Multifaceted Interception of 2-chloro-2-oxoacetic Anhydrides: A Direct Asymmetric Synthesis of β-lactams

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Supporting Information

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I. General experimental

General information: Dichloromethane was distilled from calcium hydride under nitrogen. Toluene and benzene were distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Other reagents were used as purchased from Aldrich. VANOL and VAPOL were prepared according to a literature procedure and were determined to be at least 99% optical purity. Preparation of aziridine esters have been previously reported.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. $^1$H NMR and $^{13}$C NMR were recorded on a Varian Inova-300 MHz, Varian UnityPlus-500 MHz or Varian Inova-600 MHz instrument in CDCl$_3$ unless otherwise noted. CDCl$_3$ was used as the internal standard for both $^1$H NMR ($\delta = 7.24$) and $^{13}$C NMR ($\delta = 77.0$). HR-MS was performed in the department of Biochemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C.

Although we have not experienced any problems with the use of ethyl diazoacetate herein, we note that diazo compounds in general are heat sensitive and potentially explosive and should be handled with due care.
II. Preparation of acids

Preparation of acid 8:

To a suspension of ester 88\(^4\) (62% ee, 170 mg, 0.600 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (170 mg, 3.00 mmol, 5.00 equiv) in H\(_2\)O (2 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, aq citric acid (2N, 2 mL) was added. The white precipitate was collected by filtration. The product was obtained as a white solid (150 mg, 0.593 mmol) in 99% yield; mp 123-125 °C; R\(_f\) = 0.10 (hexane:EtOAc 4:1). Spectral data for 8: \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 2.74 (d, 1H, \(J = 6.0\) Hz), 3.18 (d, 1H, \(J = 6.5\) Hz), 3.60 (d, 1H, \(J = 14.0\) Hz), 3.81 (d, 1H, \(J = 14.0\) Hz), 7.12-7.48 (m, 10H), 12.20 (brs, 1H); \(^13\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 46.22, 46.74, 62.06, 126.90, 127.03, 127.63, 127.69, 128.23, 135.98, 138.73, 168.78 (One sp\(^2\) C not located); IR (thin film) 1718(s) 1224(s) cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{16}\)NO\(_2\) (M+H, ESI\(^+\)) m/z 254.1181, meas 254.1163; [\(\alpha\)]\(^20\)D 18.2° (c 1.0, CH\(_2\)Cl\(_2\)) on 62% ee material.

Preparation of acid 10:

To a 50 mL round bottom flask containing ester 9\(^2\) (98% ee, 1.07 g, 3.00 mmol, 1.00 equiv) and ethanol (5 mL) was added an aqueous solution of KOH (840 mg, 15.0 mmol, 5.00 equiv) in H\(_2\)O (5 mL). The resulting suspension was refluxed for 1 h during which time it became a homogeneous solution. After it was cooled to rt, ethanol was removed by rotary evaporation. To the remaining aqueous solution was added aq citric acid (2N, 10 mL). The resulting white precipitate was collected by filtration and washed with H\(_2\)O and hexane to obtain the pure acid 10 (976 mg, 2.98 mmol, 99%) as a white solid; mp 143-145 °C; R\(_f\) = 0.10 (hexane:EtOAc 4:1). Spectral data for acid 10: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 2.78 (d, 1H, \(J = 7.2\) Hz), 3.40 (d, 1H, \(J = 6.6\) Hz), 4.04 (s, 1H), 7.20-7.30 (m, 8H), 7.32 (q, 4H, \(J = 7.2\) Hz), 7.47 (t, 4H, \(J = 8.4\) Hz); \(^1\)H NMR
(600 MHz, DMSO-$d_6$) $\delta$ 2.77 (d, 1H, $J = 7.2$ Hz), 3.32 (d, 1H, $J = 6.6$ Hz), 4.17 (s, 1H), 7.14-7.30 (m, 7H), 7.34 (t, 2H, $J = 7.8$ Hz), 7.41 (d, 2H, $J = 7.8$ Hz), 7.49 (d, 2H, $J = 8.4$ Hz), 7.61 (d, 2H, $J = 7.8$ Hz), 12.22 (bres, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 46.39, 47.14, 75.34, 126.94, 126.99, 127.05, 127.08, 127.25, 127.59, 127.63, 128.31, 128.34, 135.70, 143.07, 143.20, 168.58; IR (thin film) 1705(s), 1244(m) cm$^{-1}$; HRMS calcd for C$_{22}$H$_{20}$NO$_2$ (M+H, ESI$^+$) m/z 330.1494, meas 330.1506; $[\alpha]_{20}^D$ 19.6$^\circ$ (c 0.5, CH$_2$Cl$_2$) on 98% ee material.

**Preparation of acid 90:**

To a suspension of ester 89 (90% ee, 872 mg, 2.00 mmol, 1.00 equiv) in ethanol (5 mL) was added a solution of KOH (560 mg, 10.00 mmol, 5.00 equiv) in H$_2$O (5 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The white precipitate was collected by filtration and washed with H$_2$O and hexanes. The solid was dissolved in Et$_2$O (25 mL), dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated to afford the product 90 as a white solid (810 mg, 1.985 mmol) in 99% yield; mp 140-142 °C; $R_f$ = 0.20 (hexane:EtOAc 4:1). Spectral data for acid 90: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.79 (d, 1H, $J = 7.0$ Hz), 3.32 (d, 1H, $J = 7.0$ Hz), 4.03 (s, 1H), 7.17 (d, 2H, $J = 8.5$ Hz), 7.22-7.60 (m, 13H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 45.45, 48.15, 77.23, 122.04, 126.98, 127.40, 127.77, 127.88, 128.75, 128.84, 129.30, 131.45, 133.02, 141.14, 141.55, 169.82; IR (thin film) 1711(s), 1265(m) cm$^{-1}$; HRMS calcd for C$_{22}$H$_{19}$NO$_2$Br (M+H, ESI$^+$) m/z 408.0599, meas 408.0576; $[\alpha]_{20}^D$ 3.5$^\circ$ (c 1.0, CH$_2$Cl$_2$) on 90% ee material.

**Preparation of acid 92:**

![Diagram](attachment:image_url)
To a 50 mL round bottom flask containing ester 91 (racemic, 250 mg, 0.674 mmol, 1.00 equiv), ethanol (2 mL) and THF (1 mL) was added an aqueous solution of KOH (189 mg, 3.37 mmol, 5.00 equiv) in H$_2$O (2 mL). The resulting suspension was refluxed for 2 h during which time it became a homogeneous solution. After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration and washed with H$_2$O and hexane to obtain the pure acid 92 (230 mg, 0.670 mmol, 99%) as a white solid; mp 147-149 °C; R$_f$ = 0.10 (hexane:EtOAc 4:1). Spectral data for acid 92: $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 2.23 (s, 3H), 2.72 (d, 1H, $J$ = 6.5 Hz), 3.26 (d, 1H, $J$ = 6.5 Hz), 4.14 (s, 1H), 7.00-7.40 (m, 10H), 7.46 (d, 2H, $J$ = 7.5 Hz), 7.58 (d, 2H, $J$ = 7.5 Hz), 12.16 (brs, 1H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 20.67, 46.33, 47.03, 75.32, 126.92, 127.00, 127.20, 127.48, 128.24, 128.31, 132.64, 136.19, 143.09, 143.21, 168.58 (Two $sp^2$ carbon not located); IR (thin film) 1705(s), 1244(m) cm$^{-1}$; HRMS calcd for C$_{23}$H$_{22}$NO$_2$ (M+H, ESI$^+$) m/z 344.1651, meas 344.1679.

Preparation of acid 26:

Alkylation: General procedure for alkylation, illustrated for the acid 26: To a flame-dried 50 mL round bottom flask filled with N$_2$ was charged with dry i-Pr$_2$NH (0.050 mL, 0.33 mmol, 2.1 equiv) and dry THF (3 mL). The vacuum adapter was quickly replaced with a septum to which a N$_2$ balloon was attached via a needle. The flask was cooled in a dry ice-acetone bath (–78 °C). n-BuLi (2.3M, 0.14 mL, 0.32 mmol, 2.0 equiv) was added dropwise via syringe. After it was stirred at –78 °C for 5 min, the solution was stirred at 0 °C for 15 min. After the flask was cooled to –78 °C again, a solution of ester 93 (99% ee, 100 mg, 0.160 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise. The resulting yellow solution was stirred at –78 °C for 30 min. Then CH$_3$I (0.030 mL, 0.48 mmol, 3.0 equiv) was added via syringe. The resulting mixture was stirred at –78 °C for 1 h, and then dry ice-acetone bath was removed. And the reaction mixture was allowed to warm up to rt slowly over a period of 1 h. Then aq sat NaHCO$_3$ (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 x 5 mL). The combined
organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated to afford the methylated ester 18 used directly in the next step.

**Hydrolysis:** To the mixture of the methylated ester in THF (1 mL) and ethanol (1 mL) was added an aqueous solution of KOH (45 mg, 0.80 mmol, 5.0 equiv) in H$_2$O (1 mL). The resulting mixture was refluxed overnight (~17 h). After it was cooled to rt, the volatiles were evaporated and aq citric acid (2N, 2 mL) was added. The mixture was extracted with ether (10 mL + 2 × 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product 26 was obtained as a white solid (85 mg, 0.14 mmol) in 87% yield over 2 steps; mp 72-74 °C; $R_f = 0.30$ (hexane:EtOAc 4:1). Spectral data for 26: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.36, 1.38 (2s, 36H), 1.63 (s, 3H), 3.24 (s, 1H), 3.638, 3.642 (2s, 6H), 4.31 (s, 1H), 6.96-7.00 (m, 2H), 7.14-7.18 (m, 3H), 7.24 (s, 2H), 7.29 (s, 2H), 10.00 (brs, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 12.14, 32.01, 32.09, 35.80, 35.82, 49.48, 53.65, 64.19, 64.24, 71.06, 125.00, 126.08, 127.28, 128.03, 128.36, 134.54, 135.49, 135.85, 143.83, 143.90, 158.72, 159.15, 170.50; IR (thin film) 2963(s), 1768(m), 1414(m) cm$^{-1}$; HRMS calcd for C$_{41}$H$_{58}$NO$_4$ (M+H, ESI$^+$) m/z 628.4366, meas 628.4321; $[\alpha]^{20}_D$ 23.6 $^\circ$(c 1.0, Et$_2$O) on 99% ee material.

**Preparation of acid 25:**

![Chemical Structure](image)

Alkylation: The general procedure for the alkylation described for acid 26 was followed with ester 9$^2$ (98% ee, 357 mg, 1.00 mmol, 1.00 equiv), $i$-Pr$_2$NH (0.30 mL, 2.1 mmol, 2.1 equiv), $n$-BuLi (2.3M, 0.87 mL, 2.0 mmol, 2.0 equiv) and CH$_3$I (0.20 mL, 3.0 mmmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

**Hydrolysis:** To the mixture of the above methylated ester in ethanol (2 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H$_2$O (5 mL). The resulting mixture was refluxed overnight (~12 h). After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration. The product was obtained as a slightly brown solid
(250 mg, 0.730 mmol) in 73% yield over 2 steps; mp 155-156 °C; R_f = 0.10 (hexane:EtOAc 4:1).

Spectral data for acid 25: ¹H NMR (500 MHz, DMSO-d_6) δ 1.45 (s, 3H), 3.15 (s, 1H), 4.68 (s, 1H), 7.08-7.44 (m, 11H), 7.56 (d, 2H, J = 7.5 Hz), 7.71 (d, 2H, J = 7.5 Hz), 12.0 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d_6) δ 13.22, 50.26, 51.56, 68.86, 126.58, 126.63, 126.77, 126.96, 127.17, 127.54, 127.68, 128.19, 128.27, 136.63, 143.92, 144.20, 170.84; IR (thin film) 1720(s), 1265(m) cm⁻¹; HRMS calcd for C_{23}H_{22}NO_2 (M+H, ESI⁺) m/z 344.1651, meas 344.1626; [α]_{D}^{20} 110.3° (c 0.67, CH_2Cl_2) on 98% ee material.

Preparation of acid 27:

**Alkylation:** The general procedure for the alkylation described for acid 26 was followed with ester 94 (99% ee, 656 mg, 1.00 mmol, 1.00 equiv), i-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), n-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH₃I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

**Hydrolysis:** To the mixture of the crude product in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (2.5 mL). The resulting mixture was refluxed for 42 h. After it was cooled to rt, the volatiles were evaporated and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product was obtained as a white solid (602 mg, 0.937 mmol) in 94% yield over 2 steps; mp 82-85 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for acid 27: ¹H NMR (500 MHz, CDCl₃) δ 1.40, 1.41 (2s, 3H), 1.65 (s, 3H), 2.26 (s, 3H), 3.24 (s, 1H), 3.67, 3.68 (2s, 6H), 4.32 (s, 1H), 6.89 (d, 2H, J = 8.0 Hz), 6.99 (d, 2H, J = 8.0 Hz), 7.28 (s, 2H), 7.34 (s, 2H), 9.50 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.07, 21.07, 32.02, 32.08, 35.79, 35.80, 49.33, 53.48, 64.17, 64.24, 71.08, 124.99, 126.09, 127.17, 129.02, 131.59, 135.60, 135.92, 137.73, 143.78, 143.85, 158.68, 159.12, 170.66;
IR (thin film) 2961(s), 1718(s), 1224(s) cm\(^{-1}\); HRMS calcd for C\(_{42}\)H\(_{60}\)NO\(_4\) (M+H, ESI\(^+\)) m/z 642.4522, meas 642.4482; \([\alpha]\)\(^{20}\)_D 9.3° (c 2.0, CH\(_2\)Cl\(_2\)) on 99% ee material.

**Preparation of acid 28:**

\[
\begin{align*}
\text{BUDAM} & \quad \text{COOEt} \quad 95 \quad 99\% \text{ ee} \\
\text{N} & \quad \downarrow \quad 1) \text{LDA, MeI} \quad \uparrow \\
\text{BUDAM} & \quad \text{COOH} \quad 28 \quad 99\% \text{ ee}
\end{align*}
\]

**Alkylation:** The general procedure for the alkylation described for acid 26 was followed with ester 95\(^4\) (96% ee, 656 mg, 1.00 mmol, 1.00 equiv), i-Pr\(_2\)NH (0.30 mL, 2.1 mmol, 2.1 equiv), n-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH\(_3\)I (0.19 mL, 3.0 mmmol, 3.0 equiv). After workup, the methlylated ester was obtained which was used directly in the next step.

**Hydrolysis:** To the mixture of the methylated ester in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H\(_2\)O (5 mL). The resulting mixture was refluxed for 22 h. After it was cooled to rt, the volatiles were evaporated and aq HCl (6N, 5 mL) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 \times 10 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 180 mm, hexane:acetone 9:1). The product 28 was obtained as a white solid (507 mg, 0.780 mmol) in 78% yield over 2 steps; mp 76-78 °C; R\(_f\) = 0.50 (hexane:acetone 4:1). Spectral data for acid 28: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.43, 1.46 (2s, 36H), 1.71 (s, 3H), 2.30 (s, 3H), 3.23 (s, 1H), 3.68, 3.71 (2s, 6H), 4.40 (s, 1H), 7.00-7.20 (m, 4H), 7.34 (s, 2H), 7.39 (s, 2H), 9.80 (brs, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 11.91, 18.86, 31.98, 32.08, 35.74, 35.78, 49.09, 53.75, 64.13, 64.15, 71.32, 124.92, 125.49, 126.00, 127.04, 127.93, 129.94, 132.96, 135.56, 135.83, 136.55, 143.72, 143.86, 158.66, 159.07, 170.32; IR (thin film) 2961(s), 1767(s), 1414(m) cm\(^{-1}\); HRMS calcd for C\(_{42}\)H\(_{60}\)NO\(_4\) (M+H, ESI\(^+\)) m/z 642.4522, meas 642.4491; \([\alpha]\)\(^{20}\)_D 31.3° (c 1.0, CH\(_2\)Cl\(_2\)) on 99% ee material.

**Preparation of acid 29:**

\[
\begin{align*}
\text{BUDAM} & \quad \text{COOEt} \quad 96 \quad 99\% \text{ ee} \\
\text{N} & \quad \downarrow \quad 1) \text{LDA, Mel} \quad \uparrow \\
\text{BUDAM} & \quad \text{COOH} \quad 29 \quad 99\% \text{ ee}
\end{align*}
\]
**Alkylation:** The general procedure for the alkylation described for acid 26 was followed with ester 96\(^\dagger\) (99\% ee, 720 mg, 1.00 mmol, 1.00 equiv), \(\text{i-Pr}_2\text{NH}\) (0.30 mL, 2.1 mmol, 2.1 equiv), \(\text{n-BuLi}\) (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and \(\text{CH}_3\text{I}\) (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the methylated ester was obtained which was used directly in the next step.

**Hydrolysis:** To the mixture of the methylated ester in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in \(\text{H}_2\text{O}\) (2.5 mL). The resulting mixture was refluxed for 3 h. After it was cooled to rt, \(\text{CH}_2\text{Cl}_2\) (5 mL) was added and the mixture was refluxed for 66 hours until it became a homogeneous solution. After it was cooled to rt, the volatiles were removed by rotary evaporation and \(\text{aq}\) HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (\(\text{Na}_2\text{SO}_4\)) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 250 mm, hexane:acetone 9:1). The product 29 was obtained as a white solid (383 mg, 0.54 mmol) in 54\% yield over 2 steps; mp 78-80 °C; \(R_f = 0.30\) (hexane:acetone 9:1). Spectral data for acid 29: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 1.45, 1.47 (2s, 36H), 1.71 (s, 3H), 3.26 (s, 1H), 3.73 (s, 6H), 4.40 (s, 1H), 6.94 (d, 2H, \(J = 8.4\) Hz), 7.30-7.40 (m, 6H), 9.60 (brs, 1H); \(^{13}\text{C NMR}\) (150 MHz, CDCl\(_3\)) \(\delta\) 12.11, 32.01, 32.07, 35.78, 35.80, 49.63, 52.83, 64.17, 64.26, 70.91, 122.08, 124.96, 126.01, 129.04, 131.45, 133.75, 135.29, 135.75, 143.90, 143.92, 158.73, 159.17, 170.34; IR (thin film) 2961(s), 1769(m), 1414(m) cm\(^{-1}\); HRMS calcd for \(\text{C}_{41}\text{H}_{57}\text{NO}_{4.79}\text{Br}\) (M+H, ESI\(^+\)) \(m/z\) 706.3471, meas 706.3450; \([\alpha]_{D}^{20}\) 18.6° (c 1.0, \(\text{CH}_2\text{Cl}_2\)) on 99\% ee material.

**Preparation of acid 30:**

\[
\begin{align*}
\text{COOEt} & \quad \text{BUDAM} & \quad \text{N} \\
\begin{array}{c}
\text{BUDAM} \\
\text{N}
\end{array} & \quad \text{COOH}
\end{align*}
\]

1) LDA, MeI then H\(^+\)

2) KOH, EtOH

**Alkylation:** The general procedure for the alkylation was followed with ester 97\(^\dagger\) (96\% ee, 432 mg, 0.600 mmol, 1.00 equiv), \(\text{i-Pr}_2\text{NH}\) (0.18 mL, 1.3 mmol, 2.1 equiv), \(\text{n-BuLi}\) (2.3M, 0.51 mL, 1.3 mmol, 2.0 equiv) and \(\text{CH}_3\text{I}\) (0.12 mL, 1.8 mmol, 3.0 equiv). After workup, the methylated ester was obtained which was used directly in the next step.
Hydrolysis: To the mixture of the methylated ester in THF (2 mL) and ethanol (2 mL) was added an aqueous solution of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 12 h. And another portion of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H₂O (2 mL) was added. The resulting mixture was refluxed for 48 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq citric acid (2N, 5 mL) was added. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1). The product was obtained as a white solid (240 mg, 0.340 mmol) in 57% yield over 2 steps; mp 76-80 °C; Rₚ = 0.50 (hexane:acetone 5:1).

Spectral data for acid 30: ¹H NMR (500 MHz, CDCl₃) δ 1.37, 1.40 (2s, 36H), 1.71 (s, 3H), 3.27 (s, 1H), 3.63, 3.67 (2s, 6H), 4.38 (s, 1H), 7.00-7.16 (m, 3H), 7.27, 7.30 (2s, 4H), 7.44-7.50 (dd, 1H, J = 7.5, 1.5 Hz), 9.80 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.12, 32.00, 32.10, 35.79, 35.83, 49.88, 55.31, 64.19, 64.21, 71.03, 123.73, 124.98, 125.95, 126.95, 128.91, 129.55, 132.47, 134.44, 135.21, 135.71, 143.86, 143.95, 158.77, 159.12, 169.57; IR (thin film) 2961(s), 1773(m), 1414(m) cm⁻¹; HRMS calcd for C₄₁H₅₇NO₄⁻⁷⁹Br (M⁺H, ESI⁺) m/z 706.3471, meas 706.3497; [α]²⁰D 12.0° (c 1.0, CH₂Cl₂) on 96% ee material.

Preparation of acid 31:

Alkylation: The general procedure for the alkylation described for acid 26 was followed with ester 98 (98% ee, 691 mg, 1.00 mmol, 1.00 equiv), i-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), n-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH₃I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the methylated ester was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (2.5 mL). The resulting mixture was refluxed for 6 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The
combined organic extracts were dried (\(\text{Na}_2\text{SO}_4\)) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 9:1). The product 31 was obtained as a white solid (380 mg, 0.560 mmol) in 56% yield over 2 steps; mp 88-91 °C; \(R_f = 0.45\) (hexane:EtOAc 4:1). Spectral data for 31: \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta 1.37\) (s, 18H), 1.41 (s, 18H), 1.83 (s, 3H), 3.27 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.46 (s, 1H), 7.12 (d, 1H, \(J = 7.0\) Hz), 7.20-7.26 (m, 1H), 7.32, 7.35 (2s, 4H), 7.44-7.54 (m, 2H), 7.70 (d, 1H, \(J = 8.5\) Hz), 7.80 (d, 1H, \(J = 7.5\) Hz), 7.85 (d, 1H, \(J = 7.5\) Hz), 9.80 (brs, 1H); \(^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\) \(\delta 12.13\), 32.02, 32.13, 32.23, 35.81, 35.85, 49.32, 53.18, 64.23, 71.47, 123.18, 124.86, 125.06, 125.15, 126.14, 126.17, 126.72, 128.62, 128.68, 130.76, 131.24, 133.38, 135.40, 135.81, 143.87, 143.98, 158.79, 159.20, 170.14; IR (thin film) 2963(s), 1770(m), 1414(m cm\(^{-1}\); HRMS calcd for \(C_{45}H_{60}NO_4\) (M+H, ESI\(^+\)) m/z 678.4522, meas 678.4510; \([\alpha]^{20}_D\) 9.0° (c 1.0, CH\(_2\)Cl\(_2\)) on 98% ee material.

**Preparation of acid 32:**

**Alkylation:** The general procedure for the alkylation described for acid 26 was followed with ester 96\(^4\) (99% ee, 720 mg, 1.00 mmol, 1.00 equiv), i-Pr\(_2\)NH (0.30 mL, 2.1 mmol, 2.1 equiv), n-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and ethyl iodide (0.24 mL, 3.0 mmol, 3.0 equiv). After workup, the ethylated ester was obtained which was used directly in the next step.

**Hydrolysis:** To the mixture of the ethylated ester in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H\(_2\)O (2.5 mL). The resulting mixture was refluxed for 16 h. After it was cooled to rt, additional THF (2.5 mL) was added and the mixture was refluxed for 48 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (\(\text{Na}_2\text{SO}_4\)) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product 32 was obtained as a white solid (382 mg, 0.530 mmol) in 53%
yield over 2 steps; mp 83-87 °C; \( R_f = 0.50 \) (hexane:EtOAc 4:1). Spectral data for 32: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 0.80 (t, 3H, \( J = 7.0 \) Hz), 1.38, 1.40 (2s, 36H), 1.74 (dq, 1H, \( J = 7.5, 7.5 \) Hz), 2.31 (dq, 1H, \( J = 7.5, 7.5 \) Hz), 3.14 (s, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.35 (s, 1H), 6.79 (d, 2H, \( J = 8.0 \) Hz), 7.28 (d, 2H, \( J = 8.0 \) Hz), 7.30 (s, 4H), 9.00 (brs, 1H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 11.27, 20.09, 31.99, 32.07, 35.78, 35.79, 51.42, 54.64, 64.26, 64.30, 70.62, 122.03, 124.97, 126.01, 128.98, 131.44, 133.74, 135.17, 135.79, 143.95, 144.00, 158.83, 159.23, 169.38; IR (thin film) 2961(s), 1710(s), 1224(s) cm\(^{-1}\); HRMS calcd for C\(_{42}\)H\(_{59}\)NO\(_4\)Br (M+H, ESI\(^+\)) \( m/z \) 720.3627, meas 720.3578; \([\alpha]\)\(^{20}\)D 6.4° (c 1.0, CH\(_2\)Cl\(_2\)) on 99% ee material.

**Preparation of acid 100:**

![Chemical Structure of 100](image)

To a solution of ester 99 (99% ee, 287 mg, 1.00 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H\(_2\)O (2 mL). The resulting mixture was refluxed for 2 h. After cooling to rt, aq citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration. The product 100 was obtained as a white solid (217 mg, 0.838 mmol, 84%); mp 195-196 °C; \( R_f = 0.05 \) (hexane:EtOAc 4:1). Spectral data for acid 100: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 0.84-1.24 (m, 6H), 1.50-1.70 (m, 5H), 1.84 (t, 1H, \( J = 8.0 \) Hz), 2.45 (d, 1H, \( J = 7.0 \) Hz), 3.48 (d, 1H, \( J = 13.0 \) Hz), 3.69 (d, 1H, \( J = 13.0 \) Hz), 7.10-7.40 (m, 5H), 7.70 (brs, 1H); \(^1\)H NMR (600 MHz, DMSO-d\(_6\)) \( \delta \) 0.80-1.28 (m, 6H), 1.50-1.70 (m, 5H), 1.70-1.80 (m, 1H), 2.24 (d, 1H, \( J = 7.2 \) Hz), 3.32 (d, 1H, \( J = 13.2 \) Hz), 3.54 (d, 1H, \( J = 13.2 \) Hz), 7.20-7.40 (m, 5H), 11.80 (s, 1H); \(^1\)C NMR (125 MHz, DMSO-d\(_6\)) \( \delta \) 25.11, 25.19, 25.76, 29.50, 30.74, 35.68, 41.88, 50.76, 62.91, 126.97, 128.08, 128.28, 138.76, 170.91; IR (thin film) 2924(w), 1755(s) cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{22}\)NO\(_2\) (M+H, ESI\(^+\)) \( m/z \) 260.1651, meas 260.1667; \([\alpha]\)\(^{20}\)D 52° (c 0.5, DMSO) on 99% ee material.
Preparation of acid 102:

To a suspension of ester 101² (99% ee, 363 mg, 1.00 mmol, 1.00 equiv) in ethanol (3 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (3 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, the volatiles were removed by rotary evaporation. Then aq citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration and washed with H₂O, affording the product 102 as a white solid (306 mg, 0.913 mmol) in 93% yield; mp 151-152 °C; Rf = 0.25 (hexane:EtOAc 4:1). Spectral data for acid 102: ¹H NMR (500 MHz, DMSO-d₆) δ 0.46 (q, 1H, J = 10.5 Hz), 0.90-1.10 (m, 5H), 1.16-1.28 (m, 1H), 1.30-1.70 (m, 4H), 1.89 (t, 1H, J = 7.0 Hz), 2.22 (d, 1H, J = 7.0 Hz), 3.80 (s, 1H), 7.16-7.40 (m, 8H), 7.45 (d, 2H, J = 7.5 Hz), 12.40 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 24.92, 25.09, 25.63, 29.44, 30.26, 35.60, 42.27, 51.07, 75.77, 126.67, 126.71, 127.20, 127.96, 128.13, 128.19, 143.08, 143.28, 170.79; IR (thin film) 2926(s), 1705(m), 1450(m) cm⁻¹; HRMS calcd for C₂₂H₂₆NO₂ (M+H, ESI⁺) m/z 336.1964, meas 336.1950; [α]²⁰ 75.2° (c 0.5, CH₂Cl₂) on 99% ee material.

Preparation of acid 104:

To a solution of ester 103³ (23% ee, 200 mg, 0.420 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (117 mg, 2.09 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 1 h. After cooling to rt, aq citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28 × 280 mm, hexane:acetone 4:1 to 3:1) to afford the product 104 (180 mg, 0.400 mmol) as a white solid in 96% yield; mp 85-90 °C; Rf = 0.30 (hexane:acetone 4:1). Spectral data for 104: ¹H NMR (300 MHz, CDCl₃) δ 0.50-0.70 (m, 1H), 0.90-1.70 (m, 10H),
1.88 (dd, 1H, $J = 9.3$, 6.9 Hz), 2.22, 2.23 (2s, 12H), 2.37 (d, 1H, $J = 6.9$ Hz), 3.48 (s, 1H), 3.66, 3.67 (2s, 6H), 6.97 (s, 4H), 9.00 (brs, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 16.11, 16.22, 25.28, 25.34, 25.95, 29.87, 30.97, 37.26, 43.16, 53.15, 59.58, 59.67, 76.72, 127.15, 127.98, 130.70, 131.06, 136.56, 137.12, 156.24, 156.41, 170.75; IR (thin film) 2928(s), 1710(w) cm$^{-1}$; HRMS calcd for C$_{28}$H$_{38}$N$_{4}$O$_4$ (M+H, ESI$^+$) m/z 452.2801, meas 452.2791; $[\alpha]_{D}^{20}$ 10.6° (c 0.5, CH$_2$Cl$_2$) on 23% ee material.

Preparation of acid 55:

trans-ester formation$^{6,7}$: A mixture of trans-epoxide 105$^6$ (racemic, 500 mg, 2.50 mmol, 1.00 equiv), NH$_4$Cl (400 mg, 7.50 mmol, 3.00 equiv) and benzylamine (1.35 mL, 12.5 mmol, 5.00 equiv) in absolute ethanol (5 mL) was refluxed for 8 h. After cooling, the solvent was evaporated and H$_2$O (10 mL) was added. And the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28 × 280 mm, hexane: EtOAc 4:1) to give the ring-opening product (404 mg, 1.32 mmol, 53%). To a solution of the ring-opening product and triphenylphosphine (694 mg, 2.65 mmol, 2.00 equiv) in THF (5 mL) at 0 °C was added diethylazodicarboxylate (DEAD, 0.420 mL, 2.65 mmol, 2.00 equiv) dropwise under N$_2$. After it was stirred at 0 °C for 1 h, the resulting mixture was stirred at rt for 20 h. The reaction mixture was concentrated and purified by column chromatography (1$^{st}$ column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2$^{nd}$ column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) afforded the trans-aziridine 106 (100 mg, 0.348 mmol) as a colorless oil in 14% over 2 steps; $R_f$ = 0.60 (hexane:EtOAc 4:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.86-1.30 (m, 9H), 1.50-1.80 (m, 5H), 2.07 (dd, 1H, $J = 7.0$, 2.5 Hz), 2.50 (d, 1H, $J = 3.0$ Hz), 3.87 (d, 1H, $J = 13.5$ Hz), 3.92 (d, 1H, $J = 13.5$ Hz), 4.10 (q, 2H, $J = 7.5$ Hz), 7.20-7.4 (m, 1H), 7.26-7.38 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.12, 25.62, 25.64, 26.22, 29.93, 30.71, 39.0, 40.71, 52.70, 55.64, 60.89, 126.94, 128.24,
128.54, 139.32, 169.77; IR (thin film) 2926(s), 1728(s) cm⁻¹; HRMS calcd for C₁₈H₂₆NO₂ (M+H, ESI⁺) m/z 288.164, meas 288.1972.

**Hydrolysis:** To solution of ester 106 (100 mg, 0.348 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (97 mg, 1.7 mmol, 5.0 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 30 min. After cooling, aq citric acid (2N, 2 mL) was added. The resulting white precipitate was collected by filtration. Then the white solid was dissolved in ether (20 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated to give the product trans-aziridine acid 55 (85 mg, 0.33 mmol, 94%) as a white solid; mp 135-136 °C (decomposition); Rf = 0.05 (hexane:EtOAc 4:1); ¹H NMR (500 MHz, DMSO-d₆) δ 0.80-1.30 (m, 11H), 1.98 (d, 1H, J = 2.5 Hz), 2.37 (d, 1H, J = 2.5 Hz), 3.81 (d, 1H, J = 13.5 Hz), 3.86 (d, 1H, J = 13.0 Hz), 7.20-7.40 (m, 5H), 12.52 (brs, 1H); ¹³C NMR (125 MHz, DCMSO-d₆) δ 25.14, 25.24, 25.78, 29.36, 30.03, 38.82, 39.77, 51.63, 54.69, 126.79, 128.12, 128.33, 139.60, 170.74; IR (thin film) 2924(s), 1722(s) cm⁻¹; HRMS calcd for C₁₆H₂₂NO₂ (M+H, ES⁺) m/z 260.1651, meas 260.1660.

**Preparation of 109:**

**Imine formation:** The mixture of iso-butyraldehyde (173 mg, 0.220 mL, 2.40 mmol, 1.20 equiv) benzhydryl amine (378 mg, 2.00 mmol, 1.00 equiv), MgSO₄ (960 mg, 8.00 mmol, 4.00 equiv) and dry CH₂Cl₂ (10 mL) was stirred under N₂ for 2 h. After the reaction was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the product 107 (450 mg, 1.90 mmol, 95%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 1.04 (d, 6H, J = 6.9 Hz), 2.40-2.54 (m, 1H), 5.24 (s, 1H), 7.08-7.30 (m, 10H), 7.64 (d, 1H, J = 5.1 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 19.34, 34.18, 77.74, 126.79, 127.54, 128.32, 143.95, 169.83.

**Aziridination:** A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N₂ and charged with 5 mol% (R)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H₂O (9 µL) and dry toluene (1 mL). The Teflon valve was
closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine 107 (237 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (0.25 mL, 2.4 mmol, 2.4 equiv) was added via syringe in one portion. The solution was stirred at rt for 17 h. The reaction was quenched with hexane (5 mL) and concentrated. After column chromatography (silica gel, 28 × 280 mm, hexane:EtOAc 15:1), ester 108 was obtained as a white solid (230 mg, 0.712 mmol) in 71% yield. The optical purity was determined to be 72% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R\textsubscript{t} = 3.24 min (major enantiomer) and R\textsubscript{t} = 5.98 min (minor enantiomer); mp 102-104 °C; R\textsubscript{f} = 0.40 (hexane:EtOAc 4:1); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 0.56 (d, 3H, \(J = 6.0\) Hz), 0.85 (d, 3H, \(J = 7.0\) Hz), 1.29 (t, 3H, \(J = 7.0\) Hz), 1.60-1.70 (m, 1H), 1.81 (dd, 1H, \(J = 9.5, 7.0\) Hz), 2.32 (d, 1H, \(J = 7.0\) Hz), 3.68 (s, 1H), 4.14-4.32 (m, 2H), 7.20-7.26 (m, 2H), 7.28-7.36 (m, 4H), 7.38-7.44 (m, 2H), 7.55 (d, 2H, \(J = 8.0\) Hz); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 14.18, 19.53, 20.32, 27.25, 43.58, 53.52, 60.59, 78.01, 126.83, 126.97, 127.43, 128.21, 128.25, 128.29, 142.29, 142.75, 169.48; IR (thin film) 961(m), 1734(s) cm\textsuperscript{–1}; HRMS calcd for C\textsubscript{21}H\textsubscript{26}NO\textsubscript{2} (M+H, ESI\textsuperscript{+})\(m/z\) 324.1964, meas 324.1964; \([\alpha]\)\textsubscript{20}\textsuperscript{D} –123.5\textdegree (c 0.5, CH\textsubscript{2}Cl\textsubscript{2}) on 72% ee material.

Hydrolysis: To the mixture of ester 108 (100 mg, 0.310 mmol, 1.00 equiv) in ethanol (0.5 mL) was added a solution of KOH (87 mg, 1.6 mmol, 5.0 equiv) in H\textsubscript{2}O (1 mL). The resulting mixture was refluxed for 30 min. After cooling to rt, aq citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and filtered. The filtrate was concentrated to give the crude product as a white solid. CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was added to the solid and this mixture was filtered and washed well with CH\textsubscript{2}Cl\textsubscript{2}. The filtrate was concentrated to give the product 109 as a white foamy solid (80 mg, 0.27 mmol, 88%); mp 84-86 °C; R\textsubscript{f} = 0.005 (hexane:EtOAc 4:1). Spectral data for acid 109: \textsuperscript{1}H NMR (600 MHz, DMSO-d\textsubscript{6}) \(\delta\) 0.41 (d, 3H, \(J = 6.6\) Hz), 0.75 (d, 3H, \(J = 7.2\) Hz), 1.44-1.56 (m, 1H), 1.84 (dd, 1H, \(J = 9.0, 6.0\) Hz), 2.22 (d, 1H, \(J = 6.6\) Hz), 3.82 (s,
1H), 7.14-7.54 (m, 10H), 12.40 (brs, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 19.30, 20.25, 26.67, 42.59, 52.70, 75.71, 126.70, 127.18, 127.97, 128.12, 128.18, 143.06, 143.32, 170.75 (One sp$^2$ carbon not located); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 19.52, 20.50, 28.15, 43.47, 54.55, 77.48, 126.83, 127.55, 127.84, 127.93, 128.52, 128.74, 141.25, 141.82, 171.03; IR (thin film) 2963(m), 1720(s) cm$^{-1}$; HRMS calcd for C$_{19}$H$_{22}$NO$_2$ (M+H, ESI$^+$) $m/z$ 296.1651, meas 296.1640; [$\alpha$]$^2$$_D$ – 51.1° (c 0.5, CH$_2$Cl$_2$) on 72% ee material.

**Preparation of acid 111:**

To a solution of ester 110 (80% ee, 70 mg, 0.22 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (60 mg, 1.54 mmol, 5.00 equiv) in H$_2$O (1 mL). After the mixture was refluxed for 30 min, THF (1 mL) was added. And the resulting mixture was refluxed for another 30 min. After it was cooled to rt, the volatiles were removed by rotary evaporation and ether (5 mL) was added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:CH$_2$Cl$_2$:EtOAc 2:2:1 to 1:1:1) to obtain the product 111 (45 mg, 0.15 mmol) as a white foamy solid in 71% yield; mp 50-52 °C; $R_f$ = 0.20 (hexane:CH$_2$Cl$_2$:EtOAc 2:2:1). Spectral data for acid 111: $^1$H NMR (500 MHz, CDCl$_3$) δ 0.77 (t, 3H, $J$ = 7.0 Hz), 1.10-1.28 (m, 2H), 1.38-1.48 (m, 1H), 1.56-1.64 (m, 1H), 2.19 (q, 1H, $J$ = 7.0 Hz), 2.48 (d, 1H, $J$ = 7.0 Hz), 3.80 (s, 1H), 7.00-8.00 (m, 11H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 13.57, 20.18, 31.45, 43.22, 47.71, 77.02, 127.05, 127.37, 127.65, 127.70, 128.56, 128.81, 141.35, 141.74, 170.61; IR (thin film) 1720(s) cm$^{-1}$; HRMS calcd for C$_{19}$H$_{22}$NO$_2$ (M+H, ESI$^+$) $m/z$ 296.1651, meas 296.1626; [$\alpha$]$^2$$_D$ – 51.1° (c 0.5, CH$_2$Cl$_2$) on 72% ee material.

**Preparation of acid 114:**

![Diagram](image-url)
**Imine formation**: The mixture of hydrocinnamaldehyde (90% by weight, 328 mg, 2.20 mmol, 1.10 equiv), BhNH$_2$ (378 mg, 2.00 mmol, 1.00 equiv) and MgSO$_4$ (960 mg, 8.00 mmol, 4.00 equiv) in CH$_2$Cl$_2$ (10 mL) was stirred at rt for 1.5 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine 112 as a colorless oil which was put on the vacuum for 10 sec prior to use.

**Aziridination**: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N$_2$ and charged with 5 mol% (S)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H$_2$O (9 µL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine 112 (306 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (311 µL, 3.00 mmol, 3.00 equiv) was added via syringe in one portion. The solution was stirred at rt for 22 h. The reaction was quenched with n-hexane (5 mL) and concentrated by removing all volatiles. After column chromatography (1$^{st}$ column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2$^{nd}$ column, silica gel, 28 × 280 mm, benzene:EtOAc 50:1), ester 113 was obtained as a white solid (262 mg, 0.680 mmol) in 68% yield. The optical purity was determined to be 78% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: $R_t$ = 5.06 min (minor enantiomer) and $R_t$ = 10.16 min (major enantiomer). A single recrystallization of 78% ee material afforded the product (141 mg, 0.366 mmol) with 37% recovery and 99.1% ee; mp 114-115 °C; $R_f$ = 0.50 (hexane:EtOAc 4:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 1.27 (t, 3H, $J$ = 7.5 Hz), 1.82-2.00 (m, 2H), 2.08 (q, 1H, $J$ = 6.5 Hz), 2.28-2.40 (m, 2H), 2.44-2.54 (m, 1H), 3.71 (s, 1H), 4.14-4.26 (m, 2H), 6.98 (d, 2H, $J$ = 7.5 Hz), 7.14-7.40 (m, 9H), 7.49 (d, 2H, $J$ = 8.0 Hz), 7.53 (d, 2H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.22, 29.58, 33.22, 43.19, 46.07, 60.72, 77.79, 125.70, 126.98, 127.02, 127.44, 127.83, 128.16, 128.31, 128.33, 128.39, 141.28, 142.40, 142.88, 169.33; IR (thin film) 2918(m), 1734(s)
cm⁻¹; Anal calcd for C_{26}H_{27}NO₂: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.86; H, 7.06; N, 3.63; [α]_{D}^{20} 86.2° (c 0.5, CH₂Cl₂) based on 99.1% ee material.

Hydrolysis: To a suspension of ester 113 (100 mg, 0.260 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (73 mg, 1.3 mmol, 5.0 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 45 min. After cooling to rt, aq citric acid (2N, 2 mL) was added. The resulting precipitate was collected by filtration. The product 114 was obtained as a white solid (91 mg, 0.26 mmol, 98%); mp 70-72 °C; R_{f} = 0.13 (hexane:EtOAc 4:1). Spectral data for 114: ¹H NMR (600 MHz, DMSO-d₆) δ 1.72-1.90 (m, 2H), 2.15-2.24 (m, 1H), 2.28-2.38 (m, 1H), 2.38-2.50 (m, 2H), 3.97 (s, 1H), 6.98-7.04 (m, 2H), 7.20-7.60 (m, 13H), 12.50 (brs, 1H); ¹³C NMR (150 MHz, DMSO-d₆) δ 29.52, 32.71, 42.23, 45.23, 75.42, 125.69, 126.78, 127.14, 127.52, 128.01, 128.02, 128.19, 128.21, 128.30, 128.45, 141.20, 143.49, 170.61; IR (thin film) 1734(s) cm⁻¹; HRMS calcd for C_{24}H_{24}NO₂ (M+H, ES⁺) m/z 358.1807, meas 358.1834; [α]_{D}^{20} 30.5° (c 0.5, CH₂Cl₂) on 99% ee material.

Preparation of acid 41:

Imine formation: The mixture of iso-pentaldehyde (189 mg, 2.20 mmol, 1.10 equiv), BhNH₂ (378 mg, 2.00 mmol, 1.00 equiv) and MgSO₄ (960 mg, 8.00 mmol, 4.00 equiv) in CH₂Cl₂ (10 mL) was stirred at rt for 2 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine 115 as a colorless oil which was put on the vacuum for 10 sec prior to use.

Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N₂ and charged with 5 mol% (S)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H₂O (9 µL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon
value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine 115 (251 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. Then EDA (375 µL, 3.60 mmol, 3.60 equiv) was added via syringe in one portion. The solution was stirred at rt for 19 h. The reaction was quenched with n-hexane (5 mL) and concentrated by removing all volatiles. After column chromatography (silica gel, 28 x 280 mm, hexane:acetone 9:1), ester 116 was obtained as a white solid (205 mg, 0.608 mmol) in 61% yield. The optical purity was determined to be 86% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: R\textsubscript{f} = 3.26 min (minor enantiomer) and R\textsubscript{f} = 6.01 min (major enantiomer); mp 105-106 °C; [\alpha]_D^{20} 94.7° (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}) on 86% ee material.

**Hydrolysis:** To a mixture of ester 116 (60 mg, 0.18 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (50 mg, 0.90 mmol, 5.0 equiv) in H\textsubscript{2}O (1 mL). The resulting mixture was refluxed for 30 min. After the reaction mixture was cooled to rt, aq citric acid (2N, 2 mL) was added. And the mixture was extracted with ether (3 x 10 mL). The organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and filtered. The filtrate was concentrated to give a white viscous foamy solid (50 mg, 0.16 mmol, 91%); mp 124-125 °C; [\alpha]_D^{20} = 0.50 (hexane:acetone 2:1). Spectral data for acid 117: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 0.71 (d, 3H, J = 6.7 Hz), 2.49 (d, 1H, J = 7.2 Hz), 3.83 (s, 1H), 7.00-8.00 (m, 11H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 21.79, 22.76, 26.67, 37.25, 43.32, 46.88, 127.05, 127.24, 127.71, 127.83, 128.62, 128.89, 141.25, 141.59, 169.86; IR (thin film) 1734(s) cm\textsupersccent{-1}; HRMS calcd for C\textsubscript{20}H\textsubscript{24}NO\textsubscript{2} (M+H, ESI\textsuperscript{+}) m/z 310.1810, meas 310.1811; [\alpha]_D^{20} 26.7° (c 1.0, Et\textsubscript{2}O) on 86% ee material.
**Preparation of acid 119:**

To the mixture of ester 118 \(^2\) (98% ee, 270 mg, 0.800 mmol, 1.00 equiv) in ethanol (4 mL) was added a solution of KOH (224 mg, 4.00 mmol, 5.00 equiv) in \(\text{H}_2\text{O} (4 \text{ mL})\). After the mixture was refluxed for 1.5 h, THF (1 mL) was added. The resulting mixture was refluxed for another 1.5 h. After it was cooled to rt, \(\text{aq citric acid} (2\text{N}, 5 \text{ mL})\) was added. The resulting white precipitate was collected by filtration. The solid was then dissolved in ether (30 mL) and washed with \(\text{H}_2\text{O} (3 \times 5 \text{ mL})\). The organic layer was dried (\(\text{Na}_2\text{SO}_4\)) and concentrated to obtain the product 119 (234 mg, 0.757 mmol, 95%) as a white solid; mp 164-166 °C; \(R_f = 0.25\) (hexane:EtOAc 4:1). Spectral data for acid 119: \(^1\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 0.80 \text{ (s, 9H), 2.00 (d, 1H, } J = 7.5 \text{ Hz), 2.36 (d, 1H, } J = 8.0 \text{ Hz), 3.69 (s, 1H), 7.22-7.28 (m, 3H), 7.30-7.34 (m, 4H), 7.40-7.46 (m, 4H); } \(^1\text{H NMR} (600 \text{ MHz, DMSO-d}_6) \delta 0.66 \text{ (s, 9H), 1.81 (d, 1H, } J = 7.2 \text{ Hz), 2.20 (d, 1H, } J = 7.8 \text{ Hz), 3.78 (s, 1H), 7.18-7.22 (m, 2H), 7.26-7.30 (m, 4H), 7.38 (dd, 2H, } J = 8.4, 1.2 \text{ Hz), 7.60 (dd, 2H, } J = 8.4, 1.2 \text{ Hz), 12.40 (s, 1H); } ^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 27.57, 31.61, 42.98, 59.16, 78.86, 127.03, 127.60, 127.80, 127.86, 128.55, 128.97, 141.33, 141.81 (\text{The carbonyl peak not located}); ^{13}\text{C NMR} (150 \text{ MHz, DMSO-d}_6) \delta 27.34, 31.29, 42.58, 54.89, 76.94, 126.92, 127.04, 127.98, 128.08, 128.24, 143.14, 143.87, 170.86 (\text{One } \text{sp}^2 \text{ carbon not located}); \text{IR (thin film) 2961(s), 1705(s) cm}^{-1}; \text{HRMS calcd for C}_{20}\text{H}_{24}\text{NO}_2 (\text{M+H, ESI}^+)m/z 310.1807, \text{meas 310.1781; } [\alpha]^{20}_D 30.6\degree (c 0.5, \text{CH}_2\text{Cl}_2)\text{ on 98% ee material.}

**Preparation of acid 121:**

To the mixture of ester 120 (90% ee, 800 mg, 1.30 mmol, 1.00 equiv) in THF (2.5 mL) and ethanol (2.5 mL) was added a solution of KOH (364 mg, 6.50 mmol, 5.00 equiv). The resulting mixture was refluxed for 24 h. After cooling to rt, \(\text{aq HCl} (6\text{N})\) was added to pH ~2. The mixture
was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1) to give the product 121 (565 mg, 0.976 mmol, 75%) as a white foamy solid; mp 73-76 °C; R$_f$ = 0.25 (hexane:EtOAc 4:1). Spectral data for 121: $^1$H NMR (500 MHz, CDCl$_3$) δ 0.65 (t, 3H, J = 7.5 Hz), 1.30-1.52 (m, 38H), 1.54 (s, 3H), 1.96 (t, 1H, J = 7.0 Hz), 3.67 (s, 6H), 4.14 (s, 1H), 7.20 (s, 2H), 7.22 (s, 2H), 9.60 (brs, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 10.68, 11.91, 21.97, 31.80, 35.52, 35.54, 48.00, 53.60, 63.89, 63.97, 70.24, 124.78, 125.61, 135.57, 135.67, 143.32, 143.51, 158.37, 158.73, 171.17 (One sp$^3$ carbon not located); IR (thin film) 2964(s), 1774(m) cm$^{-1}$; HRMS calcd for C$_{37}$H$_{58}$NO$_4$ (M+H, ESI$^+$) m/z 580.4366, meas 580.4296; [α]$_{20}$$^0$ 33.1° (c 1.0, CH$_2$Cl$_2$) on 90% ee material.

_Preparation of acid 123:_

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{COOEt} & \quad \text{KOH, EtOH} & \quad \text{then H}^+ \\
\text{122} & \quad \text{123} & \quad \text{> 99% ee} & \quad \text{> 99% ee} & \quad \text{150 mg, 0.500 mmol, 1.00 equiv} & \quad \text{130 mg (0.487 mmol, 94%). mp 48-50 °C; R$_f$ = 0.10 (hexane:EtOAc 4:1). Spectral data for acid 123: $^1$H NMR (500 MHz, CDCl$_3$) δ 1.61 (d, 3H, J = 7.0 Hz), 2.80 (d, 1H, J = 7.0 Hz), 3.07 (q, 1H, J = 6.5 Hz), 3.28 (d, 1H, J = 7.0 Hz), 7.20-7.80 (m, 11H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 22.60, 44.88, 47.71, 68.44, 126.95, 127.41, 127.78, 127.92, 128.33, 128.69, 133.96, 142.16, 175.51; IR (thin film) 3400(m), 1775(s) cm$^{-1}$; HRMS calcd for C$_{17}$H$_{18}$NO$_2$ (M+H, ESI$^+$) m/z 268.1338, meas 268.1331; [α]$_{20}$$^0$ 16.6° (c 1.0, CH$_2$Cl$_2$) on > 99% ee material.}
\end{align*}
\]
Preparation of acid 125:

To a suspension of ester 124 (> 99% ee, 187 mg, 0.500 mmol, 1.00 equiv) in EtOH (1 mL) was added an aqueous solution KOH (140 mg, 2.50 mmol, 5.00 equiv) in H$_2$O (2 mL). The resulting mixture was refluxed for 30 min. After it was cooled to rt, aq citric acid (2N, 2 mL) was added, followed by the addition of ether (10 mL). The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated to give a white foamy solid 175 mg (0.505 mmol, 101%); mp 80–82 °C; $R_f$ = 0.10 (hexane:EtOAc 4:1). Spectral data for acid 125: $^1$H NMR (500 MHz, CDCl$_3$) δ 1.55 (d, 3H, $J = 6.5$ Hz), 2.74 (d, 1H, $J = 7.0$ Hz), 2.98 (q, 1H, $J = 6.5$ Hz), 3.12 (d, 1H, $J = 7.0$ Hz), 7.00-7.40 (m, 10H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 22.91, 45.71, 46.16, 67.62, 120.13, 126.58, 127.02, 128.30, 129.75, 130.49, 135.51, 143.97, 168.78; IR (thin film) 3408(m), 1770(s) cm$^{-1}$; HRMS calcd for C$_{17}$H$_{17}$NO$_2$Br (M+H, ESI$^+$) m/z 346.0443, meas 346.0435; $[\alpha]_{20}^{20}$ = −19.4° (c 1.0, CH$_2$Cl$_2$) on > 99% ee material.

III. Formation of morpholine-2,3,5-triones (Scheme 3 and 4)

The formation of morpholine-2,3,5-trione 7:

Formation of 5: To a solution of acid 8 (62% ee, 38 mg, 0.15 mmol, 1.0 equiv) in acetone (0.5 mL) was added a NaOH solution (6.0 mg in 0.3 mL of H$_2$O, 0.15 mmol, 1.0 equiv). The resulting solution was stirred at rt for 2 h. Then the volatiles were removed by evaporation (acetone was added and evaporated several times) until a white solid was obtained.

Reaction of 5 with oxalyl chloride and NEt$_3$ (Scheme 3): To a solution of NEt$_3$ (12 mg, 0.12 mmol, 1.2 equiv) in benzene (1 mL) under N$_2$ was added (COCl)$_2$ (0.012 mL, 0.14 mmol, 1.4...
Upon the addition of \((\text{COCl})_2\), the solution turned from colorless to dark orange. Then 28 mg (0.10 mmol, 1.0 equiv) of the above sodium salt was added to the mixture of Et\(_3\)N and \((\text{COCl})_2\) all at once. After it was stirred at rt for 45 min under N\(_2\), CH\(_2\)Cl\(_2\) (10 mL) and HCl (2N, 2 mL) were added carefully. The organic layer was separated, washed with NaHCO\(_3\) (2 mL) and H\(_2\)O (2 mL), dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated to give the crude mixture whose \(^1\text{H} \text{NMR} \) spectrum showed the major product was compound 7 in a yield of 34% as determined with the aid of an internal standard (Ph\(_3\)CH). Absorptions for the lactam 6 were not observed in the \(^1\text{H} \text{NMR} \) spectrum of the crude mixture.

**Reaction of 8 with oxalyl chloride in CH\(_2\)Cl\(_2\) (Scheme 3):**

To a flame-dried 25 mL round bottom flask filled with N\(_2\) was added acid 8 (28 mg, 0.11 mmol, 1.0 equiv) and CH\(_2\)Cl\(_2\) (1 mL). The vacuum adapter was replaced with a septum to which a N\(_2\) balloon was attached via a needle. The flask was cooled in an ice bath. And \((\text{COCl})_2\) (0.020 mL, 0.23 mmol, 2.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and the ice bath was removed. After the mixture was stirred at rt for 1 h, the volatiles were removed by rotary evaporation to give a foamy solid. Hexane was then added and the solid was collected by filtration and washed with a mixture of CH\(_2\)Cl\(_2\) and hexane (v/v 1:10, 2 mL). The product 7 was obtained as a yellow solid (31 mg, 82%). The yield of this yellow solid was checked by NMR and found to be 91% with the aid of triphenylmethane as an internal standard. Spectral data for 7: \(^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3\)) \(\delta\) 3.21 (d, 1H, \(J = 15.0\) Hz), 4.77 (d, 1H, \(J = 3.0\) Hz), 5.18 (d, 1H, \(J = 15.0\) Hz), 5.39 (d, 1H, \(J = 2.5\) Hz), 6.80-7.60 (m, 10H); IR (thin film) 1830(s), 1780(s), 1701(s) cm\(^{-1}\). Unfortunately, the product as obtained was contaminated with some impurities. Thus, a clean \(^{13}\text{C} \text{NMR} \) could not be obtained.
The formation of morpholine-2,3,5-trione 11:

General procedure for the formation of morpholine-2,3,5-trione: Illustrated for the formation of 11: To a flame-dried 25 mL round bottom flask filled with N₂ was added acid 10 (98% ee, 33 mg, 0.10 mmol, 1.00 equiv) and CH₂Cl₂ (1 mL). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. The flask was cooled in an ice bath and then (COCl)₂ (25.1 mg, 0.017 mL, 0.20 mmol, 2.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and concentrated by rotary evaporator to afford a foamy solid. The amount of 11 present in this yellow solid was checked by the 1H NMR spectrum and found to be 92% yield with the aid of triphenylmethane as an internal standard. Hexane was then added and the solid was collected by filtration and washed with a mixture of CH₂Cl₂ and hexane (v/v 1:10). This gave the product 11 as a pale yellow solid (31 mg, 0.074 mmol, 74%); mp 129-131 °C. Spectral data for 11: ¹H NMR (300 MHz, CDCl₃) δ 3.77 (d, 1H, J = 3.9 Hz), 5.02 (d, 1H, J = 3.9 Hz), 6.98-7.10 (m, 4H), 7.15 (s, 1H), 7.28-7.46 (m, 6H), 7.40-7.62 (m, 5H); ¹³C NMR (150 MHz, CDCl₃) δ 58.35, 62.30, 64.51, 126.39, 128.40, 128.82, 129.26, 129.70, 130.08, 130.38, 130.47, 131.01, 131.05, 135.73, 136.27, 148.33, 151.23, 157.65; IR (thin film) 1832 (m), 1782 (s), 1705 (s) cm⁻¹; HRMS calcd for C₂₄H₁₉NO₄Cl (M⁺H, ESI⁺) m/z 420.1003, meas 420.0970; [α]₂⁰_D = −164.5° (c 0.5, CH₂Cl₂) on 98% ee material. Recrystallization from CH₂Cl₂ and hexane gave X-ray quality crystals. The crystallographic data for 11 has been deposited at the Cambridge Crystallographic Data Center (CCDC 884446).

The formation of morpholine-2,3,5-trione 13:
The general procedure for the formation of morpholine-2,3,5-trione 11 was followed with acid 92 (racemic, 35 mg, 0.10 mmol, 0.10 equiv), (COCl)$_2$ (0.030 mL, 0.35 mmol, 3.5 equiv) and CH$_2$Cl$_2$ (1 mL). The product 13 was obtained as a yellow solid. The NMR yield was 82% as determined on this yellow solid with the aid of PH$_3$CH as an internal standard. Spectral data for 13: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 2.34 (s, 3H), 3.73 (d, 1H, $J = 4.0$ Hz), 5.00 (d, 1H, $J = 3.5$ Hz), 6.90 (d, 2H, $J = 7.8$ Hz), 7.03 (d, 2H, $J = 7.5$ Hz), 7.10-7.60 (m, 11H); IR (thin film) 1832(s), 1782(s), 1708(s) cm$^{-1}$. Unfortunately, this product was contaminated with some impurities and a clean $^{13}$C NMR spectrum was not obtained.

The formation of morpholine-2,3,5-trione 12:

The general procedure for the formation of morpholine-2,3,5-trione 11 was followed with acid 90 (90% ee, 40.8 mg, 0.10 mmol, 1.0 equiv), (COCl)$_2$ (0.010 mL, 0.12 mmol, 1.2 equiv) and CH$_2$Cl$_2$ (1 mL). The product 12 was obtained as a yellow solid (42.3 mg, 0.085 mmol, 85%). The NMR yield was determined to be 95% with the aid of PH$_3$CH as an internal standard. This procedure was repeated to give 12 in 75% isolated yield; mp 120-122 °C. Spectral data for 12: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.72 (d, 1H, $J = 4$ Hz), 5.00 (d, 1H, $J = 4$ Hz), 6.89 (d, 2H, $J = 8.5$ Hz), 7.02 (d, 2H, $J = 7$ Hz), 7.13 (s, 1H), 7.32-7.42 (m, 4H), 7.46-7.60 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 57.81, 62.47, 64.38, 125.65, 126.41, 128.48, 129.30, 130.12, 130.17, 130.25, 130.37, 130.45, 132.91, 135.53, 136.24, 148.60, 151.13, 157.38; IR (thin film) 1832(m), 1784(s), 1708(s) cm$^{-1}$; HRMS calcd for C$_{24}$H$_{18}$NO$_4$ $^{79}$Br$^{35}$Cl (M+H, ESI$^+$) m/z 498.0108, meas 498.0150; $[\alpha]_{D}^{20} = -90.3^\circ$ (c 0.5, CH$_2$Cl$_2$).
IV. Formation of N-carboxy anhydrides (NCAs) (Table 1)

The formation of NCA 33:

General procedure for N-carboxy anhydride (NCA) formation: Illustrated for the formation of NCA 33. A flame-dried 25 mL round bottom flask filled with N\textsubscript{2} was charged with the acid 25 (98% ee, 69 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N\textsubscript{2} balloon was attached via a needle. Dry CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)\textsubscript{2} (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and at rt for 1 h, the volatiles were removed. The product was purified from the crude mixture by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to give the product 33 as a white foamy solid (44 mg, 0.11 mmol) in 54% yield; mp 49-50 °C; R\textsubscript{f} = 0.30 (hexane:EtOAc 4:1). Spectral data for NCA 33: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.62 (s, 3H), 5.13 (s, 1H), 5.30 (s, 1H), 7.10-7.16 (m, 2H), 7.22-7.48 (m, 13H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 22.02, 62.73, 65.45, 71.33, 127.63, 127.94, 128.33, 128.44, 128.49, 128.64, 128.76, 129.33, 129.73, 133.11, 137.89, 139.16, 150.23, 170.09; IR (thin film) 1848(s), 1780(s) cm\textsuperscript{-1}; HRMS calcd for C\textsubscript{24}H\textsubscript{21}NO\textsubscript{3}Cl (M+H, ESI\textsuperscript{+}) m/z 406.1210, meas 406.1235; [\alpha]_{20}^{D} = 21.3° (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}) on 98% ee material.

The formation of NCA 34:

The general procedure for NCA formation was followed with acid 26 (99% ee, 70 mg, 0.11 mmol, 1.0 equiv), (COCl)\textsubscript{2} (0.020 mL, 0.23 mmol, 2.1 equiv) and CH\textsubscript{2}Cl\textsubscript{2} (2 mL). After purification by column chromatography (1\textsuperscript{st} column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1; 2\textsuperscript{nd} column, silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product 34 was obtained as a white solid (54 mg, 0.078 mmol) in 69% yield; mp 41-42 °C; R\textsubscript{f} = 0.50 (hexane:EtOAc 4:1). Spectral data for 34:
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.31 (s, 18H), 1.42 (s, 18H), 1.68 (s, 3H), 3.64 (s, 3H), 3.75 (s, 3H), 5.06 (s, 1H), 5.27 (s, 1H), 6.89 (s, 2H), 7.18-7.26 (m, 6H), 7.35 (t, 1H, $J = 7.2$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 22.00, 31.93, 32.10, 35.70, 35.89, 62.61, 64.20, 64.33, 65.21, 71.33, 126.79, 127.34, 128.38, 128.82, 129.48, 132.17, 132.96, 133.44, 143.24, 143.43, 149.70, 158.78, 159.07, 170.39; IR (thin film) 2960(m), 1847(m), 1785(s) cm$^{-1}$; HRMS calcd for C$_{42}$H$_{57}$NO$_5$35Cl (M, ESI$^+$) m/z 690.3925, meas 690.3954; $[\alpha]_{D}^{20}$ 5.8° (c 0.5, CH$_2$Cl$_2$) on 99% ee material. Recrystallization of 34 gave X-ray quality single crystals. The crystallographic data for 34 has been deposited at the Cambridge Crystallographic Data Center (CCDC 884444).

The formation of NCA 35:

The general procedure for NCA formation was followed with acid 27 (99% ee, 129 mg, 0.200 mmol, 1.00 equiv), (COCl)$_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH$_2$Cl$_2$ (2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product 35 was obtained as a white foamy solid (106 mg, 0.0150 mmol) in 75% yield; mp 71-78 °C; $R_f$ = 0.60 (benzene:EtOAc 100:1). Spectral data for NCA 35: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.28 (s, 18H), 1.39 (s, 18H), 1.63 (s, 3H), 2.31 (s, 3H), 3.61 (s, 3H), 3.72 (s, 3H), 5.08 (s, 1H), 5.21 (s, 1H), 6.86 (s, 2H), 7.01 (d, 2H, $J = 8.0$ Hz), 7.04 (d, 2H, $J = 8.5$ Hz), 7.21 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 20.79, 21.82, 31.66, 31.84, 35.43, 35.62, 62.20, 63.95, 64.07, 64.85, 71.08, 126.58, 127.05, 128.43, 128.78, 130.18, 131.96, 132.69, 139.23, 142.94, 143.14, 149.44, 158.50, 158.79, 170.19; IR (thin film) 2961(m), 1847(m), 1784(s) cm$^{-1}$; HRMS calcd for C$_{43}$H$_{59}$NO$_5$35Cl (M+H, ESI$^+$) m/z 704.4082, meas 704.4030; $[\alpha]_{D}^{20}$ 3.2° (c 1.0, CH$_2$Cl$_2$) on 99% ee material.

The formation of NCA 36:
The general procedure for NCA formation was followed with acid \(28\) (129 mg, 0.200 mmol, 1.00 equiv), \((\text{COCl})_2\) (0.040 mL, 0.46 mmol, 2.3 equiv) and \(\text{CH}_2\text{Cl}_2\) (2 mL). After purification by column chromatography (silica gel, 18 x 180 mm, benzene:EtOAc 100:1), the product \(36\) was obtained as a white foamy solid (100 mg, 0.0142 mmol) in 71% yield; mp 72-78 °C; \(R_f = 0.60\) (benzene:EtOAc 100:1). Spectral data for \(36\):

\[
^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \delta 1.29 (s, 18\text{H}), 1.38 (s, 18\text{H}), 1.62 (s, 3\text{H}), 2.35 (s, 3\text{H}), 3.62 (s, 3\text{H}), 3.70 (s, 3\text{H}), 5.33 (s, 1\text{H}), 5.59 (s, 1\text{H}), 6.94-7.00 (m, 3\text{H}), 7.15 (d, 1\text{H}, \text{J} = 7.2 \text{ Hz}), 7.20-7.24 (m, 3\text{H}), 7.42 (d, 1\text{H}, \text{J} = 7.8 \text{ Hz});
\]

\[
^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \delta 20.15, 20.79, 32.16, 32.30, 35.93, 36.07, 62.39, 63.25, 64.40, 64.50, 71.63, 126.55, 126.70, 128.13, 129.40, 129.62, 131.02, 132.37, 132.98, 133.55, 134.21, 143.45, 150.13, 158.74, 159.25, 170.81; \text{IR (thin film)} \text{ 2961(m), 1846(m), 1784(s) cm}^{-1}; \text{HRMS calcd for C}_{43}\text{H}_{59}\text{NO}_{35}\text{Cl (M+H, ESI') m/z 704.4082, meas 704.4040; [\alpha]^{20}_{D} -9.0^\circ (c 1.0, \text{CH}_2\text{Cl}_2) on 99\% ee material.}
\]

The formation of NCA \(37\):

The general procedure for NCA formation was followed with acid \(29\) (141 mg, 0.200 mmol, 1.00 equiv), \((\text{COCl})_2\) (0.040 mL, 0.46 mmol, 2.3 equiv) and \(\text{CH}_2\text{Cl}_2\) (2 mL). After purification by column chromatography (silica gel, 18 x 180 mm, benzene:EtOAc 100:1), the product \(37\) was obtained as a white foamy solid (120 mg, 0.0156 mmol) in 78% yield; mp 78-80 °C; \(R_f = 0.60\) (benzene:EtOAc 100:1). Spectral data for \(37\):

\[
^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 1.29 (s, 18\text{H}), 1.40 (s, 18\text{H}), 1.73 (s, 3\text{H}), 3.62 (s, 3\text{H}), 3.73 (s, 3\text{H}), 4.99 (s, 1\text{H}), 5.15 (s, 1\text{H}), 6.88 (s, 2\text{H}), 6.94 (d, 2\text{H}, \text{J} = 8.4 \text{ Hz}), 7.22 (s, 2\text{H}), 7.29 (d, 2\text{H}, \text{J} = 8.7 \text{ Hz});
\]

\[
^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \delta 21.74, 31.91, 32.09, 35.71, 35.91, 62.67, 64.18, 64.39, 64.41, 71.24, 123.72, 126.85, 127.35, 130.38, 131.51, 132.20, 132.40, 132.48, 143.37, 143.57, 149.55, 158.97, 159.09, 169.95; \text{IR (thin film)} \text{ 2963(m), 1848(m), 1784(s) cm}^{-1}; \text{HRMS calcd for C}_{42}\text{H}_{56}\text{NO}_{37}\text{BrCl (M+H, ESI') m/z 768.3030, meas 768.2977; [\alpha]^{20}_{D} -11.3^\circ (c 2.0, \text{CH}_2\text{Cl}_2) on 99\% ee material.}
The formation of NCA 38:

The general procedure for NCA formation was followed with acid 30 (96% ee, 71 mg, 0.10 mmol, 1.0 equiv), (COCl)_2 (0.020 mL, 0.23 mmol, 2.3 equiv) and CH_2Cl_2 (1 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product 38 was obtained as a white foamy solid (56 mg, 0.073 mmol) in 73% yield; mp 75–80 °C; R_f = 0.75 (benzene:EtOAc 100:1). Spectral data for 38: ^1^H NMR (500 MHz, CDCl_3) δ 1.35 (s, 18H), 1.43 (s, 18H), 1.80 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 5.39 (s, 1H), 5.96 (s, 1H), 7.03 (s, 2H), 7.12-7.18 (m, 1H), 7.22-7.32 (m, 3H), 7.49 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 8.0 Hz); ^1^C NMR (125 MHz, CDCl_3) δ 20.23, 31.96, 32.11, 35.74, 35.88, 62.89, 64.20, 64.32, 64.57, 71.17, 124.56, 126.39, 127.80, 127.86, 130.97, 131.07, 132.14, 133.02, 133.06, 134.15, 143.15, 143.22, 149.78, 158.64, 159.04, 169.72; IR (thin film) 2961(m), 1848(m), 1784(s) cm^{-1}; HRMS calcd for C_{42}H_{56}NO_{57}BrCl (M+H, ESI^+) m/z 768.3030, meas 768.3070; [α]^20_D −6.4° (c 0.5, CH_2Cl_2) on 96% ee material.

The formation of NCA 39:

The general procedure for NCA formation was followed with acid 31 (98% ee, 136 mg, 0.200 mmol, 1.00 equiv), (COCl)_2 (0.040 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). After purification by column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product 39 was obtained as a white foamy solid (118 mg, 0.016 mmol) in 80% yield; mp 89-91 °C; R_f = 0.65 (benzene:EtOAc 50:1). Spectral data for 39: ^1^H NMR (500 MHz, CDCl_3) δ 1.21 (s, 18H), 1.41 (s, 18H), 1.52 (s, 3H), 3.56 (s, 3H), 3.71 (s, 3H), 5.12 (s, 1H), 6.31 (s, 1H), 6.82 (s, 2H), 7.12 (t, 1H, J = 8.0 Hz), 7.26 (s, 2H), 7.52 (t, 1H, J = 7.0 Hz), 7.60 (t, 2H, J = 8.5 Hz), 7.83 (d, 1H, J =8.0 Hz), 7.89 (d, 1H, J = 8.5 Hz), 8.03 (d, 1H, J = 8.5 Hz); ^1^C NMR (125 MHz, CDCl_3)
The formation of NCA 40:

\[
\text{BUDAM}^\text{NCOOH} \xrightarrow{(\text{COCl})_2 (2.3 \text{ equiv})} \xrightarrow{\text{CH}_2\text{Cl}_2 0 {\degree} \text{C}, 5 \text{ min}, 1 \text{h}} \text{BUDAM}^\text{OCl} \text{Br}
\]

The general procedure for NCA formation was followed with acid 32 (99% ee, 144 mg, 0.200 mmol, 1.00 equiv), (COCl)\textsubscript{2} (0.040 mL, 0.46 mmol, 2.3 equiv) and CH\textsubscript{2}Cl\textsubscript{2} (2 mL). After column chromatography (1\textsuperscript{st} silica gel, 18 x 180 mm, benzene:EtOAc 100:1; 2\textsuperscript{nd} silica gel, 18 x 180 mm, benzene:EtOAc 100:1), the product 40 was obtained as a white foamy solid (30 mg, 0.038 mmol) in 20% yield; mp 60-61 \degree C; R\textsubscript{f} = 0.725 (benzene:EtOAc 100:1). Spectral data for 40:

\begin{align*}
^1\text{H NMR} (500 \text{ MHz, CDCl}_3) & \delta 0.42 (t, 3H, J = 7.5 \text{ Hz}), 1.28 (s, 18H), 1.36 (s, 18H), 1.74 (dq, 1H, J = 7.5, 7.5 \text{ Hz}), 2.02 (dq, 1H, J = 7.5, 7.5 \text{ Hz}), 3.58 (s, 3H), 3.70 (s, 3H), 4.94 (s, 1H), 5.35 (s, 1H), 6.93 (s, 2H), 7.18 (s, 2H), 7.23 (d, 2H, J = 8.5 \text{ Hz}), 7.40 (d, 2H, J = 8.5 \text{ Hz}); \\
^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) & \delta 7.73, 27.97, 31.90, 32.11, 35.67, 35.91, 62.87, 64.25, 64.32, 64.72, 76.19, 123.86, 126.19, 128.29, 130.41, 131.55, 131.71, 132.75, 133.12, 143.07, 143.64, 150.01, 158.54, 159.42, 169.60; \\
\text{IR (thin film)} & 2963\text{(m), 1846\text{(m), 1782\text{(s) cm}^{-1}}; \\
\text{HRMS calcd for C}_{43}\text{H}_{58}\text{NO}_{5}^{35}\text{Cl (M+H, ES}^+\text{) m/z 782.3187, meas 782.3253; [\alpha]^{20}_D 9.8{\degree} (c 1.0, CH}_2\text{Cl}_2 \text{ on 99% ee material.}}
\end{align*}

V. Formation of β-lactams with (COCl)\textsubscript{2} (Table 2)

The formation of β-lactam 42:

\[
\text{Ph}^\text{NCOOH} \xrightarrow{(\text{COCl})_2 (2.3 \text{ equiv})} \xrightarrow{\text{CH}_2\text{Cl}_2 0 {\degree} \text{C}, 5 \text{ min}, 1 \text{h}} \text{Ph}^\text{NCl}
\]
The general procedure for β-lactam formation with (COCl)₂ illustrated for 42: A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid 102 (99% ee, 67 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Dry CH₂Cl₂ (2 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)₂ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and 1 h at rt. After the volatiles were removed, the crude mixture was placed under high vacuum (0.1 mmHg) to give the product 42 (70 mg, 0.198 mmol, 99%) as a white foamy solid; The optical purity was determined to be >99% ee by HPLC analysis (Chiralpak AS column, 90:10 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: Rᵣ = 9.57 min ((3S, 4R)-42, major enantiomer) and Rᵣ = 32.35 min ((3R, 4S)-42, minor enantiomer); mp 113-114 °C; Rᵢ = 0.50 (hexane:EtOAc 4:1). Spectral data for 42: \(^1^H\) NMR (500 MHz, CDCl₃) \(\delta\) 0.84-0.98 (m, 1H), 1.02-1.36 (m, 4H), 1.62-1.94 (m, 6H), 3.57 (dd, 1H, \(J = 8.5, 5.0\) Hz), 4.80 (d, 1H, \(J = 5.0\) Hz), 5.62 (s, 1H), 7.26-7.46 (m, 10H); \(^{13}^C\) NMR (125 MHz, CDCl₃) \(\delta\) 25.55, 25.80, 26.23, 29.94, 30.01, 38.96, 58.69, 62.94, 64.88, 127.92, 128.21, 128.39, 128.55, 128.70, 128.88, 138.28, 139.25, 165.08; IR (thin film) 2927(m), 1764(s) cm⁻¹; HRMS calcd for C₂₂H₂₅NO₃Cl (M⁺H, ESI⁺) m/z 354.1625, meas 354.1638; \([\alpha]^{20}_D\) –96.6° (c 1.0, CH₂Cl₂) on 99% ee material.

The formation of β-lactam 41:

The general procedure for β-lactam formation with (COCl)₂ was followed with acid 100 (99% ee, 52 mg, 0.20 mmol, 1.0 equiv), (COCl)₂ (0.040 mL, 0.46 mmol, 2.3 equiv) and CH₂Cl₂ (2 mL). The ratio of cis:trans was determined to be ≥ 50:1 from the \(^1^H\) NMR spectrum of the crude reaction mixture with the aid of an authentic sample of the trans-isomer 56. The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1). The product 41 was obtained as a white crystalline solid (46 mg, 0.17 mmol) in 83% yield; mp 118-119 °C from hexane and benzene; Rᵢ = 0.40 (hexane:EtOAc 4:1). Spectral data for 41: \(^1^H\) NMR (500 MHz,
CDCl$_3$ δ 0.80 (qd, 1H, J = 11.0, 3.5 Hz), 0.98 (qd, 1H, J = 12.0, 3.5 Hz), 1.10 (qt, 1H, J = 13.0, 3.5 Hz), 1.18-1.32 (m, 2H), 1.62-1.80 (m, 6H), 3.33 (dd, 1H, J = 9.0, 5.0 Hz), 4.08 (d, 1H, J = 15.0 Hz), 4.81 (d, 1H, J = 5.0 Hz), 4.86 (d, 1H, J = 15.0 Hz), 7.18-7.22 (m, 2H), 7.26-7.36 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 25.29, 25.54, 25.95, 29.78, 29.80, 38.63, 47.06, 58.93, 61.18, 127.95, 128.20, 128.90, 135.06, 165.44; IR (thin film) 2924(m), 1755(s) cm$^{-1}$; HRMS calcd for C$_{16}$H$_{21}$NO$_3$Cl (M+H, ESI$^+$) m/z 278.1312, meas 278.1313; $[^\alpha]_{20}D$ –20.3° (c 0.5, CH$_2$Cl$_2$) on 99% ee material. Recrystallization of 41 gave X-ray quality single crystals. The crystallographic data for 41 has been deposited at the Cambridge Crystallographic Data Center (CCDC 884445).

The formation of β-lactam 43:

A flame-dried 25 mL round bottom flask filled with N$_2$ was charged with acid 104 (23% ee, 45 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N$_2$ balloon was attached via a needle. Dry CH$_2$Cl$_2$ (1 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)$_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 10 min, the reaction mixture was concentrated on a rotary evaporator to dryness. The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1) to afford the β-lactam 43 as a white solid (42 mg, 0.090 mmol) in 89% yield; mp 58-60 °C; R$_f$ = 0.30 (hexane:EtOAc 4:1). Spectral data for 43: $^1$H NMR (500 MHz, CDCl$_3$) δ 0.89 (qd, 1H, J = 12.0, 2.0 Hz), 1.00-1.30 (m, 4H), 1.60-1.90 (m, 6H), 2.23, 2.24 (2s, 12H), 3.52 (dd, 1H, J = 8.5, 5.5 Hz), 3.69, 3.70 (2s, 6H), 4.78 (d, 1H, J = 5.5 Hz), 5.37 (s, 1H), 6.87, 6.88 (2s, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 16.24, 16.29, 25.41, 25.70, 26.06, 29.68, 29.71, 38.79, 58.34, 59.62, 62.40, 63.85, 128.45, 128.64, 130.73, 130.99, 133.42, 134.48, 156.30, 156.53, 164.85 (One sp$^3$ carbon not located); IR (thin film) 2928(s), 1765(w) cm$^{-1}$; HRMS calcd for C$_{28}$H$_{37}$NO$_3$Cl (M+H, ESI$^+$) m/z 470.2462, meas 470.2459; $[^\alpha]_{20}D$ 10.6° (c 0.5, CH$_2$Cl$_2$) on 23% ee material.
The formation of β-lactam 44 and 45:

A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid 102 (99% ee, 67 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Dry CH₂Cl₂ (2 mL) was added via syringe. The flask was cooled to 0 °C and (COBr)₂ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 15 min, the reaction mixture was concentrated on a rotary evaporator to dryness. The ¹H NMR spectrum of the crude reaction mixture showed a 2:1 trans:cis ratio of 45:44. Purification by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 5:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) gave the major product 45 (22 mg, 0.055 mmol) in a pure form as a colorless oil in 28% yield and a mixture of 44 and 45 in 66% yield. The overall yield for cis and trans-isomers was 94%. Extended reaction times or increased temperatures do not enhance the trans/cis ratio past 2:1. Spectral data for 45:

Rᵣ = 0.35 (hexane:EtOAc 4:1); ¹H NMR (500 MHz, CDCl₃) δ 0.60-1.80 (m, 11H), 3.72 (dd, 1H, J = 5.0, 2.0 Hz), 4.51 (d, 1H, J = 2.0 Hz), 5.78 (s, 1H), 7.20-7.60 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 25.36, 25.76, 26.03, 26.47, 29.31, 38.86, 43.53, 62.25, 69.23, 127.81, 128.02, 128.05, 128.36, 128.59, 128.69, 138.09, 138.17, 163.76; IR (thin film) 1765(s), 1265(m) cm⁻¹; HRMS calcd for C₂₃H₂₅NO⁷⁸Br (M+H, ESI⁺) m/z 398.1120, meas 398.1117; [α]₂₀D −8.3° (c 1.0, CH₂Cl₂) on 99% ee material.

A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid 102 (99% ee, 34 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂
balloon was attached via a needle. Dry CH_2Cl_2 (1 mL) was added via syringe. The flask was cooled to 0 °C and (COBr)_2 (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, aq sat NaHCO_3 (1 mL) was added at 0 °C via syringe along with CH_2Cl_2 (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 7:1 cis:trans ratio of 44:45. The major product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1). The pure cis-isomer 44 (100:1 cis:trans ratio by ^1H NMR, 33 mg, 0.083 mmol) was obtained as a colorless oil in 83% yield and a mixture of cis- and trans-isomers was obtained in 12% yield. The overall yield for the cis and trans-isomers was 95%. Spectral data for 44: solidified in the refrigerator, mp 83-85 °C; R_f = 0.35 (hexane:EtOAc 4:1); ^1H NMR (600 MHz, CDCl_3) δ 0.86 (qd, 1H, J = 11.4, 3.0 Hz), 1.02-1.32 (m, 4H), 1.62-1.74 (m, 3H), 1.78-1.90 (m, 3H), 3.48 (dd, 1H, J = 9.0, 5.4 Hz), 4.86 (d, 1H, J = 5.4 Hz), 5.61 (s, 1H), 7.20-7.40 (m, 10H); ^13C NMR (150 MHz, CDCl_3) δ 25.21, 25.52, 25.98, 29.84, 30.01, 40.02, 47.94, 61.30, 64.78, 127.70, 127.99, 128.17, 128.36, 128.48, 128.66, 138.04, 139.04, 165.00; IR (thin film) 1765(s) cm^-1; HRMS calcd for C_{22}H_{25}NO_{79}Br (M+H, ESI^+) m/z 398.1120, meas 398.1125; [α]_D^20 −33.9° (c 0.5, CH_2Cl_2) on 99% ee material.

The formation of β-lactam 56:

The general procedure for β-lactam formation with (COCl)_2 was followed with trans-acid 55 (racemic, 50 mg, 0.193 mmol, 1.0 equiv), (COCl)_2 (0.04 mL, 0.46 mmol, 2.3 equiv) and CH_2Cl_2 (2 mL). The ratio of trans:cis was determined to be ≥ 100:1 from the ^1H NMR spectrum of the crude reaction mixture with the aid of an authentic sample of the cis-isomer 41. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product trans-56 was obtained as a colorless oil (45 mg, 0.162 mmol) in 85% yield; R_f = 0.33.
(hexane:EtOAc 4:1). Spectral data for trans-56: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.88-1.26 (m, 5H), 1.48-1.78 (m, 6H), 3.33 (dd, 1H, $J$ = 6.0, 2.0 Hz), 4.06 (d, 1H, $J$ =15.5 Hz), 4.48 (d, 1H, $J$ = 2.0 Hz), 4.80 (d, 1H, $J$ = 15.0 Hz), 7.20-7.40 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 25.46, 25.55, 25.96, 27.52, 29.45, 39.17, 45.82, 57.22, 67.73, 127.95, 128.10, 128.89, 134.86, 164.15; IR (thin film) 2928(m), 1770(s) cm$^{-1}$; HRMS calcd for C$_{16}$H$_{21}$NO$_3$Cl (M+H, ESI$^+$) m/z 278.1312, meas 278.1316.

The formation of $\beta$-lactam 46:

The general procedure for $\beta$-lactam formation with (COCl)$_2$ was followed with acid 109 (72% ee, 30 mg, 0.10 mmol, 1.0 equiv), (COCl)$_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH$_2$Cl$_2$ (1 mL). The crude product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1). The product 46 was obtained as a white solid (30 mg, 0.096 mmol) in 96% yield; mp 110-112 °C; $R_f$ = 0.35 (hexane:EtOAc 4:1). Spectral data for 46: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.95 (d, 3H, $J$ = 6.6 Hz), 0.99 (d, 3H, $J$ = 7.2 Hz), 2.08-2.18 (m, 1H), 3.56 (dd, 1H, $J$ = 9.0, 5.4 Hz), 4.82 (d, 1H, $J$ = 5.4 Hz), 5.62 (s, 1H), 7.24-7.40 (m, 10H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 19.55, 19.71, 29.36, 58.49, 64.25, 64.31, 127.78, 128.00, 128.23, 128.29, 128.55, 128.66, 138.09, 138.89, 164.69; IR (thin film) 1759(s) cm$^{-1}$; HRMS calcd for C$_{19}$H$_{21}$NO$_3$Cl (M+H, ESI$^+$) m/z 314.1312, meas 314.1299; $[\alpha]_{D}^{20}$ 66.9° (c 0.5, CH$_2$Cl$_2$) on 72% ee material.

The formation of $\beta$-lactam 47:

The general procedure for $\beta$-lactam formation with (COCl)$_2$ was followed with acid 111 (80% ee, 30 mg, 0.10 mmol, 1.0 equiv), (COCl)$_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) and CH$_2$Cl$_2$ (1 mL). The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc
The β-lactam 47 was obtained as a colorless oil (25 mg, 0.080 mmol) in 81% yield; \( R_f = 0.30 \) (hexane:EtOAc 4:1). Spectral data for 47: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 0.83 (t, 3H, \( J = 7.0 \) Hz), 1.04-1.18 (m, 1H), 1.26-1.40 (m, 1H), 1.44-1.54 (m, 1H), 1.70-1.82 (m, 1H), 3.64-3.74 (m, 1H), 4.88 (d, 1H, \( J = 5.0 \) Hz), 5.96 (s, 1H), 7.18-7.42 (m, 10H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 13.69, 18.98, 31.57, 57.71, 59.15, 61.04, 127.83, 127.85, 128.13, 128.58, 128.69, 128.77, 137.60, 138.57, 164.07; IR (thin film) 1765(s) cm\(^{-1}\); HRMS calcd for C\(_{19}\)H\(_{21}\)NO\(_3\)Cl (M+H, ESI') \( m/z \) 314.1312, meas 314.1313; [\( \alpha \)]\(_D\)\(^{20}\) =\(-28.5^\circ\) (c 1.0, CH\(_2\)Cl\(_2\)) on 80% ee material.

The formation of β-lactam 49:

The general procedure for β-lactam formation with (COCl)\(_2\) was followed with acid 114 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), (COCl)\(_2\) (0.020 mL, 0.23 mmol, 2.3 equiv) and CH\(_2\)Cl\(_2\) (1 mL). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product 49 was obtained as a white solid (27 mg, 0.072 mmol) in 72% yield; mp 93-94 °C; \( R_f = 0.13 \) (hexane:EtOAc 4:1). Spectral data for 49: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.72-1.88 (m, 1H), 2.00-2.16 (m, 1H), 2.28-2.44 (m, 1H), 2.58-2.72 (m, 1H), 3.64-3.76 (m, 1H), 4.90 (d, 1H, \( J = 5.1 \) Hz), 5.94 (s, 1H), 6.94-7.02 (m, 2H), 7.20-7.40 (m, 13H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 31.12, 31.72, 57.03, 58.96, 60.92, 126.20, 127.78, 127.87, 128.18, 128.23, 128.50, 128.64, 128.66, 128.81, 137.33, 138.39, 140.31, 163.94; IR (thin film) 1765(s) cm\(^{-1}\); HRMS calcd for C\(_{24}\)H\(_{23}\)NO\(_3\)Cl (M+H, ESI') \( m/z \) 376.1468, meas 376.1441; [\( \alpha \)]\(_D\)\(^{20}\) =\(-50.8^\circ\) (c 1.0, CH\(_2\)Cl\(_2\)) on 99% ee material.

The formation of β-lactam 50:
The general procedure for $\beta$-lactam formation with (COCl)$_2$ was followed with acid 117 (86% ee, 31 mg, 0.10 mmol, 1.0 equiv), (COCl)$_2$ (0.02 mL, 0.23 mmol, 2.3 equiv) and CH$_2$Cl$_2$ (1 mL) with a reaction time to be 30 min at rt. The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1). The product 50 was obtained as a pale yellow solid (24 mg, 0.074 mmol) in 75% yield; solidified in the refrigerator, mp 72-73 °C; $R_f = 0.25$ (hexane:EtOAc 4:1). Spectral data for 50: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.68 (d, 3H, $J = 6.3$ Hz), 0.81 (d, 3H, $J = 6.6$ Hz), 1.22-1.34 (m, 1H), 1.40-1.56 (m, 1H), 1.72-1.82 (m, 1H), 3.66-3.76 (m, 1H), 4.86 (d, 1H, $J = 4.8$ Hz), 5.96 (s, 1H), 7.14-7.20 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 21.64, 23.04, 25.06, 37.97, 56.27, 59.40, 60.90, 127.77, 127.81, 128.21, 128.60, 128.77, 128.85, 137.50, 138.55, 164.19; IR (thin film) 1767(s) cm$^{-1}$; HRMS calcd for C$_{20}$H$_{23}$NO$_3$Cl (M+H, ESI$^+$) m/z 328.1468, meas 328.1475; $[^\alpha]_D^{20} -10.4^\circ$ (c 1.0, CH$_2$Cl$_2$) on 86% ee material.

The formation of $\beta$-lactam 51:

A flame-dried 25 mL round bottom flask filled with N$_2$ was charged with acid 119 (98% ee, 62 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N$_2$ balloon was attached via a needle. Dry CH$_2$Cl$_2$ (2 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)$_2$ (0.040 mL, 0.46 mmol, 2.3 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and rt for 5 h, it was concentrated and kept at rt for 3 months. The products were purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 9:1). The pure cis-51 (40 mg, 0.12 mmol) was obtained as a white solid in 62% yield and the pure trans-52 (10 mg, 0.031 mmol) was obtained as a white solid in 15% yield. If this reaction was repeated for 24 h at 25 °C and then quenched with aq NaHCO$_3$ before concentration, a 38% yield of 51 was isolated. The 1H NMR spectrum of the crude reaction mixture indicated the presence of a 4% yield of the trans-isomer 52 along with a 46% yield of the acid chloride 53.
Spectral data for cis-51: mp 136-138 °C; Rf = 0.33 (hexane:EtOAc 4:1); 1H NMR (600 MHz, CDCl3) δ 1.12 (s, 9H), 3.74 (d, 1H, J = 6.0 Hz), 4.82 (d, 1H, J = 5.4 Hz), 5.48 (s, 1H), 7.18-7.44 (m, 10H); 13C NMR (150 MHz, CDCl3) δ 26.84, 34.10, 57.58, 65.60, 67.63, 127.73, 128.03, 128.15, 128.41, 128.53, 128.72, 138.24, 138.87, 164.69; IR (thin film) 1763(s) cm⁻¹; HRMS calcd for C20H23NO35Cl (M+H, ESI⁺) m/z 328.1468, meas 328.1476; [α]D²⁰ –89.5° (c 0.5, CH₂Cl₂) on 98% ee material;

Spectral data for trans-52: mp 101-103 °C; Rf = 0.40 (hexane:EtOAc 4:1); 1H NMR (600 MHz, CDCl3) δ 0.98 (s, 9H), 3.51 (d, 1H, J = 2.4 Hz), 4.41 (d, 1H, J = 2.4 Hz), 5.44 (s, 1H), 7.24-7.38 (m, 10H); 13C NMR (150 MHz, CDCl3) δ 26.08, 33.11, 56.30, 65.44, 73.80, 127.86, 127.91, 127.98, 128.54, 128.79, 138.29, 138.41, 163.77; IR (thin film) 2963(m), 1768 (s) cm⁻¹; HRMS calcd for C20H23NO35Cl (M+H, ESI⁺) m/z 328.1468, meas 328.1453; [α]D²⁰ –15.4° (c 1.0, CH₂Cl₂) on 98% ee material.

The formation of acid chloride 53:

A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid 119 (98% ee, 93 mg, 0.30 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Dry CH₂Cl₂ (3 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)₂ (0.15 mL, 1.75 mmol, 5.8 equiv) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 5 min and rt for 1 h, it was concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1) to give the acid chloride 53 (20 mg, 0.033 mmol) as a white solid in 22% yield; mp 85-86 °C; Rf = 0.70 (hexane:EtOAc 4:1). Spectral data for 53: 1H NMR (600 MHz, CDCl₃) δ 0.78 (s, 9H), 2.07 (d, 1H, J = 7.0 Hz), 2.67 (d, 1H, J = 7.0 Hz), 3.66 (s, 1H), 7.20-7.42 (m, 8H), 7.57 (d, 2H, J = 7.5 Hz); 13C NMR (150 MHz, CDCl₃) δ 27.77, 32.83, 52.33, 60.27, 79.18, 127.20, 127.55, 127.98, 128.25, 128.72, 128.81, 141.93, 142.66, 170.36; IR (thin film) 1790(s) cm⁻¹; Anal calcd for C20H22ClO3:
C, 73.27; H, 6.76; N, 4.27. Found: C, 72.84; H, 6.71; N, 4.18. \([\alpha]_D^{20} 139.2^\circ (c 0.5, \text{CH}_2\text{Cl}_2)\) on 98% ee material.

*The formation of \(\beta\)-lactam 54:*

\[
\begin{align*}
\text{BUDAM COOH} & \quad \text{(COCl)}_2 \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

The general procedure for \(\beta\)-lactam formation with (COCl)\(_2\) was followed with acid 121 (90% ee, 58 mg, 0.10 mmol, 1.0 equiv), (COCl)\(_2\) (0.020 mL, 0.23 mmol, 2.3 equiv) and CH\(_2\)Cl\(_2\) (1 mL). The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 15:1). The \(\beta\)-lactam 54 was obtained as a white foamy solid (23 mg, 0.39 mmol) in 39% yield; mp 73-76 °C; \(R_f = 0.30\) (hexane:EtOAc 4:1). Spectral data for 54: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.74 (t, 3H, \(J = 7.2\) Hz), 1.26-1.50 (m, 37H), 1.64-1.80 (m, 4H), 3.10 (dd, 1H, \(J = 10.2, 3.3\) Hz), 3.65, 3.66 (2s, 6H), 5.94 (s, 1H), 7.00 (s, 2H), 7.06 (s, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 10.35, 24.13, 24.41, 32.05, 32.08, 35.79, 35.85, 59.59, 64.26, 64.28, 67.11, 71.60, 125.98, 127.23, 131.51, 132.41, 143.34, 143.74, 158.79, 158.94, 166.94; IR (thin film) 2964(s), 1770(s) cm\(^{-1}\); HRMS calcd for C\(_{37}\)H\(_{57}\)NO\(_3\)\(_35\)Cl (M+H, ES\(^+\)) m/z 598.4027, meas 598.4039; \([\alpha]_D^{20} -7.1^\circ (c 0.5, \text{CH}_2\text{Cl}_2)\) on 90% ee material.

**VI. Formation of \(\beta\)-lactams with SOCl\(_2\) (Scheme 3 and Table 2)**

*The formation of \(\beta\)-lactam 6:*

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \quad \text{NaOH} & \quad \text{H}_2\text{O/Acetone} & \quad \text{rt, 1h} & \quad \text{NaH, SOCl}_2 & \quad \text{THF, rt, 75 min}
\end{align*}
\]

_Formation of 5:_ To a solution of acid 8 (62% ee, 222 mg, 0.88 mmol, 1.0 equiv) in acetone (3 mL) was added a NaOH solution (35.1 mg in 2.4 mL of H\(_2\)O, 0.88 mmol, 1.0 equiv). The resulting solution was stirred at rt for 1 h. Then the volatiles were removed by evaporation (acetone was added and evaporated several times) until a white solid was obtained.
Reaction of 5 with thionyl chloride and NaH (Scheme 3): To a flame-dried 5 mL round bottom flask was added NaH (2 mg, 60% dispersion in mineral oil, 0.05 mmol, 0.29 equiv) which was washed three times with hexane (0.5 ml \times 3) (hexane was added to the flask and the top clear solution was carefully removed by a syringe). The remaining volatiles were removed by vacuum and the flask was filled with N\textsubscript{2}. To the flask containing dry NaH was added THF (freshly distilled, 0.5 ml) to form a slurry. Then 46.8 mg of the above sodium salt 5 (0.17 mmol, 1 equiv) was added to the slurry followed by the dropwise addition of thionyl chloride (19 µL, 0.25 mmol, 1.5 equiv) to form an orange reaction mixture. After the mixture was stirred at rt for 75 min under N\textsubscript{2}, the solvent was removed by rotary evaporation and EtOAc (3 mL) was added followed by the careful addition of water (0.7 mL). The organic layer was separated, washed with H\textsubscript{2}O (1 mL), dried with Na\textsubscript{2}SO\textsubscript{4} and filtered. The filtrate was concentrated to give the crude mixture whose \textsuperscript{1}H NMR spectrum showed that the major product was compound 6 in a yield of 56% as determined with the aid of an internal standard (Ph\textsubscript{3}CH).

The formation of β-lactam 42:

![Diagram of the formation of β-lactam 42]

To a 10 mL flame-dried round bottom flask equipped with a stir bar and filled with N\textsubscript{2} was added acid 102 (99% ee, 34 mg, 0.1 mmol, 1.0 equiv). The vacuum adapter was replaced by a septum to which a N\textsubscript{2} balloon was attached via a needle. Then dry CH\textsubscript{2}Cl\textsubscript{2} (1mL) was added via a syringe. After the solution was cooled to 0 °C, SOCl\textsubscript{2} (15 µL, 0.2 mmol, 2.0 equiv) was added to the reaction flask in a dropwise manner. The reaction mixture was stirred at 0 °C for 5 min and then at room temperature for 1h. Then it was concentrated on a rotary evaporator to dryness. The product was purified by column chromatography (silica gel, 18 \times 180 mm, hexane:EtOAc 5:1) to afford the β-lactam 42 (22 mg, 0.062 mmol, 62%) as a off-white solid.
VII. Reaction of 3-phenylaziridine 10 with (COCl)$_2$ in the presence of DMF (Table 3)

The general procedure for the reaction of 3-phenylaziridine 10 with (COCl)$_2$ in the presence of DMF illustrated for entry 3 in Table 3: To a 10 mL flame-dried round bottom flask equipped with a stir bar and filled with N$_2$ was added acid 10 (98% ee, 33 mg, 0.1 mmol, 1.0 equiv) and dry CH$_2$Cl$_2$ (1ml) followed by the addition of dry DMF (7.8 µL, 0.1 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N$_2$ balloon was attached via a needle. The mixture was cooled to 0 °C. Then (COCl)$_2$ (17 µL, 0.2 mmol, 2.0 equiv) was added to the reaction flask in a dropwise manner. The reaction mixture was stirred at 0 °C for 15 min and then concentrated on a rotary evaporator to dryness. The NMR yields for 65 and 11 were 7% and 28%, respectively, determined from the $^1$H NMR spectrum of the crude reaction mixture with the aid of Ph$_3$CH as internal standard in CDCl$_3$.

VIII. Formation of β-lactam and acid chloride with Vilsmeier reagent (Table 3 and Table 4)

Procedure A for β-lactam formation with Vilsmeier reagent illustrated for β-lactam 65:

The formation of β-lactam 65:

Vilsmeier reagent preparation: To a flame-dried 10 mL round bottom flask filled with N$_2$ was added dry DMF (22.5 µL, 0.29 mmol, 2.9 equiv) and dry CH$_2$Cl$_2$ (0.2 mL) via syringe. The vacuum adapter was replaced with a septum to which a N$_2$ balloon was attached via a needle. Then (COCl)$_2$ (20 µL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use.
Lactam formation: To an oven-dried 5 mL round bottom flask filled with N₂ was added acid 10 (98% ee, 33 mg, 0.10 mmol, 1.0 equiv) and dry CH₂Cl₂ (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner via syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CH₂Cl₂ (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. The reaction mixture was stirred at 0 °C for 20 min and concentrated by rotovap. The NMR yield of 65 was 82% as determined from the ¹H NMR spectrum of the crude reaction mixture with the aid of Ph₃CH as internal standard in CDCl₃. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam 65 (28.7 mg, 0.083 mmol, 83%) as a white solid; mp 107-108 °C; Rᵣ = 0.20 (hexane:EtOAc 4:1). Spectral data for 65: ¹H NMR (500 MHz, CDCl₃) δ 4.95 (d, 1H, J = 5.0 Hz), 5.13 (d, 1H, J = 5.0 Hz), 5.65 (s, 1H), 7.20-7.46 (m, 15H); ¹³C NMR (125 MHz, CDCl₃) δ 60.28, 61.86, 62.89, 127.92, 127.96, 128.17, 128.26, 128.41, 128.56, 128.61, 128.64, 128.91, 133.14, 137.52, 138.22, 164.31; IR (thin film) 1767(s) cm⁻¹; HRMS calcd for C₂₂H₁₉NO₃Cl (M+H, ES⁺) m/z 348.1155, meas 348.1161; [α]²⁰D −59.2° (c 1.0, CH₂Cl₂) on 98% ee material.

The formation of acid chloride 14:

Procedure A for β-lactam formation with Vilsmeier reagent was followed with acid 10 (98% ee, 164.7 mg, 0.50 mmol, 1.0 equiv), Vilsmeier reagent (1.16 mmol, 2.3 equiv) in 2.2 mL dry CH₂Cl₂ (0.6 mL for making Vilsmeier reagent and 1.6 mL for transferring the starting material aziridine acid 10 to Vilsmeier reagent 61) with a reaction time of 1 min at 0 °C. Then the reaction mixture was quickly loaded onto a chromatography column without concentration (silica gel 20 × 180 mm, hexane:EtOAc 7:1). Elution afforded the acid chloride 14 (99.6 mg, 0.286 mmol, 57%) as a white solid; mp 103-105 °C; Rᵣ = 0.31 (hexane:EtOAc 7:1). Spectral data for 14: ¹H NMR (500 MHz, CDCl₃) δ 3.17 (d, 1H, J = 7.0 Hz), 3.50 (d, 1H, J = 6.5 Hz), 4.00 (s, 1H), 7.15-7.19 (m, 1H), 7.22-7.30 (m, 6H), 7.32-7.36 (m, 2H), 7.37-7.40 (m, 2H), 7.41-7.45 (m, 2H), 7.51-7.55 (m,
2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 51.34, 54.40, 77.34, 127.04, 127.33, 127.64, 127.71, 127.75, 128.21, 128.22, 128.66, 128.77, 133.03, 141.53, 141.63, 167.95; IR (thin film) 1799 (s), 1028 (s), 698 (s) cm$^{-1}$; HRMS calcd for C$_{22}$H$_{19}$NO$_{35}$Cl (M+H, ES$^+$) m/z 348.1155, meas 348.1147; [$\alpha$]$^{20}_D$ +72.8° (c 1.0, CH$_2$Cl$_2$) on 98% ee material.

**The formation of $\beta$-lactam 70:**

![Chemical Structure](image)

Procedure A for $\beta$-lactam formation with Vilsmeier reagent was followed with acid 92 (racemic, 34.4 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23 mmmol, 2.3 equiv) with a reaction time of 1 h at 0 °C. After the column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1), the product was obtained as white foamy solid (21.7 mg, 0.06 mmol, 60%); mp 117-118 °C; R$_f$ = 0.30 (hexane:EtOAc 4:1). Spectral data for 70: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.30 (s, 3H), 4.89 (d, 1H, $J = 5.4$ Hz), 5.08 (d, 1H, $J = 5.0$ Hz), 5.58 (s, 1H), 7.05 (d, 2H, $J = 8.4$ Hz), 7.10 (d, 2H, $J = 7.8$ Hz), 7.20-7.46 (m, 10H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 21.22, 60.40, 61.76, 62.96, 127.36, 127.87, 127.95, 128.19, 128.54, 128.62, 128.65, 128.94, 130.05, 137.55, 138.45, 138.88, 164.34; IR (thin film) 1767 (s) cm$^{-1}$; HRMS calcd for C$_{23}$H$_{21}$NO$_{35}$Cl (M+H, ES$^+$) m/z 362.1312, meas 362.1303.

**The formation of $\beta$-lactam 71:**

![Chemical Structure](image)

Procedure A for $\beta$-lactam formation with Vilsmeier reagent was followed with acid 90 (90% ee, 41 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23 mmmol, 2.3 equiv) with a reaction time of 1h. The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1) to afford the $\beta$-lactam 71 (36.1 mg, 0.085 mmol, 85%) as a white foamy solid;
mp 48-50 °C; Rf = 0.30 (hexane:EtOAc 4:1). Spectral data for 71: 1H NMR (600 MHz, CDCl₃) δ 4.89 (d, 1H, J = 5.4 Hz), 5.12 (d, 1H, J = 4.8 Hz), 5.68 (s, 1H), 6.96-7.01 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.26 (m, 5H), 7.28-7.34 (m, 3H), 7.36-7.40 (m, 2H); 13C NMR (150 MHz, CDCl₃) δ 60.06, 61.41, 62.78, 123.04, 128.04, 128.10, 128.31, 128.34, 128.67, 130.25, 131.35, 132.37, 137.33, 137.95, 164.12 (One sp² carbon not located); IR (thin film) 1767(s) cm⁻¹; HRMS calcd for C₂₂H₁₈NO₃ClBr (M+H, ES⁺) m/z 426.0260, meas 426.0274; [α]₂⁰ºD –85.0° (c 1.0, CH₂Cl₂) on 90% ee material.

Procedure B for β-lactam formation with Vilsmeier reagent illustrated for β-lactam 73:

The formation of β-lactam 73:

Vilsmeier reagent preparation: To a flame-dried 50 mL round bottom flask filled with N₂ was added dry DMF (0.10 mL, 1.2 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Dry CH₂Cl₂ (5 mL) was added via syringe. Then (COCl)₂ (0.10 mL, 1.2 mmol, 1.0 equiv) was added dropwise at rt. The resulting solution was stirred at rt for at least 5 min prior to use. The concentration of Vilsmeier reagent is 0.23 M in CH₂Cl₂.

Lactam formation: To a flame-dried 25 mL round bottom flask filled with N₂ was added acid 25 (98% ee, 34 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. The flask was cooled to 0 °C and the Vilsmeier reagent (0.23M, 2 mL, 0.46 mmol, 4.6 equiv) was added to the flask via syringe all at once at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, it was concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1) to afford the β-lactam 73 (8 mg, 0.022 mmol, 22%) as a white solid; mp 130-132 °C; Rf = 0.50 (hexane:EtOAc 4:1). Spectral data for 73: 1H NMR (500 MHz, CDCl₃) δ 1.84 (s, 3H), 4.57 (s, 1H), 5.53 (s, 1H), 7.15-7.40 (m, 15H); 13C NMR (125 MHz, CDCl₃) δ 24.38, 62.80, 69.72, 72.91,
The formation of $\beta$-lactam 6:

Procedure B for $\beta$-lactam formation with Vilsmeier reagent was followed with acid 8 (62% ee, 26 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23 M, 1.0 mL, 0.23 mmmol, 1.0 equiv) with a reaction time of 15 min at 0 °C. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product 6 (20 mg, 0.074 mmol, 74%) as a viscous oil; $R_f = 0.35$ (hexane:EtOAc 4:1). Spectral data for 6: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.90 (d, 1H, $J = 14.5$ Hz), 4.78 (d, 1H, $J = 5.0$ Hz), 4.90 (d, 1H, $J = 14.5$ Hz), 5.07 (d, 1H, $J = 5.0$ Hz), 7.10-7.42 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 44.96, 60.26, 61.15, 128.13, 128.25, 128.55, 128.62, 128.93, 129.14, 132.69, 134.34, 163.99; IR (thin film) 2922(m), 1770(s) cm$^{-1}$; $[\alpha]_D^{20} = -9.6^\circ$ (c 1.0, CH$_2$Cl$_2$) on 98% ee material. Spectral data match those previously reported data. 

The formation of $\beta$-lactam 69:

Procedure B for $\beta$-lactam formation with Vilsmeier reagent was followed with acid 123 (> 99% ee, 27 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmmol, 2.3 equiv). The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), to afford the $\beta$-lactam 69 (22 mg, 0.077 mmol, 77%) as a white foamy solid; mp 95-96 °C; $R_f = 0.30$ (hexane:EtOAc 4:1). Spectral data for 69: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.43 (d, 3H, $J = 7.0$ Hz), 4.69 (d, 1H, $J = 5.0$ Hz), 4.98 (d, 1H, $J = 5.0$ Hz), 5.07 (q, 1H, $J = 7.0$ Hz), 127.93, 127.94, 128.17, 128.30, 128.50, 128.55, 128.88, 134.19, 137.64, 138.63, 167.28; IR (thin film) 1767(s) cm$^{-1}$; HRMS calcd for C$_{23}$H$_{21}$NO$_3$Cl (M+H, ESI$^+$) m/z 362.1312, meas 362.1299; $[\alpha]_D^{20} = -56.0^\circ$ (c 1.0, CH$_2$Cl$_2$) on 62% ee material.
Hz), 7.20-7.40 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 19.08, 53.04, 60.29, 60.42, 127.28, 128.15, 128.72, 128.81, 129.08, 134.21, 138.99, 164.22 (One sp$^2$ carbon not located); IR (thin film) 1761(s) cm$^{-1}$; HRMS calcd for C$_{17}$H$_{17}$NO$_3$Cl (M+H, ESI$^+$) $m/z$ 286.0999, meas 286.0975; $\left[\alpha\right]_{D}^{20}$ $-84.5^\circ$ (c 1.0, CH$_2$Cl$_2$) on > 99% ee material.

The formation of $\beta$-lactam 72:

![](image)

Procedure B for $\beta$-lactam formation with Vilsmeier reagent was followed with acid 125 (> 99% ee, 35 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmmol, 2.3 equiv). The crude product was purified by column chromatography (silica gel, 18 x 180 mm, hexane:EtOAc 5:1), affording the product 72 (25 mg, 0.069 mmol, 69%) as a white foamy solid; mp 102-103 °C; $R_f = 0.20$ (hexane:EtOAc 4:1). Spectral data for 72: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.41 (d, 3H, $J = 7.5$ Hz), 4.60 (d, 1H, $J = 5.0$ Hz), 4.94 (d, 1H, $J = 5.0$ Hz), 5.01 (q, 1H, $J = 7.0$ Hz), 7.08-7.14 (m, 2H), 7.16-7.20 (m, 2H), 7.28-7.34 (m, 3H), 7.46-7.50 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 19.08, 53.18, 59.86, 60.10, 123.22, 127.25, 128.27, 128.88, 130.31, 131.40, 133.36, 138.77, 164.00; IR (thin film) 1767(s) cm$^{-1}$; HRMS calcd for C$_{17}$H$_{16}$NO$_3$Cl$^{79}$Br (M+H, ESI$^+$) $m/z$ 364.0104, meas 364.0078; $\left[\alpha\right]_{D}^{20}$ $-116.3^\circ$ (c 1.0, CH$_2$Cl$_2$) on > 99% ee material.

IX. Conversion of acid chloride 14 to $\beta$-lactam 65

i. Thermolysis of acid chloride 14:

The acid chloride 14 was relatively stable in CD$_2$Cl$_2$ solution at room temperature. Acid chloride 14 (0.1 mmol) was dissolved in dry CD$_2$Cl$_2$ (0.7 mL) and the $^1$H NMR spectrum was taken at certain intervals with quantitation aided by an internal standard (Ph$_3$CH). After 23 hours at room temperature, there was 72% acid chloride 14 remaining, only a 5% yield of the lactam 65 and 23% conversion to other compounds.
To a flame-dried 5 mL Schlenk flask was added the acid chloride 14 (98% ee, 34.8 mg, 0.1 mmol) and dry CH$_2$Cl$_2$ (1 mL). The flask was sealed and heated at 80 °C for an hour. Then the mixture was allowed to cool to room temperature and a small amount of the mixture was taken out and dissolved in CDCl$_3$. The $^1$H NMR spectrum of the crude reaction revealed that a mixture of the acid chloride 14 and lactam 65 in a ratio of 1: 0.13 was obtained along with other unknown side products.

ii. The conversion of acid chloride 14 to β-lactam 65 with HCl:

To a flame-dried 10 mL round bottom flask filled with N$_2$ was added the acid chloride 14 (98% ee, 48 mg, 0.14 mmol, 1.0 equiv) and dry CH$_2$Cl$_2$ (1.5 mL). Then dry HCl was passed through the reaction flask for 5 min. More CH$_2$Cl$_2$ was added to replenish the solvent loss during passing through dry HCl. The reaction mixture was stirred at 0 °C for 1h and then warmed up to rt. The reaction mixture was stirred for another 4h at rt and then concentrated by rotary evaporator. The $^1$H NMR spectrum of the crude reaction was taken which revealed that the lactam 65 was formed in 18% yield and only 16% of the acid chloride 14 was unreacted by comparing the integrations of the methine and aromatic protons.

iii. The conversion of acid chloride 14 to β-lactam 65 with HCl in the presence of a chloride source:

To a flame-dried 10 mL round bottom flask filled with N$_2$ was added benzyltriethylammonium chloride (22 mg, 0.096 mmol, 1.2 equiv), the acid chloride 14 (98% ee,
27.7 mg, 0.080 mmol, 1.0 equiv) and dry CH₂Cl₂ (1.5 mL). The reaction mixture was stirred at rt for 1h. Then dry HCl was passed through the reaction flask until the acidity of the vapor inside the flask was pH ~1. More CH₂Cl₂ was added to replenish the solvent loss during the purge with dry HCl. The mixture was stirred at rt for another 3h and then concentrated by rotary evaporator. After the addition of Ph₃CH as an internal standard, the ¹H NMR spectrum of the crude reaction was taken which revealed that the lactam 65 was formed in 20% yield and only 9% of the acid chloride 14 was unreacted.

iv. The conversion of acid chloride 14 to β-lactam 65 with HOTf in the presence of a chloride source:

![Chemical Structure]

To a flame-dried 10 mL round bottom flask filled with N₂ was added benzyltriethylammonium chloride (28 mg, 0.12 mmol, 1.2 equiv), a 1 M solution of the acid chloride 14 (34.8 mg, 0.10 mmol, 1.0 equiv) in dry CH₂Cl₂ and a certain amount of TfOH from the stock solution. The reaction mixture was stirred at rt for 15 min and then concentrated by rotary evaporator. Then NMR yield of the β-lactam 65 and the amount of leftover acid chloride 14 and were determined from the ¹H NMR spectrum of the crude reaction mixture in CDCl₃ with the aid of Ph₃CH as an internal standard. The results are listed in Table 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>TfOH (equiv)</th>
<th>Yield of lactam (%)</th>
<th>Acid Chloride (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>2</td>
<td>0.08</td>
<td>11</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>19</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>14</td>
<td>52</td>
</tr>
</tbody>
</table>
v. The conversion of acid chloride 14 to β-lactam 65 with Vilsmeier reagent 61:

![Chemical structure]

**Vilsmeier reagent preparation**: To a flame-dried 10 mL round bottom flask filled with N₂ was added dry DMF (22.5 µL, 0.29 mmol, 2.9 equiv) and dry CH₂Cl₂ (0.2 mL) via syringe. The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Then (COCl)₂ (20 µL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use.

**Lactam formation**: To an oven-dried 5 mL round bottom flask filled with N₂ was added the acid chloride 14 (98% ee, 34.7 mg, 0.10 mmol, 1.0 equiv) and dry CH₂Cl₂ (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner via syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CH₂Cl₂ (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. The reaction mixture was stirred at 0 °C for 20 min and concentrated by rotary evaporator. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the β-lactam 65 (23.6 mg, 0.068 mmol) in 68% isolated yield.

X. Sequential multi-component catalytic asymmetric aziridination and ring expansion to β-lactam 48 (Scheme 9)

![Chemical structure]

**Multi-component catalytic asymmetric aziridination**: To a 25 mL flame-dried Schlenck flask equipped with a stir bar and filled with N₂ was added (S)-VAPOL (13.7 mg, 0.025 mmol), B(OPh)₃ (21.8 mg, 0.075 mmol) and amine 79 (149.7 mg, 0.5 mmol). Dry toluene (1 mL) was added under
an N₂ atmosphere to dissolve the reagents. The reaction mixture was stirred at room temperature for 1 h. Then 4Å Molecular Sieves (150 mg, freshly flame-dried) were added. After the reaction mixture was cooled to –10 °C, the aldehyde 80 (47.0 µL, 0.522 mmol, 1.04 equiv) was added followed by the addition of ethyl diazoacetate (EDA) 81 (125 µL, 1.0 mmol, 2.0 equiv). The resulting mixture was stirred for 24 h at –10 °C. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (3 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine 82 as a viscous yellow oil.

*Hydrolysis:* To the solution of the crude aziridine 82 in ethanol (2 mL) was added a solution of KOH (140.3 mg, 2.5 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 1 h and then cooled to rt. Then aq citric acid (2N, 2.5 mL) and ether (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated to afford the crude aziridine acid as a yellow foamy solid.

*Ring-expansion:* To a flame-dried round bottom flask equipped with a stir bar and filled with N₂ was added dry DMF (147.5 µL, 1.9 mmol, 3.8 equiv) and dry CH₂Cl₂ (1 mL). The flask was fitted with a rubber septum and a nitrogen balloon. Then (COCl)₂ (131 µL, 1.53 mmol, 3.06 equiv) was added dropwise to the reaction flask with stirring and the Vilsmeier salt precipitated out as a white solid. The mixture was stirred for 20 min at room temperature and cooled to 0 °C. A solution of the crude aziridine acid in dry CH₂Cl₂ (5 mL) was added dropwise to the reaction flask containing the Vilsmeier salt (1.53 mmol, 3.06 equiv) over 5 min. The reaction mixture was stirred for 10 min at 0 °C and concentrated to afford a foamy crude product. The yield of lactam 48 was 59% (over three steps) as determined from the with ¹H NMR spectrum of the crude reaction mixture in CDCl₃ with the aid of Ph₃CH as an internal standard. The product was purified by column chromatography (silica gel, 25 × 210 mm, hexane: CH₂Cl₂: ethyl acetate 8:8:1) to afford β-lactam 48 (124 mg, 0.29 mmol) as a colorless semi-solid in 58% isolated yield (over three steps); The optical purity was determined to be 96% ee by HPLC analysis (Chiralcel OD-H
column, 98:2 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: \( R_t = 7.06 \) min (major enantiomer, 48) and \( R_t = 11.73 \) min (minor enantiomer, \textit{ent}-48). \( R_f = 0.25 \) (hexane:CH\(_2\)Cl\(_2\):ethyl acetate 8:8:1). Spectral data for 48: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 0.80 (t, 3H, \( J = 7.2 \) Hz), 1.04-1.16 (m, 1H), 1.24-1.36 (m, 1H), 1.42-1.50 (m, 1H), 1.68-1.76 (m, 1H), 2.241 (s, 6H), 2.242 (s, 6H), 3.63-3.68 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 4.83 (d, \( J = 5.5 \) Hz, 1H), 5.70 (s, 1H), 6.82 (s, 2H), 6.85 (s, 2H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \) 13.65, 16.19, 16.20, 31.43, 57.39, 59.01, 59.62, 59.63, 60.19, 128.13, 128.95, 130.84, 131.06, 132.92, 133.82, 156.44, 156.60, 163.99; IR (thin film) 2934(w), 1767(s), 1485(w), 1221(w) cm\(^{-1}\); HRMS calcd for C\(_{25}\)H\(_{33}\)NO\(_3\)Cl (M+H, ESI\(^+\)) \( m/z \) 430.2149, meas 430.2141; \([\alpha]^{20}\)\(D\) – 13.7° (c 1.0, CH\(_2\)Cl\(_2\)) on 96% ee material.

**XI. Transformations of \( \beta \)-lactam 42 (Scheme 10)**

Substitution of \( \beta \)-lactam 42 with sodium iodide:

![Scheme 10](image_url)

To a flame-dried test tube sized Schlenck flask filled with N\(_2\) were added the lactam 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), NaI (150 mg, 1.00 mmol, 10.0 equiv) and DMSO-d\(_6\) (0.40 mL). The resulting mixture was stirred at 100 °C for 66 h. After cooling to rt, H\(_2\)O (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 \( \times \) 5 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 18 \( \times \) 180 mm, hexane:EtOAc 5:1) to afford the \( \beta \)-lactam 83 (34 mg, 0.076 mmol) as a viscous oil in 76% yield; \( R_t = 0.50 \) (hexane:EtOAc 4:1). Spectral data for 83: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.78-1.30 (m, 6H), 1.42-1.70 (m, 5H), 3.78 (dd, 1H, \( J = 5.1, 2.1 \) Hz), 4.60 (d, 1H, \( J = 1.8 \) Hz), 5.75 (s, 1H), 7.20-7.40 (m, 10H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 15.65, 25.33, 25.80, 26.07, 26.32, 29.34, 39.82, 62.22, 70.05, 127.76, 128.02, 128.19, 128.36, 128.55, 128.64, 138.21, 138.36, 164.89; IR (thin film)
2926(m), 1759(s) 1265(s) cm⁻¹; HRMS calcd for C₂₂H₂₅NOI (M+H, ESI⁺) m/z 446.0981, meas 446.0948; [α]²⁰D –12.8° (c 1.0, CH₂Cl₂) on 99% ee material.

Reduction of β-lactam 42 with Bu₃SnH:

![Reduction of β-lactam 42 with Bu₃SnH](image)

To a flame-dried Schlenk flask filled with N₂ was added 3-chlorolactam 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), AIBN (10 mg), and dry benzene (1 mL), then tri-butyltin hydride (119 mg, 0.100 mL, 0.400 mmol, 4.00 equiv) was quickly added under a N₂ stream. Then the Schlenk flask was sealed and the reaction was stirred at 80 °C for 19 h. After it was cooled to rt, aq sat KF (3 mL) and CH₂Cl₂ (10 mL) were added. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to give the β-lactam 84 as a white solid (31 mg, 0.097 mmol, 97%). mp 74-76 °C; Rₚ = 0.50 (hexane:EtOAc 4:1). Spectral data for 84: ¹H NMR (500 MHz, CDCl₃) δ 0.78-1.12 (m, 5H), 1.22-1.32 (m, 1H), 1.46-1.68 (m, 5H), 2.69 (dd, 1H, J = 2.5, 15.0 Hz), 2.85 (dd, 1H, J = 5.5, 15.0 Hz), 3.55 (td, 1H, J = 5.5, 2.5 Hz), 5.78 (s, 1H), 7.22-7.38 (m, 10H); ¹³C NMR (150 MHz, CDCl₃) δ 25.52, 25.90, 26.23, 26.37, 29.76, 38.21, 39.34, 57.07, 62.19, 127.47, 127.65, 128.17, 128.43, 128.49, 139.01, 139.30, 167.72 (One sp² C not located); IR (thin film) 2924(m), 1749(s) cm⁻¹; HRMS calcd for C₂₂H₂₆NO (M+H, ESI⁺) m/z 320.2014, meas 320.2007; [α]²⁰D – 82.8° (c 1.0, CH₂Cl₂) on 99% ee material.

Reductive ring opening of β-lactam 42 with LiAlH₄:

![Reductive ring opening of β-lactam 42 with LiAlH₄](image)

To a flame-dried 25 mL round bottom flask filled with N₂ was added LiAlH₄ (20 mg, 0.50 mmol, 5.0 equiv). The vacuum adapter was quickly replaced with a septum to which a N₂ balloon...
was attached via a needle. Dry THF (0.5 mL) was added and the resulting solution was cooled to 0 °C. A solution of 3-chlorolactam 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise via syringe. After the mixture was stirred at 0 °C for 5 min, the ice bath was removed. After the reaction mixture was stirred at rt for 2 h, H2O (0.1 mL) was added carefully at 0 °C. The mixture was stirred at 0 °C for 15 min, and then filtered through Na2SO4 on a Celite pad on a sintered glass funnel. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 3:1) to give the amino alcohol 85 as a white solid (29 mg, 0.090 mmol, 90%). mp 92–94 °C; Rf = 0.30 (hexane:EtOAc 3:1). Spectral data for 85: 1H NMR (600 MHz, CDCl3) δ 0.44-0.54 (m, 1H), 0.90-1.20 (m, 5H), 1.28 (d, 1H, J =12.6 Hz), 1.42-1.64 (m, 6H), 1.79 (q, 1H, J = 6.0 Hz), 3.52-3.60 (m+s, 2H), 3.67-3.74 (m, 1H), 7.16-7.30 (m, 6H), 7.37 (d, 2H, J = 7.2 Hz), 7.43 (d, 2H, J = 7.2 Hz); 13C NMR (150 MHz, CDCl3) δ 25.62, 25.74, 26.19, 30.92, 31.42, 36.93, 44.68, 50.58, 60.66, 78.90, 127.07, 127.17, 127.25, 127.95, 128.23, 128.59, 143.15, 143.55; IR (thin film) 3400(m), 2926(s) cm⁻¹; HRMS calcd for C22H30NO (M+H, ESI⁺) m/z 324.2327, meas 324.2303; [α]₂₀° D 4.0° (c 1.0, CH₂Cl₂) on 99% ee material.

**Trans-Chloro β-lactam 67 under Suzuki coupling conditions:**

To a flame-dried test-tube size Schlenk flask filled with N₂ was added (S)-prolinol (5 mg, 0.048 mmol, 0.48 equiv), NiCl₂•glyme (5 mg, 0.024 mmol, 0.24 equiv), phenylboronic acid (24 mg, 0.20 mmol, 2.0 equiv), KHMDS (40 mg, 0.20 mmol, 2.0 equiv) and i-PrOH (0.5 mL). Then the mixture was stirred at rt for 5 min. The starting material 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv) was added. Then the Teflon valve was closed and the flask was heated at 80 °C for 24 h. 1H NMR spectrum of the crude reaction mixture indicated a 95% conversion of the cis-chloro β-lactam 42 to the trans-chloro β-lactam 67. The trans-chloro-lactam 67 was tentatively identified in the 1H NMR spectrum of the crude reaction mixture by the following absorptions: 3.60 (dd, 1H, J = 5.0, 2.0 Hz), 4.49 (d, 1H, J =1.5 Hz), 5.77 (s, 1H).
The transformation of β-lactam 42 with allyltributyltin:

To a flame-dried test tube size Schlenk flask filled with N₂ was added 3-chlorolactam 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), AIBN (10 mg) and dry benzene (0.5 mL). Allyl tri-butyltin (134 mg, 0.130 mL, 0.400 mmol, 4.00 equiv) was added under a N₂ stream. Then the Teflon valve was closed the reaction mixture was heated at 80 °C for 17 h. After the mixture was cooled to rt, it was concentrated and the product was purified by column chromatography (silica gel, 18 × 18 mm, hexane:EtOAc 5:1) to give the β-lactam 86 (32 mg, 0.089 mmol, 89%) as a colorless oil which solidified during storage; mp 62-64 °C; Rᵢ = 0.50 (hexane:EtOAc 4:1). Spectral data for 86: ¹H NMR (500 MHz, CDCl₃) δ 0.78-1.12 (m, 5H), 1.26-1.34 (m, 1H), 1.46-1.70 (m, 5H), 2.26-2.34 (m, 1H), 2.42-2.50 (m, 1H), 2.88-2.94 (m, 1H), 3.24 (dd, 1H, J = 2.5, 5.5 Hz), 5.01 (dd, 1H, J = 10.0, 2.0 Hz), 5.07 (dt, 1H, J = 17.0, 1.5 Hz), 5.68-5.78 (m+s, 2H), 7.20-7.50 (m, 10H); ¹³C NMR (150 MHz, CDCl₃) δ 25.67, 25.99, 26.23, 27.27, 30.24, 33.27, 39.37, 50.49, 62.11, 63.41, 117.23, 127.44, 127.60, 128.27, 128.36, 128.42, 128.43, 134.91, 139.06, 139.36, 170.01; IR (thin film) 2926(m), 1747(s) cm⁻¹; HRMS calcd for C₂₅H₃₀NO (M+H, ESI⁺) m/z 360.2327, meas 360.2334; [α]₂⁰° –42.7° (c 1.0, CH₂Cl₂) on 99% ee material.

Substitution of β-lactam 42 with NaN₃:

To a flame-dried test tube sized Schlenk flask filled with N₂ were added the lactam 42 (99% ee, 36 mg, 0.10 mmol, 1.0 equiv), NaN₃ (66 mg, 1.0 mmol, 10 equiv) and DMSO-d₆ (0.20 mL). The resulting mixture was stirred at 80 °C for 48 h and 100 °C for 12 h. H₂O (2 mL) was added
and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were washed with H₂O (2 × 1 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated and the product as purified by column chromatography (silica gel, 18 × 150 mm, hexane:EtOAc 5:1) to afford the azido-β-lactam 87 (31 mg, 0.086 mmol) as a white solid in 86% yield; mp 105-107 °C; Rᵣ = 0.50 (hexane:EtOAc 4:1). Spectral data for 87: ¹H NMR (300 MHz, CDCl₃) δ 0.78-1.40 (m, 6H), 1.46-1.76 (m, 5H), 3.42 (dd, 1H, J = 5.4, 2.4 Hz), 4.31 (d, 1H, J = 2.1 Hz), 5.73 (s, 1H), 7.20-7.40 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 25.48, 25.77, 26.06, 26.89, 29.53, 37.91, 62.36, 64.80, 65.39, 127.84, 128.04, 128.16, 128.33, 128.59, 128.72, 138.08, 138.24, 164.36; IR (thin film) 2928(m), 2106(s) 1765(s) cm⁻¹; HRMS calcd for C₂₂H₂₅N₄O (M+H, ES⁺) m/z 361.2028, meas 361.2041; [α]₂⁰ D 74.4° (c 0.5, CH₂Cl₂) on 99% ee material.

XII. NMR studies on lactam formation with Vilsmeier reagent or with (COCl)₂

i. Formation of β-lactam 65 from acid 10 and Vilsmeier reagent 61.

![Diagram](image_url)

**Vilsmeier reagent preparation:** To a flame-dried 10 mL round bottom flask filled with N₂ was added dry DMF (22.5 µL, 0.29 mmol, 2.9 equiv) and dry CD₂Cl₂ (0.2 mL) via syringe. The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Then (COCl)₂ (20 µL, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use. Ph₃CH was added as an internal standard.

**Lactam formation:** To an oven-dried 5 mL round bottom flask filled with N₂ was added acid 10 (98% ee, 33 mg, 0.10 mmol, 1.0 equiv) and dry CD₂Cl₂ (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner via syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CD₂Cl₂ (0.2 mL, 0.1 mL) which were also
transferred to the reaction flask containing the Vilsmeier reagent. After the acid 10 was completely transferred to the Vilsmeier reagent over ~2 min at 0 °C, the reaction mixture was transferred to a cold dry NMR tube filled with N₂ and pre-cooled to 0 °C. The ¹H NMR spectrum was taken at certain intervals at 0 °C in the first 20 min. Subsequently the NMR tube was warmed to rt and the collection of NMR data continued for 80 min. The results are shown in Table 6 and Chart 1.

The first data point at 6 minutes reveals that there is rapid conversion of the acid 10 to the acid chloride 14 (83% yield). In the first 20 minutes at 0 °C there is very little β-lactam 65 formed (3%) and it is not until the temperature is raised to 25 °C that substantial amount of the acid chloride 14 is consumed with concomitant β-lactam formation. In addition, two intermediates are observed to grow in then completely disappear after 100 minutes, but neither accumulates in any significant amount. These intermediates were not identified. The following ¹H NMR absorptions were observed: intermediate A: ¹H NMR (500 MHz, CD₂Cl₂) δ 4.52 (d, J = 10 Hz, 1H), 5.22 (s, 1H), 6.58 (d, J = 10.5 Hz, 1H); intermediate B ¹H NMR (500 MHz, CD₂Cl₂) δ 3.92 (d, J = 3.5 Hz, 1H), 4.93 (s, 1H), 5.75 (d, J = 3.5 Hz, 1H).

Table 6. Time course of the reaction of 10 with Vilsmeier reagent 61

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>14 (%)</th>
<th>65 (%)</th>
<th>Intermediate A (%)</th>
<th>Intermediate B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>83</td>
<td>1</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
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<td>7</td>
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<td>20</td>
<td>77</td>
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<td>12</td>
<td>6</td>
</tr>
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<td>38</td>
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<td>14</td>
<td>3</td>
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<td>11</td>
<td>2</td>
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<td>8</td>
<td>1</td>
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<tr>
<td>55</td>
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<td>58</td>
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<td>0.5</td>
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<td>62</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
<td>63</td>
<td>2</td>
<td>0</td>
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<tr>
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<td>64</td>
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<td>0</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ii. Formation of β-lactam 42 from acid 102 and (COCl)$_2$

\[
\text{Acid chloride 14} \quad \text{(COCl)$_2$ (2.3 equiv)} \quad \text{CD$_2$Cl$_2$} \quad 0 °C, 50 min \quad \text{25 °C, 40 min} \quad \text{Lactam 42}
\]

A flame-dried 25 mL round bottom flask filled with N$_2$ was charged with acid 102 (99% ee, 33.5 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N$_2$ balloon was attached via a needle. Dry CD$_2$Cl$_2$ (1 mL) was added via syringe. The flask was cooled to 0 °C and (COCl)$_2$ (0.020 mL, 0.23 mmol, 2.3 equiv) was added dropwise at 0 °C. The reaction mixture was immediately transferred to a NMR tube filled with N$_2$ and pre-cooled to 0 °C. The $^1$H NMR spectrum was taken at certain intervals at 0 °C in the first 50 min. Subsequently the NMR tube was warmed to rt and the collection of NMR data was continued. The results are shown in Table 7 and Chart 2.

In contrast to the phenyl substituted aziridine carboxylic acid 10, the cyclohexyl substituted aziridine carboxylic acid 102 is converted to corresponding β-lactam 42 at a much faster rate at 0
°C. After the temperature is raised to 25 °C, β-lactam formation is complete within 40 minutes (90 min in total) (88% yield). Two intermediates are observed to grow in but both are consumed as β-lactam formation proceeds. These intermediates have not been identified but neither are considered to be the acid chloride 126 (See below, Part iii). The following 1H NMR absorptions were observed for intermediates A′ and B′: intermediate A′: 1H NMR (500 MHz, CD2Cl2) δ 2.35 (br, 1H), 3.10 (br, 1H), 3.94 (br, 1H); intermediate B′: 1H NMR (500 MHz, CD2Cl2) δ 2.61 (br, t, J = 12 Hz, 1H), 3.82 (br, t, J = 3.8 Hz, 1H).

Table 7. Time course of the reaction of 102 with (COCl)2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>42 (%)</th>
<th>Intermediate A′ (%)</th>
<th>Intermediate B′ (%)</th>
</tr>
</thead>
<tbody>
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</tr>
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<td>32</td>
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</tr>
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<td>10</td>
<td>46</td>
</tr>
<tr>
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<td>42</td>
<td>7</td>
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<tr>
<td>90</td>
<td>88</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Chart 2. Time course of the reaction of 102 with (COCl)2

Yield/%

0 °C to rt

0 20 40 60 80 100

0 10 20 30 40 50 60 70 80 90 100

t/min

Electronic Supplementary Material (ESI) for Chemical Science
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iii. Formation of β-lactam \(42\) from acid \(102\) and Vilsmeier reagent \(61\)

![Chemical Reaction](image)

**Vilsmeier reagent preparation:** To a flame-dried 10 mL round bottom flask filled with \(N_2\) was added dry DMF (22.5 \(\mu\)L, 0.29 mmol, 2.9 equiv) and dry CD\(_2\)Cl\(_2\) (0.2 mL) via syringe. The vacuum adapter was replaced with a septum to which a \(N_2\) balloon was attached via a needle. Then \((\text{COCl})_2\) (20 \(\mu\)L, 0.23 mmol, 2.3 equiv) was added in a dropwise manner at rt with stirring to form Vilsmeier reagent which precipitated as a white solid. Stirring was continued at rt for 20 min. Then the preformed Vilsmeier reagent was cooled to 0°C prior to use. Ph\(_3\)CH was added as an internal standard.

**Lactam formation:** To an oven-dried 5 mL round bottom flask filled with \(N_2\) was added acid \(102\) (99% ee, 33.5 mg, 0.10 mmol, 1.0 equiv) and dry CD\(_2\)Cl\(_2\) (0.6 mL) at rt. The resulting solution was transferred to the preformed Vilsmeier reagent in a dropwise manner via syringe at 0 °C. The 5 mL flask was rinsed with another two portions of dry CD\(_2\)Cl\(_2\) (0.2 mL, 0.1 mL) which were also transferred to the reaction flask containing the Vilsmeier reagent. After the acid \(102\) was completely transferred to the Vilsmeier reagent over ~2 min at 0 °C, the reaction mixture was transferred to a cold dry NMR tube filled with \(N_2\) and pre-cooled to 0 °C. The \(^1\text{H}\) NMR spectrum was taken at certain intervals at 0 °C in the first 20 min. Subsequently the NMR tube was warmed to rt and the collection of NMR data continued for 25 min. The results are shown in Table 8 and Chart 3.

Compared to the phenyl substituted aziridine carboxylic acid \(10\), the cyclohexyl substituted aziridine carboxylic acid \(102\) is converted to corresponding β-lactam \(42\) at a much faster rate at 0 °C by Vilsmeier reagent. After the temperature is raised to 25 °C, β-lactam formation is complete within 14 minutes (45 min in total) (95% yield). Acid Chloride \(126\) and intermediate \(A''\) are observed to grow in but both are consumed as β-lactam formation proceeds. The following \(^1\text{H}\)
NMR absorptions were observed for acid chloride 126 and intermediates A": acid chloride 126: $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 2.22 (dd, 1H, $J = 9.3, 6.5$ Hz), 2.97 (d, 1H, $J = 7$ Hz), 3.81 (s, 1H); intermediate A": $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 5.84 (s, 1H), 5.98 (d, 1H, $J = 8$ Hz). The assignment of the major intermediate in this reaction as the acid chloride 126 was made on the basis of the close similarities of the absorptions observed for this intermediate with those of the isolated and characterized acid chlorides 14 and 53.

Table 8. Time course of the reaction of 102 with Vilsmeier reagent 61

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>42 (%)</th>
<th>Intermediate A'' (%)</th>
<th>Acid Chloride (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>38</td>
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</tr>
<tr>
<td>45</td>
<td>95</td>
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<td>0</td>
</tr>
</tbody>
</table>

Chart 3. Time course of the reaction of 102 with Vilsmeier reagent 61
The cyclohexyl substituted aziridine carboxylic acid 102 can be converted to the β-lactam 42 with both (COCl)$_2$ and Vilsmeier reagent but via different intermediates. The $^1$H NMR spectra of the reaction mixture in the early stages of each reaction are shown in Figures 1 and 2. The intermediate in the reaction with the Vilsmeier reagent is assigned as the acid chloride 126 and this intermediate does not appear to be present in the reaction mixture with oxalyl chloride.

Figure 1. $^1$H NMR spectrum of reaction between acid 102 and (COCl)$_2$ at 10 min at 0 °C

Figure 2. $^1$H NMR spectrum of the reaction between acid 102 and Vilsmeier reagent at 8 min at 0 °C
XIII. References:


