Organic Syntheses

# Preparation of Methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate

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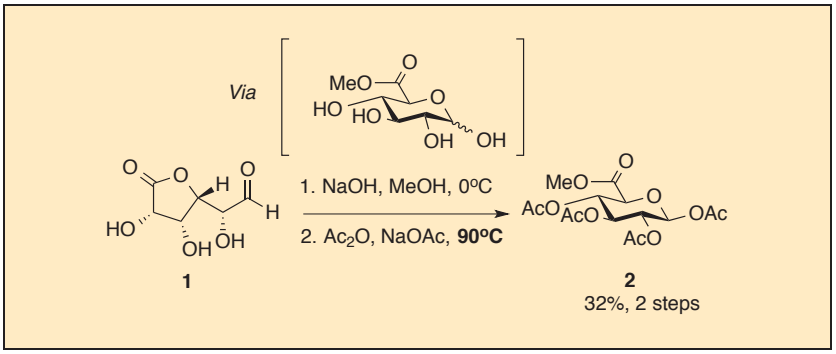
*Checked by Michal Achmatowicz and Margaret Faul*




## Procedure

A. *Methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate* **2.** A three-necked 250-mL round-bottomed flask on a stirrer plate is equipped with a 2-cm Teflon coated magnetic stirrer bar, rubber septum, thermometer (with insert to monitor the internal reaction temperature) and a connection to a nitrogen line (Figure 1).

**Figure 1. Reaction set-up**

Under inert atmosphere the flask is charged with methanol (MeOH) (50 mL) (Note 1), NaOH (20 mg, 0.5 mmol, 0.02 equiv) (Note 2) and then stirred vigorously for 10 min to complete dissolution of NaOH. The clear solution is cooled to 0 °C with an ice/water bath and to this is added D-glucuronolactone **1** (5.0 g, 28 mmol, 1.0 equiv) portion-wise (Note 3) over 25 min (Note 4). The solution is stirred for an additional 30 min, while maintaining the internal temperature at 0 °C. Upon complete dissolution of **1**, the reaction solution is transferred to a one-necked 250-mL round-bottomed flask and the solvent removed by rotary evaporation (30 °C, 20 mmHg) (Note 5) to yield a pale yellow foam which is dried under vacuum (5 mmHg) for 2 h to remove the majority of residual MeOH (Figure 2).

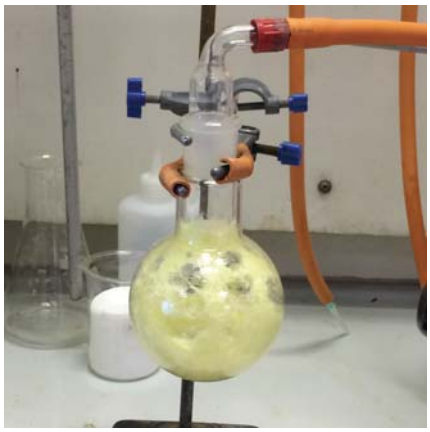


**Figure 2. Pale yellow foam after removal of methanol**

The flask (Note 6) containing the foam is charged with a 2-cm Teflon coated magnetic stirrer bar, acetic anhydride (54 g, 50 mL, 530 mmol, 19 equiv) and anhydrous NaOAc (9.5 g, 116 mmol, 4.1 equiv) (Note 7). A reflux condenser is attached, the reaction placed under nitrogen and the mixture heated (Note 8) to 90 °C for 1.5 h (Note 9). The light-brown suspension (Figure 3) is then allowed to cool. The solution is no longer stirred and is left standing overnight.

**Figure 3. Light brown suspension**

The resulting precipitate is diluted with EtOAc (100 mL) and any solids broken up carefully with a spatula. This enables stirring of the suspension, which is continued vigorously for 5 min. The suspension is then filtered through a 100-mL medium porosity sintered glass funnel into a 0.5 L flask, washing the solids with an additional portion of EtOAc (100 mL). This filtrate is retained. Sodium bicarbonate ($NaHCO_3$) (90 g, 1.1 mol, 38 equiv) is weighed into a 1.0 L beaker on a stirrer plate and distilled water (250 mL) added. A 4-cm Teflon coated stirrer bar is added and stirring commenced to dissolve the majority of the $NaHCO_3$. The reaction filtrate is added slowly to this stirred solution (Note 10) and stirring is continued for >30 min, or until all effervescence had ceased. The solution is then transferred to a 1.0 L separating funnel and the organic/aqueous layers separated. The aqueous phase is extracted once with EtOAc (50 mL) and the organics combined, washed with $H_2O$ (50 mL), dried over $MgSO_4$ (10.0 g) for 10 min, and filtered through a sintered glass funnel into a flask. The solvent is removed on a rotary evaporator (40 °C, 20 mmHg) to reveal a sticky, brown oil mixed

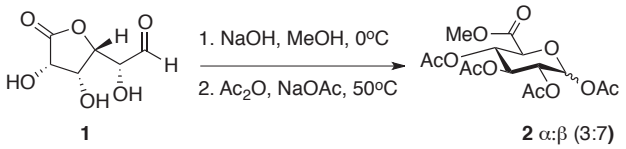
with solids. This residue is dissolved in hot (70 °C) EtOH (50 mL) and allowed to cool, which induces crystallisation of **2**. The solids are collected by vacuum filtration (Note 11) and dried under vacuum for 2 h (5 mmHg) furnishing 3.40 g (32%) of **2** as a light tan solid (Figure 4) (Notes 12 and 13).

**Figure 4. Product (2) as a light tan solid**

## Notes

1. Methanol (MeOH, HPLC Grade) was obtained from Sigma-Aldrich and used as received.
2. Sodium hydroxide (NaOH) was obtained from Fisher Scientific in pellet form and was used as received. For this procedure a pellet of NaOH was ground in a pestle with a mortar and the required amount weighed out into a small sample vial for transfer to the stirred MeOH solution.
3. D-Glucuronolactone **1** [D-(+)-glucuronic acid-□-lactone, >99%] was purchased from Sigma Aldrich and used as received.
4. D -Glucuronolactone **1** was added to the solution in 5 x 1.0 g portions in 5 minute intervals. The solution color may turn from clear to very pale yellow during this addition process.
5. Upon complete dissolution of **1** into solution the evaporation of MeOH should be completed with a rotary evaporator bath temperature not exceeding 30 °C as this may lead to decomposition of the intermediate free sugar. As the last traces of MeOH are removed, the residue may begin to foam inside the flask and the intermediate material will appear as a light yellow foam.

6. As necessary and depending on the heating setup in use, the flask can be fitted with a Y-shaped adapter for a flexible thermocouple or a 2-necked flask used.
7. Acetic anhydride (ReagentPlus, ≥99%) and anhydrous NaOAc (ReagentPlus, ≥99%) were both obtained from Sigma Aldrich and used as received.
8. The pale yellow foam is quite sticky and may not immediately dissolve upon addition of the acetic anhydride and NaOAc. Heating from ambient temperature up to 90 °C is required to achieve this. As the solvent warms, the reagents will dissolve and a pale brown suspension results. The mixture was heated using a Drysyn™ heating block and temperature thermocouple.
9. If lower heating temperature of 50 °C is applied for 4 h and then the solution is allowed to cool to room temperature overnight, the reaction delivers an improved yield of **2** (4.8–6.0 g, 45–60%) as white solid, but with a reduced diastereomeric preference for the $\beta$ anomer. Experiments run at 50 °C gave approximately 3/7 ($\alpha/\beta$) diastereomeric mixtures, as judged by $^1$H NMR analysis.




**1** **2** α:β (3:7)

**Scheme 1. Reaction performed at 50 °C**

10. This step requires a careful addition of the filtrate to control the effervescence of $CO_2$ upon destruction of excess $Ac_2O$ and neutralization of AcOH. Approximately 50 mL of filtrate should be added to the $NaHCO_3$ solution every 5 minutes.
11. Following filtration, the solids should be washed with 10-20 mL of ice-cold diethyl ether.
12. Analytical data for **2**[2]: TLC $R_f$ 0.15 (3/1, hexane:EOAc) visualised with phosphomolybdic acid (PMA) stain. mp 175–177 °C; $[\alpha]_D^{20}$ +0.70° (*c* 0.55, $CH_2Cl_2$). D-(+)-Glucuronic acid γ-lactone $[\alpha]_D^{20}$ +18.0° (*c* 8.0, $H_2O$) (lit. 18.8°. IR (film): 2955, 1751, 1371, 1202, 1144, 1115, 1087, 1177, 1037 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 2.05 (s, 6H), 2.13 (s, 3H), 3.75 (s, 3H), 4.19 (d, *J* = 9.4 Hz, 1H), 5.15 (t, *J* = 8.3 Hz, 1H), 5.26 (t, *J* = 9.3

Hz, 1H), 5.32 (t, $J$ = 9.1 Hz, 1H), 5.78 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 20.4, 20.5, 20.6, 20.8, 53.0, 68.9, 70.2, 71.8, 73.0, 91.4, 166.8, 168.8, 169.1, 169.4, 169.9. MS $m/z$ 399 (100, [M+Na$^+$]); [M+Na$^+$] calcd for $C_{15}H_{20}NaO_{11}$: 399.08978. Found: 399.08980 (0.1 ppm). The $\beta$ anomer is identified by a large $^3$J ($H_1$-$H_2$) coupling ($J$ = 7.8 Hz). The product can be stored on the shelf for prolonged periods.

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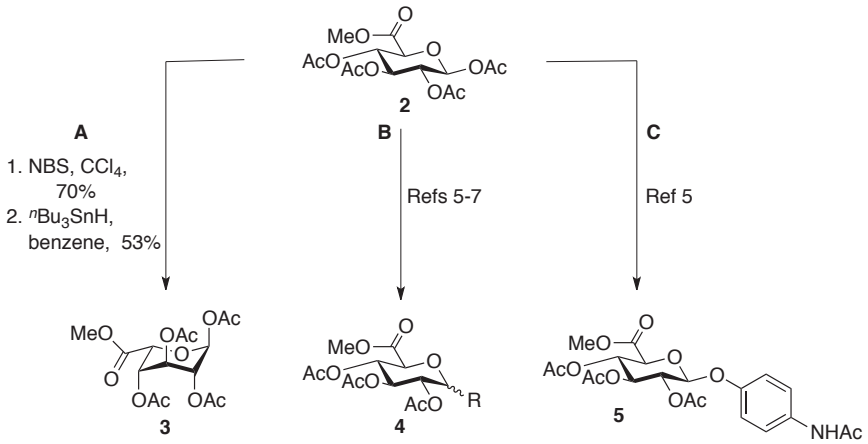
## Discussion

The synthesis of methyl 1,2,3,4-tetra-*O*-acetyl-□-D-glucopyranuronate **2** described builds on an original report by Bollenback *et al.*[2] In their article the authors prepare **2** using acid (periodic acid) or base (pyridine) catalyzed acetylation of the intermediate pyranouronate, obtained from methanolysis of **1**. While this is a useful procedure on large scale (the original scale was >2.3 mol, 400 g of **1**) we did not find it reliably reproducible on small to medium scales (often producing brown tars needing multiple repetitive chromatographic steps to isolate low % yields of **2**), and we also sought to eliminate the use of periodic acid and/or pyridine. The use of NaOAc in acetic anhydride proved a convenient alternative for the acetylation step and the process could be reliably scaled to 10 g of **1**. This method further provides an economic alternative to **2** derived from the commercially available, but more expensive D-glucuronic acid.[3]

D-Glucuronate **2** is a commonly required uronate building block (Scheme 2). For example, it has been used to access non-readily available L-IdoA units for the construction of complex heparin-related disaccharides,[4] *via* an intermediate C5-bromide (Scheme 2, A). It has also seen utility for access to and characterization of the important glucuronide-containing metabolite **5** (Scheme 2, C).[5] Importantly, **2** also serves as a vital precursor for the formation of alternative C-1 anomeric derivatives **4** (complicit to wider glycosylation applications and methodologies) including trichloroacetimidates,[5] hemi-acetals,[6] and glycosyl bromides[7] (Scheme 2, B).




**Scheme 2. Synthetic applications of glucuronate building block 2. R = Br (*via* $TiCl_4$, DCM), R = OH (*via* $^nBu_3SnOMe$, benzene), R=OC(O)$CCl_3$ (*via* $ClC(O)CCl_3$, DBU, DCM).**

## References


1. Email: g.j.miller@keele.ac.uk. This work was supported by Keele University, Keele, Staffordshire, ST5 5BG, U.K.
2. Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310–3315.
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## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

D-Glucuronolactone: D-(+)-glucuronic acid-□-lactone; (32449-92-6)
Acetic anhydride: acetic anhydride; (108-24-7)
Sodium acetate: Sodium acetate; (127-09-3)

Gavin Miller was born in Newport, Wales and read a MChem in Chemistry at UMIST. He then undertook a Ph.D. in carbohydrate chemistry at the University of Manchester, followed by PDRA positions at Brown University, USA and at St Andrews, UK. Gavin then moved to industry, firstly at Ferring Pharmaceuticals and secondly at Peakdale Molecular. He returned to the University of Manchester in 2009 as a PDRA in the Manchester Institute of Biotechnology and secondly as a fixed-term lecturer in 2013, within the School of Chemistry. He took up his current Lectureship in Organic Chemistry at Keele University in 2015.

Aisling Ní Cheallaigh undertook a BSc. in Medicinal Chemistry and Chemical Biology at University College Dublin (UCD) and graduated with first class honours. Upon receipt of a prestigious IRCSET scholarship she began her postgraduate studies through which she obtained a Ph.D. in Synthetic Carbohydrate Chemistry. She then held a PDRA position at the University of Manchester carrying out organic synthesis of monoterpenoid derivatives for use in a synthetic biology programme. She currently holds a Senior Scientist position in Chemical Development at AstraZeneca.

Garrett Potter pursued a B.S. in Biochemistry/Chemistry at The University of California, San Diego (UCSD). He then worked for biopharmaceutical start-up companies Actimis Pharmaceuticals and Axikin Pharmaceuticals prior to pursuing postgraduate studies with a Ph.D. in carbohydrate chemistry at the University of Manchester. He held a PDRA position at the University of Manchester, synthesizing carbohydrate building blocks toward heparan sulfate-derived bioactive scaffolds. Currently, he is a Postdoctoral Research Scholar at Stanford University in the ChEM-H Medicinal Chemistry Knowledge Center.

John Gardiner received his undergraduate education and his Ph.D. (Martin Bryce's lab) working on total synthesis of alkaloids, from Durham University. He joined Mike Jung's group at the University of California, Los Angeles (UCLA) for 2 years working on nucleoside and de novo carbohydrate syntheses. He moved to Manchester (UMIST) then the University of Manchester and Manchester Institute of Biotechnology (MIB) where his group's research has focused on carbohydrate methods, oligosaccharide syntheses, glycosylaminoglycans and mimetics, biocatalytic reductions, synthesis / biotransformations of terpenoids, polyaromatic dendrimers and heterocyclic medicinal chemistry.

Michal Achmatowicz received his undergraduate education at the University of Warsaw, Poland where he completed his undergraduate thesis in Chemistry in 1997. He then joined Professor Janusz Jarczak's research group at the Institute of Organic Chemistry of the Polish Academy of Sciences in Warsaw to pursue his Ph.D. in organic chemistry. From 2001 to 20013 he was a post-doctoral research fellow with Professor Louis S. Hegedus at the Colorado State University. Subsequently he joined the Chemical Process Research and Development at Amgen at Thousand Oaks, California, where he has been developing robust processes toward active pharmaceutical ingredients, coauthoring several publications, and enjoying rock climbing in his spare time.

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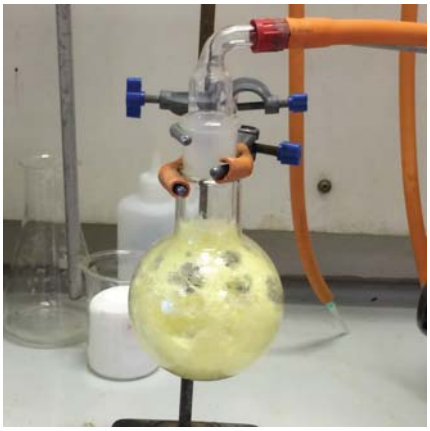

**Figure 2. Pale yellow foam after removal of methanol**

The flask (Note 6) containing the foam is charged with a 2-cm Teflon coated magnetic stirrer bar, acetic anhydride (54 g, 50 mL, 530 mmol, 19 equiv) and anhydrous NaOAc (9.5 g, 116 mmol, 4.1 equiv) (Note 7). A reflux condenser is attached, the reaction placed under nitrogen and the mixture heated (Note 8) to 90 °C for 1.5 h (Note 9). The light-brown suspension (Figure 3) is then allowed to cool. The solution is no longer stirred and is left standing overnight.

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**Figure 4. Product (2) as a light tan solid**

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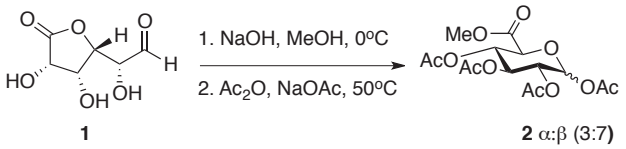


**1** **2** α:β (3:7)

**Scheme 1. Reaction performed at 50 °C**

10. This step requires a careful addition of the filtrate to control the effervescence of $CO_2$ upon destruction of excess $Ac_2O$ and neutralization of AcOH. Approximately 50 mL of filtrate should be added to the $NaHCO_3$ solution every 5 minutes.
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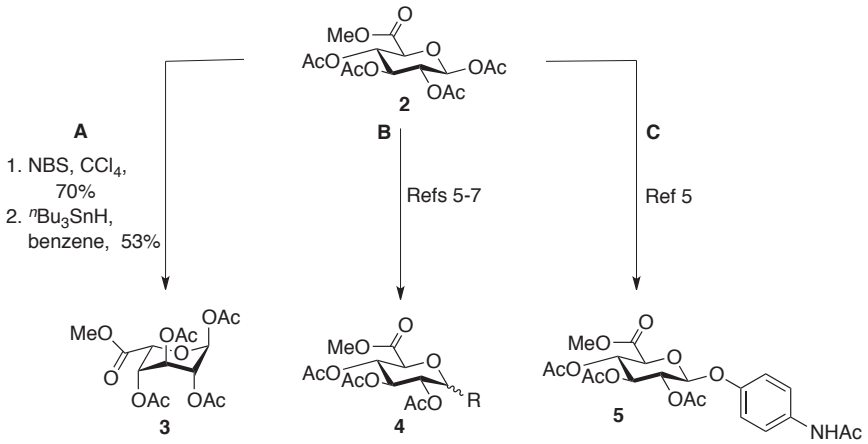


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## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

D-Glucuronolactone: D-(+)-glucuronic acid-γ-lactone; (32449-92-6)
Acetic anhydride: acetic anhydride; (108-24-7)
Sodium acetate: Sodium acetate; (127-09-3)

Gavin Miller was born in Newport, Wales and read a MChem in Chemistry at UMIST. He then undertook a Ph.D. in carbohydrate chemistry at the University of Manchester, followed by PDRA positions at Brown University, USA and at St Andrews, UK. Gavin then moved to industry, firstly at Ferring Pharmaceuticals and secondly at Peakdale Molecular. He returned to the University of Manchester in 2009 as a PDRA in the Manchester Institute of Biotechnology and secondly as a fixed-term lecturer in 2013, within the School of Chemistry. He took up his current Lectureship in Organic Chemistry at Keele University in 2015.

Aisling Ní Cheallaigh undertook a BSc. in Medicinal Chemistry and Chemical Biology at University College Dublin (UCD) and graduated with first class honours. Upon receipt of a prestigious IRCSET scholarship she began her postgraduate studies through which she obtained a Ph.D. in Synthetic Carbohydrate Chemistry. She then held a PDRA position at the University of Manchester carrying out organic synthesis of monoterpenoid derivatives for use in a synthetic biology programme. She currently holds a Senior Scientist position in Chemical Development at AstraZeneca.

Garrett Potter pursued a B.S. in Biochemistry/Chemistry at The University of California, San Diego (UCSD). He then worked for biopharmaceutical start-up companies Actimis Pharmaceuticals and Axikin Pharmaceuticals prior to pursuing postgraduate studies with a Ph.D. in carbohydrate chemistry at the University of Manchester. He held a PDRA position at the University of Manchester, synthesizing carbohydrate building blocks toward heparan sulfate-derived bioactive scaffolds. Currently, he is a Postdoctoral Research Scholar at Stanford University in the ChEM-H Medicinal Chemistry Knowledge Center.

John Gardiner received his undergraduate education and his Ph.D. (Martin Bryce's lab) working on total synthesis of alkaloids, from Durham University. He joined Mike Jung's group at the University of California, Los Angeles (UCLA) for 2 years working on nucleoside and de novo carbohydrate syntheses. He moved to Manchester (UMIST) then the University of Manchester and Manchester Institute of Biotechnology (MIB) where his group's research has focused on carbohydrate methods, oligosaccharide syntheses, glycosylaminoglycans and mimetics, biocatalytic reductions, synthesis / biotransformations of terpenoids, polyaromatic dendrimers and heterocyclic medicinal chemistry.

Michal Achmatowicz received his undergraduate education at the University of Warsaw, Poland where he completed his undergraduate thesis in Chemistry in 1997. He then joined Professor Janusz Jarczak's research group at the Institute of Organic Chemistry of the Polish Academy of Sciences in Warsaw to pursue his Ph.D. in organic chemistry. From 2001 to 20013 he was a post-doctoral research fellow with Professor Louis S. Hegedus at the Colorado State University. Subsequently he joined the Chemical Process Research and Development at Amgen at Thousand Oaks, California, where he has been developing robust processes toward active pharmaceutical ingredients, coauthoring several publications, and enjoying rock climbing in his spare time.

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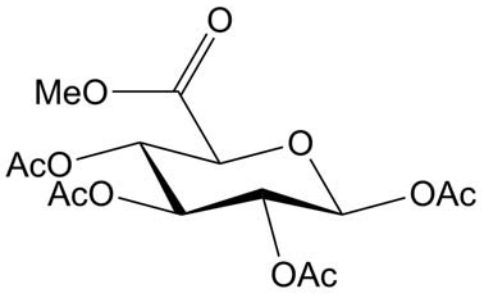


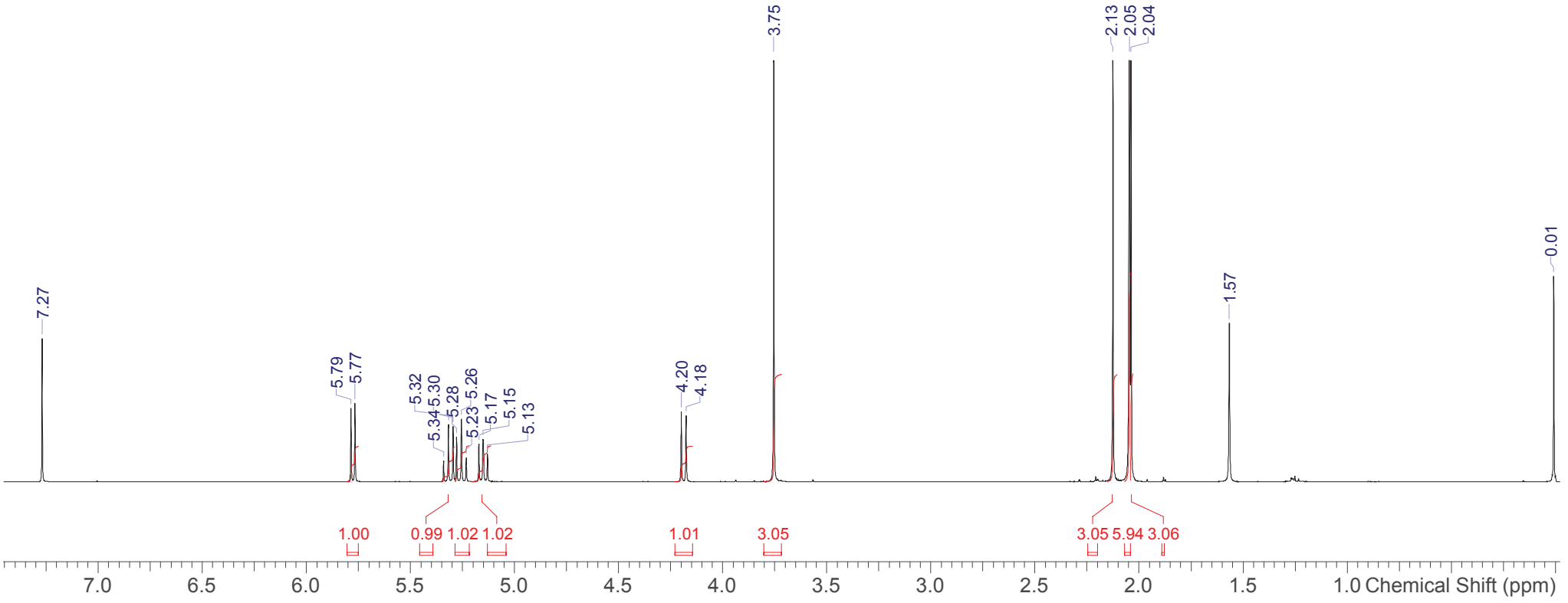

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