Synthesis of *N*-Glycosyl Conjugates through a Multicomponent Domino Process

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Dedicated to Professor Stefano Servi on the occasion of his retirement

Introduction

The synthesis of carbohydrates linked to a peptide backbone has become a principal focus for synthetic bioorganic and medicinal chemists. Indeed, there is a growing interest in understanding the role of glycopeptides and glycoconjugates in a range of biochemical processes, such as cellular recognition, adhesion, and signalling, as well as in the synthesis of potential drug candidates. In many of these applications, the sugar moiety is able to induce specific interactions with the bioreceptor, generating new properties in terms of activity, selectivity, tissue permeability and pharmacodynamic effects.[1] For these reasons, the development of combinatorial approaches to obtain diverse sugar-based scaffolds in a rapid manner has attracted the attention of organic chemists. Much effort has focused on the synthesis and assembly of native *N*- and *O*-linked glycopeptides, as well as *C*- and *S*-linked glycopeptides,[2] because protein glycosylation is not under direct genetic control.[3] In natural *N*-linked glycoproteins, the sugar moiety is often tethered to an asparagine residue through a β-*N*-glycosylic linkage. However, several *N*-glycopeptide mimetics have been synthesized in which the *N*-glycosyl linkage is replaced by non-native bonds such as urea,[4] retroamide,[5] triazole,[6] and others.[7] Another strategy used for the synthesis of novel building blocks for *N*-linked glycoconjugates involves the use of *N*-glycosylamines and suitably protected and activated amino acids as starting materials.[8] However, all the above strategies are stepwise synthetic procedures, which are not ideal for the combinatorial and diversity-oriented synthesis of *N*-linked glycoconjugates in general, due to economic and environmental concerns. In this context, multicomponent (MC)[9] and domino[10] reactions have attracted much interest in recent years. Indeed, the possibility of building even elaborate scaffolds in a single step starting from three or more simple reactants is very attractive for combinatorial and diversity oriented synthetic programs, thus this approach is playing an increasingly central role in the development of modern synthetic methodology for pharmaceutical and drug discovery research. However, although many MC reactions have been developed in the past decade, only a few can be applied to the synthesis of glycopeptide mimetics.[11] Thus, despite these advances, there remains a need to discover new carbohydrate-based MC reactions to broaden the possible scaffold diversity.

Recently, within the framework of developing novel domino process for the synthesis of heterocycles starting from suitable carboxylic acids such as fumaric acid monoesters **2** and carbodiimides **3** (Scheme 1, path a),[12] we have discovered a novel three-component regioselective domino process for the synthesis of urea-peptide (Scheme 1, R^1 and R^2 = alkyl or aryl) and glyco-peptide (R^1 = sugar) conjugates

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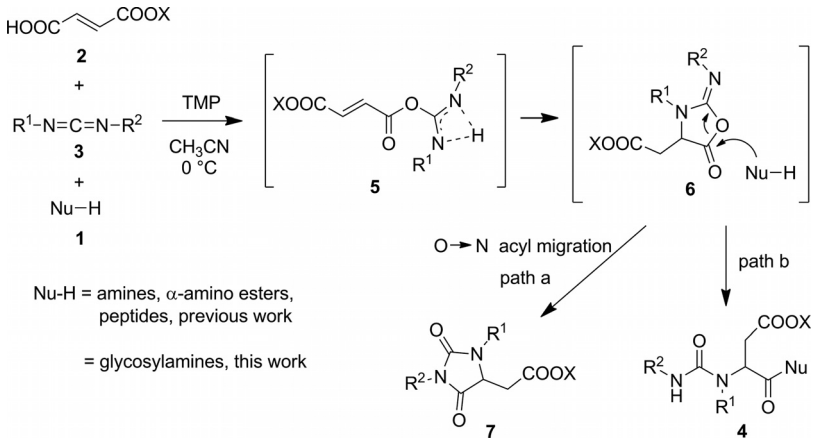


Scheme 1. Proposed mechanism for the synthesis of compounds **4**.

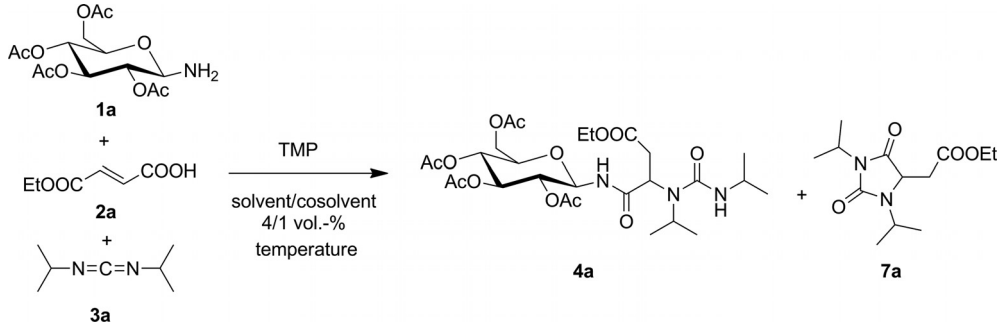
that takes place when the reaction is carried out in the presence of N-nucleophiles **1** such as amines, α-amino esters, and peptides (Scheme 1, path b).[13]

Herein, we report on the synthesis of a novel class of *N*-glycosyl conjugates, i.e., *N*-glycosyl-Asp-urea conjugates, by exploiting the same MC domino process with *N*-glycosylamines as nucleophiles. The reaction conditions have been optimised to minimise the formation of hydantoin byproduct **7** (Scheme 1, path a), which occurs due to the lower nucleophilicity of glycosylamines compared with amines or α-amino esters. The process is highly regioselective when *N*-primary alkyl, *N*′-tertiary alkyl asymmetric carbodiimides[12] are used and the synthesis could be accomplished through a four-component sequential domino process when the carbodiimide reactant is generated in situ by the Staudinger reaction.

Results and Discussion

The reaction with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**1a**), fumaric acid monoethyl ester (**2a**) and commercially available diisopropylcarbodiimide (DIC; **3a**) was conducted under the same optimised conditions used in the previous work for the synthesis of glyco-peptide conjugates, namely stoichiometric TMP (2,4,6-trimethylpyridine), CH_3CN as solvent at 0 °C (Table 1, entry 1).[13] However, in this case, we obtained the desired product **4a** in only 40% yield and in ca. 2:1 diastereoisomeric ratio (*dr*), along with the corresponding hydantoin byproduct **7a** in almost the same molar quantity (43% yield). To increase the yield of the desired product, the reaction conditions were reoptimised in terms of solvent and temperature. We hypothesised that the modest yields obtained in the first

Table 1. Process optimization.



Entry	Solvent	Cosolvent	Temp. [°C]	Yield of **4a** [%][a]	Yield of **7a** [%][a]
1	CH_3CN	–	0	40[b]	43
2	CH_3CN	MeOH	0	–[c]	–
3	CH_3CN	*t*BuOH	0	43[b]	39
4	CH_3CN	DMF	0	65[b]	21
5	DMF	–	0	56[d]	33
6	CH_3CN	DMF	–30	n.r.[e]	–
7	CH_3CN	DMF	25	15[b]	70

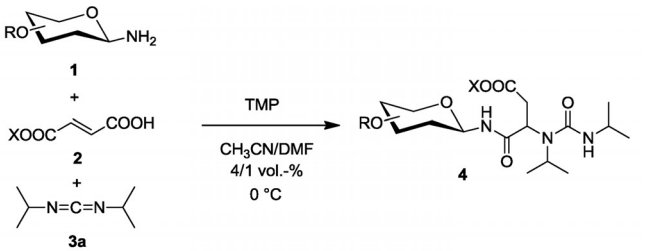
[a] Isolated yield. [b] Formed as a mixture of diastereoisomers (ca. 2:1). [c] Nucleophilic addition of MeOH to intermediate of type **6** occurred. [d] Equimolecular mixture of diastereoisomers. [e] No reaction occurred.

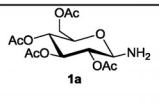
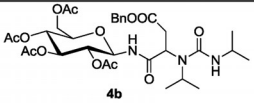
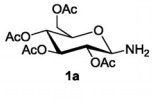
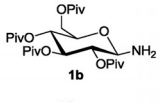
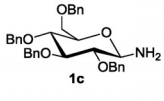
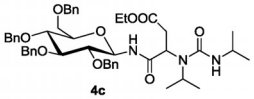
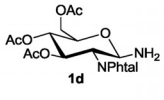
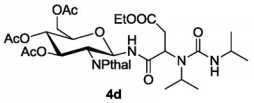
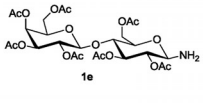
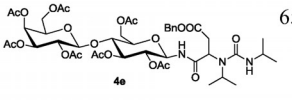
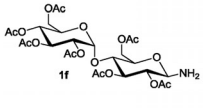
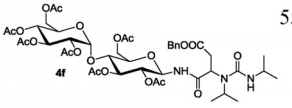
attempt were probably due to two factors: (1) poor nucleophilicity of the glycosylamine, which renders the O→N acyl migration mechanism very competitive, and (2) relatively low solubility of the nucleophile in CH_3CN. In an attempt to improve the yield, the concentration of the solution was adjusted, but no improvement in yield was achieved under either more dilute conditions (favouring the solubility of the nucleophile) or with more concentrated solutions (favouring the intermolecular process vs. the intramolecular rearrangement; data not shown). The use of polar solvents as co-solvent was also investigated with the aim of increasing both the nucleophilicity and the solubility of the glycosamine reagent. However, by using a 4:1 (v/v) mixture of CH_3CN/MeOH (Table 1, entry 2) under the same reaction conditions, the formation of **4a** was not observed; instead, the product arising from nucleophilic attack of methanol to the intermediate **6** was recovered in very good yield (87%; see Scheme 1). To avoid the nucleophilic attack of the co-solvent, the more bulky additive *t*BuOH was employed (Table 1, entry 3) and, indeed, the *N*-glycosyl-Asp-urea conjugate **4a** was obtained, again in a 2:1 *dr*, albeit in modest yields (43%). To our delight, by using a more polar but non-nucleophilic cosolvent, such as *N*,*N*-dimethylformamide (DMF) (Table 1, entry 4), the desired compound **4a** was produced in acceptable yield (ca. 2:1 *dr*; 65% yield) along with hydantoin **7a** as a minor byproduct (21%). This result confirms that the presence of a polar solvent in the reaction leads to an increase in the rate of nucleophilic attack to the intermediate **6**. However, when the reaction was carried out in DMF as solvent (Table 1, entry 5) the desired product **4a** was formed in slightly lower yields (56%) and as an equimolecular mixture of two diastereoisomers, demonstrating that the polar solvent also accelerates the O→N acyl migration mechanism.

Having optimised the reaction conditions in terms of solvents, we investigated the influence of the temperature on the process. By lowering the temperature to –30 °C, the formation of intermediate **5** did not occur and the starting materials were recovered (Table 1, entry 6), whereas when the reaction was performed at room temperature an acceleration of the O→N acyl migration mechanism was observed with the consequent formation of hydantoin **7a** in 70% yield along with the desired product **4a** in only 15% yield (Table 1, entry 7). Thus, as observed in previous work,[13] the process works most efficiently when conducted at 0 °C.

We were very surprised to find that when the reaction was carried out in CH_3CN as solvent, with or without a cosolvent, a ca. 2:1 mixture of two isomeric products was always formed. These products were identified as two diastereoisomers that differed at the newly formed stereocenter, i.e., the α-carbon of the aspartic acid unit.[14] These isomers could have been, instead, either diastereoisomers at the anomeric carbon or rotamers, however, the ^{1}H NMR spectrum of **4a** displayed a triplet at δ = 5.18 ppm (J = 9.2 Hz), arising from the anomeric protons of the two isomers, with the same chemical shift and the same coupling constant with the NH and the vicinal *anti*-axial proton, thus confirming that the two isomers are not anomeric diastereoisomers (see the Supporting Information).[15] Moreover, variable-temperature ^{1}H NMR spectroscopic analysis conducted with **4a** in [D_6]dimethyl sulfoxide (DMSO) over a range of 25–65 °C did not show any coalescence of the signals, indicating the absence of restricted rotation and thus the absence of rotamers (see the Supporting Information). Our surprise at obtaining a certain diastereoselection in this process arose from considering that, according to the proposed mechanism (Scheme 1), the new stereocenter is already formed before the chiral *N*-glycosylamine is involved in the reaction.[16] It may be that during the intramolecular aza-Michael reaction, the sugar interacts with intermediate **5** through hydrogen bonds and acts as an organocatalyst.[17] Such a complex is likely disrupted in the presence of a large amount of polar solvents because when the reaction was

Table 2. Synthesis of *N*-glycosyl-Asp-urea conjugates with DIC.



Entry	Sugar	X	Product[a]	Yield (%)[b]
1	 1a	Bn	 4b	68[c]
2	 1a	*t*Bu	–	–[d]
3	 1b	Et	–	–[d]
4	 1c	Et	 4c	73[c]
5	 1d	Et	 4d	61[c]
6	 1e	Bn	 4e	65[c]
7	 1f	Bn	 4f	55[c]

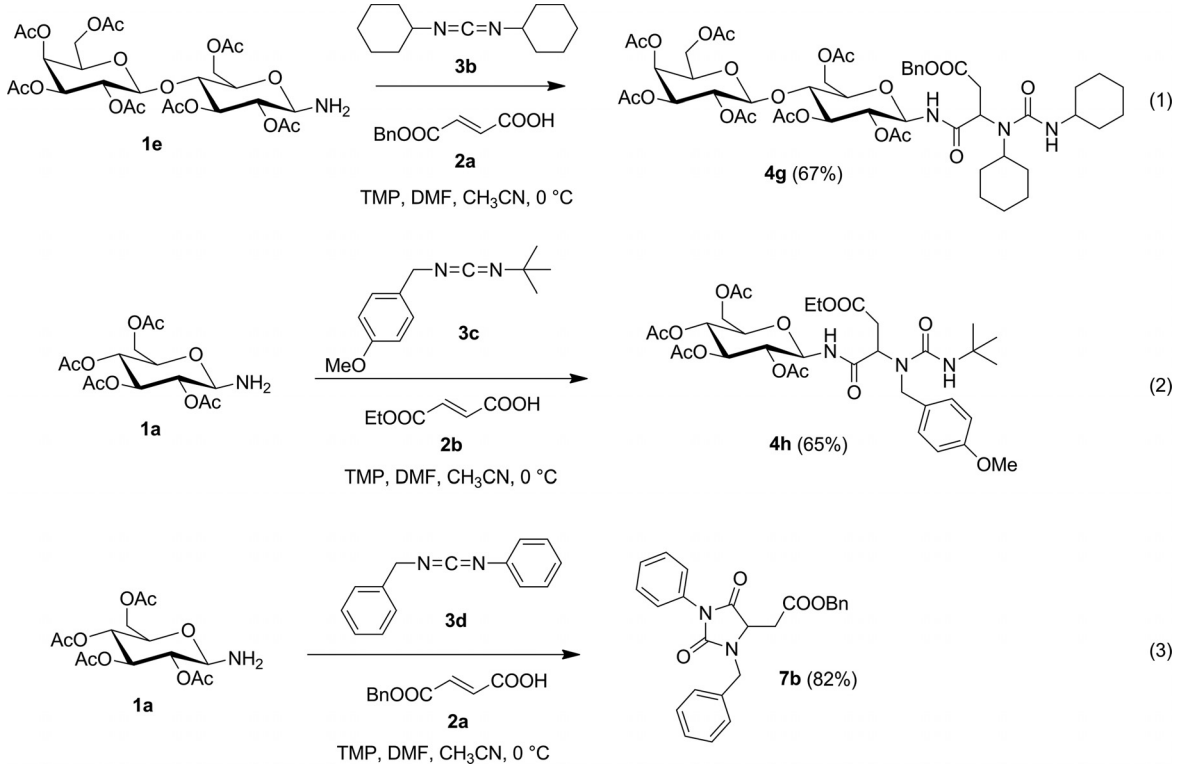
[a] Formed as a mixture of diastereoisomers (ca. 2:1). [b] Isolated yield. [c] The corresponding hydantoins were formed in ca. 20% yield. [d] The corresponding hydantoin was recovered as the only product in high yields.

carried out in DMF no diastereoselectivity was observed (Table 1, entry 5).[18]

With these results in hand, we studied in more depth the reactivity of fumaric acid monoesters with a range of glycosylamines to establish the versatility of the process (Table 2). Because *N*-glycosyl-Asp-urea conjugates of type **4** are very intriguing synthons since they could be further functionalized at the ester moiety after simple hydrolysis (see below), we explored the reactivity of other derivatives with different ester protecting groups, such as benzyl and *tert*-butyl esters, to allow chemoselective hydrolysis of the ester function with respect to the protecting groups of the sugar moiety. As expected, fumaric acid monobenzyl ester (**2b**) reacted with nucleophile **1a** and DIC **3a** under the optimised conditions [DMF/CH_3CN (20% v/v), 0 °C], affording conjugate **4b** in similar yield (68%) and with almost the same *dr* (Table 2, entry 1). Unfortunately, the same result was not obtained with acid **2c**, having a bulky *tert*-butyl ester group, probably because this substrate was too sterically hindered (Table 2, entry 2). For the same reason explained above, we also investigated the compatibility of different protecting groups on the sugar moiety. Again, 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**1b**) did not react in the presence of DIC **3a** and acid **2a**, presumably for steric reasons (Table 2, entry 3), whereas 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosylamine (**1c**) produced, under the same conditions, conjugate **4c** in excellent yields, again as a ca. 2:1 mixture of diastereoisomers (Table 2, entry 4). The process is highly versatile and worked nicely with a range of *N*-glycosylamines. Accordingly, the reaction between 2-*N*-phthaloyl-3,4,6-tri-*O*-acetyl-β-D-glucopyranosylamine (**1d**) and acid **2a** in the presence of **3a** led to the formation of conjugate **4d** in acceptable yields (Table 2, entry 5), whereas disaccharides **1e** and **1f** produced *N*-glycosylconjugated products **4e** and **4f**, respectively, with fumaric acid monobenzyl ester **2b** in good yields (Table 2, entries 6 and 7). It is worth noting that all the above reactions generate a mixture of two diastereoisomers with a 2:1 *dr* along with the formation of the corresponding hydantoin byproduct in ca. 20% yield.

Having established that the process works efficiently with a range of fumaric acid monoesters and *N*-glycosyl nucleophiles, we investigated the use of symmetric and asymmetric carbodiimides (Scheme 2). Commercially available symmetric *N*,*N*-dicyclohexylcarbodiimide (DCC; **3b**) reacted nicely with acid **2b** and sugar **1e**, affording the desired conjugate **4g** in good yields, again as a ca. 2:1 mixture of diastereoisomers, along with the corresponding hydantoin (19%), demonstrating that the process works efficiently with symmetric *N*,*N*′-dialkyl carbodiimides in general [Scheme 2, Equation (1)].

Surprisingly, asymmetric carbodiimides reacted differently in this process depending on the nature of the carbodiimide substituents. Indeed, the use of carbodiimides having the two N-substituents very different in terms of steric hindrance, such as *N*-*p*-methoxybenzyl *N*′-*tert*-butyl carbodiimide (**3c**), in the presence of acid **2b** and nucleophile **1a**, as expected, gave rise to a completely regioselective pro-



Scheme 2. Reaction with symmetric and asymmetric carbodiimides.

cess producing *N*-glycosyl-Asp-urea conjugate **4h** as the only regioisomer, again as a ca. 2:1 mixture of diastereoisomers [Scheme 2, Equation (2)].[19] This result was in complete agreement with those obtained in previous work when fumaric acid monoesters were found to react with *N*-primary alkyl, *N′*-tertiary alkyl asymmetric carbodiimides in the absence[12] or presence of N-nucleophiles.[13] Accordingly, the condensation between the two starting reagents produced a mixture of O-acylisoureas **5-A** and **5-B** in equilibrium (Figure 1). Subsequent intramolecular nucleophilic attack of the less congested nitrogen bearing the primary alkyl substituent to the activated carbon–carbon double bond is exclusive, resulting in the formation, after nucleophilic addition of the *N*-glycosylamine, of the only regioisomeric conjugate **4h**.

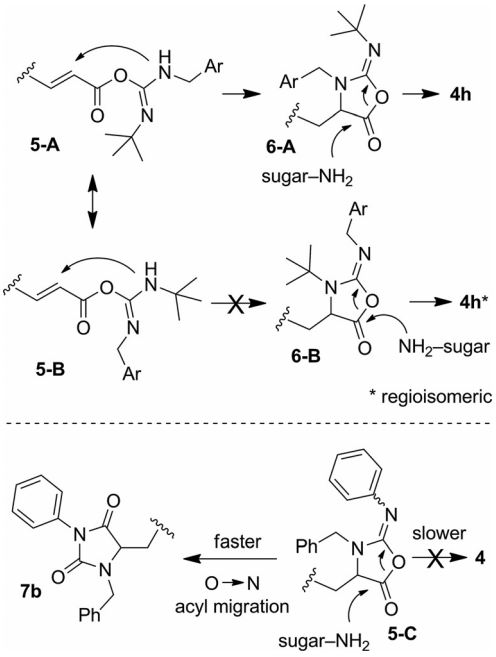


Figure 1. Reaction mechanism with asymmetric carbodiimides.

Unfortunately, asymmetric carbodiimides having *N*-alkyl and *N′*-aryl substituents, such as *N*-benzyl *N′*-phenyl carbodiimide (**3d**), did not afford the desired product but gave the corresponding hydantoin **7b** in excellent yields [Scheme 2, Equation (3)].

The above result was unexpected because, in previous works, similar reactions between *N*-alkyl, *N′*-aryl asymmetric carbodiimides, fumaric acid monoesters and stronger N-nucleophiles produced the corresponding conjugates in a regiospecific way in high yields.[17] In this case, the reaction between poorly nucleophilic *N*-glycosylamines and intermediates of type **5-C**, which is more stable and therefore less reactive due to conjugation between the C=N double bond and the aromatic ring, is likely very slow, and the faster O→N acyl migration mechanism becomes exclusive, resulting in the formation of hydantoin **7b** (Figure 1).

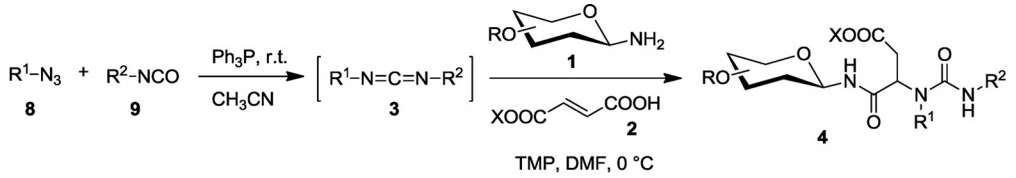
Finally, to investigate whether the process could be used effectively for the combinatorial synthesis of interesting *N*-glycosyl-Asp-urea conjugates **4**, we explored the reaction of acids **2a** and **2b** and a range of *N*-glycosyl nucleophiles with asymmetric *N*,*N′*-dialkyl carbodiimides, with the latter being generated in situ through the Staudinger reaction (Table 3).

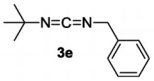
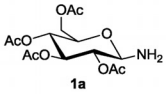
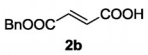
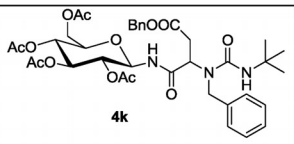
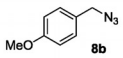
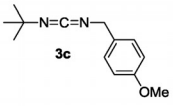
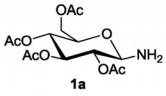
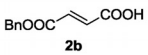
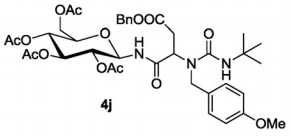
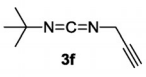
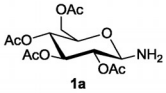
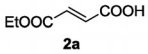
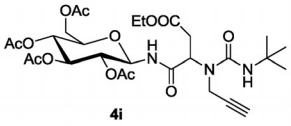
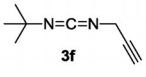
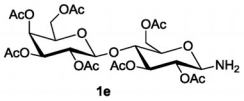
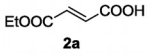
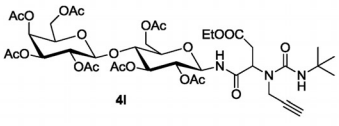
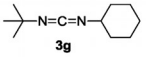
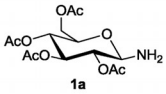
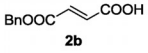
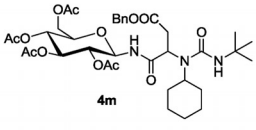
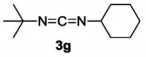
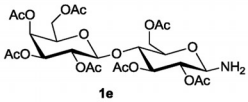
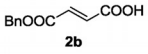
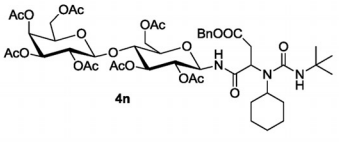
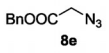
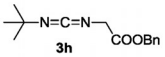
Accordingly, benzyl azide **8a** was treated with *tert*-butyl isocyanate **9a** in CH_3CN as solvent in the presence of 1 equiv. Ph_3P, affording carbodiimide **3e** along with Ph_3PO byproduct (reaction monitored by TLC). Thus the solution was diluted with DMF (20% in volume) and TMP, cooled to 0 °C and nucleophile **1a** followed by acid **2b** were added, producing a 2:1 diastereoisomeric mixture of the desired conjugate **4k** in good yields and as the only regioisomer (Table 3, entry 1). Analogously, starting from *p*-methoxybenzyl azide **8b**, conjugate **4j** was obtained with almost the same *dr*, regiospecificity, and yield (Table 3, entry 2). Propargyl azide **8c** also reacted smoothly with isocyanate **9a**, giving carbodiimide **3f**, which reacted in situ with acid **2a** in the presence of *N*-glycosyl monosaccharide and disaccharide **1a/e** producing good yields of the very interesting clickable *N*-glycosyl-Asp-urea conjugates **4i/l**, respectively (Table 3, entries 3 and 4).

The behaviour of carbodiimides bearing *N*-secondary alkyl and *N′*-tertiary alkyl substituents was then investigated to check whether a totally regioselective process could also be achieved in this case. To our delight, *N*-cyclohexyl *N′*-*tert*-butyl carbodiimide (**3g**), obtained by reaction of the corresponding azide **8d** and isocyanate **9a**, reacted with acid **2b** and nucleophiles **1a** and **1e** to afford conjugates **4m** and **4n**, respectively, as mixtures of diastereoisomers (ca. 2:1 *dr*) but as single regioisomers (Table 3, entries 5 and 6). Finally, we investigated the possibility of synthesising even more intriguing conjugates, such as *N*-glycosyl-peptide mimetics and disaccharide mimetics, by incorporating an α-amino acid or a sugar moiety, respectively, in the carbodiimide framework. Accordingly, starting from azidoglycine benzyl ester **8e** and *tert*-butyl isocyanate **9a**, we were able to produce regiospecifically *N*-glycopeptide **4o** (Table 3, entry 7), which could be further elongated by selective hydrogenolysis of the benzyl ester functionality. In this case, the yield was lower (53%), although still acceptable, likely due to the less nucleophilic nature of α-amino esters than amines in both the Staudinger reaction and in the intramolecular aza-Michael process. On the other hand, glycoazide **8f** reacted under the same conditions with isocyanate **9a**, acid **2b** and *N*-glycosylamine **1a**, producing, in good yields and total regiocontrol, a diastereoisomeric mixture (ca. 2:1 *dr*) of novel disaccharide mimetic **4p**, in which two sugar moieties are tethered through an Asp-urea linkage (Table 3, entry 8).

The *N*-glycosyl-Asp-urea conjugates **4** described above are interesting synthons because their structure could be further modified by simple chemoselective transformations. Accordingly, by choosing the appropriate starting alkyl azide reactant **8** we were able to obtain products that could be selectively deprotected, affording conjugates having a free urea framework, which is known to be of special interest because of its promising features in drug discovery and

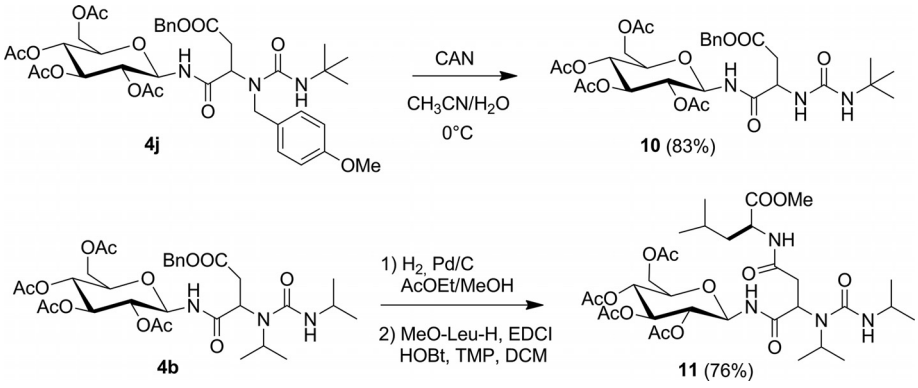
Table 3. Four-component synthesis of *N*-glycosyl-Asp-urea conjugates **4**.



Entry	Azide	Isocyanate	Carbodiimide	Sugar	Acid	Product[a,b]	Yield (%)[c]
1	 **8a**	 **9a**	 **3e**	 **1a**	 **2b**	 **4k**	61
2	 **8b**	 **9a**	 **3c**	 **1a**	 **2b**	 **4j**	63
3	 **8c**	 **9a**	 **3f**	 **1a**	 **2a**	 **4i**	59
4	 **8c**	 **9a**	 **3f**	 **1e**	 **2a**	 **4l**	60
5	 **8d**	 **9a**	 **3g**	 **1a**	 **2b**	 **4m**	66
6	 **8d**	 **9a**	 **3g**	 **1e**	 **2b**	 **4n**	63
7	 **8e**	 **9a**	 **3h**	**1a**	**2a**	**4o**	53
8	**8f**	**9a**	**8k**	**1a**	**2b**	**4p**	61

[a] Formed as a mixture of diastereoisomers (ca. 2:1). [b] The corresponding hydantoins were formed in ca. 20% yield. [c] Isolated yield.

interesting hydrogen-bonding properties.[20] For instance, starting from azide **8b**, derivatives having an *N*-*p*-methoxybenzyl urea moiety, such as **4j**, were obtained, which could be easily removed by oxidative cleavage with cerium(IV) ammonium nitrate (CAN) [Scheme 3, Equation (1)].[21] Moreover, because the MC domino process works well with sugars **1** and fumaric acid monesters **2** having different protecting groups, a synthetic plan can almost always be envisaged in which selective deprotection could be achieved. For example, derivative **4b** was selectively hydrolysed at the benzyl ester function by hydrogenolysis. Subsequent coupling with an α-amino ester, such as H-Leu-OMe, mediated by 1-hydroxybenzotriazole (HOBt) / *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC), afforded *N*-glycosylpeptide **11** in good overall yields [Scheme 3, Equation (2)].



Scheme 3. Chemoselective functionalization of synthons **4**.

Conclusions

We have developed a MC sequential domino process for the synthesis of a novel class of *N*-glycosyl conjugates, i.e., *N*-glycosyl-Asp-urea conjugates, starting from readily accessible reactants, such as azides, isocyanates, fumaric acid monoesters, and *N*-glycosylamines. Because the latter compounds are poor nucleophiles, fine-tuning of the reaction conditions in terms of solvent and temperature was required to achieve the target compounds in good yields. The reaction works nicely with either symmetric or asymmetric *N*,*N*′-dialkyl carbodiimides, giving rise in the latter case to completely regioselective reactions. By applying this process, we obtained a small library of multifunctional compounds that could be used to increase the diversity of sugar frameworks and may find application as synthons in the synthesis of potential glycomimetics and/or glycopeptidomimetics. Moreover, starting from suitable azides, such as α-azido esters or azido sugars, it is possible to synthesise, respectively, novel *N*-glycosyl-urea-peptides or disaccharide mimetics in which two sugar moieties are tethered by an Asp-urea linkage. The operational simplicity and the mild conditions combined with favourable atom economy and environmental aspects render this strategy attractive and promising for the preparation of novel classes of glycoconjugates; it is particularly suitable for solid-phase/combinatorial chemistry. Investigations into these latter issues are in progress in our laboratories.

Experimental Section

General Methods: Commercially available reagent-grade solvents were employed without purification. TLC were run on silica gel 60 F_{254} Merck. Flash chromatography (FC) was performed with silica gel 60 (60–200 μm, Merck). ^{1}H NMR spectra were recorded with 400 MHz spectrometers. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00 ppm). Glycosylamines **1a**–**f** were prepared by catalytic hydrogenation of the corresponding azides obtained as reported in ref.[22]

Three-Component Synthesis of 4a; Typical Procedure: To a stirred solution of carbodiimide **3a** (1 equiv., 0.17 mmol, 26 μL) in a mixture of CH_3CN/DMF (4:1, 2.5 mL) glycosylamine **1a** (1 equiv., 0.17 mmol, 60.0 mg) followed by TMP (1 equiv., 0.17 mmol, 23 μL) and a solution of acid **2a** (1 equiv., 0.17 mmol, 24.5 mg) in a minimum amount of CH_3CN were added at 0 °C. The resulting solution was stirred until the reaction was complete (TLC monitoring, ca. 3 h.). A 1 N HCl aqueous solution was added and the mixture was extracted three times with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, concentrated under vacuum, and the crude material was purified by flash chromatography (FC) to obtain an approximate 2:1 mixture of diastereoisomers **4a** (68.2 mg, 65%).

Four-Component Synthesis of 4j; Typical Procedure: To a stirred solution of benzyl azide **8a** (1.1 equiv., 0.19 mmol, 25.3 mg) and *tert*-butyl isocyanate **9a** (1.1 equiv., 0.19 mmol, 21.7 μL) in CH_3CN (2.0 mL), Ph_3P (1.1 equiv., 0.19 mmol, 49.0 mg) was added at room temp. and the solution stirred overnight. The solution was diluted with DMF (500 μL), the temperature was lowered to 0 °C, and glycosylamine **1a** (1 equiv., 0.17 mmol, 60.0 mg) followed by TMP (1 equiv., 0.17 mmol, 23 μL) and a solution of acid **2b** (1 equiv., 0.17 mmol, 35.0 mg) in a minimum amount of CH_3CN were added. The resulting solution was stirred until the reaction was complete (TLC monitoring, ca. 3 h.). A 1N HCl aqueous solution was added and the mixture was extracted three times with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, concentrated under vacuum, and the crude material was purified by flash chromatography (FC) to give an approximate 2:1 mixture of diastereoisomers **4j** (85.9 mg, 61%).

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-[2-(1,3-diisopropylureido)-4-ethoxy-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4a): Obtained as a mixture of two diastereoisomers; R_f = 0.25 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3360, 1743, 1721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.25 (d, *J* = 9.2 Hz, 1 H, amidic NH), 5.25 (dd, *J* = 9.2, 9.2 Hz, 1 H, 3-H), 5.18 (dd, *J* = 9.2, 9.2 Hz, 1 H, 1-H), 5.04 (dd, *J* = 9.2, 9.2 Hz, 1 H, 4-H), 4.92 (dd, *J* = 9.2, 9.2 Hz, 1 H, 2-H), 4.47 (d, *J* = 7.2 Hz, 1 H, ureido NH), 4.39 (m, 1 H, Asp Cα-H), 4.27 (dd, *J* = 12.4, 4.4 Hz, 1 H, 6-H), 4.14 (q, *J* = 7.2 Hz, 2 H, $COCH_2CH_3$), 4.06 (dd, *J* = 12.4, 2.4 Hz,1 H, H′-6), 3.92 [m, 2 H, -$NCH(CH_3)_2$], 3.78 (m, 1 H, 5-H), 3.36 (dd, *J* = 16.8, 7.6 Hz, 1 H, Asp Cβ-H), 2.45 (dd, *J* = 16.8, 4.8 Hz, 1 H, Asp Cβ-H′), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1–30–1.11 (m, 15 H) ppm; δ [minor diastereoisomer (*R*)] = 7.43 (d, *J* = 9.2 Hz, 1 H, amidic NH), 5.26 (dd, *J* = 9.2, 9.2 Hz, 1 H, 3-H), 5.18 (dd, *J* = 9.2, 9.2 Hz, 1 H, 1-H), 5.04 (dd, *J* = 9.2, 9.2 Hz, 1 H, 4-H), 4.94 (dd, *J* = 9.2, 9.2 Hz, 1 H, 2-H), 4.47 (d, *J* = 7.2 Hz, 1 H, ureido NH), 4.39 (m, 1 H, Asp Cα-H), 4.21 (dd, *J* = 12.4, 4.4 Hz, 1 H, 6-H), 4.13 (q, *J* = 7.2 Hz, 2 H, $COCH_2CH_3$), 4.06 (m, 1 H, H′-6), 3.92 [m, 2 H, -NC*H*-

$(CH_3)_2$], 3.78 (m, 1 H, 5-H), 3.22 (dd, J = 16.8, 8.4 Hz, 1 H, Asp Cβ-H), 2.55 (dd, J = 16.8, 4.8 Hz, 1 H, Asp Cβ-H′), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.30–1.11 (m, 15 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 171.6, 171.2, 170.7, 170.5, 170.4, 170.3, 169.8, 169.4, 169.3, 157.0, 156.5, 78.5, 78.3, 73.5, 73.4, 73.1, 72.9, 70.4, 70.1, 68.3, 61.7, 60.8, 60.7, 53.7, 47.8, 47.4, 42.8, 42.6, 42.1, 35.9, 35.4, 23.45, 23.42, 23.2, 23.1, 23.0, 21.4, 21.3, 21.1, 20.9, 20.6, 20.5, 20.4, 14.1 ppm. ESI: m/z (%) = 656.6 (2) [M^+ + K], 640.6 (100) [M^+ + Na], 618.4 (1) [M^+ + 1]. $C_{27}H_{43}N_3O_{13}$ (617.65): calcd. C 52.50, H 7.02, N 6.80; found C 52.52, H 7.05, N 6.81.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-[4-(benzyloxy)-2-(1,3-diisopropylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4b): Obtained as a mixture of two diastereoisomers; R_f = 0.32 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3344, 1763, 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.33 (m, 6 H), 5.25 (dd, J = 9.2, 9.2 Hz, 1 H), 5.18 (m, 1 H), 5.14 (d, J = 12.4 Hz, 1 H), 5.08 (d, J = 12.4 Hz, 1 H), 5.03 (dd, J = 10.0, 10.0 Hz, 1 H), 4.92 (dd, J = 9.6, 9.6 Hz, 1 H), 4.47 (m, 1 H), 4.38 (m, 1 H), 4.26 (dd, J = 12.4, 4.4 Hz, 1 H), 4.03 (d, J = 12.4 Hz, 1 H), 3.91 (m, 1 H), 3.83 (m, 1 H), 3.76 (m, 1 H), 3.42 (dd, J = 16.8, 7.2 Hz, 1 H), 2.53 (dd, J = 16.8, 5.2 Hz, 1 H), 2.04 (s, 3 H), 1.99 (s, 6 H), 1.97 (s, 3 H), 1.27 (d, J = 6.8 Hz, 3 H), 1.16–1.01 (m, 9 H) ppm: δ [minor diastereoisomer (*R*)] = 7.43 (d, J = 9.6 Hz, 1 H), 7.32 (m, 5 H), 5.26 (dd, J = 9.6, 9.6 Hz, 1 H), 5.18 (m, 1 H), 5.13 (d, J = 12.4 Hz, 1 H), 5.06 (d, J = 12.4 Hz, 1 H), 5.03 (dd, J = 10.0, 10.0 Hz, 1 H), 4.93 (dd, J = 9.2, 9.2 Hz, 1 H), 4.47 (m, 1 H), 4.38 (m, 1 H), 4.20 (dd, J = 12.4, 4.4 Hz, 1 H), 4.03 (d, J = 12.4 Hz, 1 H), 3.91 (m, 1 H), 3.83 (m, 1 H), 3.76 (m, 1 H), 3.28 (dd, J = 16.8, 8.4 Hz, 1 H), 2.63 (dd, J = 16.8, 5.2 Hz, 1 H), 2.02 (s, 3 H), 1.99 (s, 6 H), 1.98 (s, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.16–1.01 (m, 9 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.4, 171.4, 171.1, 170.6, 170.4, 170.3, 169.8, 169.4, 169.3, 157.1, 156.5, 135.7, 128.5, 128.4, 128.2, 128.15, 128.11, 78.5, 78.3, 73.6, 73.5, 73.1, 73.0, 70.4, 70.2, 68.4, 66.6, 53.9, 47.9, 47.5, 42.8, 42.6, 42.1, 35.9, 35.4, 23.4, 23.3, 23.2, 23.0, 22.9, 21.5, 21.3, 21.1, 20.8, 20.6, 20.5, 20.4 ppm. ESI: m/z (%) = 718.7 (11) [M^+ + K], 702.7 (100) [M^+ + Na]. $C_{32}H_{45}N_3O_{13}$ (679.72): calcd. C 56.54, H 6.67, N 6.18; found C 56.58, H 6.63, N 6.19.

Ethyl 3-(1,3-Diisopropylureido)-4-oxo-4-[(2*R*,3*S*,4*S*,5*R*)-3,4,5-tris-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-ylamino]-butanoate (4c): Obtained as a mixture of two diastereoisomers; R_f = 0.35 (hexane/EtOAc, 60:40). FTIR (neat): $\tilde{\nu}$ = 3340, 1747, 1714 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.30 (m, 21 H), 5.12 (dd, J = 9.2, 9.2 Hz, 1 H), 4.85 (m, 4 H), 4.54 (m, 6 H), 4.14 (m, 2 H), 3.91 (m, 2 H), 3.74 (m, 4 H), 3.49 (m, 2 H), 3.18–2.88 (m, 2 H), 1.27–1.11 (m, 15 H) ppm: δ [minor diastereoisomer (*R*)] = 7.30 (m, 21 H), 5.16 (dd, J = 9.2, 9.2 Hz, 1 H), 4.85 (m, 4 H), 4.54 (m, 6 H), 4.14 (m, 2 H), 3.91 (m, 2 H), 3.74 (m, 4 H), 3.49 (m, 2 H), 3.18–2.88 (m, 2 H), 1.27–1.11 (m, 15 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.9, 172.3, 171.1, 171.0, 157.8, 138.2, 138.1, 138.0, 128.3, 128.2, 128.1, 127.9, 127.8, 127.78, 127.70, 127.6, 127.59, 127.53, 127.4, 85.8, 85.7, 81.6, 81.1, 79.6, 79.4, 75.5, 75.4, 74.9, 74.8, 74.6, 73.5, 68.6, 68.5, 60.8, 55.2, 54.7, 54.4, 48.1, 47.6, 44.9, 42.9, 42.7, 35.5, 35.2, 35.2, 23.3, 23.1, 21.5, 21.4, 21.2, 21.1 ppm. ESI: m/z (%) = 832.7 (100) [M^+ + Na], 810.7 (1) [M^+ + 1]. $C_{47}H_{59}N_3O_9$ (810.00): calcd. C 69.69, H 7.34, N 5.19; found C 69.70, H 7.37, N 5.21.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2-(Acetoxymethyl)-6-[2-(1,3-diisopropylureido)-4-ethoxy-4-oxobutanamido]-5-(1,3-dioxoisoindolin-2-yl)tetrahydro-2*H*-pyran-3,4-diyl Diacetate (4d): Obtained as a mixture of two diastereoisomers; R_f = 0.22 (hexane/EtOAc, 30:70). FTIR (neat): $\tilde{\nu}$ = 3361, 1745, 1726 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.82 (m, 2 H), 7.71 (m, 2 H), 7.46 (d, J = 9.6 Hz, 1 H), 6.03 (dd, J = 9.6, 9.6 Hz, 1 H), 5.89 (dd, J = 9.6, 9.6 Hz, 1 H), 5.14 (dd, J = 9.6, 9.6 Hz, 1 H), 5.34 (dd, J = 9.6, 9.6 Hz, 1 H), 4.12 (m, 1 H), 4.31 (m, 2 H), 4.06 (q, J = 7.2 Hz, 2 H), 3.96 (m, 1 H), 3.94 (m, 1 H), 3.69 (m, 1 H), 3.59 (m, 1 H), 3.00 (dd, J = 16.4, 7.2 Hz, 1 H), 2.46 (dd, J = 16.4, 6.0 Hz, 1 H), 2.08 (s, 3 H), 2.01 (s, 3 H), 1.82 (s, 3 H), 1.20–0.95 (m, 15 H) ppm; δ [minor diastereoisomer (*R*)] = 7.82 (m, 2 H), 7.71 (m, 3 H), 5.99 (dd, J = 9.6, 9.6 Hz, 1 H), 5.89 (dd, J = 9.6, 9.6 Hz, 1 H), 5.14 (dd, J = 9.6, 9.6 Hz, 1 H), 5.39 (m, 1 H), 4.31 (m, 2 H), 4.12 (m, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 3.96 (m, 1 H), 3.94 (m, 1 H), 3.69 (m, 1 H), 3.59 (m, 1 H), 3.00 (dd, J = 16.4, 7.2 Hz, 1 H), 2.58 (dd, J = 16.4, 6.0 Hz, 1 H), 2.06 (s, 3 H), 2.01 (s, 3 H), 1.83 (s, 3 H), 1.20–0.95 (m, 15 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$), δ = 172.3, 171.1, 170.9, 170.6, 170.5, 169.8, 169.4, 167.3, 162.5, 157.3, 156.9, 134.2, 131.5, 123.7, 76.1, 76.0, 73.5, 71.0, 70.9, 68.9, 68.8, 61.9, 60.7, 60.6, 54.2, 54.1, 54.0, 53.8, 47.5, 42.8, 42.5, 36.4, 35.4, 23.3, 23.1, 23.0, 21.2, 20.8, 20.6, 20.5, 20.3, 20.2, 14.0, 13.9 ppm. ESI: m/z (%) = 743.6 (9) [M^+ + K], 727.6 (100) [M^+ + Na], 705.5 (6) [M^+ + 1] ppm. $C_{33}H_{44}N_4O_{13}$ (704.73): calcd. C 56.24, H 6.29, N 7.95; found C 56.21, H 6.33, N 7.97.

(3*S*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-{(3*R*,4*S*,5*S*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-[4-(benzyloxy)-2-(1,3-diisopropylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3-yloxy}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4e): Obtained as a mixture of two diastereoisomers; R_f = 0.26 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3345, 1744, 1721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.30 (m, 6 H), 5.33 (d, J = 2.8 Hz, 1 H), 5.22 (dd, J = 9.2, 9.2 Hz, 1 H), 5.12–5.03 (m, 4 H), 4.93 (d, J = 2.8 Hz, 1 H), 4.83 (dd, J = 9.2, 9.2 Hz, 1 H), 4.46–4.35 (m, 4 H), 4.07 (m, 3 H), 4.85 (m, 3 H), 3.75 (dd, J = 9.6, 9.6 Hz, 1 H), 3.69 (m, 1 H), 3.35 (dd, J = 16.8, 7.2 Hz, 1 H), 2.58 (dd, J = 16.8, 5.6 Hz, 1 H), 2.11 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 6 H), 1.92 (s, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.14–1.08 (m, 9 H) ppm; δ [minor diastereoisomer (*R*)] = 7.47 (d, J = 9.6 Hz, 1 H), 7.30 (m, 5 H), 5.33 (d, J = 2.8 Hz, 1 H), 5.23 (dd, J = 9.2, 9.2 Hz, 1 H), 5.12–5.03 (m, 4 H), 4.93 (d, J = 2.8 Hz, 1 H), 4.84 (dd, J = 9.2, 9.2 Hz, 1 H), 4.46–4.35 (m, 4 H), 4.07 (m, 3 H), 4.85 (m, 3 H), 3.75 (dd, J = 9.6, 9.6 Hz, 1 H), 3.69 (m, 1 H), 3.21 (dd, J = 16.8, 7.2 Hz, 1 H), 2.64 (dd, J = 16.8, 5.6 Hz, 1 H), 2.11 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 6 H), 1.92 (s, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.14–1.08 (m, 9 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.4, 172.3, 171.3, 170.9, 170.7, 170.2, 170.1, 170.0, 169.9, 169.3, 168.8, 157.2, 156.7, 135.7, 135.6, 128.5, 128.4, 128.2, 128.1, 100.8, 78.3, 78.2, 76.0, 75.9, 74.4, 74.3, 72.8, 72.7, 70.8, 70.6, 69.1, 66.8, 66.5, 61.0, 54.0, 47.8, 47.4, 42.8, 42.6, 42.4, 36.3, 35.7, 35.2, 31.3, 23.3, 23.2, 23.1, 23.0, 22.9, 21.2, 20.8, 20.7, 20.6, 20.5, 20.3 ppm. ESI: m/z (%) = 990.7 (1000) [M^+ + Na]. $C_{44}H_{61}N_3O_{21}$ (967.97): calcd. C 54.60, H 6.35, N 4.34; found C 54.57, H 6.33, N 4.36.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{(3*R*,4*S*,5*S*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-[4-(benzyloxy)-2-(1,3-diisopropylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3-yloxy}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4f): Obtained as a mixture of two diastereoisomers; R_f = 0.21 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3355, 1749, 1722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.34 (m, 6 H), 5.38–5.30 (m, 3 H), 5.22 (dd, J = 8.8, 8.8 Hz, 1 H), 5.17 (d, J = 12.4 Hz, 1 H), 5.11 (d, J = 12.4 Hz, 1 H), 5.05 (dd, J = 9.2, 9.2 Hz, 1 H), 4.86 (dd, J = 10.8, 4.0 Hz, 1 H), 4.80 (dd, J = 9.2, 9.2 Hz, 1 H), 4.45 (m, 1 H), 4.40 (d, J = 12.4 Hz, 1 H), 4.24 (d, J = 2.4 Hz, 1 H), 4.21 (d, J = 2.4 Hz, 1 H), 4.05 (dd, J = 12.4, 2.4 Hz, 1 H), 3.94 (m, 3 H), 3.84 (m, 1 H), 3.77

(m, 1 H), 3.36 (dd, J = 16.8, 7.2 Hz, 1 H), 2.61 (dd, J = 16.8, 5.6 Hz, 1 H), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.26–1.11 (m, 12 H) ppm; δ [minor diastereoisomer (*R*)] = 7.50 (d, J = 9.6 Hz, 1 H), 7.34 (m, 5 H), 5.38–5.30 (m, 3 H), 5.25 (dd, J = 8.8, 8.8 Hz, 1 H), 5.14 (d, J = 12.4 Hz, 1 H), 5.07 (d, J = 12.4 Hz, 1 H), 5.05 (dd, J = 9.2, 9.2 Hz, 1 H), 4.86 (dd, J = 10.8, 4.0 Hz, 1 H), 4.81 (dd, J = 9.2, 9.2 Hz, 1 H), 4.45 (m, 1 H), 4.39 (d, J = 12.4 Hz, 1 H), 4.24 (d, J = 2.4 Hz, 1 H), 4.21 (d, J = 2.4 Hz, 1 H), 4.05 (dd, J = 12.4, 2.4 Hz, 1 H), 3.94 (m, 3 H), 3.84 (m, 1 H), 3.77 (m, 1 H), 3.24 (dd, J = 16.8, 8.0 Hz, 1 H), 2.68 (dd, J = 16.8, 5.2 Hz, 1 H), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.26–1.11 (m, 12 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.3, 171.3, 170.6, 170.5, 170.4, 170.3, 169.7, 169.6, 169.3, 162.5, 156.7, 135.7, 128.5, 128.4, 128.2, 128.1, 95.6, 78.0, 77.9, 75.4, 75.2, 74.0, 73.9, 73.0, 72.9, 71.2, 71.0, 70.0, 69.4, 68.6, 68.2, 66.6, 62.9, 62.8, 61.6, 54.1, 47.9, 47.5, 42.9, 42.7, 36.4, 35.7, 35.1, 31.4, 23.3, 23.2, 23.1, 23.0, 21.6, 21.2, 21.1, 20.8, 20.6, 20.57, 20.52, 20.48, 20.41 ppm. ESI: *m*/*z* (%) = 990.7 (100) [M^+ + Na]. $C_{44}H_{61}N_3O_{21}$ (967.97): calcd. C 54.60, H 6.35, N 4.34; found C 54.55, H 6.36, N 4.33.

(3*S*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-{(3*R*,4*S*,5*S*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-[4-(benzyloxy)-2-(1,3-dicyclohexylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3-yloxy}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4g): Obtained as a mixture of two diastereoisomers; R_f = 0.26 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3368, 1741, 1724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.33 (m, 5 H), 7.22 (d, J = 8.8 Hz, 1 H), 5.33 (d, J = 2.8 Hz, 1 H), 5.24 (dd, J = 9.2, 9.2 Hz, 1 H), 5.15–5.05 (m, 4 H), 4.93 (dd, J = 10.4, 3.6 Hz, 1 H), 4.83 (dd, J = 9.6, 9.6 Hz, 1 H), 4.46–4.36 (m, 4 H), 4.10 (m, 3 H), 3.85 (dd, J = 6.8, 6.8 Hz, 1 H), 3.75 (d, J = 8.8 Hz, 1 H), 3.67 (m, 1 H), 3.58 (m, 1 H), 3.43 (m, 1 H), 3.38 (dd, J = 16.4, 7.6 Hz, 1 H), 2.53 (dd, J = 16.4, 5.2 Hz, 1 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H),2.01 (s, 6 H), 1.99 (s, 3 H), 1.94 (s, 3 H), 1.92–1.08 (m, 20 H) ppm; δ [minor diastereoisomer (*R*)] = 7.48 (d, J = 8.8 Hz, 1 H), 7.33 (m, 5 H), 5.33 (d, J = 2.8 Hz, 1 H), 5.24 (dd, J = 9.2, 9.2 Hz, 1 H), 5.15–5.05 (m, 4 H), 4.93 (dd, J = 10.4, 3.6 Hz, 1 H), 4.85 (dd, J = 9.6, 9.6 Hz, 1 H), 4.46–4.36 (m, 4 H), 4.10 (m, 3 H), 3.85 (dd, J = 6.8, 6.8 Hz, 1 H), 3.77 (dd, J = 10.0, 5.6 Hz, 1 H), 3.67 (m, 1 H), 3.58 (m, 1 H), 3.38 (m, 1 H), 3.25 (dd, J = 16.8, 8.0 Hz, 1 H), 2.68 (dd, J = 16.8, 5.2 Hz, 1 H), 2.13 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H),2.01 (s, 6 H), 1.99 (s, 3 H), 1.94 (s, 3 H), 1.92–1.08 (m, 20 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 172.4, 171.4, 170.9, 170.7, 170.3, 170.2, 170.1, 170.0, 169.9, 169.3, 169.2, 168.9, 157.1, 156.5, 135.8, 135.6, 128.5, 128.4, 128.2, 128.1, 100.8, 78.4, 78.1, 77.2, 76.7, 76.0, 75.8, 74.4, 74.3, 72.8, 72.7, 71.0, 70.8, 70.6, 69.1, 66.7, 66.6, 66.5, 62.1, 61.0, 60.3, 58.7, 56.7, 54.5, 54.4, 49.6, 49.5, 49.1, 35.8, 35.4, 33.9, 33.8, 33.5, 33.4, 33.3, 31.8, 31.7, 31.5, 26.1, 26.0, 25.6, 25.2, 25.1, 25.0, 24.9, 24.8, 20.7, 20.6, 20.5, 20.4 ppm. ESI: *m*/*z* (%) = 1070.9 (100) [M^+ + Na]. $C_{50}H_{69}N_3O_{21}$ (1048.10): calcd. C 57.30, H 6.64, N 4.01; found C 57.32, H 6.62, N 4.04.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{2-[3-*tert*-butyl-1-(4-methoxybenzyl)ureido]-4-ethoxy-4-oxobutanamido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4h): Obtained as a mixture of two diastereoisomers; R_f = 0.15 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3289, 1741, 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.33 (d, J = 9.6 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.4 Hz, 2 H), 5.25 (dd, J = 9.6, 9.6 Hz, 1 H),5.24 (dd, J = 9.6, 9.6 Hz, 1 H), 5.15 (dd, J = 6.8, 6.8 Hz, 1 H), 5.02 (dd, J = 10.0, 10.0 Hz, 1 H), 4.91 (dd, J = 9.6, 9.6 Hz, 1 H), 4.53 (s, 1 H), 4.21 (m, 2 H), 4.08 (m, 4 H), 3.78 (s, 3 H), 3.75 (m, 1 H), 2.97 (dd, J = 16.8, 8.0 Hz, 1 H), 2.56 (dd, J = 16.8, 6.8 Hz, 1 H), 2.06 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.20 (s, 9 H), 1.86 (m, 3 H) ppm; δ [minor diastereoisomer (*R*)] = 7.40 (d, J = 9.6 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 5.25 (dd, J = 9.6, 9.6 Hz, 1 H),5.24 (dd, J = 9.6, 9.6 Hz, 1 H), 5.15 (dd, J = 9.8, 6.8 Hz, 1 H), 5.02 (dd, J = 10.0, 10.0 Hz, 1 H), 4.93 (dd, J = 6.4, 6.4 Hz, 1 H), 4.48 (s, 1 H), 4.21 (m, 2 H), 4.08 (m, 4 H), 3.77 (s, 3 H), 3.75 (m, 1 H), 3.00 (dd, J = 16.4, 9.2 Hz, 1 H), 2.50 (dd, J = 16.4, 5.2 Hz, 1 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.86 (m, 3 H), 1.16 (s, 9 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.7, 171.5, 170.7, 170.6, 170.5, 170.4, 170.2, 169.9, 169.6, 169.4, 159.3, 158.0, 129.1, 129.0, 127.9, 127.6, 114.6, 114.5, 78.2, 78.1, 73.6, 73.3, 73.1, 70.7, 70.4, 68.4, 68.2, 61.9, 61.8, 60.8, 60.6, 55.7, 55.3, 54.6, 51.2, 51.1, 48.9, 48.5, 34.3, 33.8, 29.1, 29.0, 20.6, 20.4, 14.0, 13.9 ppm. ESI: *m*/*z* (%) = 732.7 (100) [M^+ + Na]. $C_{33}H_{47}N_3O_{14}$ (709.75): calcd. C 55.84, H 6.67, N 5.92; found C 55.82, H 6.67, N 5.93.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-[2-(1-benzyl-3-*tert*-butyl-ureido)-4-(benzyloxy)-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4k): Obtained as a mixture of two diastereoisomers; R_f = 0.23 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3342, 1748, 1724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.33 (m, 10 H, ArH), 7.18 (d, J = 7.2 Hz, 1 H, amidic NH), 5.31 (dd, J = 9.2, 9.2 Hz, 1 H, 3-H), 5.28 (dd, J = 9.2, 9.2 Hz, 1 H, 1-H), 5.24 (dd, J = 9.2, 9.2 Hz, 1 H, 4-H), 5.11 (d, J = 12.4 Hz, 1 H, -OC*H*HPh), 5.10 (m, 1 H, Asp Cα-H), 5.08 (d, J = 12.4 Hz, 1 H, -OC*H*HPh), 4.94 (d, J = 9.6, 9.6 Hz, 1 H, 2-H), 4.46 (s, 1 H, ureido NH), 4.32 (d, J = 17.6 Hz, C*H*HPh), 4.28 (dd, J = 12.4, 4.4 Hz, 1 H, 6-H), 4.17 (d, J = 17.6 Hz, C*H*HPh), 4.08 (dd, J = 12.4, 2.0 Hz, 1 H, 6′-H), 3.79 (m, 1 H, 5-H), 3.06 (dd, J = 16.8, 7.6 Hz, 1 H, Asp Cβ-H), 2.67 (dd, J = 16.8, 6.8 Hz, 1 H, Asp Cβ-H′), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.22 (s, 9 H) ppm: δ [minor diastereoisomer (*R*)] = 7.33 (m, 10 H), 7.22 (d, J = 7.2 Hz, 1 H), 5.28 (dd, J = 9.2, 9.2 Hz, 1 H), 5.24 (m, 2 H), 5.09 (m, 3 H), 4.97 (d, J = 9.6 Hz, 1 H), 4.93 (d, J = 9.6 Hz, 1 H), 4.47–4.14 (m, 3 H), 4.08 (dd, J = 12.0, 2.0 Hz, 1 H), 3.79 (m, 1 H), 3.11 (dd, J = 16.8, 9.2 Hz, 1 H), 2.62 (dd, J = 16.8, 5.2 Hz, 1 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.18 (s, 9 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 171.6, 170.5, 169.9, 169.6, 169.4, 158.1, 137.1, 135.6, 129.2, 128.5, 128.3, 128.2, 127.9, 126.3, 78.1, 73.7, 73.3, 70.8, 68.2, 66.7, 61.8, 55.9, 51.3, 49.6, 34.2, 29.1, 20.7, 20.5 ppm. ESI: *m*/*z* (%) = 780.6 (21) [M^+ + K], 764.7 (100) [M^+ + Na]. $C_{37}H_{47}N_3O_{13}$ (741.79): calcd. C 59.91, H 6.39, N 5.66; found C 59.95, H 6.41, N 5.65.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{4-(Benzyloxy)-2-[3-*tert*-butyl-1-(4-methoxybenzyl)ureido]-4-oxobutanamido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4j): Obtained as a mixture of two diastereoisomers; R_f = 0.39 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3360, 1751, 1729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.32 (m, 6 H), 7.09 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 5.27 (dd, J = 9.6, 9.6 Hz, 1 H), 5.26 (dd, J = 9.6, 9.6 Hz, 1 H), 5.19 (m, 1 H), 5.09 (m, 3 H), 4.96 (d, J = 9.6 Hz, 1 H), 4.91 (d, J = 9.6 Hz, 1 H), 4.50 (s, 1 H), 4.26 (m, 2 H), 4.10 (m, 2 H), 3.78 (s, 3 H), 3.07 (dd, J = 16.8, 7.2 Hz, 1 H), 2.66 (dd, J = 16.8, 7.2 Hz, 1 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.22 (s, 9 H) ppm; δ [minor diastereoisomer (*R*)] = 7.42 (d, J = 9.6 Hz, 1 H),7.32 (m, 5 H), 7.13 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 5.28 (dd, J = 9.6, 9.6 Hz, 1 H), 5.25 (dd, J = 9.6, 9.6 Hz, 1 H), 5.19 (m, 1 H), 5.09 (m, 3 H), 4.96 (d, J = 9.6 Hz, 1 H), 4.91 (d, J = 9.6 Hz, 1 H), 4.47 (s, 1 H), 4.26 (m, 2 H), 4.10 (m, 2 H), 3.78 (s, 3 H), 3.11 (dd, J = 16.8, 8.8 Hz, 1 H), 2.66 (dd, J = 16.8, 5.6 Hz, 1 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.18 (s, 9 H) ppm; ^{13}C NMR (100.6 MHz,

$CDCl_3$): δ = 171.6, 171.4, 170.6, 170.5, 170.4, 170.3, 169.9, 169.6, 169.4, 159.3, 158.0, 135.6, 135.5, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 114.6, 114.5, 78.2, 78.1, 73.6, 73.5, 73.3, 73.1, 70.8, 70.4, 68.4, 68.2, 66.7, 66.5, 61.9, 61.8, 55.8, 55.3, 54.6, 51.2, 51.1, 49.1, 48.5, 34.2, 33.7, 29.1, 29.0, 20.65, 20.62, 20.5, 20.4 ppm. ESI: *m*/*z* (%) = 794.7 (100) [M^+ + Na]. $C_{38}H_{49}N_3O_{14}$ (771.82): calcd. C 59.13, H 6.40, N 5.44; found C 59.16, H 6.41, N 5.46.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-{2-[3-*tert*-butyl-1-(prop-2-ynyl)ureido]-4-ethoxy-4-oxobutanamido}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4i): Obtained as a mixture of two diastereoisomers; R_f = 0.46 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3371, 1767, 1741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.22 (d, *J* = 9.2 Hz, 1 H), 5.28–5.20 (m, 2 H), 5.08–5.02 (m, 2 H), 4.97–4.88 (m, 2 H), 4.26 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.08 (d, *J* = 12.8 Hz, 1 H), 3.96 (dd, *J* = 18.8, 2.4 Hz, 1 H), 2.87 (dd, *J* = 18.8, 2.4 Hz, 1 H), 3.77 (m, 1 H), 3.07 (dd, *J* = 16.8, 7.6 Hz, 1 H), 2.75 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.39 (t, *J* = 2.4 Hz, 1 H), 2.08 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.37 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm: δ [minor diastereoisomer (*R*)] = 7.20 (d, *J* = 9.2 Hz, 1 H), 5.28–5.20 (m, 2 H), 5.08–5.02 (m, 2 H), 4.97–4.88 (m, 2 H), 4.21 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.08 (d, *J* = 12.8 Hz, 1 H), 4.02 (dd, *J* = 18.8, 2.4 Hz, 1 H), 3.77 (m, 2 H), 3.12 (dd, *J* = 16.8, 8.0 Hz, 1 H), 2.68 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.43 (t, *J* = 2.4 Hz, 1 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.99 (s, 3 H), 1.35 (s, 9 H), 1.25 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.3, 171.2, 170.6, 170.5, 170.4, 170.3, 169.8, 169.4, 156.8, 156.6, 79.2, 78.3, 78.2, 73.9, 73.8, 73.7, 73.2, 73.0, 70.7, 70.4, 68.4, 68.2, 61.8, 61.7, 60.8, 60.7, 55.5, 55.1, 51.5, 35.2, 35.1, 33.8, 33.6, 29.4, 29.2, 29.1, 20.6, 20.5, 14.0 ppm. ESI: *m*/*z* (%) = 666.6 (2) [M^+ + K], 650.6 (100) [M^+ + Na]. $C_{28}H_{41}N_3O_{13}$ (627.64): calcd. C 53.58, H 6.58, N 6.69; found C 53.60, H 6.57, N 6.71.

(3*S*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-((3*R*,4*S*,5*S*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-{2-[3-*tert*-butyl-1-(prop-2-ynyl)ureido]-4-ethoxy-4-oxobutanamido}tetrahydro-2*H*-pyran-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4l): Obtained as a mixture of two diastereoisomers; R_f = 0.12 (hexane/EtOAc, 60:40). FTIR (neat): $\tilde{\nu}$ = 3358, 1734, 17216 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.18 (d, *J* = 8.8 Hz, 1 H), 5.34 (d, *J* = 3.2 Hz, 1 H), 5.24 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.17 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.07 (dd, *J* = 7.6 Hz, 1 H), 4.98–4.91 (m, 2 H), 4.82 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.49–4.39 (m, 2 H), 4.12 (m, 6 H),3.87–3.76 (m, 4 H), 3.69 (m, 1 H), 3.05 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.73 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.38 (t, *J* = 2.4 Hz, 1 H), 2.14 (s, 3 H), 2.12 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 6 H), 1.99 (s, 3 H), 1.95 (s, 3 H), 1.37 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm: δ [minor diastereoisomer (*R*)] = 7.16 (d, *J* = 8.8 Hz, 1 H), 5.34 (d, *J* = 3.2 Hz, 1 H), 5.25 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.17 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.07 (dd, *J* = 7.6 Hz, 1 H), 4.98–4.91 (m, 2 H), 4.85 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.49–4.39 (m, 2 H), 4.12 (m, 6 H),3.87–3.76 (m, 4 H), 3.69 (m, 1 H), 3.09 (dd, *J* = 16.8, 8.4 Hz, 1 H), 2.66 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 2.14 (s, 3 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.95 (s, 3 H), 1.34 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.1, 171.0, 170.6, 170.4, 170.2, 170.0, 169.9, 169.4, 168.9, 156.9, 156.7, 100.9, 79.1, 78.1, 78.0, 74.5, 73.8, 72.8, 71.0, 70.8, 69.1, 66.7, 62.0, 61.8, 60.9, 60.8, 55.2, 54.9, 51.5, 35.0, 34.9, 33.7, 33.6, 29.2, 29.1, 20.7, 20.67, 20.61, 20.5, 20.4, 14.0 ppm. ESI: *m*/*z* (%) = 938.7 (100) [M^+ + Na]. $C_{40}H_{57}N_3O_{21}$ (915.90): calcd. C 52.45, H 6.27, N 6.69; found C 52.46, H 6.29, N 4.57.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-[4-(benzyloxy)-2-(3-*tert*-butyl-1-cyclohexylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4m): Obtained as a mixture of two diastereoisomers; R_f = 0.41 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3335, 1731, 1722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.49 (d, *J* = 8.8 Hz, 1 H), 7.32 (m, 5 H), 5.26–5.03 (m, 5 H), 4.93 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.67 (s, 1 H), 4.40 (m, 1 H), 4.26 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.04 (d, *J* = 12.4 Hz, 1 H), 3.76 (m, 1 H), 3.37 (m, 1 H), 3.29 (dd, *J* = 16.8, 7.6 Hz, 1 H), 2.60 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.83–1.44 (m, 8 H), 1.30 (s, 9 H), 1.07 (m, 2 H) ppm; δ [minor diastereoisomer (*R*)] = 7.32 (m, 6 H), 5.26–5.03 (m, 5 H), 4.91 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.67 (s, 1 H), 4.40 (m, 1 H), 4.18 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.05 (d, *J* = 12.4 Hz, 1 H), 3.76 (m, 1 H), 3.55 (m, 1 H), 3.29 (dd, *J* = 16.8, 7.6 Hz, 1 H), 2.56 (dd, *J* = 16.8, 4.4 Hz, 1 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.83–1.44 (m, 8 H), 1.30 (s, 9 H), 1.07 (m, 2 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.0, 172.6, 171.1, 170.5, 170.46, 170.41, 170.2, 169.8, 169.7, 169.4, 156.9, 135.7, 128.5, 128.25, 128.22, 128.1, 78.5, 78.3, 73.5, 73.4, 73.3, 73.0, 70.4, 70.3, 68.3, 68.2, 66.7, 61.8, 57.0, 56.3, 54.7, 54.0, 51.2, 51.1, 35.8, 35.7, 32.0, 31.8, 31.7, 29.3, 29.2, 26.2, 26.0, 25.2, 20.6, 20.5, 20.4, 14.1 ppm. ESI: *m*/*z* (%) = 756.7 (100) [M^+ + Na]. $C_{36}H_{51}N_3O_{13}$ (733.81): calcd. C 58.92, H 7.01, N 5.73; found C 58.90, H 7.00, N 5.77.

(3*S*,4*S*,5*S*,6*S*)-2-(Acetoxymethyl)-6-{(3*R*,4*S*,5*S*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-[4-(benzyloxy)-2-(3-*tert*-butyl-1-cyclohexylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3-yloxy}tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4n): Obtained as a mixture of two diastereoisomers; R_f = 0.27 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3326, 1728, 1725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.51 (d, *J* = 8.8 Hz, 1 H, amidic NH), 7.35 (m, 5 H, ArH), 5.35 (dd, *J* = 3.6, 1.2 Hz, 1 H, Gal 4-H), 5.25 (dd, *J* = 9.2, 9.2 Hz, 1 H, Glu 3-H), 5.16 (dd, *J* = 9.2, 9.2 Hz, Glu 1-H), 5.15 (d, *J* = 12.4 Hz, 1 H, O*CH*HPh), 5.11 (d, *J* = 12.4 Hz, 1 H, O*CH*HPh), 5.10 (dd, *J* = 10.4, 8.0 Hz, 1 H, Gal 2-H), 4.96 (dd, *J* = 10.4, 3.6 Hz, 1 H, Gal 3-H), 4.88 (dd, *J* = 9.2, 9.2 Hz, 1 H, Glu 2-H), 4.66 (s, 1 H, ureido NH), 4.48 (d, *J* = 8.0 Hz, 1 H, Gal 1-H), 4.39 (m, 1 H, Asp Cα-H), 4.40 (dd, *J* = 12.0, 2.0 Hz, 1 H, Glu 6-H), 4.13 (m, 1 H, Glu 6′-H), 4.12 (m, 1 H, Gal 6-H), 4.11 (dd, *J* = 6.8, 6.8 Hz, 1 H, Gal 6′-H), 3.88 (dd, *J* = 6.8, 1.2 Hz, 1 H, Gal 5-H), 3.80 (dd, *J* = 9.2, 9.2 Hz, 1 H, Glu 4-H), 3.71 (m, 1 H, Glu 5-H), 3.37 (m, 1 H, NC*H*), 3.26 (dd, *J* = 16.4, 7.2 Hz, 1 H, Asp Cβ-H), 2.65 (dd, *J* = 16.4, 6.0 Hz, 1 H, Asp Cβ-H′), 2.15 (s, 3 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 2.044 (s, 3 H), 2.041 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.85–1.50 (m, 8 H), 1.31 (s, 9 H), 1.12 (m, 2 H) ppm: δ [minor diastereoisomer (*R*)] = 7.35 (m, 6 H), 5.35 (d, *J* = 3.2 Hz, 1 H), 5.27 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.18–5.08 (m, 4 H), 4.95 (dd, *J* = 10.4, 3.6 Hz, 1 H), 4.83 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.66 (s, 1 H), 4.49–4.39 (m, 3 H), 4.15–4.06 (m, 3 H), 3.86 (dd, *J* = 6.8, 6.8 Hz, 1 H), 3.79 (dd, *J* = 9.6, 9.6 Hz, 1 H), 3.68 (m, 1 H), 3.60 (m, 1 H), 3.26 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.59 (dd, *J* = 16.8, 4.8 Hz, 1 H), 2.15 (s, 3 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 2.044 (s, 3 H), 2.041 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.85–1.50 (m, 8 H), 1.30 (s, 9 H), 1.12 (m, 2 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 172.9, 171.1, 170.3, 170.2, 170.0, 169.9, 168.9, 157.1, 135.7, 128.6, 128.5, 128.3, 128.2, 100.9, 78.3, 76.0, 74.4, 73.0, 71.0, 70.8, 70.7, 70.6, 69.1, 66.7, 66.6, 62.0, 60.9, 56.9, 54.7, 51.1, 35.6, 31.9, 31.7, 29.3, 26.2, 26.1, 25.3, 20.8, 20.7, 20.6, 20.5, 20.4 ppm. ESI: *m*/*z* (%) = 1060.8 (34) [M^+ + K], 1044.8 (100) [M^+ + Na]. $C_{48}H_{67}N_3O_{21}$ (1022.06): calcd. C 56.41, H 6.61, N 4.11; found C 56.38, H 6.60, N 4.15.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(2-{1-[2-(benzyloxy)-2-oxoethyl]-3-*tert*-butylureido}-4-ethoxy-4-oxobutanamido)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4o): Obtained as a mixture of two

diastereoisomers; R_f = 0.28 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3321, 1731, 1726 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 8.45 (d, *J* = 8.8 Hz, 1 H), 7.37 (m, 5 H), 5.28–5.17 (m, 4 H), 5.09 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.97 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.66 (dd, *J* = 8.4, 5.6 Hz, 1 H), 4.46 (m, 1 H), 4.24 (dd, *J* = 12.0, 4.4 Hz, 1 H), 4.17–4.08 (m, 4 H), 3.84–3.78 (m, 2 H), 3.06 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.69 (dd, *J* = 16.8, 8.4 Hz, 1 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H), 1.29 (s, 9 H), 1.23 (t, *J* = 7.2 Hz, 3 H) ppm; δ [minor diastereoisomer (*R*)] = 8.70 (br. s, 1 H), 7.37 (m, 5 H), 5.28–5.17 (m, 4 H), 5.07 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.98 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.62 (m, 1 H), 4.46 (m, 1 H), 4.17–4.08 (m, 5 H), 3.84–3.78 (m, 2 H), 3.06 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.67 (dd, *J* = 16.8, 7.6 Hz, 1 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.27 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.1, 171.9, 171.2, 171.0, 170.9, 170.5, 170.4, 169.94, 169.91, 169.7, 169.6, 169.3, 156.4, 155.7, 134.94, 134.91, 128.8, 128.7, 128.6, 128.59, 128.51, 128.4, 78.5, 78.4, 73.6, 73.5, 73.4, 70.6, 70.5, 70.4, 68.6, 68.3, 68.2, 68.1, 67.7, 67.6, 62.0, 61.9, 61.8, 61.0, 60.3, 58.2, 57.8, 51.5, 51.3, 49.7, 48.9, 34.2, 34.0, 29.1, 29.0, 28.9, 20.6, 20.5, 20.4, 14.1, 14.0 ppm. ESI: *m*/*z* (%) = 776.6 (1) [M$^+$ + K], 760.6 (100) [M$^+$ + Na]. $C_{34}H_{47}N_3O_{15}$ (737.76): calcd. C 55.35, H 6.42, N 5.70; found C 55.37, H 6.43, N 5.72.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-[4-(benzyloxy)-2-(3-*tert*-butyl-1-{[(3*aR*,4*R*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]methyl}ureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4p): Obtained as a mixture of two diastereoisomers; R_f = 0.21 (hexane/EtOAc, 50:50). FTIR (neat): $\tilde{\nu}$ = 3333, 1727, 1718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.50 (d, *J* = 9.6 Hz, 1 H), 7.30 (m, 5 H), 5.25 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.22 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.08 (d, *J* = 2.4 Hz, 2 H), 5.04–4.88 (m, 3 H), 4.77 (m, 1 H), 4.62 (dd, *J* = 6.0, 1.2 Hz, 1 H), 4.54 (d, *J* = 6.4 Hz, 1 H), 4.45 (dd, *J* = 6.0, 2.0 Hz, 1 H), 4.23–4.16 (m, 2 H), 4.01 (dd, *J* = 12.4, 2.4 Hz, 1 H), 3.75 (m, 1 H), 3.34 (s, 3 H), 3.28 (dd, *J* = 10.4, 6.8 Hz, 1 H), 3.19 (m, 2 H), 2.77 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.95 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.29 (s, 9 H) ppm; δ [minor diastereoisomer (*R*)] = 7.30 (m, 6 H), 5.27 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.23 (dd, *J* = 9.2, 9.2 Hz, 1 H), 5.07 (d, *J* = 2.4 Hz, 2 H), 5.04–4.88 (m, 3 H), 4.77 (m, 1 H), 4.62 (dd, *J* = 6.0, 1.2 Hz, 1 H), 4.56 (d, *J* = 6.4 Hz, 1 H), 4.49 (dd, *J* = 6.0, 2.0 Hz, 1 H), 4.23–4.16 (m, 2 H), 4.01 (dd, *J* = 12.4, 2.4 Hz, 1 H), 3.75 (m, 1 H), 3.32 (s, 3 H), 3.28 (dd, *J* = 10.4, 6.8 Hz, 1 H), 3.19 (m, 1 H), 3.00 (dd, *J* = 16.8, 8.8 Hz, 1 H), 2.66 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.26 (s, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.9, 171.6, 170.9, 170.8, 170.5, 170.4, 169.8, 169.5, 169.4, 157.5, 157.4, 135.7, 135.6, 128.5, 128.4, 128.2, 128.1, 113.4, 112.8, 112.2, 110.4, 110.2, 109.9, 87.2, 86.7, 86.5, 85.4, 84.3, 84.2, 82.1, 82.0, 81.6, 78.2, 78.1, 73.6, 73.5, 73.4, 73.3, 70.6, 70.5, 68.2, 66.6, 61.8, 56.1, 55.8, 55.0, 51.2, 51.1, 50.3, 43.0, 34.3, 33.6, 29.5, 29.2, 29.0, 26.6, 26.5, 26.4, 25.1, 24.9, 24.8, 20.5, 20.4 ppm. ESI: *m*/*z* (%) = 860.7 (100) [M$^+$ + Na], 838.7 (1) [M$^+$ + H]. $C_{39}H_{55}N_3O_{17}$ (837.87): calcd. C 55.91, H 6.62, N 5.02; found C 55.88, H 6.60, N 5.03.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-[4-(benzyloxy)-2-(3-*tert*-butylureido)-4-oxobutanamido]tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (10): R_f = 0.43 (hexane/EtOAc, 40:60). FTIR (neat): $\tilde{\nu}$ = 3325, 1730, 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.35 (m, 7 H), 5.32 (dd, *J* = 9.6, 9.6 Hz, 1 H), 5.20 (dd, *J* = 9.2 Hz, 1 H), 5.10 (m, 3 H), 4.94 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.71 (br. s, 1 H), 4.30 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.10 (dd, *J* = 12.4, 2.4 Hz, 1 H), 3.25 (dd, *J* = 17.6, 4.0 Hz, 1 H), 2.63 (dd, *J* = 17.6, 4.4 Hz, 1 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.36 (s, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 172.1, 171.7, 170.5, 169.7, 169.4, 155.9, 135.4, 128.6, 128.3, 127.9, 78.3, 73.7, 72.7, 71.0, 68.3, 66.6, 50.8, 49.8, 35.4, 29.4, 20.6 ppm. ESI: *m*/*z* (%) = 674.6 (100) [M$^+$ + Na]. $C_{30}H_{41}N_3O_{13}$ (651.67): calcd. C 55.29, H 6.34, N 6.45; found C 55.30, H 6.36, N 6.44.

(3*R*,4*S*,5*S*,6*R*)-2-(acetoxymethyl)-6-{2-(1,3-diisopropylureido)-4-[(*S*)-1-methoxy-4-methyl-1-oxopentan-2-ylamino]-4-oxobutanamido}tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (11): Obtained as a mixture of two diastereoisomers; R_f = 0.25 (hexane/EtOAc, 30:70). FTIR (neat): $\tilde{\nu}$ = 3312, 1722, 1721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereoisomer (*S*)] = 7.27 (d, *J* = 8.8 Hz, 1 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 5.25 (dd, *J* = 9.6, 9.6 Hz, 1 H), 5.20 (dd, *J* = 9.6, 9.6 Hz, 1 H), 5.03 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.91 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.56 (m, 2 H), 4.24 (m, 2 H), 4.04 (dd, *J* = 12.8, 2.4 Hz, 1 H), 3.92–3.76 (m, 3 H), 3.70 (s, 3 H), 3.23 (dd, *J* = 14.8, 6.8 Hz, 1 H), 2.46 (dd, *J* = 14.8, 4.8 Hz, 1 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.62 (m, 2 H), 1.52 (m, 1 H), 1.28–1.11 (m, 12 H), 0.91 (m, 6 H) ppm; δ [minor diastereoisomer] = 7.78 (d, *J* = 9.2 Hz, 1 H), 6.09 (d, *J* = 8.0 Hz, 1 H), 5.22 (dd, *J* = 9.6, 9.6 Hz, 1 H), 5.19 (dd, *J* = 9.6, 9.6 Hz, 1 H), 5.04 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.92 (dd, *J* = 9.6, 9.6 Hz, 1 H), 4.56 (m, 2 H), 4.24 (m, 2 H), 4.04 (dd, *J* = 12.8, 2.4 Hz, 1 H), 3.92–3.76 (m, 3 H), 3.67 (s, 3 H), 3.02 (dd, *J* = 14.8, 6.8 Hz, 1 H), 2.46 (dd, *J* = 14.8, 6.4 Hz, 1 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.62 (m, 2 H), 1.52 (m, 1 H), 1.28–1.11 (m, 12 H), 0.91 (m, 6 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.1, 173.0, 170.8, 170.6, 170.5, 170.1, 170.0, 169.8, 169.7, 169.4, 169.3, 78.5, 78.3, 73.5, 73.1, 70.5, 70.2, 68.4, 68.3, 61.8, 61.7, 54.6, 54.2, 52.1, 52.0, 50.9, 48.5, 48.3, 42.8, 42.6, 42.1, 41.3, 41.2, 38.7, 37.8, 23.5, 23.4, 23.2, 23.1, 22.9, 22.7, 21.9, 21.8, 21.3, 21.0, 20.8, 20.7, 20.6, 20.5, 20.4 ppm. ESI: *m*/*z* (%) = 739.7 (100) [M$^+$ + Na]. $C_{32}H_{52}N_4O_{14}$ (716.78): calcd. C 53.62, H 7.31, N 7.82; found C 53.61, H 7.33, N 7.80.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H NMR, ^{13}C NMR, and ESI-MS spectra of all new compounds. Copies of ^{1}H-^{1}H COSY spectra of **4a** and (*S*)-**4n**. Variable-temperature ^{1}H NMR spectra of **4a** in [D_6]DMSO.

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[14] The stereochemistry of the major diastereoisomer was assessed by chemical correlation.

[15] The exact assignment of the ^{1}H NMR signals of both diastereoisomers **4a** was achieved on the basis of ^{1}H-^{1}H COSY spectra (see the Supporting Information).

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[18] To investigate whether *N*-glycosylamine **1a** acts as a base to produce the thermodynamic mixture of diastereoisomers, we treated the equimolar mixture of **4a** obtained in the reaction carried out in DMF (entry 5, Table 1) with **1a** under the reaction conditions (0 °C, CH_3CN/DMF). After 3 h, the mixture of diastereoisomers was recovered with the same equimolar ratio. Moreover, in a separate experiment, when a ca. 2:1 diastereoisomeric mixture of **4a** was treated with secondary and tertiary amines, under the same reaction condition, we did not observe any change in the diastereoisomeric ratio. Only by treating a ca. 2:1 diastereoisomeric mixture of **4a** with stronger bases, such as aqueous NaOH, was epimerisation detected. These results suggest that the process is irreversible, leading to the formation of the kinetic mixture of diastereoisomers.

[19] In this reaction we also detected the regioselective formation of the corresponding hydantoin derivative.

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[21] Compound **10** was also synthesised by using a multistep procedure to determine the stereochemical outcome and to confirm the regiochemistry of the process. Accordingly, commercially available (*S*)-*N*-Boc-Asp(OBzl)-OH (**12**) was coupled with glycosylamine **1a**, affording conjugate (*S*)-**13**, which, after Boc-deprotection, was treated with *tert*-butyl isocyanate **10a** to produce (*S*)-**10**, which corresponds to the major diastereoisomer obtained with our MC process.

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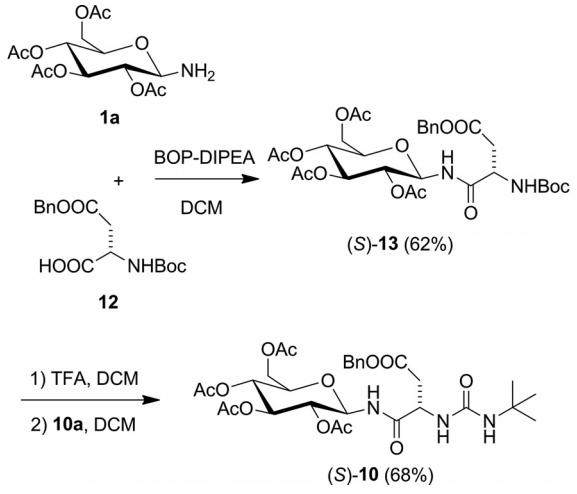

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