Electrochemical Synthesis of Phthalides via Anodic Activation of Aromatic Carboxylic Acids.

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1. General information

- All reagents and solvents were purchased from Acros or Sigma-Aldrich and used directly as received without any further purification.
- Thin layer chromatography was performed on prepared thin layers precoated plates: Silicagel Merck 60 F254. The visualisation of spots on TLC plates was effected by exposure to UV or by using basic KMnO4 solution. Column chromatography was performed over ROCC Silica gel 60 (40 – 63μ mesh) using relevant eluent.
- JEOL JNM-ECX400 and ECA500 spectrometers were used for NMR measurements. Chloroform (δ = 7.24) was used as an internal standard for 1H NMR and CDCl3 (δ = 77.0) for 13C NMR. Coupling constants are reported and expressed in Hz, splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), ddd (doublet of doublet of doublet), m (multiplet). Structures of known compounds were confirmed by comparison with data reported in literature.
- NMR Fourier transform, integration and pick picking were done with MestRenova software or ACD NMR software.
- Infrared spectra were recorded on Shimadzu FTIR-8400S spectrometer and the absorption bands are reported in reciprocal centimeters (cm⁻¹).
- The mass spectra were recorded on a Finigan TSQ 7000 or Varian Matt 44S or Finnigan Exactive Orbitrap
- HPLC separations were performed with a reversed phase C18 LiChroCART® column (250 mm × 4 mm i.d.; particle size: 5 m) (Merck, Darmstadt, Germany), a HPLC Waters 2690 separation module (Waters, Milford, MA, USA) coupled to a UV spectrophotometric detector Kromaton (Angers, France); all controlled by Borwin software (Borwin, Rostock, Germany). The column was maintained at 30 °C.
- The electrochemical cells were purchased from the Institute of Creative Chemistry Japan. The 10ml cells were double jacketed and equipped with a stir bar and two 2.0 cm² platinum sheet electrodes separated apart by 5 mm.

2. Synthesis of starting materials

General procedure for synthesis of 2-(2-carboxyvinyl)-benzoic acid derivatives 1

**Phosphonium salts.** To a solution of triphenylphosphine (10.2g, 42mmol, 1.15 eq.) in acetonitrile (100mL) ester or amide of halogenacetic acid (38mmol, 1eq.) was added and the mixture was refluxed for 12h. The solvent was evaporated under reduced pressure, to the residue THF (100mL) was added and sonicated for 30 minutes. The precipitate was filtered off, washed with THF and dried in vacuo to afford pure phosphonium salt in 60-96% yield.

**2-(2-Carboxyvinyl)-benzoic acid derivatives 1.** The appropriate phosphonium salt (20mmol, 1eq.) was suspended in THF and KOBu (2.24g, 20mmol, 1eq.) was added portionwise and the mixture was stirred for 1 hour at ambient temperature. 2-Carboxybenzaldehyde (3.00g, 20mmol, 1eq.) was added and the mixture was stirred overnight. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100mL), extracted with 10% K₂CO₃ (4x50mL), the combined aqueous phases were washed with DCM (4x50mL), and carefully acidified with 5% HCl.
to pH 3. In case of precipitation the product was filtered off, washed with water and dried in vacuo.
In case of oil formation the aqueous phase was extracted with DCM (3x50mL), the combined
organic phases were washed with water, dried over Na$_2$SO$_4$, evaporated and dried in vacuo.

**(E)-2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)benzoic acid**(1a). Yield 70%, white powder. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.48 (d, $J = 16.0$Hz, 1H), 8.09 (dd, $J = 7.7$, 1.4Hz, 1H), 7.63-7.62 (m, 1H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 1H), 6.27 (d, $J = 16.0$Hz, 1H), 1.54 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 172.3, 166.2, 142.8, 137.4, 133.3, 131.7, 129.4, 128.7, 128.2, 123.3, 80.9, 28.3 ppm. IR (neat, cm$^{-1}$) 1708, 1691, 1149, 762. HRMS (ESI) calcd for C$_{14}$H$_{16}$O$_4$Na (M+Na$^+$) 271.09408, found: 271.09387

**(E)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)benzoic acid**(1b). E/Z = 85:15. Yield 76%. Although such
a mixture is sufficient for lactonisation reaction, pure E isomer can be obtained after
recrystallisation from hexane/ethyl acetate. White powder. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.55 (d, $J = 16.0$Hz, 1H), 8.11 (d, $J = 7.4$Hz, 1H), 7.62-7.57 (m, 2H), 7.49-7.45 (m, 1H), 6.33 (d, $J = 15.5$Hz, 1H), 4.28 (q, $J = 7.3$Hz, 2H), 1.34 (t, $J = 7.2$Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 172.1, 166.8, 143.9, 137.4, 133.4, 131.8, 129.6, 128.7, 128.3, 121.5, 60.8, 14.4 ppm. IR (neat, cm$^{-1}$) 1694, 1214, 748, 668. HRMS(ESI) calcd for C$_{12}$H$_{13}$O$_4$ (M+H$^+$) 221.08084, found: 221.08086

**(E)-2-(3-oxo-3-propoxyprop-1-en-1-yl)benzoic acid**(1c). Yield 65%, white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.55 (d, $J = 15.5$Hz, 1H), 8.11 (d, $J = 7.4$Hz, 1H), 7.64-7.58 (m, 2H), 7.49-7.46 (m, 1H), 6.34 (d, $J = 16.0$Hz, 1H), 4.19 (t, $J = 6.6$Hz, 2H), 1.74 (sxt, $J = 7.1$Hz, 2H), 1.00 (t, $J = 7.4$Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 171.9, 166.9, 143.9, 137.4, 133.4, 131.8, 129.6, 128.6, 128.3, 121.5, 66.4, 22.2, 10.6 ppm. IR (neat, cm$^{-1}$)1694, 1214, 748, 668. HRMS(ESI)calcd for C$_{13}$H$_{15}$O$_4$(M+H$^+$) 235.09649, found: 235.09645

**(E)-2-(3-isopropoxy-3-oxoprop-1-en-1-yl)benzoic acid**(1d). Yield 64%, white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.53 (d, $J = 16.0$Hz, 1H), 8.11-8.10 (m, 1H), 7.63-7.57 (m, 2H), 7.49-7.46 (m, 1H), 6.31 (d, $J = 16.0$Hz, 1H), 5.15 (spt, $J = 6.3$, 1H), 1.32 (d, $J = 6.3$Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 171.9, 166.9, 143.9, 137.4, 133.4, 131.8, 129.6, 128.6, 128.3, 121.5, 66.4, 22.2, 10.6 ppm. IR (neat, cm$^{-1}$)1713, 1687, 1106, 750, 668. HRMS(ESI)calcd for C$_{13}$H$_{15}$O$_4$(M+H$^+$) 235.09649, found: 235.09645

**(E)-2-(3-(allyloxy)-3-oxoprop-1-en-1-yl)benzoic acid**(1e). Yield 55%, white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.59 (d, $J = 16.0$Hz, 1H), 8.12 (d, $J = 7.4$Hz, 1H), 7.64-7.58 (m, 2H), 7.49-7.46 (m, 1H), 6.31 (d, $J = 16.0$Hz, 1H), 5.42-4.38 (m, 1H), 5.29-5.27 (m, 1H), 4.74 (d, $J = 5.7$Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 172.2, 166.4, 144.4, 137.3, 133.5, 132.3, 131.9, 129.7, 128.6, 128.3, 121.1, 118.4, 65.4 ppm. IR (neat, cm$^{-1}$) 1715, 1274, 1175, 764. HRMS(ESI)calcd for C$_{13}$H$_{13}$O$_4$(M+H$^+$) 233.08084, found: 233.08083
(E)-2-(3-(diethylamino)-3-oxoprop-1-en-1-yl)benzoic acid (1f). Yield 87%, white powder. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.63 (d, $J$ = 15.5 Hz, 1H), 7.99 (dd, $J$ = 8.0, 1.1 Hz, 1H), 7.58-7.56 (m, 1H), 7.49-7.46 (m, 1H), 7.40-7.37 (m, 1H), 6.71 (d, $J$ = 15.5 Hz, 1H), 3.54-3.51 (m, 4H), 1.28-1.23 (m, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 169.3, 166.8, 143.1, 137.1, 131.9, 131.2, 131.2, 129.0, 127.6, 119.6, 42.8, 41.6, 15.0, 13.2 ppm. IR (neat, cm$^{-1}$) 2976, 2932, 1710, 1640, 1571, 1486, 1449, 1246, 1139, 1074, 966, 756. HRMS (ESI) calcd for C$_{14}$H$_{18}$O$_3$N(M+H$^+$) 248.12812, found: 248.12812

(E)-2-(3-(diallylamino)-3-oxoprop-1-en-1-yl)benzoic acid (1g). Yield 84%, after recrystallisation from ethyl acetate white needles. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.62 (d, $J$ = 15.6 Hz, 1H), 8.00 (dd, $J$ = 7.8, 1.4 Hz, 1H) 7.54-7.52 (m, 1H), 7.48 (td, $J$ = 7.4, 1.1 Hz, 1H), 7.41-7.37 (m, 1H), 6.65 (d, $J$ = 15.6 Hz, 1H), 5.91-5.81 (m, 2H), 5.29-5.18 (m, 4H), 4.15 (d, $J$ = 6.0 Hz, 2H), 4.05-4.04 (m, 2H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 169.5, 167.6, 143.4, 137.0, 133.1, 132.9, 132.1, 130.9, 129.1, 127.6, 119.8, 118.1, 117.3, 49.4, 49.2 ppm HRMS (ESI) calcd for C$_{16}$H$_{18}$O$_3$N(M+H$^+$) 272.128120, found: 272.12833

3. Electrochemical lactonisation reaction

**General procedure for electrochemical lactonisation reaction**

Standard electrolysis procedure: A pre-cooled to 10°C 10mL undivided electrochemical cell, equipped with two platinum electrodes (2 cm$^2$ – separated from each other by 5 mm) was charged with a solution of 2-(2-carboxyvinyl)-benzoic acid derivative 1 (0.4mmol) in 10 mL of methanol and with an aliphatic carboxylic co-acid (2.0 mmol, 5 equivalents). Then, MeONa (0.12 mmol, 0.3 equivalent, 40 µL of 3M solution in MeOH) was added and the solution was electrolyzed at a constant current of 200 mA. The mixture was vigorously stirred and electrolysed until full consumption of starting material 1 as shown by TLC. Typically, 30-40 minutes (9.3-12.3 F/mol) was required for complete transformation. The solvent was then removed under reduced pressure and the residue was dissolved in DCM, washed with water, in the case of acetic acid, or with 10% K$_2$CO$_3$ for higher aliphatic acids. The organic solution was then dried with Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The diastereoisomeric ratio was determined directly from the crude mixture by $^1$H NMR analysis. The mixture was then purified over silica gel using column chromatography along with a petroleum ether/ethyl acetate mixture as the eluent in order to yield the pure lactones 2.
2a. Following the general procedure from 1a and acetic acid, yield 58\%, dr = 1:1 $R_f = 0.13$ (petroleum ether/EtOAc 9:1), colourless oil. $^1$H NMR (500 MHz, CDCl$_3$)$\delta = 7.88$ (d, $J = 7.4$ Hz, 1H), 7.55-7.51 (m, 1H), 7.67-7.63 (m, 1H), 7.48 (d, $J = 7.4$Hz, 0.52H), 7.45 (d, $J = 8.0$ Hz, 0.57H), 5.78-5.75 (m, 1H), 3.09 (qd, $J = 7.1$, 4.6 Hz, 0.49H), 2.83-2.78 (m, 0.56H), 1.44 (s, 4.73H), 1.37 (s, 4.27H), 1.13 (d, $J = 6.9$Hz, 1.59H), 1.06 (d, $J = 6.9$Hz, 1.41H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$)$\delta = 171.8$, 171.3, 170.3, 170.4, 148.3, 147.6, 134.3, 134.1, 129.5, 129.4, 127.0, 126.5, 125.8, 125.7, 122.9, 122.3, 81.8, 81.7, 81.5, 81.4, 44.8, 43.8, 28.1, 28.0, 12.0, 11.6 ppm. IR (neat, cm$^{-1}$)1765, 1726, 1154, 138. HRMS (ESI)calcd for C$_{15}$H$_{19}$O$_4$ (M+H$^+$) 263.12779, found: 263.12775

Gram scale synthesis of 2a: A pre-cooled to 10°C 50mL undivided electrochemical cell, equipped with two platinum electrodes (2 cm$^2$ – separated from each other by 5 mm) was charged with a solution of $(E)$-2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)benzoic acid (1a) (8.0 mmol, 1.99g) and acetic acid (40 mmol, 2.4 g, 2.3 mL) in 46 mL of methanol. Then, MeONa (2.4 mmol, 0.3 equivalent, 0.8 mL of 3M solution in MeOH) was added and the mixture was vigorously stirred while being electrolyzed at a 200 mA constant current during 10 hours (9.3 F/mol of substrate). The solvent was removed under reduced pressure and the residue was dissolved in DCM. The solution was then washed with water, dried with Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product was purified over silica gel using column chromatography along with a petroleum ether/ethyl acetate 9:1 mixture as the eluent to afford 1.09g of pure 2a as colorless oil with a yield of 52%.
2b. Following the general procedure from 1a and propionic acid, yield 45%, dr = 1:1, Rf = 0.15, 0.20 (petroleum ether/EtOAc 9:1), colourless oil. ^1H NMR (500 MHz, CDCl_3) δ = 7.87 (d, J = 7.4 Hz, 1H), 7.66-7.62 (m, 1H), 7.53-7.44 (m, 2H), 5.63-5.61 (m, 1H), 2.78 (dt, J = 9.7, 4.9 Hz, 0.46H), 2.53-1.49 (m, 0.53H), 1.92-1.62 (m, 2H), 1.43 (s, 4.72H), 1.25 (s, 4.08H), 0.98 (t, J = 7.4 Hz) and 0.98 (t, J = 7.4 Hz, 3H) ppm. ^13C NMR (125 MHz, CDCl_3) δ = 171.6, 170.6, 170.3, 170.2, 148.6, 147.8, 134.2, 133.9, 129.5, 129.4, 126.9, 126.2, 125.8, 125.6, 122.9, 122.8, 81.9, 81.5, 80.8, 80.6, 52.7, 51.7, 28.1, 27.8, 22.5, 21.3, 12.0, 11.4 ppm. IR (neat, cm⁻¹) 1765, 1723, 1153, 1157. HRMS (ESI) calcd for C_{16}H_{21}O_4(M+H⁺) 277.14344, found: 277.14341

2c. Following the general procedure from 1a and isovaleric acid, yield 46%, dr = 1:1, Rf = 0.13, 0.18 (petroleum ether/EtOAc 20:1), white solid. ^1H NMR (500 MHz, CDCl_3) δ = 7.90-7.88 (m, 1H), 7.67-7.63 (m, 1H), 7.55-7.44 (m, 2H), 5.60-5.58 (m, 1H), 2.98-2.94 (m, 0.48H), 2.70 (ddd, J = 10.9, 7.2, 3.7 Hz, 0.52H), 1.85 (ddd, J = 13.5, 10.6, 4.6 Hz, 0.55H), 1.75-1.59 (m, 2), 1.47-1.42 (m) and 1.42 (s) (5H), 1.35-1.28 (m, 1H), 1.25 (s, 4.28H), 0.91 (d, J = 6.9 Hz) and 0.86 (d, J = 6.3 Hz) (6H) ppm. ^13C NMR (125 MHz, CDCl_3) δ = 171.7, 170.8, 170.3, 170.2, 148.3, 147.7, 134.1, 133.9, 129.6, 129.5, 127.0, 126.4, 125.9, 125.7, 123.0, 122.7, 81.9, 81.6, 81.5, 81.0, 49.3, 48.2, 38.0, 36.8, 28.1, 27.8, 26.1, 23.6, 23.2, 21.9, 21.4 ppm. IR (neat, cm⁻¹) 1769, 1726, 1153. HRMS (ESI) calcd for C_{18}H_{20}NaO_4(M+Na⁺) 327.15668, found: 327.15656

2d. Following the general procedure from 1a and 3,3-dimethylbutyric acid, yield 31%, dr = 1:1, Rf = 0.13 (petroleum ether/EtOAc 20:1), white solid. ^1H NMR (500 MHz, CDCl_3) δ = 7.90 (d, J = 6.46Hz) and 7.88 (d, J = 4.6 Hz) (1H), 7.67-7.64 (m, 1H), 7.55-7.47 (m, 2H), 5.58 (d, J = 5.7Hz, 0.52H), 5.56 (d, J = 4.6 Hz, 0.47H), 3.00 (ddd, J = 10.0, 4.3, 1.7 Hz, 0.48H), 2.82 (ddd, J = 9.6, 5.6, 1.4 Hz, 0.51H), 1.96 (dd, J = 14.3, 9.7 Hz, 0.52H), 1.85 (dd, J = 14.3, 10.3 Hz, 0.49H), 1.39 (s, 4.53H), 1.26 (s, 4.52H), 0.89 (s, 4.45H), 0.85 (s, 4.59H) ppm. ^13C NMR (125 MHz, CDCl_3) δ = 171.9, 171.3, 170.2, 170.1, 147.8, 147.3, 133.9, 133.8, 129.6, 129.5, 127.1, 126.8, 125.8, 125.6, 123.1, 122.8, 82.4, 81.9, 81.8, 81.4, 47.2, 46.5, 40.7, 40.4, 30.7, 29.5, 29.4, 28.0, 27.7 ppm. IR (neat, cm⁻¹) 2955, 1766, 1727, 1467, 1367, 1286, 1146, 1061, 742. HRMS (ESI) calcd for C_{18}H_{20}NaO_4(M+Na⁺) 319.19039, found: 319.19057

2m. Following the general procedure from 1a and mono-methyl-hydrogen succinate, yield 55%, dr = 1:1, Rf = 0.15, 0.22 (petroleum ether/EtOAc 4:1), colourless oil, after column chromatography dr = 2.0:1 ^1H NMR (500 MHz, CDCl_3) δ = 7.90-7.88 (m, 1H), 7.68-7.64 (m, 1H), 7.55-7.46 (m, 2H), 5.70 (d, J = 6.3Hz) and 5.65 (d, J = 4.6 Hz) (1H), 3.66 (s) and 3.64 (s) (3H), 3.02-2.99 (m, 0.35H), 2.77 (ddd, J = 10.0, 6.6, 4.0 Hz, 0.64H), 2.52-2.27 (m, 2H), 2.10-1.87 (m, 2H), 1.44 (s, 5.84H), 1.24 (s, 3.11H) ppm. ^13C NMR (125 MHz, CDCl_3) δ = 173.4, 173.2, 173.1, 170.8, 170.1, 170.0, 169.8, 148.0, 147.5, 134.3, 134.1, 129.7, 129.6, 126.8, 126.3, 125.9, 125.8, 122.8, 122.6, 82.4, 82.0, 81.0, 80.6, 51.9, 51.8, 49.5, 48.8, 31.6, 31.4, 28.1, 27.8, 23.2, 23.1 ppm. IR (neat, cm⁻¹)
1) 2978, 1768, 1730, 1368, 1149, 1060, 742. **HRMS (ESI)** calcd for C_{18}H_{23}O_{6} (M+H^+) 335.14891, found: 335.14898

2n. Following the general procedure from 1a and 3-chloropropionic acid, yield 42%, dr = 1:1, R_f = 0.12 (petroleum ether/EtOAc 9:1), white solid. **^1H NMR (400 MHz, CDCl_3)** \( \delta = 7.92-7.88 \text{ (m, 1H)}, 7.72-7.65 \text{ (m, 1H)}, 7.58-7.47 \text{ (m, 2H)}, 5.83 \text{ (d, } J = 5.0 \text{ Hz, 0.48H)}, 5.68 \text{ (d, } J = 3.7 \text{ Hz, 0.52H)}, 3.74-3.56 \text{ (m, 2H)}, 3.34-3.28 \text{ (m, 0.5H)}, 3.07-3.03 \text{ (m, 0.5H)}, 2.31-2.22 \text{ (m, 1H)}, 2.04-1.95 \text{ (m, 0.5H)}, 1.76-1.68 \text{ (m, 0.5H)}, 1.48 \text{ (s, 3.5H)}, 1.44 \text{ (s, 1.1H)}, 1.22 \text{ (s, 4.5H) ppm. **^13C NMR (100 MHz, CDCl_3)** \( \delta = 170.2, 169.7, 169.1, 168.1, 147.5, 147.3, 134.0, 129.7, 129.5, 126.6, 126.3, 125.8, 125.6, 122.6, 122.3, 82.5, 81.9, 80.8, 80.0, 47.0, 46.5, 42.6, 42.4, 30.6, 29.6, 28.0, 27.6 ppm.**}

HRMS (ESI) calcd for C_{18}H_{23}O_{6} (M+H^+) 335.14891, found: 335.14898

2e. Following the general procedure from 1a and acetic acid, yield 65%, dr = 1:1, R_f = 0.13 (petroleum ether/EtOAc 9:1), colourless oil. **^1H NMR (500 MHz, CDCl_3)** \( \delta = 7.91-7.89 \text{ (m, 1H)}, 7.72-7.64 \text{ (m, 1H)}, 7.56-7.53 \text{ (m, 1H)}, 7.48-7.42 \text{ (m, 1H)}, 5.66-5.64 \text{ (m, 1H)}, 4.25-4.17 \text{ (m, 2H)}, 3.17-3.16 \text{ (m, 0.5H)}, 3.92-3.87 \text{ (m, 0.5H)}, 1.28 \text{ (td, } J = 7.2, 1.1 \text{ Hz, 1.5H)}, 1.25-1.22 \text{ (m, 1.5H)}, 1.15-1.14 \text{ (m, 1.5H)}, 1.06 \text{ (d, } J = 8.0 \text{ Hz, 1.5H) ppm. **^13C NMR (125 MHz, CDCl_3)** \( \delta = 172.6, 172.4, 170.2, 148.1, 134.4, 134.1, 129.6, 129.6, 126.5, 126.0, 125.9, 123.0, 122.2, 81.2, 80.9, 61.4, 61.3, 44.1, 43.0, 14.3, 14.2, 11.6, 11.1 \text{ ppm. **IR (neat, cm}^{-1}\text{)** 1763, 1730, 1466, 1190, 1039, 743. HRMS (ESI) calcd for C_{12}H_{12}O_{4} (M+H^+) 235.09649, found: 235.09645


2f. Following the general procedure from 1b and acetic acid, yield 55%, dr = 1:1, R_f = 0.16 (petroleum ether/EtOAc 9:1), colourless oil. **^1H NMR (500 MHz, CDCl_3)** \( \delta = 7.91-7.89 \text{ (m, 1H)}, 7.62-7.64 \text{ (m, 1H)}, 7.56-7.53 \text{ (m, 1H)}, 7.48-7.42 \text{ (m, 1H)}, 5.86-5.84 \text{ (m, 1H)}, 4.25-4.17 \text{ (m, 2H)}, 3.21-3.16 \text{ (m, 0.5H)}, 3.92-3.87 \text{ (m, 0.5H)}, 1.28 \text{ (td, } J = 7.3, 1.7 \text{ Hz, 1H)}, 1.25-1.22 \text{ (m, 1.5H)}, 1.15-1.14 \text{ (m, 1.5H)}, 1.06 \text{ (d, } J = 8.0 \text{ Hz, 1.5H) ppm. **^13C NMR (125 MHz, CDCl_3)** \( \delta = 172.6, 172.4, 170.2, 148.1, 134.4, 134.1, 129.6, 129.6, 126.5, 126.0, 125.9, 123.0, 122.2, 81.2, 80.9, 61.4, 61.3, 44.1, 43.0, 14.3, 14.2, 11.6, 11.1 \text{ ppm. **IR (neat, cm}^{-1}\text{)** 1763, 1730, 1466, 1190, 1039, 743. HRMS (ESI) calcd for C_{12}H_{12}O_{4} (M+H^+) 235.09649, found: 235.09645


2g. Following the general procedure from 1b and propionic acid, yield 52%, dr = 1:1, R_f = 0.19 (petroleum ether/EtOAc 9:1), colourless oil. **^1H NMR (500 MHz, CDCl_3)** \( \delta = 7.90 \text{ (d, } J = 7.4 \text{ Hz, 1H), 7.66-7.61 \text{ (m, 1H)}, 7.53-7.49 \text{ (m, 1.5H)}, 7.37 \text{ (d, } J = 6.9 \text{ Hz, 0.5H)}, 5.68-5.65 \text{ (m, 1H)}, 4.21 \text{ (qd, } J = 7.3, 1.7 \text{ Hz, 1H)}, 4.07 \text{ (q, } J = 6.9 \text{ Hz, 1H)}, 2.87-2.84 \text{ (m, 0.5H)}, 2.59 \text{ (ddd, } J = 9.2, 8.0, 4.0 \text{ Hz, 0.5H)}, 1.95-1.85 \text{ (m, 0.5H)}, 1.83-1.75 \text{ (m, 0.5H)}, 1.73-1.59 \text{ (m, 1H)}, 1.25 \text{ (t, } J = 7.2 \text{ Hz, 1.6H)}, 1.11 \text{ (t, } J = 6.9 \text{ Hz, 1.4H)}, 0.97-0.93 \text{ (m, 3H) ppm. **^13C NMR (125 MHz, CDCl_3)** \( \delta = 172.3, 171.7, 170.1, 148.3, 147.4, 134.3, 134.0, 129.6, 126.8, 126.1, 125.9, 125.8, 123.0, 122.5, 80.6, 80.4, 61.1, 61.0, 52.0, 50.8, 22.2, 20.9, 14.3, 14.1, 12.0, 11.5 \text{ ppm. **IR (neat, cm}^{-1}\text{)** 1765, 1728, 1215, 908, 752. HRMS (ESI) calcd for C_{14}H_{17}O_{4} (M+H^+) 249.11214, found: 249.11200

2h. Following the general procedure from 1c and acetic acid, yield 42%, dr = 1:1, Rf = 0.10 (petroleum ether/EtOAc 9:1), colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.90$ (d, $J =$8.0 Hz, 1H), 7.69-7.64 (m, 1H), 7.54-7.51 (m, 1H), 7.47-7.42 (m, 1H), 5.81 (d, $J =$5.2Hz, 0.5H), 5.79 (d, $J =$4.6Hz, 0.5H), 5.10-5.04 (m, 0.5H, 5.03-4.97 (m, 0.5H), 3.13 (qd, $J =$7.3, 4.6 Hz, 0.5H), 2.85 (qd, $J =$7.2, 5.4 Hz, 0.5H), 1.25 (d, $J =$6.3 Hz, 1.5H), 1.21 (d, $J =$6.3Hz, 1.5H), 1.18 (d, $J =$5.7Hz, 1.5H), 1.15 (d, $J =$6.3Hz, 1.5H), 1.13 (d, $J =$6.9Hz, 1.5H), 1.06 (d, $J =$7.4Hz, 1.5H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 172.1$, 171.7, 170.3, 170.2, 148.1, 147.3, 134.3, 134.1, 129.6, 129.5, 126.9, 126.5, 125.9, 125.8, 123.0, 122.2, 81.3, 81.1, 68.9, 68.8, 44.1, 43.2, 21.8, 21.7, 11.7, 11.4 ppm. IR (neat, cm$^{-1}$)2982, 1766, 1728, 1466, 1287, 1213, 1107, 744. HRMS (ESI)calcd for C$_{14}$H$_{17}$O$_4$ (M+H$^+$) 249.11214, found: 249.11204

2i. Following the general procedure from 1d and acetic acid, yield 54%, dr = 1:1, Rf = 0.12 (petroleum ether/EtOAc 9:1), colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.88$ (d, $J =$7.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.54-7.51 (m, 1H), 7.47-7.42 (m, 1H), 5.81 (d, $J =$5.2Hz, 0.5H), 5.79 (d, $J =$4.6Hz, 0.5H), 5.10-5.04 (m, 0.5H, 5.03-4.97 (m, 0.5H), 3.13 (qd, $J =$7.3, 4.6 Hz, 0.5H), 2.85 (qd, $J =$7.2, 5.4 Hz, 0.5H), 1.25 (d, $J =$6.3 Hz, 1.5H), 1.21 (d, $J =$6.3Hz, 1.5H), 1.18 (d, $J =$5.7Hz, 1.5H), 1.15 (d, $J =$6.3Hz, 1.5H), 1.13 (d, $J =$6.9Hz, 1.5H), 1.06 (d, $J =$7.4Hz, 1.5H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 172.1$, 171.7, 170.3, 170.2, 148.1, 147.3, 134.3, 134.1, 129.6, 129.5, 126.9, 126.5, 125.9, 125.8, 123.0, 122.2, 81.3, 81.1, 68.9, 68.8, 44.1, 43.2, 21.8, 21.7, 11.7, 11.4 ppm. IR (neat, cm$^{-1}$)2982, 1766, 1728, 1466, 1287, 1213, 1107, 744. HRMS (ESI)calcd for C$_{14}$H$_{17}$O$_4$ (M+H$^+$) 249.11214, found: 249.11207

2j. Following the general procedure from 1e and acetic acid, yield 43%, dr = 1:1, Rf = 0.11 (petroleum ether/EtOAc 9:1), colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.90$ (d, $J =$6.9 Hz, 1H), 7.69-7.63 (m, 1H), 7.56-7.52 (m, 1H), 7.47-7.41 (m, 1H), 5.95-5.83 (m, 2H), 5.36-5.23 (m, 2H), 4.67 (d, $J =$5.7Hz, 1H), 4.63 (dt, $J =$5.7, 1.4 Hz, 1H), 3.22 (qd, $J =$7.2, 4.9 Hz, 0.5H), 2.94 (qd, $J =$7.1, 5.2Hz, 0.5H), 1.14 (d, $J =$6.9Hz, 1.5H), 1.06 (d, $J =$7.4Hz, 1.5H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 172.2$, 172.0, 170.1, 147.9, 147.0, 134.4, 134.2, 131.7, 131.6, 131.0, 119.1, 81.1, 80.8, 66.0, 65.9, 44.0, 43.0 ppm. IR (neat, cm$^{-1}$)1766, 1735, 1466, 1287, 1190, 1041, 744. HRMS (ESI)calcd for C$_{14}$H$_{15}$O$_4$ (M+H$^+$) 247.09649, found: 247.09639
Following the general procedure from 1f and acetic acid, yield 33%, dr = 1:1, R<sub>f</sub> = 0.18, 0.28 (petroleum ether/EtOAc 2:1), after column chromatography dr = 2.33:1, colourless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.88 (d, <i>J</i> = 7.4Hz) and 7.85 (d, <i>J</i> = 8.0Hz) (1H), 7.43-7.41 (m, 0.7H), 5.73 (d, <i>J</i> = 6.3Hz, 0.3H), 5.68 (d, <i>J</i> = 9.7Hz, 0.7H), 3.51-3.43 (m, 1H), 3.41-3.28 (m, 1.8H), 3.20-3.12 (m, 0.7H), 2.64 (dq, <i>J</i> = 9.7, 6.7Hz, 0.7H), 1.51 (d, <i>J</i> = 6.9Hz, 2H), 1.19-1.10 (m, 5H), ppm. 1<sup>3</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.3, 172.1, 170.5, 170.2, 149.0, 147.9, 134.1, 133.9, 129.5, 129.4, 126.9, 125.8, 125.7, 125.7, 124.6, 123.6, 83.3, 82.5, 42.8, 42.4, 42.1, 40.7, 40.6, 16.7, 14.9, 14.7, 13.2 ppm. IR (neat, cm<sup>-1</sup>) 1763, 1630, 1465, 1285, 1215, 1061, 993, 757, 689. HRMS (ESI) calcd for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>N(M+H<sup>+</sup>) 262.14377, found: 262.14387

Following the general procedure from 1f and propionic acid, yield 40%, dr = 1:1, <i>R_f</i> = 0.22, 0.29 (petroleum ether/EtOAc 2:1), after column chromatography dr = 1.43:1, colourless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.89 (d, <i>J</i> = 7.4Hz) and 7.86 (d, <i>J</i> = 8.0Hz) (1H), 7.22-7.21 (m, 0.6H), 7.68-7.64 (m, 0.6H), 7.59-7.48 (m, 1.6H), 7.40-7.39 (m, 0.4H), 5.66 (d, <i>J</i> = 9.2Hz, 0.4H), 5.62 (d, <i>J</i> = 9.6Hz, 0.6H), 3.66-3.53 (m, 1H), 3.40-3.30 (m, 2H), 3.26-3.18 (m, 1H), 1.21-1.14 (m, 5H), 0.99 (t, <i>J</i> = 7.4Hz, 1.2H), 0.86 (t, <i>J</i> = 7.4Hz, 1.8H), 0.70 (t, <i>J</i> = 7.2Hz, 1.2H) ppm. 1<sup>3</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 171.3, 171.0, 170.5, 170.1, 148.8, 147.9, 133.9, 133.8, 129.5, 129.4, 126.8, 125.8, 125.7, 124.4, 123.7, 82.6, 82.3, 48.9, 47.1, 42.5, 42.1, 41.1, 40.7, 24.9, 21.3, 14.9, 14.4, 13.2, 13.1, 11.5, 11.2 ppm. IR (neat, cm<sup>-1</sup>) 1765, 1632, 1465, 1288, 1068. HRMS (ESI) calcd for C<sub>16</sub>H<sub>22</sub>O<sub>3</sub>N(M+H<sup>+</sup>) 276.15943, found: 276.15961

Scheme S3

Double cyclization experiment. Following the general procedure from 1g (0.40 mmol, 108.5 mg) and acetic acid (5eq.) after workup 113.0 mg of complex mixture of compounds was obtained. The mixture was analysed by <sup>1</sup>H NMR (Fig S-1), TLC and HPLC (Fig S-2) and subsequently subjected to preparative HPLC. Three major fractions were isolated and analysed by NMR and HRMS. The complexity of the crude mixture due to the presence of several diastereoisomers makes the identification and assignation of each NMR signals a complex task and that even in the enriched
fractions. Nevertheless, we are confident in the formation of the product 8a (as a mixture of diastereoisomers) due to:

1) The presence of appropriate high resolution mass spectrum m/z ratios that correspond to 8a as well as 8b
2) The presence of multiplets at 0.79 and 1.17 ppm that can be assigned to Me group of 8b (it matches very well the signals for a similar Me group in 2k)
3) The presence of a characteristic highly shielded triplet at 0.63 ppm (3H) that corresponds to the aliphatic ethyl fragment of 8a as well as a doublet at 6.10 ppm (1H) that could be assigned to the benzylic proton of 8a.
Fig S-1. $^1$H NMR spectrum of the crude mixture from double cyclization experiment.
Fig S-2. HPLC analysis of the crude mixture from double cyclization experiment.
Produit de départ :

Chemical Formula: C_{21}H_{13}NO_{3}
Exact Mass: 271.12084
Molecular Weight: 271.31600

Produit d’arrivée :

Chemical Formula: C_{21}H_{13}NO_{3}
Exact Mass: 285.13649
Molecular Weight: 285.34300

Présents également toute une série d’intermédiaires de réaction...

3 fractions contenant chaque fois entre 2 et 4 composés : pré-séparation réalisée en HPLC semi-préparative.