Site-selective Electrochemical Oxidation of Glucosides

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ABSTRACT: Quinuclidine-mediated electrochemical oxidation of glycopyranosides provides C3-ketosaccharides with excellent selectivity. The method is a versatile alternative to Pd-catalyzed oxidation, and to photochemical oxidation, and is complementary to the TEMPO-mediated C6-selective oxidation. Contrary to the electrochemical oxidation of methylene and methine groups, the reaction does not require oxygen.

Carbohydrates are an important class of compounds, both in biology, in food and feed, and as raw materials for industry. The monosaccharide building blocks mostly occur in their glucopyranoside form.1 Despite the application of carbohydrates, their selective functionalization
is difficult, mainly because of the necessity to discriminate between the virtually identical secondary hydroxyl groups. In synthesis, protection-group strategies are mostly applied but this is not feasible for large scale industrial application.

Over the past years, significant progress has been made in the site-selective modification of unprotected and partially protected carbohydrates. Because of its versatility regarding further modifications, regioselective oxidation is particularly noteworthy. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO)-mediated oxidation of glycopyranosides leads to selective oxidation of the primary C6 hydroxy group, most often producing the corresponding uronic acids. Palladium-catalyzed oxidation and hydrogen atom-transfer (HAT) reactions show a strong preference for the secondary C3 hydroxy group (Scheme 1), and a rationale for this has been provided.

**Scheme 1.** Site-selective oxidation of methyl-a-D-glucopyranoside (1).

The C3 selective oxidation, in particular the palladium-catalyzed version, has shown to be versatile and scalable, but for many applications a precious metal-free protocol would be a gain. The photochemical oxidation mediated by an organo-sensitizer provides this, and we showed the related photochemical alkylation reaction to be scalable in a flow system.
Baran and co-workers reported on the electrochemical quinuclidine-mediated C-H activation of methylene and methine groups. We realized that generating the quinuclidine radical cation by electrochemical means instead of using light and a photosensitizer, might overcome some of the limitation of photochemical oxidation and could be an attractive alternative. We assumed initially that the fate of the generated carbon-centered radical would be identical to that in the photochemical process, e.g. reaction with oxygen or superoxide and subsequent collapse to the carbonyl function.

Electrochemical oxidation of the primary and the anomeric hydroxy group in sugars is well-described. TEMPO and 4-acetamido-TEMPO are the mediators of choice, and Pt and Au based electrodes have mainly been applied. Similar results were obtained under heterogeneous conditions, in which a TEMPO immobilized Nafion perfluorinated film was deposited onto graphite electrodes.

As electrochemical, quinuclidine-mediated oxidation of glycosides had not been studied, we started by adopting the reaction conditions of Baran et al., and subjected methyl-α-D-glucopyranoside (1) to electrolysis with RVC (anode) and Ni foam (cathode) electrodes. Quinuclidine (1 eq), tetramethylammonium tetrafluoroborate (Me₄NBF₄, 1 eq) and hexafluoroisopropanol (HFIP, 10 eq) were dissolved in acetonitrile and a constant current was set at 5 mA. Upon electrolysis, the initial suspension of 1 turned homogeneous over 24 h. TLC analysis showed an incomplete but clean conversion, and NMR analysis revealed 80% conversion to 3-keto product 1a. In particular, the apparent full selectivity for the C3-position and the clean conversion to the keto-sugar demonstrated the potential of this method. The use of graphite electrodes, being inexpensive, pleasingly led to full oxidation of 1 within the same reaction time (Scheme 2). Moreover, the same results were obtained when the amount of quinuclidine was reduced to 0.3 eq.
The isolated yield of 1a after column chromatography was 56%, comparable to the reported yield for the photochemical oxidation reaction. 6c

**Scheme 2:** Regioselective electrochemical oxidation of methyl-α-D-glucopyranoside (1).

With these first results in hand, we investigated the substrate scope of the oxidation reaction, employing graphite electrodes. In order to facilitate solubility and chromatographic purification, partly protected glycosides were used, leading to the corresponding products in moderate to good yields (Table 1).

**Table 1.** Scope of the electrochemical oxidation of mono- and disaccharides.
Reaction conditions: glycoside (0.32 mmol, 1 eq), quinuclidine (0.3 eq), Me₄NBF₄ (1 eq), HFIP (10 eq), 5 mL ACN, graphite electrodes, 5 mA (constant current, 2.00 mA/cm²), 16 h, yields after column chromatography. a Reaction on 0.56 mmol scale. b Reaction on 0.16 mmol scale for 24 h. c NMR yield using 1,4-difluorobenzene as internal standard.

Silyl-equipped 2 was smoothly converted to ketone 2a in 62% isolated yield. Noteworthy, the presence of a trityl group, potentially susceptible to Birch reduction,¹⁴ had no effect on the reaction
outcome, and 3 underwent selective oxidation in 70% yield. In addition, substrate 4, with a tosyl group at C6, provided 4a in 55% yield. The methyl ester of glucuronic acid 5, xyloside 6, 2-deoxyglucoside 7, and 6-deoxy-glucoside 8 were smoothly oxidized in moderate to good yields. 4,6-Protected monosaccharide 9 was oxidized in merely 95% NMR yield (60% isolated yield). Somewhat to our surprise, the presence of a benzylidene function had no detrimental effect on the reaction outcome, and glucose derivative 10 provided the C3 oxidation product in 60% isolated yield. We previously observed significant acetal cleavage in the photochemical alkylation reaction.9 Acetal-protected sorbose 11 provided product 11a in a somewhat disappointing 34% yield, and oxidation of unprotected methyl-β-D-glucopyranoside 12 led to a mixture of unidentified products. The acetal derivative 13 did, however, yield the desired product, albeit in an isolated yield of 21%. Hydrogen atom transfer at the anomeric position is most probably a competing reaction in β-glucosides.15 Oxidation of methyl N-acetyl glucosamine 14 was incomplete, probably due to its low solubility, and to mitigate this restriction, the acetone derivatives 15 and 16 were synthesized. We were pleased to see that for 15 this led to a high 67% yield in the oxidation reaction. A hypothesis to explain the 33% yield yield for 16a is that hydrogen abstraction by the quinuclidine radical cation is hampered by steric hindrance of the bulky iso-propyl substituent. The method is not restricted to monosaccharides, as trehalose derivative 17 produced 17a in a rewarding 42% yield in a double oxidation reaction.

To illustrate the scalability of our methodology, 2 was oxidized on a 1 g scale. Product 2a was isolated in 50% yield (Scheme 3).

**Scheme 3.** Oxidation of 2 on a gram scale.
In the proposed mechanism, the reaction starts with the formation of the quinuclidinium radical cation (Qu⁺⁺) at the anode, followed by hydrogen abstraction of the C3-H bond (Scheme 4). In both the electro-oxidation of methylene/methine units according to Baran et al., and in the photochemical alcohol oxidation according to Taylor et al., oxygen or superoxide traps the formed carbon-centered radical. The formed hydroperoxide (radical) reacts then subsequently to the carbonyl function.

As expected, no reaction occurred in the absence of quinuclidine, while the absence of HFIP resulted in a significant decrease in yield. Surprisingly, however, when we subjected 2 to electrochemical oxidation under an argon atmosphere and rigorous exclusion of oxygen, this hardly effected the reaction! As a control, and to exclude the inadvertent presence of oxygen, we reproduced the C-H activation reaction reported by Baran et al. using the benchmark substrate sclareolide. As expected, this reaction clearly required oxygen, and the yield dropped dramatically to less than 5% upon exclusion of oxygen.

Based on these observations we propose that radical 2b is trapped by Qu⁺⁺, instead of oxygen/superoxide, leading to the unstable aminal cation 2c. This aminal collapses to keto-sugar 2a releasing Qu (Scheme 4). Additional support for this mechanism is provided by the observation that with 2.5 F/mol the reaction under argon provided 70% conversion and with 1 F/mol 29% conversion was obtained.
**Scheme 4.** Proposed mechanism for the electrochemical oxidation reaction.

In conclusion, glycopyranosides can be electro-oxidized selectively at the C3 position in a quinuclidine-mediated process, which is highly complementary to the known electrochemical oxidation at C6 mediated by TEMPO. Whereas the quinuclidinium radical cation attacks the weakest C-H bond in a HAT process, TEMPO in its oxoammonium form oxidizes the primary hydroxy group because it is sterically most accessible.

The use of graphite electrodes and the absence of any metal-based catalysts and sensitizers provides an asset in the scale up of this method, required for its application in carbohydrate chemistry. An additional advantage is the observation that no oxygen is required for the oxidation. This is a distinct advantage for electrochemistry-in-flow, as the supply of sufficient oxygen in a flow process is technically challenging because of its low solubility and because of safety.
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REFERENCES


Supporting Information

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General Information

All solvents used were of commercial grade and used without further purification. Quinuclidine, Me₄NBF₄ and 1,1,1,3,3,3-hexafluoro-2-propanol were purchased from Sigma-Aldrich and TCI and were used without further purification. Electrochemical reactions were performed in a ElectraSyn 2.0 device with IKA graphite electrodes. Large-scale oxidation was performed with a VSP-300 (BioLogic) potentiostat using graphite electrodes (SIGRAFINE®, SGL Carbon SE). Flash chromatography was performed manually with silica gel (SiliaFlash P60, 230-400 mesh, Silicycle) or performed with automated column chromatography using a Reveleris flash chromatography system purchased from Buchi. TLC was performed on Merck silica gel 60, 0.25 mm plates and visualization was done by staining with anisaldehyde stain. NMR spectra were recorded on a Varian AMX400 spectrometer using CD₃OD, CD₃CN or CDCl₃. Data are reported as follows: Chemical shifts (δ), multiplicity (s = singlet, d = doublet, m = multiplet, br = broad), coupling constants J (Hz), and integration. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL.

Starting materials that were synthesized:

Compounds 1, 6, 8 and 12 are commercially available. Compounds 2, 3, 4, 5, 7, 9, 10, 11, 13, 14, 15, 16 and 17 were synthesized according to known literature procedures and the characterization data are in full agreement.
Synthesis of compound 16.

To a stirred solution of compound 16' in 10 mL DMF were added (S)-camphorsulfonic acid (0.01 eq.) and 2,2-dimethoxypropane (1 eq.). The resulting mixture was stirred at room temperature for 48 h, upon which water and EtOAc were added. The resulting phases were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with water (3x), dried over MgSO₄ and evaporated under reduced pressure. Compound 16 was isolated upon column chromatography (10/1 DCM : MeOH) as a white solid (55%).

**1H-NMR** (400 MHz, CD₃OD) δ 4.89 (d, J = 3.9 Hz, 1H), 3.94 (dd, J = 10.3, 3.9 Hz, 1H), 3.83 (p, J = 6.2 Hz, 1H), 3.80-3.74 (m, 2H), 3.73-3.64 (m, 2H), 3.64-3.53 (m, 1H), 1.98 (s, 3H), 1.52 (s, 3H), 1.47 (s, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H).

**13C-NMR** (101 MHz, CD₃OD) δ 173.6, 100.9, 97.7, 76.3, 71.8, 69.9, 65.1, 63.4, 56.0, 29.5, 23.7, 22.5, 21.8, 19.4.


**General Procedure for the Regioselective Electrochemical Oxidation**

A mixture of starting material (1 equiv.), quinuclidine (0.3 equiv.), Me₄NBF₄ (1 equiv.) and HFIP (10 equiv.) in CH₃CN (5 mL) was placed in an ElectraSyn vial, equipped with two IKA graphite electrodes, and electrolyzed in a Electrasyn 2.0 at room temperature, under constant current (5 mA, j = 2.00 mA/cm²). The reaction progress was monitored by TLC (10% MeOH in DCM). Acetonitrile and HFIP were subsequently co-evaporated with water under reduced pressure, upon which celite and MeOH were added and the slurry was concentrated to dryness at 40 °C. The resulting mixture was pulverized, loaded on top of a silica gel column and subsequently eluted (5 to 10% MeOH in DCM). Fractions containing the desired product were collected and the solvent was removed in vacuo.

**Procedure for the Large Scale Oxidation**

To a 30 mL beaker-type electrolysis cell (Scheme 1) were added 1 g of glucoside 2 (3.24mmol, 1.0 eq.), quinuclidine (0.973 mmol, 0.3 eq.), Me₄NBF₄ (3.24 mmol, 1.0 eq.), HFIP (5.45 mmol, 10 eq.) and MeCN (25 mL). Graphite electrodes (2.0 cm x 6.0 cm) were immersed in the solution and electrolysis was conducted under constant current (5 mA). Electrolysis was conducted for 96 h, upon which the mixture was transferred into a round-bottom flask. MeCN and HFIP were evaporated under reduced pressure, celite and MeOH were added and the slurry was concentrated to dryness at 40
°C. The resulting mixture was pulverized, loaded on a silica gel column and eluted (5 % MeOH in DCM). The fractions containing the product were combined and the solvent was evaporated in vacuo.

Figure 1. Gram-scale electrochemical oxidation.
Data of the Products

\((2R,3R,5S,6S)-3,5\text{-Dihydroxy-2-(hydroxymethyl)-6-methoxytetracyclo}-4H\text{-pyran-4-one (1a).}\)

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{OMe}
\end{align*}
\]

Isolated as a white solid (55 mg, 0.52 mmol, 56\%) after column chromatography (10\% MeOH in DCM).

\(^{1}H\ \text{NMR} (400\text{ MHz, CD}_{3}\text{OD}) \delta 5.05 (d, J = 4.2\text{ Hz, 1H}), 4.40 (dd, J = 4.3, 1.5\text{ Hz, 1H}), 4.23 (dd, J = 9.7, 1.6\text{ Hz, 1H}), 3.88 (dd, J = 12.1, 2.2\text{ Hz, 1H}), 3.83-3.73 (m, 1H) 3.65 (ddd, J = 9.8, 4.7, 2.2\text{ Hz, 1H}), 3.40 (s, 3H).
\]

\(^{13}C\ \text{NMR} (101\text{ MHz, CD}_{3}\text{OD}) \delta 207.0, 103.8, 76.7, 76.1, 73.3, 62.5, 55.7.\)

Spectroscopic data correspond to those reported in literature.\(^{12}\)

\(\text{Isolated as a white solid (62 mg, 0.20 mmol, 62\%) after column chromatography (5\% MeOH in DCM).}\)

\(^{1}H\ \text{NMR} (400\text{ MHz, CD}_{3}\text{CN}) \delta 5.03 (d, J = 4.3\text{ Hz, 1H}), 4.34 (dd, J = 4.3, 1.6\text{ Hz, 1H}), 4.23 (dd, J = 9.7, 1.6\text{ Hz, 1H}), 4.03-3.81 (m, 2H), 3.54 (ddd, J = 9.7, 4.2, 2.1\text{ Hz, 1H}), 3.34 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).
\]

\(^{13}C\ \text{NMR} (101\text{ MHz, CD}_{3}\text{CN}) \delta 207.3, 103.2, 76.2, 75.8, 72.9, 63.3, 55.7, 28.8, 26.2, 19.0, -5.1, -5.2.\)

Spectroscopic data correspond to those reported in literature.\(^{13}\)

\((2S,3S,5S,6S)-3,5\text{-Dihydroxy-2-methoxy-6-((trityloxy)methyl)tetrahydro-4H-pyran-4-one (3a).}\)

\[
\begin{align*}
\text{HO} & \quad \text{OTr} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{OMe}
\end{align*}
\]
Reaction was run on 0.46 mmol scale. Isolated as white solid (118 mg, 0.32 mmol, 70%) after column chromatography (5% MeOH in DCM).

\textbf{1}^H \textbf{NMR} (400 MHz, CD$_3$CN) $\delta$ 7.52-7.46 (m, 6H), 7.37-7.31 (m, 6H), 7.30-7.24 (m, 3H), 5.11 (d, $J = 4.3$ Hz, 1H), 4.50-4.38 (m, 1H), 4.28 (d, $J = 9.8$, 5.1, 1.5 Hz, 1H), 3.77-3.72 (m, 1H), 3.62 (d, $J = 5.3$ Hz, 1H), 3.57(d, $J = 7.9$ Hz, 1H), 3.42 (s, 3H), 3.40-3.28 (m, 2H).

\textbf{13C NMR} (101 MHz, CD$_3$CN) $\delta$ 206.8, 145.0, 129.6, 128.9, 128.1, 103.2, 87.3, 75.9, 75.3, 73.6, 64.4, 55.8.

Spectroscopic data correspond to those reported in literature.\textsuperscript{13}

\begin{center}
\includegraphics[width=0.2\textwidth]{compound1.png}
\end{center}

Reaction was run on 0.57 mmol scale. Isolated as a yellow sticky oil (105 mg, 0.30 mmol, 53%) after column chromatography (3% MeOH in DCM).

\textbf{1}^H \textbf{NMR} (400 MHz, CD$_3$OD) $\delta$ 7.82 (d, $J = 8.35$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 4.94 (d, $J = 4.2$ Hz, 1H), 4.37 (dd, $J = 11.0$, 2.1 Hz, 1H), 4.34 (dd, $J = 4.3$, 1.5 Hz, 1H), 4.30 (dd, $J = 11.0$, 5.3 Hz, 1H), 4.11 (dd, $J = 10.0$, 1.5 Hz, 1H), 3.77 (ddd, $J = 10.0$, 5.5, 2.1 Hz, 1H), 3.34 (s, 3H), 2.45 (s, 3H).

\textbf{13C NMR} (101 MHz, CD$_3$OD) $\delta$ 205.8, 146.6, 134.3, 131.1, 129.1, 103.6, 75.9, 73.7, 73.1, 70.6, 55.9, 21.6.

\textbf{HRMS} (ESI$^+$) calculated for C$_{14}$H$_{18}$O$_8$S$_1$Na$_1$ ([M+Na]$^+$): 369.06146, found: 369.06079.

Methyl \((2R,3R,5S,6S)-3,5\text{-Dihydroxy-6-methoxy-4-oxotetrahydro-2H-pyran-2-yl})\text{methyl 4-methylbenzenesulfonate (4a).}

\begin{center}
\includegraphics[width=0.2\textwidth]{compound2.png}
\end{center}

Isolated as a white solid (24.3 mg, 0.11 mmol, 49%) after column chromatography (10% MeOH in DCM).

\textbf{1}^H \textbf{NMR} (400 MHz, CD$_3$CN) $\delta$ 5.11 (d, $J = 4.1$ Hz, 1H), 4.48-4.39 (m, 2H), 4.06 (dd, $J = 9.7$, 0.6 Hz, 1H), 3.79 (s, 3H), 3.39 (s, 3H).

\textbf{13C NMR} (101 MHz, CD$_3$CN) $\delta$ 205.0, 169.8, 103.9, 75.8, 74.7, 74.6, 56.4, 53.3.
Spectroscopic data correspond to those reported in literature.\(^4\)

\((2S,3S,5R)-3,5\text{-Dihydroxy-2-methoxytetrahydro-4H-pyran-4-one (6a)}\).

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{CH}_2 & \quad \text{OH} \\
\text{OMe} & \quad \text{OH}
\end{align*}
\]

Isolated as a white solid (20.2 mg, 0.12 mmol, 41\%) after column chromatography (5\% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CD\(_3\)OD) \(\delta\) 4.97 (d, \(J = 4.2\) Hz, 1H), 4.41-4.34 (m, 2H), 3.97 (dd, \(J = 10.3, 7.9\) Hz, 1H), 3.58 (t, \(J = 10.4\) Hz, 1H), 3.35 (s, 3H).

\(^{13}\text{C NMR}\) (101 MHz, CD\(_3\)OD) \(\delta\) 206.6, 104.4, 76.3, 73.1, 65.2, 55.7.

Spectroscopic data correspond to those reported in literature.\(^{13}\)

\((2R,3R,6S)-3\text{-Hydroxy-2-(hydroxymethyl)-6-methoxytetrahydro-4H-pyran-4-one (7a)}\).

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

Isolated as a white solid (62 mg, 0.27 mmol, 62\%) after column chromatography (10\% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CD\(_3\)OD) \(\delta\) 5.13 (d, \(J = 4.2\) Hz, 1H), 4.17 (d, \(J = 9.9\) Hz, 1H), 3.87 (dd, \(J = 12.0, 2.3\) Hz, 1H), 3.80 (dd, \(J = 12.0, 4.7\) Hz, 1H), 3.68 (ddd, \(J = 9.8, 4.6, 2.2\) Hz, 1H), 3.34 (s, 2H), 2.87 (ddd, \(J = 14.1, 4.5, 1.0\) Hz, 1H), 2.49 (d, \(J = 14.1\) Hz, 1H).

\(^{13}\text{C NMR}\) (101 MHz, CD\(_3\)OD) \(\delta\) 207.3, 101.2, 76.4, 74.1, 62.6, 55.0, 46.6.

Spectroscopic data correspond to those reported in literature.\(^{13}\)

\((2S,3S,5R,6R)-3,5\text{-dihydroxy-2-methoxy-6-methyltetrahydro-4H-pyran-4-one (8a)}\).

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Me} & \quad \text{OMe}
\end{align*}
\]

Isolated as a colorless sticky oil (60.2 mg, 0.34 mmol, 61\%) after column chromatography (5\% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CD\(_3\)CN) \(\delta\) 4.98 (d, \(J = 4.4\) Hz, 1H), 4.37 (ddd, \(J = 8.2, 4.2, 1.6\) Hz, 1H), 3.86 (ddd, \(J = 9.4, 5.0, 1.7\) Hz, 1H), 3.68-3.57 (m, 2H), 3.49 (br d, \(J = 8.0\) Hz, 1H, OH), 3.34 (s, 3H), 1.36 (d, \(J = 6.2\) Hz, 3H).

The spectrum was also recorded in CD\(_3\)OD.
$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 4.98 (d, $J = 4.3$ Hz, 1H), 4.40 (dd, $J = 4.4$, 1.7 Hz, 1H), 3.88 (dd, $J = 9.4$, 1.5 Hz, 1H), 3.71 (dq, $J = 9.4$, 6.2 Hz, 1H), 3.38 (s, 3H), 1.39 (d, $J = 6.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN) $\delta$ 206.6, 103.1, 78.5, 75.8, 72.0, 55.7, 18.9.

Spectroscopic data correspond to those reported in literature.$^{13}$

(4$a$R,6$S,7$S,8$a$R)-7-Hydroxy-6-methoxy-2,2-dimethyltetrahydropyrano[3,2-d][1,3]dioxin-8(4$H$)-one (9a).

Isolated as a white solid (29.2 mg, 0.12 mmol, 60%) after column chromatography (5% MeOH in DCM).

$^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 5.08 (d, $J = 4.3$ Hz, 1H), 4.49 (dd, $J = 10.0$, 1.6 Hz, 1H), 4.34 (ddd, $J = 8.4$, 4.2, 1.5 Hz, 1H), 3.92 (m, 2H), 3.72 (td, $J = 9.5$, 6.4 Hz, 1H), 3.51 (d, $J = 8.8$ Hz, 1H), 3.36 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN) $\delta$ 201.1, 104.6, 100.8, 76.2, 76.0, 67.6, 63.4, 56.0, 29.1, 19.3.

Spectroscopic data correspond to those reported in literature.$^{13}$

(2$R,4$a$R,6$S,7$S,8$a$R)-7-hydroxy-6-methoxy-2-phenyltetrahydropyrano[3,2-d][1,3]dioxin-8(4$H$)-one (10a).

Isolated as a white solid (59.8 mg, 0.21 mmol, 60%) after column chromatography (5% MeOH in DCM).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.50 (m, 2H), 7.38-7.36 (m, 3H), 5.58 (s, 1H), 5.17 (d, $J = 4.4$ Hz, 1H), 4.44 – 4.39 (m, 2H), 4.35 (dd, $J = 9.5$, 1.6 Hz, 1H), 4.06 (td, $J = 9.8$, 4.5 Hz, 1H), 3.95 (t, $J = 10.2$ Hz, 1H), 3.46 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.4, 136.4, 129.6, 128.5, 126.5, 103.5, 102.2, 82.2, 75.2, 69.7, 66.1, 56.0.

Spectroscopic data correspond to those reported in literature.$^{14}$

(5$S,8$S,10$S$)-8,10-Dihydroxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]decan-9-one (11a).
Isolated as colorless sticky oil (15.3 mg, 0.08 mmol, 34%) after column chromatography (5% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CD\(_3\)OD) \(\delta\) 4.43 (dd, \(J = 10.6, 7.9, 1\)H), 4.32 (d, \(J = 1.5\) Hz, 1H), 4.19 (d, \(J = 8.8\) Hz, 1H), 4.08-4.03 (m, 2H), 3.70 (t, \(J = 10.5\) Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H).

\(^{13}\text{C NMR}\) (101 MHz, CD\(_3\)OD) \(\delta\) 206.2, 114.0, 109.9, 75.1, 73.1, 66.2, 27.3, 26.1.

\(^{13}\text{C NMR}\) (ESI\(^-\)) calculated for C\(_9\)H\(_{13}\)O\(_6\) ([M-H]\(^{-}\): 217.07176, found: 217.07156.

\((4aR,6R,7S,8aR)-7\text{-Hydroxy-6-methoxy-2,2-dimethyltetrahydropyrano}[3,2-d][1,3]\text{-dioxin-8(4H)}\)-one (13a).

Isolated as white solid (10.3 mg, 0.05 mmol, 21%) after column chromatography (5% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 4.44 (dd, \(J = 10.2, 1.9\) Hz, 1H), 4.35 (d, \(J = 7.4\) Hz, 1H), 4.13 (dd, \(J = 7.5, 1.9\) Hz, 1H), 4.09 (dd, \(J = 11.0, 5.2\) Hz, 1H), 3.96 (t, \(J = 10.4\) Hz, 1H), 3.63 (s, 3H), 3.41 (ddd, \(J = 15.3, 10.2, 5.2\) Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 199.8, 107.2, 100.7, 77.4, 75.4, 68.0, 62.6, 57.9, 28.8, 18.9.

Spectroscopic data correspond to those reported in literature.\(^{13}\)

\(N\-\{(4aR,6S,7S,8aR)-6\text{-Methoxy-2,2-dimethyl-8-oxohexahydropyrano}[3,2-d][1,3]\text{-dioxin-7(7H)}\}\)-yl)acetamide (15a).

Isolated as colorless sticky oil (33.5 mg, 0.12 mmol, 67%) after column chromatography (5% MeOH in DCM).

\(^1\text{H NMR}\) (400 MHz, CD\(_3\)CN) \(\delta\) 6.67 (d, \(J = 8.4\) Hz, 1H), 5.08 (d, \(J = 4.2\) Hz, 1H), 4.86 (ddd, \(J = 8.3, 4.2, 1.4\) Hz, 1H), 4.61 (dd, \(J = 10.1, 1.4\) Hz, 1H), 4.19-3.83 (m, 2H), 3.76 (td, \(J = 10.0, 5.5\) Hz, 1H), 3.34 (s, 3H), 1.95 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H).
\( ^{13}C \text{ NMR} \) (101 MHz, CD\(_3\)CN) \( \delta \) 197.9, 171.0, 103.1, 101.0, 76.7, 67.8, 63.3, 59.9, 56.0, 29.2, 22.7, 19.3.

HRMS (ESI\(^{-}\)) calculated for C\(_{12}\)H\(_{18}\)NO\(_6\) ([M-H]\^-): 272.11396, found: 272.11397.

\( N-((4aR,6S,7S,8aR)-6\text{-isopropoxy-2,2-dimethyl-8-oxohexahydropyrano[3,2-d][1,3]dioxin-7-yl})\text{acetamide (16a).} \)

Isolated as sticky yellow oil (32.8 mg, 0.11 mmol, 33%) after column chromatography (5% MeOH in DCM).

\( ^{1}H \text{ NMR} \) (400 MHz, CD\(_3\)OD) \( \delta \) 5.36 (d, \( J = 4.4 \) Hz, 1H), 4.96 (dd, \( J = 4.5, 1.4 \) Hz, 1H), 4.66 (dd, \( J = 9.6, 1.5 \) Hz, 1H), 4.08-3.97 (m, 1H), 3.96-3.84 (m, 3H), 2.03 (s, 3H), 1.53 (s, 3H), 1.42 (s, 3H), 1.21 (d, \( J = 6.2 \) Hz, 3H), 1.14 (d, \( J = 6.1 \) Hz, 3H).

\( ^{13}C \text{ NMR} \) (101 MHz, CD\(_3\)OD) \( \delta \) 198.6, 173.4, 101.6, 100.8, 77.1, 72.4, 68.3, 63.7, 60.4, 29.1, 23.4, 22.2, 21.5, 19.3.

HRMS (ESI\(^{-}\)) calculated for C\(_{14}\)H\(_{22}\)NO\(_6\) ([M-H]\^-): 300.14526, found: 300.14474.

\( (4aR,4a'R,6R,6'R,7S,7'S,8aR,8a'R)-6,6'-\text{Oxybis(7-hydroxy-2,2-dimethyltetrahydropyrano[3,2-d][1,3]dioxin-8(4\(H\))\text{-one (17a).}} \)

Isolated as white solid (21.4 mg, 0.05 mmol, 42%) after column chromatography (5% MeOH in DCM).

\( ^{1}H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 5.50 (d, \( J = 4.6 \) Hz, 2H), 4.55-4.34 (m, 4H), 4.10 (td, \( J = 10.1, 5.0 \) Hz, 2H), 3.99 (dd, \( J = 10.6, 5.1 \) Hz, 2H), 3.91 (t, \( J = 10.4 \) Hz, 2H), 1.51 (s, 6H), 1.51 (s, 6H).

\( ^{13}C \text{ NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 199.0, 100.7, 98.4, 75.5, 74.1, 67.7, 62.7, 28.7, 19.0

Spectroscopic data correspond to those reported in literature.\(^{13}\)
Figure 2. Crude $^1$H NMR for the oxidation of Me-α-D-glucopyranoside.
Oxidation of sclareolide was conducted as described by Baran et. al. (ref. 10 in the manuscript).

**Figure 3.** Control reaction on sclareolide. (A) representation of the reaction. (B) GCMS trace of the starting material, (C) GCMS trace of the reaction performed in the presence of oxygen, (D) GCMS trace of the reaction performed under oxygen free conditions.
$^{1}H$, $^{13}C$ –NMR and HRMS Spectra of the New Compounds
Found: 369.06079

Calculated: 369.06146

C_{14}H_{18}O_{8}SNa:

\text{C}_{14} \text{H}_{18} \text{O}_{8} \text{S}1 \text{Na}1 

\text{pa Chrg 1}
Found: 272.11397

Calculated: 272.11396
Found: 302.16046

Calculated: 302.16091

C14 H24 NO6:

[50.00-500.00]
Found: 300.14474

Calculated: 300.14526

C 14 H22 NO6:

NHAc

16a
References