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Directed Dehydrogenative Copper-Catalyzed C-H Thiolation in *Pseudo-Anomeric* Position of Glycals using Thiol and Thiosugar Partners

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Abstract. A novel approach to 1-thiotrehalose analogs and thioglycals was described by a directed copper-catalyzed dehydrogenative C–H thiolation of the pseudo-anomeric bond of glycals. The use of aminoquinoline-containing glycals as well as thiosugars or thiols as coupling partners

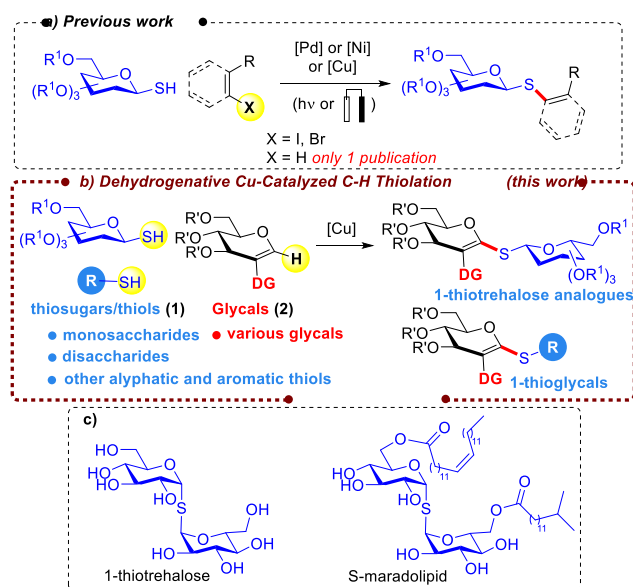
led to the synthesis of a library of triglycosides in moderate to good yields.

Keywords: C-H thiolation; thioglycosides; glycals; copper catalysis; directing group

Introduction

Serving a therapeutic purpose, the strategy consisting of mimicking natural biomolecules in order to reach drug candidates with an interesting pharmacokinetic profile (stability, solubility, activity, etc.) presents a popular methodology in medicinal chemistry.^[1] For instance, the synthetic conception of an unnatural avatar, sufficiently close in structure to interact with the target enzyme but different enough to be saved from degradation pathway is generally sought. In glycochemistry, most bioactive mimics were conceived by replacing the natural anomeric link (generally a C–O or a C–N bond) with an unnatural one.^[2] Among these analogs, thioglycosides, where the anomeric link is a C–S bond, offered an interesting balance between structural homology versus better stability compared to the native glycoside. Indeed, current literature shows the plethora of biological activities of developed thioglycosides: such as, glycosidase inhibitors, cytotoxic Hsp90 inhibitors, hSGLT1 inhibitors, antimicrobial agents or even lectin A ligands.^[3] From a synthetic point of view, the formation of an anomeric C–S bond has been mainly proposed using an acid-catalyzed glycosylation reaction^[4] with thiols or by nucleophilic substitution of a haloglycoside with a thiolate anion.^[5] However, these two methods suffer from poor substrate scopes

(mostly in terms of thiols) and use often harsh conditions. Recently, the use of metal-catalyzed reactions allowed proposing alternative access to thioglycosides *via* copper-,^[6] nickel-,^[7] or palladium^[8]-catalyzed cross-couplings with halide partners^[9] or glycals^[10] (Scheme 1a).



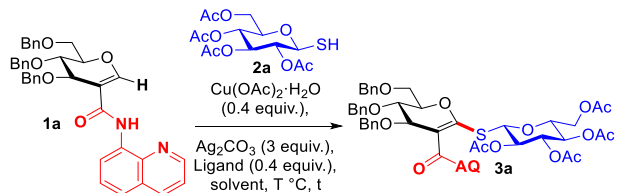
Scheme 1. Metal-catalyzed synthesis of thioglycosides

Very recently, our group reported other emergent and competitive activation processes toward thioglycosides such as photocatalysis^[11] or electrocatalysis^[12] (Scheme 1a). However, the use of non-activated partners faced with thiosugars via a C–H dehydrogenative cross-coupling pathway^[13] is very scarce. Only one example of dehydrogenative C–H thiolation of benzamides using thiosugars has been described by our group in 2016 (Scheme 1).^[6c] Moreover, we proposed a few years ago that aminoquinoline-containing glycals are suitable starting substrates for the C–H functionalization of the pseudo-anomeric position of glycals. Palladium- or nickel-catalysis has been successfully used on this compound with aryl iodide^[14] or alkynyl bromide partners.^[15] C–H activation methods involving sugars emerge very recently as a new option in the glycochemistry toolbox.^[16] However, examples where the sugar is the C–H activated partner remain very rare due to the complexity of the sugar structure and the difficulty to target only one specified C–H bond. Accordingly, we believe that developing a dehydrogenative C(sp²)–H thiolation method of glycals to readily access 1-thiotrehaloses (Scheme 1c) and 1-thiolated glycals would find widespread utility. Herein, we described the first Cu-catalyzed C–H thiolation of the pseudo-anomeric position of glycals bearing an 8-amidoquinoline directing group with thiosugars and thiols as partners (Scheme 1b).

Results and Discussion

Inspired by our previous works,^[6c] we started our investigation by reacting the perbenzylated C2-amidoglycal **1a** with an excess of peracetylated thiosugar **2a** (2 equiv.) in the presence of Cu(OAc)₂·H₂O (0.4 equiv.), Ag₂CO₃ (3 equiv.) in DMSO (0.1 M) at 120 °C for 1 h (Table 1, entry 1). Satisfyingly, the corresponding disaccharide **3a** was obtained in a modest 24% yield. The replacement of the thermic activation by microwave irradiation had no improvement on the observed yield (Table 1, entry 2), but a decrease in the temperature from 120 °C to 100 °C led to a slight gain in terms of yield of **3a** after 18 h (Table 1, entry 3). Good yields of 60% were obtained by adding the bidentate ligands bathophen or neocuproine (Table 1, entries 4 and 6), whereas the use of phenanthroline was less efficient (Table 1, entry 5 and SI). The best yield of **3a** was found when the reaction temperature was fixed at 90 °C (70% yield, Table 1, entry 7), however, performing the reaction at 80 °C furnished the desired **3a** in only 55% yield even if the reaction time was increased at 40 h (Table 1, entry 8). For practical reasons (avoiding the extraction step), we considered the use of acetonitrile as a solvent substitute for DMSO, which gave a comparable yield (67% instead of 70%) after 24 h of reaction time (Table 1, entries 9 and 10). According to the literature,^[17] the mechanism is expected to run as follows (Scheme 2): chelation of the copper salt with the ligand (L) generates the active catalyst. Thanks to the silver salt,

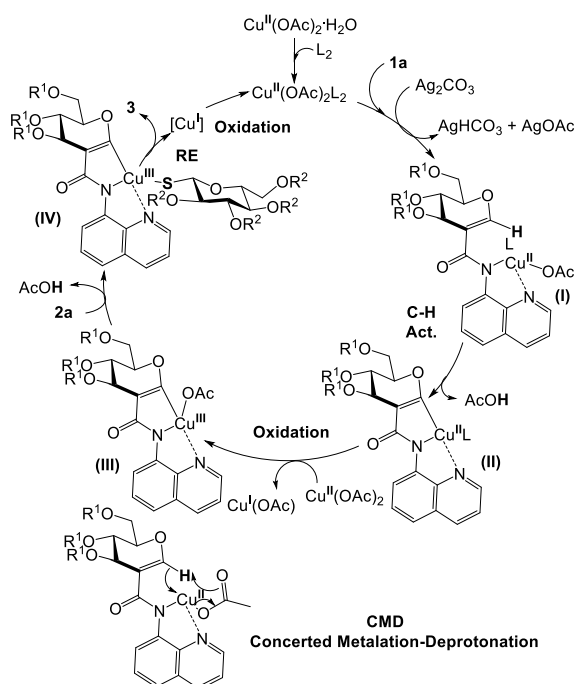
Table 1. Optimization of the C–H thiolation conditions^{a)}



N°	Ligand	Solvent	Conditions	Yield ^{b)} 3a
1	-	DMSO	120 °C/ 1 h	24%
2	-	DMSO	120 °C MW/ 1 h	25%
3	-	DMSO	100 °C/ 18 h	32%
4	Bathophen	DMSO	100 °C/ 16 h	60%
5	Phenanthroline	DMSO	100 °C/ 16 h	ND
6	Neocuproine	DMSO	100 °C/ 16 h	58%
7	Neocuproine	DMSO	90 °C/ 24 h	70%
8	Neocuproine	DMSO	80 °C/ 40 h	55%
9	Neocuproine	ACN	90 °C/ 24 h	67%
10	Neocuproine	ACN	90 °C/ 46 h	61%

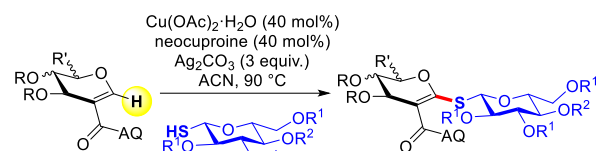
^{a)} Conditions: 0.085 mmol of **1a** (1 equiv.), **2a** (2 equiv.), Cu(OAc)₂·H₂O (40 mol%), ligand (40 mol%), Ag₂CO₃ (3 equiv.), solvent, at T°C during the indicating time under argon. ^{b)} Isolated yields. ND: not determined

this last species could coordinate with the amidoquinolyl moiety to form intermediate (I). Then, the C–H activation process occurs following a concerted metalation-deprotonation mechanism helped by the proximity of the acetate ligand of the copper species to the *pseudo*-anomeric C–H bond forming the intermediate (II). Activated Cu(III) species (intermediate III) is then generated via an oxidation step involving a Cu(OAc)₂ partner. From (III), a ligand exchange with thiosugar **2** is supposed to lead to intermediate (IV), which, after reductive elimination (RE) forms compound **3** and a Cu(I) salt. Finally, an oxidation step let the reformation of active Cu(II) species. This mechanism was supported by the fact that the use of the corresponding disulfide as starting substrate failed to obtain the desired product. The versatility of this reaction was explored to reach diverse di- or trisaccharides (Scheme 2). The selected conditions were revealed to be successful using **1a** with diverse thiosugar partners including peracetylated thio-D-glucose (compound **3a**), peracetylated thio-D-galactose (compound **3d**) as well as the disaccharide thio-cellobiose (compound **3e**) which were obtained in 67%, 52%, and 40% yields, respectively. However, the use of the perbenzoylated or perbenzylated thio-D-glucose instead of the acetylated one proved to be less reactive leading to the desired products **3b** and **3c** in moderate yields. This

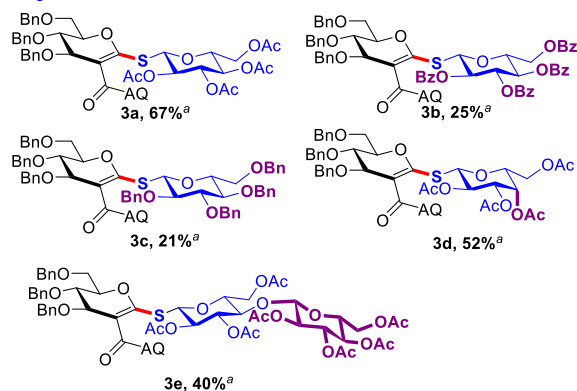


Scheme 2. Proposed mechanism for the developed C-H thiolation.

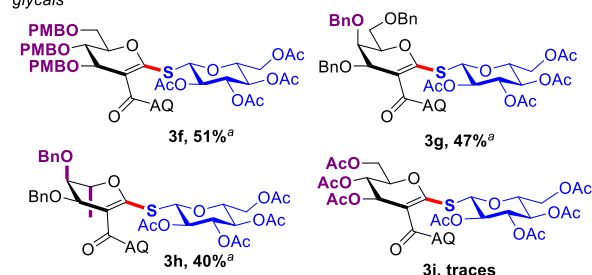
drop in terms of reactivity for these two partners could be explained by the lower accessibility of the thiol function of these structures due to the steric hindrance generated by the benzoyl or the benzyl group present in the close position 2. Concerning the glycal partner, the *per*-PMB-protected analog showed a similar reactivity (Scheme 3, 3f) as well as the two D-galactal- and L-rhamnall examples (Scheme 3, 3g and 3h respectively). The use of the peracetylated D-glucal analog was examined but without success due to a probable deactivation of the glycal double bond by the electron-withdrawing character of the acetyl groups (Scheme 3, 3i). We next investigated the possibility to extend the scope of the developed conditions to other thiol partners (Scheme 4). We were delighted to see that both aliphatic and aromatic thiols furnished the corresponding thiosugars in modest to excellent yields (thioglycals 4). Thiophenols bearing electron-donating or electron-withdrawing groups were revealed to be excellent coupling partners furnishing the desired aryl thioglycals 4a-c in yields ranging from 48 to 67% yields. The thioglucal 4c bearing a C-Cl bond may be used in further post-functionalization reactions under transition metal-catalysis. Other tested aliphatic thiols such as propyl ester or benzylthiol led to the desired products 4d and 4e in 50% and 76% yield, respectively. Interestingly, exotic thiol partners such as Boc-protected cysteine, C₁₈-long chain- or adamantylthiols were also suitable partners (thioglycals 4f, 4g and 4h) albeit modest yields were obtained under our optimized conditions.



thiosugars



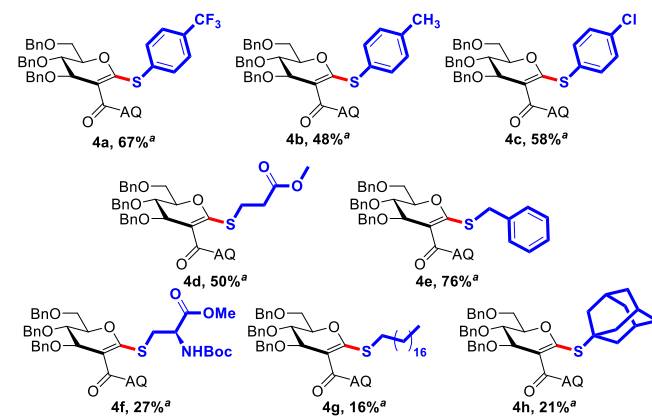
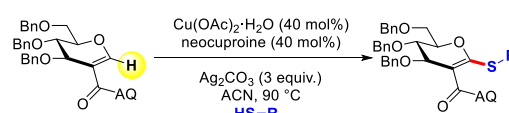
glycals



Reaction conditions: A sealable tube was charged with 0.085 mmol of 1a (1 equiv.), 2 (2 equiv.), Cu(OAc)₂·H₂O (40 mol%), neocuproine (40 mol%), Ag₂CO₃ (3 equiv.), solvent, at 90 °C under argon. a) Isolated yields.

Scheme 3. Scope of the C-H thiolation with various glycals and thiosugars

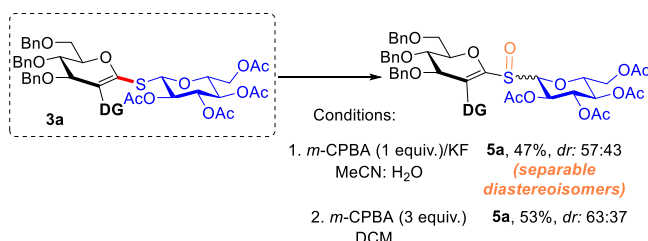
Thioethers are highly valuable intermediates in organic synthesis as they can be involved in a wide range of reactions at the sulfur atom, such as oxidation



Reaction conditions: A sealable tube was charged with 0.085 mmol of 1a (1 equiv.), thiol (2 equiv.), Cu(OAc)₂·H₂O (40 mol%), neocuproine (40 mol%), Ag₂CO₃ (3 equiv.), solvent, at T °C during the indicating time under argon. a) Isolated yields

Scheme 4. Scope of the C-H thiolation using other thiols as partners

into sulfoxide,^[18] sulfone^[19], or sulfoximines.^[20] To further show the synthetic utility of our protocol, we evaluated whether the thioglycoside **3a** could be oxidized under various reported conditions (Scheme 5). Thus, sulfoxide **5a** was isolated in 47% yield and a 57:43 diastereomeric ratio when *m*-CPBA (1 equiv)/KF was used as the oxidant system. Interestingly, using a large excess of *m*-CPBA (3 equiv) did not produce the desired sulfone but only the sulfoxide **5a** was obtained in 53% yield and a 63:37 diastereomeric ratio.



Scheme 5. Tentative oxidation of the thioglycoside **3a**

Conclusion

In summary, we described here the first catalytic approach for the C–H thiolation of the pseudo-anomeric position of glycols with various thiosugars and thiols via copper catalysis. This method provides unprecedented access to thiotrehalose analogs and thioglycols. We believe that this method not only opens a new way for Cu-catalyzed functionalization of pseudo-anomeric C–H bond of glycols, but also provides a versatile and convergent approach for the synthesis of complex sulfoxide glycosides.

Experimental Section

Materials and methods

All the solvents and reagents were obtained from commercial sources and were used without further purification. Unless otherwise noted, all reactions were carried out under an argon atmosphere. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (15 g of vanillin in 250 mL ethanol and 2.5 mL of concentrated sulfuric acid). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The ¹H NMR and ¹³C NMR J-MOD spectra were recorded in either CDCl₃ or *d*₆-acetone or *d*₃-acetonitrile on Bruker Avance 300, 400 spectrometers. The ¹⁹F NMR Decoupled spectra were recorded in *d*₆-acetone on Bruker Avance 200 spectrometers. The chemical shifts of ¹H, ¹³C and ¹⁹F are reported in ppm relative to the solvent residual peaks. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected. IR spectra were recorded on an IR-Affinity-1S. High-resolution mass spectra (HR-MS) were recorded on a Micro Mass LCT Premier Spectrometer. Optical rotations were obtained with a Polarimeter-MCP100.

Synthetic procedures

General procedure for the aminocarbonylation reaction [14] (general procedure 1):

In a Schlenk tube were added Pd(OAc)₂ (0.1 equiv.), PPh₃ (0.2 equiv.), K₂CO₃ (2 equiv.), Mo(CO)₆ (4.2 equiv.), and the corresponding 2-iodoglycol (1 equiv.). Dioxane (1 mL) and the amine (2 equiv.) were then added. The resulting mixture was stirred at 80 °C overnight. The mixture was concentrated under vacuum and the crude was finally purified on silica gel using the indicated solvent. The product was washed with HCl (1M) to remove excess of aminoquinoline

General procedure for the C–H thiolation reaction (general procedure 2):

In a Schlenk tube were added compound **1** (1 equiv.) Cu(OAc)₂·H₂O (0.4 equiv.), Ag₂CO₃ (3 equiv.), Neocuproine (0.4 equiv.), the corresponding Thiol (2 equiv.) and ACN (0.1 M) was then added. The reaction vessel was purged with argon and sealed, the resulting mixture was stirred at 90 °C for 24 h, 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 oxidation reaction [21]:

To a solution of KF (6.1 mg, 0.1054 mmol) in CH₃CN/H₂O (0.6 mL; v/v 5:1), 70% *m*-CPBA (18.2 mg, 0.1054 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. To the ice-cooled reaction mixture was added (**3a**, 50 mg, 0.0527 mmol) and the mixture was stirred at 0 °C for 30 min. After completion of the reaction, it was quenched with aq FeSO₄ solution and extracted with CH₂Cl₂. The organic layer was washed with aq NaHCO₃ and water successively, dried (MgSO₄) and concentrated under reduced pressure. Product **5a** was isolated after flash chromatography as a white solid (totally 23.7 mg, 47%, **5a-1** is 13.5 mg, **5a-2** is 10.2 mg). *Rf* = 0.5 (EtOAc / DCM /cyclohexane: 5/0.5/5).

To a stirred solution of compound (**3a**, 0.08 mmol) in freshly dried DCM (0.8 mL), 1.1 equivalent of 70% *m*-CPBA were added to a stirred solution. The reaction mixture was cooled to -10 °C and allowed to stir for 30 min, after the completion of the reaction diluted with 20 mL of DCM. The organic layer was washed with NaHCO₃ (aq.) and dried over MgSO₄, concentrated under reduced pressure. The residue was purified over SiO₂ to give a pure compound. Product **5a** was isolated after flash chromatography as a white solid (totally 40.8 mg, 53%, **5a-1** is 25.8 mg, **5a-2** is 15 mg). *Rf* = 0.5 (EtOAc / DCM /cyclohexane: 5/0.5/5).

Characterization data

(*2R,3S,4S*)-3,4-bis((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide (**1b**). According to general procedure 1, (*2R,3R,4R*)-5-iodo-3,4-bis((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)-3,4-dihydro-2H-pyran (300 mg, 1 equiv.) was allowed to react for 16 h. Product **1b** was isolated after flash chromatography as yellow oil (294.7 mg, 92%). *Rf* = 0.45 (AcOEt/Cyclo 4:6); [α]_D²⁰ = +3.4 (*c* = 1.23, CHCl₃); **IR** (neat, cm⁻¹): 2834, 1610, 1524, 1485, 1324, 1300, 1192, 1111; **¹H NMR** (300 MHz, CDCl₃) δ 10.33 (s, 1H), 8.71 (d, *J* = 9.0 Hz, 1H), 8.39 (dd, *J* = 3.0 Hz; *J* = 6.0 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.64 (s, 1H), 7.43–7.32 (m, 2H), 7.26–7.22 (m, 1H), 7.14–7.10 (m, 4H), 7.04 (d, *J* = 9 Hz, 2H), 6.75–6.71 (m, 4H), 6.64 (d, *J* = 9 Hz, 2H), 4.87 (d, *J* = 12 Hz, 1H), 4.50–4.38 (m, 5H), 4.32–4.21 (m, 2H), 3.90–3.88 (m, 1H), 3.67–3.59 (m, 10H), 3.52–3.47 (m, 1H); **¹³C NMR** (**J**-MOD, 75 MHz, CDCl₃) δ. 165.5 (C), 159.6 (C), 159.4 (C), 159.3 (C), 153.4 (CH), 147.8 (CH), 138.6 (C), 136.5 (CH), 135.2 (CH), 130.2 (C), 130.0 (C), 129.7 (C), 129.6 (CH), 129.4 (CH), 129.2 (CH), 128.1(C), 127.6 (CH), 121.5

(CH), 121.2 (CH), 117.1 (CH), 114.1 (CH), 113.0 (CH), 113.8 (CH), 108.5 (C), 76.6 (CH), 73.1(CH₂), 71.5 (CH₂), 70.8 (CH₂), 70.5 (2CH), 67.5 (CH₂), 55.3 (3CH₃); **HRMS** for C₄₀H₄₀N₂NaO₈ [M+Na]⁺ (m/z): calcd. 699.2677, found 699.2674.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3a).

According to general procedure 2, (2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate **2a**^[22] (61.9 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3a** was isolated after flash chromatography as a yellow oil (54 mg, 67%). **Rf** = 0.34 (EtOAc/cyclohexane: 4/6); $[\alpha]_D^{20} = +22.5$ ($c = 0.24$, CHCl₃); **IR** (neat, cm⁻¹): 3021, 2865, 2005, 1941, 1652, 1484, 1369, 1214; **¹H NMR** (400 MHz, CDCl₃) δ 10.63 (s, 1H), 8.81 (dd, $J = 3.0$ Hz; $J = 9.0$ Hz, 1H), 8.41 (dd, $J = 3.0$ Hz; $J = 6.0$ Hz, 1H), 8.10 (dd, $J = 3.0$ Hz; $J = 9.0$ Hz, 1H), 7.55–7.28 (m, 15H), 7.23–7.18 (m, 3H), 5.23–5.04 (m, 4H), 4.97 (d, $J = 12$ Hz, 1H), 4.79–4.68 (m, 3H), 4.64–4.44 (m, 4H), 4.16–4.05 (m, 2H), 4.01–3.68 (m, 2H), 3.68 (dd, $J = 3.0$ Hz; $J = 9.0$ Hz, 1H), 3.49–3.43 (m, 1H), 2.02 (s, 3H), 1.91 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); **¹³C NMR** (J-MOD, 100 MHz, d₆-acetone) δ 170.9 (C), 170.6 (C), 170.2(C), 170 (C), 166.4 (C), 162.2 (C), 149.4 (CH), 139.7 (C), 139.5(2C), 139.3 (C), 137.5 (CH), 136.6 (C), 129.6 (CH), 129.5 (CH), 129.3 (C), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.9 (2CH), 128.5 (2CH), 128.4 (CH), 122.9 (CH), 122.2 (CH), 117.2 (CH), 105.9 (C), 81.3 (CH), 80.6 (CH), 76.8 (CH), 75.2 (CH), 74.3 (CH), 74.0 (CH₂), 72.8 (CH₂), 71.9 (CH), 70.9 (CH₂), 70.9(CH), 69.6 (CH), 68.7(CH₂), 63.3 (CH₂), 20.9 (3CH₃), 20.8 (CH₃); **HRMS** for C₅₁H₅₃N₂O₁₄S [M+H]⁺ (m/z): calcd 949.3212, found 949.3216.

(2R,3R,4S,5R,6S)-2-((benzyloxy)methyl)-6-(((2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (3b).

According to general procedure 2, (2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and (2R,3R,4S,5R,6S)-2-((benzyloxy)methyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl tribenzoate **2b**^[8b] (104.2mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3b** was obtained after flash chromatography as a white solid (25 mg, 25%). **Rf** = 0.3 (Et₂O/DCM/cyclohexane: 1/3/6); **mp**: 86.4–87.5 °C; $[\alpha]_D^{20} = +63.6$. ($c = 0.36$, CHCl₃); **IR** (neat, cm⁻¹): 1732, 1654, 1525, 1487, 1452, 1265, 1089, 1068; **¹H NMR** (300 MHz, CDCl₃) δ 10.50 (s, 1H), 8.66 (d, $J = 6.9$ Hz, 1H), 8.30 (d, $J = 2.7$ Hz, 1H), 7.99–7.72 (m, 10H), 7.37–7.16 (m, 26H), 7.08–7.07 (m, 3H), 5.79 (t, $J = 9.0$ Hz, 1H), 5.61–5.43 (m, 3H), 4.77–4.23 (m, 10H), 4.02–4.00 (m, 1H), 3.75–3.68 (m, 2H), 3.57–3.54 (m, 1H); **¹³C NMR** (J-MOD, 75 MHz, CDCl₃) δ 166.2 (C), 166.0 (C), 165.3 (C), 165.1 (C), 165.0 (C), 161.5 (C), 147.7 (CH), 138.7 (C), 138.1 (C), 137.8 (2C), 136.4 (CH), 135.1 (C), 133.6 (CH), 133.5 (CH), 133.2 (CH), 133.1 (2CH), 130.0 (2CH), 129.9 (2CH), 129.4 (C), 129.2 (C), 129.10 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (4CH), 128.2 (CH), 128.1(CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 121.3 (CH), 121.2 (CH), 117.4 (CH), 106.6 (C), 80.7 (CH), 79.8 (CH), 76.2 (CH), 75.7 (CH), 74.8 (CH), 73.5 (CH₂), 72.6 (CH₂), 71.9 (CH), 70.5 (CH), 69.8 (CH), 69.3 (CH₂), 67.8 (CH₂), 63.5 (CH₂); **HRMS** (ESI): m/z calc. for C₇₁H₆₁N₂O₁₄S [M+H]⁺ 1197.3838; found 1197.3840

(2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-6-(((2S,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)thio)-3,4-dihydro-2H-pyran-5-carboxamide (3c).

According to general procedure 2, (2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085

mmol, 1 equiv) and 2,3,4,6-tetra-*O*-benzyl-1-thio- α - β -D-glucopyranose **2c**^[22] (94.6 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3c** was obtained after flash chromatography as a yellow oil (22.5 mg, 23%). **Rf** = 0.4 (Actone/DCM/cyclohexane: 1/0.4/8); $[\alpha]_D^{20} = +87.2$ ($c = 0.25$, CHCl₃); **IR** (neat, cm⁻¹): 1654, 1521, 1487, 1456, 1087, 1074, 736, 696; **¹H NMR** (300 MHz, d₃-acetonitrile) δ 10.79 (s, 1H), 8.85–8.79 (m, 1H), 8.36 (dd, $J = 1.8$ Hz; $J = 4.2$ Hz, 1H), 8.19 (dd, $J = 1.8$ Hz; $J = 8.4$ Hz, 1H), 7.58–7.51 (m, 2H), 7.41–7.19 (m, 29H), 7.13–7.12 (m, 4H), 7.08–7.03 (m, 2H), 6.35 (d, $J = 5.4$ Hz, 1H), 4.92–4.88 (m, 1H), 4.83–4.65 (m, 8H), 4.58–4.54 (m, 1H), 4.51–4.40 (m, 4H), 4.37–4.27 (m, 3H), 4.22–4.17 (m, 1H), 4.13–4.10 (m, 1H), 3.95–3.89 (m, 1H), 3.86–3.74 (m, 2H), 3.71–3.65 (m, 1H), 3.63–3.54 (m, 2H), 3.52–3.46 (m, 1H); **¹³C NMR** (J-MOD, 100 MHz, d₃-acetonitrile) δ 166.5 (C), 156.8 (C) 149.6 (CH), 139.9 (C), 139.6 (C) 139.5 (C), 139.4 (C), 139.3 (C), 139.2 (C) 139.1 (C), 139.0 (C), 137.3 (CH), 136.3(C), 129.5 (CH), 129.3 (2CH), 129.2 (6CH), 129.1 (CH), 129.1 (C), 129.0 (CH), 128.9 (2CH), 128.7 (3CH), 128.6 (CH), 128.5 (3CH), 128.4 (CH), 128.2 (CH), 122.7 (CH), 122.4 (CH), 117.1 (CH), 110.7 (C), 83.1 (2CH), 80.0 (CH), 79.7 (CH), 78.4 (CH), 75.9 (CH₂), 75.4 (CH₂), 73.7 (CH₂), 73.6 (CH₂), 72.9 (CH), 72.8 (CH₂), 72.7 (CH), 72.3 (CH₂), 71.8 (CH₂), 71.3 (CH), 69.8 (CH₂), 68.9 (CH₂); **HRMS** (ESI): m/z calc. for C₇₁H₆₉N₂O₁₀S [M+H]⁺ 1141.4667; found 1141.4651.

(2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3d).

According to general procedure 2, (2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and (2R,3S,4S,5R,6S)-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate **2d**^[8b] (61.9 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3d** was isolated after flash chromatography as a yellow oil (42 mg, 52%). **Rf** = 0.34 (EtOAc/cyclohexane: 4/6); $[\alpha]_D^{20} = +17.5$ ($c = 1.00$, CHCl₃); **IR** (neat, cm⁻¹): 3064, 2362, 2326, 1712, 1521, 1424, 1326, 1080; **¹H NMR** (400 MHz, CDCl₃) δ 10.65 (s, 1H), 8.81 (dd, $J = 1.2$ Hz; $J = 7.6$ Hz, 1H), 8.39 (dd, $J = 1.2$ Hz; $J = 4.4$ Hz, 1H), 8.10 (dd, $J = 1.2$ Hz; $J = 8.0$ Hz, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.47–7.44 (m, 1H), 7.43–7.28 (m, 14H), 7.21–7.19 (m, 2H), 5.33–5.25 (m, 2H), 5.19 (d, $J = 12.0$ Hz, 1H), 5.00–4.95 (m, 2H), 4.82–4.72 (m, 3H), 4.60 (dd, $J = 12.0$ Hz; $J = 20$ Hz, 2H), 4.49–4.42 (m, 2H), 4.16–4.13 (m, 1H), 4.00–3.96 (m, 2H), 3.90 (dd, $J = 8.0$ Hz; $J = 12$ Hz, 1H), 3.71 (dd, $J = 4.0$ Hz; $J = 12$ Hz, 1H), 3.54–3.51 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H). **¹³C NMR** (J-MOD, 100 MHz, CDCl₃) δ 170.5 (C), 170.4 (C), 170.3 (C), 169.3 (C), 165.2 (C), 162.2 (C), 148.0 (CH), 138.9 (C), 137.9 (C), 137.6 (2C), 136.3 (CH), 135.2 (C), 128.8 (CH), 128.7 (CH), 128.4 (2CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (C), 127.6 (2CH), 127.5 (CH), 121.5 (CH), 121.2 (CH), 117.1 (CH), 105.4 (C), 80.4 (CH), 79.6 (CH), 75.1 (CH), 74.1 (CH), 73.6 (CH₂), 72.5 (CH₂), 72.5 (CH), 71.4 (CH), 69.3(CH₂), 67.6(CH₂), 67.5(CH), 66.9 (CH), 61.7 (CH₂), 21.0 (CH₃), 20.8 (3CH₃); **HRMS** for C₅₁H₅₃N₂O₁₄S [M+H]⁺ (m/z): calcd. 949.3212, found 949.3207

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-(((2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate(3e).

According to general procedure 2, (2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2R,3R,4S,5R,6S)-4,5-diacetoxy-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate **2e**^[22] (110.9 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3e** was isolated after flash chromatography as a white solid (42 mg, 40%). **Rf** = 0.4 (EtOAc/cyclohexane: 1/1); **mp**: 89.9–92.3 °C; $[\alpha]_D^{20} = -1.2$ ($c = 0.33$, CHCl₃); **IR** (neat, cm⁻¹):

1751, 1654, 1525, 1487, 1373, 1327, 1230, 1041; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.68 (s, 1H), 8.85-8.82 (m, 1H), 8.50 (d, *J* = 3.0 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 7.63-7.27 (m, 18H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.29-5.18 (m, 3H), 5.12-4.97 (m, 3H), 4.93-4.75 (m, 9H), 4.85-4.37 (m, 6H), 4.17-3.67 (m, 9H), 2.07 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H); ¹³C NMR (J-MOD, 100 MHz, *d*₆-acetone) δ 171.1 (C), 170.9 (C), 170.5 (C), 170.4 (C), 170.1 (C), 170.0 (C), 169.9 (C), 166.3 (C), 162.2 (C), 149.3 (CH), 139.5 (C), 139.4 (C), 139.3 (C), 139.2 (C), 137.4 (CH), 136.5 (C), 129.5 (CH), 129.4 (CH), 129.2 (C), 129.1 (2CH), 128.9 (CH), 128.8 (2CH), 128.3 (2CH), 128.2 (CH) 122.8 (CH), 122.1 (CH), 117.1 (CH), 105.4 (C), 101.6 (CH), 80.9 (CH), 80.5 (CH), 77.7 (CH), 77.6 (CH), 74.9 (CH), 74.0 (CH), 73.9 (CH), 73.9 (CH₂), 72.7 (CH₂), 72.7 (CH), 72.6 (CH), 71.7 (CH), 71.1 (CH), 70.8 (CH₂), 69.1 (CH), 68.4 (CH₂), 63.5 (CH₂), 62.6 (CH₂), 21.0 (CH₃), 20.9 (2CH₃), 20.8 (2CH₃), 20.7 (2CH₃); HRMS (ESI): *m/z* calc. for C₆₃H₆₈N₂NaO₂₂S [M+Na]⁺ 1259.3877; found 1259.3878

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,3*S*,4*S*)-3,4-bis((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3*f*). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1b** (50 mg, 0.074 mmol, 1 equiv) and (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate **2a**^[8b, 22] (53.9 mg, 0.148 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3f** was isolated after flash chromatography as a white solid (39 mg, 51%). *R_f* = 0.2 (EtOAc/cyclohexane: 1/3); mp: 81.4-83.5 °C; [α]_D²⁰ = +5.7 (c = 0.23, CHCl₃); IR (neat, cm⁻¹): 2926, 1755, 1654, 1612, 1516, 1369, 1247, 1035; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.68 (s, 1H), 8.85-8.82 (m, 1H), 8.50 (d, *J* = 3.0 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 7.63-7.27 (m, 18H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.29-5.18 (m, 3H), 5.12-4.97 (m, 3H), 4.93-4.75 (m, 9H), 4.85-4.37 (m, 6H), 4.17-3.67 (m, 9H), 2.07 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H); ¹³C NMR (J-MOD, 100 MHz, *d*₆-acetone) δ 170.8 (C), 170.4 (C), 170.1 (C), 169.8 (C), 166.2 (C), 161.9 (C), 160.6 (C), 160.5 (C), 160.3 (C), 149.3 (CH), 139.5 (C), 137.4 (CH), 136.4 (C), 131.2 (2C), 131.0 (C), 130.7 (CH), 130.4 (CH), 130.0 (CH), 129.2 (C), 128.2 (CH), 122.8 (CH), 122.0 (CH), 117.0 (CH), 114.8 (CH), 114.7 (CH) 114.5 (CH), 105.8 (C), 81.1 (CH), 80.6 (CH), 76.6 (CH), 75.1 (CH), 73.8 (CH), 73.5 (CH₂), 72.2 (CH₂), 71.3 (CH), 70.8 (CH), 70.6 (CH₂), 69.3 (CH), 68.4 (CH₂), 63.0 (CH₂), 55.6 (CH₃), 55.5 (2CH₃), 20.7 (2CH₃), 20.6 (2CH₃); HRMS (ESI): *m/z* calc. for C₅₄H₅₉N₂O₁₇S [M+H]⁺ 1039.3529; found 1039.3518.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*R*,3*R*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-yl)carbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3*g*). According to general procedure 2, (2*R*,3*R*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1c** (50 mg, 0.085 mmol, 1 equiv) and (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate **2a**^[8b, 22] (61.9 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3g** was isolated after flash chromatography as a yellow oil (38.1 mg, 47%). *R_f* = 0.34 (EtOAc/cyclohexane: 4/6); [α]_D²⁰ = -14.9 (c = 1.00, CHCl₃); IR (neat, cm⁻¹): 3028, 2359, 2325, 1710, 1522, 1522, 1422, 1218; ¹H NMR (400 MHz, CDCl₃) δ 10.54 (s, 1H), 8.79 (dd, *J* = 1.6 Hz; *J* = 7.6 Hz, 1H), 8.25 (dd, *J* = 1.6 Hz; *J* = 4.0 Hz, 1H), 8.10 (dd, *J* = 1.6 Hz; *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.43-7.30 (m, 14H), 7.25-7.24 (m, 2H), 5.29-5.27 (m, 1H), 5.19-5.11 (m, 5H), 4.80-4.74 (m, 2H), 4.70-4.65 (m, 2H), 4.57-4.48 (m, 2H), 4.24-4.16 (m, 2H), 4.11-4.02 (m, 2H), 3.84 (dd, *J* = 2.4 Hz; *J* = 12 Hz, 1H), 3.56-3.53 (m, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H). ¹³C NMR (J-MOD, 100 MHz, CDCl₃) δ 170.9 (C), 170.4 (C), 169.4 (C), 169.3 (C), 165.5 (C), 160.0 (C), 147.9 (CH), 138.8 (C), 138.5 (C), 137.9 (C), 137.3 (C), 136.3 (CH), 135.1 (C), 128.7 (2CH), 128.3 (2CH),

128.2 (CH), 128.1 (CH), 128.0 (C), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 121.5 (CH), 121.3 (CH), 117.1 (CH), 106.3 (C), 80.5 (CH), 78.2 (CH), 75.7 (CH), 74.7 (CH), 73.8 (CH), 73.6 (CH₂), 73.3 (CH₂), 72.9 (CH₂), 70.9 (CH), 69.8 (CH), 68.0 (CH), 67.7 (CH₂), 61.9 (CH₂), 20.9 (CH₃), 20.8 (2CH₃), 20.7 (CH₃); HRMS (ESI): *m/z* calc. for C₅₁H₅₂N₂NaO₁₄S [M+Na]⁺ 971.3037; found 971.3048.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(((2*S*,3*S*)-3,4-bis(benzyloxy)-2-methyl-5-(quinolin-8-yl)carbonyl)-3,4-dihydro-2H-pyran-6-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3*h*). According to general procedure 2, (2*S*,3*S*)-3,4-bis(benzyloxy)-2-methyl-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1d** (50 mg, 0.104 mmol, 1 equiv) and (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate **2a**^[8b, 22] (75.8 mg, 0.208 mmol, 2.0 equiv) were allowed to react for 24 h. Product **3h** was isolated after flash chromatography as a yellow oil (35 mg, 40%). *R_f* = 0.27 (EtOAc/cyclohexane: 4/6); [α]_D²⁰ = +20.7 (c = 1.00, CHCl₃); IR (neat, cm⁻¹): 3029, 2355, 2340, 1744, 1710, 1654, 1650, 1518; ¹H NMR (400 MHz, *d*₆-acetone) δ 10.84 (s, 1H), 8.83 (dd, *J* = 2.3 Hz; *J* = 6.7 Hz, 1H), 8.32-8.27 (m, 2H), 7.58-7.52 (m, 2H), 7.50-7.43 (m, 5H), 7.38-7.25 (m, 6H), 5.64 (d, *J* = 12 Hz, 1H), 5.38 (t, *J* = 8.0 Hz, 1H), 5.28 (d, *J* = 12.0 Hz, 1H), 5.08-5.02 (m, 2H), 4.97-4.92 (m, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.82 (s, 2H), 4.61 (t, *J* = 1.6 Hz, 1H), 4.21-4.16 (m, 2H), 4.08-4.02 (m, 2H), 2.04 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.92 (s, 3H), 1.57 (d, *J* = 8.0 Hz, 3H). ¹³C NMR (100 MHz, *d*₆-acetone) δ 170.7, 170.3, 170.0, 169.8, 166.7, 160.2, 149.0, 139.4, 139.3, 139.1, 137.2, 136.5, 129.2, 129.0, 128.9, 128.8, 128.6, 128.1, 128.0 (2C), 122.6, 121.8, 116.8, 104.7, 80.0, 77.2, 76.2, 74.6, 73.6, 73.1, 71.9, 70.7, 70.1, 69.3, 63.2, 20.6 (3C), 20.5, 16.2; HRMS (ESI): *m/z* calc. for C₄₄H₄₇N₂O₁₃S [M+H]⁺ 843.2799; found 843.2817.

(2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-6-((4-(trifluoromethyl)phenyl)thio)-3,4-dihydro-2H-pyran-5-carboxamide (4*a*). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and 4-(trifluoromethyl)benzenethiol **2k** (30.3 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4a** was isolated after flash chromatography as a white solid (43.7 mg, 67%). *R_f* = 0.3 (EtOAc/cyclohexane: 1/6); mp: 57.0-59.1 °C; [α]_D²⁰ = -75.0 (c = 0.30, CHCl₃); IR (neat, cm⁻¹): 2927, 1749, 1604, 1521, 1386, 1122, 1062, 825; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.77 (s, 1H), 8.90-8.87 (m, 1H), 8.40 (d, *J* = 3.0 Hz, 1H), 8.32 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.60-7.24 (m, 21H), 5.23 (d, *J* = 12 Hz, 1H), 4.86-4.66 (m, 5H), 4.49-4.29 (m, 3H), 4.05-3.99 (m, 1H), 3.70-3.65 (m, 1H); ¹³C NMR (J-MOD, 100 MHz, *d*₆-acetone) δ 166.6 (C), 160.8 (C), 149.3 (CH), 139.6 (C), 139.4 (C), 139.2 (C), 137.5 (CH), 136.6 (C), 135.4 (2CH), 130.4 (C, q, *J* = 30 Hz), 129.4 (CH), 129.2 (2CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.3 (CH, q, *J* = 4 Hz), 125.4 (C, q, *J* = 270 Hz), 122.8 (CH), 122.1 (CH), 117.0 (CH), 105.2 (C), 80.2 (CH), 73.8 (CH₂), 73.3 (CH), 72.2 (CH₂), 71.4 (CH₂), 71.1 (CH), 68.7 (CH₂). ¹⁹F NMR (200 MHz, *d*₆-acetone) δ -62.6; HRMS (ESI): *m/z* calc. for C₄₄H₃₈F₃N₂O₅S [M+H]⁺ 763.2448; found 763.2460.

(2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-6-(*p*-tolylthio)-3,4-dihydro-2H-pyran-5-carboxamide (4*b*). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2H-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and 4-methylbenzenethiol (21.1 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4b** was isolated after flash chromatography as a white solid (29 mg, 48%). *R_f* = 0.4 (EtOAc/DCM/cyclohexane: 1/1/6); mp: 115.9-116.5 °C; [α]_D²⁰ = -90.7 (c = 0.28, CHCl₃); IR (neat, cm⁻¹): 3736, 2921, 2870, 1654, 1521, 1485, 1327, 1250; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.78 (s, 1H), 8.90 (t, *J* = 4.5 Hz, 1H), 8.40 (d, *J* = 3.0 Hz, 1H), 8.31 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 3.0 Hz, 2H), 7.50-7.09 (m, 21H), 5.20 (d, *J* = 12 Hz, 1H), 4.83-

4.77 (m, 3H), 4.68-4.64 (m, 2H), 4.38-4.27 (m, 3H), 3.89-3.82 (m, 1H), 3.71-3.66 (m, 1H), 2.28 (s, 3H); ¹³C NMR (J-MOD, 100 MHz, *d*₆-acetone) δ 166.8 (C), 163.0 (C), 149.2 (CH), 139.6 (C), 139.5 (3C), 139.3 (C), 137.5 (CH), 136.9 (C), 135.8 (CH), 130.5 (CH), 129.4 (CH), 129.3 (C), 129.2 (2CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (2CH), 128.3 (CH), 128.3 (C), 122.8 (CH), 121.9 (CH), 116.9 (CH), 104.0 (C), 80.0 (CH), 73.7 (CH₂), 73.5 (CH), 72.2 (CH₂), 71.2 (CH₂), 68.9 (CH₂), 21.4 (CH₃). HRMS (ESI): *m/z* calc. for C₄₄H₄₁N₂O₅S [M+H]⁺ 709.2731; found 709.2723.

(2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-((4-chlorophenyl)thio)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide (4c). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and 4-chlorobenzenthio (28.6 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4c** was isolated after flash chromatography as a white solid (37.2mg, 58%). *R_f* = 0.4 (EtOAc / DCM / cyclohexane: 1/1/6); *mp*: 80.7-82.5 °C; [α]_D²⁰ = -79.7 (c = 0.31, CHCl₃); IR (neat, cm⁻¹): 1653, 1521, 1485, 1384, 1327, 1205, 1093, 1043; ¹H NMR (300 MHz, *d*₃-acetonitrile) δ 10.64 (s, 1H), 8.78-8.75 (m, 1H), 8.34-8.33 (m, 1H), 8.21-8.18 (m, 1H), 7.56-7.15 (m, 22H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.70-4.48 (m, 5H), 4.35-4.26 (m, 2H), 4.10-4.04 (m, 1H), 3.83-3.77 (m, 1H), 3.53-3.48 (m, 1H); ¹³C NMR (J-MOD, 100 MHz, *d*₃-acetonitrile) δ 166.8 (C), 161.8 (C), 149.3 (CH), 139.4 (C), 139.2 (C), 139.1 (2C), 138.9 (C), 137.4 (CH), 137.2 (CH), 136.3 (C), 135.3 (C), 130.3 (C), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 122.8 (CH), 122.2 (CH), 116.9 (CH), 104.1 (C), 80.4 (CH), 73.7 (CH₂), 73.0 (CH), 72.3 (CH₂), 71.2 (CH₂), 71.0 (CH), 68.6 (CH₂); HRMS (ESI): *m/z* calc. for C₄₃H₃₈ClN₂O₅S [M+H]⁺ 729.2184; found 729.2177.

Methyl 3-(((2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2*H*-pyran-6-yl)thio)propanoate (4d). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and methyl 3-mercaptopropanoate (18.6 μL, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4d** was isolated after flash chromatography as a yellow oil (30 mg, 50%). *R_f* = 0.62 (EtOAc / cyclohexane: 4/6); [α]_D²⁰ = -2.3 (c = 1.00, CHCl₃); IR (neat, cm⁻¹): 3028, 2360, 1738, 1654, 1484, 1358, 1326, 1219; ¹H NMR (400 MHz, *d*₆-acetone) δ 10.66 (s, 1H), 8.86-8.83 (m, 1H), 8.38-8.35 (m, 1H), 8.32-8.27 (m, 1H), 7.57-7.54 (m, 1H), 7.49-7.41 (m, 5H), 7.38-7.25 (m, 12H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.97-4.93 (m, 1H), 4.85-4.79 (m, 3H), 4.58-4.52 (m, 2H), 4.48-4.45 (m, 1H), 4.30 (t, *J* = 4.0 Hz, 1H), 4.02 (dd, *J* = 8.0 Hz, *J* = 12.0, 1H), 3.65 (dd, *J* = 4.0 Hz, *J* = 12.0, 1H), 3.60 (s, 3H), 3.25-3.18 (m, 1H), 3.00-2.93 (m, 1H), 2.84-2.69 (m, 2H). ¹³C NMR (100 MHz, *d*₆-acetone) δ 172.8, 166.7, 163.4, 149.1, 139.4, 139.2 (2C), 137.3, 136.8, 129.3, 129.2, 129.1 (2C), 128.9, 128.7 (2C), 128.5, 128.3, 128.2 (2C), 122.7, 121.7, 116.7, 102.9, 79.8, 73.7, 72.9, 72.1, 70.9, 70.8, 68.7, 51.9, 35.7, 25.6. HRMS (ESI): *m/z* calc. for C₄₁H₄₀N₂NaO₇S [M+Na]⁺ 727.2454; found 727.2466.

(2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-(benzylthio)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide (4e). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and phenylmethanethiol (21.1 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4e** was isolated after flash chromatography as a white solid (45.8 mg, 76%). *R_f* = 0.3 (EtOAc / cyclohexane: 1/6); *mp*: 83.1-84.7 °C; [α]_D²⁰ = +20.8 (c = 0.36, CHCl₃); IR (neat, cm⁻¹): 3736, 3566, 2378, 2347, 2320, 1517, 1489, 1458; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.65 (s, 1H), 8.85 (t, *J* = 4.5 Hz, 1H), 8.39 (d, *J* = 3.0 Hz, 1H), 8.27 (d, *J* = 6.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.46-

7.19 (m, 21H), 5.23-5.19 (m, 1H), 4.90-4.81 (m, 4H), 4.66-4.59 (m, 1H), 4.51-4.43 (m, 2H), 4.36-4.29 (m, 1H), 4.21-4.11 (m, 2H), 3.90- 3.83 (m, 1H), 3.74-3.69 (m, 1H); ¹³C NMR (J-MOD, 75 MHz, *d*₆-acetone) δ 166.9 (C), 164.7(C), 149.2 (CH), 139.6 (2C), 139.5 (C), 139.4 (2C), 137.4 (CH), 137.0 (C), 130.2 (CH), 129.5 (2CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (2CH), 128.3 (CH), 128.0 (CH), 122.8 (CH), 121.8 (CH), 116.9 (CH), 103.1 (C), 79.8 (CH), 73.9 (CH₂), 73.4 (CH), 72.3 (CH₂), 71.2 (CH), 71.0 (CH₂), 68.6 (CH₂), 35.3 (CH₂); HRMS (ESI): *m/z* calc. for C₄₄H₄₁N₂O₅S [M+H]⁺ 709.2731; found 709.2724.

Methyl S-(((2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2*H*-pyran-6-yl)-*N*-(tert-butoxycarbonyl)-l-cysteinate (4f). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and methyl (tert-butoxycarbonyl)-l-cysteinate (40 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4f** was isolated after flash chromatography as a white solid (18.8mg, 27%). *R_f* = 0.3 (EtOAc/DCM / cyclohexane: 2/1/8); *mp*: 52.4-54.0 °C; [α]_D²⁰ = +0.9 (c = 0.33, CHCl₃); IR (neat, cm⁻¹): 2927, 2870, 1714, 1654, 1521, 1487, 1327, 1165; ¹H NMR (300 MHz, *d*₆-acetone) δ 10.69 (s, 1H), 8.87-8.84 (m, 1H), 8.49-8.42 (m, 1H), 8.30 (d, *J* = 6.0 Hz, 1H), 7.57-7.55 (m, 2H), 7.52-7.29 (m, 16H), 6.42-6.39 (m, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.96-4.94 (m, 1H), 4.81-4.78 (m, 3H), 4.68-4.50 (m, 5H), 4.30-4.20 (m, 2H), 3.64 (s, 3H), 3.41-3.24 (m, 2H), 1.34 (s, 9H); ¹³C NMR (J-MOD, 100 MHz, *d*₆-acetone) δ 172.4 (C), 166.8 (C), 163.1 (C), 156.4 (C), 149.2 (CH), 139.6 (C), 139.4 (C), 139.3 (2C), 139.2 (C), 137.4 (CH), 136.9 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 122.8 (CH), 121.8 (CH), 116.9 (CH), 103.3 (C), 80.1 (CH), 79.8 (C), 73.7 (CH₂), 73.3 (CH), 72.3 (CH₂), 71.2 (CH₂), 71.2 (CH), 68.4 (CH₂), 55.5 (CH), 52.6 (CH₃), 31.7 (CH₂), 28.7 (CH₃); HRMS (ESI): *m/z* calc. for C₄₆H₅₀N₃O₉S [M+H]⁺ 820.3262; found 820.3256

(2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-(octadecylthio)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide (4g). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and octadecane-1-thiol (48.8 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4g** was isolated after flash chromatography as a yellow oil (12 mg, 16%). *R_f* = 0.66 (EtOAc / cyclohexane: 2/8); [α]_D²⁰ = +2.3 (c = 1.00, CHCl₃); IR (neat, cm⁻¹): 2921, 1746, 1517, 1464, 1422, 1367, 1260, 1105; ¹H NMR (400 MHz, *d*₆-acetone) δ 10.68 (s, 1H), 8.87-8.85 (m, 1H), 8.38 (dd, *J* = 1.6 Hz, *J* = 4.0, 1H), 8.30 (dd, *J* = 1.6 Hz, *J* = 8.4, Hz, 1H), 7.56-7.55 (m, 1H), 7.49-7.45 (m, 1H), 7.44-7.40 (m, 4H), 7.37-7.26 (m, 12H), 5.24 - 5.14 (m, 1H), 4.92-4.89 (m, 1H), 4.81-4.79 (m, 3H), 4.60-4.59 (m, 1H), 4.50 (g, *J* = 12.0 Hz, 2H), 4.29 (t, *J* = 4.0 Hz, 1H), 4.00 (dd, *J* = 8 Hz, *J* = 12.0 Hz, 1H), 3.70 (dd, *J* = 4Hz, *J* = 12 Hz, 1H), 3.01-2.94 (m, 1H), 2.79-2.73 (m, 1H), 1.71-1.63 (m, 2H), 1.43-1.36 (m, 2H), 1.26 (m, 28H), 0.89-0.85 (m, 3H). ¹³C NMR (100 MHz, *d*₆-acetone) δ 166.8, 164.4, 149.1, 139.5 (2C), 139.4, 139.3, 137.4, 136.9, 129.3, 129.2, 129.1 (2C), 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 122.7, 121.6, 116.7, 103.3, 79.6, 73.7, 73.1, 72.1, 71.1, 70.9, 68.79.9, 32.8, 30.5 (2C), 30.4(2C), 30.2 (2C), 30.1, 30.0, 29.9, 29.9, 29.7, 23.5, 14.5; HRMS for C₅₅H₇₁N₂O₅S [M+H]⁺ (m/z): calcd 871.5078, found 871.5065

(2*R*,3*S*,4*S*)-6-((adamantan-1-yl)thio)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide (4h). According to general procedure 2, (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-*N*-(quinolin-8-yl)-3,4-dihydro-2*H*-pyran-5-carboxamide **1a** (50 mg, 0.085 mmol, 1 equiv) and adamantan-1-thiol (28.6 mg, 0.17 mmol, 2.0 equiv) were allowed to react for 24 h. Product **4h** was isolated after flash

chromatography as a white solid (13.6mg, 21%). *R_f* = 0.3 (EtOAc /cyclohexane: 1/5); *mp*: 48.8-50.0°C ; [α]_D²⁰ = +20.0 (c = 0.13, CHCl₃); **IR** (neat, cm⁻¹) : 2906, 2852, 1647, 1521, 1487, 1456, 1097, 1070; **¹H NMR** (300 MHz, *d*₆-acetone) δ 10.95 (s, 1H), 8.95-8.93 (m, 1H), 8.81-8.80 (m, 1H), 8.34-8.31 (m, 1H), 7.59-7.55 (m, 3H), 7.39-7.20 (m, 15H), 4.78-4.52 (m, 8H), 4.12-4.05 (m, 2H), 3.77-3.73 (m, 1H), 2.31-2.15 (m, 7H), 1.74-1.69 (m, 8H); **¹³C NMR** (J-MOD, 100 MHz, *d*₆-acetone) δ 166.6 (C), 156.3 (C), 149.4 (CH), 139.8 (C), 139.7 (C), 139.5 (2C), 137.5 (CH), 136.8 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (3CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 123.0 (CH), 122.1 (CH), 116.9 (CH), 114.6 (C), 79.5 (CH), 73.8 (CH₂), 73.7 (CH), 73.1 (CH), 72.9 (CH₂), 72.3 (CH₂), 69.3 (CH₂), 52.1 (C), 44.6 (CH₂), 37.0 (CH₂), 31.3 (CH); **HRMS** (ESI): m/z calc. for C₄₇H₄₈N₂NaO₅S [M+Na]⁺ 775.3176; found 775.3160

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-(((2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-(quinolin-8-ylcarbonyl)-3,4-dihydro-2*H*-pyran-6-yl)sulfinyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (5a). 5a-1: *mp*: 63.1-64.4 °C; [α]_D²⁰ = +140.3 (c = 0.077, CHCl₃); **IR (neat, cm⁻¹) : 3736, 2349, 2320, 1749, 1508, 1373, 1226, 1062; **¹H NMR** (300 MHz, *d*₃-acetonitrile) δ 10.78 (s, 1H), 8.71 (dd, *J* = 3.0 Hz; *J* = 9.0 Hz, 1H), 8.35 (dd, *J* = 3.0 Hz; *J* = 6.0 Hz, 1H), 8.24 (dd, *J* = 3.0 Hz; *J* = 9.0 Hz, 1H), 7.61-7.51 (m, 2H), 7.45-7.21 (m, 16H), 5.47-5.30 (m, 3H), 5.27-4.19 (m, 5H), 4.80-4.69 (m, 3H), 4.54-4.51 (m, 1H), 4.42 (s, 2H), 4.29-4.03 (m, 4H), 4.01-3.93 (m, 1H), 3.79-3.72 (m, 1H), 3.60-3.54 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H); **¹³C NMR** (J-MOD, 100 MHz, *d*₆-acetone) δ 171.0 (C), 170.8 (C), 170.2 (C), 169.7 (C), 166.4 (C), 165.7 (C), 149.6 (CH), 139.6 (C), 139.5 (C), 139.0 (C), 138.9 (C), 137.6 (CH), 136.0 (C), 129.6 (CH), 129.3 (2CH), 129.3 (C), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 123.1 (CH), 122.9 (CH), 117.5 (CH), 108.7 (C), 97.3 (CH), 81.3 (CH), 77.4 (CH), 75.8 (CH), 73.9 (CH₂), 72.5 (CH₂), 71.8 (CH), 71.8 (CH₂), 71.2 (CH), 69.0 (CH), 67.6 (CH₂), 67.1 (CH), 63.1 (CH₂), 21.2 (CH₃), 21.0 (CH₃), 20.9 (CH₃), 20.8 (CH₃); **HRMS** (ESI): m/z calc. for C₅₁H₅₂N₂NaO₁₅S [M+Na]⁺ 987.2981; found 987.2991. **5a-2: mp**: 67.2-69.3°C; [α]_D²⁰ = -131.4 (c = 0.14, CHCl₃); **IR** (neat, cm⁻¹) : 3736, 2374, 2349, 2322, 1749, 1734, 1508, 1224; **¹H NMR** (300 MHz, *d*₃-acetonitrile) δ 10.52 (s, 1H), 8.70-8.67 (m, 2H), 8.30 (dd, *J* = 3.0 Hz; *J* = 9.0 Hz, 1H), 7.66-7.57 (m, 2H), 7.54-7.50 (m, 1H), 7.42-7.27 (m, 12H), 7.18-7.15 (m, 3H), 5.34-5.28 (m, 2H), 5.18-5.15 (m, 1H), 5.04-4.93 (m, 3H), 4.78-4.70 (m, 4H), 4.52-4.44 (m, 2H), 4.35 (t, *J* = 3 Hz, 1H), 4.18-4.12 (m, 1H), 3.95-3.78 (m, 4H), 2.12 (s, 3H), 1.92 (s, 6H), 1.72 (s, 3H); **¹³C NMR** (J-MOD, 100 MHz, *d*₃-acetonitrile) δ 171.2 (C), 171.0 (C), 170.4 (C), 170.1 (C), 166.0 (C), 165.4 (C), 149.8 (CH), 139.3 (C), 139.2 (C), 138.8 (C), 138.6 (C), 137.6 (CH), 135.3 (C), 129.5 (CH), 129.4 (CH), 129.2 (2CH), 129.1 (C), 129.0 (2CH), 128.7 (CH), 128.6 (2CH), 128.1 (CH), 123.2 (CH), 123.1 (CH), 117.4 (CH), 108.4 (C), 91.5 (CH), 80.8 (CH), 77.6 (CH), 74.5 (CH), 73.6 (CH₂), 73.5 (CH), 72.9 (CH₂), 71.5 (CH₂), 70.8 (CH), 68.5 (CH), 68.2 (CH), 67.6 (CH₂), 62.7 (CH₂), 21.0 (CH₃), 20.9 (CH₃), 20.8 (2CH₃); **HRMS** (ESI): m/z calc. for C₅₁H₅₂N₂NaO₁₅S [M+Na]⁺ 987.2981; found 987.2989.**

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Directed Dehydrogenative Copper-Catalyzed C-H Thiolation in *Pseudo*-Anomeric Position of Glycals using Thiol and Thiosugar Partners*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

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