Supplementary Information

Direct Synthesis of 2-Pyrone-4,6-Dicarboxylic Acid and *trans*-Aconitic Acid from Renewable Gallic Acid and Tannic Acid

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1 Contents

2 General Information

All used chemicals were commercially available. Ethylacetate and cyclohexane were purchased in technical grade and distilled prior to use.

NMR

NMR experiments were carried out on a Bruker Avance II 400 (Bruker, Karlsruhe, Germany) at 298 K and the chemical shifts were referenced to the signal of the corresponding non-deuterated solvent according to data by Cambridge Isotope Laboratories.

Chromatography

Thin layer chromatography was performed using Silica 60 F_{254} on aluminium plates purchased from Merck KGaA (Darmstadt, Germany). An UV lamp (λ = 254 nm, NU-4 KL, Benda, Wiesloch, Germany), (2,4-dinitrophenyl)hydrazine solution (1.0 g 2,4-DNPH in 250 mL 1 M HCl_{aq}) and cer-molybdenum (0.38 g ammonium cerium(IV) sulfate, 0.8 g ammonium molybdate, 100 mL 2 M H_2SO_4) were used for substance detection. The retention factors given are referring to the noted solvent mixtures. Preparative column chromatography was performed on silica gel 60 M (0.040–0.063 mm, Macherey-Nagel GmbH & Co, Düren, Germany).

High Resolution Mass Spectrometry

Mass spectra via electrospray-ionization (ESI–) were recorded using an Agilant 6545 QTOF-MS (Agilant, Santa Clara (CA), USA). Mass-charge ratios (m/z) were obtained for the characterised compounds.

3 General Procedures

3.1 General Procedure 1

50 mg (0.294 mmol) gallic acid (**1**) and 113 mg (2.5 equiv., 0.735 mmol) $NaBO_3$•4 H_2O were weighed into a pressure tube. 3 mL acetic acid was added, and the resulting solution stirred at 50 °C for 4 h. After that the mixture was partitioned between 1 M hydrochloric acid (10 mL) and ethyl acetate (EA, 10 mL) and the aqueous phase extracted three times with EA (3x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. A defined amount of 1,3,5-trimethoxybenzene was added to the residue and dissolved in deuterated DMSO and analysed by ^{1}H NMR.

3.2 General Procedure 2

158 mg (3.5 equiv., 1.029 mmol) $NaBO_3$•4 H_2O were weighed into a round-bottom flask (25 mL) and 9 mL acetic acid were added. 50 mg (0.294 mmol) gallic acid (**1**) were dissolved in 0.7 mL EtOH and added dropwise over 1 h at 70 °C. After the addition the mixture was stirred for another hour at 70 °C. After that, acetic acid was removed with a rotary evaporator (p = 50 mbar, T_{bath} = 50 °C) and the residue was partitioned between 1 M hydrochloric acid (10 mL) and EA (10 mL) and the aqueous phase was extracted three more times with EA (3x 10 mL) . The combined organic fractions were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure.

4 Optimization

4.1 Influence of the Reaction Temperature

Table S1. Conversion of **1** and yield of **2** and **3** in dependence of the reaction temperature. The reaction was conducted according to GP 1 with the constant parameters: 4 h, 2.5 eq. of sodium perborate, 0.1 M. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

T / °C	Conversion of **1**	Yield **2**	Yield **3**
25	66%	6%	31%
30	81%	7%	28%
40	81%	12%	29%
50	86%	11%	21%
60	86%	12%	18%
70	91%	13%	14%
80	84%	13%	13%

4.2 Influence of the Reaction Time

Table S2. Conversion of **1** and yield of **2** and **3** in dependence of the reaction time. The reaction was conducted according to GP 1 with the constant parameters: 2.5 equivalents of sodium perborate, 70 °C, 0.1 M. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

t / h	Conversion of **1**	Yield **2**	Yield **3**
0.25	44%	2%	9%
0.50	58%	7%	22%
1	88%	12%	25%
2	82%	10%	22%
4	86%	11%	25%
8	86%	11%	26%
16	86%	12%	20%
23	73%	11%	27%
48	80%	13%	25%
120	81%	13%	20%

4.3 Influence of the Equivalents Oxidant

Table S3. Conversion of **1** and yield of **2** and **3** in dependence of the equivalents of sodium perborate. The reaction was conducted according to GP 1 with the constant parameters: 4 h, 70 °C, 0.1 M. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Equivalents of Sodium Perborate	Conversion of **1**	Yield **2**	Yield **3**
0	0%	n.d.	n.d.
0.5	25%	2%	4%
1	45%	6%	8%
1.5	60%	10%	17%
2	76%	11%	20%
2.5	86%	11%	21%
3	88%	11%	27%
3.5	100%	16%	32%
4	99%	12%	32%
4.5	100%	11%	35%

4.4 Influence of the Substrate Concentration

Table S4. Conversion of **1** and yield of **2** and **3** in dependence of the substrate concentration. For these experiments, the volume of the solvent was varied and the amount of starting material kept constant. The reaction was conducted according to GP 1 with the constant parameters: 4 h, 70 °C, 2.5 eq. sodium perborate. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Concentration of **1** / mol/L	Conversion of **1**	Yield **2**	Yield **3**
0.294	67%	4%	27%
0.098	86%	11%	21%
0.049	92%	19%	19%
0.033	90%	20%	11%
0.025	90%	23%	10%
0.012	89%	33%	8%
0.0061	78%	17%	1%

4.5 Influence of the Solvent

Table S5. Conversion of **1** and yield of **2** and **3** in dependence of solvent. The reaction was conducted according to GP 1. Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Solvent	Conversion of **1**	Yield **2**	Yield **3**
Volume ratio of HFIP in AcOH			
100%	17%	n.d.	n.d.
80%	55%	2%	8%
60%	62%	4%	26%
40%	78%	6%	28%
20%	80%	8%	30%
10%	79%	9%	27%
Volume ratio of trifluoro-ethanol in AcOH			
40%	75%	6%	26%
30%	77%	8%	24%
20%	83%	11%	26%
pivalic acid	58%	traces	8%
propionic acid	80%	4%	32%
formic acid	52%	1%	1%
TFA	77%	n.d.	4%
MeOH	56%	n.d.	traces

5 Green Metrics

5.1 Methodology

A combination of different metrics was chosen to evaluate the greenness of the reported procedure. Even though there is no reported literature method to access pyrone **2**, a reaction employing a similar strategy was chosen for comparison, which uses a similar substrate and receives a somewhat similar product.[1]

For economic considerations, it should be noted again, that the generated product is not commercially available, even though it is of high academic and industrial interest. Therefore, as a metric the price per gram, only considering the used reactants was calculated, determined by the lowest price found for the substance on scifinder.

$$Eco\ Factor = \frac{1}{yield} * reagent\ cost\ per\ mol * eq.\ used$$

The atom economy was calculated according to the following formula:[2]

$$AE = \frac{molecular\ mass\ of\ desired\ product}{molecular\ mass\ of\ all\ reactants}$$

The excess reactant factor was calculated by formula:[2]

$$excess\ reactant\ factor = \frac{stoichiometric\ mass\ of\ reactants + \cdot\ excess\ mass\ of\ reactants}{stoichiometric\ mass\ of\ reactants}$$

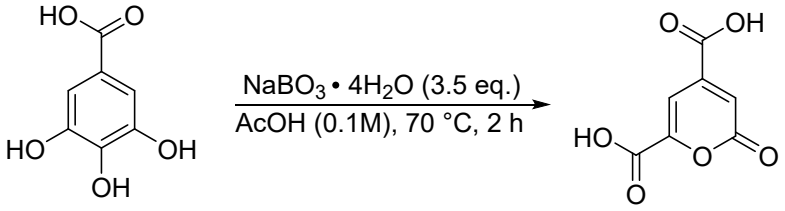
The safety of the reaction was calculated, by categorizing the used reagents according to table S6 and calculating the mean value:[2, 3]

Table S6. Ranking of reagents according to GHS classifications.

GHS ranking	classification
1	explosive, oxidizing, toxic, health hazard
2	harmful, flammable, environmental, corrosive (combination of 3 hazards)
3	harmful, flammable, environmental, corrosive (combination of 2 hazards)
4	harmful, flammable, environmental, corrosive (1 hazard)
5	-

The EcoScale score was calculated according to the procedure developed by Van Aken et al.[4]

5.2 Our Method



34%

Table S7. Batch table for the synthesis of pyrone **2**.

Substance	M / g/mol	GHS classification	GHS ranking	Price €/g	Price €/mol	Specifications
Gallic acid	170.12	none	5	0.03 (Aaron Chemicals)	5.10	500 g, 95–98%
Sodium perborate tetrahydrate	153.86	corrosive, health hazard	1	0.02 (Hayashi Pure Chemicals)	3.08	500 g, 95–98%
Acetic acid, glacial	60.05	flammable, corrosive	3	0.01 (Oakwood Chemicals)		200 L, 99%

Average GHS: 3.

Calculations:

$$AE = \frac{184.10\,\frac{g}{mol}}{170.12\,\frac{g}{mol} + 3.5 * 153.86\frac{g}{mol}} \cdot = 26\%$$

The AE is relatively low, which also stems from the use of an excess of oxidant, but also the crystal water of sodium perborate.

$$Eco = \frac{1}{0.34} * \left(\frac{5.10\ €}{mol} + \left(\frac{3.08\ €}{mol} * 3.5\right)\right) = 46.71\frac{€}{mol}$$

The solvent costs were not taken into consideration, as acetic acid was removed by evaporation after the reaction and can be reused. Meanwhile the other starting materials are very inexpensive.

$$excess\ reactant\ factor = \frac{170.12 + \ 153.86 * 2\ eq\ + 153.86 * 1.5\ eq}{170.12 + 153.86 * 2\ eq} = 1.48$$

EcoScale penalty points:

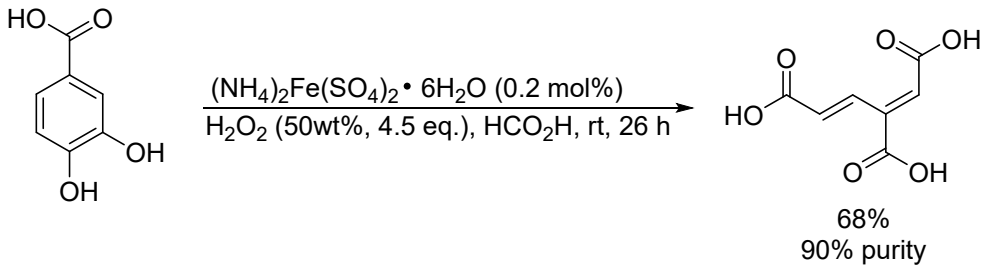
Table S8. Calculation of the penalty points for the determination of EcoScale score.

Parameter	Penalty points
yield	32.5
reagent costs	0
reagent safety	5 (AcOH, flammable)
equipment	0
conditions	3 (heating, > 1 h)
work up	4 (liq.-liq. extraction; crystallization and filtration)
Sum	44.5

The actual score is 55.5, with most penalty points originating from the poor yield, which is made up for by the accessibility of the starting materials from renewable resources and their low price.

5.3 Comparable Method

Tabelle S9. Batch table for the comparable method.



Substance	M / g/mol	GHS classification	GHS ranking	Price €/g	Price €/mol	Specification
Protocate-chuic acid	154.12	none	5	0.07 (1stScientific)	10.78	1 kg, 95–98%
H_2O_2, 50 wt%	34.01	oxidizing, corrosive	1	0.05 (Oakwood Chemicals)	3.40	1 L, 95–98%
Formic acid	46.03	flammable, corrosive, toxic	1	0.10 (Oakwood Chemicals)	6.40	250 g, 99%

Average GHS: 2.3.

Calculations:

Due to H_2O_2 being in a concentration of 50 wt%, the corresponding values were multiplied by 2, and due to the extremely low loading, the catalyst was not taken into consideration. Additionally the solvent costs were also disregarded, as formic acid was removed by evaporation after the reaction and, depending on thermal degradation can be reused.

$$AE = \frac{186.12\,\frac{g}{mol}}{154.12\frac{g}{mol} + 2 * 4.5 * 34.01\frac{g}{mol}} = 39\%$$

$$Eco = \frac{1}{0.61} * \left(\frac{10.78\,€}{mol} + \left(\frac{3.40\,€}{mol} * 4.5 * 2\right)\right) = 67.8\frac{€}{mol}$$

$$Excess\ Reactant\ Factor = \frac{154.12 + 34.01 * 2 * 4.5\ eq}{154.12 + 34.01 * 2 * 2\ eq} = 1.59$$

EcoScale penalty points:

Table S10. Calculation of the penalty points for the determination of EcoScale score.

Parameter	Penalty points
yield	19.5
reagent costs	3
reagent safety	5 + 5 (formic acid), 10 (H_2O_2, 50 wt%)
equipment	1 (syringe pump)
conditions	1 (> 24 h)
work up	4 (liq.-liq. extraction; crystallization and filtration)
Sum	48.5

The actual score is 51.5, with most penalty points stemming from the toxicity and hazardous nature of the reagents.

5.4 Comparison

For a comparison, both methods were plotted in a spider plot (Figure S1). The reactions perform somewhat similar, but our protocol avoids the use of toxic and dangerous chemicals like highly concentrated H_2O_2, which is not easily available in high concentrations due to homeland security reasons Additionally, the starting materials of our method are less expensive, a lower amount of excess reactant needed and a higher score on the EcoScale is realized.

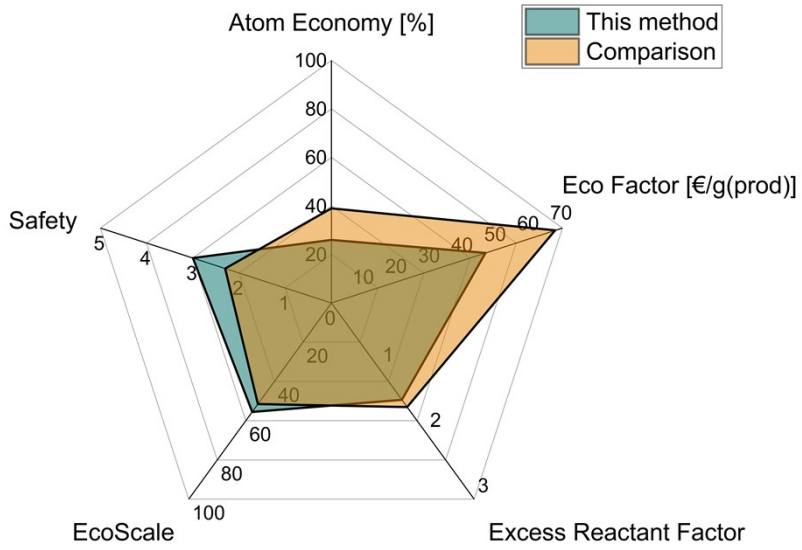
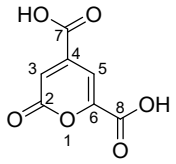


Figure S1. Comparison of this method and a comparable method by different green chemistry metrics in a spider plot.

6 Compound Characterization

6.1 Characterisation of 2*H*-2-Oxo-pyran-4,6-dicarboxylic acid (2)



2

The compound was synthesized according to GP2 on a fivefold scale using 250 mg (1.47 mmol) gallic acid (**1**). To isolate the product, a procedure according to Michinobu et al. was used, dissolving the residue after evaporation in 0.3 ml H_2O followed by addition of 50 mg NaCl and cooling to 2 °C over 17 h. The precipitated salt was filtrated and washed with ethyl acetate and then dissolved in 1 M hydrochloric acid and the product extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated yielding 78.8 mg (0.428 mmol, 36%) of the product as an off-white solid.[5]

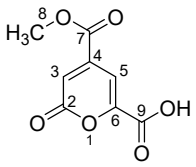
R_f ($CHCl_3$: ethyl acetate:HCOOH = 10:8:1): 0.4 (broad).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.00 (d, $^4J_{3,5}$ = 1.5 Hz, 1H, *H*-3), 7.25 (d, $^4J_{5,3}$ = 1.5 Hz, 1H, *H*-5).

^{13}C NMR (101 MHz, DMSO-d_6) δ = 107.9 (*C*-5), 121.2 (*C*-3), 144.2 (*C*-4), 149.7 (*C*-6), 160.0 (C-2), 160.2 (*C*-8), 163.9 (*C*-7) ppm.

MS for $C_7H_4O_6$ (ESI-) [M^--H]: 182.99.

6.1.1 Characterisation of 2*H*-4-(Methoxycarbonyl)-2-oxo-pyran-6-carboxylic acid (2a)



2a

The compound was synthesised according to GP2 on a fivefold scale using 260 mg (1.47 mmol) methyl gallate (**1a**). The crude product was purified via flash chromatography using MeOH:CH_2Cl_2 (2.5:97.5; *v*:*v*) with 0.25% AcOH as the eluent yielding 186 mg (0.937 mmol, 54%) of the product as a pale yellow coloured solid.

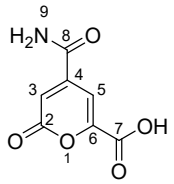
R_f (CH_2Cl_2:MeOH = 9:1 + 1 drop AcOH): 0.35.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.88 (s, 3H, *H*-8), 7.06 (d, $^4J_{3,5}$ = 1.5 Hz, 1H, *H*-3), 7.26 (d, $^4J_{5,3}$ = 1.5 Hz, 1H, *H*-5) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 53.44 (*C*-8), 107.5 (*C*-5), 121.5 (*C*-3), 142.8 (*C*-4), 149.9 (*C*-6), 159.9 (*C*-2), 160.0 (*C*-9), 163.9 (*C*-7) ppm.

MS for $C_7H_6O_6$ (ESI-) [M^--H]: 197.01.

6.1.2 Characterisation of 2*H*-4-Carbamoyl-2-oxo-pyran-6-carboxylic acid (2b)



2b

The compound was synthesised according to GP2 on a fivefold scale using 254 mg (1.47 mmol) 3,4,5-trihydroxybenzamide (**1b**). After the reaction finished, parts of the product precipitated and were isolated by filtration. After extractive work-up, the combined organic fractions were concentrated under reduced pressure and the flask placed in a freezer, allowing the remaining product to precipitate, yielding overall 150 mg (0.750 mmol, 51%) of the product as a pale yellow solid.

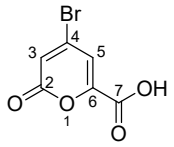
R_f (CH_2Cl_2:MeOH = 5:1 + 1 drop AcOH): 0.1.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.83 (d, $^4J_{3,5}$ = 1.6 Hz, 1H, *H*-3), 7.24 (d, $^4J_{5,3}$ = 1.6 Hz, 1H, *H*-5), 7.88 (s, 1H, *H*-9), 8.31 (s, 1H, *H*-9) ppm.

^{13}C NMR (126 MHz, DMSO-d_6) δ = 105.1 (*C*-5), 115.4 (*C*-3), 147.6 (*C*-6), 154.6 (*C*-8), 160.3 (*C*-7), 161.1 (*C*-2), 164.1 (*C*-4) ppm.

HRMS for $C_7H_5N_1O_5$ (ESI-) [M^--H]: 182.01

6.1.3 Characterisation of 2*H*-4-Bromo-2-oxo-pyran-6-carboxylic acid (2c)



2c

The compound was synthesised according to GP2 on a fivefold scale using 308 mg (1.47 mmol) 5-bromopyrogallol (**1c**). The crude product was purified via flash chromatography using MeOH: CH_2Cl_2 (5:95; *v*:*v*) with 0.1% AcOH as the eluent yielding 217 mg (0.991 mmol, 66%) of the product as a pale yellow solid.

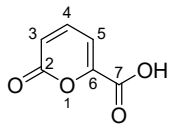
R_f (CH_2Cl_2:MeOH = 5:1 + 1 drop AcOH): 0.25.

^{1}H NMR (500 MHz, acetone-d_6) δ = 6.98 (d, $^4J_{3,5}$ = 1.7 Hz, 1H, *H*-3), 7.28 (d, $^4J_{5,3}$ = 1.7 Hz, 1H, *H*-5) ppm.

^{13}C NMR (126 MHz, acetone-d_6) δ = 114.9 (*C*-5), 122.6 (*C*-3), 139.6 (*C*-4), 149.6 (*C*-6), 158.7 (*C*-2), 159.8 (*C*-7) ppm.

MS for $C_6H_3Br_1O_4$ (ESI-) [M^--H]: 218.91.

6.1.4 Characterisation of 2*H*-2-Oxo-pyran-6-carboxylic acid (2d)



2d

The compound was synthesised according to GP2 on a fivefold scale using 189 mg (1.47 mmol) pyrogallol (**1d**). The crude product was purified via flash chromatography using MeOH: CH_2Cl_2 (5:95; *v*:*v*) with 0.1% AcOH as the eluent yielding 113 mg (0.807 mmol, 54%) of the product as a pale yellow solid.

R_f (CH_2Cl_2:MeOH = 5:1 + 1 drop AcOH): 0.2.

^{1}H NMR (500 MHz, acetone-d_6) δ = 6.55 (dd, $^3J_{3,4}$ = 9.4 Hz, $^4J_{3,5}$ = 1.0 Hz, 1H, *H*-3), 7.18 (dd, $^3J_{5,4}$ = 6.6 Hz, $^4J_{3,5}$ = 1.0 Hz, 1H, *H*-5), 7.65 (dd, $^3J_{4,3}$ = 9.4 Hz, $^3J_{4,5}$ = 6.6 Hz, 1H, *H*-4) ppm.

^{13}C NMR (126 MHz, MeOH-d_6) δ = 111.4 (*C*-5), 121.2 (*C*-3), 144.4 (*C*-4), 151.3 (*C*-6), 162.0 (*C*-2), 162.4 (*C*-7) ppm.

MS for $C_6H_4O_4$ (ESI-) [M^--H]: 139.00.

7 NMR Spectra

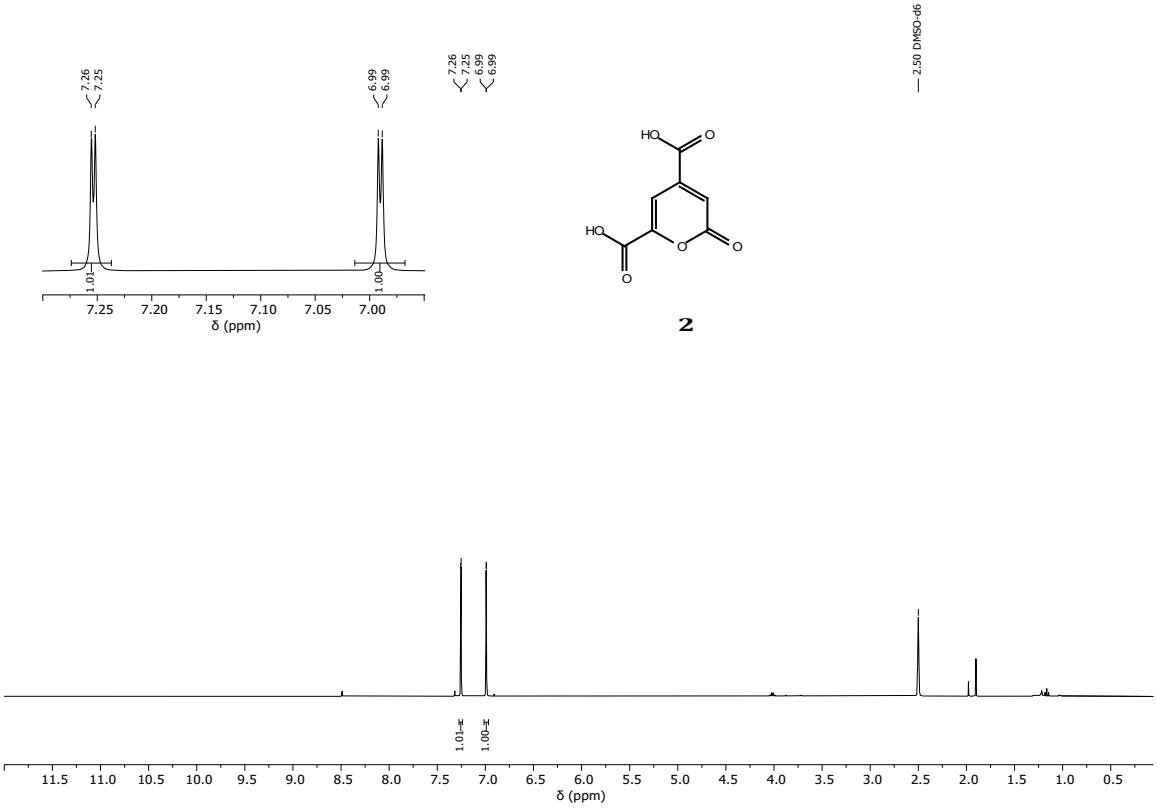


Figure S2. ^{1}H NMR (400 MHz, DMSO-d_6) of 2*H*-2-oxo-pyran-4,6-dicarboxylic acid (**2**).

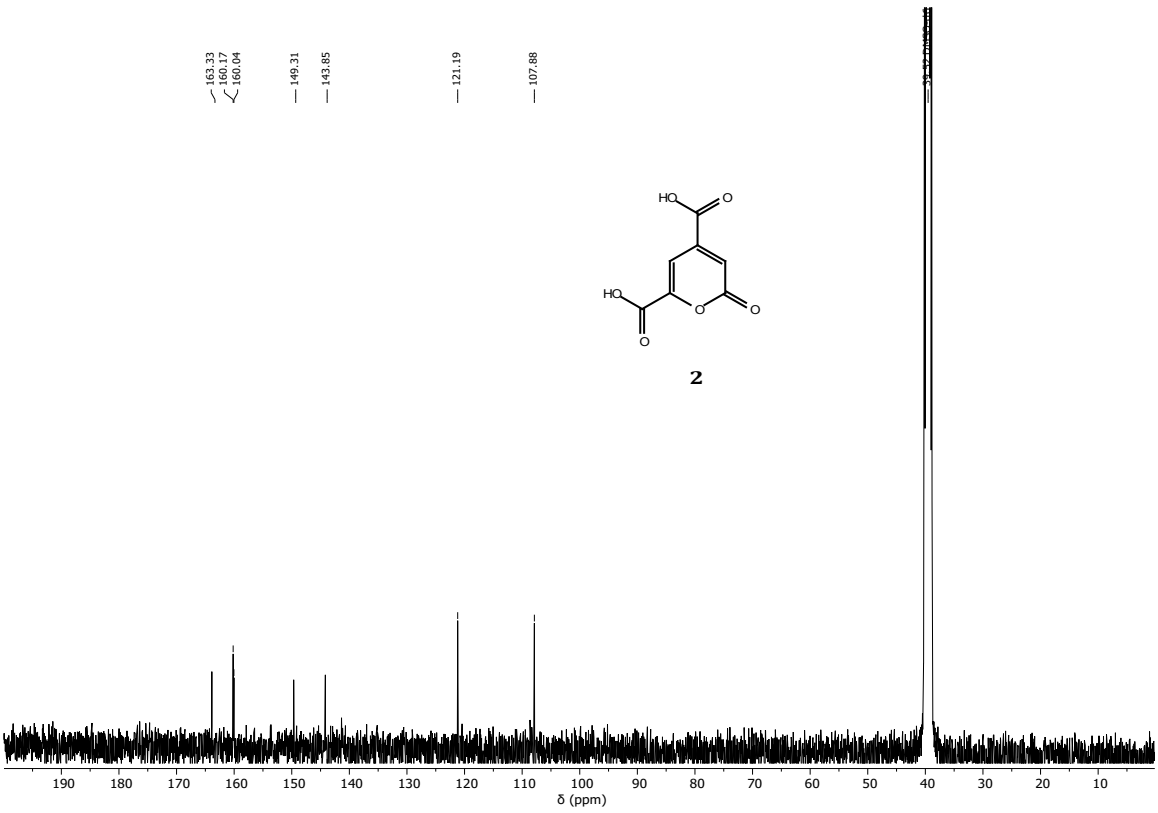


Figure S3. ^{13}C NMR (101 MHz, DMSO-d_6) of 2*H*-2-oxo-pyran-4,6-dicarboxylic acid (**2**).

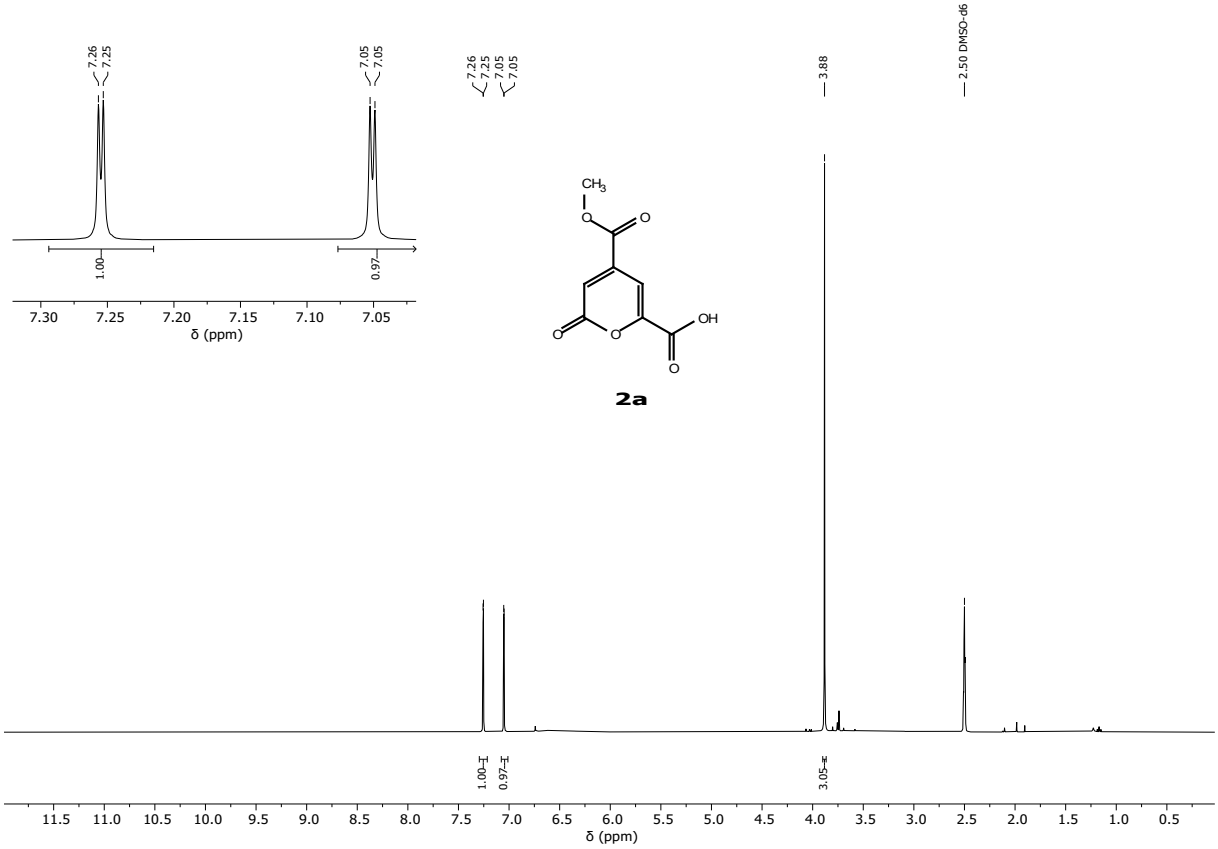


Figure S4. ^{1}H NMR (400 MHz, DMSO-d_6) of 2*H*-4-(methylcarbonyl)-2-oxo-pyran-6-carboxylic acid (**2a**).

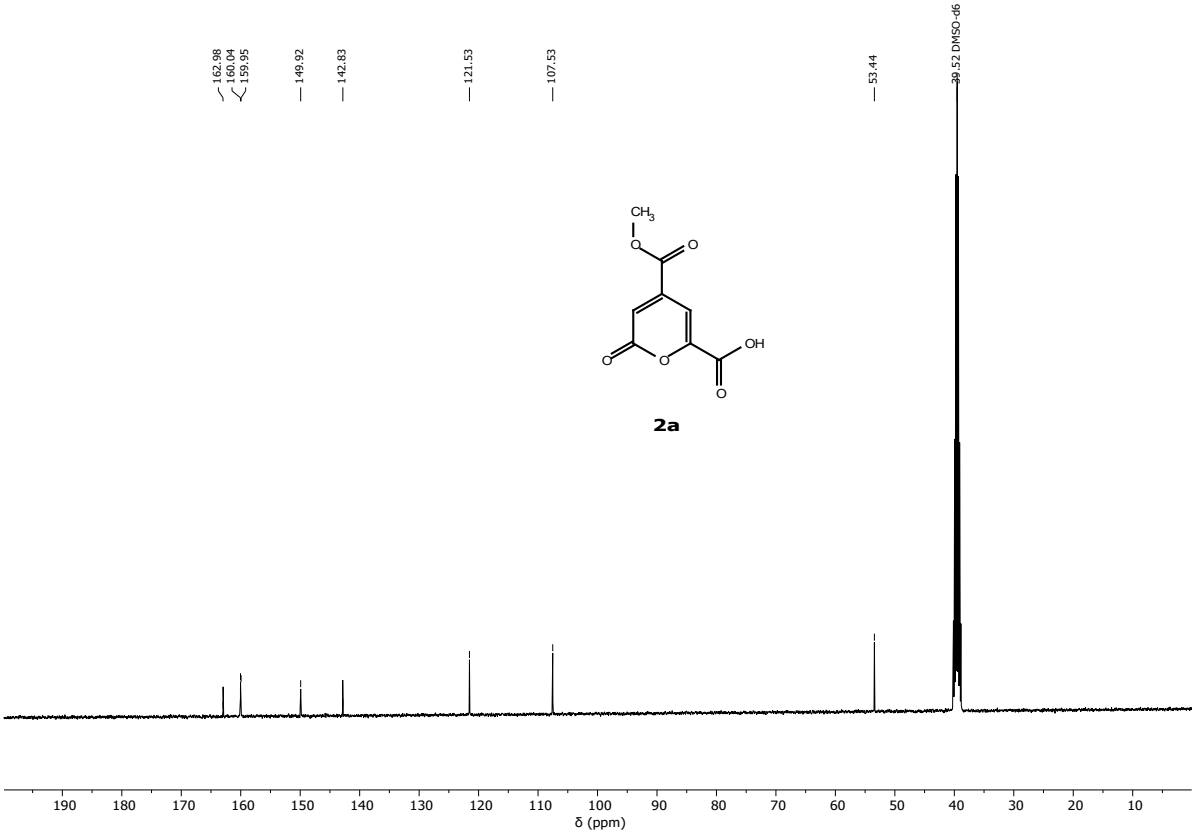


Figure S5. ^{13}C NMR (101 MHz, DMSO-d_6) of 2*H*-4-(methylcarbonyl)-2-oxo-pyran-6-carboxylic acid (**2a**).

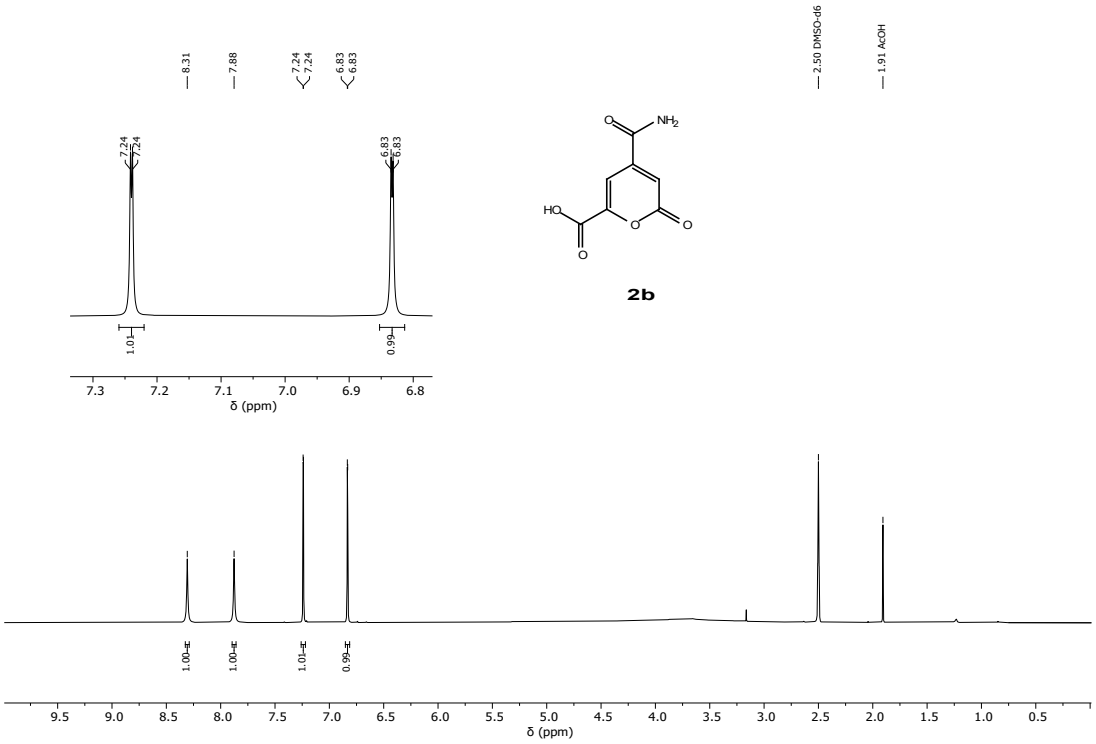


Figure S6. ^{1}H NMR (500 MHz, DMSO-d_6) of 2*H*-4-carbamoyl-2-oxo-pyran-6-carboxylic acid (**2b**).

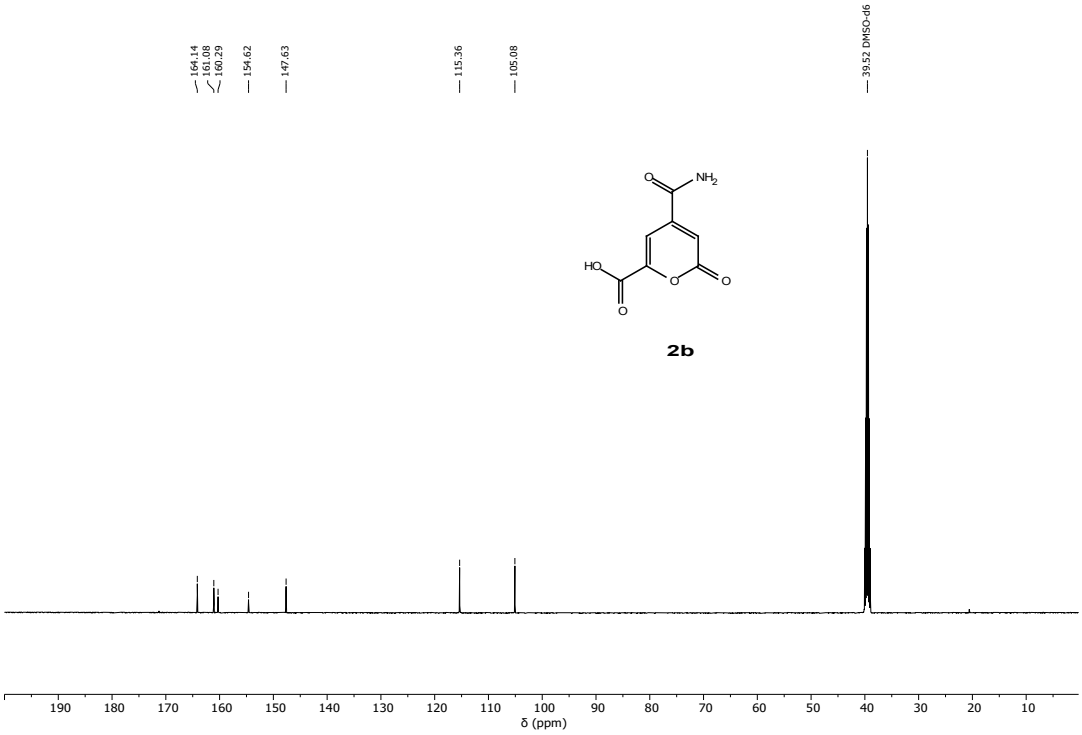


Figure S7. ^{13}C NMR (126 MHz, DMSO-d_6) of 2H-4-carbamoyl-2-oxo-pyran-6-carboxylic acid (**2b**).

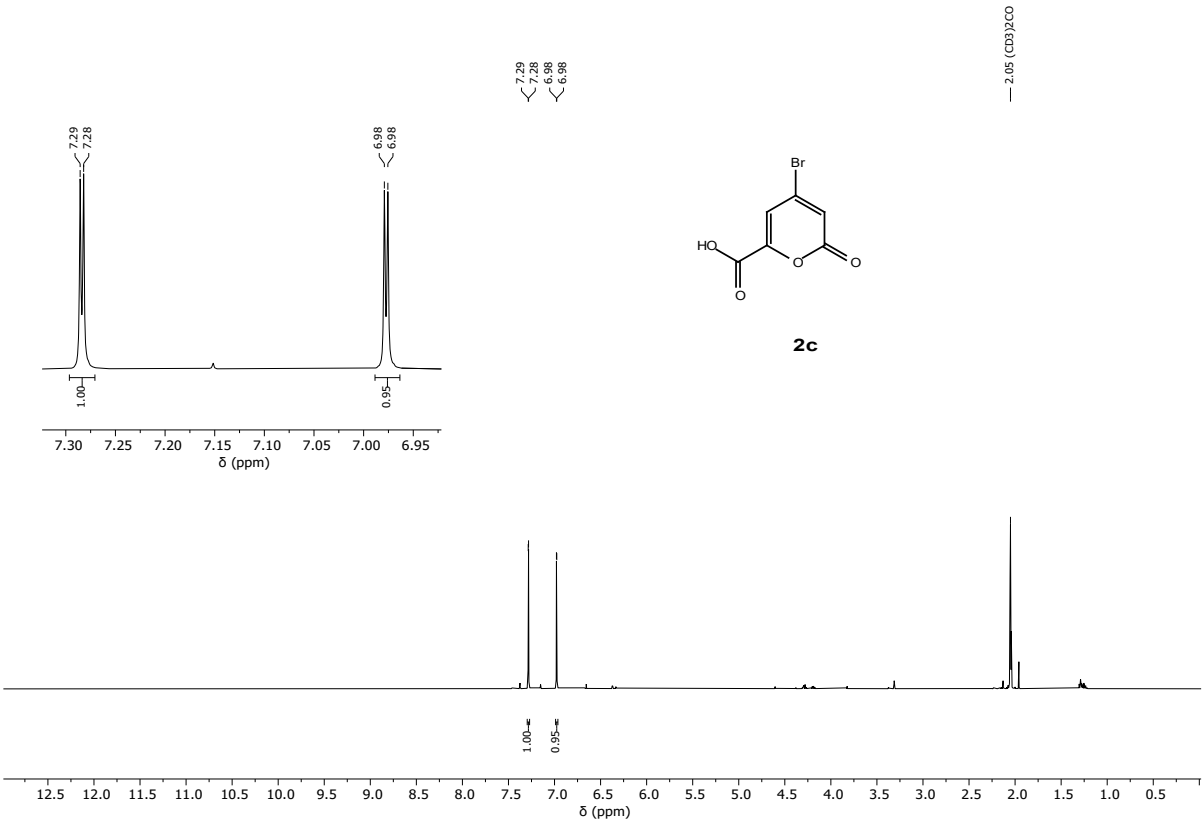


Figure S8. ^{1}H NMR (500 MHz, acetone-d_6) of 2*H*-4-bromo-2-oxo-pyran-6-carboxylic acid (**2c**).

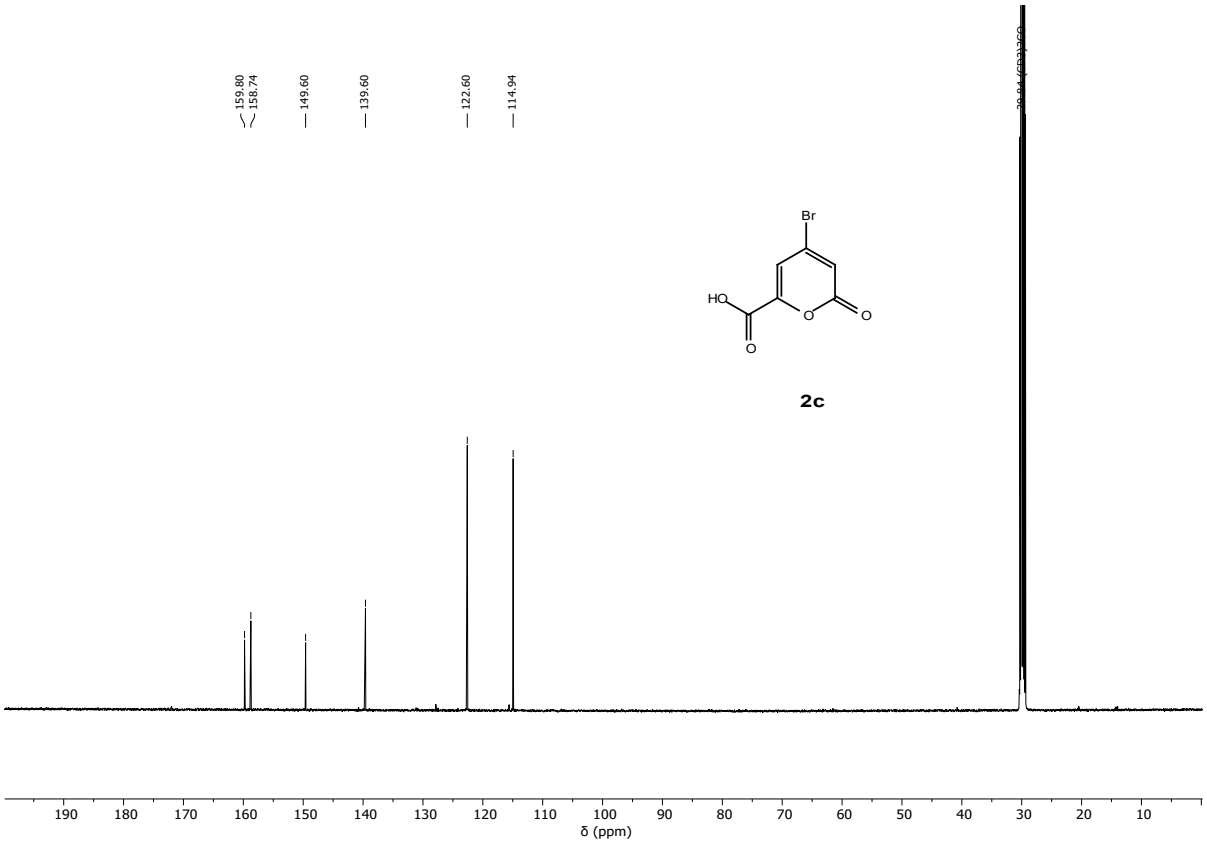


Figure S9. ^{13}C NMR (126 MHz, acetone-d_6) of 2*H*-4-bromo-2-oxo-pyran-6-carboxylic acid (**2c**).

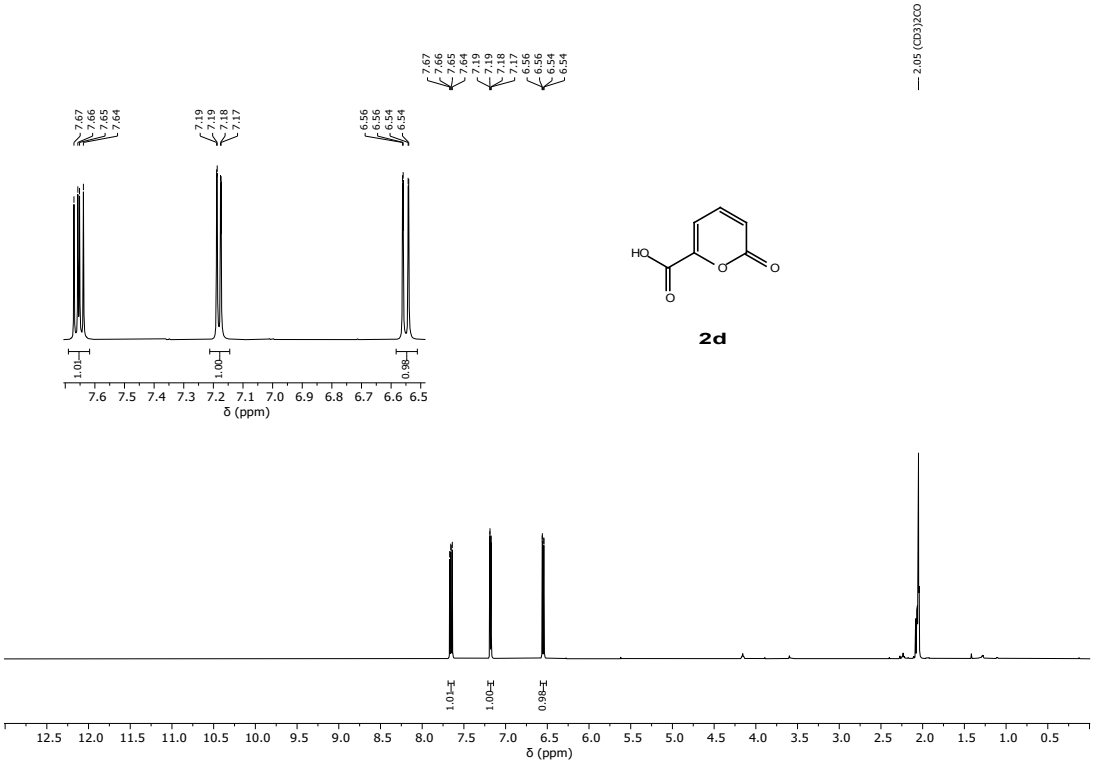


Figure S10. ^{1}H NMR (500 MHz, acetone-d_6) of 2*H*-2-oxo-pyran-6-carboxylic acid (**2d**).

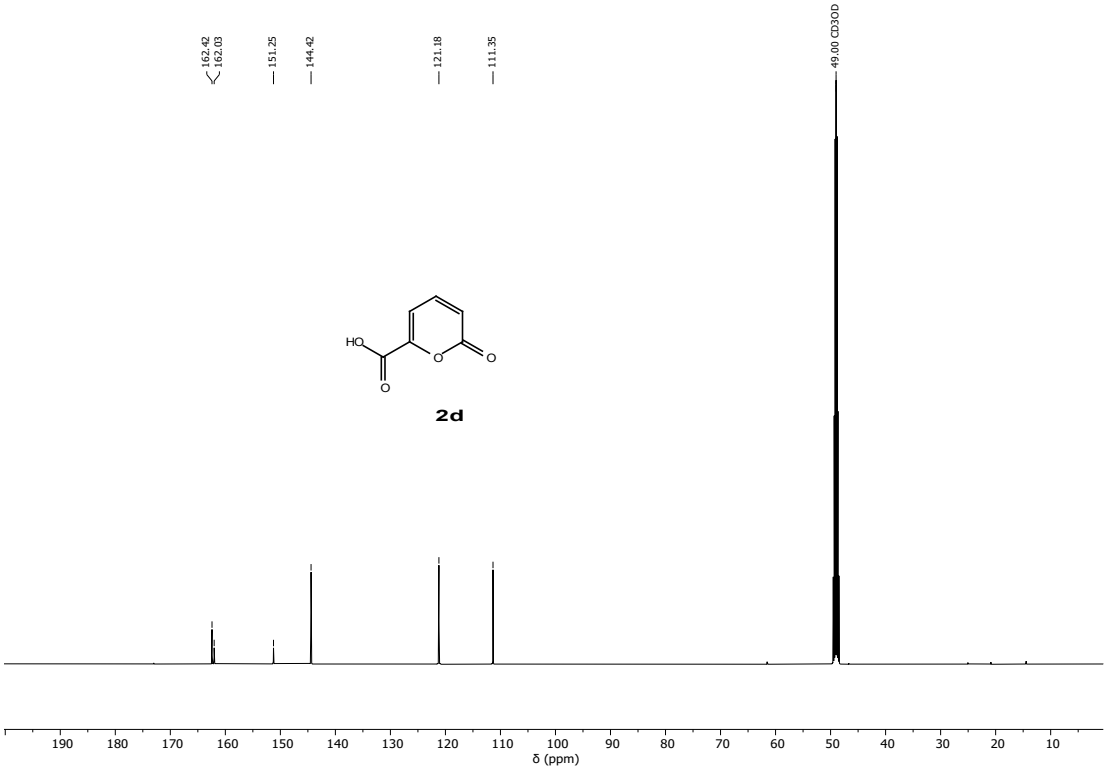


Figure S11. ^{13}C NMR (126 MHz, MeOH-d_4) of 2*H*-2-oxo-pyran-6-carboxylic acid (**2d**).

8 Literature

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