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Supporting Information

Catalyst-free photo-induced aerobic radical synthesis of lactams from *N*-alkenyl trichloroacetamides in 2-methyl tetrahydrofuran as the radical initiator under violet light

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1. General information

Unless otherwise stated, all reactions were carried out under air atmosphere with commercially available solvents. Photocatalyzed reactions were carried out in a 10 mL flask closed with a rubber stopper using violet light ($\lambda = 395-405$ nm). Reagents and solvents were used as received without further purification. All product mixtures were analyzed by thin-layer chromatography performed on SiO₂ (Merck silica gel 60 F254) and the spots were located by UV light (λ 254 nm) and/or a 1% KMnO₄ aqueous solution. Flash chromatography was carried out on SiO₂ (Carlo Erba silica gel 60A, 35–70 μ). Drying of organic extracts during the reaction workup was performed over anhydrous Na₂SO₄ and solvent evaporation was accomplished with a rotatory evaporator. ¹H and ¹³C NMR spectra were recorded on a Bruker 400 and a Bruker 500 spectrometers in CDCl₃. Chemical shifts are reported as δ values (ppm) relative to internal Me₄Si, ¹³C NMR spectra are referenced to the deuterated solvent signal (CDCl₃: 77.00 ppm). All NMR data assignments are supported by COSY and HSQC experiments. The following abbreviations (or combinations) were used to describe 1 H-NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. Melting points were recorded on a Gallenkamp melting point apparatus. Electrochemical characterizations (Cyclic Voltammetry) were carried out in acetonitrile (MeCN)/0.1 M tetrabutylammonium hexafluorophosphate (98%) at room temperature, on a BASi Epsilon EClipseTM (Metrohm, The Netherlands) in a glass cell. A three-electrode cell was employed, which was composed of a glassy carbon (GC) working electrode (3 mm diameter), a platinum wire as a counter electrode and an Ag/AgCl as a reference electrode (RE). Oxygen was removed by purging the solution with high purity Nitrogen. The GC electrode was polished before any measurement with diamon paste and ultrasonically rinsed with deionized water for 15 minutes. The electrode was electrochemically activated in the background solution by means of several voltammetric cycles at 100 mV/s between the anodic and cathodic solvent /electrolyte discharges.¹ UV-Visible absorbances spectra were recorded with Secomam UVIKON XS UV/Vis Spectrometer.

¹ We thank Dr. Xavier Companyó for letting us use the machine and Paula Rodríguez for her help.



2. Preparation and characterization of trichloroacetamides 1a-1s

For the preparation and characterization of trichloroacetamides **1a**, **1b**, **1c**, **1d**, **1g**, **1h**, **1i**, **1k**, **1m**, **1n** see our previous work.² Preparation and characterization of **1e** has been reported previously.³ **1j** was prepared from *t*-butylamine and propargyl bromide using the two-step sequence described in ref.2. Synthesis and characterization of **1f** and **1s** is reported in our previous work.⁴ **1I** was prepared from the corresponding secondary amine⁵ and trichloroacetyl chloride using the conditions reported in ref.2. **1o** and **1q** were prepared by oxidation with IBX of the corresponding amides⁶ using the protocol

² G. Trenchs, F. Diaba, Org. Biomol. Chem., 2022, **20**, 3118-3123.

³ M. L. Marin, R. J. Zaragoza, M. A. Miranda, F. Diaba, J. Bonjoch, *Org. Biomol. Chem.*, 2011, **9**, 3180-3187.

⁴ F. Diaba, E. Gomez-Bengoa, J. M. Cuerva, J. Bonjoch, J. Justicia, *RSC Adv.*, 2016, **6**, 55360-55365.

⁵ S. Rodriguez, E. Castillo, M Carda, J. A. Marco, *Tetrahedron*, 2002, **58**, 1185-1192.

⁶ F.Diaba, J. A. Montiel, G. Serban, J. Bonjoch, Org. Lett., 2015, **17**, 3860-3863.

described previously.² Finally, the preparation and characterization of **1r** and **1p** were reported in our previous work.^{7,8}

N-(tert-Butyl)-2,2,2-trichloro-N-(prop-2-yn-1-yl)acetamide (1j)

Physical State: colorless oil

¹H NMR (400 MHz,CDCl₃) δ 4.53 (br s, 2H), 2.37 (t, *J* = 2.4 Hz, 1H), 1.58 (s, 9H, *t*Bu); ¹³C NMR (101 MHz, CDCl₃) δ 159.6 (C=O), 94.7 (CCl₃), 80.2 (C), 73.3 (CH), 61.4 (C), 36.9 (CH₂), 27.8 (CH₃); IR (NaCl) 2975, 2930, 2122, 1686 cm⁻¹; HRMS (ESI-TOF) calcd. for C₉H₁₃Cl₃NO 256.0057 [M+H]⁺, found 256.0055. Calcd. for C₉H₁₆Cl₃N₂O 273.0323 [M+NH₄]⁺, found 273.0323.

N-Benzyl-2,2,2-trichloro-N-(1-phenylbut-3-en-1-yl)acetamide (11)



Physical State: colorless oil

¹H NMR (400 MHz,CDCl₃) δ 3.02-2.64 (m, 2H), 4.12 and 5.12-4.64 (m, 5H), 5.91 and 5.68 (2 br s, 1H), 7.61-6.94 (m, 10H); ¹³C NMR (101 MHz, CDCl₃) δ 160.8 (C=O), 137.8, 137.0, 135.6 (C), 134.6, 133.7 (CH), 128.7, 128.4, 128.2, 127.9, 127.2 (Ar-CH), 117.9 (CH₂), 93.9 (CCl₃), 63.8 and 60.9 (CH), 53.1 and 49.5 (CH₂), 36.1 (CH₂); IR (NaCl) 1686 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₉H₁₉Cl₃NO 382.0527 [M+H]⁺, found 382.0530.

2,2,2-Trichloro-*N*-methyl-*N*-(4-oxocyclohex-2-en-1-yl)acetamide (10)



Physical State: white solid, m.p.: 110-113 °C

⁷ For **1r** see: J. Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. Heterocycles, 1999, **50**, 731-738.

⁸ For **1p** see: S. Jansana, F. Diaba, J. Bonjoch, *Org. Lett.*, 2019, **21**, 5757–5761.

¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, *J* = 10.3 Hz, 1H), 6.17 (ddd, *J* = 10.3, 2.8, 1.1 Hz, 1H), 5.45 and 5.35 (2 br s, 1H), 3.23 and 2.91 (2 br s, 3H, CH₃), 2.62-2.40 and 2.35-2.09 (2 m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 197.1 (C=O), 160.7 (C=O), 149.3 (CH), 132.0 (CH), 92.9 (CCl₃), 56.1 and 55.8 (CH), 36.5 (CH₂), 34.2 and 32.5 (CH₃), 27.6 and 26.1 (CH₂); IR (NaCl) 3056, 2986, 1681 cm⁻¹; HRMS (ESI-TOF) calcd. for C₉H₁₁Cl₃NO₂ [M+H]⁺ 269.9850, found 269.9851. Calcd for C₉H₁₀Cl₃NNaO₂ [M+Na]⁺ 291.9669, found 291.9670.

N-Benzyl-2,2,2-trichloro-N-((4-oxocyclohex-2-en-1-yl)methyl)acetamide (1q)



Physical state: amorphous solid

¹H NMR (400 MHz, CDCl₃) δ 7.43-7.30 (m, 3H, ArH), 7.28-7.22 (m, 2H, ArH), 6.71 (d, J = 10.2 Hz, 1H), 6.03 (dd, J = 10.2, 2.5 Hz, 1H), 5.06 (s, 2H, CH₂Ar), 3.51 – 3.28 (m, 2H, CH₂), 2.97 (m, 1H), 2.52 (dt, J = 16.9, 5.0 Hz, 1H), 2.36 (ddd, J = 16.9, 12.0, 4.9 Hz, 1H), 2.10 (m, 1H), 1.74 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 198.7 (CO), 161.5 (CO), 150.1 (CH), 134.7 (C), 130.3 (CH), 129.1 (CH), 128.2 (CH), 127.0 (CH), 92.9 (CCl₃), 54.3 (CH₂), 51.2 (CH₂), 36.3 (CH₂), 34.0 (CH), 26.5 (CH₂); IR (NaCl) 3060, 3033, 2942, 2871, 1678 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₆H₁₇Cl₃NO₂ [M+H]⁺ 360.0319, found 360.0317.

3. Photocatalyzed synthesis of lactams 2 in the presence of ammonia

A mixture of trichloroacetamide **1** (0.2 mmol) and *fac*-Ir(ppy)₃ (1.3 mg, 0.002 mmol, 1 mol%) in a THF/Acetone solution (4 mL, 1:1) saturated with NH₃ (4-11 equiv.) was stirred at rt under blue LEDs irradiation for 0.5-24 h. The mixture was then concentrated and purified by chromatography using a mixture of Hexane/EtOAc (1:0 to 1:1) or cyclohexane/AcOEt (1:0 to 1:1) as eluent to provide the corresponding lactams **2**. The results obtained for the different substrates is indicated in the following Table 1.



Table 1. Scope of the photocatalyzed synthesis of lactams **2** in the presence of Ir(ppy)₃ and ammonia^a

^a Except for 2i, 2f and 2j, lactams 2 were already characterized in our previous work (see ref. 2).

4. Photocatalyzed synthesis of lactams 2 in THF or 2-MeTHF alone under violet irradiation



Trichloroacetamide **1** (0.2-2 mmol) in THF or 2-MeTHF (4–40 mL) was stirred at rt under violet LEDs irradiation for the time indicated. The reaction mixture was then concentrated and purified by chromatography using a mixture of Hexane/EtOAc (1:0 to 1:1) or cyclohexane/EtOAc (1:0 to 1:1) as eluent, to provide the corresponding lactams **2** and/or **3**.

(*R*)-3,3-Dichloro-4-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (2e, diastereomer less polar)



Physical state: colourless oil $[\alpha]_D^{23}$ = -102.5 (*c* 1, MeOH)

¹H NMR (400, MHz CDCl₃) δ 7.40-7.26 (m, 5H, ArH), 5.47 (q, *J* = 7.1 Hz, 1H), 2.98 (dd, *J* = 9.8, 7.1 Hz, 1H, H-5), 2.92 (dd, *J* = 9.8, 8.5 Hz, 1H, H-5), 2.59 (dquint, *J* = 8.4, 6.7 Hz, 1H, H-4), 1.54 (d, *J* = 7.1 Hz, 3H, CH₃), 1.27 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.6 (C-2), 138.7 (*ipso*-C), 128.8, 128.0, 127.1 (Ar-CH), 87.6 (C-3), 50.5 (CH), 45.4 (C-4 and C-5), 15.5 (CH₃), 11.6 (CH₃); IR (NaCl) 3059, 2978, 2937, 1713 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₃H₁₆Cl₂NO [M+H]⁺ 272.0603, found 272.0604.

(S)-3,3-Dichloro-4-methyl-1-((S)-1-phenylbut-3-en-1-yl)pyrrolidin-2-one (*epi*-2e, diastereomer more polar)



Physical state: white solid, m.p.: 89-91 °C

[α]²³_D = -150.1 (*c* 1, MeOH)

¹H NMR (400 MHz CDCI₃) δ 7.38-7.25 (m, 5H, ArH), 5.49 (q, *J* = 7.1 Hz, 1H), 3.25 (dd, *J* = 9.9, 6.8 Hz, 1H, H-5), 2.73 (dquintet, *J* = 8.4, 6.7 Hz, H-4), 2.53 (dd, *J* = 9.9, 8.4 Hz, 1H, H-5), 1.58 (d, *J* = 7.1 Hz, 3H, CH₃), 1.22 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCI₃) δ 166.6 (C-2), 138.5 (*ipso*-C), 128.7, 128.0, 127.0 (Ar-CH), 87.5 (C-3), 50.2 (CH), 45.4 (C-5), 45.3 (C-4), 15.8 (CH₃), 11.8 (CH₃); IR (NaCI) 3054, 2981, 2939, 1705 cm⁻¹; HRMS (ESI-TOF) calcd. C₁₃H₁₆Cl₂NO [M+H]⁺ 272.0603, found 272.0602.



(*RS*)-3,3-Dichloro-4-methyl-1-((*SR*)-1-phenylbut-3-en-1-yl)pyrrolidin-2-one (2f, diastereomer less polar)



Physical state: colourless oil

¹H NMR (400 MHz CDCl₃) δ 7.41-7.24 (m, 5H, ArH), 5.79 (dddd, *J* = 17.6, 10.3, 7.7, 5.7 Hz, 1H, =CH), 5.41 (dd, *J* = 10.2, 5.8 Hz, 1H), 5.19 (dq, *J* = 17.1, 1.6 Hz, 1H, =CH₂), 5.11 (dq, *J* = 10.2, 1.3 Hz, 1H, =CH₂), 3.03 (dd, *J* = 9.6, 7.0 Hz, 1H, H-5), 2.94 (dd, *J* = 9.6, 8.5 Hz, 1H, H-5), 2.85-2.2.64 (m, 2H), 2.56 (m, 1H, H-4), 1.26 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.1 (CO), 137.6 (*ipso*-C), 133.4 (=CH), 128.9, 128.2, 127.5 (Ar-CH), 118.4 (=CH₂), 87.4 (C-3), 54.4 (CH), 45.6 (C-4 and C-5), 34.5 (CH₂), 11.7 (CH₃); IR (NaCl) 3064, 3031, 2978, 2936, 2879, 1719 cm⁻¹; HRMS (ESI-TOF) calc. for

C₁₅H₁₈Cl₂NO 298.0760 [M+H]⁺, found 298.0755. Calcd. for C₁₅H₁₇Cl₂NNaO 320.0579 [M+Na]⁺, found 320.0576.

(*RS*)-3,3-Dichloro-4-methyl-1-((*RS*)-1-phenylbut-3-en-1-yl)pyrrolidin-2-one (*epi*-2f, diastereomer more polar)



Physical state: amorphous solid

¹H NMR (400 MHz, CDCl₃) δ 7.43-7.22 (m, 5H, ArH), 5.80 (dddd, *J* = 17.1, 10.2, 8.0, 5.5 Hz, 1H, =CH), 5.40 (dd, *J* = 10.2, 6.0 Hz, 1H), 5.16 (dq, *J* = 16.9, 1.5 Hz, 1H, =CH₂), 5.11 (dq, *J* = 10.2, 1.3 Hz, 1H, =CH₂), 3.24 (dd, *J* = 9.7, 6.7 Hz, 1H, H-5), 2.88-2.62 (m, 3H), 2.56 (dd, *J* = 9.7, 8.4 Hz, 1H, H-5), 1.21 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.1 (C-2), 137.4 (*ipso*-C), 133.9 (=CH), 128.8, 128.1, 127.4 (Ar-CH), 118.0 (=CH₂), 87.4 (C-3), 54.3 (CH), 45.7 (C-5), 45.2 (C-4), 34.2 (CH₂), 11.7 (CH₃); IR (NaCl) 3062, 3032, 2979, 2937, 2881, 1717 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₅H₁₈Cl₂NO 298.0760 [M+H]⁺, found 298.0756. Calcd. for C₁₅H₁₇Cl₂NNaO 320.0579 [M+Na]⁺, found 320.0579.

1-(tert-Butyl)-3,3-dichloro-4-methylenepyrrolidin-2-one (2j)



Physical state: White solid, m.p.: 90-95 °C

¹H NMR (400 MHz, CDCl₃) δ 5.91 (td, *J* = 2.1, 1.0 Hz, 1H, =CH₂), 5.45 (td, *J* = 1.8, 1.0 Hz, 1H, =CH₂), 4.12 (t, *J* = 1.9 Hz, 2H, CH₂-5), 1.47 (s, 9H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 165.4 (C-2), 141.5 (C-4), 115.1 (=CH₂), 79.9 (C-3),55.5 (C), 47.3 (C-5), 27.2 (CH₃); IR (NaCl) 3104, 2977, 2936, 2872, 1713, 1669 cm⁻¹; HRMS (ESI-TOF) calcd. for C₉H₁₄Cl₂NO 222.0447 [M+H]⁺, found 222.0446. Calcd. for C₉H₁₃Cl₂NNaO 244.0266 [M+Na]⁺, found 244.0273.

(4*RS*,6*SR*)-1-Benzyl-3,3-dichloro-4-methyl-6-phenylpiperidin-2-one (2I, diastereomer less polar)



Physical state: amorphous solid

¹H NMR (400 MHz, CDCl₃) δ 7.46-7.26 (m, 6H, ArH), 7.21-7.10 (m, 4H, ArH), 5.59 (d, *J* = 14.8 Hz, 1H, CH₂Ar), 4.51 (dd, *J* = 6.1, 2.2 Hz, 1H, H-6), 3.46 (d, *J* = 14.8 Hz, 1H, CH₂Ar), 2.68 (dqd, *J* = 12.8, 6.4, 2.8 Hz, 1H, H-4), 2.31 (ddd, *J* = 14.2, 12.4, 6.1 Hz, 1H, H-5), 1.77 (dt, *J* = 14.3, 2.5 Hz, 1H, H-5), 1.22 (d, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 165.1 (C-2), 139.7 (*ipso*-C), 136.1(*ipso*-C), 129.2, 128.8, 128.1, 128.0, 127.8, 126.3 (Ar-CH), 89.2 (C-3), 58.3 (C-6), 49.4 (CH₂Ar), 39.2 (C-4), 35.1 (C-5), 16.5 (CH₃); IR (NaCl) 3155, 3022, 2928, 2899, 1669 cm⁻¹; HRMS (ESI-TOF) calc. for C₁₉H₂₀Cl₂NO [M+H]⁺ 348.0916, found 349.0918.

(4*RS*,6*RS*)-1-Benzyl-3,3-dichloro-4-methyl-6-phenylpiperidin-2-one (*epi*-2l, diastereomer more polar)



¹H NMR (400 MHz, CDCl₃) δ 7.46-7.08 (m, 8H, ArH), 7.05-6.98 (m, 2H, ArH), 5.35 (d, *J* = 14.6 Hz, 1H, CH₂Ar), 4.30 (dd, *J* = 11.2, 6.4 Hz, 1H, H-6), 3.54 (d, *J* = 14.6 Hz, 1H, CH₂Ar), 2.59 (dqd, *J* = 12.7, 6.4, 3.6 Hz, 1H, H-4), 2.10 (ddd, *J* = 14.7, 12.4, 11.2 Hz, 1H, H-5), 2.02 (ddd, *J* = 14.7, 6.4, 3.6 Hz, 1H, H-5), 1.33 (d, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 165.1 (C-2), 140.4 (*ipso*-C), 136.2 (*ipso*-C), 129.1, 128.6, 128.4, 127.6, 127.0 (Ar-CH), 89.4 (C-3), 60.2 (C-6), 48.2 (CH₂Ar), 42.8 (C-4), 37.1 (C-5), 16.2 (CH₃).



(3aRS,7aSR)-3,3-Dichloro-1-methylhexahydro-2H-indole-2,5(3H)-dione (20)



Physical state: amorphous solid

¹H NMR (400 MHz CDCl₃) δ 3.91 (ddd, *J* = 8.8, 7.1, 5.0 Hz, 1H, H-7a), 3.36 (q, 1H, *J* = 7.2 Hz, H-3a), 3.01 (s, 3H, CH₃), 2.83 (dd, *J* = 16.5, 6.8 Hz, 1H, H-4), 2.72 (ddd, *J* = 16.5, 7.8, 0.9 Hz, 1H, H-4), 2.49-2.42 (m, 1H), 2.36-2.24 (m, 2H), 2.19-2.08 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 206.5 (C-5), 166.2 (C-2), 85.2 (C-3), 55.0 (C-7a), 48.7 (C-3a), 38.4 (C-4), 35.6 (C-6), 29.0 (CH₃), 24.3 (C-7); IR (NaCl) 2950, 2919, 2851, 1716, 1674 cm⁻¹; HRMS (ESI-TOF) calcd. for C₉H₁₂Cl₂NO₂ [M+H]⁺ 236.0240, found 236.0238.

(3aRS,4RS,7aRS)-3,3,4-Trichloro-1-methylhexahydro-2H-indole-2,5(3H)-dione (3o)



Physical state: amorphous solid

¹H NMR (400 MHz, CDCl₃) δ 4.85 (d, *J* = 4.9 Hz, 1H, H-4), 3.86 (ddd, *J* = 11.3, 8.2, 5.0 Hz, 1H, H-7a), 3.49 (ddd, *J* = 8.3, 5.0, 0.6 Hz, 1H, H-3a), 2.94 (s, 3H, CH₃), 2.76 (ddd, *J* = 16.9, 13.0, 5.9 Hz, 1H, H-6), 2.48 (dddd, *J* = 16.9, 4.8, 3.5, 0.9 Hz, 1H, H-6), 2.36 (ddddd, *J* = 13.8, 5.9. 4.5, 3.6, 0.9 Hz, 1H, H-7), 2.06 (tdd, *J* = 13.8, 11.3, 5.1 Hz, 1H, H-7)

7); ¹³C NMR (101 MHz, CDCl₃) δ 199.2 (C-5), 165.2 (C-2), 82.2 (C-3), 57.2 (C-3a and C-4), 54.6 (C-7a), 32.7 (C-6), 29.3 (CH₃), 24.4 (C-7); IR (NaCl) 1717 cm⁻¹; HRMS (ESI-TOF) calcd. for C₉H₁₁Cl₃NO₂ [M+H] + 269.9850, found 269.9853.

β-Lactam 4p



Physical state: colourless oil

¹H NMR (400 MHz, CDCl₃) δ 7.73-7.66 (m, 1H, ArH), 7.39-7.28 (m, 5H, ArH), 7.27-7.20 (m, 2H, ArH), 7.12-7.07 (m, 1H, ArH), 6.02 (s, 1H, =CH₂), 5.22 (s, 1H, =CH₂), 4.94 (d, *J* = 15.4 Hz, 1H, CH₂Ar), 4.04 (d, *J* = 15.4 Hz, 1H, CH₂Ar), 3.28 (ddd, *J* = 17.6, 12.6, 5.7 Hz, 1H), 2.84 (ddd, *J* = 17.6, 5.9, 2.6 Hz, 1H), 2.11 (ddd, *J* = 13.6, 5.5, 2.5 Hz, 1H), 1.99 (ddd, *J* = 13.6, 12.6, 5.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 161.9 (CO), 139.6, 135.9, 134.8, 132.0 (C), 129.0, 128.8, 128.6, 128.3, 128.2, 126.6, 125.0 (Ar-CH), 112.4 (=CH₂), 88.4 (CCl₂), 75.4 (C), 44.6 (CH₂Ar), 30.0 (CH₂), 26.4 (CH₂); IR (NaCl) 3068, 3032, 2926, 2854, 1781 cm⁻¹; HRMS (ESI-TOF) calcd. for C₂₀H₁₈Cl₂NO [M+H]⁺ 358.0760, found 358.0758.

γ-Lactam 2p'



¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.60-7.02 (m, 8H, ArH), 5.33 (dd, *J* = 4.5, 3.7 Hz, 1H, =CH), 4.85 (d, *J* = 4.8 Hz, 1H, CH₂Ar), 4.79 (d, *J* = 4.8 Hz, 1H, CH₂Ar), 3.41 (d, *J* = 4.1 Hz, 2H, CH₂), 1.47 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.4 (CO), 139.6, 136.3, 135.0, 134.3 (C),128.8, 128.2, 127.9, 127.2, 126.6, 125.8 (ArCH), 100.7 (=CH), 88.3 (CCl₂), 51.9 (C), 45.0 (CH₂Ar), 28.7 (CH₂), 28.1 (CH₃).

γ-Lactam 5p



Physical state: colourless viscous oil

¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.36-7.14 (m, 8H, ArH), 5.24 (dd, *J* = 6.2, 2.3 Hz, 1H, =CH), 4.98 (s, 1H), 4.90 (d, *J* = 15.3 Hz, 1H, CH₂Ar), 4.63 (d, *J* = 15.3 Hz, 1H, CH₂Ar), 3.41 (br d, *J* = 20.1 Hz, 1H), 3.32 (dd, *J* = 20.1 Hz, 1H), 1.35 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.0 (CO), 142.5, 140.6, 135.4 (C), 128.7, 128.0, 127.7, 127.4, 127.0, 126.9, 124.3 (ArCH), 98.5 (=CH), 64.6 (CHCl), 45.5 (C), 44.5 (CH₂Ar), 29.0 (CH₂), 24.1 (CH₃); HRMS (ESI-TOF) calcd. for C₂₀H₁₉CINO [M+H]⁺ 324.1150, found 324.1153.

(4aRS,8aSR)-2-Benzyl-4,4-dichlorohexahydroisoquinoline-3,6(2H,4H)-dione (2q)



Physical state: amorphous solid

¹H NMR (400 MHz CDCl₃) δ 7.39-7.25 (m, 5H, ArH), 4.77 (d, *J* = 14.5 Hz, 1H, CH₂Ar), 4.57 (d, *J* = 14.5 Hz, 1H, CH₂Ar), 3.48 (dd, *J* = 13.1, 10.6 Hz, 1H), 3.36 (dd, *J* = 13.1, 7.0 Hz, 1H), 3.04-2.90 (m, 3H), 2.43-2.27 (m, 3H), 2.01-1.83 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 207.1 (CO), 162.5 (CO), 135.6 (*ipso*-C), 129.0, 128.2, 128.1, 85.6 (C), 51.7 (CH₂Ar), 50.0 (CH), 46.8 (CH₂), 40.0 (CH₂), 35.9 (CH₂), 28.8 (CH), 25.5 (CH₂); IR (NaCl) 3061, 3029, 2929, 1714, 1673 cm⁻¹; HRMS (ESI-TOF) calc. for C₁₆H₁₈Cl₂NO₂ [M+H]⁺ 326.0709, found 326.0713.

(1*RS*,5*SR*)-2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1]nonan-3-one (2r)

Physical state: White solid, m.p.: 116-120 °C

¹H NMR (400 MHz CDCl₃) δ 7.36-7.24 (m, 5H, ArH), 5.36 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 3.86 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 3.53 (br s, 1H, H-1), 2.84 (m, 1H, H-5), 2.57 (dm, *J* = 13.7, 1H), 2.43 (dm, *J* = 13.6, 1H), 1.85 (m, 1H), 1.80 (ddd, *J* = 13.7, 3.5, 2.4 Hz, 1H), 1.70-1.53 (m, 2H), 1.50-1.37 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 165.6 (CO), 136.6 (*ipso*-C), 128.8, 127.8, 127.7 (ArCH), 87.9 (C-4), 52.1 (C-1), 49.1 (CH₂Ar), 45.8 (C-5), 29.8 (CH₂), 28.9 (CH₂), 27.9 (CH₂), 16.1 (CH₂); IR (NaCl) 3060, 3031, 2958, 2929, 2870, 1662, 1601 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₅H₁₈Cl₂NO [M+H]⁺ 298.0760, found 298.07061.⁹

(1*RS*,5*RS*,6*RS*)-2-Benzyl-4,4,6-trichloro-6-methyl-2-azabicyclo[3.3.1]nonan-3-one (3s)



Physical state: white solid, m.p.: 72-74 °C

¹H NMR (400 MHz, CDCl₃) δ 7.39-7.21 (m, 5H, ArH), 5.34 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 3.90 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 3.52 (br s, 1H, H-1), 3.07 (br s, 1H, H-5), 2.80-2.67 (m, 2H, CH₂-9), 2.12 (s, 3H, CH₃), 2.05-1.94 (m, 2H, H-7 and H-8), 1.88-1.71 (m, 2H, H-7 and H-8); ¹³C NMR (101 MHz, CDCl₃) δ 164.1 (CO), 136.2 (*ipso*-C), 128.9, 127.9, 127.8 (ArCH), 85.7 (C-4), 75.6 (C-6), 56.5 (C-5), 50.7 (C-1), 49.2 (CH₂Ar), 35.4 (CH₃), 33.1 (C-7), 29.4 (C-9), 25.3 (C-8); IR (NaCl) 3054, 3030, 2982, 2941, 1673 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₆H₁₉Cl₃NO [M+H]⁺ 346.0527, found 346.0526. Calcd. for C₁₆H₁₈Cl₃NNaO [M+Na]⁺ 368.0346, found 368.0350.

(1*RS*,5*RS*)-2-Benzyl-4,4-dichloro-6-methylene-2-azabicyclo[3.3.1]nonan-3-one (4s)



⁹ For the characterization of **3r** see: F. Diaba , A. Martínez-Laporta , J. Bonjoch , A. Pereira , J. M. Muñoz-Molina , P. J. Pérez and T. R. Belderrain , *Chem. Commun.*, 2012, **48** , 8799-8801.

¹H NMR (400 MHz, CDCl₃) δ 7.37-7.24 (m, 5H, ArH), 5.38 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 4.96 (dm, *J* = 6.3 Hz, 2H, =CH₂), 3.93 (d, *J* = 14.9 Hz, 1H, CH₂Ar), 3.59 (br s, 1H, H-1), 3.40 (br s, 1H, H-5), 2.66 (ddt, *J* = 13.7, 4.0, 2.7 Hz, 1H, H-9), 2.33-2.25 (m, 1H, H-7), 2.23-2.10 (m, 1H, H-7), 1.95 (dm, 1H, *J* = 13.4, 1H, H-8), 1.86 (ddd, *J* = 13.7, 3.7, 2.4 Hz, 1H, H-9), 1.51 (tdd, *J* = 13.4, 5.2, 2.4 Hz, 1H, H-8); ¹³C NMR (101 MHz, CDCl₃) δ 165.1 (CO), 144.2 (C-6), 136.4 (*ipso*-C), 128.9, 127.8 (ArCH), 114.4 (=CH₂), 85.3 (C-4), 55.9 (C-5), 51.9 (C-1), 49.3 (CH₂Ar), 31.2 (C-9), 29.4 (C-7), 25.4 (C-8); IR (NaCl) 3061, 3031, 2938, 2857, 1667, 1604, 1584 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₆H₁₇Cl₂NO [M+H]⁺ 309.0682, found 309.0685.



5. Reactions achieved from 2e and epi-2e

5.1. Reductive dechlorination of 2e and epi-2e

To a solution **2e** (465.4 mg, 1.7 mmol) in MeOH (18 mL) was added NH₄Cl (540 mg, 10.1 mmol) and Zn (1.12 g, 17.1 mmol) and the mixture was stirred at 0 °C for 1 h and then at rt overnight. The reaction mixture was filtered through a short celite pad and the filter cake was washed with MeOH. The solution was then concentrated and purified by chromatography using a mixture of Hexane/EtOAc (1:0 to 1:1) to yield **7e** (291.8 mg, 84%). Operating from *epi-2e* and following the same procedure *epi-7e* was isolated (70%).

(S)-4-Methyl-1-((S)-1-phenylethyl)pyrrolidin-2-one (7e)

Physical state: colourless viscous oil

[α]²³_D = -134.6 (*c* 1, MeOH)

¹H NMR (400 MHz, CDCl₃) δ 7.38-7.22 (m, 5H, ArH), 5.49 (q, *J* = 7.1 Hz, 1H), 3.09 (dd, *J* = 9.6, 7.6 Hz, 1H, H-5), 2.87 (dd, *J* = 9.6, 6.3 Hz, 1H, H-5), 2.56 (dd, *J* = 16.5, 8.4 Hz, 1H, H-3), 2.30 (octet, *J* = 7.1 Hz, 1H, H-4), 2.07 (dd, *J* = 16.5, 7.4 Hz, 1H, H-3), 1.51 (d, *J* = 7.1 Hz, 3H, CH₃), 1.09 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 174.0 (CO), 140.3 (*ipso*-C), 128.4, 127.3, 127.0 (ArCH), 49.6 (C-5), 48.7 (CH), 39.8 (C-3), 26.5 (C-4), 19.5 (CH₃), 16.1 (CH₃). IR (NaCl) 3030, 2961, 2932, 2873, 1667 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₃H₁₈NO [M+H]⁺ 204.1383, found 204.1385.

(*R*)-4-Methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (*epi*-7e)

Physical state: colourless viscous oil

 $[\alpha]_{D}^{23}$ = -141.3 (*c* 1, MeOH)

¹H NMR (400 MHz, CDCl₃) δ 7.39-7.22 (m, 5H, ArH), 5.50 (q, *J* = 7.1 Hz, 1H), 3.42 (dd, *J* = 9.5, 7.5 Hz, 1H, H-5), 2.59 (dd, *J* = 16.5, 8.4 Hz, 1H, H-3), 2.51 (dd, *J* = 9.5, 5.6 Hz, 1H, H-5), 2.37 (m, 1H, H-4), 2.03 (dd, *J* = 16.5, 6.4 Hz, 1H, H-3), 1.51 (d, *J* = 7.2 Hz, 3H, CH₃), 0.97 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 174.0 (CO), 140.1 (*ipso*-C), 128.5, 127.4, 127.1 (ArCH), 49.4 (C-5), 48.7 (CH), 39.8 (C-3), 26.4 (C-4), 19.6 (CH₃), 16.1 (CH₃); IR (NaCl) 3030, 2961, 2932, 2872, 1667cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₃H₁₈NO [M+H]⁺ 204.1383, found 204.1379.





Epi-7e

5.2. Reduction of amides 7e and epi-7e

To a solution of AlCl₃ (39 mg, 0.29 mmol) in THF (0.86 mL) was added a 1 M solution of LiAlH₄ in THF (0.46 mL, 0.46 mmol) and the mixture was stirred at rt for 15 min. A solution of **6e** (39 mg, 0.19 mmol) in THF (0.75 mL) was then added dropwise and the mixture was stirred at rt for 4 h under argon atmosphere. The mixture was cooled to 0 °C and quenched with a NaOH aqueous solution until basic PH, extracted with CHCl₃ and the organics were dried and concentrated to yield **8e** (26.6 mg, 73%). Operating from *epi*-**7e** and following the same procedure *epi*-**8e** was isolated (68%).

(S)-3-Methyl-1-((S)-1-phenylethyl)pyrrolidine (8e)



Physical state: colourless viscous oil

 $[\alpha]_{D}^{23}$ = -47.2 (*c* 1, MeOH)

¹H NMR (400 MHz, CDCl₃) δ 7.37-7.17 (m, 5H, ArH), 3.18 (q, *J* = 6.6 Hz, 1H), 2.93 (dd, *J* = 9.1, 7.6 Hz, 1H, H-2), 2.51-2.40 (m, 2H, CH₂-5), 2.31-2.18 (m, 1H, H-3), 2.97 (m, 1H, H-4), 1.94 (dd, *J* = 9.0, 7.3 Hz, 1H, H-2), 1.37 (d, *J* = 6.6 Hz, 3H, CH₃), 1.30 (ddt, *J* = 12.5, 8.2, 6.2 Hz, 1H, H-4), 1.00 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.8 (*ipso*-C), 128.2, 127.2, 126.7 (ArCH), 66.0 (CH), 61.0 (C-2), 53.0 (C-5), 32.6 (C-4), 31.7 (C-3), 23.2 (CH₃), 20,5 (CH₃); IR (NaCl) 3025, 2954, 2926, 2870, 2774 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₃H₂₀N [M+H]⁺ 190.1590, found 190.1592.

(R)-3-Methyl-1-((S)-1-phenylethyl)pyrrolidine (epi-8e)



Physical state: colourless viscous oil

 $[\alpha]_{D}^{23}$ = -63.0 (*c* 1, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.35-7.19 (m, 5H, ArH), 3.16 (q, *J* = 6.6 Hz, 1H), 2.87 (m, 1H, H-5), 2.65 (dd, *J* = 9.1, 7.3 Hz, 1H, H-2), 2.33 (td, *J* = 9.0, 6.5 Hz, 1H, H-5), 2.26-2.09 (m, 1H, H-4), 2.03 (dddd, *J* = 12.5, 9.4, 8.0, 6.5, H-4), 1.87 (dd, *J* = 9.1, 7.9 Hz, 1H,

H-2), 1.37 (d, J = 6.6 Hz, 3H, CH₃),1.36-1.27 (m, 1H, H-3), 0.96 (d, J = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.8 (*ipso*-C), 128.2, 127.2, 126.8 (ArCH), 66.1 (CH), 61.3 (C-2), 52.7 (C-5), 32.5 (C-4), 31.8 (C-3), 23.0 (CH₃), 20.1 (CH₃); IR (NaCl) 3026, 2956, 2927, 2870, 2777 cm⁻¹; HRMS (ESI-TOF) calcd. for C₁₃H₂₀N [M+H]⁺ 190.1590, found 190.1592.

5.3. Debenzylation of amines 8e and epi-8e

To a solution **8e** (465.4 mg, 1.7 mmol) in MeOH (18 mL) was added NH₄Cl (540 mg, 10.1 mmol) and Zn (1.12 g, 17.1 mmol) and the mixture was stirred at 0 °C for 1 h and then at rt overnight. The reaction mixture was filtered through a short celite pad and the filter cake was washed with MeOH. The solution was then carefully concentrated to yield **9e** (208 mg, 60%). Operating from *epi-8e* and following the same procedure *epi-9e* was isolated (59%).¹⁰

 ¹⁰ The ¹H and ¹³C NMR as well as the specific rotation data of **9** and *epi-9* are in accordance with the litterature see: (a) K. Kondo; H. Ogawa, T. Shinohara, M. Kurimura, Y. Tanada, K. Kan, H. Yamashita, S. Nakamura, T. Hirano, Y. Yamamura, T. Mori, M. Tominaga, A. Itai, *J. Med. Chem.*, 2000, **43**, 4388–4397; (b) B. Ringdahl, R. Dahlbom, *Acta Pharm. Suec.*, 1978, **15**, 255-263.

6. ¹H and ¹³C NMR spectra of new compounds

ÇCl₃ ≥0 Ņ 1j ⁱBu



100 90 f1 (ppm)











S22



S23











100 90 f1 (ppm)









f1 (ppm)







GT818-47-14/1H Equip: B400F / N.Inv: 1037597 N.Reg: 23020177 Usuari: san / Mostra: XGT818-47-14 Nom: GISELA TRENCHS MIR Data: 06/02/2023 10:10:37 h./ Ope.: AUTOSERVEI Experiment: A-H1-zg30 Solvent: CDCI3

































GT807-22/1H Equip: B400F / N.Inv: 1037597 N.Reg: 23010536 Usuari: san / Mostra: KOT807-22 Nom: GISELA TRENCHS MIR Data: 19/01/2023 14:54:46 h./ Ope.: AUTOSERVEI Experiment: A-H1-zg30 Solvent: CDCI3

ſ ſ Ĵ ſ н **I-68.0** 0.72 2.63 2.02 2.05 5.29 9 -36.0 46:0 -98 5.0 4.5 f1 (ppm) 0.0 9.5 7.5 3.5 2.5 9.0 8.5 8.0 7.0 6.5 6.0 5.5 4.0 3.0 2.0 1.5 1.0 0.5 0.0 GT807-22/13C Equip: B400F / N.Inv: 1037597 N.Reg: 23010536 Usuari: san / Mostra: XGT807-22 Nom: GISELA TRENCHS MIR Data: 20/01/2023 00:47:07 h./ Ope.: AUTOSERVEI Experiment: A-C13-zgpg30 Solvent: CDCl3 00.77 128.88 127.79 56.53 50.70 49.16 35.40 33.10 29.37 25.29 - 136.18 / 30.93 164.10 85.74

0 00 190 100 90 f1 (ppm) 30 20 180 170 160 150 140 130 120 110 80 70 60 50 40 10



^{4s} with evolution products











100 90 f1 (ppm)





100 90 f1 (ppm)



23070654_B400FA_21072023_XGT938-10-B,1512 2020 Equip: B400F / N.Inv: 1037597 N.Reg: 23070654 Usuari: san / Mostra: XGT938-10-B Nom: GISELA TRENCHS MIR Data: 21/07/2023 13:14:56 h./ Ope.: AUTOSERVEI Experiment: A-H1-zg30 Solvent: CDCI3





