Supporting Information

2,7-Diazabicyclo[2.2.1]heptanes: Novel Asymmetric Access and Controlled Bridge-Opening

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**General Methods**

All reactions were carried out under an atmosphere of nitrogen and using dry solvents unless otherwise stated. All reagents were used as received from commercial suppliers without further purification.

Microwave reactions were carried out in a CEM Discover-S microwave reactor using 150 Watts in dynamic mode.

The progress of reactions was monitored by thin layer chromatography using Merck silica gel 60 F$_{254}$ plates, which were visualized with UV light and potassium permanganate. Flash column chromatography was carried out using Geduran 60 Å silica gel and the indicated solvent systems.

NMR data were recorded on a Bruker AVIII300, AVIII400, AVIII400neo or AVIII500neo spectrometer in deuterated chloroform (unless otherwise indicated) and spectra were calibrated using residual solvent peaks (\(^{1}H = 7.26 \text{ ppm} ; \ ^{13}C = 77.16 \text{ ppm}\)). The multiplicities of \(^{1}H\) NMR signals are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and combinations thereof.

Mass spectra were recorded on either a Waters Xevo G2-XS Tof or Synapt G2-S mass spectrometer using Zspray in ESI positive mode.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Varian 660-IR FT-IR spectrometer using Agilent Resolutions Pro for processing data. Absorption maxima (\(v_{\text{max}}\)) are reported in wavenumbers (cm$^{-1}$).

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected.

Optical rotations were measured using a Bellingham and Stanley ADP450 Series Peltier polarimeter at 20 °C using the sodium D line (589.3 nm) and the indicated concentration and solvent.

High performance liquid chromatography (HPLC) analysis was performed using an LC-20 prominence system from Shimazdu, Chromelone client, version 6.80 SR15 Build 4656, Phenomenex Lux Cellulose-1 (250 x 4.6 mm), Phenomenex Lux Cellulose-3 (250 x 4.6 mm), Phenomenex Lux Amylose-2 (250 x 4.6 mm) and Shimazdu SPD-M20A diode Array Detector for the UV detection, monitored at 220 nm or 230 nm.

Some signals in the C-H aromatic region of the \(^{13}C\) NMR spectra are not observed due to having equivalent resonances.
Preparation of Catalysts and Reagents

Catalysts 3+S2 were prepared according to literature procedure.¹

Catalyst S1 was prepared according to literature procedure.²

Catalyst S3 was commercially available and purchased from Strem Chemicals, inc.

Triketopiperazine S11 was prepared according to literature procedure.³

1,1’-(1,2-Dioxoethane-1,2-diyl)bis-1H-benzotriazole (OxBzt) was prepared according to literature procedure.⁴

Phenyl vinyl ketone (PhVK) was prepared according to literature procedure.⁵
## Optimisation Tables

### Asymmetric Michael Additions

![Chemical structures](image)

**Figure 1.** Optimisation of asymmetric Michael additions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>2a (%)</th>
<th>er</th>
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<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>r.t.</td>
<td>16 h</td>
<td>98</td>
<td>90:10</td>
</tr>
<tr>
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<td>22</td>
<td>77:23</td>
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<tr>
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<td>S3</td>
<td>r.t.</td>
<td>4 days</td>
<td>37</td>
<td>82:18</td>
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<tr>
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<td>r.t.</td>
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<td>82</td>
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<tr>
<td>5</td>
<td>3</td>
<td>3</td>
<td>16 h</td>
<td>90</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>−30</td>
<td>12 days</td>
<td>83</td>
<td>92:8</td>
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**Reductive Ring Opening**

![Diagram](image)

<table>
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<th>Entry</th>
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<tr>
<td>1</td>
<td>NaBH₄</td>
<td>1.0:3.2</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄/CeCl₃</td>
<td>1.0:2.0</td>
</tr>
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<td>NaCNBH₃</td>
<td>1.0:1.8</td>
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<td>4</td>
<td>Na(OAc)₃BH</td>
<td>2.7:1.0</td>
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<tr>
<td>5</td>
<td>DIBAL</td>
<td>4.5:1.0</td>
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<td>DIBAL (-78 °C)</td>
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<td>7</td>
<td>L-selectride</td>
<td>NR</td>
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<td>NR</td>
</tr>
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<td>9</td>
<td>H-cube, H₂ Pd/C</td>
<td>NR</td>
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<tr>
<td>10</td>
<td>NH₄CO₂H, Pd/C</td>
<td>NR</td>
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General Procedures

General procedure A for the synthesis of amino amides (S6-S8)

To a 2-necked round bottomed flask containing phenylacetic acid derivative (1 eq.) was added thionyl chloride (0.5 M) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 1 hour then allowed to cool to room temperature followed by the addition of NBS (1.5 eq.) and HBr (3 drops). The reaction mixture was then heated at 80 °C for 4 hours. Excess thionyl chloride was removed under reduced pressure and the resulting crude compound was heated with hexane (20 mL), filtered while hot and then washed with hot hexane (4 x 20 mL). The washings were concentrated under reduced pressure to give the crude α-bromo acid chloride as an oil. The acid chloride was then added dropwise to a solution of benzylamine (5 eq.) in MeCN (1 M) at 0 °C under a nitrogen atmosphere and stirred for 16 hours at room temperature. The reaction mixture was filtered, washed with MeCN and the filtrate was concentrated under reduced pressure. The reaction was purified by flash column chromatography using the indicated solvent system.

General procedure B for the synthesis of aryl triketopiperazines (1a-g)

To a microwave vial containing a suspension of 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (1.5 eq.) in THF (0.2 M) was added N-benzyl-2-(benzylamino)-2-phenylacetamide (1 eq.) in THF (0.2 M). The reaction mixture was stirred for 10 minutes then irradiated for 1 hour at 150 °C. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using the indicated solvent system.

General procedures Ci and Cii for the racemic and enantioselective Michael additions of α-aryl triketopiperazines (2a-q)

General procedure Ci for the racemic Michael additions of α-aryl triketopiperazines (2a-q)

To a solution of triketopiperazine 1a-j (1 eq.) in CH$_2$Cl$_2$ (0.1 M) was added triethylamine (1 eq.) followed by the Michael acceptor (2.5 eq.) at room temperature. The mixture was left to react until the starting material was consumed. The reaction was directly purified by flash column chromatography using the indicated solvent system.
General procedure Cii for the enantioselective Michael additions of α-aryl triketopiperazines (2a-q)

To a mixture of triketopiperazine 1a-j (1 eq.) and catalyst 3 (10 mol%) in CH₂Cl₂ (0.1 M) at -78 °C, the Michael acceptor (2.5 eq.) was added neat. The reaction mixture was allowed to warm to 3 °C and left to react. After the starting material was consumed the reaction was directly purified by flash column chromatography using the indicated solvent system.

General procedure D for the synthesis of diazabicycles (4a-m)

To a solution of triketopiperazine 2a-k, 2n and 2q (1 eq.) in THF (0.2 M) was added ethanolamine (0.2 M). The reaction mixture was heated under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure and directly purified by flash column chromatography using the indicated solvent system.
Synthesis of Amino Amides (S4-S10)

N-benzyl-2-(benzylamino)-2-phenylacetamide S4

![Chemical structure of S4]

To a microwave vial containing a solution of benzylamine (0.55 mL, 5 mmol) in MeCN (4 mL) was added α-chlorophenylacetyl chloride (0.16 mL, 1 mmol) dropwise at 0 °C. TBAI (185 mg, 0.5 mmol) dissolved in MeCN (1 mL) was added and the reaction mixture was irradiated for 1 hour in the microwave at 150 °C. The reaction mixture was filtered, washed with MeCN (5 mL) and the filtrate concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (2:1)) to afford S4 (307 mg, 93%) as an orange oil.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 3302, 3061, 3028, 2845, 1657, 1515, 1453, 1028, 730, 694; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52 – 7.19 (m, 16H), 4.46 (d, \(J = 5.9\) Hz, 2H), 4.30 (s, 1H), 3.77 (s, 2H), 2.05 (br s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.0, 139.3, 139.2, 138.5, 129.0, 128.8, 128.7, 128.3, 127.8, 127.6, 127.5, 127.5, 67.1, 52.7, 43.4; \(m/z\) (ES HRMS) C\(_{22}\)H\(_{23}\)N\(_2\)O requires 331.1810, found [MH]\(^+\) 331.1813.

N-benzyl-2-(benzlamino)-2-(4-methoxyphenyl)acetamide S5

![Chemical structure of S5]

To a 2-necked round bottomed flask containing 4-methoxyphenylacetic acid (1.81 g, 10 mmol), NBS (1.87 g, 10.5 mmol) and AIBN (330 mg, 2 mmol) was added CCl\(_4\) (15 mL). The reaction mixture was heated under reflux for 16 hours then allowed to cool to room temperature, filtered, washed with CCl\(_4\) and concentrated under reduced pressure. To the resulting oil was added thionyl chloride (15 mL) and the reaction mixture was heated under reflux for 1 hour. The solvent was removed under reduced pressure to give crude 2-bromo-2-(4-methoxyphenyl)acetyl chloride as an orange oil. The crude product was diluted with MeCN (5 mL) and added dropwise to a solution of benzylamine (5.4 mL, 50 mmol) in MeCN...
(50 mL) at 0 °C and stirred for 16 hours at room temperature. The reaction mixture was filtered, washed with MeCN (10 mL) and the filtrate was concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford S5 (1.79 g, 50%) as an orange oil.

\textbf{IR} \ \nu_{\text{max}}/\text{cm}^{-1} \ 3289, 3030, 2931, 2838, 1511, 1453, 1251, 1177, 1026, 751, 694; \ \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \ \delta \ 7.42 (br s, 1H), 7.35 – 7.18 (m, 12H), 6.87 (d, J = 8.4 Hz, 2H), 4.46 (d, J = 5.9 Hz, 2H), 4.25 (s, 1H), 3.80 (s, 3H), 3.75 (d, J = 3.5 Hz, 2H) 1.80 (br s, 1H); \ \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \ \delta \ 172.4, 159.6, 139.4, 138.5, 131.5, 128.8, 128.7, 128.6, 128.3, 127.8, 127.6, 127.5, 114.4, 66.5, 55.5, 52.6, 43.4; \ \\textit{m/z} (ESI HRMS) C\textsubscript{23}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}Na requires 383.1735, found [MNa]\textsuperscript{+} 383.1732.

\textit{N-benzyl-2-(benzylamino)-2-(4-nitrophenyl)acetamide S6}

\[
\text{O} \hspace{1cm} \text{N} \\
\text{NO}_2 \\
\text{HO} \hspace{1cm} \text{BnNH} \\
\text{NHBn} \\
\text{S6}
\]

Following procedure A using 4-nitrophenylacetic acid (1.81 g, 10 mmol), NBS (2.67 g, 15 mmol), HBr (3 drops) and benzylamine (5.4 mL, 50 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (2:1)) to afford S6 (1.85 g, 68%) as an orange oil.

\textbf{IR} \ \nu_{\text{max}}/\text{cm}^{-1} \ 3347, 3258, 3033, 2933, 2846, 1668, 1519, 1452, 1343, 750, 734, 689; \ \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \ \delta \ 8.23 – 8.16 (m, 2H), 7.57 – 7.53 (m, 2H), 7.40 (br s, 1H), 7.37 – 7.19 (m, 10H), 4.45 (d, J = 5.9 Hz, 2H), 4.40 (s, 1H), 3.77 (s, 2H), 2.06 (br s, 1H); \ \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \ \delta \ 170.6, 147.8, 146.3, 138.6, 138.0, 128.9, 128.8, 128.4, 128.3, 127.8, 127.8, 124.1, 66.3, 52.4, 43.5; \ \\textit{m/z} (ESI HRMS) C\textsubscript{22}H\textsubscript{22}N\textsubscript{3}O\textsubscript{3} requires 376.1661, found [MH]\textsuperscript{+} 376.1665.

\textit{N-benzyl-2-(benzylamino)-2-(4-bromophenyl)acetamide S7}

\[
\text{O} \hspace{1cm} \text{Br} \\
\text{N} \\
\text{Br} \\
\text{HN} \\
\text{NHBn} \\
\text{S7}
\]

1) SOCl\textsubscript{2}, reflux, 1 h then NBS, HBr, reflux, 4 h

2) BnNH\textsubscript{2}, MeCN 0 °C - r.t., 16 h
Following general procedure A using 4-bromophenylacetic acid (860 mg, 4 mmol), NBS (1 g, 6 mmol), HBr (3 drops) and benzylamine (2.2 mL, 20 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford S7 (708 mg, 45%) as an orange oil.

IR ν<sub>max</sub>/cm<sup>-1</sup> 3299, 3062, 3028, 2924, 2848, 1652, 1517, 1486, 1453, 1071, 1010, 907, 727, 696; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 – 7.46 (m, 3H), 7.38 – 7.22 (m, 12H), 4.46 (d, J = 6.0 Hz, 2H), 4.27 (s, 1H), 3.77 (s, 2H), 2.06 (br s, 1H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.5, 139.0, 138.3, 132.0, 128.8, 128.7, 128.3, 127.9, 127.5, 127.4, 127.3, 127.2, 127.1, 126.5, 52.4, 43.3; m/z (ES HRMS) C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>OBr requires 409.0916, found [MH]<sup>+</sup> 409.0924.

N-benzyl-2-(benzylamino)-2-(2-bromophenyl)acetamide S8

Following general procedure A using 2-bromophenylacetic acid (430 mg, 2 mmol), NBS (530 mg, 3 mmol), HBr (3 drops) and benzylamine (1.1 mL, 10 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford S8 (474 mg, 58%) as an orange oil.

IR ν<sub>max</sub>/cm<sup>-1</sup> 3315, 3061, 3027, 2922, 2844, 1658, 1514, 1453, 1080, 1025, 748, 697; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 – 7.49 (m, 2H), 7.38 – 7.22 (m, 12H), 4.69 (s, 1H), 4.51 (dd, J = 6.0, 2.1 Hz, 2H), 3.85 (d, J = 12.7 Hz, 1H), 3.71 (d, J = 12.7 Hz, 1H), 2.27 (br s, 1H);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.1, 139.1, 138.5, 138.2, 133.4, 129.8, 129.6, 128.6, 128.3, 127.9, 127.8, 127.5, 124.3, 65.8, 52.6, 43.4; m/z (ES HRMS) C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>OBr requires 409.0916, found [MH]<sup>+</sup> 409.0911.

N-benzyl-2-(benzylamino)-2-(furan-2-yl)acetamide S9

To a solution of glyoxylic acid monohydrate (460 mg, 5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (33 mL) was added benzylamine (0.55 mL, 5 mmol) and 2-furylboronic acid (560 mg, 5 mmol). The flask was
purged with argon and stirred at room temperature for 4 hours. The resulting precipitate was filtered, dried under reduced pressure and used without further purification. To a round bottomed flask containing the crude amino acid was added CH₂Cl₂ (25 mL) and the reaction mixture was cooled to 0 °C, followed by the addition of PyBOP (2.8 g, 5.5 mmol), triethylamine (1.1 mL, 7.5 mmol) and benzylamine (1.4 mL, 12.5 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford S9 (1.24 g, 78%) as an orange oil.

IR νmax/cm⁻¹ 3304, 3061, 3028, 2949, 2849, 1657, 1520, 1453, 1147, 1073, 1010, 734, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (br s, 1H), 7.38 (dd, J = 1.9, 0.9 Hz, 1H), 7.36 – 7.23 (m, 10H), 6.38 – 6.29 (m, 2H), 4.50 (d, J = 5.9 Hz, 2H), 4.40 (s, 1H), 3.82 (d, J = 13.1 Hz, 1H), 3.74 (d, J = 13.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 151.6, 142.6, 139.0, 138.3, 128.8, 128.7, 128.4, 127.8, 127.6, 127.6, 110.7, 108.5, 60.4, 52.4, 43.5; m/z (ES HRMS) C₂₀H₂₁N₂O₂ requires 321.1603, found [MH]+ 321.1604.

N-benzyl-2-(benzylamino)-2-(thiophen-2-yl)acetamide S10

To a solution of glyoxylic acid monohydrate (368 mg, 4 mmol) in CH₂Cl₂ (26 mL) was added benzylamine (0.44 mL, 4 mmol) and 2-thiopheneboronic acid (512 mg, 4 mmol). The flask was purged with argon and stirred at room temperature for 72 hours. The resulting precipitate was filtered, dried under reduced pressure and used without further purification. To a round bottomed flask containing the crude amino acid was added CH₂Cl₂ (20 mL) and the reaction mixture was cooled to 0 °C, followed by the addition of PyBOP (2.3 g, 4.4 mmol), triethylamine (0.84 mL, 6 mmol) and benzylamine (1.1 mL, 10 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford S10 (749 mg, 56%) as an orange oil.

IR νmax/cm⁻¹ 3318, 3061, 2922, 2851, 1654, 1517, 1452, 1359, 1234, 1078, 1028, 847, 731, 694; ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.16 (m, 12H), 7.01 (d, J = 3.4 Hz, 1H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 4.54 (s, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.77 (d, J = 13.2 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 2.27 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 142.2, 139.0, 138.2, 128.7, 128.6,
Synthesis of α-Aryl Triketopiperazines (1a-j)

1,4-dibenzyl-6-phenylpiperazine-2,3,5-trione 1a

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (394 mg, 1.35 mmol) in THF (2 mL), N-benzyl-2-(benzylamino)-2-phenylacetamide S4 (307 mg, 0.9 mmol) in THF (3 mL). The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$) to afford 1a (247.9 mg, 72%) as a white solid.

m.p. 159 – 161 °C; IR $\nu_{\text{max}}$/cm$^{-1}$ 3034, 1748, 1673, 1437, 1253, 1188, 720, 698; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 – 7.18 (m, 15H), 5.57 (d, $J = 14.5$ Hz, 1H), 5.15 (s, 1H), 5.07 (d, $J = 13.7$ Hz, 1H), 4.89 (d, $J = 13.7$ Hz, 1H), 3.63 (d, $J = 14.4$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.8, 156.4, 153.0, 135.0, 134.1, 134.0, 130.0, 129.8, 129.3, 129.2, 128.9, 128.7, 128.2, 127.0, 63.8, 48.0, 44.7; m/z (ESI HRMS) C$_{24}$H$_{20}$N$_2$O$_3$Na requires 407.1372, found [MNa]$^+$. 407.1370.

1,4-dibenzyl-6-(4-methoxyphenyl)piperazine-2,3,5-trione 1b

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (438 mg, 1.5 mmol) in THF (2 mL), N-benzyl-2-(benzylamino)-2-(4-methoxyphenyl)acetamide S5 (360 mg, 1.0 mmol) in THF (3 mL). The residue was purified by column chromatography on silica gel (gradient: CH$_2$Cl$_2$:acetone = (1:0) to (95:5)) to afford 1b (117.8 mg, 28%) as a white solid.
m.p. 184 – 186 °C; IR ν<sub>max</sub>/cm<sup>-1</sup> 2966, 2842, 2358, 1749, 1515, 1352, 1251, 1176, 1022, 831, 728, 695; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.30 (m, 2H), 7.31 – 7.14 (m, 8H), 7.14 – 7.09 (m, 2H), 6.93 – 6.88 (m, 2H), 5.52 (d, <i>J</i> = 14.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.85 (d, <i>J</i> = 13.7 Hz, 1H), 3.82 (s, 3H), 3.59 (d, <i>J</i> = 14.4 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.1, 160.9, 156.5, 153.0, 135.1, 134.1, 129.3, 128.8, 128.7, 128.3, 128.2, 125.8, 115.2, 63.2, 55.6, 47.8, 44.7; m/z (ESI HRMS) C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Na requires 437.1477, found [MNa]<sup>+</sup> 437.1482.

**1,4-dibenzyl-6-(4-nitrophenyl)piperazine-2,3,5-trione 1c**

![Chemical structure of 1c](image)

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzo[1H]triazole (438 mg, 1.5 mmol) in THF (2 mL), N-benzyl-2-(benzylamino)-2-(4-nitrophenyl)acetamide S6 (375 mg, 1.0 mmol) in THF (3 mL). The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) to afford 1c (163 mg, 38%) as a white solid.

m.p. 167 – 169 °C; IR ν<sub>max</sub>/cm<sup>-1</sup> 3089, 3030, 1754, 1684, 1518, 1346, 1254, 976, 727, 702; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.27 – 8.20 (m, 2H), 7.43 – 7.10 (m, 12H), 5.51 (d, <i>J</i> = 14.5 Hz, 1H), 5.23 (s, 1H), 5.02 (d, <i>J</i> = 13.6 Hz, 1H), 4.87 (d, <i>J</i> = 13.6 Hz, 1H), 3.66 (d, <i>J</i> = 14.5 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.6, 155.8, 152.8, 148.9, 140.9, 134.7, 133.3, 129.5, 129.3, 129.2, 128.8, 128.5, 128.2, 124.9, 63.3, 48.6, 45.0; m/z (ESI HRMS) C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>Na requires 452.1222, found [MNa]<sup>+</sup> 452.1219.

**1,4-dibenzyl-6-(4-bromophenyl)piperazine-2,3,5-trione 1d**

![Chemical structure of 1d](image)

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzo[1H]triazole (86 mg, 0.30 mmol) in THF (1 mL), N-benzyl-2-(benzylamino)-2-(4-bromophenyl)acetamide S7 (100 mg, 0.25 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) to afford 1d (23 mg, 21%) as an off white solid.
m.p. 159 – 162 °C; IR ν\textsubscript{max}/cm\textsuperscript{-1} 3028, 2918, 1744, 1491, 1434, 1365, 1251, 1188, 1072, 1010, 823, 741, 695; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.56 – 7.50 (m, 2H), 7.37 – 7.31 (m, 3H), 7.28 – 7.20 (m, 5H), 7.19 – 7.12 (m, 2H), 7.10 – 7.05 (m, 2H), 5.51 (d, J = 14.5 Hz, 1H), 5.07 (s, 1H), 5.02 (d, J = 13.7 Hz, 1H), 4.85 (d, J = 13.7 Hz, 1H), 3.60 (d, J = 14.5 Hz, 1H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 166.3, 156.2, 152.9, 134.9, 133.7, 133.1, 133.0, 129.3, 129.2, 129.0, 128.7, 128.6, 128.4, 124.3, 63.3, 48.1, 44.8; m/z (ES HRMS) C\textsubscript{24}H\textsubscript{19}N\textsubscript{2}O\textsubscript{3}BrNa requires 485.0477, found [MNa]\textsuperscript{+} 485.0476.

1,4-dibenzyl-6-(furan-2-yl)piperazine-2,3,5-trione 1e

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (225 mg, 0.77 mmol) in THF (2 mL), N-benzyl-2-(benzylamino)-2-(furan-2-yl)acetamide S9 (204 mg, 0.64 mmol) in THF (2 mL). The residue was purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}) to afford 1e (94.2 mg, 40%) as an off white solid.

m.p. 144 – 146 °C; IR ν\textsubscript{max}/cm\textsuperscript{-1} 3062, 3033, 2925, 1748, 1688, 1496, 1430, 1361, 1255, 1208, 1013, 730, 699; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.30 – 7.11 (m, 11H), 6.34 (dd, J = 3.4, 0.8 Hz, 1H), 6.30 (dd, J = 3.3, 1.8 Hz, 1H), 5.33 (d, J = 14.6 Hz, 1H), 5.10 (s, 1H), 4.99 (d, J = 13.9 Hz, 1H), 4.87 (d, J = 13.9 Hz, 1H), 3.72 (d, J = 14.6 Hz, 1H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 164.7, 156.4, 153.0, 145.8, 144.3, 135.0, 133.9, 129.2, 129.1, 129.1, 128.8, 128.7, 128.2, 111.6, 111.2, 57.8, 48.0, 44.9; m/z (ES HRMS) C\textsubscript{22}H\textsubscript{18}N\textsubscript{2}O\textsubscript{4}Na requires 397.1164, found [MNa]\textsuperscript{+} 397.1166.

1,4-dibenzyl-6-(thiophen-2-yl)piperazine-2,3,5-trione 1f

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (105 mg, 0.36 mmol) in THF (1 mL), N-benzyl-2-(benzylamino)-2-(thiophen-2-yl)acetamide S10 (100 mg, 0.30 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}) to afford 1f (40 mg, 34%) as an off white solid.
m.p. 135 – 137 °C; IR ν<sub>max</sub>/cm<sup>-1</sup> 3033, 2923, 2853, 1747, 1688, 1495, 1431, 1361, 1253, 1207, 1087, 971, 729, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.23 (m, 11H), 7.06 – 7.02 (m, 2H), 5.56 (d, J = 14.6 Hz, 1H), 5.37 (s, 1H), 5.05 (d, J = 13.7 Hz, 1H), 4.91 (d, J = 13.7 Hz, 1H), 3.81 (d, J = 14.6 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.9, 156.1, 152.5, 136.9, 134.9, 133.9, 129.3, 129.2, 128.9, 128.7, 128.3, 127.9, 127.6, 59.4, 48.0, 44.9; m/z (ES HRMS) C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>SNa requires 413.0936, found [MNa]<sup>+</sup> 413.0926.

1,4-dibenzyl-6-(2-bromophenyl)piperazine-2,3,5-trione 1g

Following general procedure B using 1,1'-((1,2-dioxaethane-1,2-diyl)bis-1H-benzotriazole (85 mg, 0.30 mmol) in THF (1 mL), N-benzyl-2-(benzylamino)-2-(2-bromophenyl)acetamide S8 (100 mg, 0.25 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) to afford 1g (43 mg, 38%) as an off white solid.

m.p. 153 – 155 °C; IR ν<sub>max</sub>/cm<sup>-1</sup> 3062, 3032, 2932, 1744, 1682, 1494, 1429, 1363, 1257, 1190, 1027, 908, 728, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 (dd, J = 7.7, 1.6 Hz, 1H), 7.40 – 7.23 (m, 10H), 7.21 – 7.15 (m, 2H), 7.07 (dd, J = 7.4, 1.9 Hz, 1H), 5.64 (br s, 1H), 5.36 (d, J = 14.6 Hz, 1H), 5.07 (d, J = 13.6 Hz, 1H), 4.93 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 14.5 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.9, 156.3, 153.1, 134.9, 134.6, 134.0, 133.5, 131.4, 129.7, 129.3, 129.1, 128.7, 128.4, 128.3, 124.0, 63.8, 48.2, 44.8; m/z (ES HRMS) C<sub>24</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>BrNa requires 485.0477, found [MNa]<sup>+</sup> 485.0474.

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)piperazine-2,3,5-trione 1h and 1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)piperazine-2,3,5-trione 1i

To a round bottomed flask containing triketopiperazine S11 (100 mg, 0.32 mmol), NBS (87 mg, 0.49 mmol) and AIBN (11 mg, 65 µmol, 20 mol%) was added diethylcarbonate (1.6 mL)
and the reaction mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, filtered, washed with diethylcarbonate (3 x 2 mL) and the filtrate concentrated under reduced pressure. The crude α-bromo triketopiperazine was then used without further purification. To the crude residue was added diethylcarbonate (2 mL) and N-methyl pyrrole (58 µL, 0.65 mmol) and the reaction mixture was stirred for 7 days at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 1h (66.6 mg, 52%) as a colourless waxy solid and 1i (10.4 mg, 8%) as a colourless waxy solid.

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)piperazine-2,3,5-trione 1h

IR ν<sub>max</sub>/cm<sup>-1</sup> 3062, 3032, 2944, 1745, 1684, 1493, 1427, 1359, 1301, 1251, 1207, 1089, 908, 723, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.22 (m, 8H), 7.15 – 7.08 (m, 2H), 6.62 (dd, J = 2.7, 1.8 Hz, 1H), 6.13 (dd, J = 3.8, 2.7 Hz, 1H), 6.06 (dd, J = 3.9, 1.7 Hz, 1H), 5.47 (d, J = 14.4 Hz, 1H), 5.12 (s, 1H), 5.03 (d, J = 13.8 Hz, 1H), 4.86 (d, J = 13.9 Hz, 1H), 3.84 (d, J = 14.4 Hz, 1H), 3.39 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.3, 156.2, 153.1, 135.1, 133.8, 129.4, 129.2, 129.1, 128.8, 128.7, 128.2, 125.3, 124.1, 109.0, 108.3, 56.5, 48.1, 44.6, 34.2; m/z (ES HRMS) C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>Na requires 410.1481, found [MNa]<sup>+</sup> 410.1489.

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)piperazine-2,3,5-trione 1i

IR ν<sub>max</sub>/cm<sup>-1</sup> 3062, 3031, 2942, 1745, 1683, 1495, 1429, 1357, 1253, 1207, 1155, 1088, 1029, 909, 726, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.29 (m, 5H), 7.28 – 7.21 (m, 5H), 6.55 (t, J = 2.5 Hz, 1H), 6.52 (t, J = 2.1 Hz, 1H), 5.92 (dd, J = 2.8, 1.9 Hz, 1H), 5.48 (d, J = 14.5 Hz, 1H), 5.06 – 5.01 (m, 2H), 4.87 (d, J = 13.8 Hz, 1H), 3.81 (d, J = 14.5 Hz, 1H), 3.60 (s, 3H);<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.8, 156.9, 153.1, 135.3, 134.6, 129.5, 129.3, 129.2, 128.7, 128.6, 128.1, 123.5, 120.7, 117.5, 106.6, 56.2, 47.6, 44.6, 36.6; m/z (ES HRMS) C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>Na requires 410.1481, found [MNa]<sup>+</sup> 410.1484.

1,4-dibenzyl-6-(1H-indol-3-yl)piperazine-2,3,5-trione 1j

To a round bottomed flask containing triketopiperazine S11 (308 mg, 1.0 mmol), NBS (267 mg, 1.5 mmol) and AIBN (30 mg, 0.20 mmol, 20 mol%) was added diethylcarbonate (5 mL) and the reaction mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, filtered, washed with diethylcarbonate (3 x 3 mL) and
the filtrate concentrated under reduced pressure. The crude α-bromo triketopiperazine was then used without further purification. To the crude residue was added DMF (5 mL) and indole (177 mg, 1.5 mmol) and the reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with EtOAc (5 mL), washed with water (5 × 10 mL) and brine (10 mL) and the organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (1:1)) to afford 1j (329 mg, 78%) as a white solid.

**m.p.** 178 – 180 °C; **IR** \( \nu_{\text{max}}/\text{cm}^{-1} \) 3270, 3059, 1747, 1691, 1661, 1548, 1494, 1425, 1360, 1272, 1201, 1147, 1100, 1077, 970, 735, 695; \(^1\text{H NMR} \) (400 MHz, CDCl₃) \( \delta \) 8.56 (s, 1H), 7.46 – 7.37 (m, 2H), 7.36 – 7.08 (m, 13H), 5.54 (d, \( J = 14.5 \text{ Hz} \), 1H), 5.45 (s, 1H), 5.08 (d, \( J = 13.7 \text{ Hz} \), 1H), 4.88 (d, \( J = 13.7 \text{ Hz} \), 1H), 3.79 (d, \( J = 14.5 \text{ Hz} \), 1H), 3.79 (d, \( J = 13.7 \text{ Hz} \), 1H); \(^13\text{C NMR} \) (101 MHz, CDCl₃) \( \delta \) 167.1, 156.8, 153.1, 136.7, 135.1, 134.5, 129.4, 129.2, 129.2, 128.7, 128.6, 128.2, 124.9, 124.0, 123.5, 121.2, 118.7, 112.0, 109.8, 57.6, 47.8, 44.8; \( m/z \) (ES HRMS) \( \text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_3\text{Na} \) requires 446.1481, found \([\text{MNa}]^+ \) 446.1480.

**Asymmetric Michael Additions (2a-q)**

1,4-dibenzyl-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione \( 2a \)

Following general procedure \( \text{Ci}i \) using triketopiperazine \( 1a \) (38 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 \( \mu \text{mol} \), 10 mol%), \( \text{CH}_2\text{Cl}_2 \) (1 mL) and methyl vinyl ketone (\( \mu \text{L}, 0.25 \text{ mmol} \)). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford \( 2a \) (44.6 mg, 98%) as a colourless oil in 8:92 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, \( \lambda \) 220 nm, t(minor) = 20.5 min, t(major) = 22.4 min].

**IR** \( \nu_{\text{max}}/\text{cm}^{-1} \) 3067, 3035, 1744, 1682, 1495, 1419, 1358, 1266, 1144, 1074, 1029, 707, 693; \(^1\text{H NMR} \) (400 MHz, CDCl₃) \( \delta \) 7.43 – 7.18 (m, 15H), 5.22 (d, \( J = 14.8 \text{ Hz} \), 1H), 5.09 (d, \( J = 13.6 \text{ Hz} \), 1H), 4.93 (d, \( J = 13.6 \text{ Hz} \), 1H), 3.64 (d, \( J = 14.8 \text{ Hz} \), 1H), 3.04 – 2.93 (m, 1H), 2.40 (ddd, \( J = 14.8, 9.2, 6.0 \text{ Hz} \), 1H), 1.84 – 1.76 (m, 2H), 1.60 (s, 3H); \(^13\text{C NMR} \) (101 MHz, CDCl₃) \( \delta \) 205.1, 169.1, 155.8, 155.1, 138.0, 136.6, 135.1, 129.7, 129.6, 129.2, 129.2, 128.9, 128.7, 128.3,
128.2, 126.3, 72.8, 48.9, 44.7, 37.1, 30.1, 29.4; \textit{m/z} (ESI HRMS) C$_{28}$H$_{26}$N$_2$O$_4$Na requires 477.1790, found [MNa]$^+$ 477.1792; [$\alpha$]$^D_{20}$ = −23.4 (c 1.0, CHCl$_3$).

1,4-dibenzy-6-(4-methoxyphenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2b

Following general procedure Cii using triketopiperazine 1b (41 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH$_2$Cl$_2$ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2b (40.0 mg, 83%) as a colourless oil in 7:93 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 13.9 min, t(major) = 16.9 min].

\textbf{IR} \nu_{\text{max}}$/cm^{-1}$ 3036, 2959, 1739, 1683, 1512, 1420, 1358, 1260, 1229, 1184, 1077, 1031, 824, 698; \textbf{\textit{1}H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.21 (m, 12H), 6.95 – 6.89 (m, 2H), 5.22 (d, \(J = 14.7\) Hz, 1H), 5.11 (d, \(J = 13.6\) Hz, 1H), 4.95 (d, \(J = 13.6\) Hz, 1H), 3.84 (s, 3H), 3.70 (d, \(J = 14.8\) Hz, 1H), 3.02 – 2.91 (m, 1H), 2.38 (ddd, \(J = 14.8, 9.2, 6.1\) Hz, 1H), 1.84 – 1.76 (m, 2H), 1.62 (s, 3H); \textbf{\textit{13}C NMR} (101 MHz, CDCl$_3$) $\delta$ 205.2, 169.4, 160.4, 155.9, 155.1, 136.8, 135.2, 129.8, 129.3, 129.2, 128.9, 128.7, 128.3, 128.2, 127.6, 115.0, 72.4, 55.6, 48.8, 44.7, 37.2, 30.2, 29.4; \textit{m/z} (ES HRMS) C$_{29}$H$_{28}$N$_2$O$_5$Na requires 507.1896, found [MNa]$^+$ 507.1898; [$\alpha$]$^D_{20}$ = −18.5 (c 1.0, CHCl$_3$).

1,4-dibenzy-6-(4-nitrophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2c

S17
Following general procedure Cii using triketopiperazine 1c (43 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2c (34.6 mg, 70%) as a colourless oil in 5:95 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 45:55, 1.0 ml/min, λ 220 nm, t(minor) = 23.2 min, t(major) = 27.1 min].

**IR** ν max/cm⁻¹ 3080, 3033, 2939, 1751, 1680, 1517, 1417, 1345, 1229, 1109, 1079, 1030, 854, 730, 703; ¹H NMR (400 MHz, CDCl₃) δ 8.29 – 8.23 (m, 2H), 7.63 – 7.57 (m, 2H), 7.40 – 7.22 (m, 10H), 5.20 – 5.11 (m, 2H), 5.02 (d, J = 13.6 Hz, 1H), 3.86 (d, J = 14.8 Hz, 1H), 3.03 (ddd, J = 14.4, 10.7, 5.8 Hz, 1H), 2.56 (ddd, J = 14.7, 10.8, 4.3 Hz, 1H), 1.99 – 1.82 (m, 2H), 1.73 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 204.7, 168.2, 155.4, 154.7, 148.4, 144.6, 136.1, 134.8, 129.4, 129.1, 129.0, 128.8, 128.6, 128.4, 127.9, 124.5, 49.0, 45.0, 36.9, 30.5, 29.5; m/z (ES HRMS) C₂₈H₂₅N₃O₆Na requires 522.1641, found [MNa]⁺ 522.1638; [α]₂⁰D = −7.5 (c 1.0, CHCl₃).

1,4-dibenzyl-6-(4-bromophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2d

Following general procedure Cii using triketopiperazine 1d (46 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2d (46.7 mg, 88%) as a colourless oil in 9:91 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 21.6 min, t(major) = 24.3 min].

**IR** ν max/cm⁻¹ 3063, 3032, 1743, 1716, 1680, 1491, 1360, 1228, 1077, 908, 727, 701; ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.49 (m, 2H), 7.30 – 7.16 (m, 12H), 5.16 (d, J = 14.7 Hz, 1H), 5.08 (d, J = 13.6 Hz, 1H), 4.93 (d, J = 13.5 Hz, 1H), 3.69 (d, J = 14.8 Hz, 1H), 2.91 (ddd, J = 14.4, 10.0, 6.8 Hz, 1H), 2.38 (ddd, J = 14.8, 9.8, 5.4 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.61 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 204.9, 168.8, 155.6, 155.0, 137.1, 136.4, 135.0, 132.8, 129.3, 129.2, 128.9, 128.8, 128.5, 128.3, 128.1, 124.1, 72.4, 48.9, 44.9, 37.0, 30.2, 29.4; m/z (ES HRMS) C₂₉H₂₅N₂O₄NaBr requires 555.0895, found [MNa]⁺ 555.0900; [α]₂⁰D = −4.7 (c 1.0, CHCl₃).
1,4-dibenzyl-6-(furan-2-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2e

Following general procedure Cii using triketopiperazine 1e (37 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2e (44 mg, 99%) as a colourless oil in 94:6 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 35:65, 1.0 ml/min, λ 220 nm, t(major) = 24.4 min, t(minor) = 27.8 min].

IR νmax/cm⁻¹ 3036, 2935, 1746, 1684, 1459, 1365, 1342, 1231, 1147, 1015, 908, 731, 700; ¹H NMR (400 MHz, CDCl3) δ 7.37 – 7.17 (m, 11H), 6.57 (dd, J = 3.4, 0.8 Hz, 1H), 6.36 (dd, J = 3.4, 1.9 Hz, 1H), 5.12 (d, J = 13.7 Hz, 1H), 5.05 – 4.97 (m, 2H), 3.92 (d, J = 14.9 Hz, 1H), 2.74 (ddd, J = 14.7, 10.4, 6.5 Hz, 1H), 2.44 (ddd, J = 14.9, 10.0, 5.1 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.67 (s, 3H); ¹³C NMR (101 MHz, CDCl3) δ 205.0, 167.1, 155.8, 154.9, 149.8, 143.7, 136.3, 135.1, 129.2, 128.8, 128.8, 128.7, 128.3, 128.0, 111.1, 110.7, 68.5, 47.7, 44.9, 36.6, 29.5, 28.6; m/z (ES HRMS) C₂₆H₂₄N₂O₅Na requires 467.1583, found [MNa]⁺ 467.1590; [α]D²⁰ = −12.1 (c 1.0, CHCl₃).

1,4-dibenzyl-6-(3-oxobutyl)-6-(thiophen-2-yl)piperazine-2,3,5-trione 2f

Following general procedure Cii using triketopiperazine 1f (39 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2f (42.7 mg, 93%) as a colourless oil in 6:94 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 21.4 min, t(major) = 23.4 min].
IR $\nu_{max}/cm^{-1}$ 2924, 1742, 1687, 1495, 1416, 1363, 1227, 1079, 1028, 701; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (dd, $J = 5.1$, 1.2 Hz, 1H), 7.34 – 7.21 (m, 10H), 7.06 (dd, $J = 3.7$, 1.3 Hz, 1H), 7.01 (dd, $J = 5.1$, 3.7 Hz, 1H), 5.37 (d, $J = 14.8$ Hz, 1H), 5.08 (d, $J = 13.7$ Hz, 1H), 4.95 (d, $J = 13.7$ Hz, 1H), 3.84 (d, $J = 14.9$ Hz, 1H), 2.96 (ddd, $J = 14.6$, 11.6, 5.3 Hz, 1H), 2.48 (ddd, $J = 14.8$, 11.5, 3.5 Hz, 1H), 1.83 (ddd, $J = 17.1$, 11.5, 5.3 Hz, 1H), 1.72 (ddd, $J = 17.8$, 11.6, 3.5 Hz, 1H), 1.58 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 204.9, 167.9, 155.4, 154.8, 142.8, 136.7, 135.0, 129.1, 129.1, 129.0, 128.7, 128.3, 128.3, 127.8, 127.6, 126.9, 70.8, 48.8, 44.9, 37.3, 31.6, 29.3; $m/z$ (ES HRMS) C$_{26}$H$_{24}$N$_2$O$_4$NaS requires 483.1354, found [MNa]$^+$ 483.1353; $\left[\alpha\right]_{D}^{20} = -33.5$ (c 1.0, CHCl$_3$).

1,4-dibenzyl-6-(2-bromophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2g

Following general procedure Cii using triketopiperazine 1g (46 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH$_2$Cl$_2$ (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2g (47.1 mg, 88%) as a colourless oil in 45:55 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 19.4 min, t(major) = 23.5 min].

IR $\nu_{max}/cm^{-1}$ 3064, 3033, 1741, 1717, 1680, 1494, 1419, 1361, 1262, 1227, 1075, 1027, 908, 727, 700; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.32 – 7.23 (m, 4H), 7.18 – 7.04 (m, 2H), 5.18 (d, $J = 13.3$ Hz, 1H), 5.03 (d, $J = 13.3$ Hz, 1H), 4.69 (d, $J = 14.7$ Hz, 1H), 3.96 (d, $J = 14.7$ Hz, 1H), 2.55 (ddd, $J = 14.0$, 11.4, 4.2 Hz, 1H), 2.44 (ddd, $J = 14.1$, 11.0, 5.2 Hz, 1H), 1.90 (ddd, $J = 17.6$, 11.0, 4.2 Hz, 1H), 1.73 – 1.60 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 204.6, 169.3, 156.5, 155.0, 136.2, 135.9, 135.3, 134.9, 131.2, 130.4, 129.8, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 124.5, 117.6, 47.7, 44.6, 36.4, 33.0, 29.7; $m/z$ (ES HRMS) C$_{26}$H$_{25}$N$_2$O$_4$BrNa requires 555.0895, found [MNa]$^+$ 555.0898; $\left[\alpha\right]_{D}^{20} = 1.9$ (c 1.0, CHCl$_3$).
1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2h

Following general procedure Cii using triketopiperazine \(1h\) (39 mg, 0.10 mmol), chiral catalyst \(3\) (4 mg, 10 µmol, 10 mol%), \(\text{CH}_2\text{Cl}_2\) (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford \(2h\) (45.0 mg, 99%) as a colourless oil in 49:51 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 40:60, 1.0 ml/min, \(\lambda\) 220 nm, t(minor) = 15.9 min, t(major) = 18.3 min].

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\text{IR} \nu_{\text{max}}/\text{cm}^{-1} 3063, 3033, 2947, 1742, 1717, 1681, 1491, 1416, 1358, 1306, 1261, 1074, 908, 724, 699; \quad ^1\text{H NMR} (400 MHz, CDCl_3) \delta 7.48 – 7.41 (m, 2H), 7.30 – 7.23 (m, 3H), 7.19 – 7.09 (m, 3H), 6.91 – 6.86 (m, 2H), 6.46 (dd, \(J = 3.8, 1.8\) Hz, 1H), 6.39 (dd, \(J = 2.8, 1.8\) Hz, 1H), 6.14 (dd, \(J = 3.8, 2.8\) Hz, 1H), 6.10 (d, \(J = 13.3\) Hz, 1H), 5.05 (d, \(J = 13.3\) Hz, 1H), 4.55 (d, \(J = 13.9\) Hz, 1H), 4.32 (d, \(J = 13.9\) Hz, 1H), 2.70 – 2.60 (m, 4H), 2.52 (ddd, \(J = 14.5, 9.9, 5.6\) Hz, 1H), 2.15 – 1.93 (m, 2H), 1.86 (s, 3H); \quad ^13\text{C NMR} (101 MHz, CDCl_3) \delta 204.9, 168.8, 156.1, 154.2, 135.8, 135.0, 130.1, 129.7, 128.7, 128.6, 128.3, 128.0, 126.9, 125.4, 112.2, 107.4, 67.6, 47.5, 44.9, 37.0, 34.0, 33.2, 29.9; \quad m/z \quad (\text{ES HRMS}) \quad \text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_4\text{Na} \quad \text{requires} \quad 480.1899, \quad \text{found \text{[MNa]}^+} \quad 480.1904; \quad [\alpha]_D^{20} = 5.7 \quad (c \quad 1.0, \text{CHCl}_3).
\]

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2i

Following general procedure Cii using triketopiperazine \(1i\) (34 mg, 90 µmol), chiral catalyst \(3\) (3.5 mg, 9 µmol 10 mol%), \(\text{CH}_2\text{Cl}_2\) (1 mL) and methyl vinyl ketone (18 µL, 0.21 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford \(2i\) (25.1 mg, 63%) as a colourless oil in 77:23 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 35:65, 1.0 ml/min, \(\lambda\) 220 nm, t(major) = 19.5 min, t(minor) = 21.1 min].
IR $\nu_{\text{max}}$/cm$^{-1}$ 3062, 3031, 1741, 1682, 1495, 1419, 1362, 1227, 1166, 1080, 911, 729, 701; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 – 7.20 (m, 10H), 6.59 (t, $J$ = 2.1 Hz, 1H), 6.55 (t, $J$ = 2.5 Hz, 1H), 5.90 (dd, $J$ = 2.9, 1.9 Hz, 1H), 5.29 (d, $J$ = 14.9 Hz, 1H), 5.08 (d, $J$ = 13.7 Hz, 1H), 4.95 (d, $J$ = 13.7 Hz, 1H), 3.91 (d, $J$ = 14.8 Hz, 1H), 3.61 (s, 3H), 2.81 (ddd, $J$ = 14.8, 11.8, 5.3 Hz, 1H), 2.30 (ddd, $J$ = 14.9, 11.6, 3.4 Hz, 1H), 1.82 (ddd, $J$ = 17.1, 11.7, 5.3 Hz, 1H), 1.70 (ddd, $J$ = 17.9, 11.8, 3.4 Hz, 1H), 1.57 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 205.7, 169.7, 156.1, 155.3, 137.4, 135.4, 129.2, 129.1, 128.8, 128.6, 128.1, 128.0, 123.3, 122.9, 120.4, 106.5, 69.5, 48.3, 44.7, 37.4, 36.7, 30.4, 29.4; m/z (ES HRMS) C$_{27}$H$_{28}$N$_3$O$_4$ requires 458.2080, found [MH]$^+$ 458.2082; $[\alpha]_D^{20} = -21.2$ (c 1.0, CHCl$_3$).

1,4-dibenzyl-6-(1H-indol-3-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione 2j

Following general procedure Cii using triketopiperazine 1j (12 mg, 30 µmol), chiral catalyst 3 (1 mg, 3 µmol, 10 mol%), CH$_2$Cl$_2$ (1 mL) and methyl vinyl ketone (6 µL, 80 µmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2j (12.5 mg, 91%) as a colourless oil in 27:73 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 60:40, 1.0 ml/min, λ 220 nm, t(minor) = 5.8 min, t(major) = 9.9 min].

IR $\nu_{\text{max}}$/cm$^{-1}$ 3343, 1739, 1715, 1676, 1496, 1416, 1362, 1225, 1166, 1017, 980, 909, 728, 699; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.84 – 8.76 (m, 1H), 7.43 – 7.34 (m, 4H), 7.25 – 7.13 (m, 9H), 7.07 (d, $J$ = 7.9 Hz, 1H), 7.01 – 6.96 (m, 1H), 5.23 – 5.14 (m, 2H), 5.00 (d, $J$ = 13.5 Hz, 1H), 3.94 (d, $J$ = 14.7 Hz, 1H), 2.83 (ddd, $J$ = 14.4, 11.5, 5.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 1.90 (ddd, $J$ = 17.6, 11.5, 3.7 Hz, 1H), 1.77 (ddd, $J$ = 17.3, 11.7, 5.2 Hz, 1H), 1.66 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 205.3, 169.6, 156.4, 154.8, 136.9, 136.8, 135.2, 129.6, 129.1, 128.7, 128.4, 128.0, 124.8, 124.1, 123.3, 121.2, 118.4, 114.1, 112.2, 69.4, 48.0, 44.9, 36.7, 31.9, 29.6; m/z (ES HRMS) C$_{30}$H$_{27}$N$_3$O$_4$Na requires 516.1899, found [MNa]$^+$ 516.1901; $[\alpha]_D^{20} = -14.5$ (c 1.0, CHCl$_3$).
1,4-dibenzyl-6-(3-oxopentyl)-6-phenylpiperazine-2,3,5-trione 2k

Following general procedure Cii using triketopiperazine 1a (38 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2k (41.3 mg, 91%) as a colourless oil in 4:96 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 28.1 min, t(major) = 30.6 min].

IR νmax/cm⁻¹ 2938, 1743, 1680, 1495, 1416, 1362, 1261, 1222, 1144, 1077, 1030, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.17 (m, 15H), 5.21 (d, J = 14.8 Hz, 1H), 5.09 (d, J = 13.6 Hz, 1H), 4.93 (d, J = 13.6 Hz, 1H), 3.64 (d, J = 14.8 Hz, 1H), 3.06 – 2.94 (m, 1H), 2.48 – 2.37 (m, 1H), 1.93 – 1.81 (m, 1H), 1.81 – 1.65 (m, 3H), 0.76 (t, J = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 207.9, 169.2, 155.9, 155.2, 138.0, 136.7, 135.1, 129.7, 129.6, 129.2, 128.8, 128.7, 128.3, 128.1, 126.3, 72.8, 48.9, 44.7, 35.8, 35.4, 30.1, 7.7; m/z (ES HRMS) C₂₉H₂₈N₂O₄Na requires 491.1947, found [MNa⁺] 491.1949; [α]D²⁰ = −23.9 (c 1.0, CHCl₃).

1,4-dibenzyl-6-(4-methoxyphenyl)-6-(3-oxopentyl)piperazine-2,3,5-trione 2l

Following general procedure Cii using triketopiperazine 1b (41 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2l (37 mg, 75%) as a colourless oil in 3:97 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 220 nm, t(minor) = 22.1 min, t(major) = 27.4 min].
IR $\nu_{\text{max}}$/cm$^{-1}$ 2970, 2936, 1744, 1682, 1608, 1525, 1495, 1415, 1349, 1221, 1113, 1078, 1030, 852, 729, 700; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 – 7.18 (m, 12H), 6.94 – 6.89 (m, 2H), 7.32 – 7.14 (m, 10H), 5.13 – 5.04 (m, 2H), 4.94 (d, $J$ = 13.5 Hz, 1H), 3.79 (d, $J$ = 14.8 Hz, 1H), 2.51 (ddd, $J$ = 14.7, 10.2, 5.1 Hz, 1H), 1.91 (dq, $J$ = 17.6, 7.4 Hz, 1H), 1.82 (d, $J$ = 12.6 Hz, 1H), 1.76 – 1.66 (m, 3H), 0.79 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.0, 169.4, 160.4, 156.0, 155.2, 136.8, 135.2, 129.8, 129.3, 128.9, 128.3, 128.7, 128.3, 127.7, 115.0, 72.5, 55.6, 48.8, 44.7, 35.9, 35.5, 30.2, 7.7; m/z (ES HRMS) C$_{30}$H$_{30}$N$_2$O$_5$Na requires 521.2052, found [MNa]$^+$ 521.2048; $[\alpha]_D^{20}$ = −4.8 (c 1.0, CHCl$_3$).

1,4-dibenzyl-6-(4-nitrophenyl)-6-(3-oxopentyl)piperazine-2,3,5-trione 2m

Following general procedure Cii using triketopiperazine 1c (43 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH$_2$Cl$_2$ (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2m (31.5 mg, 63%) as a colourless oil in 3:97 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, $\lambda$ 230 nm, t(minor) = 19.3 min, t(major) = 22.7 min].

IR $\nu_{\text{max}}$/cm$^{-1}$ 2980, 2933, 1744, 1682, 1608, 1525, 1495, 1415, 1349, 1221, 1113, 1078, 1030, 852, 729, 700; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.22 – 8.16 (m, 2H), 7.56 – 7.49 (m, 2H), 7.32 – 7.14 (m, 10H), 5.13 – 5.04 (m, 2H), 4.94 (d, $J$ = 13.5 Hz, 1H), 3.79 (d, $J$ = 14.8 Hz, 1H), 2.51 (ddd, $J$ = 14.7, 10.2, 5.1 Hz, 1H), 1.91 (dq, $J$ = 17.6, 7.4 Hz, 1H), 1.82 (d, $J$ = 12.6 Hz, 1H), 1.76 – 1.66 (m, 3H), 0.79 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 207.5, 168.3, 155.4, 154.7, 148.4, 144.7, 136.1, 134.8, 129.4, 129.1, 128.9, 128.3, 128.7, 128.3, 127.9, 124.5, 72.4, 49.0, 45.0, 35.5, 30.6, 7.7; m/z (ES HRMS) C$_{29}$H$_{27}$N$_3$O$_6$Na requires 536.1798, found [MNa]$^+$ 536.1800; $[\alpha]_D^{20}$ = −7.2 (c 1.0, CHCl$_3$).
1,4-dibenzyl-6-(3-oxo-3-phenylpropyl)-6-phenylpiperazine-2,3,5-trione 2n

Following general procedure Cii using triketopiperazine 1a (38 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2n (46 mg, 90%) as a colourless oil in 85:15 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(major) = 61.3 min, t(minor) = 70.3 min].

IR ν max/cm⁻¹ 3064, 3029, 1742, 1678, 1597, 1494, 1415, 1361, 1262, 1228, 1138, 1073, 1002, 746, 690; ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.29 (m, 12H), 7.25 – 7.17 (m, 5H), 7.06 – 6.99 (m, 2H), 6.96 – 6.89 (m, 1H), 5.23 (d, J = 14.8 Hz, 1H), 5.13 (d, J = 13.5 Hz, 1H), 4.98 (d, J = 13.6 Hz, 1H), 3.73 (d, J = 14.8 Hz, 1H), 3.18 (ddd, J = 14.4, 9.9, 6.6 Hz, 1H), 2.63 (ddd, J = 14.7, 9.4, 5.6 Hz, 1H), 2.41 – 2.25 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 196.8, 169.3, 155.9, 155.2, 138.1, 136.4, 136.1, 135.2, 133.2, 129.7, 129.6, 129.3, 128.9, 128.8, 128.4, 128.3, 128.0, 127.7, 126.4, 72.9, 49.0, 44.7, 32.5, 30.6; m/z (ES HRMS) C₂₃H₂₈N₂O₄Na requires 539.1947, found [MNa⁺] 539.1957; [α]D²⁰ = −12.5 (c 1.0, CHCl₃).

1,4-dibenzyl-6-(4-methoxyphenyl)-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione 2o

Following general procedure Cii using triketopiperazine 1b (41 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2o (52 mg, 95%) as a colourless oil in 87:13 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 60:40, 1.0 ml/min, λ 220 nm, t(major) = 22.1 min, t(minor) = 26.0 min].
IR \( \nu_{\text{max}}/\text{cm}^{-1} \) 3061, 2958, 1741, 1678, 1603, 1511, 1447, 1415, 1362, 1256, 1227, 1182, 1077, 1030, 832, 733, 697; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.53 – 7.46 (m, 1H), 7.38 – 7.27 (m, 8H), 7.25 – 7.18 (m, 5H), 7.07 – 6.98 (m, 2H), 6.96 – 6.89 (m, 3H), 5.21 (d, \( J = 14.8 \) Hz, 1H), 5.13 (d, \( J = 13.5 \) Hz, 1H), 4.97 (d, \( J = 13.6 \) Hz, 1H), 3.83 (s, 3H), 3.76 (d, \( J = 14.8 \) Hz, 1H), 3.14 (ddd, \( J = 14.4, 9.9, 6.5 \) Hz, 1H), 2.58 (ddd, \( J = 14.6, 9.4, 5.6 \) Hz, 1H), 2.39 – 2.23 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 196.9, 169.5, 160.4, 156.0, 136.5, 136.1, 135.3, 133.2, 129.9, 129.4, 128.9, 128.8, 128.3, 128.0, 127.7, 115.0, 72.6, 55.6, 48.8, 44.7, 32.5, 30.7; m/z (ES HRMS) \( \text{C}_{34}\text{H}_{30}\text{N}_{2}\text{O}_{5}\text{Na} \) requires 569.2052, found [MNa\(^+\)] 569.2048; \( \delta = -7.9 \) (c 1.0, CHCl\(_3\)).

1,4-dibenzyl-6-(4-nitrophenyl)-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione 2p

Following general procedure Cii using triketopiperazine 1c (43 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 \( \mu \)mol, 10 mol%), CH\(_2\)Cl\(_2\) (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford 2p (49.5 mg, 88%) as a colourless oil in 4:96 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, \( \lambda \) 230 nm, \( t(\text{minor}) = 42.8 \) min, \( t(\text{major}) = 50.2 \) min].

IR \( \nu_{\text{max}}/\text{cm}^{-1} \) 3064, 3034, 2744, 1744, 1679, 1597, 1521, 1495, 1417, 1348, 1263, 1227, 1140, 1077, 907, 851, 727, 702; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.24 – 8.18 (m, 2H), 7.60 – 7.56 (m, 2H), 7.55 – 7.50 (m, 1H), 7.41 – 7.31 (m, 6H), 7.24 – 7.19 (m, 3H), 7.19 – 7.14 (m, 2H), 7.05 – 6.98 (m, 2H), 6.98 – 6.93 (m, 1H), 5.16 – 5.05 (m, 2H), 4.99 (d, \( J = 13.5 \) Hz, 1H), 3.90 (d, \( J = 14.8 \) Hz, 1H), 3.22 – 3.12 (m, 1H), 2.78 – 2.69 (m, 1H), 2.45 – 2.31 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 196.4, 168.4, 155.5, 154.8, 148.4, 144.8, 135.9, 134.9, 133.5, 129.5, 128.9, 128.8, 128.6, 128.3, 127.9, 127.8, 124.5, 72.5, 49.0, 45.0, 32.2, 31.0; m/z (ES HRMS) \( \text{C}_{33}\text{H}_{32}\text{N}_{3}\text{O}_{6}\text{Na} \) requires 584.1798, found [MNa\(^+\)] 584.1803; \([\alpha]_D^{20} = -5.5\) (c 1.0, CHCl\(_3\)).
3-(1,4-dibenzyl-3,5,6-trioxo-2-phenylpiperazin-2-yl)propanal 2q

Following general procedure Cii using triketopiperazine 1a (38 mg, 0.10 mmol), chiral catalyst 3 (4 mg, 10 µmol, 10 mol%), CH₂Cl₂ (1 mL) and acrolein (17 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford 2q (37.2 mg, 85%) as a colourless oil.

IR ν max/cm⁻¹ 3035, 2943, 1738, 1711, 1680, 1495, 1418, 1361, 1265, 1148, 1072, 911, 754, 692; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 7.47 – 7.17 (m, 15H), 5.29 (d, J = 14.8 Hz, 1H), 5.07 (d, J = 13.6 Hz, 1H), 4.93 (d, J = 13.6 Hz, 1H), 3.64 (d, J = 14.8 Hz, 1H), 3.05 (ddd, J = 14.4, 11.2, 5.3 Hz, 1H), 2.45 (ddd, J = 14.7, 11.1, 3.8 Hz, 1H), 1.97 – 1.75 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 198.2, 169.0, 155.7, 155.2, 137.8, 136.6, 135.0, 129.8, 129.7, 129.1, 129.1, 129.0, 128.7, 128.3, 126.2, 72.8, 49.0, 44.9, 38.1, 28.5; m/z (ES HRMS) C₂₇H₂₄N₂O₄Na requires 463.1634, found [MNa]⁺ 463.1631.

6-(2-(1,3-dioxolan-2-yl)ethyl)-1,4-dibenzyl-6-phenylpiperazine-2,3,5-trione S12

To a vial containing aldehyde 2q (37 mg, 85 µmol) was added 2-ethyl-2-methyl-1,3-dioxolane (0.25 mL) and PTSA (5 mg) and the reaction mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford S12 (40 mg, 98%) as a colourless oil in 42:58 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 25.7 min, t(major) = 28.1 min].

IR ν max/cm⁻¹ 3062, 2951, 2885, 1742, 1683, 1494, 1418, 1363, 1263, 1234, 1128, 1076, 1029, 732, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.20 (m, 15H), 5.15 (d, J = 13.6 Hz, 1H), 5.07 –
4.98 (m, 2H), 4.35 (t, J = 4.9 Hz, 1H), 3.95 (d, J = 14.8 Hz, 1H), 3.81 – 3.67 (m, 4H), 2.93 (ddd, J = 13.8, 11.6, 5.1 Hz, 1H), 2.30 (ddd, J = 13.8, 11.7, 4.2 Hz, 1H), 1.35 – 1.13 (m, 2H); 13C NMR (101 MHz, CDCl3) δ 169.5, 156.0, 154.9, 138.5, 136.5, 135.1, 129.5, 129.4, 129.3, 128.6, 128.6, 128.2, 127.9, 126.4, 103.1, 73.1, 64.8, 64.8, 48.8, 44.7, 30.7, 28.6; m/z (ES HRMS) C29H28N2O4Na requires 507.1896, found [MNa]+ 507.1897.

2,7-Diazabicyclo[2.2.1]heptanes (4a-m)

2,7-dibenzyl-1-methyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4a

Following general procedure D using triketopiperazine 2a (19 mg, 40 µmol), THF (0.1 mL) and ethanolamine (0.1 mL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4a (13.9 mg, 87%) as a colourless oil in 92:8 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 70:30, 1.0 ml/min, λ 220 nm, t(major) = 8.1 min, t(minor) = 9.8 min].

IR νmax/cm⁻¹ 3060, 3028, 2979, 2943, 1692, 1494, 1453, 1405, 1318, 1182, 955, 700; 1H NMR (400 MHz, CDCl3) δ 8.07 – 7.99 (m, 2H), 7.41 – 7.24 (m, 8H), 7.24 – 7.09 (m, 5H), 4.58 (d, J = 15.2 Hz, 1H), 4.30 (d, J = 15.2 Hz, 1H), 3.46 (d, J = 15.6 Hz, 1H), 3.37 (d, J = 15.6 Hz, 1H), 2.29 – 2.16 (m, 1H), 1.98 – 1.86 (m, 2H), 1.60 – 1.49 (m, 1H), 1.12 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 175.6, 140.8, 138.6, 136.5, 128.8, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 126.5, 84.1, 75.3, 46.8, 43.7, 35.3, 35.2, 18.2; m/z (ES HRMS) C26H27N2O requires 383.2123, found [MH]+ 383.2121; [α]D²⁰ = 15.4 (c 1.0, CHCl₃).
2,7-dibenzyl-4-(4-methoxyphenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4b

Following general procedure D using triketopiperazine 2b (26 mg, 53 µmol), THF (0.14 mL) and ethanolamine (0.14 mL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4b (11.2 mg, 51%) as a colourless oil.

IR ν max/cm⁻¹ 2979, 2940, 2837, 1689, 1514, 1494, 1454, 1404, 1319, 1246, 1177, 1028, 831, 728, 699; ¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.90 (m, 2H), 7.41 – 7.26 (m, 5H), 7.22 – 7.10 (m, 5H), 6.93 – 6.87 (m, 2H), 4.57 (d, J = 15.2 Hz, 1H), 4.29 (d, J = 15.2 Hz, 1H), 3.80 (s, 3H), 3.43 (d, J = 15.6 Hz, 1H), 3.35 (d, J = 15.5 Hz, 1H), 2.27 – 2.16 (m, 1H), 1.95 – 1.84 (m, 2H), 1.57 – 1.48 (m, 1H), 1.12 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.8, 159.2, 140.8, 138.6, 129.3, 128.7, 128.3, 128.2, 128.1, 127.7, 127.6, 126.5, 113.9, 84.0, 75.0, 55.4, 46.7, 43.7, 35.2, 34.9, 18.2; m/z (ES HRMS) C₂₈H₂₂N₂O₂ requires 413.2229, found [MH]^+ 413.2231.

2,7-dibenzyl-1-methyl-4-(4-nitrophenyl)-2,7-diazabicyclo[2.2.1]heptan-3-one 4c

Following general procedure D using triketopiperazine 2c (25 mg, 50 µmol), THF (125 µL) and ethanolamine (125 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4c (13.1 mg, 61%) as a colourless oil.

IR ν max/cm⁻¹ 2940, 2925, 2853, 1692, 1601, 1517, 1494, 1406, 1347, 1317, 1182, 1028, 956, 909, 852, 729, 698; ¹H NMR (400 MHz, CDCl₃) δ 8.26 – 8.15 (m, 4H), 7.39 – 7.28 (m, 5H), 7.24 – 7.13 (m, 5H), 4.56 (d, J = 15.2 Hz, 1H), 4.35 (d, J = 15.2 Hz, 1H), 3.45 (d, J = 15.7 Hz, 1H), 3.36 (d, J = 15.7 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.01 – 1.91 (m, 2H), 1.62 – 1.54 (m, 1H),
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.5, 147.4, 144.2, 139.8, 138.1, 128.9, 128.4, 128.2, 127.8, 127.5, 126.9, 123.6, 84.4, 74.9, 47.2, 43.9, 35.8, 35.5, 18.0; $m/z$ (ES HRMS) C$_{26}$H$_{26}$N$_3$O$_3$ requires 428.1744, found [MH]$^+$ 428.1975.

2,7-dibenzyl-4-(4-bromophenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4d

Following general procedure D using triketopiperazine 2d (45 mg, 85 µmol), THF (215 µL) and ethanolamine (215 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4d (23.1 mg, 60%) as a colourless oil.

IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3030, 2923, 2850, 1693, 1493, 1405, 1318, 1182, 1011, 955, 823, 703; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 – 7.88 (m, 2H), 7.50 – 7.45 (m, 2H), 7.38 – 7.27 (m, 5H), 7.23 – 7.11 (m, 5H), 4.55 (d, $J = 15.2$ Hz, 1H), 4.30 (d, $J = 15.2$ Hz, 1H), 3.38 (s, 2H), 2.19 – 2.10 (m, 1H), 1.95 – 1.86 (m, 2H), 1.55 – 1.49 (m, 1H), 1.13 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.2, 140.4, 138.4, 135.6, 131.6, 129.8, 128.8, 128.3, 128.2, 127.7, 127.6, 126.6, 122.0, 84.1, 74.9, 46.9, 43.8, 35.3, 18.1; $m/z$ (ES HRMS) C$_{28}$H$_{26}$N$_2$OBr requires 461.1229, found [MH]$^+$ 461.1226.

2,7-dibenzyl-4-(furan-2-yl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4e

Following general procedure D using triketopiperazine 2e (59 mg, 0.13 mmol), THF (325 µL) and ethanolamine (325 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4e (36.6 mg, 75%) as a colourless oil.
IR $\nu_{\text{max}}$/cm$^{-1}$ 3028, 2945, 1697, 1494, 1454, 1405, 1312, 1185, 1006, 910, 729, 697; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39 – 7.27 (m, 6H), 7.19 – 7.13 (m, 2H), 7.13 – 7.08 (m, 3H), 6.92 (dd, $J = 3.3$, 0.9 Hz, 1H), 6.34 (dd, $J = 3.3$, 1.8 Hz, 1H), 4.52 (d, $J = 15.2$ Hz, 1H), 4.35 (d, $J = 15.2$ Hz, 1H), 3.49 – 3.36 (m, 2H), 2.57 (ddd, $J = 12.1$, 10.4, 4.1 Hz, 1H), 1.88 (ddd, $J = 11.5$, 10.4, 4.2 Hz, 1H), 1.74 (ddd, $J = 12.1$, 9.2, 4.3 Hz, 1H), 1.49 (ddd, $J = 11.4$, 9.2, 4.2 Hz, 1H), 1.21 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.2, 148.1, 142.9, 140.1, 138.3, 128.8, 128.2, 128.0, 127.7, 126.4, 111.8, 110.4, 84.3, 72.7, 47.1, 43.8, 35.1, 30.0, 17.9; m/z (ES HRMS) C$_{24}$H$_{25}$N$_2$O$_2$ requires 373.1916, found [MH]$^+$ 373.1919.

2,7-dibenzyl-1-methyl-4-(thiophen-2-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one 4f

Following general procedure D using triketopiperazine 2f (12 mg, 26 µmol), THF (65 µL) and ethanolamine (65 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4f (5 mg, 50%) as a colourless oil in 93:7 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 70:30, 1.0 ml/min, $\lambda$ 220 nm, t(major) = 7.8 min, t(minor) = 9.4 min].

IR $\nu_{\text{max}}$/cm$^{-1}$ 3062, 2928, 2851, 1699, 1484, 1454, 1405, 1296, 1182, 1028, 842, 700; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (dd, $J = 3.6$, 1.2 Hz, 1H), 7.38 – 7.28 (m, 6H), 7.22 – 7.10 (m, 5H), 7.02 (dd, $J = 5.1$, 3.6 Hz, 1H), 4.53 (d, $J = 15.2$ Hz, 1H), 4.35 (d, $J = 15.2$ Hz, 1H), 3.49 (d, $J = 15.4$ Hz, 1H), 3.34 (d, $J = 15.3$ Hz, 1H), 2.30 (ddd, $J = 12.2$, 10.3, 4.2 Hz, 1H), 1.98 (ddd, $J = 12.2$, 9.1, 4.3 Hz, 1H), 1.90 (ddd, $J = 11.6$, 10.3, 4.3 Hz, 1H), 1.49 (ddd, $J = 11.6$, 9.2, 4.3 Hz, 1H), 1.12 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.5, 140.6, 138.3, 128.8, 128.3, 128.1, 127.9, 127.7, 126.9, 126.5, 126.2, 84.5, 73.9, 46.7, 43.9, 36.0, 35.2, 18.2; m/z (ES HRMS) C$_{24}$H$_{25}$N$_2$O$_2$S requires 389.1688, found [MH]$^+$ 389.1685; [$\alpha$]$^\circ_{D}$ = −7.3 (c 1.0, CHCl$_3$).
2,7-dibenzyl-4-(2-bromophenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4g

Following general procedure D using triketopiperazine 2g (36 mg, 68 µmol), THF (175 µL) and ethanolamine (175 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4g (9 mg, 29%) as a colourless oil.

IR ν<sub>max</sub>/cm<sup>-1</sup> 2921, 2850, 1688, 1494, 1455, 1406, 1313, 1028, 755, 698; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.61 (d, <i>J</i> = 7.9 Hz, 1H), 7.47 – 7.08 (m, 13H), 4.65 (br s, 1H), 4.27 (d, <i>J</i> = 15.5 Hz, 1H), 3.32 (d, <i>J</i> = 15.1 Hz, 1H), 3.23 (d, <i>J</i> = 15.5 Hz, 1H), 1.99 (ddd, <i>J</i> = 11.8, 10.2, 4.5 Hz, 1H), 1.85 (br s, 1H), 1.62 (br s, 2H), 1.10 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 175.1, 140.1, 138.5, 135.5, 133.9, 132.0, 129.9, 128.7, 128.4, 128.1, 128.0, 127.5, 127.2, 126.6, 84.0, 77.4, 48.0, 43.4, 34.8, 29.2, 18.2; m/z (ES HRMS) C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>OBr requires 461.1229, found [MH]<sup>+</sup> 461.1233.

2,7-dibenzyl-1-methyl-4-(1-methyl-1H-pyrrol-2-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one 4h

Following general procedure D using triketopiperazine 2h (34.7 mg, 76 µmol), THF (190 µL) and ethanolamine (190 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4h (7.5 mg, 26%) as a colourless oil.

IR ν<sub>max</sub>/cm<sup>-1</sup> 3029, 2924, 2852, 1702, 1494, 1453, 1404, 1322, 1274, 1225, 1179, 1028, 950, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 – 7.25 (m, 5H), 7.21 – 7.10 (m, 3H), 7.06 – 7.01 (m, 2H), 6.66 (s, 1H), 6.53 (dd, <i>J</i> = 2.7, 1.8 Hz, 1H), 6.09 (dd, <i>J</i> = 3.7, 2.7 Hz, 1H), 4.54 (d, <i>J</i> = 15.4 Hz, 1H), 4.39 (d, <i>J</i> = 15.4 Hz, 1H), 3.58 (s, 3H), 3.35 (d, <i>J</i> = 15.2 Hz, 1H), 3.23 (d, <i>J</i> = 15.2 Hz, 1H), 2.43 (ddd, <i>J</i> = 13.6, 10.4, 3.9 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.57 – 1.50 (m, 1H), 1.26 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 175.0, 140.0, 138.4, 128.8, 128.1, 127.9, 127.5, 126.5,
124.7, 112.1, 107.0, 84.0, 72.6, 47.4, 43.3, 35.2, 33.5, 29.4, 17.7; \textit{m/z} (ES HRMS) C_{25}H_{28}N_{3}O requires 386.2232, found [MH]^+ 386.2230.

2,7-dibenzyl-1-methyl-4-(1-methyl-1H-pyrrol-3-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one 4i

![Diagram of 2,7-dibenzyl-1-methyl-4-(1-methyl-1H-pyrrol-3-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one 4i]

Following general procedure D using triketopiperazine 2i (16 mg, 35 µmol), THF (100 µL) and ethanolamine (100 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4i (3.3 mg, 25%) as a colourless oil.

IR \textit{v}_{\text{max}}/\text{cm}^{-1} 2922, 2852, 1693, 1494, 1453, 1410, 1272, 1207, 1079, 1028, 793, 733, 700; \textsuperscript{1}H NMR (400 MHz, CDCl$_3$) \( \delta \) 7.38 – 7.23 (m, 7H), 7.19 – 7.15 (m, 3H), 7.14 – 7.09 (m, 1H), 6.55 (t, \( J = 2.5 \) Hz, 1H), 6.27 (dd, \( J = 2.7, 1.7 \) Hz, 1H), 4.54 (d, \( J = 15.4 \) Hz, 1H), 4.27 (d, \( J = 15.2 \) Hz, 1H), 3.64 (s, 3H), 3.58 (d, \( J = 15.5 \) Hz, 1H), 3.27 (d, \( J = 15.3 \) Hz, 1H), 2.29 – 2.19 (m, 1H), 1.86 – 1.74 (m, 2H), 1.48 – 1.41 (m, 1H), 1.08 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl$_3$) \( \delta \) 176.5, 141.6, 138.8, 128.7, 128.2, 128.0, 127.5, 126.2, 122.4, 122.0, 117.8, 107.8, 84.2, 72.9, 46.4, 43.8, 36.3, 35.1, 34.1, 18.3; \textit{m/z} (ES HRMS) C$_{25}$H$_{28}$N$_{3}$O requires 386.2232, found [MH]^+ 386.2233.

2,7-dibenzyl-4-(1H-indol-3-yl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4j

![Diagram of 2,7-dibenzyl-4-(1H-indol-3-yl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4j]

Following general procedure D using triketopiperazine 2j (9.5 mg, 19 µmol), THF (50 µL) and ethanolamine (50 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4j (2 mg, 21%) as a colourless oil.
IR $\nu_{\text{max}}$/cm$^{-1}$ 3300, 2924, 2852, 1680, 1494, 1455, 1409, 1351, 1217, 1074, 942, 741, 700; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.28 – 8.19 (m, 2H), 7.40 – 7.31 (m, 5H), 7.31 – 7.26 (m, 1H), 7.19 – 7.09 (m, 6H), 7.07 – 7.03 (m, 1H), 4.56 (d, $J = 15.2$ Hz, 1H), 4.37 (d, $J = 15.2$ Hz, 1H), 3.46 (d, $J = 15.2$ Hz, 1H), 3.30 (d, $J = 15.1$ Hz, 1H), 2.72 (ddd, $J = 12.4$, 10.3, 4.0 Hz, 1H), 1.96 (ddd, $J = 11.6$, 10.3, 4.4 Hz, 1H), 1.73 (ddd, $J = 12.4$, 9.3, 4.4 Hz, 1H), 1.57 – 1.49 (m, 1H), 1.11 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 176.4, 140.9, 138.6, 136.4, 128.8, 128.2, 128.0, 127.6, 126.3, 126.2, 125.4, 122.2, 120.9, 119.7, 111.3, 109.7, 84.2, 73.0, 47.2, 43.7, 35.5, 31.8, 18.6; $m/z$ (ES HRMS) C$_{28}$H$_{28}$N$_3$O requires 422.2232, found [MH]$^+$ 422.2235.

2,7-dibenzyl-1-ethyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4k

Following general procedure D using triketopiperazine 2k (24 mg, 50 µmol), THF (125 µL) and ethanolamine (125 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4k (9.8 mg, 50%) as a colourless oil.

IR $\nu_{\text{max}}$/cm$^{-1}$ 3030, 2931, 2850, 1692, 1494, 1453, 1399, 1314, 1074, 1028, 760, 734, 700; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 – 7.99 (m, 2H), 7.42 – 7.21 (m, 8H), 7.17 – 7.07 (m, 5H), 4.63 (d, $J = 15.4$ Hz, 1H), 4.27 (d, $J = 15.3$ Hz, 1H), 3.37 (s, 2H), 2.28 – 2.19 (m, 1H), 2.10 (ddd, $J = 11.7$, 10.4, 4.0 Hz, 1H), 1.90 (ddd, $J = 12.1$, 9.3, 3.9 Hz, 1H), 1.71 (dq, $J = 14.9$, 7.5 Hz, 1H), 1.54 (dq, $J = 14.7$, 7.4 Hz, 1H), 1.44 – 1.35 (m, 1H), 0.55 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.3, 140.1, 138.8, 136.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 126.5, 88.1, 75.7, 47.1, 43.7, 34.2, 30.8, 23.0, 7.8; $m/z$ (ES HRMS) C$_{27}$H$_{29}$N$_2$O requires 397.2280, found [MH]$^+$ 397.2281.
2,7-dibenzyl-1,4-diphenyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4l

Following general procedure D using triketopiperazine 2n (18 mg, 35 µmol), THF (90 µL) and ethanolamine (90 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4l (13 mg, 84%) as a colourless oil.  

IR ν\textsubscript{max}/cm\textsuperscript{-1} 3059, 3031, 2926, 1705, 1494, 1450, 1398, 1322, 1198, 1074, 1029, 951, 911, 752, 731, 695; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.52 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.31 – 7.14 (m, 9H), 6.96 – 6.87 (m, 5H), 6.75 – 6.68 (m, 2H), 4.56 (d, J = 14.6 Hz, 1H), 3.82 (d, J = 14.7 Hz, 1H), 3.16 (d, J = 14.4 Hz, 1H), 3.07 (d, J = 14.4 Hz, 1H), 2.63 – 2.48 (m, 2H), 2.10 (ddd, J = 11.9, 8.7, 3.2 Hz, 1H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 175.7, 139.4, 137.6, 134.6, 133.1, 130.3, 129.7, 129.5, 128.8, 129.5, 128.2, 127.4, 126.5, 126.1, 88.6, 77.5, 48.3, 44.2, 30.3, 26.5; m/z (ES HRMS) C\textsubscript{31}H\textsubscript{29}N\textsubscript{2}O requires 445.2280, found [MH]\textsuperscript{+} 445.2281.

2,7-dibenzyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one 4m

Following general procedure D using triketopiperazine 2q (19 mg, 44 µmol), THF (110 µL) and ethanolamine (110 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford 4m (4.4 mg, 28%) as a colourless oil.  

IR ν\textsubscript{max}/cm\textsuperscript{-1} 2916, 2854, 1694, 1494, 1451, 1411, 1330, 1249, 701; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.07 – 8.02 (m, 2H), 7.46 – 7.30 (m, 8H), 7.16 – 7.11 (m, 3H), 6.85 – 6.79 (m, 2H), 4.84 (d, J = 14.7 Hz, 1H), 4.26 (d, J = 2.4 Hz, 1H), 3.91 (d, J = 14.7 Hz, 1H), 3.33 (d, J = 13.0 Hz, 1H), 3.02 (d, J = 13.0 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.00 – 1.91 (m, 2H), 1.65 – 1.59 (m, 1H); \textsuperscript{13}C NMR
Reduction of 4a

\[
\text{N},1\text{-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide 5a and 5b}
\]

To a solution of diazabicycle 4a (29 mg, 77 µmol) in CH\(_2\)Cl\(_2\) (0.5 mL) was added DIBAL (65 µL, 77 µmol) at −78 °C. After 1 hour a further equivalent of DIBAL (65 µL, 77 µmol) was added and the reaction mixture was allowed to warm to 0 °C over 1 hour. The reaction mixture was then diluted with CH\(_2\)Cl\(_2\) (2 mL) followed by the addition of aqueous Rochelle’s salt (3 mL, 20% w/w) and stirred vigorously for 1 hour. The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 3 mL) and the combined organic layers were washed with brine (5 mL), dried over MgSO\(_4\), concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane:EtOAc = 9:1) to afford 5a (11.4 mg, 39%) and 5b (5.4 mg, 18%) as colourless oils.

**Major (2R, 5S) or (2S, 5R) N,1-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide 5a**

**Minor (2R, 5R) or (2S, 5S) N,1-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide 5b**
Formation of Iminium 6

1-benzyl-2-(benzylcarbamoyl)-5-methyl-2-phenyl-3,4-dihydro-2H-pyrrol-1-ium chloride 6

To a round bottomed flask containing diazabicycle 4a (39 mg, 0.1 mmol) was added HCl in dioxane (0.2 mL, 4 M) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to afford 6 (quant.) as a colourless residue.

IR $\nu_{\text{max}}$/cm$^{-1}$ 3169, 3030, 1666, 1530, 1496, 1452, 1359, 1271, 1127, 1079, 1028, 957, 729, 696; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.04 (t, $J = 6.0$ Hz, 1H), 7.50 – 7.43 (m, 2H), 7.42 – 7.33 (m, 2H), 7.31 – 7.15 (m, 6H), 7.14 – 7.03 (m, 3H), 6.66 – 6.58 (m, 2H), 5.31 (d, $J = 16.2$ Hz, 1H), 4.72 (d, $J = 16.2$ Hz, 1H), 4.55 – 4.43 (m, 2H), 3.80 – 3.67 (m, 1H), 3.27 (d, $J = 14.1$ Hz, 3H), 2.53 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.5, 168.2, 138.6, 133.8, 131.2, 130.4, 129.2, 129.0, 128.7, 128.5, 127.3, 126.9, 89.0, 54.1, 44.1, 40.5, 33.4, 21.4; m/z (ES HRMS) C$_{26}$H$_{27}$N$_2$O requires 383.2123, found [M]$^+$ 383.2124.
Synthesis of harmicine Amide 10

*N-benzyl-2-chloro-2-phenylacetamide S13*

\[
\begin{align*}
\text{Cl} & \quad \text{Et}_3\text{N} \quad \text{MeCN} \\
\text{BnNH}_2 & \quad 0 \degree \text{C to r.t., 1 h} \\
\text{Cl} & \quad \text{BnN} \\
\end{align*}
\]

To a solution of benzylamine (0.69 mL, 6.33 mmol) and triethylamine (1.06 mL, 7.60 mmol) in MeCN (30 mL) was added α-chlorophenylacetyl chloride (1.0 mL, 6.33 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 hour then filtered, washed with MeCN (3 x 5 mL) and the filtrate was concentrated under reduced pressure. The residue was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with 1 M HCl (20 mL), the organic layer was dried with MgSO\(_4\), filtered and concentrated under reduced pressure to afford S13 as a pale yellow solid (1.55 g, 95%).

**IR** \(\nu_{\text{max}}/\text{cm}^{-1}\) 3289, 3064, 3031, 1659, 1496, 1454, 1213, 1029, 730, 695; **\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 – 7.05 (m, 10H), 6.91 (Br s, 1H), 5.33 (s, 1H), 4.42 (d, \(J = 5.7\) Hz, 2H); **\(^{13}\text{C NMR}\)** (101 MHz, CDCl\(_3\)) \(\delta\) 167.5, 137.5, 137.2, 129.3, 129.1, 129.0, 127.9, 61.9, 44.3; **m/z** (ES) C\(_{15}\)H\(_{14}\)NO\(_2\)Na requires 282.7, found [MNa]\(^+\) 282.3. Data is in agreement with literature.\(^6\)

**2-((2-(1H-indol-3-yl)ethyl)amino)-N-benzyl-2-phenylacetamide S14**

\[
\begin{align*}
\text{BnNH}_2 & \quad \text{Et}_3\text{N}, \text{tryptamine, MeCN} \\
\text{Cl} & \quad \text{BnNH}_2 \quad \text{r.t., 72 h} \\
\end{align*}
\]

To a solution of S13 (457 mg, 1.76 mmol) and triethylamine (0.98 mL, 7.04 mmol) in MeCN (9 mL) was added tryptamine (705 mg, 4.40 mmol) in one portion. The reaction mixture was stirred for 72 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH\(_2\)Cl\(_2\) (15 mL), washed with 1 M HCl (15 mL), and the organic layer was dried with MgSO\(_4\), filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (CH\(_2\)Cl\(_2\):Acetone = 9:1) to afford S14 (215 mg, 32%) as a brown oil.

**IR** \(\nu_{\text{max}}/\text{cm}^{-1}\) 3297, 3059, 2924, 2846, 1654, 1520, 1454, 1230, 908, 731; **\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) 8.05 (s, 1H), 7.57 – 7.50 (m, 1H), 7.35 – 7.24 (m, 8H), 7.17 (ddd, \(J = 8.2, 7.0, 1.2\) Hz,
1H), 7.14 – 7.06 (m, 3H), 6.88 (d, J = 2.3 Hz, 1H), 4.36 (dd, J = 14.9, 6.2 Hz, 1H), 4.26 (s, 1H), 4.19 (dd, J = 14.9, 5.8 Hz, 1H), 3.05 – 2.87 (m, 4H), 1.99 (br s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.3, 139.4, 138.5, 136.5, 128.9, 128.7, 128.2, 127.6, 127.4, 122.2, 119.5, 118.9, 113.5, 111.4, 67.7, 48.8, 43.1, 25.9; m/z (ES HRMS) C$_{25}$H$_{26}$N$_3$O requires 384.2076, found [MH]$^+$ 384.2084.

1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-phenylpiperazine-2,3,5-trione 7

Following general procedure B using 1,1’-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole (171 mg, 0.59 mmol) in THF (1.5 mL), S14 (187 mg, 0.49 mmol) in THF (2 mL). The residue was purified by flash column chromatography on silica gel (gradient: CH$_2$Cl$_2$/MeOH = (1:0) to (99:1)) to afford 7 (67.5 mg, 32%) as a waxy yellow solid.

IR $\nu_{\text{max}}$/cm$^{-1}$ 3332, 3057, 3034, 2937, 1744, 1683, 1454, 1428, 1362, 1198, 908, 732; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.08 (s, 1H), 7.44 (dd, J = 7.9, 1.0 Hz, 1H), 7.40 – 7.27 (m, 4H), 7.25 (d, J = 8.9 Hz, 5H), 7.18 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.11 – 7.04 (m, 2H), 7.05 – 6.93 (m, 2H), 4.99 (d, J = 13.8 Hz, 1H), 4.85 – 4.77 (m, 2H), 4.20 (ddd, J = 13.1, 7.8, 4.4 Hz, 1H), 3.19 (dt, J = 13.8, 7.9 Hz, 1H), 3.08 (dt, J = 13.2, 7.4 Hz, 1H), 2.96 (ddd, J = 13.6, 7.1, 4.5, 0.9 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.7, 156.6, 153.0, 136.4, 135.2, 134.5, 129.8, 129.6, 129.2, 128.7, 128.2, 127.1, 126.9, 122.6, 122.3, 119.9, 118.4, 112.0, 111.6, 66.3, 47.1, 44.6, 23.0; m/z (ES HRMS) C$_{27}$H$_{23}$N$_3$O$_3$Na requires 460.1637, found [MNa]$^+$ 460.1635.

1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione 8
Following general procedure Cii using triketopiperazine 7 (66 mg, 0.15 mmol), triethylamine (20 µL, 0.15 mmol), CH₂Cl₂ (1.5 mL) and methyl vinyl ketone (30 µL, 0.375 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford 8 (75 mg, 99%) as a yellow oil.

**IR** ν<sub>max</sub>/cm<sup>-1</sup> 3339, 2950, 1741, 1712, 1677, 1419, 1362, 1227, 907, 726; **<sup>1</sup>H NMR** (400 MHz, CDCl₃) δ 8.16 (br s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.42 – 7.36 (m, 5H), 7.35 – 7.28 (m, 6H), 7.15 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 5.20 (d, J = 13.5 Hz, 1H), 4.98 (d, J = 13.5 Hz, 1H), 3.49 (ddd, J = 13.5, 11.5, 4.7 Hz, 1H), 3.16 (ddd, J = 13.4, 11.4, 5.6 Hz, 1H), 3.01 – 2.75 (m, 3H), 2.61 (ddd, J = 14.3, 11.8, 3.6 Hz, 1H), 2.23 (ddd, J = 17.7, 11.5, 3.6 Hz, 1H), 2.04 (ddd, J = 17.3, 11.8, 5.1 Hz, 1H), 1.96 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl₃) δ 205.4, 169.7, 156.0, 153.8, 138.0, 136.2, 135.3, 129.5, 128.8, 128.5, 127.0, 126.6, 122.4, 122.3, 119.7, 118.9, 112.1, 111.3, 71.7, 47.4, 44.7, 37.3, 30.1, 30.0, 23.3; **m/z** (ES HRMS) C₃₁H₂₉N₃O₄Na requires 530.2056, found [MNa]<sup>+</sup> 530.2057.

7-(2-(1H-indol-3-yl)ethyl)-2-benzyl-1-methyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one 9

Following general procedure D using triketopiperazine 8 (54 mg, 0.11 mmol), THF (0.27 mL) and ethanolamine (0.27 mL). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford 9 (24 mg, 52%) as a colourless oil.

**IR** ν<sub>max</sub>/cm<sup>-1</sup> 3408, 3298, 3057, 2923, 2852, 1685, 1494, 1455, 1318, 1182, 961, 908, 739; **<sup>1</sup>H NMR** (400 MHz, CDCl₃) δ 7.99 – 7.94 (m, 2H), 7.86 (br s, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.24 (m, 7H), 7.15 – 7.08 (m, 2H), 6.97 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 6.73 (d, J = 2.3 Hz, 1H), 4.54 (d, J = 15.3 Hz, 1H), 4.29 (d, J = 15.3 Hz, 1H), 2.69 – 2.45 (m, 4H), 2.25 – 2.16 (m, 1H), 1.95 – 1.81 (m, 2H), 1.59 – 1.54 (m, 1H), 1.52 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl₃) δ 176.0, 138.5, 136.5, 136.2, 128.8, 128.5, 128.4, 128.2, 127.9, 127.5, 127.4, 122.0, 121.4, 119.3, 119.0, 114.4, 111.1, 83.9, 76.0, 44.0, 43.8, 35.1, 34.1, 27.1, 17.7; **m/z** (ES HRMS) C₂₉H₃₀N₃O requires 436.2389, found [MH]<sup>+</sup> 436.2392.
N-benzyl-11b-methyl-3-phenyl-2,3,5,6,11b-hexahydro-1H-indolizino[8,7-b]indole-3-carboxamide 10

To a round bottomed flask containing 9 (16 mg, 38 µmol) was added HCl in dioxane (0.5 ml) and the reaction mixture was heated at 90 °C for 16 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in CH₂Cl₂ (3 mL), washed with sat. aq. NaHCO₃ (5 mL), the aqueous layer was extracted with CH₂Cl₂ (2 x 3 mL), the organic layers were combined and washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford 10 (10.4 mg, 63%) as a pale yellow oil.

IR νmax/cm⁻¹ 3284, 2960, 2922, 2852, 1651, 1499, 1449, 1331, 1275, 1117, 908, 732; ¹H NMR (400 MHz, CDCl₃) δ 8.80 (t, J = 6.0 Hz, 1H), 7.81 (br s, 1H), 7.41 (d, J = 4.3 Hz, 4H), 7.36 – 7.23 (m, 7H), 7.14 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.05 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.70 (dd, J = 14.7, 6.6 Hz, 1H), 4.54 (dd, J = 14.7, 5.3 Hz, 1H), 3.17 (dd, J = 8.4, 2.8 Hz, 2H), 2.56 – 2.39 (m, 2H), 2.29 (ddd, J = 12.4, 6.1, 2.2 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.68 – 1.55 (m, 2H), 1.48 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 177.0, 139.1, 139.0, 137.8, 135.7, 129.1, 128.9, 128.2, 128.1, 128.0, 127.7, 127.5, 121.9, 119.4, 118.3, 110.9, 109.9, 76.6, 62.5, 44.0, 39.9, 37.4, 33.6, 28.4, 19.4; m/z (ES HRMS) C₂₉H₃₀N₃O requires 436.2389, found [MH]^+ 436.2388.
### References

Appendix

$^1$H and $^{13}$C NMR
HPLC Traces

Racemic 2a

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Enantioenriched 2a

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Racemic 2b

Enantioenriched 2b
Racemic 2c

Enantioenriched 2c
Racemic 2d

Enantioenriched 2d
Racemic 2e

![Racemic 2e Graph]

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Enantioenriched 2e

![Enantioenriched 2e Graph]

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S105
Racemic 2f

Enantiomeric 2f
Racemic 2g

![Racemic 2g](image1)

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Enantioenriched 2g

![Enantioenriched 2g](image2)

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Racemic 2h

![Graph showing racemic 2h with chromatogram and table data]

Enantioenriched 2h

![Graph showing enantioenriched 2h with chromatogram and table data]
Racemic 2i

![Graph of racemic 2i with peaks at retention times and corresponding areas and relative areas.]

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<td></td>
<td></td>
<td>883.219</td>
<td>768.522</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Enantioenriched 2i

![Graph of enantioenriched 2i with peaks at retention times and corresponding areas and relative areas.]

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret. Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel. Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.50</td>
<td>n.a.</td>
<td>761.853</td>
<td>730.578</td>
<td>76.98</td>
<td>n.a.</td>
<td>BM</td>
</tr>
<tr>
<td>2</td>
<td>21.07</td>
<td>n.a.</td>
<td>263.065</td>
<td>218.440</td>
<td>23.03</td>
<td>n.a.</td>
<td>MB</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1014.918</td>
<td>949.018</td>
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</tbody>
</table>
Racemic 2j

Enantioenriched 2j
### Racemic 2k

![Chromatogram](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.99</td>
<td>n.a.</td>
<td>456.057</td>
<td>518.128</td>
<td>47.41</td>
<td>n.a.</td>
<td>BM*</td>
</tr>
<tr>
<td>2</td>
<td>30.78</td>
<td>n.a.</td>
<td>416.599</td>
<td>574.849</td>
<td>52.59</td>
<td>n.a.</td>
<td>MB*</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>872.656</td>
<td>1092.976</td>
<td>100.00</td>
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</tr>
</tbody>
</table>

### Enantioenriched 2k

![Chromatogram](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.16</td>
<td>n.a.</td>
<td>54.747</td>
<td>53.896</td>
<td>4.28</td>
<td>n.a.</td>
<td>BM*</td>
</tr>
<tr>
<td>2</td>
<td>30.60</td>
<td>n.a.</td>
<td>828.738</td>
<td>1205.445</td>
<td>95.72</td>
<td>n.a.</td>
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<tr>
<td><strong>Total</strong></td>
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<td></td>
<td>883.485</td>
<td>1259.341</td>
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<td>0.000</td>
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</tbody>
</table>
Racemic 2l

Enantioenriched 2l
Racemic 2m

Enantioenriched 2m
Racemic 2n

Enantioenriched 2n
Racemic 2o

![Graph of Racemic 2o](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.41</td>
<td>n.a.</td>
<td>809.199</td>
<td>773.125</td>
<td>49.67</td>
<td>n.a.</td>
<td>BM</td>
</tr>
<tr>
<td>2</td>
<td>25.84</td>
<td>n.a.</td>
<td>581.731</td>
<td>777.194</td>
<td>50.13</td>
<td>n.a.</td>
<td>MB</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1390.930</td>
<td>1550.319</td>
<td>100.00</td>
<td>0.000</td>
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</tbody>
</table>

Enantioenriched 2o

![Graph of Enantioenriched 2o](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.16</td>
<td>n.a.</td>
<td>2511.561</td>
<td>3130.746</td>
<td>86.65</td>
<td>n.a.</td>
<td>BM*</td>
</tr>
<tr>
<td>2</td>
<td>28.84</td>
<td>n.a.</td>
<td>392.916</td>
<td>452.446</td>
<td>13.35</td>
<td>n.a.</td>
<td>MB*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>2904.477</td>
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</tr>
</tbody>
</table>
Racemic 2p

![Graph of racemic 2p](image1)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.43</td>
<td>n.a.</td>
<td>130.933</td>
<td>378.436</td>
<td>50.31</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>51.54</td>
<td>n.a.</td>
<td>102.868</td>
<td>373.771</td>
<td>49.69</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
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<td></td>
<td>233.802</td>
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</tr>
</tbody>
</table>

Enantioenriched 2p

![Graph of enantioenriched 2p](image2)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.81</td>
<td>n.a.</td>
<td>21.392</td>
<td>64.970</td>
<td>3.93</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>50.24</td>
<td>n.a.</td>
<td>349.274</td>
<td>1343.057</td>
<td>96.07</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
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<td></td>
<td>360.666</td>
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</tr>
</tbody>
</table>
Racemic S12

![Graph for racemic S12](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.84</td>
<td>n.a.</td>
<td>623.566</td>
<td>665.571</td>
<td>n.a.</td>
<td>BM</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28.28</td>
<td>n.a.</td>
<td>876.879</td>
<td>1038.263</td>
<td>n.a.</td>
<td>M</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>0.000</td>
</tr>
</tbody>
</table>

Enantioenriched S12

![Graph for enantioenriched S12](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.71</td>
<td>n.a.</td>
<td>708.026</td>
<td>700.257</td>
<td>41.90</td>
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<td>BM</td>
</tr>
<tr>
<td>2</td>
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<td>967.396</td>
<td>58.01</td>
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<td></td>
<td></td>
<td>100.00</td>
<td>0.000</td>
</tr>
</tbody>
</table>
**Racemic 4a**

![Graph showing chromatogram with peak at 8.212 and 9.600 minutes]

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.21</td>
<td>n.a.</td>
<td>150.872</td>
<td>56.766</td>
<td>50.62</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td>2</td>
<td>9.80</td>
<td>n.a.</td>
<td>112.994</td>
<td>54.341</td>
<td>49.18</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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<td>269.866</td>
<td>111.707</td>
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<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

**Enantioenriched 4a**

![Graph showing chromatogram with peak at 8.132 and 9.766 minutes]

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.13</td>
<td>n.a.</td>
<td>641.599</td>
<td>267.022</td>
<td>91.89</td>
<td>n.a.</td>
<td>MB²</td>
</tr>
<tr>
<td>2</td>
<td>9.78</td>
<td>n.a.</td>
<td>49.799</td>
<td>23.656</td>
<td>8.11</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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<td>691.388</td>
<td>290.678</td>
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</tr>
</tbody>
</table>
Enantioenriched sample of 2f used to generate diazabicycle 4f

![Graph and Table]

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.20</td>
<td>n.a.</td>
<td>144.430</td>
<td>113.348</td>
<td>6.95</td>
<td>n.a.</td>
<td>BM*</td>
</tr>
<tr>
<td>2</td>
<td>23.57</td>
<td>n.a.</td>
<td>1426.436</td>
<td>1516.427</td>
<td>93.05</td>
<td>n.a.</td>
<td>MB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1570.867</td>
<td>1629.776</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structure]
Racemic 4f

Enantioenriched 4f
X-ray Crystal Structures

The datasets were measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collections were driven and processed and absorption corrections were applied using CrysAlisPro.[51] The structure of 2f was solved using ShelXT[52] and that of 4a was solved using ShelXS[53] and both structures were refined by a full-matrix least-squares procedure on F² in ShelXL.[54] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (Ueq) of the parent atom. Figures and reports were produced using OLEX2.[55]

The structure of 2f occupies a chiral space group and the absolute structure has been determined from the diffraction data, with the Flack parameter being -0.004 (6).

In 2f the thiophene ring, C(7)-S(8)-C(9)-C(10)-C(11), (C(7′)-S(8′)-C(9′)-C(10′)-C(11′)) is disordered over two positions at a refined percentage occupancy ratio of 63.9(3) : 36.1 (3).

The structure of 4a occupies a centrosymmetric space group. Thus in one molecule in the unit cell C(6) is R and C(9) is S while in the other molecule C(6) is S and C(9) is R. The relative stereochemistry is the same in all molecules.

The CIFs for the crystal structures of 2f and 4a have been deposited with the CCDC and have been given the deposition numbers: CCDC 1880502 and CCDC 1880503 respectively.

Crystal structure determination of 2f:

Crystal Data for C₂₆H₂₄N₂O₄S (M =460.53 g/mol): monoclinic, space group P2₁ (no. 4), a = 7.27000(10) Å, b = 11.16340(10) Å, c = 14.17310(10) Å, β = 96.9580(10)°, V = 1141.79(2) Å³, Z = 2, T = 100.01(10) K, μ(CuKα) = 1.556 mm⁻¹, Dcalc = 1.340 g/cm³, 21276 reflections measured (12.264° ≤ 2Θ ≤ 144.218°), 4388 unique (Rint = 0.0209, Rsigma = 0.0147) which were used in all calculations. The final R₁ was 0.0227 (I > 2σ(I)) and wR₂ was 0.0582 (all data). Flack = -0.004(6).
Crystal structure determination of 4a:

**Crystal Data** for C\(_{26}\)H\(_{26}\)N\(_2\)O (\(M = 382.49\) g/mol): triclinic, space group P-1 (no. 2), \(a = 9.9803(5)\) Å, \(b = 10.7055(5)\) Å, \(c = 11.0770(7)\) Å, \(\alpha = 76.953(5)^\circ\), \(\beta = 64.440(6)^\circ\), \(\gamma = 72.474(4)^\circ\), \(V = 1011.80(11)\) Å\(^3\), \(Z = 2\), \(T = 100.01(10)\) K, \(\mu(\text{MoK}\alpha) = 0.076\) mm\(^{-1}\), \(D_{\text{calc}} = 1.255\) g/cm\(^3\), 8126 reflections measured (7.212° ≤ 2\(\Theta\) ≤ 53.462°), 4266 unique (\(R_{\text{int}} = 0.0201\), \(R_{\text{sigma}} = 0.0362\)) which were used in all calculations. The final \(R_1\) was 0.0451 (I > 2\(\sigma(I)\)) and \(wR_2\) was 0.1063 (all data).


