***Supporting Information for*:**

# Continuous-flow preparation of γ-butyrolactone scaffolds from renewable fumaric and itaconic acids under photosensitized conditions

Romaric Gérardy,[†] Marc Winter,[‡] Clemens R. Horn,[‡] Alessandra Vizza,[‡] Kristof Van Hecke[§] and Jean-Christophe M. Monbaliu*[,†]

[†] Center for Integrated Technology and Organic Synthesis, Department of Chemistry, University of Liège, B-4000 Liège (Sart Tilman), Belgium

e-mail: jc.monbaliu@ulg.ac.be

[‡] Corning Reactor Technologies, Corning SAS, 7 bis Avenue de Valvins, CS 70156 Samois sur Seine, 77215 Avon Cedex, France

[§] XStruct, Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281-S3, B-9000 Ghent, Belgium

Contents

## 1. Equipment

### 1.1 Microfluidic setup (92 μL internal volume)

A commercial continuous-flow reactor (FutureChemistry® FlowStart Evo™) was used for preliminary photoaddition experiments. The setup included a borosilicate glass chip microreactor (92 μL internal volume, 500 μm channel depth, 600 μm channel width) and was equipped with the photochemistry module (2 LEDs, 365 nm wavelength, 15 nm FWHM, 320 mW radiant flux). The microfluidic chip was mounted on a Pelletier for temperature control (temperature accuracy +/- 0.5 °C). The feed solution was loaded in a plastic syringe protected from direct light exposure (thin foil), and conveyed to the microfluidic chip through a section of high purity DuPont® PFA tubing (1/16" o.d., 1/32" i.d.) with a syringe pump. The outlet of the microfluidic chip was connected to a BPR (2 bar) through an additional section of PFA tubing. The reactor effluent was collected, processed and analyzed.

### 1.2 Mesofluidic setup (2.6 mL internal volume, lab scale)

The reactions were conducted in a commercial continuous-flow reactor (Corning® Advanced-Flow™ Lab Photo Reactor) featuring a compact glass mesofluidic module (155 x 125 mm size, 0.4 mm channel height, 2.6 mL internal volume) integrated with a high capacity heat-exchanger (2 layers, 22 mL, 1 W $mL^{-1}$ $K^{-1}$). LED panels were mounted on both sides of the fluidic module (40 mm from the center of the reactive layer), and each LED panel was equipped with 20 × 365 nm LEDs and a heat exchanger (T = 10 °C). The thermoregulation of both the glass fluidic module and the LED panels was carried out with LAUDA® Proline RP 845 thermostats. Ethylene glycol, which is transparent at 365 nm, was utilized as thermofluid. The feed solution was conveyed to the photoreactor with a FLOM HPLC pump (0.01 – 100 mL $min^{-1}$; wetted-parts: PTFE, PCTFE, FFKM and ruby) through a section of 1/8" PFA tubing (Swagelok®). The feed solution was installed on a precision scale for accurate flow rate monitoring. A dome-type back-pressure regulator (BPR, Zaiput Flow Technologies®) was inserted downstream the reactor (set point: 2 bar). The reactor effluents were conveyed through PFA capillaries (1/8" O.D.) towards an inline 43 MHz Spinsolve™ Carbon NMR spectrometer from Magritek® equipped with the flow-through module, and finally to a collection tank (Figure S1).

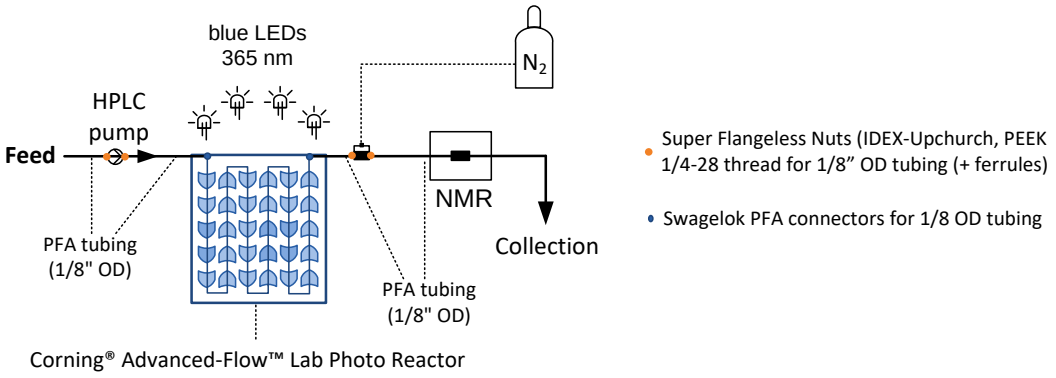



**Figure S1.** Simplified flow chart

1.3 Mesofluidic setup (41 mL internal volume, pilot scale)

The reactions were conducted in a commercial continuous-flow reactor (Corning® Advanced-Flow™ G1 Photo Reactor) equipped with 5 glass fluidic modules connected in series (8.2 mL internal volume each). Each fluidic module was integrated with a heat exchanger, and sandwiched between two thermoregulated (T = 10 °C) LED panels (365 nm, 30 LEDs per panel, 300 LEDs in total). A dome-type back-pressure regulator (BPR, Zaiput Flow Technologies®) was inserted downstream the reactor (set point: 2 bar). The feed solution was conveyed to the photoreactor with a FLOM HPLC pump (0.01 – 100 mL $min^{-1}$; wetted-parts: PTFE, PCTFE, FFKM and ruby) through a section of 1/8" PFA tubing (Swagelok®). The reactor effluents were conveyed through PFA capillaries (1/8" O.D.) towards a collection tank.

1.4 Nuclear Magnetic Resonance (NMR)

In-line NMR (qualitative) analysis was carried out with a 43 MHz Spinsolve™ Carbon NMR spectrometer from Magritek® equipped with the flow-through module. Analytical samples were collected, processed and analyzed by $^{1}H$ NMR at 400 MHz on a Bruker Avance III HD spectrometer (9.4 Tesla). $^{13}C$ NMR spectra were recorded at 100.6 MHz. The chemical shifts are reported in ppm relative to TMS as internal standard or to solvent residual peak.

1.5 X-ray diffraction

For the structure of **4a**, X-ray intensity data were collected at 100 K on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro.[S1] Using Olex2,[S2] the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on $F^2$ using the ShelXL program package.[S3,S4] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl and hydroxyl groups).

1.6 Other characterization and purification methods

HRMS spectra were recorded on a FTMS (ESI) apparatus (Thermo® Scientific Q Exactive™). IR spectra were recorded using ATR technique on a Thermo Scientific® Nicolet iS5 iD7 FT-IR spectrometer with a diamond window. Melting points were determined with an Electrothermal® 9100 melting point apparatus (uncorrected values). TLC was performed on POLYGRAM® SIL G/$UV_{254}$ silica gel precoated plates. Column chromatography was performed on Davisil® LC60A 70-200 μm silica gel.

## 2. Additional experimental details

### 2.1 Chemicals

Fumaric acid, itaconic acid, benzophenone, 4,4'-dimethoxybenzophenone, isopropanol, cyclohexanol and methanol were purchased from commercial sources and used as received.

- Fumaric acid (CAS 110-17-8, > 99.0%, TCI, MSDS)
- Itaconic acid (CAS 97-65-4, > 99.0%, TCI, MSDS)
- Benzophenone (CAS 119-61-9, > 99.0%, TCI, MSDS)
- 4,4'-Dimethoxybenzophenone (CAS 90-96-0, 97%, Aldrich, MSDS)
- Isopropanol (CAS 67-63-0, > 98%, VWR, MSDS)
- Cyclohexanol (CAS 108-93-0, 99%, Alfa Aesar, MSDS)
- Methanol (CAS 67-56-1, 99.9%, VWR, MSDS)

### 2.2 Residence (irradiation) time

Residence (irradiation) time within the reactor time was calculated according Equation S1:

$$\text{Residence (irradiation) time (min)} = \frac{\text{Internal volume (mL)}}{\text{Flow rate (mL min}^{-1}\text{)}} \textbf{ (Equation S1)}$$

### 2.3 In-line NMR monitoring

Reaction monitoring was carried out by following the relative variations of selected characteristic peaks in the $^{1}$H NMR spectrum corresponding to the olefinic protons from the substrate and to the aromatic protons from the sensitizer (acting as an internal reference). Representative NMR spectra are depicted in Figures S7 and S8. The conversion was qualitatively determined with Equation S2:

$$\text{conv.} = \left(1 - \frac{n_{PS} \times [PS] \times A_{sub}}{n_{sub} \times [sub] \times A_{PS}}\right) \times 100 \textbf{ (Equation S2)}$$

where conv. = conversion (%)

$n_{PS}$ = number of aromatic protons in the photosensitizer

[PS] = photosensitizer concentration in the feed (mol $L^{-1}$)

$A_{PS}$ = sum of the areas of the photosensitizer aromatic proton peaks

$n_{sub}$ = number of olefinic protons in the substrate

[sub] = substrate concentration in the feed (mol $L^{-1}$)

$A_{sub}$ = sum of the areas of the substrate olefinic proton peaks

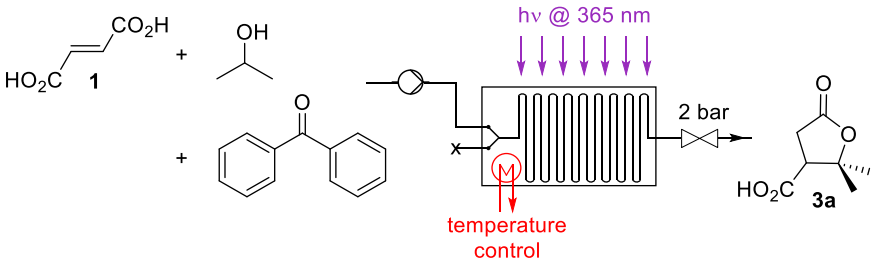
For fumaric acid (**1**), irradiation at 365 nm triggers an equilibrium between the *E* (fumaric acid) and *Z* (maleic acid) isomers, and both isomers were taken into account in the calculation

of the conversion. Reaction conversions presented in this manuscript were obtained by high field NMR.

2.4 Photosensitized addition of isopropanol to fumaric acid (**1**) in the microfluidic setup

**Typical experimental procedure.** A solution of **1** and benzophenone in 10 mL of isopropanol, was prepared under sonication, and degassed with argon for 15 min. The feed solution was loaded in a plastic syringe protected from direct light exposure (thin foil). The solution was delivered to the glass microfluidic photoreactor using the syringe pump included in the commercial setup. A back pressure regulator set at 2 bar was connected downstream the reactor. The solution was irradiated at 365 nm, and collected after equilibration of the system. The solvent was removed under reduced pressure and the sample was analyzed by off-line $^{1}$H NMR (400 MHz).

**Table S1.** Preliminary attempts of photosensitized addition of isopropanol to fumaric acid (**1**) in a 92 µL continuous microfluidic reactor (FutureChemistry® FlowStart Evo™).




| Entry | [**1**] (mol/L) | Benzophenone (equiv.) | Res. time | T (°C) | Conv.[a] (%) |
|---|---|---|---|---|---|
| 1 | 0.1 | 0.2 | 5 min | 25 | 14 |
| 2 | 0.1 | 0.2 | 10 min | 25 | 31 |
| 3 | 0.1 | 0.2 | 20 min | 25 | 60 |
| 4 | 0.2 | 0.2 | 20 min | 25 | 55 |
| 5 | 0.3 | 0.2 | 20 min | 25 | -[b] |
| 6 | 0.1 | 0.1 | 20 min | 25 | 28 |
| 7 | 0.1 | 0.2 | 20 min | 50 | 97 |

Conditions: LED power = 100%. [a] Off-line $^{1}$H NMR. [b] Heterogeneous feed solution.

2.5 Photosensitized addition of alcohols to fumaric acid (**1**) in the mesofluidic setup (lab scale)

**Table S2.** Optimization of the photosensitized addition of isopropanol, cyclohexanol and methanol to fumaric acid (**1**); (lab scale experiments performed in a Corning® Advanced-Flow Lab Photo Reactor™).

| Entry | Substrate | Solvent | Benzophenone (equiv.) | Res. time | T (°C) | Product | Conv.[a] (%) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | **1** | *i*PrOH | 0.2 | 20 min | 40 | **3a** | 95 | - |
| 2 | **1** | *i*PrOH | 0.2 | 25 min | 40 | **3a** | >99 | - |
| 3 | **1** | *i*PrOH | 0.4 | 10 min | 40 | **3a** | >99 | 76 |
| 4[c] | **1** | CyOH | 0.4 | 10 min | 40 | **3b** | >99 | 75 |
| 5 | **1** | MeOH | 0.4 | 10 min | 40 | **3c** | 22 | - |
| 6 | **1** | MeOH | 0.8 | 10 min | 40 | **3c** | 34 | - |
| 7 | **1** | MeOH | 1.2 | 10 min | 40 | **3c** | 36 | - |
| 8 | **1** | MeOH | 1.6 | 10 min | 40 | **3c** | 40 | - |
| 9 | **1** | MeOH | 3 | 10 min | 40 | **3c** | 64 | - |
| 10 | **1** | MeOH | 3 | 10 min | 55 | **3c** | 72 | - |
| 11 | **1** | MeOH | 3 | 20 min | 55 | **3c** | >99 | 47 |

Conditions: fumaric acid (**1**, 0.2 M) + benzophenone in alcohol, LED power = 100%. [a] Off-line $^1$H NMR. [b] Isolated yield after purification by column chromatography. [c] The solvent was a 9:1 v/v mixture of CyOH/MeOH.

2.6 Photosensitized addition of alcohols to itaconic acid (**2**) in the mesofluidic setup (lab scale)

**Table S3.** Optimization of the photosensitized addition of isopropanol, cyclohexanol and methanol to itaconic acid (**2**); (lab scale experiments performed in a Corning® Advanced-Flow Lab Photo Reactor™).

| Entry | Substrate | Solvent | Benzophenone (equiv.) | Res. time | T (°C) | Product | Conv.[a] (%) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **2** | *i*PrOH | 0.4 | 10 min | 40 | **4a** | 64 | - |
| 2 | **2** | *i*PrOH | 0.4 | 10 min | 70 | **4a** | 88 | - |
| 3 | **2** | *i*PrOH | 0.5 | 10 min | 40 | **4a** | 73 | - |
| 4 | **2** | *i*PrOH | 0.5 | 10 min | 70 | **4a** | >99 | - |
| 4 | **2** | *i*PrOH | 0.7 | 10 min | 40 | **4a** | >99 | 52 |
| 6[c] | **2** | CyOH | 0.4 | 10 min | 40 | **4b** | 85 | - |
| 7[c] | **2** | CyOH | 0.4 | 10 min | 70 | **4b** | >99 | - |
| 8[c] | **2** | CyOH | 0.5 | 10 min | 40 | **4b** | 95 | 72 |
| 9 | **2** | MeOH | 3 | 10 min | 55 | **4c** | clogging | - |
| 10[d] | **2** | MeOH | 3 | 10 min | 55 | **4c** | n.c. | - |
| 11[d] | **2** | MeOH | 3.5 | 10 min | 40 | **4c** | n.c. | - |
| 12[d] | **2** | MeOH | 3.5 | 10 min | 55 | **4c** | n.c. | - |
| 13[d] | **2** | MeOH | 3.5 | 20 min | 55 | **4c** | >99 | traces |

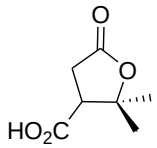
Conditions: itaconic acid (**2**, 0.2 M) + benzophenone in alcohol, LED power = 100%. [a] Off-line $^1$H NMR. [b] Isolated yield after purification by column chromatography.[c] The solvent was a 9:1 v/v mixture of CyOH/MeOH. [d] 0.1 M substrate.

2.7 Scaling-out

A solution of **1** (0.2 M) and benzophenone (0.08 M, 0.4 equiv.) in 250 mL of isopropanol, was prepared under sonication, and degassed with argon for 15 min. The feed solution was loaded in a brown glass feed tank and kept under an argon atmosphere. The solution was delivered to the glass mesofluidic reactor (41 mL internal volume) through a HPLC pump set at 4.1 mL min$^{-1}$. A back pressure regulator set at 2 bar was connected downstream the reactor. The solution was irradiated at 365 nm and at 40 °C, and collected after 20 min equilibration.

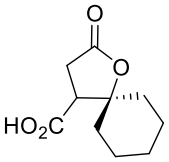
The solvent was removed under reduced pressure and the sample was analyzed by off-line $^1$H NMR (400 MHz). Output (**3a**): 83 g day$^{-1}$.

2.8 Characterization of compounds **3a-c** and **4a,b**



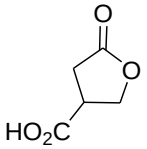
$C_7H_{10}O_4$
Mol. Wt.: 158.15

**Terebic acid (3a). $^1$H NMR (DMSO-d$_6$, 400 MHz):** $\delta$ = 3.23 (t, *J* = 8.5 Hz, 1H), 2.83 (dd, *J* = 17.7, 8.4 Hz, 1H), 2.72 (dd, *J* = 17.7, 8.7 Hz, 1H), 1.50 (s, 3H), 1.28 (s, 3H) ppm. **$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz):** $\delta$ = 174.5, 171.9, 84.0, 49.7, 31.7, 27.9, 23.1 ppm. The NMR data matched those reported in the literature.[S5] **ESI HRMS** *m/z* $C_7H_9O_4^-$ [M-H]$^-$: calcd 157.0495. Found: 157.0495.



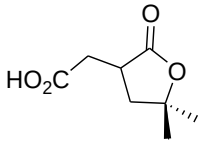
$C_{10}H_{14}O_4$
Mol. Wt.: 198.22

**2-Oxo-1-oxaspiro[4.5]decane-4-carboxylic acid (3b). $^1$H NMR (DMSO-d$_6$, 400 MHz):** $\delta$ = 3.11 (t, *J* = 7.8 Hz, 1H), 2.76 (d, *J* = 8.0 Hz, 2H), 1.95 – 1.09 (m, 10H) ppm. **$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz):** $\delta$ = 174.5, 172.1, 85.2, 49.3, 36.1, 31.8, 31.5, 24.4, 22.2, 21.7 ppm. The $^1$H NMR data matched those reported in the literature.[S6] **ESI HRMS** *m/z* $C_{10}H_{14}O_4Na^+$ [M+Na]$^+$: calcd 221.0784. Found 221.0784.



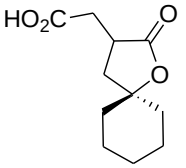
$C_5H_6O_4$
Mol. Wt.: 130.1

**Paraconic acid (3c). $^1$H NMR (DMSO-d$_6$, 400 MHz):** $\delta$ = 4.44 (t, *J* = 8.5 Hz, 1H), 4.35 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.44 (ddd, *J* = 14.4, 8.7, 5.8 Hz, 1H), 2.75 (dd, *J* = 17.6, 9.4 Hz, 1H), 2.64 (dd, *J* = 17.5, 6.2 Hz, 1H) ppm. **$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz):** $\delta$ = 176.3, 173.9, 69.2, 39.8, 30.7 ppm. The NMR data matched those reported in the literature.[S5] **ESI HRMS** *m/z* $C_5H_5O_4^-$ [M-H]$^-$: calcd 129.0182. Found 129.0181.



$C_8H_{12}O_4$
Mol. Wt.: 172.18

**2-(5,5-Dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (4a). $^1$H NMR (DMSO-d$_6$, 400 MHz):** $\delta$ = 3.20 – 3.10 (m, 1H), 2.62 (dd, *J* = 17.1, 4.4 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.31 – 2.21 (m, 1H), 1.84 (t, *J* = 12.0 Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H) ppm. **$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz):** $\delta$ = 177.2, 172.5, 82.2, 39.8, 36.7, 34.0, 28.4, 26.6 ppm. The $^1$H NMR data did not match those reported in the literature.[S7] **IR (neat)**: $\nu_{max}$ = 2980, 2935, 1728, 1707 cm$^{-1}$. **MP:** 132.1-133.8 °C (lit.[S8] 137-140 °C). **ESI HRMS** *m/z* $C_8H_{11}O_4^-$ [M-H]$^-$: calcd 171.0652. Found 171.0653.



$C_{11}H_{16}O_4$
Mol. Wt.: 212.25

**2-(2-Oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (4b). $^1$H NMR (DMSO-d$_6$, 400 MHz):** $\delta$ = 3.14 – 3.03 (m, 1H), 2.61 (dd, *J* = 17.1, 4.4 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.31 (dd, *J* = 12.4, 9.4 Hz, 1H), 1.87 – 1.07 (m, 11H) ppm. **$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz):** $\delta$ = 177.1, 172.5, 83.6, 39.8, 38.0, 37.4, 35.9, 35.1, 34.1, 24.5, 22.3 ppm. **IR (neat)**: $\nu_{max}$ = 2981, 2935, 2870, 1731, 1719 cm$^{-1}$. **MP:** 134.7-136.5 °C (lit.[S9] 133.5-134.5 °C). **ESI HRMS** *m/z* $C_{11}H_{17}O_4^+$ [M+H]$^+$: calcd 213.1121. Found 213.1122.

## 3. Structure assignment for compounds 4a,b

### 3.1 Structure assignment for **4a** and **4b** by HMBC

The assignments of $^{13}C=O$ chemical shifts were made by comparison with literature data for the analogous isoparaconic acid **4c**.[S10]

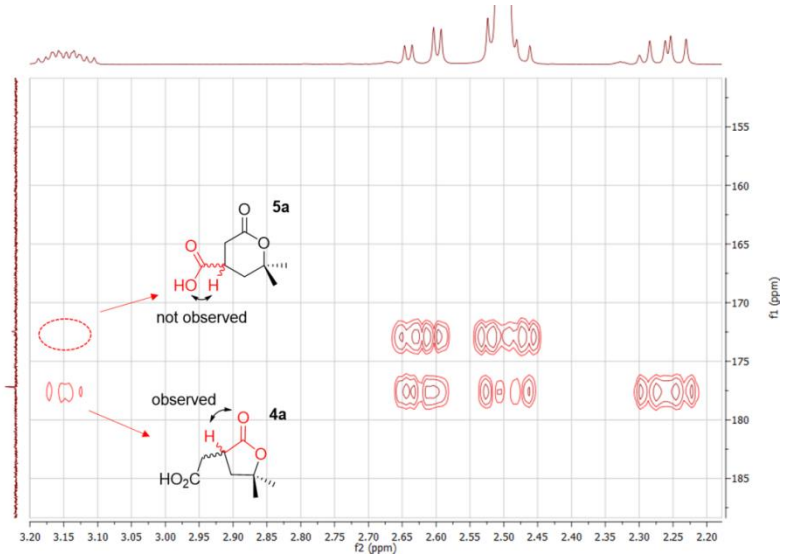



**Figure S2**. HMBC spectrum of 2-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (**4a**) in DMSO-$d_6$. The interaction between the lactone $^{13}C=O$ and the $^{1}H$ positioned on the stereogenic center is emphasized.

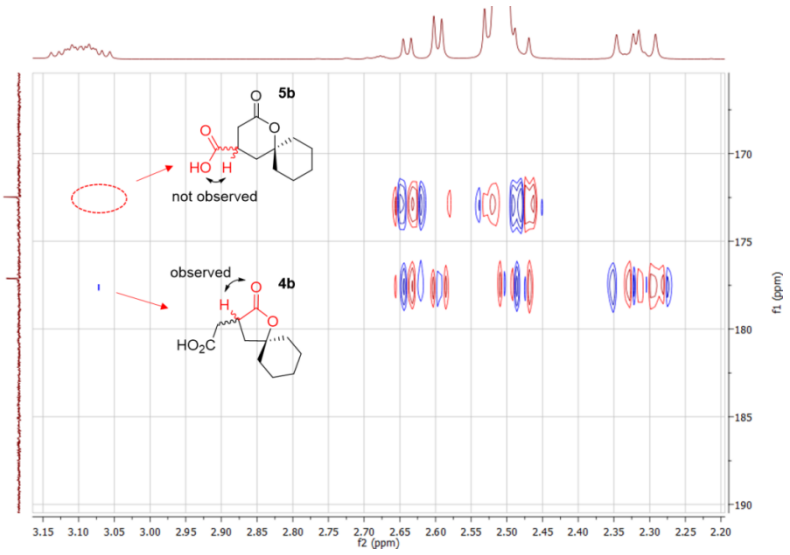



**Figure S3**. HMBC spectrum of 2-(2-oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (**4b**) in DMSO-$d_6$. The interaction between the lactone $^{13}C=O$ and the $^{1}H$ positioned on the stereogenic center is emphasized.

3.2 Structure assignment for **4a** by X-ray diffraction

White crystals of **4a** were obtained from recrystallization in petroleum spirit 40-60/toluene/methanol (10:10:1 v/v/v).

*Crystal data for compound* **4a**. $C_8H_{12}O_4$, $M$ = 172.18, monoclinic, space group $P2_1/c$ (No. 14), $a$ = 5.3618(6) Å, $b$ = 15.150(2) Å, $c$ = 10.5728(11) Å, $\beta$ = 92.826(9)°, $V$ = 857.80(17) Å$^3$, $Z$ = 4, $T$ = 100 K, $\rho_{calc}$ = 1.333 g cm$^{-3}$, $\mu$(Cu-Kα) = 0.906 mm$^{-1}$, $F$(000) = 368, 7976 reflections measured, 1745 unique ($R_{int}$ = 0.0445) which were used in all calculations. The final $R1$ was 0.0756 ($I > 2\sigma(I)$) and $wR2$ was 0.1956 (all data).

The asymmetric unit has chirality at C4A (*R*), but obviously, because of the centro-symmetric space group ($P2_1/c$), also the inverse configuration (*S*) is present in the crystal. Additionally, there is also clear positional disorder of the γ-butyrolactone ring in the asymmetric unit, which could be modeled in two parts (the first part with C4A configuration (*R*) and the second part with C4B (*S*), with occupancy factors of 0.785 and 0.215, respectively) (Figure S4).

Furthermore, hydrogen bonds are formed in the crystal packing between C=O and COOH groups, forming chains along the [-1 0 1] direction (Figure S5).

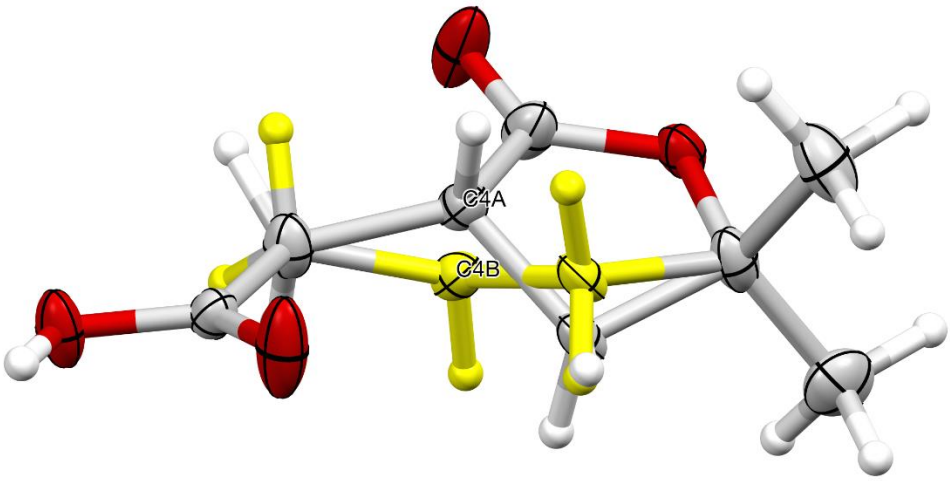



**Figure S4.** Asymmetric unit of the crystal structure of **4a**, showing thermal displacement ellipsoids at the 50% probability level and atom labeling scheme of the chiral C-atoms. The positional disorder of the γ-butyrolactone ring is shown in yellow.

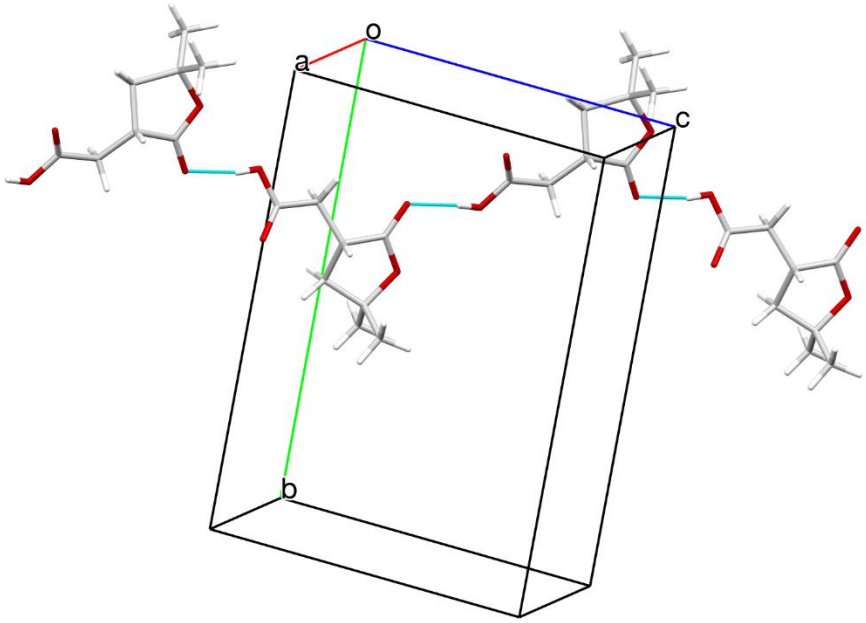



**Figure S5.** Hydrogen bonds (blue dashed lines) observed in the crystal packing of the structure of **4a**, between C=O and COOH groups, forming chains along the [-1 0 1] direction. The disorder of the γ-butyrolactone ring is omitted for clarity.

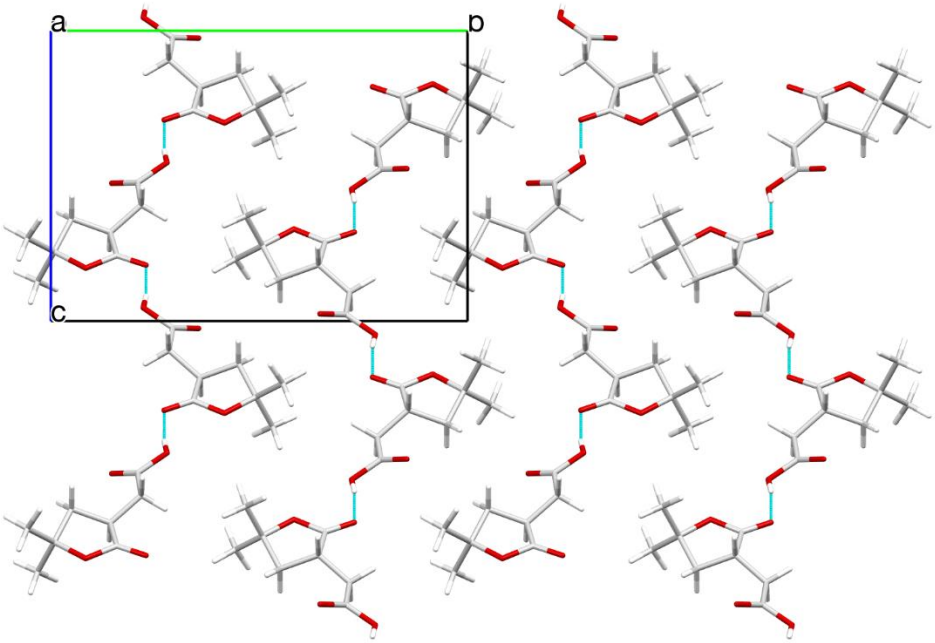



**Figure S6.** Packing diagram of the structure of **4a**, viewed down the crystallographic *a*-axis. Hydrogen bonds between C=O and COOH groups are indicated (blue dashed lines). The disorder of the γ-butyrolactone ring is omitted for clarity.

CCDC 1554500 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

## 4. Representative NMR spectra

4.1 In-line $^{1}$H NMR

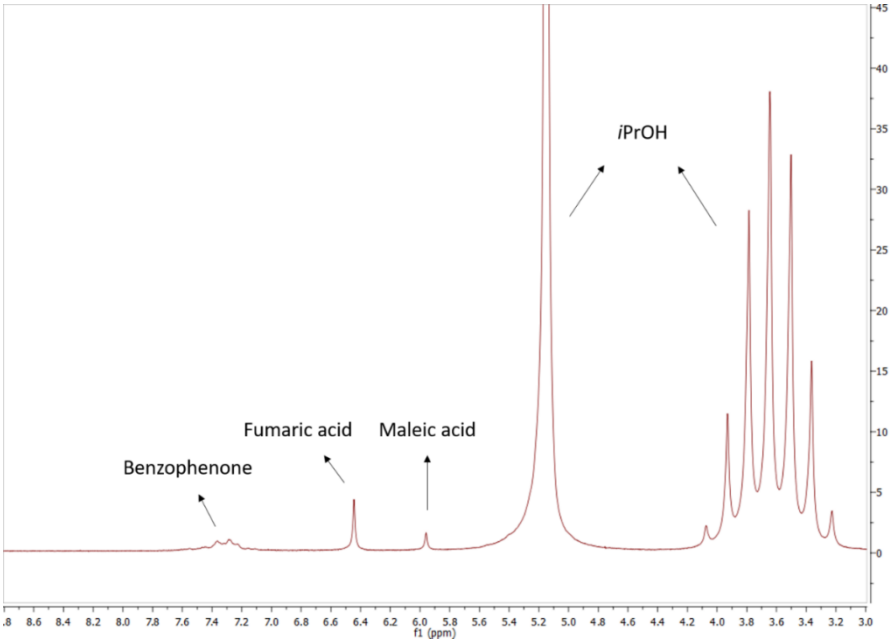



**Figure S7**. Representative in-line $^{1}$H NMR spectrum (43 MHz) obtained during the optimization of *i*PrOH addition to fumaric acid (**1**).

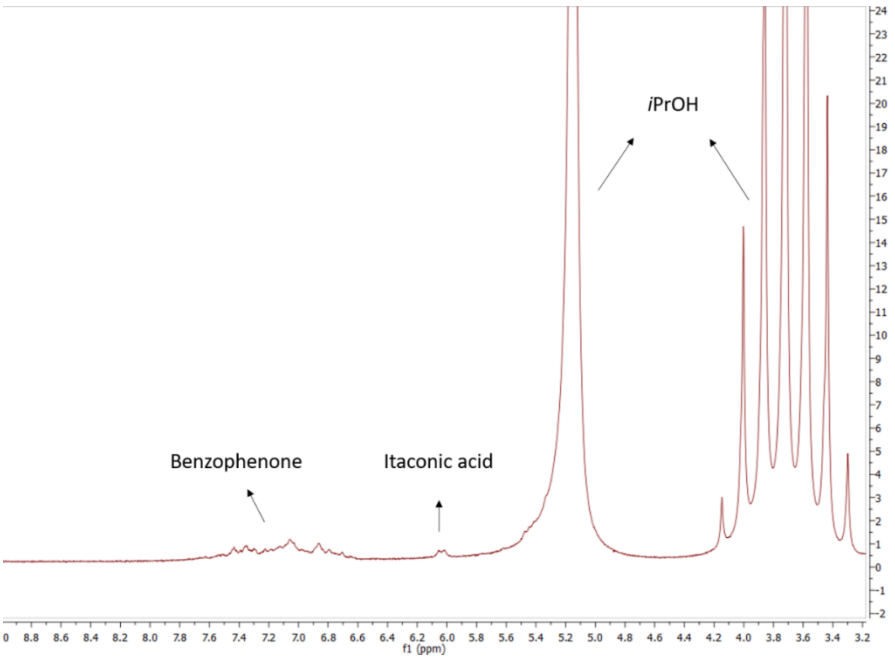



**Figure S8**. Representative in-line $^{1}$H NMR spectrum (43 MHz) obtained during the optimization of *i*PrOH addition to itaconic acid (**2**).

4.2 Copies of $^{1}H$, $^{13}C$, COSY and HSQC NMR spectra of compounds **3a-c** and **4a,b**

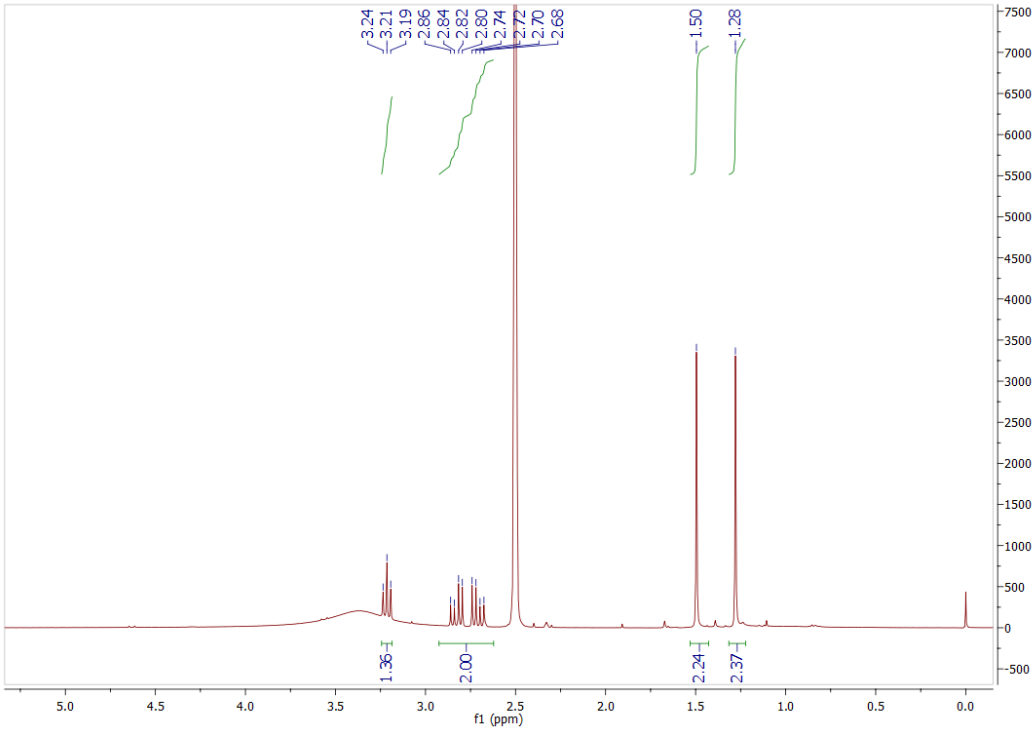



**Figure S9**. $^{1}H$ NMR spectrum (400 MHz) of terebic acid (**3a**) in DMSO-$d_6$.

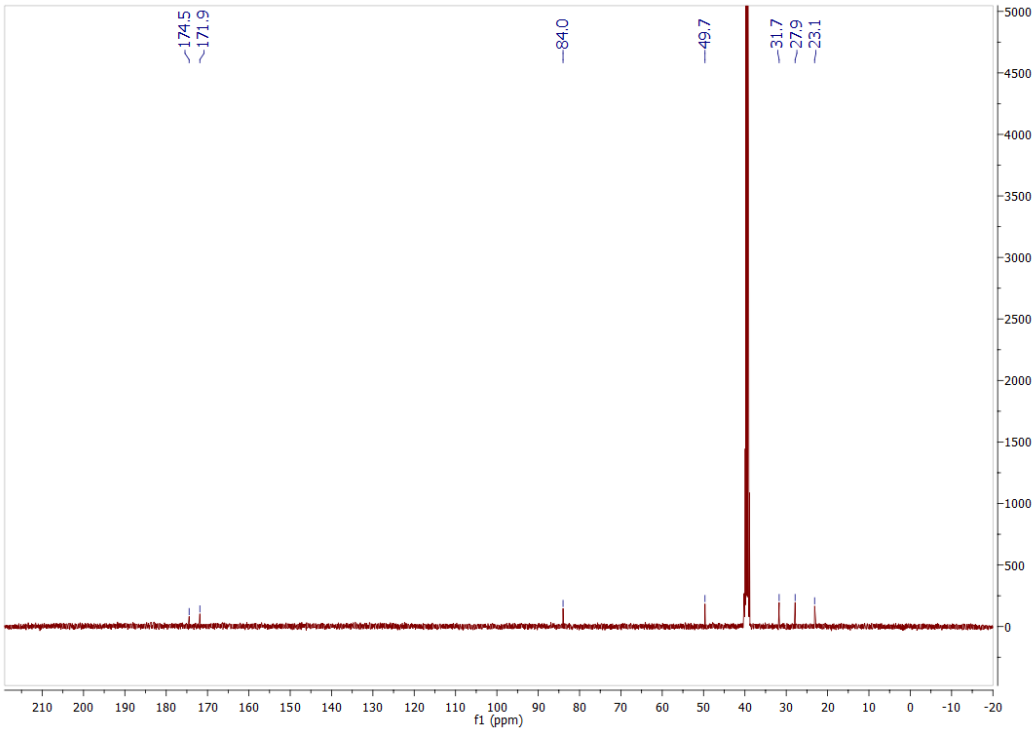



**Figure S10**. $^{13}C$ NMR spectrum (100.6 MHz) of terebic acid (**3a**) in DMSO-$d_6$.

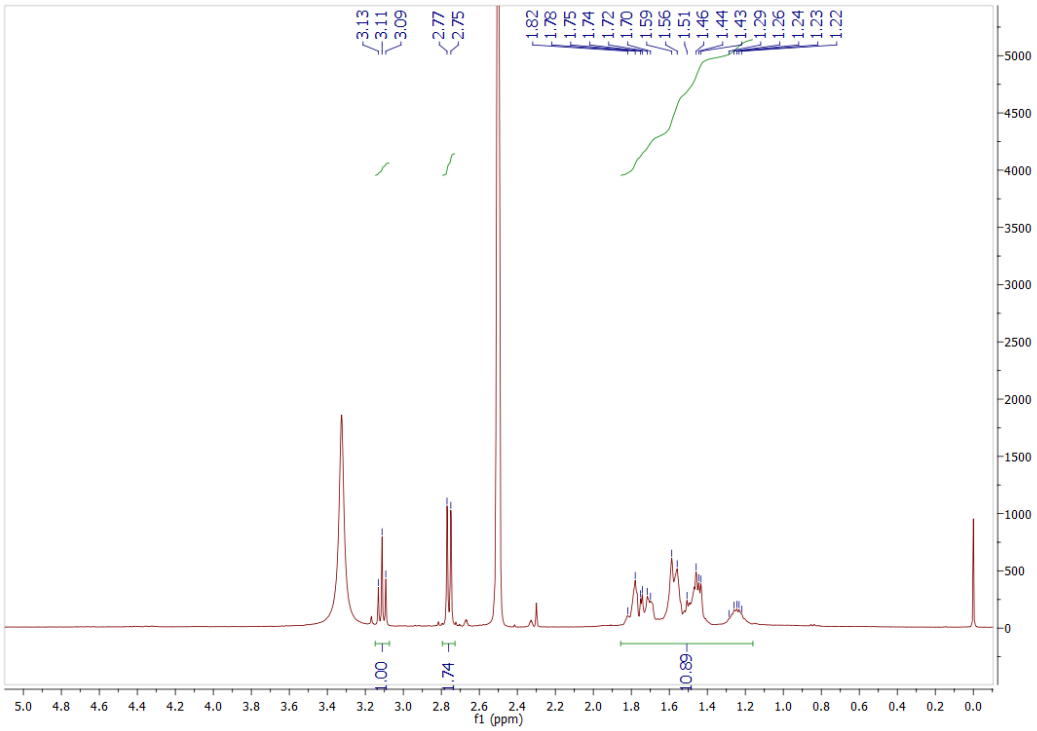



**Figure S11**. $^{1}$H NMR spectrum (400 MHz) of 2-oxo-1-oxaspiro[4.5]decane-4-carboxylic acid (**3b**) in DMSO-$d_6$.

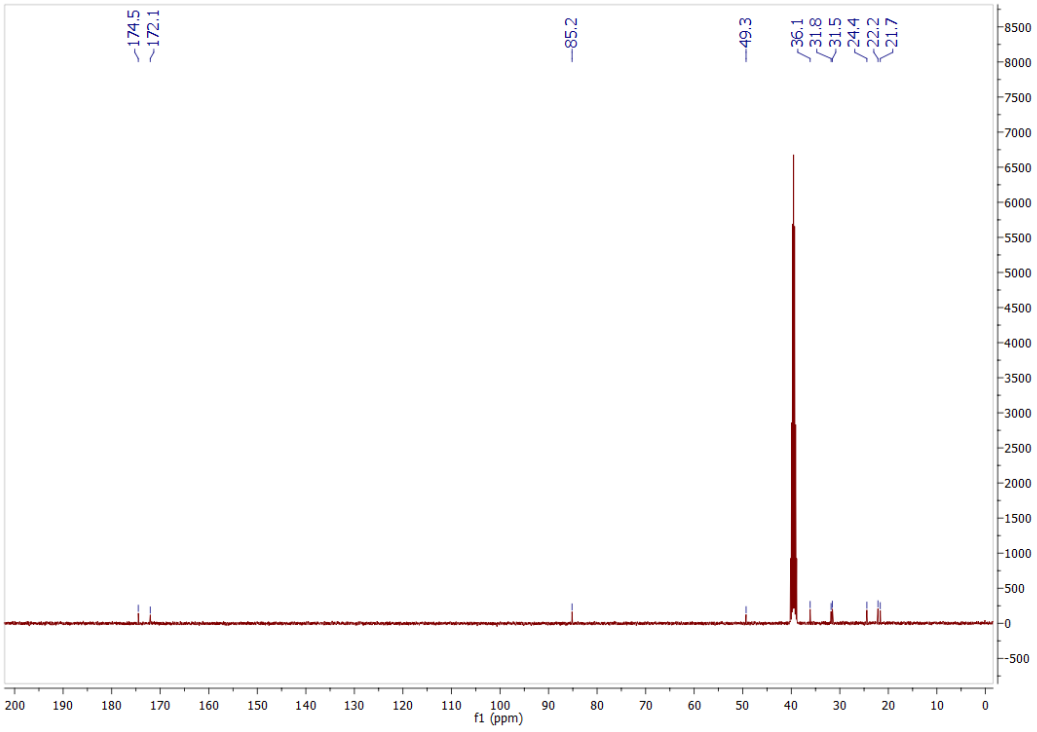



**Figure S12**. $^{13}$C NMR spectrum (100.6 MHz) of 2-oxo-1-oxaspiro[4.5]decane-4-carboxylic acid (**3b**) in DMSO-$d_6$.

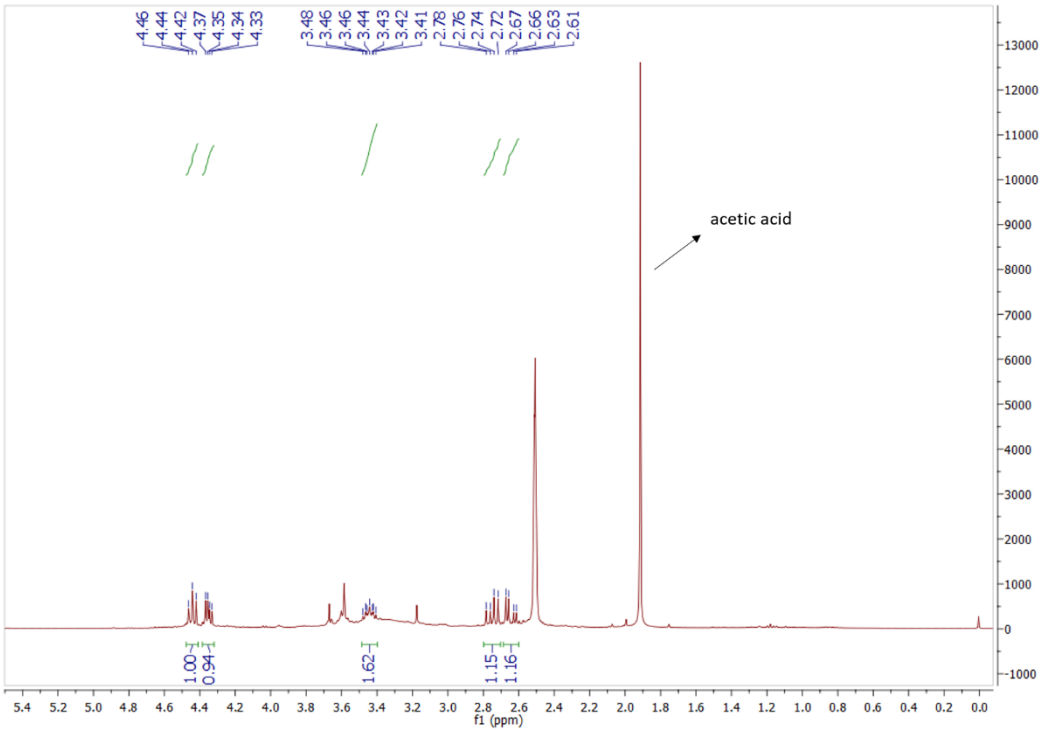



**Figure S13**. $^{1}$H NMR spectrum (400 MHz) of paraconic acid (**3c**) in DMSO-$d_6$.

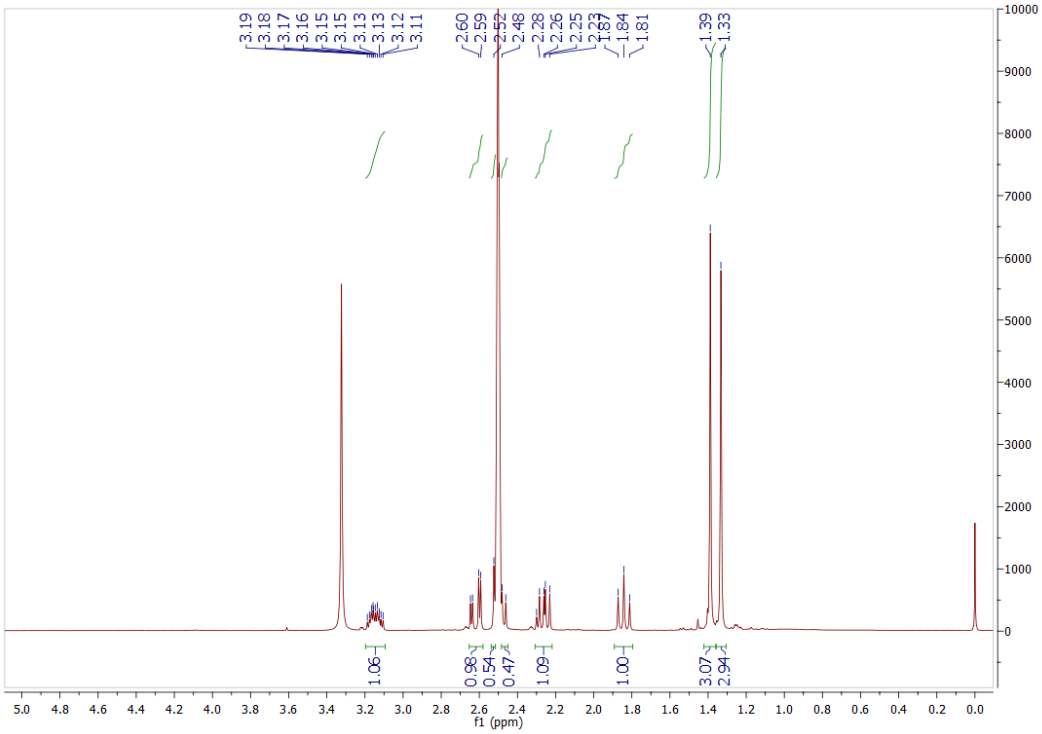



**Figure S14**. $^{1}$H NMR spectrum (400 MHz) of 2-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (**4a**) in DMSO-$d_6$.

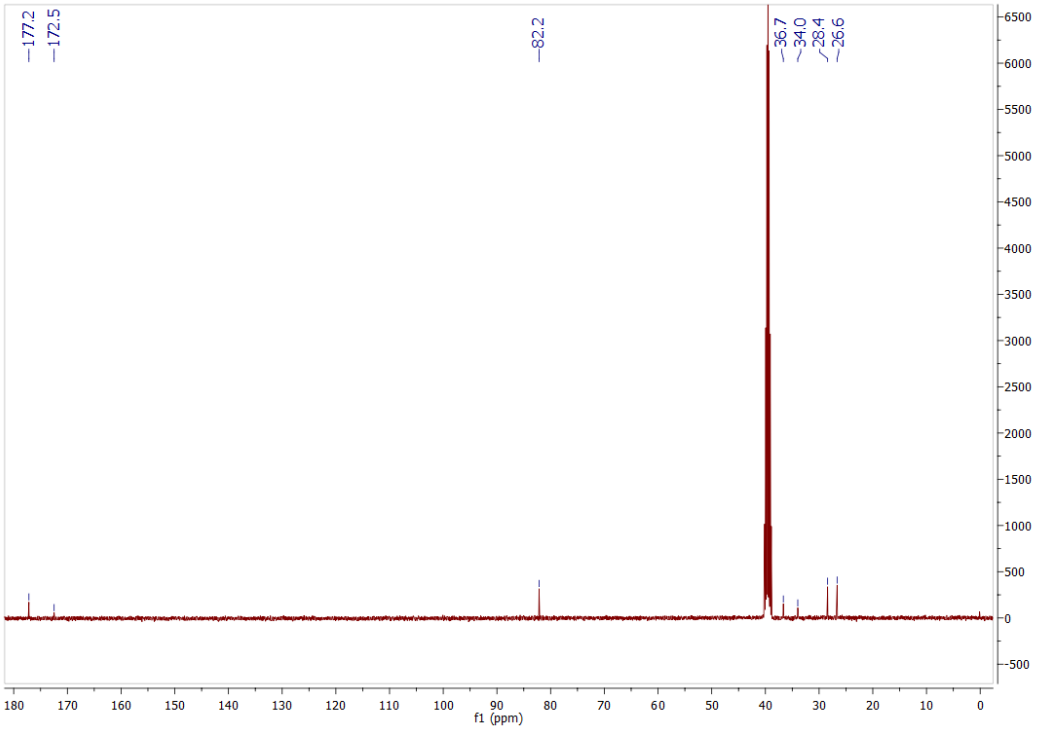



**Figure S15**. $^{13}$C NMR spectrum (100.6 MHz) of 2-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (**4a**) in DMSO-$d_6$.

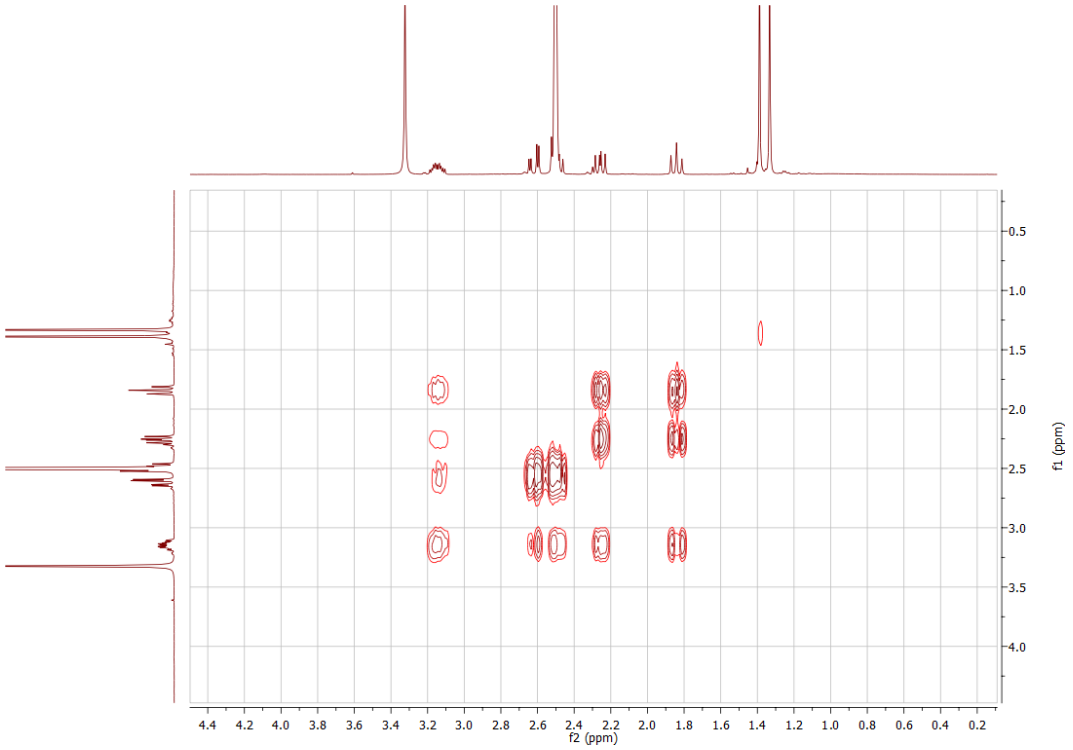



**Figure S16**. COSY NMR spectrum of 2-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (**4a**) in DMSO-$d_6$.

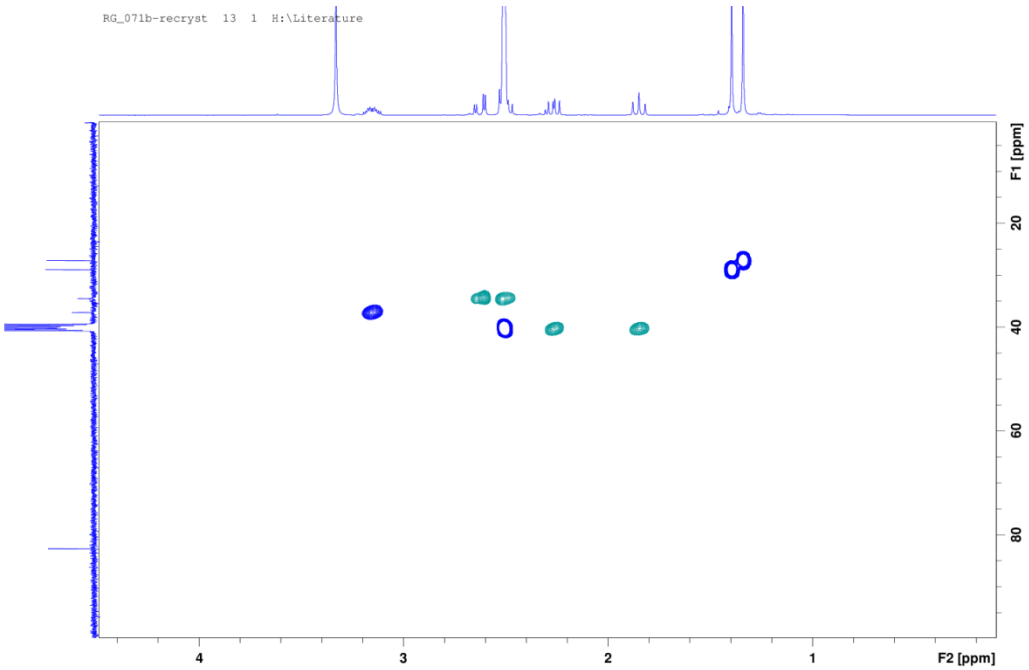



**Figure S17**. HSQC NMR spectrum of 2-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)acetic acid (**4a**) in DMSO-$d_6$.

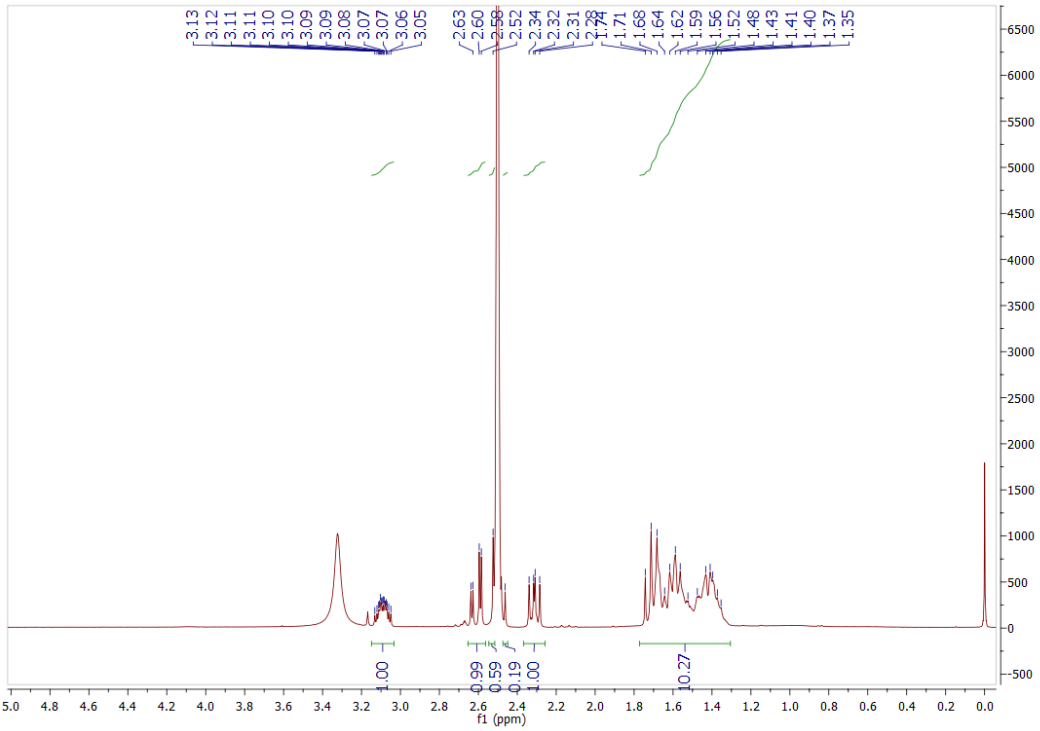



**Figure S18**. $^{1}$H NMR (400 MHz) spectrum of 2-(2-oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (**4b**) in DMSO-$d_6$.

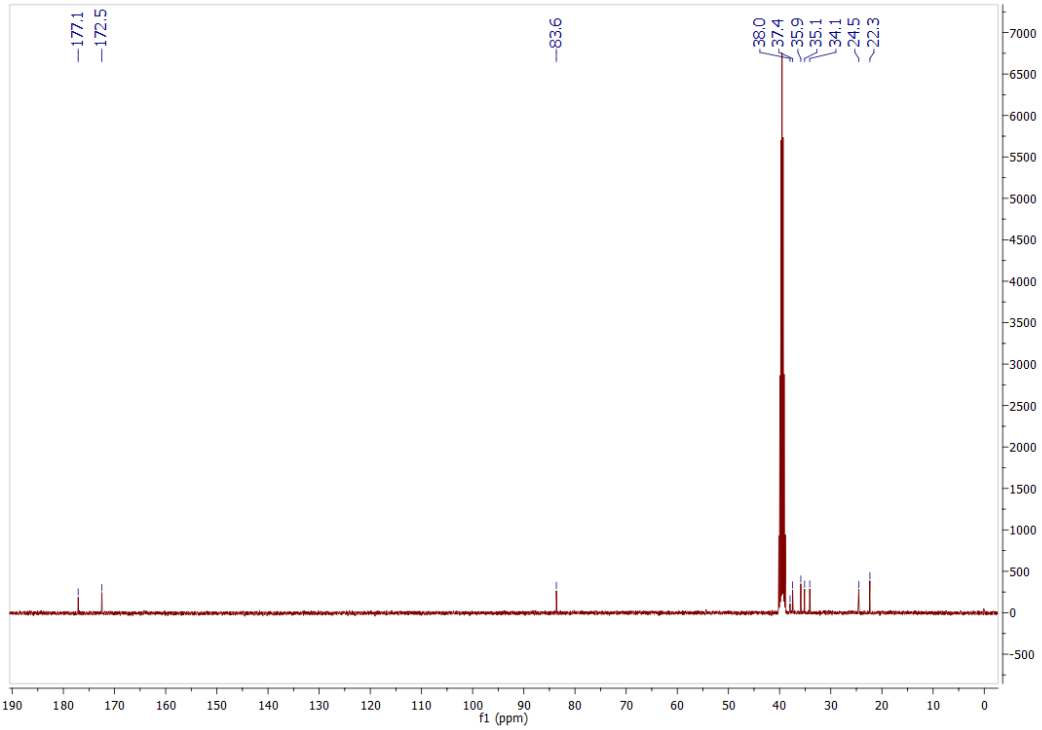



**Figure S19**. $^{13}$C NMR spectrum (100.6 MHz) of 2-(2-oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (**4b**) in DMSO-$d_6$.

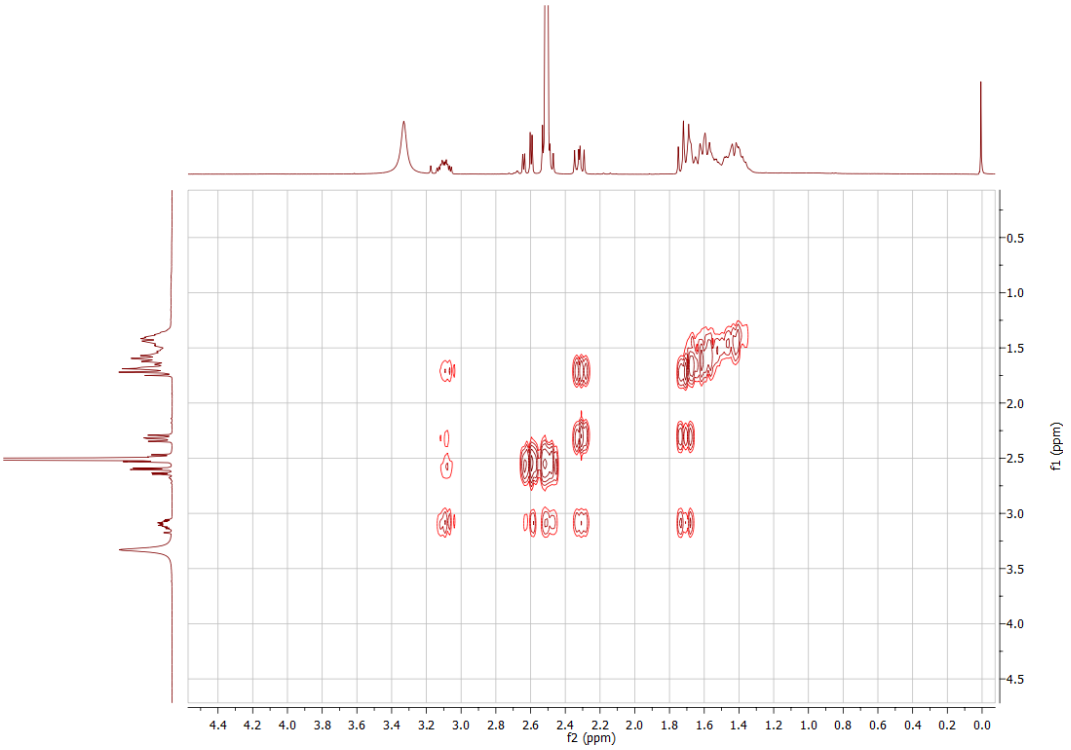



**Figure S20**. COSY NMR spectrum of 2-(2-oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (**4b**) in DMSO-$d_6$.

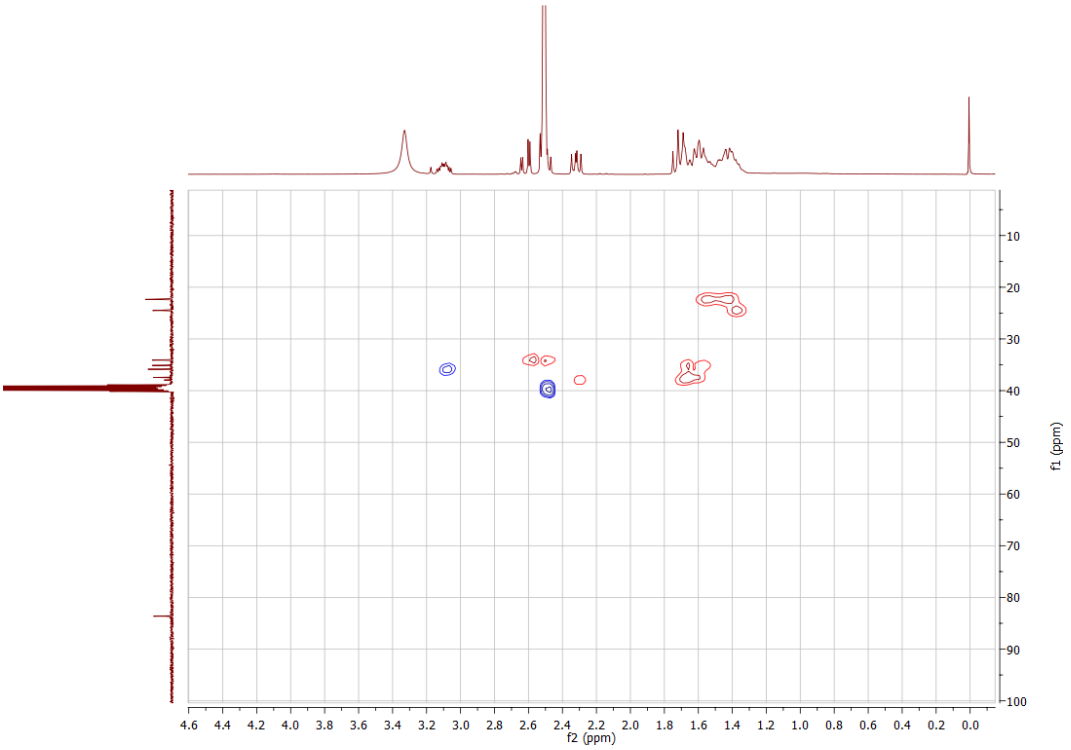



**Figure S21**. HSQC NMR spectrum of 2-(2-oxo-1-oxaspiro[4.5]decan-3-yl)acetic acid (**4b**) in DMSO-$d_6$.

## 5. References


[S1] Rigaku Oxford Diffraction, CrysAlisPro, Rigaku Oxford Diffraction, Yarnton, England, **2015**.

[S2] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, 42, 339-341.

[S3] Sheldrick, G.M. *Acta Cryst*. **2008**, A64, 112-122.

[S4] Sheldrick, G.M. *Acta Cryst*. **2015**, C71, 3-8.

[S5] Ouchi, A.; Liu, C.; Kaneda, M.; Hyugano, T. *Eur. J. Org. Chem.* **2013**, 3807–3816.

[S6] Tanaka, K.; Sugino, T.; Toda, F. *Green Chem.* **2000**, *2*, 303–304.

[S7] Kochikyan, T. V.; Arutyunyan, E. V.; Arutyunyan, V. S.; Avetisyan, A. A. *Russ. J. Org. Chem.* **2002**, *38*, 390–393.

[S8] Phillips, D. D.; Johnson, W. A. *J. Am. Chem. Soc.* **1955**, *77*, 5977–5982.

[S9] Torii, S.; Okamoto, T.; Oida, T. *J. Org. Chem.* **1978**, *43*, 2294–2296.

[S10] Felluga, F.; Forzato, C.; Mazzeo, G.; Nitti, P.; Pitacco, G.; Superchi, S. *Chirality* **2014**, *26*, 640–650.