Supporting Information

Development of a modular photoreactor for the upscaling of continuous flow photochemistry.

Johannes G. H. Hermens, Mathieu L. Lepage, Arjan Kloekhorst, Erik Keller, Robin Bloem, Maurice Meijer, Ben L. Feringa*

The upscaling of biphasic photochemical reactions is challenging because of the inherent constraints of liquid-gas mixing and light penetration. Using semi-permeable coaxial flow chemistry within a modular photoreactor, the photooxidation of the platform chemical furfural was scaled up to produce routinely 29 gram per day of biobased building block hydroxybutenolide, precursor to acrylate alternatives.

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General Considerations

Commercial reagents and solvents: Unless stated otherwise, all reagents and solvents were obtained from the commercial sources: Sigma–Aldrich and Linde-gas and were used as received.

Reagents: Furfural (99%) and methylene blue were purchased from *Sigma–Aldrich* (Zwijndrecht, The Netherlands).
Oxygen compressed (technical grade) was purchased from *Linde-gas* (Schiedam, The Netherlands).

Solvents: Methanol (MeOH, 99%, AR grade), diethyl ether (Et$_2$O, stabilized with BHT, AR grade), and pentane (*n*-pentane, HPLC grade) were purchased from *Macron* (Arnhem, The Netherlands).

Equipment: A detailed description of the construction of the photochemical reactor (Supporting Information Construction Manual OctoColor) and the setup of the tube in tube continuous flow system is given *vide infra* (Supporting Information pages S3–S4).
8 x 50 W red light LEDs (for emission spectrum see Supporting Information page S8).
8 x 50 W blue light LEDs (for emission spectrum see Supporting Information page S8).

General Analytical Information: Nuclear Magnetic Resonance spectra were measured with an Agilent Technologies 400-MR (400/54 Premium Shielded) spectrometer (400 MHz). All spectra were measured at room temperature (22–24 °C). Chemical shifts for the specific NMR spectra were reported relative to the residual solvent peak [in ppm; CDCl$_3$: δH = 7.26; CDCl3: δC = 77.16]. The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad signal), app (apparent). All ^{13}C-NMR spectra are ^{1}H-broadband decoupled.

Coaxial flow construction manual

Equipment

- Vapourtec SF-10 (peristaltic) reagent pump, Vapourtec part no. 50-1345 (**Figure S1A**).
- *Outer tubing*: PTFE tubing, l x OD x ID = 50 ft (≈15.2 m) x 1/8 in. (≈3.2 mm) x 0.085 in. (≈2.2 mm), Merck Life Science N.V. product no. 20532 (**Figure S1B**).
- *Inner tubing:* Teflon AF 2400 tubing, l x OD x ID = 14 m x 1/16 in. (≈1.6 mm) x 1/25 in. (≈1.0 mm), Biogeneral, custom part (**Figure S1B**).
- 2x SS Tube Fitting, Bored-Through Reducer, 1/16 in. x 1/8 in., Swagelok part no. SS-100-R-2BT (**Figure S1C**).
- 2x SS Tube Fitting, Union Tee, 1/8 in., Swagelok part no. SS-200-3 (**Figure S1D**).
- Nut ferrules set of 5, 1/16 in., Swagelok part no. SS-100-NFSET (**Figure S1E**).
- Nut ferrules set of 5, 1/8 in., Swagelok part no. SS-200-NFSET (**Figure S1F**).
- SS Tube Fitting, Male O-Seal Connector, 1/8 in., Swagelok part no. SS-200-1-2-OR (**Figure S1G**).
- Back pressure regulator, Stainless Steel PR Regulator, 0 to 250 psig (17.2 bar), 500 psig (34.4 bar) inlet, A Config, PCTFE Seat, 1/8 in. FNPT, 0.06 Cv, Swagelok non-standard part no. KCP1GJA2A2P10000 (**Figure S1H**).
- 1/4 in. stainless steel pipe.
- SS Swagelok Tube Fitting, Bulkhead Male Connector, 1/4 in. Tube OD x 1/8 in. Male NPT, Swagelok part no. SS-400-11-2 (**Figure S1I**).
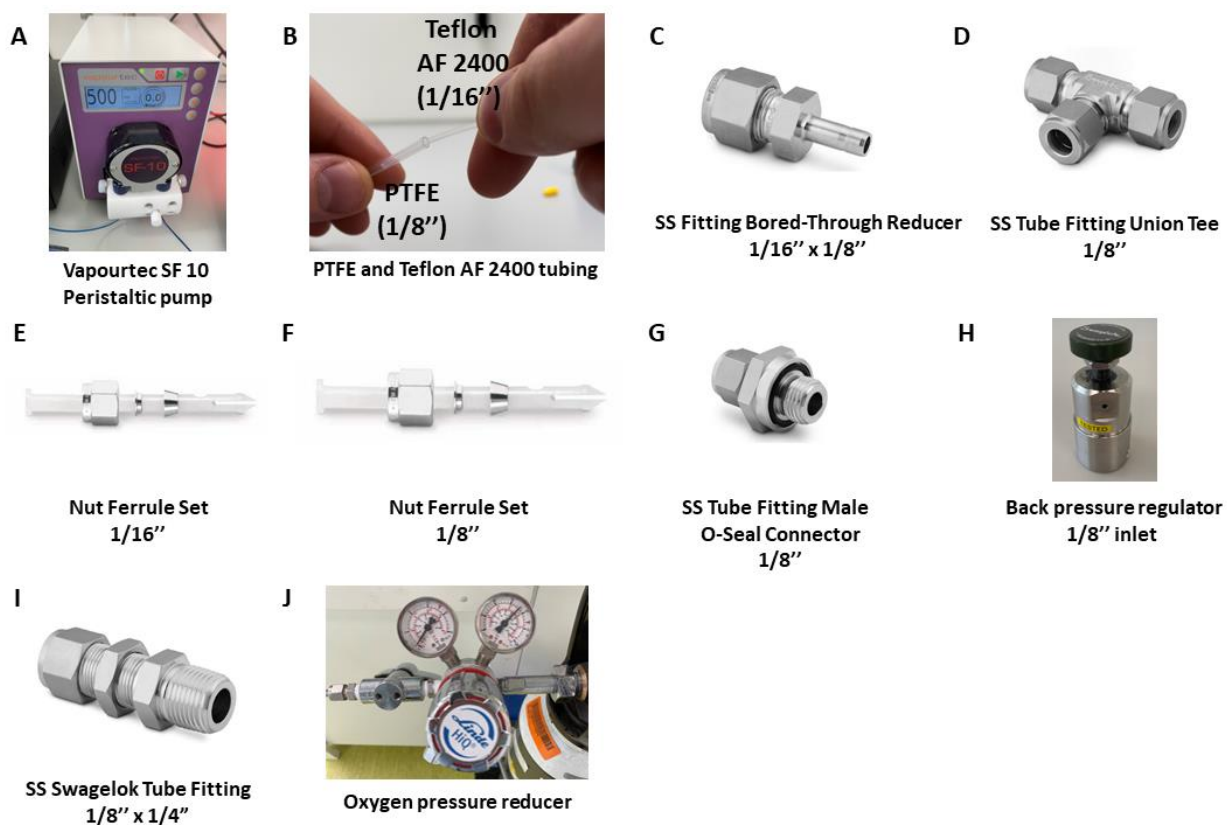- Oxygen pressure reducer, Linde-gas, type: R200/1-14B (**Figure S1J**).

Figure S1 Components for the assembly of the coaxial flow setup

Procedure setup of the coaxial flow reactor.

- The 15 meters PTFE outer tubing (OD = 1/8 in.) was cut to a length of 12 meters.
- The Teflon AF 2400 inner tubing (14 meters) was carefully inserted in the 12 meters of PTFE outer tubing in which 1 meter of Teflon AF 2400 inner tubing sticks out of both ends of the PTFE outer tubing.
- On both ends, the Teflon AF 2400 tubing was threaded through the Swagelok SS Tube Fitting Union Tee (1/8 in.) and the outer PTFE tubing (1/8 in.) was directly connected.
- A SS Tube Fitting Bored-Through Reducer (1/16 in. x 1/8 in.) on the outside ports of the SS Tube Fitting Union Tee was used to connect the Teflon AF 2400 tubing.
  - ! The ferrules and nuts used for connecting the tubing to the SS Tube Fitting Union Tee are hand-tightened, followed by a 3/4 turn with the appropriate wrench.
- 10 Meters of coaxial tubing was coiled around a plastic cylinder (∅ = 16 cm) from bottom to top and held in place by electrical tape.
- The remaining ports of the SS Tube Fitting Union Tee were connected to 1/8 in. PTFE tubing used for gas feed and gas outlet.
- The gas feed tubing was connected using a SS Tube Fitting to a 1/4 in. stainless steel pipe which was directly connected to an oxygen cylinder with pressure reducer.
- The gas outlet tubing was connected to a Back Pressure Regulator (Stainless Steel PR Regulator) using a SS Tube Fitting Male O-Seal Connector in order to pressurize (closed) or depressurize (opened) the outer tubing.
- The Teflon AF 2400 tubing end, before the gas feed Union Tee, was connected to the Vapourtec SF-10 peristaltic pump.
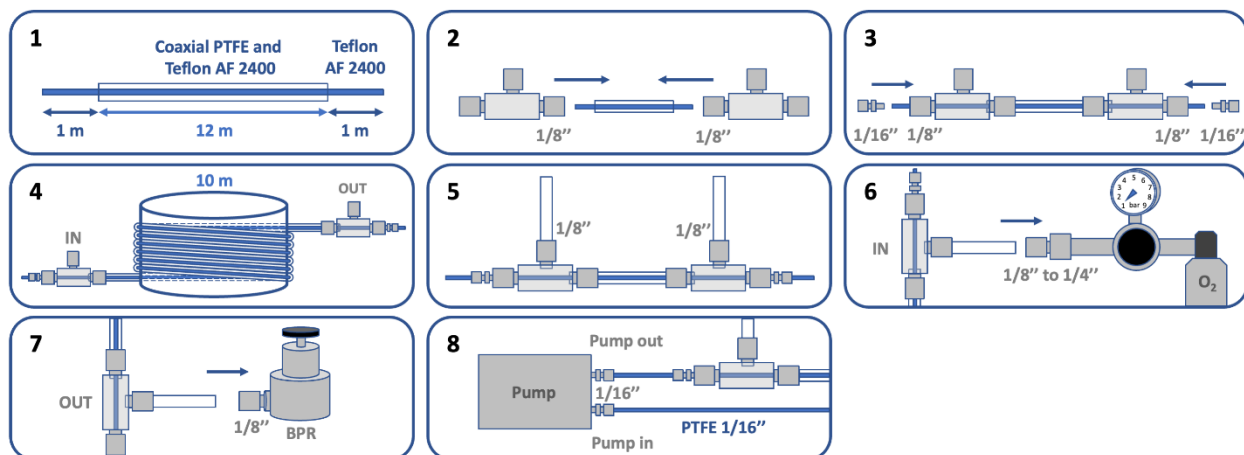

Figure S2 Construction manual of the coaxial flow setup.

Optimization of the segmented flow setup

A segmented flow setup (**Figure S3**) was built and placed inside the photochemical reactor. 25 meter of Fluorenated Ethylene Propylene (FEP) tubing (ID = 1/16'', total volume = 49.5 mL) was wrapped around a 1 liter glass bottle and connected via a T-piece to a tube containing oxygen and a tube containing the solution (furfural and methylene blue in methanol). The oxygen was down regulated to 7 bar pressure and the flow was controlled with a Brooks mass flow controller. The solution was pumped by a Vapourtech SF10 peristaltic pump.

Using segmented flow, we started with the optimized conditions obtained from the previous segmented flow system of FEP tubing around a TL-bulb[1] (i.e. 0.05 M of furfural, 4 mol% methylene blue 0.5 mL/min solution flow speed and 2.5 mL/min oxygen flow). Using these conditions, full conversion towards the desired hydroxybutenolide was achieved (**Table S1**, Entry 1). Studying the concentration of furfural, the concentration of furfural could be increased to 0.2 M, which still resulted in full conversion (**Table S1**, entry 2, 3). In order to establish the importance of the residence time, the solution flow was increased from 0.05 to 2 mL/min. At the lowest concentration of 0.05 M, excellent conversion was still obtained, however with increasing concentrations of furfural at higher flow speeds, lower conversions were obtained with an overall increase in productivity (**Table S1**, entry 4–7).

As the amount of oxygen could be the limiting reagent, using 0.05 M of furfural and a solution flow of 2 mL/min, the flow of oxygen was doubled to 5 mL/min. This resulted however in a lower conversion, supposedly due to the decreased residence time (**Table S1**, entry 8).

Using the OctoColor reactor the productivity of the original segmented flow setup was increased from 1.5 mmol/h to 6 mmol/h, due to the utilization of high power LEDs with better overlap between the absorption spectrum of the photosensitizer and emission spectrum of the lamp (**Figure S10**). Under optimal conditions with the highest concentration of furfural in the segmented flow setup (0.2 M furfural, 4 mol% methylene blue, 0.5 mL/min solution flow, 2.5 mL/min oxygen flow) a continuous production of 14.4 g/day of hydroxybutenolide was possible.

Table S1 Optimization table for continuous segmented flow photooxidation of furfural towards hydroxybutenolide. Reaction conditions: furfural, methylene blue (4 mol%), MeOH, rt, oxygen (7 bar), 635 nm, 49.5 mL internal volume.
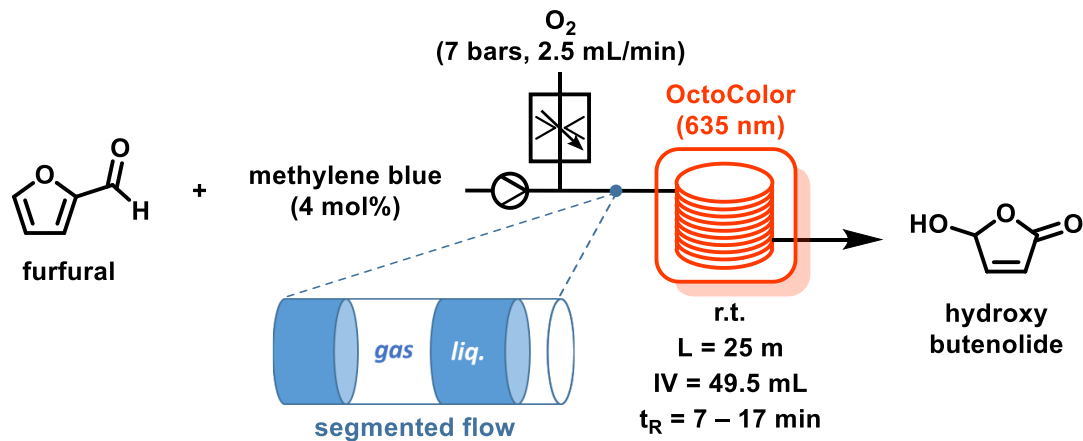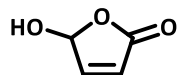

Entry	Furfural (M)	Flow solution (mL/min)	Flow O₂ (mL/min)	Yield (%)[a]	Productivity (mmol/h)
1	0.05	0.5	2.5	>99	1.5
2	0.1	0.5	2.5	>99	3.0
3	0.2	0.5	2.5	>99	6.0
4	0.05	1.0	2.5	>99	3.0
5	0.05	2.0	2.5	98	5.9
6	0.1	2.0	2.5	64	7.7
7	0.2	2.0	2.5	49	11.8
8	0.05	2.0	5.0	94	5.6

[a] Conversion determined by ^{1}H-NMR spectroscopy in $CDCl_3$.

Experimental

5-hydroxy-2(5H)-furanone (hydroxybutenolide) segmented flow

A solution of freshly distilled (65°C, 4 mbar) furfural (14.0 g, 146 mmol) and methylene blue (1.86 g, 6 mmol, 4 mol%) in 730 mL of methanol was prepared in a 1 L glass bottle. The solution was stirred at 500 rpm and pumped by a Vapourtech SF10 peristaltic pump at a flow rate of 0.5 mL/min into the segmented flow setup. The flow of oxygen, pressurized at 7 bar, was set at 2.5 mL/min and the segmented flow setup was irradiated with red light (200 W) inside the OctoColor reactor. The reacted mixture was collected for 24 h, and then processed according to isolation guidelines (*vide infra*, page S10) to provide hydroxybutenolide or reacted further to another derivative.
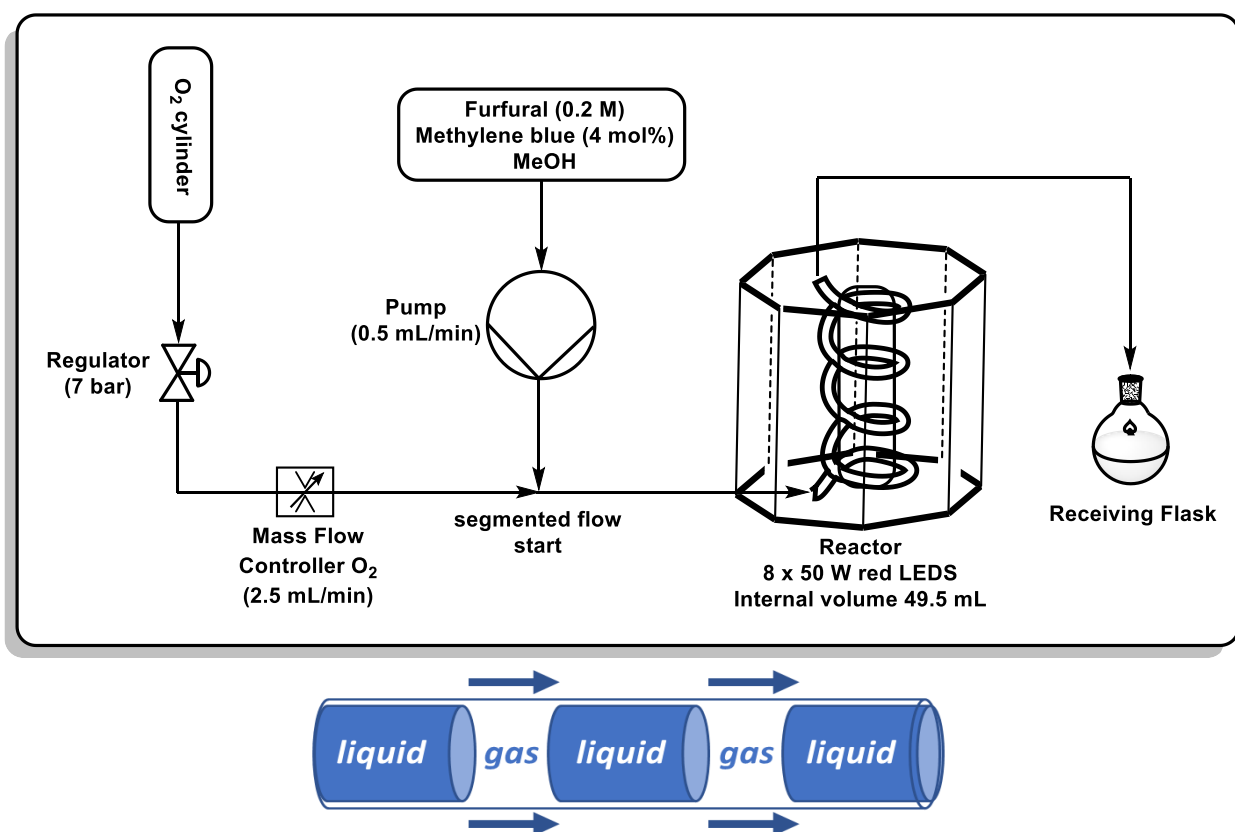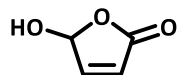
Figure S3 Flow scheme for the segmented flow photooxidation of furfural (top) and schematic representation of segmented flow (bottom).

5-hydroxy-2(5H)-furanone (hydroxybutenolide) coaxial flow setup ("tube-in-tube")

A solution of freshly distilled (65°C, 4 mbar) furfural (96.0 g, 1 mol) and methylene blue (1.60 g, 5 mmol, 0.5 mol%) in 2.5 L of methanol was prepared in a 2.5 L glass bottle. The solution was stirred at 500 rpm and pumped by a Vapourtech SF10 peristaltic pump at a flow rate of 0.5 mL/min into the coaxial flow reactor. The oxygen pressure was set at 1 bar and the coaxial flow setup was irradiated with red light (200 W) inside the OctoColor reactor. The reacted mixture was collected for 83 h, and then processed according to isolation guidelines (*vide infra*, page S10) to provide hydroxybutenolide or reacted further to another derivative.
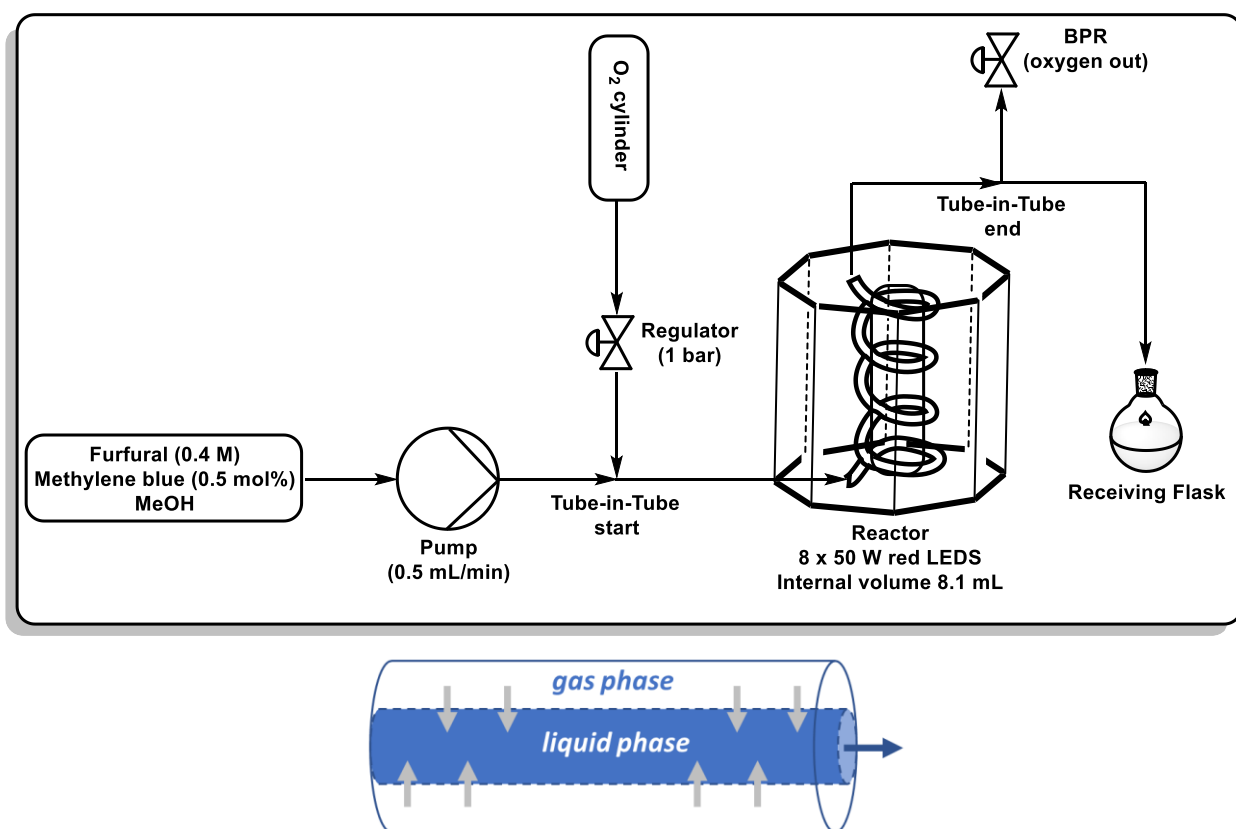

Figure S4 Flow scheme for the tube in tube flow photooxidation of furfural (top) and schematic representation of tube in tube flow (bottom).
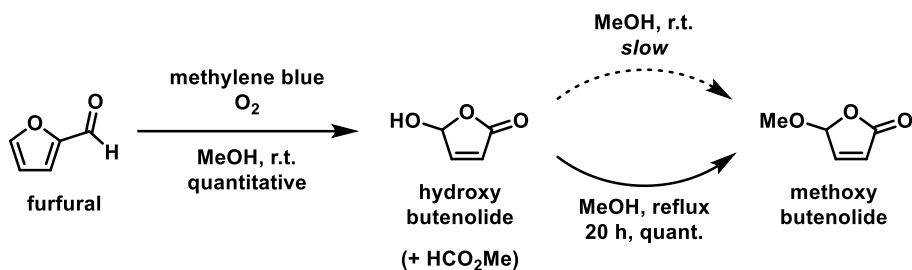
Isolation of hydroxybutenolide

Figure S5 Photooxidation of furfural towards hydroxybutenolide and methyl formate and subsequent condensation process over time, if left standing at room temperature in methanol unattended (*slow*) or with quantitative conversion towards methoxybutenolide if refluxed overnight.

Under the optimized conditions for each setup described above, hydroxybutenolide is quantitatively produced with >99% selectivity (see **Figure S6**, top). The collected solution thus contains hydroxybutenolide (0.2 to 0.4 M), methyl formate (max. 1 eq., produced during reaction) and methylene blue (0.002 to 0.016 M) in methanol.
This solution can be used directly for further transformations compatible with these components. In particular, condensation with methanol to obtain methoxybutenolide (see **Figure S5**) can be performed directly by refluxing the collected mixture over night.[1]

For other purposes, methanol and methyl formate can be removed by rotary evaporation.

It is important to note that condensation of hydroxybutenolide with methanol (forming methoxy butenolide, see **Figure S5**) will slowly occur at room temperature if the collected reaction mixture is left unattended. Cooling of the collection flask (*e.g.* with an ice bath) will effectively prevent this condensation from happening. Similarly, rotary evaporation should be performed under 25°C. Following these guidelines, hydroxybutenolide stained with methylene blue can be obtained quantitatively as a blue oil in > 97% purity (see **Figure S6**, middle). Note that methylene blue is present in such small amount (0.5 mol%) that it is not detectable by ^{1}H-NMR.

Most of the methylene blue can be precipitated by slowly diluting the well-stirred crude blue oil at room temperature with diethyl ether (10 mL per gram of crude). Filtration of the supernatant solution on neutral aluminum oxide (1 g per gram of crude) (**Figure S7**, A-C), rinsing with more diethyl ether (5 mL per gram of crude) affords a lightly colored filtrate (**Figure S7** B), which is then concentrated, re-dissolved in chloroform (1 mL per gram of residue) and cooled to −18°C (*e.g.* in a freezer). Addition of a seed of solid hydroxybutenolide triggers crystallization, which is allowed to proceed at −18°C for a few hours (typically overnight). The crystallized material is then filtered, rinsing with a minimal amount of ice-cold chloroform (1 mL per gram of residue) or pentane (excess). Hydroxybutenolide is then obtained as a white solid of high purity (see **Figure S6**, bottom and **Figure S7** D), albeit with a loss of yield (typically 60% isolated).

Alternatively, removing the methylene blue can be done by silica gel column chromatography (gradient: AcOEt/pentane 10% to 60% over 25 column volumes).[1]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, J = 5.7 Hz, 1H), 6.25 (s, 1H), 6.23 (d, J = 5.7 Hz, 1H), 5.04 (s, 1H).
^{13}C NMR (101 MHz, CDCl^3) δ 171.80 (1C), 152.31 (1C), 124.70(1C), 99.05(1C).
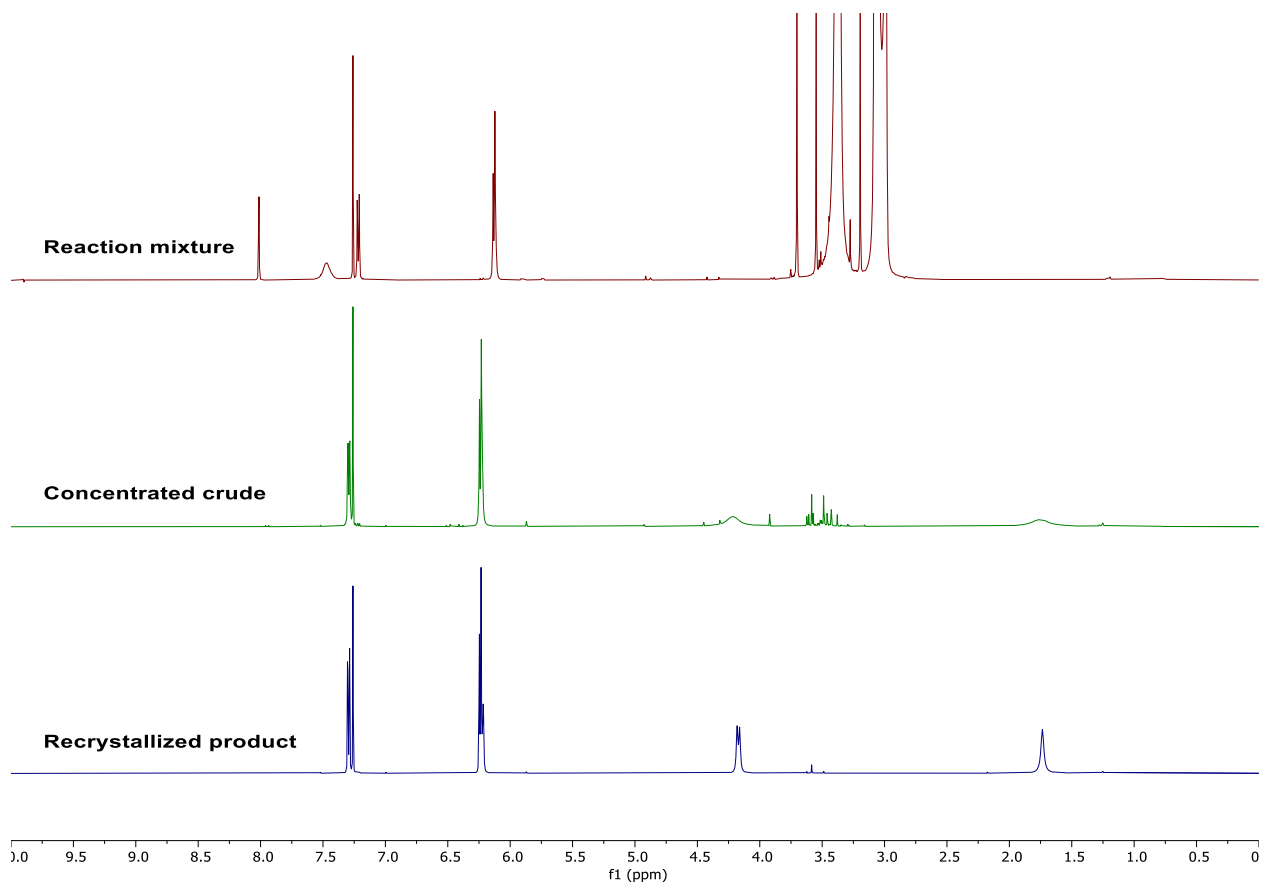HRMS calculated 99.0088, found 99.0090.

Figure S6 Stacked ^{1}H-NMR spectra of hydroxybutenolide (measured at 293 K in CDCl$_3$). Top: reaction mixture containing hydroxybutenolide, methyl formate and methylene blue in methanol; methylene blue is not detectable by ^{1}H-NMR (0.5 mol%). Middle: concentrated reaction mixture containing >95% hydroxybutenolide. Bottom: Recrystallized hydroxybutenolide.
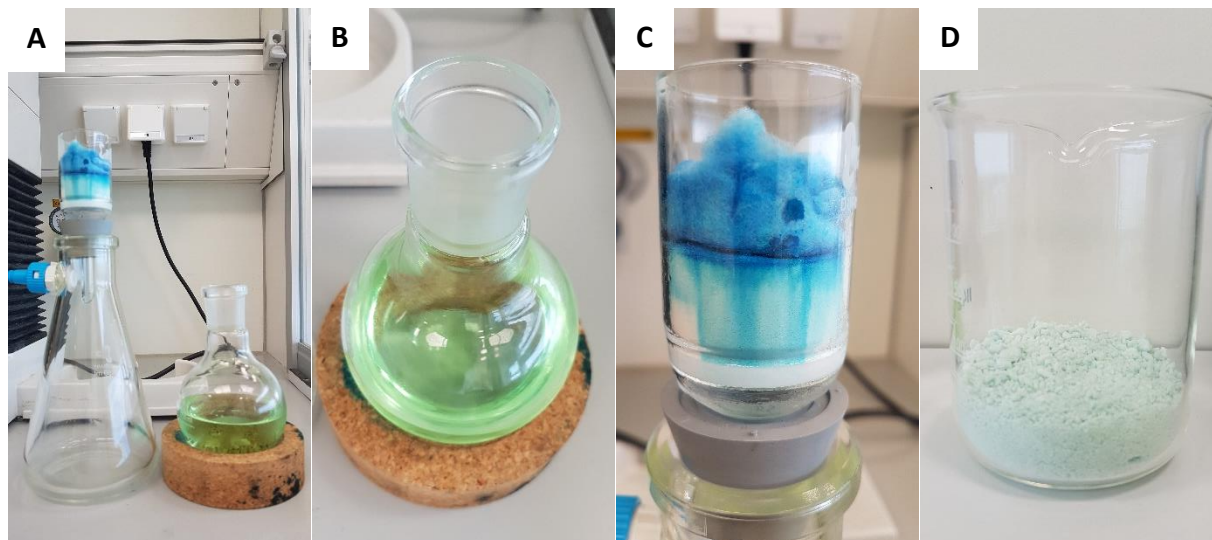

Figure S7 (A) Filtration of diethyl ether supernatant over neutral aluminum oxide. (B) Lightly colored filtrate containing purified hydroxybutenolide. (C) Aluminum oxide filter plug onto which methylene blue was trapped. (D) Recrystallized hydroxybutenolide.
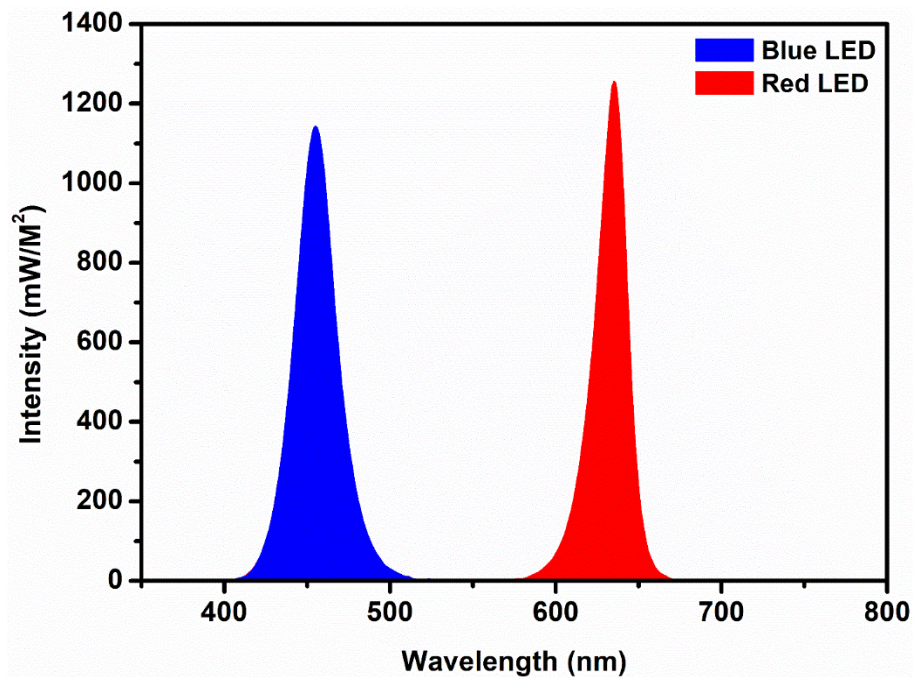
Emission spectrum LEDs

Figure S8 Emission spectrum of 50 W red and blue LEDs expressed in intensity (mW/M^2) versus wavelength (nm).

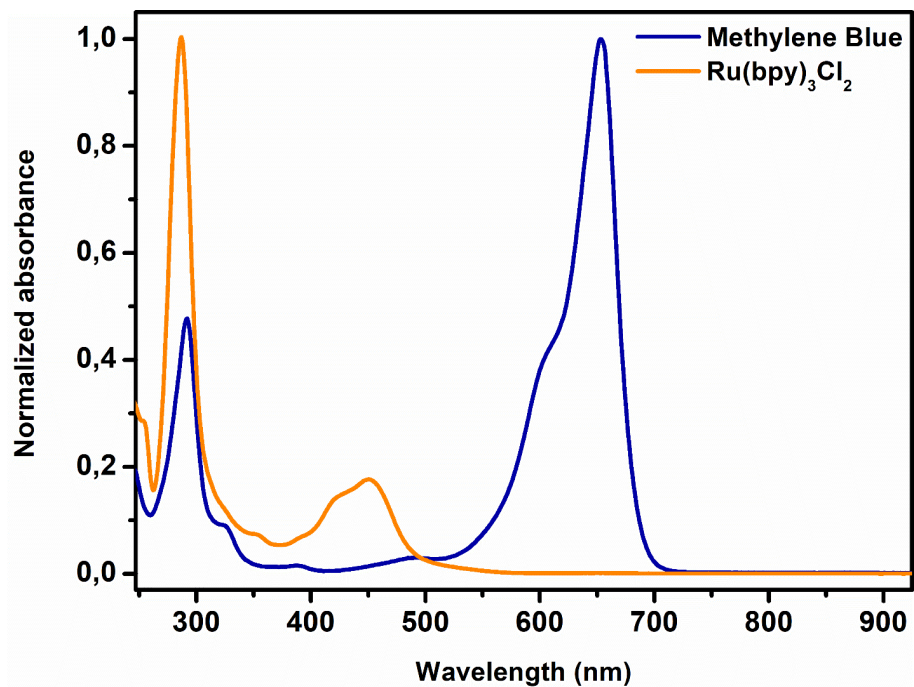# Normalized absorption of photosensitizers

Figure S9 Normalized absorption spectra of methylene blue (5.0 · 10^{-6} M) and Ru(bpy)$_3$Cl$_2$ (1.3 · 10^{-5} M) in MeOH at 293K.

Comparison normalized absorption spectra of photosensitizers and emission spectra of LEDs
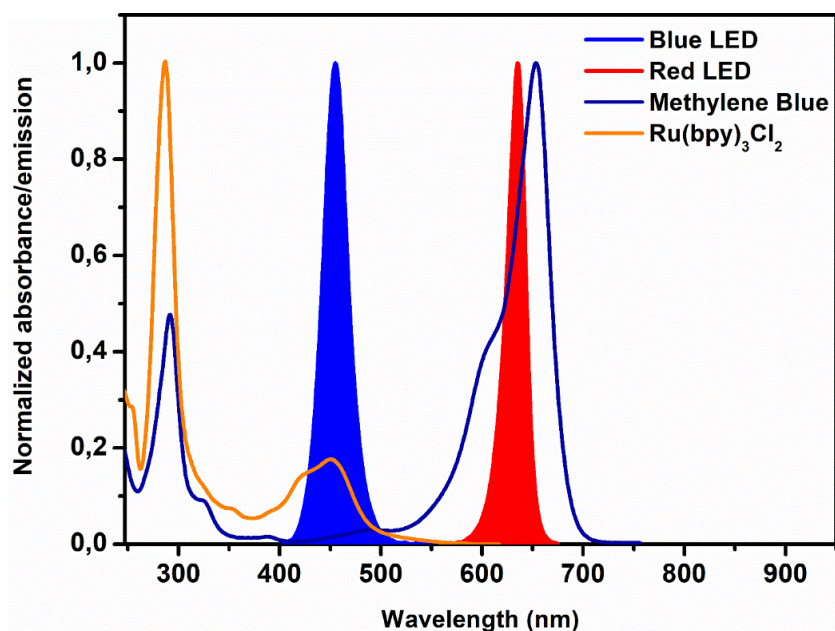

Figure S10 Normalized absorption spectra of methylene blue ($5.0 \cdot 10^{-6}$ M) and Ru(bpy)$_3$Cl$_2$ ($1.3 \cdot 10^{-5}$ M) in MeOH at 293K and normalized emission spectra of blue and red LEDs of OctoColor reactor.

Conversion of furfural and productivity of hydroxybutenolide versus residence time in tube in tube setup

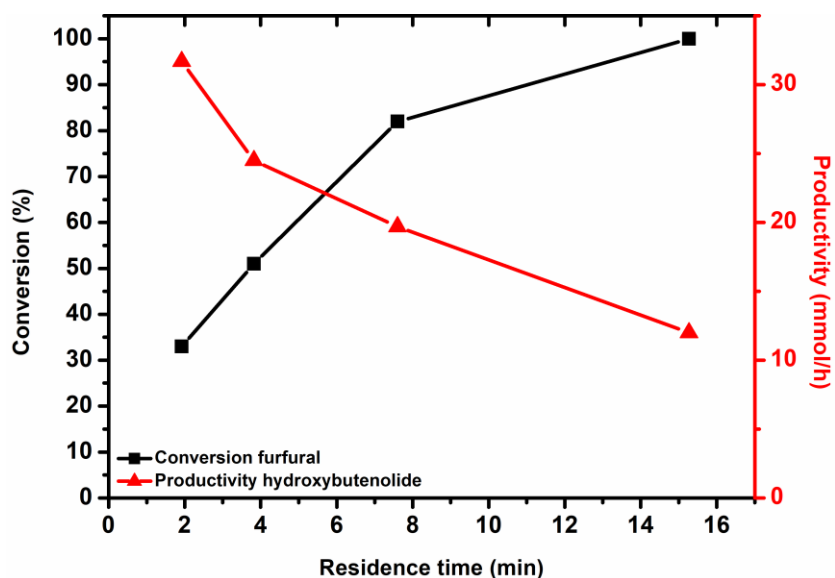**Figure S11** Conversion of furfural versus residence time inside the tube in tube reactor (black) determined by ^{1}H-NMR spectroscopy. Productivity (mmol/h) of hydroxybutenolide versus residence time inside the tube in tube reactor. Reaction conditions tube in tube: 0.4 M furfural in methanol, 4 mol% methylene blue, 1 bar O$_2$, flow speed 4, 2, 1 and 0.5 mL/min for 1.9, 3.8, 7.6 and 15.3 min residence time, respectively.

Estimation of the maximum photon flux and singlet oxygen equivalents

We propose below an estimation of the maximum theoretical amounts of photons actually converted to singlet oxygen, the active species in the studied reaction, and compare this to the flow rate of furfural.

Table S2 Parameters of the red LED OctoColor setup.

Nominal power of one red LED	P	50 W
Fraction of nominal power used	f_P	50%
Number of LEDs	N	8
Molar energy of photons at 635 nm	$E_{M,635}$	$1.88 \cdot 10^{-5}$ J / mol

Maximal photon flux to the reaction mixture:
Equation S1 Photon flux of 8 red LEDs at 50% power.

$$Q_{h\nu} = N \times P \times f_p \times \frac{1}{E_{M,635}} = 1.06 \; mmol/s$$

Only a fraction of this maximal photon flux will actually reach the reaction mixture. However, this fraction is difficult to approximate, so this value for the maximal photon flux is used as an upper boundary.

The absorbance of the reaction mixture at λ = 635 nm is calculated based on methylene blue (MB).

Table S3 Parameters absorptivity under optimized reaction conditions.

Molar extinction coefficient of MB at λ = 635 nm	ε_{635}	50260 L·mol^{-1}·cm^{-1}
Concentration of MB	c	2 mM
Internal diameter of tubing	l	0.10 cm

Absorbance of the reaction mixture at λ = 635 nm, taking the internal diameter of tubing as a typical path length:
Equation S2 Absorbance of methylene blue under optimized reaction conditions.

$$A_{635} = \varepsilon_{635} \times c \times l = 10.05 \gg 1$$

It is thus reasonably assumed that all the photons reaching the reaction mixture will be absorbed by methylene blue, which will then partially be converted to singlet oxygen *via* photosensitization.

The maximal molar flow rate of singlet oxygen in the reaction mixture is calculated, which is compared to the molar flow rate of furfural (*i.e.* the productivity in hydroxybutenolide).

Table S4 Parameters molar flow rate $^1O_2$.

Maximal photon flux	$Q_{h\nu}$	1.06 mmol·s^{-1} (see above)
Quantum yield of photosensitization $^1MB \rightarrow {}^1O_2$	Φ_{PS}	50%
Molar flow rate of furfural	$Q_{furfural}$	0.20 mmol/min
		3.33 µmol/s

Maximal molar flow rate of singlet oxygen:
Equation S3 Maximal molar flow rate $^1O_2$ under optimized conditions.

$$Q_{(^1O_2)} = Q_{h\nu} \times \Phi_{PS} = 531 \; \mu mol/s$$

Maximal singlet oxygen equivalents:

Equation S4 Maximal equivalents of $^1O_2$ produced under optimized conditions.

$$Max.Eq_{(^1O_2)} = \frac{Q_{(^1O_2)}}{Q_{furfural}} = 159$$

Conclusion: Since the conversion of furfural to hydroxybutenolide is > 99%, the number of singlet oxygen equivalents versus furfural is thus comprised between 1 and 159. In reality, it is likely that not all of the emitted photons reach the reaction mixture. To test this, we provide in the next section the results of experiments where the power supply to the LEDs was decreased.

Variation of power supply to red LEDs

According to the supplier of the LEDs, a power of 50 W per LED is obtained with a forward voltage of 20-24 V and a forward current of 1.5 A. In our initial settings we purposely applied a total of 6 A for 8 red LEDs (0.75 A per LED), that is 200 W total (25 W per LED).

In the optimized conditions using the OctoColor semi-permeable coaxial flow setup (0.4 M furfural in methanol, 0.5 mol% methylene blue, 1 bar O_2, 0.5 mL/min flow rate), we tested the impact of the LED power on the conversion. The setup was started and allowed to reach steady-state over 30 min and then a 10 mL sample was collected over 20 min (**Table S5**, entry 1). The current intensity was reduced by 50% (that is 12.5 W per LED), the setup was allowed to reach steady-state over 30 min and then a 10 mL sample was collected over 20 min (**Table S5**, entry 2). This operation was repeated once more for **Table S5**, entry 3 (that is 6.25 W per LED).

Table S5 Optimization of the light intensity of red LEDs of the continuous flow photooxidation of furfural towards hydroxybutenolide.

Entry	Forward current (A)	Conversion (%)
1	6.0	>99
2	3.0	77
3	1.5	45

Results: With our initial parameters (Entry 1), the conversion was > 99%, but with a 50% lower current intensity, conversion was decreased by 25%. Conversion was even lower when halving the current intensity once more.

Conclusion: Our initial settings for power supply are optimal.

Operational energy cost hydroxybutenolide

We provide below a table for the calculation of the operational time and energy cost of the reactor using the optimized conditions (**Table 1**, entry 11) and the current electricity price[2] in the Netherlands of €0.33/kWh for the production of 1 kg hydroxybutenolide. In addition, we compare these values to the operational time and energy cost of our previously described segmented flow setup.[1]

	Coaxial flow (this work)	Segmented flow (previous work)
Power lamps (W)	50 (per LED, 8 total)	18 (per TL-bulb, 1 total)
Power fans (W)	1.56 (per fan, 12 total)	n/a
Total (kW)	0.22	0.018
Productivity hydroxybutenolide (mmol/h)	$1.20\cdot10^{-2}$	$1.50\cdot10^{-3}$
Time to produce 1 kg hydroxybutenolide (days)	35	278
Energy required for 1 kg hydroxybutenolide (kWh)	182.23	119.98
Current electricity price (€/kWh)	0.33	0.33
Energy cost for 1 kg hydroxybutenolide (€)	60.14	39.59

<u>**Results:**</u> Under optimized conditions, the production of 1 kg of hydroxybutenolide using the OctoColor reactor and continuous coaxial flow would cost €60.14 in 35 days. The production of 1 kg hydroxybutenolide using the previously described segmented flow setup would cost €39.59 in 278 days.

<u>**Conclusion:**</u> **The productivity of hydroxybutenolide using the OctoColor and coaxial continuous flow is increased 8-fold as opposed to the segmented flow setup while the energy cost for production is similar (same order of magnitude).**
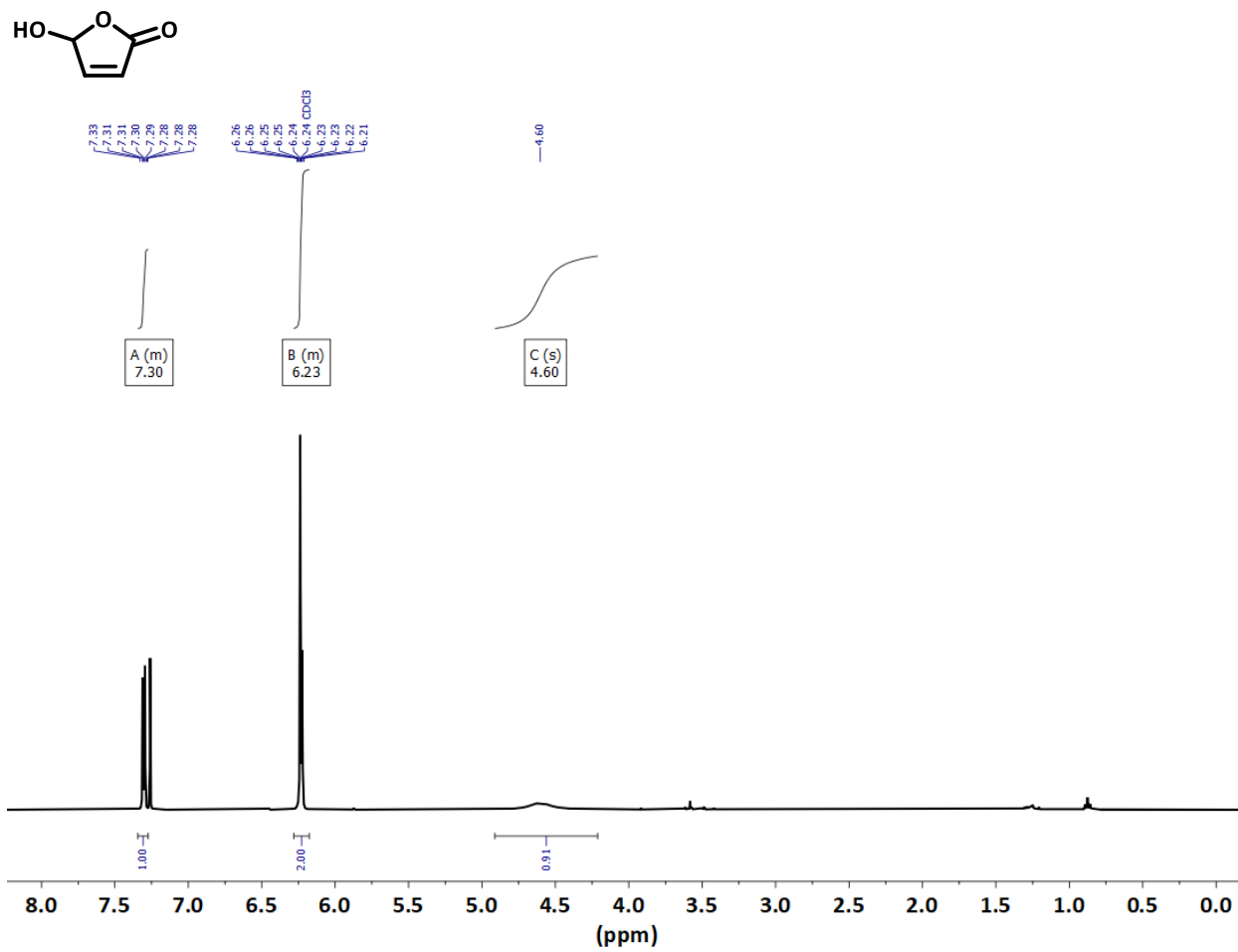
NMR spectra hydroxybutenolide

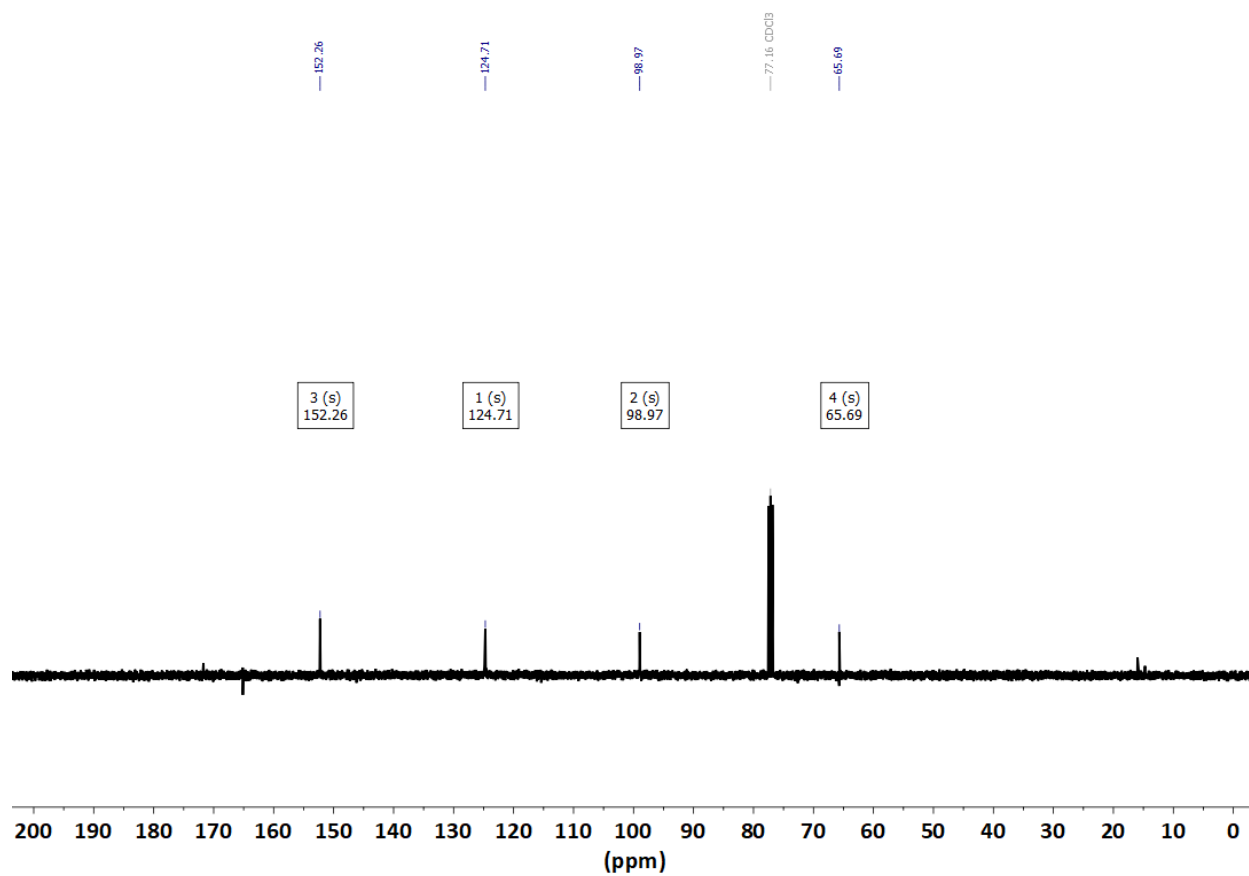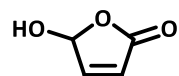**Figure S12** ^{1}H-NMR spectrum of hydroxybutenolide measured at 293 K in CDCl$_3$.

Figure S13 ^{13}C-NMR spectrum of hydroxybutenolide measured at 293 K in CDCl$_3$.

References

1. J. G. H. Hermens, T. Freese, K. J. v. d. Berg, R. v. Gemert and B. L. Feringa, *Sci. Adv.*, 2020, **6**, eabe0026.
2. *Average energy prices for consumers*, https://www.cbs.nl/en-gb/figures/detail/84672ENG (accessed on 2022/07/24).