Supporting Information for:

Levoglucosenone as Starting Material for Cascade Continuous-Flow Synthesis of (*R*)-γ-Carboxy-γ-butyrolactone

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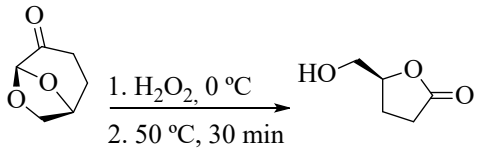
COMPOUND DATA CONTENT:

Summary

EXPERIMENTAL

1. Batch Reactions

1.1. Synthesis of lactone 2H-HBO (3) from Cyrene™ (2)



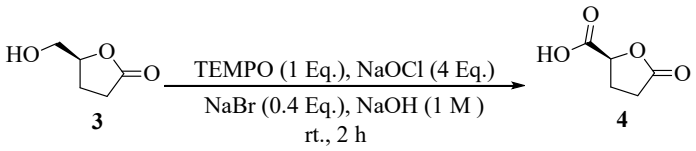
Cyrene™ (**2**) 2H-HBO (**3**)

The synthesis of (S)-γ-Hydroxymethyl-γ-butyrolactone (2H-HBO, **3**) from Cyrene™ (**2**) was performed by a previously established method.[i]

The synthesis of 2H-HBO were performed in a 50 mL round bottom flask, a solution containing by slow dripping Hydrogen Peroxide 30 % (0.81 mL, 7.11 mmol, 1.08 Eq.) into a 6.6 M solution of Cyrene™ at 0 ºC (0.844 g, 6.59 mmol, 1 Eq.) in 1 mL H_2O. Than the solution was heated to 50 °C for 30 min and reaction progression was tracked through thin layer chromatography (ethyl acetate/cyclohexane 8:2). At the end, the reaction was heated to 90 °C to kill any hydrogen peroxide excess. The reaction was dried through rotatory evaporation, using cyclohexane as azeotrope then lyophilized. Obtaining the product in the form of a colorless oil of 0.75 g mass with an isolated yield of 98 % (Conv.: >99 %, Selec.: 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.59 (tdd, J = 7.4, 4.6, 2.8 Hz, H 4), 3.86 (dd, J = 12.5, 2.8 Hz, H 5b), 3.64 – 3.55 (m, H 5a), 2.89 (s, H 6), 2.64 – 2.45 (m, H 2), 2.27 – 2.04 (m, H 3). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 177.84 (s, C1), 80.87 (s, C4), 64.10 (s, C5), 28.70 (s, C2), 23.15 (s, C3).

i. Bonneau, G., Peru, A. A. M., Flourat, A. L. and Allais, F. *Green Chemistry* **2018**, *20*, 2455–2458.

1.2. Synthesis of oxidation of 2H-HBO (3) towards carboxylic acid 4



The synthesis of carboxylic acid **4** from 2H-HBO (**3**) was performed by a previously established method.[ii]

The synthesis of **4** was carried out in a 50 mL round bottom flask, containing 4 mL of distilled water and 232 mg of 2H-HBO (2 mmol, 1 Eq.), to this solution were added 312 mg of 2,2,6 ,6-tetramethylpiperidine 1-oxy (TEMPO, 2 mmol, 1 Eq.), 82 mg of sodium bromide (0.8 mmol, 0.4 Eq.), and 550 mL of 10 % sodium hypochlorite solution (8 mmol, 4 Eq.). The pH of the solution was adjusted to 10 with 1 M sodium hydroxide and then stirred for two hours, monitored by thin layer chromatography (ethyl acetate/cyclohexane 8:2). After the total consumption of 2H-HBO (**3**), the reaction was quenched with 1 mL of ethanol. The pH was then reduced to 1 by a 6 M hydrochloric acid solution. For purification, a liquid-liquid extraction was carried out with dichloromethane, followed by rotary evaporation of the aqueous phase. The solid obtained was then resuspended with hot ethanol and subsequently filtered through a sintered funnel to remove inorganic salts. Obtaining the product in the form of 0.403g g of mass with an isolated yield of 82 % (Conv.: 82 %, Select.: 95 %). IR ν_{max} (KBr) cm^{-1}: 3550-3200, 1775, 1723, 1175. ^1H NMR (400 MHz, D_2O) δ (ppm) δ 2.4-2.6 (4H, m,-CH_2-CH_2), 4.85-5.15 (H, m, ring-H), 5.1 (H, s, -COOH).

ii. Kraus, T., Buděšínský, M., Z., Jiří. *J. Org. Chem.* **2001**, *66*, 4595–4600.

Figure S1. H-Cube® Mini Plus continuous flow hydrogenation reactor (ThalesNano).

2. Chomatographic Analysis

2.1. Gas Chromatography-Mass Spectrometry (GC-MS): Continuous-flow hydrogenation of LGO (**1**) for the production of Cyrene™(**2**).

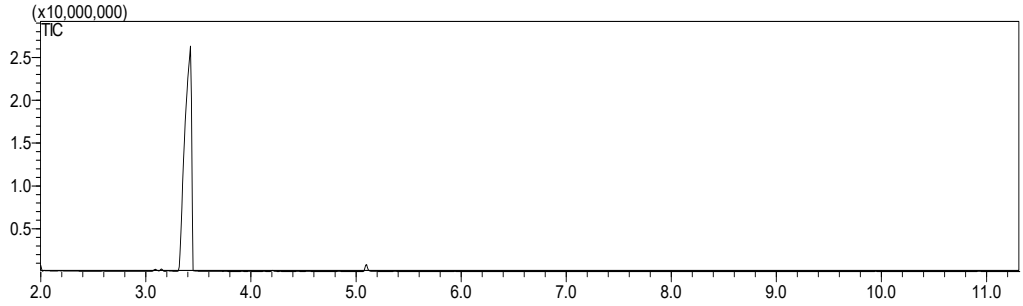


Figure S2. GC−MS chromatograms of standard Levoglucosenone, LGO (**1**) (3.4 min).

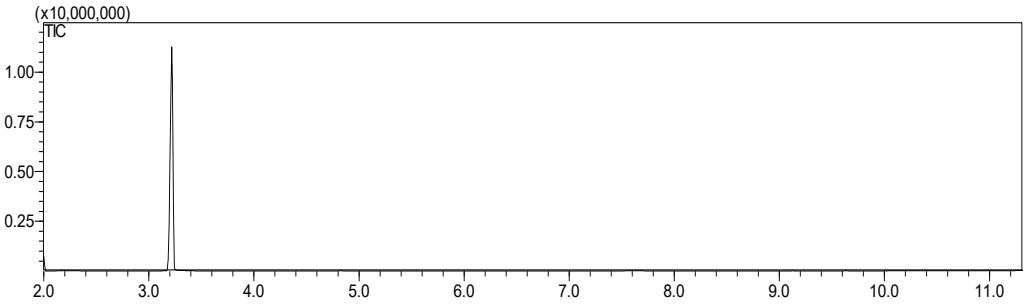


Figure S3. GC−MS chromatograms of standard Cyrene™ (**2**) (3.2 min).

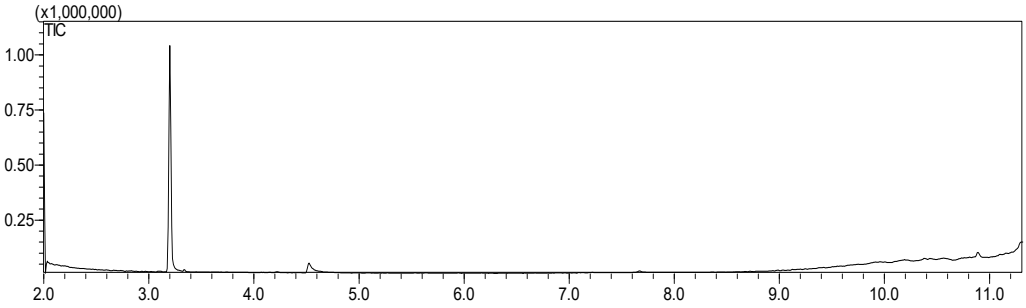


Figure S4. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 1).

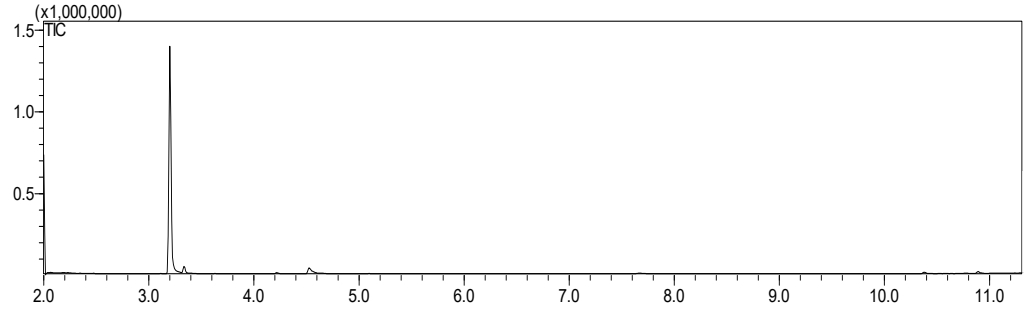


Figure S5. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 2).

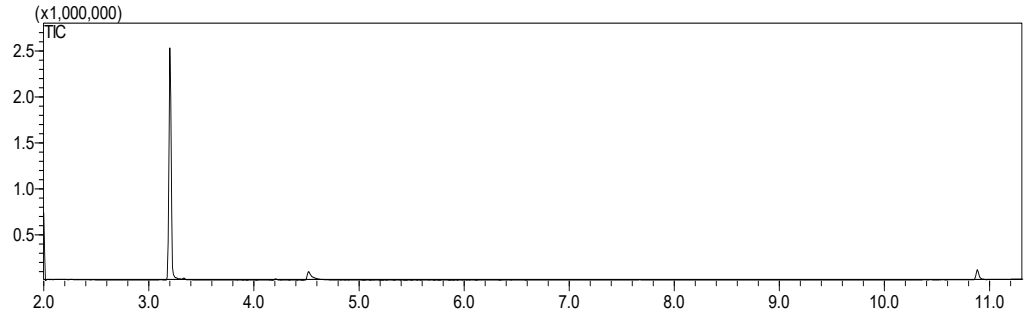


Figure S6. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 3).

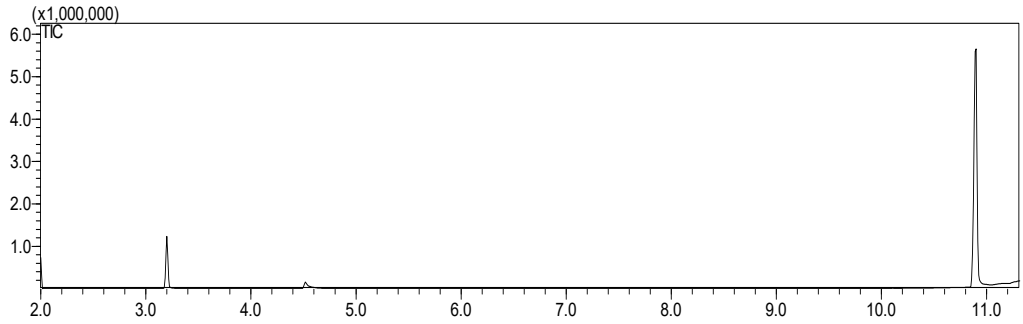


Figure S7. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 4).

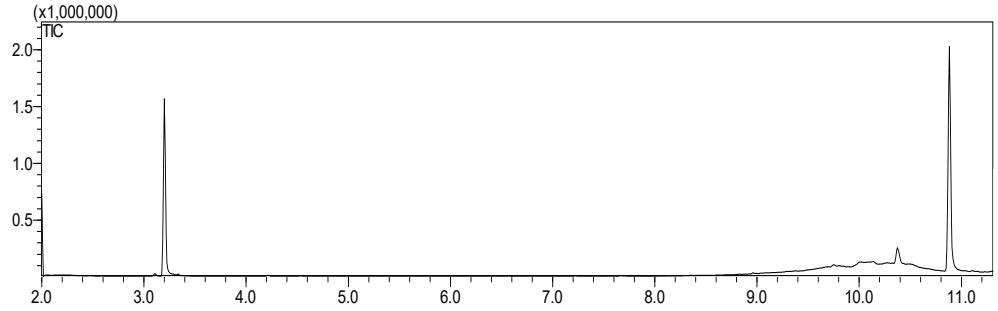


Figure S8. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 5).

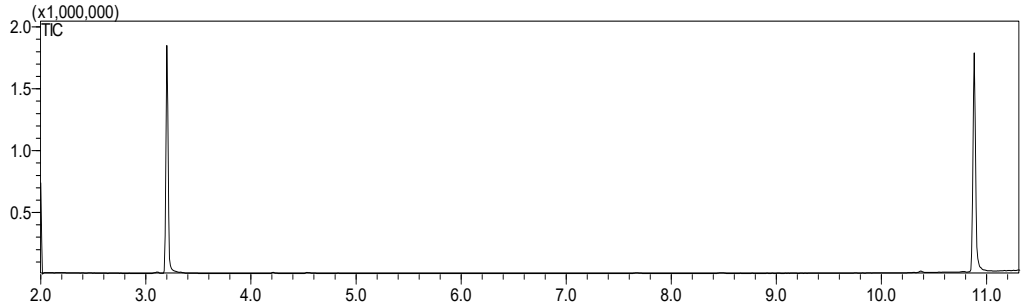


Figure S9. GC−MS chromatograms of continuous-flow hydrogenation of LGO (**1**) using Pd/C 10% (Table 1, entry 6).

2.2. Gas Chromatography-FID Spectrometry (GC-FID): Continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**).

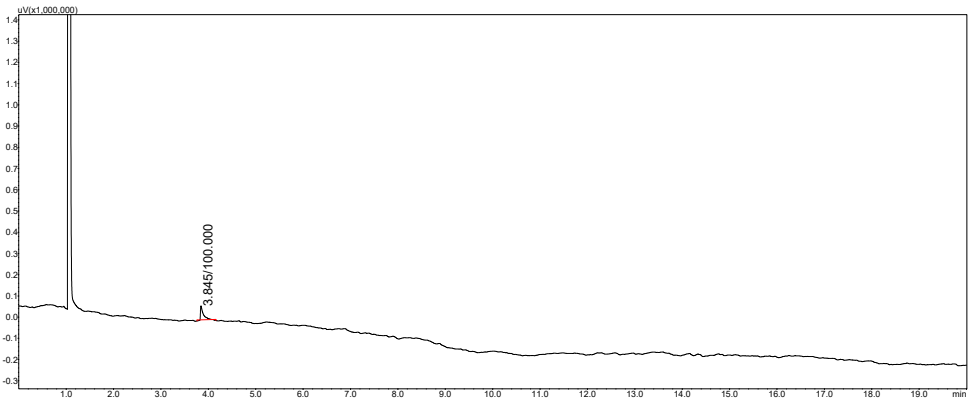


Figure S10. GC−FID standard Cyrene™ (**2**).

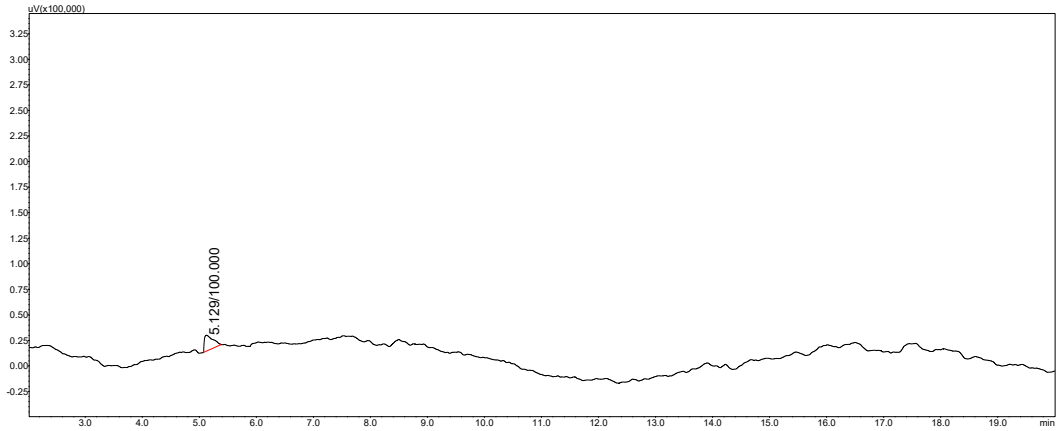


Figure S11. GC−FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 1).

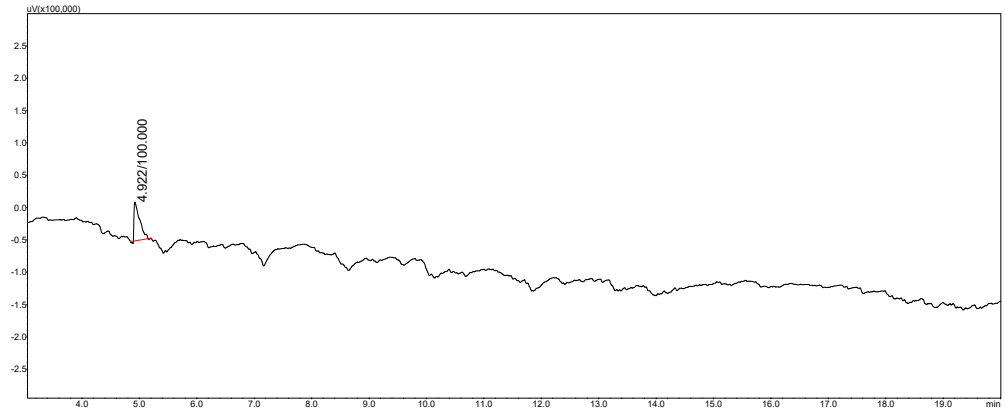


Figure S12. GC−FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 2).

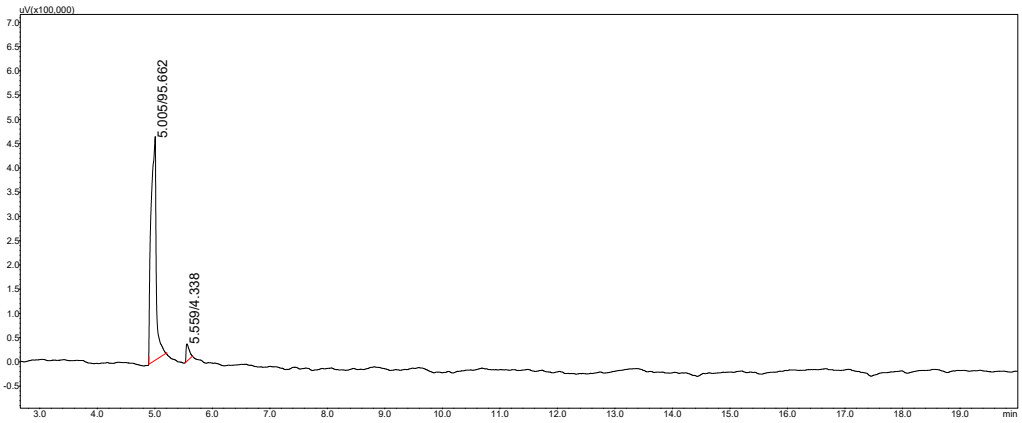


Figure S13. GC–FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 3).

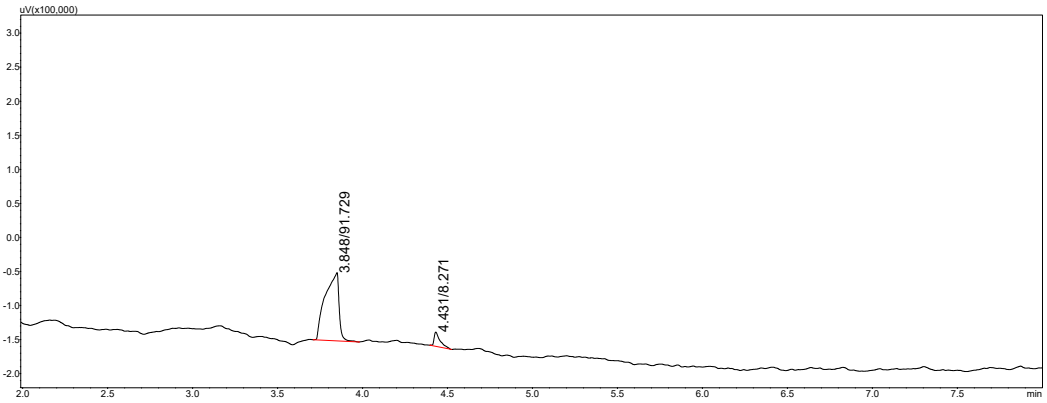


Figure S14. GC–FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 4).

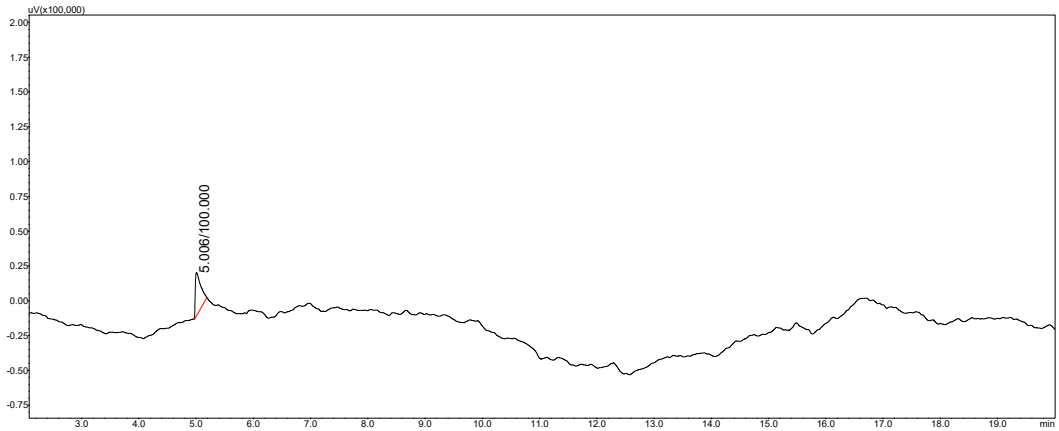


Figure S15. GC–FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 5).

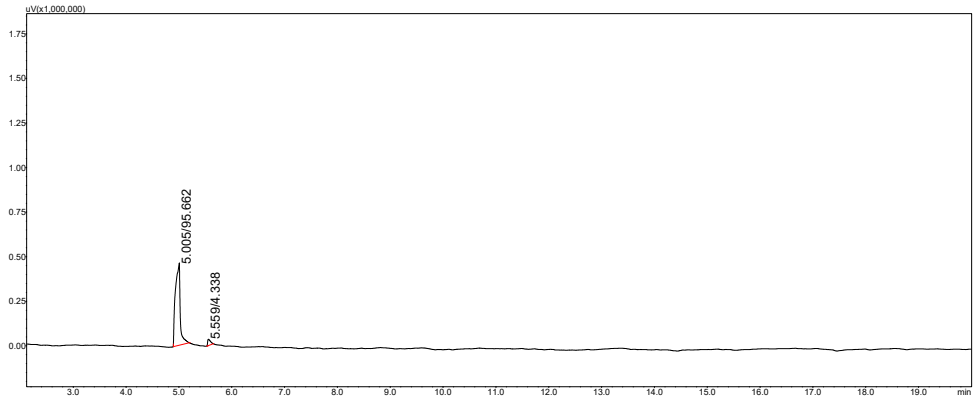


Figure S16. GC−FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 6).

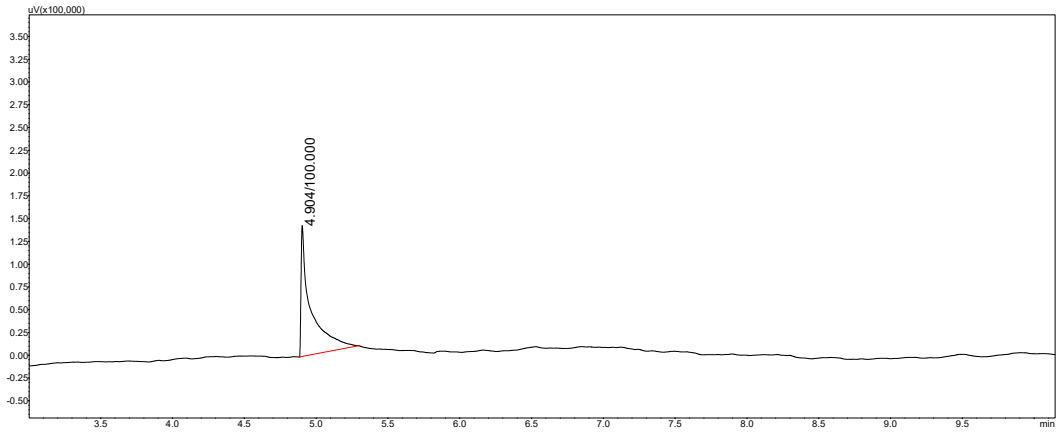


Figure S17. GC−FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 7).

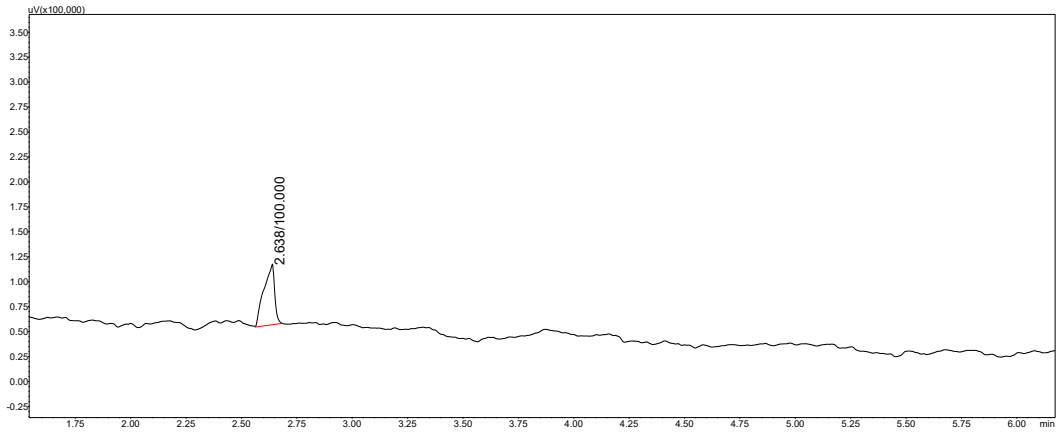


Figure S18. GC−FID chromatograms of continuous-flow Baeyer-Villiger oxidation of Cyrene™ (**2**) towards 2H-HBO (**3**) (Table 2, entry 8).

2.3. Gas Chromatography-Mass Spectrometry (GC-MS): Carboxylic acid **4**

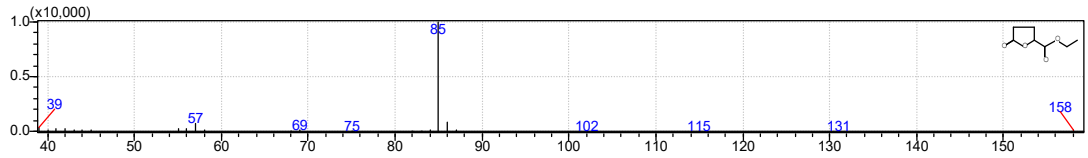


Figure S19. Chromatogram for batch oxidation of 2H-HBO (**3**) towards carboxylic acid **4**.

2.4. Gas Chromatography-FID Spectrometry (GC-FID): Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4**.

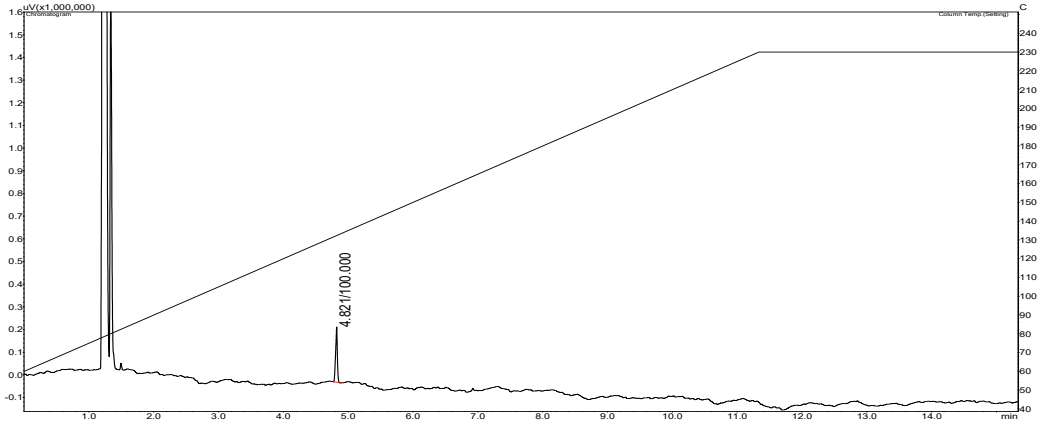


Figure S20. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 3, entry 1).

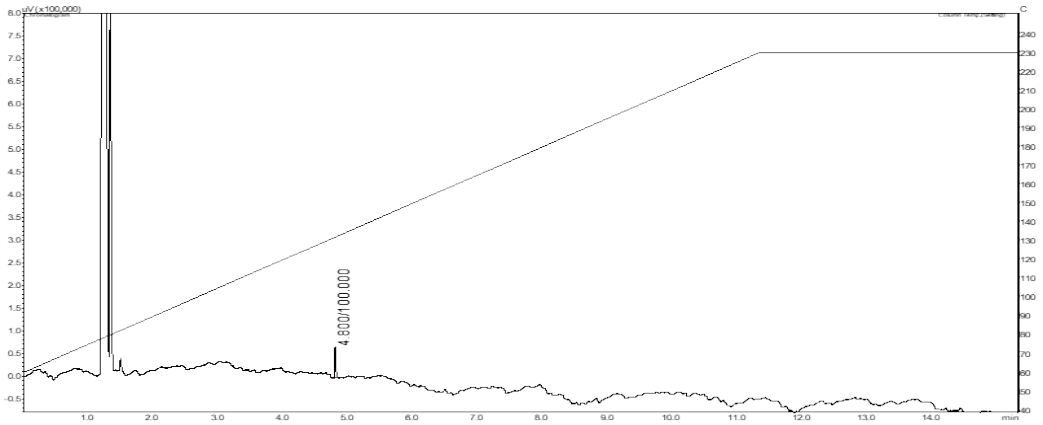


Figure S21. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 3, entry 2).

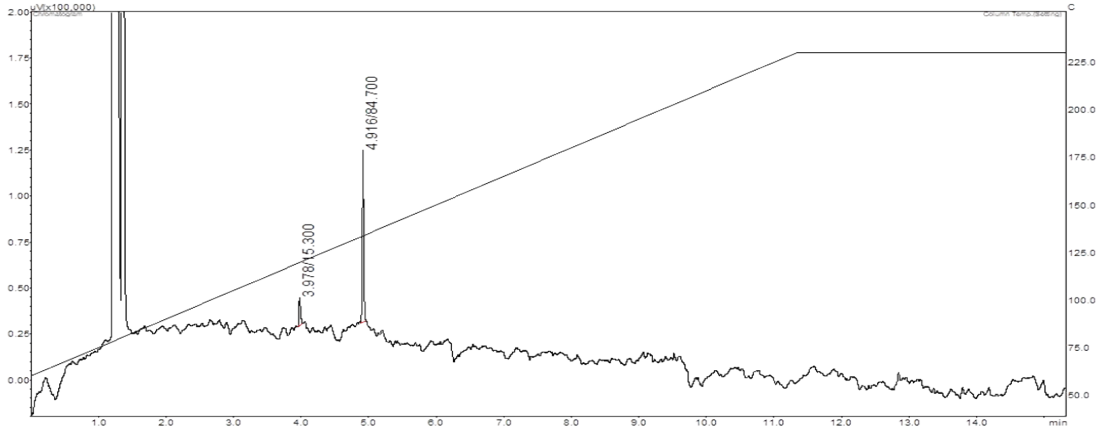


Figure S22. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 3, entry 3).

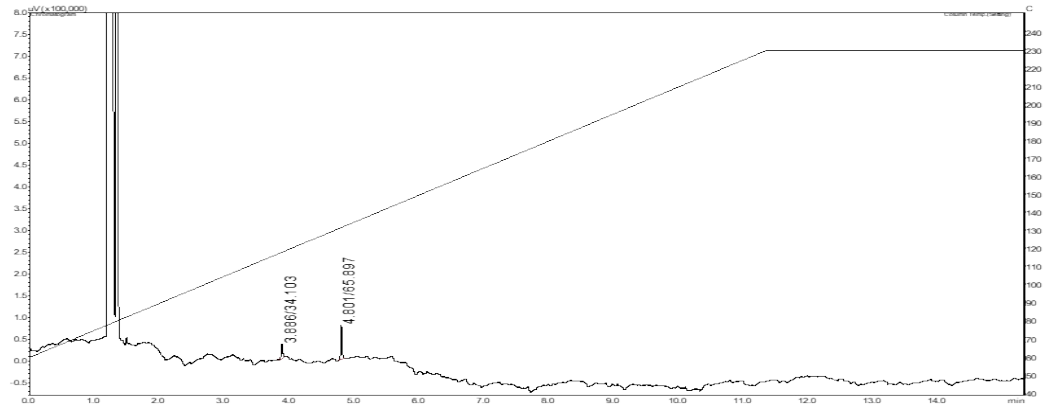


Figure S23. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 3, entry 4).

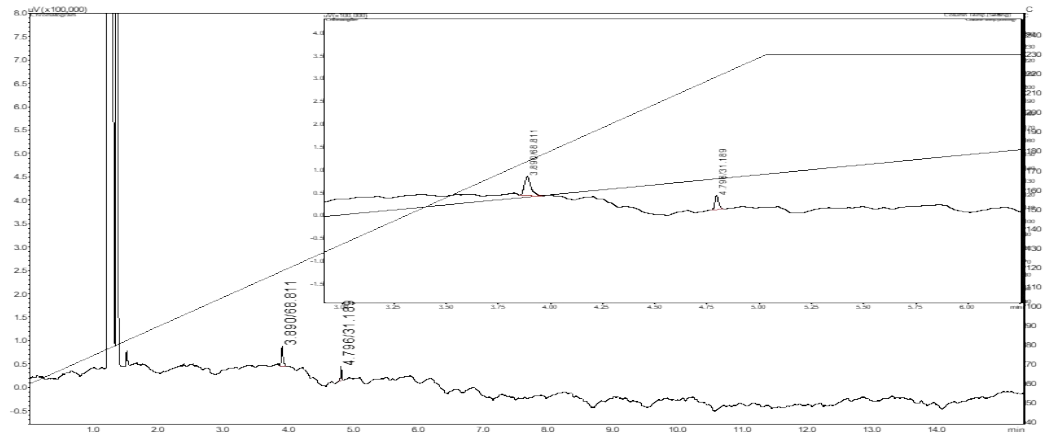


Figure S24. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 3, entry 5).

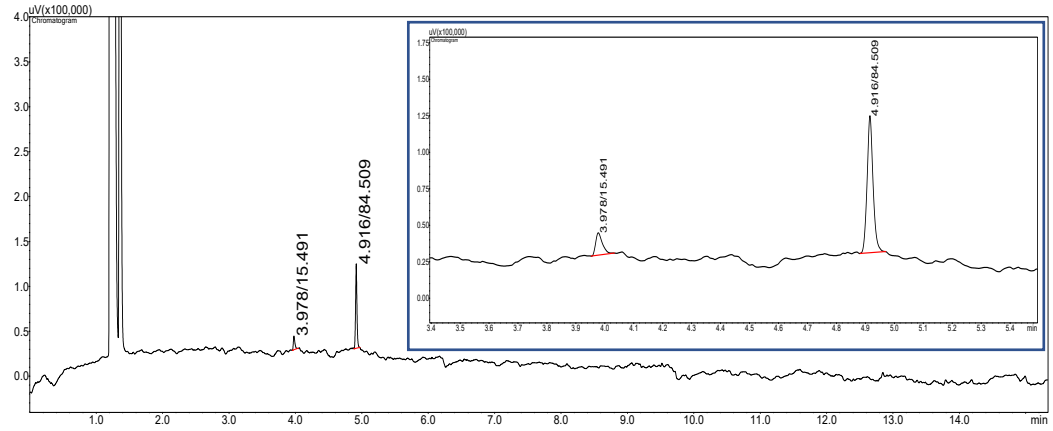


Figure S25. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 1).

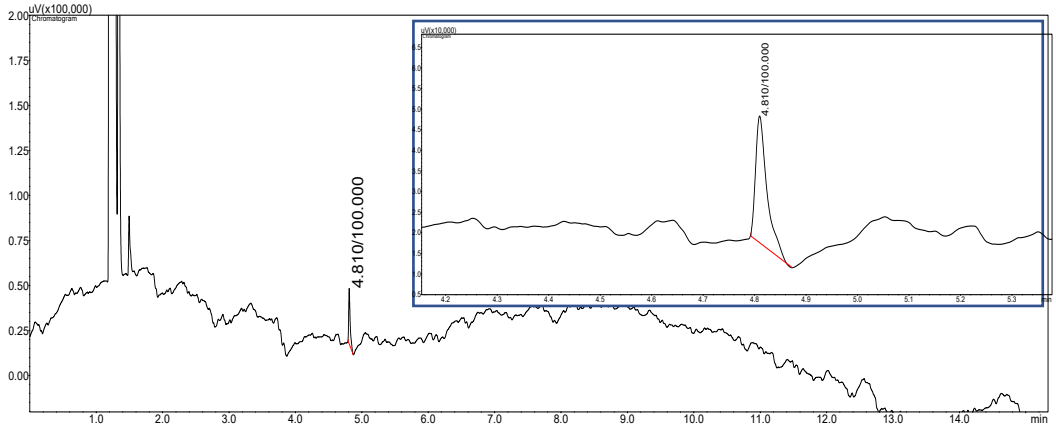


Figure S26. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 2).

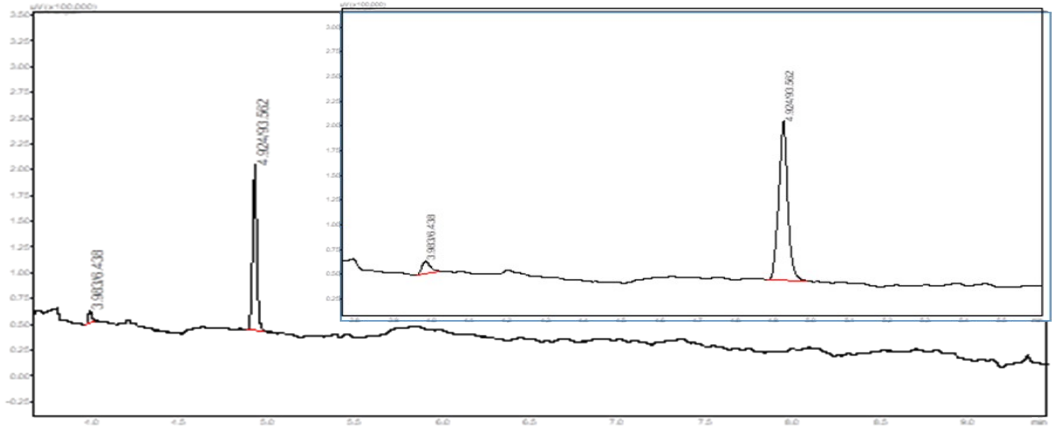


Figure S27. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **5** (Table 4, entry 3).

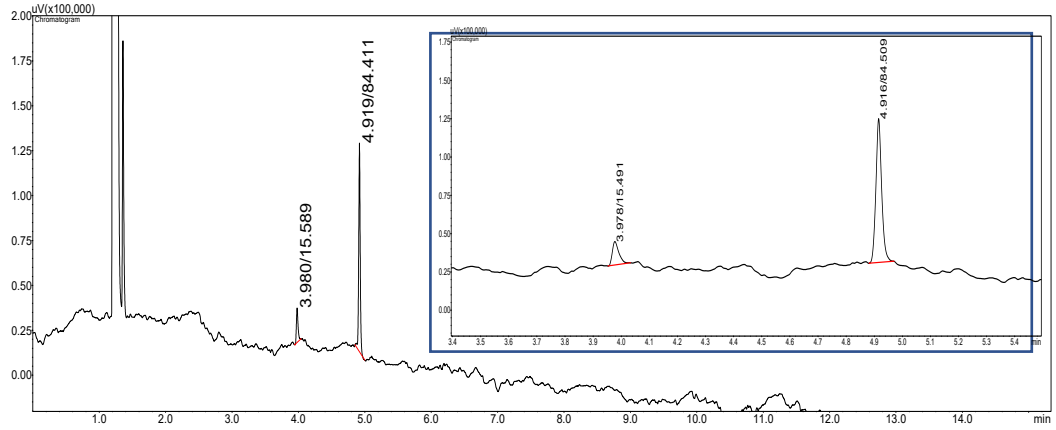


Figure S28. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 4).

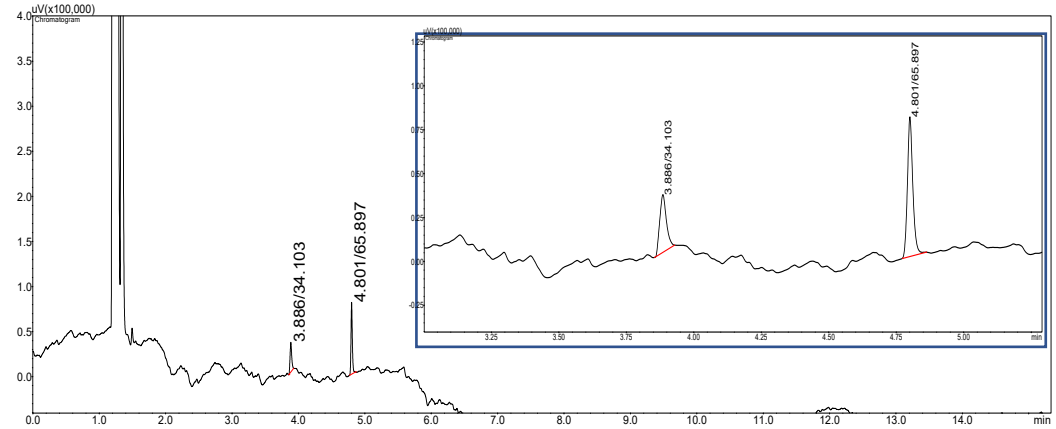


Figure S29. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 5).

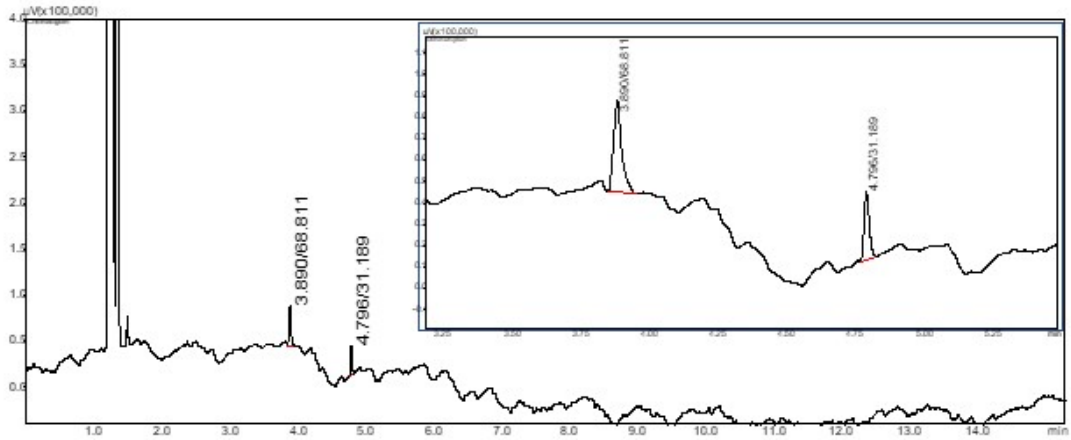


Figure S30. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 6).

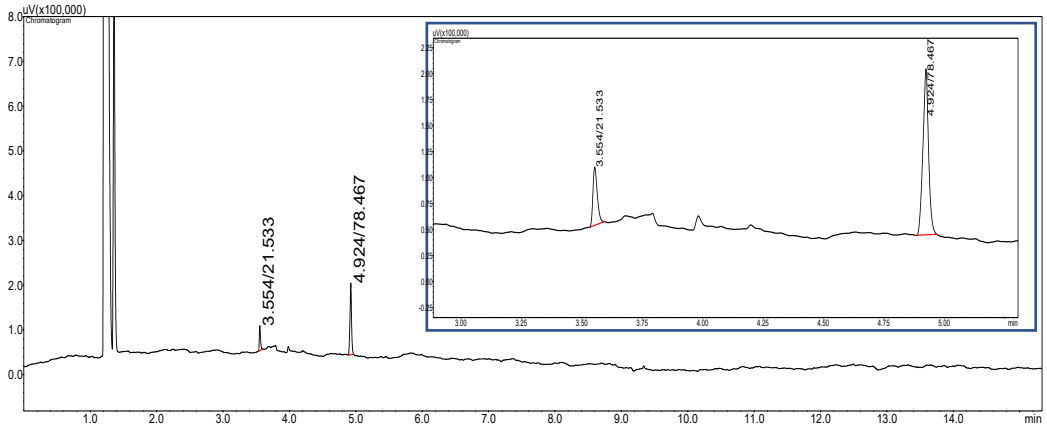
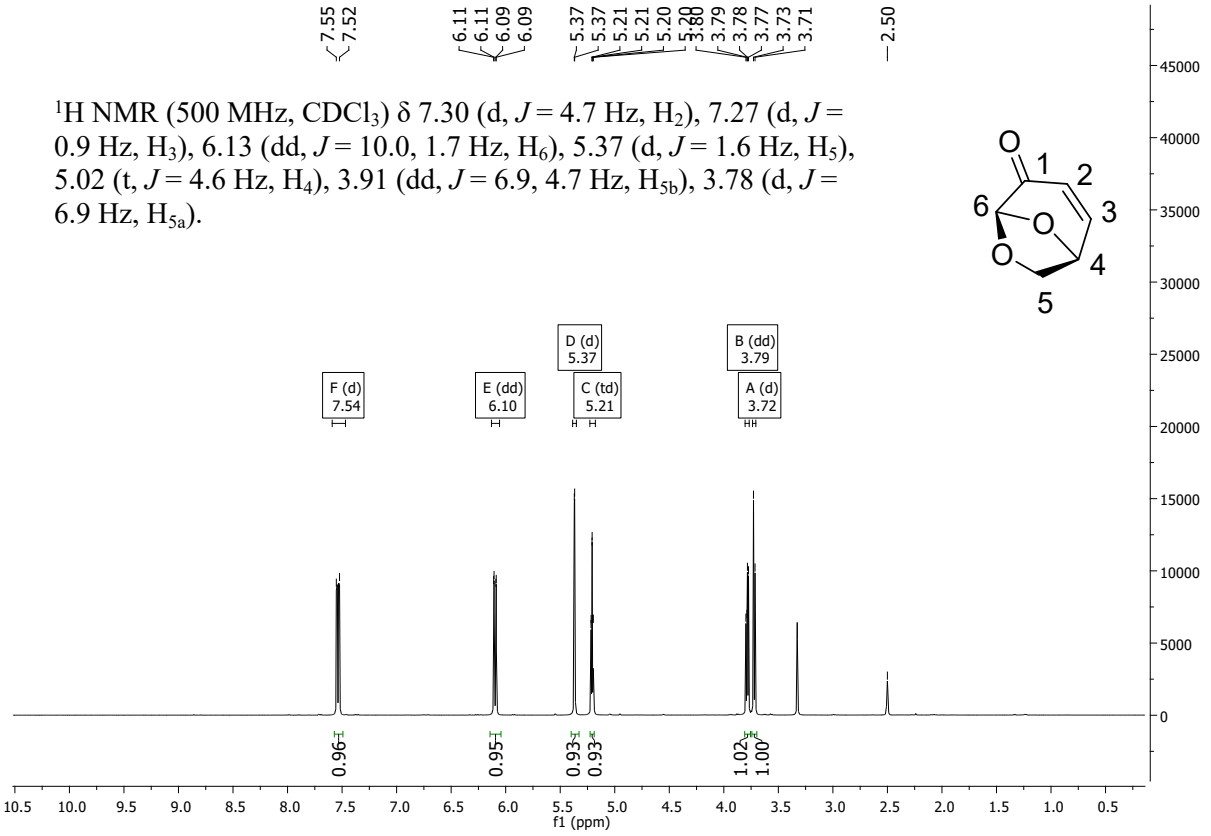


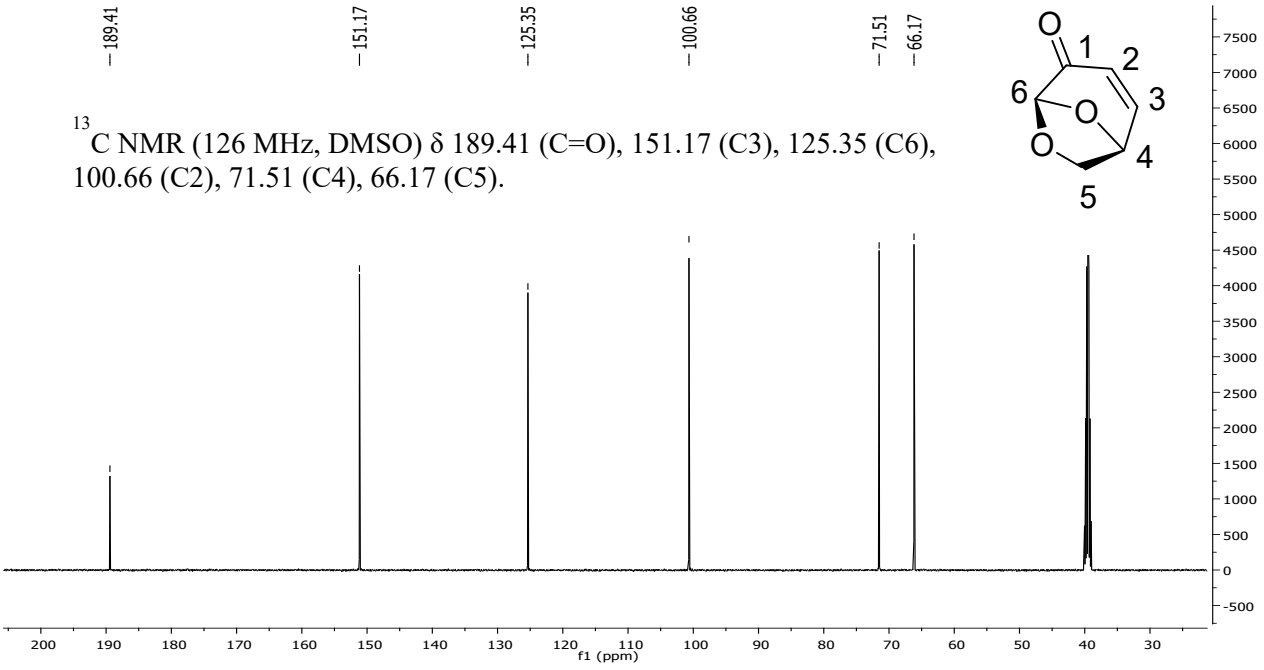
Figure S31. Chromatogram for Continuous-flow oxidation of 2H-HBO (**3**) towards carboxylic acid **4** (Table 4, entry 7).

3. Spectral data



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 4.7 Hz, H_2), 7.27 (d, J = 0.9 Hz, H_3), 6.13 (dd, J = 10.0, 1.7 Hz, H_6), 5.37 (d, J = 1.6 Hz, H_5), 5.02 (t, J = 4.6 Hz, H_4), 3.91 (dd, J = 6.9, 4.7 Hz, H_{5b}), 3.78 (d, J = 6.9 Hz, H_{5a}).

Figure S32. ^{1}H NMR spectrum of Levoglucosenone (LGO, **1**) in $CDCl_3$.



^{13}C NMR (126 MHz, DMSO) δ 189.41 (C=O), 151.17 (C3), 125.35 (C6), 100.66 (C2), 71.51 (C4), 66.17 (C5).

Figure S33. ^{13}C NMR spectrum of Levoglucosenone (LGO, **1**) in $CDCl_3$.

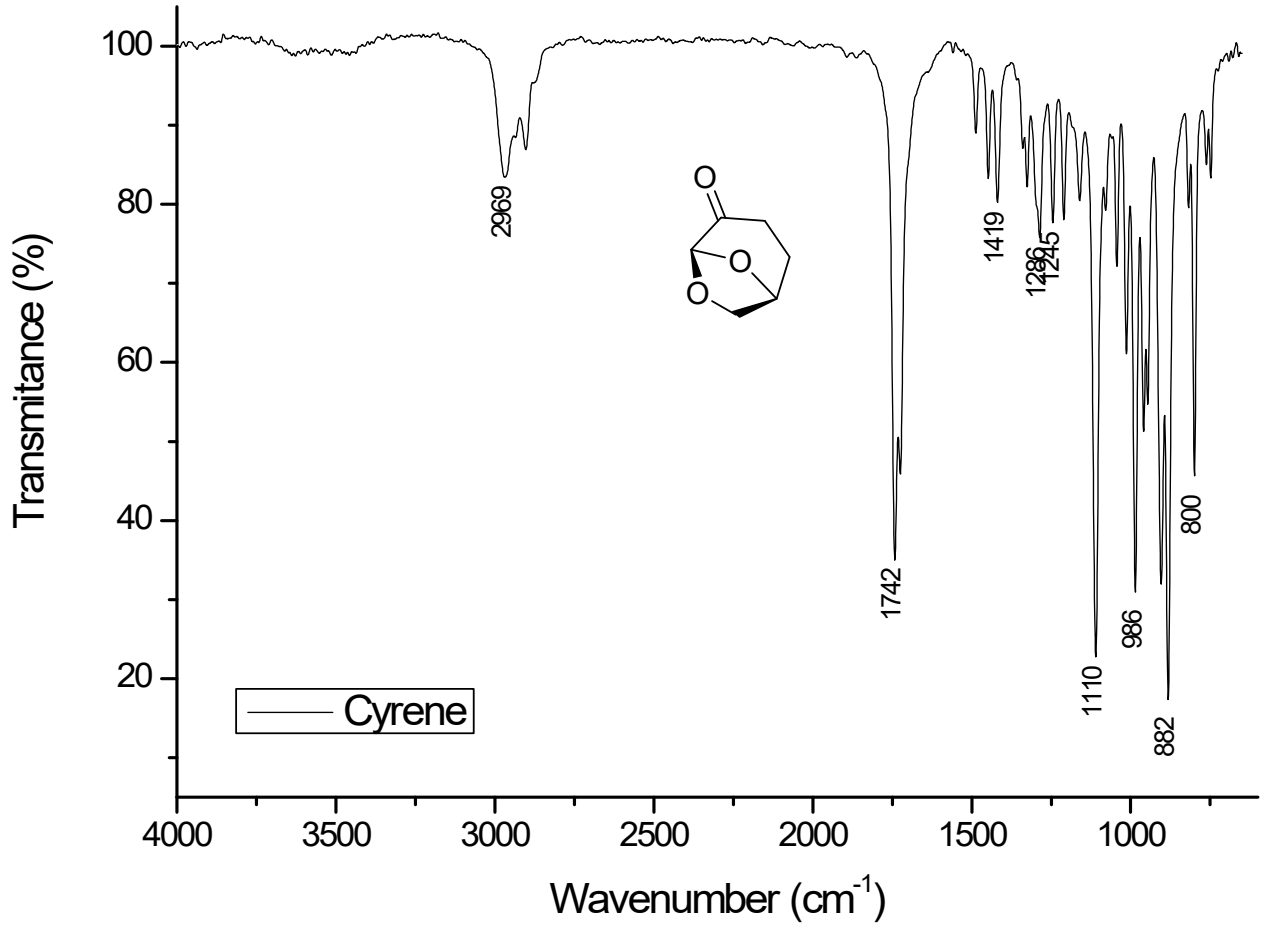
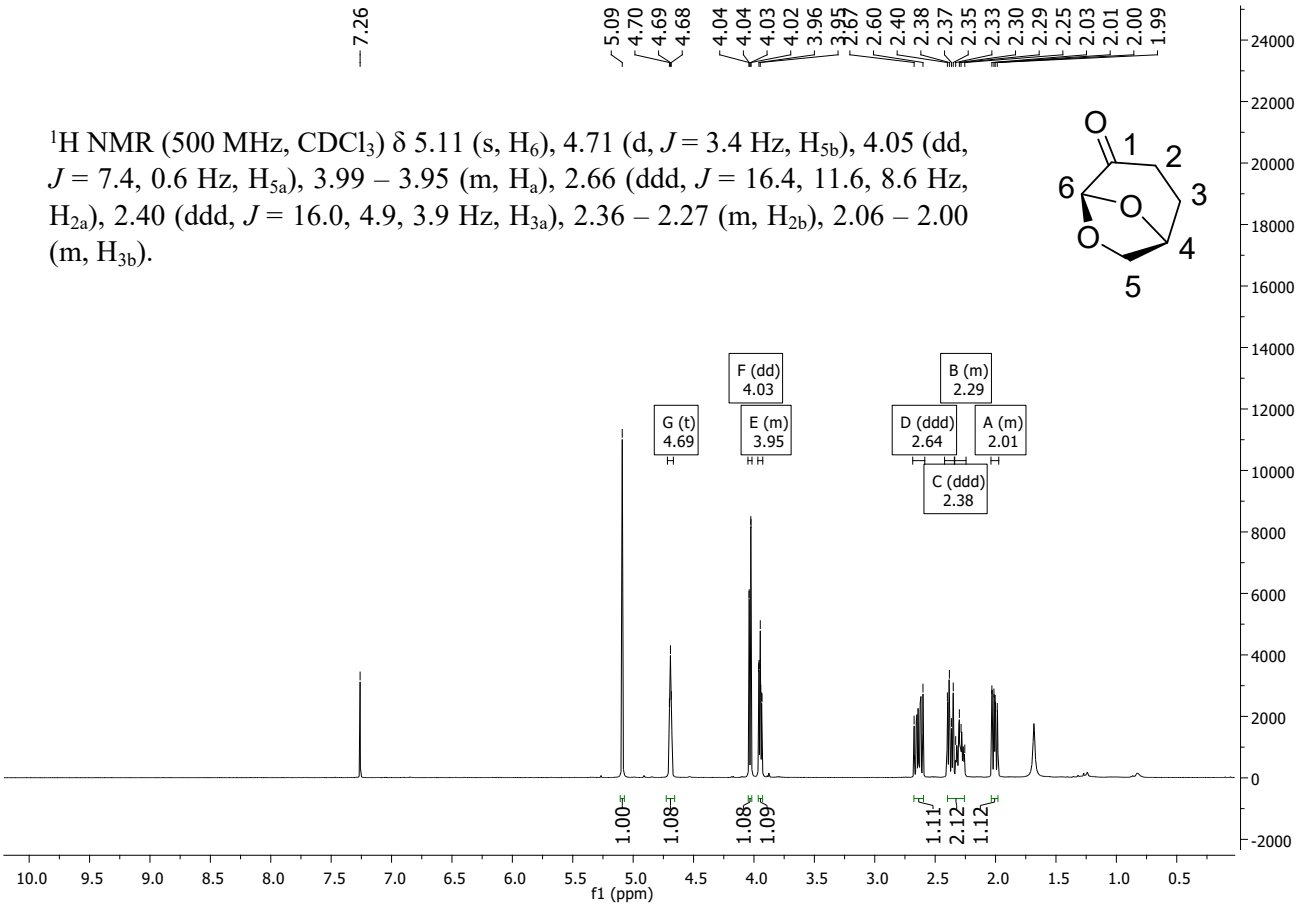
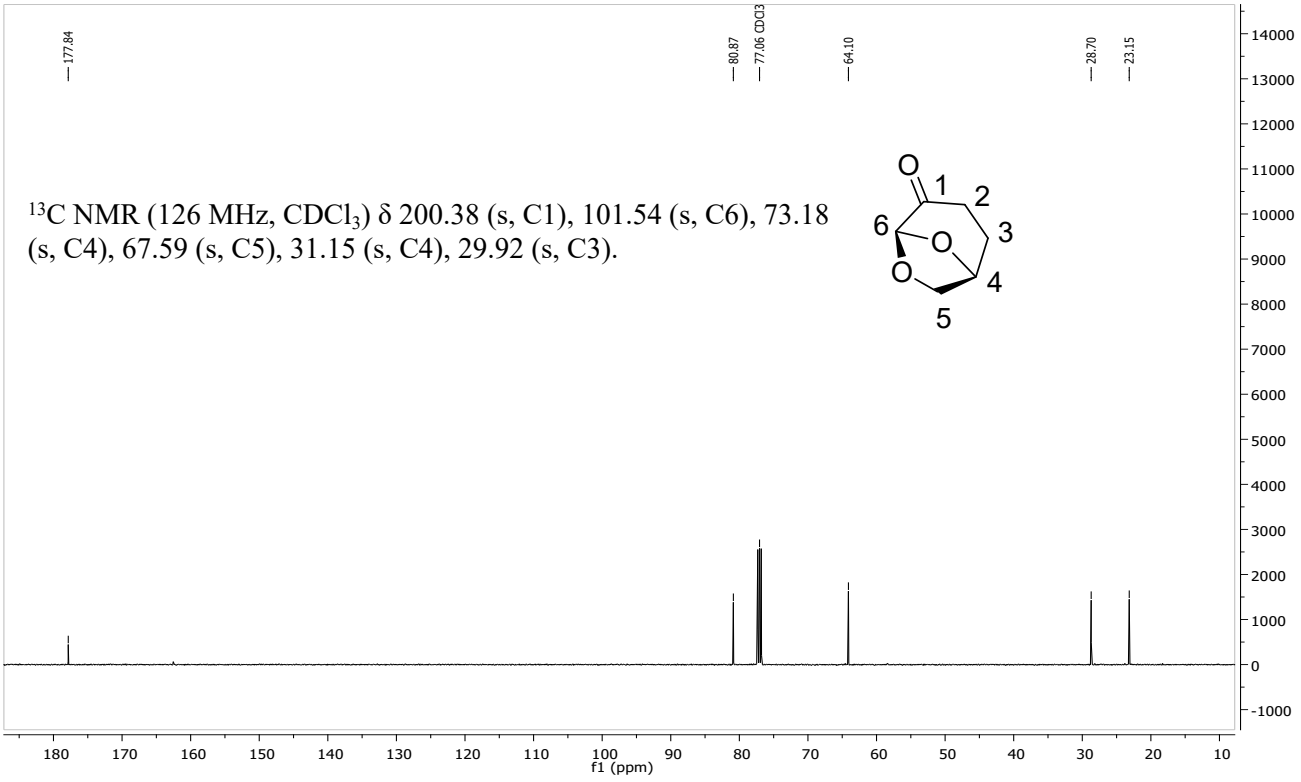


Figure S34. Infrared spectrum Cyrene™ (**2**).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (s, H_6), 4.71 (d, J = 3.4 Hz, H_{5b}), 4.05 (dd, J = 7.4, 0.6 Hz, H_{5a}), 3.99 – 3.95 (m, H_a), 2.66 (ddd, J = 16.4, 11.6, 8.6 Hz, H_{2a}), 2.40 (ddd, J = 16.0, 4.9, 3.9 Hz, H_{3a}), 2.36 – 2.27 (m, H_{2b}), 2.06 – 2.00 (m, H_{3b}).

Figure S35. ^{1}H NMR spectrum of Cyrene™ (**2**) in $CDCl_3$.



^{13}C NMR (126 MHz, $CDCl_3$) δ 200.38 (s, C1), 101.54 (s, C6), 73.18 (s, C4), 67.59 (s, C5), 31.15 (s, C4), 29.92 (s, C3).

Figure S36. ^{13}C NMR spectrum of Cyrene™ (**2**) in $CDCl_3$.

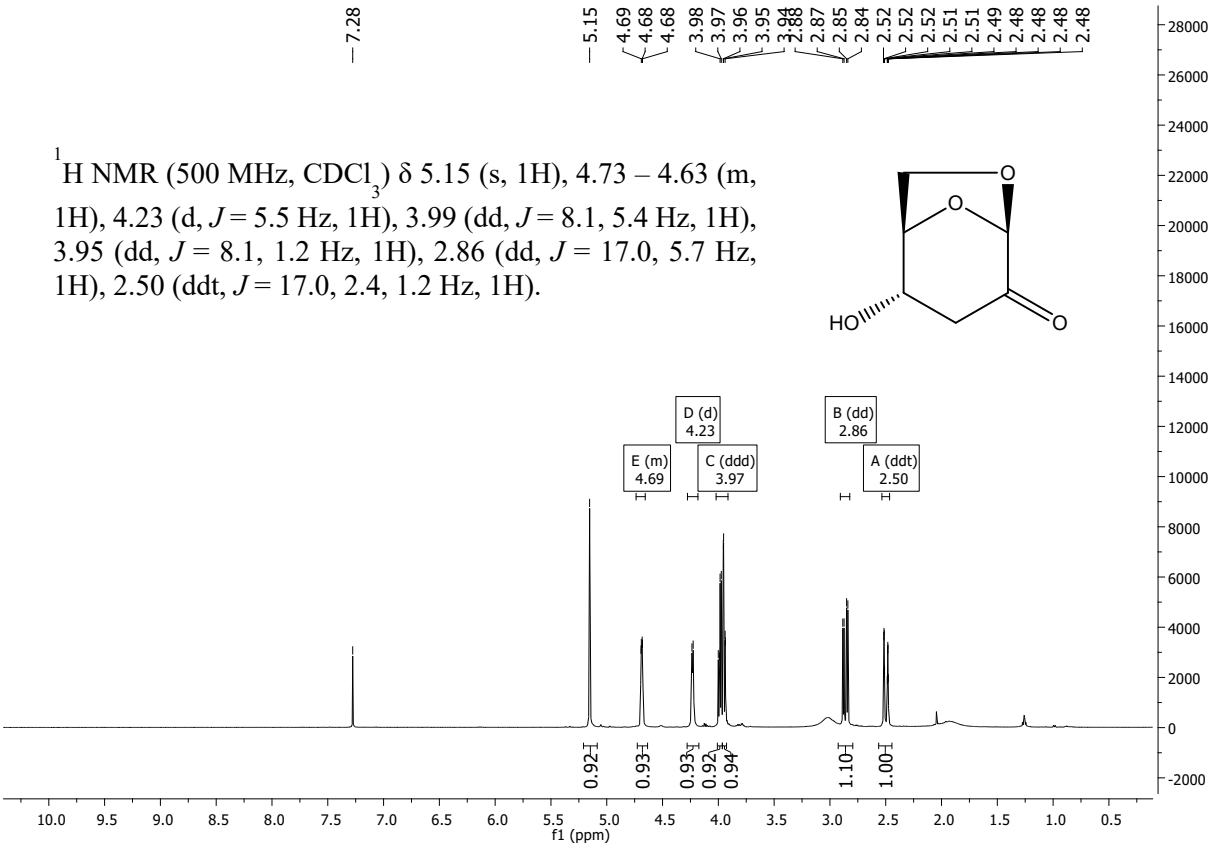
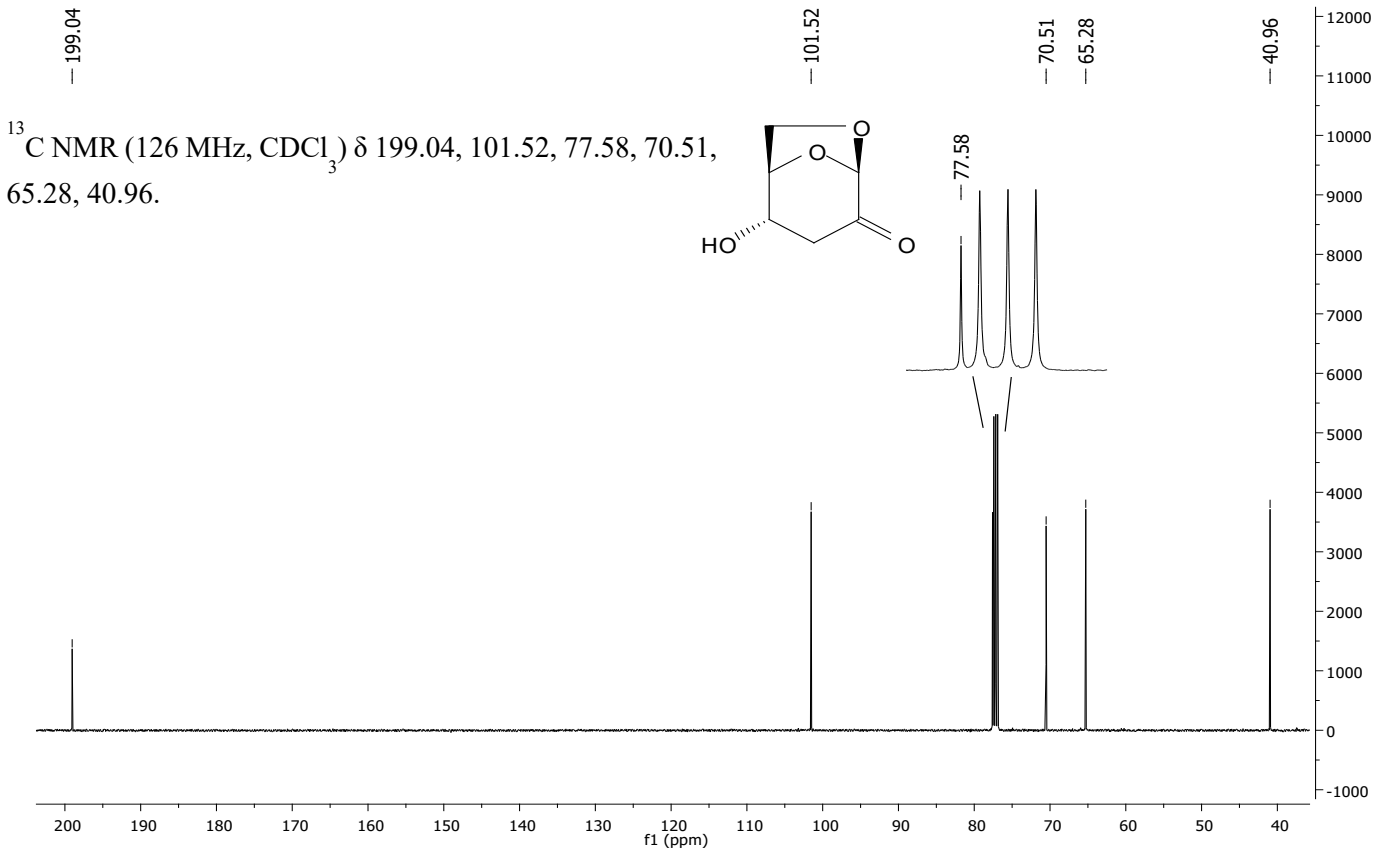


Figure S37. ^{1}H NMR spectra of the 1,4-addition product **5** (500 MHz, $CDCl_3$).



^{13}C NMR (126 MHz, $CDCl_3$) δ 199.04, 101.52, 77.58, 70.51, 65.28, 40.96.

Figure S38. ^{13}C NMR spectra of the 1,4-addition product **5** (500 MHz, $CDCl_3$).

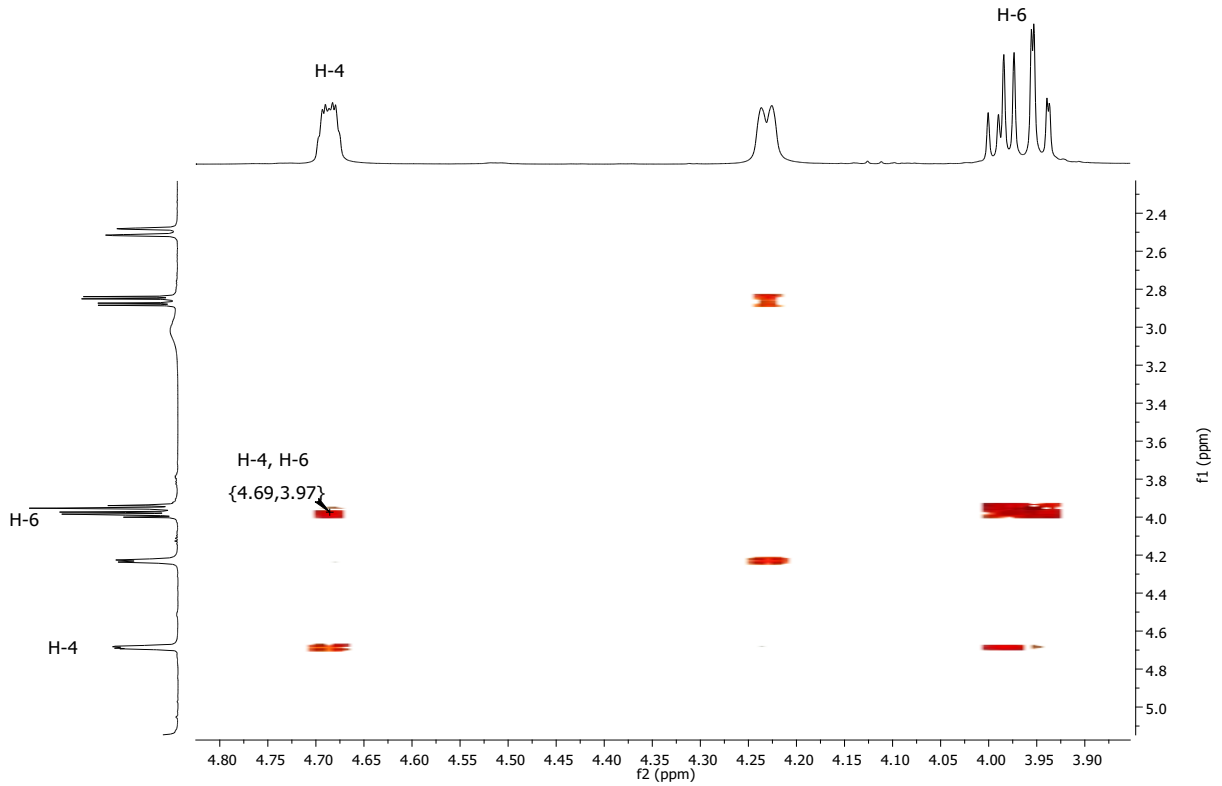


Figure S39. Expansion of H-H COSY spectra of the 1,4-addition product **5** (500 MHz, $CDCl_3$).

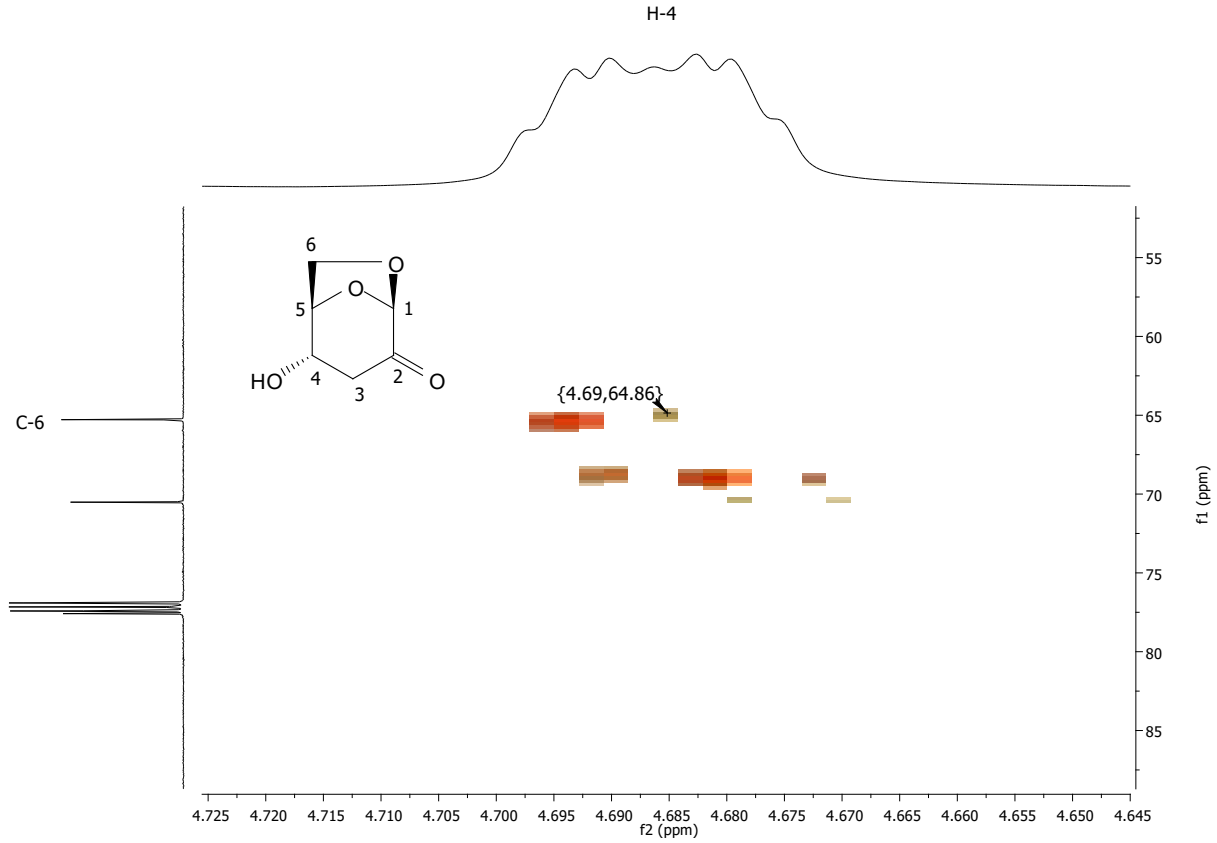


Figure S40. Expansion of HMBC H-C (J_2-J_3) spectra of the 1,4-addition product **5** (500 MHz, $CDCl_3$).

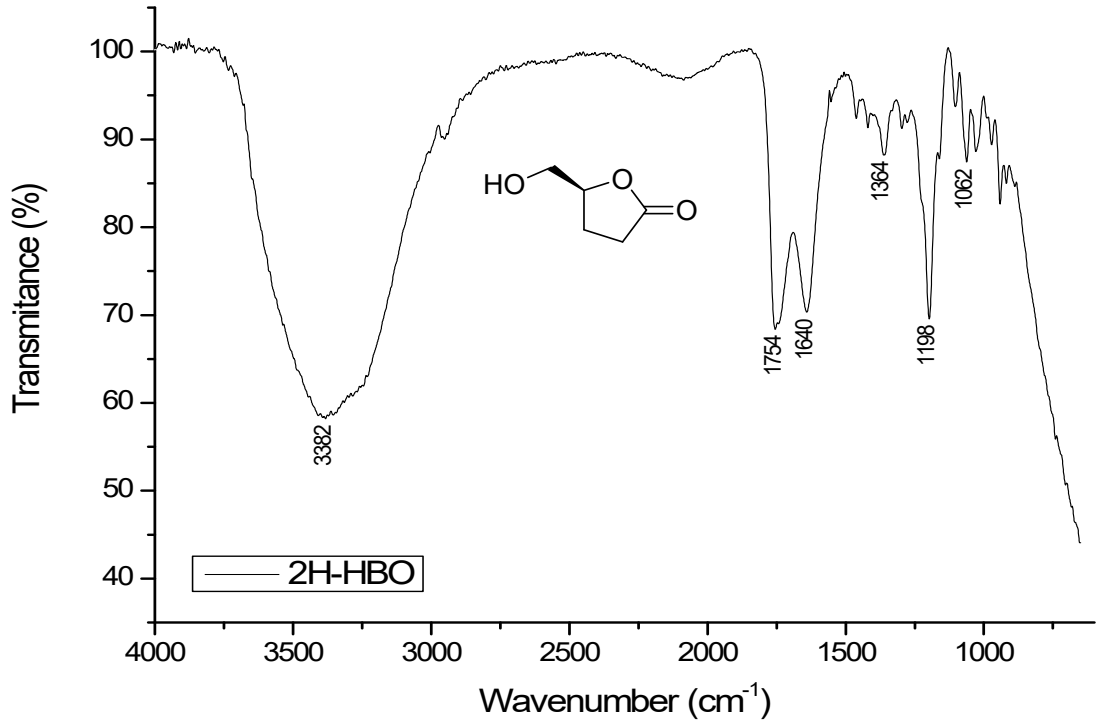


Figure S41. Infrared spectrum 2H-HBO (**3**).

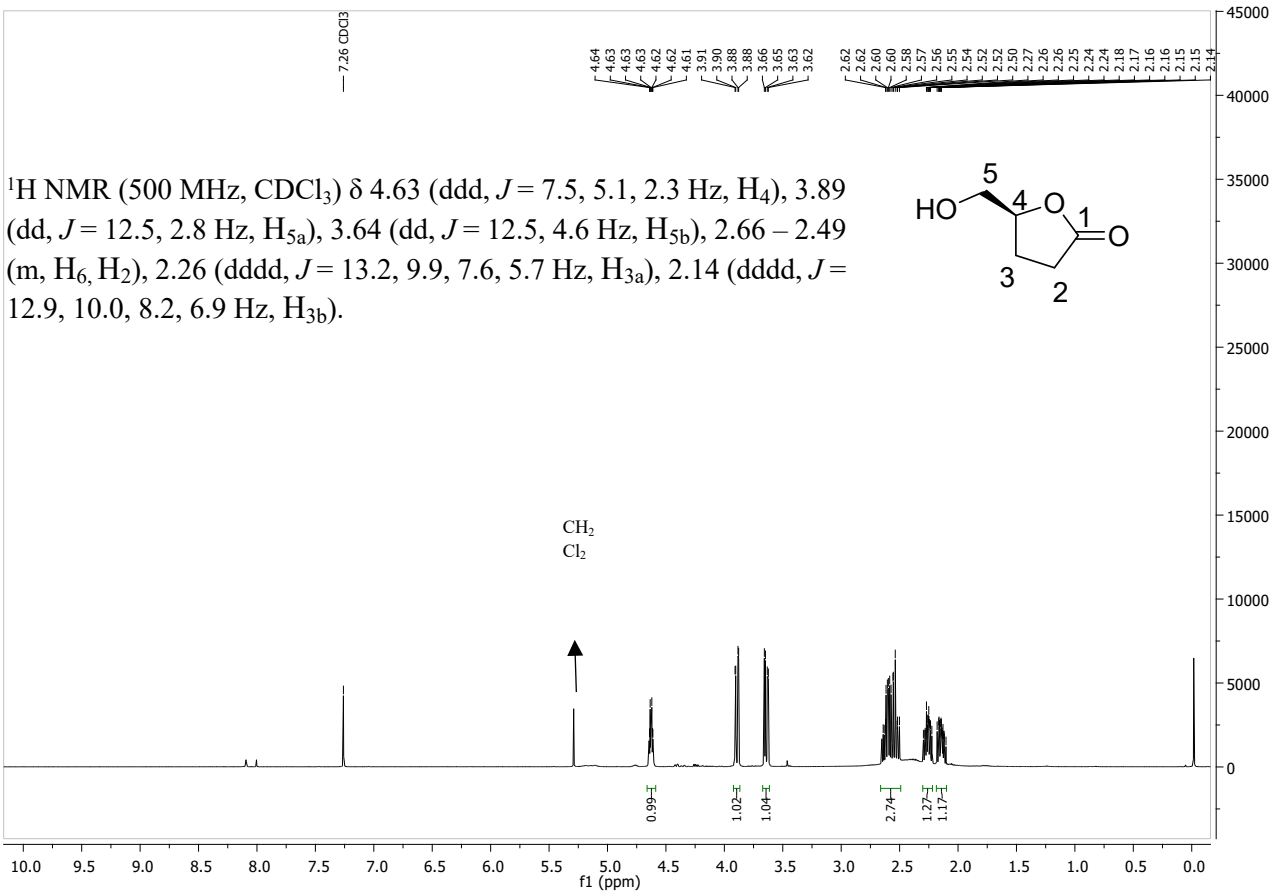


Figure S42. [1]H NMR spectrum of 2H-HBO (**3**) in $CDCl_3$.

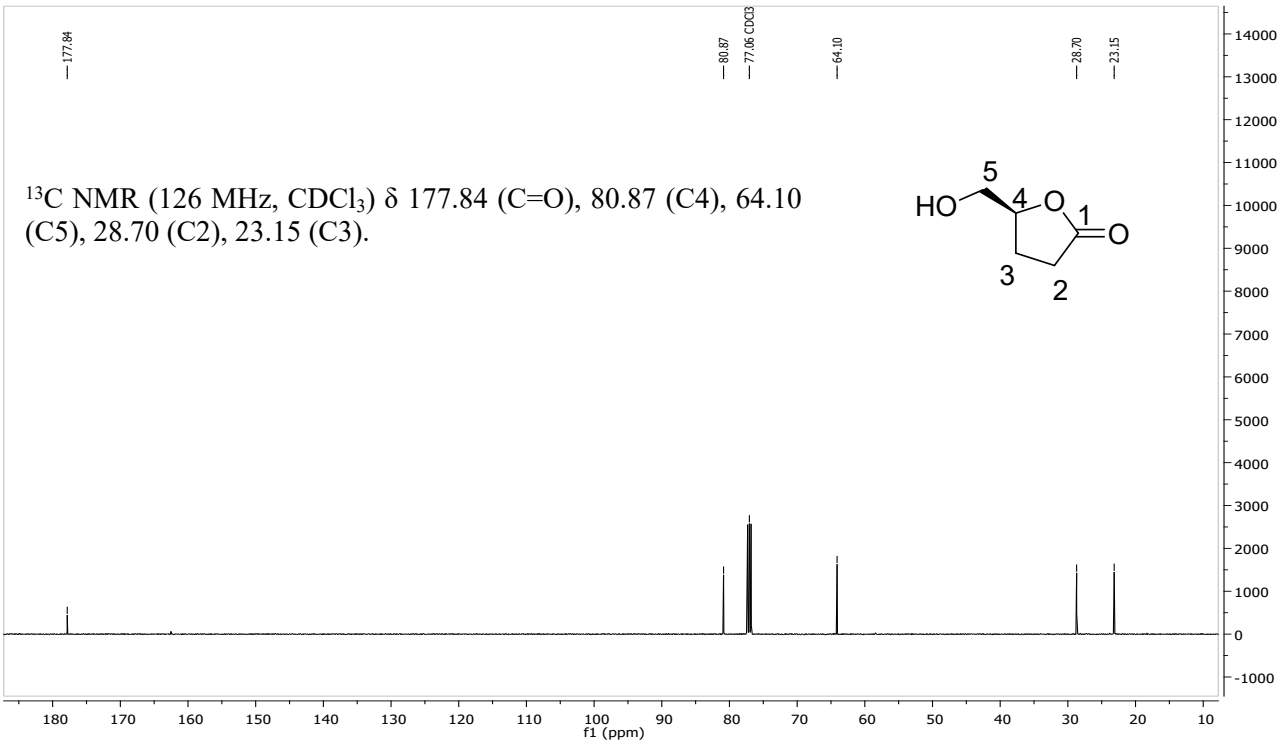


Figure S43. [13]C NMR spectrum of 2H-HBO (**3**) in $CDCl_3$.

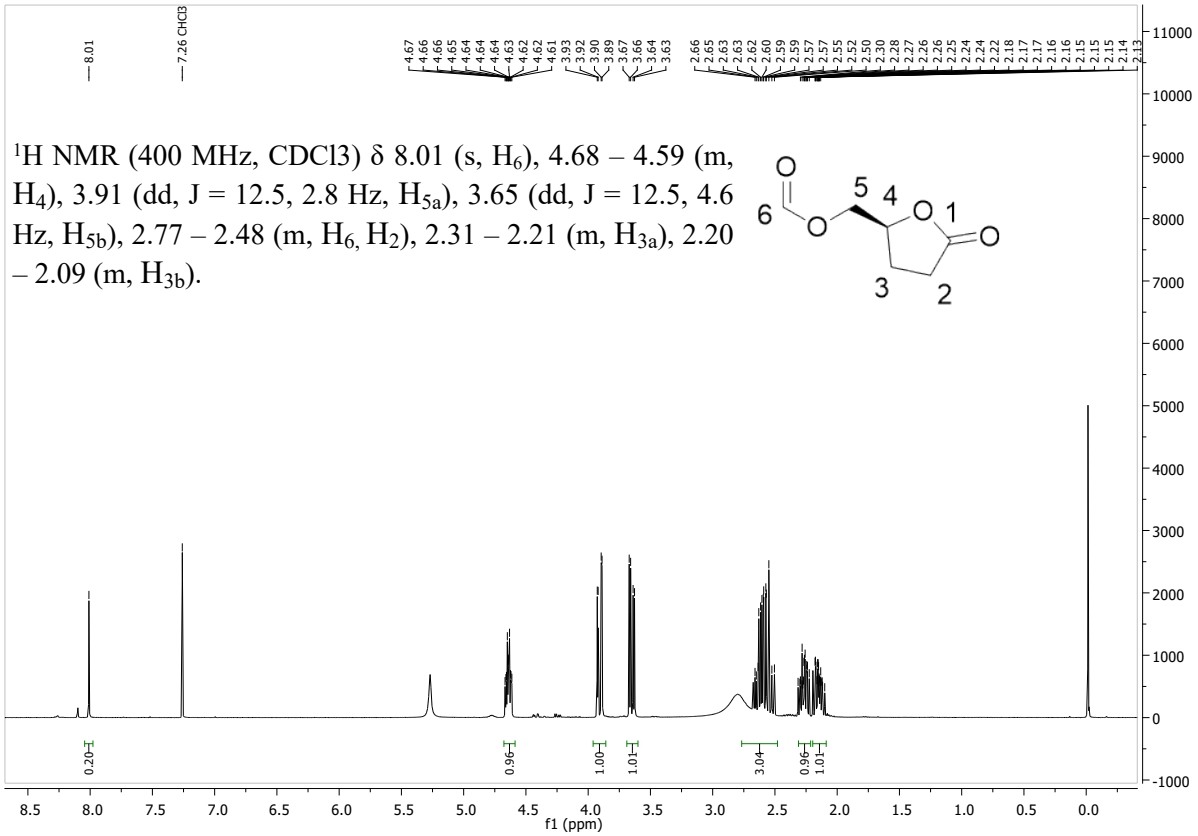


Figure S44. [1]H NMR spectrum showing FBO (**3**) evidence in $CDCl_3$.