

Supporting Information For

Modular Continuous Flow Synthesis of Orthogonally Protected 6-Deoxy Glucose Glycals

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S1.1 Materials and Methods

Continuous flow equipment was assembled from commercially available components supplied from IDEX Health & Science Technologies. Static mixers were purchased from StaMixCo (Part #HT-40-1.70-10-PTFE). Reactors were constructed from high-purity perfluoroalkoxy (PFA) tubing. For reactions under 1-gram scale of starting material, PFA tubing with a 1/16" outside diameter and a 0.03" internal diameter (Part #1912), with complementary PEEK fittings, were used. For reaction larger than 1-gram scale of starting material, PFA tubing with a 1/8" outside diameter and a 1/16" internal diameter (Part #1921), with complementary PEEK fittings, were used. Harvard Apparatus PhD Ultra syringe pumps were used to infuse solutions within NORM-JECT syringes with 1/16" Leur Adaptors that were purchased from Chromtech (Part #P-624 and P-630).

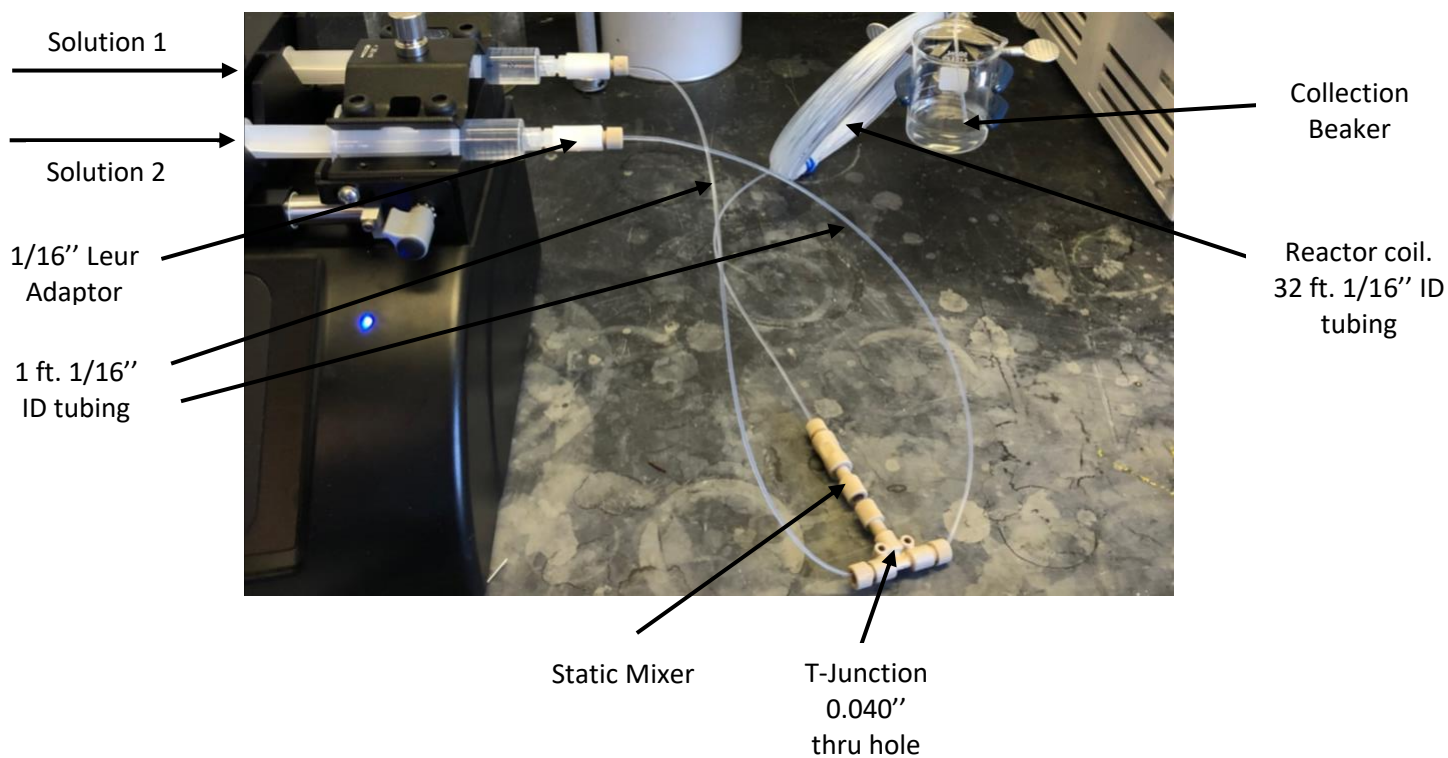
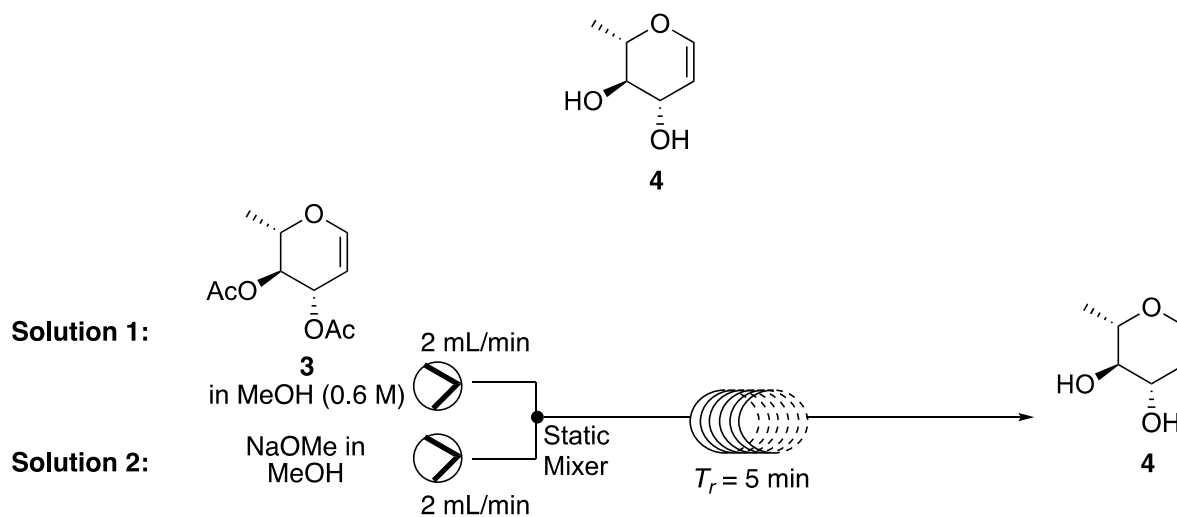
Solvents were rendered anhydrous through a commercial solvent purification system immediately prior to use. All other chemicals were purchased at the highest possible quality and used as received. Flash column chromatography was performed on 230–400 mesh silica gel. Analytical and thin layer chromatography was carried out on silica gel 60 F-254 plates. Products were visualized using UV or by staining with 5% aqueous sulfuric acid. NMR spectra were recorded on a NMR spectrometer at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR. Chemical shifts are reported in ppm relative to TMS (for ^1H NMR in CDCl_3) or CDCl_3 (for ^{13}C NMR in CDCl_3). For ^1H NMR spectra, data are reported as follows: δ shift, multiplicity (s = singlet, m = multiplet, t = triplet, d = doublet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dq = doublet of quartets), coupling constants are reported in Hz. Low-resolution mass spectra (LRMS) were recorded using a ESI-MS with an additional APCI source. High-resolution mass spectra (HRMS) were obtained on ElectroSpray Ionization (ESI) on a Waters Qtof Premier instrument in the positive mode or Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT- ICR-MS) with direct analysis in real time (DART) ionization source. Optical rotations were measured at 589 nm in a 5 cm cell at 24 °C.

S2. Experimental Procedure

S2.1 General Experimental

Prior to running each reaction, the reactor was equilibrated with an identical volume of anhydrous solvent. For example, if 20 mL of anhydrous DMF was used to dissolve a solution, then 20 mL of anhydrous DMF was used to equilibrate the reactor immediately prior to running the reaction.

S2.2 Synthesis of (3,4-dihydroxy-L-rhamnol 4).



Solution 1: In a flame-dried 50-mL round bottom flask, commercially available 3,4-*O*-diacetyl-L-rhamnal (5.0 g, 23.3 mmol) was added and dissolved into 39 mL anhydrous methanol (0.6 M).

Solution 2: In a flame-dried 50-mL round bottom flask, NaOMe (1.01 g, 18.6 mmol) was added and dissolved into 39 mL anhydrous methanol (0.48 M).

Solutions 1 and 2 were loaded into separate NORM-JECT syringes and mounted into a Harvard syringe pump.

The syringe pump was set to infuse at 2 mL/min (total flow rate = 4 mL/min).

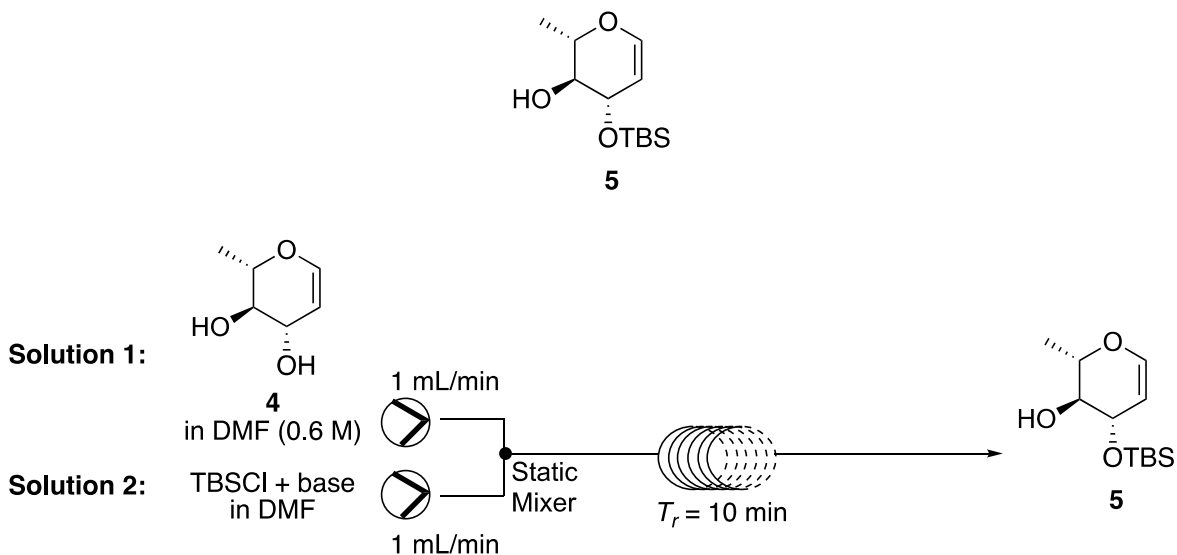
After the solution was dispensed, 40 mL total (20 mL in each line) of anhydrous methanol was used to flush the reactor. After the collection time had subsided, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (5 to 10% methanol in dichloromethane) to afford **4** (2.98 g, 98%) as a white solid. The spectroscopic data was in good agreement with previously reported values.¹

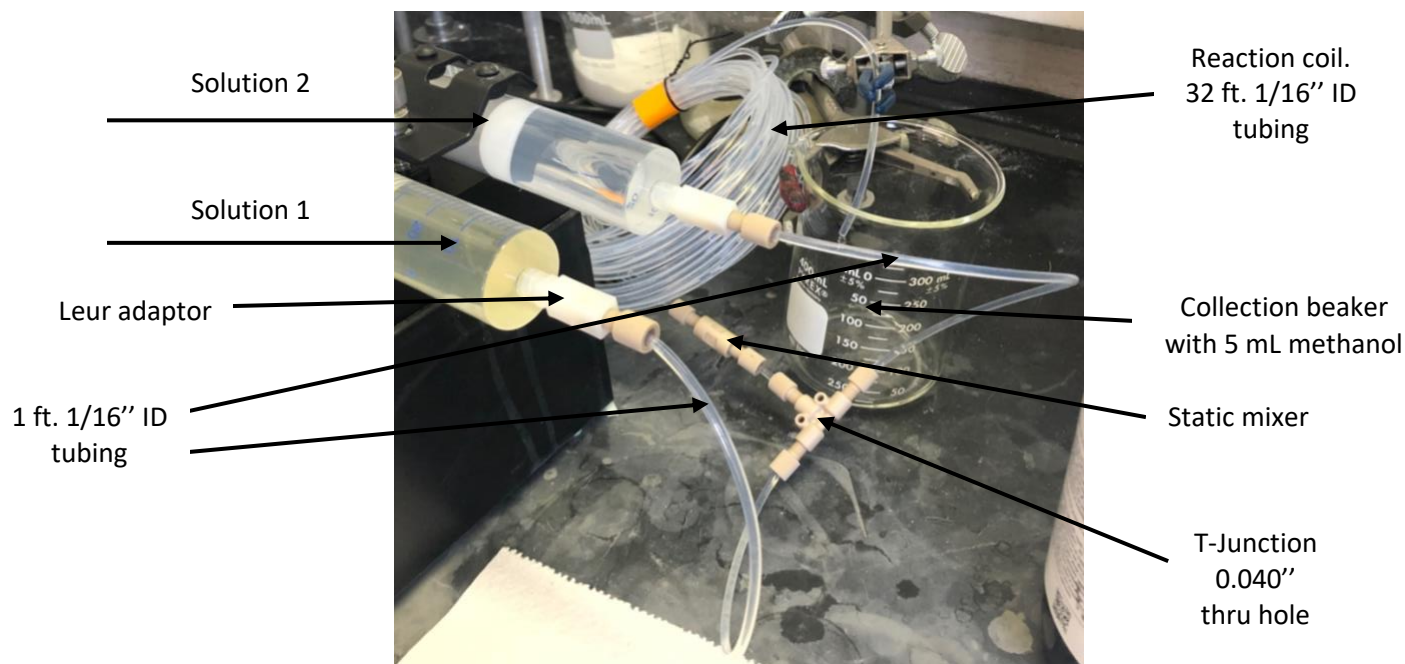
¹H NMR (500 MHz, CDCl₃) δ 6.32 (dd, *J* = 6.0, 1.6 Hz, 1H), 4.72 (dd, *J* = 6.0, 2.0 Hz, 1H), 4.23 – 4.19 (m, 1H), 3.87 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.45 – 3.40 (m, 1H), 2.44 (d, *J* = 26.7 Hz, 1H), 1.91 (d, *J* = 24.4 Hz, 1H), 1.39 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 144.9, 102.7, 75.6, 74.4, 70.4, 17.1.

LRMS (ESI) *m/z*: [M+Na]⁺ Calcd. for C₆H₁₀O₃Na 153.05; found 154.12

S2.3 Synthesis of 3-*O*-(*tert*-butyldimethylsilyl)oxy-L-rhamnal **5**





5 mL of MeOH was added to the collection beaker before infusion began to quench the reaction as it proceeded.

Solution 1: Compound **4** (2.97 g, 22.8 mmol) was dissolved into 38 mL anhydrous DMF (0.6 M).

Solution 2: In a flame-dried round bottom flask, *tert*-butyldimethylsilyl chloride (3.78 g, 25.1 mmol) and 4-dimethylaminopyridine (4.18 g, 34.2 mmol) were dissolved in anhydrous DMF (38 mL).

Solutions 1 and 2 were loaded into separate NORM-JECT syringes and mounted into a Harvard syringe pump.

Syringe pump was set to infuse at 1 mL/min (total flow rate = 2 mL/min).

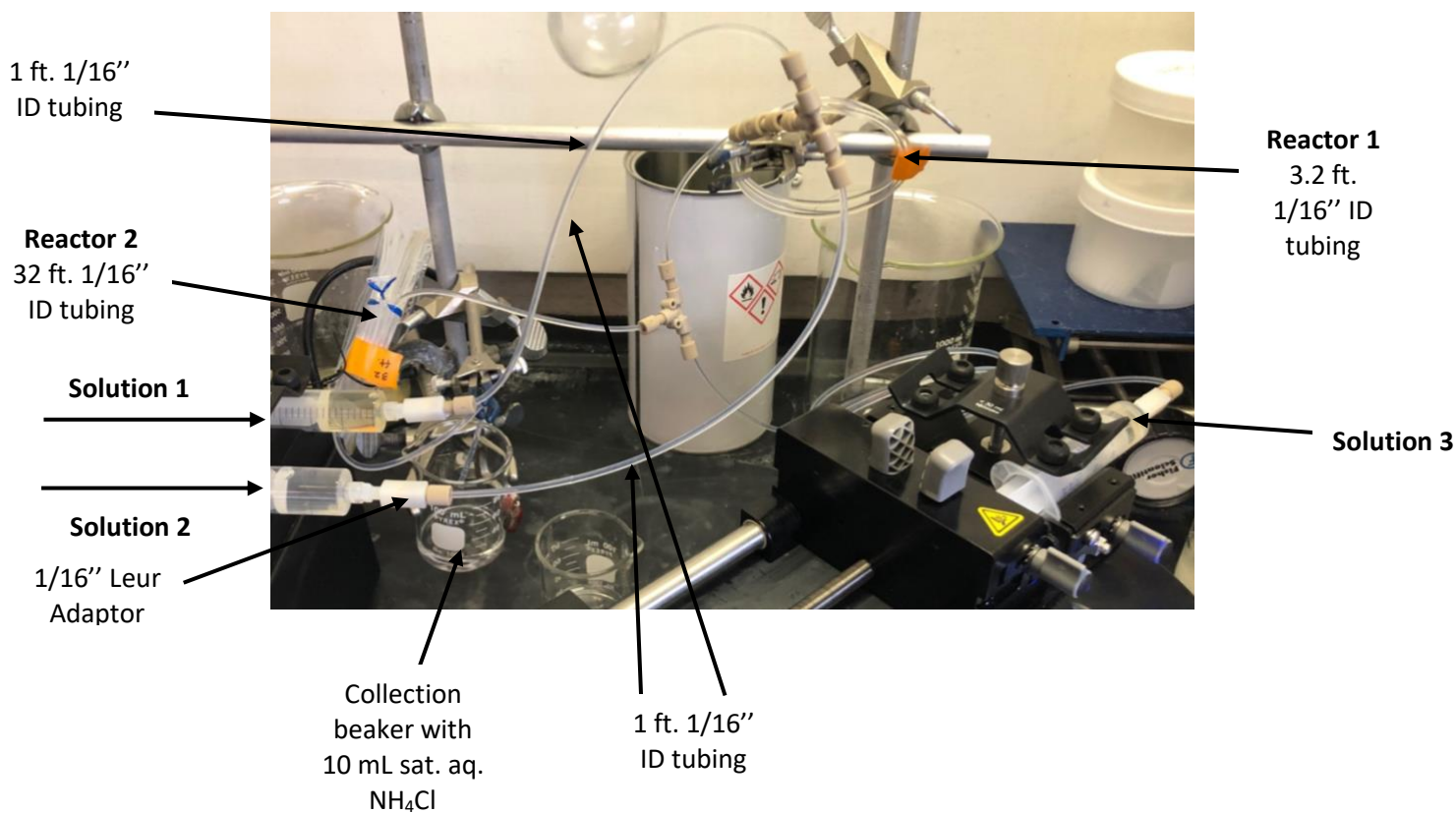
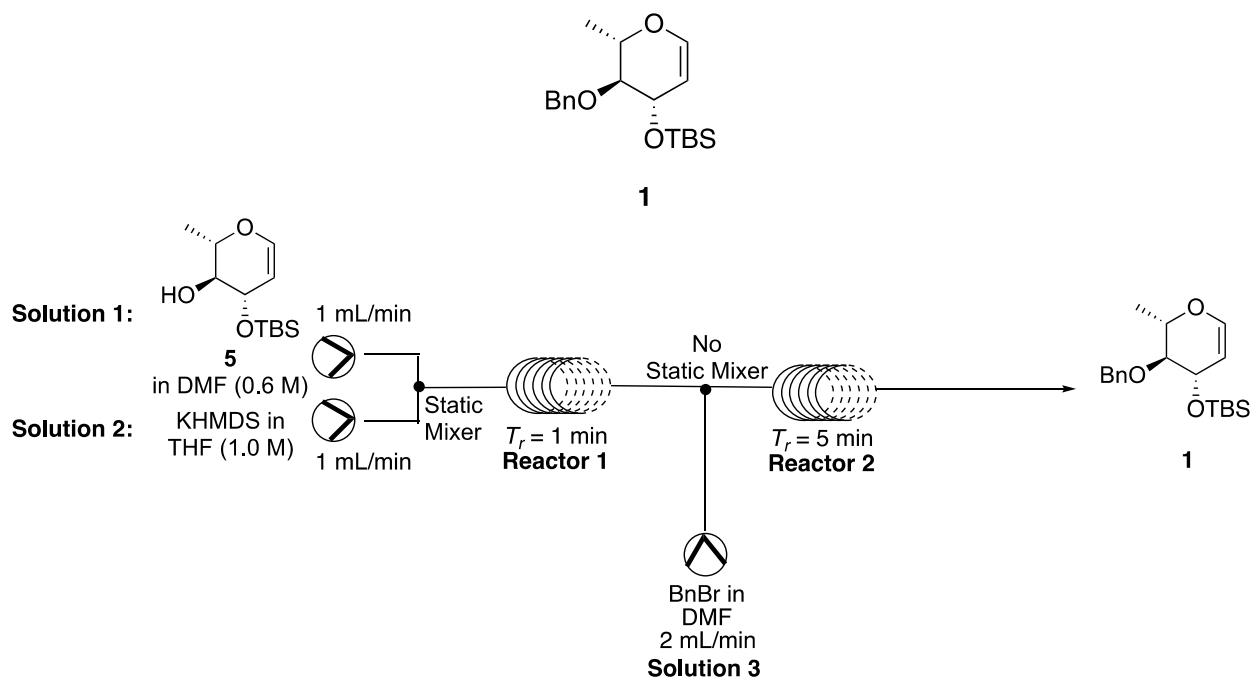
After the solution was dispensed, 40 mL total (20 mL in each line) of anhydrous DMF was used to flush the reactor. After the collection time had subsided, the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (3x). The pooled organic layers were washed with 1M LiCl (2x), brine (1x), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (5 to 10% ethyl acetate in hexanes) afforded **5** (4.90 g, 88%) as a clear oil. The spectroscopic data is in good agreement with previously reported values.²

¹H NMR (500 MHz, CDCl₃) δ 6.26 (dd, *J* = 6.1, 1.6 Hz, 1H), 4.62 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.21 (dt, *J* = 6.8, 1.9 Hz, 1H), 3.91 (dq, *J* = 9.2, 6.4 Hz, 1H), 3.47 (ddd, *J* = 9.2, 6.8, 3.9 Hz, 1H), 2.11 (d, *J* = 3.9 Hz, 1H), 1.38 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 143.6, 103.4, 74.9, 74.3, 70.5, 25.8, 18.1, 17.2, -4.3, -4.5.

LRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{12}H_{24}O_3SiNa$ 267.14; found 268.01

S2.4 Synthesis of 3-O-(tert-butyltrimethylsilyloxy)-4-O-benzyl-L-rhamnal 1



10 mL of sat. aq. NH_4Cl was added to the collection beaker prior to infusion to quench the reaction as it proceeded.

Solution 1: Compound **5** (2.69 g, 11.0 mmol) was dissolved in 18.3 mL anhydrous DMF (0.6 M).

Solution 2: In a flame-dried round bottom flask, potassium bis(trimethylsilyl)amide (1.0 M in THF, 11 mL, 11.0 mmol) was added and brought to 18.3 mL with an additional 7.3 mL anhydrous DMF.

Solution 3: In a flame-dried round bottom flask, benzyl bromide (6.54 mL, 55.0 mmol) was added and brought to ~36.6 mL with an additional 30 mL anhydrous DMF (1.8 M).

Reactors 1 and 2 were assembled and connected with a T-Mixer. In this setup, a static mixer was not included to avoid clogging from precipitate that would form overtime.

Solutions 1 and 2 were loaded into separate NORM-JECT syringes and mounted into a Harvard syringe pump. The syringe pump was set to infuse at 1 mL/min (total flow rate = 2 mL/min).

Solution 3 was loaded into a NORM-JECT syringe and mounted into a Harvard syringe pump. The syringe pump was set to infuse at 2 mL/min (total flow rate = 4 mL/min).

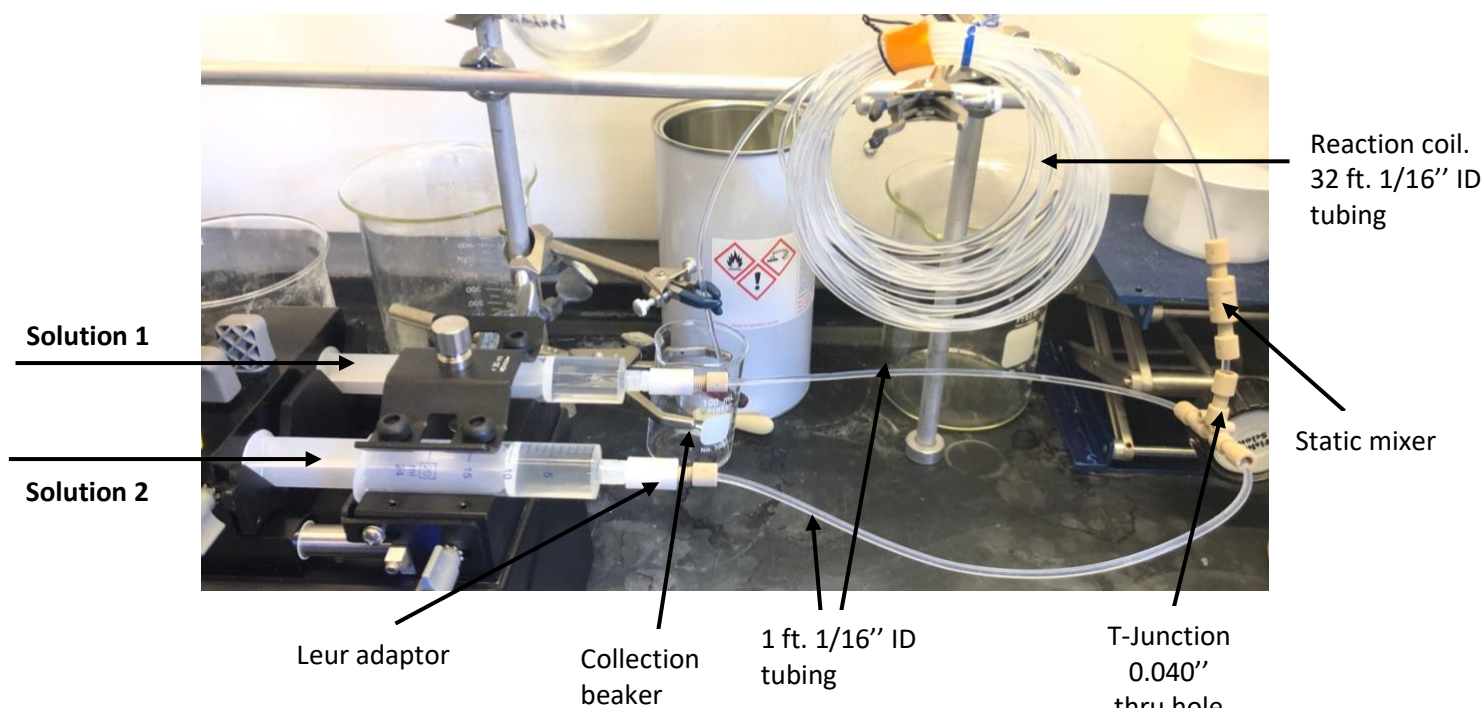
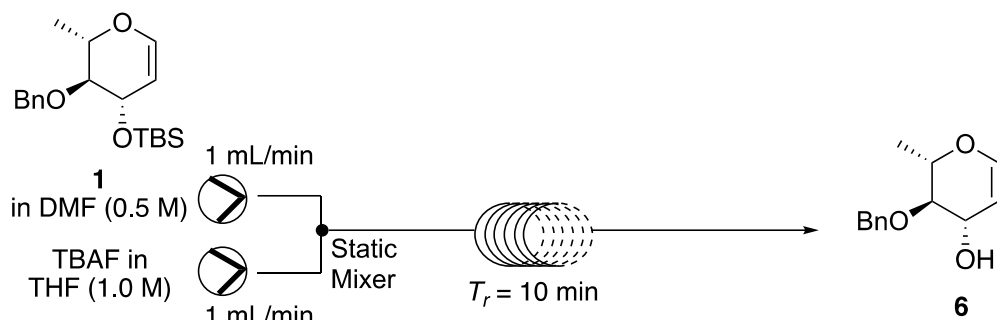
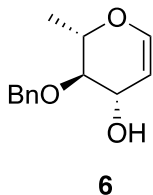
After all of the solutions were dispensed, 60 mL total (20 mL in each line) of anhydrous DMF was used to flush the reactors. After the collection time had subsided, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3x). The pooled organic layers were washed with 1M LiCl (2x), brine (1x), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2 to 5% ethyl acetate in hexanes) afforded **1** (3.16 g, 86%) as a clear oil. The spectroscopic data is in good agreement with previously reported values.³

^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 6.27 (dd, $J = 6.1, 1.5$ Hz, 1H), 4.88 (d, $J = 11.2$ Hz, 1H), 4.67 (d, $J = 11.2$ Hz, 1H), 4.63 (dd, $J = 6.1, 2.5$ Hz, 1H), 4.37 (dt, $J = 6.4, 1.9$ Hz, 1H), 3.94 (dq, $J = 8.8, 6.5$ Hz, 1H), 3.34 (dd, $J = 8.9, 6.4$ Hz, 1H), 1.34 (d, $J = 6.4$ Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 143.5, 138.3, 128.4, 127.9, 127.7, 103.9, 81.8, 74.5, 73.9, 69.9, 25.9, 18.0, 17.4, -4.3, -4.6.

LRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{SiNa}$ 357.19; found 358.06

S2.5 Synthesis of 4-O-benzyl-L-rhamnol 6



Solution 1: Compound 1 (1.73 g, 5.17 mmol) was dissolved in 10.3 mL DMF (0.5 M).

Solution 2: Tetra-butylammonium fluoride (1.0 M in THF, 10.3 mmol, 10.3 mL).

Solutions 1 and 2 were loaded into separate NORM-JECT syringes and mounted into a Harvard syringe pump.

Syringe pump was set to infuse at 1 mL/min (total flow rate = 2 mL/min).

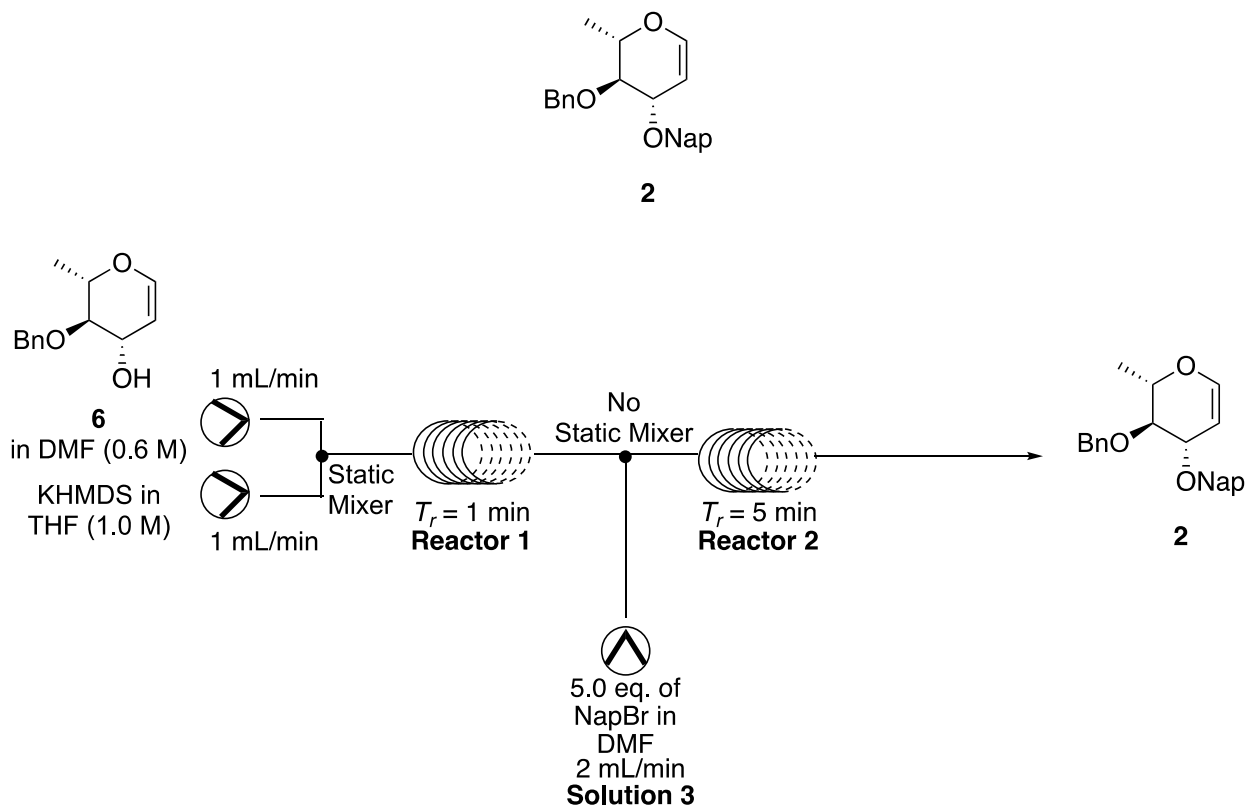
After the solution was dispensed, 40 mL total (20 mL in each line) of anhydrous DMF was used to flush the reactor. After the collection time had subsided, the solution was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (20 to 30% ethyl acetate in hexanes) to afford **6** (1.06 g, 93%) as a white solid. The spectroscopic data is in good agreement with previously reported values.⁴

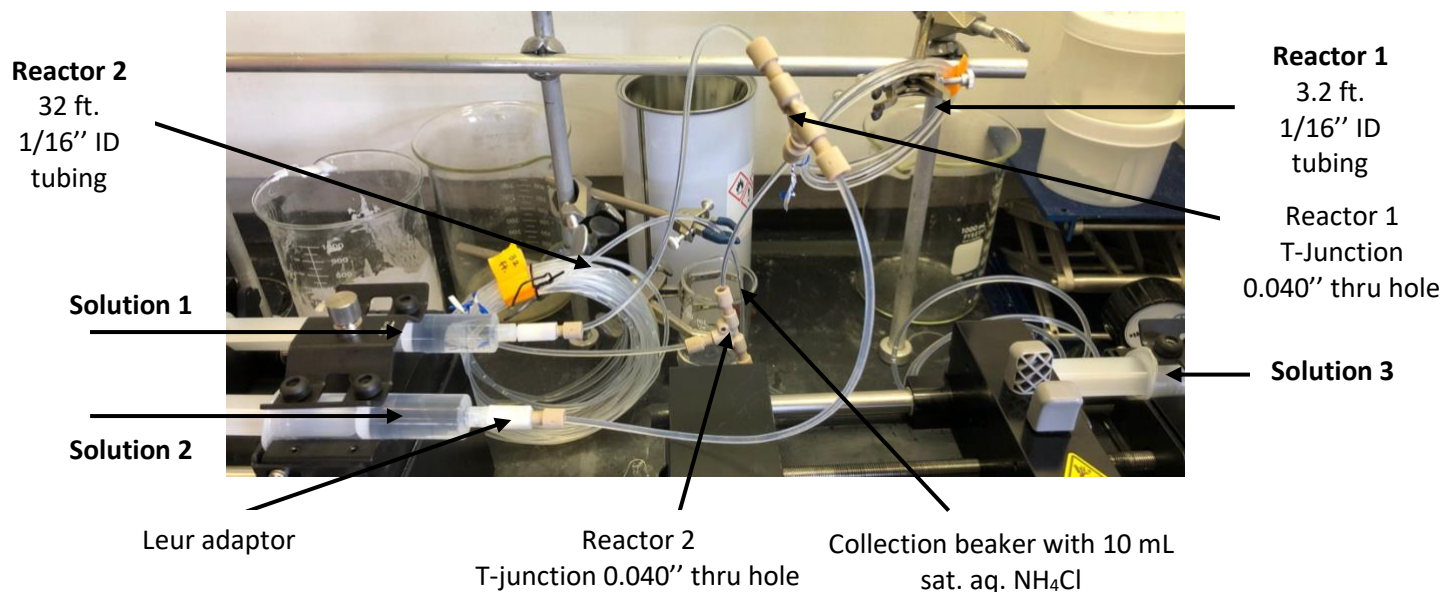
¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.27 (m, 5H), 6.33 (dd, *J* = 5.9, 1.7 Hz, 1H), 4.87 – 4.77 (m, 2H), 4.70 (dd, *J* = 6.0, 2.3 Hz, 1H), 4.41 – 4.29 (m, 1H), 3.91 (dq, *J* = 9.6, 6.4 Hz, 1H), 3.28 (dd, *J* = 9.6, 6.9 Hz, 1H), 1.65 (d, *J* = 5.8 Hz, 1H), 1.41 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 144.7, 138.3, 128.6, 128.0, 103.1, 82.5, 74.3, 74.1, 70.0, 17.6.

LRMS (ESI) *m/z*: [M+Na]⁺ Calcd. for C₁₃H₁₆O₃Na 243.10; found 243.96

S2.6 Synthesis of 3-*O*-naphthyl-4-*O*-benzyl-*L*-rhamnol **2**





10 mL of sat. aq. NH_4Cl was added to the collection beaker prior to infusion to quench the reaction as it proceeded.

Solution 1: Compound **6** (1.07 g, 4.86 mmol) was dissolved into 8.1 mL DMF (0.6 M). The solution was taken up into a syringe and connected to a syringe pump.

Solution 2: In a flame-dried round bottom flask, potassium bis(trimethylsilyl)amide (1.0 M in THF, 4.86 mL, 4.86 mmol) was added and brought to ~8.1 mL with an additional 3.2 mL anhydrous DMF. The solution was taken up into a syringe and connected to the same syringe pump as Solution 1.

Solution 3: In a flame-dried round bottom flask, 2-(bromomethyl)naphthalene (5.37 g, 24.3 mmol) was added and dissolved into 16.2 mL DMF (1.5 M). The solution was taken up into a syringe and connected to a different syringe pump than Solutions 1 and 2.

Reactors 1 and 2 were assembled and connected with a T-Mixer. In this setup, a static mixer was not included to avoid clogging from precipitate that would form overtime.

Solutions 1 and 2 were loaded into separate NORM-JECT syringes and mounted into a Harvard syringe pump. The syringe pump was set to infuse at 1 mL/min (total flow rate = 2 mL/min).

Solution 3 was loaded into a NORM-JECT syringe and mounted into a Harvard syringe pump. The syringe pump was set to infuse at 2 mL/min (total flow rate = 4 mL/min).

After the solutions were dispensed, 60 mL total (20 mL in each line) of anhydrous DMF was used to flush the reactors. After the collection time had subsided, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3x). The pooled organic layers were washed with 1M LiCl (2x), brine (1x), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*.

Purification by flash column chromatography (2 to 5% ethyl acetate in hexanes) afforded **2** (1.44 g, 82%) as an amorphous solid.

^1H NMR (500 MHz, CDCl_3) δ 7.90–7.67 (m, 4H), 7.57–7.37 (m, 3H), 7.37–7.17 (m, 5H), 6.37 (d, $J = 6.1, 1.4$ Hz, 1H), 4.98–4.83 (m, 2H), 4.82 (d, $J = 12.0$ Hz, 1H), 4.76–4.69 (m, 2H), 4.27 (dd, $J = 6.6, 1.4$ Hz, 1H), 3.96 (dq, $J = 9.1, 6.5$ Hz, 1H), 3.52 (dd, $J = 9.0, 6.5$ Hz, 1H), 1.39 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 144.9, 138.5, 135.8, 133.4, 133.1, 128.5, 128.3, 128.0, 127.9, 127.79, 127.75, 126.8, 126.2, 126.1, 126.0, 100.2, 79.5, 76.6, 74.2, 74.1, 70.6, 17.7.

LRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{Na}$ 383.16; Found 383.92

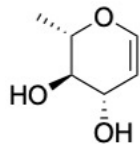
HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{Na}$ 383.1623; Found 383.1628

$[\alpha]^{25}_{\text{D}} = +29.8$ ($c = 1.22$, CH_2Cl_2)

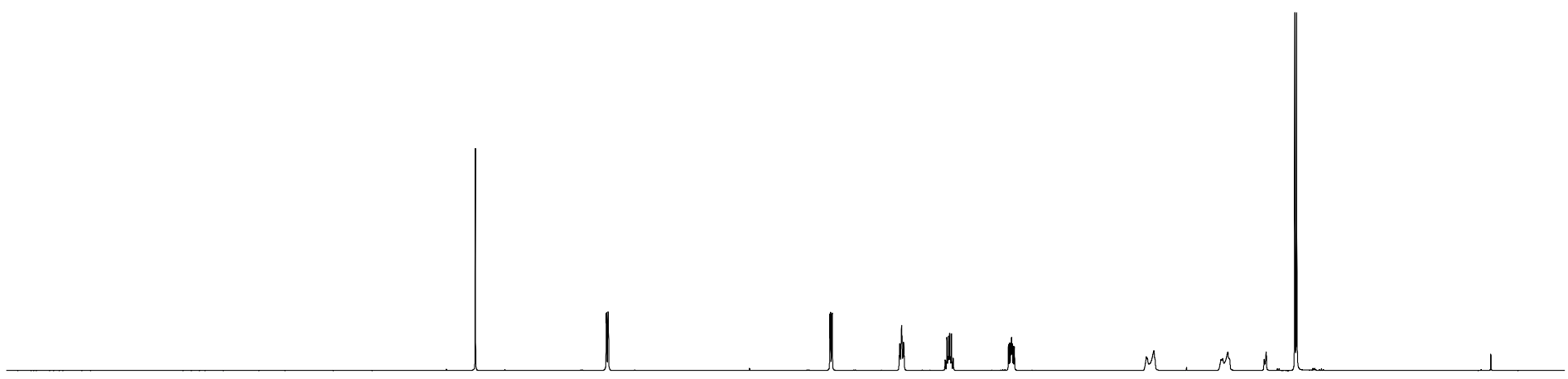
References:

- (1) Timmons, S. C.; Jakeman, D. L. *Carbohydr. Res.* 2007, **342**, 2695–2704.
- (2) Donnard, M.; Tschamber, T.; Eustache, J. *Tetrahedron Lett.* 2008, **49**, 7325–7327.
- (3) Wandzik, I.; Bieg, T. *Carbohydr. Res.* 2006, **341**, 2702–2707.
- (4) Kirschning, A.; Hary, U.; Plumeier, C.; Ries, M.; Rose, L. *J. Chem. Soc. Perkin Trans. 1* 1999, **4**, 519–528.

¹H NMR of 4 (500 MHz, CDCl₃)



7.263
6.326
6.323
6.314
6.311
4.726
4.722
4.714
4.710
4.231
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4.213
4.203
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3.889
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2.457
2.410
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1.918
1.881
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1.606
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10

9

8

7

6

5

4

3

2

1

0

ppm

0.97

1.00

1.02

1.03

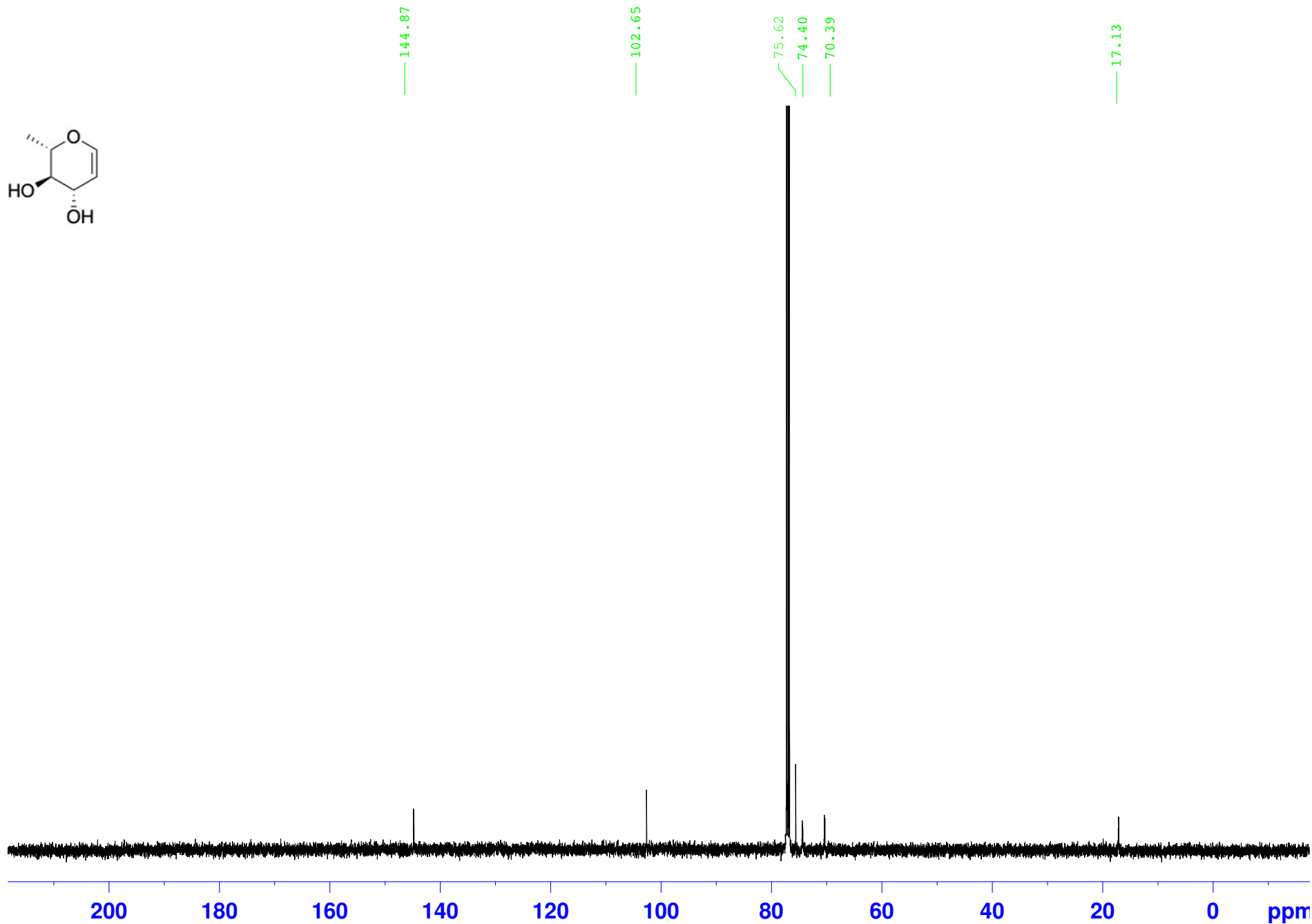
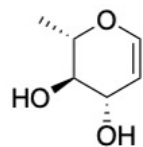
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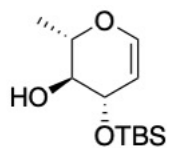
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3.15

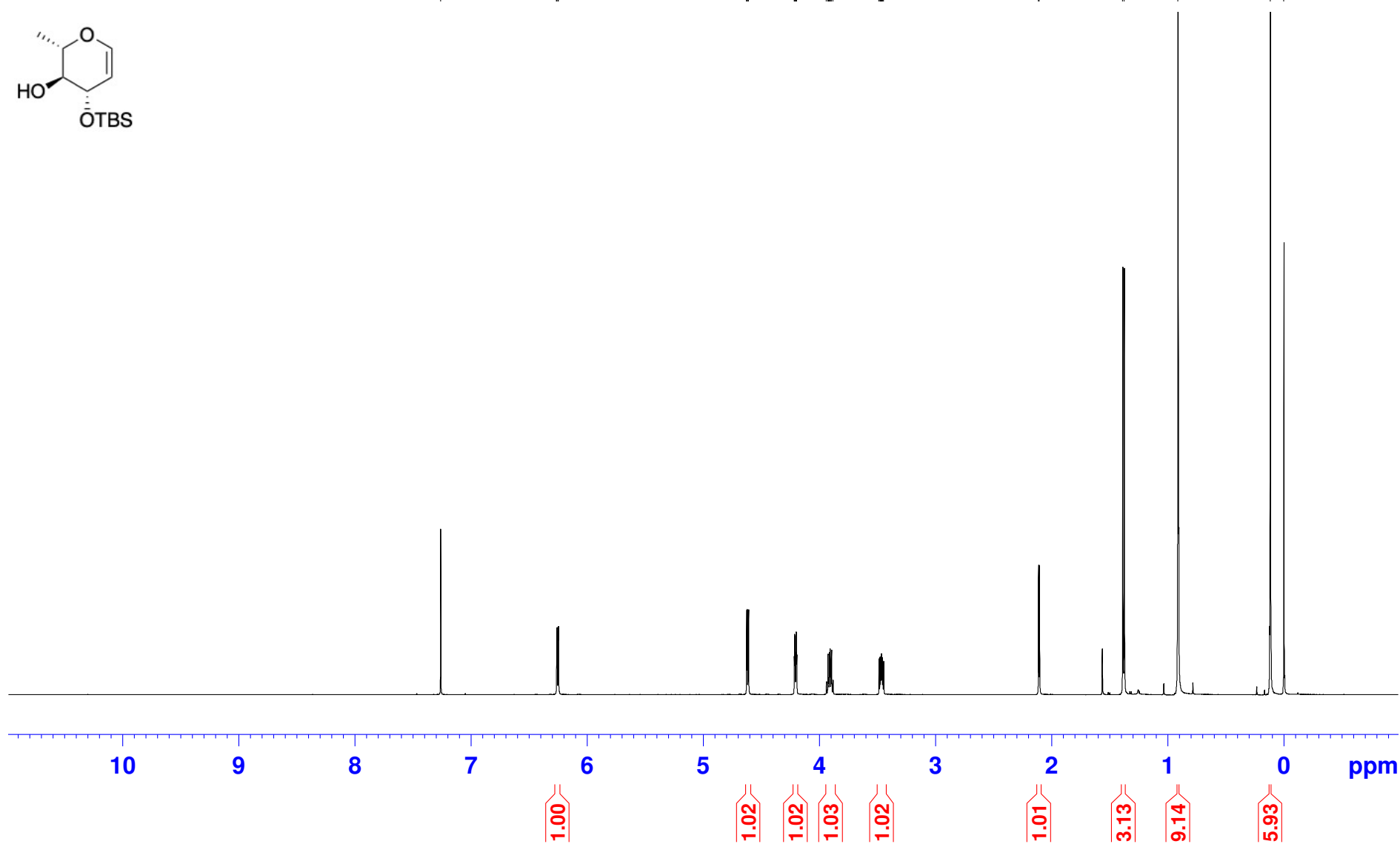
¹³C NMR of 4 (125 MHz CDCl₃)



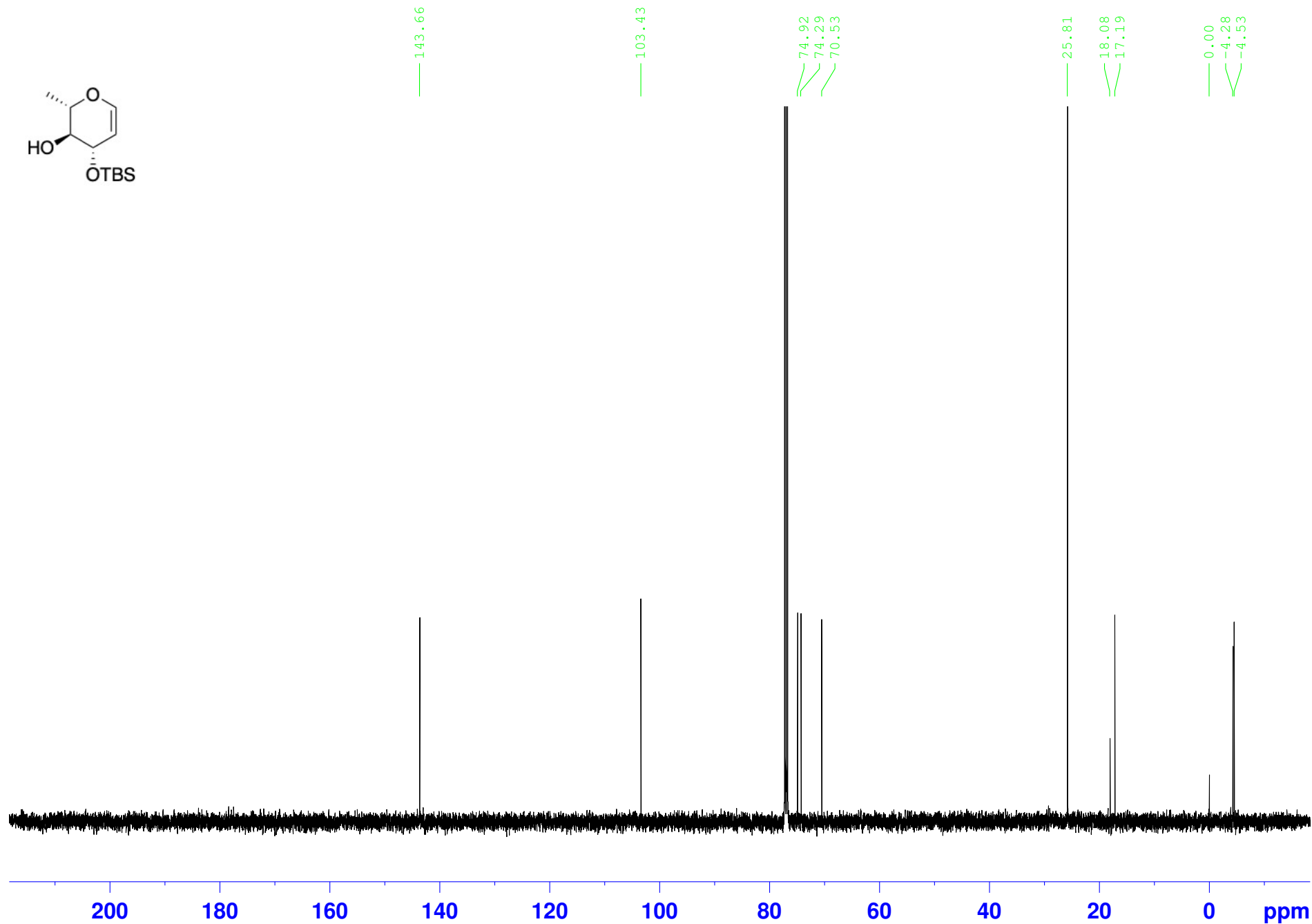
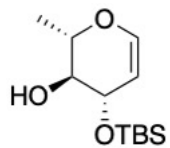
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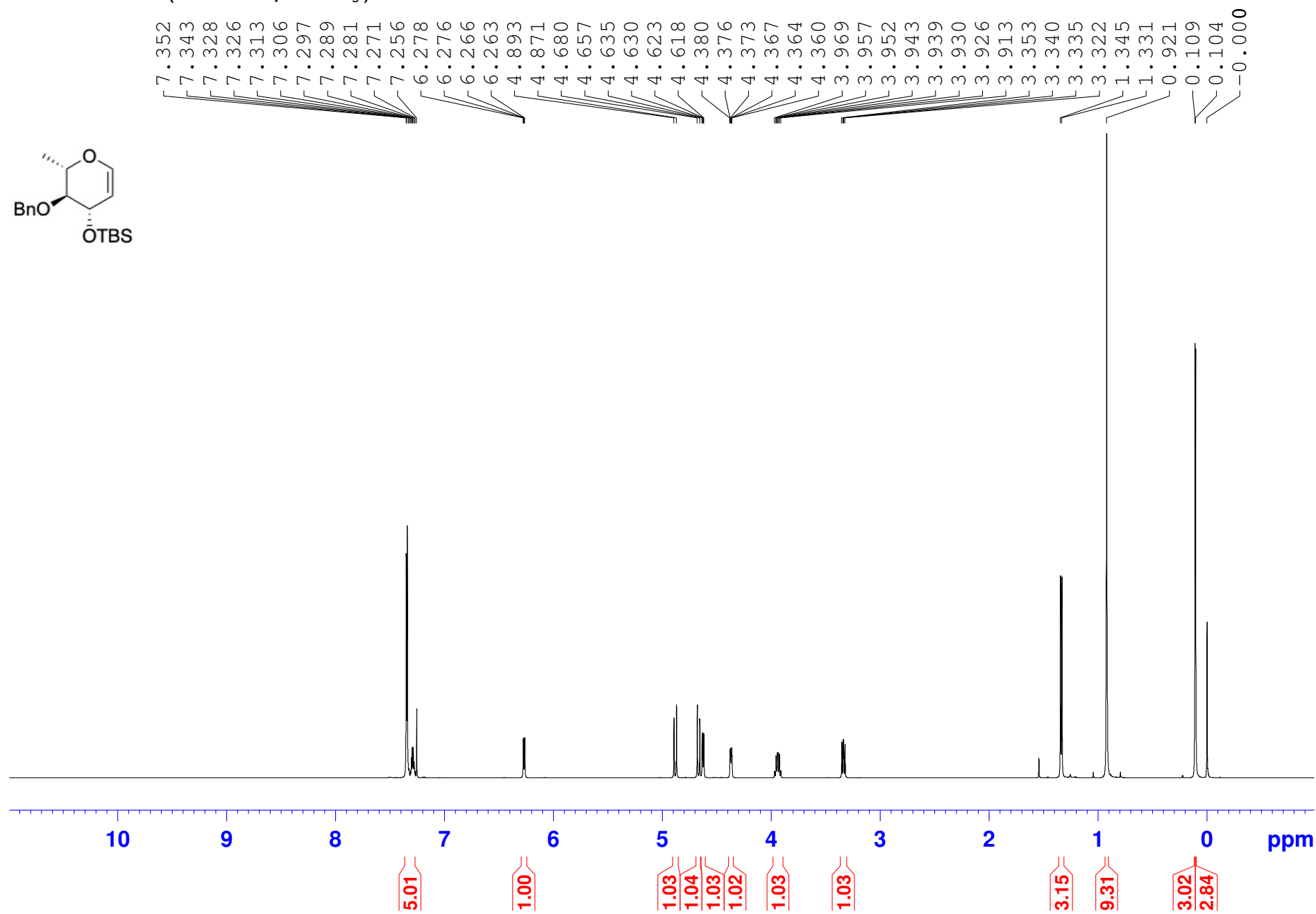
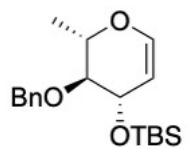
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4.200
4.196
3.940
3.927
3.921
3.914
3.909
3.901
3.896
3.883
3.487
3.479
3.473
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0.000



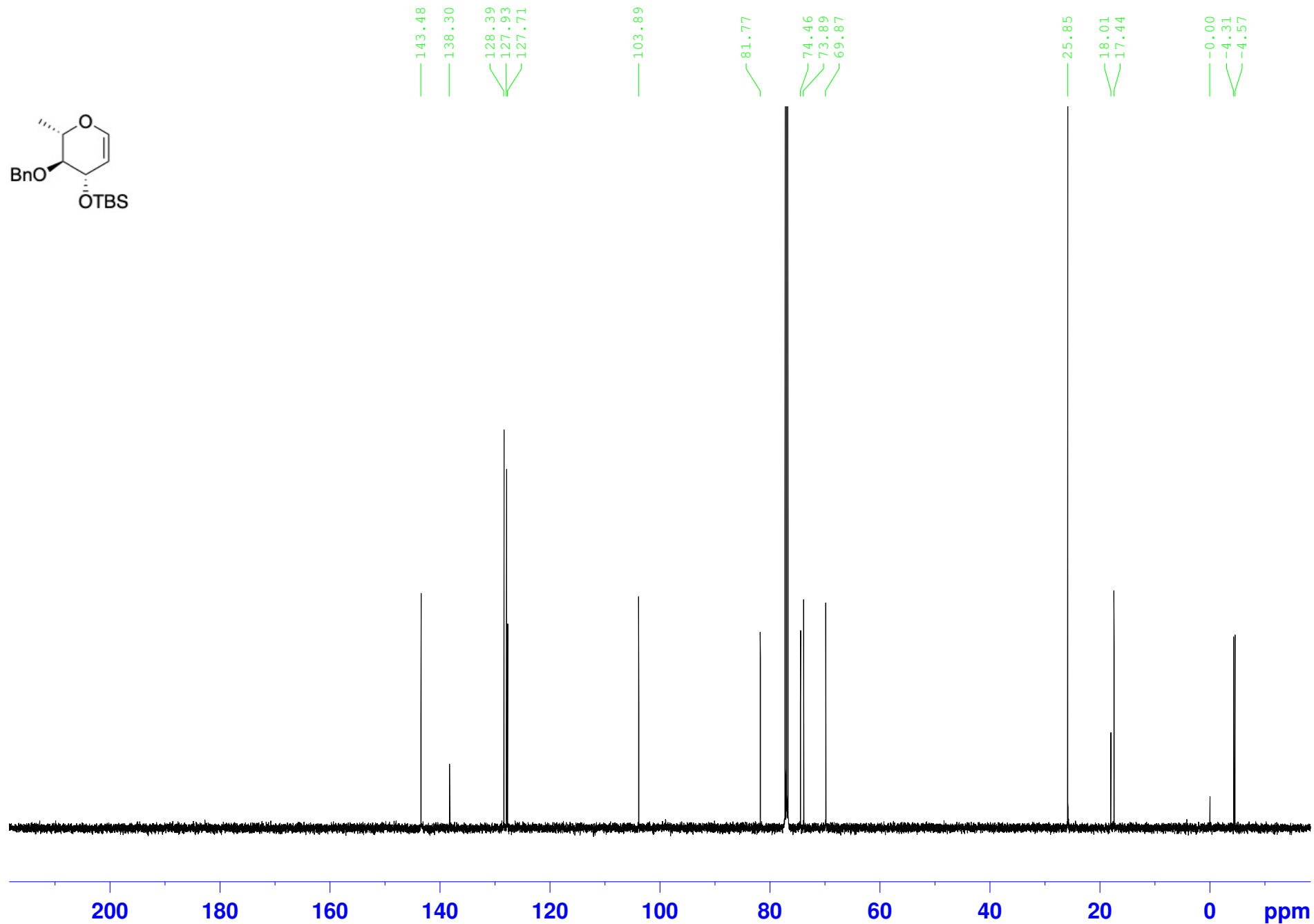
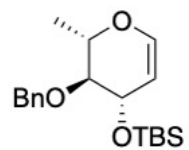
¹³C NMR of 5 (125 MHz, CDCl₃)



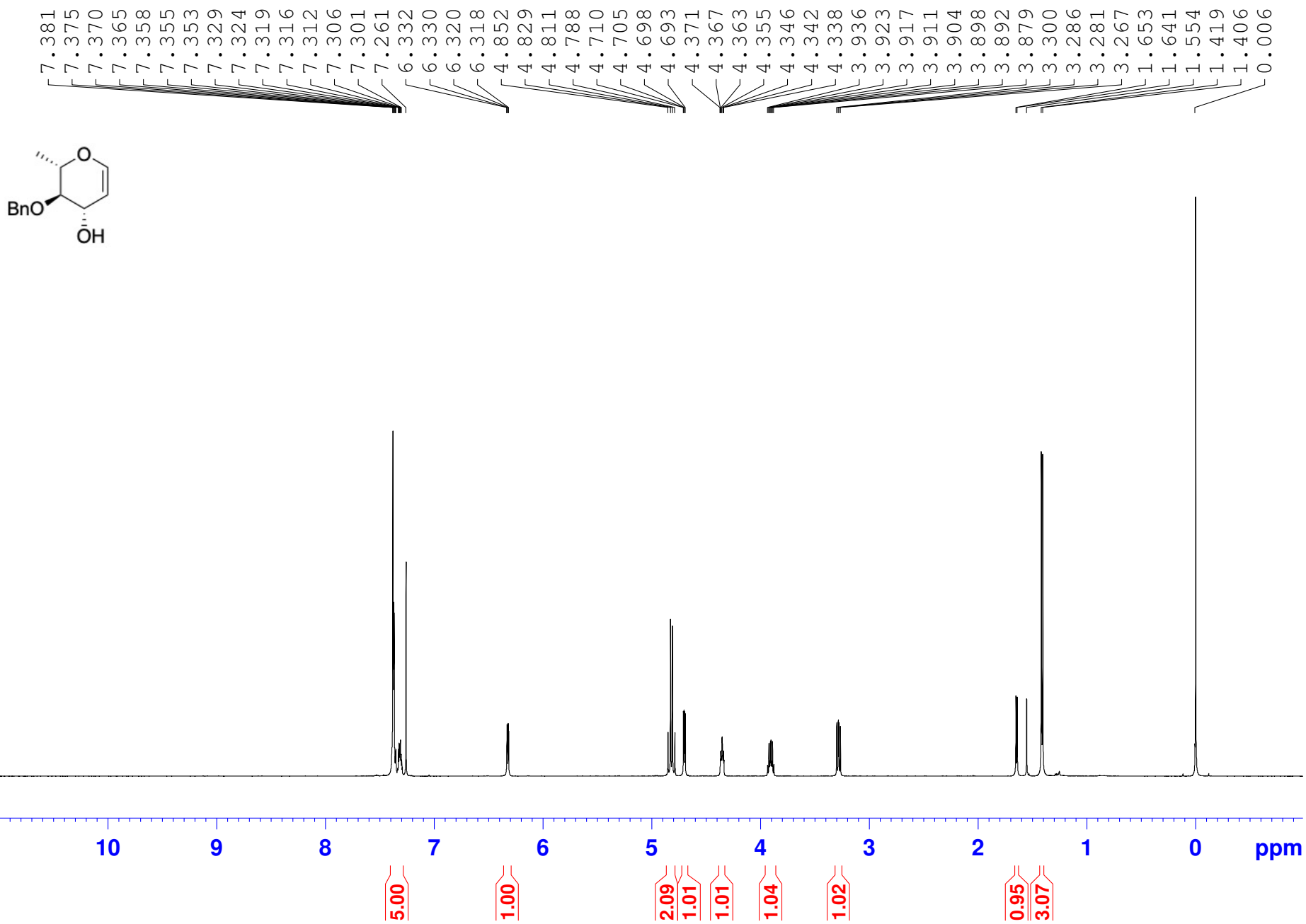
¹H NMR of **1** (500 MHz, CDCl₃)



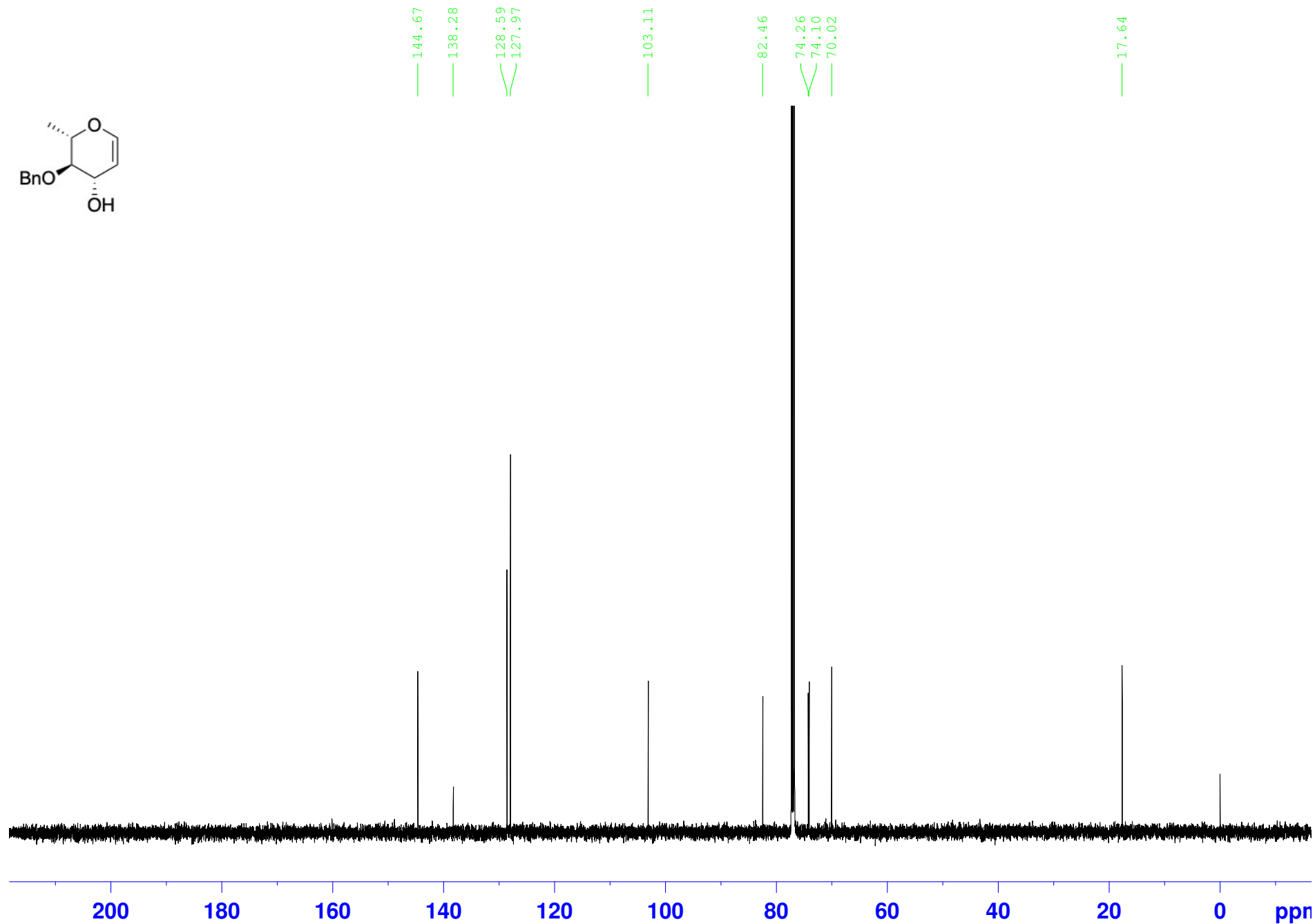
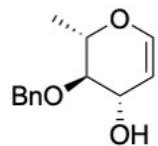
¹³C NMR of **1** (125 MHz, CDCl₃)



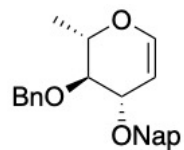
¹H NMR of 6 (500 MHz, CDCl₃)



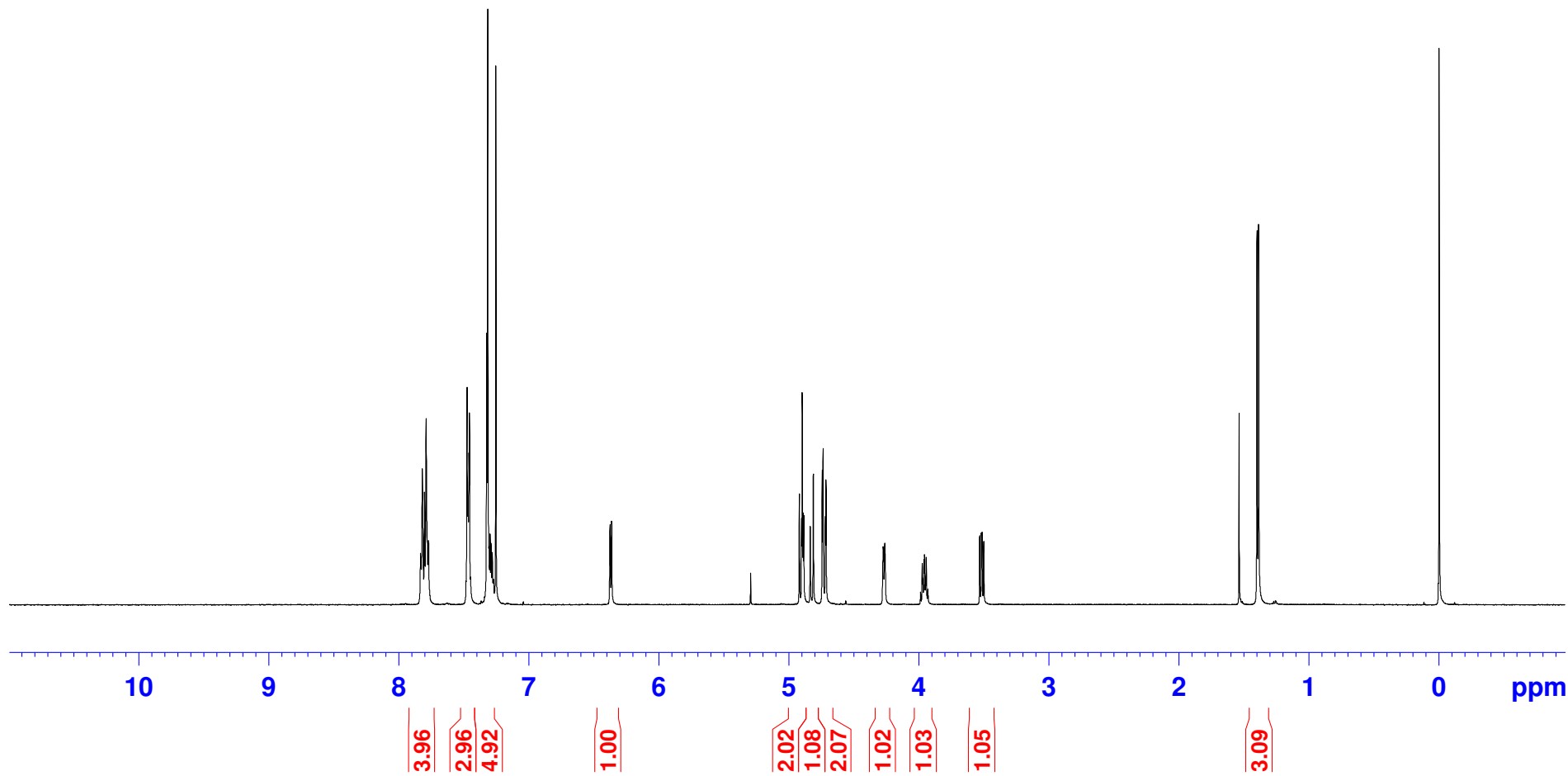
¹³C NMR of 6 (125 MHz, CDCl₃)



¹H NMR of 2 (500 MHz, CDCl₃)



7.835
7.822
7.804
7.792
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7.476
7.472
7.469
7.465
7.463
7.458
7.327
7.318
7.308
7.300
7.293
6.376
6.364
4.920
4.903
4.898
4.891
4.886
4.836
4.813
4.744
4.738
4.720
4.715
4.279
4.275
4.272
4.266
4.262
4.259
3.987
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3.970
3.962
3.957
3.949
3.944
3.931
3.533
3.519
3.515
3.502
1.399
1.386



¹³C NMR of 2 (125 MHz, CDCl₃)

