N-Alkylated C-Glycosyl Amino Acid Derivatives: Synthesis by a One-Pot Four-Component Ugi Reaction

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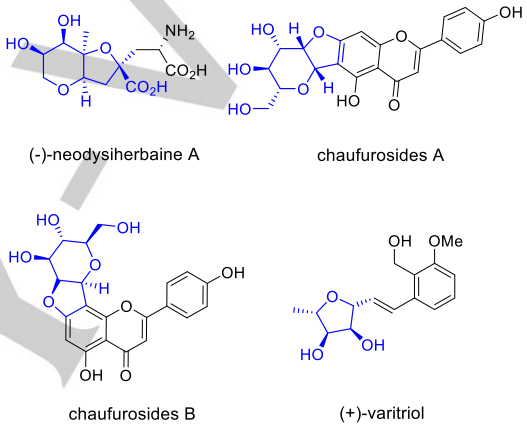
Abstract: *C*-glycosides represent an important group of naturally occurring glycosylation derivatives but also efficient mimetics of native *O*-glycosides. We describe here a one-pot four-component methodology toward a library of *N*-alkylated *C*-glycosyl amino acid derivatives comprising seven different isopropylidene-protected carbohydrate units. The applied methodology tolerates different amines and isocyanides and provides access to Ugi products in yields up to 85 %. X-ray analysis of selected products bearing three different carbohydrate motifs and comparison of their crystal structures with similar ones deposited in Cambridge Crystallographic Database revealed that four structures adopt different conformations, mostly not typical for peptide structures. This property opens the possibility to exploit here described *N*-alkylated *C*-glycosyl amino acid derivatives as templates for accessing different biotic and abiotic secondary structures.

Introduction

Glycosylation is the most ubiquitous posttranslational modification of proteins, responsible for diversity in structure and function of glycoproteins, like modulation of membrane receptor signalling, transmembrane receptor function, protection from proteases and immune response, anti-adhesive action, nutrient storage, epigenetic histone modification and many others.[1] Although *N*- and *O*-glycosides represent the majority of naturally occurring glycosylation derivatives, *C*-glycosides also occupy an important part of the natural product pool with significant biological activities.[2] Some examples include neodysiherbaine A, an amino acid isolated from the Dysidea herbacea Micronesian sponge, a highly selective agonist for the kainate glutamate receptors,[3] chaufurosides A and B, *C*-glycosyl flavones isolated from oolong tea leaves, with anti-inflammatory and chemopreventive activities,[4] and (+)-varitriol, isolated from a marine-derived strain of the fungus Emericella varicolo showing strong cytotoxicity against renal, breast, and central nervous system cancer cell lines (Scheme 1).[5] Compared to *O*-glycosylation counterparts, *C*-glycosides are resistant toward hydrolytic enzymes and therefore traditionally selected as mimics of native *O*-glycosides in drug development process. To cope with diversity in structure of the naturally occurring *C*-glycosides and *O*-glycosides, a variety of methods have been developed for the synthesis of *C*-glycosides.[6] The majority of them rely on the direct formation of glycosidic C-C linkages with carbohydrate building blocks as the "donor" precursors. In addition, intramolecular rearrangements leading to *C*-glycosylation or construction of carbohydrate rings after the installation of the glycosidic C-C bonds were used for the synthesis of this important group of compounds.



Scheme 1. Some examples of naturally occurring *C*-glycosides.

Multicomponent reactions (MCRs) have also been widely used for the formation of C-C bond between a carbohydrate molecule and an aromatic or aliphatic aglycon.[7] Actually, carbohydrate-based MCRs are considered to be one of the most versatile methods for the preparation of compound libraries.[8,9] Among others, these include synthesis of modified nucleosides with antiviral, antitumor and antibacterial activities,[9] depsipeptides bearing carbohydrate moieties,[10] or *N*-glycosyl conjugates.[11] Dondoni exploited versatile reactivity of carbohydrate-related compounds to gain new classes of chiral molecules of biological relevance; *C*-nucleosides by asymmetric Biginelli and Hantzsch three-component reactions (3CRs), *C*-glycosyl β-amino esters by Mannich and Reformatsky reactions, glycosyl β-lactams and heterocyclic α-amino acids,[9] and functionalized thioimidazoles through a variant of the Marckwald reaction.[12] Carbohydrate-derived amines were utilized in the synthesis of cyclic depsipeptides,[13] neoglycoconjugates,[11a,b, 14] and glycopeptidomimetics,[15] while structurally diverse glycopeptidomimetics were also afforded utilizing carbohydrates equipped with a carboxylic acid in the Ugi reaction.[16] Sugar isocyanides have been sporadically used in MCRs, owing to a challenging synthetic procedure, and low stability.[17] However, recently we have successfully used 1-, 2-, and 6-isocyanoglycosyl derivatives derivatives in the diastereoselective Passerini reaction.[18] Although carbohydrate-derived aldehydes were often

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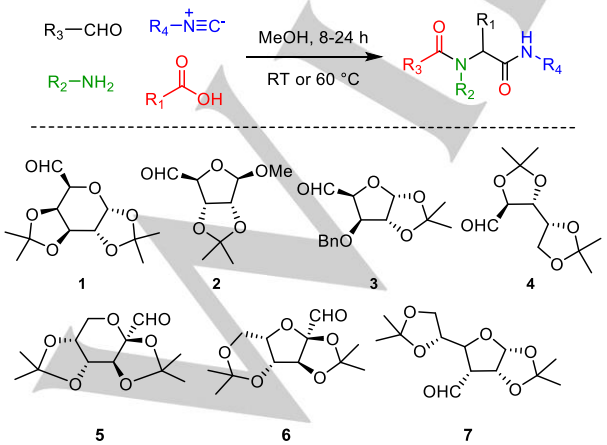
used in MCRs,[8,9] due to their reported influence on the stereochemical outcome of the reactions, they are almost neglected in isocyanide-based MCRs, a widely exploited strategy for the generation of drug-like molecules. Of particular interest is the Ugi reaction, where peptide-like structures, α-acylaminoamides can be prepared in a single step from suitable building blocks equipped with an aldehyde, an amine, a carboxylic acid and an isocyanide group. The Ugi reaction facilitates rapid access to structurally diverse compound libraries, and is thus exploited in diversity-oriented synthesis with application in drug discovery.

As a part of our ongoing project on utilization of carbohydrate-derived aldehydes in multicomponent reactions,[18] in this study we evaluated the potential of the Ugi reaction in the synthesis of various *N*-alkylated *C*-glycosyl amino acid derivatives. *N*-Alkylation of amino acids and peptides is a valuable tool for overcoming unfavorable pharmacokinetic properties of natural peptides, mainly enzymatic degradation and limited ability to cross biological membranes. *N*-Alkylation increases the proteolytic stability towards enzymes, reduces the polar character of the amide bond and often facilitates better interaction with receptors by increasing rigidity of the peptide. Therefore, a robust, single-pot access toward *N*-alkylated non-natural amino acid building blocks is highly relevant for utilization in medicinal chemistry.

Results and Discussion

We selected seven carbohydrate-derived aldehydes carrying one or two isopropylidene-type of protecting groups: 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-derived aldehyde **1**, methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside-derived aldehyde **2**, 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose-derived aldehyde **3**, 2,3:4,6-di-*O*-isopropylidene-D-arabinose-derived aldehyde **4**, 2,3,4,5-di-*O*-isopropylidene β-D-fructopyranose-derived aldehyde **5**, 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose-derived aldehyde **6**, and 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-derived aldehyde **7** (Scheme 2).

Scheme 2. Selection of carbohydrate-derived aldehydes utilized in the Ugi reaction.

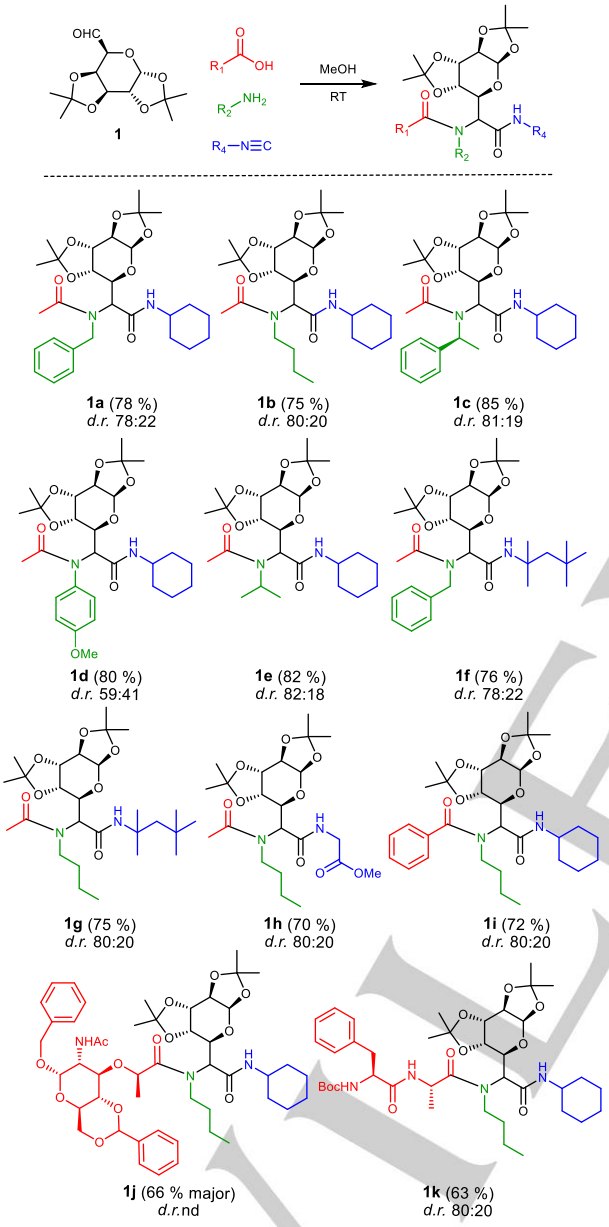


All aldehydes were easily obtained by the oxidation of the corresponding alcohols with Dess−Martin periodinane (details are provided in the Supporting Information file). The selected collection of aldehydes contains structurally diverse compounds with aldehyde group attached to either tertiary carbon atom (in aldehydes **1**-**4** and **7**) or quaternary carbon atom (aldehydes **5** and **6**). Selected aldehydes are in pyranose or furanose forms, while aldehyde **4** is in open chain form.

Our initial experiments aimed on probing the robustness of the selected methodology were performed with D-galactose derived aldehyde **1**. Formation of the Schiff base between an aldehyde and an amine is the first step of the Ugi reaction; therefore, we selected aromatic and aliphatic, chiral and achiral components: benzyl amine, butyl amine, *S*-phenylethyl amine, phenyl amine, and isopropyl amine in the reaction with acetic acid and cyclohexyl isocyanide. All reactions were performed in methanol at room temperature until the consumption of the aldehyde was seen on TLC, typically for 6-24h. All five products were isolated in very good yields, 75-85 % (products **1a**-**1e**, Scheme 3). Next, Ugi reactions were carried out with two additional commercially available isocyanides, 1,1,3,3-tetramethylbutyl isocyanide and methyl isocyanoacetate. Products obtained from benzyl amine (**1f**) and butyl amine (**1g** and **1h**) were isolated again in very good yields, 70-76 % (Scheme 3). Finally, along with simple acetic acid, three products were obtained by using benzoic acid (**1i**, 72 %) fully protected *N*-acetylmuramic acid (**1j**, 66 %) and dipeptide Boc-Phe-Ala-OH (**1k**, 63 %). Comparison of the results revealed that the reaction is tolerant to different amines, carboxylic acids and isocyanides, and highly robust; all products were obtained in very good yields, up to 85 %. Diastereoselectivity of the Ugi reaction was determined by the ^{1}H NMR spectroscopy of the reaction mixture of the product **1b** (80:20 *d.r.*); for all other products it was determined as the ratio of isolated diastereoisomers. Only the major diastereoisomer of product **1j** was isolated, while the minor diastereoisomer partially overlapped with the major one, therefore purification was unsatisfactory. It is interesting to note that the *d.r.* remains almost constant throughout all performed reactions, indicating the predominant influence of the carbonyl component structure on the diastereoselectivity outcome of the Ugi reaction.

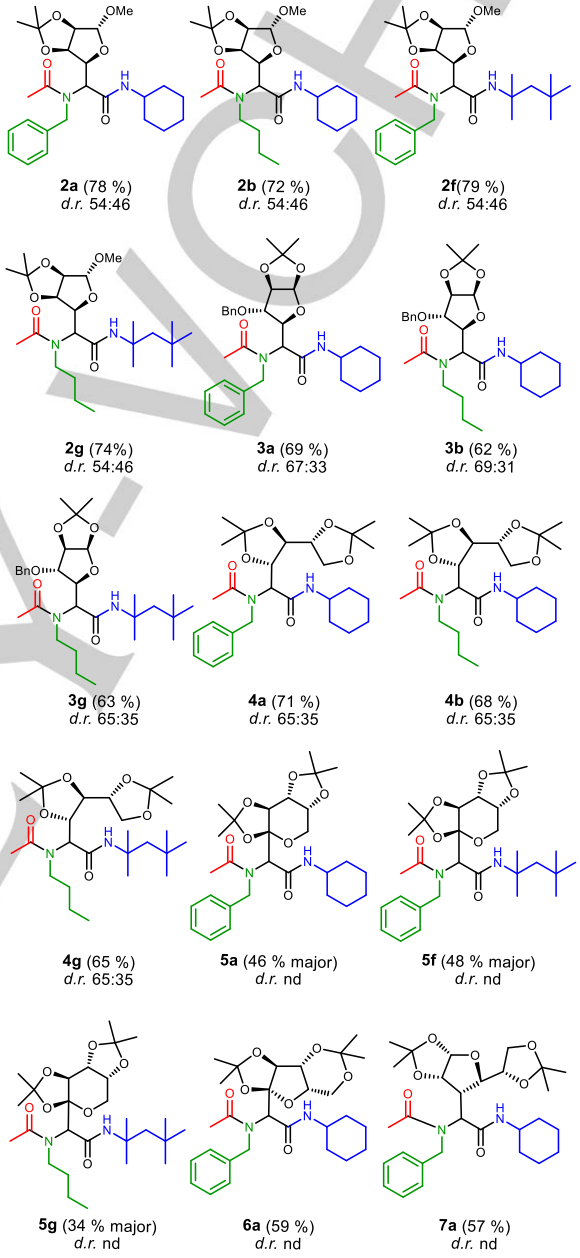
To explore the substrate scope of the carbonyl components in the Ugi reaction, we proceeded with a group of selected isopropylidene-protected aldehydes (Scheme 2). In all further experiments, acetic acid was the constant carboxylic component, while benzylamine and butylamine were used in combination with either cyclohexyl or 1,1,3,3-tetramethylbutyl isocyanide. Reactions performed with methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside-derived aldehyde **2** furnished Ugi products **2a**, **2b**, **2f**, and **2g** in very good yields (72-79 %, Scheme 4), but with poor diastereoselectivity, 54:46 *d.r.* Ugi products **3a**, **3b** and **3g** derived from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose-related aldehyde **3**, were obtained in slightly lesser yields (62-69 %) but with better diastereoselectivity; up to 69:31 *d.r.* (Scheme 4). An open chain 2,3:4,6-di-*O*-isopropylidene-D-arabinose-derived aldehyde **4** was utilized in the Ugi reaction giving products **4a**, **4b**, and **4g** in good yields (up to 71 %). The ratio of two diastereoisomers was found to be constant, 65:35 *d.r.* in all three

reactions performed with aldehyde **4**. The next set of reactions was carried out with D-fructose-derived aldehyde **5**, where the aldehyde group is attached to the quaternary carbon atom. Major diastereoisomers were isolated for all three products (**5a**, **5f**, and **5g**) in 34-48 % yields, while purification of minor diastereoisomers was not satisfactory due to the partial overlapping with the major isomer and some reaction byproducts.



Scheme 3. Products of the Ugi reaction performed with galactose-derived aldehyde **1**.

Reaction performed with 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose-derived aldehyde **6**, acetic acid, benzyl amine and cyclohexyl isocyanide furnished Ugi product **6a**, where the major isomer was isolated in 59 % yield and purification of minor isomer was again incomplete. Finally, in the reaction with 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-derived aldehyde **7** the major isomer of the Ugi product **7a** was isolated in 57 % yield.

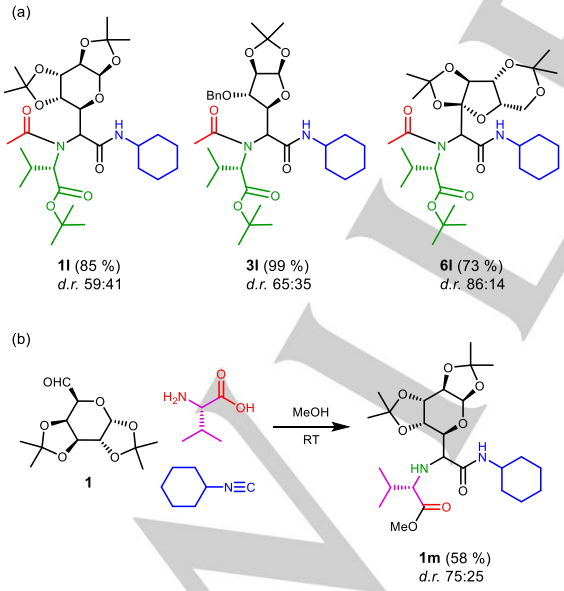


Scheme 4. Products of the Ugi reaction performed with aldehydes **2**-**7**.

Obtained results allowed us to conclude that the applied methodology is quite robust; it tolerates different amines and isocyanides and provides access to α-acylamino carboxamides in very good yields. Although observed diastereoselectivities are not impressive, two diastereoisomers were separated and isolated as pure compounds in most cases. Despite many efforts, to date, no general solution for the problem of stereocontrol in the Ugi

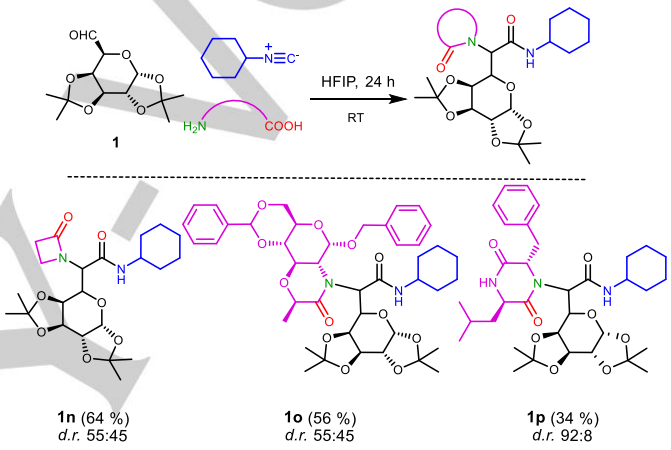
reaction has been found. The most promising results have been obtained with either chiral amines in the four-component reaction (U-4CR) or chiral imines in the three-component Ugi reaction (U-3CR). Using this approach, reactions performed with chiral α- and β-amino acids showed the best diastereoselectivities, while the utilization of chiral aldehydes, acids or isocyanides generally gave poor results.[19]

To determine the influence of chiral α-amino acids on the diastereoselective outcome of the reaction, we performed the Ugi reaction with L-valine *tert*-butyl ester, acetic acid, cyclohexyl isocyanide and three different aldehydes. As presented in the Scheme 5a, galactose-derived product **1l** was obtained in 85 % yield, with the ratio of two isolated distereoisomers *d.r.* 59:41. Slight decrease in *d.r.* compared to other Ugi products in the galactose series can be due to somewhat problematic purification of the product **1l**. Two diastereoisomers of the Ugi product **3l** were isolated in *d.r.* 65:35 and almost quantitative yield. Comparison with other products obtained in the reaction with aldehyde **3** (Scheme 4), revealed that the influence of the chiral amine on the diastereoselectivity is minimal. In the reaction with aldehyde **6** the corresponding Ugi product **6l** was isolated in 73 % yield and very good diastereoselectivity, *d.r.* 86:14 (Scheme 5a). Finally, we performed a three-component Ugi reaction with unprotected valine as a bifunctional component (Scheme 5b). Ugi product **1m** was isolated in 58 % yield, and the ratio of two diastereoisomers after purification was 75:25 *d.r.* Insight into obtained results with chiral amines revealed that, contrary to the literature,[19] the influence of the chiral amine components on the diastereoselectivity of the Ugi reaction is unsubstantial and the stereocontrol of the reaction is mainly determined by the chiral aldehyde.



Scheme 5. Ugi reactions performed with chiral amines; (a) a four-component reaction with H-Val-OtBu; (b) a three-component reaction with H-Val-OH.

Finally, we examined further the utility of carbohydrate aldehydes in the Ugi reaction by performing reactions with bifunctional components to gain more complex structures. A simple β-amino acid, 3-aminopropanoic acid and more complex δ-amino acid, protected muramic acid, were tested. Reactions were carried out with galactose-derived aldehyde **1** and cyclohexyl isocyanide in hexafluoroisopropanol (HFIP) at the room temperature for 24 hours. Both products, **1n** and **1o** were obtained in fair yields (64 % and 56 %, respectively) and 55:45 *d.r.* (Scheme 6). Next, we performed reaction with dipeptide H-Phe-Leu-OH as bifunctional component. Ugi product **1p** bearing diketopiperazine ring was obtained in moderate yield (34 %) but very good diastereoselectivity, 92:8 *d.r.* (Scheme 6).

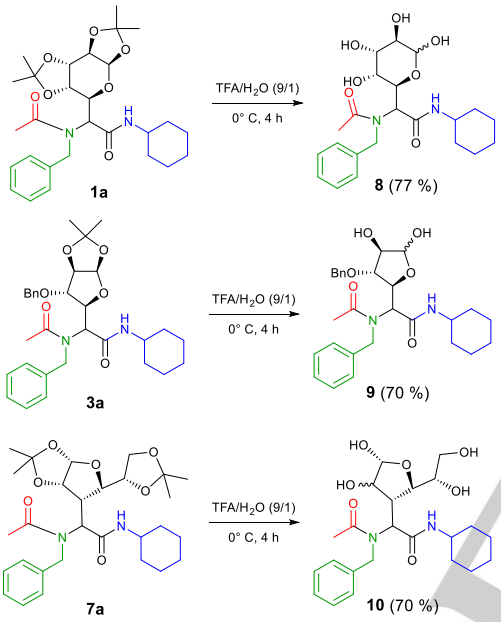


Scheme 6. Ugi products obtained with aldehyde **1**, cyclohexyl isocyanide and bifunctional derivatives.

Having the general scope of the Ugi reaction with different aldehydes in hand, we probed the access to deprotected derivatives. We selected Ugi products bearing different C-glycosyl units to verify the robustness of the deprotection procedure. Treatment of compounds **1a**, **3a** and **7a** with TFA/H_2O (9/1) at 0° C resulted in removal of isopropylidene groups after 4 h, and derivatives **8**-**10** were obtained in 70-77 % as a mixture of different anomeric forms (Scheme 7).

A very important feature of peptides and peptidomimetics with incorporated *N*-alkylated amino acids is their propensity to adopt specifically folded secondary structures.[20] Turn-like conformations are especially important in the design of peptidomimetics aimed to target protein-protein and protein-receptor interactions.[21,22] Turn-topology is mainly influenced by the amino acid side-chain, therefore an access to structural motifs able to induce different secondary structures is a great advantage.[23] We hypothesized that the combination of *N*-alkyl substituent and the side-chain *C*-glycosyl unit will represent interesting scaffolds able to mimic various peptide secondary structures or induce new, abiotic ones. Access to such scaffolds is highly relevant in the design of drug-like compounds and materials with biomedical application. *N*-alkylation reduces the

number of hydrogen-bond donors, influences the *cis–trans* equilibrium of the amide bond and increases steric hindrance, thus affecting the conformational freedom of the adjacent amino acids. Since our *N*-alkylated C-glycosyl amino acid derivatives are too short to adopt stable secondary structure in solution, we opted for x-ray analysis in this early stage hoping to get some insight into conformational space accessed by different derivatives. We managed to prepare crystals suitable for the x-ray analysis of four Ugi products **1b**, **1n** (galactose derivatives), **3a** (xylose derivative), and **5f** (fructose derivative). The main crystallographic data are given in Table 1, while a more detailed data report is given in the Supplementary Information file. Structures are presented at Figure 1.



Scheme 7. Deprotection of selected Ugi products.

Structures **1b** and **5f** bearing galactose and fructose units, respectively, have intramolecular hydrogen bonds between the only available hydrogen bond donor (atom N2) and oxygen acceptors on the sugar moiety (Table 2 and Figure 2). These hydrogen bonds are bifurcated with O3 and O4 atoms as acceptors in the structure **1b** and more directional in structure **5f** where only oxygen O3 acts as an acceptor. In these two structures, the intramolecular hydrogen bonds constrain and fix the positioning of the sugar part of the molecule. Contrary to that, structures **3a** and **1n** do not have intramolecular hydrogen bonds. Instead, they form intermolecular N-H···O hydrogen bond with the neighboring O1 acceptor. Thus, in case of the structure **3a** two molecules in asymmetric unit form a hydrogen bonded pair, while only one hydrogen bond is present in structure **1n** between symmetrically related molecules in the crystal packing.

Table 1. Crystallographic and refinement data for compounds **1b**, **1n**, **3a**, and **5f**.

	1b	**1n**	**3a**	**5f**
Formula	$C_{25}H_{42}N_2O_7$	$C_{22}H_{34}N_2O_7$	$C_{31}H_{40}N_2O_6$	$C_{30}H_{46}N_2O_7$
Formula Weight	482.60	438.51	536.79	546.69
Crystal System	trigonal	orthorhombic	monoclinic	monoclinic
Space group	$P\,3_2$	$P\,2_12_12_1$	$P\,2_1$	$P\,2_1$
a, b, c [Å]	22.0258(2) 22.0258(2) 15.1383(2)	9.5087(2) 12.1237(3) 20.2845(6)	16.6779(4) 11.2365(3) 17.2990(5)	9.6708(3) 15.9475(3) 11.0762(3)
α, β, γ [°]	90 90 120	90 90 90	90 111.194(3) 90	90 111.742(4) 90
V [Å^3]	6360.21(12)	2338.41(10)	3022.58(15)	1586.71(8)
Z	9	4	4	2
D(calc) [g cm^{-3}]	1.134	1.246	1.180	1.144
μ(CuKα) [mm^{-1}]	0.672	0.765	0.659	0.656
F(000)	2358	944	1153	592
Crystal Size [mm]	0.2x0.3x0.3	0.05x0.08x0.1	0.05x0.15x0.3	0.05x0.1x0.2

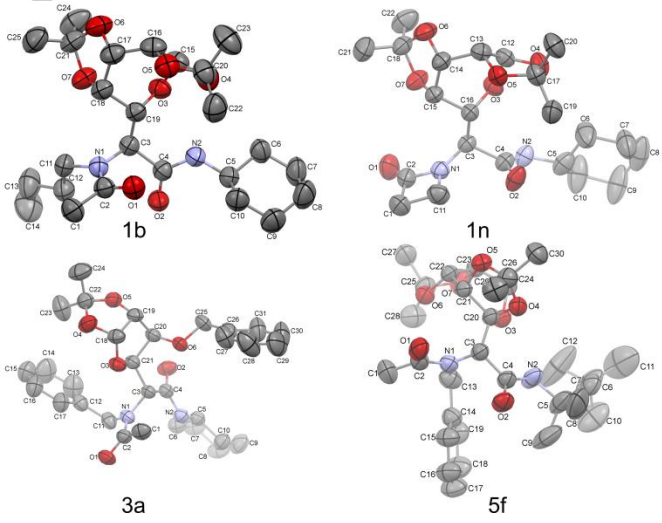


Figure 1. Thermal ellipsoid representation of the structures of compounds **1b**, **1n**, **3a** and **5f** (at 50 % probability level). In case more than one molecule in asymmetric unit is presented only one representative molecule is given. CCDC 1953263 (**1b**), 1953296 (**1n**), 1953294 (**3a**) and 1953283 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

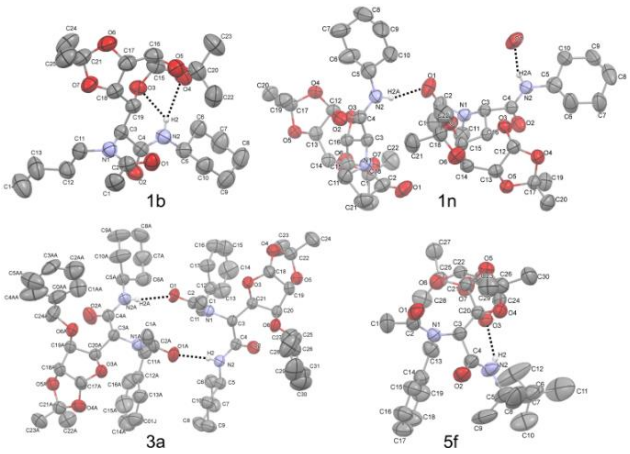


Figure 2. Hydrogen bonds in structures **1b**, **1n**, **3a** and **5f**.

Table 2. Hydrogen bond distances and angles in structures **1b**, **1n**, **3a**, and **5f**.

Hydrogen bond	d(D-H) [Å]	d(H-A) [Å]	d(D-A) [Å]	angle(D-H-A) [°]
structure 1b				
N2–H2···O3	0.86	2.0900	2.776(3)	137.00
N2A–H2A···O3A	0.86	2.1700	2.816(4)	132.00
N2A–H2A···O4A	0.86	2.4600	3.301(4)	168.00
N2B–H2B···O3B	0.86	2.1600	2.800(3)	131.00
N2B–H2B···O7B	0.86	2.5800	3.429(3)	170.00
structure 1n				
N2–H2···O1	0.86	2.1800	3.017(4)	163.00
structure 3a				
N2–H2···O1A	0.86	2.1000	2.926(4)	161.00
N2A–H2A···O1	0.86	2.2500	3.088(5)	164.00
structure 5f				
N2–H2···O3	0.86	2.0900	2.826(3)	137.00

To compare structures of compounds **1b**, **1n**, **3a** and **5f** with those deposited in Cambridge Crystallographic Database (CSD version 5.40 with updates up to May 2019) we performed the search using the query given on Figure SI-1. The care was taken for the query to be sufficiently general to yield enough structures for good statistics and to match the structures of our compounds as close as possible. The search returned 1294 hits with 3438 substructure matches with selected query. The scatter plot of the structures in the CSD search closely resembles the Ramachandran plot of protein structures (Figure 3). This is mainly a consequence of a large number of modified peptides present in the CSD database, which naturally follow the most common secondary structures of proteins. The structures in the search predominantly populate four distinct areas of the plot, which correspond to right handed and left handed α-helix structure, β-sheet and one area sparsely populated in proteins, which reflects a fairly extended chain and is largely populated by glycine, the only amino acid that can readily adopt the conformations required for the region (Figure 3).[24,25] Remarkably, our four structures fall on very different positons on the plot, indicating the difference in their conformation. The angle τ, torsional angles φ and ψ that would correspond to Ramachandran torsional angles in protein structures, are depicted on Figure 3 and listed in Table 3. Among four structures, only the structure **1n** falls into region allowed for proteins, where β-sheet structures are situated. It is possible that the β-sheet-like conformation in structure **1n** is enforced by the presence of four-membered ring C1-C2-N1-C11 which makes the oxygen atom O1 point in the opposite direction with respect to O2, quite like in the protein β-sheet.

Table 3. Torsion angles ϕ, ψ, and angle τ (deg) for compounds **1b, 1n**, **3a**, and **5f** as determined by X-ray crystallographic analysis.position

	ϕ (C2-N1-C3-C4)	ψ (N1-C3-C4-N2)	τ (N1-C3-C4)
1b	53.2(3) 55.4(3) 58.5(3)	-142.6(2) -145.4(3) -149.5(3)	110.3(2) 110.26(19) 110.1(2)
1n	-135.2(3)	132.3(2)	109.74(17)
3a	131.7(3) 127.3(3)	-54.8(3) -48.3(5)	111.1(2) 111.7(2)
5f	124.8(3)	104.7(3)	110.5(2)

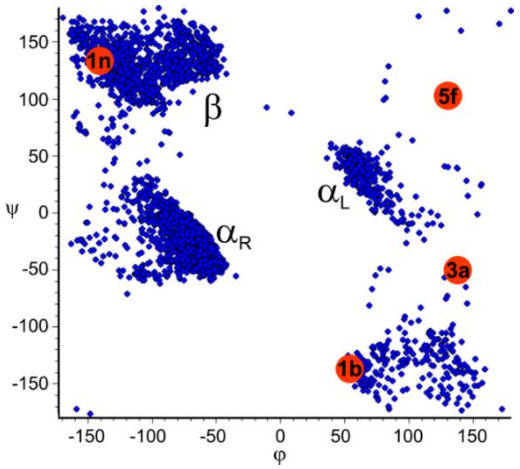


Figure 3. The graphical representation of the results of the CSD analysis corresponding to Ramachandran plot for polypeptides and protein strucutres. The regions usually populated in proteins are denoted as αL (left-handed α-helix), αR (right-handed α-helix) and β (for β-sheets). It is visible that the structures described in this paper cover completely different parts of the plot, and only the structure **1n** falls into the β region allowed for proteins.

The importance of "3D-structural diversity" to cover the broad array of peptide secondary structures during the peptidomimetic design, was nicely demonstrated by Shuto et al.[26] Computational calculations and x-ray crystallography studies showed that the incorporation of cyclopropane moiety effectively constrains the molecular conformation of the peptide. They prepared a group of cyclopropane-based peptidomimetics mimicking a wide range of peptide secondary structures, from folded to extended forms. Based on these analyses, a lead stereoisomer targeting melanocortin receptors was identified, and its potency and selectivity were improved by further derivatization. Furthermore, it was demonstrated that peptide-based catalysts,[27] nowadays implemented in myriad synthetically relevant transformations, can access diverse conformational space, and that low-barrier interconversions between conformations can be an advantage in multistep, enantioselective reactions.[28] Thus, supported by a strong literature precedent we plan to validate the utility of here described *N*-alkylated C-glycosyl scaffolds as inducers of various secondary structures. They will be incorporated in short peptide sequences and their conformational preferences in solid state and solution will be studied in details.

Conclusions

We have prepared a library of *N*-alkylated *C*-glycosyl amino acid derivatives comprising seven different isopropylidene-protected carbohydrate motifs utilizing the four-component Ugi reaction. The methodology tolerates different amines and isocyanides and provide access to α-acylamino carboxamides in yields up to 82 %. The stereochemical outcome of the reaction is mainly determined by the nature of chiral, bulky, carbohydrate-derived aldehyde components with the best diastereoselectivity being 80:20 *d.r.* observed with galactose-related aldehydes. To validate the utility of carbohydrate-derived aldehydes in accessing higher complexity structures, we also performed three-component Ugi reactions with bifunctional derivatives, and obtained Ugi products bearing an additional ring in fair yields. Access to deprotected derivatives was verified by acid-mediated removal of isopropylidene groups performed on three Ugi products bearing different C.glycosyl units. Since *N*-alkylated amino acids derivatives are versatile scaffolds known to induce different folded conformations, we performed single crystal x-ray analysis on selected Ugi products comprising three different C-glycosyl units to probe the conformational space accessible by these scaffolds. Comparison of angle τ, and torsional angles φ and ψ revealed large conformational differences between four structures, which may be exploited in the design of oligomers able to adopt different secondary structures.

Experimental Section

General procedure for Ugi reaction:

1:2,3:4-di-*O*-isopropylidene-D-galacto-dialdose 1 (0.08 mmol, 1.0 eq) and amine (1.1eq) were dissolved in methanol (0.5 mL) in a glass vial and stirred for one hour at RT. To this reaction mixture was further added acid (1.1eq) and isocyanide (1.1eq). The resulting mixture was stirred at RT until the consumption of aldehyde was seen by TLC. The reactions were concentrated under reduced pressure and the reaction mixtures purified by flash column chromatography.

Representative example of the Ugi product:

2-(N-benzylacetamido)-N-cyclohexyl-2-((3aR,5S,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)acetamide (**1a**) Yield 78 % (32 mg); colorless oil; R_f (DS1) = 0.44, R_f (DS2) = 0.27 (EtOAc/PE 1:1, v/v); *d.r.* 78:22. Chemical shifts for major isomer: ^{1}H NMR ($CDCl_3$): δ 7.51 – 7.25 (m, 5H), 6.99 (d, *J* = 6.6 Hz, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.73 (d, *J* = 16.5 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.29 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 3.82 – 3.61 (m, 2H), 2.07 (s, 3H), 1.88 (dd, *J* = 26.0, 11.9 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.15 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 173.5, 168.1, 137.2, 128.6, 128.3, 127.7, 109.9, 109.4, 97.1, 71.1, 70.9, 70.8, 66.2, 48.7, 33.4, 33.0, 26.4, 26.0, 25.9, 25.3, 25.2, 25.1, 24.4, 23.0. Chemical shifts for minor isomer: ^{1}H NMR ($CDCl_3$) δ 7.29 – 7.17 (m, 5H), 6.41 (s, 1H), 5.52 (d, *J* = 5.1 Hz, 1H), 4.70 (d, *J* = 17.4 Hz, 1H), 4.58 (dd, *J* = 7.7, 2.4 Hz, 2H), 4.56 – 4.49 (m, 1H), 4.40 – 4.33 (m, 2H), 4.31 (dd, *J* = 5.1, 2.5 Hz, 1H), 3.59 (m, 1H), 2.02 (s, 3H), 1.83 – 1.76 (m, 2H), 1.69 – 1.50 (m, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.38 – 1.24 (m, 7H), 1.19 – 1.10 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 167.9, 137.9, 128.9, 127.4, 126.8, 109.7, 109.0, 96.8, 71.6, 71.5, 71.3, 70.8, 65.1, 48.3, 32.9, 26.4, 26.1, 25.8, 25.2, 24.9, 24.8, 22.8. HRMS (MALDI TOF/TOF): Calcd. For $C_{28}H_{40}N_2O_7$ $[M+H]^+$ 517.2914; found 517.2891.

Supplementary Information file contains experimental details for all synthesized compounds, their ^{1}H and ^{13}C NMR spectra and crystallographic data.

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Keywords: amino acids • carbohydrates • *C*-glycosides • peptidomimetics • Ugi reaction

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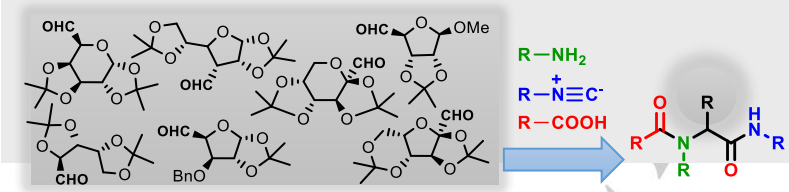

We describe a one-pot four-component methodology toward a library of *N*-alkylated *C*-glycosyl amino acid derivatives comprising seven different isopropylidene-protected carbohydrate units. The applied methodology provides access to Ugi products in yields up to 85 %.

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N-alkylated C-glycosyl amino acid derivatives accessed by one-pot-four component Ugi reaction