Organic Syntheses

Enantioselective Synthesis of α– and β–Boc-protected 6-Hydroxy-pyranones: Carbohydrate Building Blocks

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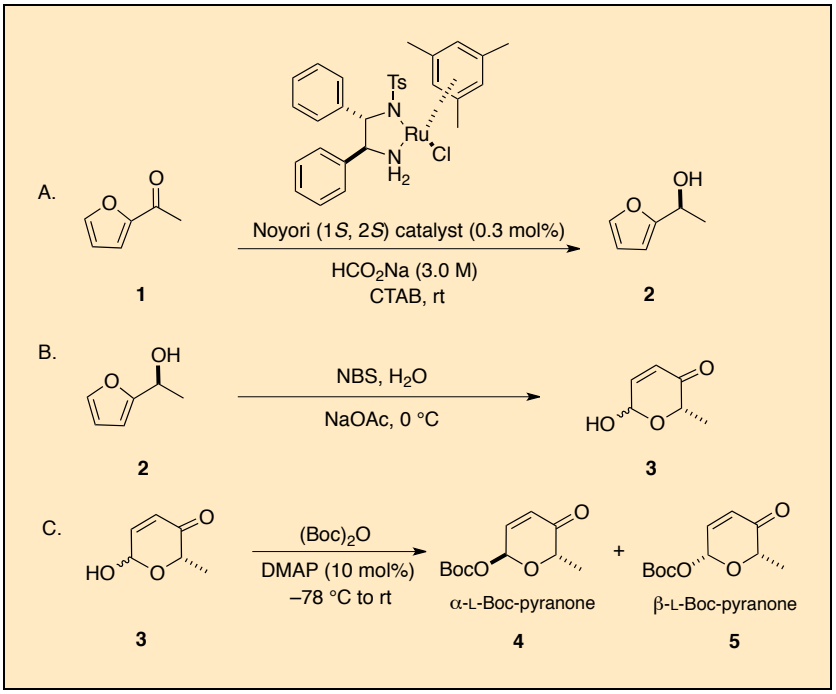

Procedure

A. *(S)-1-(Furan-2-yl)ethanol (***2***).* To a 500 mL Erlenmeyer flask equipped with a 5 cm octagonal magnetic stir bar is added sodium formate (55.0 g,

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0.801 mol) (Note 1) followed by 267 mL of deionized water to make a 3.0 M solution. The solution is stirred until all of the solid dissolves and simultaneously degassed by bubbling nitrogen gas through the solution via a needle for 5 min at room temperature. Liquid 2-acetyl furan (**1**) (16.4 mL, 18.1 g, 0.163 mol, 1 equiv) (Note 2), CH_2Cl_2 (2 mL) (Note 3), and cetyltrimethylammonium bromide (CTAB) (5.9 g, 10 mol%) (Note 4) are added, the flask loosely capped with a polyethylene cap, and the solution stirred for 20 min. To the resulting brown suspension, Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN (304 mg, 0.3 mol%) (Note 5) is added, and the Erlenmeyer flask again capped loosely with a polyethylene stopper. The resulting suspension is stirred vigorously at room temperature for 24 h (Note 6). The progress of the reaction is monitored by TLC using *p*-anisaldehyde as stain (Compound **2** has an R_f=0.26 in 20% EtOAc in hexanes. The starting 2-acetyl furan (R_f=0.37) is UV active, whereas the product alcohol is not) (Note 7). The darker brown reaction mixture is diluted with water (200 mL), the magnetic stir bar removed, and the solution is transferred to a 2-L separatory funnel. The mixture is extracted with Et_2O (4 x 500 mL) and the layers are allowed to separate over a period of 30 min for each extraction (Note 8). The combined organic layers are washed with saturated $NaHCO_3$ solution (150 mL) (Note 9), saturated NaCl solution (150 mL), dried over Na_2SO_4 (22.5 g) (Note 10), and passed through a small plug of silica gel (50 g SiO_2, vacuum filtration, 6.5 cm in diameter, 3.2 cm height, 0.5 cm sand). The Na_2SO_4 is washed with Et_2O (2 x 150 mL) and successively passed through the silica gel plug. The filtrate is concentrated under reduced pressure using a rotary evaporator (20 °C, 150 mmHg initial to 25 mmHg) yielding 16.7 g of the crude furan alcohol (**2**) as a dark grey oil (Note 11). A small amount of the representative sample is purified using silica gel flash chromatography eluting with 20-25% Et_2O/hexanes to give pure furan alcohol **2** as a colorless oil (Note 12).

B. *(2S, 6R)-6-Hydroxy-2-methyl-2H-pyran-3(6H)-one (**3**).* The crude furan alcohol (**2**) (16.57 g, 0.148 mol, 1.0 equiv) in a 500 mL 2-neck Erlenmeyer flask equipped with a thermometer and 5 cm magnetic stir bar (Note 13) is dissolved in 248 mL of THF/H_2O (3:1) (Note 14) and cooled to 1.2 °C using an ice-water bath. Solid $NaHCO_3$ (24.85 g, 0.296 mol, 2.0 equiv) (Note 9) and NaOAc•$3H_2O$ (20.2 g, 0.148 mol, 1.0 equiv) (Note 15) are added successively over the course of 1 min each, during which time the temperature lowers to –1.2 °C. After stirring for 5 min, solid *N*-bromosuccinimide (27.97 g, 0.156 mol, 1.05 equiv) (Note 16) is added to the solution portion-wise

(approx. 7 g every 5 min). The resulting orange/red color resulting from each addition of NBS quickly subsides to a green/brown suspension and the temperature is maintained between 1 °C and 10 °C. Upon the last addition of NBS, the orange/red color persists through the remainder of the reaction. The reaction mixture is stirred for an additional 2 h and the temperature maintained between 1–2 °C. Product formation is monitored by TLC (Note 7) using *p*-anisaldehyde as stain (Compound **3** possesses an R_f=0.24 in 40% EtOAc in hexanes, while the starting material's R_f=0.52). The resulting slurry is diluted with Et_2O (100 mL) and transferred to a 2-L separatory funnel containing H_2O (200 mL) and an additional Et_2O (100 mL) that were precooled to 4.5 °C in an ice/water bath. The organic layer is separated. The bottom aqueous layer, which still contains some solid material, is once again washed with Et_2O (3 x 400 mL) and the combined organics are washed with saturated aqueous NaCl (200 mL), after which the red/orange organic phase changes to a grey/faint red solution. The organic layer is then dried over sodium sulfate (30 g) (Note 10) with stirring for 30 min to give a clear grey organic phase. The sodium sulfate is filtered, washed with Et_2O (2 x 50 mL), and the combined filtrate concentrated under reduced pressure by rotary evaporator (20 °C, 150 mmHg initial to 25 mmHg final) yielding a crude mixture of alcohol diastereomers **3** as a grey/faint red oil (24.33 g) (Note 17), which is stored in a freezer at –19 °C. A small amount of the representative crude sample is purified by silica gel flash chromatography, eluting with 25-30% EtOAc/hexanes, to give a mixture of diastereomers **3** as a colorless oil (Note 18).

C. *tert-Butyl ((2S,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (**4**)* and *tert-butyl ((2R,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (**5**)*. An oven-dried, 500 mL 3-necked, round-bottomed flask with 3.5 cm octagonal stirbar is equipped on the left neck with a nitrogen inlet adapter, the middle neck a rubber septum, and the right neck a rubber thermometer adapter with thermometer (Note 19). The crude mixture of diastereomeric allylic alcohols (**3**) (24.2 g, 0.148 mol, 1 equiv) (Note 20) is added and dissolved in anhydrous DCM (185 mL) (Note 3). The solution is cooled to –67.2 °C (using a dry ice–acetone bath) under nitrogen atmosphere, the center septum removed, and solid $(Boc)_2O$ (74.25 g, 0.273 mol, 2.3 equiv) (Note 21) added via funnel over the course of one min so as to maintain stirring. A catalytic amount of DMAP (1.82 g, 14.8 mmol, 0.1 equiv) (Note 22) is then added. The resulting solution is allowed to stir for 6 h at –66.8 °C and then warmed to 2.2 °C in an ice-water bath and stirred for a 3 h period (Note 23). The ice-water bath is then removed and the reaction

stirred for 1 h, during which time the reaction warms to 7.2 ºC. The reaction is monitored by TLC using potassium permanganate as stain (Compounds **4** and **5** possess R_f=0.48 and 0.44, respectively, in 20% EtOAc in hexanes, while the starting material's R_f=0.11). The reaction mixture is then brought to 2.4 ºC (ice-water bath), diluted with Et_2O (100 mL), and quenched by the addition of saturated $NaHCO_3$ (150 mL) (Note 3) over the course of 1 min. The mixture is extracted with Et_2O (4 x 500 mL) using 2-L separatory funnel. The organic layer is washed sequentially with 1N solution of $NaHSO_4$ (to remove excess DMAP) (Note 24), saturated $NaHCO_3$ (150 mL), and saturated aqueous NaCl (150 mL), after which the solution is dried over sodium sulfate (15.0 g) and filtered. The sodium sulfate is rinsed with Et_2O (2 x 50 mL) and the combined filtrate is transferred into a 3-L round-bottomed flask and concentrated under reduced pressure by rotary evaporator (20 ºC, 150 mmHg initially to 25 mmHg), which yields a crude mixture of Boc-protected pyranones as a red-brown oil.

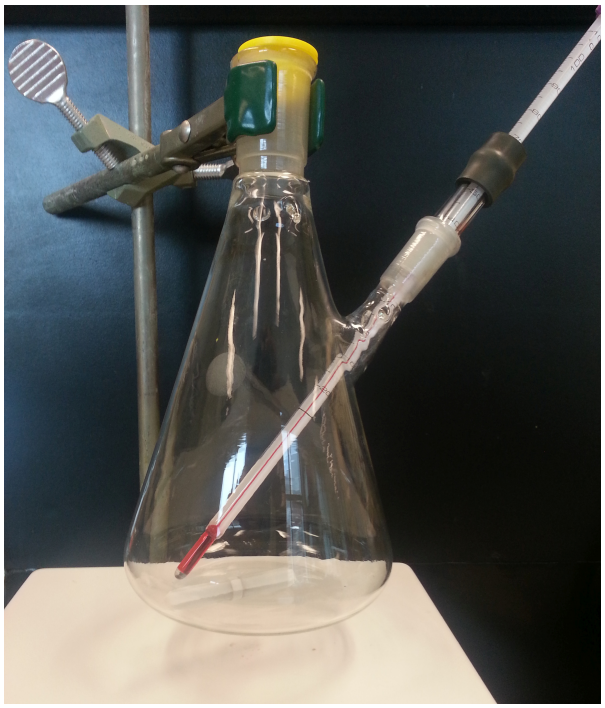
The crude product is purified by SiO_2 flash chromatography using a solvent gradient of Et_2O in hexane (0.5% to 10% Et_2O in hexane v/v). The diameter of the chromatography column is 9.0 cm, and the column is packed using silica gel (500 g) (Note 7) to a height of 14.5 cm and wetted with 0.5% Et_2O/hexanes. The oil is loaded to the top of the column and absorbed on to the silica. After placing a 0.5 cm layer of sand on top of silica, 500 mL of 0.5% Et_2O/hexanes is passed through the column. After the initial solvent is collected additional amounts of eluent are added to the top of the column with slight incremental increases in solvent polarity (e.g., 500 mL of 1% Et_2O/hexanes, followed by 500 mL of 2% Et_2O/hexane, until 500 mL of 10% Et_2O/hexanes has been passed through the column. An additional 2.5 L of 10% Et_2O/hexanes is then passed through the column). The first 4-L of solvent is collected in 500 mL fractions in Erlenmeyer flasks, after which the eluent is collected in 200 mL fractions. Fractions are monitored by TLC for product (using potassium permanganate as stain) (Note 13). The α-L-Boc-pyranone **4** elutes off of the column with the 8-10% Et_2O/hexanes wash. The fractions containing the pure α-L-Boc-pyranone **4** (least polar diastereomer, R_f (20% EtOAc/hexanes) = 0.59) are collected, concentrated on a rotary evaporator (20 ºC, 150 mmHg initially to 25 mmHg), and placed under high vacuum (1.5 mmHg)), to yield 13.02 g (57.0 mmol) of a faint yellow solid. Fractions containing a mixture of diastereomers (obtained during the 10% Et_2O/hexanes solvent system) are also collected to yield 0.50 g of a colorless oil, which can be separated by further chromatography. The β-L-Boc-pyranone **5** elutes off of the column

with the later 10% Et_2O/hexanes wash. Fractions containing the pure β-L-Boc-pyranone **5** (more polar diastereomer, R_f (20% EtOAc/hexanes) = 0.50) (Note 13) are collected, concentrated on a rotary evaporator (20 °C, 150 mmHg initially to 25 mmHg), and placed under high vacuum (1.5 mmHg) to yield 5.23 g (22.9 mmol) of a faint yellow solid (Note 25). The Boc-protected pyranones are stored in a freezer. The overall yield for the three steps is 51% (Note 26).

Notes

1. Sodium formate, BioUltra, ≥99.0%, was purchased from Sigma-Aldrich Co. and used as received.
2. 2-Acetyl furan, 99%, was purchased from Sigma-Aldrich Co. and used as received.
3. The checkers used ACS grade dichloromethane (CH_2Cl_2) purchased from Fisher Scientific and filtered through a column of activated alumina. The submitters used CH_2Cl_2 purchased from VWR International, LLC. and dried prior to use by percolation through anhydrous Al_2O_3.
4. Cetyltrimethylammonium bromide, BioXtra, ≥99.0%, was purchased from Sigma-Aldrich Co. and used as received.
5. Noyori asymmetric catalyst (*R*)-Ru(η^6-mesitylene)-(*S,S*)-TsDPEN (95%) was purchased from Sigma-Aldrich Co. and used as received.[2]
6. Sodium formate is used as a hydrogen donor source for this reaction along with cetyltrimethylammonium bromide, which functions as a phase transfer catalyst. Vigorous stirring is important for this step.
7. Silica gel SilicaFlash® F60 (40-63 μm/230-500 mesh) was purchased from Silicycle. Glass-backed extra hard layer TLC plates, 60 Å (250 μm thickness) were also purchased from Silicycle containing F-254 indicator.
8. In one instance the checkers noted an emulsion resulted without separation of the organic and aqueous phases. In this instance, an additional 200 mL deionized water was added, followed by an additional 200 mL Et_2O. The separatory funnel was shaken and the layers were allowed to separate over the course of 30 min.
9. Sodium bicarbonate, ACS reagent, 99.7–100.3%, was purchased from EMD Chemicals Inc. and used as received.

10. Sodium sulfate, ACS grade, ≥99.0%, anhydrous, granular was purchased from EMD Chemicals Inc. and used as received.
11. A ^{1}H NMR of the crude reaction mixture sample was obtained to confirm product formation prior to use in the next step. When the reaction was performed using 8.2 mL of 2-acetyl furan, 8.5 g of crude alcohol **2** was obtained.
12. The purified product **2** showed following data: R_f (25% Et_2O/hexanes) = 0.26, $[\alpha]^{24}_D$ = –22 (c = 1.0, CH_2Cl_2) (Note 27); IR (neat) 3351, 2980, 2934, 1505, 1467, 1371, 1229, 1149, 1008, 927, 877, 809, 734; 598 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55 (d, J = 6.6 Hz, 3 H), 1.93 (d, J = 5.0 Hz, 1 H), 4.88 (dq, J = 1.2, 6.4 Hz, 1 H), 6.23 (ddd, J = 3.2, 0.8, 0.8 Hz, 1 H), 6.32 (dd, J = 3.2, 1.8 Hz, 1 H), 7.37 (dd, J = 1.8, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 63.9, 105.4, 110.4, 142.2, 157.9; HRMS (ESI) Calcd for $(M+Na)^+$: 135.0422, Found: 135.0417. The enantiomeric excess of the product was determined by Mosher ester analysis (>95% ee). Absolute stereochemistry was also determined by Mosher Ester analysis according to a protocol by Hoye et al.[3] To a flame-dried vial was added *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, which was dissolved by the addition of 0.3 mL anhydrous DCM. Oxalyl chloride (43 μL, 0.48 mmol) was added, followed by DMF (2 μL, 0.026 mmol). This solution was stirred for 30 min, after which the stir bar was removed, rinsed with 0.1 mL DCM, and the vial concentrated under reduced pressure. The crude Mosher's acid chloride was then placed under high vacuum for 10 min. In a separate flame-dried 3 mL vial the crude product **2** (16.9 mg, 0.151 mmol) was dissolved in methylene chloride (0.3 mL). A 10 % DMAP pyridine solution (60 μL) was added with stirring, followed by the addition of crude Mosher's acid chloride that was dissolved in 0.2 mL DCM. The reaction was monitored by TLC. Upon completion, the crude reaction mixture was diluted with ether (1 mL), extracted with 1 N HCl (3 x 1 mL), washed with sat. $NaHCO_3$ (3 x 1 mL), dried over Na_2SO_4 and concentrated. The enantiomeric excess was determined by inspection of the crude ^{1}H NMR spectra by integration of peaks at 1.62 (d, J = 6.7 Hz, CH_3) for the (*R,R*)-isomer and 1.70 (d, J = 6.8 Hz, CH_3) for the (*R,S*)-isomer.[4] The procedure was repeated with S-(–)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid.
13. The setup is illustrated in the accompanying photograph. The checkers found it most efficient to momentarily remove the thermometer during addition of any reagents.



14. The checkers used non-stabilized tetrahydrofuran (THF) from Fisher Scientific and passed through a column of activated alumina. The submitters used THF purchased from VWR International, LLC. and dried by percolation through anhydrous Al_2O_3.
15. Sodium acetate trihydrate ReagentPlus®, ≥99.0% was purchased from Sigma-Aldrich Co. and used as received.
16. *N*-Bromosuccinimide ReagentPlus®, 99% was purchased from Sigma-Aldrich Co. and used as received.
17. A ^{1}H NMR of the crude reaction mixture sample was obtained to confirm product formation prior to use in the next step. When the reaction was performed at half scale, 14.0 g of crude material was obtained.
18. Product **3** possesses the following characterization data: R_f (40% EtOAc/hexanes) = 0.26; the mixture of α and β anomers displayed dextrorotatory chiroptic properties. The checkers observed a range of $[\alpha]^{24}{}_D$ = +76 to +103 (*c* = 1.0, CH_2Cl_2) (The submitters noted a 2.6:1 (α:β) selectivity with an $[\alpha]^{25}{}_D$ = + 44 (*c* = 1.0, CH_2Cl_2). The checkers observed

that leaving the sample in solution in an NMR tube caused the mixture to change from an initially 2.0:1 (α:β) mixture to a 3.3:1 (α:β) mixture. This variation in solution could account for the range of observed optical rotations.); IR (neat) 3377, 2988, 2940, 2875, 1690, 1447, 1373, 1234, 1159, 1016, 939 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer (α) δ: 1.38 (d, *J* = 6.8 Hz, 3 H), 3.44 (bs, 1 H), 4.66 (q, *J* = 6.8 Hz, 1 H), 5.62 (m, 1 H), 6.09 (d, *J* = 10.2 Hz, 1 H), 6.89 (dd, *J* = 10.2, 3.4 Hz, 1 H); minor isomer (β) δ: 1.45 (d, *J* = 6.7 Hz, 3 H), 3.77 (bs, 1 H), 4.22 (dq, *J* = 6.7, 1.2 Hz, 1 H), 5.66 (bm, 1 H), 6.09 (dd, *J* = 10.3, 1.6 Hz, 1 H), 6.94 (dd, *J* = 10.3, 1.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer (α) δ: 15.7, 70.8, 88.0, 127.6, 144.7, 197.3; minor isomer (β)δ: 16.6, 75.6, 91.3, 128.9, 148.4, 197.3; HRMS (ESI) Calcd. for $(C_6H_8O_3+Na)^+$: 151.0371, Found: 151.0365

19. The setup is illustrated in the accompanying photograph.

20. The number of equivalents and mmol in this step was calculated based on a theoretical quantitative yield in step B of the pyranone products **3**.

21. Di-*tert*-butyl dicarbonate ReagentPlus®, 99% was purchased from Sigma-Aldrich Co. and used as received. The number of equivalents was calculated based on a theoretical quantitative yield in step B.
22. 4-Dimethylaminopyridine ReagentPlus®, ≥99.0% was purchased from Sigma-Aldrich Co. and used as received.
23. The submitters note that in order to get good α-selectivity, the temperature should be carefully maintained between –78 ºC to –30 ºC. That is, the solution is stirred for 6 h in a dry ice-acetone bath and then warmed to – 30 ºC over a 3 h period. Finally, the reaction mixture is brought to 0 ºC (ice-water bath) diluted with Et_2O (100 mL) and quenched by the dropwise addition of saturated $NaHCO_3$ (150 mL).
24. Sodium bisulfate purum, anhydrous, ~95.0%, was purchased from Sigma-Aldrich Co. and used as received.
25. Two spots are observed on the TLC plate when using potassium permanganate as stain. The top spot is α-L-Boc-pyranone and the lower spot is β-L-Boc-protected pyranone. Pure fractions from the column are evaporated using rotary evaporator (25 ºC, 150 mmHg initial to 25 mmHg final) and dried under high vacuum (1.5 mmHg) for 6 h. Both pure α-L-Boc-pyranone and β-L-Boc-pyranone are initially viscous liquids at room temperature, but they become solid after removing residual solvent under high vacuum. The products showed the following data: Compound **4**: α-L-anomer: R_f (20% EtOAc/hexanes) = 0.59; Diastereomeric Ratio: 99.6:0.4 (α:β); HRMS $[\alpha]^{24}_D$ = +102 (*c* 1.0, CH_2Cl_2); IR (neat) 2983, 2940, 1747, 1700, 1371, 1274, 1255, 1154, 1105, 1090, 1056, 1028, 940, 859, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.41 (d, *J* = 6.7 Hz, 3 H), 1.52 (s, 9 H), 4.64 (q, *J* = 6.7 Hz, 1 H), 6.20 (d, *J* =10.2 Hz, 1 H), 6.33 (d, *J* = 3.6 Hz, 1 H), 6.87 (dd, *J* = 10.2, 3.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.6, 28.0 (3C), 72.6, 84.0, 89.5, 128.8, 141.3, 152.2, 196.1; HRMS (+ESI) Calcd. for $[C_{11}H_{16}O_5+Na^+]$: 251.0890, Found: 251.0892; Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 58.08; H, 7.08. Compound **5:** β-L-anomer: R_f (20% EtOAc/hexanes) = 0.50; $[\alpha]^{24}_D$ = –50 (*c* 0.3, CH_2Cl_2); IR (neat) 2994, 2940, 1749, 1700, 1370, 1273, 1250, 1157, 1032, 1007, 936, 852, 791 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.50 (m, 12 H), 4.37 (q, *J* = 7.1 Hz, 1 H), 6.21 (d, *J* =10.4 Hz, 1 H), 6.37 (s, 1 H), 6.88 (dd, *J* = 10.3, 2.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0, 28.0 (3C), 76.1, 84.0, 90.2, 128.6, 143.1, 152.1, 196.3. Diastereomeric Ratio: 2.4:97.6 (α:β); HRMS (+ESI) Calcd. for $[C_{11}H_{16}O_5+Na^+]$: 251.0890, Found: 251.0891. Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 58.13; H, 7.03. Diastereomeric purity is

determined by GCMS analysis. GC conditions: (column: HP-5 5% Phenyl Methyl Siloxane, 30.0 m x 250 μm x 0.50 μm nominal), Rate: 25 °C, Oven set point: 40 °C, Hold Time: 2 min. AUX Heater on: Set point: 300 °C, Hold Time: 5 min., total run time: 17 min., retention time: α-L-Boc-pyranone 7.54 min, β-L-Boc-pyranone 7.65 min. The enantiomeric excess for the α-L-Boc-pyranone was determined to be 98% by chiral HPLC (conditions: Chiralpak AD column, eluent: hexane/*i*-PrOH = 93:7, flow rate: 1.0 mL/min). The peaks were visualized at 210 nm with retention times of 5.47 min (minor isomer) and 7.37 min (major isomer).

26. The submitters report the yields obtained over the three steps range from 55-60%. The checkers report that when the reaction was performed on half scale, a 56% yield was obtained over the three steps.
27. The *S* enantiomer appears numerous times in the literature. Among these, both the + and the – optical rotations are reported. The + rotation has been found to be in error.

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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.

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and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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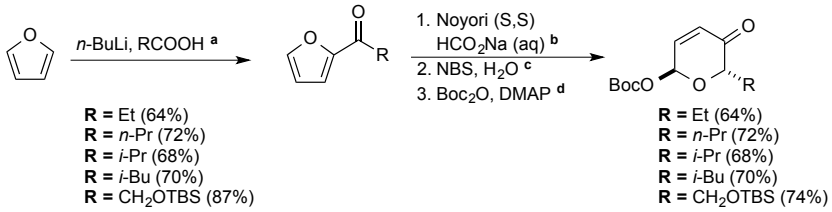
Discussion

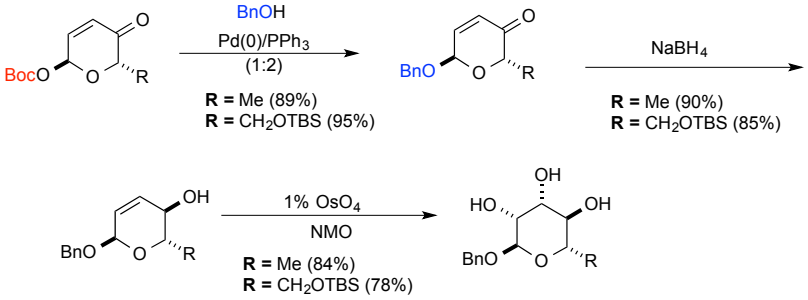
As part of a larger effort aimed at using the tools of asymmetric synthesis for medicinal chemistry, chemists have been seeking new methods for the de novo asymmetric synthesis of carbohydrates.[5] One broadly applicable asymmetric approach involves the use of α- and β-6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones as carbohydrate precursors.[6] The route begins with the asymmetric synthesis of 6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones from achiral acylfurans or vinylfurans.[7] The most practical approach begins with the acylation of furan at the 2-position and rely on the Noyori asymmetric hydrogen transfer reaction to install either the (*R*)- or (*S*)-furan alcohol stereochemistry (*i.e.*, D- or L-form respectively).[2] An NBS-promoted Achmatowicz oxidative rearrangement[8] of furan alcohols and subsequent *t*-butyl carbonate formation provides the 6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones with variable C-6 substitution as a mixture of α- and β-diastereoisomers (Scheme 1).[9]



[a]THF, 0 to -78 °C, 6-12 h; [b]10 mol% Cetyltrimethylammonium Bromide (CTAB), rt, 24 h; [c]THF/H_2O (3:1), $NaHCO_3$, $NaOAc•3H_2O$, 0 °C, 1 h; [d]CH_2Cl_2, –78 °C, 12 h

Scheme 1. Synthesis of variously substituted Boc-pyranones

The potential of the C-6 substituted α-6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones as α-mannose precursors is demonstrated by the glycosylation/post-glycosylation sequence outlined in Scheme 2. The route begins with the Pd-π-allyl catalyzed glycosylation of benzyl alcohol to stereospecifically transfer (via a double inversion mechanism) the anomeric stereocenter to the α-pyranone product. Two highly stereoselective post-glycosylation reactions install the requisite *manno*-stereochemistry. Thus, a $NaBH_4$ promoted ketone reduction installs the C-4 alcohol and an OsO_4-catalyzed Upjohn dihydroxylation installs the C-2/3 diol stereochemistry.[10]



Scheme 2. Boc-pyranones as α-mannose precursors

In addition to being mono-saccharide precursors, the Boc-pyranones are excellent building blocks for oligosacchirdes.[11] This is nicely exemplified in the syntheses of the oligo-rhamnose containing natural products, like the Cleistetrosides[12] and the Anthrax tetrasaccharide.[13] The structural range for which this methodology is applicable, is nicely demonstrated in the approach to the Anthrax tetrasaccharide, as it contains both α-L and β-D monosaccharides with the rare anthrose sugar.[14] The overall synthetic efficiency of this approach magnified when the glycosylation reaction was applied in an iterative bi-directional fashion. For example, an all *manno*-heptasaccharide with 25 stereocenters was produced in 12 steps from an achiral acylfuran.[15]

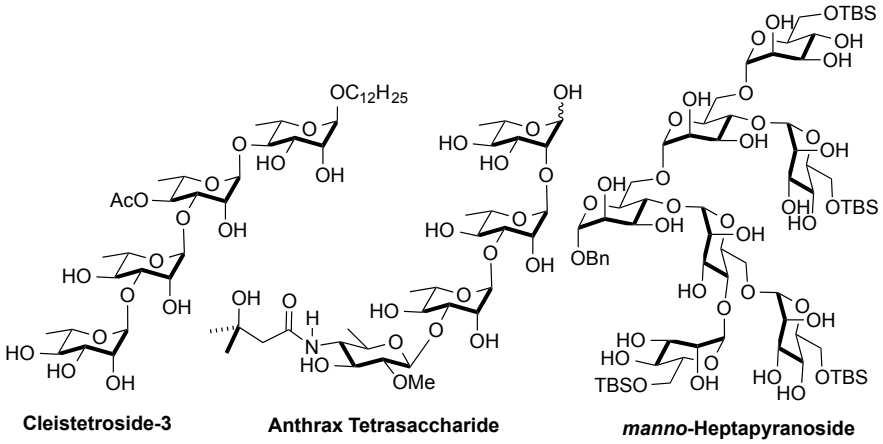


Figure 1. Oligosaccharides prepared via a Pd-catalyzed glycosylation

Finally, the ability to have myriad C-6 substitution along with the flexibility for variable substitution at the C-2,3,4 position makes these routes most readily adaptable to medicinal chemistry applications.[16] The applicability of these structurally and stereochemically divergent approaches is best suited for the synthesis of carbohydrate containing natural product libraries. Examples of this application can be seen in the syntheses of carbohydrate analogues of SL0101,[17] digitoxin[18] and methymycin[19] (Figure 2).

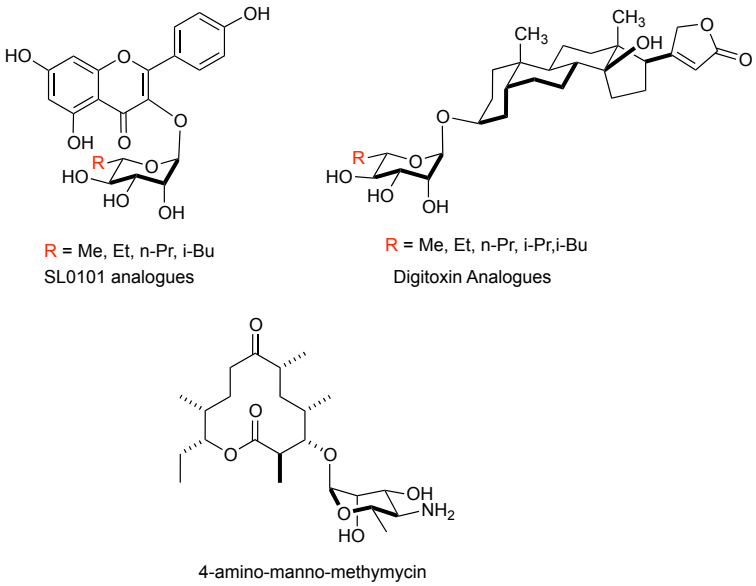


Figure 2. Pd-catalyzed glycosylation

References

1. Department of Chemistry and Chemical Biology, Northeastern University, 102 Hurtig Hall, 360 Huntington Ave, Boston, MA-02115; *Email:* G.ODoherty@neu.edu. We are grateful to NIH (GM090259) and NSF (CHE-1213596) for financial support of this research.
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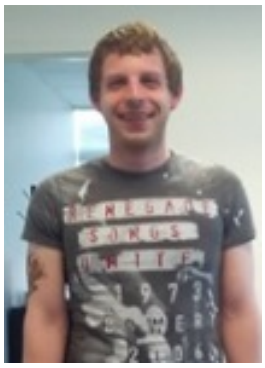
Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-1-(Furan-2-yl)ethanol (112653-32-4)
Sodium formate (141-53-7)
Cetyltrimethylammonium bromide (57-09-0)
2-Acetyl furan (1192-62-7)
(*R*)-Ru(η^6- mesitylene)-(*S,S*)-TsDPEN (174813-81-1)
N-Bromosuccinimide (128-08-5)
(2*S*, 6*R*)-6-Hydroxy-2-methyl-2H-pyran-3(6*H*)-one (138809-74-2)
(2*S*, 6*S*)-6-Hydroxy-2-methyl-2H-pyran-3(6*H*)-one (1385812-17-8)
tert-Butyl ((2*S*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (865484-73-7)
tert-Butyl ((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (916069-09-5)
N,N-Dimethylaminopyridine (1122-58-3)
$(Boc)_2O$: Di-*tert*-butyl dicarbonate; (24424-99-5)

Sumit O. Bajaj was born in Maharashtra, India. He received his Bachelor's degree (B.Sc.) in 2004 from Amravati University, Amravati and Master's degree (M.Sc. Organic chemistry) in 2006 from Sant. Gadge Baba Amravati University, Amravati, India. He began his doctoral research in the fall of 2010 at Northeastern University in Boston, MA. At Northeastern University, he is working on the synthesis of oligosaccharides natural products as anti-cancer agents under the guidance of Prof. George A. O'Doherty.

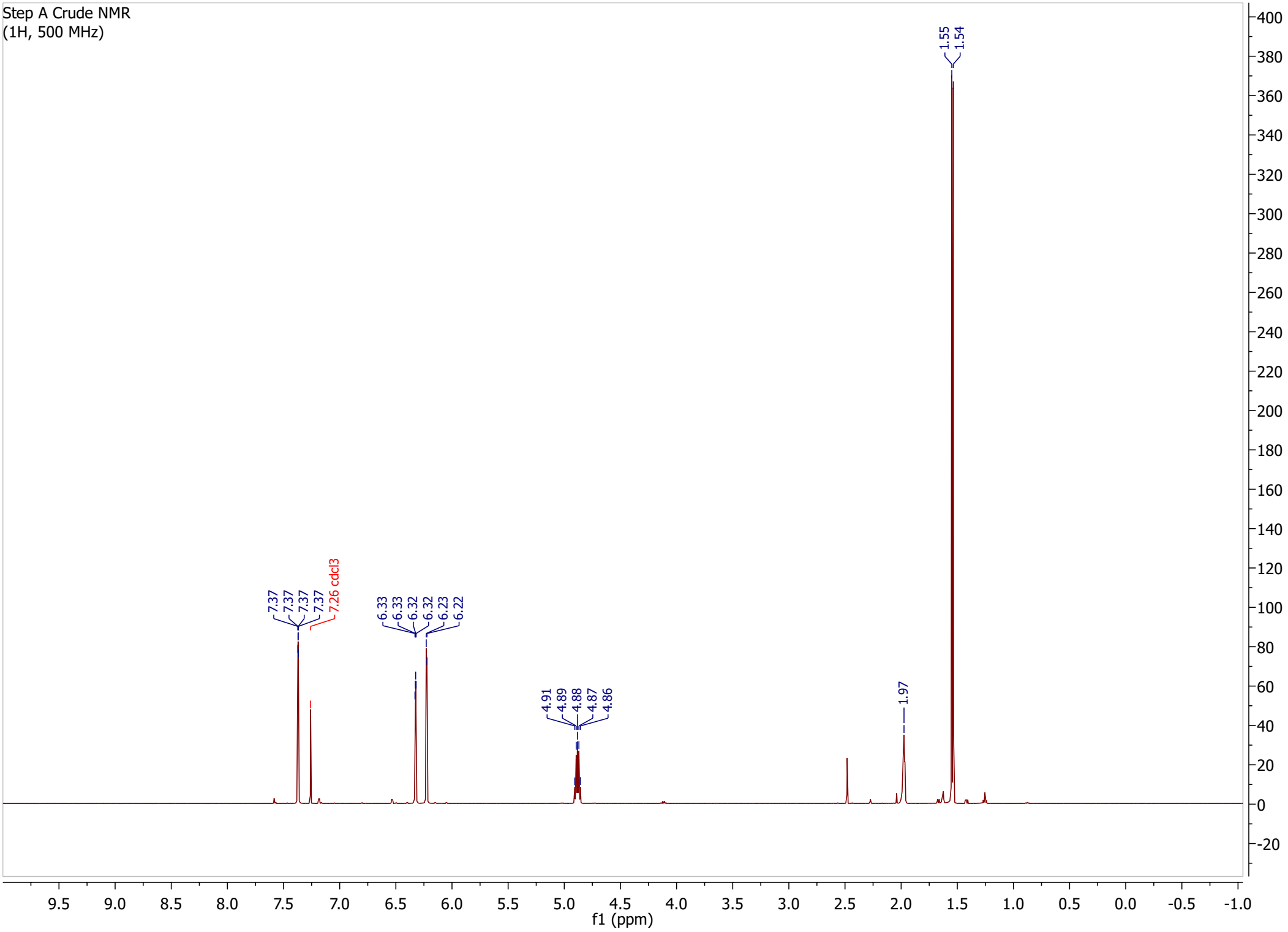


Jamison Farnsworth, originally from Northern Vermont, first attended Suffolk University, transferred after first year to Northeastern University. Majored in Chemistry while at Northeastern with a primary concentration in analytical and organic. In addition to research in the O'Doherty group, he participated in industrial CO-OPs, the first at Shire HGT and the second at Arsenal Medical. In 2012, he graduated from Northeastern with a BS in chemistry and now is currently employed in the biopharmaceutical industry as an analytical chemist.

George O'Doherty was born in Kilkenny Ireland in 1966 and received his undergraduate education from RPI with Professor Alan R. Cutler in 1987. After earning his Ph.D. with Professor Leo A. Paquette at OSU in 1993 he pursued postdoctoral studies with first Professor Barry M. Trost at Stanford and then Anthony G. M. Barrett. He began his independent career at Univ. of Minnesota in 1996 and in 2002, he moved to West Virginia University. He moved again in 2011, to Northeastern University where he has risen to the rank of Professor. His laboratory is interested in the use of asymmetric catalysis for the synthesis and medicinal chemistry study of biological important carbohydrate and natural products.

Michael T. Tudesco obtained his B.S. degree in Chemistry at the University of North Carolina at Chapel Hill in 2012, performing undergraduate research under the supervision of Professor Michel R. Gagné. After obtaining his Masters degree at Baylor University under the guidance of Professor John L. Wood, he took a position at Genentech in San Francisco.

Heemal Dhanjee obtained his BA in Mathematics and Molecular and Cell Biology at the University of California, Berkeley in 2007. He subsequently moved to California State University, Northridge and performed research in organic synthesis under the supervision of Professor Thomas Minehan. He is currently pursuing graduate research at Baylor University under the guidance of Professor John L. Wood.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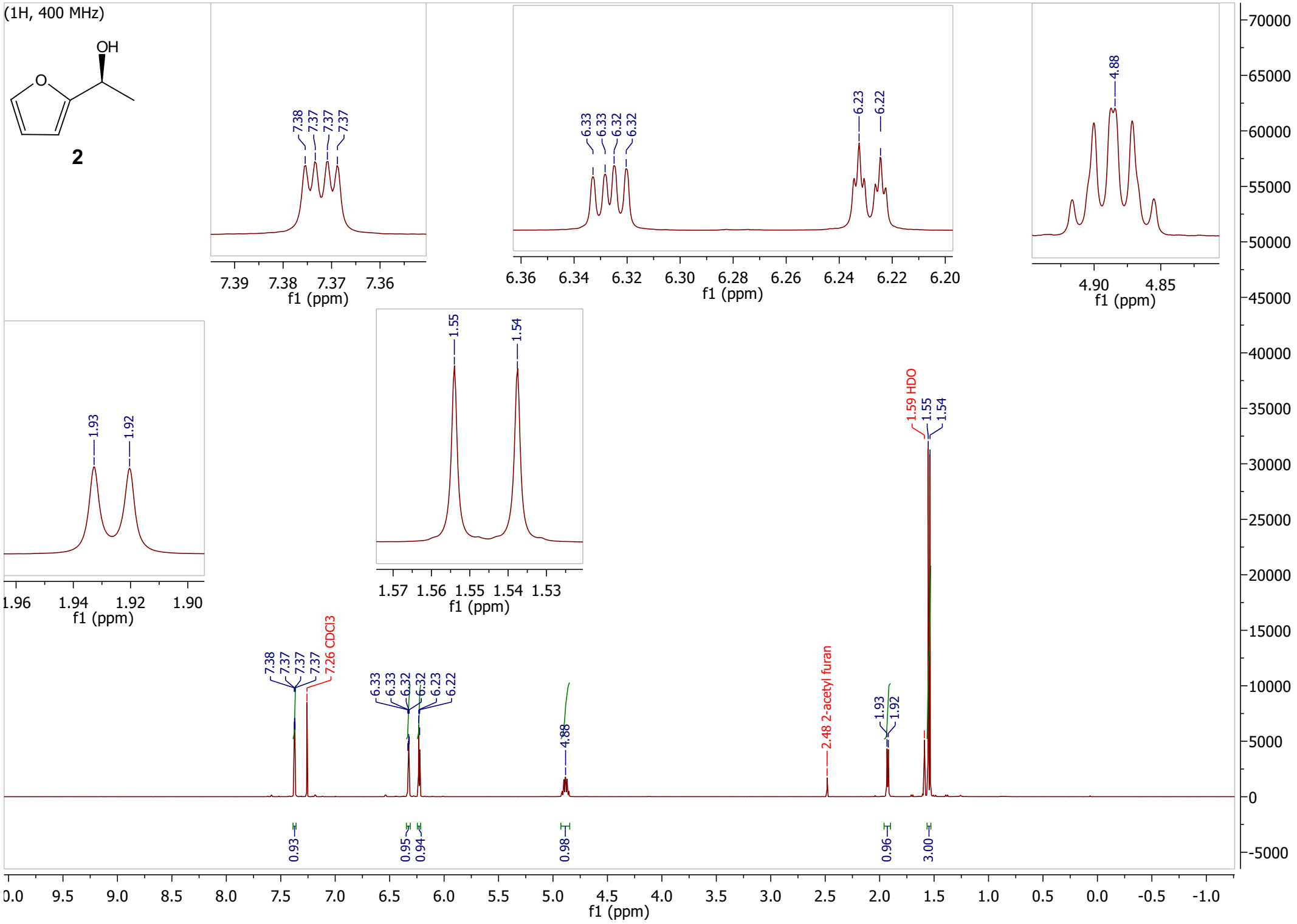
1.54
7.37
7.37
7.37
7.37
7.26 cdcl3
6.33
6.33
6.32
6.32
6.23
6.22
4.91
4.89
4.88
4.87
4.86
1.97
f1 (ppm)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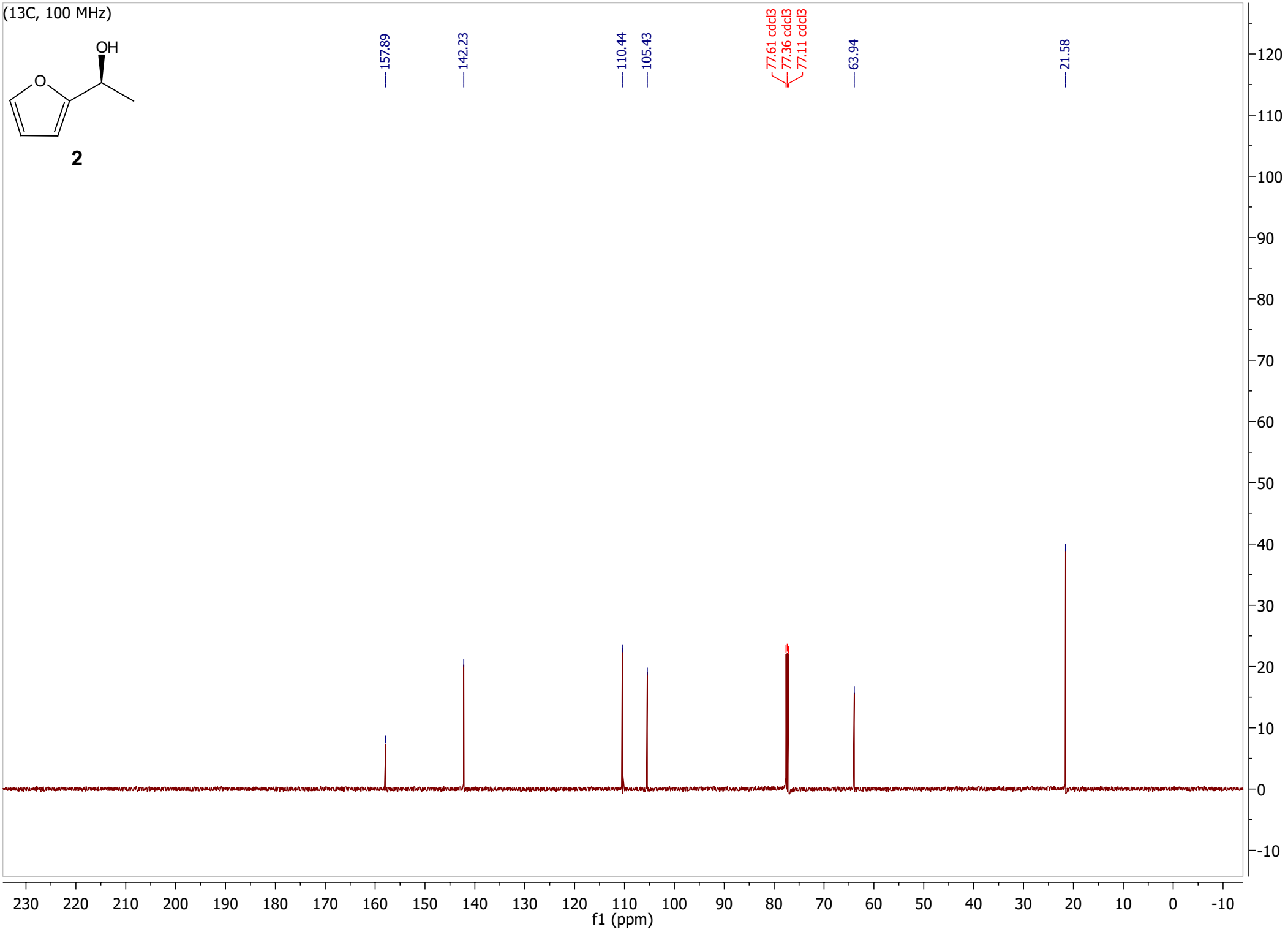
OH
O
2
7.38
7.37
7.37
7.37
6.33
6.33
6.32
6.32
6.23
6.22
4.88
1.93
1.92
1.55
1.54
1.59 HDO
7.26 CDCl3
2.48 2-acetyl furan
0.93
0.95
0.94
0.98
0.96
3.00
f1 (ppm)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O
2
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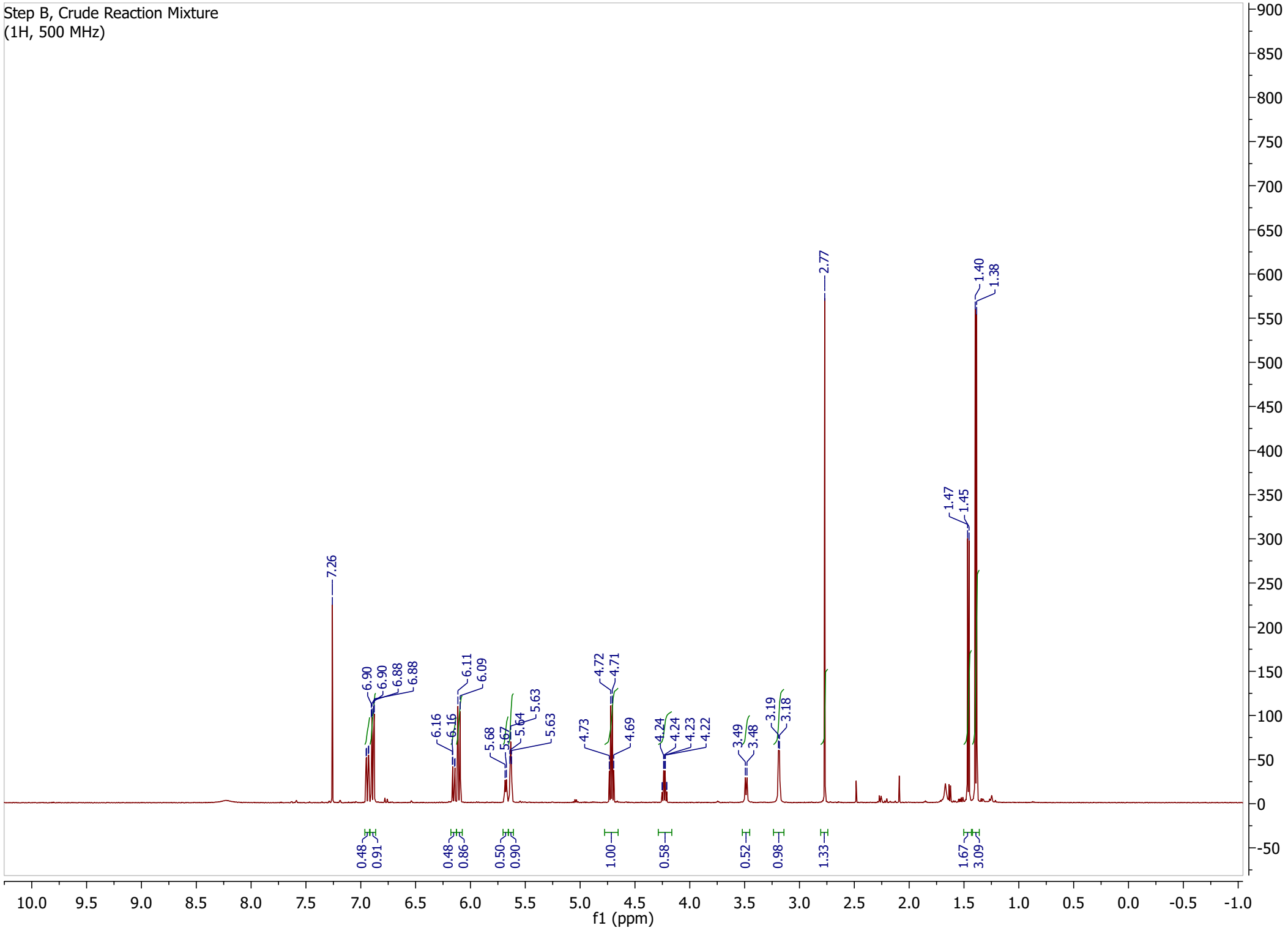
77.36 cdcl3
77.11 cdcl3
63.94
21.58
f1 (ppm)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6.90
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6.88
6.16
6.16
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6.09
5.68
5.67
5.64
5.63
5.63
4.73
4.72
4.71
4.69
4.24
4.24
4.23
4.22
3.49
3.48
3.19
3.18
2.77
1.47
1.45
1.40
1.38
0.48
0.91
0.48
0.86
0.50
0.90
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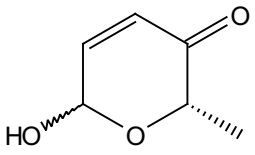
0.58
0.52
0.98
1.33
1.67
3.09
f1 (ppm)

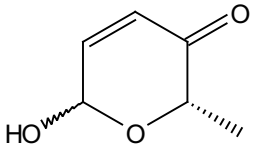
(1H, 400 MHz)


HO
O
O

3

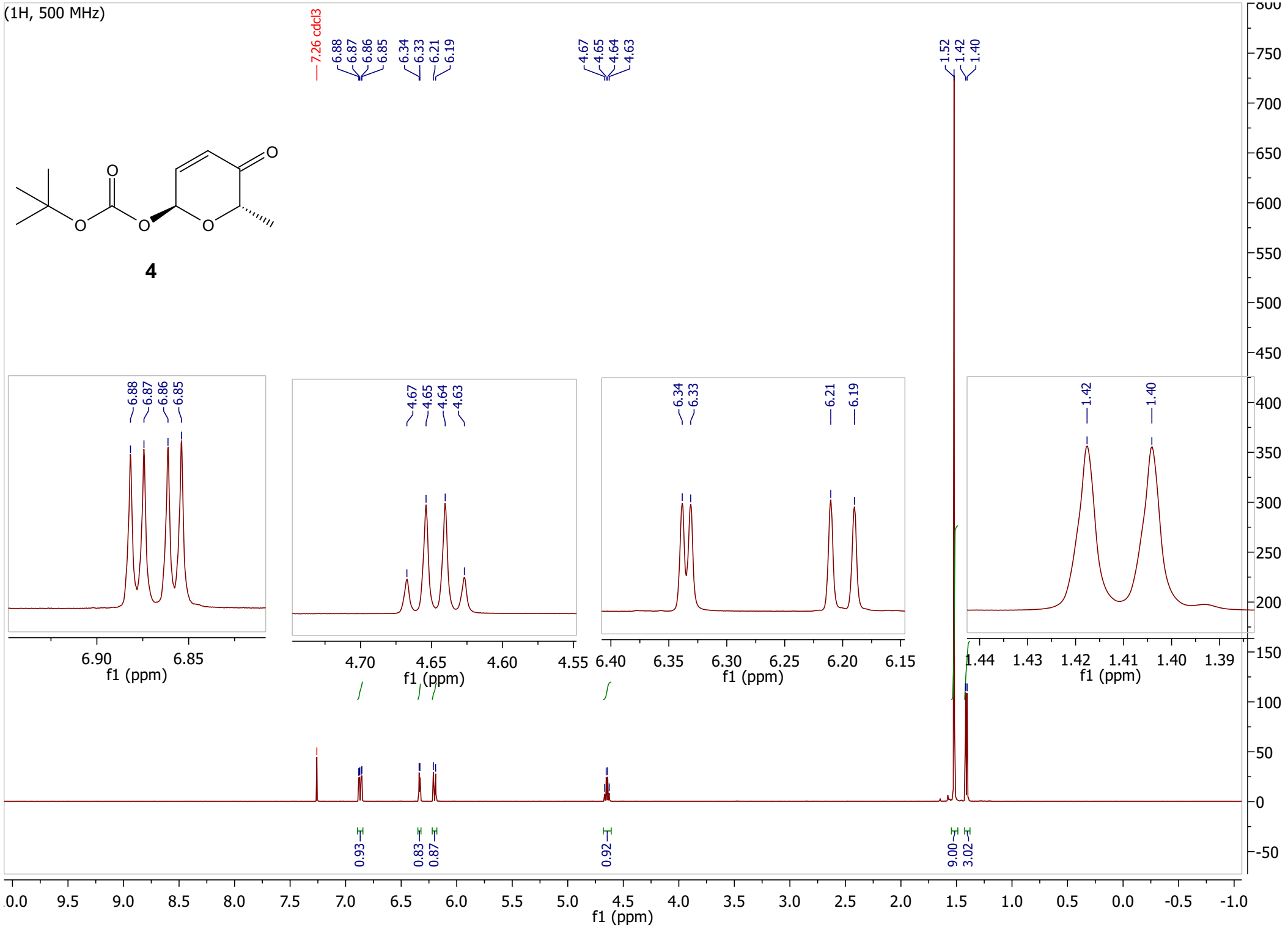
6.95 6.95 6.92 6.92 6.91 6.90 6.88 6.87
7.00 6.95 6.90 6.85
f1 (ppm)
4.73 4.71 4.70 4.68
4.76 4.74 4.72 4.70 4.68 4.66
f1 (ppm)
6.16 6.15 6.13 6.13 6.11 6.08
6.17 6.16 6.15 6.14 6.13 6.12 6.11 6.10 6.09 6.08 6.07 6.06
f1 (ppm)
4.25 4.20 4.20
4.26 4.24 4.22 4.20 4.18
f1 (ppm)
1.46 1.44 1.39 1.37
1.45 1.40 1.35
f1 (ppm)
1.46 1.44 1.39 1.37
7.26 CDCl3
6.91 6.90 6.88 6.87
6.15 6.13 6.11 6.08
5.66 5.62
4.73 4.71 4.70 4.68
4.25 4.23 4.23 4.22 4.21 4.20
3.77 3.76
3.44
1.81 HDO
0.30 0.91 0.32 0.87 0.35 0.91 0.94 0.27 0.25 0.94 0.49 0.91 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
40000 38000 36000 34000 32000 30000 28000 26000 24000 22000 20000 18000 16000 14000 12000 10000 8000 6000 4000 2000 0 -2000

(13C, 100 MHz)


HO
O
O

3

77.68 CDCl3
77.36 CDCl3
77.04 CDCl3
75.57
70.76
148.38
144.74
128.85
127.57
91.31
88.04
16.58
15.65
197.27
196.80
f1 (ppm)


(1H, 500 MHz)
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6.88
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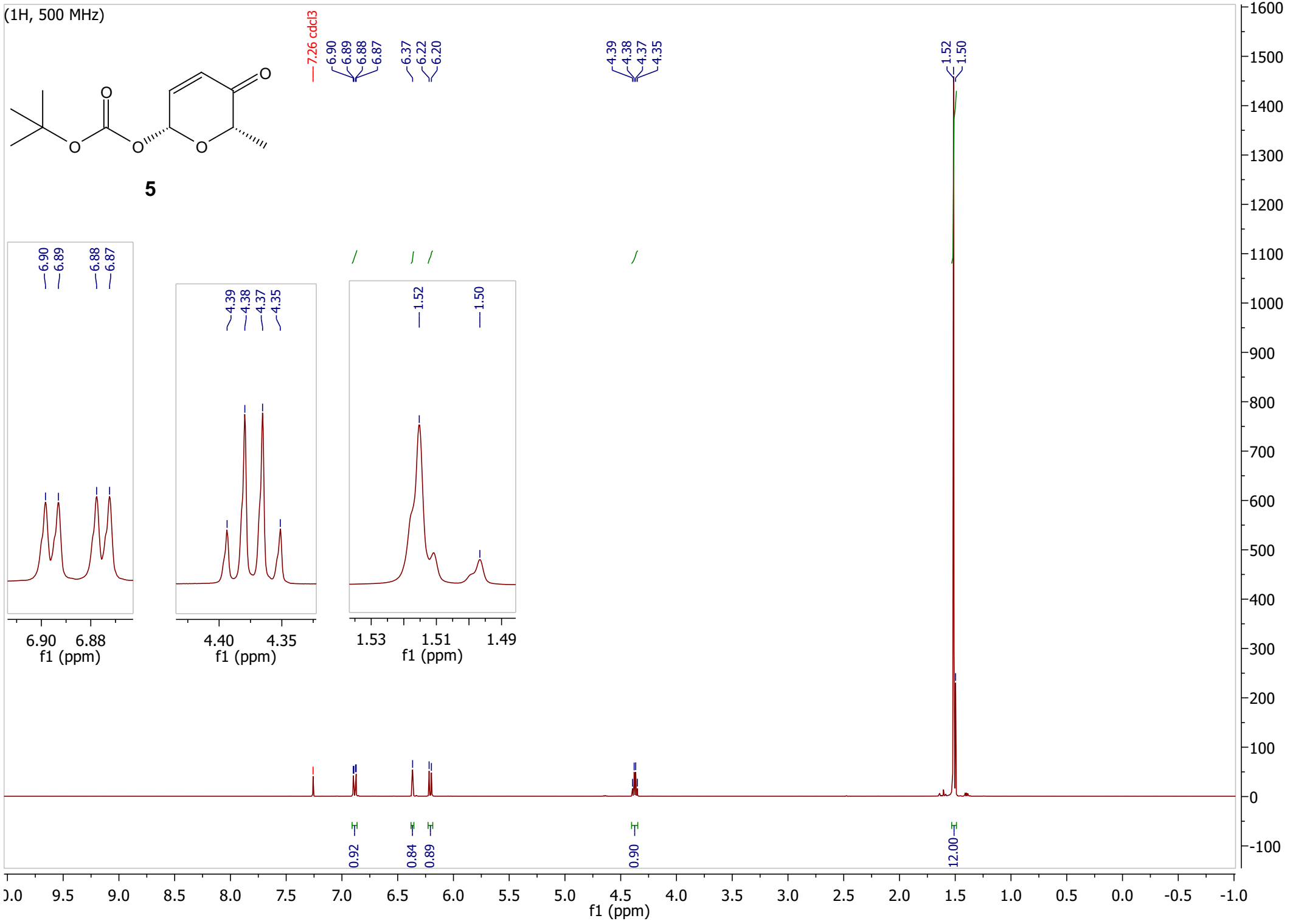
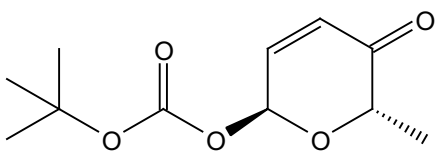
6.34
6.33
6.21
6.19
4.67
4.65
4.64
4.63
1.52
1.42
1.40
4
0.93
0.83
0.87
0.92
9.00
3.02
f1 (ppm)


(1H, 500 MHz)
7.26 cdcl3
6.90
6.89
6.88
6.87
6.37
6.22
6.20
4.39
4.38
4.37
4.35
1.52
1.50
5
f1 (ppm)
0.92
0.84
0.89
0.90
12.00

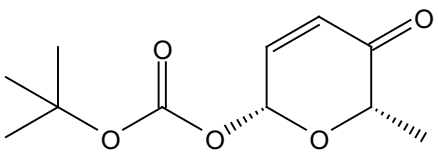
(13C, 125 MHz)



4

196.13
152.23
141.30
128.80
89.54
84.02
77.61 cdcl3
77.36 cdcl3
77.11 cdcl3
72.57
28.05
15.64
40
35
30
25
20
15
10
5
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(13C, 500 MHz)



5

196.29
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143.15
128.64
90.22
84.04
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28.03
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f1 (ppm)