Supporting Information

for

Novel amide-functionalized chloramphenicol base bifunctional organocatalysts for enantioselective alcoholysis of meso-cyclic anhydrides

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Detailed experimental procedures, $^1$H NMR files

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1. General procedure

Unless otherwise specified, all reagents and solvents were purchased from commercial sources and used as received. $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer in CDCl$_3$ or $d_6$-DMSO using tetramethylsilane (TMS) as internal standards. Coupling constant ($J$) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Melting points were measured on WRS-1B digital melting-point apparatus. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co. Ltd. Optical rotations were measured by a Rudolph AUTOPOL I Automatic Polarimeter. EI MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak IA-H column (25 cm × 4.6 mm × 5 μm).

2. Preparation of the chloramphenicol base amide bifunctional organocatalysts

**General procedure**

```
\[
\text{O}_2\text{N} \quad \text{NH}_2 \\
\text{R}^1\text{N} \quad \text{R}^1
\]

\[
\rightarrow \quad \text{R}^3\text{COCl}, \text{Et}_3\text{N} \\
\text{CH}_2\text{Cl}_2, \text{r.t.}
\]

\[
\text{O}_2\text{N} \quad \text{R}^1\text{N} \quad \text{R}^1
\]
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To a solution of chloramphenicol base (1 g, 2 mmol) and in CH$_2$Cl$_2$ (20 mL) was added the solution of Et$_3$N (1.15 mL, 8 mmol) in CH$_2$Cl$_2$ (10 mL) under N$_2$ atmosphere. After cooling to 0 °C, R$^3$COCl (3 mmol) was added dropwise over 20 min. After addition, the reaction mixture was stirred for 3 h at room temperature and then quenched by water (10 mL). The organic phase was washed with NaHCO$_3$ (20 mL), H$_2$O (20 mL), brine (20mL), dried over Na$_2$SO$_4$ and concentrated under reduced
pressure to give a yellow solid. The crude product was purified by flash chromatography using PE/EA 10:1 to give product 7.

\[ N-((1R,2R)-2-(\text{Dimethylamino})-1-(4\text{-nitrophenyl})-3-(\text{trityloxy})propyl)-4-(\text{tri-fluoromethyl})benzamide \ (7a) \]

Yellow solid, yield 80%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.20 \text{ (s, 1H)}, 8.06 \text{ (d, } J = 8.6 \text{ Hz, 2H}), 7.90 \text{ (d, } J = 8.1 \text{ Hz, 2H}), 7.72 \text{ (d, } J = 8.2 \text{ Hz, 2H}), 7.37 \text{ (d, } J = 8.5 \text{ Hz, 2H}), 7.28-7.23 \text{ (m, 15H)}, 4.69 \text{ (d, } J = 10.3 \text{ Hz, 1H}), 3.30-3.22 \text{ (m, 2H)}, 3.01-2.97 \text{ (m, 1H)}, 2.46 \text{ (s, 6H) ppm}; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 165.9, 148.8, 147.0, 143.0, 137.1, 133.2, 128.5, 128.2, 127.4, 127.1, 125.6, 123.6, 87.6, 67.7, 58.17, 54.1, 41.4 \text{ ppm}; \text{HRMS (ESI}^+\text{) calcd for C}_{38}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_4 \text{[M+H]}^+ = 654.2580, \text{found: 654.2574.}

\[ N-((1R,2R)-2-(\text{Dimethylamino})-1-(4\text{-nitrophenyl})-3-(\text{trityloxy})propyl)-4\text{-nitro-benzamide} \ (7b) \]

Yellow solid, yield 73%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.30 \text{ (d, } J = 8.7 \text{ Hz, 2H}), 8.26 \text{ (s, 1H)}, 8.07 \text{ (d, } J = 8.6 \text{ Hz, 2H}), 7.94 \text{ (d, } J = 8.7 \text{ Hz, 2H}), 7.37 \text{ (d, } J = 8.6 \text{ Hz, 2H}), 7.26-7.23 \text{ (m, 15H)}, 4.69 \text{ (dd, } J = 10.2, 1.9 \text{ Hz, 1H}), 3.31-3.22 \text{ (m, 2H)}, 3.01-2.96 \text{ (m, 1H)}, 2.47 \text{ (s, 6H) ppm}; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 165.2, 149.7,\)
148.5, 147.0, 139.4, 128.5, 128.2, 127.2, 123.8, 123.7, 87.6, 67.6, 58.1, 54.2, 41.4 ppm; HRMS (ESI$^+$) calcd for C$_{37}$H$_{34}$N$_4$O$_6$ [M+H]$^+$ = 631.2557, found: 631.2568.

$N$-((1$R$,2$R$)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-4-fluoro-benzamide (7c)

![Chemical structure of 7c]

Yellow solid, yield 85%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.12 (s, 1H), 8.06 (d, $J$ = 8.6 Hz, 2H), 7.82-7.78 (m, 2H), 7.38 (d, $J$ = 8.6 Hz, 2H), 7.25 (m, 15H), 7.11 (t, $J$ = 8.6 Hz, 2H), 4.70 (d, $J$ = 10.3 Hz, 1H), 3.29-3.22 (m, 2H), 3.02-2.99 (m, 1H), 2.46 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 166.2, 149.1, 146.9, 143.0, 129.4, 129.3, 128.5, 128.3, 127.7, 127.1, 123.6, 115.7, 115.4, 87.6, 67.6, 58.1, 53.9, 41.3 ppm; HRMS (ESI$^+$) calcd for C$_{37}$H$_{34}$FN$_3$O$_4$ [M+H]$^+$ = 604.2612, found: 604.2625.

4-Chloro-$N$-((1$R$,2$R$)-2-(dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-benzamide (7d)

![Chemical structure of 7d]

Yellow solid, yield 80%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.13 (s, 1H), 8.06 (d, $J$ = 8.6 Hz, 2H), 7.73 (d, $J$ = 8.5 Hz, 2H), 7.42 (d, $J$ = 8.6 Hz, 2H), 7.37 (d, $J$ = 8.6 Hz, 2H), 7.28-7.23 (m, 15H), 4.69 (d, $J$ = 8.7 Hz, 1H), 3.29-3.21 (m, 2H), 3.02-2.97 (m, 1H), 2.46 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 166.2, 149.0, 146.9, 143.0, 137.9, 132.2, 128.8, 128.5, 128.4, 129.2, 127.7, 127.1, 123.6, 87.6, 67.6, 58.1, 54.0,
41.3 ppm; HRMS (ESI⁺) calcd for C₃₇H₃₄ClN₃O₄ [M+H]⁺ = 620.2316, found: 620.2305.

**4-Bromo-N-((1R,2R)-2-(dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)benzamide (7e)**

![Chemical Structure](image)

Yellow solid, yield 88%; ¹H NMR (400 MHz, CDCl₃) δ = 8.09 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.27-7.23 (m, 15H), 4.66 (d, J = 10.1 Hz, 1H), 3.29-3.20 (m, 2H), 2.99-2.95 (m, 1H), 2.45 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 166.3, 149.0, 146.9, 143.0, 132.7, 131.8, 128.6, 128.5, 128.2, 127.7, 127.1, 126.4, 123.6, 87.6, 67.7, 58.1, 54.0, 41.4 ppm; HRMS (ESI⁺) calcd for C₃₇H₃₄BrN₃O₄ [M+H]⁺ = 664.1811, found: 664.1809.

**N-((1R,2R)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)benzamide (7f)**

![Chemical Structure](image)

Yellow solid, yield 75%; ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.27-7.23 (m, 15H), 4.72 (dd, J = 10.4, 2.3 Hz, 1H), 3.30-3.21 (m, 2H), 3.03-2.99 (m, 1H), 2.47 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 167.2, 149.3, 146.8, 143.1, 133.9, 131.6, 128.5, 128.3, 127.7, 127.1, 127.0, 123.6,
87.5, 67.7, 58.2, 53.9, 41.3 ppm; HRMS (ESI⁺) calcd for C_{37}H_{35}N_{3}O_{4} [M+H]⁺ = 586.2706, found: 586.2705.

N-((1R,2R)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-4-methylbenzamide (7g)

Yellow solid, yield 77%; ¹H NMR (400 MHz, CDCl₃) δ = 8.12 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.27-7.23 (m, 17H), 4.72 (d, J = 10.4 Hz, 1H), 3.28 – 3.21 (m, 2H), 3.03 – 3.01 (m, 1H), 2.46 (s, 6H), 2.41 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 167.3, 149.4, 146.8, 143.1, 142.1, 131.0, 129.2, 128.5, 128.3, 127.7, 127.1, 127.0, 123.6, 87.5, 67.6, 58.2, 53.8, 41.3, 21.4 ppm; HRMS (ESI⁺) calcd for C_{38}H_{37}N_{3}O_{4} [M+H]⁺ = 600.2862, found: 600.2859.

N-((1R,2R)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-4-methoxybenzamide (7h)

Yellow solid, yield 68%; ¹H NMR (400 MHz, CDCl₃) δ = 8.02 (d, J = 8.6 Hz, 2H), 7.98 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.24-7.21 (m, 15H), 6.92 (d, J = 8.6 Hz, 2H), 4.65 (d, J = 10.3 Hz, 1H), 3.84 (s, 3H), 3.26-3.18 (m, 2H), 2.96-2.93 (m, 1H), 2.43 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 167.1, 162.4, 148.7, 147.1, 142.9, 129.0, 128.7, 128.6, 127.9, 127.3, 126.1, 123.8, 113.7, 87.7, 66.7,
57.9, 55.3, 53.3, 41.0 ppm; HRMS (ESI⁺) calcd for C₃₈H₇₇N₃O₅ [M+H]⁺ = 616.2811, found: 616.2804.

*N-((1R,2R)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-3,5-bis-(trifluoromethyl)benzamide (7i)*

![Chemical structure of 7i]

White solid, yield 90%; ¹H NMR (400 MHz, CDCl₃) δ = 8.26 (br, 1H), 8.20 (s, 2H), 8.06 (d, J = 8.6 Hz, 2H), 8.02 (s, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.24-7.23 (m, 15H), 4.70 (d, J = 10.7 Hz, 1H), 3.30-3.22 (m, 2H), 3.04-3.03 (m, 1H), 2.47 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 164.5, 148.3, 147.1, 143.0, 136.0, 132.4, 132.0, 128.5, 128.3, 127.7, 127.2, 127.3, 123.7, 87.6, 67.6, 60.15, 54.2, 41.3 ppm; HRMS (ESI⁺) calcd for C₃₉H₃₄F₆N₅O₄ [M+H]⁺ = 722.2454, found: 722.2455.

*N-((1R,2R)-1-(4-Nitrophenyl)-2-(pyrrolidin-1-yl)-3-(trityloxy)propyl)-3,5-bis-(trifluoromethyl)benzamide (7j)*

![Chemical structure of 7j]

Light yellow solid, yield 92%; ¹H NMR (400 MHz, CDCl₃) δ = 8.37 (br, 1H), 8.16 (s, 2H), 8.08 (d, J = 8.4 Hz, 2H), 7.99 (s, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.21-7.19 (m, 15H), 5.05 (d, J = 5.5 Hz, 1H), 3.36-3.33 (m, 1H), 3.26-3.20 (m, 2H), 2.64 (d, J = 28.8 Hz, 4H), 1.73-1.69 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 164.4, 148.6, 147.2, 143.2, 136.4, 132.5, 132.2, 128.6, 128.1, 128.0, 127.4, 124.3, 123.8, 121.6,
87.8, 65.1, 60.1, 54.6, 49.7, 23.7 ppm; HRMS (ESI⁺) calcd for C₄₁H₃₅F₆N₃O₄ [M+H]⁺ = 748.2610, found: 748.2592.

\( N-((1R,2R)-1\text{-}(4\text{-Nitrophenyl})\text{-}2\text{-}(\text{piperidin}-1\text{-yl})\text{-}3\text{-}(\text{trityloxy})\text{propyl})\text{-}3,5\text{-bis}\text{(trifluoromethyl)}\text{benzamide} \) (7k)

Light yellow solid, yield 89%; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta = 8.72 \text{ (s, 1H)}, 8.29 \text{ (s, 2H)}, 8.07-8.02 \text{ (m, 3H)}, 7.36 \text{ (d, } J = 8.2 \text{ Hz, 2H)}, 7.25-7.21 \text{ (m, 15H)}, 4.60 \text{ (d, } J = 10.4 \text{ Hz, 1H)}, 3.34-3.30 \text{ (m, 1H)}, 3.24 \text{ (d, } J = 10.3 \text{ Hz, 1H)}, 2.94 \text{ (s, 1H)}, 2.80-2.76 \text{ (m, 2H)}, 2.60 \text{ (s, 2H)}, 1.63 \text{ (s, 2H)}, 1.51 \text{ (s, 4H)} \text{ ppm}; \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta = 163.8, 148.7, 147.2, 143.2, 136.0, 132.6, 132.4, 128.7, 128.5, 127.9, 127.3, 125.2, 124.5, 123.9, 87.8, 69.1, 58.8, 53.6, 27.4, 27.0, 24.5 \text{ ppm}; \) HRMS (ESI⁺) calcd for C₄₂H₃₇F₆N₃O₄ [M+H]⁺ = 762.2767, found: 762.2731.

\( N-((1R,2R)-2\text{-Morpholino}-1\text{-}(4\text{-Nitrophenyl})\text{-}3\text{-}(\text{trityloxy})\text{propyl})\text{-}3,5\text{-bis}\text{(trifluoromethyl)}\text{benzamide} \) (7l)

Yellow solid, yield 82%; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta = 8.38 \text{ (s, 1H)}, 8.26 \text{ (s, 2H)}, 8.07 \text{ (s, 1H)}, 8.04 \text{ (s, 2H)}, 7.35 \text{ (d, } J = 8.4 \text{ Hz, 2H)}, 7.25-7.21 \text{ (m, 15H)}, 4.70 \text{ (d, } J = 10.4 \text{ Hz, 1H)}, 3.76-3.73 \text{ (m, 2H)}, 3.73-3.68 \text{ (m, 2H)}, 3.35-3.31 \text{ (m, 1H)}, 3.28-3.26 \text{ (m,
1H), 3.00-2.98 (m, 1H), 2.85 (m, 2H), 2.72-2.71 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 163.8, 148.1, 147.3, 143.1, 135.8, 128.6, 128.4, 127.9, 127.4, 127.2, 124.3, 123.9, 88.0, 68.4, 68.0, 58.9, 53.3, 27.0 ppm; HRMS (ESI$^+$) calcd for C$_{41}$H$_{35}$F$_6$N$_3$O$_5$ [M+Na]$^+$ = 786.2379, found: 786.2349.

$N$-((1$R$,2$R$)-3-((tert-Butyldimethylsilyl)oxy)-2-(dimethylamino)-1-(4-nitrophenyl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7m)

![Diagram of 7m]

White solid, yield 88%; $^1$H NMR (400 MHz, CDCl$_3$) δ = 8.23-8.20 (m, 4H), 8.00 (s, 1H), 7.64 (d, $J$ = 8.3 Hz, 2H), 5.10 (d, $J$ = 9.5 Hz, 1H), 3.83 (d, $J$ = 11.4 Hz, 1H), 3.37 (dd, $J$ = 11.4, 4.1 Hz, 1H), 2.51 (s, 6H), 1.26 (s, 1H), 0.91 (s, 9H), 0.01 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 164.8, 147.5, 136.3, 132.5, 132.2, 128.6, 127.5, 125.3, 123.9, 121.6, 68.2, 56.7, 52.9, 41.8, 25.9, 18.2, -5.5 ppm; HRMS (ESI$^+$) calcd for C$_{26}$H$_{33}$F$_6$N$_3$O$_4$Si [M+H]$^+$ = 594.2223, found: 594.2209.

$N$-((1$R$,2$R$)-3-((tert-Butyldimethylsilyl)oxy)-1-(4-nitrophenyl)-2-(pyrrolidin-1-yl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7n)

![Diagram of 7n]

Yellow solid, yield 85%; $^1$H NMR (400 MHz, CDCl$_3$) δ = 8.39 (s, 1H), 8.24 (s, 2H), 8.20 (d, $J$ = 8.1 Hz, 2H), 8.03 (s, 1H), 7.60 (d, $J$ = 8.0 Hz, 2H), 5.29 (s, 1H), 3.71-3.63 (m, 2H), 3.04 (s, 1H), 2.80 (s, 2H), 2.68 (s, 2H), 1.83-1.77 (m, 4H), 0.88 (s, 9H), 0.01 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 164.1, 148.5, 147.2, 136.3, 132.4,
132.1, 127.9, 127.3, 123.6, 121.5, 66.5, 59.8, 53.5, 50.2, 25.8, 23.5, 18.1, -5.6 ppm; 
HRMS (ESI⁺) calcd for C₂₈H₃₅F₆N₃O₄Si [M+H]⁺ = 620.2379, found: 620.2377.

N-((1R,2R)-3-((tert-Butyldimethylsilyl)oxy)-1-(4-nitrophenyl)-2-(piperidin-1-yl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7o)

Light yellow solid, yield 83%; ¹H NMR (400 MHz, CDCl₃) δ = 8.68 (s, 1H), 8.31 (s, 2H), 8.20 (d, J = 8.1 Hz, 2H), 8.03 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 4.94 (d, J = 10.3 Hz, 1H), 3.79 (d, J = 11.2 Hz, 1H), 3.42 (dd, J = 11.2, 4.3 Hz, 1H), 2.86-2.81 (m, 2H), 2.74 (d, J = 8.8 Hz, 1H), 2.62 (s, 2H), 1.66 (s, 2H), 1.54 (s, 4H), 0.90 (s, 9H), 0.01 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 164.0, 149.0, 147.4, 136.1, 132.6, 132.2, 128.4, 127.3, 125.3, 123.9, 121.7, 70.0, 57.3, 52.2, 27.5, 25.9, 24.6, 18.1, -5.5 ppm; 
HRMS (ESI⁺) calcd for C₂₉H₃₇F₆N₃O₄Si [M+H]⁺ = 634.2536, found: 634.2521.

N-((1R,2R)-3-((tert-Butyldimethylsilyl)oxy)-2-morpholino-1-(4-nitrophenyl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7p)

Light yellow solid, yield 80%; ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (s, 1H), 8.28 (s, 2H), 8.21 (d, J = 8.0 Hz, 2H), 8.04 (s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 5.07 (d, J = 10.2 Hz, 1H), 3.84 (d, J = 11.4 Hz, 1H), 3.76 (d, J = 6.0 Hz, 2H), 3.68 (s, 2H), 3.41-3.38 (m, 1H), 2.87 (s, 2H), 2.79 (d, J = 10.1 Hz, 1H), 2.74-2.70 (m, 2H), 0.91 (s, 9H), 0.02
(s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 164.1, 148.3, 147.5, 136.0, 132.7, 132.3, 128.5, 127.2, 123.9, 121.6, 69.2, 68.0, 57.2, 52.0, 50.4, 25.9, 18.1, -5.5 ppm; HRMS (ESI$^+$) calcd for C$_{28}$H$_{35}$F$_6$N$_3$O$_5$Si [M+Na]$^+$ = 658.2148, found: 658.2124.

3. Typical procedure for alcoholysis of meso-cyclic anhydride
An alcohol (5 mmol) was added dropwise at room temperature under nitrogen to a stirred solution of an anhydride 8 (0.5 mmol) and 7i (36.1 mg, 0.05 mmol) in MTBE (20 mL). The reaction was monitored by using thin-layer chromatography. Once anhydride consumption was complete, the solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (10 mL). The solution was washed with saturated Na$_2$CO$_3$ (2 × 5 mL) and the combined aqueous phase were acidified with excess 2 N HCl, followed by extraction with EtOAc (3 × 10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated to afford the corresponding monoester, without further purification by flash chromatography.

4. Scale-up methanolysis of meso-cyclic anhydride 8h (4.26 g scale)
MeOH (10.1 mL, 250 mmol) was added dropwise at 0 °C under nitrogen to a stirred solution of meso-cyclic anhydride 8h (4.26 g, 25 mmol) and 7i (1.80 g, 2.5 mmol) in MTBE (2 L). The reaction was monitored by using thin-layer chromatography. After 96 h, the anhydride consumption was complete. The solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (300 mL). The solution was washed with saturated Na$_2$CO$_3$ (3 × 150 mL) and the combined aqueous layers were acidified with excess 2 N HCl, followed by extraction with EtOAc (3 × 300 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to afford the corresponding monoester 9h, without further purification by flash chromatography. Monoester 9h, light yellow oil, yield 97%, 81% ee; $[\alpha]_D^{25} = -3.5$ (c = 1.0 in CHCl$_3$); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.6 mL/min, UV detection at 220 nm, T = 30 °C, retention time: t(minor) = 50.6 min, t(major) = 56.1 min.
5. Characterization of the monooesters

All monooesters except 9h are known compounds and their NMR spectra data were identical to those reported in the literature. The enantiomeric excess of the monooester was determined by chiral HPLC, analysis of the diastereoisomeric mixture of the corresponding amide ester derived from (5)-1-phenylethylamine according to the reported procedure.

Thionyl chloride (0.6 mmol, 45 μL) was added to a solution of the monooester (0.5 mmol) in dry toluene (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes, and triethylamine (1.5 mmol, 0.14 mL) and (S)-1-phenylethylamine (0.55 mmol, 71 μL) were added successively. The mixture was stirred at 0 °C for 1 h and at room temperature for an additional 1 h. The residue was then dissolved in ethyl acetate (50 mL). The organic solution was washed with HCl (2 N, 50 mL), saturated aq NaHCO₃ (50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo to give the diastereoisomeric mixture. The enantiomeric excess was determined by comparison of chiral HPLC.

(1S,6R)-6-(Methoxycarbonyl)cyclohex-3-enecarboxylic acid (9a)

White solid, yield 98%, 95% ee; [α]D²⁵ = -4.3 (c = 1.0 in CHCl₃) (lit.[2] [α]D²⁰ = -4.9 (c = 1.5 in CHCl₃)); Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(major) = 33.1 min, t(minor) = 45.3 min; ¹H NMR (400 MHz, CDCl₃) δ = 4.93 (dd, J = 24.1, 3.6 Hz, 2H), 3.67 (s, 3H), 3.05-2.99 (m, 2H), 1.84-1.82 (m, 2H), 1.56-1.51 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 179.7, 173.7, 125.1, 125.0, 51.9, 39.6, 39.4, 25.7, 25.5 ppm.

(1S,2R)-2-(Methoxycarbonyl)cyclohexanecarboxylic acid (9b)
Colorless oil, yield 97%, 90% ee; $[\alpha]_D^{25} = +3.6$ ($c = 1.0$ in CHCl$_3$) (lit.$^{[2]}$ $[\alpha]_D^{20} = +3.5$ ($c = 1.43$ in CHCl$_3$)); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: t(minor) = 23.2 min, t(major) = 29.9 min; $^1$H NMR (400 MHz, DMSO): $\delta = 3.67$ (s, 3H), 2.84 (s, 2H), 2.00 (br, 2H), 1.78 (br, 2H), 1.54-1.47 (m, 2H), 1.42-1.39 (m, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO) $\delta = 180.2, 174.2, 51.8, 42.6, 42.4, 26.3, 26.0, 23.8, 23.7$ ppm.

(1S,2R,3S,4R)-3-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9c)

White solid, yield 94%, 73% ee; $[\alpha]_D^{25} = +6.3$ ($c = 1.0$ in CHCl$_3$) (lit.$^{[2]}$ $[\alpha]_D^{20} = +8.7$ ($c = 1.08$ in CHCl$_3$)); Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 85/15, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: t(major) = 23.8 min, t(minor) = 37.8 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.69$ (br, 1H), 6.49-6.45 (m, 2H), 5.29 (d, $J = 16.7$ Hz, 2H), 3.71 (s, 3H), 2.88-2.83 (m, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO) $\delta = 173.0, 172.5, 137.1, 137.0, 80.4, 80.1, 51.9, 47.0, 46.3$ ppm.

(1R,2S,3R,4S)-3-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9d)

White solid, yield 95%, 84% ee; $[\alpha]_D^{25} = -5.8$ ($c = 1.0$ in CHCl$_3$) (lit.$^{[2]}$ $[\alpha]_D^{20} = -7.4$ ($c = 1.53$ in CHCl$_3$)); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 96/4, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: t(minor)
= 47.8 min, t(major) = 50.7 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 6.31 (dd, $J = 5.1$, 2.9 Hz, 1H), 6.22 (dd, $J = 5.3$, 2.8 Hz, 1H), 3.59 (s, 3H), 3.35-3.26 (m, 2H), 3.18 (d, $J = 12.9$ Hz, 2H), 1.49 (d, $J = 8.6$ Hz, 1H), 1.34 (d, $J = 8.6$ Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 178.3, 172.9, 135.5, 134.3, 51.5, 48.7, 48.2, 48.0, 46.5, 46.1 ppm.

(R)-5-Methoxy-3-methyl-5-oxopentanoic acid (9e)

Yellow oil, yield 87%, 81% ee; $[\alpha]_D^{25} = +3.1$ (c = 1.0 in CHCl$_3$) (lit.$[^{[2]}]$ $[\alpha]_D^{20} = +1.1$ (c = 1.36 in CHCl$_3$)); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 96/4, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 38.3 min, t(major) = 44.1 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.67 (s, 3H), 2.50-2.39 (m, 3H), 2.31-2.24 (m, 2H), 1.05 (d, $J = 6.3$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 173.8, 172.8, 51.6, 40.6, 40.3, 27.3, 19.8 ppm.

(R)-3-Ethyl-5-methoxy-5-oxopentanoic acid (9f)

Yellow oil, yield 91%, 80% ee; $[\alpha]_D^{25} = -1.36$ (c = 1.0 in CHCl$_3$) (lit.$[^{[8]}]$ $[\alpha]_D^{20} = -0.92$ (c = 1.0 in CHCl$_3$)); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 26.7 min, t(major) = 30.3 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.67 (s, 3H), 2.39 (t, $J = 7.3$ Hz, 4H), 2.31-2.24 (m, 1H), 1.42 (p, $J = 7.3$ Hz, 2H), 0.92 (t, $J = 7.4$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 174.0, 173.0, 51.6, 38.1, 37.8, 33.4, 26.4, 11.1 ppm.

(R)-3-Isopropyl-5-methoxy-5-oxopentanoic acid (9g)
Yellow oil, yield 90%, 94% ee; $[\alpha]_D^{25} = -2.7$ ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: $t$(minor) = 24.4 min, $t$(major) = 31.0 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 10.97 (br, 1H), 2.44 (d, $J = 12.4$ Hz, 3H), 2.37-2.30 (m, 2H), 1.67-1.60 (m, 1H), 1.23 (t, $J = 6.6$ Hz, 2H), 0.91 (d, $J = 6.4$ Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 179.4, 178.1, 43.9, 38.9, 29.8, 25.1, 22.4, 20.8 ppm.

(R)-3-(Allyloxy)-5-methoxy-5-oxopentanoic acid (9h)

Light yellow oil, yield 97%, 81% ee; $[\alpha]_D^{25} = -3.5$ ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.6 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: $t$(minor) = 50.4 min, $t$(major) = 58.8 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 5.91-5.82 (m, 1H), 5.25 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.16 (d, $J = 10.4$ Hz, 1H), 4.21 (p, $J = 6.2$ Hz, 1H), 4.06 (d, $J = 5.7$ Hz, 2H), 3.69 (s, 3H), 2.68-2.57 (m, 4H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 176.6, 171.3, 134.2, 117.2, 71.9, 70.9, 51.7, 39.2, 39.1 ppm.

(R)-5-Methoxy-5-oxo-3-phenylpentanoic acid (9i)

White solid, yield 89%, 77% ee; $[\alpha]_D^{25} = +7.5$ ($c = 1.0$ in CHCl$_3$) (lit.$^{[2]}$ $[\alpha]_D^{20} = +8.1$ ($c = 1.62$ in CHCl$_3$)); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 90/10, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: $t$(minor) = 43.2 min, $t$(major) = 49.2 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.31-7.28 (m, 2H), 7.23-7.21 (m, 3H), 3.67-3.61 (m, 1H), 3.58 (s, 3H), 2.80-2.62 (m, 4H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 177.7, 172.1, 142.3, 128.7, 127.2, 127.1, 51.6, 40.4, 40.2, 37.9 ppm.

(R)-3-(4-Chlorophenyl)-5-methoxy-5-oxopentanoic acid (9j)
White solid, yield 87%, 78% ee; $[\alpha]_D^{25} = +3.2$ (c = 1.0 in CHCl$_3$) (lit.$^7$ $[\alpha]_D^{25} = -8.0$ (c = 0.88 in CHCl$_3$) for (S)-9j); Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 92/8, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 47.7 min, t(major) = 53.3 min; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.24 (s, 2H), 7.14 (d, J = 8.4 Hz, 2H), 3.63-3.57 (m, 4H), 2.77-2.56 (m, 4H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 177.3, 171.8, 140.7, 132.8, 128.8, 128.6, 51.7, 40.2, 40.0, 37.3 ppm.

(R)-5-Methoxy-5-oxo-3-(p-tolyl)pentanoic acid (9k)

White solid, yield 92%, 79% ee; $[\alpha]_D^{25} = +5.7$ (c = 1.0 in CHCl$_3$) (lit.$^8$ $[\alpha]_D^{20} = +5.2$ (c = 1.0 in CHCl$_3$)); Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 95/5, Flow rate: 1.0 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 41.1 min, t(major) = 47.8 min; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.10 (s, 4H), 3.63–3.56 (m, 4H), 2.78–2.60 (m, 4H), 2.31 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 177.6, 172.1, 139.3, 136.6, 129.3, 127.0, 51.6, 40.5, 40.3, 37.5, 21.0 ppm.

(R)-5-Methoxy-3-(4-methoxyphenyl)-5-oxopentanoic acid (9i)

White solid, yield 91%, 80% ee; $[\alpha]_D^{25} = -4.7$ (c = 1.0 in EtOH) (lit.$^6$ $[\alpha]_D^{20} = +7.6$ (c = 0.6 in EtOH) for (S)-9i); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.6 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 87.91 min, t(major) = 103.9 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.13 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.62-3.54 (m, 4H), 2.77-2.58 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 173.2, 172.2, 158.3, 135.4, 128.8, 114.0, 55.3, 51.6, 40.7, 40.6, 37.7 ppm.
(1S,6R)-6-(Ethoxycarbonyl)cyclohex-3-enecarboxylic acid (9m)

White solid, yield 97%, 93% ee; $[\alpha]_D^{25} = -1.2$ ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ C$, retention time: $t$(minor) = 25.7 min, $t$(major) = 29.5 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 11.14$ (br, 1H), 5.68 – 5.62 (m, 2H), 4.13 (q, $J = 7.0$ Hz, 2H), 3.03-3.02 (m, 2H), 2.58-2.51 (m, 2H), 2.34 (d, $J = 18.4$ Hz, 2H), 1.21 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 179.9$, 173.2, 125.2, 125.0, 60.8, 39.7, 39.6, 25.9, 25.5, 14.0 ppm.

(1S,6R)-6-(Isoproxy carbonyl)cyclohex-3-enecarboxylic acid (9n)

White solid, yield 93%, 89% ee; $[\alpha]_D^{25} = -7.5$ ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ C$, retention time: $t$(minor) = 30.4 min, $t$(major) = 36.1 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 11.18$ (br, 1H), 5.69-5.62 (m, 2H), 5.00 (dt, $J = 12.4$, 6.2 Hz, 1H), 3.02 (s, 2H), 2.58-2.50 (m, 2H), 2.33 (d, $J = 16.5$ Hz, 2H), 1.19-1.18 (m, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 180.2$, 172.6, 125.3, 125.0, 68.3, 39.7, 25.9, 25.4, 21.7, 21.6 ppm.

(1S,6R)-6-((Allyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9o)

White solid, yield 90%, 85% ee; $[\alpha]_D^{25} = -0.7$ ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ C$, retention time: $t$(minor) = 30.3 min, $t$(major) = 36.2
min; $^1$H NMR (400 MHz, CDCl$_3$) δ = 11.11 (br, 1H), 5.92-5.82 (m, 1H), 5.69-5.64 (m, 2H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.19 (d, $J = 10.5$ Hz, 1H), 4.62-4.54 (m, 2H), 3.06 (d, $J = 5.9$ Hz, 2H), 2.62-2.53 (m, 2H), 2.39-2.34 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 179.7, 172.9, 132.1, 125.2, 118.1, 65.4, 39.7, 39.6, 25.9, 25.6 ppm.

(1S,6R)-6-((Benzyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9p)

White solid, yield 98%, 86% ee; $[^\alpha]_D^{25} =$ -1.0 ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.2 mL/min, UV detection at 210 nm, $T = 30^\circ$C, retention time: t(major) = 69.6 min, t(minor) = 75.6 min; $^1$H NMR (400 MHz, CDCl$_3$) δ = 10.51 (br, 1H), 7.37-7.29 (m, 5H), 5.69 (s, 2H), 5.19-5.11 (m, 2H), 3.11 (t, $J = 5.2$ Hz, 2H), 2.66-2.57 (m, 2H), 2.42-2.35 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 179.8, 173.0, 135.9, 128.5, 128.2, 128.1, 125.2, 125.1, 66.6, 39.7, 39.6, 25.8, 25.6 ppm.

(1S,6R)-6-((Cinnamylxy)carbonyl)cyclohex-3-enecarboxylic acid (9q)

White solid, yield 99%, 90% ee; $[^\alpha]_D^{25} =$ -3.6 ($c = 1.0$ in CHCl$_3$); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 254 nm, $T = 30^\circ$C, retention time: t(minor) = 31.1 min, t(major) = 34.6 min; $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.42-7.29 (m, 5H), 6.64 (d, $J = 3.2$ Hz, 2H), 6.41-6.36 (m, 1H), 5.73 (s, 2H), 4.34-4.33 (m, 2H), 3.14-3.09 (m, 2H), 2.66-2.62 (m, 2H), 2.43-2.39 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 177.7, 173.2, 136.7, 131.0, 128.5, 127.6, 126.4, 125.1, 123.1, 65.3, 63.4, 39.7, 39.6, 25.8, 25.6 ppm.
6. Catalytic asymmetric synthesis of (S)-GABOB by 7i

Dimethyl 3-(allyloxy)pentanedioate (14)

Under N2 atmosphere, to a stirred solution of dimethyl 3-hydroxypentanedioate (40 g, 0.23 mol) and allyl 2,2,2-trichloroacetimidate (91.9 g, 0.46 mol) in 1000 mL of 4:1 c-hexane/CH2Cl2 at 0 °C was added TfOH (4 mL, 46 mmol). After addition, the reaction mixture was stirred for 24 h at room temperature and then filtered. The filtrate was washed with NaHCO3 (2 × 200 mL), dried over Na2SO4 and concentrated under reduced pressure to give yellow oil. The crude product was purified by flash chromatography using PE/EA 9:1 to give product 14 (45.6 g, 93%) as colourless oil; 1H NMR (400 MHz, CDCl3) δ = 5.90-5.81 (m, 1H), 5.24 (dd, J = 17.2, 1.3 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 4.21 (p, J = 6.3 Hz, 1H), 4.04 (d, J = 5.7 Hz, 2H), 3.68 (s, 6H), 2.60 (qd, J = 15.5, 6.3 Hz, 4H) ppm; 13C NMR (100 MHz, CDCl3) δ = 170.8, 134.0, 116.5, 71.7, 70.4, 51.1, 38.8 ppm; HRMS (ESI+) calcd for C10H16O5 [M+Na]+ = 239.0895, found: 239.0892.

3-(Allyloxy)pentanedioic acid (15)
To a stirred solution of 14 (45 g, 0.21 mol) in 750 mL of 4:1 THF/H₂O was added LiOH·H₂O (22.03 g, 0.53 mol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h before the THF was evaporated. The aqueous layer was washed with EtOAc (2 × 100 mL), acidified with 2 N HCl, and then extracted with EtOAc (3 × 200 mL). The organic phase was washed with brine (300 mL), dried over Na₂SO₄ and concentrated to afford 15 (35.6 g, 91%) as yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 9.23 (br, 2H), 5.93–5.83 (m, 1H), 5.27 (dd, J = 17.2, 1.5 Hz, 1H), 5.19–5.16 (m, 1H), 4.22 (p, J = 6.2 Hz, 1H), 4.08 (d, J = 5.7 Hz, 2H), 2.69 (qd, J = 15.8, 6.2 Hz, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 176.9, 134.1, 117.5, 71.7, 71.0, 39.1 ppm; HRMS (ESI⁺) calcd for C₈H₁₃O₅ [M+H]⁺ = 189.0763, found: 189.0757.

3-(Allyloxy)glutaric anhydride (8h)

![8h](image)

To a stirred suspension of 15 (33 g, 0.18 mol) in 500 mL of CH₂Cl₂ at 0 °C was added AcCl (124 mL, 1.8 mmol). The reaction mixture was stirred at room temperature for 12 h and concentrated. The crude product was dissolved in 500 mL of CH₂Cl₂, washed with NaHCO₃ (3 × 300 mL) and brine (300mL), dried over Na₂SO₄ and concentrated to afford 8h (26.5 g, 89%) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 5.89-5.79 (m, 1H), 5.30-5.21 (m, 2H), 4.08-4.03 (m, 3H), 3.09 (dd, J = 16.6, 3.5 Hz, 2H), 2.75 (d, J = 18.9 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 165.0, 133.4, 118.1, 69.9, 67.0, 35.7 ppm; HRMS (ESI⁺) calcd for C₈H₁₀O₄ [M+H]⁺ = 171.0657, found: 171.0652.

(R)-3-(Allyloxy)-5-methoxy-5-oxopentanoic acid (9h)

![9h](image)

MeOH (10.1 mL, 250 mmol) was added dropwise at 0 °C under nitrogen to a stirred solution of meso-cyclic anhydride 8h (4.26 g, 25 mmol) and 7i (1.80 g, 2.5 mmol) in
MTBE (2 L). The reaction was monitored by using thin-layer chromatography. After 96 h, anhydride consumption was complete, the solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (300 mL). The solution was washed with saturated Na$_2$CO$_3$ (3 × 150 mL) and the combined aqueous layers were acidified with excess 2 N HCl, followed by extraction with EtOAc (3 × 300 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to afford momoester 9h (4.9 g, yield 97%, 81% ee) as light yellow oil; $[\alpha]_D^{25} = -3.5$ (c = 1.0 in CHCl$_3$); Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.6 mL/min, UV detection at 220 nm, $T = 30$ °C, retention time: t(minor) = 50.6 min, t(major) = 56.1 min; Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH=95/5, Flow rate: 0.6 mL/min, UV detection at 220 nm, t(minor) = 50.6 min, t(major) = 56.1 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 5.91$-$5.82$ (m, 1H), $5.25$ (dd, $J = 17.2, 1.2$ Hz, 1H), $5.16$ (d, $J = 10.4$ Hz, 1H), $4.21$ (p, $J = 6.2$ Hz, 1H), $4.06$ (d, $J = 5.7$ Hz, 2H), $3.69$ (s, 3H), 2.68-2.57 (m, 4H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 176.6$, 171.3, 134.2, 117.2, 71.9, 70.9, 51.7, 39.2, 39.1 ppm; HRMS (ESI$^+$) calcd for C$_{9}$H$_{14}$O$_{5}$ [M+Na]$^+$ = 225.0739, found: 225.0733.

(S)-Methyl 3-(allyloxy)-4-(((benzylcarbonyl)amino)butanoate (11)

\[
\text{\begin{figure}
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\end{figure}}
\]

Diphenylphosphoryl azide (6.5 mL, 30 mmol) was added to a dry toluene solution (100 mL) of 9h (5 g, 25 mmol) and triethylamine (4.2 mL, 30 mmol) at room temperature. The reaction mixture was stirred for 30 min and then it was slowly warmed to 90 °C. When the evolution of nitrogen ceased (30 min), benzyl alcohol (3.1 mL, 30 mmol) was added, and the mixture was heated at reflux overnight. The reaction mixture was washed with NaNO$_2$ (1% aq., 2 × 250 mL), NaHCO$_3$ (2 × 250 mL), H$_2$O (250 mL), dried over Na$_2$SO$_4$ and concentrated to afford brown oil. The crude product was purified by flash chromatography using PE/EA 10:1 to give product 11 (5.7 g, 75%) as light yellow oil; $[\alpha]_D^{25} = +5.4$ (c = 1.0 in CHCl$_3$); $^1$H NMR
(400 MHz, CDCl$_3$) $\delta = 7.35$-$7.30$ (m, 5H), 5.89-$5.80$ (m, 1H), 5.23 (d, $J = 17.2$ Hz, 1H), 5.15 (d, $J = 10.2$ Hz, 2H), 5.09 (s, 2H), 4.02 (d, $J = 4.9$ Hz, 2H), 3.92-$3.90$ (m, 1H), 3.67 (s, 3H), 3.42-$3.37$ (m, 1H), 3.33-$3.27$ (m, 1H), 2.59-$2.45$ (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 171.4$, 156.6, 136.5, 134.4, 128.5, 128.2, 128.1, 117.4, 74.4, 70.8, 66.8, 51.8, 43.8, 37.4 ppm; HRMS (ESI$^+$) calcld for C$_{16}$H$_{21}$NO$_5$ [M+Na]$^+$ = 330.1317, found: 330.1306.

(S)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-hydroxybutanoate (12)

To a solution of 11 (0.9 g, 3 mmol) and Pd/C (450 mg) in MeOH (30 mL) was added 4-methylbenzenesulfonic acid (57 mg, 0.3 mmol). The reaction mixture was heated at reflux for 3 h and filtered. The filtrate was concentrated to afford yellow oil. The crude product was purified by flash chromatography using PE/EA 5:1 to give product 12 (0.75 g, 96%) as light yellow oil; $[\alpha]_D^{25} = +2.5$ (c = 1.0 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.34$ (s, 5H), 5.29 (br, 1H), 5.10 (s, 2H), 4.12 (br, 1H), 3.70 (s, 3H), 3.44 (s, 1H), 3.38 (s, 1H), 3.22-$3.15$ (m, 1H), 2.54-$2.44$ (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 172.9$, 157.0, 136.4, 128.6, 128.3, 128.2, 67.5, 67.0, 52.0, 45.9, 38.4 ppm.

(S)-GABOB (13)

(S)-methyl 4-(((benzyloxy)carbonyl)amino)-3-hydroxybutanoate (12, 5 g, 19 mmol) was added to 16 N HCl (60 mL) and then the reaction mixture was heated at reflux overnight. The mixture was concentrated under reduced pressure and the residue was crystallized from EtOH to give white solid, then dissolved in H$_2$O (5 mL) and added NaOH (0.54 g). The stirred suspension was added H$_2$O until the solid disappeared, then EtOH (20 mL) was added and filtered, oven dry the filter cake to afford (S)-GABOB (13, 1.63 g, 73%) as white solid; 96% ee, determined from optical
rotation, \([\alpha]_D^{25} = +19.7 \ (c = 1.4 \text{ in } \text{H}_2\text{O})\) (lit.\(^{[9]}\) \([\alpha]_D^{25} = +20.56 \ (c = 1.41 \text{ in } \text{H}_2\text{O})\), recrystallization from 78% EtOH further increased the optical purity to 99% ee, \([\alpha]_D^{25} = +20.4 \ (c = 1.5 \text{ in } \text{H}_2\text{O})\); \(^1\text{H}\) NMR (400 MHz, D\(_2\)O) \(\delta = 4.21\text{-}4.15 \ (m, 1\text{H}), 3.15 \ (dd, J = 13.1, 3.0 \text{ Hz, } 1\text{H}), 2.93 \ (dd, J = 13.1, 9.5 \text{ Hz, } 1\text{H}), 2.41 \ (d, J = 6.5 \text{ Hz, } 2\text{H}) \text{ ppm}; \(^{13}\text{C}\) NMR (100 MHz, D\(_2\)O) \(\delta = 178.6, 65.5, 44.1, 42.3 \text{ ppm}; \) HRMS (ESI\(^+\)) calcd for C\(_4\)H\(_9\)NO\(_3\) [M+H]\(^+\) = 120.0661, found: 120.0654.

7. References


8. Copies of NMR spectra and chiral HPLC spectra

\[ N-((1R,2R)-2-(\text{Dimethylamino})-1-(4\text{-nitrophenyl})-3-(\text{trityloxy})propyl)-4-(\text{tri-fluoromethyl})benzamide \ (7a) \]

\[ ^1H \text{ NMR} \]

\[ ^{13}C \text{ NMR} \]
HRMS

$N-((1R,2R)-2-(\text{Dimethylamino})-1-(4\text{-nitrophenyl})-3-(\text{trityloxy})\text{propyl})-4\text{-nitrobenzamide (7b)}$

$^1\text{H NMR}$
$^{13}$C NMR

HRMS
\( N-((1R,2R)-2-(\text{Dimethylamino})-1-(4\text{-nitrophenyl})-3-(\text{trityloxy}propyl)-4\text{-fluoro}benzamide \ (7c)) \)

\(^1\text{H NMR}\)

\(^{13}\text{C NMR}\)
4-Chloro-N-((1R,2R)-2-(dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-benzamide (7d)

$^1$H NMR
$^1^3$C NMR

HRMS
4-Bromo-N-((1R,2R)-2-(dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-benzamide (7e)

$^1$H NMR

$^{13}$C NMR
HRMS

\[ N-((1R,2R)-2-(\text{Dimethylamino})-1-(4-\text{nitrophenyl})-3-(\text{trityloxy} \text{propyl})\text{benzamide}) \] (7f)  

\(^1\text{H NMR}\)
$^{13}$C NMR

HRMS
$N$-($1R,2R$)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-4-methylbenzamide (7g)

$^1$H NMR

$^{13}$C NMR
HRMS

$N^-{(1R,2R)}-2$-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-4-methoxybenzamide (7h)

$^1H$ NMR
\( ^{13}C \text{NMR} \)

\( \text{HRMS} \)
$N$-((1$R,2R$)-2-(Dimethylamino)-1-(4-nitrophenyl)-3-(trityloxy)propyl)-3,5-bis-(trifluoromethyl)benzamide (7i)

$^1$H NMR

$^{13}$C NMR
HRMS

$N\text{-}(1R,2R)-1\text{-}(4\text{-Nitrophenyl})\text{-}2\text{-}(\text{pyrrolidin-1-yl})\text{-}3\text{-}(\text{trityloxy})\text{-}3,5\text{-bis-}$
$(\text{trifluoromethyl})\text{benzamide (7j)}$

$^1H$ NMR
$^{13}$C NMR

HRMS
N-((1R,2R)-1-(4-Nitrophenyl)-2-(piperidin-1-yl)-3-(trityloxy)propyl)-3,5-bis-(trifluoromethyl)benzamide (7k)

$^1$H NMR

$^{13}$C NMR
HRMS

\[ N-((1R,2R)-2-Morpholino-1-(4-nitrophenyl)-3-(trityloxy)propyl)-3,5-bis(trifluoro-methyl)benzamide (7l) \]

\(^1\)H NMR
$^{13}$C NMR

HRMS
$N\-((1R,2R)-3\-((tert\-Butyldimethylsilyl)oxy)\-2\-(dimethylamino)\-1\-(4\-nitrophenyl)\-propyl)\-3,5\-bis(trifluoromethyl)benzamide$ (7m)

$^1^H$ NMR

$^{13}C$ NMR
HRMS

\[ N-(1R,2R)-3-(\text{tert-Butyldimethylsilyl})\text{oxy})-1-(4-nitrophenyl)-2-(\text{pyrrolidin-1-yl})-\text{propyl})-3,5\text{-bis(trifluoromethyl)benzamide (7n)} \]

\(^1\text{H NMR}\)
$N$-((1\textit{R},2\textit{R})-3-((\text{tert-Butyldimethylsilyl})oxy)-1-(4-nitrophenyl)-2-(piperidin-1-yl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7o)

$^1\text{H}$ NMR

$^{13}\text{C}$ NMR
N-((1R,2R)-3-((tert-Butyldimethylsilyl)oxy)-2-morpholino-1-(4-nitrophenyl)-propyl)-3,5-bis(trifluoromethyl)benzamide (7p)

$^1$H NMR
$^{13}$C NMR

HRMS
(1S,6R)-6-(Methoxycarbonyl)cyclohex-3-ene-carboxylic acid (9a)

$^1$H NMR

$^{13}$C NMR
(1S,2R)-2-(Methoxycarbonyl)cyclohexanecarboxylic acid (9b)

$^1$H NMR

$^{13}$C NMR
(1S,2R,3S,4R)-3-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9c)

$^1$H NMR

$^{13}$C NMR
(1R,2S,3R,4S)-3-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9d)

$^1$H NMR

$^{13}$C NMR
(R)-5-Methoxy-3-methyl-5-oxopentanoic acid (9e)

$^1$H NMR

$^{13}$C NMR
(R)-3-Ethyl-5-methoxy-5-oxopentanoic acid (9f)

$^1$H NMR

$^{13}$C NMR
(R)-3-Isopropyl-5-methoxy-5-oxopentanoic acid (9g)

$^1$H NMR

$^{13}$C NMR
(R)-3-(Allyloxy)-5-methoxy-5-oxopentanoic acid (9h)

$^1$H NMR

$^{13}$C NMR
HRMS

(R)-5-Methoxy-5-oxo-3-phenylpentanoic acid (9i)

$^1$H NMR

$^{13}$C NMR
(R)-3-(4-chlorophenyl)-5-methoxy-5-oxopentanoic acid (9j)

$^1$H NMR
$^{13}$C NMR

(R)-5-Methoxy-5-oxo-3-(p-tolyl)pentanoic acid (9k)

$^1$H NMR
$^{13}$C NMR

(R)-5-Methoxy-3-(4-methoxyphenyl)-5-oxopentanoic acid (9l)

$^1$H NMR
$^{13}$C NMR

(1S,6R)-6-(Ethoxycarbonyl)cyclohex-3-enecarboxylic acid (9m)

$^1$H NMR
$^{13}$C NMR

(1S,6R)-6-(Isopropoxycarbonyl)cyclohex-3-enecarboxylic acid (9n)

$^1$H NMR
(1S,6R)-6-((Allyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9o)

$^1$H NMR
$^{13}$C NMR

(1S,6R)-6-((Benzyloxy)carbonyl)cyclohex-3-ene carboxylic acid (9p)

$^1$H NMR
\(^{13}\)C NMR

(1S,6R)-6-((Cinnamyl)carbonyl)cyclohex-3-enecarboxylic acid (9q)

\(^1\)H NMR
\(^{13}\)C NMR

\[
\text{Dimethyl 3-(allyloxy)pentanedioate (14)}
\]

\(^1\)H NMR
3-(Allyloxy)pentanedioic acid (15)

$^1$H NMR

$^{13}$C NMR
3-(Allyloxy)glutaric anhydride (8h)

$^1$H NMR
$^{13}$C NMR

HRMS
(S)-Methyl-3-(allyloxy)-4-(((benzyloxy)carbonyl)amino)butanoate (11)

\[ ^1\text{H NMR} \]

\[ ^{13}\text{C NMR} \]
HRMS

(S)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-hydroxybutanoate (12)

$^1$H NMR
$^{13}$C NMR

(S)-GABOB (13)

$^1$H NMR
Chiral HPLC:

$(1S,6R)$-6-(Methoxycarbonyl)cyclohex-3-enecarboxylic acid (9a)

Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.5 mL/min, UV detection at 220 nm, $T = 30^\circ$C, retention time: $t$(major) = 33.1 min, $t$(minor) = 45.3 min.
(1S,2R)-2-(Methoxycarbonyl)cyclohexanecarboxylic acid (9b)

Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 23.2 min, t(major) = 29.9 min.

(1S,2R,3S,4R)-3-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9c)

Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 85/15, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(major) = 23.8 min, t(minor) = 37.8 min.

(1R,2S,3R,4S)-3-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (9d)

Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 96/4, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 47.8 min, t(major) = 50.7 min.
**(R)-5-Methoxy-3-methyl-5-oxopentanoic acid (9e)**

Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 96/4, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 38.3 min, t(major) = 44.1 min.

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**Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 96/4, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 38.3 min, t(major) = 44.1 min.**

**(R)-3-Ethyl-5-methoxy-5-oxopentanoic acid (9f)**

Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 26.7 min, t(major) = 30.3 min.

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**(R)-3-Isopropyl-5-methoxy-5-oxopentanoic acid (9g)**

Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 24.4 min, t(major) = 31.0 min.

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**Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 24.4 min, t(major) = 31.0 min.**
(R)-3-(Allyloxy)-5-methoxy-5-oxopentanoic acid (9h)
Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.6 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 50.4 min, t(major) = 58.8 min.

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(R)-5-Methoxy-5-oxo-3-phenylpentanoic acid (9i)
Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 90/10, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 43.2 min, t(major) = 49.2 min.

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(R)-3-(4-Chlorophenyl)-5-methoxy-5-oxopentanoic acid (9j)
Chiral HPLC (Chiralcel OD-H column), Hexane/i-PrOH = 92/8, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 47.7 min, t(major) = 53.3 min.

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(R)-5-Methoxy-5-oxo-3-(p-tolyl)pentanoic acid (9k)
Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 95/5, Flow rate: 1.0 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 41.1 min, t(major) = 47.8 min.

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(R)-5-Methoxy-3-(4-methoxyphenyl)-5-oxopentanoic acid (9l)
Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 93/7, Flow rate: 0.6 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 87.91 min, t(major) = 103.9 min.

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(1S,6R)-6-(Ethoxycarbonyl)cyclohex-3-enecarboxylic acid (9m)
Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 25.7 min, t(major) = 29.5 min.

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(1S,6R)-6-(Isopropoxycarbonyl)cyclohex-3-enecarboxylic acid (9n)
Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 30.4 min, t(major) = 36.1 min.

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(1S,6R)-6-((Allyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9o)
Chiral HPLC (Chiralcel IA-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 220 nm, T = 30°C, retention time: t(minor) = 30.3 min, t(major) = 36.2 min.

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(1S,6R)-6-((Benzyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9p)
Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 95/5, Flow rate: 0.2 mL/min, UV detection at 210 nm, T = 30°C, retention time: t(major) = 69.6 min, t(minor) = 75.6 min.

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(1S,6R)-6-((Cinnamyloxy)carbonyl)cyclohex-3-enecarboxylic acid (9q)
Chiral HPLC (Chiralcel AD-H column), Hexane/i-PrOH = 94/6, Flow rate: 0.5 mL/min, UV detection at 254 nm, T = 30°C, retention time: t(minor) = 31.1 min, t(major) = 34.6 min.

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