.5 Hz, 1H), 3.61 H-6 isoc (ddd, *J* = 13.7, 7.1, 4.7 Hz, 1H), 3.42 H-6 isoc (ddd, *J* = 13.5, 8.7, 4.4 Hz, 1H), 1.59 – 1.28 CH_3-isop (24H).^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.7 CO amid, 165.4 CO ester, 133.4 benz-ε, 130.3 benz-γ, 129.9 benz-β, 128.6 benz-δ, 113.9 Cq-isop, 113.5 C-2 ald, 109.5 Cq-isop, 109.3 Cq- isop, 97.8 Cq-isop, 96.4 C-1 isoc, 85.5 C-3 ald, 74.2 C-5 ald, 73.0 C-1 ald, 72.9 C-4 ald, 71.6 C-4 isoc, 71.0 C-3, 70.9 C-2, 66.7 C-5 isoc, 60.4 C-6, 40.2 C-6, [29.0, 27.9, 27.1, 26.3, 26.2, 25.4, 24.5, 19.1] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{44}NO_{13}$ 650.2813; Found 650.2811.

(3aS,3bR,7aS,8aR)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl 2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylate (24): Yield 40 % (32 mg), mp = 160-161 °C, R_f = 0.33 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ - 27 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 NH (m, 1H), 5.47 H-1 isoc (t, *J* = 5.2 Hz, 1H), 5.44 H-1 ald (s, 1H), 4.92 H-3 ald (s, 1H), 4.57 H-3 GulA (s, 1H), 4.54 H-3 isoc (m, 1H), 4.30 H-4 (d, *J* = 2.1 Hz, 1H), 4.27 H-4 (d, *J* = 1.4 Hz, 1H), 4.25 H-2 isoc (dd, *J* = 4.9, 2.3 Hz, 1H), 4.21 H-4 isoc (dd, *J* = 7.8, 1.6 Hz, 1H), 4.18 H-5 (s, 1H), 4.15 H-5 (d, *J* = 1.5 Hz, 1H), 4.05 H-6 ald, GulA (m, 4H), 3.92 H-5 isoc (dd, *J* = 6.8, 5.1 Hz, 1H), 3.59 H-6 isoc (ddd, *J* = 13.4, 6.9, 5.0 Hz, 1H), 3.41 H-6 isoc (ddd, *J* = 13.4, 8.5, 4.6 Hz, 1H), 1.74 – 1.36 CH_3 isop. (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.42 CO, 164.95 CO, 114.53 C-2, 114.13 C-2, 113.36 Cq-isop., 110.61 Cq-isop., 109.45 Cq-isop., 109.09 Cq-isop., 97.7 Cq-isop., 96.4 C-1 isop, 88.1 C-3, 85.4 C-3, [74.3, 74.1, 73.2, 73.0, 72.6, 71.6, 71.0, 70.95] C-2 isoc, C-3 isoc, C-4 isoc, ald, GulA, C-5 ald, isoc, GulA, 66.6 C-1 ald, 60.3 C-6, 60.2 C-6, 40.1 C-6 isoc, [29.0, 28.8, 27.9, 27.2, 26.6, 26.3, 26.2, 25.9, 25.4, 24.6, 19.0, 18.9] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{56}NO_{18}$ 802.3497; Found 802.3503.

2-(((3aR,5S,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)amino)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl benzoate (25): Yield 71 % (46 mg) ; *S* configuration; mp = 171-173 °C; R_f = 0.64 (toluene:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ + 41 (*c* 0.73, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 benz-γ (dd, *J* = 8.2, 1.1 Hz, 1H), 7.56 benz-ε (t, *J* = 7.4 Hz, 1H), 7.43 benz-δ (t, *J* = 7.8 Hz, 1H), 6.97 NH (d, *J* = 9.3 Hz, 1H), 6.80 NH (m, 1H), 5.86 H-1 isoc (d, *J* = 3.8 Hz, 1H), 5.81 (m, 1H), 5.61 H-1 ald (s, 1H), 4.96 (m, 1H), 4.61 H-2 isoc (m, 1H), 4.48 H-3 ald (s, 1H), 4.39 H-5 isoc (d, *J* = 2.2 Hz, 1H), 4.37 H-5 ald (m, 1H), 4.22 H-4 ald (d, *J* = 1.2 Hz, 1H), 4.14 H-3 isoc (td, *J* = 9.5, 5.1 Hz, 1H), 4.07 H-4 isoc, H-6 (m, 2H), 3.95 H-6 (m, 1H), 1.58 – 1.32 (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.8 CO amid, 165.4 CO ester, 133.7 benz-ε, 130.2 benz-γ , 129.5 benz-β, 128.7 benz-δ , 114.2 Cq-isop, 113.1 C-2 ald, 112.6 Cq-isop, 109.5 Cq-isop, 104.7 C-1 isoc, 97.9 Cq-isop, 85.4 C-3 ald, 79.0 C-2, 78.9 C-4 isoc, 75.1 C-5 isoc, 73.9 C-4 ald, 72.9 C-1 ald, 72.7 C-5 ald, 63.9 C-6 isoc, 60.6 C-6 ald, 52.6 C-3 isoc, [29.3, 27.8, 27.1, 26.7, 26.7, 26.5, 25.7, 18.9] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{43}NO_{13}Na$ 672.2632; Found 672.2622.

2-(((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)amino)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (26): Yield 53 % (49 mg). DS1: Yield 10 % (8 mg), mp = 117-119 ºC; R_f = 0.68 (PE:EtOAc 2:3, v/v). DS2: Yield 43 % (35 mg), mp = 110-112 ºC; R_f = 0.57 (PE:EtOAc 2:3, v/v). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 Phe (m, 2H), 7.22 Phe (m, 3H), 6.93 NH (d, *J* = 9.4 Hz, 1H), 5.86 H-1 isoc (d, *J* = 3.8 Hz, 1H), 5.36 H-1 ald (s, 1H), 4.88 NH Phe (d, *J* = 8.5 Hz, 1H), 4.61 Phe-α, H-4 (m, 2H), 4.35 H-5, H-2 isoc (dd, *J* = 11.8, 9.9 Hz, 3H), 4.19 H-5 (m, 2H), 4.05 H-6, H-4 (m, 4H), 3.94 H-6 (dd, *J* = 14.4, 6.7 Hz, 2H), 3.39 Phe-β (dd, *J* = 14.2, 4.5 Hz, 1H), 3.02 Phe-β (dd, *J* = 14.1, 8.2 Hz, 1H), 1.55 – 1.32 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.0 CO, 170.6 CO, 136.5 Phe-γ, 129.8 Phe-ζ, 128.7 Phe-δ, 127.1 Phe-ε, 114.1 C-2 ald, 112.7 Cq-isop, 109.6 Cq-isop., 104.6 C-1 isoc, 97.82 Cq-isop, 85.43 C-3 ald, [80.13, 79.06, 78.82, 77.44, 77.23, 77.02, 75.19, 73.98] C-3, C-4, C-5, 72.85 C-1 ald, 72.6, 64.1 C-6 isoc, 60.5 C-6 ald, 54.6 Phe.α, 52.6 C-3 isoc, 38.4 Phe-β, [29.3, 28.5, 27.7, 26.7, 26.6, 26.5, 25.8, 18.9] CH_3-isop. HRMS (ESI-TOF): $[M+Na]^+$ Calcd for $C_{39}H_{56}N_2O_{15}Na$ 815.3578; Found 815.3575.

(3aS,3bR,7aS,8aR)-2-(((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)amino)-2-oxo-1-((3aS,3bR,7aS,8aR)-2,2,5,5-

tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl 2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylate (27): Yield 45 % (36 mg); mp = 113-115 ºC; R_f = 0.27 (PE:EtOAc 1:1, v/v). *d.r.* 72:28 (determined from the ^{1}H NMR spectrum of product isolated as a mixture of two diastereoisomers). Chemical shifts are given for major diastereisomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 NH (d, *J* = 9.4 Hz, 0.72H), 5.85 H-1 isoc (d, *J* = 3.8 Hz, 1H), 5.41 H-1 ald (s, 0.72H), 4.91 H-3 GulA (s, 0.72H), 4.60 H-3 ald (s, 1H), 4.57 H-2 isoc (m, 1H), 4.34 C-4 isoc (td, *J* = 7.0, 2.2 Hz, 1H)), 4.31 H-4 GulA (d, *J* = 2.3 Hz, 1H), 4.30 H-4 ald (d, *J* = 2.0 Hz, 1H), 4.19 H-3 isoc, (m, 3H), 4.04 H-6 isoc, H-6 ald, H-6-GulA, H-5 isoc (m, 5H), 3.93 H-6 isoc, H-6 GulA (m, 2H), 1.55 – 1.31 CH_3-isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.6, 165.0, 114.8 Cq-isop 114.2 Cq-isop, 113.2 C-2 ald, 112.6 Cq-isop,, 110.6 C-2 GulA, 109.6 Cq-isop, 104.7 C-1 isoc, 97.7 Cq-isop 88.2 C-3 GulA, 85.4 C-3 ald, 79.1 C-2 isoc, 78.9 C-5 isoc, 75.2 C-4 isoc, 74.2 C-5 GulA, 74.2 C-5 ald, 73.4 C-1 ald, 72.8 C-4 GulA, 72.6 C-4 ald, 64.1 C-6 isoc, 60.6 C-6 GulA, 60.3 C-6 ald, 52.3 C-3 isoc, 29.1 CH_3-isop, 28.8 CH_3-isop, 27.8 CH_3-isop, 27.3 CH_3-isop, 26.8 CH_3-isop , 26.6 CH_3-isop, 26.5 CH_3-isop, 26.0 CH_3-isop, 25.8 CH_3-isop, 19.0 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{37}H_{55}NO_{18}$ 824.3317; Found 824.3281.

2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-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)methyl)amino)ethyl acetate (28): Yield 64 % (38 mg); mp = 106-112 °C, R_f = 0.3 (PE:EtOAc 1:1, v/v); *d.r.* 85:15 (determined from the ^{1}H NMR spectrum); $[\alpha]_D^{22}$ - 60 (*c* 1, $CHCl_3$)

Chemical shifts are given for major diastereisomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.40 NH (t, *J* = 6.0 Hz, 1H), 5.46 H-1 ald, isoc (dd, *J* = 9.6, 4.9 Hz, 2H), 4.94 H-6 ald (d, *J* = 9.5 Hz, 1H), 4.59 H-3 (m, 1H), 4.54 H-3 (m, 1H), 4.34 – 4.29 H-4 ald, isoc, H-5 ald, H-2 isoc (m, 4H), 4.15 H-2 ald (dd, *J* = 9.5, 1.6 Hz, 1H), 3.98 H-5 isoc (m, 1H), 3.49 H-6-isoc (dt, *J* = 13.1, 6.5 Hz, 1H), 3.42 H-6 isoc (ddd, *J* = 13.5, 7.8, 5.5 Hz, 1H), 2.11 CH_3-ac. (s, 3H), 1.59 – 1.30 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 169.9 CO, 168.5 CO, 109.8 Cq-isop, 109.5 Cq-isop, 109.4 Cq-isop, 109.0 Cq-isop, 96.5 C-1, 96.3 C-1, 71.2 C-6, 71.1 C-4, 70.9 C-2, 70.9 C-4, 70.7 C-3, 70.5 C-3, 67.2 C-5 ald, 65.7 C-5 isoc, 40.0 C-6 isoc, 26.3 CH_3-isop, 26.2 CH_3-isop, 25.3 CH_3-isop, 25.3 CH_3-isop, 24.6 CH_3-isop, 24.5 CH_3-isop, 20.9 CH_3-ac. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{27}H_{42}NO_{13}$ 588.2656; Found 588.2681.

2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl benzoate (29): Yield 71 % (46 mg). DS1: Yield 8 % (5 g); mp 149-151 °C; R_f=0,42 (toluene:EtOAc 2:1, v/v). DS2: Yield 63 % (41 mg); mp 125-132 °C; R_f=0,35 (toluene:EtOAc 2:1, v/v); $[\alpha]_D^{22}$ -44 (*c* 1, $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 benz-δ (m, 2H), 7.52 benz-ε (m, 1H), 7.40 benz-γ (m, 2H), 6.86 NH (dd, *J* = 7.5, 4.7 Hz, 1H), 5.54 H-1 (d, *J* = 4.9 Hz, 1H), 5.44 H-1 (d, *J* = 5.0 Hz, 1H), 5.38 H-6 ald. (d, *J* = 8.4 Hz, 1H), 4.68 H-3 (d, *J* = 1.6 Hz, 1H), 4.66 H-3 (d, *J* = 1.6 Hz, 1H), 4.62 H-4 (d, *J* = 2.3 Hz, 1H), 4.61 (d, *J* = 2.3 Hz, 1H), 4.56 (d, *J* = 2.4 Hz, 1H), 4.55 H-4 ald. (d, *J* = 2.3 Hz, 1H), 4.32 H-2 (m, 1H), 4.25 H-2 (dt, *J* = 4.9, 2.5 Hz, 1H), 4.20 H-5; H-4 (m, 2H), 3.97 H-5 isoc (m, 1H), 3.75 H-6 isoc (ddd, *J* = 14.2, 7.8, 3.0 Hz, 1H), 3.17 H-6 isoc.(ddd, *J* = 14.2, 9.5, 4.7 Hz, 1H), 1.56 – 1.28 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 167.5 Cq-amid, 166.4 Cq-ester, 133.3 benz-ε, 130.3 benz-δ, 130.0 benz-β, 128.5 benz-γ, 109.8 Cq-isop, 109.6 C-q-isop, 109.2 Cq-isop, 109.0 Cq-isop., 96.7 C-1, 96.6 C-1, 73.9 C-6 ald, 71.7 H-5, 71.0 H-4, 70.8 H-2, 70.8 H-3, 70.75 H-3, 67.6 H-5 isoc., 40.7 C-6 isoc, [26.3, 26.2, 26.1, 25.9, 25.3, 25.25, 24.5, 24.4] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{44}NO_{13}$ 650.2813; Found 650.2791.

2-oxo-1-((3aR,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl (3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxylate (30): Yield 41 % (33 mg). DS1: Yield 7 % (6 mg), R_f = 0.4 (PE:EtOAc 1:1, v/v). DS2: yield 34 % (27 mg); mp = 121-123 °C, R_f = (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ -48.5 (*c* 0.7, $CHCl_3$). Chemical shifts are given for DS2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.54 NH (m, 1H), 5.47 H-1 ald (d, *J* = 4.8 Hz, 1H), 5.46 H-1 isoc (dd, *J* = 5.0 Hz, 1H), 5.13 H-6 ald (d, *J* = 9.2 Hz, 1H), 4.90 H-3 GulA (s, 1H), 4.56 H-3 ald (m, 1H), 4.53 H-3 isoc (dd, *J* = 8.0, 2.4 Hz, 1H), 4.43 H-4 ald (dd, *J* = 8.0, 1.6 Hz, 1H), 4.30 H-4 isoc (dd, *J* = 8.0, 1.8 Hz), 4.28 H-2 ald, H-4 GulA (m, 2H), 4.25 H-2 isoc (dd, *J* = 5.0, 2.4 Hz, 1H), 4.20 H-5 ald (dd, J = 9.2, 1.5 Hz, 2H), 4.13 H-5 GulA (m, 1H), 4.04 H-6 GulA (m, 2H), 3.97 H-5 isoc (m, 1H), 3.44 H-6 isoc (m, 2H), 1.50 – 1.27 CH_3-isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 167.4 CO, 165.2 CO, 113.9, Cq-isop, 109.6 Cq-isop, 109.4 Cq-isop, 109.0 Cq-isop, 97.7 Cq-isop, 96.5 C-1, 96.3 C-1, 87.5 C-3 GulA, 74.1 C-5 GulA, 73.3 C-4 GulA, 71.7 C-6, 71.2 C-4 isoc, 71.0 C-2 isoc, 70.9 C-2 ald, 70.5 C-3 ald, 70.2 C-3 isoc, 67.2 C-5 ald, 65.7 C-5 isoc, 59.9 C-6 GulA, 40.0 C-6 isoc, 28.8 CH_3-isop, 27.0 CH_3-isop, 26.2 CH_3-isop, 26.1 CH_3-isop, 25.8 CH_3-

isop, 25.2 CH_3-isop, 24.5 CH_3-isop, 24.2 CH_3-isop, 19.1 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{37}H_{55}NO_{18}$ 802.3497 Found 802.3519.

(3aR,5R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(((3aR,5S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)carbamoyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate (31): Yield 18 % (11 mg); mp = 152-156 °C; R_f = 0.4 (toluene:EtOAc 1:1); *d.r.* 87:13 (determined from the ^{1}H NMR spectrum); $[\alpha]_D^{22}$ + 57 (c 1, $CHCl_3$).Chemical shifts are given for major DS. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 NH (d, *J* = 8.9 Hz, 1H), 5.89 H-1 keton (d, *J* = 3.6 Hz, 1H), 5.84 H-1 isoc. (d, *J* = 3.8 Hz, 1H), 4.86 H-2 keton (d, *J* = 3.6 Hz, 1H), 4.54 H-4 keton (dd, *J* = 4.9, 3.9 Hz, 1H), 4.46 H-2 isoc (d, *J* = 2.9 Hz, 1H), 4.42 H-5 keton, (td, *J* = 6.4, 2.9 Hz, 1H), 4.33 – 4.28 H-5 isoc (m, 1H), 4.17 – 4.13 H-3 isoc, H-4 isoc, H-6 (m, 3H), 4.06 – 4.00 H-3 isoc, H-4 isoc, H-6 (m, 4H), 3.94 – 3.91 H-6 (m, 1H), 2.09 CH_3-ac. (s, 3H), 1.62 – 1.31 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 169.5 Cq-ac, 164.9 CO amid, 114.2 Cq-isop, 112.8 Cq-isop, 109.8 Cq-isop, 108.78 Cq-isop, 105.6 C-1, 104.6 C-1, 85.3 C-3 keton, 82.7 C-2 keton, 82.2 1 C-2 isoc, 79.3 C-4, 78.9 C-4, 75.3 C-5, 73.5 C-4, 65.2 C-6, 64.4 C-6, 52.9 C-3, [27.1, 26.9, 26.8, 26.75, 26.7, 26.67, 26.5, 26.49, 25.6, 25.5] CH_3-isop, 21.4 CH_3-ac. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{41}NO_{13}Na$ 610.2476; Found 610.2449.

(3aR,5R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(((3aR,5S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)carbamoyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl benzoate (32): Yield 12 % (8 mg); R_f = 0.31 (toluene:EtOAc 3:1, v/v); $[\alpha]_D^{22}$ + 34.8 (*c* 0.66 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 NH (d, *J* = 8.8 Hz, 1H), 7.93 benz-γ (dd, *J* = 8.2, 1.1 Hz, 2H), 7.58 benz-ε (dd, *J* = 11.8, 4.3 Hz, 1H), 7.43 benz-δ (t, *J* = 7.8 Hz, 2H), 6.12 H-1 impurity (d, *J* = 4.5 Hz, 1H), 5.94 H-1(d, *J* = 3.6 Hz, 1H), 5.87 H-1 (d, *J* = 3.8 Hz, 1H), 4.97 H-2 keton (d, *J* = 3.7 Hz, 1H), 4.60 H-5 (m, 1H), 4.57 H-4 (m, 1H), 4.55 H-2 isoc (d, *J* = 3.1 Hz, 1H), 4.41 H-5 (td, *J* = 6.8, 2.6 Hz, 1H), 4.37 H-6, H-4 (m, 1.5H), 4.23 – 3.39 H-3 isoc, H-4, H-6 (m, 5.5H), 1.64 – 1.33 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 165.5 CO amid, 165.0 CO ester, 134.0 benz-ε, 129.9 benz-γ, 129.4 benz-β, 128.8 benz-δ, 114.3 Cq-isop., 112.7 Cq-isop., 109.7 Cq-isop, 109.0 Cq-isop, 105.5 C-1, 104.7 C-1, 103.3 C-1 impurity, 85.7 C-3 keton, 83.0 C-2, 82.0 C-2, 79.2 C-4, 78.9 C-4, 75.1 C-5, 73.4 C-5, 65.4 C-6, 64.2 C-6, 52.7 C-3 keton, [27.1, 26.8, 26.81, 26.53, 26.51, 25.50, 25.4] CH_3-isop. HRMS: Calcd. for $C_{32}H_{43}NO_{13}$ $[M+Na]^+$ 672.2632 found 672.2627. Purification of the compound was not completely satisfying and compound contained truncated sugar component with 6.12 H-1 and 103.3 C-1.

General procedure for Ugi reactions: Aldehyde (0.1 mmol) and amine (0.1 mmol, 1 eq.) component were dissloved in 100 µL anhydrous MeOH in a glass vial and allowed to react for 1h, followed by the addition of acid (0.1 mmol, 1 eq.) and isocyanide (0.1 mmol, 1 eq.) component. The solution was allowed to stir for 24 h in closed vial at room temperature. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

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-(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)-2-(N-(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)acetamido)acetamide (33) Yield 72 % (60 mg). DS1: Yield 46 % (38 mg); *R* configuration; mp = 202-204 °C; R_f = 0.45 (benzin:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ -5 (c 1, $CHCl_3$).^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.54 H-4, H-1 (dd, J=8.0, 2.4, 3H), 4.23 – 4.01 H-1, H-5, H-3 (m, 8H), 3.95 – 3.87 H-6 (m, 3H), 3.78 H-6 (s, 1H), 3.73 – 3.58 H-1; H-6 (m, 3H), 2.87 H-1 (d, J=11.8, 1H), [2.26 (s, 3H), 1.51 (s, 3H), 1.48 (d, J=4.9, 8H), 1.45 (s, 9H), 1.33 (s, J=8.7, 6H), 1.31 (s, 6H), 1.28 (s, 3H)] CH_3 isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 110.1, 109.4, 108.9, 108.8, 73.0, 71.2, 70.7, 70.5, 70.3, 61.9, 61.2, 43.6, 27.1, 26.7, 26.2, 25.1, 24.3, 24.1, 23.2. Presence of rotamers. DS2: Yield 27 % (22 mg); mp = 158-161 °C; R_f=0.24 (PE:EtOAc 1:1); $[\alpha]_D^{22}$ - 24 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, CDCl3) d 6.47 NH (dd, J = 9.7, 3.2 Hz, 1H), 4.95 H-4 ald. (d, J = 3.0 Hz, 1H), 4.74 H-1 ald (s, 1H), 4.61 (ddd, J = 14.4, 8.3, 6.2 Hz, 2H), 4.56 H-5 ald (d, J = 2.9 Hz, 1H), 4.54 H-1 amine (d, J = 3.0 Hz, 1H), [4.53 (s, 1H), 4.28 (d, J = 2.8 Hz, 1H), 4.20 (m, 4H)] H-3, H-4, H-5, 4.11 H-1 isoc (m, 3H), 3.94 H-6 ald (dd, J = 12.8, 1.7 Hz, 1H), 3.81 (ddd, J = 12.6, 8.8, 1.6 Hz, 2H), 3.74 H-1 amine (d, J = 3.0 Hz, 1H), 3.71 H-6 ald (s, J = 15.6 Hz, 2H), 3.63 (dd, J = 26.4, 12.9 Hz, 3H), 3.09 H-1 isoc (dd, J = 14.7, 3.5 Hz, 1H), 2.36 CH3-ac (s, 3H), 1.69 - 1.15 CH3-isop (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 174.2, 166.5, 110.8, 110.1, 109.4, 109.1, 109.1, 108.7, 103.1, 103.0, 102.9, 73.1, 71.4, 71.2, 71.1, 70.7, 70.7, 70.6, 70.3, 70.1, 62.1, 62.1, 61.5, 49.9, 44.9, 27.0, 26.9, 26.8, 26.3, 26.2, 26.1, 26.0, 25.1, 24.5, 24.4, 24.3, 23.1. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{39}H_{61}N_2O_{17}$ 829.3970; Found 829.3970.***N*-(2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)-*N*-(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)benzamide (34)**: Yield 89 % (79 mg); mp 145-147 °C; R_f = 0.26 (PE:EtOAc 1:1), 0.55

(PE:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ - 46 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 benz (s, 1H), 7.43 benz (s, 1H), 7.37 – 7.29 benz (m, 3H), 6.66 NH (d, *J* = 6.9 Hz, 1H), 5.20 C-1 ald (s, 1H), 4.97 (s, 1H), 4.81 H-1 amine (d, *J* = 15.2 Hz, 1H), 4.77 H-3* (s, 1H), 4.61-4.10 H-5, H-4, H-3 (m), 3.99-3.88 H-1 amin (m, 4H), 3.78-3.14 H-6 (m, 6H), 1.57-1.25 CH_3-isop (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 174.5 CO, 166.8 CO, 135.5 benz, 130.3 benz, 129.7 benz, 128.6 benz, 128.4 benz, 110.8 Cq-isop., 109.5 Cq-isop, 109.2 Cq-isop, 108.8 Cq-isop, 103.6 C-2, 103.1 C-2, 103.0 C-2, [72.9, 71.4, 71.3, 71.0, 70.9, 70.8, 70.6, 70.2] C-5, C-4, C-3, 67.0 C-1 ald, 62.6 C-6, 62.2 C-6, 61.7 C-6, 50.2 C-1 amine, 45.3 C-1 isoc, 44.0 C-1 isoc, 27.3 CH_3-isop, 27.0 CH_3-isop, 26.8 CH_3-isop, 26.5 CH_3-isop, 26.3 CH_3-isop, 26.3 CH_3-isop, 26.1 CH_3-isop, 24.5 CH_3-isop., 24.33 CH_3-isop, 24.3 CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{44}H_{63}N_2O_{17}$ 891.4127; Found 891.4131.

tert-butyl (1-oxo-1-((2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)-3-phenylpropan-2-yl)carbamate (35): Yield 67 % (71 mg). DS1: Yield 38 % (40 mg); mp 168-170 °C; R_f = 0.37 (toluene:EtOAc 3:2, v/v); $[\alpha]_D^{22}$ - 49 (*c* 1 $CHCl_3$).^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39 – 7.35 Phe (m, 1H), 7.21 Phe (d, *J*=6.6, 4H), 7.15 NH (d, *J*=6.2, 1H), 4.96 H-1 ald., Phe-α, NH (d, *J*=28.6, 3H), 4.68 – 4.42 H-3, H-4, H-5 (m, 4H), 4.26 – 4.08 H-3, H-4, H-5 (m, 7H), 3.89 H-6, H-1 (t, *J*=28.2, 3H), 3.83 – 3.51 H-6, H-1 (m, 6H), 3.13 H-1 (d, *J*=72.2, 3H), 1.50 CH_3 (dd, *J*=24.4, 13.2, 16H), 1.43 CH_3 (d, *J*=9.3, 5H), 1.34 – 1.26 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 128.6 Phe, 128.3 Phe, 126.4 Phe, 110.3 Cq-isop, 109.4 Cq-isop, 109.2 Cq-isop, 108.6 Cq-isop, 102.6 C-2, 102.2 C-2, 72.4 C-1 ald, [71.3, 71.2, 71.0, 70.8, 70.5, 70.5] C-3, C-4, C-5, 61.7 C-6, 61.6 C-6 , 52.2 Phe- α, 44.5 C-1 amine, 38.4 Phe β, [29.9, 28.5, 27.0, 26.7, 26.2, 25.7, 24.4] CH_3 isop. HRMS ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{51}H_{75}N_3O_{19}Na$ 1056.4892; Found 1056.4899. DS2: Yield 29 % (31 mg); mp 150-152 °C; R_f = 0.22 (toluene:EtOAc 3:2, v/v); $[\alpha]_D^{22}$ - 31 (*c* 1 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 Phe (d, *J*=6.1, 1H), 7.33 Phe (dd, *J*=7.8, 3.9, 1H), 7.26 NH (d, *J*=7.4, 1H), 7.18 Phe (d, *J*=7.2, 1H), 7.15 Phe (d, *J*=7.6, 2H), 5.68 H-1 ald. (s, 1H), 5.26 Phe-α (dd, *J*=13.6, 5.5, 1H), 5.19 H-4 (d, *J*=2.8, 1H), 4.75 NH (d, *J*=8.2, 1H), 4.57 C-3 (dd, *J*=7.8, 2.9, 1H), 4.54 – 4.46 C-4 (m, 1H), 4.37 H-1 Fru amin (d, *J*=15.4, 1H), 4.13 H-1 isoc, H-3, H-4 (ddd, *J*=21.1, 11.3, 5.0, 3H), 4.07 – 3.99 H-4 (m, 1H), 3.86 – 3.77 H-6 (m, 1H), 3.69 H-6 amine, H-5, H-3 (ddd, *J*=42.0,

24.2, 14.8, 3H), 3.05 Phe-β (t, *J*=16.0, 1H), 2.91 CH_2 Phe (dd, *J*=14.8, 11.3, 1H), 1.56 – 1.09 CH_3 Boc, CH_3 isop (49H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 175.1 CO, 166.5 CO, 156.1 Phe, 138.0 Phe, 129.2 Phe, 129.0 Phe, 128.8 Phe, 128.8 Phe, 128.6 Phe, 126.6 Phe, 109.3 Cq-isop, 109.3 Cq-isop, 109.2 Cq-isop., 109.1 Cq- isop, 108.3 Cq-isop, 108.2 Cq-isop, 104.8 C-2, 103.1 C-2, 102.5 C-2, 80.3 Cq-Boc, [72.8, 72.7, 71.3, 70.9, 70.7, 70.6] C-5, C-4, C-3, 63.1 C-1 ald, [62.4, 61.9, 61.5] C-6, 51.1 Phe-α, 50.8 C-1 amin, 47.8 C-1 isoc, 37.4 Phe-β, [28.6, 27.6, 27.1, 26.5, 26.4, 25.9, 25.9, 25.6, 25.4, 24.3, 24.3, 23.7] CH_3-Boc, isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{51}H_{75}N_3O_{19}Na$ 1056.4892; Found 1056.4895.

(3aS,3bR,7aS,8aR)-2,2,5,5-tetramethyl-*N*-(2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)-*N*-(((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)hexahydro [1,3]dioxolo[4',5':4,5]cyclopenta[1,2-d][1,3]dioxine-8a-carboxamide (36): Yield 32 % (34 mg). DS1: Yield 17 % (18 mg); mp = 165-167 °C, R_f = 0.375 (PE:EtOAc 2:3, v/v); $[\alpha]_D^{22}$ - 15 (*c* 0.6, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.22 – 7.14 NH (m, 1H), 5.28 H-1 ald (s, 1H), 5.25 H-3 GulA (s, 1H), 4.91 H-3 ald* (d, *J*=2.9, 1H), 4.60 – 4.55 H-3 (m, 1H), 4.49 H-4, H-3 (ddd, *J*=24.0, 7.7, 2.3, 2H), 4.34 H-1 amine (d, *J*=15.5, 1H), 4.25 H-5 (s, 1H), 4.14 H-6, H-5, H-4, (ddd, *J*=23.5, 19.1, 7.6, 7H), 4.02 H-5, H-4 (dt, *J*=13.9, 6.9, 2H), 3.98 – 3.81 H-6 (m, 4H), 3.79 – 3.58 H-1 ald, H-1 isoc, H-6 (m, 6H), 3.42 – 3.36 H-1 isoc (m, 1H), 1.75 – 1.11 CH_3-isop (64H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 169.7 CO, 167.9 CO, 113.3 C-2 GulA, 113.1 Cq-isop, 109.2 Cq-isop., 108.9 Cq-isop., 108.6 Cq-isop., 105.6 C-2, 103.1 C-2, 102.9 C-2, 97.9 Cq-isop, 89.0 C-3 GulA, [74.2, 74.1, 73.5, 73.2, 72.1, 71.2, 71.0, 70.9, 70.7, 70.5] C-5, C-4, C-3, 66.0 C-1 ald, 61.8 C-6, 61.6 C-6, 59.5 C-6, 52.5 C-1 amine, 46.9 C-1 isoc, [28.6, 27.5, 27.4, 27.2, 26.6, 26.4, 26.3, 25.3, 24.6, 24.3, 19.3] CH_3-isop. DS2: Yield 15 % (16 mg); mp = 164-165 ºC; R_f = 0.24 (PE:EtOAc 2:3, v/v); $[\alpha]_D^{22}$ + 18 (c 0.65, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 NH (m, 2H), 5.52 H-3 GulA (s, 1H), 5.05 H-3 ald (d, *J* = 2.2 Hz, 1H), 5.01 H-1 ald. (s, 1H), 4.72 H-1 amine (m, 1H), 4.53 H-6 (m, 3H), 4.40 H-5 ald.(m, 1H), 4.28 H-5 GulA (m, 1H), 3.88 H-6; H-1 amine, H-4 ald. (m, 16H), 3.34 H-6 (d, *J* = 12.8 Hz, 1H), 2.76 H-1 isoc (dd, *J* = 14.6, 4.8 Hz, 1H), 1.48 – 1.17 CH_3-isop (64H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 166.6 CO, 165.7 CO, 114.0 C-2 GulA, 113.7 Cq-isop, 109.4 Cq-isop, 109.1 Cq-isop, 108.44 Cq-isop, 108.4 Cq-isop, 108.3 Cq-isop, 108.2 Cq-isop, 105.9 C-2, 103.9 C-2, 102.8 C-2, 97.9 Cq-isop GulA, 88.3 C-3 GulA, 75.8 C-4 GulA, [74.6, 74.0, 72.5, 72.4, 71.3, 71.2, 71.0, 70.9, 70.8, 70.7, 70.7, 70.5, 69.5] C-5, C-4, C-3, 63.9 C-1 ald, 62.1, 61.8, 61.6,

60.7, 59.4, 51.6, 47.5, 45.5, 28.4 CH_3-isop, 27.7 CH_3-isop, 27.0 CH_3-isop, 26.9 CH3-izop, 26.85 CH3-izop, 26.58 CH3-izop, 26.45 CH3-izop, 26.36 CH3-izop, 26.04 CH_3-isop, 26.0 CH_3-isop, 25.7 CH_3-isop, 24.5 CH_3-isop, 24.3 CH_3-isop, 23.8 CH_3-isop, 23.3 CH_3-isop, 18.95 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{49}H_{74}N_2O_{22}Na$ 1065.4631; Found 1065.4613.

(3aS,3bR,7aS,8aR)-*N*-benzyl-2,2,5,5-tetramethyl-*N*-(2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)tetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxamide (37): Yield 47 % (42 mg). DS1: *R* configuration; Yield 24 % (21 mg), mp = 160-162 °C, R_f = 0.34 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 11 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 Ph (d, *J* = 7.2 Hz, 1H), 7.20 Ph (t, *J* = 7.4 Hz, 2H), 7.12 Ph (t, *J* = 7.4 Hz, 2H), 7.05 – 7.02 NH (m, 1H), 5.43 H-3 GulA (s, *J* = 13.6 Hz, 1H), 5.19 H-4 ald (s, 1H), 5.11 CH_2-benzyl (d, *J* = 15.5 Hz, 1H), 5.08 H-1 ald (s, 1H), 4.87 CH_2 benzyl (d, *J* = 15.4 Hz, 1H), 4.52 H-3 isoc (d, *J* = 7.8 Hz, 1H), 4.45 H-3 ald (d, *J* = 7.6 Hz, 1H), 4.28 – 4.00 H-3, H-4, H-5 (m), 3.95 H-6 ald (dd, *J* = 26.9, 12.1 Hz, 1H), 3.87 – 3.74 H-6 GulA, H-6 isoc (m, 1H), 3.74 – 3.55 H-1 isoc (m, 1H), 2.67 H-1 isoc (m, 1H), 1.63 – 1.23 CH_3-isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 166.4 CO, 165.8 CO, 138.7 Ph, 137.9 Ph, 128.5 Ph, 127.8 Ph, 126.5 Ph, 114.0 Cq-isop., 113.4 C-2 GulA, 109.4 Cq-isop, 108.7 Cq-isop, 108.4 Cq isop, 105.4 C-2 ald, 102.6 C-2 isoc, 97.9 Cq-isop, 88.0 C-3 GulA, [75.9, 72.3, 72.2, 71.5, 71.2, 71.1, 71.0, 70.4, 69.6] C-3, C-4, C-5, 63.9 C-1 ald, 61.9 C-6, 61.6 C-6, 59.5 C-6, 49.6 CH_2 benzyl, 45.3 C-1 isoc, [28.4, 27.2, 26.9, 26.8, 26.7, 26.4, 26.2, 25.7, 25.7, 24.4, 23.5, 19.0] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3969. DS2: Yield 23 % (20 mg), mp = 165-168 °C, Rf = 0.25 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 4 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.36 Ph (m, 1H), 7.17 – 7.11 Ph (m, 3H), 7.04 Ph, NH (m, 1H), 5.42 C-3 GulA (s, 1H), 5.38 H-1 ald (s, 1H), 5.34 H-4 ald (d, *J* = 2.8 Hz, 1H), 5.12 CH_2 benzyl (d, *J* = 16.2 Hz, 1H), 4.93 CH_2 benzyl (d, *J* = 16.2 Hz, 1H), 4.63 – 4.53 H-3 ald (m, 1H), 4.47 H-3 isoc (m, 1H), 4.24 – 3.95 H-5, H-6 (m), 1.84 – 1.04 CH_3-isop (m, H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 167.7 CO, 165.7 CO, 138.6 Ph, 128.0 Ph, 127.3 Ph, 126.8 Ph, 113.3 Cq-isop, 113.1 C-2 GulA, 109.8 Cq-isop, 109.6 Cq-isop, 109.3 Cq-isop, 108.7 Cq-isop, 104.2 C-2 ald, 102.5 C-2 ald, 97.5 Cq-isop, 87.5 C-3 GulA, [75.2, 74.3, 72.9, 72.8, 72.3, 71.6, 71.4, 71.4, 71.2, 71.1, 71.1, 71.0, 70.9, 70.8, 70.7, 70.5], 62.8 C-1 ald, 62.6 C-6, 62.1 C-6, 59.8 C-6, 49.9 CH_2-benzyl, 46.8 C-1 isoc, [28.8, 27.1, 27.0, 26.6, 26.5, 26.5, 26.0, 25.6, 24.6, 18.8] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3909.

methyl (2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)-L-phenylalaninate (38a): Yield 67 % (46 mg). DS1: Yield 36 % (25 mg), mp = 115-116 ºC, R_f = 0.44 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ - 4 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.22 Phe-ε (d, *J*=7.5, 2H), 7.17 Phe-ζ (dd, *J*=10.5, 4.2, 1H), 7.14 Phe-δ (d, *J*=7.1, 2H), 6.63 NH-amid (dd, *J*=8.6, 2.9, 1H), 4.78 H-3 (d, *J*=2.7, 1H), 4.60 – 4.54 H-4 (m, 2H), 4.21 – 4.15 H-5, H-3 (m, 3H), 4.03 – 3.93 H-1 isoc (m, 1H), 3.91 – 3.81 H-6 (m, 2H), 3.75 – 3.66 H-6 (m, 2H), 3.64 – 3.58 Phe-α (m, 1H), 3.57 CH_3-methyl (s, 3H), 3.33 H-1 ald. (d, *J*=9.1, 1H), 3.19 H-1 isoc (dd, *J*=14.1, 3.3, 1H), 3.02 Phe-β (dd, *J*=13.5, 8.1, 1H), 2.92 Phe-β (dd, *J*=13.5, 6.4, 1H), 2.51 NH-amine (dd, *J*=9.1, 5.0, 1H), 1.50 CH_3-isop (s, 3H), 1.48 CH_3-isop (s, 3H), 1.44 CH_3-isop (s, 3H), 1.42 CH_3-isop (s, 3H), 1.37 CH_3-isop (s, 3H), 1.35 CH_3-isop (s, 3H), 1.32 CH_3-isop (s, 3H), 1.31 CH_3-isop. (s, 3H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 173.6 CO, 170.4 CO, 137.4 Phe-γ, 129.4 Phe-δ, 128.6 Phe-ε, 126.9 Phe-ζ, 109.5 Cq-isop, 109.2 Cq-isop, 109.0 Cq-isop, 108.7 Cq isop., 103.8 C-2, 102.6 C-2, [71.9, 71.7, 71.3, 71.2, 71.1, 70.8, 70.8, 70.7, 70.7, 70.6, 70.6, 70.5] C-3, C-4, C-5, 64.1 C-1 ald., 62.1 Phe-α, 61.8 C-6, 61.5 C-6, 51.7 CH_3, 45.5 C-1 isoc, 39.4 Phe-β, 26.9 CH_3 isop, 26.8 CH_3 isop, 26.7 CH_3-isop, 26.6 CH_3-isop, 26.3 CH_3-isop., 26.2 CH_3-isop, 26.1 CH_3-isop, 25.8 CH_3-isop, 24.5 CH_3-isop, 24.4 CH_3 isop, 24.2 CH_3 isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{35}H_{50}N_2O_{13}Na$ 707.3391; Found 707.3376.DS2: Yield 31 % (21 mg), mp = 112-113 ºC, R_f = 0.39 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 18 (*c* 1 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.62 – 7.54 NH amide (m, 1H), 7.22 Phe-ε (d, *J*=7.2, 2H), 7.18 – 7.15 Phe-ζ, Phe-δ (m, 3H), 4.78 H-3 (d, *J*=2.7, 1H), 4.58 – 4.49 H-4 (m, 2H), 4.17 H-5, H-3 (ddd, *J*=10.7, 6.8, 5.2, 3H), 3.87 – 3.77 H-1 isoc., H-6 (m, 3H), 3.70 – 3.60 H-6, Phe-α (m, 3H), 3.53 H-1 ald, CH_3-methyl (d, *J*=8.6, 4H), 3.28 H-1 isoc. (dd, *J*=13.8, 3.4, 1H), 3.02 – 2.94 Phe-β (m, 1H), 2.90 Phe-β (dt, *J*=13.5, 6.8, 1H), 2.74 NH amine (d, *J*=6.0, 1H), 1.49 CH_3-isop (s, 3H), 1.44 CH_3-isop (d, *J*=3.0, 6H), 1.43 CH_3-isop (s, 3H), 1.39 CH_3-isop (s, 3H), 1.32 CH_3-isop (s, 3H), 1.30 CH_3-isop (s, 3H), 1.20 CH_3-isop (s, 2H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 173.5 CO, 170.6 CO, 137.4 Phe-γ, 129.7 Phe-δ, 128.5 Phe-ε, 126.8 Phe-ζ, 109.3 Cq-isop, 108.9 Cq-isop, 108.5 Cq-isop, 102.8 C-2, 102.5 C-2, [71.9, 71.7, 71.1, 70.8, 70.6, 70.5 C-3, C-4, C-5, 67.7 C-1 ald, 62.0 Phe-α, 61.8 C-6, 61.5 C-6, 51.7 CH_3-methyl, 46.5 C-1 isoc, 38.2 Phe-β, 26.7 CH_3-isop, 26.6 CH_3-isop, 26.3 CH_3-isop, 26.2 CH_3-isop, 25.5 CH_3-isop, 25.4 CH_3-isop, 24.4 CH_3-isop, 24.2 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{35}H_{50}N_2O_{13}Na$ 707.3391; Found 707.3374.

benzyl *N*-acetyl-*N*-(2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)-L-tyrosinate (40): Yield 73 % (61 mg). DS1: Yield 54 % (45 mg), R_f = 0.51 (PE:EtOAc 1:2, v/v). NMR and MS spectra indicate presence of a three-component Ugi product along with DS1 of **40**. Chemical data are therefore given for DS2. DS2: Yield 19 % (16 mg), mp = 136-138 ºC, R_f = 0.41 (PE:EtOAc 1:2, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 NH (dd, *J* = 8.8, 3.4 Hz, 1H), 7.41 – 7.26 benz (m, 3H), 7.23 benz (dd, *J* = 7.5, 1.8 Hz, 2H), 7.08 Tyr (d, *J* = 8.4 Hz, 2H), 6.64 Tyr (d, *J* = 8.5 Hz, 2H), 5.18 (m, 2H), 5.05 – 4.99 (m, 1H), 4.61 (dd, *J* = 7.9, 2.7 Hz, 1H), 4.55 (dd, *J* = 7.9, 3.1 Hz, 1H), 4.26 – 4.18 (m, 4H), 4.14 (s, 1H), 4.09 (dd, *J* = 14.2, 8.8 Hz, 1H), 4.01 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.91 – 3.83 (m, 2H), 3.80 – 3.65 (m, 5H), 3.29 – 3.21 Tyr (m, 2H), 2.02 (s, 3H) CH_3 ac, [1.49 (d, *J* = 7.0 Hz, 6H), 1.46 (d, *J* = 8.8 Hz, 3H), 1.33 (d, *J* = 3.9 Hz, 3H), 1.30 (d, *J* = 7.4 Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.03 (s, 3H)]CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 174.2 CO, 170.4 CO, 166.3 CO, 154.2 Tyr, 135.5 Tyr, 132.0 benz, 131.1 Tyr, 130.7 Tyr, 128.8 benz, 128.6 benz, 128.4 Tyr, 115.1 Tyr, 110.4 Cq isop, 109.6 Cq isop, 109.5 Cq isop, 108.9 Cq isop, 103.2 C-2, 102.5 C-2, [71.4, 70.9, 70.6, 70.3, 70.2, 69.7, 69.0, 68.7] C-1, C-3, C-4, C-5, 67.5 benz, 62.5 C-6, 61.7 C-6, 45.5 Tyr, 33.7 C-1, [26.7, 26.6, 26.1, 25.9, 25.9, 25.5, 24.2, 23.8] CH_3-isop, 23.8 CH_3 ac. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{56}N_2O_{15}Na$ 863.3578; Found 863.3545.

benzyl 2-(2-((tert-butoxycarbonyl)amino)-3-(4-((tert-butoxycarbonyl)oxy)phenyl)-*N*-(2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)propanamido)-3-(4-hydroxyphenyl)propanoate (41): Yield 49 % (58 mg), mp = 128-130 °C, R_f = 0.28 (PE:EtOAc 3:2, v/v), $[\alpha]_D^{22}$ = + 25 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 Tyr, Ph (m), 7.26 Tyr (m), 7.21 Tyr (m), 7.17 Tyr (m), 7.03 Tyr, NH (m), 6.66 Tyr (m), 6.44 NH (s, 1H), 5.55 (s, 1H), 5.50 (s, 1H), 5.22 (d, *J* = 9.3 Hz, 1H), 5.12 (s, 1H), 5.08 (d, *J* = 9.9 Hz, 1H), 5.00 (t, *J* = 12.1 Hz, 1H), 4.91 (m, 1H), 4.84 (s, 1H), 4.59 (s, 1H), 4.54 (d, *J* = 5.2 Hz, 1H), 4.14 (m, 1H), 4.06 (d, *J* = 2.1 Hz, 1H), 3.80 (d, *J* = 12.9 Hz, 1H), 3.67 (m, 1H), 3.45 (m, 1H), 3.37 (d, *J* = 11.1 Hz, 1H), 3.28 (dd, *J* = 28.3, 12.3 Hz, 1H), 3.19 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.79 (dd, *J* = 13.6, 8.9 Hz, 1H), 2.70 (m, 1H), 1.64 – 1.22 CH_3-Boc, CH_3-isop (42H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 154.7 Tyr, 131.3 Tyr, 131.1 Tyr, 130.6 Tyr, 128.6 Tyr, 128.4 Tyr, 128.1 Tyr, 120.9 Tyr, 115.3 Tyr, 115.0 Tyr, 108.6 Cq-isop, 79.5 Cq-Boc, 79.2 Cq-Boc, 72.1, 71.0, 70.97, 70.5, 66.6 CH_2-benzyl, 61.8 C-6, 61.6 C-6, 51.5 Tyr-α, 47.3 C-1 isoc, 47.0 Tyr-β, 40.4 Tyr-β, [28.6, 28.4, 27.9] CH_3-Boc, [27.1 , 26.6, 26.4, 26.2,

26.0, 25.4, 24.7, 24.5] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{60}H_{79}N_3O_{20}Na$ 1184.5155; Found 1184.5170.

benzyl (2-oxo-1-((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)amino)ethyl)-L-tyrosinate (41a): Yield 16 % (13 mg), mp = 118-120 °C, Rf = 0.17 (PE:EtOAc 3:2, v/v), $[\alpha]_D^{22}$ = - 6 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.29 - 7.25 Tyr (m), 7.15 - 6.99 Tyr (m), 6.69 - 6.63 Tyr (m), 5.13, 5.07, 4.82, 4.80, 4.77, 4.75, 4.63, 4.56, 4.48, 4.43, 4.42, 4.42, 4.41, 4.41, 4.12, 4.11, 3.84, 3.82, 3.82, 3.72, 3.70, 3.68, 3.67, 3.66, 3.64, 3.64, 3.59, 3.57, 2.98, 2.95, 1.61 – 1.15 CH_3-Boc, CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 172.4 CO, 134.5 Tyr, 151.8 Tyr, 130.5 Tyr, 128.5 Tyr, 128.4 Tyr, 121.3 Tyr, 115.3 Tyr, 109.0 Cq-isop, 81.3 Cq-Boc, 71.2, 70.7, 70.1, 66.4 CH_2-benzyl, 65.1, 62.4 C-6, 61.6 C-6, 60.0, 50.3 Tyr-α, 47.4 C-1 isoc, 38.3 Tyr-β, 36.2 Tyr-β, [28.5, 27.9] CH_3-Boc, [26.8, 26.6, 25.8, 24.9, 24.3] CH_3-isop. HRMS: Calcd. for $C_{60}H_{79}N_3O_{20}$ $[M+Na]^+$ 1184.5155 found 1184.5138. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{55}N_2O_{14}$ 799.3653; Found 799.3652.

3aS,3bR,7aS,8aR)-*N*-benzyl-2,2,5,5-tetramethyl-*N*-(2-oxo-2-((((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethylhexahydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole)-3a-yl)methyl)amino)-1-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl)tetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxamide (42): Yield 60 % (54 mg). DS1: Yield 30 % (27 mg); mp = 179-180 °C; R_f = 0.32 (toluene:EtOAc 1:1, v/v$[\alpha]_D^{22}$ + 4.19 (*c* 0.77, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 Ph (dt, *J* = 16.2, 7.7 Hz, 1H), 7.12 – 7.03 Ph (m, 1H), 6.94 NH (d, *J* = 4.5 Hz, 1H), 5.60 H-3 GulA (s, 1H), 5.55 H-1 ald (s, 1H), 5.38 H-3 ald (s, 1H), 5.36 CH_2-benzyl (s, 1H), 5.23 CH_2-benzyl (d, *J* = 16.1 Hz, 1H), 4.60 H-3 isoc (s, 1H), 4.48 – 4.40 (m, 1H), 4.33 – 3.80 (m, 4H), 3.79 – 3.74 (m, 1H), 3.66 H-6 isoc (d, *J* = 12.9 Hz, 1H), 3.61 H-6 isoc (d, *J* = 13.1 Hz, 1H), 3.42 H-1 isoc (dd, *J* = 14.0, 8.6 Hz, 1H), 2.63 H-1 isoc (dd, *J* = 14.0, 3.8 Hz, 1H), 1.68 – 1.03 (m, 24H) CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 167.7 CO, 167.3 CO, 138.3 Ph, 128.09 Ph, 127.4 Ph, 126.4 Ph, 115.1 C-2 ald, 113.5 Cq-isop, 113.3 C-2 GulA, 112.0 Cq-isop, 109.0 Cq-isop, 108.1 Cq-isop, 102.9 C-2 isoc, 98.6 Cq-isop, 97.8 Cq-isop, 88.3 C-3 ald, 86.0 C-3, [75.4, 74.9, 73.0, 72.97, 72.9, 72.3, 70.6, 70.5] C-3, C-4, C-5, 61.5 C-1 ald, 61.4 C-6, 60.8 C-6, 59.3 C-6, 48.9 CH_2-benzyl, 46.2 C-1 ald, [29.0, 29.0, 27.3, 27.2, 26.9, 26.3, 26.3, 25.9, 25.24, 24.3, 20.7, 19.2, 18.9] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3945. DS2: *R* configuration,

Yield 30 % (27 mg); mp = 150-154 °C; R_f = 0.21 (toluene:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 24 (*c* 1 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.24 Ph (m, 2H), 7.12 Ph (t, *J* = 7.5 Hz, 2H), 7.06 Ph (t, *J* = 7.3 Hz, 1H), 7.01 – 6.94 NH (m, 1H), 5.38 H-3 GulA (s, 1H), 5.29 H-1 ald (s, 1H), 5.27 H-3 GulA (s, 1H), 5.13 CH_2-benzyl (d, *J* = 15.8 Hz, 1H), 4.96 CH_2-benzyl (d, *J* = 15.8 Hz, 1H), 4.53 H-3 ald (dd, *J* = 7.9, 2.5 Hz, 1H), 4.28 H-4 GulA (s, 1H), 4.19 H-6 ald, GulA (ddd, *J* = 16.6, 15.7, 6.2 Hz, 4H), 4.13 H-4 ald, isoc (s, 2H), 4.07 H-5 ald, isoc, GulA (ddd, *J* = 14.9, 9.3, 2.4 Hz, 3H), 3.81 H-6 isoc (dd, *J* = 12.8, 1.4 Hz, 1H), 3.72 – 3.69 H-1 isoc (m, 1H), 3.66 H-6 isoc (d, *J* = 13.2 Hz, 1H), 2.73 – 2.67 H-1 isoc (m, 1H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 166.5 CO, 165.5 CO, 138.8 Ph, 128.7 Ph, 127.75 Ph, 126.5 Ph, 115.2 C-2 ald, 113.9 Cq-isop., 113.4 C-2 GulA, 112.2 Cq-isop., 109.4 Cq-isop, 108.4 Cq-isop., 102.7 C-2 isoc, 97.8 Cq-isop, 97.6 Cq-isop., 87.9 C-3, 87.7 C-3, [75.7, 74.0, 73.0, 72.1, 71.6, 71.1, 70.4] C-5, C-4, C-3, C-2, 62.1 C-1 ald, 61.6 C-6, 60.4 C-6, 59.4 C-6, 49.1 CH_2-benzyl, 45.3 C-1 isoc, [29.0, 28.6, 28.2, 26.8, 26.7, 26.2, 25.7, 25.67, 24.4, 19.3, 18.9] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}$ 913.3946; Found 913.3904.

***N*-(2-oxo-1-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)-2-((((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)amino)ethyl)-*N*-(((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)methyl)benzamide (43)**: Yield 64 % (57 mg), mp = 235-237 ºC; R_f = 0.25 (PE:EtOAc 1:1, v/v); *d.r.* 74:26; $[\alpha]_D^{22}$ - 25 (*c* 1, $CHCl_3$).Chemical shifts are given for the major diastereoisomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.58 NH (s, 1H), 7.33 benz (d, *J*=15.7, 5H), 5.02 H-1 ald (s, *J*=11.9, 1H), 5.00 H-3 (s, 1H), 4.88 H-3 (s, 1H), 4.69 H-1 amine (m, 1H), 4.54 H-3 (s, 1H), 4.32 H-1 isoc, H-5, H-4 (m, 15H), 4.06 H-1 amine, H-6, H-4, H-5 (m, 4H), 3.59 H-1 isoc (m, 1H), 1.39 CH_3-isop. (m, 36 H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 174.5 CO, 166.7 CO, 136.7 benz, 130.6 benz, 128.8 benz, 128.2 benz, 114.73 Cq-isop, 114.5 Cq-isop, 114.3 C-2, 113.0 Cq-isop., 112.4 C-2, 112.3 Cq-isop, 97.6 Cq-isop, 97.6 Cq-isop, 97.4 Cq-isop, 87.4 C-3, 86.3 C-3, 84.5 C-3, [75.3, 73.9, 73.8, 73.6, 73.3, 73.0, 72.9, 72.7, 71.7, 71.5, 70.8, 70.4, 68.7] C-4, C-5, 67.7 C-1 ald, 62.1 C-6, 60.8 C-6, 60.6 C-6, 60.2 C-6, 48.8 C-1, 43.0 C-1, 42.2 C-1, 29.9 CH_3-isop, 29.2 CH_3-isop, 29.1 CH_3-isop, 28.8 CH_3-isop, 28.6 CH_3-isop, 28.2 CH_3-isop, 28.0 CH_3-isop, 27.8 CH_3-isop, 27.6 CH_3-isop, 27.4 CH_3-isop, 26.6 CH_3-isop, 19.3 CH_3-isop, 18.9 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3922.

***N*-((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-2-(*N*-((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)acetamido)-2-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)acetamide (44):** Yield 55 % (46 mg). DS1: Yield 31 % (26 mg); mp = 145-148 ºC; R_f = 0.41 (perolether:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ + 78.9 (*c* 0.646, $CHCl_3$). ^{1}H NMR (600 MHz, CDCl3) δ 6.52 NH (d, *J* = 9.4 Hz, 1H), 5.85 H-1 amine (d, *J* = 3.7 Hz, 1H), 5.71 H-1 isoc (d, *J* = 3.9 Hz, 1H), 4.61 H-2 isoc (m, 1H), 4.59 H-3 ald (s, 1H), 4.54 H-2 amine (m, 1H), 4.39 H-5 amine (dd, *J* = 6.8, 1.8 Hz, 1H), 4.31 H-5 isoc (dd, *J* = 7.0, 3.0 Hz, 3H), 4.05 H-3 isoc, H-6 isoc (m, 2H), 3.81 H-4 isoc (dd, *J* = 8.9, 3.7 Hz, 1H), 3.67 H-1 ald (1H), 2.87 H-3 amine (m, 1H), 2.18 CH_3-ac (s, 3H), 1.41 CH_3-isop. (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 171.9 CO, 114.4 Cq-isop, 113.8 C-2-Sor, 112.7 Cq-isop., 112.2 Cq-isop, 109.8 Cq-isop, 109.4 Cq-isop, 104.8 C-1 amine, 104.2 C-1 isoc, 97.7 Cq-isop, 85.6 C-3 ald, 80.7 C-4, 79.6 C-4, 79.1 C-2, 78.8 C-2, 75.7 C-5, 75.0 C-4, 73.3 C-5, 72.9 C-2, 65.5 C-6 amine, 64.7 C-1 ald, 63.7 C-6 ald, 61.0 C-3 isoc, 60.7 C-6 isoc, 52.9 C-3 amine, [29.7, 27.9, 26.9, 26.9, 26.7, 26.7, 26.6, 26.5, 25.5, 25.1, 18.8] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{60}N_2O_{17}Na$ 851.3790; Found 851.3760.DS2: Yield 24 % (20 mg); mp = 139-142 ºC; R_f = 0.26 (benzin:EtOAc 1:2, v/v); $[\alpha]_D^{22}$ + 90 (*c* 0.66, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 NH (d, *J* = 7.5 Hz, 1H), 5.81 H-1 amine (m, 2H), 5.75 H-1 isoc (d, *J* = 3.8 Hz, 1H), 4.94 H-3 ald (s, 2H), 4.74 H-2 isoc (m, 1H), 4.65 H-2 amine (m, 2H), 4.06 H-3 isoc, H-4; H-5, H-6 (m), 3.67 H-1 ald (s, 1H), 2.93 (d, *J* = 11.2 Hz, 1H), 2.86 H-3 amine (m, 1H), 1.54 – 1.32 CH_3-isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 170.8 CO, 113.8 C-2, 112.9 Cq-isop, 112.7 Cq-isop, 112.5 Cq-isop., 109.9 Cq-isop, 109.7 Cq-isop, 104.8 C-1 amine, 104.7 C-1 isoc, 97.8 Cq-isop, 86.0 C-3 ald, 79.5 C-4 isoc, 79.1 C-2 amine, 78.5 C-4 amine, 77.7 C-2 isoc, 76.8 C-5, 75.89 C-5, 73.4 C-4, 73.0 C-4, 66.5 C-1 ald, 65.7 C-6 amine, 65.11 C-6 ald, 63.25 C-3 isoc, 60.54 C-6 isoc, 54.08 C-3 amine, [29.02, 27.7, 27.0, 26.8, 26.8, 26.8, 26.6, 26.5, 26.4, 26.1, 25.6, 19.2] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{60}N_2O_{17}Na$ 851.3790; Found 851.3748.

***N*-((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-*N*-(2-(((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)amino)-2-oxo-1-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl)benzamide (45)**: Yield 14 % (13 mg); R_f = 0.41 (toluene:EtOAc 1:1, v/v); ^{1}H NMR (600 MHz, CDCl3) δ 7.85 NH (m, 1H), 7.57 benz (d, J = 7.3 Hz, 2H), 7.32 benz (dd, J = 13.7, 6.9 Hz, 2H), 7.27 benz (t, J = 7.2 Hz, 2H), 6.02 NH (m, 1H), 5.89 H-1 (s), 5.79 H-1 (d, J = 3.4 Hz), 5.75 H-1 (m), 5.23 H-3 (s, 1H), 4.90 H-4 (d, J = 18.7 Hz, 2H), 4.79 H-3 ald (s, 1H), 4.65 (s, 1H), 4.55

(s, 1H), 4.47 H-3 ald (s, 1H), 4.39 H-3 (d, J = 4.1 Hz, 1H), 4.32 H-4 (s, 1H), 4.29 H-4 (s, 1H), 4.24 H-1 (s, 1H), 4.15 H-3 (d, J = 14.1 Hz, 2H), 4.02 H-6, H-5, H-2 (m), 3.77 H-6 (m), 1.39 CH_3-isop (m). ^{13}C NMR{1H} (151 MHz, CDCl3) δ 174.7 CO, 168.1 CO, 137.4 benz, 129.6 benz, 128.9 benz, 126.8 benz, 113.7 C-2 ald, 113.2 Cq-isop, 112.9 Cq-isop, 109.8 Cq-isop, 104.4 C-1, 104.3 C-1, 104.1 C-1, 97.62 Cq-isop, 88.5 C-3, 85.6 C-3, 85.1 C-3, 79.7, 79.4, 78.8, 78.0, 77.8, 76.7, 76.2, 75.8, 75.2, 73.6 C-1, 73.4, 73.3, 73.0, 72.3, 67.1 C-6, 65.5 C-6, 65.2 C-6, 65.18 C-1, 63.8 C-3, 62.5 C-3, 62.2 C-3, 60.8 C-6, 60.51 C-6, 60.4 C-6, 55.3 C-3, 52.4 C-3, [28.9, 28.5, 27.3, 26.7, 26.7, 26.4, 25.7, 25.2, 19.0] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}$ 913.3946; Found 913.3913.

N-((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)-N-(2-(((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)amino)-2-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)acetyl)benzamide (45b): Yield 36 % (32 mg); mp = 185-186 ºC; R_f = 0.64 (toluene:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 156 (*c* 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 benz (m, 1H), 7.54 benz (m, 1H), 7.42 benz (dt, *J*=5.6, 4.4, 1H), 7.32 benz (m, 2H), 5.88 H-1 (d, *J*=3.9, 0.56H), 5.67 H-1 (d, *J*=3.2, 0.96H), 5.61 H-1 (d, *J*=3.5, 0.48H), 5.26 H-4 (d, *J*=10.5), 4.96 H-3 (s, 0.45H), 4.92 H-2 (m, 0.55H), 4.76 H-2, H-5 (m, 1H), 4.66 H-3 (s, 0.55H), 4.58 H-6 (m, 0.45H), 4.52 H-2 (m, 0.45H), 4.32 H-4 ald (s, 0.45H), 4.26 H-4 ald (s, 0.55H), 4.20 – 3.73 H-4, H-5, H-6 (m), 3.59 H-6 (t, *J*=7.3), 3.52 H-6 (t, *J*=7.2), 3.36 H-1 (d, *J*=9.2, 0.5H), 3.07 H-3 (m, 0.44H), 2.96 NH (m, 1H), 1.35 CH_3 (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 177.1 CO, 175.2 CO, 173.9 CO, 173.2 CO, 137.8 benz, 135.3 benz., 133.0 benz., 132.4 benz., 129.8 benz., 128.4 benz., 116.1 C-2, 115.8 C-2, 114.1 Cq-isop, 113.2 Cq-isop, 112.8 Cq-isop, 112.6 Cq-isop, 112.4 Cq-isop., 112.1 Cq-isop., 110.7 Cq-isop., 109.6 Cq-isop, 109.1 Cq-isop, 104.3 C-1, 104.2 C-1, 103.9 C-1, 103.7 C-1, 98.03 Cq-isop., 97.2 Cq-isop., 86.2 C-3, 81.5, 80.35, 80.2, 79.6, 79.3, 78.4, 78.3, 76.5, 76.4, 75.6, 75.4, 74.4, 73.8, 73.4 C-1 Sor, 73.3, 72.8, 68.5 C-6, 68.3 C-6, 66.9 C-6, 64.5 C-6, 63.7 C-6, 62.6 C-3, 62.2 C-3, 61.4 C-3, 61.1 C-3, 60.6 C-6, 60.4 C-6, [29.8, 29.1, 28.3, 27.9, 27.2, 27.1, 27.0, 26.7, 26.6, 26.5, 26.3, 26.1, 26.0, 25.6, 25.5, 25.2, 18.7] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3954.

tert-butyl (1-((S)-N-((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-(((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)amino)-2-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-

d][1,3]dioxin-8a-yl)acetamido)-1-oxo-3-phenylpropan-2-yl)carbamate (46b): Yield 29 % (30 mg), mp = 134-138 ºC; R_f = 0.79 (PE:EtOAc 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 Phe (m, 2H), 7.23 Phe (m, 2H), 7.15 (m, 1H), 5.81 (d, *J* = 3.7 Hz, 0.24H), 5.77 (d, *J* = 3.6 Hz, 0.12H), 5.65 (m, 1.62H), 5.25 Phe-NH (d, *J* = 10.5 Hz, 1H), 4.98 Phe-α (m, 1H), 4.86 H-3 ald (s, 1H), 4.70 H-2 amine (t, J=4.0, 1H), 4.67 – 4.58 H-2 isoc (m, 1H), 4.33 Phe-α (m, 1H), 4.26 H-1 ald (s, 1H), 4.15 – 3.96 H-4, H-5, H-6 (m) 3.89 – 3.66 H-6 (m, 1H), 3.74 H-3 isoc (m, 1H), 3.47 Phe-β (m, 1H), 3.25 – 3.16 H-3 amine (m, 1H), 3.07 – 2.90 Phe-β (m, 1H), 1.57 – 1.18 (m, 45H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ = 182.5 CO, 175.3 CO, 138.9 Phe, 129.8 Phe, 129.5 Phe, 128.3 Phe, 126.4 Phe, 115.5 C-2 ald, 114.0 Cq-isop, 113.5 Cq-isop, 112.4 Cq-isop, 110.7 Cq-isop, 109.7 Cq-isop, 104.5 C-1, 103.7 C-1, 98.0 Cq-isop, 86.4 C-3 ald, 81.9, 80.2, 79.7, 78.9, 78.3 Cq-Boc, 78.1, 76.1, 75.7, 73.9, 73.0, 68.2 C-6, 67.8 C-6, 66.3 C-6, 63.4 C-5, 61.6 C-3, 61.1 C-3, 60.6 Phe-α, 60.4 C-6, 40.9 Phe-β, [29.8, 28.6, 28.4, 27.3, 26.9, 26.8, 26.7, 26.4, 26.1, 25.8, 25.5, 25.4, 18.7] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{51}H_{75}N_3O_{19}Na$ 1056.4892; Found 1056.4912.

N-((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-(((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)amino)-2-((3aS,3bR,7aS,8aS)-2,2,5,5-tetramethyltetrahydro-8aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)acetamide (45a): DS1: Yield = 43 % (20 mg); R_f = 0.3 (toluene:EtOAc 2:3 v/v), $\alpha]_D^{22}$ + 72 (*c* 1, $CHCl_3$). ^{1}H NMR (600 MHz, CDCl3) δ 6.52 NH (d, *J* = 9.4 Hz, 1H), 5.85 H-1 amine (d, *J* = 3.8 Hz, 1H), 5.71 H-1 isoc (d, *J* = 3.9 Hz, 1H), 4.61 H-2 isoc (m, 1H), 4.59 H-3 ald (s, 1H), 4.55 H-2 amine (m, 1H), 4.40 H-6 (m, 1H), 4.32 H-4 ald (d, *J* = 2.2 Hz, 1H), 4.30 H-6 (dd, *J* = 7.0, 3.8 Hz, 1H), 4.09 H-6, H-5, H-4, H-3 amine, H-2 (s, 9H), 3.81 H-4 isoc (dd, *J* = 8.9, 3.7 Hz, 1H), 3.68 H-1 ald (d, *J* = 10.7 Hz, 1H), 2.89 H-3 isoc (m, 1H), 2.85 NH (m, 1H), 1.58 – 1.28 CH_3-isop 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 171.9 CO, 114.4 C-2 ald, 113.8 Cq-isop, 112.7 Cq-isop, 112.3 Cq-isop, 109.8 Cq-isop, 109.4 Cq-isop, 104.8 C-1 isoc, 104.27 C-1 amine, 97.7 Cq-isop, 85.7 C-3, 80.8, 79.7, 79.2, 78.8, 75.8, 75.1, 73.3, 73.0, 65.6 C-6, 64.8 C-1 ald, 63.7 C-6, 61.1, 60.7 C-6, 52.9 C-3 amine, [29.7, 27.9, 26.9, 26.9, 26.8, 26.7, 26.6, 26.5, 25.6, 25.1, 18.8] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{37}H_{58}N_2O_{16}Na$ 809.3684; Found 809.3698. DS2: Yield = 18 % (14 mg), R_f = 0.21 (toluene:EtOAc 2:3 v/v), $[\alpha]_D^{22}$ + 93 (*c* 0.46, $CHCl_3$). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{37}H_{58}N_2O_{16}$ 809.3684; Found 809.3699.

(3aS,3bR,7aS,8aR)-*N*-benzyl-*N*-(2-(((3aR,5S,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)amino)-2-oxo-1-((3aS,3bR,7aS,8aS)-

2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxin-8a-yl)ethyl)-2,2,5,5-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine-8a-carboxamide (48): Yield 50 % (45 mg). DS1: Yield 20 % (18 mg); mp = 204-208 °C, R_f = 0.4 (PE:EtOAc 1:1, v/v$[\alpha]_D^{22}$ + 53 (*c* 0.546, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 Ph (m, 5H), 6.34 NH (d, *J* = 8.9 Hz, 1H), 5.74 H-1 isoc (m, 1H), 5.53 H-1 ald (s, 1H), 5.36 H-3 GulA (s, 1H), 5.28 CH_2-benzyl (d, *J* = 16.3 Hz, 1H), 5.15 H-3 ald (s, 1H), 5.04 CH_2-benzyl (d, *J* = 16.2 Hz, 1H), 4.57 (s, 1H), 4.40 – 3.98 H-4, H-5, H-6 (m), 3.90 – 3.78 (m, 2H), 3.71 – 3.67 (m, 1H), 1.54 – 1.24 CH_3-isop (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 167.2 CO, 166.4 CO, 166.0 CO, 138.9 Ph, 128.1 Ph, 127.4 Ph, 126.1 Ph, 125.8 Ph, 115,1 C-2 ald, 114.6 C-2 ald, 114.2 C-2 ald, 113.5 Cq-isop, 113.4 Cq-isop, 112.9 C-2 GulA, 109.2 Cq-isop, 109.15 Cq-isop, 104.8 C-1 isoc, 104.5 C-1 isoc, 97.7 Cq-isop, 97.4 Cq-isop, 88.1 C-3 GulA, 87.6 C-3 GulA, 85.1 C-3 ald, 84.6 C-3 ald, [79.2, 79.1, 79.0, 78.8, 75.5, 75.1, 75.0, 74.3, 73.8, 73.2, 73.2, 73.1, 72.8] C-2, C-4, C-5, 64.0 C-6, 63.6 C-6, 63.3 C-6, 61.3 C-1 ald, 60.5 C-6, 60.3 C-6, 59.8 C-6, 59.7 C-6, 52.4 C-3 isoc, 52.1 C-3 isoc, 49.5 CH_2-benzyl, [29.9, 29.6, 29.4, 28.9, 28.8, 28.3, 27.9, 27.1, 27.0, 26.9, 26.7, 26.6, 26.5, 26.2, 25.6, 25.5, 19.1, 18.9] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3925.DS2: Yield 30 % (27 mg); mp = 142-146 °C, R_f = 0.29 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ + 42.3 (*c* 0.59, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 Ph (d, *J* = 7.6 Hz, 1H), 7.18 Ph (d, *J* = 7.1 Hz, 1H), 7.16 Ph (d, *J* = 4.0 Hz, 2H), 7.13 NH (d, *J* = 8.0 Hz, 1H), 5.68 H-1 isoc (d, *J* = 3.6 Hz, 0.59H), 5.56 H-1 isoc (d, *J* = 3.7 Hz, 0.41H), 5.46 H-1 ald (s, 1H), 5.42 H-3 GulA (s, 1H), 5.39 H-3 ald (s, 1H), 5.36 H-3 GulA (s, 1H), 5.15 CH_2-benzyl (dd, *J* = 17.3, 8.4 Hz, 1H), 5.00 CH_2-benzyl (m, 1H), 4.50 H-3 ald (s), 4.27 – 3.79 C-4, C-5, C-6 (m), 1.58 – 1.22 CH_3 isop (36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 166.7 CO, 166.0 CO, 138.6 Ph, 138.4 Ph, 128.2 Ph, 127.7 Ph, 127.2 Ph, 126.7 Ph, 126.2 Ph, 115.3 C-2 ald, 114.5 Cq-isop, 114.0 C-2 ald, 113.4 Cq-isop, 113.2 C-2 GulA, 112.5 Cq-isop, 112.5 Cq-isop, 109.5 Cq-isop, 104.3 C-1 isoc, 104.2 C-1 isoc, 97.8 Cq-isop, 97.7 C-q-isop, 88.3 C-3 GulA, 87.8 C-3 GulA, 87.6 C-3 ald, 86.7 C-3 ald, [79.3, 78.7, 78.4, 75.5, 75.3, 75.2, 74.8, 74.1, 73.0, 72.6, 72.2] C-4, C-5, 64.2 C-6, 64.0 C-6, 63.1 C-1 ald, 60.4 C-6, 59.4 C-6, 59.4 C-6, 52.8 C-3 isoc, 51.7 C-3 isoc, 49.1 CH_2-benzyl, [29.9, 29.4, 29.2, 29.0, 28.6, 28.4, 28.2, 27.4, 27.2, 27.1, 27.0, 26.9, 26.8, 26.7, 26.5, 26.5, 26.1, 26.0, 25.6, 19.2, 19.17, 19.0, 18.8] CH_3-isop. Presence of rotamers. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{44}H_{62}N_2O_{17}Na$ 913.3946; Found 913.3932.

2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-*N*-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)-2-(N-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-

tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)acetamido)acetamide (49): Yield 78 % (65 mg), mp = 130-134 ºC; R_f = 0.35 (PE:EtOAc 1:2, v/v); *d.r.* 77:23; $[\alpha]_D$ = - 43 ° c1 $CHCl_3$. Chemical shifts are given for major diastereoisomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 NH (covered with solvent), 5.53 H-1 ald. (d, J = 4.9 Hz, 1H), 5.47 H-1 isoc, H-1 amine (dd, J = 5.0, 1.9 Hz, 2H), 4.92 H-6 ald. (d, J = 9.0 Hz, 1H), 4.56 H-3, H-4 (m, 3H), 4.27 H-4, H-2 (m, 2H), 4.08 H-4 ald (dd, J = 8.0, 1.4 Hz, 1H), 4.05 H-5 amine (m, 1H), 3.96 H-5 isoc (m, 1H), 3.82 H-6 amine (dd, J = 15.3, 9.0 Hz, 1H), 3.63 H-5 ald (s, 1H), 3.57 H-6 isoc (m, 1H), 3.43 H-6 amine (dd, J = 15.3, 4.7 Hz, 1H), 3.30 H-6 isoc (m, 1H), 2.16 CH_3-ac (s, 1H), 1.66, 1.57, 1.50, 1.43, 1.28 CH_3-isop (36 H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 173.8 CO, 169.5 CO, 109.8 Cq-isop, 109.5 Cq-isop., 109.4 Cq- isop, 109.1 Cq-isop, 108.9 Cq-isop, 97.0 C-1 ald, 96.6 C-1 amine, 96.5 C-1 isoc, [72.6, 72.2, 71.5, 71.2, 71.1, 71.1, 71.0, 70.8, 70.6, 67.3] C-2 , C-3, C-4, 66.4 C-5, 66.3 C-6 ald., 65.8 C-5, 63.0 C-5 ald, 51.8 C-6 amine, 40.2 C-6 isoc, [26.5, 26.3, 26.2, 26.1, 25.4, 25.2, 25.1, 24.8, 24.7, 24.6] CH_3-isop, 22.3 CH_3-ac. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{60}N_2O_{17}Na$ 851.3790; Found 851.3823.

***N*-((S)-2-oxo-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)-*N*-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)benzamide (50):** Yield 83 % (72 mg). DS1: Yield 31 % (27 mg); mp 146-148 °C; R_f=0.55 (PE:EtOAc 1:1); $[\alpha]_D^{22}$ - 12 (*c* 0.66, $CHCl_3$). DS2: Yield 52 % (45 mg); mp 125-132 °C; R_f=0.53 (PE:EtOAc 1:1); $[\alpha]_D^{22}$ - 72 (*c* 0.66, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 NH (m, 1H), benz-ε (s, 2H), 7.33 benz-γ, benz-δ (d, *J* = 7.3 Hz, 3H), 5.56 H-1 ald.(d, *J* = 4.4 Hz, 1 H), 5.49 H-1 isoc (d, *J* = 4.6 Hz, 1 H), 5.38 H-1 amine (d, *J* = 4.7 Hz, 1 H), 5.10 H-5 ald. (d, *J* = 8.3 Hz, 1 H), 4.63 H-3 (d, *J* = 5.8 Hz, 1H), 4.55 H-3 (d, *J* = 7.2 Hz, 1H), 4.43 H-3 (d, *J* = 7.5 Hz, 1H), 4.34 H-2 (d, *J* = 7.5 Hz, 1H), 4.31 H-2, H-4 (d, *J* = 6.4 Hz, 2H), 4.23 H-2, H-4 (d, *J* = 11.6 Hz, 2H), 3.95 H-5, H-4 (m, 2H), 3.88 H-6 ald. (d, *J* = 7.9 Hz, 1H), 3.75 H-6 (dd, *J* = 14.6, 7.7 Hz, 1H), 3.64 H-6 (m, 1H), 3.36 H-6 (d, *J* = 6.5 Hz, 1H), 1.64 - 1.04 CH_3-isop (m, 36H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 174.3 CO, 169.2 CO, 136.4 benz-β, 129.3 benz-ε, 128.3 benz-δ, 127.0 benz-γ, 109.8 Cq-isop., 109.6 Cq-isop, 108.9 Cq-isop, 97.0 C-1, 96.6 C-1, 96.3 C-1 ald, [71.5, 71.1, 71.0, 70.7] C-2, C-3, C-4, 66.7 C-5, 66.4 C-5, 65.6 C-5, 63.2 C-6 ald, 51.8 C-6 amine, 40.1 C-6 isoc, 26.3 CH_3-isop, 25.4 CH_3-isop , 25.1 CH_3-isop, 24.8 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{62}N_2O_{17}Na$ 891.4127; Found 891.4129.

methyl (2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)-L-phenylalaninate (51a): Yield 50 % (35 mg). DS1: Yield 40 % (28 mg), mp = 100-102 ºC; R_f = 0.32 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ - 33.75 (c 0.8, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 Phe (m, 2H), 7.18 Phe, NH (dd, *J* = 7.2, 5.2 Hz, 4H), 5.48 H-1 (d, *J* = 4.9 Hz, 1H), 5.43 H-1 (d, *J* = 5.0 Hz, 1H), 4.54 H-3 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.48 H-4 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.43 H-4 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.25 H-2 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.19 H-2 (m, 1H), 4.16 H-3 (m, 1H), 4.06 H-5 (d, *J* = 5.3 Hz, 1H), 4.01 Phe-α (m, 1H), 3.63 CH_3-methyl (s, 3H), 3.36 H-5, H-6 ald, H-6 isoc (m, 3H), 3.11 NH (s, 1H), 2.90 Phe-β, H-6 isoc (m, 2H), 2.78 Phe-β (dd, *J* = 13.5, 8.2 Hz, 1H), 1.49 – 1.27 CH_3-isop (24H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 174.2 CO, 172.1 CO, 138.2 Phe, 129.7 Phe, 128.5 Phe, 126.73 Phe, 109.6 Cq-isop, 109.1 Cq-isop, 109.0 Cq-isop, 108.8 Cq-isop, 97.0 C-1, 96.8 C-1, [71.9, 71.3, 71.2, 71.2, 71.1, 70.7] C-2, C-3, C-4, 67.1 C-6, 65.3 α-Phe, 64.3 C-5, 63.6 C-5, 51.8 CH_3-methyl, 40.2 C-6, 40.2 β-Phe, [26.4, 26.3, 26.2, 26.0, 25.4, 25.3, 24.8, 24.0] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{35}H_{50}N_2O_{13}$ 707.3391; Found 707.3395. DS2: Yield 10 % (7 mg), R_f = 0.24 (PE:EtOAc 1:1, v/v). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{35}H_{50}N_2O_{13}$ 707.3391; Found 707.3380.

methyl 2-(2-((tert-butoxycarbonyl)amino)-*N*-(2-oxo-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)-3-phenylpropanamido)-3-phenylpropanoate (52): Yield 14 % (13 mg), R_f = 0.57 (PE:EtOAc 1:1, v/v); $[\alpha]_D^{22}$ - 48.5 (*c* 0.515, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.60 impurities (s), 7.23 Phe (m, under solvent), 7.02 Phe (d, *J* = 7.1 Hz, 2H), 5.66 C-1 (m, 0.24H), 5.50 C-1 (d, *J* = 5.0 Hz, 0.76H), 5.35 (m, 1H), 5.26 Phe-α (m, 1H), 5.20 C-1 (m, 1H), 5.06 (m, 1H), 4.99 (m, 1H), 4.87 Phe-α (m, 1H), 4.76 H-6 ald (s, 1H), 4.59 (m, 2H), 4.37 (m, 1H), 4.28 (m, 3H), 4.14 (d, *J* = 35.2 Hz, 2H), 4.00 (dd, *J* = 4.6, 2.1 Hz, 1H), 3.86 (m, 2H), 3.66 (d, *J* = 18.6 Hz, 1H), 3.61 CH_3-methyl (s, 3H), 3.47 (m, 3H), 3.20 (m, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.95 (m, 1H), 1.63 – 1.24 CH_3-isop, CH_3-Boc (32H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 129.8 Phe, 129.5 Phe, 129.1 Phe, 128.6 Phe, 126.7 Phe, 109.1 Cq-isop, 96.7 Cq-isop, 80.7 Cq-Boc, 71.23, 66.1, 65.3, 59.8 Phe-α, 58.9 C-6 ald, 52.4 CH_3-methyl, 39.6 C-6 isoc, 37.8 Phe-β, 35.4 Phe-β, 28.5 CH_3-Boc, 26.3 CH_3-isop, 25.5 CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{49}H_{67}N_3O_{16}Na$ 976.4419 found 976.4451.

benzyl *N*-acetyl-*N*-(2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)-L-tyrosinate (53) and benzyl (2-oxo-1-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)-L-tyrosinate (53a) Compound **53** and **53a** are isolated as inseparable mixture with Rf = 0.54 (PE:EtOAc 1:2, v/v) in 80 % yield (66 mg). Ratio of two products was determined from the ^{1}H NMR spectrum (chemical shifts for H1 Gal). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 – 8.51 NH (m), 7.37 – 7.24 Tyr, NH (m), 7.20 – 7.16 Tyr (m), 7.15 – 7.08 Tyr (m, 1H), 7.08 – 7.04 Tyr (m), 7.00 (t, *J* = 8.0 Hz), 6.74 (d, *J* = 8.5 Hz), 6.67 (t, *J* = 6.0 Hz), 6.61 (d, *J* = 8.5 Hz), 6.23 (s), 5.96 NH (d, *J* = 8.4 Hz, 1H), 5.56 H-1 (d, *J* = 5.2 Hz, 1H), 5.50 H-1 (d, *J* = 5.0 Hz, 1H), 5.48 h-1 (d, *J* = 5.0 Hz, 1H), 5.46 H-1 (d, *J* = 4.9 Hz, 1H), 5.28 H-1 (d, *J* = 4.7 Hz, 1H), 5.02 (ddt, *J* = 29.5, 21.7, 12.3 Hz), 4.79 – 4.74 (m), 4.62 (dd, *J* = 8.1, 2.1 Hz), 4.55 (ddd, *J* = 12.6, 6.5, 3.6 Hz), 4.38 (dd, *J* = 9.9, 1.3 Hz), 4.32 (dt, *J* = 12.4, 6.2 Hz), 4.29 – 4.22 (m), 4.09 (dddd, *J* = 19.6, 9.6, 6.1, 2.1 Hz), 3.96 – 3.88 (m), 3.83 – 3.69 (m), 3.67 – 3.59 (m), 3.52 (dd, *J* = 14.2, 10.1 Hz), 3.48 – 3.37 (m), 3.31 – 3.12 (m), 3.09 (d, *J* = 13.9 Hz), 2.26 CH_3 Ac (d, *J* = 6.4 Hz), 2.04 CH_3 Ac (d, *J* = 7.3 Hz), 1.94 CH_3 Ac (d, *J* = 7.0 Hz, 4H), 1.63 – 1.10 (m) CH_3 isop, 0.88 – 0.83 CH_3 isop (m). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 173.5 CO, 172.8 CO, 172.2 CO, 170.1 CO, 169.8 CO, 167.2 CO, 154.9 Tyr, 154.4 Tyr, 136.1 Tyr, 135.1 Tyr, 132.2 Tyr, 130.8 Tyr, 130.8 Tyr, 128.7 Tyr, 128.7 Tyr, 128.6 Tyr, 128.5 Tyr, 128.4 Tyr, 128.1 Tyr, 128.0 Tyr, 116.0 Tyr, 115.6 Tyr, 115.1 Tyr, 109.6 Cq isop, 109.6 Cq isop, 109.3 Cq isop, 109.3 Cq isop, 109.1 Cq isop, 109.0 Cq isop, 108.96 Cq isop, 108.9 Cq isop, 108. 8 Cq isop, 108.6 Cq isop, 96.5 C-1, 96.5 C-1, 96.4 C-1, 96.3 C-1, 96.0 C-1, 72.2, 71.8, 71.6, 71.4, 71.2, 71.0, 70.9, 70.8, 70.81, 70.7, 70.6, 70.5, 68.3, 67.7, 67.3, 67.1, 67.05, 66.5, 66.0, 65.8, 65.5, 60.8, 60.3, 40.1 C-6, 39.9 C-6, 35.6 C-6, 35.3 C-6, 31.8 Tyr, [27.1, 26.4, 26.2, 26.1, 26.0, 25.9, 25.3, 25.2, 25.2, 24.9, 24.4, 24.4, 24.2, 24.2, 23.9, 23.3, 23.0, 22.9, 22.2] CH_3 isop, 14.40.

benzyl 2-(2-((tert-butoxycarbonyl)amino)-3-(4-((tert-butoxycarbonyl)oxy)phenyl)-*N*-((S)-2-oxo-1-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl)amino)ethyl)propanamido)-3-(4-hydroxyphenyl)propanoate (54): Yield 78 % (91 mg). DS1: Yield 52 % (61 mg); mp = 150-152

ºC; R_f = 0.4 (PE:EtOAc 3:2, v/v); $[\alpha]_D^{22}$ - 92 (c 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 Tyr-δ (m, 1H), 7.07 Tyr-ε (m, 1H), 6.83 NH (s, 1H), 6.73 Tyr-δ (d, *J* = 8.4 Hz, 1H), 6.57 Tyr-ε (d, *J* = 8.5 Hz, 1H), 5.52 H-1 (d, *J* = 5.1 Hz, 1H), 5.33 Tyr-α (d, *J* = 10.1 Hz, 1H), 5.29 NH (s, 1H), 5.23 H-1 (d, *J* = 4.5 Hz, 1H), 5.19 (d, *J* = 6.8 Hz, 1H), 5.15 CH_2-benzyl (m, 1H), 5.00 CH_2-benzyl (d, *J* = 12.5 Hz, 1H), 4.81 Tyr-α (dd, *J* = 10.8, 5.5 Hz, 1H), 4.59 H-6 ald.(d, *J* = 10.4 Hz, 1H), 4.55 H-3 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.28 H-2 (dd, *J* = 5.1, 2.3 Hz, 1H), 4.18 H-4 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.12 H-5 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.05 H-2; H-3 (m, 2H), 3.72 H-5 (d, *J* = 10.3 Hz, 1H), 3.45 H-6 isoc (dd, *J* = 14.1, 10.8 Hz, 1H), 3.33 Tyr-β (m, 1H), 3.22 Tyr-β (m, 1H), 3.09 Tyr-β (m, 1H), 2.95 Tyr-β (m, 1H), 1.87 – 1.03 CH_3-Boc, CH_3-isop. ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 172.8 CO, 169.7 CO, 167.6 CO, 156.0 Tyr-ε, 154.8 Tyr-ε, 152.4 Tyr, 149.9 Tyr), 136.2 Tyr-γ, 135.5 Tyr-γ, 130.9 Tyr-δ, 130.7 Tyr-δ, 130.4 benzyl, 128.7 benzyl 128.2 benzyl, 128.1 benzyl, 121.3 Tyr-ε, 115.9 Tyr-ε, 109.3 Cq-isop, 109.2 Cq-isop, 96.6 C-1, 96.2 C-1, 84.0 Cq-Boc, 80.9 Cq-Boc, 71.2 C-3, 70.8 C-3, 68.6 C-4, 67.1 CH_2-benzyl, 66.0 C-2, C-5 ald, 65.4 C-2, 60.1 Tyr-α, 58.5 C-6 ald, 51.7 Tyr-α, 39.6 C-6, 37.9 Tyr-β, 34.5 Tyr-β, 28.4 CH_3-Boc, 28.0 CH_3-Boc, [26.5 26.3, 26.0, 25.4, 25.4, 25.0, 24.3] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{60}H_{79}N_3O_{20}Na$ 1184.5155; Found 1184.5139. DS2: Yield 26 % (30 mg); mp = 151-154 ºC; R_f = 0.31 (PE:EtOAc 3:2, v/v); $[\alpha]_D^{22}$ - 32.7 ° (*c* 0.764, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.59 (t, *J* = 10.4 Hz, 1H), 6.46 (m, 1H), 5.44 (d, *J* = 4.9 Hz, 1H), 5.41 (d, *J* = 4.7 Hz, 1H), 5.30 (s, 1H), 5.21 (m, 1H), 5.14 (m, 1H), 5.06 (m, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.89 (m, 1H), 4.78 (s, 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 4.55 (m, 1H), 4.46 (m, 1H), 4.25 (s, 1H), 4.20 (s, 1H), 4.16 (d, *J* = 9.4 Hz, 1H), 4.05 (m, 1H), 3.98 (m, 1H), 3.93 (d, *J* = 7.9 Hz, 1H), 3.57 (m, 1H), 3.35 (m, 1H), 3.21 (m, 1H), 3.05 (m, 1H), 2.89 (m, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 2.67 (m, 1H), 1.56 (d, *J* = 9.6 Hz, 2H), 1.54 (d, *J* = 4.8 Hz, 1H), 1.52 (t, *J* = 8.4 Hz, 3H), 1.47 (s, 1H), 1.44 (s, 1H), 1.41 (s, 1H), 1.37 (s, 2H), 1.31 (t, *J* = 8.3 Hz, 3H), 1.26 (s, 1H), 1.22 (m, 2H), 1.14 (d, *J* = 1.4 Hz, 1H), 1.05 (d, *J* = 16.2 Hz, 1H). ^{13}C NMR{1H} (151 MHz, $CDCl_3$) δ 150.0 Tyr, 146.9 Tyr, 135.5 Tyr, 131.4 Tyr, 131.0 Tyr, 128.6 Tyr, 128.4 Tyr, 128.2 Tyr, 121.3 Tyr, 115.0 Tyr, 109.7 Cq-isop, 108.9 Cq-isop, 108.7 Cq-isop, 96.6 H-1, 79.6 Cq-Boc, 71.8, 71.1, 70.8, 67.5, 66.0, 41.0 C-6 isoc, 40.3 Tyr-β, 28.6 CH_3-Boc, 28.5 CH_3-Boc, [27.9, 26.3, 26.2, 25.3, 24.7, 24.5] CH_3-isop. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{60}H_{79}N_3O_{20}Na$ 1184.5155; Found 1184.5170.

Synthesis of 2-((2R,3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-*2H*-pyran-2-yl)-*N*-(((2R,3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)methyl)-2-(*N*-(((2R,3S,4R,5R)-2,3,4,5-tetrahydroxytetrahydro-*2H*-pyran-2-

yl)methyl)acetamido)acetamide (**55**): Compound **33** (DS1) (50 mg, 0.06 mmol) was dissolved in TFA/H_2O mixture (9:1, v/v) and stirred for 3h at room temperature. The reaction was monitored by TLC in EtOAc/EtOH/AcOH/H_2O 7:4:2:2. The product was precipitated with cold diisopropylether and centrifuged. The precipitate was dried, dissolved in water and passed through C-18 silica gel Bond Elute patron, eluted with water to give compound **55** as a mixture of diastereomers in 89 % yield (31 mg). ^{13}C NMR{1H} (151 MHz, DMSO-d_6) δ 158.12, 157.92, 101.70, 101.51, 99.61, 98.06, 95.51, 95.12, 82.97, 82.48, 82.07, 81.41, 78.56, 77.70, 77.39, 76.83, 75.97, 75.59, 75.55, 74.89, 74.68, 73.86, 72.40, 71.08, 70.88, 70.50, 70.22, 69.46, 69.26, 69.14, 68.99, 68.89, 68.71, 66.04, 63.76, 63.28, 63.22, 63.07, 63.01, 62.86, 62.51, 62.30, 61.73, 60.46, 60.20, 44.75, 44.13, 43.60, 43.00, 27.66, 26.06, 21.35, 21.30, 21.05. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H37N_2O_{17}$ 589.2092; Found 589.2080.

Keywords: multicomponent reactions, glycoconjugates, multivalent ligands, heterovalent ligands, carbohydrates

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ^{1}H and ^{13}C NMR spectra of all compounds, MS/MS spectra of selected Ugi products, x-ray data.

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