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Site-selective Electrochemical Oxidation of Glucosides

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Keywords: Glucosides, site-selective, oxidation.

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.[2] Because of its versatility regarding further modifications,[3] 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.[4] Palladium-catalyzed oxidation[5] and hydrogen atom-transfer (HAT) reactions[6] show a strong preference for the secondary C3 hydroxy group (Scheme 1), and a rationale for this has been provided.[7]

Scheme 1. Site-selective oxidation of methyl-a-D-glucopyranoside (**1**).
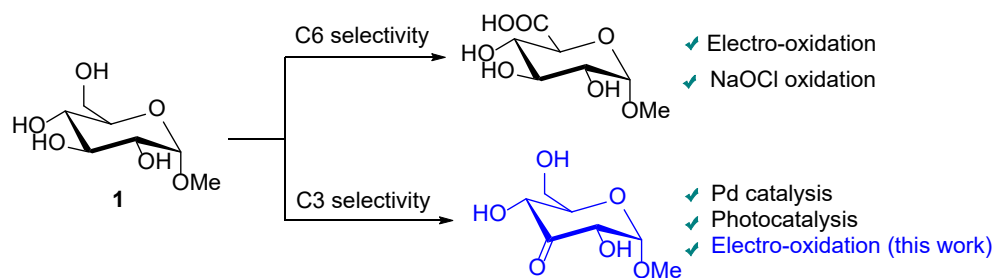
The C3 selective oxidation, in particular the palladium-catalyzed version, has shown to be versatile[8] and scalable,[3] but for many applications a precious metal-free protocol would be a gain. The photochemical oxidation mediated by an organo-sensitizer provides this,[6c, d] and we showed the related photochemical alkylation reaction to be scalable in a flow system.[9]

Baran and co-workers reported on the electrochemical quinuclidine-mediated C-H activation of methylene and methine groups.[10] 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,[11] and Pt and Au based electrodes have mainly been applied.[12] Similar results were obtained under heterogeneous conditions, in which a TEMPO immobilized Nafion perfluorinated film was deposited onto graphite electrodes.[13]

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 (Me$_4$NBF$_4$, 1 eq) and hexafluoro isopropanol (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.
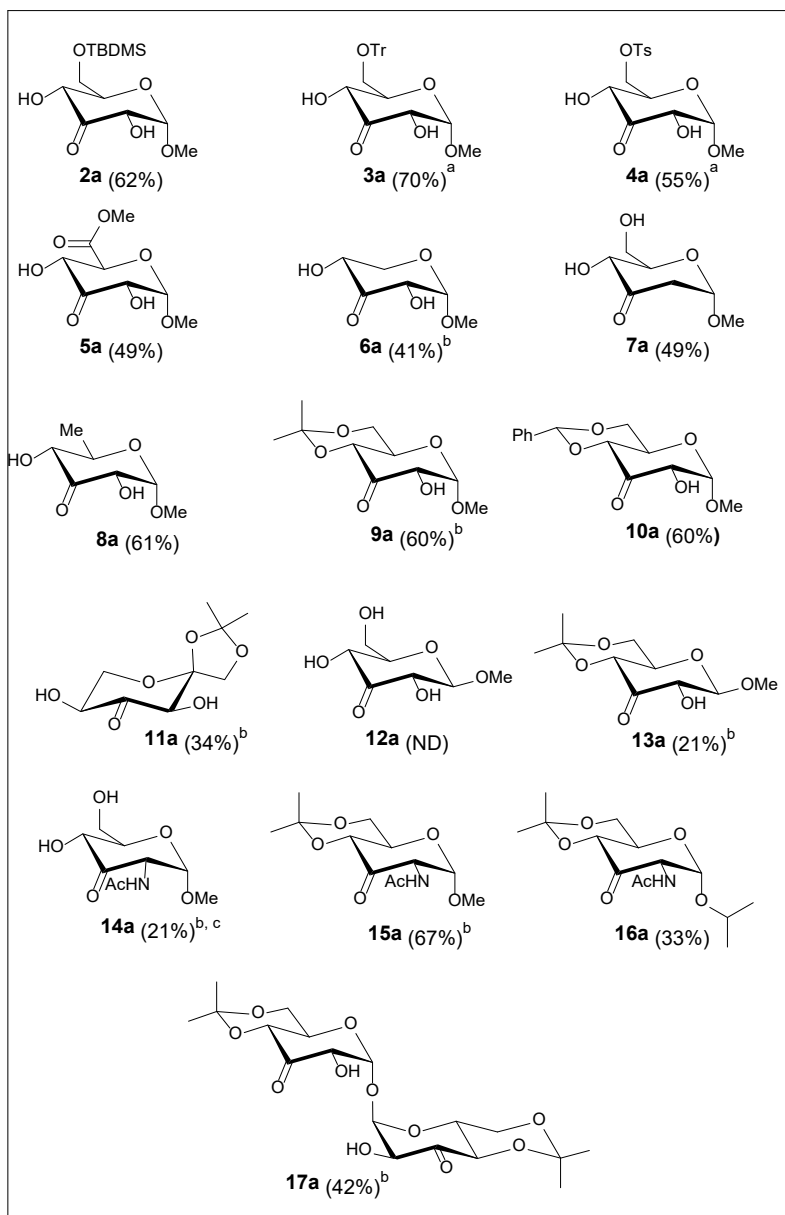
The isolated yield of **1a** after column chromatography was 56%, comparable to the reported yield for the photochemical oxidation reaction.[6c]

Scheme 2: Regioselective electrochemical oxidation of methyl-α-D-glucopyranoside (**1**).
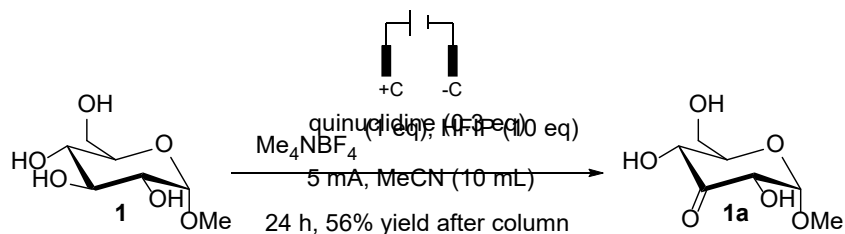
With these first results in hand, we investigated the substrate scope of the oxidation reaction, employing graphite electrodes. In order to facilitate solubility and chromatographic purification, partly protected glycosides were used, leading to the corresponding products in moderate to good yields (Table 1).

Table 1. Scope of the electrochemical oxidation of mono- and disaccharides.
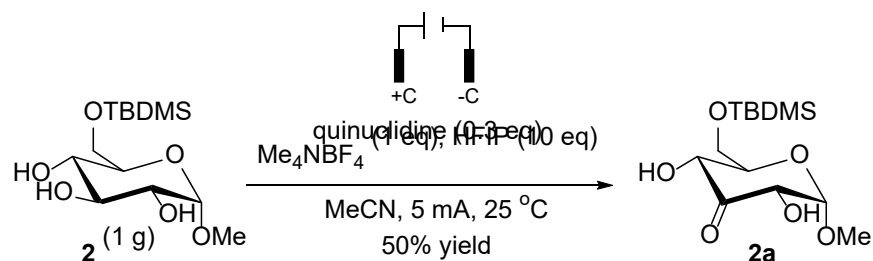
2a (62%)   **3a** (70%)[a]   **4a** (55%)[a]

5a (49%)   **6a** (41%)[b]   **7a** (49%)

8a (61%)   **9a** (60%)[b]   **10a** (60%)

11a (34%)[b]   **12a** (ND)   **13a** (21%)[b]

14a (21%)[b, c]   **15a** (67%)[b]   **16a** (33%)

17a (42%)[b]

Reaction conditions: glycoside (0.32 mmol, 1 eq), quinuclidine (0.3 eq), Me_4NBF_4 (1 eq), HFIP (10 eq), 5 mL ACN, graphite electrodes, 5 mA (constant current, 2.00 mA/cm^2), 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.

Scheme showing conversion of **2** (1 g) bearing OTBDMS, HO, HO, OH, OMe groups to **2a** under conditions: quinuclidine (0.3 eq), HFIP (10 eq), Me$_4$NBF$_4$ (1 eq), MeCN, 5 mA, 25 °C, 50% yield.

In the proposed mechanism, the reaction starts with the formation of the quinuclidinium radical cation (Qu$^{+\bullet}$) 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.[10] 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$^{+\bullet}$, 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.
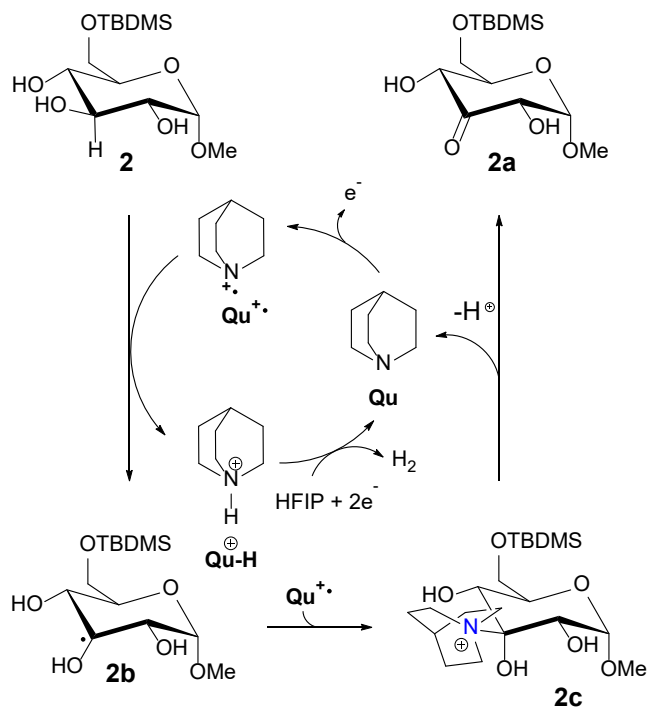
In conclusion, glycopyranosides can be electro-oxidized selectively at the C3 position in a quinuclidine-mediated process, which is highly complementary to the known electrochemical oxidation at C6 mediated by TEMPO. Whereas the quinuclidinium radical cation attacks the weakest C-H bond in a HAT process, 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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Notes

Any additional relevant notes should be placed here.

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Supporting Information

Site-selective electrochemical oxidation of glycosides

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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 CD_3OD, CD_3CN or $CDCl_3$. 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 where synthesized:
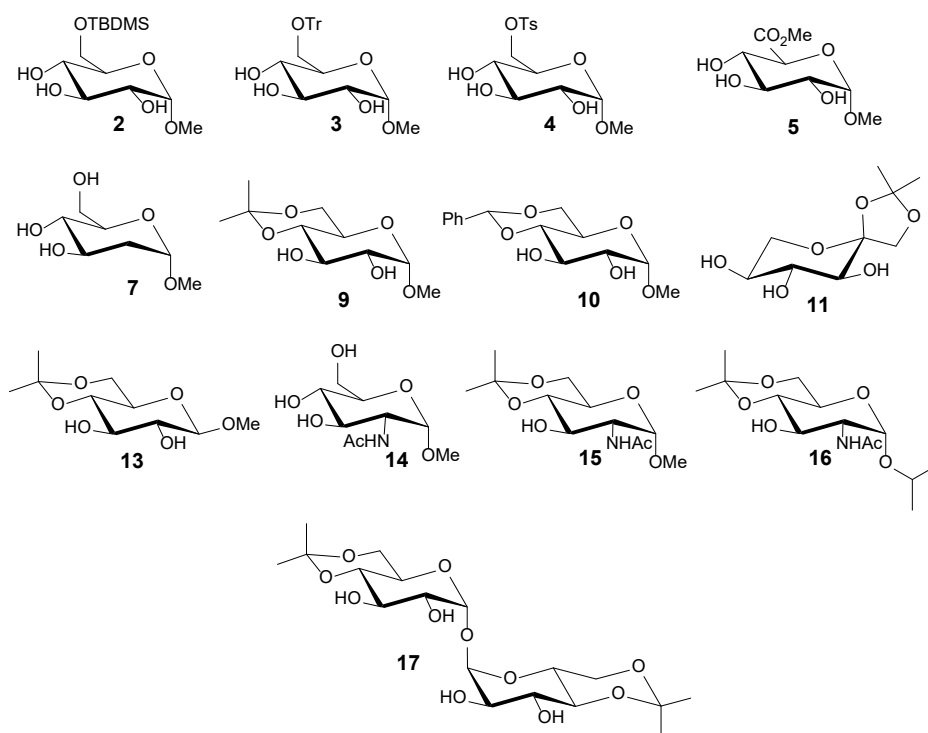
Compounds **1**, **6**, **8** and **12** are commercially available. Compounds **2**,[1] **3**,[2] **4**,[3] **5**,[4] **7**,[5] **9**,[6] **10**,[7] **11**,[8] **13**,[6] **14**,[9] **15**,[10] and **17**[11] were synthesized according to known literature procedures and the characterization data are in full agreement.

Synthesis of compound **16**.
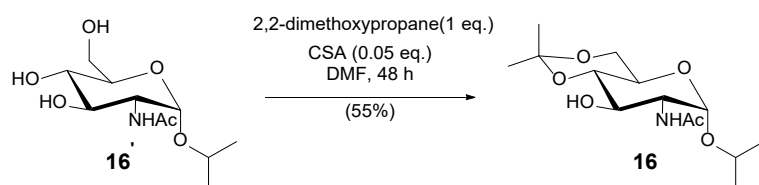
To a stirred solution of compound **16'** in 10 mL DMF were added (*S*)-camphorsulfonic acid (0.01 eq.) and 2,2-dimethoxypropane (1 eq.). The resulting mixture was stirred at room temperature for 48 h, upon which water and EtOAc were added. The resulting phases were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with water (3x), dried over $MgSO_4$ and evaporated under reduced pressure. Compound **16** was isolated upon column chromatography (10/1 DCM : MeOH) as a white solid (55%).

^{1}H-NMR (400 MHz, CD_3OD) 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).

^{13}C-NMR (101 MHz, CD_3OD) 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.

HRMS (ESI⁻) calculated for $C_{14}H_{24}N_1O_6$ ([M-H]⁻): 302.16091, found: 302.16046.

General Procedure for the Regioselective Electrochemical Oxidation

A mixture of starting material (1 equiv.), quinuclidine (0.3 equiv.), Me_4NBF_4 (1 equiv.) and HFIP (10 equiv.) in CH_3CN (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/cm^2). 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.), Me_4NBF_4 (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
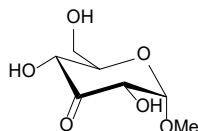
ºC. The resulting mixture was pulverized, loaded on a silica gel column and eluted (5 % MeOH in DCM). The fractions containing the product were combined and the solvent was evaporated in vacuo.

Figure 1. Gram-scale electrochemical oxidation.

Data of the Products

(2*R*,3*R*,5*S*,6*S*)-3,5-Dihydroxy-2-(hydroxymethyl)-6-methoxytetrahydro-4*H*-pyran-4-one (**1a**).


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

¹H NMR (400 MHz, CD$_3$OD) δ 5.05 (d, *J* = 4.2 Hz, 1H), 4.40 (dd, *J* = 4.3, 1.5 Hz, 1H), 4.23 (dd, *J* = 9.7, 1.6 Hz, 1H), 3.88 (dd, *J* = 12.1, 2.2 Hz, 1H), ,3.83-3.73 (m, 1H) 3.65 (ddd, J = 9.8, 4.7, 2.2 Hz, 1H), 3.40 (s, 3H).

¹³C NMR (101 MHz, CD$_3$OD) δ 207.0, 103.8, 76.7, 76.1, 73.3, 62.5, 55.7.

Spectroscopic data correspond to those reported in literature.[12]

(2*R*,3*R*,5*S*,6*S*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,5-dihydroxy-6-methoxytetrahydro-4*H*-pyran-4-one (**2a**).
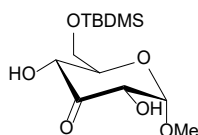
Isolated as a white solid (62 mg, 0.20 mmol, 62%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD$_3$CN) δ 5.03 (d, *J* = 4.3 Hz, 1H), 4.34 (dd, *J* = 4.3, 1.6 Hz, 1H), 4.23 (dd, *J* = 9.7, 1.6 Hz, 1H), 4.03-3.81 (m, 2H), 3.54 (ddd, *J* = 9.7, 4.2, 2.1 Hz, 1H), 3.34 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

¹³C NMR (101 MHz, CD$_3$CN) δ 207.3, 103.2, 76.6, 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]

(2*S*,3*S*,5*R*,6*R*)-3,5-Dihydroxy-2-methoxy-6-((trityloxy)methyl)tetrahydro-4*H*-pyran-4-one (**3a**).
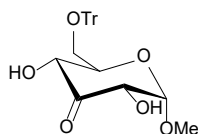
Reaction was run on 0.46 mmol scale. Isolated as white solid (118 mg, 0.32 mmol, 70%) after column chromatography (5% MeOH in DCM).

^{1}H NMR (400 MHz, CD$_3$CN) δ 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).

^{13}C NMR (101 MHz, CD$_3$CN) δ 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.[13]

((2R,3R,5S,6S)-3,5-Dihydroxy-6-methoxy-4-oxotetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (**4a**).
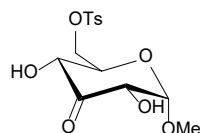
Reaction was run on 0.57 mmol scale. Isolated as a yellow sticky oil (105 mg, 0.30 mmol, 53%) after column chromatography (3% MeOH in DCM).

^{1}H NMR (400 MHz, CD$_3$OD) δ 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).

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

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

Methyl (2S,3R,5S,6S)-3,5-Dihydroxy-6-methoxy-4-oxotetrahydro-2H-pyran-2-carboxylate (**5a**).
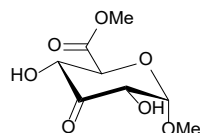
Isolated as a white solid (24.3 mg, 0.11 mmol, 49%) after column chromatography (10% MeOH in DCM).

^{1}H NMR (400 MHz, CD$_3$CN) δ 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).

^{13}C NMR (101 MHz, CD$_3$CN) δ 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]

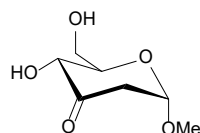(2*S*,3*S*,5*R*)-3,5-Dihydroxy-2-methoxytetrahydro-4*H*-pyran-4-one (**6a**).
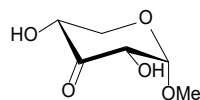
Isolated as a white solid (20.2 mg, 0.12 mmol, 41%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD₃OD) δ 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).

¹³C NMR (101 MHz, CD₃OD) δ 206.6, 104.4, 76.3, 73.1, 65.2, 55.7.

Spectroscopic data correspond to those reported in literature.[13]

(2*R*,3*R*,6*S*)-3-Hydroxy-2-(hydroxymethyl)-6-methoxytetrahydro-4*H*-pyran-4-one (**7a**).

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

¹H NMR (400 MHz, CD₃OD) δ 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).

¹³C NMR (101 MHz, CD₃OD) δ 207.3, 101.2, 76.4, 74.1, 62.6, 55.0, 46.6.

Spectroscopic data correspond to those reported in literature.[13]

(2*S*,3*S*,5*R*,6*R*)-3,5-dihydroxy-2-methoxy-6-methyltetrahydro-4*H*-pyran-4-one (**8a**).
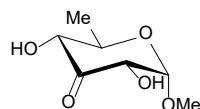
Isolated as a colorless sticky oil (60.2 mg, 0.34 mmol, 61%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD₃CN) δ 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).
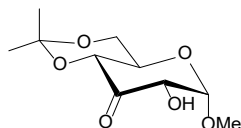
The spectrum was also recorded in CD₃OD.

¹H NMR (400 MHz, CD₃OD) δ 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).

¹³C NMR (101 MHz, CD₃CN) δ 206.6, 103.1, 78.5, 75.8, 72.0, 55.7, 18.9.

Spectroscopic data correspond to those reported in literature.[13]

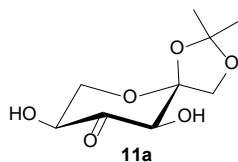(4a*R*,6*S*,7*S*,8a*R*)-7-Hydroxy-6-methoxy-2,2-dimethyltetrahydropyrano[3,2-d][1,3]dioxin-8(4*H*)-one (**9a**).

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

¹H NMR (400 MHz, CD₃CN) δ 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).

¹³C NMR (101 MHz, CD₃CN) δ 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*,4a*R*,6*S*,7*S*,8a*R*)-7-hydroxy-6-methoxy-2-phenyltetrahydropyrano[3,2-d][1,3]dioxin-8(4*H*)-one (**10a**).
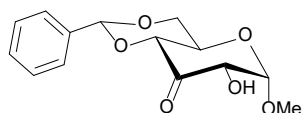
Isolated as a white solid (59.8 mg, 0.21 mmol, 60%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CDCl₃) δ 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).

¹³C NMR (101 MHz, CDCl₃) δ 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**).

11a

Isolated as colorless sticky oil (15.3 mg, 0.08 mmol, 34%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD₃OD) δ 4.43 (dd, J = 10.6, 7.9, 1H), 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).

¹³C NMR (101 MHz, CD₃OD) δ 206.2, 114.0, 109.9, 75.1, 73.1, 66.2, 27.3, 26.1.

HRMS (ESI⁻) calculated for $C_9H_{13}O_6$ ([M-H]⁻): 217.07176, found: 217.07156.

(4a*R*,6*R*,7*S*,8a*R*)-7-Hydroxy-6-methoxy-2,2-dimethyltetrahydropyrano[3,2-d][1,3]dioxin-8(4*H*)-one (**13a**).
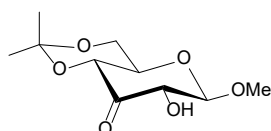
Isolated as white solid (10.3 mg, 0.05 mmol, 21%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CDCl₃) δ 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).

¹³C NMR (101 MHz, CDCl₃) δ 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*-((4a*R*,6*S*,7*S*,8a*R*)-6-Methoxy-2,2-dimethyl-8-oxohexahydropyrano[3,2-d][1,3]dioxin-7-yl)acetamide (**15a**).
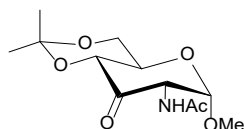
Isolated as colorless sticky oil (33.5 mg, 0.12 mmol, 67%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD₃CN) δ 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).

¹³C NMR (101 MHz, CD₃CN) δ 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-((4a*R*,6*S*,7*S*,8a*R*)-6-isopropoxy-2,2-dimethyl-8-oxohexahydropyrano[3,2-d][1,3]dioxin-7-yl)acetamide (**16a**).
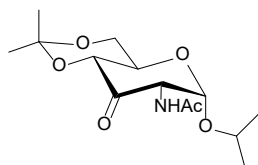

Isolated as sticky yellow oil (32.8 mg, 0.11 mmol, 33%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CD₃OD) δ 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).

¹³C NMR (101 MHz, CD₃OD) δ 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.

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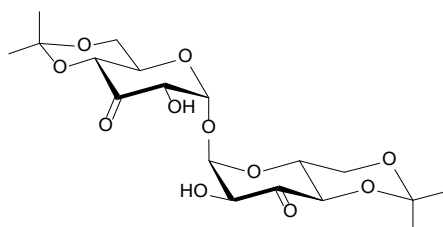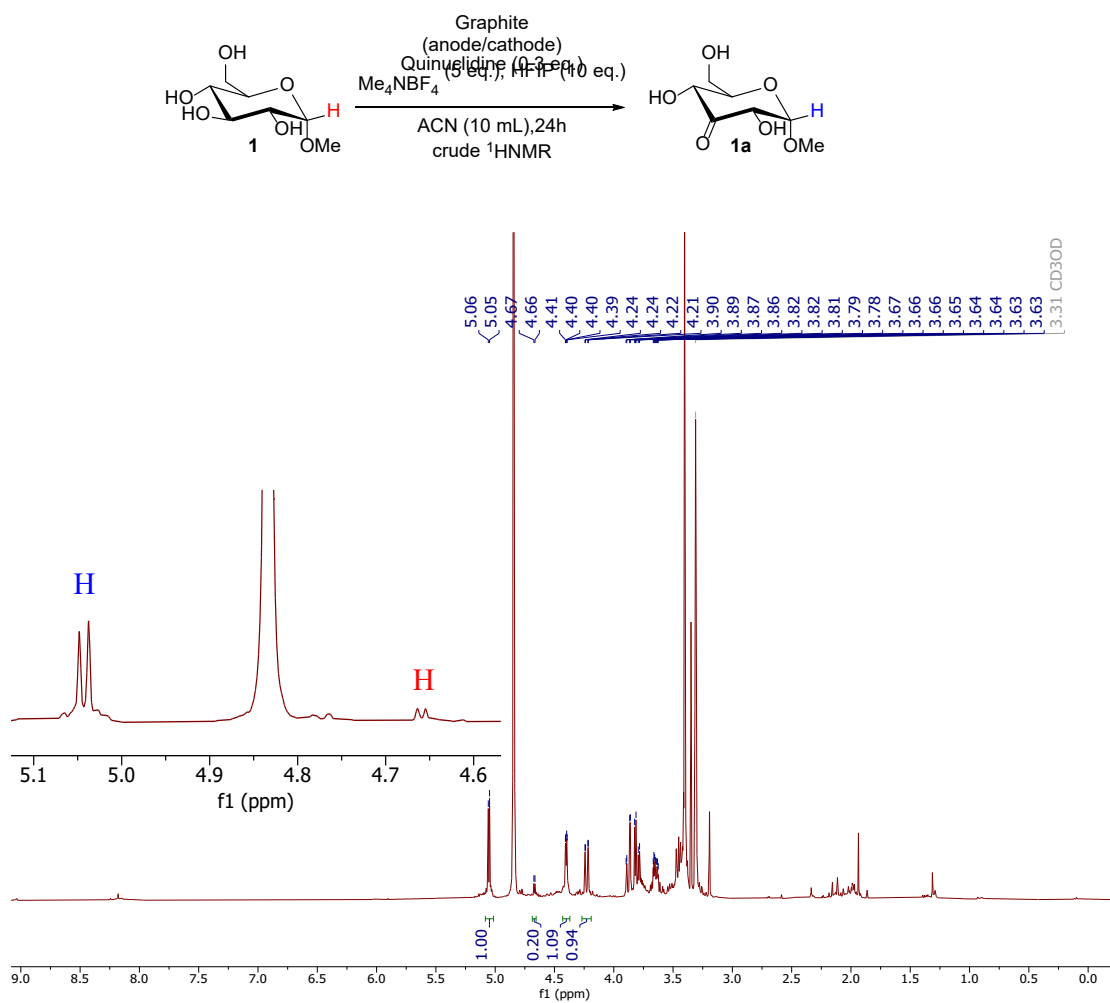

Isolated as white solid (21.4 mg, 0.05 mmol, 42%) after column chromatography (5% MeOH in DCM).

¹H NMR (400 MHz, CDCl₃) δ 5.50 (d, *J* = 4.6, 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).

¹³C NMR (101 MHz, CDCl₃) δ 199.0, 100.7, 98.4, 75.5, 74.1, 67.7, 62.7, 28.7, 19.0

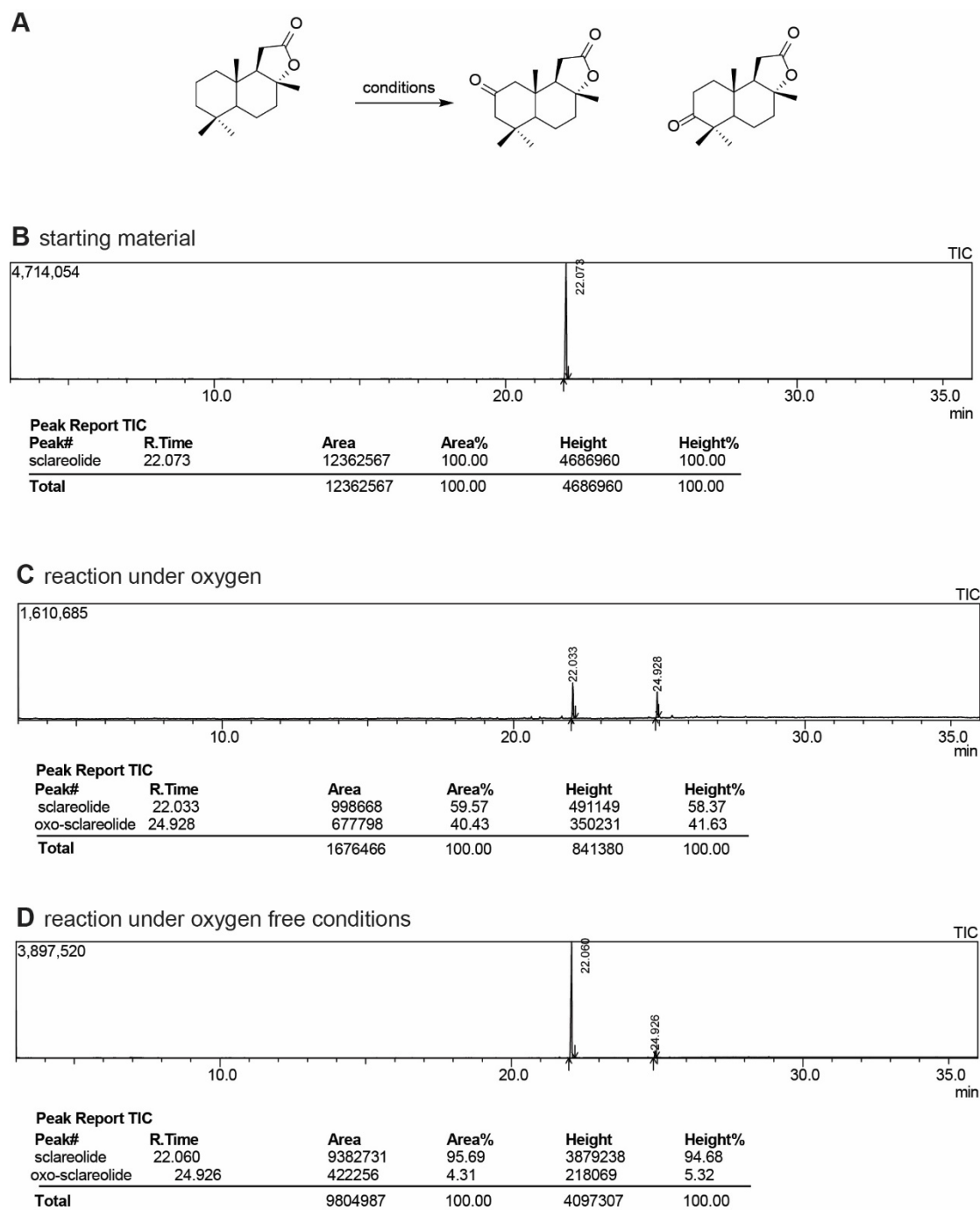Spectroscopic data correspond to those reported in literature.[13]

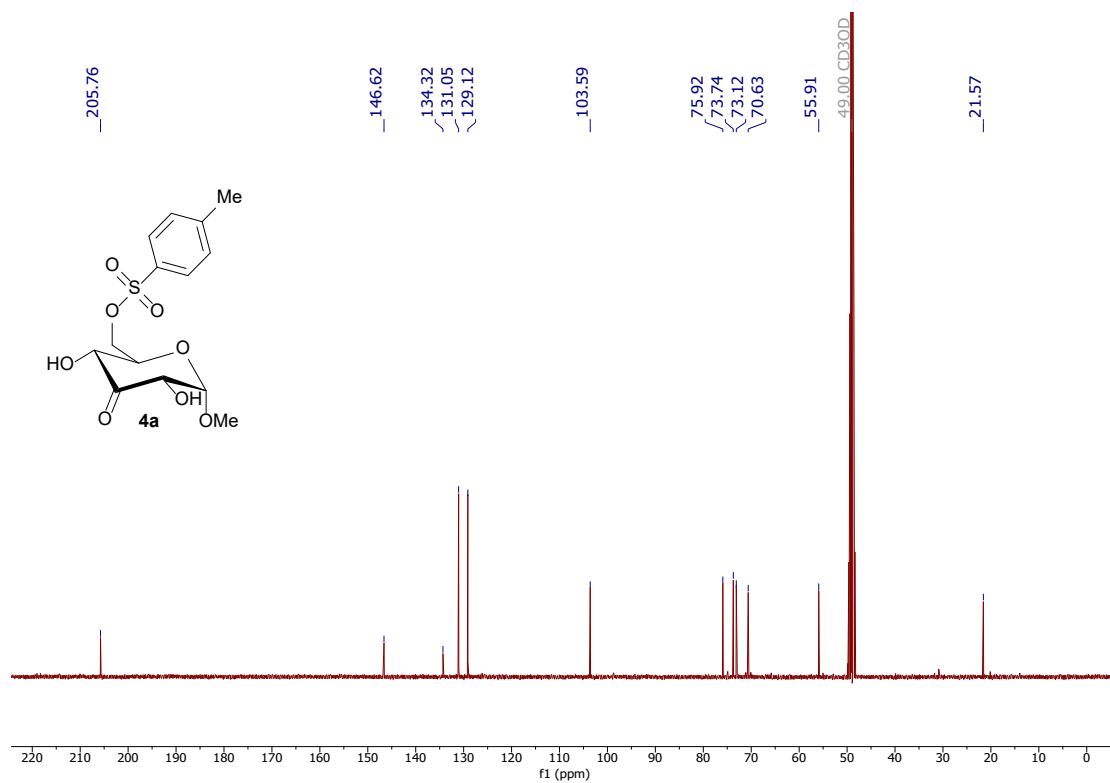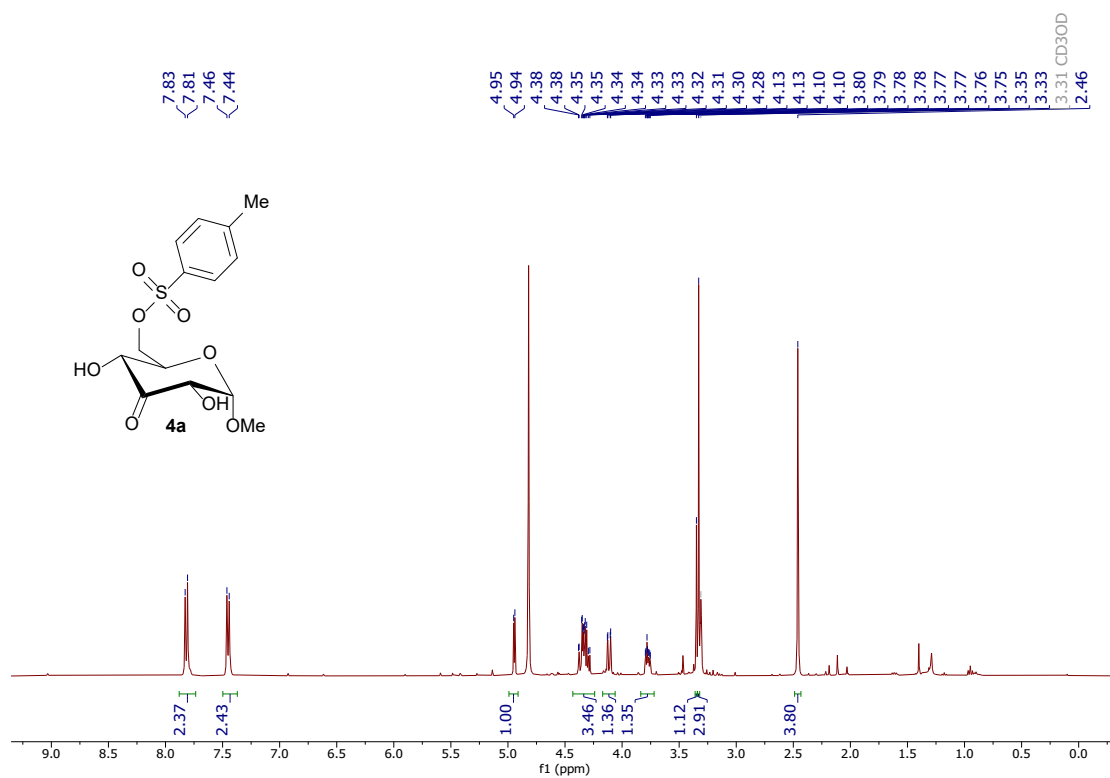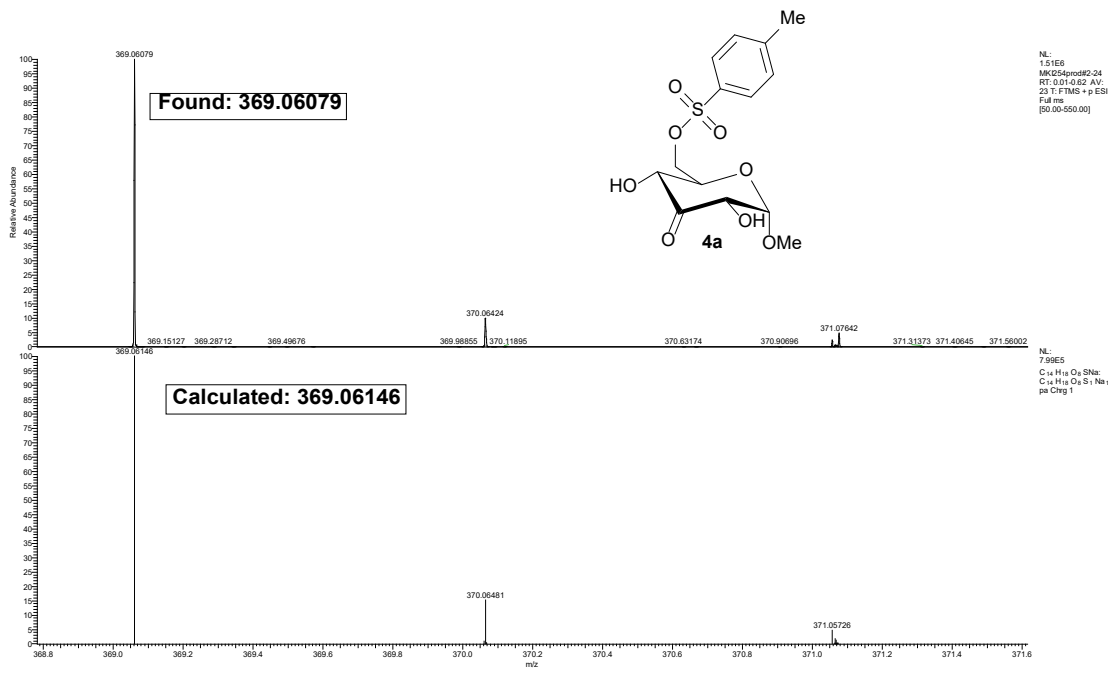**Figure 2.** Crude ¹H NMR for the oxidation of Me-α-D-glucopyranoside.

Oxidation of sclareolide was conducted as described by Baran et. al. (ref. 10 in the manuscript).

A

B starting material

Peak Report TIC

Peak#	R.Time	Area	Area%	Height	Height%
sclareolide	22.073	12362567	100.00	4686960	100.00
Total		12362567	100.00	4686960	100.00

C reaction under oxygen

Peak Report TIC

Peak#	R.Time	Area	Area%	Height	Height%
sclareolide	22.033	998668	59.57	491149	58.37
oxo-sclareolide	24.928	677798	40.43	350231	41.63
Total		1676466	100.00	841380	100.00

D reaction under oxygen free conditions

Peak Report TIC

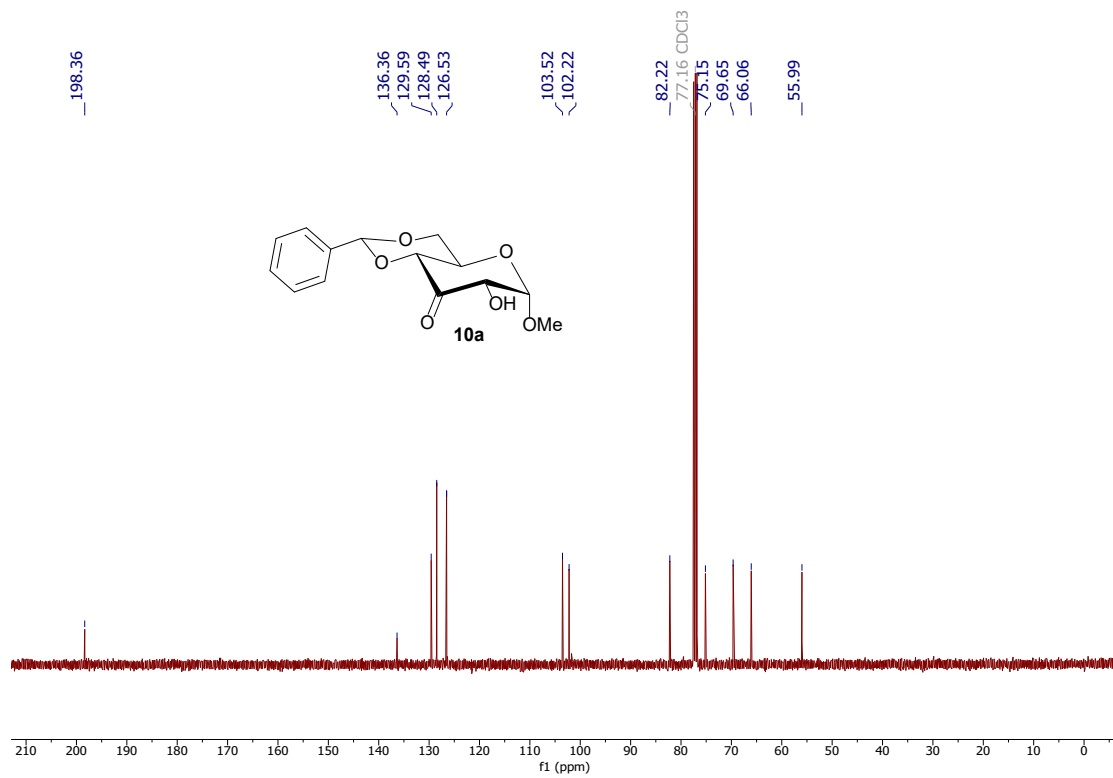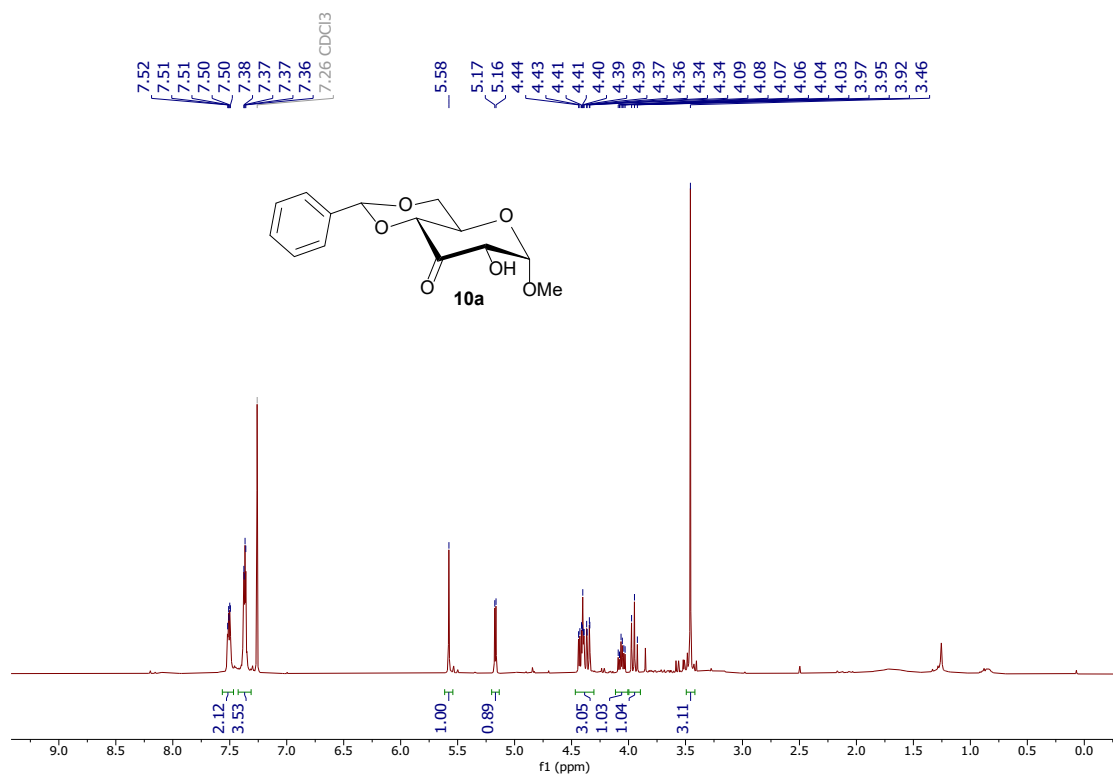| Peak#	R.Time	Area	Area%	Height	Height%
sclareolide	22.060	9382731	95.69	3879238	94.68
oxo-sclareolide	24.926	422256	4.31	218069	5.32
Total		9804987	100.00	4097307	100.00

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.
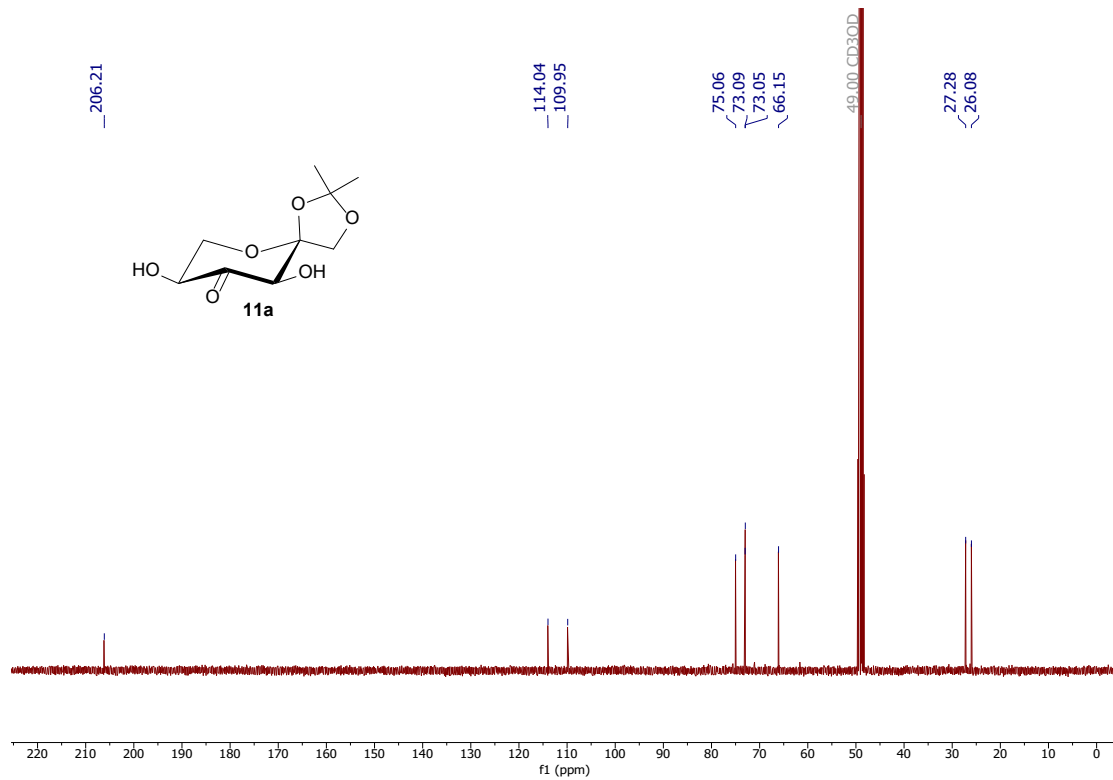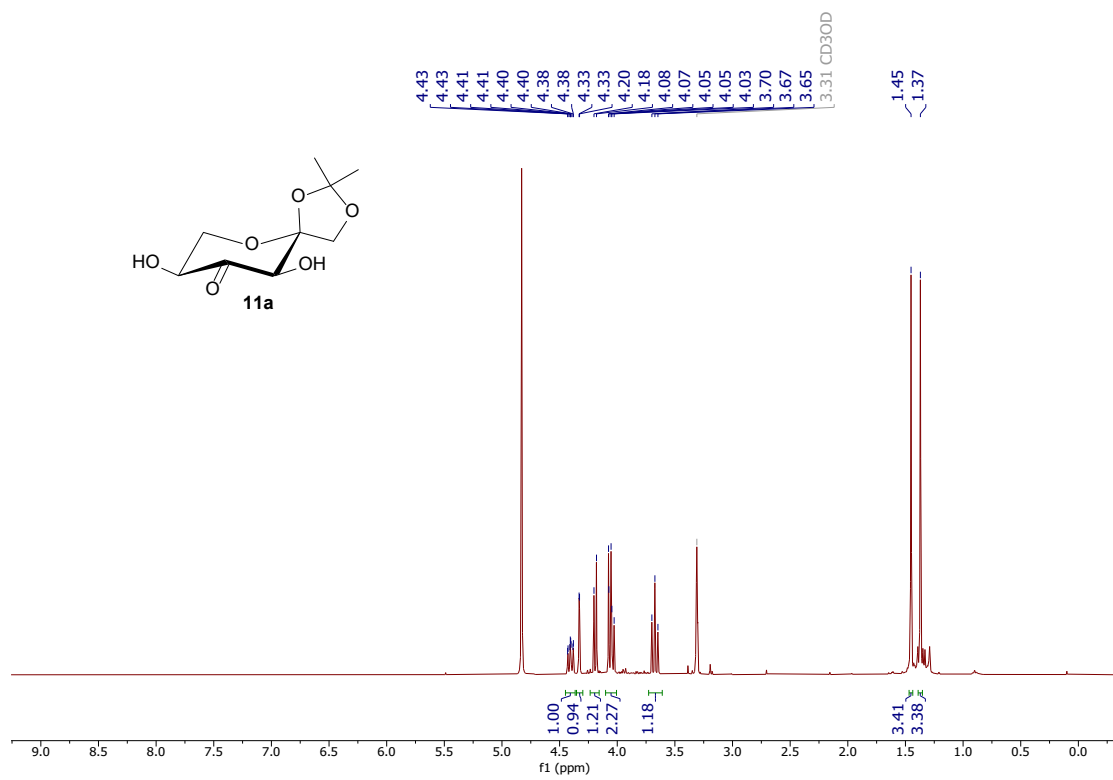
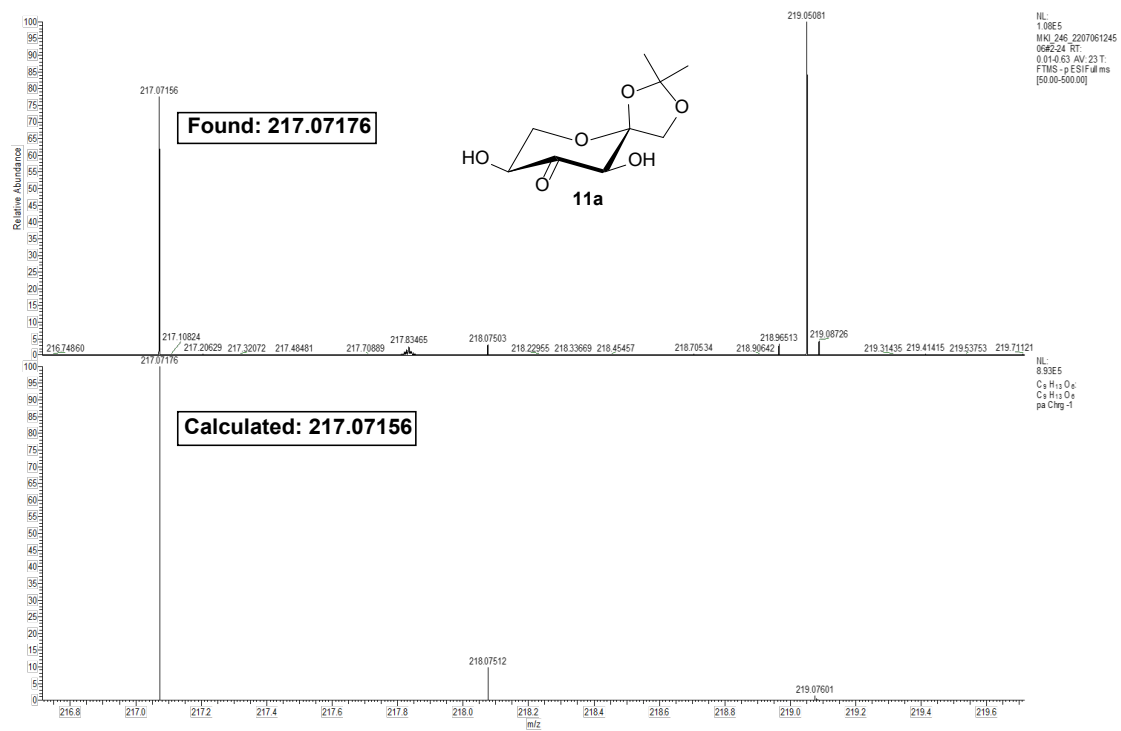# ¹H, ¹³C –NMR and HRMS Spectra of the New Compounds

Found: 369.06079

Calculated: 369.06146

Found: 217.07176
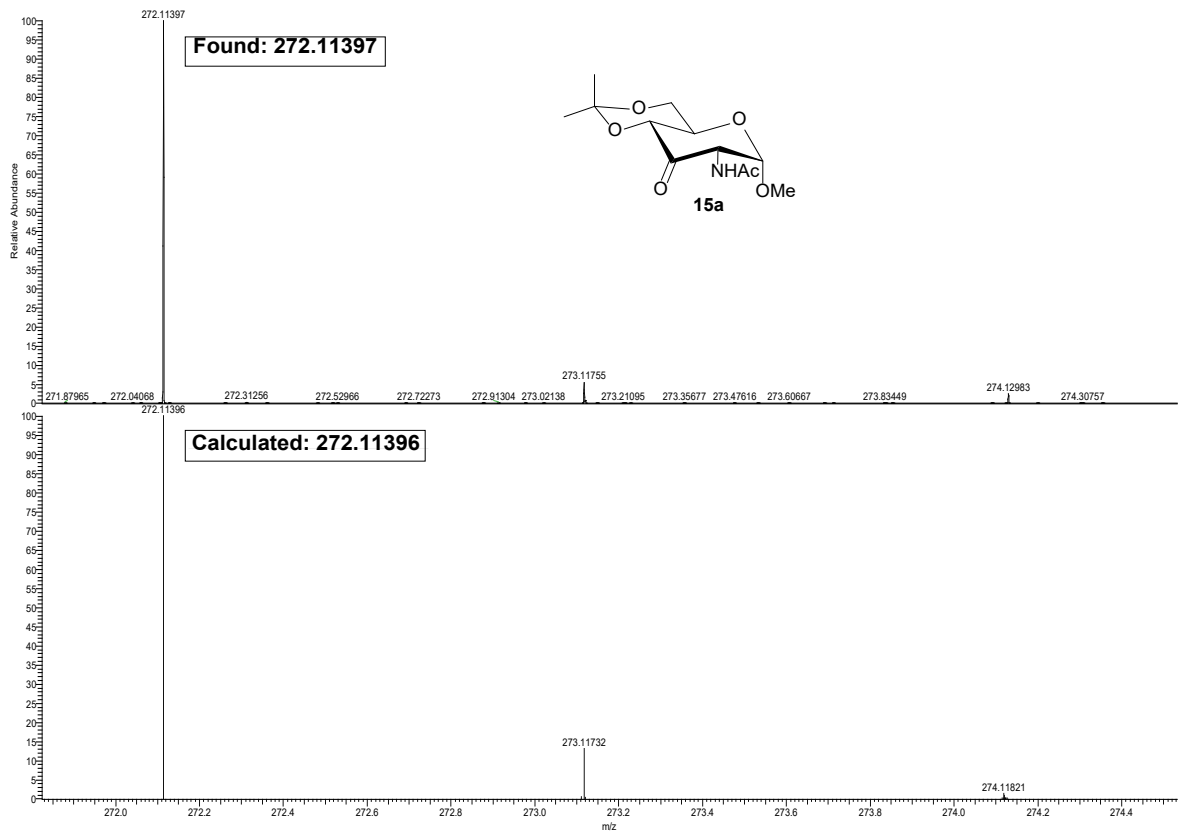
Calculated: 217.07156
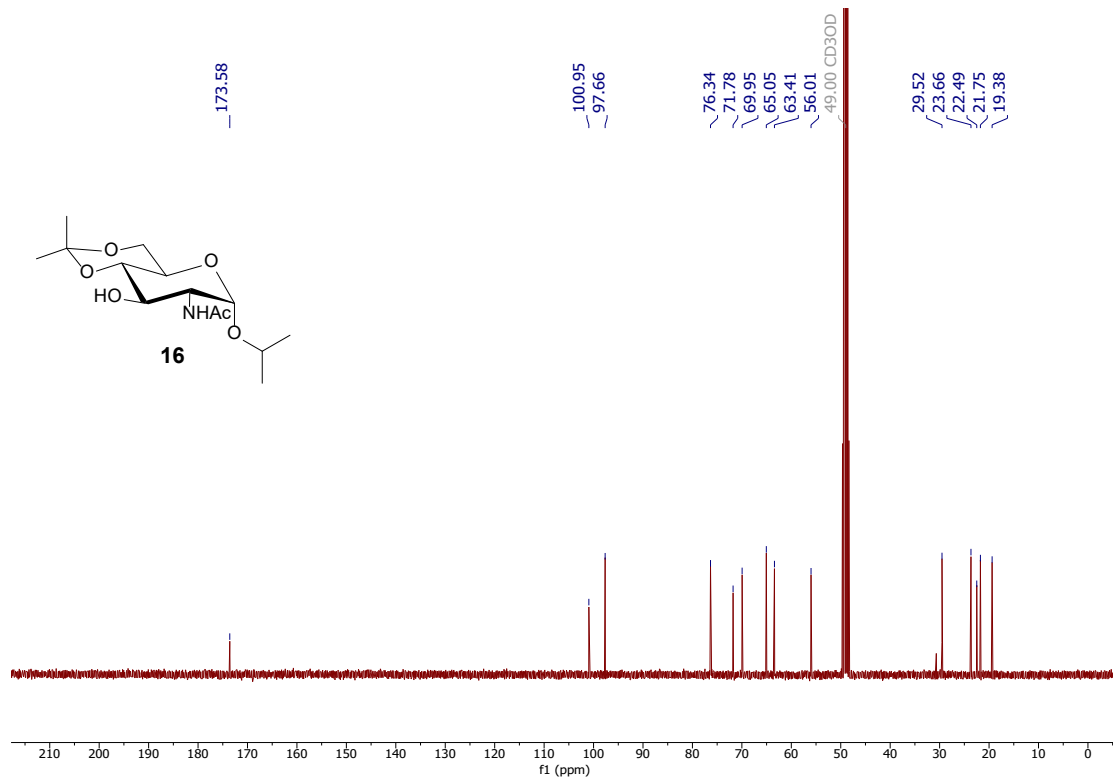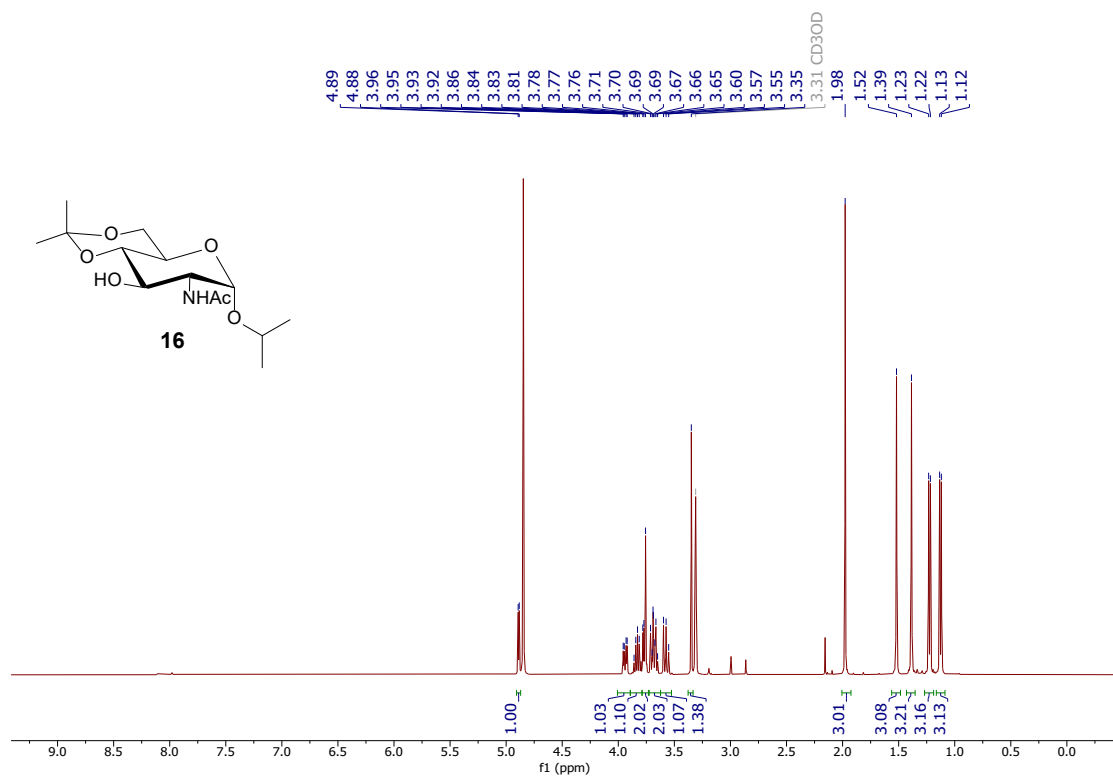
Found: 272.11397

Calculated: 272.11396

15a
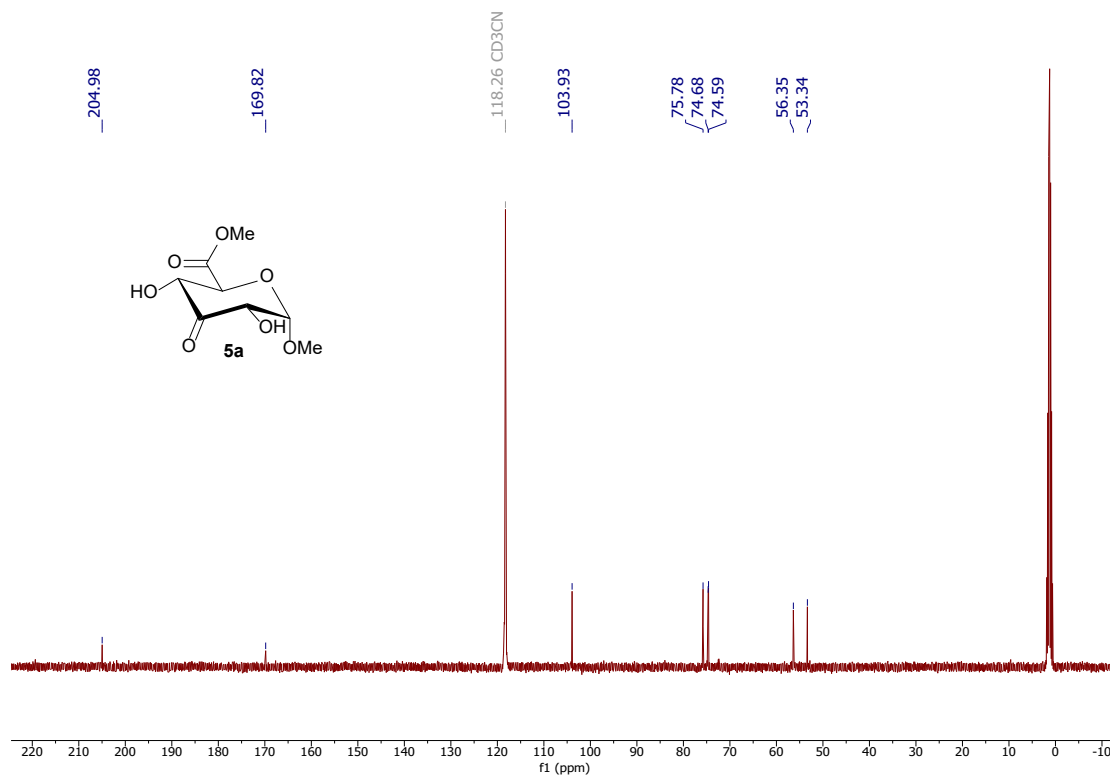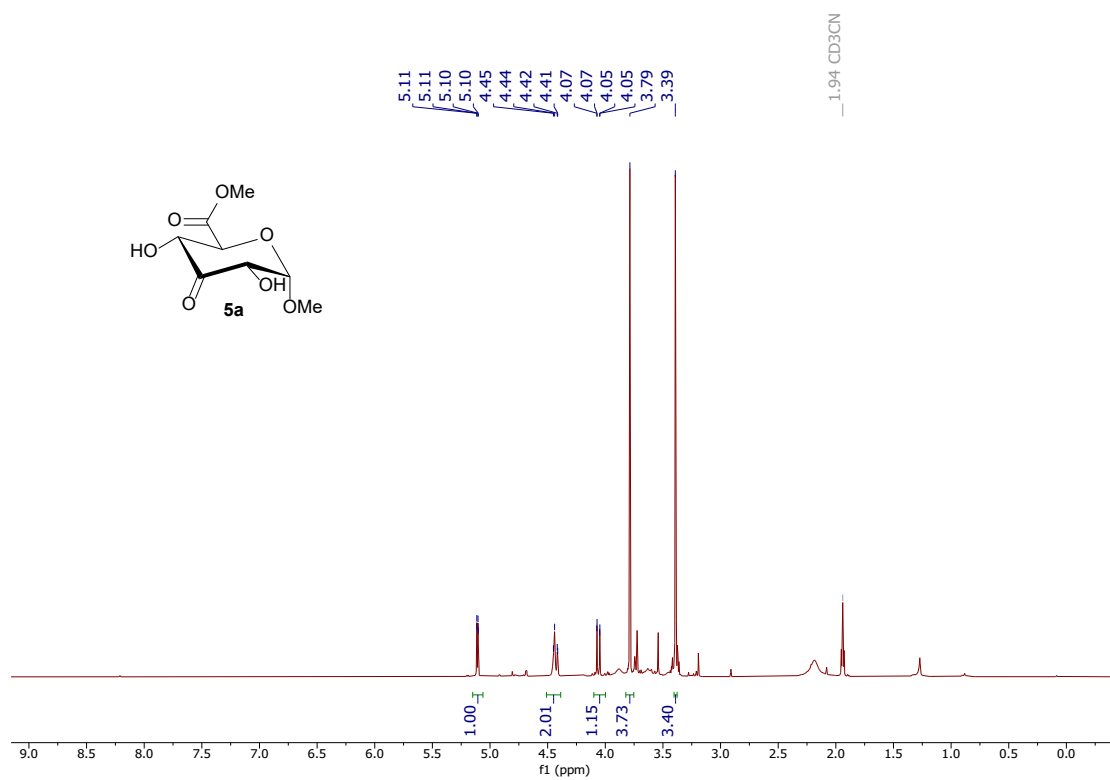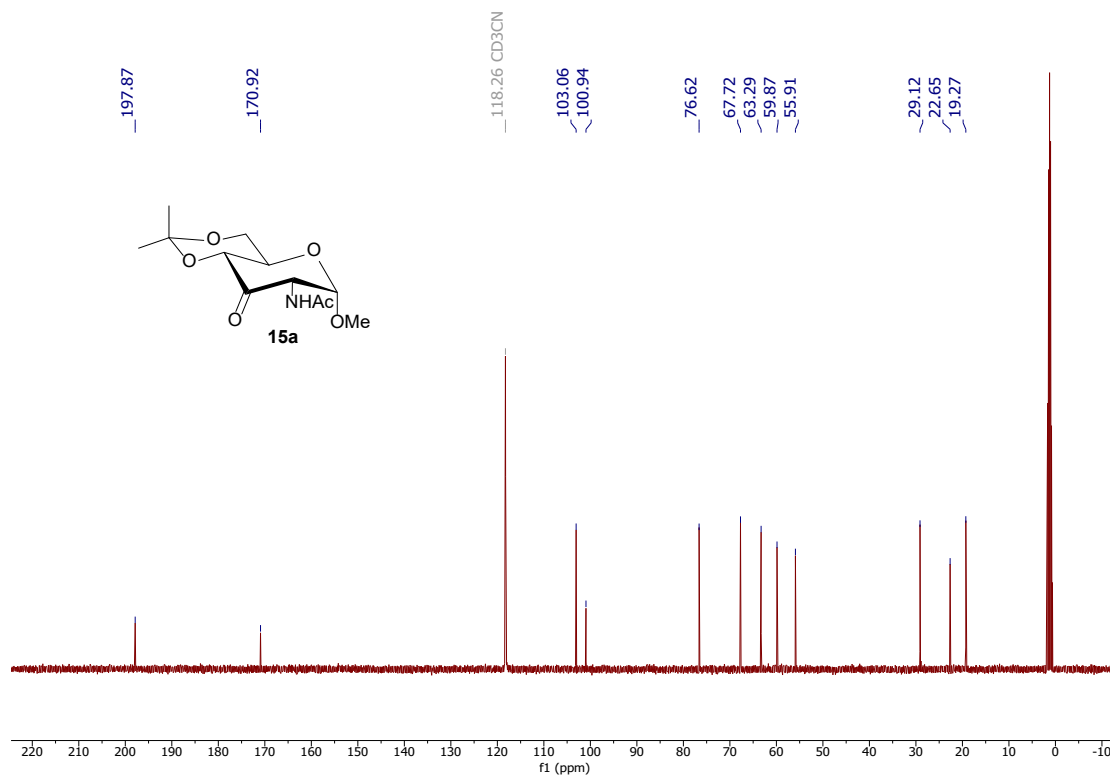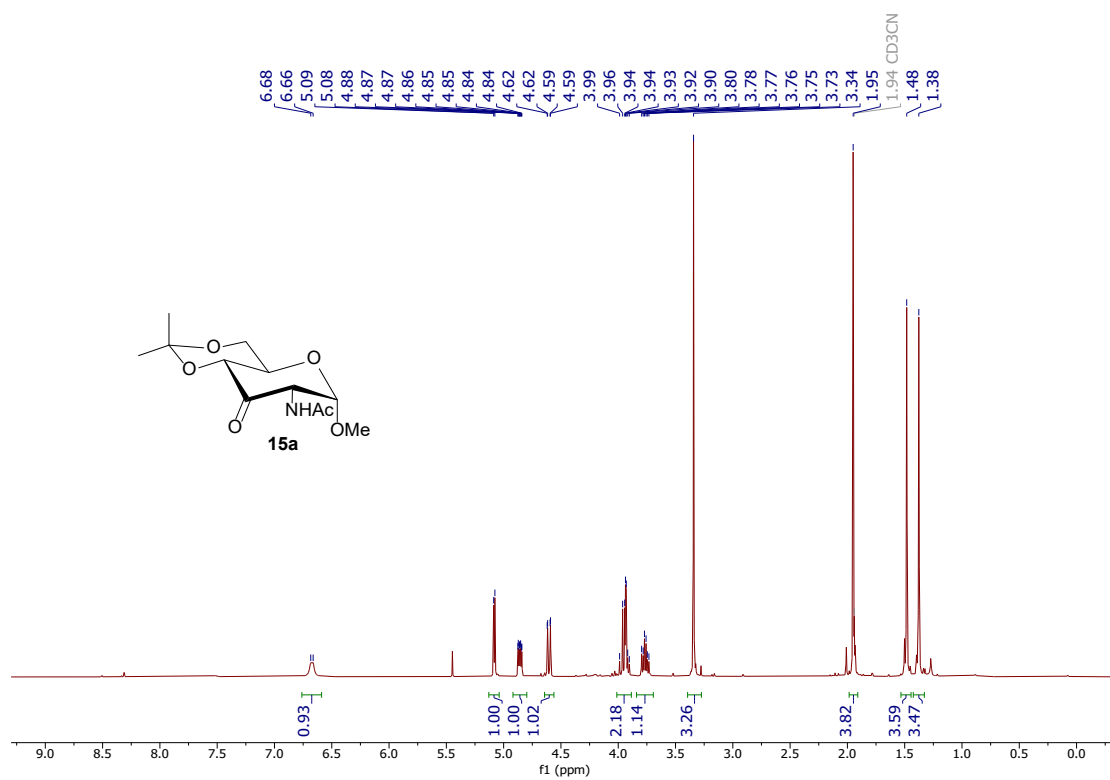
NL:
2.89E5
MK269_2207061239
3C#2-24 RT:
0.01-0.63 AV: 23 T:
FTMS - p ESI Full ms
[50.00-500.00]

272.11397

273.11755

274.12983

271.87965 272.04068 272.31256 272.52966 272.72273 272.91304 273.02138 273.21095 273.35677 273.47616 273.60667 273.83449 274.30757

NL:
8.61E5
C$_{12}$H$_{18}$NO$_6$:
C$_{12}$H$_{18}$N$_1$O$_6$
pa Chrg -1

272.11396

273.11732

274.11821

m/z

Found: 302.16046

Calculated: 302.16091

16

Found: 300.14474

Calculated: 300.14526

16a

300.14474

302.16049

301.14807

299.88053 300.24008 300.53842 300.94882 301.09876 301.27951 301.44090 301.67404 301.88417 302.12643 302.26733 302.43120

300.14526

301.14862

302.14951

Relative Abundance

m/z
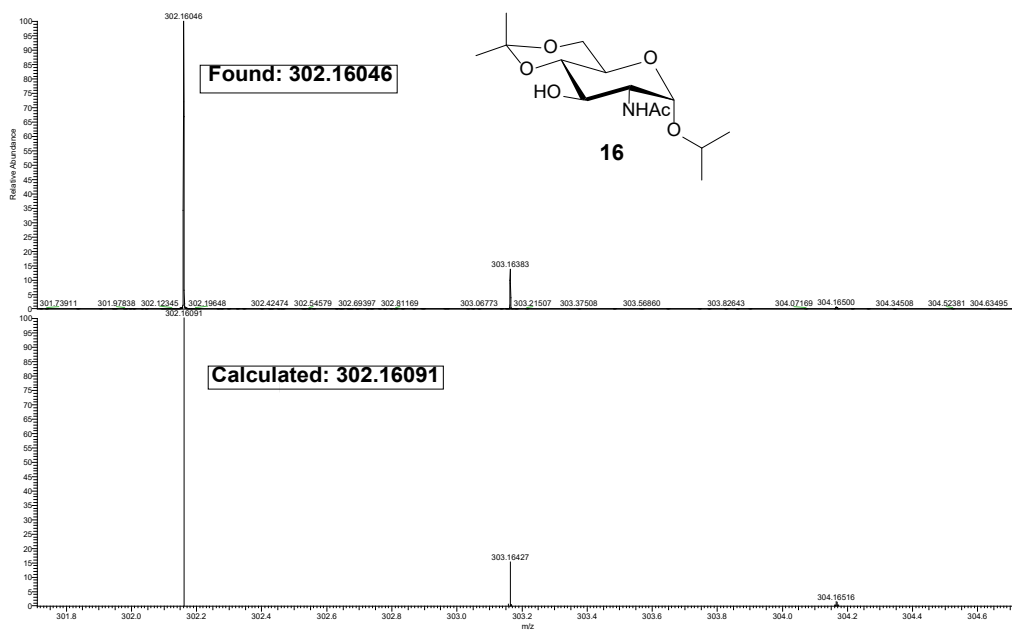
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8#2-24 RT: 0.01-0.63
AV: 23 T: FTMS - p
ESI Full ms
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$C_{14} H_{22} N_1 O_6$
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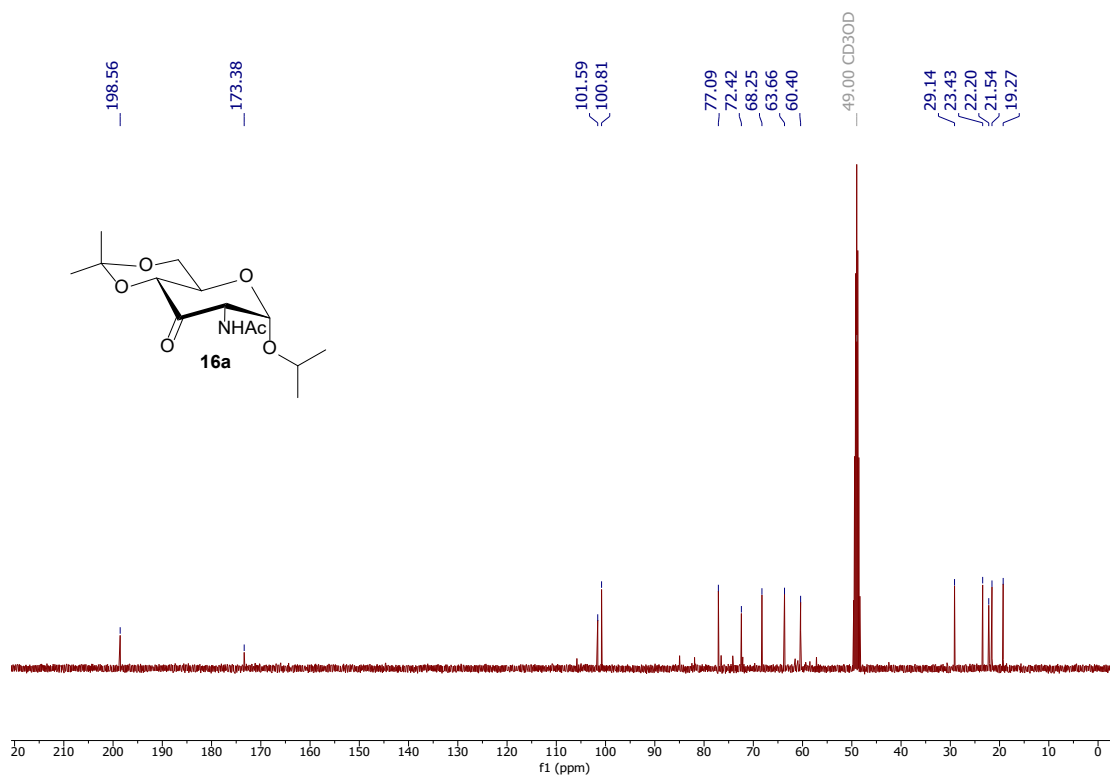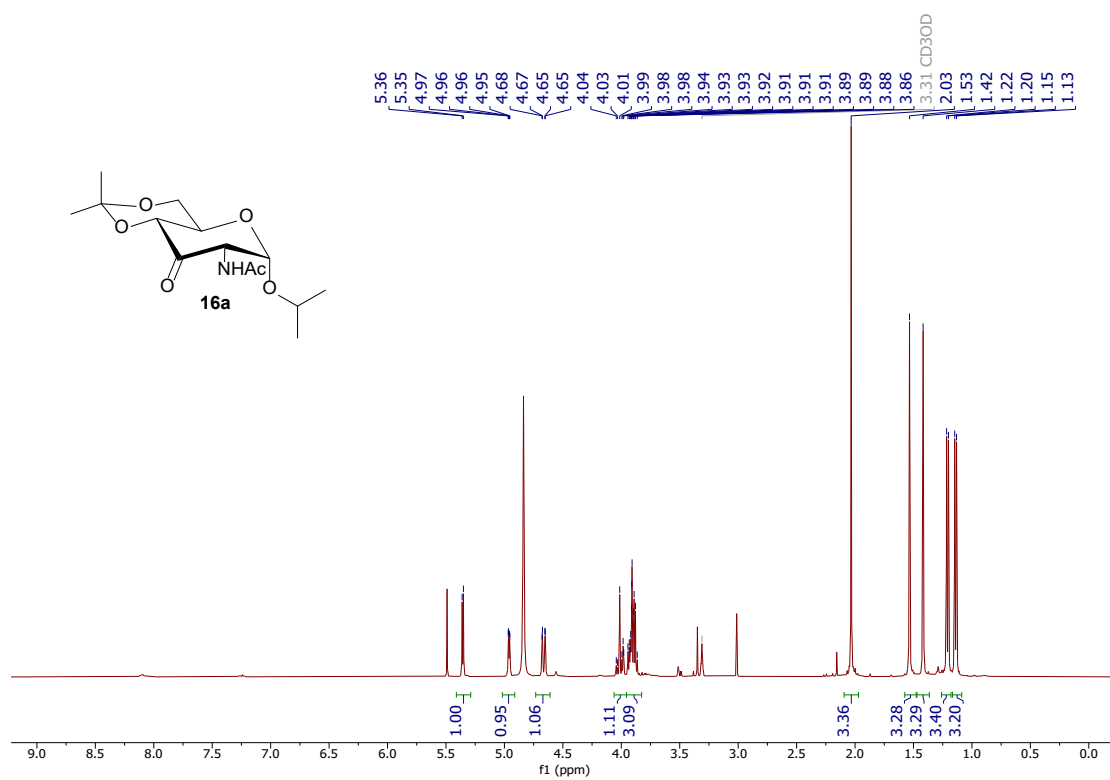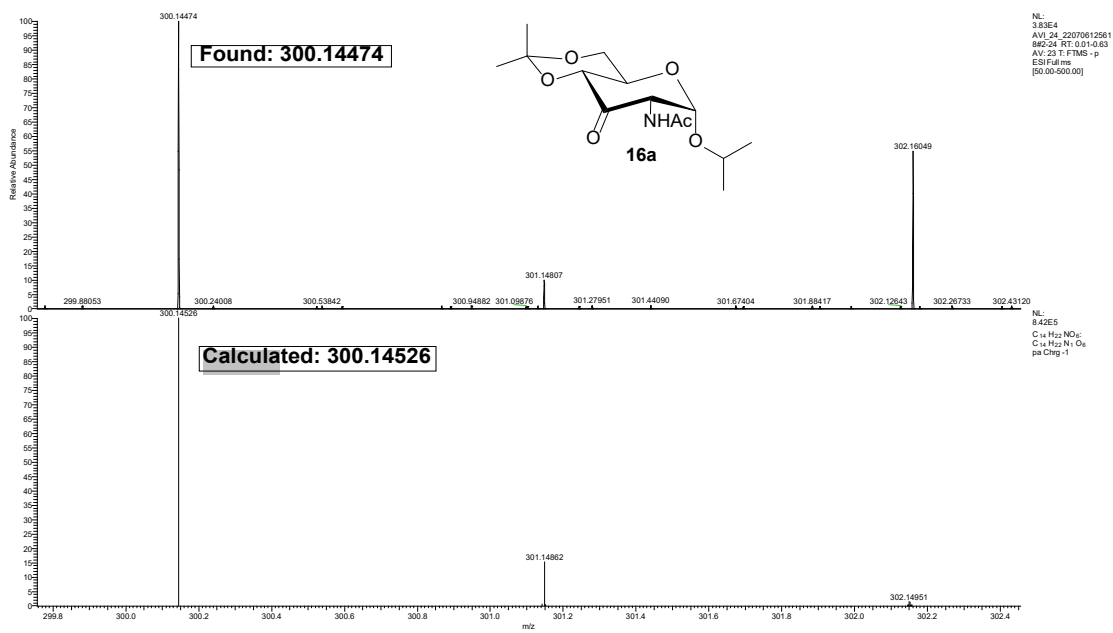
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