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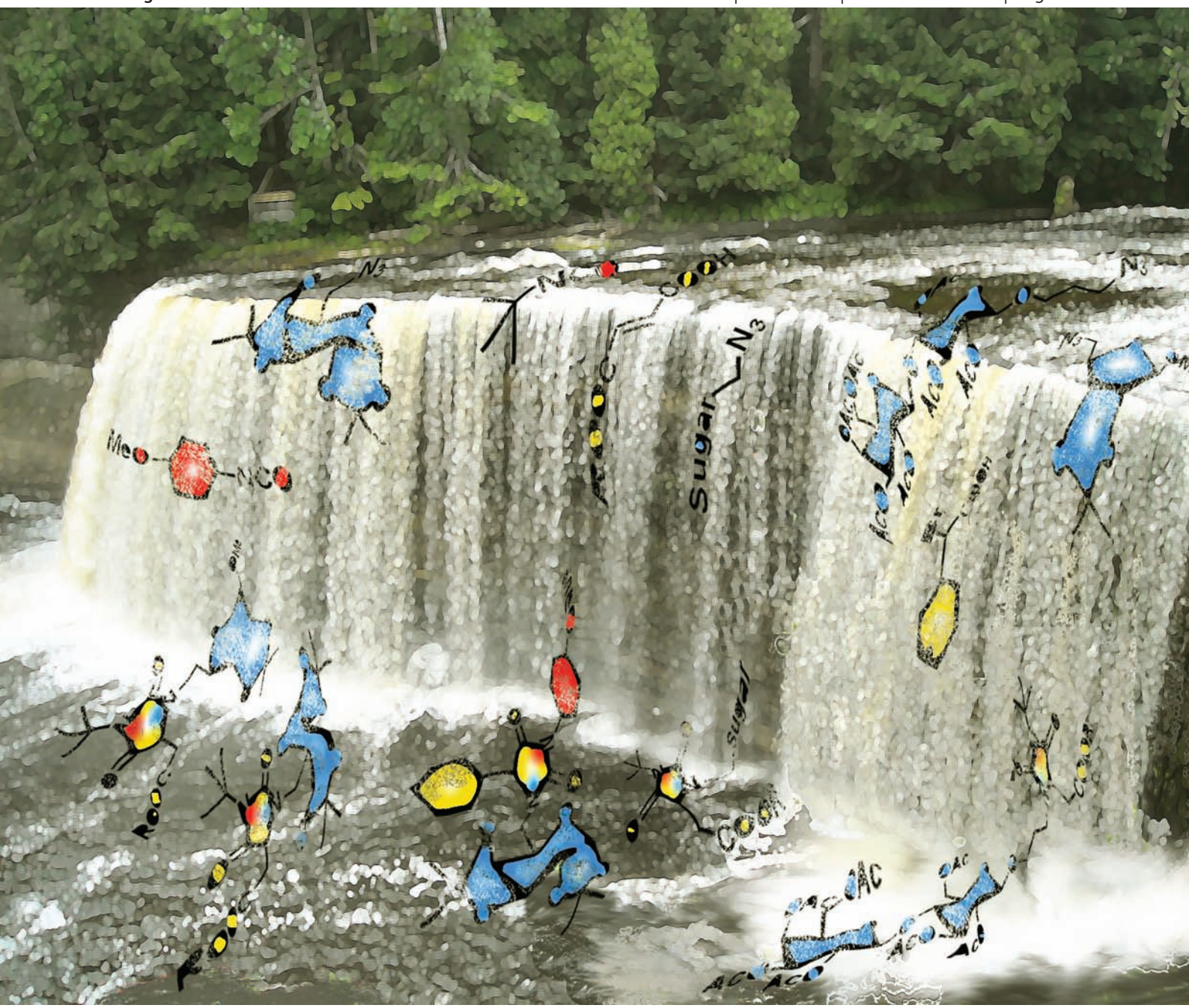

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FULL PAPER
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PAPER

Three-component, one-pot sequential synthesis of glyco-hydantoin conjugates†

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The development of new methods for linking sugars to heterocycles and peptides is an attractive area of research because glyco-conjugates play important roles in biology and medicine and are indispensable tools for probing several processes. Herein we report a one-pot, three-component sequential procedure for the synthesis of a novel class of glyco-conjugates, *i.e.* glyco-hydantoin conjugates, in high yields and very mild conditions, using readily accessible starting materials. We also demonstrated that some of the glyco-hydantoin conjugates obtained are synthons for the preparation of a novel class of glyco-pseudopeptides in which the amino acid is tethered to the sugar through the hydantoin ring.

Introduction

The development of new multicomponent (MC) coupling processes has attracted intense interest in recent years.[1] Such processes allow the efficient construction of elaborate molecules from simple precursors in a minimum number of steps, and many are ideally suited for the generation of structurally diverse libraries of small molecules. In particular, "one-pot" MC sequential syntheses, in which a number (≥2) of synthetic steps involving three or more reactants are carried out in the same flask without isolation of any intermediate, feature a high degree of reaction mass efficiency and are especially suitable in combinatorial chemistry and diversity-oriented synthesis programs, thus playing a central role in the development of modern synthetic methodology for pharmaceutical and drug discovery research.[2] In this context, since carbohydrates have secured their place in pharmaceutical chemistry, in biopharmaceuticals as well as in small molecule chemistry, development of new methods for linking sugars to heterocycles, peptides or proteins is an active area of research.[3] However, despite the advances made recently in discovering new MC reactions for the construction of different arrays of heterocyclic compounds,[4] there is a need to broaden the scope of carbohydrate-based one-pot MC processes for the construction of novel carbohydrate conjugates. In fact, the resulting sugar-heterocycle conjugates are expected to be important structural scaffolds in drug discovery because, apart from their different pharmacodynamic effects, these hybrid molecules often exhibit unusual pharmacokinetic properties, such as tissue permeability.[5] In addition, new biological properties, both in terms of activity and/or selectivity, may appear due to specific interactions between glycoside residues and bioreceptors.[6]

Among different heterocycles, hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications. In fact, many derivatives have been identified as anti-convulsants[7] and antimuscarinics,[8] antiulcer and antiarrythmics,[9] antiviral, antidiabetics,[10] serotonin and fibrinogen receptor antagonists,[11] inhibitors of the glycine binding site of the NMDA receptor,[12] and antagonists of leukocyte cell adhesion acting as allosteric inhibitors of the protein–protein interaction.[13] Moreover, substituted hydantoins are important building blocks for the synthesis of non-natural amino acids both in racemic form by alkaline degradation[14] and in an enantioselective way by enzymatic resolution.[15] The observed activities usually do not arise from the heterocycle itself but from the different ligands that have been attached to it. For this reason, there is a lot of interest in developing new strategies for a straightforward synthesis of selectively substituted hydantoins both in solution and in solid phase.[16] However, quite surprisingly, the synthesis of hydantoin glycoconjugates is an issue that has been almost ignored so far, except for spirohydantoins incorporated at the anomeric position of the carbohydrates.[17]

Within the frame of a project aimed at developing new domino processes for the synthesis of small heterocycles, we recently demonstrated that carbodiimides, when treated with suitable carboxylic acids such as activated α,β-unsaturated and α-bromo carboxylic acids, are useful reagents for the synthesis, in very mild conditions, of diversely substituted hydantoins through a regiospecific domino condensation–aza-Michael–N→O acyl migration one-pot process (Scheme 1).[18]

Herein we wish to report on the extension of this chemistry to the synthesis of a large array of interesting glyco-hydantoin conjugates, some of them have been further functionalized for the synthesis of novel glyco-hydantoin-pseudopeptide conjugates. We envisioned that the transformation of easily accessible sugar-azides and isocyanates to glyco-hydantoin conjugates could be accomplished in a one-pot, MC sequential fashion by forming

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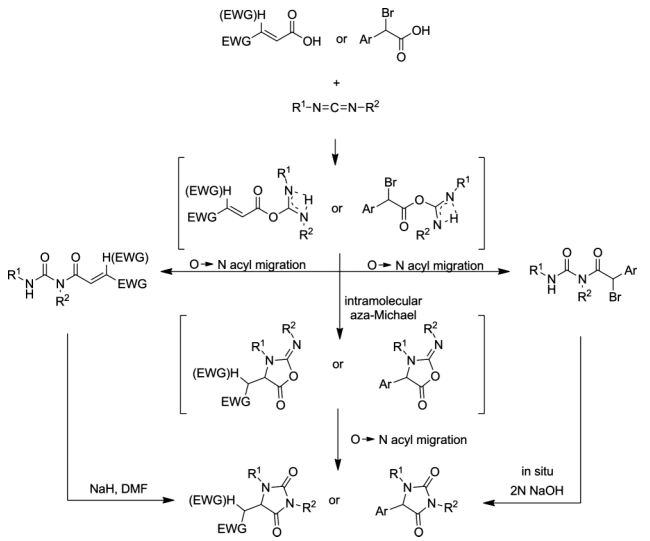
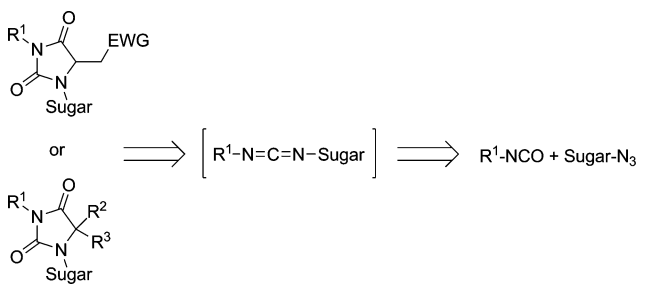
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c1ob06312j



Scheme 1 One-pot domino process for the synthesis of substituted hydantoins.

in situ the reactant carbodiimide through the Staudinger (aza-Wittig) reaction[19] (Scheme 2).



Scheme 2 Retrosynthetic analysis.

Results and discussion

In a previous work, we have defined "strongly asymmetric" those carbodiimides that have two *N*-substituents very different in terms of electronic features, such as an aromatic and an alkyl substituent, and "weakly asymmetric" those carbodiimides that have two alkyl substituents at the nitrogen atoms very different in terms of steric bulkiness.[18b] We have demonstrated that both strongly and weakly asymmetric carbodiimides react with suitable carboxylic acids giving rise to the formation of hydantoins with total regioselectivity in most cases. Thus, we decided to exploit such reactivity for the synthesis of glyco-hydantoin conjugates in a highly regioselective manner starting from carbodiimides having a *N*-primary glyco-substituent, such as 6-aminohexoses and 5-aminopentoses, and a *N′*-tertiary or -aryl substituent.[20] Apart from regiochemical concern, the choice to use *N*-primary glyco-substituents is very intriguing because linking heterocycles or peptides at the primary positions of 6-aminohexoses and 5-aminopentoses provides conjugates with enzymatically stable artificial linkages, also considering the fact that the $–CHNH_2$ moiety present in these sugars might mimic some elements of the glycine structure.[21]

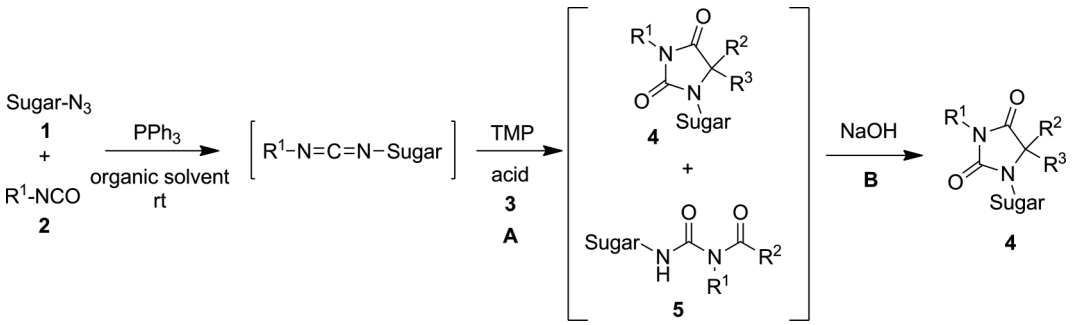
Since carbodiimides could be easily synthesized in high yield by Staudinger reaction, we decided to exploit such reaction in order to perform our synthesis in a MC sequential fashion. The first attempts were made by using 4,4,4-trifluoro-3-trifluoromethyl (Tfm)-crotonic acid **3a** since it was already known that this acid readily reacts with glyco-carbodiimides giving rise to the formation, in the presence of a nucleophile, of peptide-sugar conjugates incorporating hexafluorovaline.[22] Accordingly, when azido-galactose **1a** was reacted with *tert*-butyl isocyanate **2a** in CH_3CN and in the presence of triphenylphosphine, carbodiimide and triphenylphosphine oxide were cleanly formed (TLC monitoring).[23] By adding to the resulting solution 2,4,6-trimethylpyridine (*sym*-collidine, TMP) followed by acid **3a** we were able to obtain in high yield the desired diastereoisomeric conjugates **4a** in a 3.5 to 1.0 diastereoisomeric ratio (d.r.) (entry 1, Table 1).[24] As expected, the reaction was completely regioselective, with only compounds **4a** formed by the nucleophilic attack of the less sterically hindered primary alkyl carbodiimide *N*-substituent, *i.e.* the glycosyl substituent, during the intramolecular aza-Michael step.

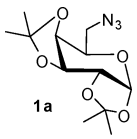
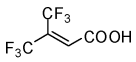
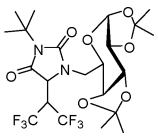
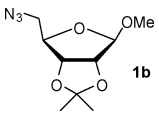
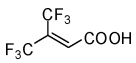
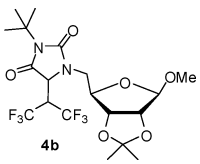
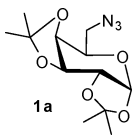
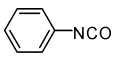
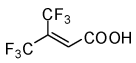
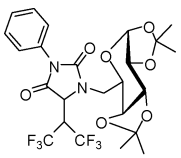
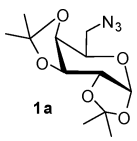
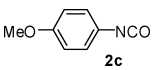
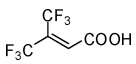
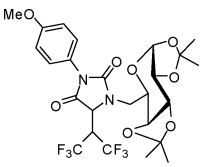
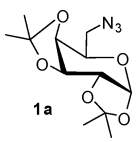
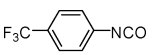
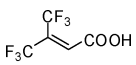
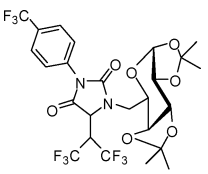
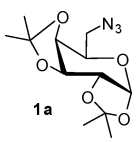
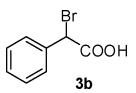
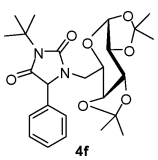
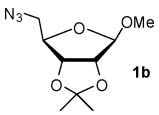
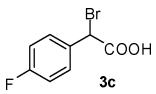
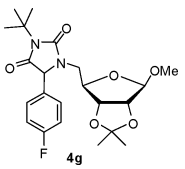
Starting with another primary glycosyl azide, namely methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-ribofuranoside **1b**, the reaction worked nicely as well, producing only the regioisomeric glyco-hydantoin conjugates **4b** in high yield and in an almost equimolecular d.r. (entry 2, Table 1).

We then tried the reaction with *in situ* generated "strongly asymmetric" carbodiimides. Accordingly, by treating glyco-azide **1a** with phenyl isocyanate **2b** in the presence of triphenylphosphine we detected the clean formation of the corresponding carbodiimide after 3 h in CH_3CN at rt. After the addition of TMP followed by acid **3a** we obtained the formation, in high yields and with complete control of the regioselection, of the corresponding diastereoisomeric glyco-hydantoins **4c** (d.r. 3.2 to 1.0) arising from the nucleophilic attack of the *N*-alkyl carbodiimide substituent in the aza-Michael step (entry 3, Table 1). The reaction with strongly asymmetric carbodiimides was shown to be highly versatile since it worked well with either electron-rich *N*-aryl carbodiimides, such as *N*-*p*-methoxyphenyl, *N′*-galactosyl carbodiimide (entry 4, Table 1), and with electron-poor *N*-aryl carbodiimides, such as *N*-*p*-trifluoromethylphenyl, *N′*-galactosyl carbodiimide (entry 5, Table 1) giving rise to the formation of adducts **4d**,**e** respectively, with almost the same d.r. obtained with the unsubstituted *N*-phenyl carbodiimide. However, while the reaction with electron poor *N*-*p*-trifluoromethylphenyl carbodiimide derivative was totally regioselective, in the reaction with the carbodiimide bearing the more nucleophilic *N*-*p*-methoxyphenyl group a small amount (less than 15%) of the regioisomer arising from the nucleophilic attack of the aniline moiety was observed.

In order to expand the scope of this methodology, we decided to explore the reaction with other acids, starting with differently substituted α-bromo acetic acids. In this context, α-bromo phenylacetic acid **3b** and α-bromo-4-fluorophenylacetic acid **3c** were already known to be very reactive in the presence of carbodiimides even in low polarity solvents such as DCM.[18c] Thus, azides **1a** and **1b** were reacted with *t*-butyl isocyanate **2a** and Ph_3P in CH_2Cl_2 as a solvent, giving rise to the formation of the corresponding carbodiimides as well. The resulting solutions were treated with TMP followed by acids **3b**,**c**, respectively, affording an equimolar diastereoisomeric mixture of only the regioisomeric

Table 1 Three-component sequential synthesis of glyco-hydantoin conjugates



Entry	Azide	Isocyanate	Acid	Solvent	Method	Product	d.r.	Yield(%)[a]
1	 1a	 2a	 3a	CH_3CN	**A**	 4a	3.5 : 1.0	89
2	 1b	 2a	 3a	CH_3CN	**A**	 4b	1.5 : 1.0	83
3	 1a	 2b	 3a	CH_3CN	**A**	 4c	3.2 : 1.0	65
4	 1a	 2c	 3a	CH_3CN	**A**	 4d	3.2 : 1.0	69[b]
5	 1a	 2d	 3a	CH_3CN	**A**	 4e	3.2 : 1.0	64
6	 1a	 2a	 3b	CH_2Cl_2	**A**	 4f	1.0 : 1.0	78
7	 1b	 2a	 3c	CH_2Cl_2	**A**	 4g	1.0 : 1.0	64

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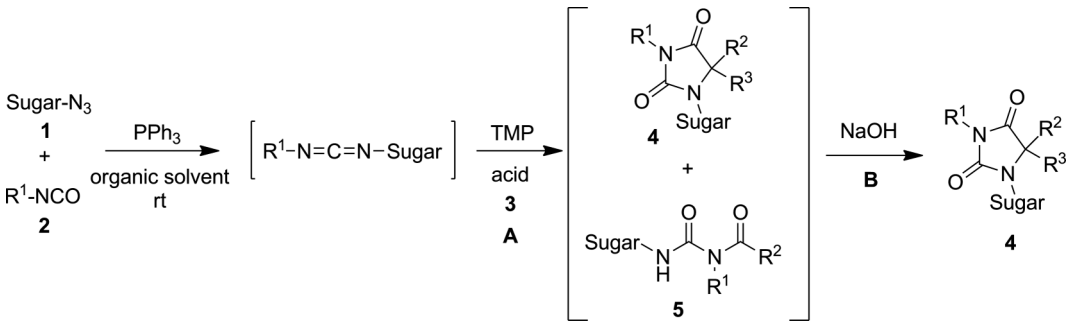


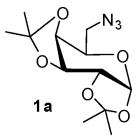
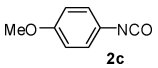
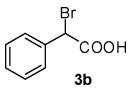
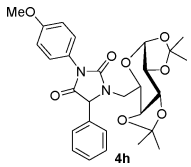
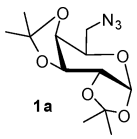
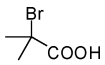
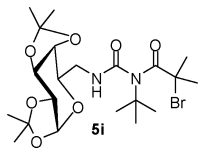
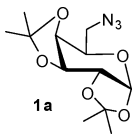
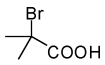
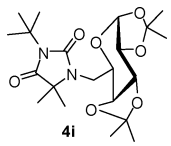
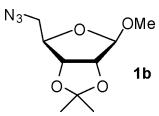
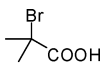
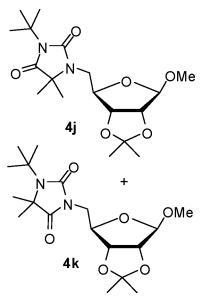
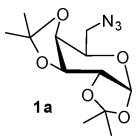
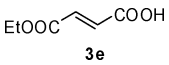
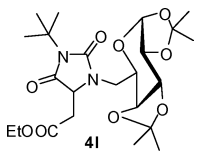
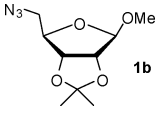
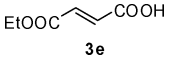
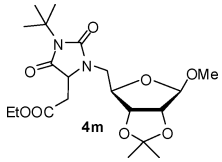
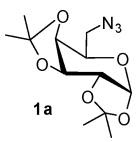
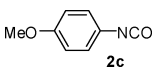
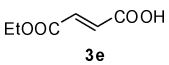
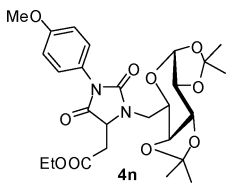
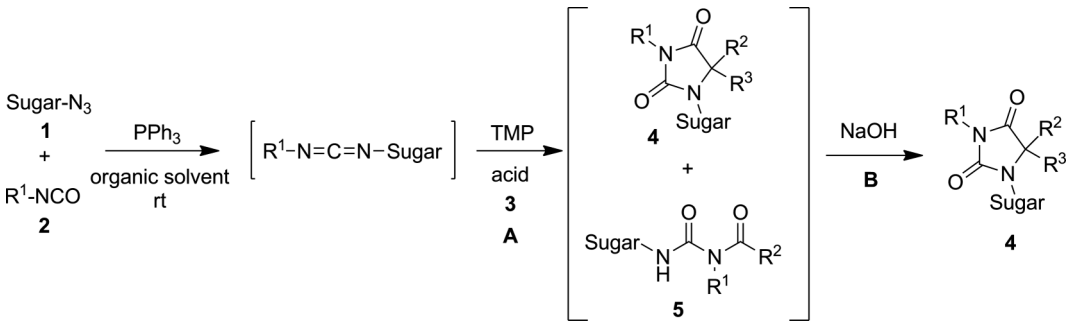
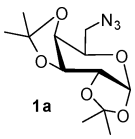
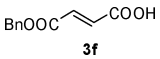
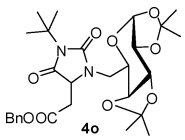
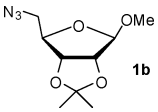
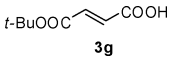
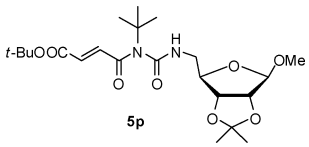
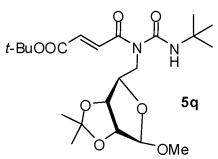
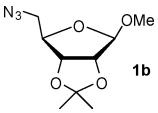
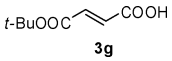
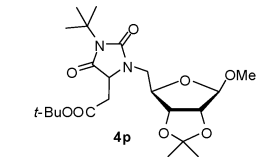
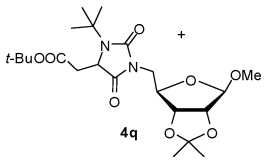
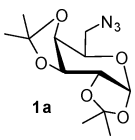
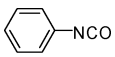
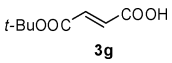
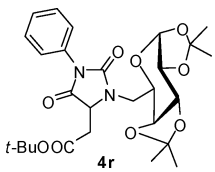
Entry	Azide	Isocyanate	Acid	Solvent	Method	Product	d.r.	Yield(%)[a]
8	 1a	 2c	 3b	CH_2Cl_2	**A**	 4h	1.0 : 1.0	73[b]
9	 1a	 2a	 3d	DMF	**A**	 5i	/	89
10	 1a	 2a	 3d	DMF	**B**	 4i	/	69
11	 1b	 2a	 3d	DMF	**B**	 4j + 4k	/	71
12	 1a	 2a	 3e	CH_3CN	**A**	 4l	2.5 : 1.0	87
13	 1b	 2a	 3e	CH_3CN	**A**	 4m	1.0 : 1.0	82
14	 1a	 2c	 3e	CH_3CN	**A**	 4n	1.2 : 1.0	76[b]

Table 1 (*Contd.*)



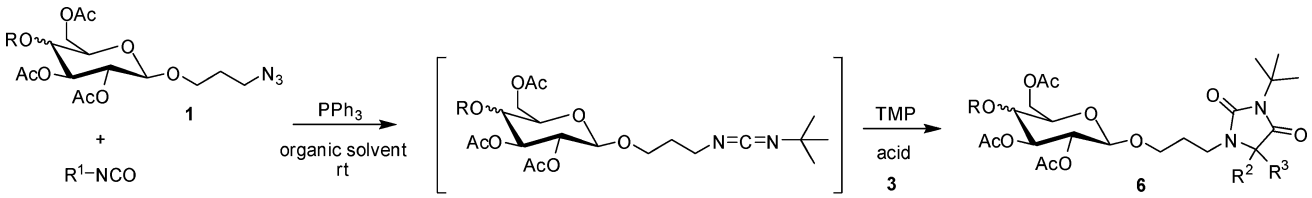
Entry	Azide	Isocyanate	Acid	Solvent	Method	Product	d.r.	Yield(%)[a]
15	 1a	 2a	 3f	CH_3CN	**A**	 4o	2.5 : 1.0	81
16	 1b	 2a	 3g	CH_3CN	**A**	 5p +  5q	/	95
17	 1b	 2a	 3g	CH_3CN	**B**	 4p +  4q	1.0 : 1.0	69
18	 1a	 2b	 3g	CH_3CN	**B**	 4r	1.0 : 1.0	72

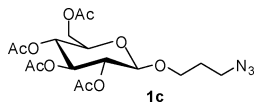
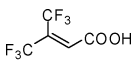
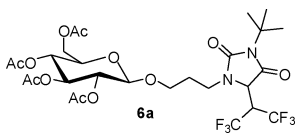
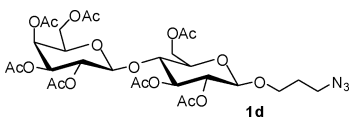
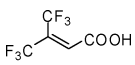
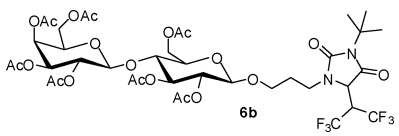
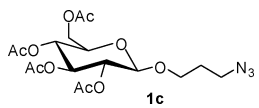
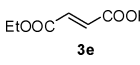
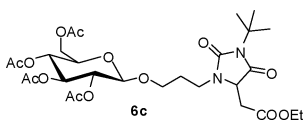
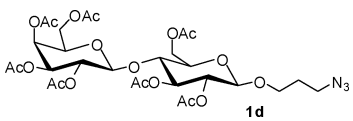
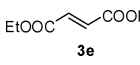
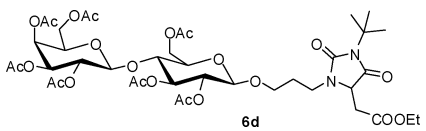
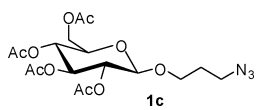
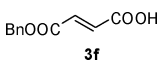
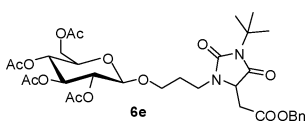
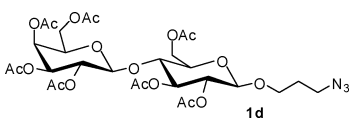
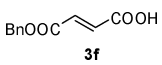
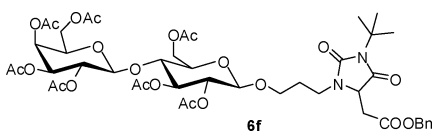
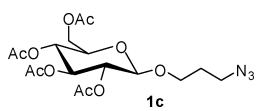
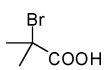
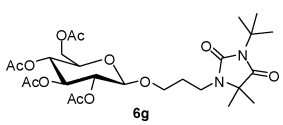
[a] Overall yields. [b] A small amount of the other regioisomers was detected by ^{1}H NMR.

glyco-hydantoin conjugates **4f**,**g**, respectively, which arose from the nucleophilic attack of the primary glycosyl amine moiety. Also with these acids, the reaction with "strongly asymmetric" carbodiimides resulted to be regioselective. In fact, *in situ* formed *N*-galactosyl, *N′*-*p*-methoxyphenyl carbodiimide reacted with acid **3b** in the same conditions described above, *i.e.* in DCM at rt, producing the regioisomers **4h** in an equimolar ratio and almost quantitative yields (entry 8, Table 2).[25]

α-Bromo dimethylacetic acid **3d**, considering the inductive electron donating effect of the two methyl groups, was expected to be much less reactive than the corresponding arylacetic acids **3b**,**c** in the intramolecular aza-Michael step. Indeed, when reacted

Table 2 Three-component sequential synthesis of glycosyl-hydantoin conjugates



Entry	Azide	Isocyanate	Acid	Solvent	Product[a]	Yield (%)[b]
1	 **1c**	 **2a**	 **3a**	CH_3CN	 **6a**	75
2	 **1d**	 **2a**	 **3a**	CH_3CN	 **6b**	71
3	 **1c**	 **2a**	 **3e**	CH_3CN	 **6c**	78
4	 **1d**	 **2a**	 **3e**	CH_3CN	 **6d**	68
5	 **1c**	 **2a**	 **3f**	CH_3CN	 **6e**	72
6	 **1d**	 **2a**	 **3f**	CH_3CN	 **6f**	69
7	 **1c**	 **2a**	 **3d**	DMF	 **6g**	65

[a] Equimolecular mixture of diastereoisomers. [b] Overall yields.

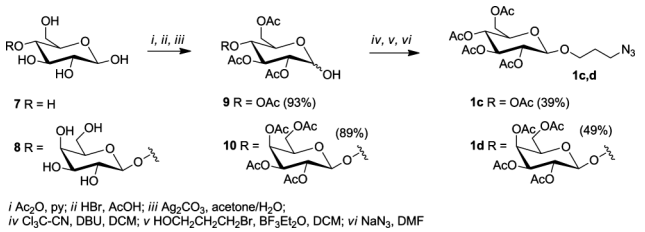
with the carbodiimide arising from Staudinger reaction between galactose-azide **1a** and isocyanate **2a**, we obtained the formation of only the regioisomeric *N*-acylurea derivative **5i** in high yields even when the reaction was performed in highly polar solvent such as DMF (entry 9, Table 1). Evidently, in this case the O→N acyl migration process is favorable compared to the slow intramolecular aza-Michael step (see the mechanism depicted in Scheme 1). However, treatment of compound **5i** with a base, such as NaOH, triggered the formation of the corresponding hydantoin **4i** in almost quantitative yields (data not shown). Moreover, the cyclization step could be performed *in situ* by adding the base solution to the reaction mixture once the formation of the *N*-acylurea intermediate has occurred. Indeed, through a three component sequential procedure consisting of the formation of the carbodiimide starting from azide **1a** and isocyanate **2a**, reaction with acid **3d**, and cyclization of the resulting *N*-acylurea intermediate **5i** triggered by the addition of a 2 N aqueous solution of NaOH, we obtained the direct formation of the regioisomeric glyco-hydantoin **4i**, as the only product, in high yield (entry 10, Table 1). To our surprise, when the latter methodology was used starting with azide **1b**, we obtained, at the end of the process, an equimolar mixture of the two regioisomeric glyco-hydantoin

conjugates **4j**,**k** (entry 11, Table 1). Probably, the sterically and electronic features of the ribose moiety and the *t*-butyl substituent are not different enough to render the O→N acyl migration step regioselective, on the contrary to what happens in the aza-Michael step (see for instance entries 2 and 7, Table 1).

Finally, we decided to explore the reactivity of fumaric acid monoesters. As expected, fumaric acid ethyl ester **3e** reacted smoothly with carbodiimides arising from Staudinger reaction between primary glyco-azides **1a**,**b** and *t*-butyl isocyanate **2a**, giving rise to the formation of glyco-conjugates **4l**,**m**, respectively, as the only regioisomers and in high yields by performing the reaction in CH_3CN as solvent (entries 12 and 13, Table 1). These reactions were slightly less diastereoselective (2.5 to 1.0 and 1.0 to 1.0 d.r. respectively) compared to the corresponding reactions with acid **3a**, probably because the activating ester moiety is less sterically hindered that the two trifluoromethyl groups.[26] Similarly, "strongly asymmetric" carbodiimide *in situ* generated from azide **1a** and *p*-methoxyisocyanate **2c** produced an equimolar mixture of two diastereoisomeric glyco-hydantoins **4n** as the major regioisomers[27] (entry 14, Table 1).

Since glyco-hydantoin conjugates arising from the reaction of fumaric acid monoesters are very intriguing synthons because they could be further functionalized at the ester moiety after simple hydrolysis (see below), we decided to explore the reactivity of other derivatives having different ester protecting groups, such as benzyl and *t*-butyl esters. In such a way, it is possible to design glyco-hydantoin conjugates having orthogonal protecting groups at the glyco and ester moieties. Accordingly, fumaric acid monobenzyl ester **3f** reacted efficiently with carbodiimide derived from the reaction between azide **1a** and isocyanate **2a** producing in the same condition, *i.e.* CH_3CN as solvent, regioisomeric hydantoins **4o** in very good yields (entry 15, Table 1). To our surprise, fumaric acid mono-*t*-butyl ester **3f** reacted with the same kind of carbodiimides leading to the formation of an equimolar mixture of the two regioisomeric *N*-acylurea derivatives **5p**,**q** in almost quantitative yield (entry 16, Table 1). Probably, the sterically hindered *t*-butyl ester hampers the nucleophilic aza-Michael addition, rendering the O→N acyl migration the only operative mechanism. Moreover, as occurred with acid **3d**, the O→N acyl migration mechanism involving *N*-ribofuranosyl, *N*′-*t*-butyl carbodiimide was not regioselective. Also in this case, by treating the solution mixture at 0 °C with a 2 N aqueous solution of NaOH, we obtained the direct formation of the regioisomeric glyco-hydantoins **4p**,**q** in quantitative yields and as an equimolecular mixture of two diastereoisomers[28] (entry 17, Table 1). The same three component sequential procedure could be used for the synthesis of *N*-glyco, *N*′-aryl hydantoins such as **4r** in high yield and with total control of the regioselectivity (entry 18, Table 1).

The preparation of compounds in which a glycosyl residue is linked to another sugar or nonsugar moiety, such as amino acids and heterocyles, through the anomeric carbon is very important since the resulting compounds have application in medicinal chemistry as leads for new drug discovery and for improvement of known drugs acting as inhibitors of carbohydrate processing enzymes, and in glycobiology for studying the role of carbohydrates in biological process.[5,6] Although through this procedure we can have access to a large array of glyco-hydantoin derivatives in which the conjugation arises at the primary positions of 6-aminohexoses and 5-aminopentoses, we could not prepare glycosyl-hydantoin conjugates at the anomeric carbon since the corresponding carbodiimides were not reactive at all. Thus, we decided to synthesize glycosyl-azides **1c**,**d** in which the anomeric carbons of the sugars are tethered to a simple linker bearing a primary azido group (Scheme 3).

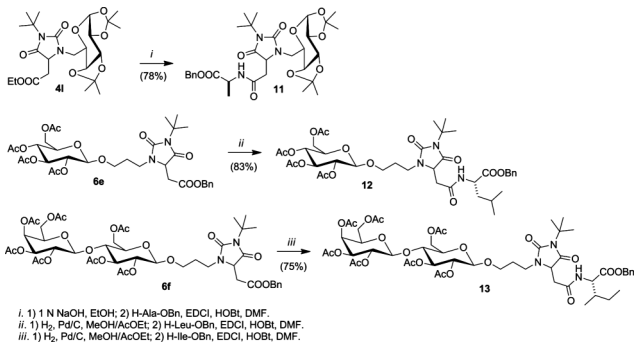


Scheme 3 Synthesis of glyco-azides **1c**,**d**.

Accordingly, acetylation of glucose **7** and lactose **8** followed by selective bromination of the anomeric carbons and hydrolysis, led us to prepare derivatives **9**,**10**, respectively, which were submitted to *O*-glycosylation, *via* trichloroacetimidate, with 3-Br-propanol and finally transformed to the targets glycosyl-azides **1c**,**d** by nucleophilic displacement of the bromine atom. By the use of the 3-azido-propanol linker, we were able to synthesize glycosyl-hydantoin conjugates **6** in a very efficient way (Table 2). Accordingly, glucosyl-azide **1c** and lactosyl-azide **1d** reacted smoothly with *t*-butyl isocyanate **2a** in the presence of Ph_3P leading to the clean formation of the corresponding carbodiimide (TLC monitoring) along with Ph_3PO. After addition of TMP followed by acid **3a**, two pairs of diastereoisomers **6a** and **6b**, respectively, were obtained in high yields (entries 1 and 2, Table 2). Also in this case, the reactions were completely regioselective giving rise to the formation of only the regioisomers arising from the nucleophilic attack of the nitrogens bearing the primary *N*-alkyl substituents, *i.e.* the glycosyl substituents. On the contrary, the process was completely non stereoselective (d.r. 1.0 : 1.0 in both cases). However, this was not surprising since the chiral sugar moieties in these reactions are quite far from the incipient new stereogenic center forming during the intramolecular aza-Michael step. Gratifyingly, the process worked very well also with fumaric acid monoesters **3e**,**f** producing only the regioisomeric glycosyl-hydantoin conjugates **6c–f** in high yields (entries 3–6, Table 2). Finally, 1-bromo-dimethylacetic acid **3d** also reacted efficiently with weakly asymmetric carbodiimide produced from azide **1c** and isocyanate **2a**, giving rise to the formation of the only regioisomeric glycosyl-hydantoin conjugate **6g** (entry 8, Table 2). It is worth noting that in this case we did not observe the intermediate formation of the corresponding *N*-acyl urea derivative, so it was not necessary to treat the solution with a base to trigger the cyclization of the latter, as happened when azido-galactose **1a** was used (entry 18, Table 1). Probably, the distance between the bulky glyco moiety and the reactive site allows the intramolecular aza-Michael reaction to occur even if the electrophilic carbon on the acid is not so reactive.

Some of the derivatives described above, namely the glyco-hydantoin conjugates derived from the reaction of fumaric acid monoesters **3e–g**, could be further modified to synthesize a novel

class of pseudopeptide-sugar conjugates where the glyco moiety is tethered to the peptidic chain through the hydantoin ring. This could be accomplished by hydrolyzing the ester function and coupling the resulting acid with amino acids or peptides. Accordingly, glyco-hydantoin conjugate **4l** was treated with a 1 N aqueous solution of NaOH and the resulting acid coupled with alanine benzyl ester to obtain the sugar-pseudopeptide conjugate **11**, while benzyl ester derivatives **6e**,**f** were hydrolyzed by catalytic hydrogenation and coupled with leucine and isoleucine benzyl esters, respectively, giving rise to the formation of glycosyl-pseudopeptides conjugates **12** and **13**, in all cases with very good overall yields (Scheme 4). It is worth noting that since the MC sequential process works efficiently with fumaric acid monoethyl, monobenzyl, and mono-*t*-butyl esters, one can always have the possibility to hydrolyze chemoselectively the ester function while maintaining the protecting groups on the glyco moiety, or *vice versa*, by choosing suitable starting materials. While for the synthesis of the pseudoglycopeptides described above this is not necessary, the possibility to accomplish a chemoselective deprotection on our glyco-conjugates is a surplus value of our strategy because selective and efficient protection and deprotection often plays a central role in the completion of multistep syntheses of organic molecules.



Scheme 4 Synthesis of sugar-pseudopeptide conjugates.

Conclusions

In conclusion, we have developed an efficient process for the synthesis of libraries of glyco-hydantoin conjugates through a MC sequential process involving simple and readily accessible starting materials such as glyco-azides, isocyanates and suitable carboxylic acids. The reaction is totally regioselective in almost all cases when both strongly and weakly carbodiimide intermediates are involved. These multifunctional compounds could be used to increase the diversity of sugar frameworks and may find applications as potential glycomimetics and/or peptidomimetics. For instance, it is worth noting that β-ribofuranose is the central sugar of many aminoglycoside antibiotics, such as neomycin and paromomycin, and that their 5″ position (5 position of ribofuranose) has been often functionalized in order to obtain more potent/selective antibiotics.[29] The functionalization of such a position by our MC methodology is currently in progress in our laboratories.

Finally, we have also demonstrated that glyco-hydantoin conjugates arising from fumaric acid monoesters are intriguing synthons for the synthesis of a novel class of glycosyl-pseudopeptides through a simple chemoselective hydrolysis–coupling procedure. The operational simplicity, the very good chemical yields and the mild conditions combined with favorable atom economy aspects and a small number of synthetic steps, render this strategy attractive and promising for the preparation of a novel class of glyco-conjugates and particularly suitable for solid phase/combinatorial chemistry. Also investigation of these latter issues are currently in progress.

Experimental section

General methods

Commercially available reagent-grade solvents were employed without purification. Primary glyco-azides **1a**,**b**[30] and fumaric acid monoesters **3e–g**[31] were prepared following reported procedures. ^{1}H NMR spectra were run on spectrometers 250, 400 or 500 MHz. 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). High-resolution MS spectra were recorded with a FT-ICR (Fourier Transform Ion Ciclotorn Resonance) instrument, equipped with an ESI source, or a standard MS instrument, equipped with an EI source.

General procedure for the three-component sequential synthesis of glyco-hydantoin conjugates, METHOD A

To a stirred solution of glycosyl azide (1.2 equiv.) in the organic solvent (0.1 M), neat isocyanate (1.2 equiv.) followed by a solution of Ph_3P (1.2 equiv.) in a minimum amount of the same solvent were added at rt. After the formation of the corresponding carbodiimide was complete (TCL monitoring), TMP (1 equiv.) followed by a solution of the acid (1 equiv.) in a minimum amount of the same solvent were added. The resulting solution was stirred until the reaction was complete (TLC monitoring) leaving the temperature at rt. A 1 N HCl aqueous solution was added and the mixture extracted three times with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the crude purified by flash chromatography.

General procedure for the three-component sequential synthesis of glyco-hydantoin conjugates, METHOD B

To a stirred solution of glycosyl azide (1.2 equiv.) in the organic solvent (0.1 M), neat isocyanate (1.2 equiv.) followed by a solution of Ph_3P (1.2 equiv.) in a minimum amount of the same solvent were added at rt. After the formation of the corresponding carbodiimide was complete (TCL monitoring), TMP (1 equiv.) followed by a solution of the acid (1 equiv.) in a minimum amount of the same solvent were added. The resulting solution was stirred until the reaction was complete and the formation of the *N*-acylurea derivative was detected (TLC monitoring). The solution was cooled to 0 °C and a 2 N aqueous solution of NaOH (10% in volume) was added and the mixture stirred for 30 min at the same temperature. A 1 N HCl aqueous solution was added until acidic pH was obtained, the temperature raised to rt, and the mixture extracted three times with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the crude purified by flash chromatography.

3-*tert*-Butyl-5-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidine-2,4-dione, 4a

Major diastereoisomer, R_f 0.52 (hexane : AcOEt 80 : 20); $[\alpha]_D^{25}$: –34.3 (*c* 0.5, $CHCl_3$); FTIR (neat) *ν* 1789, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.40 (d, *J* = 5.2 Hz, 1H), 4.51 (dd, *J* = 7.6 and 2.0 Hz, 1H), 4.37 (s, 1H), 4.19–4.12 (m 2H), 4.09 (dd, *J* = 8.0 and 1.6 Hz, 1H), 3.79 (m, 1H), 3.75 (septet, *J* = 8.8 Hz, 1H), 3.20 (dd, *J* = 15.2 and 3.6 Hz, 1H), 1.51 (s, 9H), 1.41 (s, 3H), 1.34 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): *δ* = 170.3, 157.9, 122.9 (q, *J* = 280.7 Hz), 122.3 (q, *J* = 282.7), 109.5, 108.5, 96.3, 71.4, 71.1, 70.4, 64.6, 58.6, 55.1, 49.7, 49.4, 49.1, 42.1, 28.3, 25.9, 25.8, 24.7, 24.1; ESI (*m*/*z*) 571.2 [M^++Na, (100)], 549.1 [M^++1, (32)]; HRMS calcd for [$C_{22}H_{30}F_6N_2O_7$]: 548.1957, found: 548.1944. *Minor diast.*: R_f 0.30 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: –15.4 (*c* 0.3, $CHCl_3$); FTIR (neat) *ν* 1775, 1726 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.36 (d, *J* = 5.0 Hz, 1H), 4.74 (s, 1H), 4.53 (dd, *J* = 7.6 and 2.6 Hz, 1H), 4.21 (dd, *J* = 5.0 and 2.3 Hz, 1H), 4.08 (d, *J* = 8.2 Hz, 2H), 3.73–3.69 (m, 2H), 3.34 (dd, *J* = 15.4 and 10.6 Hz, 1H), 1.50 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): *δ* = 170.7, 157.5, 109.9, 109.0, 96.1, 71.5, 70.8, 70.3, 66.6, 58.8, 56.9, 49.4, 49.1, 41.9; ESI (*m*/*z*) 571.2 [M^++Na, (100)], 549.1 [M^++1, (12)]; HRMS calcd for [$C_{22}H_{30}F_6N_2O_7$]: 548.1957, found: 548.1947.

3-*tert*-Butyl-5-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)imidazolidine-2,4-dione, 4b

Major diastereoisomer, R_f 0.25 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: –23.4 (*c* 0.5, $CHCl_3$); FTIR (neat) *ν* 1775, 1715 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 4.94 (s, 1H), 4.66 (dd, *J* = 5.9 and 1.5 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.37 (s, 2H), 4.29 (m, 1H), 3.98–3.88 (m, 2H), 3.31 (s, 3H), 3.29 (dd, *J* = 14.6 and 3.3 Hz, 1H), 1.58 (s, 9H), 1.47 (s, 3H), 1.32 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): *δ* = 170.2, 157.7, 123.4 (q, *J* = 280.7 Hz), 121.1 (q, *J* = 279.7 Hz), 113.6, 110.3, 85.5, 83.4, 82.6, 56.3, 54.9, 50.0 (septet, *J* = 28.2 Hz), 45.9, 28.7, 26.9, 25.5; ESI (*m*/*z*) 515.0 [M^++Na, (100)], 493.1 [M^++1, (10)]; HRMS calcd for [$C_{19}H_{26}F_6N_2O_6$]: 492.1695, found: 492.1693. *Minor diast.*: R_f 0.30 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: –15.0 (*c* 0.6, $CHCl_3$); FTIR (neat) *ν* 1767, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 4.89 (s, 1H), 4.54 (d, *J* = 6.0 Hz, 1H), 4.49 (dd, *J* = 6.0 and 0.9 Hz, 1H), 4.45 (s, 1H), 4.31 (t, *J* = 7.2 Hz, 1H), 3.95 (dd, *J* = 15.2 and 6.8 Hz, 1H), 3.78 (septet, *J* = 8.8 Hz, 1H), 3.28 (s, 3H), 2.98 (dd, *J* = 15.2 and 7.6 Hz, 1H), 1.52 (s, 9H), 1.39 (s, 3H), 1.23 (s, 3H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): *δ* = 169.8, 156.8, 112.9, 110.1, 84.7, 83.4, 81.9, 59.1, 54.8, 53.4, 49.3 (septet, *J* = 27.2 Hz), 44.3, 28.3, 26.4, 24.9, the CF_3 signal was obscured due to its low intensity; ESI (*m*/*z*) 515.1 [M^++Na, (100)], 493.1 [M^++1, (8)]; HRMS calcd for [$C_{19}H_{26}F_6N_2O_6$]: 492.1695, found: 492.1690.

5-(1,1,1,3,3,3-Hexafluoropropan-2-yl)-3-phenyl-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidine-2,4-dione, 4c

Major diastereoisomer, R_f 0.33 (hexane : AcOEt 80 : 20); $[\alpha]_D^{25}$: –43.8 (*c* 0.9, $CHCl_3$); FTIR (neat) *ν* 1774, 1743 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 5.49 (d, *J* = 4.8 Hz, 1H), 5.16 (s, 1H), 4.63 (dd, *J* = 7.6 and 2.4 Hz, 1H), 4.33 (dd, *J* = 4.9 and 2.4 Hz, 1H), 4.27 (d, *J* = 10.0 Hz, 1H), 4.20 (dd, *J* = 8.0 and 1.8 Hz, 1H), 3.94 (m, 2H), 3.55 (dd, *J* = 15.2 and 10.4 Hz, 1H), 1.46 (s, 6H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): *δ* = 169.2, 155.9, 131.4, 129.3, 128.8, 126.3, 110.1, 109.2, 96.3, 71.5, 70.9, 70.5, 66.8, 57.5, 49.6 (septet, *J* = 28.4 Hz), 42.5, 25.9, 25.8, 25.0, 24.6, the CF_3 signal was obscured due to its low intensity; ESI (*m*/*z*) 591.0 [M^++Na, (100)], 569.1 [M^++1, (20)]; HRMS calcd for [$C_{24}H_{26}F_6N_2O_7$]: 568.1644, found: 568.1650. *Minor diast.*: R_f 0.27 (hexane : AcOEt 80 : 20); $[\alpha]_D^{25}$: –12.6 (*c* 0.5, $CHCl_3$); FTIR (neat) *ν* 1792, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.46 (m, 2H), 7.37 (m, 3H), 5.50 (d, *J* = 4.9 Hz, 1H), 4.82 (s, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.41 (dd, *J* = 15.2 and 6.9 Hz, 1H), 4.28 (m, 2H), 4.04 (m, 1H), 3.97 (septet, *J* = 8.7 Hz, 1H), 3.42 (dd, *J* = 15.2 and 3.1 Hz, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.32 (s, 6H); ^{13}C-NMR (125.7 MHz, $CDCl_3$); δ = 168.8, 156.6, 131.6, 129.2, 128.5, 128.2, 109.6, 108.7, 96.4, 71.6, 71.3, 70.6, 70.5, 64.8, 55.7, 49.5 (septet, *J* = 28.4 Hz), 42.7, 25.9, 24.7, 24.3, the CF_3 signal was obscured due to its low intensity; ESI (*m*/*z*) 591.0 [M^++Na, (100)], 569.1 [M^++1, (13)]; HRMS calcd for [$C_{24}H_{26}F_6N_2O_7$]: 568.1644, found: 568.1652.

5-(1,1,1,3,3,3-Hexafluoropropan-2-yl)-3-(4-methoxyphenyl)-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]-dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidine-2,4-dione, 4d

Mixture of two diast., R_f 0.22 (hexane : AcOEt 80 : 20); FTIR (neat) *ν* 1778, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), *one diast.*: *δ* = 7.11 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.39 (d, *J* = 4.9 Hz, 1H), 4.87 (s, 1H), 4.55 (m, 1H), 4.28–4.03 (m, 4H), 3.74 (s, 3H), 3.65 (septet, *J* = 7.8 Hz, 1H), 3.47 (t, *J* = 13.8 Hz, 1H), 1.53 (s, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.27 (s, 3H); ^{1}H-NMR (400 MHz, $CDCl_3$), *other diast.*: *δ* = 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.43 (d, *J* = 4.9 Hz, 1H), 4.84 (s, 1H), 4.55 (m, 1H), 4.28–4.03 (m, 4H), 3.74 (s, 3H), 3.65 (septet, *J* = 7.8 Hz, 1H), 3.46 (t, *J* = 13.8 Hz, 1H), 1.53 (s, 3H), 1.43 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): *δ* = 159.2, 159.0, 155.9, 155.4, 127.9, 127.5, 127.2, 126.8, 114.8, 114.7, 110.2, 110.1, 109.1, 96.5, 96.4, 71.7, 70.7, 64.8, 64.4, 55.7, 40.7, 40.6, 26.1, 26.0, 25.3, 25.2, 24.9, 24.8; ESI (*m*/*z*) 621.2 [M^++Na, (100)], 599.1 [M^++1, (19)]; HRMS calcd for [$C_{25}H_{28}F_6N_2O_8$]: 598.1750, found: 598.1755.

3-*tert*-Butyl-5-phenyl-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)-imidazolidine-2,4-dione, 4f

Mixture of two diast., R_f 0.52 (hexane : AcOEt 70 : 30); FTIR (neat) *ν* 1768, 1715 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.14 (m, 10H), 5.52 (s, 1H), 5.44 (d, *J* = 4.8 Hz, 1H), 5.43 (s, 1H), 5.38 (d, *J* = 4.8 Hz, 1H), 4.55 (t, *J* = 2.4 Hz, 1H), 4.53 (t, *J* = 2.4 Hz, 1H), 4.22–3.93 (m, 8H), 3.40 (dd, *J* = 14.0 and 3.2 Hz, 2H), 1.47 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.23 (s, 9H), 1.22 (s, 3H), 1.20 (s, 9H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): *δ* = 170.4, 170.2, 144.7, 144.5, 135.1, 134.1, 129.3, 129.1, 128.8, 128.7, 128.1, 127.2, 126.9, 126.3, 109.8, 109.7, 108.7, 108.5, 96.3, 96.2, 80.9, 80.2, 71.6, 71.0, 70.9, 70.5, 70.4, 64.7, 64.2, 52.6, 40.6, 40.5, 30.5, 30.4, 28.6, 26.4, 26.1, 26.0, 25.0, 24.9, 24.7, 24.6; ESI (*m*/*z*) 517.2 [M^++Na, (100)], 475.1 [M^++1, (12)]; HRMS calcd for [$C_{25}H_{34}N_2O_7$]: 474.2366, found: 474.2372.

3-*tert*-Butyl-5-(4-fluorophenyl)-1-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)imidazolidine-2,4-dione, 4g

Mixture of two diast., R_f 0.45 (hexane : AcOEt 80 : 20); FTIR (neat) ν 1768, 1731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5H), 7.02 (m, 5H), 5.49 (s, 2H), 4.87 (d, J = 4.8 Hz, 2H), 4.80 (d, J = 6.0 Hz, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.54 (dd, J = 12.0 and 6.0 Hz, 2H), 4.45 (m, 2H), 3.61 (m, 4H), 3.27 (s, 3H), 3.20 (s, 3H),1.40 (s, 3H), 1.39 (s, 3H), 1.26 (s, 9H), 1.25 (s, 9H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.1, 163.2 (d, J = 248.5 Hz), 143.5, 143.3, 129.7, 128.0, 127.9, 115.9 (d, J = 22.1 Hz), 112.3, 109.8, 85.3, 85.2, 83.1, 82.9, 82.4, 82.3, 79.6, 55.3, 55.2, 52.8, 43.1, 43.0, 30.5, 29.6, 26.4, 24.9; ESI (m/z) 459.2 [M^++Na, (100)], 437.2 [M^++1, (47)]; HRMS calcd for [$C_{22}H_{29}FN_2O_6$]: 436.2010, found: 436.2017.

3-(4-Methoxyphenyl)-5-phenyl-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidine-2,4-dione, 4h

One diast: R_f 0.31 (toluene : AcOEt 80 : 20); $[\alpha]_D^{25}$: −27.7 (c 0.8, $CHCl_3$); FTIR (neat) ν 1757, 1717 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 2H), 7.42 (m, 3H), 7.37 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 5.76 (s, 1H), 5.55 (d, J = 7.9 Hz, 1H), 4.61 (dd, J = 7.9 and 2.2 Hz, 1H), 4.31 (dd, J = 5.0 and 3.2 Hz, 1H), 4.25 (dd, J = 8.0 and 1.8 Hz, 1H), 3.98 (m, 1H), 3.82 (s, 3H), 3.69 (dd, J = 14.1 and 6.9 Hz, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.4, 159.6, 133.9, 129.7, 129.3, 128.3, 128.2, 126.4, 125.2, 114.7, 109.5, 108.9, 108.8, 96.9, 96.8, 80.3, 72.0, 71.2, 71.1, 68.5, 55.8, 46.2, 26.5, 26.4, 26.3, 25.4, 24.9, 24.8; ESI (m/z) 547.0 [M^++Na, (100)], 525.1 [M^++1, (31)]; HRMS calcd for [$C_{28}H_{32}N_2O_8$]: 524.2159, found: 524.2153. *Other diast.*: R_f 0.24 (toluene : AcOEt 80 : 20); $[\alpha]_D^{25}$: −17.9 (c 0.3, $CHCl_3$); FTIR (neat) ν 1755, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 2H), 7.41 (m, 3H), 7.37 (d, J = 9.0 Hz, 2H), 6. 93 (d, J = 9.0 Hz, 2H), 5.75 (s, 1H), 5.54 (d, J = 5.0 Hz, 1H), 4.61 (dd, J = 8.0 and 2.3 Hz, 1H), 4.31 (dd, J = 4.9 and 2.3 Hz, 1H), 4.26 (m, 1H), 3.81 (s, 3H), 3.54 (dd, J = 12.9 and 6.3 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.5, 159.6, 131.2, 129.7, 129.6, 129.3, 128.3, 128.2, 128.19, 128.11, 126.4, 114.6, 109.6, 108.8, 96.8, 80.3, 72.1, 71.3, 68.6, 67.5, 55.8, 46.2, 26.5, 26.4, 25.4, 24.9; ESI (m/z) 547.1 [M^++Na, (100)], 525.1 [M^++1, (11)]; HRMS calcd for [$C_{28}H_{32}N_2O_8$]: 524.2159, found: 524.2162.

2-Bromo-*N*-*tert*-butyl-2-methyl-*N*-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methylcarbamoyl)propanamide, 5i

R_f 0.49 (hexane : AcOEt 80 : 20); FTIR (neat) ν 1776, 1711 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 (br s, 1H), 5.50 (d, J = 3.9 Hz, 1H), 4.62 (dd, J = 6.3 and 2.0 Hz, 1H), 4.31 (dd, J = 3.9 and 2.0 Hz, 1H), 4.24 (dd, J = 6.3 and 1.1 Hz, 1H), 4.10 (m, 2H), 3.67 (dd, J = 12.0 and 8.1 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.36 (s, 12H), 1.31 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 174.1, 154.7, 109.6, 109.4, 96.2, 71.6, 70.9, 70.7, 66.1, 60.8, 51.0, 48.5, 33.4, 33.0, 28.3, 26.1, 26.0, 25.0, 24.4; ESI (m/z) 507.0 [M^++1, (100)]; HRMS calcd for [$C_{21}H_{35}BrN_2O_7$]: 506.1628, found: 506.1633.

3-*tert*-Butyl-5,5-dimethyl-1-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidine-2,4-dione, 4i

R_f 0.37 (hexane : AcOEt 80 : 20); $[\alpha]_D^{25}$: −10.5 (c 0.8, $CHCl_3$); FTIR (neat) ν 1789, 1725 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.47 (d, J = 3.9 Hz, 1H), 4.61 (dd, J = 6.3 and 1.9 Hz, 1H), 4.27 (m, 2H), 4.23 (d, J = 6.6 Hz, 1H), 3.56 (dd, J = 11.8 and 2.1 Hz, 1H), 3.10 (dd, J = 11.8 and 6.8 hz, 1H), 1.59 (s, 9H), 1.49 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 156.5, 109.4, 108.8, 96.4, 71.9, 71.0, 70.6, 65.6, 60.7, 57.4, 41.3, 28.7, 26.0, 25.8, 25.1, 24.4, 24.1, 22.9; ESI (m/z) 449.1 [M^++Na, (100)], 427.1 [M^++1, (7)]; HRMS calcd for [$C_{21}H_{34}N_2O_7$]: 426.2366, found: 426.2361.

1-*tert*-Butyl-3-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione, 4j

R_f 0.54 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: −48.7 (c 0.5, $CHCl_3$); FTIR (neat) ν 1759, 1721 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.78 (d, J = 5.9 Hz, 1H), 4.52 (d, J = 5.9 Hz, 1H), 4.38 (t, J = 7.0 Hz, 1H), 3.55 (m, 2H), 3.28 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H), 1.19 (s, 9H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 176.2, 148.2, 112.2, 109.8, 85.3, 83.1, 82.6, 54.6, 42.7, 30.3, 26.4, 25.0, 24.9, 24.1, 23.9; ESI (m/z) 393.2 [M^++Na, (52)], 371.1 [M^++1, (100)]; HRMS calcd for [$C_{18}H_{30}N_2O_6$]: 370.2104, found: 370.2113.

3-*tert*-Butyl-1-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione, 4k

R_f 0.39 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: −43.7 (c 0.3, $CHCl_3$); FTIR (neat) ν 1775, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.88 (s, 1H), 4.80 (d, J = 5.9 Hz, 1H), 4.59 (d, J = 5.9 Hz, 1H), 4.19 (dd, J = 9.8 and 5.0 Hz, 1H), 3.64 (dd, J = 14.6 and 9.9 Hz, 1H), 3.28 (s, 3H), 3.01 (dd, J = 17.2 and 5.0 Hz, 1H), 1.52 (s, 9H), 1.38 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.2, 156.9, 112.3, 109.8, 85.8, 85.2, 82.3, 60.5, 57.8, 55.2, 42.6, 29.3, 28.6, 26.5, 25.0, 24.3, 23.0; ESI (m/z) 393.2 [M^++Na, (100)], 371.1 [M^++1, (13)]; HRMS calcd for [$C_{18}H_{30}N_2O_6$]: 370.2104, found: 370.2111.

Ethyl 2-(1-*tert*-butyl-2,5-dioxo-3-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidin-4-yl)acetate, 4l

Mixture of two diast., R_f 0.43 (hexane:AcOEt 70 : 30); FTIR (neat) ν 1784, 1756, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), *major diast*: δ = 5.32 (d, J = 5.0 Hz, 1H), 4.48 (dd, J = 7.9 and 2.5 Hz, 1H), 4.16 (dd, J = 5.0 and 2.4 Hz, 1H), 4.03 (m, 4H), 3.92 (m, 1H), 3.48 (dd, J = 14.8 and 8.3 Hz, 1H), 3.31 (dd, J = 14.8 and 3.1 Hz, 1H), 3.78 (m, 2H), 1.49 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.95 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{1}H-NMR (400 MHz, $CDCl_3$), *minor diast*: δ = 5.33 (d, J = 5.1 Hz, 1H), 4.47 (m, 1H), 4.21 (t, J = 4.4 Hz, 1H), 4.16 (m, 1H), 4.03 (m, 4H), 3.67 (dd, J = 15.0 and 2.4 Hz, 1H), 2.99 (dd, J = 15.0 and 9.4 Hz, 1H), 2.81 (dd, J = 17.2 and 4.3 Hz, 1H), 2.74 (dd, J = 17.2 and 5.5 Hz, 1H), 1.50 (s, 12H), 1.35 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.13 (t,

J = 7.1 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$), *major diast.*: δ = 173.2, 169.6, 157.6, 109.4, 108.7, 96.2, 71.6, 71.0, 70.5, 65.8, 60.7, 57.7, 56.8, 42.9, 35.1, 28.6, 25.9, 25.0, 24.3, 14.1; ^{13}C-NMR (100.6 MHz, $CDCl_3$), *minor diast.*: δ = 173.3, 169.1, 157.6, 109.5, 108.8, 96.2, 71.6, 70.8, 70.4, 67.1, 60.8, 57.1, 56.8, 41.3, 33.4, 28.6, 25.8, 25.0, 24.7, 14.1; ESI (m/z) 507.1 [M^++Na, (100)], 485.1 [M^++1, (41)]; HRMS calcd for [$C_{23}H_{36}N_2O_9$]: 484.2421, found: 484.2434.

Ethyl 2-(1-*tert*-butyl-3-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-2,5-dioxoimidazolidin-4-yl)acetate, 4m

Mixture of two diast., R_f 0.52 (hexane : AcOEt 70 : 30); FTIR (neat) ν 1775, 1741, 1712 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.93 (s, 1H), 4.92 (s, 1H), 4.72 (dd, J = 5.9 and 1.0 Hz, 1H), 4.61 (s, 1H), 4.31 (t, J = 7.3 Hz, 1H), 4.20–4.12 (m, 4H), 4.07 (t, J = 4.8 Hz, 1H), 3.87 (dd, J = 14.6 and 7.5 Hz, 1H), 3.44 (d, J = 7.4 Hz, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 2.94–2.86 (m, 4H), 1.59 (s, 9H), 1.58 (s, 9H), 1.43 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 173.0, 172.8, 169.4, 169.2, 158.0, 157.4, 112.9, 112.7, 110.4, 110.2, 85.5, 85.2, 84.8, 84.7, 82.4, 82.2, 61.4, 61.3, 58.3, 58.2, 56.8, 55.8, 55.7, 55.5, 45.3, 43.6, 35.2, 33.8, 28.7, 28.6, 28.5, 26.7, 25.3, 25.2, 14.3, 14.2; ESI (m/z) 393.2 [M^++Na, (100)], 371.1 [M^++1, (13)]; HRMS calcd for [$C_{20}H_{32}N_2O_8$]: 428.2159, found: 428.2151.

Ethyl 2-(1-(4-methoxyphenyl)-2,5-dioxo-3-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidin-4-yl)acetate, 4n

Mixture of two diast., R_f 0.36 (hexane : AcOEt 70 : 30); FTIR (neat) ν 1769, 1733, 1716 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 4H), 6.96–6.89 (m, 4H), 5.48 (m, 2H), 4.76 (m, 2H), 4.61 (m, 2H), 4.30–4.25 (m, 4H), 4.17–4.01 (m, 8H), 3.81 (s, 3H), 3.79 (s, 3H), 3.59 (t, J = 3.1 Hz, 1H), 3.55 (dd, J = 4.5 and 3.1 Hz, 1H), 3.07 (m, 2H), 2.80 (m, 2H), 1.52–1.29 (m, 30H); ESI (m/z) 557.1 [M^++Na, (100)], 535.1 [M^++1, (25)]; HRMS calcd for [$C_{26}H_{34}N_2O_{10}$]: 534.2213, found: 534.2206.

Benzyl 2-(1-*tert*-butyl-2,5-dioxo-3-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidin-4-yl)acetate, 4o

Mixture of two diast., R_f 0.19 (hexane : AcOEt 80C: 20); FTIR (neat) ν 1779, 1756, 1726 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), *major diast*: δ = 7.26 (m, 5H), 5.29 (d, J = 4.9 Hz, 1H), 5.07 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.49 (dd, J = 7.7 and 2.4 Hz, 1H), 4.16 (dd, J = 5.0 and 2.4 Hz, 1H), 4.10 (dd, J = 7.8 and 1.6 Hz, 1H), 4.04 (m, 1H), 3.94 (br d, J = 7.6 Hz, 1H), 3.45 (dd, J = 14.9 and 8.2 Hz, 1H), 3.36 (dd, J = 14.9 and 3.0 Hz, 1H), 2.91 (dd, J = 17.2 and 4.2 Hz, 1H), 2.83 (dd, J = 17.2 and 5.4 Hz, 1H), 1.50 (s, 9H), 1.39 (s, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{1}H-NMR (400 MHz, $CDCl_3$), *minor diast*: δ = 7.26 (m, 5H), 5.34 (d, J = 5.0 Hz, 1H), 5.02 (s, 2H), 4.48 (dd, J = 7.8 and 2.6 Hz, 1H), 4.25 (t, J = 4.4 Hz, 1H), 4.18 (dd, J = 5.0 and 2.4 Hz, 1H), 4.06–4.01 (m, 2H), 3.67 (dd, J = 16.0 and 2.4 Hz, 1H), 3.01 (dd, J = 16.0 and 9.4 Hz, 1H), 2.87 (m, 2H), 1.49 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$), *major diast.*: δ = 173.1, 169.5, 157.7, 135.7, 128.5, 128.2, 128.0, 109.4, 108.7, 96.2, 71.6, 71.0, 70.6, 66.6, 65.9, 57.8, 56.9, 43.0, 35.1, 28.5, 26.0, 25.0, 24.3; ESI (m/z) 547.1 [M^++1, (100)]; HRMS calcd for [$C_{28}H_{38}N_2O_9$]: 546.2577, found: 546.2571.

(*E*)-*tert*-Butyl 4-(1-*tert*-butyl-3-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)ureido)-4-oxobut-2-enoate, 5p

R_f 0.30 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: −38.6 (c = 0.6, $CHCl_3$); FTIR (neat) ν 1768, 1731, 1704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, J = 15.1 Hz, 1H), 6.65 (d, J = 15.1 Hz, 1H), 6.48 (br s, 1H), 4.90 (s, 1H), 4.56 (d, J = 5.9 Hz, 1H), 4.46 (d, J = 5.9 Hz, 1H), 4.38 (t, J = 4.6 Hz, 1H), 3.46 (m, 1H), 3.68 (m, 1H), 3.29 (s, 3H), 1.42 (s, 9H), 1.39 (s, 3H), 1.38 (s, 9H), 1.24 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 164.5, 162.4, 155.1, 134.2, 133.4, 112.8, 110.2, 85.5, 85.3, 82.1, 81.5, 57.9, 55.6, 44.1, 28.1, 27.9, 26.4, 24.8; ESI (m/z) 479.3 [M^++Na, (100)], 457.2 [M^++1, (3)]; HRMS calcd for [$C_{22}H_{36}N_2O_8$]: 456.2472, found: 456.2479.

(*E*)-*tert*-Butyl 4-(3-*tert*-butyl-1-(((3a*S*,4*R*,6*S*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)ureido)-4-oxobut-2-enoate, 5q

R_f 0.53 (hexane : AcOEt 70 : 30); $[\alpha]_D^{25}$: −27.4 (c = 1.0, $CHCl_3$); FTIR (neat) ν 1787, 1730 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.71 (br s, 1H), 7.35 (d, J = 15.2 Hz, 1H), 6.68 (d, J = 15.2 Hz, 1H), 4.87 (s, 1H), 4.68 (d, J = 5.9 Hz, 1H), 4.54 (d, J = 5.9 Hz, 1H), 4.21 (m, 2H), 3.56 (m, 1H), 3.28 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H), 1.30 (s, 9H), 1.21 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 168.1, 164.0, 152.6, 135.4, 133.8, 112.5, 110.3, 85.7, 85.1, 82.1, 81.9, 55.5, 51.4, 46.5, 28.6, 27.9, 26.4, 24.9; ESI (m/z) 479.3 [M^++Na, (100)]; HRMS calcd for [$C_{22}H_{36}N_2O_8$]: 456.2472, found: 456.2462.

***tert*-Butyl 2-(1-*tert*-butyl-3-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-2,5-dioxoimidazolidin-4-yl)acetate, 4p**

Mixture of diast., R_f 0.18 (hexane : AcOEt 80 : 20); FTIR (neat) ν 1775, 1736, 1712 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.86 (s, 1H), 4.70 (d, J = 5.9 Hz, 1H), 4.56 (m, 3H), 4.25 (t, J = 7.4 Hz, 1H), 4.12 (m, 2H), 4.02 (dd, J = 5.7 and 4.2 Hz, 1H), 3.83 (dd, J = 14.6 and 8.2 Hz, 1H), 3.43 (dd, J = 14.4 and 6.7 Hz, 1H), 3.34 (dd, J = 14.4 and 7.9 Hz, 1H), 3.27 (s, 3H), 3.24 (s, 3H), 2.85 (dd, J = 14.6 and 6.5 Hz, 1H), 2.79–2.71 (m, 2H), 2.68–2.60 (m, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.38 (s, 6H), 1.37 (s, 9H), 1.36 (s, 9H), 1.24 (s, 3H), 1.23 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.8, 172.7, 168.6, 168.3, 157.7, 157.2, 112.6, 112.5, 110.1, 109.9, 85.3, 85.1, 84.44, 84.40, 82.3, 82.1, 81.9, 81.8, 58.1, 56.8, 55.7, 55.4, 55.2, 45.1, 43.3, 36.4, 35.1, 28.6, 27.9, 26.5, 26.4, 25.1, 25.0; ESI (m/z) 479.3 [M^++Na, (100)]; HRMS calcd for [$C_{22}H_{36}N_2O_8$]: 456.2472, found: 456.2481.

***tert*-Butyl 2-(3-*tert*-butyl-1-(((3a*S*,4*R*,6*R*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-2,5-dioxoimidazolidin-4-yl)acetate, 4q**

Mixture of diast., R_f 0.43 (hexane : AcOEt 70C: 30); FTIR (neat) ν 1773, 1756, 1715 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.86 (s, 1H), 4.70 (d, J = 5.8 Hz, 1H), 4.68 (d, J = 5.9 Hz, 1H), 4.56 (t, J = 6.0 Hz, 2H), 4.35 (m, 2H), 4.07 (m, 2H), 3.54 (m, 4H), 3.28 (s, 3H), 3.26 (s, 3H), 2.98 (dd, J = 5.8 and 2.2 Hz,

1H), 2.94 (dd, J = 5.8 and 2.2 Hz, 1H), 2.72 (dd, J = 6.2 and 4.6 Hz, 1H), 2.68 (dd, J = 6.2 and 4.6 Hz, 1H), 1.38 (s, 18H), 1.36 (s, 6H), 1.33 (s, 9H), 1.32 (s, 9H), 1.21 (s, 3H), 1.20 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 172.3, 167.7, 156.6, 156.4, 112.2, 109.9, 109.8, 85.4, 85.3, 83.7, 83.6, 82.5, 82.3, 81.8, 56.2, 55.7, 55.6, 55.1, 55.0, 41.6, 38.7, 38.6, 28.5, 28.4, 27.9, 26.5, 26.4, 25.1, 25.0; ESI (m/z) 479.3 [M^++Na, (100)]; HRMS calcd for [$C_{22}H_{36}N_2O_8$]: 456.2472, found: 456.2476.

tert-Butyl 2-(2,5-dioxo-1-phenyl-3-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidin-4-yl)acetate, 4r

Mixture of diast., R_f 0.53 (hexane : AcOEt 70 : 30); FTIR (neat) ν 1749, 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 8H), 7.25 (m, 2H), 5.42 (d, J = 5.3 Hz, 1H), 5.41 (d, J = 5.5 Hz, 1H), 4.52 (m, 3H), 4.40 (t, J = 4.7 Hz, 1H), 4.22 (m, 2H), 4.17 (t, J = 8.2 Hz, 1H), 4.16 (t, J = 8.2 Hz, 1H), 4.05 (m, 2H), 3.94 (dd, J = 14.6 and 7.6 Hz, 1H), 3.89 (dd, J = 15.1 and 2.2 Hz, 1H), 3.29 (dd, J = 14.6 and 3.7 Hz, 1H), 3.17 (dd, J = 15.0 and 9.6 Hz, 1H), 2.92 (m, 2H), 2.89 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.35 (s, 12H), 1.37 (s, 9H), 1.27 (s, 3H), 1.24 (s, 6H), 1.22 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 171.8, 171.7, 168.6, 168.1, 156.0, 132.1, 128.9, 127.8, 126.0, 125.9, 109.6, 109.5, 108.9, 108.7, 96.3, 96.2, 81.8, 81.7, 71.5, 70.8, 70.4, 67.5, 65.3, 57.8, 57.0, 42.1, 41.3, 35.7, 34.4, 28.0, 27.9, 26.0, 25.96, 25.91, 24.9, 24.9, 24.4, 24.2; ESI (m/z) 555.1 [M^++Na, (100)], 533.2 [M^++1, (21)]; HRMS calcd for [$C_{27}H_{36}N_2O_9$]: 532.2421, found: 532.2429.

(3*R*,4*S*,5*S*,6*R*)-2-(acetoxymethyl)-6-(3-(3-*tert*-butyl-5-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6a

Mixture of diast., R_f 0.38 (hexane : AcOEt 70 : 30); FTIR (neat) ν 1788, 1765, 1735, 1721 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.11 (m, 2H), 4.99–4.90 (m, 2H), 4.83 (t, J = 8.4 Hz, 2H), 4.39 (dd, J = 13.0 and 7.9 Hz, 2H), 4.24 (m, 2H), 4.15 (m, 2H), 4.04 (m, 2H), 3.77 (m, 6H), 3.60 (m, 2H), 3.51 (m, 1H), 3.40 (m, 1H), 3.06 (m, 2H), 2.00 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.91, (s, 3H), 1.78–1.70 (m, 4H), 1.51 (s, 9H), 1.50 (s, 9H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.5, 170.1, 170.0, 169.9, 169.3, 169.2, 169.0, 157.3, 157.2, 101.1, 100.9, 100.7, 72.7, 72.6, 71.9, 71.8, 71.2, 71.0, 68.4, 68.0, 67.3, 65.5, 63.3, 61.8, 58.9, 58.7, 54.6, 54.2, 49.7 (septet, J = 28.2 Hz), 49.4 (septet, J = 28.9 Hz), 40.2, 39.5, 28.3, 28.2, 27.1, 26.6, 20.5, 20.4, the CF_3 signal was obscured due to its low intensity; ESI (m/z) 555.1 [M^++Na, (100)], 533.2 [M^++1, (21)]; HRMS calcd for [$C_{27}H_{36}F_6N_2O_{12}$]: 694.2172, found: 694.2177.

(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-(3-(3-*tert*-butyl-5-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6b

Mixture of diast., *mixture of diast.*, R_f 0.36 (AcOEt : hexane 50 : 50); FTIR (neat) ν 1759, 1747, 1725, 1708 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.19 (d, J = 2.9 Hz, 2H), 5.03 (t, J = 9.2 Hz, 1H), 5.02 (t, J = 9.2 Hz, 1H), 4.94 (m, 2H), 4.82 (m, 2H), 4.66 (m, 2H), 4.37–4.28 (m, 6H), 4.23 (s, 1H), 4.12 (s, 1H), 3.96 (m, 6H), 3.74–3.61 (m, 10H), 3.46 (m, 3H), 3.32 (septet, J = 5.3 Hz, 1H), 2.98 (m, 2H), 2.02 (s, 3H), 1.99 (s, 6H), 1.96 (s, 6H), 1.90 (s, 6H), 1.89 (s, 12H), 1.87 (s, 3H), 1.86 (s, 3H), 1.80 (s, 6H), 1.72–1.60 (m, 4H), 1.44 (s, 18H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 170.1, 170.0, 169.9, 169.8, 169.5, 169.2, 168.9, 157.2, 157.1, 123.0 (q, J = 279.7 Hz), 122.2 (q, J = 283.7 Hz), 100.9, 100.6, 76.0, 72.8, 71.4, 70.9, 70.7, 69.1, 68.2, 66.9, 66.7, 61.9, 60.8, 58.7, 58.6, 54.6, 54.3, 53.9, 49.6 (septet, J = 28.7 Hz), 40.2, 39.4, 31.5, 30.2, 29.2, 28.2, 28.1, 27.0, 26.5, 20.6, 20.5, 20.4, 20.3; ESI (m/z) 1005.1 [M^++Na, (100)]; HRMS calcd for [$C_{39}H_{52}F_6N_2O_{20}$]: 982.3018, found: 982.3013.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(3-(3-*tert*-butyl-5-(2-ethoxy-2-oxoethyl)-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6c

Mixture of diast., R_f 0.35 (AcOEt : hexane 60 : 40); FTIR (neat) ν 1781, 1754, 1741, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.11 (t, J = 9.5 Hz, 1H), 5.10 (t, J = 9.5 Hz, 1H), 4.97 (t, J = 9.5 Hz, 2H), 4.88 (dd, J = 8.0 and 2.2 Hz, 1H), 4.86 (dd, J = 8.0 and 2.2 Hz, 1H), 4.41 (dd, J = 8.0 and 3.8 Hz, 2H), 4.18 (dd, J = 4.8 and 1.8 Hz, 1H), 4.15 (dd, J = 4.7 and 1.8 Hz, 1H), 4.04 (m, 6H), 3.94 (t, J = 4.6 Hz, 1H), 3.91 (t, J = 4.7 Hz, 1H), 3.78 (m, 2H), 3.61 (m, 2H), 3.50–3.35 (m, 4H), 3.10 (m, 1H), 2.98 (m 1H), 2.75 (m, 4H), 2.00 (s, 6H), 1.97 (s, 3H), 1.96 (s, 3H), 1.93 (s, 6H), 1.91 (s, 6H), 1.75 (m, 4H), 1.51 (s, 18H), 1.16 (t, J = 7.1 Hz, 3H), 1.59 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.8, 170.6, 170.2, 169.3, 169.2, 169.1, 157.3, 157.2, 100.75, 100.72, 72.8, 72.7, 71.8, 71.2, 68.4, 67.3, 66.9, 61.9, 61.8, 61.1, 61.0, 57.9, 57.8, 56.1, 55.7, 38.7, 37.8, 34.4, 34.1, 29.2, 28.6, 28.5, 27.9, 20.66, 20.61, 20.5, 14.1; ESI (m/z) 653.1 [M^++Na, (100)], 631.2 [M^++1, (13)]; HRMS calcd for [$C_{28}H_{42}N_2O_{14}$]: 630.2636, found: 630.2625.

(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-(3-(3-*tert*-butyl-5-(2-ethoxy-2-oxoethyl)-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6d

Mixture of diast., R_f 0.45 (AcOEt : hexane 70 : 30); FTIR (neat) ν 1787, 1753, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.26 (d, J = 3.0 Hz, 2H), 5.11 (t, J = 9.3 Hz, 1H), 5.10 (t, J = 9.2 Hz, 1H), 5.02 (dd, J = 10.4 and 7.9 Hz, 2H), 4.89 (dd, J = 10.4 and 3.4 Hz, 2H), 4.78 (m, 2H), 4.42–4.38 (m, 6H), 3.99 (m, 10H), 3.94 (q, J = 4.6 Hz, 2H), 3.78–3.70 (m, 6H), 3.52–3.40 (m, 5H), 3.06 (m, 1H), 2.98 (m,1H), 2.74 (m, 3H), 2.06 (s, 6H), 2.03 (s, 6H), 1.98 (s, 6H), 1.97 (s, 6H), 1.96 (s, 12H), 1.87 (s, 6H), 1.80–1.68 (m, 4H), 1.52 (18H), 1.17 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 170.1, 170.0, 169.8, 169.5, 168.9, 157.2, 101.0, 100.5, 77.2, 76.1, 72.7, 71.8, 70.9, 70.7, 69.2, 66.6, 61.9, 61.0, 60.8, 56.0, 55.7, 38.6, 37.9, 34.4, 34.1, 28.5, 28.0, 20.6, 20.4, 20.3, 14.1; ESI (m/z) 941.1 [M^++Na, (100)], 957.3 [M^++K, (21)]; HRMS calcd for [$C_{40}H_{58}N_2O_{22}$]: 918.3481, found: 918.3486.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(3-(5-(2-(benzyloxy)-2-oxoethyl)-3-*tert*-butyl-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6e

Mixture of diast., R_f 0.20 (AcOEt : hexane 50 : 50); FTIR (neat) ν 1782, 1773, 1754, 1729 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 10H), 5.10 (m, 2H), 5.03 (s, 4H), 4.96 (t, J = 9.8 Hz, 2H),

4.86 (t, J = 8.4 Hz, 2H), 4.38 (d, J = 3.9 Hz, 1H), 4.35 (d, J = 3.8 Hz, 1H), 4.16 (dd, J = 12.3 and 4.6 Hz, 2H), 4.02 (m, 4H), 3.93 (m, 2H), 3.72 (m, 2H), 3.57 (m, 2H), 3.46–3.29 (m, 4H), 3.08 (m, 1H), 2.93 (m, 1H), 2.81 (m, 2H), 1.98 (s, 3H), 1.97 (s, 3H), 1.94 (s, 6H), 1.93 (s, 6H), 1.92 (s, 3H), 1.90 (s, 3H), 1.48 (s, 18H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 170.6, 170.2, 169.4, 169.2, 157.3, 135.2, 128.6, 128.5, 100.7, 100.6, 72.7, 72.6, 71.8, 71.2, 67.3, 66.8, 61.8, 56.1, 55.7, 38.7, 37.8, 34.4, 28.5, 27.9, 20.7, 20.6, 14.2; ESI (m/z) 715.1 [M$^+$+Na, (100)]; HRMS calcd for [$C_{33}H_{44}N_2O_{14}$]: 692.2793, found: 692.2784.

(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-(3-(5-(2-(benzyloxy)-2-oxoethyl)-3-*tert*-butyl-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6f

Mixture of diast., R_f 0.28 (AcOEt : hexane 70 : 30); FTIR (neat) ν 1784, 1765, 1735, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 10H), 5.25 (d, J = 3.3 Hz, 2H), 5.08 (t, J = 9.4 Hz, 1H), 5.07 (t, J = 9.2 Hz, 1H), 5.03 (m, 5H), 4.91–4.85 (m, 4H), 4.78–4.70 (m, 2H), 4.41–4.33 (m, 5H), 4.04–4.94 (m, 10H), 3.78 (m, 2H), 3.67 (m, 3H), 3.53–3.36 (m 5H), 3.21 (m, 1H), 3.05–2.90 (m, 2H), 2.78 (m, 3H), 2.03 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.94 (s, 9H), 1.93 (s, 9H), 1.92 (s, 6H), 1.90 (s, 3H), 1.85 (s, 6H), 1.65 (m, 4H), 1.47 (s, 18H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 170.2, 170.0, 169.9, 169.6, 168.9, 157.2, 135.9, 135.3, 133.1, 132.1, 131.9, 131.8, 128.6, 128.5, 128.4, 125.4, 101.0, 100.4, 72.7, 71.0, 70.0, 69.2, 68.3, 66.9, 66.7, 61.9, 60.8, 60.2, 57.9, 55.8, 34.2, 30.3, 28.5, 22.8, 20.9, 20.8, 20.5, 20.4, 14.1; ESI (m/z) 1003.3 [M$^+$+Na, (100)]; HRMS calcd for [$C_{45}H_{60}N_2O_{22}$]: 980.3638, found: 980.3643.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(3-(3-*tert*-butyl-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 6g

R_f 0.33 (AcOEt : hexane 60 : 40); $[\alpha]_D^{25}$: −52.0 (c 0.4, $CHCl_3$); FTIR (neat) ν 1777, 1752, 1727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.10 (t, J = 9.4 Hz, 1H), 4.97 (t, J = 9.8 Hz, 1H), 4.88 (t, J = 9.5 Hz, 1H), 4.42 (d, J = 7.9 Hz, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.48 (m, 2H), 1.98 (s, 6H), 1.95 (s, 3H), 1.92 (s, 3H), 1.91 (s, 3H), 1.90 (s, 3H), 1.85 (s, 3H), 1.28 (s, 9H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 174.0, 170.5, 170.1, 169.3, 169.1, 153.4, 100.7, 72.9, 72.8, 71.9, 71.8, 71.3, 68.5, 67.5, 62.0, 58.6, 51.3, 44.0, 32.8, 30.7, 29.2, 28.6, 28.4, 20.6; ESI (m/z) 595.1 [M$^+$+Na, (57)], 573.1 [M$^+$+1, (100)]; HRMS calcd for [$C_{26}H_{40}N_2O_{12}$]: 572.2581, found: 572.2596.

(2*S*)-Benzyl 2-(2-(1-*tert*-butyl-2,5-dioxo-3-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)methyl)imidazolidin-4-yl)acetamido)propanoate, 11

Mixture of two diast., R_f 0.32 (hexane : AcOEt 60 : 40); FTIR (neat) ν 1774, 1724 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), *major diast*: δ = 7.23 (m, 5H), 6.47 (d, J = 7.2 Hz, 1H), 5.34 (d, J = 5.0 Hz, 1H), 5.09 (d, J = 12.3 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1H), 4.47 (m, 2H), 4.25 (dd, J = 5.6 and 3.9 Hz, 1H), 4.16 (dd, J = 4.9 and 2.4 Hz, 1H), 4.08 (m, 1H), 4.02 (m, 1H), 3.66 (dd, J = 15.1 and 2.0 Hz, 1H), 3.07 (dd, J = 15.1 and 9.6 Hz, 1H), 2.66 (m, 2H), 1.49 (s, 9H), 1.36–1.16 (m, 15H); ^{1}H-NMR (400 MHz, $CDCl_3$), *minor diast*: δ = 7.23 (m, 5H), 6.39 (d, J = 7.2 Hz, 1H), 5.31 (d, J = 4.9 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.47 (m, 2H), 4.13 (dd, J = 4.9 and 2.3 Hz, 1H), 4.08 (m, 1H), 4.02 (m, 2H), 3.52 (dd, J = 15.0 Hz, 1H), 3.30 (dd, J = 15.0 and 2.6 Hz, 1H), 2.66 (m, 2H), 1.49 (s, 9H), 1.36–1.16 (m, 15H);^{13}C-NMR (100.6 MHz, $CDCl_3$), *major diast.*: δ = 173.8, 172.6, 167.6, 157.3, 135.3, 128.5, 128.3, 128.1, 109.5, 108.8, 96.2, 71.6, 70.8, 70.4, 67.0, 57.8, 57.6, 48.2, 41.4, 35.5, 28.6, 25.8, 24.9, 24.3, 18.4; ^{13}C-NMR (100.6 MHz, $CDCl_3$), *minor diast.*: δ = 173.2, 172.7, 168.1, 157.6, 135.3, 128.4, 128.3, 128.1, 109.3, 108.7, 96.2, 71.6, 70.9, 70.6, 65.8, 57.8, 56.8, 48.2, 42.9, 36.8, 28.6, 25.9, 24.9, 24.2, 18.4;ESI (m/z) 618.1 [M$^+$+1, (100)]; HRMS calcd for [$C_{31}H_{43}N_3O_{10}$]: 617.2948, found: 617.2956.

(3*R*,4*S*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(3-(5-(2-((*S*)-1-(benzyloxy)-4-methyl-1-oxopentan-2-ylamino)-2-oxoethyl)-3-*tert*-butyl-2,4-dioxoimidazolidin-1-yl)propoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 12

Mixture of diast., R_f 0.35 (AcOEt : hexane 60 : 40); FTIR (neat) ν 1783, 1755, 1717 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (10H), 6.32 (d, J = 8.3 Hz, 1H), 6.28 (d, J = 8.2 Hz, 1H), 3.14 (t, J = 9.5 Hz, 1H), 5.12 (t, J = 9.4 Hz, 1H), 5.06 (m, 2H), 5.05 (m, 2H), 4.97 (t, J = 9.8 Hz, 1H), 4.96 (t, J = 9.6 Hz, 1H), 4.88 (t, J = 9.8 Hz, 1H), 4.86 (t, J = 8.0 Hz, 1H), 4.53 (m, 2H), 4.41 (d, J = 5.2 Hz, 1H), 4.39 (d, J = 5.3 Hz, 1H), 4.14 (m, 2H), 4.06–3.95 (m, 4H), 3.75 (m, 2H), 3.61 (m, 2H), 3.52 (m, 1H), 3.42 (m, 3H), 3.07 (m, 1H), 2.97 (m, 1H), 2.75 (dd, J = 15.9 and 4.8 Hz, 1H), 2.62 (m, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.92 (s, 3H), 1.91 (s, 3H), 1.90 (s, 3H), 1.72 (m, 4H), 1.55-1.46 (m, 6H), 1.51 (s, 9H), 1.50 (s, 9H), 0.84–0.80 (m, 6H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 170.5, 170.1, 169.8, 169.5, 169.3, 168.1, 167.9, 157.2, 157.1, 135.4, 128.5, 128.3, 128.1, 100.8, 72.7, 72.6, 71.9, 71.4, 66.8, 61.9, 60.3, 56.04, 56.00, 50.9, 41.3, 37.4, 35.5, 28.6, 28.0, 24.8, 21.8, 20.6, 20.5, 14.1; ESI (m/z) 828.1 [M$^+$+Na, (100)], 806.1 [M$^+$+1, (2)]; HRMS calcd for [$C_{39}H_{55}N_3O_{15}$]: 805.3633, found: 805.3625.

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