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Advanced Synthesis & Catalysis

Directed Nickel-Catalyzed *pseudo*-Anomeric C–H Alkynylation of Glycals as an Approach towards *C*-Glycoconjugate Synthesis

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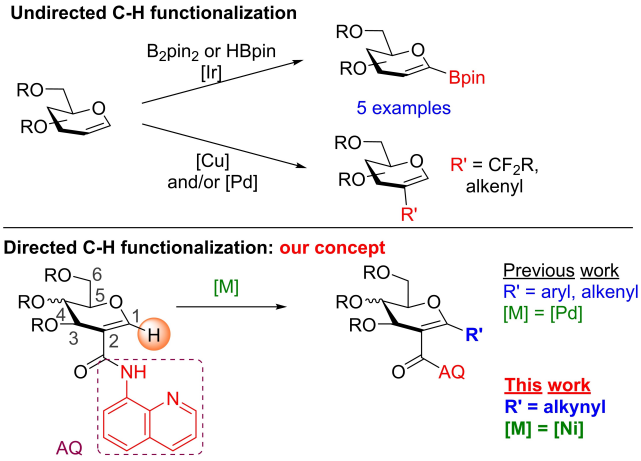
Abstract: The synthesis of complex *C*-glycoconjugates is presented here using a key directed nickel-catalyzed C–H alkynylation step. Thanks to a bidentate amidoquinoline-type directing group, the insertion of diverse alkynyl moieties onto the *pseudo*-anomeric position of glycal substrates was performed on ten examples in moderate to good yields. These platforms were used as starting substrates in a click reaction with complex azides to form original *C*-glycoconjugates. By this route, a *C*-glycosylated amino acid, a *C*-linked disaccharide and a *C*-glycosylated biotin derivative were synthesized. Preliminary conditions to remove the directing group are also proposed.

Keywords: C–H functionalization; Glycals; Alkynylation; Nickel catalysis; Directing group

Introduction

Natural hybrids between sugars and complex molecules, namely glycoconjugates, are diverse in biology and play crucial roles in many important cellular pathways. Glycolipids and glycoproteins are the most famous members of this family, suitably exposed on the cell surface to enable cell adhesion and communication processes.[1] The design of non-natural glycoconjugates which mimic natural analogues is thus an important research area for therapeutic applications.[2] Moreover, the discovery of the click reaction was a major breakthrough to conjugate biomolecules by an easy and powerful way.[3] Especially, the Huisgen cycloaddition between an alkyne and an azide has been the most commonly used in this field.[4] The synthesis of glycoconjugates using this reactivity mainly involves 1-azidoglycoside partners giving rise, after click reaction, to conjugates where the sugar part is linked to an aglycon via a hydrolyzable C–N anomeric bond.[5] Alternatively to this strategy, the sugar can be fixed to carry the alkyne functionality, generally introduced by a glycosylation reaction in the presence of propargylic alcohol leading to a hydrolyzable C–O anomeric link.[6] To ensure stability, which is one of the success factor for potential drug candidates, the development of *C*-glycoconjugates, where the glycoside moiety and the aglycon are linked by a C–C bond, has been a point of focus. However, they are still underrepresented in the literature due to the difficulty to create such bonds. Indeed, the description of synthesis of *C*-glycoconjugates by click chemistry is scarce. These structures could be obtained by using 1-alkynyl-glycoside platforms,[7] commonly synthesized by the addition of a metallic alkynide onto an electrophilic sugar (lactone, epoxide, etc.)[8] or by Lewis acid-catalyzed reaction between a stannylated alkyne and a halogenated sugar.[9] Other methods exist employing Ferrier type rearrangement on glycal substrates.[10] Recently, we proposed an access to *C*-glycosides through a palladium-catalyzed C–H functionalization of glycal substrates, directed by a suitable bidentate amide-type directing group placed at the position 2 (Scheme 1).[11] This strategy enabled to target the desired *pseudo*-anomeric position (position 1). This work represents the unique example of a directed C–H functionalization process on glycals. However, this proof of concept was limited only to aryl and activated alkenyl iodide partners. The introduction of alkyne moieties was unsuccessful in these conditions. In the literature, C–H functionalization of sugars are very limited.[12] This reactivity, applied on glycals in the absence of a



Scheme 1. The proposed methodology versus previous works on C–H functionalization of glycals.

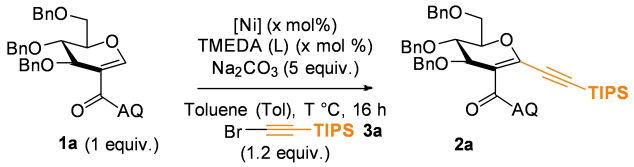
directing group, led almost exclusively to the functionalization of the position 2 with perfluoroalkylated, alkene-type or borylated functionalities only (Scheme 1).

Recently, Li *et al.* described the introduction of an alkyne on a single example of dihydropyran scaffold using a nickel-catalyzed process directed by an amidoquinoline group.[13] The literature on C–H alkynylation reactions has mostly developed over this last decade but is still limited.[14] Most of the described methodologies use palladium or rhodium catalysis[15] and only a few examples cover nickel-catalyzed reactivity.[16] Due to the failure of alkyne moiety introduction by our previous palladium-catalyzed C–H functionalization, we present, herein, a directed nickel-catalyzed C–H alkynylation of the *pseudo*-anomeric position of *C2*-amidoglycals. The resulting 1-alkynyl-glycosides are ready-to-use for the synthesis of complex *C*-glycoconjugates (Scheme 1).

Results and Discussion

Based on the work of Li *et al.*,[13] we started our investigation by heating glycal **1a** (obtained in four steps from commercial 2,4,6-tri-OAc-D-glucal) up to 120 °C in toluene in the presence of $NiCl_2$ as catalyst, TMEDA as a ligand, Na_2CO_3 as a base and bromo (triisopropylsilyl)acetylene (**3a**) as an electrophile (Table 1). Under these conditions, the desired compound **2a** was obtained. However, the yield was limited to 17% by ^{1}H NMR due to a low conversion (70% of the remaining starting material **1a**, Table 1, entry 1). Testing of different temperatures revealed that the optimal balance between reactivity and degradation is obtained at 140 °C (Table 1, entries 1–3). In terms of catalysts, 20 mol% of $Ni(OAc)_2.4H_2O$ or $Ni(NO_3)_2.6H_2O$ provided the best yields of **2a** with a

Table 1. Optimization of the C–H functionalization conditions.[a]



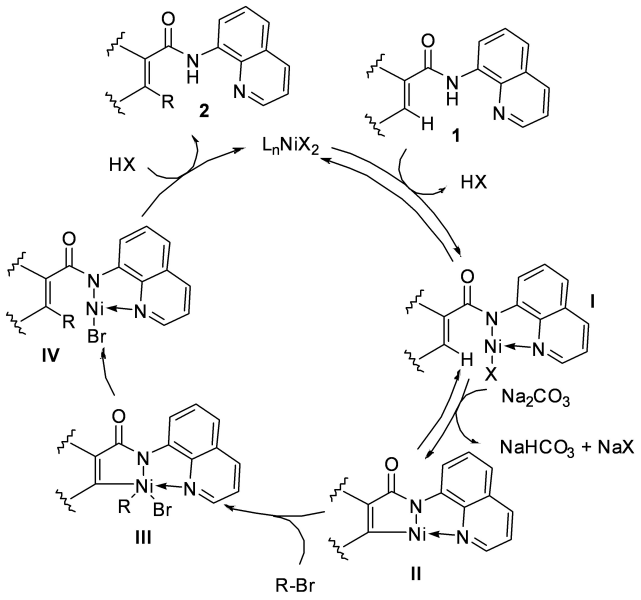
N°	[Ni] (mol%)	L (mol%)	Tol (mL)	T (°C)	^{1}H NMR Yield **2a**/**1a**
1	$NiCl_2$ (10)	40	0.85	120	17%/70%
2	–	–	–	140	25%/37%
3	–	–	–	150	15%/45%
4	$Ni(acac)_2$ (10)	–	–	140	21%/59%
5	$Ni(acac)_2$ (20)	80	–	–	30%/53%
6	$Ni(OAc)_2.4H_2O$ (20)	–	–	–	42%/traces
7	$Ni(NO_3)_2.6H_2O$ (20)	–	–	–	46%/27%
8	–	–	0.43	–	48%/0%
9	–	–	1.7	–	25%/45%
10	–	w/o	0.43	–	38%/43%
11[b]	–	–	–	–	58%/25%
12[b]	$Ni(OAc)_2.4H_2O$ (20)	–	–	–	65%[c]/25%

[a] The reaction was performed on 0.085 mmol scale of **1a**.
[b] [Ni] was added after 4 h of stirring at 140 °C.
[c] 64% isolated.

higher degree of degradation with $Ni(OAc)_2.4H_2O$ compared to $Ni(NO_3)_2.6H_2O$ (Table 1, entries 4–7). The quantity of solvent can be reduced by half without loss of yield but the reactivity was lower if the quantity of solvent is doubled (Table 1, entries 8 and 9). The absence of ligand resulted in a slight decrease in the observed yield, but the presence of reactivity in this case (38% yield in **2a**) allowed us to consider further investigations without ligand (Table 1, entry 10). Finally, the key parameter was the postponed addition of the nickel reagent after four hours of heating (where **1a**, **3a** and the base were stirred in toluene at 140 °C) leading to **2a** in a good yield of 58% using $Ni(NO_3)_2.6H_2O$ and 65% (64% isolated) using $Ni(OAc)_2.4H_2O$ (Table 1, entries 11 and 12). The role of this pre-heating step in the reactivity is quite unclear. The first plausible hypothesis is that the reaction proceeds if some amount of the base is solubilized in the medium. However, the solubilization of Na_2CO_3 is slow and limited in the chosen solvent, namely toluene. Another explanation may be that the process only works when the sugar **1a** adopts a particular conformation, formed at high temperature due to the presence of other electron π-enriched reagents such as **3a** or by the presence of the base. It should be noticed that chloro(triisopropylsilyl)acetylene is completely unreactive under the optimized conditions and only

20% of **2a** (^{1}H NMR) was observed using iodo (triisopropylsilyl)acetylene as electrophilic partner.

According to Liu's hypothesis,[13] the mechanism is supposed to start with the complexation of the Ni(II) species to the amidoquinoline-type directing group forming the intermediate **I** (Scheme 2). With the help of the base, the nickel species would insert into the close C–H bond, providing intermediate **II**. Then, the oxidative addition step leads to the Ni(IV) complex **III**. Finally, reductive elimination leads to the formation of the desired product **2** and releases the Ni(II) catalyst via **IV**.



Scheme 2. Proposed mechanistic pathway.

Under these optimal conditions, versatility in terms of electrophilic partners and glycal structures was explored (Table 2).

Generally, silylated alkynyl bromides are well tolerated and allow access to the corresponding 1-alkynylglycosides in moderate to good yields (Table 2, **2a-e**). Alkynyl partners bearing alkyl or aryl moieties led to low yields (<10% in ^{1}H NMR) except for bromocyclopropylacetylene, which formed the corresponding product **2f** in moderate yield. While D-galactal showed similar reactivity to that observed with the D-glucal analogues (Table 2, **4a** and **4b**), the L-rhamnal examples led to lower yields (Table 2, **5a** and **5b**). From these *C*-alkynylglycosides, the synthesis of *C*-glycoconjugates by click chemistry was then explored. The removal of the silylated part of **2a** using a fluorinated reagent was tested without success. Indeed, a complex mixture was observed by ^{1}H-NMR in the crude. We expected that the proximity of the nitrogen-containing amide function could give rise to undesired intramolecular reactivities. A preliminary protection of the amide-type directing group by a *tert*-butoxycarbonyl group was thus performed, forming the product **6** in a very good yield (Table 3).

Sequential one-pot cleavage of the silylated moiety followed by the copper-catalyzed click reaction with

Table 2. Scope of the C–H alkynylation.

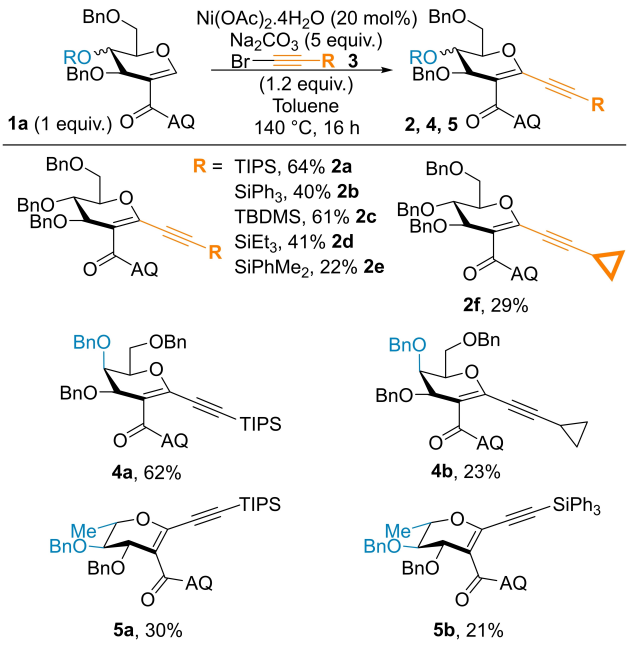
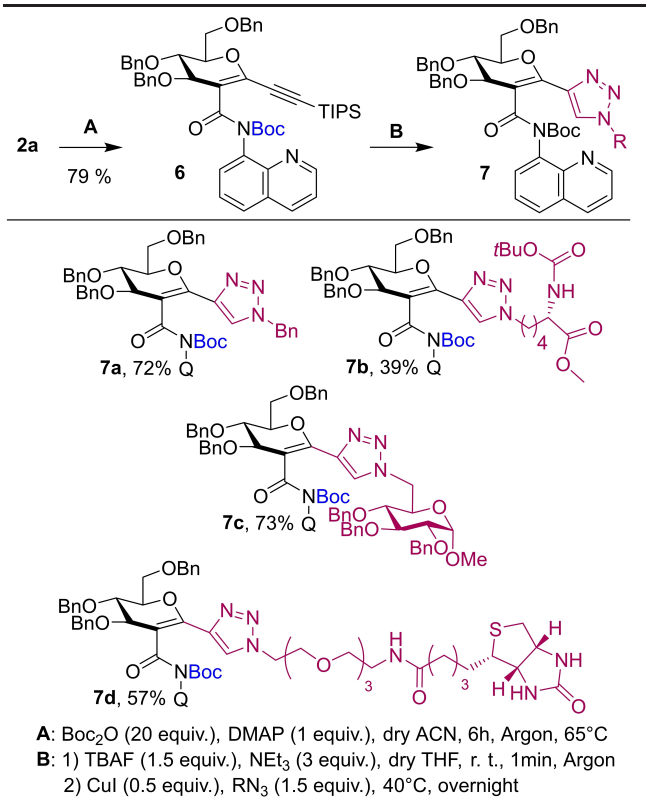


Table 3. Functionalization of **2a** by click reaction.

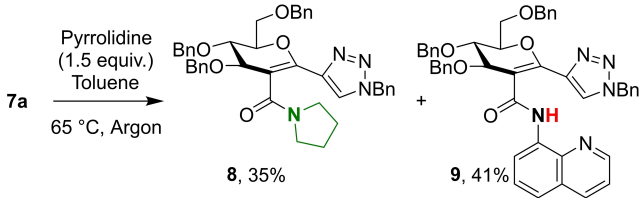


A: Boc_2O (20 equiv.), DMAP (1 equiv.), dry ACN, 6h, Argon, 65°C
B: 1) TBAF (1.5 equiv.), NEt_3 (3 equiv.), dry THF, r. t., 1min, Argon
2) CuI (0.5 equiv.), RN_3 (1.5 equiv.), 40°C, overnight

benzyl azide successfully generated the corresponding *C*-glycoconjugate in a very good yield of 72% (Table 3, **7a**). This sequence was repeated with diverse complex azide partners. A *C*-glycosylated amino acid analogue (Table 3, **7b**), a *C*-linked disaccharide (Table 3, **7c**) and a *C*-glycosylated biotin derivative (Table 3, **7d**) were synthesized in moderate to good yields (39–73%). We then investigated the possibility of removing the amidoquinoline-type directing group on **7a**. Conventional conditions described for transforming amidoquinoline moieties into amide, carboxylic acid, ester, etc. using basic, acidic or reductive conditions[17] did not yield the desired product. We finally partially solved the problem by using pyrrolidine in toluene at 65 °C, which formed the desired amido-glycal **8** in 35% yield but accompanied by 41% of an undesired compound **9** coming from the competitive deprotection of the *tert*-butoxycarbonyl group (Scheme 3).

Conclusion

A novel approach towards 1-alkynylglycosides has been presented using a directed nickel-catalyzed C–H alkynylation process between *C2*-amidoglycal starting substrates and alkynyl bromides as electrophilic reagents. Various examples bearing diversely substituted alkyne moieties and possessing different glycal configurations were successfully synthesized in moderate to good yields using this procedure. The addition of the nickel catalyst after 4 hours of heating was crucial to obtain good reactivity. A mechanistic investigation to explain this particularity is planned in the near future. After a preliminary protection step of the amide-type directing group and the removal of the silylated moiety, these alkynylated compounds were engaged in a copper-catalyzed click reaction with azides. Complex amino acid, glycosidic and biotin-type azides were chosen to give rise to original *C*-glycoconjugates. A procedure to remove the amidoquinoline group was finally presented.



Scheme 3. Removal of the directing group.

Experimental Section

Materials and Methods

All chemical operations were carried out using standard screw sealed tubes. Acetonitrile was purified before use by distillation under an argon atmosphere. Other solvents were used without further purification. The "Cyclo" abbreviation will be used to name cyclohexane. Commercially available chemicals were used as received unless otherwise stated. Reactions were monitored by thin-layer chromatography on silica gel plates (60 F254 aluminum sheets) which were rendered visible by ultraviolet and/or spraying with vanillin (15%) + sulfuric acid (2,5%) in EtOH followed by heating. ^{1}H NMR (400 MHz), and ^{13}C NMR (100.5 MHz) were recorded on a BRUKER AVANCE NEO 400 MHz spectrometer at 298 K unless otherwise stated. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants *J* are given in Hz. Infrared spectra (IR) were recorded on BRUKER TENSOR 27 on a FT-IR system using diamond window Dura SamplIR II, and the data are reported in reciprocal centimeters (cm^{-1}) in the range 4000−600 cm^{-1}. Optical rotations were measured on an Anton Paar MCP 200 polarimeter at 589 nm. [α] is expressed in $deg.cm^3.g^{-1}.dm^{-1}$, and c is expressed in g/100 cm^3. HRMS were determined on a QTOF mass analyzer coupled with electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) with a resolution of 12000.

Synthetic Procedures

Compounds 2-iodo-3,4,6-tri-*O*-benzyl-D-glucal and 2-iodo-3,4,6-tri-*O*-benzyl-D-galactal were prepared according to the literature:[18] corresponding glycal was dissolved in dry acetonitrile (8 mL/mmol) under argon, and the resulting mixture was heated to 80 °C. At this temperature, *N*-iodosuccinimide (1.2 equiv.) and silver nitrate (20 mol%) were added. The resulting mixture was stirred at 80 °C for 1–2 h. The mixture was filtrated on Celite with EtOAc and concentrated with silica. The obtained crude was purified on silica gel and furnished the corresponding 2-iodo-tri-*O*-benzylglycal. Compounds 2-*N*-(quinolin-8-yl)carbamoyl-3,4,6-tri-*O*-benzyl-D-glucal and 2-*N*-(quinolin-8-yl)carbamoyl-3,4,6-tri-*O*-benzyl-D-galactal were prepared according to the literature:[11] in a sealed tube were added $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), K_2CO_3 (2 equiv.), $Mo(CO)_6$ (4.2 equiv.), 8-aminoquinoline (2 equiv.) and the corresponding 2-iodoglucal (1 equiv.). Dioxane (9.8 mL/mmol) was then added and the resulting mixture was stirred at 80 °C overnight. The mixture was filtered on celite, concentrated under vacuum and the crude was finally purified on silica gel using the indicated solvent. The product was washed with HCl (1 M) to remove excess of aminoquinoline and then with a saturated aqueous solution of $NaHCO_3$. Bromo (triisopropylsilyl)acetylene, (bromoethynyl)triphenylsilane, 1-bromo-2-(*tert*-butyldimethylsilyl)acetylene, bromo(triethylsilyl) acetylene, (bromoethynyl)cyclopropane, (bromoethynyl) dimethyl(phenyl)silane were prepared according to the literature:[19] corresponding alkyne was dissolved in acetone

(5.4 mL/mmol), NBS (1.2 equiv.) and $AgNO_3$ (0.1 equiv.) were added and the resulting mixture was stirred 2 h at room temperature. The reaction was quenched with water, the crude was extracted with pentane (×3) and the combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum.

General Procedures

General Procedure for the C–H Functionalization Reaction (Compounds 2, 4, 5)

In a sealed tube were added Na_2CO_3 (5 equiv.), alkyne bromide (1.2 equiv.), compound **1a** (1 equiv.) and toluene (5.1 mL/mmol). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (20 mol%) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. The crude was finally purified on silica gel using the indicated solvent.

General Procedure for the ^{1}H NMR Yield Determination

The NMR yield of **2a** was determined with acetophenone as internal reference: 1 equiv. of acetophenone compared to compound **1a** was added after filtration of the crude on celite, and then the crude was concentrated. The NMR yield of **2a** on the ^{1}H NMR spectra could be determined by analytical signals:

- s at 2.6 ppm (CH_3 of acetophenone – calibrated for 3H) compared with the integrations of product signals: s at 10.35 ppm (NH of product **2a**), dd at 8.75 ppm, dd at 8.65 ppm and dd at 8.07 ppm (aromatic H of aminoquinoline of **2a**)

The reaction yield was determined with the mean value of these integrations. Conversion of starting material **1a** was determined in the same mixture by integration of:

- s at 10.55 ppm (amide proton of **1a**)
- dd at 8.83 ppm, at 8.37 ppm and at 8.12 ppm (aromatic H of aminoquinoline of **1a**)

The mean value of these integrations was calculated determining the conversion of reaction.

General Procedure for the Click Reaction (Compounds 7)

In a flask, starting material was dissolved in dry THF (11 mL/mmol) under argon. Then triethylamine (3 equiv.) and TBAF (1.5 equiv.) were added and the reaction was stirred at room temperature. The color of the reaction mixture changed in purple and after that, CuI (0.5 equiv.) and azide partner (1.5 equiv.) were added. The reaction was stirred at 40 °C overnight. The mixture was concentrated under vacuum and the crude was finally purified on silica gel using the indicated solvent.

Characterization Data

2-*N*-(quinolin-8-yl)carbamoyl-1-((triisopropylsilyl)ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2a). **2a** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (31.6 mg, 5 equiv., 0.298 mmol), bromo (triisopropylsilyl)acetylene (17.4 µL, 1.2 equiv., 0.072 mmol), compound **1a** (35 mg, 1 equiv., 0.060 mmol) and toluene (0.3 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (3 mg, 20 mol%, 0.012 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2a** was obtained after purification on silica gel (eluent: Cyclo/EtOAc 85:15) as yellowish oil (29.4 mg; 0.038 mmol; 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.75 (dd, J=7.4, 1.3 Hz, 1H), 8.64 (dd, J=4.2, 1.6 Hz, 1H), 8.07 (dd, J=8.3, 1.5 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.42 (dd, J=8.2, 1.3 Hz, 1H), 7.34 (dd, J=8.3, 4.2 Hz, 1H), 7.28–7.18 (m, 11H), 7.10 (dd, J=6.8, 2.7 Hz, 2H), 7.05 (dd, J=5.2, 1.7 Hz, 2H), 4.70 (dd, J=4.0, 1.1 Hz, 1H), 4.66 (d, J=11.2 Hz, 1H), 4.64 (d, J=11.8 Hz, 1H), 4.55 (d, J=11.8 Hz, 1H), 4.52–4.49 (m, 3H), 4.42–4.37 (m, 1H), 3.92 (dd, J=4.8, 4.4 Hz, 1H), 3.81 (dd, J=10.9, 5.9 Hz, 1H), 3.71 (dd, J=10.9, 4.5 Hz, 1H), 0.75–0.69 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 148.2, 138.9, 138.8, 138.3, 138.2, 137.9, 136.3, 135.0, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.8, 127.8, 127.6, 127.5, 121.6, 121.5, 117.2, 117.1, 99.4, 98.4, 77.6, 73.4, 73.3, 73.3, 72.6, 72.5, 67.7, 18.4, 18.3, 11.1; IR (cm^{-1}): 2925, 2859, 2363, 1684, 1559, 1526, 1487, 1457, 1374, 1326, 1261, 1208, 1145, 1091; $[\alpha]^{20}_D$ = +36.1 (0.33, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{48}H_{55}N_2O_5Si^+$ (*m/z*): calc. 767.3880; found 767.3889.

2-*N*-(quinolin-8-yl)carbamoyl-1-((triphenylsilyl)ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2b). **2b** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (45.1 mg, 5 equiv., 0.426 mmol), (bromoethynyl)triphenylsilane (37.1 mg, 1.2 equiv., 0.102 mmol), compound **1a** (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2b** was obtained after purification on silica gel (eluent: Toluene/EtOAc 98:2) as yellowish oil (29.9 mg; 0.034 mmol; 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.82–8.80 (m, 1H), 7.93 (dd, J=4.2, 1.5 Hz, 1H), 7.89 (dd, J=8.3, 1.5 Hz, 1H), 7.58 (dd, J=7.9, 1.4 Hz, 1H), 7.49 (t, J=8.0 Hz, 1H), 7.39 (d, J=7.4 Hz, 1H), 7.34–7.32 (m, 7H), 7.29–7.27 (m, 4H), 7.23–7.18 (m, 5H), 7.14–7.09 (m, 6H), 7.06–7.00 (m, 8H), 4.80 (dd, J=3.6, 1.2 Hz, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.57–4.47 (m, 5H), 3.95 (t, J=4.1 Hz, 1H), 3.84 (dd, J=10.7, 6.2 Hz, 1H), 3.71 (dd, J=10.7, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 148.2, 138.7, 138.7, 138.3, 138.1, 137.7, 135.8, 135.6, 135.1, 134.9, 132.1, 130.2, 130.0, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.6, 127.3, 121.7, 121.4, 117.9, 116.8, 100.2, 98.1, 77.6, 73.4, 73.2, 72.4, 72.3, 72.2, 67.7; IR (cm^{-1}): 3067, 3029, 2913, 2865, 2359, 1660, 1598, 1577, 1559, 1524, 1486, 1454, 1429, 1387, 1327, 1262, 1207, 1115, 1071, 1028; $[\alpha]^{20}_D$ = +175.4 (1.00, $CHCl_3$);

HRMS (TOF ES+) for $(M+H)^+$ $C_{57}H_{49}N_2O_5Si^+$ (*m/z*): calc. 869.3411; found 869.3406.

2-*N*-(quinolin-8-yl)carbamoyl-1-((*tert*-butyldimethylsilyl) ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2c). **2c** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (41.5 mg, 5 equiv., 0.426 mmol), 1-Bromo-2-(*tert*-butyldimethylsilyl)acetylene (19.7 µL, 1.2 equiv., 0.102 mmol), compound **1a** (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2c** was obtained after purification on silica gel (eluent: Toluene/EtOAc 95:5) as yellowish oil (37.9 mg; 0.052 mmol; 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.86 (dd, *J*=7.5, 1.2 Hz, 1H), 8.76 (dd, *J*=4.2, 1.6 Hz, 1H), 8.16 (dd, *J*=8.3, 1.5 Hz, 1H), 7.57 (t, *J*=7.9 Hz, 1H), 7.51 (dd, *J*=8.2, 1.2 Hz, 1H), 7.43 (dd, *J*=8.3, 4.2 Hz, 1H), 7.37–7.30 (m, 10H), 7.22–7.15 (m, 5H), 4.81 (dd, *J*=3.7, 1.2 Hz, 1H), 4.75 (d, *J*=11.4 Hz, 1H), 4.72 (d, *J*=12.4 Hz, 1H), 4.64–4.57 (m, 4H), 4.54–4.50 (m, 1H), 4.00 (t, *J*=4.2 Hz, 1H), 3.89 (dd, *J*=10.7, 6.0 Hz, 1H), 3.78 (dd, *J*=10.7, 4.8 Hz, 1H), 0.66 (s, 9H), −0.16 (s, 3H), −0.26 (s, 3H).^{13}C NMR (101 MHz, CDCl3) δ 165.2, 148.3, 138.9, 138.9, 138.2, 138.1, 137.8, 136.3, 134.9, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 127.5, 121.6, 117.2, 116.9, 101.2, 97.3, 77.4, 73.4, 73.2, 72.7, 72.4, 72.3, 67.6, 25.8, 16.5, −5.3, −5.4; IR (cm^{-1}) : 3030, 2953, 2928, 2858, 2360, 1662, 1598, 1577, 1524, 1486, 1471, 1455, 1425, 1386, 1327, 1250, 1206, 1090, 1071, 1028; $[\alpha]^{20}_D$= +207.6 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{45}H_{49}N_2O_5Si^+$ (*m/z*): calc. 725.3411; found 725.3418.

2-*N*-(quinolin-8-yl)carbamoyl-1-((triethylsilyl)ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2d). **2d** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (48.9 mg, 5 equiv., 0.426 mmol), bromo (triethylylsilyl)acetylene (19.7 µL, 1.2 equiv., 0.102 mmol), compound **1a** (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2d** was obtained after purification on silica gel (eluent: Toluene/EtOAc 98:2) as yellowish oil (25.6 mg; 0.035 mmol; 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.86 (dd, *J*=7.5, 1.1 Hz, 1H), 8.77 (dd, *J*=4.1, 1.5 Hz, 1H), 8.16 (dd, *J*=8.3, 1.4 Hz, 1H), 7.58–7.54 (m, 1H), 7.51 (dd, *J*=8.2, 1.2 Hz, 1H), 7.44 (dd, *J*=8.3, 4.2 Hz, 1H), 7.40–7.37 (m, 2H), 7.35–7.31 (m, 8H), 7.21–7.16 (m, 5H), 4.81 (dd, *J*=3.6, 1.1 Hz, 1H), 4.74 (d, *J*=11.2 Hz, 1H), 4.71 (d, *J*=11.8 Hz, 1H), 4.63–4.57 (m, 4H), 4.54–4.51 (m, 1H), 3.99 (t, *J*=4.1 Hz, 1H), 3.89 (dd, *J*=10.7, 6.1 Hz, 1H), 3.77 (dd, *J*=10.7, 4.7 Hz, 1H), 0.68 (t, *J*=7.9 Hz, 9H), 0.35–0.19 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) 192.6, 165.3, 148.2, 139.0, 138.9, 138.3, 138.1, 137.8, 136.3, 135.0, 134.6, 129.9, 129.1, 129.1, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 127.6, 121.6, 121.6, 117.1, 116.9, 100.8, 97.7, 77.4, 73.4, 73.2, 72.5, 72.4, 72.2, 67.6, 7.1, 3.7; IR (cm^{-1}): 3063, 3030, 2957, 2933, 2874, 2360, 1734, 1662, 1598, 1577, 1559, 1525, 1487, 1455, 1425, 1386, 1327, 1264, 1206, 1124, 1088, 1072, 1028; $[\alpha]^{20}_D$= +201.5 (1.00, $CHCl_3$); HRMS (TOF ES+) for (M+H)+ $C_{45}H_{49}N_2O_5Si^+$ (*m/z*): calc. 725.3411; found 725.3415.

2-*N*-(quinolin-8-yl)carbamoyl-1-((dimethyl(phenyl)silyl) ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2e). **2e** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (45.2 mg, 5 equiv., 0.426 mmol), (bromoethynyl)dimethyl(phenyl)silane (19.3 µL, 1.2 equiv., 0.102 mmol), compound **1a** (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2e** was obtained after purification on silica gel (eluent: Toluene/EtOAc 98:2) as yellowish oil (14.4 mg; 0.019 mmol; 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.86 (dd, *J*=7.6, 1.2 Hz, 1H), 8.51 (dd, *J*=4.2, 1.6 Hz, 1H), 8.10 (dd, *J*=8.3, 1.6 Hz, 1H), 7.56 (t, *J*=7.9 Hz, 1H), 7.49 (dd, *J*=8.3, 1.1 Hz, 1H), 7.35–7.29 (m, 13H), 7.20–7.16 (m, 6H), 7.07 (t, *J*=7.4 Hz, 2H), 4.83 (dd, *J*=3.6, 1.4 Hz, 1H), 4.74 (d, *J*=11.2 Hz, 1H), 4.70 (d, *J*=11.9 Hz, 1H), 4.60 (d, *J*=11.8 Hz, 1H), 4.58 (d, *J*=11.3 Hz, 1H), 4.57–4.52 (m, 3H), 3.98 (t, *J*=3.9 Hz, 1H), 3.88 (dd, *J*=10.7, 6.3 Hz, 1H), 3.75 (dd, *J*=10.7, 4.8 Hz, 1H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 148.3, 139.0, 138.8, 138.3, 138.1, 137.8, 136.2, 135.3, 134.9, 133.6, 129.5, 128.6, 128.6, 128.3, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7, 127.5, 121.6, 121.6, 117.4, 116.8, 101.1, 98.0, 77.4, 73.4, 73.2, 72.3, 72.1, 72.1, 67.7, −1.6, −1.7; IR (cm^{-1}): 3063, 3030, 2960, 2919, 2865, 2359, 2339, 1734, 1718, 1700, 1654, 1598, 1577, 1559, 1525, 1497, 1487, 1455, 1427, 1387, 1327, 1251, 1206, 1178, 1118,1091, 1071, 1028; $[\alpha]^{20}_D$= +171.7 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{47}H_{45}N_2O_5Si^+$ (*m/z*): calc. 745.3098; found 745.3105.

2-*N*-(quinolin-8-yl)carbamoyl-1-(cyclopropylethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (2f). **2f** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (45.2 mg, 5 equiv., 0.426 mmol), (bromoethynyl)cyclopropane (9.6 µL, 1.2 equiv., 0.102 mmol), compound **1a** (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **2f** was obtained after purification on silica gel (eluent: Toluene/EtOAc 98:2) as yellowish oil (15.9 mg; 0.024 mmol; 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.71 (dd, *J*=7.1, 2.2 Hz, 2H), 8.10 (dd, *J*=8.3, 1.4 Hz, 1H), 7.52–7.45 (m, 2H), 7.40–7.37 (m, 3H), 7.31–7.26 (m, 8H), 7.23–7.21 (m, 5H), 5.08 (d, *J*=4.2 Hz, 1H), 4.85 (d, *J*=11.9 Hz, 2H), 4.57–4.54 (m, 3H), 4.21–4.17 (m, 1H), 3.92 (dd, *J*=8.9, 1.7 Hz, 1H), 3.78–3.71 (m, 2H), 3.43 (d, *J*=4.2 Hz, 1H), 0.76–0.70 (m, 1H), 0.43–0.25 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 148.5, 140.7, 138.6, 138.4, 138.2, 137.7, 136.3, 134.3, 128.5, 128.4, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 126.1, 121.9, 121.8, 121.5, 116.6, 80.2, 78.8, 77.9, 77.0, 73.6, 71.4, 69.2, 62.1, 54.1, 7.8, 6.2; IR (cm^{-1}): 3318, 3064, 3030, 3008, 2925,

2865, 2360, 2339, 1718, 1681, 1596, 1577, 1527, 1486, 1454, 1425, 1386, 1328, 1264, 1208, 1179, 1153, 1095, 1071, 1028; $[\alpha]^{20}_{D}$=-40.8 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{42}H_{39}N_2O_5^+$ (*m/z*): calc. 651.2859; found 651.2865.

2-*N*-(quinolin-8-yl)carbamoyl-1-((triisopropylsilyl)ethynyl)-3,4,6-tri-*O*-benzyl-D–galactal (4a). **4a** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (36.1 mg, 5 equiv., 0.341 mmol), bromo (triisopropylsilyl)acetylene (19.9 µL, 1.2 equiv., 0.082 mmol), 2-*N*-(quinolin-8-yl)carbamoyl-3,4,6-tri-*O*-benzyl-D-galactal (40 mg, 1 equiv., 0.068 mmol) and toluene (0.34 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (3.4 mg, 20 mol%, 0.014 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **4a** was obtained after purification on silica gel (eluent: Cyclo/EtOAc 9:1) as yellowish oil (32.5 mg; 0.042 mmol; 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.75 (dd, *J*=7.3, 1.0 Hz, 1H), 8.65 (dd, *J*=4.1, 1.4 Hz, 1H), 8.06 (dd, *J*=8.3, 1.4 Hz, 1H), 7.49–7.45 (m, 1H), 7.44–7.42 (m, 1H), 7.34 (dd, *J*=8.3, 4.2 Hz, 1H), 7.31 (d, *J*=4.2 Hz, 4H), 7.27–7.21 (m, 6H), 7.19–7.17 (m, 2H), 7.13–7.09 (m, 3H), 4.79 (d, *J*=3.1 Hz, 1H), 4.72 (d, *J*=12.0 Hz, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.67 (d, *J*=11.5 Hz, 1H), 4.56 (d, *J*=12.0 Hz, 1H), 4.56 (d, *J*=12.1 Hz, 1H), 4.49 (d, *J*=12.1 Hz, 1H), 4.46–4.45 (m, 1H), 3.99–3.91 (m, 2H), 3.83 (dd, *J*=11.4, 3.4 Hz, 1H), 0.74–0.68 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 148.2, 138.9, 138.6, 138.4, 138.3, 137.9, 136.2, 135.0, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.7, 127.4, 121.6, 121.5, 117.7, 116.9, 99.3, 98.3, 77.0, 74.1, 73.4, 72.6, 72.4, 70.5, 67.6, 18.4, 18.3, 11.0; IR (cm^{-1}): 3030, 2942, 2865, 2359, 1744, 1663, 1597, 1577, 1559, 1524, 1497, 1486, 1456, 1425, 1386, 1327, 1209, 1102, 1028; $[\alpha]^{20}_{D}$=+186.2 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{48}H_{55}N_2O_5Si^+$ (*m/z*): calc. 767.3880; found 767.3869.

2-*N*-(quinolin-8-yl)carbamoyl-1-(cyclopropylethynyl)-3,4,6-tri-*O*-benzyl-D–galactal (4b). **4b** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (45.1 mg, 5 equiv., 0.426 mmol), (bromoethynyl)cyclopropane (9.2 µL, 1.2 equiv., 0.102 mmol), 2-*N*-(quinolin-8-yl)carbamoyl-3,4,6-tri-*O*-benzyl-D-galactal (50 mg, 1 equiv., 0.085 mmol) and toluene (0.43 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (4.2 mg, 20 mol%, 0.017 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **4b** was obtained after purification on silica gel (eluent: Toluene/EtOAc 95:5) as yellowish oil (12.5 mg; 0.019 mmol; 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.76 (dd, *J*=4.2, 1.7 Hz, 1H), 8.71 (dd, *J*=6.8, 2.1 Hz, 1H), 8.15 (dd, *J*=8.3, 1.6 Hz, 1H), 7.54–7.52 (m, 2H), 7.45–7.28 (m, 16H), 5.06 (d, *J*=4.1 Hz, 1H), 4.85–4.81 (m, 2H), 4.67 (d, *J*=12.0 Hz, 1H), 4.63 (d, *J*=12.1 Hz, 1H), 4.62 (d, *J*=11.8 Hz, 1H), 4.59–4.55 (m, 1H), 4.37 (dd, *J*=11.3, 8.5 Hz, 1H), 4.16 (dd, *J*=5.9, 2.9 Hz, 1H), 4.08 (dd, *J*=11.3, 1.5 Hz, 1H), 3.50 (d, *J*=4.1 Hz, 1H), 0.93–0.88 (m, 1H), 0.44–0.26 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 148.6, 139.4, 138.6, 138.5, 138.2, 137.7, 136.3, 134.2, 133.3, 129.1, 128.8, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.4, 125.9, 121.9, 121.8, 116.4, 82.1, 79.7, 74.1, 73.6, 73.1, 72.2, 68.0, 62.7, 53.4, 8.3, 7.8, 5.7; IR (cm^{-1}): 3017, 2926, 2856, 2360, 1734, 1674, 1597, 1577, 1528, 1487, 1455, 1426, 1387, 1329, 1215, 1180, 1093, 1044, 1028; $[\alpha]^{20}_{D}$=-51.7 (0.88, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{42}H_{39}N_2O_5^+$ (*m/z*): calc. 651.2859; found 651.2860.

2-*N*-(quinolin-8-yl)carbamoyl-1-((triisopropylsilyl)ethynyl)-3,4-*O*-benzyl-L–rhamnal (5a). 3,4-di-*O*-benzyl-L-rhamnal was prepared according to the literature.[20] 2-Iodo-3,4-di-*O*-benzyl-L-rhamnal (**S1**) was synthesized following the described procedure:[18] 3,4-di-*O*-benzyl-L-rhamnal (1 g, 1 equiv., 3.22 mmol) was dissolved in dry acetonitrile (22 mL) under argon and the resulting mixture was heated to 80 °C. At this temperature, *N*-iodosuccinimide (870 mg, 1.2 equiv., 3.87 mmol) and silver nitrate (109 mg, 20 mol%, 0.64 mmol) were added. The resulting mixture was stirred at 80 °C for 2 h. The mixture was filtrated on celite with EtOAc and concentrated with silica. The obtained crude was purified on silica gel (eluent: Cyclo/EtOAc 95:5) and furnished **S1** as a colorless oil (942 mg, 2.16 mmol, 67%) which was directly engaged in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.39–7.31 (m, 8H), 6.70 (s, 1H), 4.78 (d, *J*=10.9 Hz, 1H), 4.77 (d, *J*=11.5 Hz, 1H), 4.66 (d, *J*=10.9 Hz, 1H), 4.65 (d, *J*=11.5 Hz, 1H), 4.23–4.16 (m, 1H), 4.13 (d, *J*=5.4 Hz, 1H), 3.64 (dd, *J*=7.4, 5.5 Hz, 1H), 1.38 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 137.9, 137.8, 128.7, 128.5, 128.3, 128.1, 128.0, 128.0, 79.8, 79.1, 74.3, 73.7, 72.5, 71.1, 17.0; IR (cm^{-1}): 3089, 3063, 3030, 2975, 2936, 2873, 1734, 1718, 1624, 1497, 1454, 1380, 1365, 1350, 1236, 1208, 1166, 1138, 1100, 1072, 1055, 1029; $[\alpha]^{20}_{D}$=-20.8 (1.00, $CHCl_3$). 2-*N*-(quinolin-8-yl)carbamoyl-3,4-di-*O*-benzyl-L-rhamnal (**S2**) was obtained according to the literature:[11] in a sealed tube were added $Pd(OAc)_2$ (46.3 mg; 0.1 equiv.; 0.206 mmol), PPh_3 (108.2 mg; 0.2 equiv.; 0.413 mmol), K_2CO_3 (570.2 mg; 2 equiv.; 4.126 mmol), $Mo(CO)_6$ (2.3 g; 4.2 equiv.; 8.664 mmol), 8-aminoquinoline (594.8 mg; 2 equiv.; 4.126 mmol), **S1** (879 mg; 1 equiv.; 2.063 mmol) and dioxane (23 mL). The resulting mixture was stirred at 80 °C overnight. The mixture was filtrated on celite with EtOAc and concentrated under vacuum. **S2** was purified on silica gel (eluent: Toluene/EtOAc 95:5) and was washed with HCl (1 M) to remove excess of 8-aminoquinoline and then with a saturated aqueous solution of $NaHCO_3$. **S2** was obtained as yellowish oil (727 mg; 1.513 mmol; 75%) and was directly engaged in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.84 (dd, *J*=7.6, 1.0 Hz, 1H), 8.34 (dd, *J*=4.2, 1.6 Hz, 1H), 8.11 (dd, *J*=8.3, 1.5 Hz, 1H), 7.76 (s, 1H), 7.54 (t, *J*=7.9 Hz, 1H), 7.47 (dd, *J*=8.2, 0.9 Hz, 1H), 7.39–7.28 (m, 11H), 5.14 (d, *J*=11.5 Hz, 1H), 4.74 (d, *J*=11.5 Hz, 1H), 4.68 (s, 2H), 4.58–4.55 (m, 2H), 3.79 (t, *J*=2.9 Hz, 1H), 1.43 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 153.5, 148.0, 138.9, 138.3, 137.7, 136.3, 135.4, 128.7, 128.5, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 121.5, 121.2, 116.9, 107.9, 74.3, 73.8, 71.9, 71.5, 70.9, 16.3; IR (cm^{-1}): 2970, 1734, 1718, 1700, 1675, 1653, 1647, 1636, 1617, 1577, 1559, 1540, 1526, 1507, 1497, 1489, 1473, 1457, 1424, 1375, 1325, 1281, 1198, 1145, 1070, 1045, 1028; $[\alpha]^{20}_{D}$=+0.23 (0.026, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{30}H_{29}N_2O_4^+$ (*m/z*): calc. 481.2127; found 481.2126. **5a** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (55 mg, 5 equiv., 0.520 mmol), bromo

(triisopropylsilyl)acetylene (30.4 μL, 1.2 equiv., 0.125 mmol), compound **S2** (50 mg, 1 equiv., 0.104 mmol) and toluene (0.5 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (5.2 mg, 20 mol%, 0.021 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **5a** was obtained after purification on silica gel (eluent: Toluene/EtOAc 95:5) as yellowish oil (20.3 mg; 0.031 mmol; 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.76 (dd, J = 7.4, 1.4 Hz, 1H), 8.64 (dd, J = 4.2, 1.6 Hz, 1H), 8.06 (dd, J = 8.3, 1.6 Hz, 1H), 7.49–7.45 (m, 1H), 7.42 (dd, J = 8.3, 1.5 Hz, 1H), 7.33 (dd, J = 8.3, 4.2 Hz, 1H), 7.30–7.28 (m, 2H), 7.24–7.18 (m, 3H), 7.16–7.13 (m, 2H), 7.08–7.06 (m, 3H), 4.73–4.67 (m, 3H), 4.57 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.31–4.25 (m, 1H), 3.59 (dd, J = 5.8, 4.7 Hz, 1H), 1.39 (d, J = 6.7 Hz, 3H), 0.74–0.68 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 148.3, 138.9, 138.4, 137.9, 136.2, 135.0, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 127.6, 127.5, 121.6, 121.5, 117.8, 117.0, 98.8, 98.5, 77.4, 75.0, 74.6, 73.6, 73.0, 18.4, 18.3, 16.9, 11.1; IR (cm^{-1}): 2926, 2866, 2360, 2339, 1734, 1662, 1597, 1577, 1559, 1525, 1487, 1457, 1425, 1383, 1340, 1327, 1216, 1137, 1092, 1072, 1028; $[\alpha]^{20}_D$ = -157.1 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{41}H_{49}N_2O_4Si^+$ (*m/z*): calc. 661.3462; found 661.3461.

2-*N*-(quinolin-8-yl)carbamoyl-1-((triphenylsilyl)ethynyl)-3,4-*O*-benzyl-L–rhamnal (5b). 3,4-di-*O*-benzyl-L-rhamnal was prepared according to the literature.[20] 2-Iodo-3,4-di-*O*-benzyl-L-rhamnal (**S1**) was synthesized following the described procedure:[18] 3,4-di-*O*-benzyl-L-rhamnal (1 g, 1 equiv., 3.22 mmol) was dissolved in dry acetonitrile (22 mL) under argon and the resulting mixture was heated to 80 °C. At this temperature, *N*-iodosuccinimide (870 mg, 1.2 equiv., 3.87 mmol) and silver nitrate (109 mg, 20 mol%, 0.64 mmol) were added. The resulting mixture was stirred at 80 °C for 2 h. The mixture was filtrated on celite with EtOAc and concentrated with silica. The obtained crude was purified on silica gel (eluent: Cyclo/EtOAc 95:5) and furnished **S1** as a colorless oil (942 mg, 2.16 mmol, 67%) which was directly engaged in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.39–7.31 (m, 8H), 6.70 (s, 1H), 4.78 (d, J = 10.9 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 10.9 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.23–4.16 (m, 1H), 4.13 (d, J = 5.4 Hz, 1H), 3.64 (dd, J = 7.4, 5.5 Hz, 1H), 1.38 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 137.9, 137.8, 128.7, 128.5, 128.3, 128.1, 128.0, 128.0, 79.8, 79.1, 74.3, 73.7, 72.5, 71.1, 17.0; IR (cm^{-1}): 3089, 3063, 3030, 2975, 2936, 2873, 1734, 1718, 1624, 1497, 1454, 1380, 1365, 1350, 1236, 1208, 1166, 1138, 1100, 1072, 1055, 1029; $[\alpha]^{20}_D$ = -20.8 (1.00, $CHCl_3$). 2-*N*-(quinolin-8-yl)carbamoyl-3,4-di-*O*-benzyl-L-rhamnal (**S2**) was obtained according to the literature:[11] in a sealed tube were added $Pd(OAc)_2$ (46.3 mg; 0.1 equiv.; 0.206 mmol), PPh_3 (108.2 mg; 0.2 equiv.; 0.413 mmol), K_2CO_3 (570.2 mg; 2 equiv.; 4.126 mmol), $Mo(CO)_6$ (2.3 g; 4.2 equiv.; 8.664 mmol), 8-aminoquinoline (594.8 mg; 2 equiv.; 4.126 mmol), **S1** (879 mg; 1 equiv.; 2.063 mmol) and dioxane (23 mL). The resulting mixture was stirred at 80 °C overnight. The mixture was filtrated on celite with EtOAc and concentrated under vacuum. **S2** was purified on silica gel (eluent: Toluene/EtOAc 95:5) and was washed with HCl (1 M) to remove excess of 8-aminoquinoline and then with a saturated aqueous solution of $NaHCO_3$. **S2** was obtained as yellowish oil (727 mg; 1.513 mmol; 75%) and was directly engaged in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.84 (dd, J = 7.6, 1.0 Hz, 1H), 8.34 (dd, J = 4.2, 1.6 Hz, 1H), 8.11 (dd, J = 8.3, 1.5 Hz, 1H), 7.76 (s, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.47 (dd, J = 8.2, 0.9 Hz, 1H), 7.39–7.28 (m, 11H), 5.14 (d, J = 11.5 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.68 (s, 2H), 4.58–4.55 (m, 2H), 3.79 (t, J = 2.9 Hz, 1H), 1.43 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 153.5, 148.0, 138.9, 138.3, 137.7, 136.3, 135.4, 128.7, 128.5, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 121.5, 121.2, 116.9, 107.9, 74.3, 73.8, 71.9, 71.5, 70.9, 16.3; IR (cm^{-1}): 2970, 1734, 1718, 1700, 1675, 1653, 1647, 1636, 1617, 1577, 1559, 1540, 1526, 1507, 1497, 1489, 1473, 1457, 1424, 1375, 1325, 1281, 1198, 1145, 1070, 1045, 1028; $[\alpha]^{20}_D$ = +0.23 (0.026, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{30}H_{29}N_2O_4^+$ (*m/z*): calc. 481.2127; found 481.2126. **5b** was obtained following the general procedure of C–H functionalization: in a sealed tube were added Na_2CO_3 (55 mg, 5 equiv., 0.520 mmol), (bromoethynyl)triphenylsilane (45.4 mg, 1.2 equiv., 0.125 mmol), compound **S2** (50 mg, 1 equiv., 0.104 mmol) and toluene (0.5 mL). The resulting mixture was stirred for 4 h at 140 °C. Then $Ni(OAc)_2.4H_2O$ (5.2 mg, 20 mol%, 0.021 mmol) was added at room temperature in the sealed tube. The resulting mixture was stirred at 140 °C overnight. The mixture was filtrated on celite with EtOAc and then concentrated under vacuum. **5b** was obtained after purification on silica gel (eluent: Toluene/EtOAc 95:5) as yellowish oil (16.8 mg; 0.022 mmol; 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.80 (dd, J = 7.7, 0.9 Hz, 1H), 7.92 (dd, J = 4.2, 1.6 Hz, 1H), 7.86 (dd, J = 8.3, 1.5 Hz, 1H), 7.56 (dd, J = 7.9, 1.4 Hz, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.38–7.35 (m, 2H), 7.32–7.29 (m, 9H), 7.18–7.15 (m, 5H), 7.09 (dd, J = 5.0, 2.0 Hz, 3H), 7.04–7.00 (m, 6H), 4.80 (dd, J = 4.1, 0.9 Hz, 1H), 4.73 (d, J = 11.2 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.36–4.30 (m, 1H), 3.62–3.59 (m, 1H), 1.40 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 148.2, 138.6, 138.5, 138.4, 137.8, 135.8, 135.7, 135.5, 135.3, 135.2, 135.1, 134.9, 132.2, 130.2, 129.9, 128.7, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.3, 121.7, 121.4, 118.5, 116.8, 100.4, 97.5, 77.0, 75.2, 73.7, 73.6, 72.7, 16.9; IR (cm^{-1}): 2920, 2865, 2360, 2343, 1734, 1718, 1684, 1669, 1654, 1647, 1636, 1617, 1597, 1578, 1559, 1497, 1457, 1429, 1375, 1340, 1328, 1262, 1217, 1135, 1115, 1071, 1028; $[\alpha]^{20}_D$ = -143.4 (0.49, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{50}H_{43}N_2O_4Si^+$ (*m/z*): calc. 763.2992; found 763.2994.

2-*N*-*tert*-butoxycarbonyl-*N*-((quinolin-8-yl)carbamoyl)-1-((triisopropylsilyl)ethynyl)-3,4,6-tri-*O*-benzyl-D–glucal (6). **6** was obtained according to the literature:[21] compound **2a** (408 mg, 1 equiv., 0.532 mmol) was dissolved in dry acetonitrile (13 mL) under argon. Then DMAP (32.5 mg, 0.5 equiv., 0.266 mmol) and Boc_2O (1.2 g, 10 equiv., 5.319 mmol) were added. The resulting mixture was stirred at 65 °C for 3 h under argon. DMAP (32.5 mg, 0.5 equiv., 0.266 mmol) and Boc_2O (1.2 g, 10 equiv., 5.319 mmol) were added one more time. The reaction was stirred again at 65 °C for 3 h more. The mixture was concentrated under vacuum and **6** was obtained after purification on silica gel (eluent: Toluene/EtOAc 95:5) as yellowish oil (364.4 mg; 0.420 mmol; 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 3.9 Hz, 1H), 8.06 (dd,

J=8.3, 1.3 Hz, 1H), 7.72 (d, J=8.2 Hz, 1H), 7.45–7.41 (m, 1H), 7.35–7.34 (m, 2H), 7.31–7.26 (m, 6H), 7.24–7.19 (m, 7H), 7.15 (d, J=7.7 Hz, 2H), 4.89 (d, J=10.9 Hz, 1H), 4.57 (d, J=12.0 Hz, 2H), 4.53 (d, J=11.8 Hz, 2H), 4.43–4.31 (m, 3H), 3.96–3.86 (m, 2H), 3.77 (dd, J=11.2, 3.2 Hz, 1H), 1.26 (s, 9H), 1.07–1.06 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 150.1, 144.5, 138.9, 138.5, 138.0, 137.1, 136.0, 129.2, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.8, 127.8, 127.6, 127.4, 126.1, 125.4, 121.5, 99.2, 82.7, 81.2, 78.2, 73.6, 73.5, 72.9, 72.8, 68.2, 27.9, 18.8, 18.8, 11.4; IR (cm^{-1}): 2942, 2865, 2360, 2344, 1743, 1718, 1696, 1684, 1669, 1654, 1647, 1636, 1617, 1577, 1559, 1540, 1522, 1507, 1498, 1490, 1472, 1457, 1437, 1368, 1271, 1217, 1157, 1117, 1069, 1028; $[\alpha]^{20}_D$=-44.5 (0.45, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{53}H_{63}N_2O_7Si^+$ (*m/z*): calc. 867.4405; found 867.4409.

2-*N*-*tert*-butoxycarbonyl-*N*-((quinolin-8-yl)carbamoyl)-1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3,4,6-tri-*O*-benzyl-D–glucal (7a). **7a** was obtained following the general procedure of the click reaction: compound **6** (474 mg, 1 equiv., 0.577 mmol) was dissolved in dry THF (6.3 mL) under argon. Then triethylamine (241 µL, 3 equiv., 1.730 mmol) and TBAF (0.87 mL, 1.5 equiv., 0.865 mmol) were added and the reaction was stirred at room temperature. The color of the reaction mixture changed in purple, and after that CuI (55 mg, 0.5 equiv., 0.288 mmol) and benzyl azide (108 µL, 1.5 equiv., 0.865 mmol) were added. The reaction was stirred at 40 °C overnight. The mixture was concentrated under vacuum and **7a** was obtained after purification on silica gel (eluent: Cyclo/EtOAc 7:3) as yellowish oil (332 mg; 0.393 mmol; 72%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.73 (d, J=3.8 Hz, 1H), 8.34 (d, J=8.2 Hz, 1H), 8.20 (s, 1H), 7.92 (d, J=8.2 Hz, 1H), 7.63–7.59 (m, 1H), 7.48 (dd, J=8.4, 4.3 Hz, 1H), 7.44–7.24 (m, 21H), 5.70 (s, 2H), 4.98 (d, J=10.8 Hz, 1H), 4.76–4.53 (m, 8H), 4.09 (s, 1H), 3.87 (dd, J=11.2, 3.8 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 153.0, 150.7, 145.7, 145.5, 143.7, 140.1, 139.8, 139.3, 138.6, 136.9, 136.7, 129.7, 129.5, 129.2, 129.1, 129.0, 129.0, 128.8, 128.6, 128.3, 128.3, 128.1, 128.0, 127.1, 125.1, 122.3, 109.9, 81.6, 77.7, 74.3, 73.9, 72.7, 72.1, 68.9, 54.3, 27.6.; IR (cm^{-1}): 3064, 3030, 3008, 2979, 2929, 2865, 1743, 1684, 1669, 1654, 1636, 1617, 1456, 1437, 1388, 1368, 1323, 1273, 1254, 1217, 1155, 1120, 1092, 1071, 1046, 1028; $[\alpha]^{20}_D$=-56.8 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{51}H_{50}N_5O_7^+$ (*m/z*): calc. 844.3710; found 844.3731.

2-*N*-*tert*-butoxycarbonyl-*N*-((quinolin-8-yl)carbamoyl)-1-(methyl (S)-2-((*tert*-butoxycarbonyl)amino)-6-(1*H*-1,2,3-triazol-4-yl)hexanoyl)-3,4,6-tri-*O*-benzyl-D–glucal (7b). **7b** was obtained following the general procedure of the click reaction: compound **6** (51.6 mg, 1 equiv., 0.060 mmol) was dissolved in dry THF (0.63 mL) under argon. Then triethylamine (24 µL, 3 equiv., 0.173 mmol) and TBAF (86.5 µL, 1.5 equiv., 0.087 mmol) were added and the reaction was stirred at room temperature. The color of the reaction mixture changed in purple, and after that CuI (5.6 mg, 0.5 equiv., 0.029 mmol) and Boc-L-Lys(N_3)-OMe (24.8 mg, 1.5 equiv., 0.087 mmol) were added. The reaction was stirred at 40 °C overnight. The mixture was concentrated under vacuum and **7b** was obtained after purification on silica gel (eluent: Cyclo/EtOAc 5:5) as yellowish oil (23.4 mg; 0.023 mmol; 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.67 (dd, J=5.3, 1.0 Hz, 1H), 7.34–7.32 (m, 2H), 7.30–7.18 (m, 17H), 5.00 (d, J=8.0 Hz, 1H), 4.91–4.42 (m, 8H), 4.33–4.22 (m, 3H), 4.10–3.92 (m, 2H), 3.79–3.76 (m, 1H), 3.67 (s, 3H), 1.89–1.84 (m, 2H), 1.81–1.74 (m, 1H), 1.66–1.55 (m, 3H), 1.40 (s, 9H), 1.16–1.10 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 170.6, 155.5, 152.4, 149.6, 144.3, 138.7, 138.5, 137.9, 137.0, 136.1, 129.3, 128.8, 128.5, 128.4, 128.3, 128.1, 127.88, 127.8, 127.6, 127.6, 126.5, 121.3, 109.9, 82.1, 80.1, 77.4, 73.6, 73.2, 72.5, 72.3, 68.1, 53.1, 52.6, 50.0, 29.9, 29.8, 28.4, 27.6, 22.4; IR (cm^{-1}): 3063, 3033, 2929, 2866, 1743, 1717, 1684, 1670, 1654, 1636, 1540, 1521, 1517, 1507, 1498, 1473, 1456, 1437, 1391, 1368, 1323, 1273, 1254, 1204, 1160, 1121, 1091, 1072, 1028; $[\alpha]^{20}_D$=-62.1 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{56}H_{65}N_6O_{11}^+$ (*m/z*): calc. 997.4711; found 997.4712.

2-*N*-*tert*-butoxycarbonyl-*N*-((quinolin-8-yl)carbamoyl)-1-(1-(((2R,3R,4S,5R,6S)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-3,4,6-tri-*O*-benzyl-D–glucal (7c). **7c** was obtained following the general procedure of the click reaction: compound **6** (50.4 mg, 1 equiv., 0.058 mmol) was dissolved in dry THF (0.64 mL) under argon. Then triethylamine (24 µL, 3 equiv., 0.173 mmol) and TBAF (86 µL, 1.5 equiv., 0. 86 mmol) were added and the reaction was stirred at room temperature. The color of the reaction mixture changed in purple, and after that CuI (5.5 mg, 0.5 equiv., 0.029 mmol) and methyl 6-azido-6-deoxy-2,3,4-tri-O-benzyl-α-D-glucopyranoside (42.2 mg, 1.5 equiv., 0.086 mmol) were added. The reaction was stirred at 40 °C overnight. The mixture was concentrated under vacuum and **7c** was obtained after purification on silica gel (eluent: Toluene/EtOAc 9:1 then 85:15) as yellowish oil (50.1 mg; 0.042 mmol; 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.01 (d, J=7.6 Hz, 1H), 7.64–7.57 (m, 1H), 7.50–7.44 (m, 1H), 7.33–7.20 (m, 33H), 4.94–4.91 (m, 2H), 4.84 (d, J=10.8 Hz, 1H), 4.79–4.74 (m, 2H), 4.70–4.62 (m, 4H), 4.59–4.38 (m, 9H), 4.12–3.90 (m, 4H), 3.80–3.79 (m, 1H), 3.33 (dd, J=9.5, 3.0 Hz, 1H), 3.10–3.08 (m, 3H), 1.21–1.13 (m, 9H); ^{13}C NMR (101 MHz, $(CDCl_3)$ δ 170.6, 152.5, 149.6, 144.3, 142.1, 138.6, 138.4, 138.2, 138.0, 137.9, 136.9, 136.1, 136.0, 134.6, 129.9, 129.3, 129.1, 129.1, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.1, 126.4, 121.3, 110.1, 98.0, 82.4, 82.0, 79.9, 79.2, 78.0, 75.7, 75.1, 73.5, 73.3, 72.6, 72.3, 69.0, 67.9, 65.4, 55.6, 50.6, 27.6; IR (cm^{-1}): 3064, 3030, 3009, 2925, 1743, 1684, 1670, 1654, 1507, 1497, 1425, 1419, 1389, 1369, 1323, 1273, 1254, 1217, 1156, 1091, 1071, 1028; $[\alpha]^{20}_D$=-32.6 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{72}H_{74}N_5O_{12}^+$ (*m/z*): calc. 1200.5334; found 1200.5343.

2-*N*-*tert*-butoxycarbonyl-*N*-((quinolin-8-yl)carbamoyl)-1-(1-(13-oxo-17-((3aS,4S,6aR)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)-3,6,9-trioxa-12-azaheptadecyl)-1*H*-1,2,3-triazol-4-yl)-3,4,6-tri-*O*-benzyl-D–glucal (7d). **7d** was obtained following the general procedure of the click reaction: compound **6** (49.6 mg, 1 equiv., 0.058 mmol) was dissolved in dry THF (0.64 mL) under argon. Then triethylamine (24 µL, 3 equiv., 0.173 mmol) and TBAF (86 µL, 1.5 equiv., 0.86 mmol) were added and the reaction was stirred at room temperature. The color of the reaction mixture changed in purple, and after that CuI (5.5 mg, 0.5 equiv., 0.029 mmol) and Biotin-PEG3-azide (38.4 mg, 1.5 equiv., 0.086 mmol) were added. The reaction was stirred at 40 °C overnight. The mixture was concentrated under vacuum and **7d** was obtained after purification on silica

gel (eluent: Toluene/EtOAc 98:2 then 9:1) as yellowish oil (37.9 mg; 0.033 mmol; 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.32–8.10 (m, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.56–7.07 (m, 18H), 6.71 (s, 1H), 6.23 (s, 1H), 5.32–5.29 (m, 1H), 5.04–4.54 (m, 9H), 4.41–4.38 (m, 1H), 4.23–4.20 (m, 1H), 4.09–3.82 (m, 4H), 3.66–3.46 (m, 10H), 3.38–3.30 (m, 3H), 3.07 (dd, J = 11.8, 7.2 Hz, 1H), 2.82 (dd, J = 12.7, 4.7 Hz, 1H), 2.66 (d, J = 12.8 Hz, 1H), 2.15 (t, J = 7.4 Hz, 2H), 2.08–1.94 (m, 1H), 1.69–1.58 (m, 4H), 1.48–1.43 (m, 1H), 1.40–1.35 (m, 1H), 1.25–1.14 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 170.5, 163.8, 152.4, 149.8, 144.3, 138.7, 138.4, 137.9, 137.0, 136.1, 129.2, 128.8, 128.5, 128.5, 128.3, 128.1, 127.9, 127.7, 127.6, 126.5, 121.4, 110.4, 82.2, 77.4, 73.6, 73.3, 72.6, 72.3, 70.8, 70.5, 70.4, 70.1, 69.9, 69.5, 68.1, 61.8, 60.2, 59.2, 55.5, 50.4, 40.6, 39.2, 35.8, 28.2, 28.1, 27.6, 25.7; IR (cm^{-1}): 3007, 2930, 2866, 1744, 1701, 1654, 1559, 1540, 1522, 1507, 1498, 1472, 1456, 1388, 1369, 1324, 1272, 1254, 1215, 1153, 1121, 1072, 1028; $[\alpha]^{20}_D$ =-52.3 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{62}H_{75}N_8O_{12}S^+$ (*m/z*): calc. 1155.5225; found 1155.5208.

2-*N*-(pyrrolidinyl)carbamoyl-1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3,4,6-tri-*O*-benzyl-D–glucal (8) and 2-*N*-(quinolin-8-yl) carbamoyl-1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3,4,6-tri-*O*-benzyl-D–glucal (9). **8** and **9** were obtained with the following procedure: compound **7a** (22.5 mg, 1 equiv., 0.027 mmol) was dissolved in toluene (0.1 mL) under argon. Then pyrrolidine (4.1 µL, 1.5 equiv., 0.049 mmol) was added and the reaction was stirred at 65 °C overnight. The mixture was concentrated under vacuum and **8** and **9** were obtained after purification on silica gel (eluent: Cyclo/EtOAc 5:5 to have **9** and then 0:100 to have **8**) as yellowish oils (**8**: 6.2 mg; 0.009 mmol; 35% and **9**: 8.1 mg; 0.011 mmol; 41%). **8** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35–7.18 (m, 20H), 5.54 (d, J = 14.8 Hz, 1H), 5.41 (d, J = 14.8 Hz, 1H), 4.76 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 4.60–4.55 (m, 3H), 4.51 (d, J = 12.2 Hz, 1H), 4.42 (dd, J = 9.9, 5.3 Hz, 1H), 4.01–3.98 (m, 1H), 3.87 (dd, J = 10.7, 5.4 Hz, 1H), 3.77–3.74 (m, 1H), 3.47–3.40 (m, 2H), 3.35–3.28 (m, 1H), 2.91 (d, J = 7.2 Hz, 1H), 1.74–1.52 (m, 4H), 1.27–1.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 142.7, 138.4, 138.0, 138.0, 134.6, 129.2, 128.9, 128.6, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 122.9, 109.9, 76.9, 73.6, 73.4, 73.1, 67.6, 54.2, 47.5, 45.7, 25.6, 24.4; IR (cm^{-1}): 3029, 2971, 2926, 2855, 1734, 1718, 1706, 1700, 1684, 1669, 1663, 1653, 1647, 1636, 1617, 1577, 1570, 1559, 1550, 1540, 1534, 1522, 1517, 1507, 1497, 1490, 1473, 1457, 1437, 1419, 1395, 1387, 1374, 1363, 1340, 1229, 1217, 1091, 1028; $[\alpha]^{20}_D$ = +19.7 (0.32, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{41}H_{43}N_4O_5^+$ (m/z): calc. 671.3233; found 671.3235. **9** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.75 (dd, J = 7.4, 1.5 Hz, 1H), 8.42 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 8.3, 1.6 Hz, 1H), 7.66 (s, 1H), 7.52–7.48 (m, 1H), 7.45 (dd, J = 8.3, 1.6 Hz, 1H), 7.32 (dd, J = 8.3, 4.3 Hz, 1H), 7.30–7.23 (m, 11H), 7.17 (dd, J = 7.3, 2.2 Hz, 2H), 7.12–7.09 (m, 5H), 6.96 (d, J = 7.4 Hz, 2H), 5.33 (d, J = 14.8 Hz, 1H), 5.25 (d, J = 14.8 Hz, 1H), 4.72–4.69 (m, 1H), 4.68 (d, J = 12.3 Hz, 1H), 4.63–4.57 (m, 3H), 4.09–4.07 (m, 1H), 3.95 (dd, J = 10.5, 6.0 Hz, 1H), 3.87 (dd, J = 10.5, 5.3 Hz, 1H), 3.32–3.23 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 148.1, 146.9, 142.0, 138.6, 138.2, 137.8, 136.1, 135.0, 134.1, 129.0, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 124.7, 121.6, 121.5, 116.7, 110.4, 77.0, 73.6, 73.4, 72.5, 72.3, 72.2, 67.6, 54.1; IR (cm^{-1}): 1734, 1718, 1684, 1669, 1663, 1654, 1648, 1570, 1559, 1539, 1522, 1508, 1497, 1486, 1456, 1437, 1425, 1387, 1340, 1327, 1261, 1228, 1206, 1163, 1099, 1071, 1045, 1028, 1003; $[\alpha]^{20}_D$ = +71.6 (1.00, $CHCl_3$); HRMS (TOF ES+) for $(M+H)^+$ $C_{46}H_{42}N_5O_5^+$ (m/z): calc. 744.3186; found 744.3189.

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