# Electronic Supplementary Information

## Ultra-Fast and Sustainable Formal [3 + 3] Cycloadditions Enabled by Mixed Variable Optimization on an Automated Microscale Flow Platform

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## 1. General information

All commercially available chemicals were used as received unless otherwise noted. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 or 400 and 75 MHz or 100 MHz, respectively. $^{1}H$ and $^{13}C$ NMR spectra were referenced to the internal deuterated solvent ($CDCl_3$) at 7.26 and 77.16 ppm, respectively. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance ($\nu_{max}$) are quoted in wave numbers ($cm^{-1}$). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 $F_{254}$ plates and visualized with a UV lamp at 254 nm or stained with a basic potassium permanganate solution. Flash column chromatography was performed using silica gel 60 (40−63 μm).

## 2. Details of the experimental setup

HPLC pumps (JASCO PU2080) equipped with a RS-232 port were employed to flow the solution through the system. A sampler handler (JASCO AS 2055) equipped with a RS-232 port was used to inject the reagents in the line. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect) equipped with a RS-232 port. A 2-way 6-port valve (VICI, Cheminert C2-3006D) equipped with a RS-232 port was used to inject an aliquot of the crude mixture within the on-line HPLC unit. The HPLC column outlet was connected to a UV detector (JASCO, UV 2075) equipped with a RS-232 port. The flow outlet was connected to a programmable fraction collector (Advantec, CHF 1225C). All units equipped with a RS-232 port were autonomously controlled with MATLAB® through the use of communication protocols provided by the manufacturers.

## 3. Latin hypercube sampling (LHS) – Analysis of Variance (ANOVA) Optimization algorithm

**Latin hypercube sampling (LHS)** is a statistical method for generating a near-random sample of parameter values from a multidimensional distribution. In essence, LHS provides a representative sampling of the parameter space, thereby improving the reliability of the results obtained from experimental designs. A Latin hypercube is the n-dimensional generalization of

a Latin square, which is a squared grid containing only one experiment per row and per column. Fig. S1 represents the distribution of our DoE using LHS.

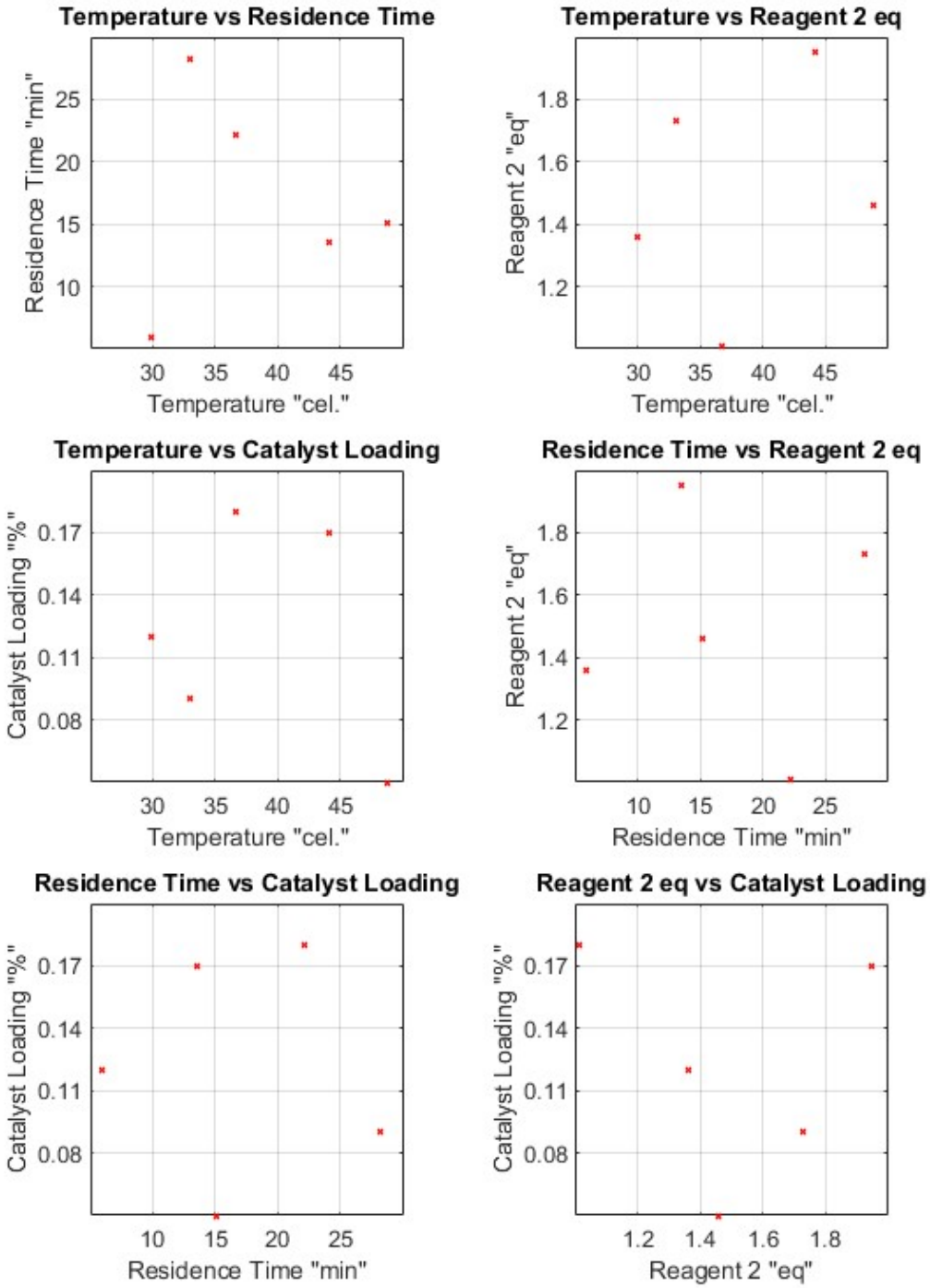



**Fig. S1** Data distribution using LHS

**Analysis of Variance (ANOVA)** is a statistical method that evaluates whether the means of groups exposed to different treatments significantly differ from each other. Specifically, ANOVA examines whether varying one or more factors in each group has a significant effect on a given response variable. ANOVA initially states the null hypothesis that there are no significant differences between the compared groups; then it tests this hypothesis by examining the variance within the groups and comparing it to the variance between the groups. If the between-groups variance significantly exceeds the within-groups variance, the null hypothesis is rejected, indicating significant differences between the groups. In ANOVA, the p-value is a probability value that measures the strength of evidence against the null hypothesis. The smaller the p-value, the stronger the evidence against the null hypothesis. Typically, a p-value of less than 0.05 is considered statistically significant, indicating that the observed data is unlikely to have occurred by chance alone.

We performed two-way ANOVA to assess the effect of two factors (i.e., type of solvent and type of catalyst). The effects of these factors were evaluated in three different response variables (throughput, yield and concentration of product at the reactor outlet). The ANOVA results for the three studies are given in Tables S1-S3, being columns the types of solvents and rows the types of catalysts.

**Table S1**. Throughput two-way ANOVA.

| **Source** | **SS** | **df** | **MS** | **F** | **Prob>F** |
|---|---|---|---|---|---|
| **Columns** | 0.359764 | 2 | 0.179882 | 1.995267 | 1.51E-01 |
| **Rows** | 0.199951 | 2 | 0.099976 | 1.108937 | 0.340916 |
| **Interaction** | 0.080089 | 4 | 0.020022 | 0.222088 | 0.924336 |
| **Error** | 3.24556 | 36 | 0.090154 | | |
| **Total** | 3.885364 | 44 | | | |

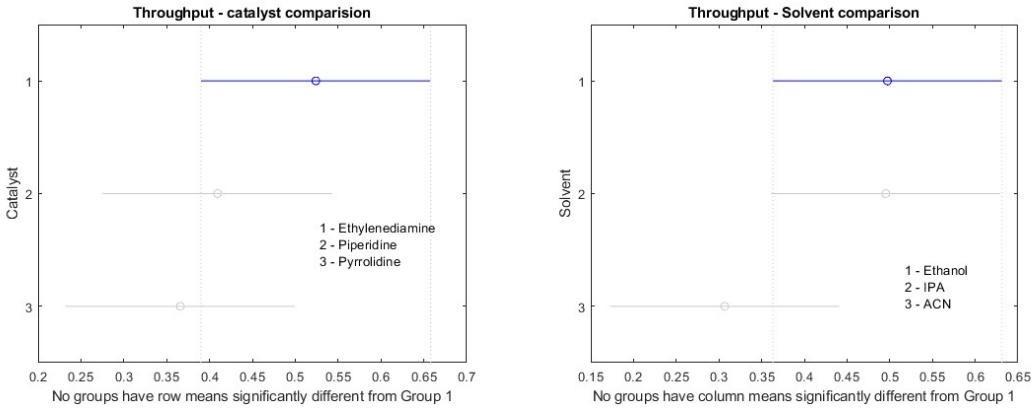



**Fig. S2** Post-hoc interpretation of the throughput two-way ANOVA

**Table S2**. Yield two-way ANOVA.

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Columns** | 2380.133 | 2 | 1190.067 | 11.75052 | 1.18E-04 |
| **Rows** | 2707.733 | 2 | 1353.867 | 13.36786 | 4.55E-05 |
| **Interaction** | 766.9333 | 4 | 191.7333 | 1.893143 | 0.132854 |
| **Error** | 3646 | 36 | 101.2778 | | |
| **Total** | 9500.8 | 44 | | | |

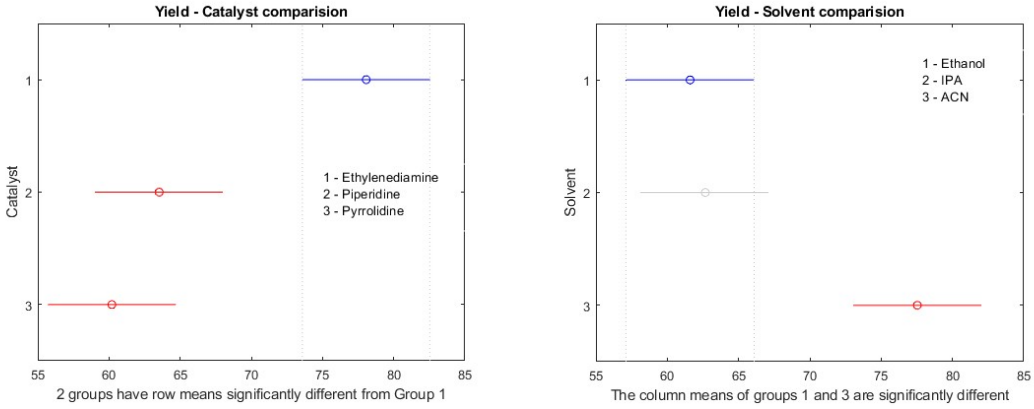



**Fig. S3** Post-hoc interpretation of the yield two-way ANOVA

**Table S3**. Concentration at the reactor outlet two-way ANOVA.

| Source | SS | Df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Columns** | 0.00416 | 2 | 0.00208 | 7.299096 | 0.002183 |
| **Rows** | 0.010394 | 2 | 0.005197 | 18.23435 | 3.39E-06 |
| **Interaction** | 0.001639 | 4 | 0.00041 | 1.437654 | 0.241547 |
| **Error** | 0.01026 | 36 | 0.000285 | | |
| **Total** | 0.026453 | 44 | | | |

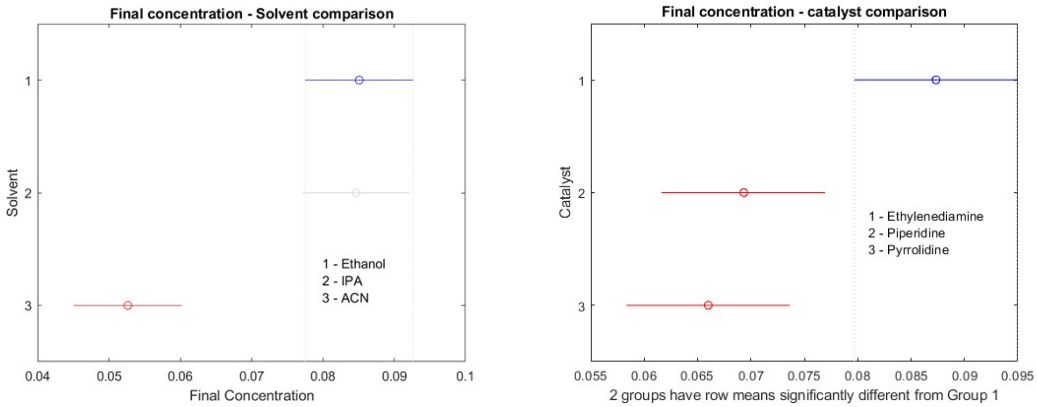



**Fig. S4** Post-hoc interpretation of the concentration at the reactor outlet two-way ANOVA

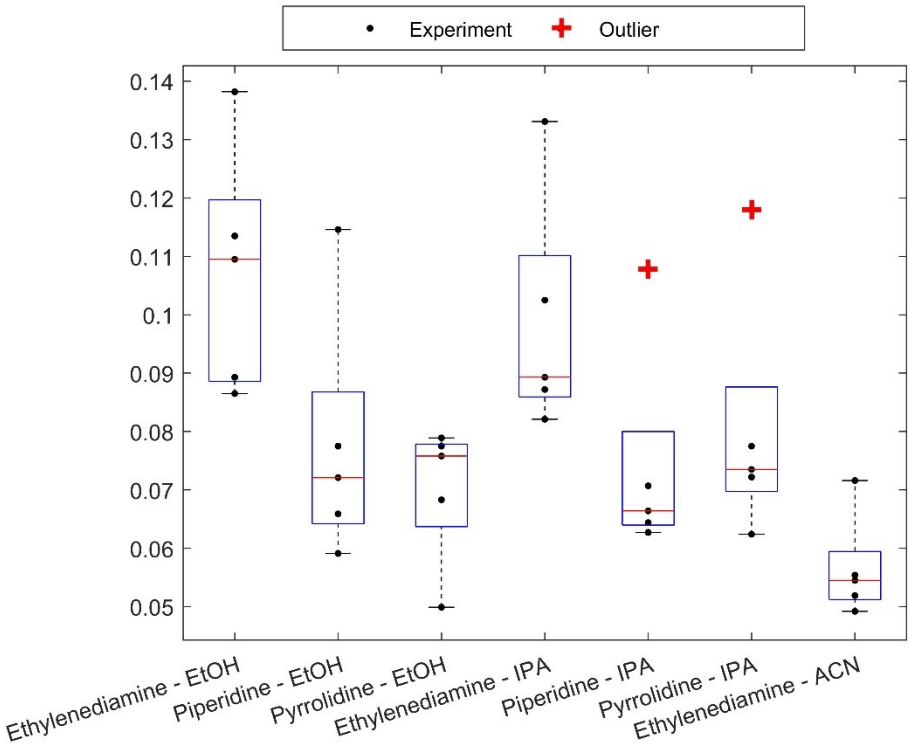



**Fig. S5** Product concentration distribution of the seven discrete combinations identified as superior by the post-hoc ANOVA interpretation. Outliers are > 1.5 times the interquartile range away from the box limits

**Table S4**. Concentration at the reactor outlet two-way ANOVA (without outliers).

| **Source** | **SS** | **Df** | **MS** | **F** | **Prob>F** |
|---|---|---|---|---|---|
| **Columns** | 0.002854 | 2 | 0.001427 | 21.00975 | 3.14E-06 |
| **Rows** | 0.006051 | 2 | 0.003025 | 44.53513 | 2.82E-09 |
| **Interaction** | 0.001064 | 4 | 0.000266 | 3.915976 | 0.012376 |
| **Error** | 0.001834 | 27 | 6.79E-05 | | |
| **Total** | 0.011803 | 35 | | | |

## 4. Optimization algorithm

The optimization algorithm here used has been described in our previous reports.[1,2]

## 5. Experimental setup of the automated flow platform for the Latin-Hypercube Sampling

An automatic sample handler prepared 190 µL of the reaction mixture from stock solutions of 1,3-cyclohexanedione **4a** (0.5 M plus xylene as the internal standard at 5 M in EtOH and *i*-PrOH or 0.25 M plus xylene as the internal standard at 2.5 M in $CH_3CN$), citral **5a** (0.5 M in EtOH and *i*-PrOH or 0.25 M in $CH_3CN$) and catalysts (0.05 M in EtOH and *i*-PrOH or 0.025 M in $CH_3CN$). The reaction mixture was injected in a stream of the corresponding solvent pumped at the required flow rate (see Table S4). The formal [3 + 3] cycloaddition occurred in a PEEK reactor coil (5 mL, 0.75 mm id) heated at the required temperature (see Table S4). The reactor outlet was connected to an automatic 2-way 6-port switch valve which injected 0.2 $\mu$L of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture of MeOH/$H_2O$ (70/30, v/v) was used as mobile phase for the HPLC analysis at a flowrate of 0.7 mL/min. A UV detector was connected to the outlet of the HPLC column (Agela Promosil C18, 3.5 mm × 150 mm, 5 µm) to follow the absorbance at a wavelength of 270 nm. Peak integration and yield calculation were under full MATLAB automation.

## 6. Results of the Latin-Hypercube Sampling (LHS)

**Table S4**. Results of the Latin-Hypercube Sampling

| Expt # | Residence time (min) | Temperature (°C) | Citral **5a** (equiv) | Catalyst loading (equiv) | Catalyst | Yield (%) | throughput ($g.h^{-1}$) | Product concentration (mol/L) |
|---|---|---|---|---|---|---|---|---|
| **$CH_3CN$** | | | | | | | | |
| 1 | 5.9 | 29.9 | 1.36 | 0.12 | **7a** | 71 | 0.64 | 0.05 |
| 2 | 5.9 | 29.9 | 1.36 | 0.12 | **7b** | 81 | 0.73 | 0.06 |
| 3 | 5.9 | 29.9 | 1.36 | 0.12 | **7c** | 59 | 0.53 | 0.04 |
| 4 | 28.2 | 33.0 | 1.73 | 0.09 | **7a** | 80 | 0.15 | 0.06 |
| 5 | 28.2 | 33.0 | 1.73 | 0.09 | **7b** | 70 | 0.13 | 0.05 |
| 6 | 28.2 | 33.0 | 1.73 | 0.09 | **7c** | 73 | 0.14 | 0.05 |
| 7 | 22.2 | 36.7 | 1.01 | 0.18 | **7a** | 83 | 0.19 | 0.05 |
| 8 | 22.2 | 36.7 | 1.01 | 0.18 | **7b** | 76 | 0.17 | 0.05 |
| 9 | 22.2 | 36.7 | 1.01 | 0.18 | **7c** | 78 | 0.17 | 0.05 |
| 10 | 13.5 | 44.2 | 1.95 | 0.17 | **7a** | 96 | 0.29 | 0.05 |
| 11 | 13.5 | 44.2 | 1.95 | 0.17 | **7b** | 83 | 0.25 | 0.04 |
| 12 | 13.5 | 44.2 | 1.95 | 0.17 | **7c** | 89 | 0.27 | 0.05 |
| 13 | 15.1 | 48.8 | 1.46 | 0.05 | **7a** | 85 | 0.36 | 0.07 |
| 14 | 15.1 | 48.8 | 1.46 | 0.05 | **7b** | 91 | 0.38 | 0.08 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15 | 15.1 | 48.8 | 1.46 | 0.05 | **7c** | 48 | 0.20 | 0.04 |
| **EtOH** | | | | | | | | |
| 16 | 5.9 | 29.9 | 1.36 | 0.12 | **7a** | 79 | 1.42 | 0.10 |
| 17 | 5.9 | 29.9 | 1.36 | 0.12 | **7b** | 52 | 0.93 | 0.07 |
| 18 | 5.9 | 29.9 | 1.36 | 0.12 | **7c** | 36 | 0.65 | 0.06 |
| 19 | 28.2 | 33.0 | 1.73 | 0.09 | **7a** | 82 | 0.30 | 0.09 |
| 20 | 28.2 | 33.0 | 1.73 | 0.09 | **7b** | 56 | 0.21 | 0.07 |
| 21 | 28.2 | 33.0 | 1.73 | 0.09 | **7c** | 56 | 0.21 | 0.08 |
| 22 | 22.2 | 36.7 | 1.01 | 0.18 | **7a** | 68 | 0.30 | 0.09 |
| 23 | 22.2 | 36.7 | 1.01 | 0.18 | **7b** | 45 | 0.20 | 0.06 |
| 24 | 22.2 | 36.7 | 1.01 | 0.18 | **7c** | 52 | 0.23 | 0.07 |
| 25 | 13.5 | 44.2 | 1.95 | 0.17 | **7a** | 80 | 0.48 | 0.08 |
| 26 | 13.5 | 44.2 | 1.95 | 0.17 | **7b** | 61 | 0.37 | 0.06 |
| 27 | 13.5 | 44.2 | 1.95 | 0.17 | **7c** | 73 | 0.44 | 0.07 |
| 28 | 15.1 | 48.8 | 1.46 | 0.05 | **7a** | 82 | 0.74 | 0.13 |
| 29 | 15.1 | 48.8 | 1.46 | 0.05 | **7b** | 68 | 0.57 | 0.11 |
| 30 | 15.1 | 48.8 | 1.46 | 0.05 | **7c** | 45 | 0.38 | 0.12 |
| ***i*-PrOH** | | | | | | | | |
| 31 | 5.9 | 29.9 | 1.36 | 0.12 | **7a** | 71 | 1.33 | 0.11 |
| 32 | 5.9 | 29.9 | 1.36 | 0.12 | **7b** | 81 | 0.91 | 0.07 |
| 33 | 5.9 | 29.9 | 1.36 | 0.12 | **7c** | 59 | 0.81 | 0.05 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 34 | 28.2 | 33.0 | 1.73 | 0.09 | **7a** | 80 | 0.23 | 0.11 |
| 35 | 28.2 | 33.0 | 1.73 | 0.09 | **7b** | 70 | 0.18 | 0.08 |
| 36 | 28.2 | 33.0 | 1.73 | 0.09 | **7c** | 73 | 0.21 | 0.08 |
| 37 | 22.2 | 36.7 | 1.01 | 0.18 | **7a** | 83 | 0.30 | 0.09 |
| 38 | 22.2 | 36.7 | 1.01 | 0.18 | **7b** | 76 | 0.22 | 0.06 |
| 39 | 22.2 | 36.7 | 1.01 | 0.18 | **7c** | 78 | 0.25 | 0.07 |
| 40 | 13.5 | 44.2 | 1.95 | 0.17 | **7a** | 96 | 0.46 | 0.09 |
| 41 | 13.5 | 44.2 | 1.95 | 0.17 | **7b** | 83 | 0.35 | 0.07 |
| 42 | 13.5 | 44.2 | 1.95 | 0.17 | **7c** | 89 | 0.41 | 0.08 |
| 43 | 15.1 | 48.8 | 1.46 | 0.05 | **7a** | 85 | 0.67 | 0.14 |
| 44 | 15.1 | 48.8 | 1.46 | 0.05 | **7b** | 91 | 0.54 | 0.11 |
| 45 | 15.1 | 48.8 | 1.46 | 0.05 | **7c** | 48 | 0.59 | 0.08 |

## 7. Experimental setup of the self-optimizing flow platform

Synthesis of 2-methyl-2-(4-methylpent-3-en-1-yl)-2,6,7,8-tetrahydro-5H-chromen-5-one **6a.** An automatic sample handler prepared 190 µL of the reaction mixture from stock solutions of 1,3-cyclohexanedione **4a** (0.5 M plus xylene as the internal standard at 5 M), citral **5a** (0.5 M) and ethylenediamine **7a** (0.05 M). The reaction mixture was injected in a stream of EtOH or *i*-PrOH pumped at the required flow (see Tables S5-6). The oxidative dimerization occurred in a PEEK reactor coil (5 mL, 0.75 mm id) heated at the required temperature. The reactor outlet was connected to an automatic 2-way 6-port switch valve which injected 0.2 $\mu$L of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture of MeOH/$H_2O$ (70/30, v/v) was used as mobile phase for the HPLC analysis at a flowrate of 0.7 mL/min. A UV detector was connected to the outlet of the HPLC column (Agela Promosil C18, 3.5 mm × 150 mm, 5 µm) to follow the absorbance at a wavelength of 270 nm. Peak integration and yield calculation were under full MATLAB automation. The calculated yield was automatically sent to the algorithm which set new experimental conditions to the units. A 4-D optimization of the throughput (g/h) was conducted using the temperature, residence time, equivalents of citral **5a** and loading of **7a** as the input variables. The initial experiment of the simplex was set at "lower bound + *d*": 30 °C, 3 min of residence time, 1.2 equivalents of citral **5a** and 8 mol% of **7a** with *d* values of 5 °C, 2 min, 0.2 equivalent and 3 mol%, respectively. The lower and upper boundaries of the research space were the following: 25-50 °C, 1-10 min, 1-2 equiv and 5-20 mol% for the temperature, residence time, equivalents of citral **5a** and catalyst loading, respectively. An optimum in EtOH giving 11.9 g/h was found in experiment 11 at 33 °C, 1 min of residence time, 1.23 equivalents of citral **5a** and 8.4 mol% of **7a** (see Table S5 for details). An optimum in *i*-PrOH giving 11.7 g/h was found in experiment 18 at 43 °C, 1 min of residence time, 1 equivalents of citral **5a** and 5.5 mol% of **7a** (see Table S6 for details).

## 8. Optimization results for the synthesis 2*H*-pyran 6a

**TABLE S5.** Maximization of the reaction yield of 2*H*-pyran **6a** in EtOH.

| Expt # | Residence time (min) | Temperature (°C) | Citral **5a** (equiv) | **7a** loading (mol%) | Throughput ($g.h^{-1}$) |
|---|---|---|---|---|---|
| 1 | 2.90 | 30 | 1.20 | 8 | 3.4 |
| 2 | 4.80 | 30 | 1.20 | 8 | 2.2 |
| 3 | 2.90 | 30 | 1.40 | 8 | 3.0 |
| 4 | 2.90 | 30 | 1.20 | 11 | 2.8 |
| 5 | 2.90 | 35 | 1.20 | 8 | 3.2 |
| 6 | 1 | 33 | 1.30 | 9.5 | 11.1 |
| 7 | 1.95 | 34 | 1.35 | 5.7 | 6.2 |
| 8 | 1.48 | 36 | 1.13 | 7.6 | 7.8 |
| 9 | 1.00 | 31 | 1.28 | 7.5 | 11.4 |
| 10 | 1.00 | 34 | 1.28 | 7.5 | 11.8 |
| **Dimension reduction** | | | | | |
| 11 | 1.00 | 33 | 1.23 | 8.4 | 11.9 |
| 12 | 1.00 | 33 | 1.22 | 6.1 | 11.7 |
| 13 | 1.00 | 36 | 1.21 | 7.1 | 11.9 |
| **Stopping criterion reached –** Similar results on the last simplex – Dimension recovery rejected | | | | | |

**TABLE S6.** Maximization of the reaction yield of 2*H*-pyran **6a** in *i*-PrOH.

| Expt # | Residence time (min) | Temperature (°C) | Citral **5a** (equiv) | **7a** loading (mol%) | Throughput ($g.h^{-1}$) |
|---|---|---|---|---|---|
| 1 | 2.90 | 30 | 1.20 | 8 | 2.5 |
| 2 | 4.80 | 30 | 1.20 | 8 | 1.5 |
| 3 | 2.90 | 30 | 1.40 | 8 | 2.2 |
| 4 | 2.90 | 30 | 1.20 | 11 | 2.4 |
| 5 | 2.90 | 35 | 1.20 | 8 | 2.8 |
| 6 | 1 | 33 | 1.30 | 9.5 | 9.5 |
| 7 | 1.95 | 34 | 1.05 | 10.2 | 4.1 |
| 8 | 1.48 | 36 | 1.18 | 6.9 | 5.7 |
| 9 | 1.00 | 37 | 1.17 | 9.2 | 9.6 |
| 10 | 1.00 | 35 | 1.17 | 9.2 | 9.9 |
| **Dimension reduction** | | | | | |
| 11 | 1.00 | 35 | 1.22 | 8.5 | 9.9 |
| 12 | 1.00 | 39 | 1.07 | 8.4 | 10.5 |
| 13 | 1.00 | 41 | 1.00 | 8.0 | 10.5 |
| 14 | 1.00 | 37 | 1.09 | 7.9 | 9.9 |
| 15 | 1.00 | 41 | 1.04 | 7.1 | 10.9 |
| 16 | 1.00 | 43 | 1.00 | 6.3 | 11.0 |
| **Dimension reduction** | | | | | |
| 17 | 1.00 | 41 | 1.00 | 7.2 | 10.6 |
| 18 | 1.00 | 43 | 1.00 | 5.5 | 11.7 |
| **Stopping criterion reached –** Similar results on the last simplex – Dimension recovery rejected | | | | | |

## 9. Experimental setup for product diversification in EtOH

The experimental setup consisted of two streams as depicted in Fig. 5. The first stream (flow rate: 2.5 ml/min) equipped with a PEEK injection loop (3 mL) loaded with a solution of 1,3-cyclohexanedione **4a** (0.5 M) and citral **5a** (0.62 M) in EtOH meet in a PEEK T-shaped piece (internal volume 0.57 µL) a second stream (flow rate: 2.5 ml/min) consisting of a solution of and ethylene diamine **7a** (4.2 mM) in EtOH loaded in a second PEEK loop (2 mL). The resulting mixture reacted in a PEEK reactor coil (5 mL, 0.75 mm id) heated at 33 °C. The crude mixture

was collected in a fraction collector purified by flash chromatography on silica gel (5% AcOEt-cyclohexane) to give the title compounds.

**2-methyl-2-(4-methylpent-3-en-1-yl)-2,6,7,8-tetrahydro-5H-chromen-5-one (6a).** Purification by flash chromatography on silica gel (5% AcOEt-cyclohexane) gave **6a** a yellow oil (211 mg, 86%, 15.9 g.h$^{-1}$). IR (ATR) *v* 2925, 1644, 1589, 1410, 1069 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm) 6.43 (d, 1H, *J* = 10.1 Hz), 5.16 (d, 1H, *J* = 10.1 Hz), 5.07 (ts, 1H, *J* = 1.4, 7.1 Hz), 2.38 (t, 2H, *J* = 6.8 Hz), 2.36 (t, 2H, *J* = 6.8 Hz), 1.91-2.08 (m, 4H), 1.50-1.72 (m, 2H), 1.65 (d, 3H, *J* = 1.0 Hz), 1.57 (br s, 3H), 1.35 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm) 194.9, 172.1, 132.1, 123.8, 121.8, 116.5, 110.4, 82.4, 41.8, 36.5, 28.7, 27.5, 25.8, 22.6, 20.8, 17.7. HRMS (ASAP+) *m/z* $[M + H]^+$ Calcd for $C_{16}H_{23}O_2$ 247.1698; Found 247.1701.

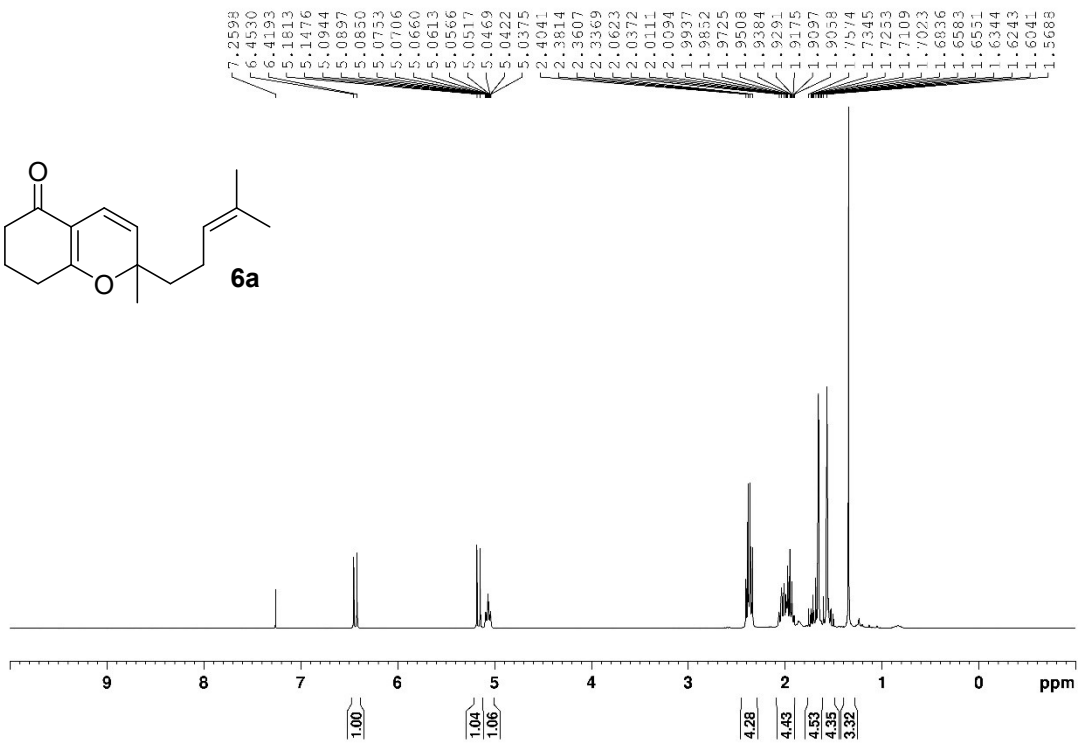
**2-methyl-2-(4-methylpent-3-en-1-yl)-7-phenyl-2,6,7,8-tetrahydro-5H-chromen-5-one (6b).** Purification by flash chromatography on silica gel (5% AcOEt-cyclohexane) gave **6b** as a mixture of two inseparable diastereoisomers (1/1) under the form of a yellow oil (264 mg, 82%, 19.8 g.h$^{-1}$). IR (ATR) *v* 3057, 3028, 2967, 2917, 1647, 1592, 1413 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm) 7.32-7.37 (m, 2H), 7.22-7.28 (m, 3H), 6.49 (d, 1H × 0.5, J = 10.1 Hz), 6.48 (d, 1H x 0.5, J = 10.1 Hz), 5.23 (d, 1H × 0.5, J = 10.1 Hz), 5.21 (d, 1H × 0.5, J = 10.1 Hz), 5.03-5.15 (m, 1H), 3.29-3.38 (m, 1H), 2.54-2.73 (m, 4H), 1.99-2.11 (m, 2H), 1.65-1.82 (m, 5H), 1.60 (s, 3H × 0.5), 1.58 (s, 3H × 0.5), 1.42 (s, 3H × 0.5), 1.35 (s, 3H × 0.5). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm) 193.9, 193.9, 171.2, 171.1, 142.8, 132.2, 132.1, 128.9, 127.1, 126.8, 123.8, 123.7, 122.0, 116.5, 116.4, 110.2, 110.1, 83.0, 82.9, 43.8, 43.7, 41.9, 41.8, 39.1, 38.8, 36.3, 36.2, 27.8, 27.4, 25.8, 22.9, 22.4, 17.8. HRMS (ASAP +) *m/z* $[M + H]^+$ Calcd for $C_{22}H_{27}O_2$ 323.2011; Found 323.2007.

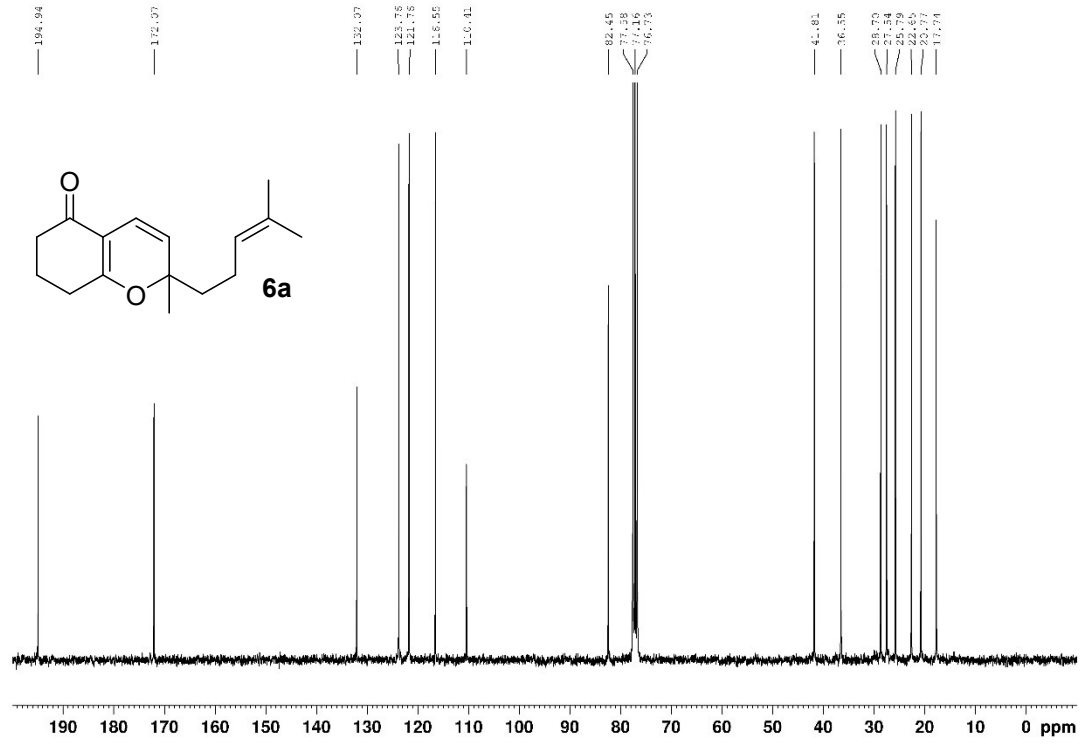
**2-methyl-2-(4-methylpent-3-en-1-yl)-2H-benzo[g]chromene-5,10-dione (6c).** Purification by flash chromatography on silica gel (5% AcOEt-cyclohexane) gave **6c** a red oil (225 mg, 73%, 16.9 g.h$^{-1}$). IR (ATR) *v* 3068, 2961, 2921, 2853, 1674, 1650, 1593, 1569, 1333, 1270 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm) 8.06-8.10 (m, 2H), 7.63-7.74 (m, 2H), 6.69 (d, 1H, *J* = 10.1 Hz), 5.66 (d, 1H, *J* = 10.1 Hz), 5.02-5.13 (m, 1H), 2.08-2.16 (m, 2H), 1.90-2.00 (m,1H), 1.65-1.73 (m, 1H), 1.61 (d, 3H, *J* = 1.0 Hz), 1.54 (s, 3H), 1.51 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm) 182.0, 179.8, 152.9, 134.1, 133.3, 132.4, 131.7, 131.6, 129.9, 126.3, 123.5, 117.6, 116.1, 83.2, 41.7, 27.7, 25.7, 22.8, 17.8. HRMS (ASAP+) *m/z* $[M + H]^+$ Calcd for $C_{20}H_{21}O_3$ 309.1491; Found 309.1488.

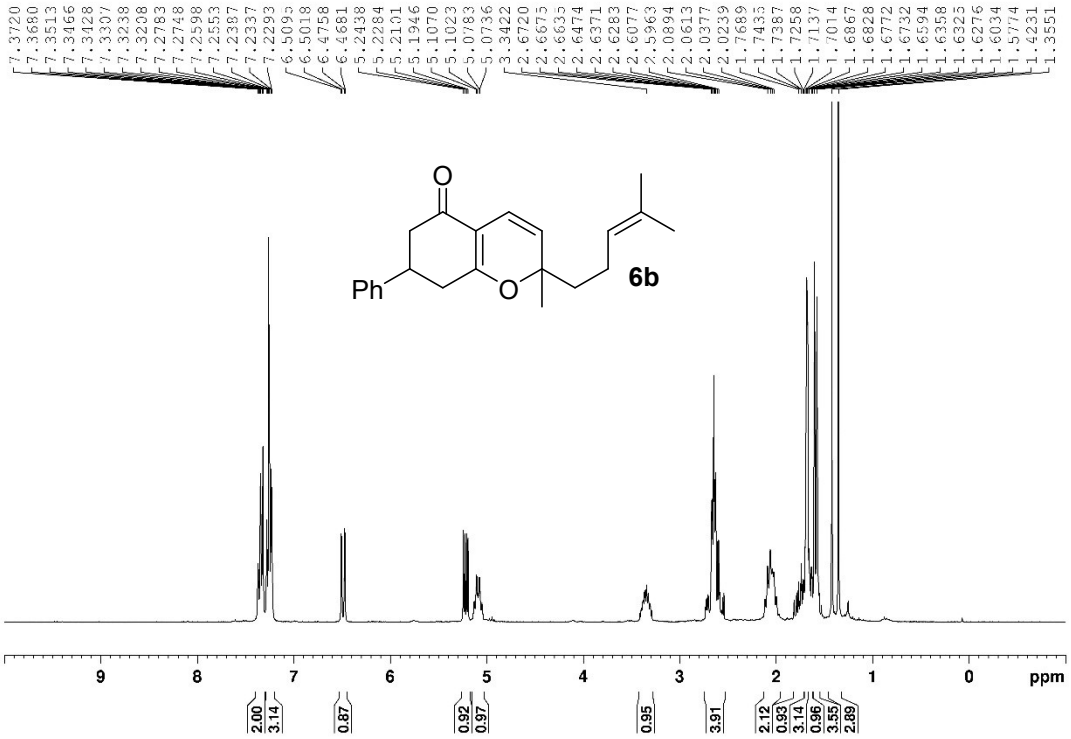
**(E)-2-(4,8-dimethylnona-3,7-dien-1-yl)-2-methyl-2H,5H-pyrano[3,2-c]chromen-5-one (6d).** Purification by flash chromatography on silica gel (5% AcOEt-cyclohexane) gave **6d** as a mixture of two inseparable (E/Z) diastereoisomers (6/4) under the form of a red oil (288 mg, 79%, 21.6 $g.h^{-1}$). IR (ATR) $\nu$ 2966, 2916, 2853, 1714, 1642, 1605, 1565, 1361, 1033 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.76-7.82 (m, 1H), 7.48-7.54 (m, 1H), 7.25-7.31 (m, 2H), 6.58 (d, 1H, $J$ = 10.0 Hz), 5.48 (d, 1H × 0.6, $J$ = 10.1 Hz), 5.47 (d, 1H × 0.4, $J$ = 10.1 Hz), 5.09-5.13 (m, 1H), 5.05-5.07 (m, 1H), 2.11-2.18 (m, 2H), 1.96-2.05 (m, 3H), 1.83-1.94 (m, 2H), 1.72-1.80 (m, 1H), 1.52-1.66 (m, 12H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 161.0 (× 0.6), 161.0 (× 0.4), 159.2 (× 1), 153.4 (× 1), 136.2 (× 0.4), 136.1 (× 0.6), 132.2 (× 1), 131.7 (× 0.4), 131.5 (× 0.6), 125.2 (× 0.6), 125.2 (× 0.4), 124.3 (× 0.6), 124.3 (× 0.4), 124.1 (× 0.4), 124.1 (× 0.6), 123.3 (× 0.4), 122.8 (× 0.6), 117.5 (× 0.4), 117.4 (× 0.6), 116.9 (× 1), 115.6 (× 0.6), 115.6 (× 0.4), 100.1 (× 1), 83.3 (× 0.6), 83.3 (× 0.4), 42.2 (× 0.4), 41.9 (× 0.6), 39.7 (× 1), 32.0 (× 0.4), 27.6 (× 0.6), 26.7 (× 0.6), 26.6 (× 0.4), 25.8 (× 0.4), 25.8 (× 0.6), 23.4 (× 1), 22.6 (× 0.6), 22.4 (× 0.4), 17.8 (× 0.6), 17.7 (× 0.4), 16.1 (× 1). HRMS (ASAP+) $m/z$ $[M + H]^+$ Calcd for $C_{24}H_{29}O_3$ 365.2117; Found 365.2108.

**10,10-dimethyl-9,10,11,11a-tetrahydro-6H,8H-9,11-methanochromeno[4,3-b]chromen-6-one (6e).** Purification by flash chromatography on silica gel (5% AcOEt-cyclohexane) gave **6e** as a mixture of two inseparable diastereoisomers (≥ 92 : 8) under the form of a yellow oil (244 mg, 83%, 18.3 $g.h^{-1}$). IR (ATR) $\nu$ 2933, 2867, 1707, 1651, 1603, 1560, 1406, 1038, 747 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz, major diastereoisomers) $\delta$ (ppm) 7.79 (dd, 1H, $J$ = 1.6, 7.9 Hz), 7.46-7.52 (m, 1H), 7.24-7.32 (m, 2H), 6.24 (d, 1H, $J$ = 2.6 Hz), 5.25-5.30 (m, 1H), 2.67-2.79 (m, 2H), 2.38-2.47 (m, 1H), 2.13-2.27 (m, 2H), 1.44 (d, 1H, $J$ = 10.5 Hz), 1.32 (s, 3H), 0.9 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz, major diastereoisomer) $\delta$ (ppm) 161.3, 159.6, 152.8, 137.3, 131.7, 124.1, 122.7, 116.8, 115.4, 112.0, 104.3, 72.4, 48.9, 42.3, 40.2, 32.0, 25.6, 25.4, 21.9. HRMS (ASAP+) $m/z$ $[M + H]^+$ Calcd for $C_{19}H_{19}O_3$ 295.1334; Found 295.1330.

## 10. NMR spectra

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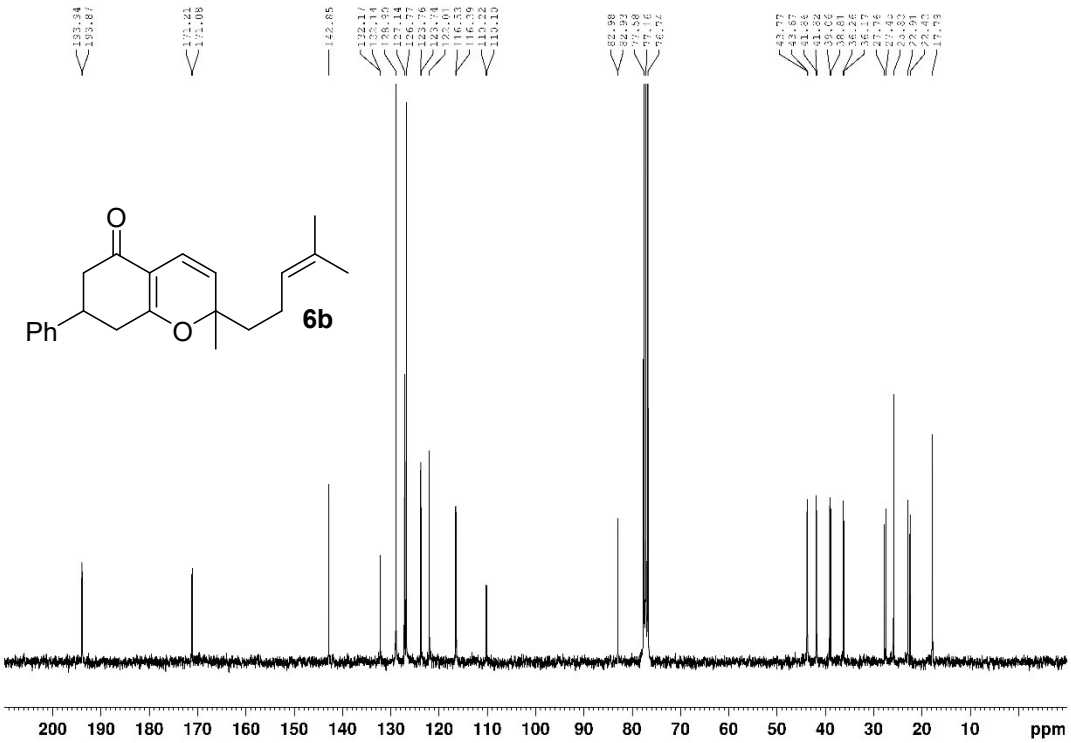
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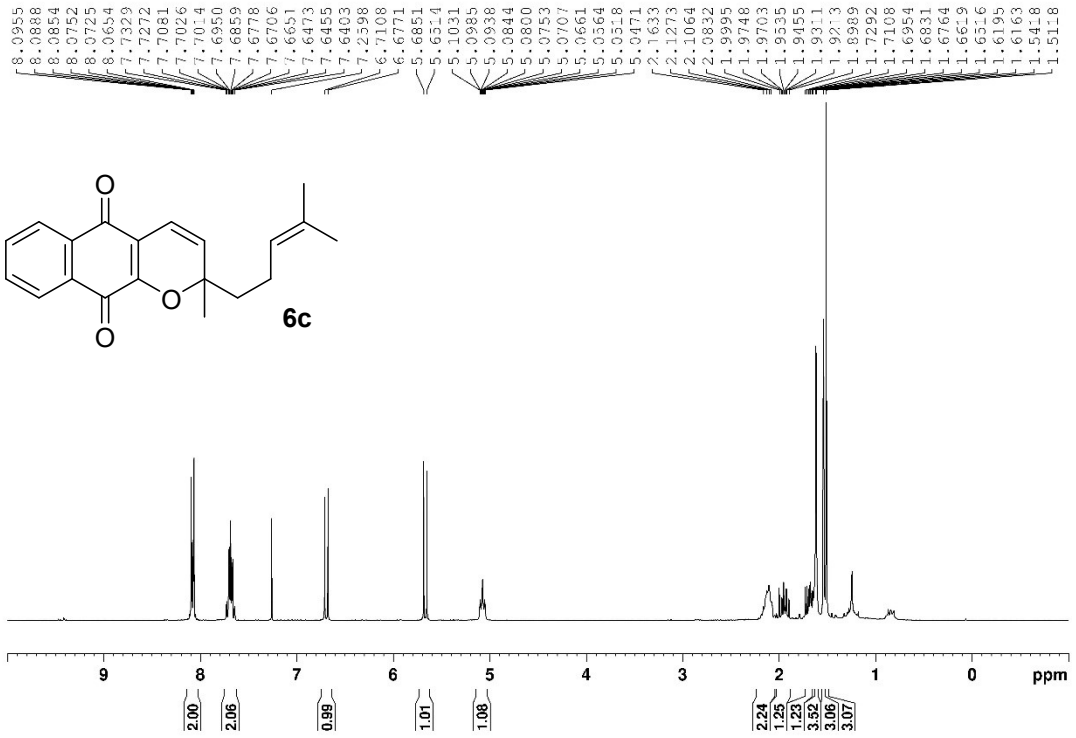
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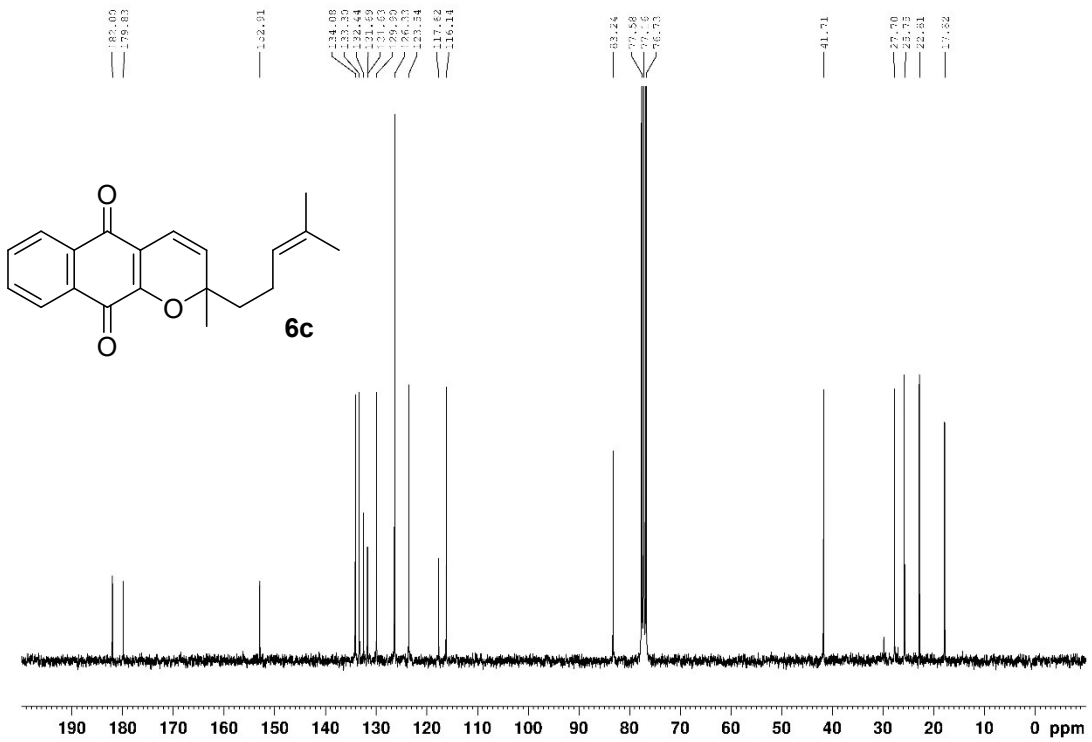
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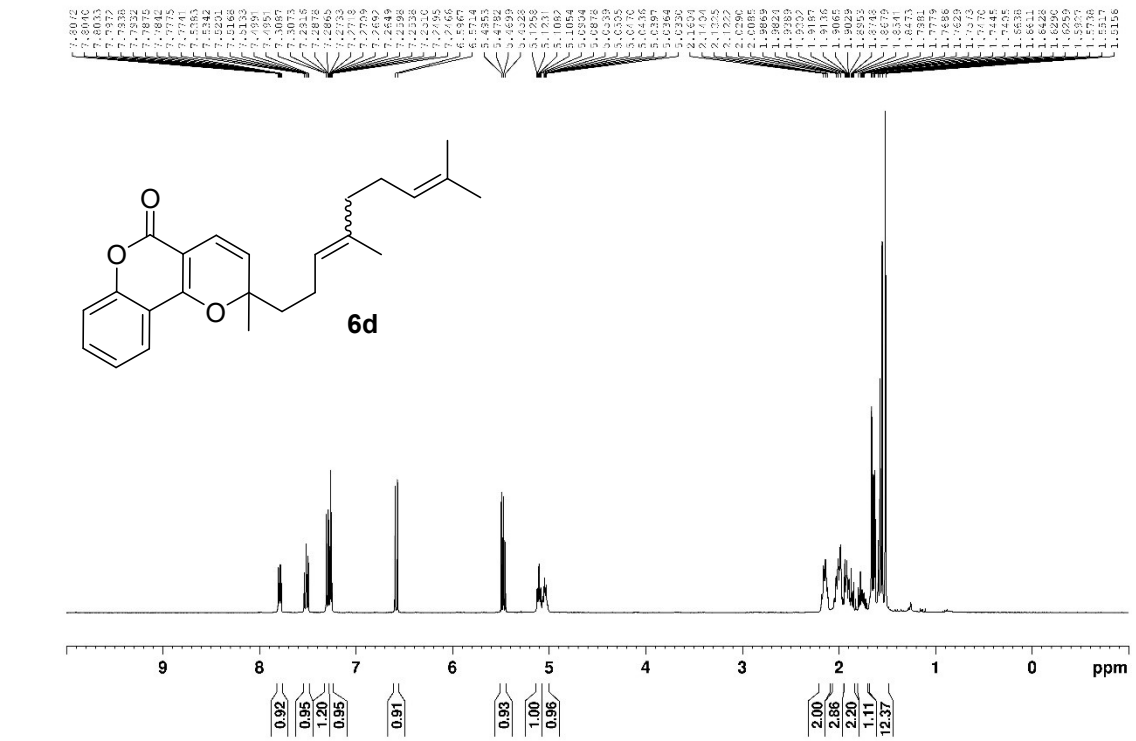
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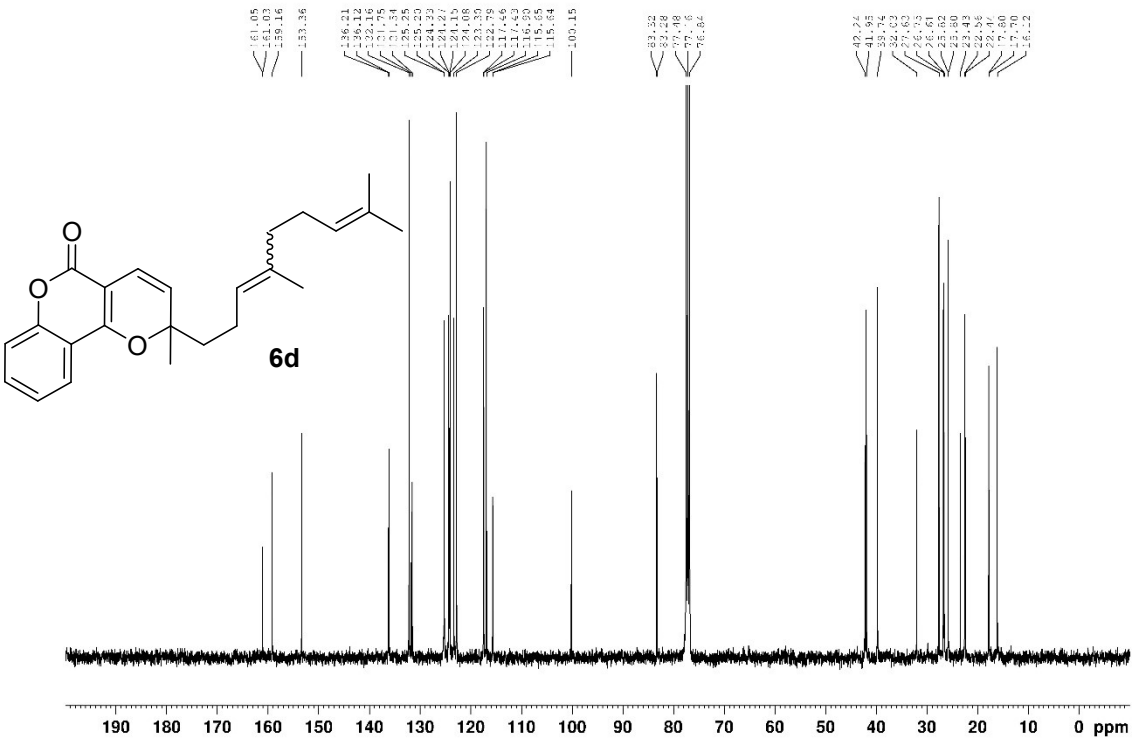
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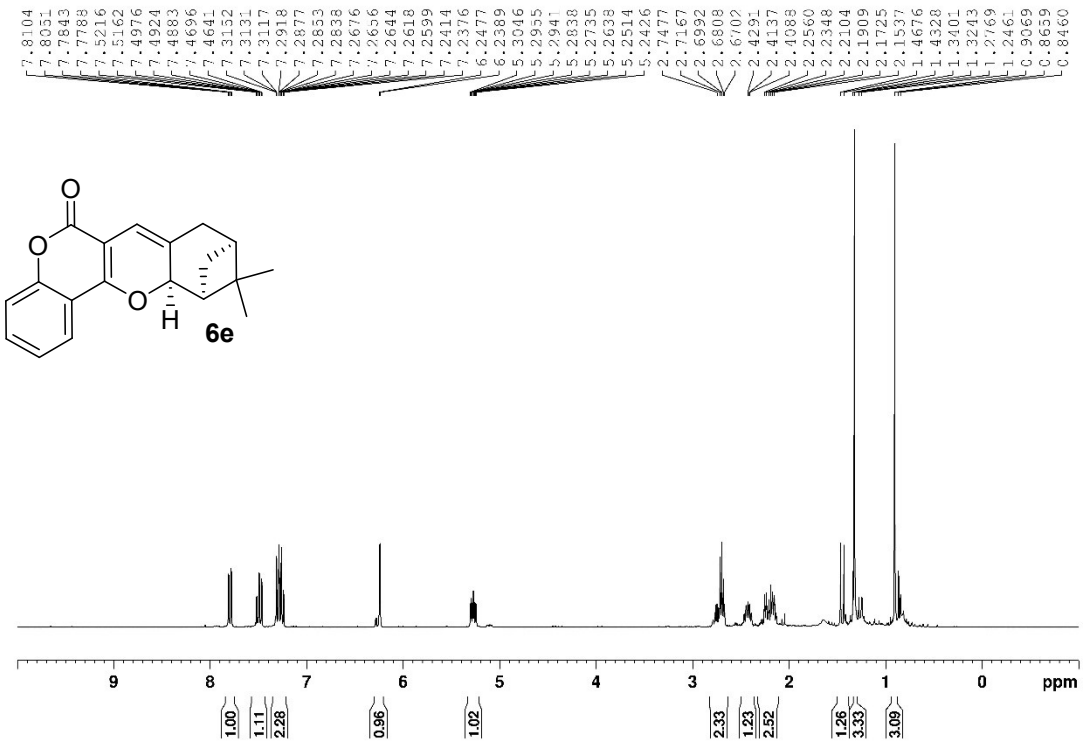
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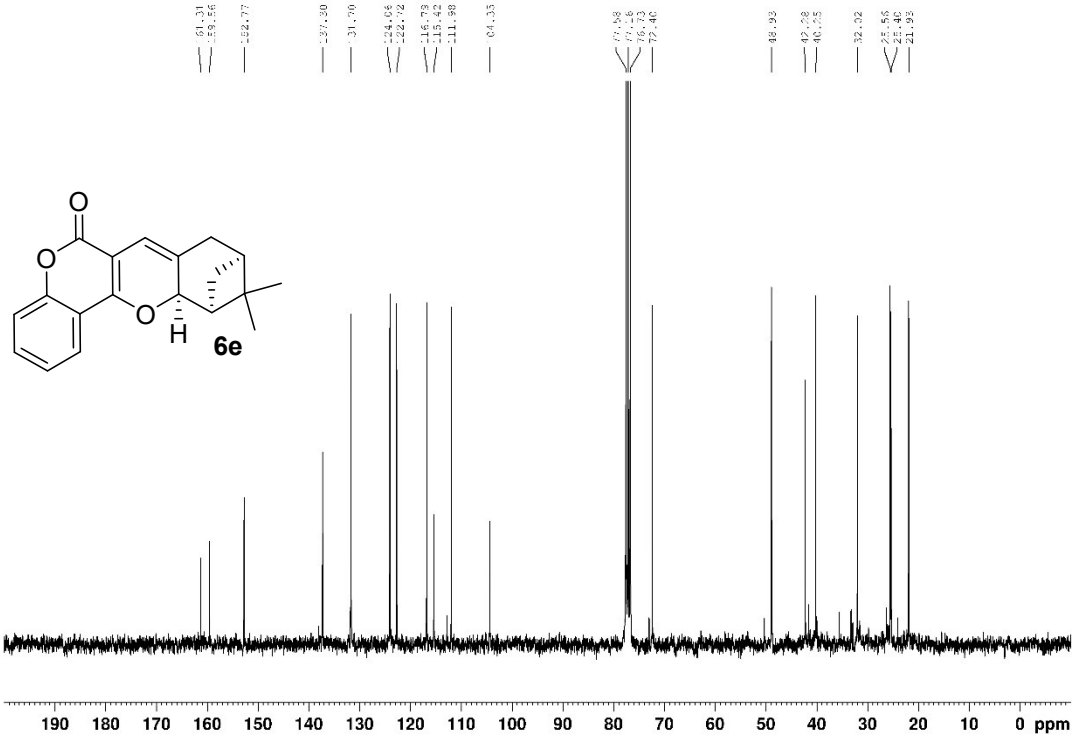
6e
ppm

## 11. References


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2 D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri and F.-X. Felpin, *Org. Process Res. Dev.*, 2016, **20**, 1979–1987.