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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).

\[\text{(Scheme 1a)}\]

**Scheme 1. Metal-catalyzed synthesis of thioglycosides**
Very recently, our group reported other emergent and competitive activation processes toward thioglycosides such as photocatalysis\(^{[14]}\) or electrocatalysis\(^{[2]}\) (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 aminooquinoline-containing glycalcs are suitable starting substrates for the C–H functionalization of the pseudo-anomeric position of glycalcs. Palladium- or nickel-catalysis has been successfully used on this compound with aryl iodide\(^{[4]}\) or alkynyl bromide partners.\(^{[9]}\) C–H activation methods involving sugars emerge very recently as a new option in the glycochemistry toolbox.\(^{[7]}\) 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(sp\(^2\))–H thiolation method of glycalcs to readily access 1-thiotrehaloses (Scheme 1c) and 1-thiolated glycalcs would find widespread utility. Herein, we described the first Cu-catalyzed C–H thiolation of the pseudo-anomeric position of glycalcs bearing an 8-amidoquinolyl directing group with thiosugars and thios 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)\(_2\)·H\(_2\)O (0.4 equiv.), Ag\(_2\)CO\(_3\) (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 bathophenanthroline 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 acetone as a solvent substitute for DMSO, which gave a comparable yield (67% instead of 70%) after 24 h of reaction (Table 1, entries 9 and 10). According to the literature\(^{[10]}\) 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, 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-cellbiose (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

<table>
<thead>
<tr>
<th>N°</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield(3a)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>DMSO</td>
<td>120 °C/1 h</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>DMSO</td>
<td>120 °C</td>
<td>25%</td>
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<tr>
<td>3</td>
<td>-</td>
<td>DMSO</td>
<td>100 °C/18 h</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>Bathophen</td>
<td>DMSO</td>
<td>100 °C/16 h</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>Phenanthroline</td>
<td>DMSO</td>
<td>100 °C/16 h</td>
<td>ND</td>
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<tr>
<td>6</td>
<td>Neocuproine</td>
<td>DMSO</td>
<td>100 °C/16 h</td>
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<tr>
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<td>Neocuproine</td>
<td>DMSO</td>
<td>90 °C/24 h</td>
<td>70%</td>
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<tr>
<td>8</td>
<td>Neocuproine</td>
<td>DMSO</td>
<td>80 °C/40 h</td>
<td>55%</td>
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<tr>
<td>9</td>
<td>Neocuproine</td>
<td>ACN</td>
<td>90 °C/24 h</td>
<td>67%</td>
</tr>
<tr>
<td>10</td>
<td>Neocuproine</td>
<td>ACN</td>
<td>90 °C/46 h</td>
<td>61%</td>
</tr>
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</table>

\(^{[a]}\) Conditions: 0.085 mmol of 1a (1 equiv.), 2a (2 equiv.), Cu(OAc)\(_2\)·H\(_2\)O (40 mol%), ligand (40 mol%), Ag\(_2\)CO\(_3\) (3 equiv.), solvent, T°C, t

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**Table 1. Optimization of the C-H thiolation conditions**

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**Scheme 1.**

[Diagram of Scheme 1 is not provided but should be included in the actual document.]
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-rhamnal examples (Scheme 3, 3g and 3h respectively). The use of the peracetylated D-glycal 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 adamantyl-thiols were also suitable partners (thioglycals 4f, 4g and 4h) albeit modest yields were obtained under our optimized conditions.

Thioglycals 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)$_2$·H$_2$O (40 mol%), neocuproine (40 mol%), Ag$_2$CO$_3$ (3 equiv.), solvent, at 90 °C under argon. a) isolated yields.

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

Scheme 4. Scope of the C-H thiolation using other thiols as partners
into sulfoxide,\(^1\) sulfoxide\(^2\) or sulfoximines.\(^2\) 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 thioles via copper catalysis. This method provides unprecedented access to thiotrehalose analogs and thiglycosides. 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 used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents unless otherwise noted. The \(^1\)H NMR and \(^13\)C NMR J-MOD spectra were recorded in either CDCl\(_3\) or \(d_6\)-acetone or \(d_6\)-acetonitrile on Bruker Avance 300, 400 spectrometers. The \(^19\)F NMR Decoupled spectra were recorded in \(d_6\)-acetone on Bruker Avance 200 spectrometers. The chemical shifts of \(^1\)H, \(^13\)C and \(^19\)F 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 (general procedure 1):

In a Schlenk tube were added Pd(OAc)\(_2\) (0.1 equiv.), PPh\(_3\) (0.2 equiv.), K\(_2\)CO\(_3\) (1 equiv.), Mo(CO)\(_6\) (1.2 equiv.) and the corresponding 2-iodoglycal (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)\(_2\)·H\(_2\)O (0.4 equiv.), Ag\(_2\)CO\(_3\) (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 (general procedure 3):

To a solution of KF (6.1 mg, 0.1054 mmol) in CH\(_3\)CN/H\(_2\)O (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 compound 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 FeSO\(_4\) solution and extracted with CH\(_2\)Cl\(_2\). The organic layer was washed with aq NaHCO\(_3\) and water successively, dried (MgSO\(_4\)) 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), 1.4 equiv. of 70% \(m\)-CPBA were added to 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 aq NaHCO\(_3\) (aq.) and dried over MgSO\(_4\) concentrated under reduced pressure. The residue was purified over SiO\(_2\) 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. In a Schlenk tube (4.2 equiv.), 3-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); \([\alpha]_D^{20} = +3.4\) (c = 1.23, CHCl\(_3\)). IR (neat, cm\(^{-1}\)) : 2934, 1610, 1524, 1485, 1324, 1300, 1192, 1111; \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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), 6.87 (d, J = 12 Hz, 1H), 5.40–5.38 (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). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 165.5 (C), 159.6 (C), 159.4 (C), 159.3 (C), 153.4 (C), 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
(2R,3R,4S,5R,6S)-2-(acetoxyethyl)-6-((2R,3S,4S,5R,6S)4,3,4-bis(benzyl)-2-((benzyl)ethyl)methyl)-5-(quinolin-8-ylcarbamoyl)-3,4-dihydro-2H-pyran-6-ylthiotetrahydro-2H-pyran-3,4,5-triyl triacetate (3e). According to general procedure 2, (2R,3R,4S,5R,6S)-4,3,4-bis(benzyl)-2-((benzyl)ethyl)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-(acetoxyethyl)-6-((2R,3S,4S,5R,6S)4,3,4-bis(benzyl)-2-((benzyl)ethyl)methyl)-5-(quinolin-8-ylcarbamoyl)-3,4-dihydro-2H-pyran-6-ylthiotetrahydro-2H-pyran-3,4,5-triyl triacetate (3e) were obtained after flash chromatography as a white solid (24 mg, 25%). Rf = 0.3 (EtOAc/DCM/cyclohexane: 1:3:6:3:1=6.5 mm; 8 mm). H NMR (400 MHz, CDCl3) δ 10.63 (s, 1H), 8.81 (dd, J = 3.0 Hz, J = 9.0 Hz, 4H), 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, 2H), 5.07 (d, J = 12 Hz, 1H), 4.97 (t, J = 12 Hz, 1H), 4.63 (m, 2H), 4.4-4.44 (m, 4H), 4.16-4.05 (m, 2H), 4.01-3.68 (m, 2H), 3.68 (d, J = 3.0 Hz, J = 9.0 Hz, 1H), 3.49-3.31 (m, 1H), 2.02 (s, 3H), 1.91 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). IR (neat cm-1): 3021, 2865, 2005, 1941, 1652, 1484, 1369, 1214. MS ([M+Na]+) 4/6; [m/z] calcd. for C14H20N3O9S [M+Na]+ 414.1467; found 414.1461.

(2R,3R,4S,5R,6S)-2-((benzoxyl)ethyl)-6-((2R,3R,4S,5R,6S)4,3,4-bis(benzyl)-2-((benzyl)ethyl)methyl)-5-(quinolin-8-ylcarbamoyl)-3,4-dihydro-2H-pyran-6-ylthiotetrahydro-2H-pyran-3,4,5-triyl triacetate (3b). According to general procedure 2, (2R,3R,4S,5R,6S)-4,3,4-bis(benzyl)-2-((benzyl)ethyl)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-((benzoxyl)ethyl)-6-((2R,3R,4S,5R,6S)4,3,4-bis(benzyl)-2-((benzyl)ethyl)methyl)-5-(quinolin-8-ylcarbamoyl)-3,4-dihydro-2H-pyran-6-ylthiotetrahydro-2H-pyran-3,4,5-triyl triacetate (3b) were obtained after flash chromatography as a white solid (22 mg, 17%). Rf = 0.3 (EtOAc/DCM/cyclohexane: 4/6); [m/z] calcd for C14H20N3O9S [M+Na]+ 414.1467; found 414.1461.
1751, 1654, 1525, 1487, 1373, 1237, 1203, 1041; 1H NMR (300 MHz, d4-acetone) δ 10.68 (S, 1H), 8.85-8.82 (m, 1H), 8.45-8.44 (m, 1H), 7.53-7.77 (m, 1H), 7.31-7.53 (m, 1H), 7.01 (m, 1H), 6.07 (m, 1H), 5.94-5.92 (m, 1H), 5.89-5.87 (m, 1H), 5.67-5.64 (m, 1H), 5.39 (d, J = 9.0 Hz, 1H), 5.29-5.28 (m, 1H), 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, d4-acetone) δ 170.13 (C), 169.12 (C), 166.33 (C), 162.23 (C), 149.33 (CH), 139.53 (C), 139.41 (C), 139.31 (C), 137.43 (CH), 136.55 (CH), 129.05 (CH), 129.04 (CH), 129.42 (C), 129.12 (C), 128.31 (CH), 127.58 (C), 127.55 (C), 127.27 (C), 77.74 (CH), 76.49 (CH), 74.00 (CH), 73.32 (CH), 72.26 (CH), 71.69 (CH), 71.06 (CH), 69.91 (CH), 68.46 (CH), 66.34 (CH), 63.26 (CH), 61.39 (C), 61.20 (C), 20.09 (CH), 20.46 (CH), 20.72 (CH). HRMS (ESI): m/z calc. for C43H34N2O2S11 [M+Na]+ 759.2201; found 759.2201.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(((2S,3S,4S)-3,4-bis(benzoxyl)-2-benzoxyl)-5-(quinolin-8-
aldehyde)-4,5-dihydro-2H-pyran-3,4,5-triytricetate (3f). According to general procedure 2, (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-5-(quinolin-8-
aldehyde)-4,5-dihydro-2H-pyran-3,4,5-triytricetate (3f) was isolated after flash chromatography as a white solid (35 mg, 48%). 

1H NMR (400 MHz, d4-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), 6.54 (d, J = 12.0 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, 4H), 4.88 (d, J = 12.0 Hz, 1H), 4.82 (t, J = 1.6 Hz, 4H), 4.39 (d, J = 16.6 Hz, 1H), 3.97 (s, 3H), 1.92 (s, 3H), 1.57 (d, J = 8.0 Hz, 3H). 13C NMR (100 MHz, d4-acetone) δ 170.71, 170.30, 170.00, 169.88, 166.17, 160.2, 149.0, 139.4, 139.3, 139.1, 137.3, 137.6, 135.9, 129.0, 129.0, 128.9, 128.8, 128.6, 128.1, 128.0 (2C), 122.6, 121.8, 116.4, 104.7, 80.7, 77.2, 76.4, 73.6, 73.1, 71.9, 70.7, 70.1, 69.3, 65.2, 62.0 (2CH), 20.6 (CH), 66.2 (CH). HRMS (ESI): m/z calc. for C42H36N2O2S10 [M+Na]+ 757.2022; found 757.2022.
(2R,3S,4S)-3,4-bis(benzoxyl)-2-((benzoxyl)methyl)-6-(4-chlorophenyl)thio)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyrano-5-carboxamide (4e). According to general procedure 2, (2R,3S,4S)-3,4-bis(benzoxyl)-2-((benzoxyl)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyrano-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 (17.8 mg, 0.024 mmol, 29%). RF = 0.4 (EtOAc / cyclohexane: 1/5); [α]22 D = -12.5 (c = 1.00, CHCl3); IR (neat, cm−1) : 3028, 2360, 1738, 1654, 1484, 1358, 1262, 1219; 1H NMR (400 MHz, d-acetone) δ 2.35 (s, 3H), 4.15 (q, J = 6.0 Hz, 2H); 3.83 (m, 1H), 3.74 (m, 1H), 3.64 (m, 1H), 3.00-2.93 (m, 2H), 2.50-2.45 (m, 2H), 2.40 (s, 4H), 1.78 (m, 1H), 0.88 (d, J = 6.0 Hz, 2H), 0.76-0.70 (m, 2H); 13C NMR (100 MHz, d-acetone) δ 172.8, 166.7, 163.3, 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), 127.7, 127.1, 116.7, 102.9, 79.8, 73.7, 72.9, 72.1, 70.9, 70.8, 68.7, 51.9, 35.5, 25.8; MS (ESI): m/z calc. for C21H17N2O2S+ [M+H]+ 373.1242, found 373.1244.

Methyl S-((2R,3S,4S)-3,4-bis(benzoxyl)-2-((benzoxyl)methyl)-5-(quinolin-8-ylcarbamoyl)-3,4-dihydro-2H-pyrano-5-carboxamide (4f). According to general procedure 2, (2R,3S,4S)-3,4-bis(benzoxyl)-2-((benzoxyl)methyl)-N-(quinolin-8-yl)-3,4-dihydro-2H-pyrano-5-carboxamide 1a (50 mg, 0.085 mmol, 1 equiv) and methyl (tert-butoxycarbonyl)-l-cysteinate (4 equiv) were allowed to react for 24 h. Product 4f was isolated after flash chromatography as a white solid (18.0 mg, 0.024 mmol, 29%). RF = 0.2 (EtOAc / cyclohexane: 1/4); [α]22 D = -20.3 (c = 0.33, CHCl3); IR (neat, cm−1) : 2927, 2870, 1714, 1654, 1521, 1477, 1327, 1165; 1H NMR (400 MHz, d-acetone) δ 1.06 (d, J = 6.0 Hz, 3H), 3.48 (m, 2H), 3.40 (m, 2H), 3.39 (m, 2H), 3.24 (m, 2H), 1.33 (S, 9H), 1.22 (m, 1H), 1.19 (m, 1H), 0.90 (m, 1H), 0.84 (m, 1H), 0.73 (m, 1H), 0.70 (m, 1H), 0.68 (m, 1H); MS (ESI): m/z calc. for C21H21N2O2S+ [M+H]+ 325.1329, found 325.1330.
References


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


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