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General Information: GC measurements were performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and autosampler, J&W HP-5MS column (20 m x 0.18 mm, 0.18 μ m) from Agilent Technologies coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source/chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scan. The source temperature was maintained at 230 °C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Microwave reactions were performed in a Biotage Initiator 60. Flow reactions were carried out on a R2/R4 Vapourtec reactor. ¹H NMR spectra were recorded on Bruker DPX-400 or Bruker AV-500 spectrometers with standard pulse sequences, operating at 400MHz and 500MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard.

General flow procedure for zinc activation A: A solution of TMSCl 2 M (2.4 mL TMSCl in 10 mL THF) was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) at 1 mL/min at room temperature. After that, a solution of 1,2-dibromoethane 1 M (0.84 mL in 10 mL of DMF) was passed through the column containing Zn (12 g) at 1 mL/min at room temperature. 20 mL of THF was then passed through the column in order to wash the activated Zn. After the activation a solution of ethyl bromoacetate 0.5M in THF was passed through the column at 0.5 mL/min and at room temperature. The solution was collected in a sealed vial under nitrogen.

An accurately weighed sample of I₂ (typically between 60.0 and 80.0 mg) is dissolved in 1 mL of THF and stirred at room temperature under nitrogen while the organozinc reagent is added slowly until the purple colour of the solution disappeared. The calculated concentration of the organozinc reagent was 0.15M.

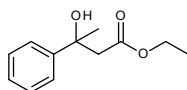
General flow procedure for zinc activation B: A solution of TMSCl 2M and 1-bromo-2-chloroethane 0.24M in 10 mL THF was passed through a column containing Zn (12g) at 1 mL/min at 40 °C. After the activation a solution of ethyl bromoacetate 0.5M in THF was passed through the column at 0.5 mL/min and at room temperature. The solution was collected in a sealed vial under nitrogen.

An accurately weighed sample of I₂ (typically between 60.0 and 80.0 mg) is dissolved in 1 mL of THF and stirred at room temperature under nitrogen while the organozinc reagent is added slowly until the purple colour of the solution disappeared. The calculated concentration of the organozinc reagent was 0.45M.

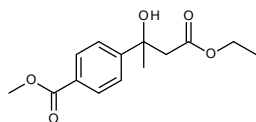
General flow procedure for Reformatsky reaction A: A solution of the correspondent acetophenone (0.1 mL, 0.86mmol) and bromoacetate (0.2mL, 1.72 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was quenched with a saturated solution of ammonium chloride and extracted with AcOEt. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 20:80. The desired fractions were collected and concentrated in vacuo to yield the final compound.

General flow procedure for Reformatsky reaction B: A solution of the ethyl bromoacetate (0.2mL, 1.82 mmol) in 0.9 mL of LiCl 0.5M of THF and a solution of acetylpyridine (0.1 mL, 0.81 mmol) in 0.9 mL in THF were passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 80°C and a flow rate of 0.25 mL/min. The outlet solution was quenched

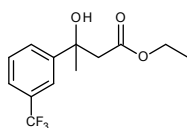
with a saturated solution of ammonium chloride and extracted with AcOEt. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 50:50. The desired fractions were collected and concentrated in vacuo to yield the final compound.



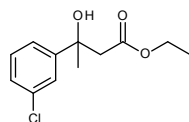
Compound 3aa was obtained as pale yellow oil (163 mg, 92% yield). MS (ESI): mass calcd. for C₁₂H₁₆O₃, 208.1099; m/z found, 209.1102 [M+H]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.45 (d, *J*=7.7 Hz, 2H), 7.33 (t, *J*=7.5 Hz, 2H), 7.21-7.27 (m, 1H), 4.37 (s, 1H), 4.00-4.18 (m, 2H), 2.97 (d, *J*=15.9 Hz, 1H), 2.79 (d, *J*=15.9 Hz, 1H), 1.55 (s, 3H), 1.08-1.18 ppm (m, 3H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 173.1, 147.3, 128.6, 127.3, 124.9, 73.2, 61.4, 46.9, 31.1, 14.4 ppm.



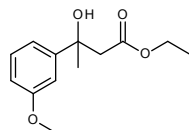
Compound 3ba was obtained as colorless oil (145 mg, 77% yield) using the general procedure A. MS (ESI): mass calcd. for C₁₄H₁₈O₅, 266.1154; m/z found, 266.1153 [M+H]⁺. ¹H NMR (400 MHz, CdCl₃) δ ppm 7.98 - 8.03 (m, 2 H), 7.50 - 7.55 (m, 2 H), 4.47 (s, 1 H), 4.05 (qd, *J*=7.17, 1.85 Hz, 2 H), 3.91 (s, 3 H), 2.98 (d, *J*=15.95 Hz, 1 H), 2.81 (d, *J*=16.18 Hz, 1 H), 1.54 (s, 3 H), 1.14 (t, *J*=7.17 Hz, 3 H). ¹³C NMR (101 MHz, CHLOROFORM-d) δ ppm 172.90, 167.31, 152.45, 130.05, 129.22, 125.03, 73.21, 61.32, 52.47, 46.54, 30.92, 14.41.



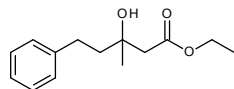
Compound 3ca was obtained as colorless oil (146 mg, 83% yield) using the general procedure A. MS (ESI): mass calcd. for C₁₃H₁₅F₃O₃, 276.0973; m/z found., 299.5808 [M+Na]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.73 (s, 1H), 7.65 (d, *J*=7.6 Hz, 1H), 7.42-7.53 (m, 2H), 4.48 (a, 1H), 4.07 (q, *J*=7.0 Hz, 2H), 2.95 (d, *J*= 12 Hz, 1H), 2.77 (d, *J*= 12 Hz, 1H), 1.55 (s, 3H), 1.13 ppm (t, *J*=7.2 Hz, 3H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 172.9, 148.4, 129.2, 128.5, 128.4, 124.2 (q, *J*=3.90 Hz, 1 C), 121.9 (q, *J*=3.90 Hz, 1 C), 73.0, 61.4, 46.6, 31.0, 14.3 ppm.



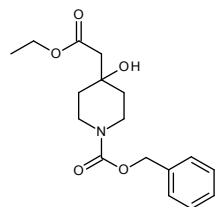
Compound 3da was obtained as colorless oil (157 mg, 84%) using the general procedure A. MS (ESI): mass calcd. for $C_{12}H_{15}ClO_3$, 242.0709; m/z found, 243.0503 $[M+H]^+$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.47 (t, J =1.8 Hz, 1H), 7.19-7.34 (m, 4H), 4.42 (s, 1H), 4.08 (q, J =7.2 Hz, 2H), 2.94 (d, J =16 Hz, 1H), 2.78 (d, J =16 Hz, 1H), 1.52 (s, 3H), 1.15 (t, J =7.2 Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 173.0, 149.5, 134.7, 130.0, 127.5, 125.5, 123.1, 72.9, 61.4, 46.5, 31.0, 14.4 ppm.



Compound 3ea was obtained as colorless oil (164 mg, 94%) using the general procedure A. MS (ESI): mass calcd. for $C_{13}H_{18}O_4$, 238.1205; m/z found, 261.1107 $[M+Na]^+$. 1H NMR (400 MHz, CHLOROFORM- d) δ ppm 7.25 (d, J =8.32 Hz, 1 H), 7.06 (m, 1 H), 6.98 (m, 1 H), 6.78 (ddd, J =8.09, 2.54, 0.92 Hz, 1 H), 4.38 (s, 1 H), 4.07 (q, J =7.17 Hz, 2 H), 3.81 (s, 3 H), 2.97 (d, J =15.95 Hz, 1 H), 2.78 (d, J =15.95 Hz, 1 H), 1.53 (s, 3 H), 1.15 (t, J =7.17 Hz, 3 H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 173.1, 160.0, 149.1, 129.6, 117.2, 112.6, 110.9, 73.1, 61.2, 55.6, 46.7, 31.1, 14.4 ppm.

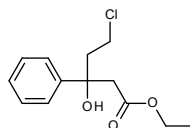


Compound 3fa was obtained as colorless oil (142 mg, 90%) using the general procedure A. MS (ESI): mass calcd. for $C_{14}H_{20}O_3$, 236.31412; m/z found, 259.1310 $[M+Na]^+$. 1H NMR (CHLOROFORM- d , 500MHz): δ = 7.26-7.30 (m, 2H), 7.16-7.21 (m, 3H), 4.19 (q, J =7.2 Hz, 2H), 3.63 (s, 1H), 2.67-2.76 (m, 2H), 2.56 (d, J =15.9 Hz, 1H), 2.50 (d, J =15.9 Hz, 1H), 1.80-1.89 (m, 2H), 1.32 (s, 3H), 1.28 ppm (t, J =7.2 Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 126MHz): δ = 173.0, 142.3, 128.4, 128.3, 125.8, 70.8, 60.7, 45.8, 43.9, 30.3, 26.7, 14.2 ppm.

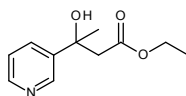


Compound 3ga was obtained as colorless oil (302 mg, 88%) using the general procedure A. MS (ESI): mass calcd. for $C_{17}H_{23}NO_5$, 321.1576; m/z found, 344.1482 $[M+Na]^+$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.29-7.40 (m, 3H), 5.12 (s, 2H), 4.18 (q, J =7.1 Hz, 2H), 3.83-4.02 (m, 2H), 3.27 (m, 2H), 2.46 (s, 2H),

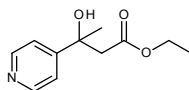
1.42-1.75 (m, 4H), 1.28 ppm (t, $J=7.1$ Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 173.0, 155.6, 137.3, 128.9, 128.4, 128.3, 68.3, 67.4, 61.3, 45.8, 40.1, 14.6 ppm.



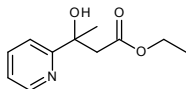
Compound 3ha was obtained as colorless oil (135 mg, 71%) using the general procedure A. MS (ESI): mass calcd. for $\text{C}_{13}\text{H}_{17}\text{ClO}_3$, 256.0866; m/z found, 279.0678 $[\text{M}+\text{Na}]^+$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.32-7.41 (m, 3H), 7.23-7.28 (m, 2H), 4.56 (s, 1H), 4.03 (q, $J=7.1$ Hz, 2H), 3.62 (td, $J=10.8$, 5.3 Hz, 1H), 3.16 (td, $J=10.7$, 5.4 Hz, 1H), 2.97 (d, $J=15.8$ Hz, 1H), 2.84 (d, $J=15.8$ Hz, 1H), 2.20-2.37 (m, 2H), 1.10 ppm (t, $J=7.1$ Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.5, 143.7, 128.5, 127.3, 124.8, 74.3, 61.0, 45.8, 45.6, 39.7, 13.9 ppm.



Compound 3ia was obtained as colorless oil (159 mg, 83%) using the general procedure B. MS (ESI): mass calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_3$, 209.1052; m/z found, 210.1162 $[\text{M}+\text{H}]^+$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 8.74 (d, $J=1.8$ Hz, 1H), 8.56 (dd, $J=4.9$, 1.6 Hz, 1H), 7.92 (dt, $J=7.9$, 2.0 Hz, 1H), 7.35 (dd, $J=8.1$, 4.9 Hz, 1H), 4.54 (s, 1H), 4.05-4.14 (m, 2H), 2.93 (d, $J=15.8$ Hz, 1H), 2.83 (d, $J=15.8$ Hz, 1H), 1.57 (s, 3H), 1.17 ppm (t, $J=7.2$ Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.7, 148.4, 146.6, 143.5, 134.2, 124.1, 72.0, 61.5, 46.4, 30.9, 14.4 ppm.

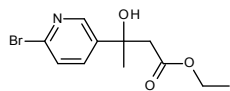


Compound 3ja was obtained as colorless oil (153 mg, 81%) using the general procedure B. MS (ESI): mass calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_3$, 209.1052; m/z found, 210.1158 $[\text{M}+\text{H}]^+$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 8.69 (d, $J=6.5$ Hz, 2H), 7.51 (d, $J=6.0$ Hz, 2H), 4.62 (s, 1H), 4.05-4.07 (m, 2H), 2.94 (d, $J=15.7$ Hz, 1H), 2.82 (d, $J=15.7$ Hz, 1H), 1.52 (s, 3H), 1.17 ppm (t, $J=7.2$ Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.5, 159.1, 149.6, 121.3, 72.5, 61.7, 45.8, 30.4, 14.4 ppm.

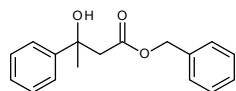


Compound 3ka was obtained as colorless oil (158 mg, 85%) using the general procedure B. MS (ESI): mass calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_3$, 209.1052; m/z found, 210.1159 $[\text{M}+\text{H}]^+$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 8.35-8.56 (m, 1H), 7.70 (td, $J=7.7$, 1.7 Hz, 1H), 7.58-7.64 (m, 1H), 7.16 (ddd, $J=7.4$, 4.9, 1.2 Hz, 1H), 4.94 (s, 1H), 3.93-4.13 (m, 2H), 3.18 (d, $J=15.7$ Hz, 1H), 2.82 (d, $J=15.7$ Hz, 1H), 1.55 (s, 3H), 1.15 ppm (t, $J=7.2$ Hz, 3H).

Hz, 3H). ^{13}C NMR (CHLOROFORM-*d*, 101MHz): δ = 172.9, 165.4, 148.3, 137.2, 122.3, 119.7, 74.1, 60.9, 46.1, 29.7, 14.4 ppm

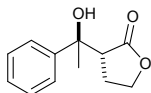


Compound 3la was obtained as colorless oil (125 mg, 69%) using the general procedure B. MS (ESI): mass calcd. for $\text{C}_{11}\text{H}_{14}\text{BrNO}_3$, 287.0157; m/z found, 288.0268 $[\text{M}+\text{H}]^+$. ^1H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.42 (dd, J =2.8, 0.7 Hz, 1H), 7.69 (dd, J =8.3, 2.5 Hz, 1H), 7.45 (dd, J =8.6, 0.7 Hz, 1H), 4.53 (s, 1H), 4.05-4.17 (m, 2H), 2.93 (d, J =15.8 Hz, 1H), 2.73-2.80 (d, J =15.8 Hz, 1H), 1.54 (s, 3H), 1.10-1.27 ppm (m, 3H). ^{13}C NMR (CHLOROFORM-*d*, 101MHz): δ = 172.7, 147.4, 142.2, 141.1, 135.9, 128.0, 71.8, 61.6, 46.2, 30.9, 14.4 ppm.

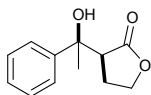


Compound 3ab was obtained as colorless oil (158 mg, 92%) using the general procedure A. MS (ESI): mass calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_3$, 270.1256; m/z found, 293.1157 $[\text{M}+\text{Na}]^+$. ^1H NMR (CHLOROFORM-*d*, 400MHz): δ = 7.42-7.47 (m, 2H), 7.29-7.35 (m, 5H), 7.22-7.27 (m, 1H), 7.14-7.18 (m, 2H), 5.03 (s, 2H), 4.31 (s, 1H), 3.05 (d, J =16.0 Hz, 1H), 2.85 (d, J =16.0 Hz, 1H), 1.51-1.57 ppm (m, 4H). ^{13}C NMR (CHLOROFORM-*d*, 101MHz): δ = 172.5, 146.7, 135.2, 128.6, 128.3, 128.3, 128.1, 126.9, 124.5, 72.8, 66.5, 46.4, 30.8 ppm.

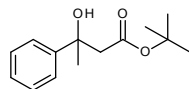
Compound 3ac was obtained as two diastereoisomers 7:4 as colorless oil (163 mg, 91%) using the general procedure A.



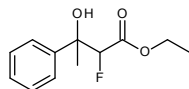
MS (ESI): mass calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3$, 206.0943; m/z found, 229.0846 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.42 (m, 2 H), 7.36 (m, 2 H), 7.26 (m, 1 H), 4.13 (m, 1 H), 4.03 (br s, 1 H), 3.14 (br d, J =9.02 Hz, 1 H), 2.99 (t, J =9.13 Hz, 1 H), 2.02 (m, 2 H), 1.85 (m, 3 H). ^{13}C NMR (CHLOROFORM-*d*, 101MHz): δ = 178.0, 145.7, 128.8, 127.5, 125.4, 75.0, 67.1, 50.3, 29.3, 26.0 ppm.



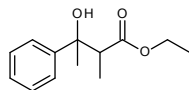
^1H NMR (CHLOROFORM-*d*, 400MHz): δ = 7.72-7.72 (m, 1H), 7.44-7.55 (m, 2H), 7.33-7.40 (m, 2H), 7.24-7.32 (m, 1H), 4.14-4.21 (m, 1H), 4.09 (td, J =9.2, 6.9 Hz, 1H), 4.01 (s, 1H), 2.97 (dd, J =10.4, 9.5 Hz, 1H), 1.99-2.19 (m, 2H), 1.70 (s, 3H). ^{13}C NMR (CHLOROFORM-*d*, 101MHz): δ = 178.7, 145.0, 128.8, 127.9, 125.6, 74.4, 66.9, 51.4, 26.2, 24.5 ppm.



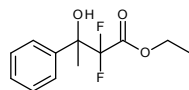
Compound 3ad was obtained as colorless oil (152 mg, 75%) using the general procedure A. MS (ESI): mass calcd. for $C_{14}H_{20}O_3$, 236.1412; m/z found, 259.1314 $[M+Na]^+$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.43-7.47 (m, 2H), 7.29-7.35 (m, 2H), 7.20-7.25 (m, 1H), 4.46 (s, 1H), 2.89 (d, $J=15.5$ Hz, 1H), 2.70 (d, $J=15.5$ Hz, 1H), 1.52 (s, 3H), 1.28 ppm (m, 9H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.4, 147.4, 128.5, 127.1, 125.0, 82.1, 73.3, 48.0, 31.1, 28.3 ppm.



Compound 3ae was obtained as a diastereoisomer mixture 1/1 as a colorless oil (162 mg, 93%) using the general procedure A. MS (ESI): mass calcd. for $C_{12}H_{15}FO_3$, 226.1005; m/z found, 249.0906 $[M+Na]^+$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.43-7.52 (m, 2H x2), 7.25-7.38 (m, 3H x2), 4.96-5.08 (m, 1H), 4.84-4.96 (m, 1H), 4.01-4.16 (m, 2H x2), 3.47 (s, 1H), 3.24 (d, $J=1.2$ Hz, 1H), 1.66-1.73 (m, 3H x2), 1.07 ppm (td, $J=7.1, 3.0$ Hz, 6H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 168.1, 167.9, 142.8, 142.1, 128.3, 128.2, 127.7, 125.4, 125.4, 125.1, 125.1, 94.4, 93.8, 92.5, 91.9, 75.1, 74.9, 74.7, 61.8, 61.7, 26.2, 26.1, 25.4, 25.4, 13.8, 13.8 ppm.

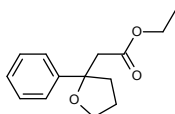


Compound 3af was obtained as a diastereoisomer mixture 1/1 as colorless oil (167 mg, 88%) using the general procedure A. MS (ESI): mass calcd. for $C_{13}H_{18}O_3$, 222.1255; m/z found, 223.1264 $[M+H]^+$. 1H NMR (400 MHz, CHLOROFORM- d) δ ppm 7.43 (m, 2H x2), 7.32 (m, 2H x2), 7.22 (m, 1H x2), 4.22 (m, 2 H), 4.09 (s, 1 H), 3.91 (m, 3 H), 3.00 (q, $J=7.17$ Hz, 1 H), 2.83 (q, $J=7.01$ Hz, 1 H), 1.57 (s, 3 H) 1.46 (s, 3 H), 1.32 (m, 3H x2), 0.96 (m, 3H x2). ^{13}C NMR (101 MHz, CHLOROFORM- d) δ ppm 177.74, 177.20, 147.99, 145.48, 128.51, 128.47, 127.16, 127.06, 125.27, 125.13, 75.06, 74.74, 61.32, 60.92, 49.72, 48.96, 30.36, 27.22, 14.6, 14.23, 13.20, 12.79.

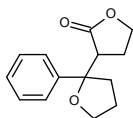


Compound 3ag. A solution of the difluoro-ethyl bromoacetate (0.1 mL, 0.81 mmol) in 0.9 mL of LiCl 0.5M in THF and a solution of acetylpyridine (0.2 mL, 1.82 mmol) in 0.9 mL in THF were passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 100°C and a flow rate of 0.25 mL/min. The outlet solution was quenched with a saturated solution of ammonium chloride and extracted with AcOEt. The organic layer was separated, dried

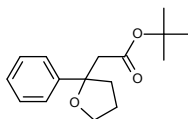
(Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 50:50. The desired fractions were collected and concentrated in vacuo to yield compound **3ag** as a pale yellow oil (112 mg, 54% yield). MS (ESI): mass calcd. for C₁₂H₁₄F₂O₃, 244.0911; m/z found, 267.0811 [M+Na]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.48-7.55 (m, 2H), 7.28-7.42 (m, 3H), 4.15 (q, *J*=7.2 Hz, 2H), 1.75 (t, *J*=1.5 Hz, 3H), 1.11 ppm (t, *J*=7.1 Hz, 3H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 167.9, 142.8, 127.7, 125.4, 93.8, 91.9, 61.7, 26.2, 25.4, 13.8 ppm.



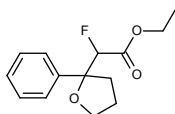
Compound 4ma was obtained as colorless oil (112 mg, 70%) using the general procedure A. MS (ESI): mass calcd. for C₁₄H₁₈O₃, 234.1256; m/z found, 257.1173 [M+Na]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.35-7.44 (m, 2H), 7.28-7.35 (m, 2H), 7.20-7.29 (m, 1H), 3.97-4.07 (m, 3H), 3.85-3.95 (m, 1H), 2.82 (dd, *J*= 12.1 and 4.2, 3H), 2.37-2.48 (m, 1H), 2.28-2.36 (m, 1H), 1.92-2.02 (m, 1H), 1.74-1.87 (m, 1H), 1.11 (t, *J*=7.1, 3H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 170.7, 146.2, 128.5, 127.2, 125.5, 85.0, 68.3, 60.6, 47.5, 37.8, 25.8, 14.5 ppm



Compound 4mc was obtained as colorless oil (87 mg, 62%) using the general procedure A. MS (ESI): mass calcd. for C₁₄H₁₆O₃, 232.1099; m/z found, 255.1002 [M+Na]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.32-7.36 (m, 4H), 7.22-7.29 (m, 1H), 4.30 (td, *J*=8.1, 6.8 Hz, 1H), 4.11 (td, *J*=8.3, 6.0 Hz, 1H), 3.91-4.01 (m, 2H), 3.10-3.20 (m, 1H), 3.05 (dd, *J*=9.5, 6.5 Hz, 1H), 2.15 (ddd, *J*=12.1, 7.8, 3.9 Hz, 1H), 1.88-2.05 (m, 3H), 1.66-1.79 ppm (m, 1H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 177.2, 146.4, 128.8, 127.3, 125.6, 87.6, 69.5, 67.2, 48.2, 36.5, 26.7, 25.8 ppm.



Compound 4md was obtained as colorless oil (101 mg, 56%) using the general procedure A. MS (ESI): mass calcd. for C₁₆H₂₂O₃, 262.1569; m/z found, 285.1470 [M+Na]⁺. ¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.36-7.46 (m, 2H), 7.29-7.36 (m, 2H), 7.19-7.29 (m, 1H), 3.96-4.07 (m, 1H), 3.90 (td, *J*=8.1, 5.5 Hz, 1H), 2.66-2.80 (m, 2H), 2.33-2.45 (m, 1H), 2.24-2.35 (m, 1H), 1.94-2.02 (m, 1H), 1.71-1.86 (m, 1H), 1.27-1.33 ppm (m, 9H). ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 170.0, 146.2, 128.4, 127.1, 125.8, 85.2, 80.7, 68.2, 48.6, 37.9, 28.3, 28.2, 25.7 ppm



Compound 4me was obtained as colorless oil (112 mg, 64%) using the general procedure A. MS (ESI): mass calcd. for $C_{14}H_{17}FO_3$, 252.1161; m/z found, 275.1070 $[M+Na]^+$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.24-7.46 (m, 5H), 4.85-5.11 (m, 1H), 3.98-4.16 (m, 3H), 3.91-3.98 (m, 1H), 2.63-2.79 (m, 1H), 2.14-2.33 (m, 1H), 1.96-2.10 (m, 1H), 1.77-1.92 (m, 1H), 1.05 ppm (dt, $J=7.9, 7.2$ Hz, 3H). ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 167.7 (dd, $J=32.75, 25.07$ Hz), 142.6, 142.6, 141.6, 141.5, 128.5, 128.1, 127.9, 126.5, 126.5, 126.1, 94.4, 94.2, 92.5, 92.3, 86.9 (d, $J=20.49$ Hz), 78.1, 78.0, 69.6, 69.3, 61.7, 61.6, 36.0, 35.9, 34.7, 34.7, 26.2, 26.0, 14.3, 14.2 ppm.

Scale up of Reformatsky Compound 3aa: A solution of acetophenone (4 mL, 34.3 mmol) and ethyl bromoacetate (4.5 mL, 41.15 mmol) in 22 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was quenched with a saturated solution of ammonium chloride and extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 90 g) from AcOEt in heptane 0:100 to 20:80. The desired fractions were collected and concentrated in vacuo to yield 6.48 g (92%) of the final compound.

	Flow	Batch ^a
Yield	92%	94%
Reaction Time	10 min	3 h
Product Throughput	10.5 g/3 h	324 mg/3 h
[1a]	1.55M	0.33M
Space-time Yield ^b	700 mg/h·mL	21.6 mg/h·mL

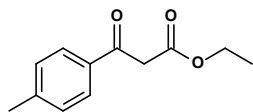
^a Batch results taken from reference.¹ ^b Calculated according to reference.²

Compound 6aa. General flow procedure for Blaise reaction: A solution of the ethyl bromoacetate (125 mg, 1 mmol) and p-tolunitrile (0.29 mL, 2.7 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was pumped through a 5 mL coil ($R_t = 10$ min) at 120°C. The final solution was collected over HCl and stirred for 1 h and then extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by

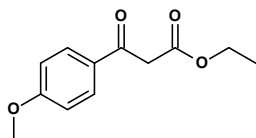
¹ H. S. Prakash Rao, N. Muthanna, *Synlett*, 2016, **27**, 2014.

² (a) S. G. Newman and K. Jenssen, *Green Chem.*, 2013, **15**, 1456; (b) H. Löwe, V. Hessel, P. Löbe and S. Hubbard, *Org. Process Res. Dev.*, 2006, **10**, 1144.

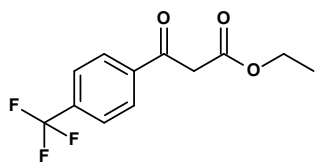
automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 50:50. The desired fractions were collected and concentrated in vacuo to yield compound **6aa** as a pale yellow oil (172 mg, 78% yield).



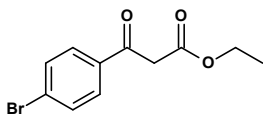
MS (ESI): mass calcd. for $C_{12}H_{14}O_3$, 206.0942; m/z found, 205.0932 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 500MHz): δ = 7.82-7.87 (m, 2H), 7.26-7.29 (m, 2H), 4.21 (q, $J=7.2$ Hz, 2H), 3.96 (s, 2H), 2.41-2.44 (m, 3H), 1.26 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 126MHz): δ = 192.2, 167.7, 144.7, 133.6, 129.4, 126.0, 86.7, 61.5, 46.0, 21.7, 14.4 ppm



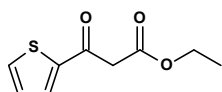
Compound 6ba was obtained as colorless oil (102 mg, 48%) using the general procedure. MS (ESI): mass calcd. for $C_{12}H_{14}O_4$, 222.0892; m/z found, 221.0816 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 500MHz): δ = 7.90-7.96 (m, 2H), 6.93-6.97 (m, 2H), 4.18-4.25 (m, 2H), 3.94 (d, $J=1.2$ Hz, 2H), 3.87 (s, 3H), 1.24-1.29 ppm (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 191.0, 167.7, 164.0, 129.1, 130.9, 113.9, 113.9, 61.4, 55.5, 45.8, 14.1 ppm.



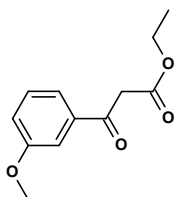
Compound 6ca was obtained as keto-enol mixture 1/1 as colorless oil (130 mg, 78%) using the general procedure. MS (ESI): mass calcd. for $C_{12}H_{11}F_3O_3$, 260.0660; m/z found, 259.0580 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 12.57 (s, 1H), 8.00-8.13 (m, 2H), 7.88 (d, $J=8.1$ Hz, 1H), 7.73-7.78 (m, 2H), 7.68 (d, $J=8.3$ Hz, 1H), 5.71 (s, 1H), 4.29 (q, $J=7.1$ Hz, 1H), 4.19-4.25 (m, 2H), 4.01 (s, 2H), 1.36 (t, $J=7.1$ Hz, 3H), 1.22-1.30 ppm (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 192.0, 173.3, 169.9, 167.4, 139.0, 135.2, 129.3, 89.4, 62.1, 61.1, 46.5, 14.6, 14.4 ppm.



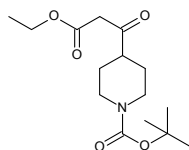
Compound 6da was obtained as keto-enol mixture 1/1 as colorless oil (125 mg, 67%) using the general procedure. MS (ESI): mass calcd. for $C_{11}H_{11}BrO_3$, 269.9891; m/z found, 268.9811 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 12.56 (s, 1H), 7.79-7.83 (m, 2H), 7.61-7.66 (m, 3H), 7.53-7.57 (m, 1H), 5.64 (s, 1H), 4.27 (q, $J=7.2$ Hz, 1H), 4.21 (q, $J=7.1$ Hz, 2H), 3.92-3.97 (m, 2H), 1.31-1.35 (t, $J=7.2$ Hz, 3H), 1.25 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 191.9, 173.4, 170.6, 167.6, 135.2, 132.8, 132.5, 132.2, 130.4, 129.5, 128.0, 126.1, 125.9, 88.1, 62.0, 60.9, 46.4, 34.6, 30.7, 14.7, 14.5 ppm



Compound 6ea was obtained as colorless oil (188 mg, 93%) using the general procedure. MS (ESI): mass calcd. for $C_9H_{10}O_3S$, 198.0350; m/z found, 197.0273 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.74 (dd, $J=3.9, 1.2$ Hz, 1H), 7.70 (dd, $J=4.9, 1.2$ Hz, 1H), 7.15 (dd, $J=4.9, 3.9$ Hz, 1H), 4.16-4.28 (m, 2H), 3.92 (s, 2H), 1.26 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 185.3, 167.4, 143.7, 135.3, 133.6, 128.7, 62.0, 46.9, 14.5 ppm.

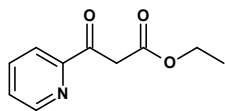


Compound 6fa was obtained as keto-enol mixture 1/1 as colorless oil (110 mg, 62%) using the general procedure. MS (ESI): mass calcd. for $C_{12}H_{14}O_4$, 222.0892; m/z found, 221.0816 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 500MHz): δ = 12.57 (s, 1H), 7.48-7.52 (m, 2H), 7.38 (t, $J=7.9$ Hz, 1H), 7.30-7.35 (m, 1H), 7.13-7.16 (m, 1H), 7.01 (ddd, $J=7.7, 2.7, 1.4$ Hz, 1H), 5.65 (s, 1H), 4.27 (q, $J=7.0$ Hz, 1H), 4.22 (q, $J=7.2$ Hz, 2H), 3.95-4.00 (m, 2H), 3.86 (s, 3H), 3.85 (s, 1H), 1.34 (t, $J=7.0$ Hz, 1H), 1.24-1.28 ppm (t, $J=7.2$ Hz, 1H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 191.0, 167.7, 164.0, 129.1, 130.9, 113.9, 113.9, 61.4, 55.5, 45.8, 14.1 ppm.

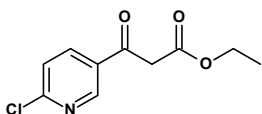


Compound 6ga was obtained as yellow oil (286 mg, 80%) using the general procedure. MS (ESI): mass calcd. for $C_{15}H_{25}NO_5$, 299.1732; m/z found, 298.1805 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ

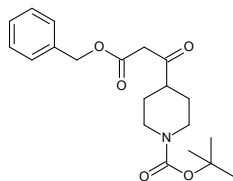
= 4.21 (m, 2H), 4.09 (m, 2H), 3.49 (s, 2H), 2.79 (br t, $J=12.1$ Hz, 2H), 2.63 (tt, $J=11.3$, 3.7 Hz, 1H), 1.85 (m, 2H), 1.55 (m, 2H), 1.43-1.48 (m, 9H), 1.27 ppm (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 204.2, 167.1, 154.6, 87.7, 79.7, 79.6, 61.5, 60.1, 48.7, 47.3, 43.1, 41.6, 28.5, 28.4, 27.3, 14.3, 14.1 ppm.



Compound 6ha was obtained as colorless oil (120 mg, 64%) using the general procedure and DMA as solvent. MS (ESI): mass calcd. for $\text{C}_{10}\text{H}_{10}\text{NO}_3$, 193.0738; m/z found, 192.0736 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 8.67 (d, $J=4.7$ Hz, 1H), 8.08 (dt, $J=7.9$, 1.0 Hz, 1H), 7.85 (td, $J=7.7$, 1.8 Hz, 1H), 7.49 (ddd, $J=7.6$, 4.8, 1.3 Hz, 1H), 4.17-4.23 (m, 4H), 1.24 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 194.7, 168.2, 152.4, 149.0, 137.0, 127.5, 122.1, 61.2, 44.9, 14.3, 14.1 ppm.

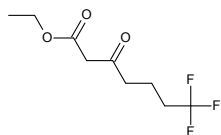


Compound 6ia was obtained as keto-enol mixture 1/1 as yellow oil (163 mg, 79%) using in the general procedure DMA as solvent. MS (ESI): mass calcd. for $\text{C}_{10}\text{H}_9\text{ClNO}_3$, 227.0349; m/z found, 226.0274 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 12.56 (s, 1H), 8.92 (d, $J=2.5$ Hz, 1H), 8.76 (d, $J=2.3$ Hz, 1H), 8.20 (dd, $J=8.4$, 2.4 Hz, 1H), 8.00 (dd, $J=8.3$, 2.5 Hz, 1H), 7.47 (dd, $J=8.3$, 0.7 Hz, 1H), 7.39 (d, $J=8.3$ Hz, 1H), 5.68 (s, 1H), 4.29 (q, $J=7.2$ Hz, 2H), 4.21 (q, $J=7.2$ Hz, 2H), 3.97 (s, 2H), 1.34 (q, $J=7.2$ Hz, 2H), 1.23-1.29 ppm (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 190.6, 173.0, 168.0, 166.9, 156.7, 150.7, 147.9, 138.8, 136.4, 130.7, 128.8, 125.1, 124.6, 89.4, 62.3, 61.2, 61.1, 46.5, 29.6, 14.6, 14.6, 14.5 ppm.

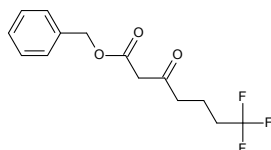


Compound 6gb was obtained as yellow oil (235 mg, 55%) using the general procedure. MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_5$, 361.1889; m/z found, 360.1902 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): δ = 4.21 (m, 2H), 4.09 (m, 2H), 3.49 (s, 2H), 2.79 (br t, $J=12.1$ Hz, 2H), 2.63 (tt, $J=11.3$, 3.7 Hz, 1H), 1.85 (m, 3H), 1.55 (m, 3H), 1.43-1.48 (m, 9H), 1.27 ppm (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ

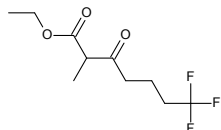
= 203.9, 167.0, 154.6, 135.2, 128.7, 128.5, 128.3, 128.2, 87.6, 79.7, 67.2, 65.9, 48.6, 47.3, 41.6, 28.4, 27.2 ppm.



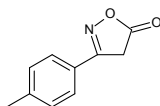
Compound 6ja was obtained as yellow oil (184 mg, 56%) using the general procedure. MS (ESI): mass calcd. for $C_9H_{13}F_3O_3$, 226.1956; m/z found, 225.1879 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 4.20 (q, $J=7.2$ Hz, 2H), 3.44 (s, 2H), 2.67 (t, $J=7.1$ Hz, 2H), 2.14 (m, 2H), 1.87 (m, 2H), 1.27 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 201.4, 167.0, 126.9 (q, $J=276.6$ Hz, 1 C), 61.5, 49.2, 41.1, 32.6 (q, $J=28.9$ Hz, 1 C), 15.9, 14.1 ppm.



Compound 6jb was obtained as yellow oil (233 mg, 55%) using the general procedure. MS (ESI): mass calcd. for $C_{14}H_{15}F_3O_3$, 288.2665; m/z found, 287.2589 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 400MHz): δ = 7.38 (m, 5H), 5.18 (m, 2H), 3.49 (s, 2H), 2.62 (t, $J=7.1$ Hz, 2H), 2.07 (m, 2H), 1.85 ppm (m, 2H); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 201.1, 166.8, 135.2, 128.7, 128.6, 128.5, 67.3, 49.2, 41.2, 32.6 (q, $J=28.85$ Hz, 1 C), 15.8 (q, $J=3.06$ Hz, 1 C) ppm.

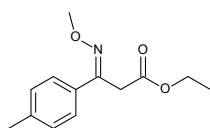


Compound 6jf was obtained as yellow oil (204 mg, 58%) using the general procedure. MS (ESI): mass calcd. for $C_{10}H_{15}F_3O_3$, 240.0973; m/z found, 239.1045 $[M-H]^-$. 1H NMR (CHLOROFORM- d , 500MHz): 4.21 (m, 2H), 3.51 (m, 1H), 2.72 (m, 1H), 2.58 (m, 1H), 2.12 (m, 2H), 1.86 (m, 2H), 1.34 (m, 3H), 1.27 ppm (m, 3H). ^{13}C NMR (126 MHz, CHLOROFORM- d) δ ppm 204.5, 170.6, 126.9 (q, $J=276.10$ Hz, 1 C), 61.5, 52.8, 39.6, 32.6 (q, $J=29.06$ Hz, 1 C), 16.0, 14.0, 12.7.

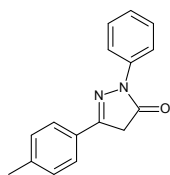


Compound 8. A solution of the ethyl bromoacetate (125 mg, 1 mmol) and p-tolunitrile (0.29 mL, 2.7 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution

was pumped through a 5 mL coil ($R_t = 10$ min) at 120°C. The final solution was collected over hydroxylamine (32.5 mg, 1.5 mmol) in EtOH (1.3 mL) and stirred for 1h at 60°C, water was added and then extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 40:60. The desired fractions were collected and concentrated in vacuo to yield compound **8** as a pale yellow oil (78 mg, 67% yield). MS (ESI): mass calcd. for $\text{C}_{10}\text{H}_9\text{NO}_2$, 175.0633; m/z found, 174.0274 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): $\delta = 7.53\text{--}7.60$ (m, 2H), 7.25-7.32 (m, 1H), 7.25-7.32 (m, 1H), 3.89 (s, 2H), 2.41 ppm (s, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): $\delta = 175.2, 163.4, 143.3, 130.3, 126.9, 125.3, 34.5, 22.0$ ppm

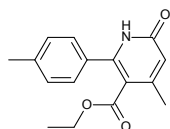


Compound 9. A solution of the ethyl bromoacetate (125 mg, 1 mmol) and p-tolunitrile (0.29 mL, 2.7 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was pumped through a 5mL coil ($R_t = 10$ min) at 120°C. The final solution was collected over o-methylhydroxylamine hydrochloride (81 mg, 1.5 mmol) in EtOH (2 mL) and stirred for 16h at 60°C, water was added and then extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 40:60. The desired fractions were collected and concentrated in vacuo to yield compound **9** as a pale yellow oil (105 mg, 69% yield). MS (ESI): mass calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_3$, 235.1208; m/z found, 234.1164 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): $\delta = 7.53$ (d, $J=7.9$ Hz, 2H), 7.17 (d, $J=7.9$ Hz, 2H), 4.12 (q, $J=7.1$ Hz, 2H), 3.96-4.02 (m, 3H), 3.70-3.77 (m, 2H), 2.32-2.38 (m, 3H), 1.25 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): $\delta = 169.3, 151.7, 139.8, 133.0, 129.6, 126.5, 62.5, 61.4, 33.6, 21.7, 14.5$ ppm.

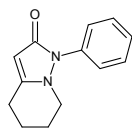


Compound 10. A solution of the ethyl bromoacetate (125 mg, 1mmol) and p-tolunitrile (0.29 mL, 2.7 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution

was pumped through a 5 mL coil ($R_t = 10$ min) at 120°C. The final solution was collected over phenylhydrazine (70 mg, 1 mmol) in EtOH (1.3 mL) and stirred for 1 h at 60°C, water was added and then extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 20:80. The desired fractions were collected and concentrated in vacuo to yield compound **10** as a pale yellow oil (125 mg, 76% yield). MS (ESI): mass calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$, 250.1106; m/z found, 249.1274 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): $\delta = 7.85$ (m, 2H), 7.64-7.69 (m, 2H), 7.39-7.46 (m, 2H), 7.24-7.28 (m, 2H), 7.21 (tt, $J=7.4$, 1.2 Hz, 1H), 3.83 (s, 2H), 2.40 (m, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): $\delta = 170.3$, 154.7, 141.2, 138.2, 129.6, 128.9, 128.2, 126.0, 125.2, 119.1, 39.7, 21.6 ppm.



Compound 11. A solution of the ethyl bromoacetate (125 mg, 1 mmol) and p-tolunitrile (0.29 mL, 2.7 mmol) in 0.7 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was pumped through a 5 mL coil ($R_t = 10$ min) at 120°C. The final solution was collected over ethyl-2-butynoate (0.128 mL, 1.1 mmol) and stirred for 16 h at 60°C, water was added and then extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 60:40. The desired fractions were collected and concentrated in vacuo to yield compound **11** as a pale yellow oil (135 mg, 49% yield). MS (ESI): mass calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_3$, 271.1208; m/z found, 270.1319 $[\text{M}-\text{H}]^-$. ^1H NMR (CHLOROFORM- d , 400MHz): $\delta = 7.19$ (s, 4H), 4.27-4.39 (m, 3H), 3.95 (q, $J=7.2$ Hz, 2H), 2.37 (s, 3H), 1.00 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CHLOROFORM- d , 101MHz): $\delta = 166.02$, 147.06, 144.2, 139.29, 133.99, 128.9, 127.8, 96.71, 59.76, 45.22, 21.4, 13.9 ppm.



Compound 12. A solution of the 5-bromovaleronitrile (200 mg, 1.23 mmol) and benzyl-2-bromoacetate (0.48mL, 3 mmol) in 3 mL of dry THF was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec R2+R4 system at 60°C and a flow rate of 0.5 mL/min. The outlet solution was pumped through a 5 mL coil ($R_t = 10$ min) at 60°C. The final solution was collected

and the solvent was evaporated in vacuo. The crude was dissolved in EtOH (2 mL) and phenylhydrazine (0.125 mL, 1.23 mmol) was added and stirred for 16 h at 60°C, water was added and then extracted with AcOEt. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude was purified by automated flash chromatography in silica gel (Si35, 4 g) from AcOEt in heptane 0:100 to 100:0 (10% of MeOH). The desired fractions were collected and concentrated in vacuo to yield compound **12** as a pale yellow oil (152 mg, 57% yield). MS (ESI): mass calcd. for C₁₃H₁₄N₂O, 214.1106; m/z found, 215.1093 [M-H]⁻. ¹H NMR (CHLOROFORM-d, 500MHz): δ = 7.43 (m, 4H), 7.25 (m, 1H), 5.39 (s, 1H), 5.30 (s, 1H), 3.23 (t, *J*=5.7 Hz, 2H), 2.69 (t, *J*=6.5 Hz, 2H), 1.98 (dt, *J*=11.3, 5.7 Hz, 2H), 1.89 ppm (m, 2H). ¹³C NMR (CHLOROFORM-d, 126MHz): δ = 166.4, 158.2, 135.1, 129.1, 126.3, 123.8, 97.9, 51.1, 24.8, 22.6 ppm.

