Organic Syntheses

Visible-light-mediated Oxidative Debenzylation of 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose

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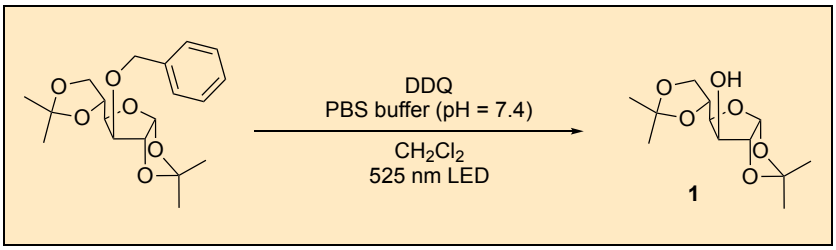

Procedure (Note 1)

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (***1***). An oven-dried, single-necked side-armed Schlenk tube (250 mL, 23 x 4.5 cm) equipped with a football-shaped Teflon-coated magnetic stir bar (2.5 cm) is charged sequentially with 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose (4.0 g, 11.4 mmol, 1 equiv) (Note 2) and dichloromethane (200 mL, 57 mM) (Note 3). Under ambient atmosphere, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3.12 g, 13.6 mmol, 1.2 equiv) (Note 4) and PBS buffer (0.2 mL, 0.1%$_{vol}$, pH 7.4) (Note 5) are added, and the flask is sealed with a rubber septum (Figure 1B). The reaction mixture is irradiated using two green LED lamps (525 nm) (Note 6) at full power while stirring at 1400 rpm (Figure 1C).

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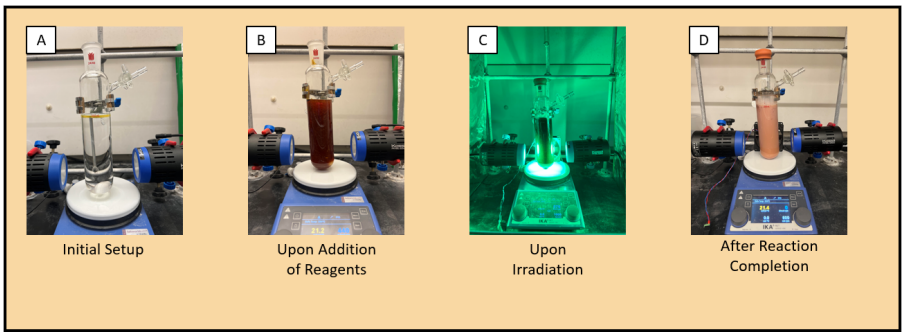


Figure 1. (A) Reaction mixture before addition of DDQ; (B) Reaction mixture after addition of DDQ; (C) Reaction mixture during irradiation; (D) Reaction mixture after the reaction (photos provided by checkers)

The reaction progress is monitored by TLC analysis (Figure 2) (Note 7), taking samples (ca. 50 μL) of the crude mixture with a syringe through the rubber septum.

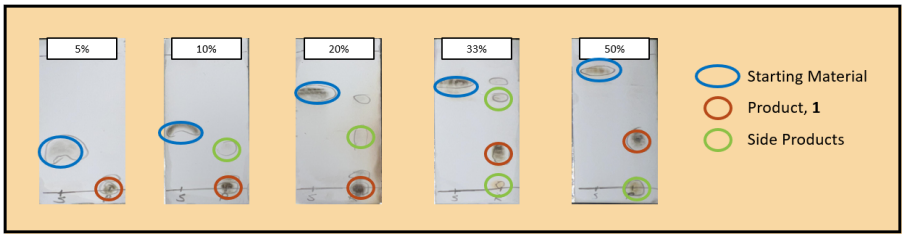


Figure 2. TLC analysis of pure starting material and reaction mixture using different percentages of ethyl acetate in *n*-hexane as mobile phase after 12 h; TLCs are stained with 10%$_{vol}$ H_2SO_4 in ethanol followed by heating (photos provided by checkers)

After 12 h (Figure 1D), TLC analysis of the reaction mixture indicates the starting material is almost completely consumed and only small amounts of undesired side-products are formed (Figure 2). The reaction mixture is vacuum filtered through a plug of celite (25 g) (Note 8) contained in a fritted funnel (7 x 6 cm) and collected in a 1000 mL Erlenmeyer flask (Figure 3A). The reaction flask is washed with CH_2Cl_2 (3 x 50 mL), which is passed through the celite bed, and the filtrate is transferred into a 500 mL separatory funnel (final volume 350 mL). The solution is then washed with saturated $NaHCO_3$ (150 mL). The aqueous layer becomes orange, while the organic layer is yellow (Figure 3B). After phase-separation, the organic layer is

removed, and the aqueous layer is extracted with additional CH_2Cl_2 (2 x 75 mL) (Note 9). Combined organic layers are passed through Na_2SO_4 (~30 g) contained in a fritted funnel into a 1000 mL round-bottomed flask. The Erlenmeyer flask is rinsed with CH_2Cl_2 (3 x 50 mL), which is passed through the Na_2SO_4 plug (~30 g) (final volume 650 mL), and the solvent is removed by rotary evaporation (35 °C, 100 mmHg) (Note 10).

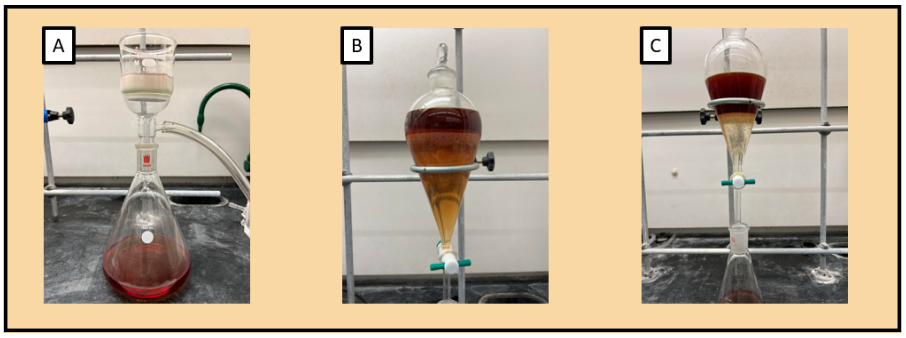


Figure 3. (A) Vacuum filter apparatus used for celite bed; (B) Reaction after washing with saturated $NaHCO_3$; (C) Extraction after washing with additional CH_2Cl_2 (photos provided by checkers)

A slurry is prepared from silica (90 g) (Note 11) and a 1:2 mixture of ethyl acetate and hexane (300 mL) (Note 12) is loaded into a fritted glass column (5 x 50 cm) (Figure 4A). The column is packed using pressurized air and an additional layer of sand (25 g) is gently added on the top of the column. The crude product is loaded on the column by dissolving the residue in a minimal amount of toluene (~5 mL) and transferring it with a glass pipette. The round-bottomed flask is rinsed with toluene (2 x 2.5 mL), and the washings are loaded on the column by pipette.

The crude product in toluene is pushed into the silica layer using air pressure, then 10 mL of ethyl acetate/hexane mixture (1:2) are carefully added to the top of the column and pushed into the silica using air pressure.

Figure 4. Glass column loaded with a slurry of silica, the crude product, and sea sand, eluted with ethyl acetate and hexane (photo provided by submitters)

A 500 mL reservoir is added to the glass column (Figure 4) and filled with the eluent system (ethyl acetate/hexane; 1:2). Fractions of 15 mL (20 x 150 mm test tubes) are collected (isocratic elution, total volume = 1.5 L). Presence of pure product is detected by TLC analysis in fractions 31 to 60 (Figure 5A). These fractions are combined in a 1000 mL round-bottomed flask, and the solvent is removed by rotary evaporation (35 °C, 50 mmHg) to obtain the title compound **1** as an off-white amorphous solid (Figure 5B, 2.46 g, 82%, purity = >99%) (Notes 13, 14, 15 and 16).

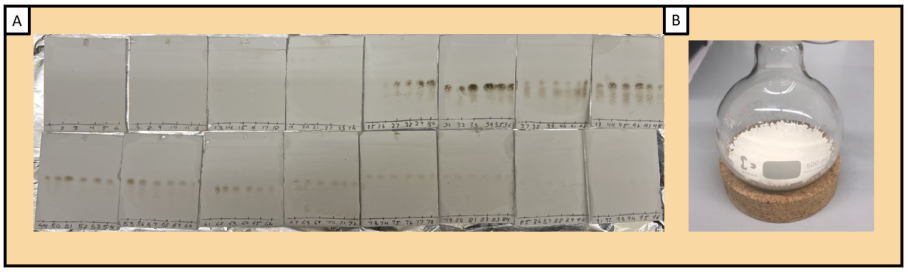


Figure 5. (A) TLC analysis of fractions obtained from chromatography; (B) Final product 1 (photo A provided by checkers and photo B provided by submitters)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dichloromethane, ethyl acetate, hexane, sulfuric acid, ethanol, sodium sulfate, sodium bicarbonate, deuterated chloroform, deuterated dimethyl sulfoxide, PBS buffer, celite, silica gel, maleic acid, toluene, sodium chloride, as well as the proper procedures for chromatographic purifications and photochemical experiments. Photochemical experiments should be carried out in a dedicated compartment (fume hood), shielded so that no light is exchanged with the surrounding environment. The operator should use light filtering goggles while such compartment is open for operations.
2. 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (97%) was purchased from Fisher Scientific and used as received.
3. Dichloromethane (stabilized with ethanol) was purchased from VWR Chemicals BDH® and used as received. Alternatively, dichloromethane (unstabilized, HPLC grade) can also be utilized if it can be acquired. Dichloromethane stabilized with amylene should not be used due to reproducibility problems. The checkers purchased dichloromethane (unstabilized, HPLC Grade) from Sigma Aldrich and used as received.

4. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (98%) was purchased from Sigma-Aldrich and used as received.
5. Phosphate-buffered saline (PBS buffer) solution was purchased from Sigma-Aldrich and used as received after verifying the pH value to be 7.4.
6. Two Kessil PR160L-525nm LED lamps at full power were used for irradiation at 525 nm. Lamps were installed 4 cm away from the reaction flask as shown in Figures 1 and 6. Lamps had linear reflectors that were aligned vertically with the reaction vessel. A high-power computer fan was used for cooling (Figure 6, left).

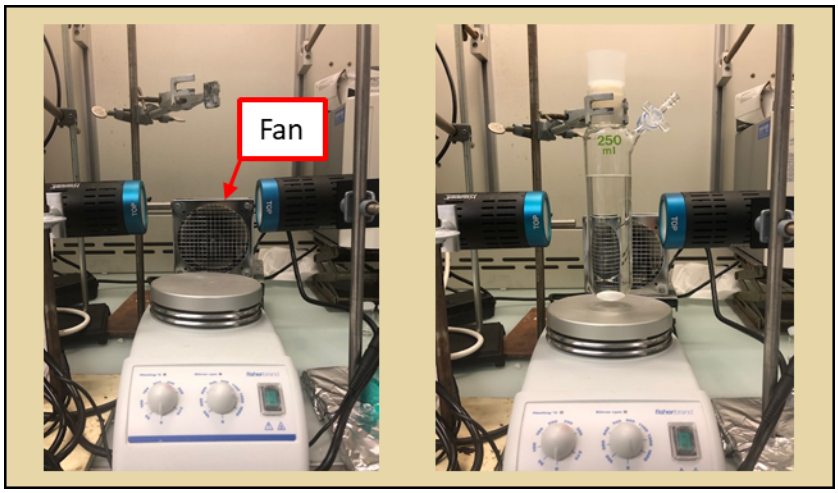


Figure 6. Irradiation setup using two lamps (525 nm) at 4 cm distance to the reaction vessel and a computer fan for cooling (photos provided by checkers)

7. TLC analysis of the crude reaction mixture is performed using pre-coated ALUGRAM Xtra SIL G/UV254 sheets from Macherey-Nagel. TLCs are eluted with ethyl acetate/hexane (1:2) and ethyl acetate/hexane (1:1) and stained using 10%$_{vol}$ of H_2SO_4 in ethanol, followed by gentle heating. The checkers performed TLC analysis using precoated TLC Silica Gel 60G F254 Glass plates from Sigma Aldrich.

33% ethyl acetate/hexane	**SM** : $R_f = 0.73$	**1** : $R_f = 0.24$
50% ethyl acetate/hexane	**SM** : $R_f = 0.88$	**1** : $R_f = 0.47$

8. Celite (Celite 535) was purchased from Carl Roth. The checkers purchased celite (Celite 535) from Thermo Fisher Scientific and used the material as received.
9. In case of emulsion formation, 50 mL of saturated brine (NaCl) solution can be added to the aqueous phase.
10. The checkers noted crystallization of the crude reaction after rotary evaporation was completed. To prevent this, a minimal amount of toluene (~5 mL) was added before rotary evaporation to prevent crystallization.
11. Silica gel (Silica 60, 0.04–0.063 mm) was purchased from Macherey-Nagel.
12. Ethyl acetate (HPLC grade, Fisher Chemical) and hexane (NORMAPUR grade, VWR) were used as received. The checkers purchased ethyl acetate (HPLC grade, Fisher Chemical) and hexane (HPLC Grade, Alfa Aesar) and used the solvents as received.
13. The checkers noted rapid decomposition of the product after a few hours of storage in non-deacidified chloroform-D. Negligible decomposition was observed of the product stored overnight in deacidified chloroform-D. The submitters purchased chloroform-D stabilized in silver foil from Carl Roth and used as received. The checkers purchased chloroform-D stabilized in silver foil from Sigma-Aldrich and used as received. Alternatively, the checkers purchased chloroform-D from Cambridge Isotope Laboratory to which 5 g of Na_2CO_3/100 mL solvent was added to deacidify the solvent.
14. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.95 (d, J = 3.6 Hz, 1H), 4.54 (d, J = 3.6 Hz, 1H), 4.38 – 4.31 (m, 2H), 4.17 (dd, J = 8.6, 6.2 Hz, 1H), 4.07 (dd, J = 7.6, 2.8 Hz, 1H), 3.98 (dd, J = 8.6, 5.4 Hz, 1H), 2.54 (d, J = 3.7 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 111.8, 109.6, 105.2, 85.1, 81.2, 74.8, 73.0, 67.6, 26.8, 26.2, 25.2. IR (neat): 3428, 2986, 2953, 2936, 2905, 2874, 1457, 1374, 1246, 1220, 1161, 1119, 1090 1059, 1030, 1003, 934, 881, 846, 783 cm^{-1}. mp = 117–119 °C; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{21}O_6$ 261.1338; found 261.1343
15. Purity was assessed by qNMR of **1** (65.5 mg) in DMSO-d_6 using maleic acid (26.1 mg) as an internal standard, with relaxation time (D1) set to 30 sec. The checkers purchased DMSO-d_6 from Cambridge Isotope laboratory, and maleic acid (99%) was purchased from ACROS Organics and used as received.
16. The reaction was repeated on an identical scale and provided 2.24 g (75%) of the product with purity >99%.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Complex molecule synthesis relies on protective groups to ensure chemo-, regio-, and stereoselectivity.[2] The construction of well-defined oligosaccharides requires selectively masking and unmasking of hydroxyl groups throughout the synthetic route using a host of protective groups.[3-5] Benzyl ethers are important protective groups in the synthesis of carbohydrates due to their excellent stability over a wide range of conditions.[2] However, benzyl ether cleavage requires harsh reduction/oxidation

processes, such as catalytic hydrogenolysis, Birch reduction, or oxidation with ozone or BCl_3, that are hazardous[6, 7] and poorly functional group tolerant[2, 8] Mild, selective, and catalytic cleavage of benzyl ethers would render them more versatile and attractive protective groups, conceptually changing the approach toward the synthesis of complex glycans and other natural products. Compared with benzyl ethers, *p*-methoxybenzyl (PMB) ethers can be selectively cleaved using mild stoichiometric oxidants or common photocatalysts due to their lower oxidation potential ($E_{Bn\text{-}O\text{-}Me}$= 2.20 V vs saturated calomel electrode (SCE)[9] and $E_{PMB\text{-}O\text{-}Me}$= 1.60 V vs SCE[9]).[2, 10-12]

A photooxidant with a sufficiently strong oxidizing excited state could facilitate the oxidative cleavage of benzyl ethers with high functional group tolerance. Indeed, using green light irradiation (LEDs centered at 525 nm) and a stoichiometric amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ,$E_{^3DDQ^*/DDQ^-}$ = 3.18 V vs SCE[15]) in wet dichloromethane, complete conversion of benzyl-protected furanose **1a** and selective formation of the desired product **1** is achieved (Figure 7).[13]

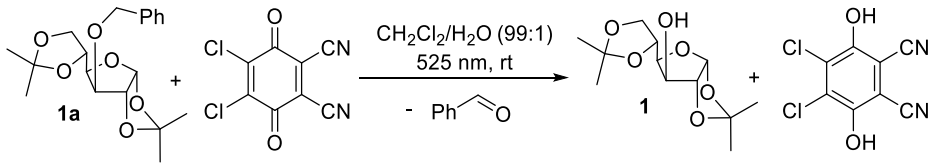
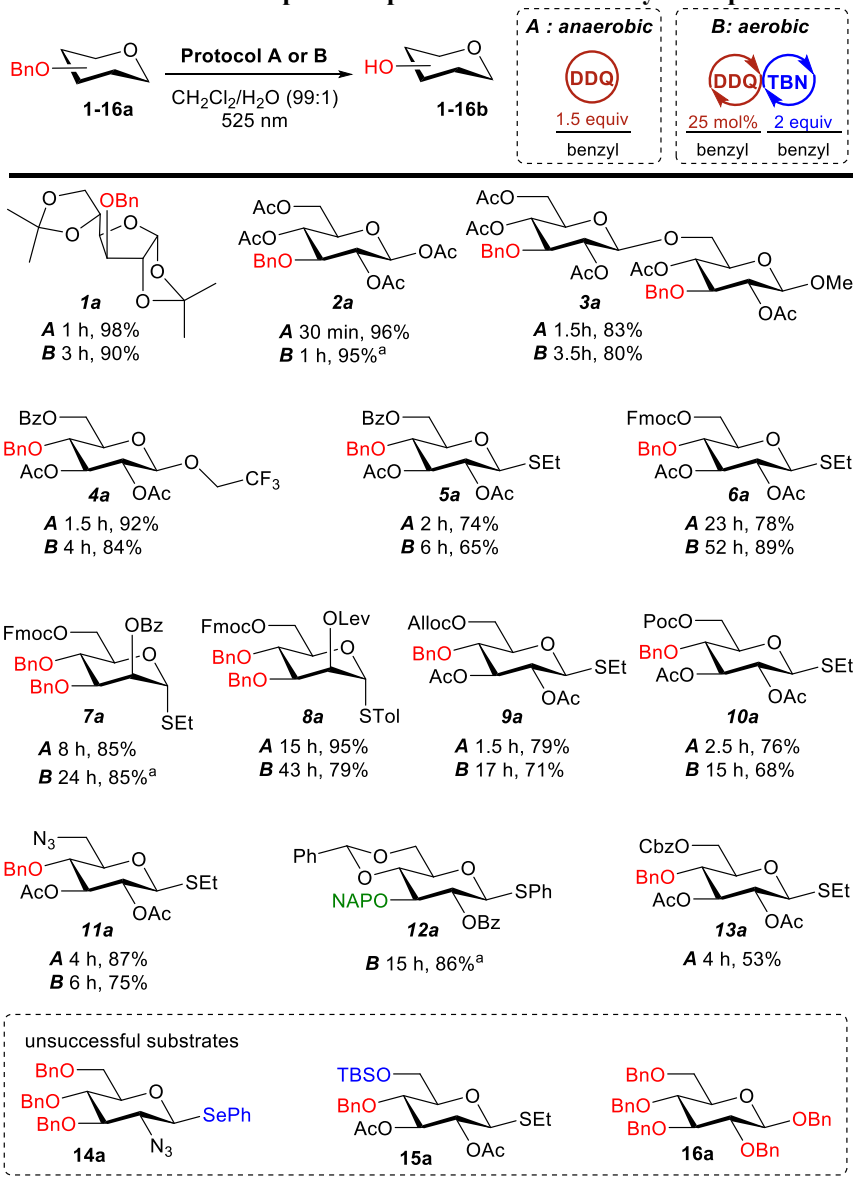


Figure 7. Photooxidative debenzylation with DDQ

Use of blue lamps (440 nm) resulted in formation of undesired side-products. To ease the tedious separation of the stoichiometric byproduct 2,3-dichloro-5,6-dicyano-1,4-hydroquinone ($DDQH_2$), we also developed a catalytic protocol using DDQ (25 mol%) in combination with *tert*-butyl nitrite (TBN, 2 equiv) and air as terminal oxidant (Table 1).[13-21] Both methods were suitable to selectively cleave benzyl ethers on substrates containing acetyl, isopropylidene, and benzoyl protecting groups (**1a**–**4a**) in less than 4 h with excellent yield on a 100 μmol scale (84–96%). Substrates presenting thioethers that potentially cause catalyst poisoning in palladium-catalyzed hydrogenolysis, also reacted smoothly and no sulfoxide or sulfone side-products were identified (**5a**–**11a**). Several common protecting groups that are not tolerated in hydrogenolysis or Birch reduction, such as fluorenylmethoxycarbonyl (Fmoc, **6a, 7a, 8a**), levulinic ester (Lev, **8a**), allyl

Table 1. Substrate scope of the photooxidative debenzylation protocol



Reaction conditions: benzyl ether (100 μmol), DDQ (protocol A: 150 μmol/benzyl, protocol B: 25 μmol/benzyl), TBN (protocol B, 200 μmol), CH_2Cl_2 (5 mL), H_2O (50 μL), 525 nm irradiation at rt (20 °C). [b]Reaction on 50 μmol scale. Isolated yields are reported.

carbonate (Alloc, **9a**), propargyl carbonate (Poc, **10a**), and benzylidene (**12a**), were well tolerated. Azides are essential handles for bio-orthogonal labeling and are stable to these photooxidative benzyl ether cleavage conditions (**11a**). The high functional group tolerance of the photooxidative debenzylation was key to selectively cleave benzyl ethers in a total synthesis of tetrodotoxin and eribulin B.[22, 23] 2-Naphtylmethylether (NAP, **12a**) is routinely removed using stoichiometric amounts of DDQ in the absence of light. We showed that the protocol using 25 mol% DDQ is also a viable option for NAP cleavage that demands less purification effort. The deprotection of a substrate presenting both benzyl ether and benzyloxycarbonyl (Cbz, **13a**) groups showed that stoichiometric amounts of DDQ are necessary in order to increase the desired reactivity, reduce reaction times and limit the competitive Cbz cleavage. Phenylselenyl (**14a**) and *tert*-butyldimethylsilyl (TBS, **15a**)[24] ethers did not withstand the photooxidative debenzylation conditions. Deprotection of per-benzylated glucose (**16a**) was not feasible due to precipitation of polar intermediates.

Application of the catalytic methodology (Protocol B) for large-scale debenzylation (11.4 mmol) of **1a** using two 525 nm LED lamps proved ineffective and was accompanied by reproducibility problems, potentially due to poor light penetration. Long reaction times are required and led to cleavage of acid-sensitive isopropylidene groups by interacting with acidic reaction intermediates ($DDQH_2$ and nitrous acid).[25] At this scale, clean separation of organic and aqueous layers was observed, which was not the case on the small-scale experiments. The water layer promoted acetal hydrolysis, which was mitigated by lowering the water content (1 to 0.1%) and introducing a buffer (PBS, pH 7.4).[26] Nevertheless, the low photon flux did not allow for efficient NO_2 generation and precipitation of $DDQH_2$ was observed along with incomplete reactions.

The method using stoichiometric amounts of DDQ (1.2 equiv, Protocol A), on the contrary, can be reproducibly carried out on a 11.4 mmol scale using two LED lamps (Figure 1). Monitoring the transformation by TLC indicated 12 h as the optimal reaction time, with the starting material being nearly consumed and side-products remaining minimal (Figure 2), ultimately yielding **1** in 82%.

This photooxidative debenzylation strategy overcomes current limitations of benzyl ethers as protecting groups that arise from the harsh conditions necessary for their cleavage. The methodology enables the use of benzyl ethers as orthogonal protective group that is installed and removed

throughout the synthesis of complex molecules and clears the path to the development of new synthetic routes in total synthesis.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose; (18685-18-2)
DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; (84-58-2)
TBN: *tert*-butyl nitrite; (540-80-7)
1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose; (582-52-5)

Amiera Madani completed her undergraduate studies in chemistry at the University of Tübingen (Germany). In 2019 she joined the Max-Planck-Institute of Colloids and Interfaces in Potsdam (Germany) to obtain her doctoral degree in 2023. Her research focuses on the development and mechanistic investigation of reactions involving reactive open-shell intermediates.

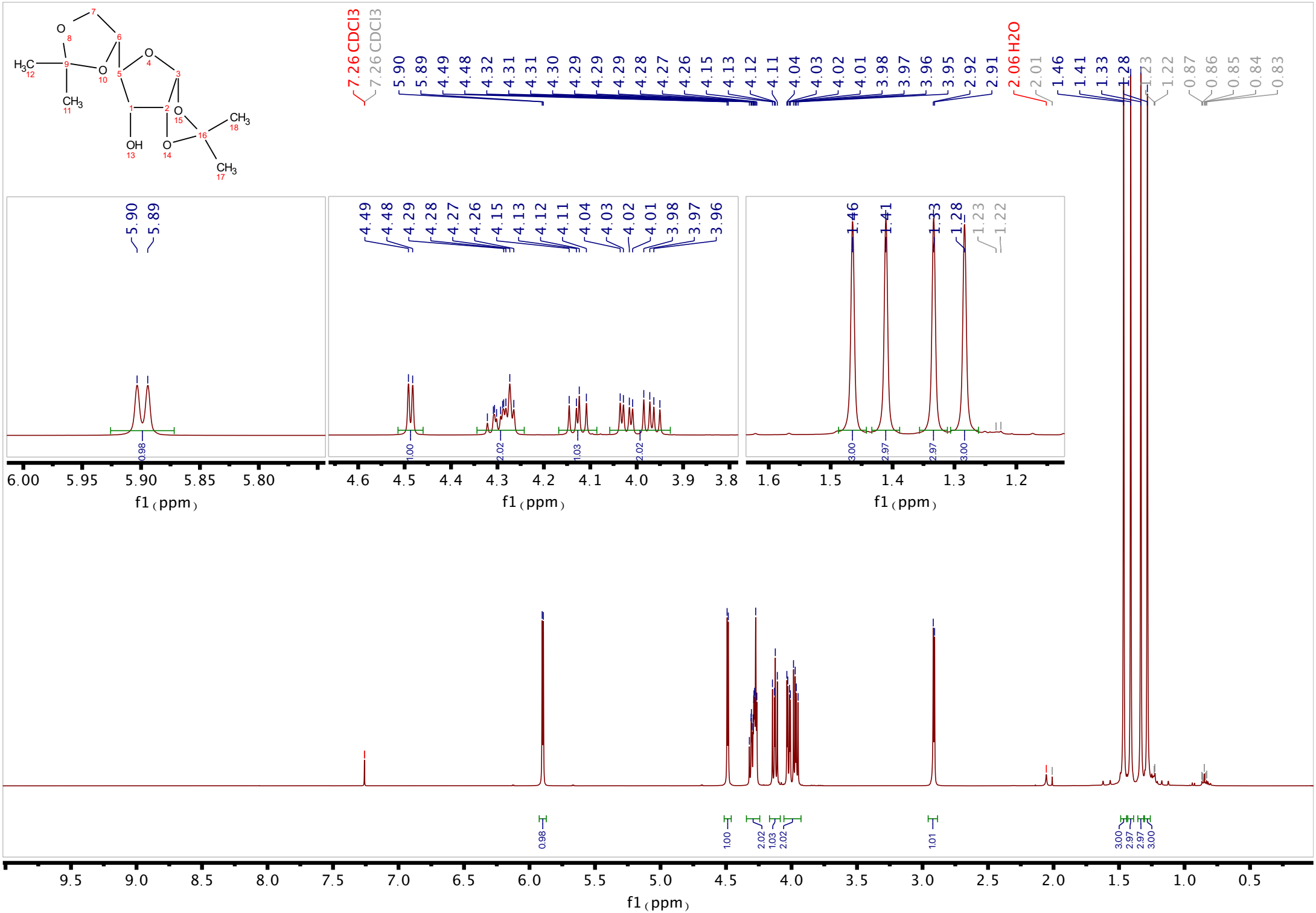
Eric T. Sletten completed his undergraduate studies in chemistry at Wartburg College (IA) in 2013. In 2013 he joined the University of Iowa Department of Chemistry and obtained his Ph.D. in 2018. In 2019, he subsequently moved to the Max-Planck-Institute of Colloids and Interfaces in Potsdam (Germany) as a postdoctoral researcher and was awarded Alexander-von-Humboldt postdoctoral research fellowship. His research focuses on the development of methodologies for glycan synthesis.

Cristian Cavedon completed his undergraduate studies in industrial chemistry at the University of Padua (Italy). In 2018 he joined the Max-Planck-Institute of Colloids and Interfaces in Potsdam (Germany) to obtain his doctoral degree in 2021. After postdoctoral research in the Jamison lab at MIT, he joined Vertex Pharmaceuticals in 2023. His research focuses on the development of organic methodologies using catalysis as well as flow and photochemistry.

Peter H. Seeberger completed his undergraduate studies in chemistry in Erlangen (Germany) and his Ph.D. in biochemistry in Boulder (CO). After postdoctoral research at the Sloan–Kettering Cancer Center in New York (95-97) and positions as Firmenich Associate Professor with tenure at MIT (98–03) and Professor at ETH Zurich (03-09), he is now a Director at the Max–Planck-Institute in Potsdam and Professor at Freie Universität Berlin. His research interests include chemistry, biology, and engineering.

Bartholomäus (Bart) Pieber studied chemistry at the University of Graz (Austria), where he completed his PhD in the group of C. Oliver Kappe in 2015. Following his doctoral work, Bart moved to Peter Seeberger's lab in Potsdam (Germany). In 2018, he started his independent research career as a group leader at the Max Planck Institute of Colloids and Interfaces (Potsdam, Germany) and was appointed as a lecturer at the University of Potsdam. In 2022, he spent time as visiting scholar at the California Institute of Technology (Pasadena, USA, Host: Prof. Greg Fu). Since June 2023, Bart is Assistant Professor at the Institute of Science and Technology Austria (ISTA).

Kevin Lee attended William Paterson University of New Jersey (United States), completing his B.S. in Chemistry and Medicinal Biochemistry in 2022 under the supervision of Yalan Xing. That same year, he joined the University of Pennsylvania to obtain his Masters in Chemical Science degree under the supervision of Dirk Trauner. His research focuses on the asymmetric total synthesis of complex natural products.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4.28
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4.26
4.15
4.13
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4.11
4.04
4.03
4.02
4.01
3.98
3.97
3.96
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2.91
2.06 H2O
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1.23
1.22
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0.85
0.84
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1.01
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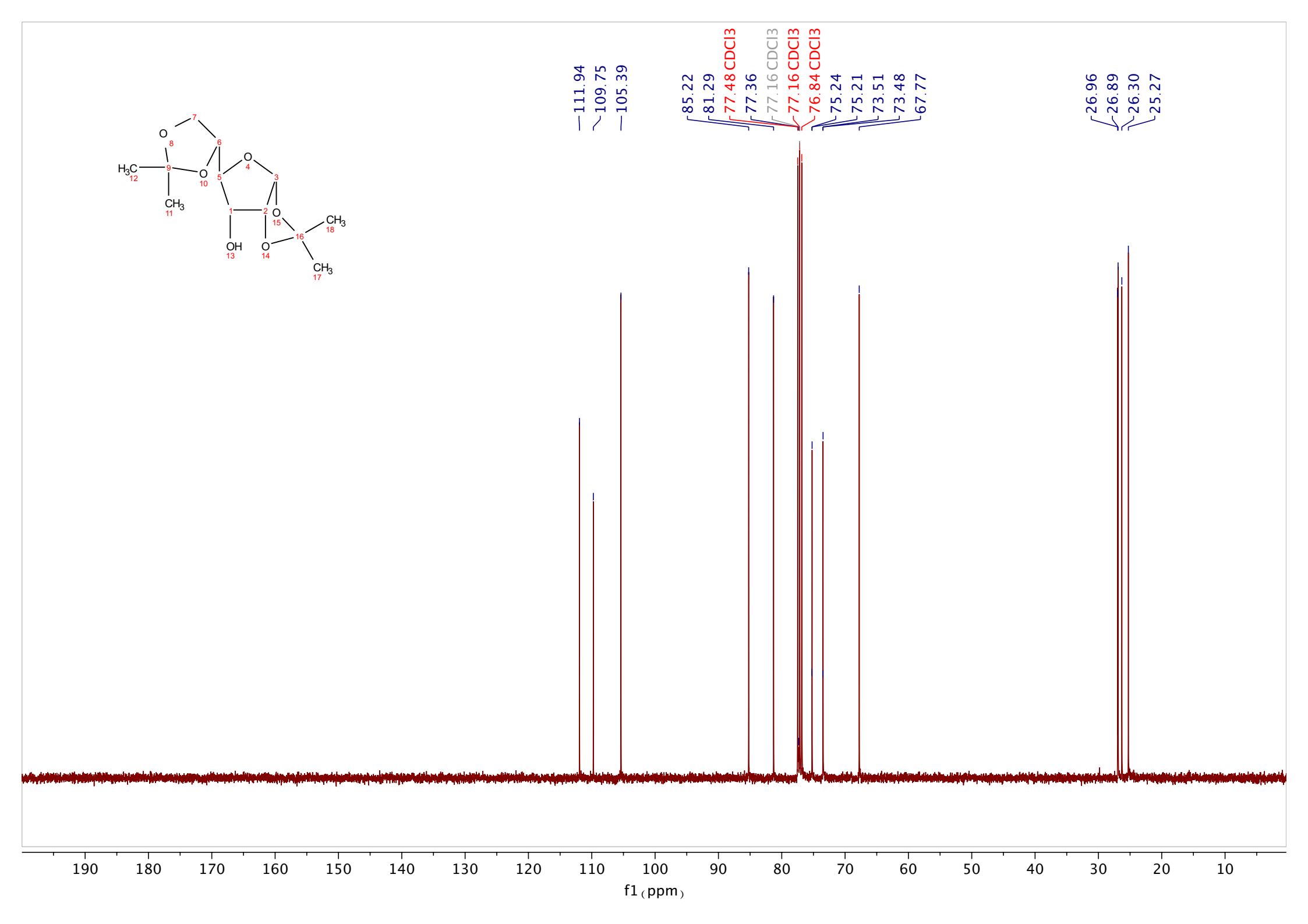
3.00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73.48
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26.30
25.27
O
8
7
6
O
4
3
H3C
12
9
O
10
5
CH3
11
1
2
O
15
CH3
18
16
OH
13
O
14
CH3
17
190
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60
50
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20
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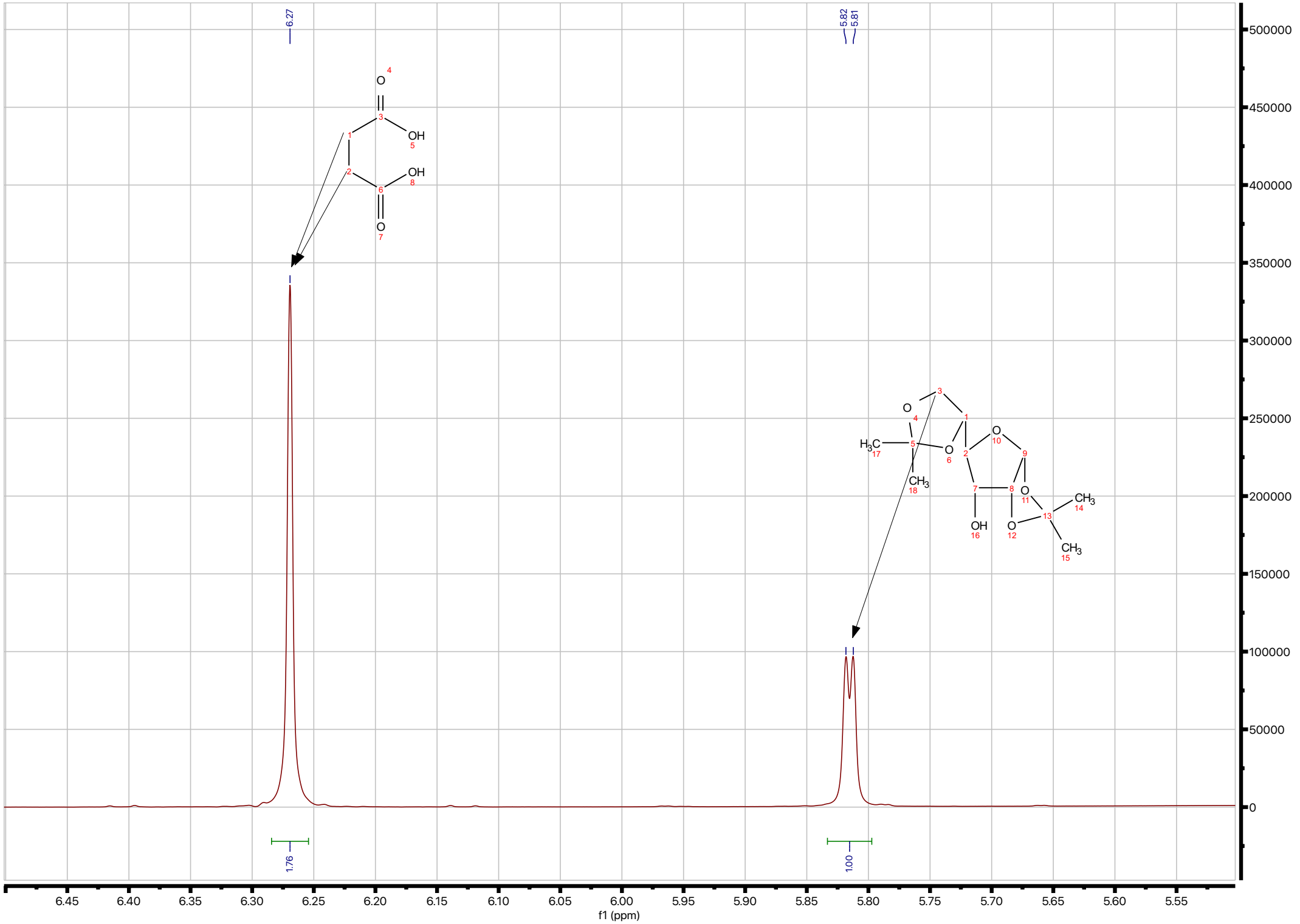
f1 (ppm)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CH3
CH3
CH3
OH