A Mild and Efficient CH₂-Extrusion Reaction for the Enantiospecific Synthesis of Highly Configurationally Stable Tröger Bases**

Sandip A. Pujari, Céline Besnard, Thomas Bürgi, and Jérôme Lacour*

anier_201500435_sm_miscellaneous_information.pdf
# Supporting Information

1. General Remarks: .................................................................................................................. S2
2. General synthesis and characterization ................................................................................. S3  
   2A: General procedure for the synthesis of ethano-Tröger base ................................................ S3  
   2B: General procedure of methylene extrusion ...................................................................... S10
3. NMR Spectra ...................................................................................................................... S21
4. CSP-HPLC traces ................................................................................................................. S50
5. Configurational stability ...................................................................................................... S66
6. ECD spectra of 2a ................................................................................................................ S67
7. Vibrational circular dichroism (VCD) and infrared (IR) analysis ........................................ S68
8. Crystallographic data for 2b ................................................................................................ S73
1. General Remarks:

NMR spectra were recorded on 300, 400 or 500 MHz spectrometer at room temperature (20 °C) otherwise mentioned. $^1$H-NMR chemical shifts are given in ppm relative to Me$_4$Si with the solvent resonance used as the internal standard (CDCl$_3$ δ = 7.26 ppm). $^{13}$C-NMR (75, 100 or 125 MHz) chemical shifts were given in ppm relative to Me$_4$Si with the solvent resonance used as the internal standard (CDCl$_3$ = 77.16 ppm). IR spectra were recorded using an ATR sampler and are reported in wave numbers (cm$^{-1}$). Melting points (M.p.) were measured in open capillary tubes and were uncorrected. Optical rotations were measured in a thermostated (20 °C) 10.0 cm long microcell at 589 nm (Na). Electro spray mass spectra (ESI) were obtained by the Department of Mass Spectrometry of the University of Geneva. All reactions involving air sensitive compounds were carried out under dry N$_2$ or argon by means of an inert gas/vacuum double manifold line. Flash column chromatography was performed with silica gel 40-63 μm or alumina (neutral Brockmann I, 50-200 μm).
2. General synthesis and characterization

2A: General procedure for the synthesis of ethano-Tröger base

Table S1. Synthesis of ethano-Tröger bases: isolated yields and ee for the major diastereomer; d.r. was determined by the $^1$H NMR of the crude reaction mixture

To a stirred solution of Tröger’s base 3 (1 mmol) in anhydrous toluene (5 mL), was added Rh$_2$(OAc)$_4$ (1 mol %) under inert atmosphere and reaction mixture was heated at 100 °C. To this solution, the corresponding diazo reagent (1.6 mmol) was added carefully over 10 min and the reaction mixture was allowed to stir at same temperature for 16 h. After being cooled to 20 °C, toluene was evaporated and the residue was purified by column chromatography to afford the ethano-TB 1.

Spectral and analytical data for 1a to 1f and 1j was reported previously.

**Compound (+)-1g**

Yield = 56.6 mg (63%, white solid) starting from 50 mg of (+)-3 (R = Me)

Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)

R$_f$ = 0.61 (15% ethyl acetate/ pentane)

M.p. = 233-235 °C

IR (neat): 2912, 1718, 1495, 1432, 1242, 1226, 1167, 1074, 774 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): 9.92 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.45-7.34 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 6.49 (s, 1H), 5.36 (d, J = 14.3 Hz, 1H), 4.77 (d, J = 17.5 Hz, 1H), 4.44 (d, J = 17.5 Hz, 1H), 4.30-4.14 (m, 3H), 3.28 (s, 3H), 2.23 (s, 3H), 2.10 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.77 (C), 147.42 (C), 145.06 (C), 138.01 (C), 136.50 (C), 136.19 (C), 134.91 (C), 134.80 (C), 134.32 (C), 131.74 (C), 129.62 (CH), 128.79 (CH), 128.77 (CH), 128.52 (CH), 128.48 (CH), 128.43 (CH), 128.18 (CH), 127.85 (CH), 127.48 (CH), 126.93 (CH), 125.61 (CH), 125.59 (CH), 124.93 (CH), 77.36 (C).65.54 (CH$_2$), 58.79 (CH$_2$), 55.78 (CH$_2$), 52.40 (CH$_3$), 21.05 (CH$_3$), 20.85 (CH$_3$);

HRMS (ESI): Calcd. for C$_{30}$H$_{29}$N$_2$O$_2$ [M+H]$^+$ = 449.2224; Observed = 449.2231

$[\alpha]_D^{20}$ = +218 (c 0.05, CHCl$_3$).

**Compound (+)-1h**

Yield = 345 mg (73%, white solid) starting from 250 mg of (+)-3 (R = Me)

Purification: By column chromatography (Silica gel, 6% ethyl acetate in pentane)

R$_f$ = 0.78 (10% ethyl acetate/ pentane)

M.p. = 97-98 °C

IR (neat): 2917, 1722, 1494, 1446, 1230, 1165, 1089, 824, 695 cm$^{-1}$;
\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.64 (d, \(J = 7.5\) Hz, 2H), 7.29-7.23 (m, 2H), 7.19 (d, \(J = 7.0\) Hz, 1H), 7.14-6.99 (m, 4H), 6.91 (d, \(J = 7.9\) Hz, 1H), 6.75 (d, \(J = 7.6\) Hz, 2H), 6.66 (d, \(J = 7.6\) Hz, 2H), 6.48 (s, 2H), 5.15 (d, \(J = 14.6\) Hz, 1H), 4.67 (d, \(J = 17.4\) Hz, 1H), 4.60, 4.53 (ABq, \(J_{AB} = 12.4\) Hz, 2H), 4.45 (d, \(J = 17.7\) Hz, 1H), 4.22 (d, \(J = 16.6\) Hz, 1H), 4.20 (d, \(J = 16.6\) Hz, 1H), 3.74 (d, \(J = 14.6\) Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.65 (C), 147.31 (C), 145.28 (C), 142.80 (C), 136.53 (C), 136.16 (C), 135.61 (C), 134.72 (C), 134.31 (C), 130.14 (CH), 128.91 (CH), 128.57 (CH), 128.30 (CH), 128.13 (CH), 127.91 (CH), 127.81 (CH), 127.73 (CH), 127.67 (CH), 127.10 (CH), 75.90 (C), 67.11 (CH\(_2\)), 62.19 (CH\(_2\)), 59.06 (CH\(_2\)), 56.19 (CH\(_2\)), 21.02 (CH\(_3\)), 20.86 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{32}\)H\(_{31}\)N\(_2\)O\(_2\) [M+H]\(^+\) = 475.2380; Observed = 475.2381

[\(\alpha\)]\(_D\)\(^{20}\) = +196 (c 0.08, CHCl\(_3\)).

**Compound 1i**

Yield = 92.1 mg (54%, yellow solid) starting from 100 mg of \(3\) (\(\text{R} = \text{Me}\))

Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)

R\(_f\) = 0.53 (10% ethyl acetate/ pentane)

M.p. = 174-176 °C

IR (neat): 2917, 1718, 1494, 1445, 1228, 1203, 1164, 1127, 1088, 919, 824, 729 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.76 (d, \(J = 7.5\) Hz, 2H), 7.39 (t, \(J = 7.7\) Hz, 2H), 7.31 (d, \(J = 8.1\) Hz, 2H), 7.05 (d, \(J = 8.0\) Hz, 1H), 6.95 (dd, \(J = 8.0, 1.2\) Hz, 1H), 6.87 (dd, \(J = 8.0, 1.0\) Hz, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 5.31-5.18 (m, 1H), 5.26 (d, \(J = 14.8\) Hz, 1H), 4.91 (dd, \(J = 10.5, 1.3\) Hz, 1H), 4.88-4.81 (m, 2H), 4.58 (d, \(J = 17.7\) Hz, 1H), 4.39 (d, \(J = 13.9\) Hz, 1H), 4.35 (d, \(J = 14.5\) Hz, 1H), 4.13 (dt, \(J = 5.6, 1.2\) Hz, 2H), 3.84 (d, \(J = 14.5\) Hz, 1H), 2.20 (s, 3H), 2.15 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.46 (C), 147.31 (C), 145.35 (C), 142.76 (C), 136.53 (C), 136.24 (C), 134.81 (C), 134.30 (C), 131.67 (CH), 130.31 (CH), 128.78 (CH), 128.54 (CH), 128.52 (CH), 128.17 (CH), 127.90 (CH), 127.71 (CH), 127.63 (CH), 127.01 (CH), 117.52 (CH\(_2\)), 75.82 (C), 65.77 (CH\(_2\)), 62.11 (CH\(_2\)), 59.10 (CH\(_2\)), 56.04 (CH\(_2\)), 20.91 (CH\(_3\)), 20.84 (CH\(_3\))

HRMS (ESI): Calcd. for C\(_{28}\)H\(_{29}\)N\(_2\)O\(_2\) [M+H]\(^+\) = 425.2224; Observed = 425.2222

**Compound (‒)-1k**
Yield = 111.5 mg (71%, white solid) starting from 100 mg of (−)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 20% ethyl acetate in pentane)

R_f = 0.50 (25% ethyl acetate/ pentane)

M.p. = 121-123 °C
IR (neat): 2924, 1724, 1609, 1494, 1325, 1142, 1040, 819, 749 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.58 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 8.7 Hz, 1H), 6.70 (dd, J = 8.7, 2.9 Hz, 1H), 6.60 (dd, J = 8.7, 2.9 Hz, 1H), 6.35 (d, J = 2.9 Hz, 1H), 6.32 (d, J = 2.9 Hz, 1H), 6.19 (d, J = 14.7 Hz, 1H), 4.81 (d, J = 17.4 Hz, 1H), 4.56 (d, J = 17.7 Hz, 1H), 4.33 (d, J = 15.4 Hz, 1H), 4.29 (d, J = 17.7 Hz, 1H), 3.77 (d, J = 14.7 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H), 2.35 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 173.53 (C), 156.98 (C), 156.67 (C), 142.92 (C), 140.76 (C), 139.63 (C), 138.19 (C), 137.83 (C), 137.39 (C), 131.56 (CH), 129.30 (CH), 128.93 (CH), 126.89 (CH), 113.68 (CH), 112.82 (CH), 112.40 (CH), 111.90 (CH), 75.76 (C), 62.38 (CH₂), 59.41 (CH₂), 56.09 (CH₂), 55.30 (CH₃), 55.27 (CH₃), 21.18 (CH₃);


[α]D²⁰ = −227 (c 0.04, CHCl₃).

Compound (+)-II

Yield = 109.4 mg (67%, pale yellow solid) starting from 100 mg of (+)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 20% ethyl acetate in pentane)

R_f = 0.53 (30% ethyl acetate/ pentane)

M.p. = 183-185 °C
IR (neat): 2909, 1719, 1605, 1497, 1452, 1303, 1252, 1233, 1166, 1028, 965, 833 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.60 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 9.1 Hz, 2H), 6.69 (dd, J = 8.7, 2.9 Hz, 1H), 6.60 (dd, J = 8.7, 2.9 Hz, 1H), 6.34 (d, J = 2.9 Hz, 1H), 6.32 (d, J = 2.9 Hz, 1H), 5.17 (d, J = 14.7 Hz, 1H), 4.79 (d, J = 17.4 Hz, 1H), 4.55 (d, J = 17.7 Hz, 1H), 4.32 (d, J = 17.2 Hz, 1H), 4.29 (d, J = 17.7 Hz, 1H), 3.81 (d, J = 14.7 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 173.63 (C), 159.12 (C), 157.01 (C), 156.71 (C), 142.96 (C), 140.79 (C), 138.22 (C), 137.84 (C), 134.59 (C), 131.56 (CH), 131.38 (CH), 128.97 (CH), 128.25 (CH), 128.07 (CH), 75.76 (C), 62.38 (CH₂), 59.41 (CH₂), 56.09 (CH₂), 55.30 (CH₃), 55.27 (CH₃), 21.18 (CH₃).
113.95 (CH), 113.88 (CH), 113.71 (CH), 112.86 (CH), 112.45 (CH), 111.93 (CH) 75.44 (C), 62.42 (CH$_2$), 59.42 (CH$_2$), 56.02 (CH$_2$), 55.40 (CH$_3$), 55.34 (CH$_3$), 55.30 (CH$_3$), 52.34 (CH$_3$);

HRMS (ESI): Calcd. for C$_{27}$H$_{29}$N$_2$O$_5$ [M+H]$^+$ = 461.2071; Observed = 461.2071
[α]$_D^{20}$ = +208 (c 0.04, CHCl$_3$).

**Compound (+)-1m**

Yield = 70.3 mg (78%, white solid) starting from 50 mg of (+)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 30% ethyl acetate in pentane)

R$_f$ = 0.38 (30% ethyl acetate/ pentane)

M.p. = 139-141 °C

IR (neat): 2923, 1726, 1608, 1493, 1235, 1142, 1040, 823, 752 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): 7.57 (d, $J$ = 8.8 Hz, 2H), 7.48 (d, $J$ = 8.8 Hz, 2H), 7.28 (d, $J$ = 8.6 Hz, 1H), 7.05 (d, $J$ = 8.6 Hz, 1H), 6.70 (dd, $J$ = 8.7, 2.9 Hz, 1H), 6.61 (dd, $J$ = 8.7, 2.9 Hz, 1H), 6.34 (d, $J$ = 2.9 Hz, 1H), 6.32 (d, $J$ = 2.9 Hz, 1H), 5.16 (d, $J$ = 14.6 Hz, 1H), 4.78 (d, $J$ = 17.5 Hz, 1H), 4.48 (d, $J$ = 17.7 Hz, 1H), 4.32 (d, $J$ = 17.5 Hz, 1H), 4.28 (d, $J$ = 17.7 Hz, 1H), 3.73 (d, $J$ = 14.6 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.90 (C), 157.16 (C), 156.83 (C), 141.67 (C), 140.31 (C), 137.81 (C), 131.77 (CH), 131.52 (CH), 128.98 (CH), 128.88 (CH), 121.94 (CH), 113.81 (CH), 113.02 (CH), 112.43 (CH), 111.99 (CH), 75.74 (C), 62.13 (CH$_2$), 59.41 (CH$_2$), 56.07 (CH$_2$), 55.36 (CH$_3$), 55.31 (CH$_3$), 52.56 (CH$_3$);

HRMS (ESI): Calcd. for C$_{26}$H$_{26}$N$_2$O$_4$Br [M+H]$^+$ = 509.1071; Observed = 509.1070
[α]$_D^{20}$ = +144 (c 0.06, CHCl$_3$).

**Compound (+)-1n**

Yield = 141.3 mg (80%, white solid) starting from 100 mg of (+)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 18% ethyl acetate in pentane)

R$_f$ = 0.56 (30% ethyl acetate/ pentane)

M.p. = 135-136 °C

IR (neat): 2945, 1744, 1613, 1493, 1241, 1163, 1121, 1065, 1015, 841 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): 7.82 (d, $J$ = 8.2 Hz, 2H), 7.63 (d, $J$ = 8.2 Hz, 2H), 7.31 (d, $J$ = 8.7 Hz, 1H), 7.06 (d, $J$ = 8.7 Hz, 1H), 6.71 (dd, $J$ = 8.7, 2.9 Hz, 1H), 6.61 (dd, $J$ = 8.7, 2.9 Hz, 1H), 6.36 (d, $J$ = 2.9 Hz, 1H), 6.32 (d, $J$ = 2.9 Hz, 1H), 5.22 (d, $J$ = 14.6 Hz, 1H), 4.79 (d, $J$ = 17.5 Hz, 1H), 4.46
(d, J = 17.7 Hz, 1H), 4.33 (d, J = 17.7 Hz, 1H), 4.32 (d, J = 17.5 Hz, 1H), 3.75 (d, J = 14.6 Hz, 1H),
3.69 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H);

\( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 172.64 (C), 157.52 (C), 156.81 (C), 146.64 (C), 142.66 (C), 140.16 (C), 137.79 (C), 137.67 (C), 131.52 (CH), 129.87 (q, \( ^2J_{C-F} = 32.4 \text{ Hz} \) (C), 129.01 (CH), 127.45 (CH),
125.57 (q, \( ^3J_{C-F} = 3.6 \text{ Hz} \) (CH), 124.19 (q, \( ^1J_{C-F} = 270 \text{ Hz} \) (C), 113.80 (CH), 113.07 (CH), 112.37 (CH), 112.00 (CH), 76.13 (C), 62.15 (CH\(_2\)), 59.40 (CH\(_2\)), 56.15 (CH\(_2\)), 55.31 (CH\(_3\)), 55.27 (CH\(_3\)),
52.61 (CH\(_3\));

\( ^{19} \text{F NMR} \) (282 MHz, CDCl\(_3\)) = \(-61.78\);

HRMS (ESI): Calcd. for C\(_{27}\)H\(_{26}\)F\(_3\)N\(_2\)O\(_4\) [M+H]\(^+\) = 499.1839; Observed = 499.1847
[\( \alpha \)]\(_D\)\(^{20}\) = +158 (c 0.11, CHCl\(_3\)).

**Compound (+)-1o**

Yield = 124.3 mg (73%, white solid) starting from 100 mg of (+)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 15% ethyl acetate in pentane)

R\(_f\) = 0.63 (40% ethyl acetate/ pentane)

M.p. = 181-182 °C

IR (neat): 2919, 1724, 1606, 1494, 1431, 1233, 1142, 1041, 806, 748 cm\(^{-1}\);

\( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)): 8.02 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.89-7.81 (m, 3H), 7.50-7.46 (m, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.74 (dd, J = 8.7, 2.8 Hz, 1H), 6.61 (dd, J = 8.7, 2.8 Hz, 1H), 6.39 (d, J = 2.8 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 5.35 (d, J = 14.6 Hz, 1H), 4.86 (d, J = 14.6 Hz, 1H), 4.60 (d, J = 17.8 Hz, 1H), 4.38 (d, J = 17.8 Hz, 1H), 4.37 (d, J = 17.8 Hz, 1H),
3.93 (d, J = 14.6 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.21 (s, 3H);

\( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 173.30 (C), 157.12 (C), 156.77 (C), 142.93 (C), 140.64 (C), 140.18 (C), 138.10 (C), 137.92 (C), 133.37 (C), 132.85 (C), 131.62 (CH), 128.97 (CH), 128.39 (CH), 128.30 (CH), 127.64 (CH), 126.40 (CH), 126.30 (CH), 126.20 (CH), 125.00 (CH), 113.81 (CH), 112.94 (CH), 112.44 (CH), 112.00 (CH), 76.12 (C), 62.61 (CH\(_2\)), 59.52 (CH\(_2\)), 56.27 (CH\(_2\)), 55.34 (2 x CH\(_3\)), 52.48 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{30}\)H\(_{29}\)N\(_2\)O\(_4\) [M+H]\(^+\) = 481.2122; Observed = 481.2141
[\( \alpha \)]\(_D\)\(^{20}\) = +147 (c 0.05, CHCl\(_3\)).
**Compound (+)-1p**

Yield = 351.3 mg (69%, white solid) starting from 282 mg of (+)-3 (R = OMe)

Purification: By column chromatography (Silica gel, 18% ethyl acetate in pentane)

R$_f$ = 0.52 (30% ethyl acetate/ pentane)

M.p. = 86-87 °C

IR (neat): 2918, 1722, 1608, 1494, 1447, 1272, 1229, 1142, 1039, 846, 696 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): 7.80 (d, $J = 7.5$ Hz, 2H), 7.41-7.42 (m, 2H), 7.38-7.31 (m, 2H), 7.26-7.18 (m, 3H), 7.12 (d, $J = 8.7$ Hz, 1H), 6.87-6.82 (m, 2H), 6.71-6.63 (m, 2H), 6.37 (d, $J = 2.9$ Hz, 1H), 6.36 (d, $J = 2.9$ Hz, 1H), 5.32 (d, $J = 14.7$ Hz, 1H), 4.85 (d, $J = 17.4$ Hz, 1H), 4.78 (d, $J = 12.4$ Hz, 1H), 4.71 (d, $J = 12.4$ Hz, 1H), 4.62 (d, $J = 17.7$ Hz, 1H), 4.37 (d, $J = 17.4$ Hz, 1H), 4.35 (d, $J = 17.7$ Hz, 1H), 3.89 (d, $J = 14.6$ Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.54 (C), 156.95 (C), 156.59 (C), 142.77 (C), 142.67 (C), 140.54 (C), 138.00 (C), 137.72 (C), 135.53 (C), 131.43 (CH), 128.83 (CH), 128.52 (CH), 128.09 (CH), 127.71 (CH), 127.69 (CH), 127.62 (CH), 127.04 (CH), 113.52 (CH), 112.79 (CH), 112.36 (CH), 112.07 (CH), 76.08 (C), 67.01 (CH$_2$), 62.29 (CH$_2$), 59.29 (CH$_2$), 56.30 (CH$_2$), 55.17 (CH$_3$), 55.06 (CH$_3$);

HRMS (ESI): Calcd. for C$_{32}$H$_{31}$N$_2$O$_4$ [M+H]$^+$ = 507.2278; Observed = 507.2276

$\text{[α]}_D^{20} = -128$ (c 0.08, CHCl$_3$).

**Compound 1q**

Yield = 31.2 mg (60%, white solid) starting from 36.6 mg of 3 (R = CO$_2$Et).

Purification: By column chromatography (Silica gel, 12% ethyl acetate in pentane)

R$_f$ = 0.52 (20% ethyl acetate/ pentane)

M.p. = 108-110 °C

IR (neat): 2950, 1710, 1606, 1492, 1446, 1277, 1237, 1173, 1103, 1020, 970, 845, 773, 698 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): 7.82 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.73-7.66 (m, 3H), 7.58 (d, $J = 1.8$ Hz, 1H), 7.51 (d, $J = 1.8$ Hz, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.32 (d, $J = 7.3$ Hz, 1H), 7.15 (d, $J = 8.3$ Hz, 1H), 5.21 (d, $J = 14.8$ Hz, 1H), 4.88 (d, $J = 17.6$ Hz, 1H), 4.62 (d, $J = 17.8$ Hz, 1H), 4.50 (d, $J = 18.4$ Hz, 1H), 4.45 (d, $J = 18.2$ Hz, 1H), 4.34-4.20 (m, 4H), 3.87 (d, $J = 14.7$ Hz, 1H), 3.04 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H);
13C NMR (75 MHz, CDCl3): δ 172.78 (C), 166.19 (C), 166.09 (C), 154.21 (C), 152.88 (C), 141.81 (C), 135.92 (C), 135.85 (C), 130.25 (CH), 130.09 (CH), 130.00 (CH), 128.90 (CH), 128.82 (CH), 128.75 (CH), 128.07 (CH), 127.86 (CH), 127.57 (C), 127.02 (C), 126.73 (CH), 75.38 (C), 61.47 (CH2), 60.93 (CH2), 60.82 (CH2), 58.75 (CH2), 55.76 (CH2), 52.58 (CH3), 14.41 (CH3), 14.37 (CH3);

HRMS (ESI): Calcd. for C30H31N2O6 [M+H]+ = 515.2177; Observed = 515.2171

2B: General procedure of methylene extrusion

To a stirred solution/suspension of ethano-Tröger base 1 (0.1 mmol) in wet nitromethane (2 mL), DDQ (0.12 mmol) was added and the reaction mixture was allowed to stir at 20 °C until TLC shows the complete consumption of starting material. Solvent was evaporated and the residue was purified by column chromatography to afford the methylene extrusion product 2.

Compound (+)-2a

Yield = 32.8 mg (85%, white solid) starting from 39.8 mg of (+)-1a

Purification: By column chromatography (Silica gel, 15% ethyl acetate in pentane)

Rf = 0.38 (20% ethyl acetate/ pentane)

M.p. = 81-83 °C

IR (neat): 2919, 1741, 1677, 1492, 1220, 1090, 1018, 804, 778 cm−1;

1H NMR (400 MHz, CDCl3): 7.84 (brs, 2H), 7.30-7.19 (m, 5H), 7.01 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.69 (s, 1H), 6.41 (s, 1H), 4.90 (d, J = 17.4 Hz, 1H), 4.32 (d, J = 14.5 Hz, 1H), 4.28 (d, J = 14.5 Hz, 1H), 4.05 (d, J = 17.4 Hz, 1H), 3.55 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H);

13C NMR (100 MHz, CDCl3): δ 170.82 (C), 146.15 (C), 145.25 (C), 137.55 (C), 133.86 (C), 133.73 (C), 128.68 (CH), 128.60 (CH), 128.35 (CH), 128.30 (CH), 128.25 (CH), 127.72 (C), 127.07 (C), 126.86 (CH), 126.74 (CH), 125.76 (CH), 125.56 (CH), 81.69 (C), 56.91 (CH2), 55.39 (CH2), 53.18 (CH3), 21.03 (CH3), 20.92 (CH3);


[α]D20 = +382 (c 0.03, CHCl3).

Similarly, compound (−)-2a was obtained starting from (−)-1a, in 83% yields with 99% ee

[α]D20 = −384 (c 0.03, CHCl3).

Compound (+)-2b
Yield = 32.1 mg (81%, white solid) starting from 41.2 mg of (+)-1b
Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)
R_f = 0.58 (15% ethyl acetate/ pentane)
M.p. = 217-218 °C

IR (neat): 2917, 1744, 1493, 1431, 1249, 1203, 1096, 937, 817 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.69 (brs, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 7.6 Hz, 2H), 7.02 (dd, J = 8.2, 1.4 Hz, 1H), 6.98 (dd, J = 8.2, 1.4 Hz, 1H), 6.69 (d, J = 0.7 Hz, 1H), 6.42 (d, J = 0.7 Hz, 1H), 4.90 (d, J = 17.4 Hz, 1H), 4.34 (d, J = 17.1 Hz, 1H), 4.27 (d, J = 17.4 Hz, 1H), 4.04 (d, J = 17.1 Hz, 1H), 3.56 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 2.12 (s, 3H);

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 171.00 (C), 146.22 (C), 145.36 (C), 138.09 (C), 134.60 (C), 133.80 (C), 133.65 (C), 129.14 (CH), 128.65 (CH), 128.56 (CH), 128.13 (CH), 127.84 (C), 127.09 (C), 126.91 (CH), 126.75 (CH), 125.78 (CH), 81.54 (C), 56.92 (CH\(_2\)), 55.37 (CH\(_2\)), 53.17 (CH\(_3\)), 21.25 (CH\(_3\)), 21.04 (CH\(_3\)), 20.96 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{26}\)H\(_{27}\)N\(_2\)O\(_2\) [M+H]\(^+\) = 399.2067; Observed = 399.2057
\([\alpha]_D^{20} = +221 (c 0.07, CHCl\(_3\)).

**Compound (+)-2c**

Yield = 31.3 mg (75%, white solid) starting from 42.8 mg of (+)-1c
Purification: By column chromatography (Silica gel, 10% ethyl acetate in pentane)
R_f = 0.48 (20% ethyl acetate/ pentane)
M.p. = 101-103 °C

IR (neat): 2927, 1740, 1607, 1493, 1436, 1244, 1204, 1093, 1020, 822 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.71 (brs, 2H), 7.27 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.02-7.00 (m, 1H), 6.97 (dd, J = 8.2, 1.4 Hz, 1H), 6.77 (d, J = 7.9 Hz, 2H), 6.69 (s, 1H), 6.43 (s, 1H), 4.88 (d, J = 17.4 Hz, 1H), 4.31 (d, J = 17.2 Hz, 1H), 4.25 (d, J = 17.4 Hz, 1H), 4.03 (d, J = 17.2 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H);

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 171.07 (C), 159.51 (C), 146.22 (C), 145.31 (C), 133.85 (C), 133.69 (C), 129.58 (CH), 129.53 (C), 128.66 (CH), 128.57 (CH), 127.84 (C), 127.11 (C), 126.90 (CH), 126.76 (CH), 125.79 (CH), 125.60 (CH), 113.77 (CH), 81.28 (C), 56.88 (CH\(_2\)), 55.37 (CH\(_2\)), 55.26 (CH\(_3\)), 53.15 (CH\(_3\)), 21.05 (CH\(_3\)), 20.96 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{26}\)H\(_{27}\)N\(_2\)O\(_3\) [M+H]\(^+\) = 415.2016; Observed = 415.2008
\([\alpha]_D^{20} = +325 (c 0.07, CHCl\(_3\)).

S11
Compound (+)-2d

Yield = 43 mg (93%, white solid) starting from 47.6 mg of (+)-1d

Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)

R_f = 0.36 (10% ethyl acetate/ pentane)

M.p. = 176-178 °C

IR (neat): 2917, 1745, 1492, 1434, 1248, 1203, 1137, 1091, 1012, 832, 818, 748 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.70 (brs, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.02 (dd, J = 8.2, 1.2 Hz, 1H), 6.98 (dd, J = 8.2, 1.2 Hz, 1H), 6.69 (s, 1H), 6.44 (s, 1H), 4.88 (d, J = 17.4 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 4.26 (d, J = 17.4 Hz, 1H), 4.05 (d, J = 17.3 Hz, 1H), 3.56 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 170.45 (C), 145.96 (C), 144.95 (C), 136.74 (C), 134.03 (C), 134.00 (C), 131.61 (CH), 130.14 (CH), 128.76 (CH), 127.47 (C), 127.09 (C), 126.79 (CH), 126.72 (CH), 125.79 (CH), 125.56 (CH), 122.73 (C), 81.38 (C), 56.80 (CH\(_2\)), 55.29 (CH\(_2\)), 53.30 (CH\(_3\)), 21.03 (CH\(_3\)), 20.93 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{25}\)H\(_{24}\)N\(_2\)O\(_2\)Br [M+H]\(^+\) = 463.1016; Observed = 463.1013

\([\alpha]\)\(_D\)^20 = +320 (c 0.02, CHCl\(_3\)).

Compound (+)-2e

Yield = 29.9 mg (66%, white solid) starting from 46.6 mg of (+)-1e

Purification: By column chromatography (Silica gel, 6% ethyl acetate in pentane)

R_f = 0.58 (15% ethyl acetate/ pentane)

M.p. = 103-104 °C

IR (neat): 2920, 1744, 1493, 1323, 1204, 1120, 1066, 1016, 820 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 8.06-7.86 (brm, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.03 (dd, J = 8.2, 1.3 Hz, 1H), 6.99 (dd, J = 8.2, 1.3 Hz, 1H), 6.70 (s, 1H), 6.43 (s, 1H), 4.88 (d, J = 17.5 Hz, 1H), 4.28 (d, J = 17.5 Hz, 1H), 4.25 (d, J = 17.4 Hz, 1H), 4.07 (d, J = 17.4 Hz, 1H), 3.56 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 170.27 (C), 145.94 (C), 144.89 (C), 141.64 (C), 134.13 (C), 134.11 (C), 130.40 (q, J\(_{CF}\) = 32.4 Hz) (C), 128.85 (CH), 128.82 (CH), 128.77 (CH), 127.35 (C), 127.10 (C),
126.83 (CH), 126.71 (CH), 125.8 (CH), 125.38 (q, 3J_C-F = 3.6 Hz) (CH), 124.07 (q, 1J_C-F = 271.0 Hz) (C), 81.58 (C), 56.84 (CH_2), 55.31 (CH_2), 53.36 (CH_3), 21.01 (CH_3), 20.91 (CH_3);

^19_F NMR (282 MHz, CDCl_3) = – 62.61

HRMS (ESI): Calcd. for C_{26}H_{24}F_3N_2O_2 [M+H]^+ = 453.1784; Observed = 453.1774

[α]_D^{20} = +117 (c 0.73, CHCl_3).

Compound (+)-2f

Yield = 16.5 mg (76%, white solid) starting from 22.4 mg of (+)-1f

Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)

R_f = 0.45 (15% ethyl acetate/pentane)

M.p. = 156-158 °C

IR (neat): 2919, 1741, 1493, 1434, 1228, 1203, 1126, 1096, 821, 746 cm\(^{-1}\);

^1H NMR (400 MHz, CDCl_3): 8.50-7.50 (m, 5H), 7.47-7.42 (m, 2H), 7.37 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 4.96 (d, J = 17.4 Hz, 1H), 4.34 (d, J = 17.4 Hz, 1H), 3.55 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H);

^13C NMR (100 MHz, CDCl_3): δ 170.70 (C), 146.05 (C), 145.16 (C), 134.03 (C), 133.85 (C), 133.20 (C), 133.15 (C), 128.78 (CH), 128.72 (CH), 128.15 (CH), 127.68 (C), 127.54 (CH), 127.15 (CH), 126.87 (C), 126.80 (CH), 126.62 (CH), 126.04 (CH), 125.59 (CH), 81.92 (C), 56.95 (CH_2), 53.30 (CH_3), 21.06 (CH_3), 20.89 (CH_3);

HRMS (ESI): Calcd. for C_{29}H_{27}N_2O_2 [M+H]^+ = 435.2067; Observed = 435.2066

[α]_D^{20} = +438 (c 0.19, CHCl_3).

Compound (+)-2g

Yield = 29.7 mg (68%, white solid) starting from 44.8 mg of (+)-1g

Purification: By column chromatography (Silica gel, 6% ethyl acetate in pentane)

R_f = 0.55 (15% ethyl acetate/pentane)

M.p. = 88-89 °C

IR (neat): 2918, 1741, 1677, 1492, 1219, 1090, 1018, 974, 778 cm\(^{-1}\);

^1H NMR (400 MHz, CDCl_3): 9.53 (d, J = 8.9 Hz, 1H), 8.02 (dd, J = 7.5, 1.2 Hz, 1H), 7.81 (dd, J = 4.6, 4.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.58 (ddd, J = 8.6, 6.8, 1.5 Hz, 1H), 7.49 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 8.0, 2.6 Hz, 2H), 7.07 (dd, J = 8.1, 1.4 Hz, 1H), ...
7.01 (dd, \( J = 8.2, 1.4 \) Hz, 1H), 6.72 (d, \( J = 0.8 \) Hz, 1H), 6.24 (d, \( J = 0.8 \) Hz, 1H), 4.77 (d, \( J = 17.5 \) Hz, 1H), 4.43 (d, \( J = 17.5 \) Hz, 1H), 3.92, 3.87 (ABq, \( J_{AB} = 14.7 \) Hz, 2H), 3.51 (s, 3H), 2.25 (s, 3H), 2.10 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 169.62 (C), 145.87 (C), 145.25 (C), 134.23 (C), 133.62 (C), 133.45 (C), 132.29 (C), 131.38 (C), 129.73 (CH), 129.38 (CH), 128.72 (CH), 128.70 (CH), 128.59 (CH), 128.48 (C), 126.85 (CH), 126.83 (CH), 126.74 (C), 126.45 (CH), 126.37 (CH), 125.66 (CH), 125.47 (CH), 125.38 (CH), 125.24 (CH), 82.64 (C), 57.12 (CH\(_2\)), 55.50 (CH\(_2\)), 53.13 (CH\(_3\)), 21.09 (CH\(_3\)), 20.91 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{29}\)H\(_{27}\)N\(_2\)O\(_2\) [M+H]\(^+\) = 435.2067; Observed = 435.2066

\([\alpha]_D^{20} = +480 \) (c 0.06, CHCl\(_3\)).

**Compound (+)-2h**

Yield = 40.8 mg (89%, white solid) starting from 47.4 mg of (+)-1h

Purification: By column chromatography (Silica gel, 8% ethyl acetate in pentane)

\( R_f = 0.51 \) (10% ethyl acetate/ pentane)

M.p. = 84-86 °C

IR (neat): 2921, 1739, 1493, 1449, 1228, 1164, 1136, 1099, 821 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.83 (brs, 2H), 7.29 (d, \( J = 8.2 \) Hz, 2H), 7.25-7.16 (m, 4H), 7.15-7.09 (m, 2H), 7.03 (dd, \( J = 8.2, 1.4 \) Hz, 1H), 6.98 (dd, \( J = 8.1, 1.5 \) Hz, 1H), 6.82-6.72 (m, 2H), 6.65 (d, \( J = 0.7 \) Hz, 1H), 6.43 (d, \( J = 0.7 \) Hz, 1H), 5.17 (d, \( J = 12.5 \) Hz, 1H), 4.89 (d, \( J = 17.5 \) Hz, 1H), 4.87 (d, \( J = 12.5 \) Hz, 1H), 4.37 (d, \( J = 17.2 \) Hz, 1H), 4.24 (d, \( J = 17.5 \) Hz, 1H), 4.07 (d, \( J = 17.2 \) Hz, 1H), 2.25 (s, 3H), 2.12 (s, 3H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 170.10 (C), 146.31 (C), 145.40 (C), 137.44 (C), 135.53 (C), 133.82 (C), 133.64 (C), 128.55 (CH), 128.33 (CH), 128.26 (CH), 128.20 (CH), 127.76 (CH), 127.70 (C), 127.57 (CH), 127.13 (CH), 127.08 (C), 126.71 (CH), 125.82 (CH), 125.70 (CH), 81.84 (C), 67.14 (CH\(_3\)), 56.85 (CH\(_2\)), 55.30 (CH\(_2\)), 21.04 (CH\(_3\)), 20.92 (CH\(_3\));

HRMS (ESI): Calcd. for C\(_{31}\)H\(_{29}\)N\(_2\)O\(_2\) [M+H]\(^+\) = 461.2214; Observed = 461.2215

\([\alpha]_D^{20} = +219 \) (c 0.12, CHCl\(_3\)).
**Compound 2i**

Yield = 34.6 mg (84%, white solid) starting from 42.5 mg of 1i

Purification: By column chromatography (Silica gel, 15% ethyl acetate in pentane)

R_f = 0.36 (15% ethyl acetate/ pentane)

M.p. = 109-110 °C

IR (neat): 2920, 1740, 1493, 1447, 1227, 1203, 1136, 1100, 986, 822, 725 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.84 (s, 2H), 7.37-7.10 (m, 5H), 7.02 (dd, J = 7.2, 1.0 Hz, 1H), 6.98 (dd, J = 7.2, 1.0 Hz, 1H), 6.70 (s, 1H), 6.42 (s, 1H), 5.55 (ddd, J = 16.0, 10.7, 5.4 Hz, 1H), 4.96 (dd, J = 10.7, 1.2 Hz, 1H), 4.94 (d, J = 17.2 Hz, 1H), 4.84 (dd, J = 17.2, 1.3 Hz, 1H), 4.59-4.51 (m, 1H), 4.41 – 4.34 (m, 1H), 4.35 (d, J = 17.0 Hz, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.06 (d, J = 17.2 Hz, 1H), 2.22 (s, 3H), 2.12 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 169.95 (C), 146.34 (C), 145.42 (C), 137.61 (C), 133.83 (C), 133.64 (C), 131.33 (CH), 128.60 (CH), 128.55 (CH), 128.37 (CH), 128.30 (CH), 128.28 (CH), 127.76 (C), 127.07 (C), 127.04 (CH), 126.73 (CH), 125.82 (CH), 125.63 (CH), 118.00 (CH₂), 81.76 (C), 65.93 (CH₃), 56.89 (CH₂), 55.34 (CH₂), 21.02 (CH₃), 20.93 (CH₃);

HRMS (ESI): Calcd. for C₂₇H₂₇N₂O₂ [M+H]^⁺ = 411.2067; Observed = 411.2069

---

**Compound (−)-2j**

Yield = 18.7 mg (90%, white solid) starting from 21.5 mg of (−)-1j

Purification: By column chromatography (Silica gel, 25% ethyl acetate in pentane)

R_f = 0.32 (30% ethyl acetate/ pentane)

M.p. = 97-99 °C

IR (neat): 2918, 1741, 1677, 1492, 1220, 1090, 804 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.86-7.77 (brm, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.29-7.19 (m, 3H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 6.14 (d, J = 2.1 Hz, 1H), 4.90 (d, J = 17.5 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 4.25 (d, J = 17.5 Hz, 1H), 4.02 (d, J = 17.3 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.87 (C), 156.34 (C), 156.16 (C), 141.66 (C), 140.76 (C), 137.50 (C), 128.89 (CH), 128.37 (C), 128.34 (CH), 128.31 (C), 128.02 (CH), 127.00 (CH), 126.85 (CH), 114.73 (CH), 114.54 (CH), 110.32 (CH), 110.14 (CH), 81.86 (C), 57.11 (CH₂), 55.59 (CH₂), 55.40 (CH₃), 55.29 (CH₃), 53.21 (CH₃);

HRMS (ESI): Calcd. for C₂₇H₂₇N₂O₄ [M+H]^⁺ = 417.1808; Observed = 417.1808
[α]_D^{20} = −280 (c 0.045, CHCl₃).

**Compound (−)-2k**

Yield = 35.5 mg (82%, white solid) starting from 44.5 mg of (−)-1k

Purification: By column chromatography (Silica gel, 30% ethyl acetate in pentane)

R_f = 0.33 (30% ethyl acetate/ pentane)

M.p. = 187-188 °C

IR (neat): 2915, 1742, 1612, 1492, 1427, 1231, 1202, 1128, 1051, 814 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.68 (brd, J = 8.2 Hz, 2H), 7.32 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.06 (d, J = 7.8 Hz, 2H), 6.79 (dd, J = 8.8, 2.9 Hz, 1H), 6.75 (dd, J = 8.8, 2.9 Hz, 1H), 6.40 (d, J = 2.9 Hz, 1H), 6.14 (d, J = 2.9 Hz, 1H), 4.90 (d, J = 17.5 Hz, 1H), 4.34 (d, J = 17.2 Hz, 1H), 4.24 (d, J = 17.5 Hz, 1H), 4.01 (d, J = 17.2 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.55 (s, 3H), 2.26 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.97 (C), 156.27 (C), 156.08 (C), 141.64 (C), 140.80 (C), 138.10 (C), 134.48 (C), 129.18 (CH), 128.92 (C), 128.14 (CH), 128.00 (C), 126.94 (CH), 126.81 (CH), 114.66 (CH), 114.41 (CH), 110.27 (CH), 110.12 (CH), 81.61 (C), 57.06 (CH₂), 55.53 (CH₂), 55.34 (CH₂), 55.22 (CH₃), 55.13 (CH₃), 21.20 (CH₃);


[α]_D^{20} = −262 (c 0.05, CHCl₃).

**Compound (+)-2l**

Yield = 30.2 mg (68%, white solid) starting from 46 mg of (+)-1l

Purification: By column chromatography (Silica gel, 30% ethyl acetate in pentane)

R_f = 0.43 (40% ethyl acetate/ pentane)

M.p. = 151-152 °C

IR (neat): 2934, 1739, 1608, 1492, 1242, 1201, 1169, 1030, 837 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.71 (brd, J = 6.9 Hz, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.82-6.72 (m, 4H), 6.40 (d, J = 2.8 Hz, 1H), 6.15 (d, J = 2.8 Hz, 1H), 4.90 (d, J = 17.5 Hz, 1H), 4.32 (d, J = 17.2 Hz, 1H), 4.23 (d, J = 17.5 Hz, 1H), 4.01 (d, J = 17.2 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 171.06 (C), 159.51 (C), 156.32 (C), 156.12 (C), 141.59 (C), 140.76 (C), 129.61 (CH), 129.39 (C), 128.94 (C), 128.01 (C), 126.97 (CH), 126.85 (CH), 114.70 (CH),
114.48 (CH), 113.76 (CH), 110.31 (CH), 110.13 (CH), 81.44 (C), 57.04 (CH₂), 55.51 (CH₂), 55.39 (CH₃), 55.29 (CH₃), 55.26 (CH₃), 53.13 (CH₃);

HRMS (ESI): Calcd. for C₂₆H₂₇N₂O₅ [M+H]+ = 447.1915; Observed = 447.1915
[a]D²⁰ = +321 (c 0.06, CHCl₃).

**Compound (+)-2m**

Yield = 39.9 mg (81%, white solid) starting from 50.8 mg of (+)-1m

Purification: By column chromatography (Silica gel, 25% ethyl acetate in pentane)

Rf = 0.39 (30% ethyl acetate/ pentane)

M.p. = 128-129 °C

IR (neat): 2940, 1737, 1611, 1492, 1432, 1237, 1200, 1044, 1010, 814, 749 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.70 (brs, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.7, 2.6 Hz, 1H), 6.75 (dd, J = 8.7, 2.6 Hz, 1H), 6.40 (d, J = 2.6 Hz, 1H), 6.15 (d, J = 2.6 Hz, 1H), 4.89 (d, J = 17.5 Hz, 1H), 4.28 (d, J = 17.7 Hz, 1H), 4.24 (d, J = 17.7 Hz, 1H), 4.03 (d, J = 17.5 Hz, 1H), 3.70 (s, 3H), 3.62 (s, 3H), 3.55 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.43 (C), 156.44 (C), 156.30 (C), 141.36 (C), 140.37 (C), 136.63 (C), 131.61 (CH), 130.16 (CH), 128.57 (C), 127.85 (C), 127.00 (CH), 126.82 (CH), 122.75 (C), 114.79 (CH), 114.73 (CH), 110.31 (CH), 110.10 (CH), 81.57 (C), 56.96 (CH₂), 55.48 (CH₂), 55.39 (CH₃), 55.29 (CH₃), 55.30 (CH₃);

HRMS (ESI): Calcd. for C₂₅H₂₄N₂O₄Br [M+H]+ = 495.0914; Observed = 495.0918
[a]D²⁰ = +276 (c 0.07, CHCl₃).

**Compound (+)-2n**

Yield = 17.5 mg (72%, white solid) starting from 25 mg of (+)-1n

Purification: By column chromatography (Silica gel, 30% ethyl acetate in pentane)

Rf = 0.39 (30% ethyl acetate/ pentane)

M.p. = 160-161 °C

IR (neat): 2927, 1728, 1610, 1495, 1324, 1236, 1163, 1120, 1067, 1041, 864 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 1.94 (brs, 2H), 7.52 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 8.8, 2.9 Hz, 1H), 6.77 (dd, J = 8.8, 2.9 Hz, 1H), 6.42 (d, J = 2.9 Hz, 1H), 6.15 (d, J = 2.9 Hz, 1H), 4.91 (d, J = 17.5 Hz, 1H), 4.26 (d, J = 17.3 Hz, 2H), 4.05 (d, J = 17.4 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 3.56 (s, 3H);
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 170.27 (C), 156.51 (C), 156.38 (C), 141.54 (C), 140.35 (C), 140.32 (C), 130.44 (q, $^2$J$_{CF}$ = 32.4 Hz) (C), 128.81 (CH), 128.49 (C), 127.85 (C), 127.04 (CH), 126.84 (CH), 125.39 (q, $^3$J$_{CF}$ = 3.6 Hz) (CH), 124.07 (q, $^1$J$_{CF}$ = 271 Hz) (C), 114.85 (CH), 114.82 (CH), 110.35 (C), 110.18 (CH), 81.77 (C), 57.01 (C), 55.76 (CH$_2$), 55.39 (CH$_3$), 55.22 (CH$_3$), 53.27 (CH$_3$);
$^{19}$F NMR (282 MHz, CDCl$_3$) = −61.87
HRMS (ESI): Calcd. for C$_{26}$H$_{24}$F$_3$N$_2$O$_4$ [M+H]$^+$ = 485.1683; Observed = 485.1686
[$\alpha$]$_{D}^{20}$ = +158 (c 0.11, CHCl$_3$).

**Compound (+)-2o**

Yield = 36.3 mg (78%, white solid) starting from 48 mg of (+)-1o
Purification: By column chromatography (Silica gel, 30% ethyl acetate in pentane)

R$_f$ = 0.32 (30% ethyl acetate/ pentane)

M.p. = 155-157 °C

IR (neat): 2935, 1741, 1612, 1492, 1431, 1203, 1124, 1061, 818, 749 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$ at 55 °C): 8.31 (brs, 1H), 7.99 (brs, 1H), 7.84-7.72 (m, 3H), 7.49-7.37 (m, 3H), 7.33 (d, $J$ = 8.8 Hz, 1H), 6.83 (dd, $J$ = 8.8, 2.8 Hz, 1H), 6.77 (dd, $J$ = 8.8, 2.8 Hz, 1H), 6.45 (d, $J$ = 2.8 Hz, 1H), 6.09 (d, $J$ = 2.8 Hz, 1H), 4.98 (d, $J$ = 17.4 Hz, 1H), 4.40 (d, $J$ = 16.5 Hz, 1H), 4.31 (d, $J$ = 17.4 Hz, 1H), 4.07 (d, $J$ = 17.3 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 3H), 3.54 (s, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$ at 55 °C): δ 170.75 (C), 156.39 (C), 156.17 (C), 141.58 (C), 140.66 (C), 134.95 (C), 133.18 (C), 133.13 (C), 128.85 (C), 128.67 (CH), 128.13 (CH), 128.00 (C), 127.52 (CH), 127.01 (CH), 126.85 (CH), 126.63 (CH), 126.05 (CH), 114.78 (CH), 114.73 (CH), 110.36 (CH), 110.05 (CH), 82.03 (C), 57.11 (CH$_2$), 55.76 (CH$_2$), 55.39 (CH$_3$), 55.22 (CH$_3$), 53.27 (CH$_3$);

HRMS (ESI): Calcd. for C$_{29}$H$_{27}$N$_2$O$_4$ [M+H]$^+$ = 467.1965; Observed = 467.1967
[$\alpha$]$_{D}^{20}$ = +312 (c 0.06, CHCl$_3$).

**Compound (+)-2p**

Yield = 39.4 mg (80%, white solid) starting from 50.6 mg of (+)-1p
Purification: By column chromatography (Silica gel, 25% ethyl acetate in pentane)

R$_f$ = 0.38 (30% ethyl acetate/ pentane)

M.p. = 85-86 °C

IR (neat): 2919, 1724, 1608, 1493, 1448, 1272, 1230, 1144, 1038, 844, 696 cm$^{-1}$;
$^1$H NMR (400 MHz, CDCl$_3$): 7.82 (brs, 2H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.27-7.21 (m, 4H), 7.20-7.17 (m, 1H), 7.15-7.11 (m, 2H), 6.82-6.79 (m, 3H), 6.75 (dd, $J = 8.8$, 2.9 Hz, 1H), 6.34 (d, $J = 2.8$ Hz, 1H), 6.15 (d, $J = 2.8$ Hz, 1H), 5.15 (d, $J = 12.5$ Hz, 1H), 4.88 (d, $J = 17.5$ Hz, 1H), 4.87 (d, $J = 12.5$ Hz, 1H), 4.36 (d, $J = 17.3$ Hz, 1H), 4.21 (d, $J = 17.5$ Hz, 1H), 4.04 (d, $J = 17.3$ Hz, 1H), 3.72 (s, 3H), 3.61 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.11 (C), 156.41 (C), 156.11 (C), 141.77 (C), 140.89 (C), 137.36 (C), 135.50 (C), 128.83 (C), 128.41 (CH), 128.33 (CH), 128.29 (CH), 128.24 (CH), 128.19 (C), 127.83 (CH), 127.64 (CH), 127.03 (CH), 126.97 (CH), 114.75 (CH), 114.48 (CH), 110.19 (CH), 110.09 (CH), 82.00 (C), 67.18 (CH$_2$), 57.02 (CH$_2$), 55.47 (CH$_2$), 55.38 (CH$_3$), 55.25 (CH$_3$);

HRMS (ESI): Calcd. for C$_{31}$H$_{29}$N$_2$O$_4$ [M+H]$^+$ = 493.2122; Observed = 493.2121

$\alpha$D$_{20}$ = –279 (c 0.03, CHCl$_3$).

**Compound 2q**

Yield = 13.3 mg (51%, white solid) starting from 25.7 mg of 1q, using 4 equivalents of DDQ.

Purification: By column chromatography (Silica gel, 15% ethyl acetate in pentane)

M.p. = 98-99 °C

IR (neat): 1710, 1611, 1277, 1256, 1174, 1099, 1017, 780 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.88 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.83-7.69 (brm, 1H), 7.64 (d, $J = 1.7$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.36 (d, $J = 1.7$ Hz, 1H), 7.27-7.21 (m, 3H), 5.00 (d, $J = 17.6$ Hz, 1H), 4.46 (d, $J = 11.2$ Hz, 1H), 4.41 (d, $J = 11.5$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.19 (d, $J = 17.6$ Hz, 1H), 3.04 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.06 (C), 166.17 (C), 166.07 (C), 153.07 (C), 152.10 (C), 136.53 (C), 129.25 (CH), 129.24 (CH), 128.81 (CH), 128.66 (CH), 128.55 (CH), 128.09 (CH), 127.90 (C), 127.02 (C), 126.73 (C), 126.62 (C), 126.01 (CH), 125.88 (CH), 81.41 (C), 60.98 (CH$_2$), 60.94 (CH$_2$), 56.78 (CH$_2$), 55.30 (CH$_2$), 53.39 (CH$_3$), 14.45 (CH$_3$), 14.37 (CH$_3$);

HRMS (ESI): Calcd. for C$_{29}$H$_{29}$N$_2$O$_6$ [M+H]$^+$ = 501.2020; Observed = 501.2024
**Compound 2r**

Yield = 21.5 mg (61%, white solid) starting from 36.8 mg of 1r, using 4 equivalents of DDQ.

Purification: By column chromatography (Silica gel, 20% ethyl acetate in pentane)

R\textsubscript{f} = 0.47 (20% ethyl acetate/ pentane)

M.p. = 56-57 °C

IR (neat): 2922, 2854, 1697, 1493, 1448, 1220, 1026, 828 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta 8.25 (d, J = 7.2 \text{ Hz}, 2H), 7.59 (t, J = 7.4 \text{ Hz}, 1H), 7.46 (t, J = 7.7 \text{ Hz}, 2H), 7.19 (d, J = 8.2 \text{ Hz}, 1H), 7.10 (d, J = 8.2 \text{ Hz}, 1H), 7.02 (d, J = 8.2 \text{ Hz}, 2H), 6.79 (s, 1H), 6.57 (s, 1H), 5.47 (s, 1H), 4.82 (d, J = 16.7 \text{ Hz}, 1H), 4.31 (d, J = 16.7 \text{ Hz}, 1H), 4.25 (d, J = 17.2 \text{ Hz}, 1H), 4.00 (d, J = 17.2 \text{ Hz}, 1H), 2.26 (s, 3H), 2.19 (s, 3H);

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta 193.10 (C), 146.65 (C), 144.11 (C), 134.61 (C), 134.20 (C), 133.73 (CH), 133.50 (C), 129.58 (CH), 128.82 (CH), 128.52 (CH), 128.36 (CH), 128.06 (C), 127.45 (CH), 127.04 (CH), 125.92 (C), 124.82 (CH), 124.75 (CH), 77.09 (CH), 60.55 (CH\textsubscript{2}), 54.30 (CH\textsubscript{2}), 21.02 (CH\textsubscript{3}), 21.01 (CH\textsubscript{3});

HRMS (ESI): Calcd. for C\textsubscript{24}H\textsubscript{23}N\textsubscript{2}O [M+H]\textsuperscript{+} = 355.1805; Observed = 355.1807
3. NMR Spectra

$^1$H NMR of 2a (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2a (100 MHz, CDCl$_3$)
$^1$H NMR of 2b (400 MHz, CDCl$_3$)

$^1$C NMR of 2b (100 MHz, CDCl$_3$)
$^1$H NMR of 2c (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2c (100 MHz, CDCl$_3$)
$^1$H NMR of 2d (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2d (100 MHz, CDCl$_3$)
$^1$H NMR of 2e (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2e (100 MHz, CDCl$_3$)
$^1$H NMR of 2f (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2f (100 MHz, CDCl$_3$)
$^1$H NMR of 1g (400 MHz, CDCl₃)

$^{13}$C NMR of 1g (100 MHz, CDCl₃)
$^1$H NMR of 2g (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2g (100 MHz, CDCl$_3$)
$^1$H NMR of 1h (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1h (100 MHz, CDCl$_3$)
$^1$H NMR of 2h (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2h (100 MHz, CDCl$_3$)
$^1$H NMR of $\textbf{II}$ (400 MHz, CDCl$_3$)

$^{13}$C NMR of $\textbf{II}$ (100 MHz, CDCl$_3$)
$^1$H NMR of 2i (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2i (100 MHz, CDCl$_3$)
$^1$H NMR of 2j (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2j (100 MHz, CDCl$_3$)
$^1$H NMR of 1k (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1k (100 MHz, CDCl$_3$)
$^1$H NMR of 2k (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2k (100 MHz, CDCl$_3$)
$^1$H NMR of II (400 MHz, CDCl$_3$)

$^{13}$C NMR of II (100 MHz, CDCl$_3$)
$^1$H NMR of 2l (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2l (100 MHz, CDCl$_3$)
$^1$H NMR of 1m (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1m (100 MHz, CDCl$_3$)
$^1$H NMR of 2m (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2m (100 MHz, CDCl$_3$)
$^1$H NMR of In (400 MHz, CDCl$_3$)

$^{13}$C NMR of In (100 MHz, CDCl$_3$)
$^1$H NMR of 2n (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2n (100 MHz, CDCl$_3$)
$^1$H NMR of 1o (400 MHz, CDCl$_3$)

$^1$C NMR of 1o (100 MHz, CDCl$_3$)
$^1$H NMR of 2o (500 MHz, CDCl$_3$, At 55 °C)

$^{13}$C NMR of 2o (125 MHz, CDCl$_3$, At 55 °C)
$^1$H NMR of 1p (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1p (100 MHz, CDCl$_3$)
$^1$H NMR of 2p (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2p (100 MHz, CDCl$_3$)
$^1$H NMR of 1q (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1q (75 MHz, CDCl$_3$)
$^1$H NMR of 2q (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2q (100 MHz, CDCl$_3$)
$^1$H NMR of 2r (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2r (100 MHz, CDCl$_3$)
4. NMR evidence for the formation of formaldehyde

NMR of crude reaction mixture of 2j (400 MHz, CD$_2$Cl$_2$). Reaction was performed with DDQ (0.1 equiv.) and MnO$_2$ (10 equiv.) in CD$_2$Cl$_2$ in a closed vial.

After addition of aq. formaldehyde in the same NMR sample.
5. CSP-HPLC traces

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:2/98; 0.7 mL/min; 23 °C, 210 nm
HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:0.7/99.3; 1 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:1/99; 1 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 1/99; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 1/99; 1 mL/min; 23 °C, 210 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 5/95; 1 mL/min; 23 °C, 210 nm
HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane:1/99; 0.5 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:7/93; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:1/99; 1 mL/min; 23 °C, 230 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 1/99; 1 mL/min; 23 °C, 230 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 7/93; 1 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 5/95; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 2/98; 1 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 230 nm
HPLC Conditions: IC (Chiral pack) column; IPA/n-Hexane:15/85; 1 mL/min; 23 °C, 210 nm
HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane:8/92; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:5/95; 1 mL/min; 23 °C, 254 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:2/98; 1 mL/min; 23 °C, 210 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 210 nm
HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane:7/93; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:5/95; 1 mL/min; 23 °C, 210 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 220 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 220 nm
HPLC Conditions: Whelk O1 column; IPA/n-Hexane:2/98; 0.7 mL/min; 23 °C, 210 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane:10/90; 1 mL/min; 23 °C, 210 nm

S65
6. Configurational stability

HPLC Conditions: IC (chiral pack) column; IPA/n-Hexane: 10/90; 1 mL/min; 23 °C, 254 nm

HPLC Conditions: Whelk O1 column; IPA/n-Hexane: 2/98; 1 mL/min; 23 °C, 210 nm
7. ECD spectra of 2a

**Fig S1:** ECD spectra of $10^{-5}$M solution of (+)-2a (red) and (‒)-2a (blue) in CH$_3$CN
8. Vibrational circular dichroism (VCD) and infrared (IR) analysis

Experimental methods. IR and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at $l/4$ retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter ($< 1800 \text{ cm}^{-1}$) in front of the photoelastic modulator was used to enhance the signal/noise ratio. A cell with CaF$_2$ windows and a 200 $\mu$m spacer was used. Solutions of (+)-2a and (−)-2a were prepared in CCl$_4$ (6 mg in 200 $\mu$l). The VCD spectrum of the solvent was subtracted from the VCD spectrum of the sample to eliminate artefacts. For both samples and solvent (reference) 33000 scans at 4 cm$^{-1}$ resolution were averaged.

Computational methods. Density functional theory (DFT) as implemented in Gaussian09 was used to study the structure of (5$S_N$, 11$S_N$)-2a and to calculate the corresponding IR and VCD spectra. The calculations were performed using the b3lyp functional and a 6-311G(d,p) basis set. Prior to the calculation of the spectra all degrees of freedom were completely relaxed. IR and VCD spectra were constructed from calculated dipole and rotational strengths assuming Gaussian band shape with a half-width at half-maximum of 5 cm$^{-1}$. All calculations were performed for the gas phase species. Frequencies were scaled by a factor of 0.98.

Results

Two conformers were found for (5$S_N$, 11$S_N$)-2a, differing by the orientation of their ester group (see below). The two conformers have similar energy (differing by about 0.6 kcal/mol) and their coexistence in solution is clearly indicated by the two carbonyl bands around 1750 cm$^{-1}$ in the infrared spectrum. Based on the relative energy Boltzmann weights of 26% (conformer 1) and 74% (conformer 2) are calculated. The IR spectrum (intensity of carbonyl bands) indicates that the fraction of conformer 1 is slightly higher than predicted by the calculations. To calculate a weighted average of the conformer spectra we therefore assumed 40% conformer 1 and 60% conformer 2. However, a large part of the VCD spectrum is insensitive to the conformation.
Conformer 1

Total Energy: -1227.374729 H
Conformer 2

Total Energy: -1227.375741 H
Infrared spectrum of (5S\textsubscript{N}, 11S\textsubscript{N})-2a (calculated, green) and (+)-2a (experimental, red). The spectrum of (−)-2a is identical. The calculated spectrum is a weighted average of 40% conformer 1 and 60% conformer 2.
9. Crystallographic data for 2b

<table>
<thead>
<tr>
<th>Property</th>
<th>Value/Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{26}H_{26}N_{2}O_{2}</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>I 2/a</td>
</tr>
<tr>
<td>a/Å</td>
<td>20.0140(4)</td>
</tr>
<tr>
<td>b/Å</td>
<td>8.70996(13)</td>
</tr>
<tr>
<td>c/Å</td>
<td>26.5870(5)</td>
</tr>
<tr>
<td>β/°</td>
<td>109.121(2)</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>(\rho_{calc} \text{ mg/mm}^3)</td>
<td>1.209</td>
</tr>
<tr>
<td>(\mu/\text{mm}^{-1})</td>
<td>0.604</td>
</tr>
<tr>
<td>F(000)</td>
<td>1696.0</td>
</tr>
<tr>
<td>Radiation</td>
<td>Cu Kα (λ = 1.5418)</td>
</tr>
<tr>
<td>2θ range for data collection</td>
<td>9.354 to 148.024°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-24 ≤ h ≤ 24, -10 ≤ k ≤ 10, -32 ≤ l ≤ 13</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>16008</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4358 [R(int) = 0.0209]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>4358/0/275</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.024</td>
</tr>
<tr>
<td>Final R indexes [I&gt;2σ (I)]</td>
<td>(R_1 = 0.0393), (wR_2 = 0.1017)</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>(R_1 = 0.0430), (wR_2 = 0.1056)</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
<td>0.23/-0.21</td>
</tr>
</tbody>
</table>

Displacement ellipsoid plot of the crystal structure of 2b. Displacement ellipsoids are drawn at 50% probability.