Supporting Information

Enantioselective Synthesis of Chiral Multicyclic \( \gamma \)-Lactones via Dynamic Kinetic Resolution of Racemic \( \gamma \)-Keto Carboxylic Acids

Zhichao Xiong, Jiangyan Tian, Peng Xue, Xumu Zhang, and Hui Lv

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1. General Information

Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on Bruker ADVANCE III (400 MHz) spectrometers for $^1$H NMR and $^{13}$C NMR. CD$_3$OD and CDCl$_3$ were the solvents used for the NMR analysis, with tetramethylsilane as the internal standard. Chemical shifts were reported upfield to TMS (0.00 ppm) for $^1$H NMR and relative to CDCl$_3$ (77.3 ppm) for $^{13}$C NMR. Optical rotation was determined using a Perkin Elmer 343 polarimeter. HPLC analysis was conducted on an Agilent 1260 Series instrument. Column Chromatography was performed with silica gel Merck 60 (300-400 mesh). All new products were further characterized by HRMS. A positive ion mass spectrum of sample was acquired on a Thermo LTQ-FT mass spectrometer with an electrospray ionization source.

2. General procedure for the synthesis of β-keto carboxylic acids

Preparation of III according to the literature$^{[1][2]}$:

To a solution of substituted benzene (I, 75 mmol) and succinic anhydride (50 mmol) dissolved in 100 mL of anhydrous CH$_2$Cl$_2$ was slowly added aluminum chloride (100 mmol) at 0 °C. After completion, the reaction mixture was warmed to room temperature and stirred overnight. Then the reaction mixture was cooled to 0 °C and 6N HCl was added carefully. When all aluminum chloride was quenched, the solution was extracted with CH$_2$Cl$_2$ three times and the combined organic phase was washed with H$_2$O and brine and dried over Na$_2$SO$_4$, filtered and concentrated under vacuum. Compound II can be used directly without further purification.

β-benzoyl propionic acid (compound II, 50 mmol) was added to a solution of 0.5M aqueous NaOH (110 mL). Formalin (37%, 4.1 mL) was added to the above solution and the reaction mixture was stirred at room temperature for 1h. Concentrated HCl (32%, 7.2 mL) was added and the solution was stirred overnight. When the reaction
was completed, the mixture was extracted with ethyl acetate three times and washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel using hexanes-ethyl acetate (5:1) as eluent to give the target compound III.

*Preparation of V (1a-1o)*[^1]:

![Chemical Structure](image)

Compound III (10 mmol) was added slowly to 5 mL concentrated H₂SO₄ at 0 °C and then heated to 85 °C for 3h. The solution was poured into a beaker containing ice-water mixture. The mixture was extracted with DCM for three times, washed with brine and dried over Na₂SO₄. The organic layer was concentrated under vacuum and the residue was purified by chromatography on silica gel using hexanes-ethyl acetate (3:1) and 0.5 % acetic acid as eluent to give the target compound.

![Chemical Structure](image)

To a round bottom flask was added ketone V (10 mmol) and glyoxylic acid (15 mmol). The mixture was stirred at 95 °C for 3h. The reaction mixture was dissolved in acetic acid (15 mL) and water (5 mL). Zinc dust (15 mL) was added over 1h to the solution and the mixture was stirred for additional 3h. The mixture was diluted with ethyl acetate and then filtered through celite. The filtration was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by chromatography on silica gel using hexanes-ethyl acetate (3:1) and 0.5 % acetic acid as eluent to give the target compound.
**2-(1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1a)**

White solid, 5 g, 41% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta 7.75\) (d, \(J = 7.6\) Hz, 1H), 7.69 (t, \(J = 7.2\) Hz, 1H), 7.58 (d, \(J = 7.6\) Hz, 1H), 7.45 (t, \(J = 7.4\) Hz, 1H), 3.51-3.47 (m, 1H), 3.05-2.88 (m, 3H), 2.76-2.72 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta 193.34, 173.57, 162.03, 135.82, 126.60, 121.05, 120.37, 117.56, 70.03, 42.45, 29.44.\) ESI-HRMS Calculated for C\(_{11}\)H\(_{10}\)O\(_3\)\(^+\) ([M+H]\(^+\)): 190.0630, found: 190.0632.

![Image](image1.png)

**2-(5-fluoro-1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1b)**

Light yellow solid, 0.48 g, 70% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta 7.74\) (dd, \(J = 8.5, 5.4\) Hz, 1H), 7.26 (dd, \(J = 8.8, 2.1\) Hz, 1H), 7.15 (td, \(J = 8.9, 2.3\) Hz, 1H), 3.52-3.35 (m, 1H), 3.05-2.80 (m, 3H), 2.77-2.65 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta 206.25, 173.86, 167.39\) (d, \(J_{C-F} = 254.5\) Hz), 157.13 (d, \(J_{C-F} = 10.1\) Hz), 132.79, 125.64 (d, \(J_{C-F} = 11.1\) Hz), 115.30, 115.06, 112.85 (d, \(J_{C-F} = 23.23\) Hz), 43.78, 33.98, 32.36, 32.34. ESI-HRMS Calculated for C\(_{11}\)H\(_9\)FO\(_3\)\(^+\) ([M+H]\(^+\)): 208.0536, found: 208.0533.

![Image](image2.png)

**2-(5-chloro-1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1c)**

Light yellow solid, 0.41 g, 71% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta 7.66\) (d, \(J = 8.2\) Hz, 1H), 7.57 (s, 1H), 7.41 (dd, \(J = 8.2, 1.6\) Hz, 1H), 3.46 - 3.40 (m, 1H), 3.03-2.81 (m, 3H), 2.76-2.70 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta 207.23, 172.76, 167.45, 166.23, 157.18, 157.08, 132.79, 125.69, 125.58, 115.30, 115.06, 112.96, 112.73, 43.78, 33.98, 32.36, 32.34. ESI-HRMS Calculated for C\(_{11}\)H\(_9\)FO\(_3\)\(^+\) ([M+H]\(^+\)): 224.0240, found: 224.0238.
2-(5-bromo-1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1d)

Light yellow solid, 0.45g, 68% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.76 (s, 1H), 7.64 - 7.51 (m, 2H), 3.52 -3.36 (m, 1H), 3.03 - 2.80 (m, 3H), 2.80 - 2.65 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 208.13, 172.76, 167.45, 166.23, 157.18, 157.08, 132.79, 125.69, 125.58, 115.30, 115.06, 112.96, 112.73, 43.78, 33.98, 32.36, 32.34. ESI-HRMS Calculated for C\(_{11}\)H\(_9\)BrO\(_3\)\(^+\) ([M+H]\(^+\)): 267.9735, found: 267.9738.

2-(5-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1e)

White solid, 0.4g, 75% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.58 (d, \(J = 7.9\) Hz, 1H), 7.34 (s, 1H), 7.26-7.17 (m, 1H), 3.41 - 3.35 (m, 1H), 2.97 - 2.91 (m, 1H), 2.89 - 2.83 (m, 2H), 2.67 - 2.61 (m, 1H), 2.43 (s, 3H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 207.78, 174.04, 154.52, 146.44, 133.80, 128.36, 126.66, 123.05, 43.71, 34.17, 32.31, 20.68. ESI-HRMS Calculated for C\(_{12}\)H\(_{12}\)O\(_3\)\(^+\) ([M+H]\(^+\)):204.0786, found: 204.0784.

2-(6-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetic acid (1f)

White solid, 0.43g, 74% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.66 - 7.14 (m, 3H), 3.41 - 3.34 (m, 1H), 2.98 - 2.81 (m, 3H), 2.71 - 2.64 (m, 1H), 2.39 (s, 3H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 208.62, 208.27, 174.03, 151.34, 137.32, 136.28, 136.04, 135.15, 127.35, 126.09, 123.01, 120.56, 43.91, 43.54, 34.19, 34.15, 32.08, 31.28, 19.67, 16.36. ESI-HRMS Calculated for C\(_{12}\)H\(_{12}\)O\(_3\)\(^+\) ([M+H]\(^+\)):204.0786, found: 204.0785.
2-(1-oxy-1,2,3,4-tetrahydronaphthalen-2-yl) acetic acid (1g)

White solid, 0.38g, 40% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.99 - 7.84 (m, 1H), 7.52 - 7.48 (m, 1H), 7.42 - 7.23 (m, 2H), 3.18 - 3.10 (m, 1H), 3.06 - 2.93 (m, 2H), 2.86 (dd, \(J = 16.6, 5.9\) Hz, 1H), 2.47 (dd, \(J = 16.6, 6.4\) Hz, 1H), 2.27 - 2.21 (m, 1H), 2.06 - 1.90 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 199.12, 174.76, 144.51, 133.30, 131.96, 128.67, 126.65, 126.24, 44.68, 34.37, 28.97, 28.80. ESI-HRMS Calculated for C\(_{12}\)H\(_{12}\)O\(_3\)\(^+\) ([M+H]\(^+\)): 204.0786, found: 204.0788.

2-(6-methoxy-1-oxy-1,2,3,4-tetrahydronaphthalen-2-yl) acetic acid (1h)

White solid, 0.51g, 50% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 8.12 - 7.68 (m, 1H), 6.95 - 6.64 (m, 2H), 3.86 (s, 3H), 3.19 - 3.02 (m, 1H), 3.02 - 2.77 (m, 3H), 2.50 - 2.35 (m, 1H), 2.33 - 2.13 (m, 1H), 2.10 - 1.85 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 202.03, 178.81, 167.98, 151.14, 133.08, 129.32, 116.98, 116.09, 58.56, 48.32, 38.39, 33.09, 32.97. ESI-HRMS Calculated for C\(_{13}\)H\(_{14}\)O\(_4\)\(^+\) ([M+H]\(^+\)): 234.0892, found: 234.0891.

2-(7-methoxy-1-oxy-1,2,3,4-tetrahydronaphthalen-2-yl) acetic acid (1i)

White solid, 0.48g, 49% yield; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.43 (d, \(J = 2.8\) Hz, 1H), 7.21 (d, \(J = 8.4\) Hz, 1H), 7.09 (dd, \(J = 8.4, 2.8\) Hz, 1H), 3.80 (s, 3H), 3.09 - 2.81 (m, 4H), 2.47 (dd, \(J = 16.5, 6.4\) Hz, 1H), 2.28 - 2.16 (m, 1H), 2.03 - 1.87 (m, 1H). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 199.31, 174.82, 156.94, 133.01, 132.93, 126.68, 118.14,
114.23, 54.82, 44.13, 34.26, 28.21, 22.33. ESI-HRMS Calculated for $\text{C}_{13}\text{H}_{14}\text{O}_4^+$ ($\text{[M+H]}^+$): 234.0892, found: 234.0889.

![Chemical Structure](image)

**2-(5-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetic acid (1j)**

White solid, 0.48g, 48% yield; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.43 (d, $J = 2.8$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.09 (dd, $J = 8.4$, 2.8 Hz, 1H), 3.80 (s, 3H), 3.10 - 2.78 (m, 4H), 2.47 (dd, $J = 16.5$, 6.4 Hz, 1H), 2.27 - 2.15 (m, 1H), 2.02 - 1.87 (m, 1H). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 199.00, 174.76, 158.42, 136.91, 132.72, 129.87, 120.96, 109.10, 54.42, 44.58, 34.42, 29.21, 27.98. ESI-HRMS Calculated for $\text{C}_{13}\text{H}_{14}\text{O}_4^+$ ($\text{[M+H]}^+$): 234.0892, found: 234.0890.

![Chemical Structure](image)

**2-(4-oxochroman-3-yl) acetic acid (1k)**

White solid, 0.45g, 40% yield; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.82 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.12 - 6.92 (m, 2H), 4.61 (dd, $J = 11.2$, 5.4 Hz, 1H), 4.33 (dd, $J = 12.3$, 11.3 Hz, 1H), 3.30 - 3.21 (m, 1H), 2.81 (dd, $J = 17.2$, 5.1 Hz, 1H), 2.48 (dd, $J = 17.2$, 7.3 Hz, 1H). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 193.34, 173.57, 162.03, 135.82, 126.60, 121.05, 120.37, 117.56, 70.03, 42.45, 29.44. ESI-HRMS Calculated for $\text{C}_{11}\text{H}_{10}\text{O}_4^+$ ($\text{[M+H]}^+$): 206.0579, found: 206.0576.

![Chemical Structure](image)

**2-(5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl) acetic acid (1l)**

White solid, 0.39g, 38% yield; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.60 (dd, $J = 8.0$, 1H), 7.52 - 7.48 (m, 1H), 7.42 - 7.36 (m, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.12 - 7.10 (m, 1H), 7.00 (dt, $J = 8.0$, 3.4 Hz, 1H), 4.79 (dd, $J = 11.2$, 7.8 Hz, 1H), 4.55 (dd, $J = 12.2$, 11.2 Hz, 1H), 3.32 - 3.21 (m, 1H), 2.11 (dt, $J = 17.2$, 7.3 Hz, 1H). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 193.34, 173.57, 162.03, 135.82, 126.60, 121.05, 120.37, 117.56, 70.03, 42.45, 29.44. ESI-HRMS Calculated for $\text{C}_{13}\text{H}_{14}\text{O}_4^+$ ($\text{[M+H]}^+$): 234.0892, found: 234.0890.
1.4 Hz, 1H), 7.43 - 7.39 (m, 1H), 7.31 - 7.23 (m, 2H), 3.41 - 3.32 (m, 1H), 3.18 - 3.05 (m, 1H), 3.02 - 2.84 (m, 2H), 2.52 - 2.47 (m, 1H), 2.15 - 2.12 (m, 1H), 1.99 - 1.94 (m, 1H), 1.73 - 1.50 (m, 2H). $^{13}$C NMR (101 MHz, CD$_3$OD) δ 206.39, 174.56, 142.37, 139.29, 131.33, 129.69, 128.01, 125.97, 45.69, 35.61, 32.98, 29.42, 25.47. ESI-HRMS Calculated for C$_{13}$H$_{14}$O$_3$ ([M+H]$^+$): 218.0943, found: 218.0941.

3. General procedure for asymmetric hydrogenation of γ-keto carboxylic acids

![Chemical Structure](image)

A suspension of γ-keto carboxylic acid (0.16 mmol), Cat (0.0032 mmol), 5:2 HCO$_2$H/Et$_3$N (1 mL) were stirred under N$_2$ at 60 ºC for 12 h until completion according to TLC detection. 5.0 mL 2N HCl was added to the reaction, the mixture was then extracted with ethyl acetate (3×5mL) three times, washed with brine, dried over Na$_2$SO$_4$ and concentrated. The desired product was purified by silica gel chromatography (hexanes: ethyl acetate = 1:1). The enantioselectivity of the products was determined by HPLC analysis. The racemic samples of diastereomeric mixtures of 2a-2i for HPLC analysis were prepared following literature procedures.

(3aR,8bS)-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (2a)

White solid, 25 mg, 90% yield, 98% ee, dr = 20:1; [α]$^D_{20}$ = +100 (c = 0.985, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 85:15; flow rate = 0.8 mL/min; UV detection at 210 nm; t$_R$ = 10.9 min (major), 12.0 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 7.4 Hz, 1H), 7.39 - 7.26 (m, 3H), 5.90 (d, J = 7.1 Hz, 1H), 3.48 - 3.21 (m, 2H), 3.04 - 2.73
(m, 2H), 2.47 - 2.27 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.97, 142.51, 138.76, 130.01, 127.60, 126.39, 125.37, 87.70, 37.93, 37.35, 35.70. ESI-HRMS Calculated for C$_{11}$H$_{10}$O$_2$$^+$ ([M+H]$^+$): 174.0681, found: 174.0680.

(3a$R$,8b$S$)-6-fluoro-3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (2b)

Light yellow solid, 27.5 mg, 90% yield, 98% ee, dr = 20:1; $[\alpha]_D^{20} = +84.8$ (c = 1.00, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 17.8 min (major), 19.2 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 - 7.37 (m, 1H), 7.09 - 6.85 (m, 2H), 5.84 (d, $J = 7.1$ Hz, 1H), 3.43 - 3.39 (m, 1H), 3.32 (dd, $J =$ 16.6, 8.5 Hz, 1H), 2.91 - 2.85 (m, 2H), 2.41 (dd, $J =$ 4.0, 8.0 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.67, 164.17 (d, $J_{C-F} = 249.47$ Hz), 145.17 (d, $J_{C-F} = 8.1$ Hz), 134.62, 127.83 (d, $J_{C-F} = 9.1$ Hz), 115.09 (d, $J_{C-F} = 23.2$ Hz), 112.15 (d, $J_{C-F} = 22.2$ Hz), 86.77, 38.02, 38.00, 37.92, 35.68. ESI-HRMS Calculated for C$_{11}$H$_9$FO$_2$$^+$ ([M+H]$^+$): 192.0587, found: 192.0585.

(3a$R$,8b$S$)-6-chloro-3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (2c)

Light yellow solid, 30.6 mg, 92% yield, 99% ee, dr = 20:1; $[\alpha]_D^{20} = +73$ (c = 0.6, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak IB column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 28.0 min (major), 30.8 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 1.8$ Hz, 2H), 5.84 (d, $J = 7.1$ Hz, 1H), 3.46 - 3.35 (m, 1H), 3.31 (dd, $J =$ 16.6, 8.4 Hz, 1H), 2.95 - 2.85 (m, 2H), 2.39 (dd, $J =$ 18.2, 5.6 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 144.49, 137.31, 128.05, 127.47, 125.56, 86.72, 37.78, 37.65, 35.54.
ESI-HRMS Calculated for $\text{C}_{11}\text{H}_{9}\text{ClO}_2^+$ ([M+H]$^+$): 208.0291, found: 208.0292.

(3aR,8bS)-6-bromo-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (2d)

Light yellow solid, 35.8 mg, 89% yield, 99% ee, dr=20:1; $\left[\alpha\right]_{D}^{20} = +62$ (c = 0.5, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak IB column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 29.6 min (major), 32.8 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J$ = 4.9 Hz, 2H), 7.35 (d, $J$ = 8.5 Hz, 1H), 5.83 (d, $J$ = 7.1 Hz, 1H), 3.43 - 3.36 (m, 1H), 3.31 (dd, $J$ = 10.7, 5.8 Hz, 1H), 2.96 - 2.87 (m, 2H), 2.40 (dd, $J$ = 13.4, 4.8 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.51, 144.78, 137.81, 130.92, 128.59, 127.80, 124.26, 86.76, 37.72, 37.57, 35.49. ESI-HRMS Calculated for $\text{C}_{11}\text{H}_{9}\text{BrO}_2^+$ ([M+H]$^+$): 251.9786, found: 251.9783.

(3aR,8bS)-6-methyl-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (2e)

White solid, 27.7 mg, 92% yield, 98% ee, dr = 20:1; $\left[\alpha\right]_{D}^{20} = +90.3$ (c = 1.00, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 23.3 min (minor), 24.3 min (major). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J$ = 7.7 Hz, 1H), 7.16 - 6.97 (m, 2H), 5.86 (d, $J$ = 7.0 Hz, 1H), 3.42 - 3.31 (m, 1H), 3.32 - 3.21 (m, 1H), 2.93 - 2.86 (m, 2H), 2.43 - 2.37 (m, 1H), 2.36 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.06, 142.80, 140.14, 135.96, 128.53, 126.08, 125.84, 87.62, 37.85, 37.57, 35.81, 21.50. ESI-HRMS Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2^+$ ([M+H]$^+$): 188.0837, found: 188.0838.
White solid, 27.3 mg, 91% yield, 99% ee, dr = 20:1; [α]$_D^{20}$ = +105.7 (c = 1.00, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95: 5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 14.9 min (major), 20.3 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (s, 1H), 7.16 (s, 2H), 5.86 (d, $J$ = 7.2 Hz, 1H), 3.38 - 3.34 (m, 1H), 3.27 (dd, $J$ = 16.1, 8.4 Hz, 1H), 2.87 (m, 2H), 2.40 (dd, $J$ = 15.4, 9.7 Hz, 1H), 2.36 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.03, 139.39, 138.90, 137.44, 130.96, 126.77, 125.06, 87.72, 37.60, 37.52, 35.73, 21.21. ESI-HRMS Calculated for C$_{12}$H$_{12}$O$_2^+$ ([M+H]$^+$): 188.0837, found: 188.0835.

White solid, 26.1 mg, 87% yield, 99% ee, dr = 20:1; [α]$_D^{20}$ = +37.4 (c = 0.5, CHCl$_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95: 5; flow rate = 1.0 mL/min; UV detection at 210 nm; $t_R$ = 19.6 min (minor), 23.0 min (minor). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 - 7.42 (m, 1H), 7.27 - 7.29 (m, 2H), 7.22 - 7.13 (m, 1H), 5.44 (d, $J$ = 5.9 Hz, 1H), 2.93 (dd, $J$ = 17.4, 8.1 Hz, 1H), 2.87 - 2.81 (m, 1H), 2.80 - 2.69 (m, 2H), 2.43 (dd, $J$ = 17.4, 2.2 Hz, 1H), 1.93 - 1.90 (m, 1H), 1.70 - 1.56 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.37, 137.51, 131.11, 130.93, 128.92, 128.77, 126.73, 78.52, 36.43, 34.74, 27.77, 25.15. ESI-HRMS Calculated for C$_{12}$H$_{12}$O$_2^+$ ([M+H]$^+$): 188.0837, found: 188.0839.
(3aR,9bS)-7-methoxy-3a,4,5,9b-tetrahydronaphtho[1,2-b]furan-2(3H)-one (2h)

White solid, 31.4 mg, 91% yield, 99% ee, dr = 20:1; \([\alpha]_D^{20} = +20.3\) (c = 0.3, CHCl_3); The enantiomeric excess was determined by HPLC on Chiralpak AD column, hexane: isopropanol = 90:10; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 14.8 min (minor), 16.6 min (major). \(^1\)H NMR (400 MHz, CDCl_3) δ 7.37 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 5.40 (d, J = 5.7 Hz, 1H), 3.81 (s, 3H), 2.92 (dd, J = 17.4, 8.0 Hz, 1H), 2.89 - 2.78 (m, 1H), 2.76 - 2.66 (m, 2H), 2.44 - 2.39 (m, 1H), 1.90 - 1.87 (m, 1H), 1.67 - 1.57 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl_3) δ 176.48, 159.81, 141.48, 132.29, 123.41, 113.16, 113.03, 78.59, 55.31, 36.67, 34.81, 28.15, 25.07. ESI-HRMS Calculated for C_{13}H_{14}O_3^+ ([M+H]^+): 218.0943, found: 218.0944.

(3aR,9bS)-8-methoxy-3a,4,5,9b-tetrahydronaphtho[1,2-b]furan-2(3H)-one (2i)

White solid, 31.4 mg, 90% yield, 99% ee, dr = 20:1; \([\alpha]_D^{20} = +47.2\) (c = 1.00, CHCl_3); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 28.4 min (major), 29.9 min (minor). \(^1\)H NMR (400 MHz, CDCl_3) δ 7.08 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.86 (dd, J = 8.4, 2.7 Hz, 1H), 5.40 (d, J = 6.0 Hz, 1H), 3.80 (s, 3H), 2.92 (dd, J = 17.4, 8.1 Hz, 1H), 2.83 - 2.72 (m, 2H), 2.72 - 2.60 (m, 1H), 2.42 (dd, J = 17.4, 2.5 Hz, 1H), 1.92 - 1.89 (m, 1H), 1.69 - 1.54 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl_3) δ 176.38, 158.19, 139.14, 132.29, 123.41, 113.16, 113.03, 78.59, 55.31, 36.67, 34.81, 28.15, 25.07. ESI-HRMS Calculated for C_{13}H_{14}O_3^+ ([M+H]^+): 218.0943, found: 218.0941.
(3aR,9bS)-6-methoxy-3a,4,5,9b-tetrahydronaphtho[1,2-b]furan-2(3H)-one (2j)

White solid, 32 mg, 92% yield, 99% ee, dr = 20:1; [α]D 20 = +25.3 (c = 0.8, CHCl3); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95: 5; flow rate = 1.0 mL/min; UV detection at 210 nm; tR = 25.3 min (major), 37.8 min (minor). 1H NMR (400 MHz, CDCl3) δ 7.24 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.42 (d, J = 5.8 Hz, 1H), 3.84 (s, 3H), 2.99 (dt, J = 17.4, 4.4 Hz, 1H), 2.90 (dd, J = 17.3, 7.9 Hz, 1H), 2.78 - 2.67 (m, 1H), 2.50 - 2.38 (m, 2H), 1.96 - 1.90 (m, 1H), 1.61 - 1.50 (m, 1H). 13C NMR (101 MHz, CDCl3) δ 176.48, 156.64, 132.08, 127.04, 126.71, 122.79, 109.85, 78.53, 55.49, 36.27, 34.35, 24.32, 20.88. ESI-HRMS Calculated for C13H14O3+ ([M+H]+): 218.0943, found: 218.0942.

(3aS,9bS)-3a,9b-dihydro-4H-furo[3,2-c]chromen-2(3H)-one (2k)

White solid, 25.9 mg, 85% yield, 96% ee, dr = 20:1; [α]D 20 = +62.5 (c = 1.00, CHCl3); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95: 5; flow rate = 1.0 mL/min; UV detection at 210 nm; tR = 27.5 min (major), 38.3 min (minor). 1H NMR (400 MHz, CDCl3) δ 7.41 (dd, J = 7.7, 1.4 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.04 - 7.00 (m, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.49 (d, J = 6.3 Hz, 1H), 4.21 (dd, J = 11.5, 4.3 Hz, 1H), 3.85 - 3.80 (m, 1H), 3.05 - 2.98 (m, 1H), 2.87 (dd, J = 17.7, 8.3 Hz, 1H), 2.46 (dd, J = 17.7, 4.2 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 175.43, 155.10, 131.44, 130.75, 121.97, 118.49, 117.45, 74.29, 64.85,
33.61, 31.17. ESI-HRMS Calculated for C_{11}H_{10}O_3^+ ([M+H]^+): 190.0630, found: 190.0631.

(3aR,10bS)-3,3a,4,5,6,10b-hexahydro-2H-benzo[6,7]cyclohepta[1,2-b]furan-2-one (2l)

White solid, 22.6 mg, 70% yield, 98% ee, dr = 20:1; [α]_D^{20} = -14.4 (c = 1.00, CHCl_3); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 12.1 min (minor), 13.2 min (major). ^1H NMR (400 MHz, CDCl_3) δ 7.36 - 7.27 (m, 3H), 7.18 - 7.10 (m, 1H), 5.86 (d, J = 9.2 Hz, 1H), 2.87 - 2.73 (m, 2H), 2.70 - 2.63 (m, 2H), 2.10 (dd, J = 17.8, 10.7 Hz, 1H), 1.72 - 1.68 (m, 3H), 1.03 - 0.87 (m, 1H). ^13C NMR (101 MHz, CDCl_3) δ 176.67, 135.67, 135.46, 128.65, 128.20, 126.90, 123.24, 81.18, 36.37, 34.06, 30.22, 27.99, 22.85. ESI-HRMS Calculated for C_{13}H_{14}O_2^+ ([M+H]^+): 202.0994, found: 202.0995.

4. Gram scale reaction

A suspension of 1a (2.5 g, 13.15 mmol), cat. C (0.082 g, 0.1315 mmol), 5:2 HCO_2H/Et_3N (10 mL) were stirred under N_2 at 60 °C for until completion according to TLC detection. 10 mL 2N HCl was added to the reaction, the mixture was then extracted with ethyl acetate (3×15 mL) three times, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (hexanes:
ethyl acetate = 1:1), affording desired product in 85% yield with 98% ee.


To a solution of 2a (1.1 g, 6.3 mmol) and methyl formate (0.82 mL, 9.45 mmol) in anhydrous THF (15 mL) was added potassium tert-butoxide (0.85 g, 7.56 mmol) in small portions at 0 °C under nitrogen. The reaction mixture was stirred at room temperature until completion. THF was removed in vacuo. The resulting solid was resolved in 20 mL anhydrous DMF under N₂. To this solution was added bromobutenolide (1.67 g, 9.45 mmol) and the reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (3×30 mL). The organic extract was then washed with brine, dried over Na₂SO₄, and the solvent removed under vacuum. The residue was purified by column chromatography, affording pure (+)-GR24 and (+)-epi-GR24.

(+)-epi-GR24

White Solid, 0.65 g, 35% yield, [α]D²⁰ = +292 (c = 0.50, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.49 (m, 1H), 7.35-7.23 (m, 1H), 6.99 (s, 1H), 6.21 (s, 1H), 5.96 (d, J = 8.0 Hz, 1H), 3.97-3.92 (m, 1H), 3.42 (dd, J = 16.9, 9.3 Hz, 1H), 3.10 (dd, J = 16.9, 3.1 Hz, 1H), 2.03 (t, J = 1.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 171.42, 170.40, 151.29, 142.69, 141.25, 138.76, 135.76, 130.05, 127.45, 126.34, 125.28, 113.26, 100.79, 86.00, 38.79, 37.42, 29.69, 10.74.
(+)-GR24

White solid, 0.65 g, 35% yield, $[\alpha]_D^{20} = 451$ (c = 0.50, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.49 (m, 2H), 7.35 (m, 3H), 7.00 (s, 1H), 6.21 (s, 1H), 5.95 (d, $J$ = 7.9 Hz, 1H), 3.97-3.92 (m, 1H), 3.44 (dd, $J$ = 16.9, 9.4 Hz, 1H), 3.11 (dd, $J$ = 16.9, 3.2 Hz, 1H), 2.03 (t, $J$ = 1.4 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.44, 170.37, 151.27, 142.66, 141.16, 138.82, 135.83, 130.04, 127.49, 126.42, 125.18, 113.14, 100.71, 85.99, 38.85, 37.31, 10.73.

6. Reference:

(3) L. J. Bromhead et al., Aust. J. Chem. 2015, 68, 1221–1227;
7. NMR spectra

NMR spectra of 1a
NMR spectra of 1b
NMR spectra of 1c
NMR spectra of 1d
NMR spectra of 1e
NMR spectra of 1f
NMR spectra of 1g
NMR spectra of 1h
NMR spectra of 1i

![NMR spectrum image]
NMR spectra of 1j
NMR spectra of 1k

![NMR Spectra Image](image-url)
NMR spectra of 11
NMR spectra of 2a
NMR spectra of 2b
NMR spectra of 2c
NMR spectra of 2d
NMR spectra of 2e
NMR spectra of 2f
NMR spectra of 2g
NMR spectra of 2h
NMR spectra of \(2i\)
NMR spectra of 2j
NMR spectra of \(2k\)
NMR spectra of 21
8. HPLC spectra of 2a-2l

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Analysis method (modified after loading)
Additional Info : Peak[s] manually integrated

[Graph of HPLC spectra]

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Area Percent Report
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Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

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Last changed: 4/6/2019 11:18:14 AM by SYSTEM
(modified after loading)
Additional Info: Peak(s) manually integrated

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Area Percent Report
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Solution : 1.0000
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Page 1 of 2
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Injection Volume : 5.000 ³L 
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Last changed : 10/30/2018 9:14:44 PM 
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Last changed : 10/30/2018 2:17:17 PM 
Extra Info : Peak(s) manually integrated

**Area Percent Report**

Sorted By : Signal 
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Solution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

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Inj Volume : 5.000 μl

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Additional Info : Peak(s) manually integrated

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Area Percent Report
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Solution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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Page 1 of 2

558
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Inj : 1
Injection Volume : 5.000 µL

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Last changed : 4/8/2019 4:52:50 PM

Additional Info : Peak(s) manually integrated

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Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

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<tr>
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<td>29.960</td>
<td>0.6173</td>
<td>132.61629</td>
<td>3.09563</td>
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</tbody>
</table>

Totals : 296.27357 7.42994

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Instrument 1 4/8/2019 4:53:09 PM
### Area Percent Report

Sorted By: Signal  
Multiplier: 1.0000  
Solution: 1.0000  
Use Multiplier & Dilution Factor with ISTDs

**Signal 1: Wavelength=210 nm**

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[min]</td>
<td>[min]</td>
<td>[nmol/u]</td>
<td>[nmol]</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
<td>-------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>1</td>
<td>25.351</td>
<td>BB</td>
<td>0.5319</td>
<td>309.75864</td>
</tr>
<tr>
<td>2</td>
<td>37.805</td>
<td>RH</td>
<td>0.6678</td>
<td>41.07934</td>
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<td><strong>Totals</strong></td>
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<td></td>
<td></td>
<td>1.09150=4</td>
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</table>

Instrument 1: 3/11/2019 3:07:30 PM
Area Percent Report

Signal 1: W101 A, Wavelength=210 nm

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<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 27.589 BB</td>
<td>0.5549</td>
<td>7052.8657</td>
<td>191.4236</td>
<td>98.2471</td>
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<tr>
<td>2 38.305 RM</td>
<td>0.5638</td>
<td>125.03205</td>
<td>3.71980</td>
<td>1.7529</td>
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</tbody>
</table>

Totals: 7178.69777 195.14416
Data File D:\DATA\XCO\XCO-DATA-91\XCO-2019-0310-1 2019-03-10 12:50:51\0001.D
Sample Name: XCO-hep-thc-1

================================================================================================

Acq. Instrument : Instrument 1  Location : Vial 2
Injection Date : 3/10/2019 3:08:02 PM  Inj : 1
Injection Volume : 5.000 μl
Last changed : 7/10/2018 8:21:33 PM
Analysis Method : D:\METHOD\QUANT TOXINO\XCO-00\VWD-00(1-6)-39-1-0.5XL-SUL-254MIN.K
Last changed : 3/11/2019 3:10:27 PM
[modified after loading]
Additional Info : Peak(s) manually integrated

================================================================================================

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Solution : 1.0000
Use Multiplier & Dilution factor with ISTDs

Signal 1: Wavelength=210 nm

Peak RetTime Type Width Area Height Area

<table>
<thead>
<tr>
<th></th>
<th>[min]</th>
<th>[min]</th>
<th>[μL/°μ]</th>
<th>[μL]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>BB</td>
<td>0.2426</td>
<td>4202.47011</td>
<td>262.73995</td>
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<tr>
<td>2</td>
<td>13.351</td>
<td>BV</td>
<td>0.3253</td>
<td>4172.71416</td>
<td>98.80999</td>
</tr>
</tbody>
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Totals : 461.53995

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Instrument 1 3/11/2019 3:10:33 PM  Page 1 of 2