Supporting Information

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One-Pot Synthesis of Diverse γ-Lactam Scaffolds Facilitated by a Nebulizer-Based Continuous Flow Photoreactor

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Part A: Reactor Set-up

Figure 1. Schematic representation of NebPhotOX continuous flow reactor set-up. The vertical pyrex cylinder dimensions are 33 cm length and 6.7 cm diameter.

Figure 2. NebPhotOX in action.
SAFETY PRECAUTIONS: Measures were taken to eliminate all possible ignition sources from the fumehood area (sparks or flames, e.g. the electricity transformer for the LEDs was kept outside of the fumehood) in which the NebPhotOX system was operated. This included operating the reactor at room temperature and pressure without any significant heat input from the low power LEDs used. In addition, the fumehood was always adequately ventilated with a high air flow. System operating conditions prevented oxygen stagnation in the system. Additional precautions included that the operator wears safety glasses with side shields and flame resistant safety clothing. When the procedure was performed on a larger scale, the two cooled collection flasks placed in series were prefilled with an excess of Me₂S in MeOH (3 equiv in the first flask and 1 equiv in the second flask) for the fast reduction of the initially formed hydroperoxides of types I and II (Scheme 1). Even higher excesses of the reducing agent can be used.
Part B: Experimental procedures

Known compounds. The following compounds were prepared as previously reported: 1a, 1c, 1d. Compound 1b is commercially available.

General experimental procedure for the preparation of compounds 3a, 3b and 4c

2-Substituted furans 1 (2.5 mmol, 380 mg in case of 1a, or 221 µL in case of 1b, or 315 mg in case of 1c) and rose Bengal (0.5 mol%, 12.7 mg) were dissolved in MeOH (total volume 5 mL, 0.5 M). The resulting solutions were transferred to the nebulizer via a liquid pump (flow rate set at 0.5 mL min⁻¹) and timing was initiated for calculation of the exact flow rate. The solutions were dispersed by the nebulizer into the reaction cylinder which was placed in a horizontal or a vertical position using oxygen or air as the nebulizing gas (50 psi back pressure). The cylinder was irradiated by LEDs (natural white light 3800–4200 K, 10 W m⁻¹, 1050 Lm m⁻¹). When all the solution had been dispersed, the timing was stopped for the calculation of the exact flow rate and the three-way valve on the uptake line was switched to pure MeOH (2 mL) to flush out the system. The crude solutions were collected in the two cooled spherical flasks placed in series. A small sample of the crude solution was concentrated in vacuo for the measurement of the conversions by ¹H NMR. Then, the solutions from the two flasks were placed into one flask and Me₂S (730 µL, 10 mmol) was added. The solution was stirred for 1 h at rt. When the reductions were completed, as indicated by tlc analysis, the appropriate amine (2.5 mmol, 278 mg of histamine, or 400 mg of tryptamine, or 273 µL of BnNH₂) was added and the solution was stirred for 1 h at rt. After the formation of the corresponding 2-pyrrolidinones of type 2, MeOH was replaced either by HCOOH (2 mL, towards 3a) or CH₂Cl₂ (6 mL, towards 3b and 4c). For the formation of 3b, TFA (1.25 mmol, 96 µL) was added, while for the formation of 4c, p-TsOH (1.25 mmol, 238 mg) was added. After completion of the reactions (15 h for 3a, or 3 h for 3b, or 1 h for 4c) the solutions were concentrated in vacuo and the products were purified by flash column chromatography (silica gel, petroleum ether : EtOAc or acetone : EtOAc).

1 G. I. Ioannou, D. Kalaitzakis, G. Vassilikogiannakis, Eur. J. Org. Chem. 2016, 3304.
2 D. Kalaitzakis, E. Antonatou, G. Vassilikogiannakis, Chem. Commun. 2014, 50, 400.
3 D. Noutsias, I. Alexopoulos, T. Montagnon, G. Vassilikogiannakis, Green Chem. 2012, 14, 601.
Glochidine (3a)\(^1\)

The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1a. Nebulization of the 5 mL reaction solution took 8.62 min (actual flow rate = 0.58 mL min\(^{-1}\)) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). When the reaction cylinder was in the vertical position and air was used as the nebulizing gas, the reaction solution was nebulized within 7.68 min (actual flow rate = 0.65 mL min\(^{-1}\)) and the conversion was 95%. Starting the reaction sequence with the cylinder placed in the horizontal position, the product 3a was isolated in 58% yield (379 mg) after purification by flash column chromatography (silica gel, EtOAc → acetone : EtOAc, 1:1).

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.49\) (s, 1H), 6.80 (s, 1H), 4.33 (ddd, \(J_1=13.5\) Hz, \(J_2=6.5\) Hz, \(J_3=1.7\) Hz, 1H), 3.09 (ddd, \(J_1=13.3\) Hz, \(J_2=11.2\) Hz, \(J_3=5.8\) Hz, 1H), 2.92–2.82 (m, 2H), 2.65–2.48 (m, 3H), 2.42 (m, 1H), 1.95 (m, 2H), 1.32–1.25 (m, 8H), 0.86 (t, \(J=6.9\) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 173.4, 132.2, 124.9, 124.7, 78.4, 41.4, 33.4, 31.4\) (2C), 29.8, 28.8, 23.6, 22.4, 20.1, 13.9 ppm.

11b-Methyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (3b)\(^4\)

The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1b. Nebulization of the 5 mL reaction solution took 8.48 min (actual flow rate = 0.59 mL min\(^{-1}\)) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). The product 3b was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 1:1). Yield 50% (300 mg).

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.34\) (brs, 1H), 7.47 (d, \(J=7.8\) Hz, 1H), 7.34 (d, \(J=8.1\) Hz, 1H), 7.17 (t, \(J=7.5\) Hz, 1H), 7.11 (t, \(J=7.4\) Hz, 1H), 4.46 (dd, \(J_1=13.1\) Hz, \(J_2=5.1\) Hz, 1H), 3.09 (m, 1H), 2.82 (m, 2H), 2.67 (m, 1H), 2.46 (ddd, \(J_1=16.8\) Hz, \(J_2=9.6\) Hz, \(J_3=1.9\) Hz, 1H), 2.29 (m, 1H), 2.17 (m, 1H) 1.59 (s, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 172.8, 137.6, 136.0, 126.7, 122.2, 119.8, 118.5, 111.0, 106.9, 59.5, 34.9, 32.8, 30.7, 25.4, 21.1\) ppm.

\(^4\) a) D. Kalaitzakis, T. Montagnon, G. I. Ioannou, E. Antonatou, G. Vassilikogiannakis, ARCIVOC 2015. (iii), 154; b) D. Kalaitzakis, T. Montagnon, E. Antonatou, N. Bardaji, G. Vassilikogiannakis, Chem. Eur. J. 2013, 19, 10119.
6-Benzyl-1-oxa-6-azaspiro[4.4]nonan-7-one (4c)

The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1c. Nebulization of the 5 mL reaction solution took 9.09 min (actual flow rate = 0.55 mL min\(^{-1}\)) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 85%). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas, the reaction solution was nebulized within 7.34 min (actual flow rate = 0.68 mL min\(^{-1}\)) and the conversion was 92%. When the reaction cylinder was in the vertical position and air was used as the nebulizing gas, the reaction solution was nebulized within 7.68 min (actual flow rate = 0.65 mL min\(^{-1}\)) and the conversion was 90%. The product 4c was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 1:1). When the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas the yield was 56% (324 mg). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas the yield was 63% (364 mg).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.27\) (m, 5H), 4.73 (d, \(J=16.0\) Hz, 1H), 4.16 (d, \(J=16.0\) Hz, 1H), 3.92 (m, 1H), 3.77 (m, 1H), 2.62 (quin, \(J=8.7\) Hz, 1H), 2.43 (ddd, \(J_1=17.1\) Hz, \(J_2=9.3\) Hz, \(J_3=3.6\) Hz, 1H), 2.20 (ddd, \(J_1=13.0\) Hz, \(J_2=9.3\) Hz, \(J_3=3.7\) Hz, 1H), 2.07 (m, 1H), 2.02–1.88 (m, 3H), 1.78 (m, 1H) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 175.3, 138.3, 128.2\) (2C), 126.8 (3C), 100.6, 67.6, 42.5, 34.3, 33.7, 29.0, 25.4 ppm.

**General experimental procedure for the preparation of pyrrolidinones 5**

2-Hexylfuran 1 (2.5 mmol, 380 mg) and rose Bengal (0.5 mol%, 12.7 mg) were dissolved in MeOH (total volume 5 mL, 0.5 M). The resulting solution was transferred to the nebulizer via a liquid pump (flow rate set at 0.5 mL min\(^{-1}\)) and timing was initiated for calculation of the exact flow rate. The solution was dispersed by the nebulizer into the reaction cylinder which was placed in a horizontal or a vertical position using oxygen or air as the nebulizing gas (50 psi back pressure). The cylinder was irradiated by the LEDs (natural white light 3800–4200 K, 10 W m\(^{-1}\), 1050 Lm m\(^{-1}\))\(^1\). When all the solution had been dispersed, the exact flow rate was calculated and the three-way valve on the uptake line was switched to pure MeOH (2 mL) to flush out the system. The crude solution was collected in the two cooled spherical flasks placed in series. A small sample of the crude solution was concentrated in vacuo for the measurement of the conversions by \(^1\)H NMR. Then, the solutions from the two flasks were placed in one flask and Me\(_2\)S (730 μL, 10 mmol) was added. The solution

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\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.27\) (m, 5H), 4.73 (d, \(J=16.0\) Hz, 1H), 4.16 (d, \(J=16.0\) Hz, 1H), 3.92 (m, 1H), 3.77 (m, 1H), 2.62 (quin, \(J=8.7\) Hz, 1H), 2.43 (ddd, \(J_1=17.1\) Hz, \(J_2=9.3\) Hz, \(J_3=3.6\) Hz, 1H), 2.20 (ddd, \(J_1=13.0\) Hz, \(J_2=9.3\) Hz, \(J_3=3.7\) Hz, 1H), 2.07 (m, 1H), 2.02–1.88 (m, 3H), 1.78 (m, 1H) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 175.3, 138.3, 128.2\) (2C), 126.8 (3C), 100.6, 67.6, 42.5, 34.3, 33.7, 29.0, 25.4 ppm.

2-Hexylfuran 1 (2.5 mmol, 380 mg) and rose Bengal (0.5 mol%, 12.7 mg) were dissolved in MeOH (total volume 5 mL, 0.5 M). The resulting solution was transferred to the nebulizer via a liquid pump (flow rate set at 0.5 mL min\(^{-1}\)) and timing was initiated for calculation of the exact flow rate. The solution was dispersed by the nebulizer into the reaction cylinder which was placed in a horizontal or a vertical position using oxygen or air as the nebulizing gas (50 psi back pressure). The cylinder was irradiated by the LEDs (natural white light 3800–4200 K, 10 W m\(^{-1}\), 1050 Lm m\(^{-1}\))\(^1\). When all the solution had been dispersed, the exact flow rate was calculated and the three-way valve on the uptake line was switched to pure MeOH (2 mL) to flush out the system. The crude solution was collected in the two cooled spherical flasks placed in series. A small sample of the crude solution was concentrated in vacuo for the measurement of the conversions by \(^1\)H NMR. Then, the solutions from the two flasks were placed in one flask and Me\(_2\)S (730 μL, 10 mmol) was added. The solution
was stirred for 1 h at rt. When the reduction was completed, as indicated by tlc analysis, the appropriate amine (2.5 mmol, 273 µL of BnNH₂, or 1.25 mL, 2.0 M solution of NH₃ in MeOH, or 216 µL of 40% w/w aqueous solution of MeNH₂) was added and the mixture was stirred for 1 h at the same temperature. After the formation of the intermediate 2-pyrrolidinone 2a, MeOH was replaced with CH₂Cl₂ (6 mL) and the appropriate nucleophile (2.5 mmol, 293 mg of indole, or 173 µL of pyrrole, or 5.0 mmol, 443 µL of 2-methylfuran) was added followed by p-TsOH (238 mg, 1.25 mmol). The reaction was stirred for 1 h at rt. After completion of the reaction, as indicated by tlc analysis, a saturated aqueous solution of NaHCO₃ (8 mL) was added and the mixture was extracted with CH₂Cl₂ (2× 8 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The products were purified by flash column chromatography (silica gel, petroleum ether : EtOAc).

In case of product 5d, the process was repeated twice on a larger scale (using either oxygen or air as the nebulizing gas and with the cylinder in the vertical position) starting with 10 mmol of furan 1a (1.52 g dissolved in 20 mL of MeOH, 0.5 M) and the results were very similar. In this case, the two cooled collection flasks placed in series were prefilled with excess of Me₂S in MeOH (3 equiv in the first flask and 1 equiv in the second flask) in order to avoid the accumulation of large amounts of hydroperoxide that formed during the initial photooxygenation step.

![Chemical structure of 1-Benzyl-5-hexyl-5-(1H-indol-3-yl)pyrrolidin-2-one (5d)](image)

### 1-Benzyl-5-hexyl-5-(1H-indol-3-yl)pyrrolidin-2-one (5d)

The reaction was accomplished according to the general experimental procedure described above. Nebulization of the 5 mL reaction solution took 8.77 min (actual flow rate = 0.57 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas, the reaction solution was nebulized within 6.67 min (actual flow rate = 0.75 mL min⁻¹) and the conversion was 99%. When the reaction cylinder was in the vertical position and air was used as the nebulizing gas, the reaction solution was nebulized within 8.48 min (actual flow rate = 0.59 mL min⁻¹) and the conversion was 92%. The product 5d was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 2:1). When the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas the yield was 56% (524 mg). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas the yield was 66% (617 mg). When the reaction cylinder was in the vertical position and air was used as the nebulizing gas the yield was 51% (477 mg).

¹H NMR (500 MHz, CDCl₃): δ = 8.50 (brs, 1H), 7.41 (t, J=8.1 Hz, 2H), 7.24-7.15 (m, 6H), 7.13 (d, J=2.6 Hz, 1H), 7.09 (t, J=7.9 Hz, 1H), 4.90 (d, J=14.8 Hz, 1H), 3.50 (d, J=14.8 Hz, 1H), 2.68 (dd, J₁=9.7 Hz, J₂=7.2 Hz, 2H), 2.51 (m, 1H), 2.15 (m, 1H), 1.78 (m, 1H).
1.92 (ddd, J₁=13.5 Hz, J₂=12.0 Hz, J₃=4.8 Hz, 1H), 1.70 (td, J₁=13.0 Hz, J₂=2.4 Hz, 1H), 1.25-1.10 (m, 3H), 1.07-0.87 (m, 5H), 0.81 (t, J=7.3 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 175.7, 138.6, 137.1, 129.0 (2C), 128.0 (2C), 127.0, 125.0, 122.4, 122.2, 120.7, 120.1, 119.5, 111.6, 66.2, 44.1, 38.5, 31.7, 31.4, 30.8, 29.2, 22.7, 22.5, 14.0 ppm; HRMS (TOF ESI): calcd for C₁₅₁₄N₂O: 375.2431 [M+H]⁺; found: 375.2441.

1-Benzyl-5-hexyl-5-(1H-pyrrol-2-yl)pyrrolidin-2-one (5e)

The reaction was accomplished according to the general experimental procedure described above. Nebulization of the 5 mL reaction solution took 8.63 min (actual flow rate = 0.58 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). The product 5e was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 2:1). Yield 55% (446 mg).

¹H NMR (500 MHz, CDCl₃): δ = 9.03 (brs, 1H), 7.21-7.15 (m, 5H), 6.71 (m, 1H), 6.16 (m, 1H), 6.11 (q, J=2.9 Hz, 1H), 4.54 (d, J=14.5 Hz, 1H), 3.67 (d, J=14.5 Hz, 1H), 2.49 (m, 2H), 2.29 (m, 1H), 2.15 (ddd, J₁=13.8 Hz, J₂=9.7 Hz, J₃=4.2 Hz, 1H), 1.87 (ddd, J₁=13.9 Hz, J₂=12.5 Hz, J₃=4.8 Hz, 1H), 1.74 (m, 1H), 1.18 (m, 3H), 1.04 (m, 3H), 0.90 (m, 1H), 0.82 (t, J=7.3 Hz, 3H), 0.78 (m, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 175.7, 138.1, 134.8, 129.0 (2C), 128.2 (2C), 127.2, 119.0, 107.3, 107.2, 66.0, 44.0, 37.1, 31.7, 31.5, 30.5, 29.2, 23.1, 22.5, 14.0 ppm; HRMS (TOF ESI): calcd for C₂₃H₂₉N₂O: 325.2274 [M+H]⁺; found: 325.2277.

5-Hexyl-5-(1H-indol-3-yl)pyrrolidin-2-one (5f)

The reaction was accomplished according to the general experimental procedure described above. Nebulization of the 5 mL reaction solution took 8.78 min (actual flow rate = 0.57 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). The product 5f was purified by flash column chromatography (silica gel, EtOAc). Yield 51% (362 mg).

¹H NMR (500 MHz, CDCl₃): δ = 8.16 (brs, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.40 (d, J=8.2 Hz, 1H), 7.22 (m, 1H), 7.13 (m, 1H), 7.05 (d, J=2.5 Hz, 1H), 6.41 (brs, 1H), 2.52 (ddd, J₁=11.8 Hz, J₂=8.6 Hz, J₃=5.4 Hz, 1H), 2.42 (m, 2H), 2.32 (m, 1H), 2.19 (m, 1H), 1.97 (m, 1H), 1.29-1.13 (m, 8H), 0.82 (t, J=7.0 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 178.4, 137.4, 124.5, 122.1, 121.0, 120.6, 119.6, 119.4, 111.6, 62.5,
5-Hexyl-1-methyl-5-(5-methylfuran-2-yl)pyrrolidin-2-one (5g)
The reaction was accomplished according to the general experimental procedure described above. Nebulization of the 5 mL reaction solution took 8.61 min (actual flow rate = 0.58 mL min\(^{-1}\)) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas, the reaction solution was nebulized within 6.03 min (actual flow rate = 0.83 mL min\(^{-1}\)) and the conversion was 99%. The product 5g was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 4:1). When the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas the yield was 53% (348 mg). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas the yield was 62% (408 mg).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) : \(\delta = 6.03 (d, J = 3.0 \text{ Hz}, 1H), 5.87 (m, 1H), 2.60 (s, 3H), 2.59 (m, 1H), 2.42 (ddd, \(J_1 = 16.7 \text{ Hz}, J_2 = 10.1 \text{ Hz}, J_3 = 4.7 \text{ Hz}, 1H), 2.30 (ddd, \(J_1 = 13.2 \text{ Hz}, J_2 = 10.0 \text{ Hz}, J_3 = 7.8 \text{ Hz}, 1H), 1.96 (m, 1H), 1.79 (ddd, \(J_1 = 13.8 \text{ Hz}, J_2 = 11.9 \text{ Hz}, J_3 = 4.4 \text{ Hz}, 1H), 1.36-1.15 (m, 8H), 0.89 (t, \(J = 6.7 \text{ Hz}, 3H) \text{ ppm; } \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) : \(\delta = 175.0, 154.1, 152.0, 107.2, 105.7, 64.5, 35.3, 31.7, 30.3, 29.5, 28.7, 25.4, 23.0, 22.6, 14.0, 13.6 ppm; HRMS (TOF ESI): calcld for C\(_{16}\)H\(_{26}\)NO\(_2\): 264.1958 [M+H]\(^+\); found: 264.1950.

General experimental procedure for the preparation of \(\gamma\)-lactams 6h, 7i, 8j and 9k

2-Substituted furan 1 (2.5 mmol, 380 mg in case of 1a or 350 mg in case of 1d) and rose Bengal (0.5 mol%, 12.7 mg) were dissolved in MeOH (total volume 5 mL, 0.5 M). The resulting solutions were transferred to the nebulizer via a liquid pump (flow rate set at 0.5 mL min\(^{-1}\)) and timing was initiated for calculation of the exact flow rate. The solutions were dispersed by the nebulizer into the reaction cylinder which was placed in a horizontal or a vertical position using oxygen or air as the nebulizing gas (50 psi back pressure). The cylinder was irradiated by the LEDs (natural white light 3800–4200 K, 10 W m\(^{-1}\), 1050 Lm m\(^{-1}\)). When all the solution had been dispersed, the exact flow rate was calculated and the three-way valve on the uptake
line was switched to pure MeOH (2 mL) to flush out the system. The crude solutions were collected in the two cooled spherical flasks placed in series. A small sample of the crude solution was concentrated \textit{in vacuo} for the measurement of the conversions by \textsuperscript{1}H NMR. Then, the solutions from the two flasks were placed into one flask and Me\textsubscript{2}S (730 \mu L, 10 mmol) was added. The solutions were stirred for 1 h at rt. When the reduction was completed, as indicated by tlc analysis, the appropriate amine (2.5 mmol, 273 \mu L of BnNH\textsubscript{2}, or 422 \mu L of 3,4-dimethoxyphenethylamine, or 216 \mu L of 40\% w/w aqueous solution of MeNH\textsubscript{2}) was added and the solutions were stirred for 1 h at the same temperature. After the formation of the intermediate 2-pyrrolidinones of type 2, methylene blue (3 mol\%, 24 mg) was added and the solutions were stirred for 3 h at rt. In case of entry h (Table 3) the reaction afforded compound 6h. After treatment with MB, in case of entry j (Table 3) MeOH was replaced by HCOOH (2 mL), while for entries i and k (Table 3), MeOH was replaced with CH\textsubscript{2}Cl\textsubscript{2} (6 mL) and p-TsOH (2.5 mmol, 476 mg towards 7i, or 1.25 mmol, 238 mg towards 9k) was added. After the addition of acid, the reactions were stirred for 1 h at rt. After completion of the reactions, as indicated by tlc analysis, the solutions were concentrated \textit{in vacuo} and the products 6h, 7i, 8j and 9k were purified by flash column chromatography (silica gel, petroleum ether : EtOAc).

1-Benzyl-5-hexyl-5-hydroxy-1H-pyrrol-2(5H)-one (6h)

The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1a. Nebulization of the 5 mL reaction solution took 9.62 min (actual flow rate = 0.52 mL min\textsuperscript{-1}) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99\%). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas, the reaction solution was nebulized within 6.48 min (actual flow rate = 0.77 mL min\textsuperscript{-1}) and the conversion was 99\%. When the reaction cylinder was in the vertical position and air was used as the nebulizing gas, the reaction solution was nebulized within 8.32 min (actual flow rate = 0.60 mL min\textsuperscript{-1}) and the conversion was 90\%. The product 6h was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 1:1). When the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas the yield was 62\% (423 mg). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas the yield was 59\% (403 mg). When the reaction cylinder was in the vertical position and air was used as the nebulizing gas the yield was 50\% (341 mg).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 7.38\ (d, J=7.2\ Hz, 2H), 7.29\ (m, 2H), 7.24\ (m, 1H), 6.85\ (d, J=6.0\ Hz, 1H), 6.14\ (d, J=6.0\ Hz, 1H), 4.55\ (d, J=15.2\ Hz, 1H), 4.47\ (d, J=15.2\ Hz, 1H), 2.22\ (brs, 1H), 1.80\ (ddd, J\_i=13.8\ Hz, J\_z=12.2\ Hz, J\_z=4.7\ Hz, 1H), 1.68\ (ddd, J\_i=13.9\ Hz, J\_z=11.9\ Hz, J\_z=4.4\ Hz, 1H), 1.15\ (quin, J=7.1\ Hz, 2H), 1.04\ (m, 3H), 0.89\ (m, 2H), 0.81\ (t, J=7.3\ Hz, 3H), 0.77\ (m, 1H)\ ppm; \textsuperscript{13}C NMR (125
(E)-1-Benzyl-5-hexylidene-1H-pyrrol-2(5H)-one (7i)
The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1a. Nebulization of the 5 mL reaction solution took 8.61 min (actual flow rate = 0.58 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). The product 7i was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 4:1). Yield 58% (370 mg). Consistent with our previously synthesized very similar compounds, the configuration of the exocyclic double bond was considered to be E.⁵

¹H NMR (500 MHz, CDCl₃): δ = 7.29 (m, 3H), 7.22 (m, 1H), 7.16 (d, J=7.1 Hz, 2H), 6.25 (dd, J₁=5.9 Hz, J₂=1.6 Hz, 1H), 5.32 (td, J₁=8.2 Hz, J₂=1.2 Hz, 1H), 4.84 (s, 2H), 2.25 (q, J=7.6 Hz, 2H), 1.36 (quin, J=7.4 Hz, 2H), 1.26 (m, 2H), 1.18 (m, 2H), 0.84 (t, J=7.2 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 170.0, 139.1, 137.3, 132.5, 128.4 (2C), 127.0, 126.6 (2C), 123.8, 116.7, 42.4, 30.9, 29.6, 27.4, 22.2, 13.8 ppm; HRMS (TOF ESI): calcd for C₁₇H₂₂NO₂: 256.1690 [M+H]+; found: 256.1690.

10b-Hexyl-8,9-dimethoxy-6,10b-dihydropyrrolo[2,1-a]isoquinolin-3(5H)-one (8j)
The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1a. Nebulization of the 5 mL reaction solution took 8.60 min (actual flow rate = 0.58 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 99%). The product 8j was purified by flash column chromatography (silica gel, petroleum ether: EtOAc = 4:1). Yield 66% (543 mg).

¹H NMR (500 MHz, CDCl₃): δ = 7.23 (d, J=5.8 Hz, 1H), 6.69 (s, 1H), 6.60 (s, 1H), 6.13 (d, J=5.8 Hz, 1H), 4.41 (dd, J₁=13.3 Hz, J₂=6.6 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.15 (m, 1H), 2.93 (ddd, J₁=16.1 Hz, J₂=11.7 Hz, J₃=6.7 Hz, 1H), 2.66 (dd, J₁=16.1 Hz, J₂=4.1 Hz, 1H), 1.93 (m, 2H), 1.24 (m, 6H), 1.10 (m, 2H), 0.85 (t, J=6.9

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⁵ D. Kalaitzakis, A. Kouridaki, D. Noutsias, T. Montagnon, G. Vassilikogiannakis, Angew. Chem. Int. Ed. 2015, 54, 6283.
1-H NMR (500 MHz, CDCl₃): δ = 7.48 (d, J=6.2 Hz, 1H), 6.19 (d, J=6.2 Hz, 1H), 4.01 (m, 1H), 3.77 (m, 1H), 2.86 (s, 3H), 1.97 (m, 2H), 1.76 (m, 1H), 1.64 (m, 2H), 1.51 (m, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 168.8, 144.7, 127.8, 91.4, 65.8, 29.9, 24.7, 23.5, 21.1 ppm; HRMS (TOF ESI): calcd for C₉H₁₄NO₂: 168.1019 [M+H]⁺; found: 168.1012.

1-Methyl-6-oxa-1-azaspiro[4.5]dec-3-en-2-one (9k)
The reaction was accomplished according to the general experimental procedure described above, utilizing furan 1d. Nebulization of the 5 mL reaction solution took 9.24 min (actual flow rate = 0.54 mL min⁻¹) when the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas (conversion 85%). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas, the reaction solution was nebulized within 6.74 min (actual flow rate = 0.74 mL min⁻¹) and the conversion was 95%. When the reaction cylinder was in the vertical position and air was used as the nebulizing gas, the reaction solution was nebulized within 7.92 min (actual flow rate = 0.63 mL min⁻¹) and the conversion was 82%. The product 9k was purified by flash column chromatography (silica gel, petroleum ether : EtOAc = 1:1). When the reaction cylinder was in the horizontal position and oxygen was used as the nebulizing gas the yield was 58% (242 mg). When the reaction cylinder was in the vertical position and oxygen was used as the nebulizing gas the yield was 53% (221 mg). When the reaction cylinder was in the vertical position and air was used as the nebulizing gas the yield was 49% (205 mg).

Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 170.8, 151.9, 148.1, 147.5, 129.7, 126.1, 125.2, 112.0, 109.1, 68.5, 56.2, 55.8, 38.9, 34.7, 31.6, 29.2, 29.0, 23.0, 22.5, 14.0 ppm; HRMS (TOF ESI): calcd for C₂₀H₂₈NO₃: 330.2064 [M+H]⁺; found: 330.2064.
Part C: Copies of $^1$H-NMR and $^{13}$C-NMR spectra

3a: glochidine
(500 MHz, CDCl$_3$)

3a: glochidine
(125 MHz, CDCl$_3$)

S13
