Asymmetric Michael Addition Reaction of α-Aryl-substituted Lactams Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchona Alkaloids: A New Short Synthesis of (+)-Mesembrine

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Table of Contents
1. General S-1
2. Experimental Section S-1
3. $^1$H & $^{13}$C NMR Spectral Data S-14
4. HPLC Data S-60
General.
All reactions were performed in oven-dried glassware under a positive pressure of nitrogen or argon. All melting points were measured on a Yanagimoto MP-S3 micro-melting point apparatus and are uncorrected. The NMR spectra were recorded on a JEOL ECA–500 (500 MHz for ^1^H NMR analysis and 125.8 MHz for ^13^C NMR analysis) instrument in CDCl₃ unless otherwise stated and are reported in parts per million (δ) downfield from TMS as an internal standard. Mass spectral analyses were performed on a JEOL JMS-700/MStaion mass spectrometer. The infrared spectra were measured with a JASCO FTIR-460plus Fourier Transform Infrared Spectrophotometer and are reported in wave-numbers (cm⁻¹).
Thin-layer chromatography (TLC) was conducted using Merck Kieselgel 60F -254 plates (0.25 mm). Kanto Chemicals silica gel 60N (spherical, neutral 63–210 µm) was used for column chromatography.
All dried solvents were stored over molecular sieves 3Å or 4Å.

The quaternary ammonium catalysts were prepared by an analogous procedure as reported by Jørgensen.¹


To a solution of LDA (1.2 equiv) in dry THF (90 mL) at -78 °C was added dropwise a solution of methyl phenylacetate (3.8 g, 25 mmol) in dry THF (10 mL) and the mixture was stirred at this temperature for 20 min. Then to this mixture was introduced a solution of BrCH₂CN (1.1 equiv) in dry THF (10 mL) and the mixture was stirred at -78 °C. After completion of the reaction (30 min), the mixture was quenched by addition of satd aq NH₄Cl and extracted with EtOAc. The combined extracts were washed with brine, dried (Na₂SO₄), and concd. The crude product was purified by silica gel column chromatography (eluted with hexane / AcOEt = 1 : 1) to give the desired product (4.7 g, 100%) as a pale yellow solid.

To a solution of this sample (946 mg, 5 mmol) in NH₃ / EtOH (2.0 M, 24 mL) was added Raney Ni (ca. 3 g) and the mixture was purged with H₂ gas, and stirred under H₂ at r.t. for 17 h. After filtration to remove Raney Ni through a pad of Celite, the mixture was refluxed for 24 h. After evaporation of the solvent, the crude product was purified by silica gel column

chromatography (eluted with hexane / acetone = 1 : 2) to give the desired lactam (701 mg, 87%) as a colorless solid.

To a solution of this lactam (806 mg, 5 mmol) in CH₂Cl₂ (50 mL) were added Et₃N (506 mg, 5 mmol), DMAP (611 mg, 5 mmol), and Boc₂O (2.2 g, 10 mmol), and the mixture was stirred at r.t. for 10 h. After concentration, the crude product was purified by silica gel column chromatography (eluted with benzene / acetone = 12 : 1) to give the desired N-Boc-lactam (1.2 g, 93%).

Colorless needles, mp 93-95 °C (from hexane-Et₂O); Rᵣ = 0.19 (hexane / acetone = 8 : 1).

FTIR (KBr) ν 1741, 1715, 1366, 1313, 1245, 1149 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 1.54 (9H, s), 2.14-2.22 (1H, m), 2.43-2.50 (1H, m), 3.69-3.78 (2H, m), 3.91 (1H, ddd, J = 11.5, 8.0, 3.5 Hz), 7.26-7.36 (5H, m).

¹³C NMR (125.8 MHz, CDCl₃) δ 26.65, 28.00 (×3), 44.40, 49.84, 83.01, 127.33, 128.02 (×2), 128.68 (×2), 137.54, 150.38, 173.76.

Anal. Calcd for C₁₅H₁₉NO₃: C, 68.94%; H, 7.33%; N, 5.36%. Found: C, 68.87%; H, 7.24%; N, 5.24%.

N-Boc-2-(4-methylphenyl)-γ-butyrolactam.

Colorless oil; Rᵣ = 0.25 (hexane / acetone = 8 : 1).

FTIR (neat) ν 1782, 1748, 1714, 1517, 1477, 1456, 1393, 1367, 1316, 1256, 1151 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 1.54 (9H, s), 2.12-2.20 (1H, m), 2.33 (3H, s), 2.41-2.47 (1H, m), 3.68-3.74 (2H, m), 3.90 (1H, ddd, J = 11.0, 8.5, 2.5 Hz) 7.15 (4H, s).

¹³C NMR (125.8 MHz, CDCl₃) δ 21.05, 26.70, 28.01 (×3), 44.39, 49.51, 82.94, 127.87 (×2), 129.38 (×2), 134.50, 137.02, 150.42, 173.96.

Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79%; H, 7.69%; N, 5.09%. Found: C, 69.53%; H, 7.64%; N, 4.94%.

N-Boc-2-(4-methoxyphenyl)-γ-butyrolactam.

Colorless needles, mp 94-96 °C (from hexane-Et₂O); Rᵣ = 0.18 (hexane / acetone = 5 : 1).

FTIR (KBr) ν 1745, 1710, 1612, 1516, 1366, 1320, 1247, 1181, 1146 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 1.54 (9H, s), 2.10-2.18 (1H, m), 2.40-2.46 (1H, m), 3.67-3.72
(2H, m), 3.79 (3H, s), 3.89 (1H, ddd, J = 11.0, 8.0, 3.0 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.18 (2H, d, J = 8.5 Hz).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 26.70, 28.02 (×3), 44.33, 49.06, 55.26, 82.92, 114.12 (×2), 129.03 (×2), 129.57, 150.43, 158.81, 173.99.

Anal. Calcd for C$_{16}$H$_{21}$NO$_4$: C, 65.96%; H, 7.27%; N, 4.81%. Found: C, 66.17%; H, 6.89%; N, 4.79%.

**Methyl 3-Cyano-2-(3,4-dimethoxyphenyl)propanoate.**

![Methyl 3-Cyano-2-(3,4-dimethoxyphenyl)propanoate](image)

Colorless plates, mp 75-77 °C (from hexane- Et$_2$O); $R_f$ = 0.25 (hexane / EtOAc = 2 : 1).

FTIR (KBr) ν 2253, 1733, 1591, 1470, 1445, 1429, 1359 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 2.81 (1H, dd, J = 16.5, 7.5 Hz), 3.01 (1H, dd, J = 16.5, 7.5 Hz), 3.73 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 3.87-3.92 (1H, m), 6.77 (1H, s), 6.82-6.86 (2H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 21.90, 47.13, 52.80, 55.87, 55.93, 110.29, 111.43, 117.58, 119.84, 127.99, 149.11, 149.32, 171.64.

Anal. Calcd for C$_{13}$H$_{15}$NO$_4$: C, 62.64%; H, 6.07%; N, 5.62%, found: C, 62.59%; H, 5.99%; N, 5.57%.

**N-Boc-2-(3,4-dimethoxyphenyl)-γ-butyrolactam.**

![N-Boc-2-(3,4-dimethoxyphenyl)-γ-butyrolactam](image)

Colorless plates, mp 63-66 °C (from hexane- Et$_2$O); $R_f$ = 0.21 (hexane / AcOEt = 2 : 1).

FTIR (KBr) ν 1782, 1749, 1713, 1607, 1591, 1519, 1464, 1367, 1316, 1253, 1146 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.54 (9H, s), 2.13-2.22 (1H, m), 2.42-2.49 (1H, m), 3.68-3.74 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 3.91 (1H, ddd, J = 11.5, 8.5, 3.0 Hz), 6.79-6.85 (3H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 26.67, 27.98 (×3), 44.33, 49.36, 55.85 (×2), 82.97, 111.15, 111.25, 119.98, 129.86, 148.26, 148.97, 150.33, 173.94.

Anal. Calcd for C$_{17}$H$_{23}$NO$_5$: C, 63.54%; H, 7.21%; N, 4.36%. Found: C, 62.88%; H, 6.91%; N, 4.39%.

**N-Boc-2-(2-naphthyl)-γ-butyrolactam.**
Colorless plates, mp 100-101 °C (from hexane-Et₂O); \( R_f = 0.22 \) (hexane / acetone = 6 : 1).

FTIR (KBr) ν 1776, 1721, 1367, 1308, 1279, 1257, 1236 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) δ 1.56 (9H, s), 2.24-2.32 (1H, m), 2.49-2.56 (1H, m), 3.74-3.79 (1H, m), 3.91-3.97 (2H, m), 7.35-7.84 (7H, m).

\(^13\)C NMR (125.8 MHz, CDCl₃) δ 26.71, 28.02 (×3), 44.50, 49.95, 83.06, 125.89, 125.98, 126.13, 126.85, 127.55, 127.73, 128.51, 132.57, 133.29, 134.95, 150.38, 173.77.

Anal. Calcd for C₁₉H₂₁NO₃: C, 73.29%; H, 6.80%; N, 4.50%. Found: C, 73.50%; H, 6.67%; N, 4.48%.

\( N \)-Boc-2-(4-chlorophenyl)-\( \gamma \)-butyrolactam.

Colorless plates, mp 113-115 °C (from hexane-Et₂O) (lit.² mp 116-117 °C); \( R_f = 0.19 \) (hexane / acetone = 12 : 1).

FTIR (KBr) ν 1780, 1765, 1495, 1380, 1369, 1319, 1162 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) δ 1.54 (9H, s), 2.10-2.16 (1H, m), 2.43-2.49 (1H, m), 3.69-3.76 (2H, m), 3.91 (1H, ddd, \( J = 11.5, 8.0, 2.5 \) Hz), 7.21 (2H, d, \( J = 8.5 \) Hz), 7.31 (2H, d, \( J = 8.5 \) Hz).

\(^13\)C NMR (125.8 MHz, CDCl₃) δ 26.55, 27.98 (×3), 44.30, 49.16, 83.16, 128.79 (×2), 129.41 (×2), 133.23, 135.90, 150.23, 173.27.

Anal. Calcd for C₁₅H₁₈ClNO₃: C, 60.91%; H, 6.13%; N, 4.74%. Found: C, 60.95%; H, 5.99%; N, 4.71%.

\( N \)-Boc-2-(2-chlorophenyl)-\( \gamma \)-butyrolactam.

Colorless needles, mp 78-81 °C (from hexane-Et₂O); \( R_f = 0.21 \) (hexane / acetone = 12 : 1).

FTIR (KBr) ν 1741, 1712, 1480, 1370, 1327, 1305, 1252, 1149 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) δ 1.56 (9H, s), 2.00-2.08 (1H, m), 2.50-2.56 (1H, m), 3.71-3.77 (1H, m), 3.89-3.93 (1H, m), 4.25 (1H, ddd, \( J = 11.5, 8.5, 3.0 \) Hz), 7.21-7.39 (4H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 26.32, 28.01 ($\times$3), 44.32, 47.76, 83.09, 127.25, 128.65, 129.46, 129.66, 134.21, 135.93, 150.23, 173.15.

Anal. Calcd for C$_{15}$H$_{18}$ClNO$_3$: C, 60.91%; H, 6.13%; N, 4.74%. Found: C, 61.02%; H, 5.87%; N, 4.71%.

**N-Boc-2-phenyl-$\delta$-valerolactam.**

This sample was prepared similarly as above using BrCH$_2$CH$_2$CN in place of BrCH$_2$CN.

Colorless plates, mp 79-81 °C (from hexane-Et$_2$O); $R_f$ = 0.23 (hexane / acetone = 12 : 1).

FTIR (KBr) $\nu$ 1724, 1688, 1394, 1369, 1287, 1257, 1238, 1174, 1149 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.52 (9H, s), 1.89-2.08 (3H, m), 2.20 (1H, dt, $J$ = 13.0, 6.0 Hz), 3.70-3.75 (1H, m), 3.77-3.79 (2H, m), 7.20-7.34 (5H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 21.66, 27.97 ($\times$3), 29.56, 46.20, 50.91, 82.96, 126.91, 128.32 ($\times$2), 128.46 ($\times$2), 139.69, 153.31, 172.23.

Anal. Calcd for C$_{16}$H$_{21}$NO$_3$: C, 69.79%; H, 7.69%; N, 5.09%. Found: C, 69.78%; H, 7.51%; N, 4.99%.

**General Procedure for the Asymmetric Michael Addition Reaction.**

The chiral ammonium catalyst was prepared by mixing a cinchona amine (0.06 mmol) and freshly distilled $p$-methoxybenzyl bromide (0.06 mmol) in toluene (0.2 mL) at r.t. for 1 h. Then, Ag$_2$O (0.06 mmol) and EtOH (0.06 mmol) were added, and the mixture was stirred at r.t. for 20 min. After cooling to $-15$ °C, lactam (0.2 mmol) in toluene (0.8 mL) followed by the Michael acceptor (1.5 eq) were added, and the reaction progress was monitored by TLC. After completion of the reaction, the mixture was directly purified by silica gel column chromatography (eluted with benzene / acetone = 12 : 1) to give the desired adduct. The ee of this compound was determined by chiral HPLC analysis.
(R)-N-Boc-2-(3-oxobutyl)-2-phenyl-γ-butyrolactam (3a).

![Structure of (R)-N-Boc-2-(3-oxobutyl)-2-phenyl-γ-butyrolactam]

Colorless needles, mp 97-99 °C (from hexane-Et₂O); $R_t = 0.17$ (hexane / acetone $= 4 : 1$). $[\alpha]_D^{19} +83.2$ (c $= 1.0$, EtOH, 79% ee).

FTIR (KBr) ν 1773, 1715, 1365, 1313, 1164 cm⁻¹.

$^1\text{H} \text{NMR}$ (500 MHz, CDCl₃) δ 1.53 (9H, s), 2.03 (3H, s), 2.10-2.16 (2H, m), 2.19-2.29 (2H, m), 2.41-2.45 (1H, m), 2.53-2.62 (1H, m), 3.48 (1H, ddd, $J = 10.0$, 8.5, 8.0 Hz), 3.75 (1H, ddd, $J = 10.0$, 8.0, 3.0 Hz), 7.26-7.41 (5H, m).

$^{13}\text{C} \text{NMR}$ (125.8 MHz, CDCl₃) δ 28.00 (×3), 29.91, 31.55, 32.17, 38.78, 42.95, 52.93, 83.02, 126.43 (×2), 127.37, 128.78 (×2), 139.04, 150.18, 175.56, 208.10.

Anal. Calcd for C₁₉H₂₅NO₄: C, 68.86%; H, 7.60%; N, 4.23%. Found: C, 68.76%; H, 7.60%; N, 4.09%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol $= 90 : 10$, 0.3 cm³ / min): $R_t$ (major) = 39.4 min; $R_t$ (minor) = 43.0 min.

(R)-N-Boc-2-(3-oxopentyl)-2-phenyl-γ-butyrolactam (3b).

![Structure of (R)-N-Boc-2-(3-oxopentyl)-2-phenyl-γ-butyrolactam]

Colorless needles, mp 90-93 °C (from hexane-Et₂O); $R_t = 0.25$ (hexane / acetone $= 3 : 1$). $[\alpha]_D^{23} +36.1$ (c $= 1.0$, EtOH, 86% ee).

FTIR (KBr) ν 1782, 1765, 1722, 1689, 1369, 1299, 1153 cm⁻¹.

$^1\text{H} \text{NMR}$ (500 MHz, CDCl₃) δ 0.97 (3H, t, $J = 7.0$ Hz), 1.52 (9H, s), 2.10-2.33 (6H, m), 2.43 (1H, ddd, $J = 13.5$, 7.0, 3.5 Hz), 2.49-2.55 (1H, m), 3.48 (1H, dq, $J = 10.0$, 1.5 Hz), 3.75 (1H, ddd, $J = 10.0$, 8.5, 3.0 Hz), 7.27-7.41 (5H, m).

$^{13}\text{C} \text{NMR}$ (125.8 MHz, CDCl₃) δ 28.00 (×3), 31.47, 32.24, 35.83, 37.45, 42.97, 53.03, 83.02, 126.49 (×2), 127.38, 128.80 (×2), 139.11, 150.25, 175.63, 210.86.

Anal. Calcd for C₂₀H₂₇NO₄: C, 69.54%; H, 7.60%; N, 4.05%. Found: C, 69.23%; H, 7.53%; N, 3.92%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol $= 90 : 10$, 0.3 cm³ / min): $R_t$ (major) = 35.5 min; $R_t$ (minor) = 29.5 min.
(R)-N-Boc-2-(2-methoxycarbonylethyl)-2-phenyl-\(\gamma\)-butyrolactam (3c).

\[
\begin{align*}
\text{CO}_2\text{Me} & & \text{N} & & \text{Ph} \\
\text{Ph} & & \text{N} & & \text{Boc}
\end{align*}
\]

Colorless plates, mp 76-85 °C (from hexane-Et\(_2\)O); \(R_t = 0.17\) (hexane / acetone = 5 : 1).
\[\alpha\]D\(_{24}^0\) +11.4 (\(c = 1.0\), EtOH, 9% ee).

FTIR (KBr) \(\nu\) 1783, 1766, 1745, 1691, 1385, 1371, 1318, 1303, 1192, 1153 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.52 (9H, s), 2.09-2.17 (3H, m), 2.30-2.41 (2H, m), 2.52 (1H, ddd, \(J = 13.0, 6.5, 2.5\) Hz), 3.48 (1H, ddd, \(J = 10.5, 9.5, 2.0\) Hz), 3.69 (3H, s), 3.77 (1H, ddd, \(J = 10.5, 8.0, 2.0\) Hz), 7.27-7.44 (5H, m).

\(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 27.99 (×3), 29.38, 30.38, 33.81, 42.98, 51.61, 52.98, 83.02, 126.50 (×2), 127.53, 128.84 (×2), 138.16, 150.25, 173.54, 175.27.

Anal. Calcd for C\(_{19}\)H\(_{25}\)NO\(_5\): C, 65.69%; H, 7.25%; N, 4.03%. Found: C, 65.58%; H, 7.25%; N, 4.00%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm\(^3\)/min): \(R_t\) (major) = 24.8 min; \(R_t\) (minor) = 28.2 min.

(R)-N-Boc-2-(2-cyanoethyl)-2-phenyl-\(\gamma\)-butyrolactam (3d).

\[
\begin{align*}
\text{CN} & & \text{O} & & \text{N} & & \text{Ph} \\
\text{Ph} & & \text{N} & & \text{Boc}
\end{align*}
\]

Colorless plates, mp 104-107 °C (from hexane-CH\(_2\)Cl\(_2\)); \(R_t = 0.23\) (hexane / acetone = 4 : 1).
\[\alpha\]D\(_{23}^0\) +44.1 (\(c = 0.14\), EtOH, 67% ee).

FTIR (KBr) \(\nu\) 2244, 1783, 1768, 1693, 1379, 1315, 1297, 1149 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.52 (9H, s), 2.01 (1H, ddd, \(J = 16.5, 9.5, 7.0\) Hz), 2.12-2.22 (2H, m), 2.42 (1H, ddd, \(J = 15.0, 9.0, 5.0\) Hz), 2.52 (1H, ddd, \(J = 16.5, 9.0, 5.0\) Hz), 2.66 (1H, ddd, \(J = 13.5, 6.0, 1.5\) Hz), 3.45 (1H, dt, \(J = 10.5, 6.0\) Hz), 3.80 (1H, ddd, \(J = 10.5, 8.0, 1.5\) Hz), 7.32-7.41 (5H, m).

\(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 12.74, 27.97 (×3), 30.96, 34.76, 43.01, 52.96, 83.41, 119.47, 126.39 (×2), 128.17, 129.27 (×2), 136.65, 150.00, 174.78.

Anal. Calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_3\): C, 64.57%; H, 7.25%; N, 8.91%. Found: C, 68.84%; H, 7.11%; N, 8.85%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm\(^3\)/min): \(R_t\) (major) = 36.0 min; \(R_t\) (minor) = 30.2 min.
(R)-N-Boc-2-(4-methylphenyl)-2-(3-oxobutyl)-γ-butyrolactam (3e).

\[
\begin{align*}
\text{Me} & \quad \text{COMe} \\
\text{N} & \quad \text{Boc} \\
\text{Me} & \quad \text{COMe} \\
\text{N} & \quad \text{Boc}
\end{align*}
\]

Colorless needles, mp 128-130 °C (from CHCl₃); \( R_t = 0.22 \) (hexane / acetone = 4 : 1).
\([\alpha]_D^{23} +83.7 \ (c = 1.0, \text{EtOH}, 78\% \text{ ee}).\)

FTIR (KBr) \( \nu \) 1775, 1737, 1711, 1364, 1315, 1290, 1258, 1172, 1157 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.52 (9H, s), 2.03 (3H, s), 2.06-2.12 (2H, m), 2.23 (2H, ABq, \( J_{AB} = 11.5 \) Hz), 2.34 (3H, s), 2.39-2.43 (1H, m), 2.57 (1H, quintet, \( J = 11.0 \) Hz), 3.46 (1H, dq, \( J = 9.0, 2.0 \) Hz), 3.72-3.75 (1H, m), 7.16 (2H, d, \( J = 7.5 \) Hz), 7.26-7.29 (2H, m).

\(^{13}\)C NMR (125.8 MHz, CDCl₃) \( \delta \) 20.92, 28.01 (×3), 29.89, 31.48, 32.24, 38.85, 42.98, 52.67, 82.97, 126.36 (×2), 129.51 (×2), 135.90, 137.16, 150.26, 175.77, 208.28.

Anal. Calcd for C₂₀H₂₇NO₄: C, 69.54%; H, 7.88%; N, 4.05%. Found: C, 69.38%; H, 7.88%; N, 4.03%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, 0.46 \times 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm³/min): \( R_t \) (major) = 32.9 min; \( R_t \) (minor) = 29.9 min.

(\( R \))-N-Boc-2-(4-methoxyphenyl)-2-(3-oxobutyl)-γ-butyrolactam (3f).

\[
\begin{align*}
\text{MeO} & \quad \text{COMe} \\
\text{N} & \quad \text{Boc} \\
\text{MeO} & \quad \text{COMe} \\
\text{N} & \quad \text{Boc}
\end{align*}
\]

Colorless needles, mp 104-107 °C (from hexane-Et₂O); \( R_t = 0.26 \) (hexane / acetone = 3 : 1).
\([\alpha]_D^{23} +78.7 \ (c = 1.0, \text{EtOH}, 73\% \text{ ee}).\)

FTIR (KBr) \( \nu \) 1785, 1766, 1736, 1714, 1608, 1516, 1466, 1369, 1310, 1257, 1187, 1155 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.52 (9H, s), 2.03 (3H, s), 2.09 (2H, dt, \( J = 11.5, 9.5 \) Hz), 2.19-2.27 (2H, m), 2.40 (1H, ddd, \( J = 12.5, 7.0, 3.5 \) Hz), 2.54 (1H, quintet, \( J = 10.5 \) Hz), 3.47 (1H, dq, \( J = 10.0, 1.5 \) Hz), 3.74 (1H, ddd, \( J = 10.0, 8.0, 3.0 \) Hz), 3.80 (3H, s), 6.88 (2H, d, \( J_{AB} = 7.5 \) Hz), 7.32 (2H, d, \( J_{AB} = 7.5 \) Hz).

\(^{13}\)C NMR (125.8 MHz, CDCl₃) \( \delta \) 28.00 (×3), 29.87, 31.42, 32.35, 38.83, 42.96, 52.31, 55.23, 82.95, 114.12 (×2), 127.62 (×2), 130.79, 150.27, 158.77, 175.78, 208.17.

Anal. Calcd for C₂₀H₂₇NO₅: C, 66.46%; H, 7.53%; N, 3.88%. Found: C, 66.14%; H, 7.31%; N, 3.78%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column,
0.46 × 25 cm, hexane / 2-propanol = 95 : 5, 0.3 cm³ / min): \( R_t (major) = 107.9 \) min; \( R_t (minor) = 101.0 \) min.

(R)-N-Boc-2-(3,4-dimethoxyphenyl)-2-(3-oxobutyl)-γ-butyrolactam (3g).

![Chemical structure of 3g](image)

Colorless needles, mp 96-98 °C (from hexane-Et₂O); \( R_t = 0.20 \) (hexane / acetone = 3 : 1). \([\alpha]_D^{27} +65.8 \) (c = 1.0, EtOH, 70% ee).

 FTIR (KBr) ν 1771, 1714, 1517, 1362, 1313, 1255, 1160 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) δ 1.52 (9H, s), 2.04 (3H, s), 2.06-2.11 (2H, m), 2.21-2.29 (2H, m), 2.42 (1H, ddd, \( J = 12.0, 7.0, 3.5 \) Hz), 2.49-2.55 (1H, m), 3.51 (1H, dq, \( J = 10.5, 2.0 \) Hz), 3.75 (1H, ddd, \( J = 10.5, 8.0, 3.0 \) Hz), 3.87(5) (3H, s), 3.88(4) (3H, s), 6.82-6.84 (1H, m), 6.89-6.90 (1H, m), 7.00 (1H, s).

\(^13\)C NMR (125.8 MHz, CDCl₃) δ 27.96 (×3), 29.91, 31.26, 32.32, 38.78, 42.99, 52.38, 55.78, 55.91, 82.92, 109.78, 110.75, 118.41, 131.12, 148.19, 149.05, 150.10, 175.69.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm³ / min): \( R_t (major) = 66.5 \) min; \( R_t (minor) = 70.1 \) min.

Anal. Calcd for C₂₁H₂₉NO₆: C, 64.43%; H, 7.47%; N, 3.58%; found: C, 64.41%; H, 7.36%; N, 3.48%.

(R)-N-Boc-2-(2-naphthyl)-2-(3-oxobutyl)-γ-butyrolactam (3h).

![Chemical structure of 3h](image)

Colorless plates, mp 132-134 °C (from hexane-CH₂Cl₂); \( R_t = 0.27 \) (hexane / acetone = 3 : 1). \([\alpha]_D^{23} +92.5 \) (c = 1.0, EtOH, 68% ee).

 FTIR (KBr) ν 1768, 1708, 1361, 1309, 1156 cm⁻¹.

\(^1\)H NMR (500 MHz, CDCl₃) δ 1.53 (9H, s), 2.00 (3H, s), 2.18-2.27 (3H, m), 2.32-2.38 (1H, m), 2.55 (1H, ddd, \( J = 12.5, 7.0, 3.5 \) Hz), 2.59-2.66 (1H, m), 3.52 (1H, dq, \( J = 10.5, 1.5 \) Hz), 3.79 (1H, ddd, \( J = 10.5, 8.0, 2.5 \) Hz), 7.47-7.54 (3H, m), 7.82-7.87 (4H, m).

\(^13\)C NMR (125.8 MHz, CDCl₃) δ 28.00 (×3), 29.87, 31.69, 32.07, 38.82, 43.02, 53.08, 83.06, 124.33, 125.37, 126.28, 126.40, 127.45, 128.08, 128.83, 132.43, 133.07, 136.38, 150.20,
Anal. Calcd for C$_2$I$_3$NO$_4$: C, 72.42%; H, 7.13%; N, 3.67%. Found: C, 72.17%; H, 7.16%; N, 3.63%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 95 : 5, 0.3 cm$^3$/min): $R_t$ (major) = 99.7 min; $R_t$ (minor) = 105.4 min.

(R)-N-Boc-2-(4-chlorophenyl)-2-(3-oxobutyl)-γ-butyrolactam (3i).

![Chemical structure of 3i](image)

Colorless plates, mp 120-121 °C (from CHCl$_3$); $R_f$ = 0.18 (hexane / acetone = 4 : 1).

[$\alpha$]$_D^{23}$ +60.2 (c = 0.94, EtOH, 65% ee).

FTIR (KBr) ν 1781, 1765, 1722, 1687, 1493, 1387, 1369, 1303, 1155 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.53 (9H, s), 2.05 (3H, s), 2.08-2.16 (2H, m), 2.22 (2H, ABq, $J_{AB} =$ 11.5 Hz), 2.38 (1H, ddd, $J = $ 13.0, 7.5, 4.0 Hz), 2.56 (1H, quintet, $J = $ 11.0 Hz), 3.50 (1H, dt, $J = $ 11.0, 7.5 Hz), 3.76 (1H, ddd, $J = $ 11.0, 8.0, 4.0 Hz), 7.32-7.37 (4H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 27.99 (×3), 29.93, 31.45, 32.04, 38.65, 42.93, 42.88, 52.48, 83.26, 127.97 (×2), 128.97 (×2), 133.40, 137.79, 150.11, 175.19, 207.84.

Anal. Calcd for C$_{19}$H$_{24}$ClNO$_4$: C, 62.38%; H, 6.61%; N, 3.83%. Found: C, 62.34%; H, 6.46%; N, 4.25%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm$^3$/min): $R_t$ (major) = 38.2 min; $R_t$ (minor) = 31.7 min.

(R)-N-Boc-2-(2-chlorophenyl)-2-(3-oxobutyl)-γ-butyrolactam (3j).

Pale yellow oil; $R_f$ = 0.18 (hexane / acetone = 6 : 1).

[$\alpha$]$_D^{23}$ +17.2 (c = 0.42, EtOH, 25% ee).

FTIR (KBr) ν 1781, 1746, 1719, 1475, 1368, 1312, 1258, 1155 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.56 (9H, s), 2.08 (3H, s), 2.09-2.16 (1H, m), 2.21-2.27 (1H, m), 2.31-2.38 (1H, m), 2.60-2.69 (2H, m), 2.81-2.88 (1H, m), 3.58-3.64 (1H, m), 3.74-3.79
(1H, m), 7.23-7.26 (2H, m), 7.35 (1H, dt, J = 7.0, 2.5 Hz), 7.41 (1H, dt, J = 6.0, 2.5 Hz).

\(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 28.06 (×3), 28.56, 30.02, 31.29, 38.93, 43.20, 53.62, 83.11, 126.97, 128.82, 129.24, 131.96, 133.57, 137.17, 150.27, 175.46, 208.02.

HRMS Calcd for C\(_{19}\)H\(_{24}\)ClNO\(_4\) 365.1394, found 365.1405.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm\(^3\)/min): \(R_t\) (major) = 40.2 min; \(R_t\) (minor) = 34.3 min.

\((R)\)-N-Boc-2-phenyl-2-(3-oxobutyl)-\(\delta\)-valerolactam (3k).

![Chemical Structure](image)

Colorless oil; \(R_t\) = 0.18 (hexane / acetone = 6 : 1).

\([\alpha]_D^{23}\) +33.3 (c = 0.3, EtOH, 26% ee).

FTIR (neat) ν 1766, 1716, 1497, 1457, 1392, 1368, 1283, 1148 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.54 (9H, s), 1.65-1.74 (1H, m), 1.75-1.82 (1H, m), 1.96 (1H, ddd, \(J = 14.0, 11.5, 5.0\) Hz), 2.03 (3H, s), 2.06-2.15 (2H, m), 2.25 (1H, ddd, \(J = 17.0, 10.0, 6.0\) Hz), 2.38 (1H, dt, \(J = 13.5, 5.0\) Hz), 2.65 (1H, ddd, \(J = 17.0, 10.0, 5.0\) Hz), 3.36 (1H, dt, \(J = 13.0, 6.0\) Hz), 3.64 (1H, ddd, \(J = 13.0, 8.0, 5.0\) Hz), 7.25-7.28 (3H, m), 7.34-7.37 (2H, m).

\(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 19.15, 27.99 (×3), 29.89, 32.10, 34.55, 39.90, 45.70, 52.77, 82.83, 126.31 (×2), 126.99, 128.81 (×2), 141.38, 153.41, 175.23, 208.81.

HRMS Calcd for C\(_{20}\)H\(_{27}\)NO\(_4\) 345.1940, found 345.1940.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 95 : 5, 0.3 cm\(^3\)/min): \(R_t\) (major) = 32.3 min; \(R_t\) (minor) = 35.2 min.

**Preparation of Cyclohexenone 4.**

![Chemical Structure](image)

To a solution of 3g (274 mg, 0.7 mmol) in dry THF (0.4 mL) at 0 °C was added dropwise \(t\)-BuOK (1.4 mL, 1.4 mmol, 1 M in THF) and the mixture was stirred at r.t. for 30 min. After quenching by addition of satd aq NH\(_2\)Cl, the organic layer was separated. The aqueous phase was extracted thoroughly with CHCl\(_3\). The combined extracts were dried (Na\(_2\)SO\(_4\)) and concd.
The ensuing crude sample was dissolved in toluene (4.5 mL) and powdered 4A MS (130 mg) and p-TsOH•H2O (26 mg, 0.07 mmol) were added, and the mixture was refluxed under N₂ for 11 h. After cooling, the mixture was quenched by addition of satd aq NaHCO₃. The organic layer was separated and the aqueous phase was extracted with CHCl₃. The combined extracts were dried (Na₂SO₄) and concd. The crude product was purified by silica gel column chromatography (eluted with hexane / AcOEt = 1 : 1) to give cyclohexenone (132 mg, 50%). Recrystallization from hexane-Et₂O gave the desired product 4 in an optically pure form. Colorless needles, mp 130-134 °C (from hexane-Et₂O); [α]D = 277.0 (c = 1.0, EtOH, >99% ee).

FTIR (KBr) ν 1719, 1647, 1616, 1517, 1383, 1319, 1164, 1147 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 1.55 (9H, s), 1.92-2.08 (2H, m), 2.14-2.23 (2H, m), 2.32 (1H, dd, J = 12.0, 5.0 Hz), 2.40-2.43 (1H, m), 3.25 (1H, dt, J = 11.0, 5.0 Hz), 3.79 (1H, dd, J = 11.0, 8.5 Hz), 3.86 (3H, s), 3.87 (3H, s), 6.56 (1H, s), 6.82 (3H, s).

¹³C NMR (125.8 MHz, CDCl₃) δ 28.14 (×3), 33.14, 36.16, 37.46, 47.73, 51.89, 55.85, 55.87, 82.98, 109.11, 109.75, 110.98, 119.34, 132.84, 148.24, 149.01, 151.55, 163.01, 199.42.

Anal. Calcd for C₂₁H₂₇NO₅: C, 67.54%; H, 7.29%; N, 3.75%. Found: C, 67.68%; H, 6.95%; N, 3.67%.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 0.3 cm³/ min): Rₜ = 72.9 min (antipode: Rₜ = 49.7 min).

Conversion of 4 to 5.

A solution of 4 (74 mg, 0.2 mmol) in (CF₃)₂CHOH (1.2 mL) was heated at 150 °C for 40 min under microwave irradiation conditions in a CEM–Discover LabMate microwave instrument. After cooling to r.t., the mixture was concd. to dryness on a rotary evaporator. The ensuing crude sample was dissolved in dry THF (3.2 mL) and added dropwise at 0 °C to NaH (60% in oil, 11 mg, 0.28 mmol) in dry THF (2.4 mL). After being stirred for 10 min, MeI (35 mg, 0.25 mmol) in dry THF (2.4 mL) was added, and the mixture was stirred at r.t. for 10 min. After quenching by addition of H₂O, the mixture was extracted with AcOEt. The combined extracts were dried (Na₂SO₄), and concd. The crude product was purified by silica gel column chromatography (eluted with CH₂Cl₂ / MeOH / i-PrNH₂ = 10 : 1 : 0.05) to give 5 (50 mg, 86%).
Pale yellow paste (lit. mp 77–78.5 °C); $R_\ell = 0.45 \ (CH_2Cl_2 / \text{MeOH} = 10 : 1)$. 
$[\alpha]_D^{26} + 132.8 \ (c = 1.0, \text{EtOH}, \text{99% ee}).$

FTIR (KBr) ν 3419, 1619, 1591, 1560, 1514, 1462, 1415 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$)  δ 1.88-1.95 (1H, m), 2.08-2.17 (3H, m), 2.27 (1H, dd, $J = 12.0$, 4.5 Hz), 2.38-2.43 (1H, m), 2.98 (3H, s), 3.27-3.35 (2H, m), 3.86 (6H, s), 5.20 (1H, s), 6.75-6.81 (3H, m).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 32.57, 32.97, 35.81, 38.86, 52.41, 52.71, 55.77, 55.85, 93.24, 109.92, 110.79, 119.24, 133.51, 147.97, 148.81, 170.75, 196.28.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane / 2-propanol = 90 : 10, 1.0 cm$^3$/min): $R_\ell = 48.2$ min (antipode: $R_\ell = 32.9$ min).

(+)-Mesembrine (6).

To a solution of 5 (41.5 mg, 0.14 mmol) and $t$-BuOH (25 mg, 0.33 mmol) in dry THF (2 mL) and liquid NH$_3$ (16 mL) at −78 °C was added a piece of metal Li (1.2 mg, 0.28 mmol) and the resulting dark-blue solution was stirred at this temperature for 30 min. After evaporation of an excess of NH$_3$ by allowing to warm to r.t., the mixture was diluted with water and extracted with EtOAc. The combined extracts were dried (Na$_2$SO$_4$) and concd. The crude product was purified by silica gel column chromatography (elution with CH$_2$Cl$_2$ / MeOH / $i$-PrNH$_2$ = 20 : 1 : 0.05) to give (+)-mesembrine (6, 31 mg, 77%).

Pale yellow oil; $R_\ell = 0.22 \ (\text{CHCl}_3 / \text{acetone} = 6 : 1)$.

$[\alpha]_D^{19} + 42.2 \ (c = 0.15, \text{MeOH}) \ {\text{litr.}^3 \ [\alpha]_D^{20} + 43 \ (c = 0.8, \text{MeOH})}$.

FTIR (neat) ν 1717, 1520, 1455, 1254, 1147, 1027 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$)  δ 2.04-2.24 (5H, m), 2.26-2.35 (1H, m, overlapping), 2.32 (3H, s), 2.40-2.47 (1H, m), 2.60 (2H, d of ABq, $J = 16.0$, 3.5 Hz), 2.95 (1H, t, $J = 3.5$ Hz), 3.13 (1H, ddd, $J = 10.0$, 7.0, 3.0 Hz), 3.88 (3H, s), 3.90 (3H, s), 6.84 (1H, d, $J = 8.0$ Hz), 6.89 (1H, d, $J = 2.0$ Hz), 6.93 (1H, dd, $J = 8.0$, 2.0 Hz).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 35.22, 36.20, 38.80, 40.03, 40.52, 47.47, 54.80, 55.85, 55.98, 70.34, 109.96, 110.99, 117.89, 140.16, 147.48, 148.99, 211.42.

1H NMR (500 MHz, CDCl3)
$\text{^13C NMR (125.8 MHz, CDCl}_3$)
None
$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
1H NMR (500 MHz, CDCl₃)
$^{13}$C NMR (125.8 MHz, CDCl$_3$)

MeO

NBoc
\[ ^1\text{H NMR} \quad (500 \text{ MHz, CDCl}_3) \]
$^{13}$C NMR (125.8 MHz, CDCl$_3$)
1H NMR
(500 MHz, CDCl₃)
\[ ^{13}\text{C} \text{ NMR} \]

(125.8 MHz, CDCl\textsubscript{3})
1H NMR (500 MHz, CDCl₃)
$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
\[ ^{13}C\text{ NMR} \quad (125.8\text{ MHz, CDCl}_3) \]
**1H NMR** (500 MHz, CDCl₃)
13C NMR
(125.8 MHz, CDCl₃)
1H NMR
(500 MHz, CDCl₃)

S-0
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(125.8 MHz, CDCl$_3$)
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SLVNT CDCl3
EXREF 0.00 ppm
RF 0.12 Hz
RGAIN 38

\[
\begin{align*}
\text{3a} & \quad \text{^1H NMR} \\
 & \quad (500 \text{ MHz, CDCl}_3)
\end{align*}
\]
$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125.8 MHz, CDCl₃)
$\text{CO}_2\text{Me}$

$\text{N}$

$\text{Boc}$

$\text{3c}$

$^1\text{H NMR}$

(500 MHz, CDCl$_3$)
**13C NMR**

(125.8 MHz, CDCl₃)
\[ \text{NBoc} \]

1H NMR (500 MHz, CDCl3)
\textbf{13C NMR} (125.8 MHz, CDCl$_3$)

\[ \text{13C} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{CN} \]

\[ \text{S-39} \]

\[ \text{S-39} \]

\[ \text{Boc} \]

\[ \text{3d} \]
$^{1}$H NMR (500 MHz, CDCl$_3$)
\( ^{13}C\) NMR

(125.8 MHz, CDCl₃)
$^{1}H$ NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125.8 MHz, CDCl$_3$)
$^{1}$H NMR 
(500 MHz, CDCl$_3$)
NBoc
O
3g

$^{13}$C NMR
(125.8 MHz, CDCl$_3$)

COMe
MeO
MeO

\[ \text{NBoc} \]

\[ \text{O} \]

\[ 3g \]

$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^3^b$H NMR

COMe$^3^h$

1H NMR (500 MHz, CDCl$_3$)
**13C NMR (125.8 MHz, CDCl₃)**

**NBoc**

**O**

**3h**
\( \text{\textsuperscript{1}H NMR} \) (500 MHz, CDCl\(_3\))
$^{13}$C NMR (125.8 MHz, CDCl$_3$)
$\text{S-50}$

$\text{3j}$

$^1$H NMR (500 MHz, CDCl$_3$)
$\text{H}$

$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
The image contains an NMR spectrum of a chemical compound, identified as 3k. The spectrum is labeled with "13C NMR (125.8 MHz, CDCl3)". The spectrum shows typical NMR peaks at various ppm values, with chemical shifts and multiplicities indicated. The compound is described as having a NBoc group and a COMe group, suggesting it is an NBoc protected compound with a methyl ester. The experimental conditions are listed at the top of the image, indicating the use of a single pulse decoupled gated acquisition method.
1H NMR (500 MHz, CDCl₃)
13C NMR (125.8 MHz, CDCl₃)

4
1H NMR (500 MHz, CDCl3)
$^{13}$C NMR
(125.8 MHz, CDCl$_3$)
**1H NMR**

$\text{MeO}$

$\text{MeO}$

(500 MHz, CDCl$_3$)
Exptl No. NNO-31 Data: 2014/04/24

Sample

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm$^3$/min
Conc. 3 mg/mL
Vol. 3 mL
UV: 254 nm

NO. RT AREA CONC
1 38.178 211103 29.9650
2 40.742 493707 70.035
TOTAL 70.4810 100.000
Exptl No. NNO-203  Data: 2015/02/13

Sample:  
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COMe

Ph

NBoc

3a (-79% ee)
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Column: Chiralpak AD-H  
Solvent: hexane / 2-propanol = 90 : 10  
Flow Speed: 0.3 cm³ / min  
Conc. 3 mg / mL  
Vol. 3 mL  
UV: 254 nm  

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S-61
Exptl No. NNO-116  Data: 2014/10/10

Sample

Column: Chiralpak AD-H  
Solvent: hexane / 2-propanol = 90 : 10  
Flow Speed: 0.3 cm³ / min  
Conc. 3 mg / mL  
Vol. 3 mL  
UV: 254 nm

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S-62
Exptl No. NNO-91  Data: 2014/07/25

Sample

Column: Chiralpak AS
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

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S-63
Sample: 3d (67% ee)

Column: Chiralpak AS
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³/min
Conc. 3 mg/mL
Vol. 3 mL
UV: 254 nm

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Exptl No. NNO-83    Data: 2014/06/26

Sample

Column: Chiralpak AS
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

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</tbody>
</table>

S-65
Exptl No. NNO-82 Data: 2014/07/24

Sample

\[ \text{Column: Chiralpak AD-H} \]
\[ \text{Solvent: hexane / 2-propanol = 95 : 5} \]
\[ \text{Flow Speed: 0.3 cm}^3 / \text{min} \]
\[ \text{Conc. 3 mg / mL} \]
\[ \text{Vol. 3 mL} \]
\[ \text{UV: 254 nm} \]

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100.972</td>
<td>233798</td>
<td>13.6575</td>
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<td>2</td>
<td>107.923</td>
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</tbody>
</table>

S-66
Sample: 

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³/min
Conc. 3 mg/mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</table>
Sample: 3h (68% ee)

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 95 : 5
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
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</table>

S-68
Exptl No. NNO-78  
Data: 2014/06/30

Sample

Column: Chiralpak AS
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm$^3$/min
Conc. 3 mg/mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

S-69
Sample

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
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Exptl No. NNO-90  Data: 2014/08/30

Sample

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 95 : 5
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
Sample column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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</tbody>
</table>
Exptl No. NNO-111  Data: 2014/10/21

Sample

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 0.3 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
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</table>

S-73
Exptl No. NNO-297  Data: 2015/06/27

Sample

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 1.0 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2</td>
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</table>

TOTAL 767744  100.000
Sample

Exptl No. NNO-291 Data: 2015/06/20

Column: Chiralpak AD-H
Solvent: hexane / 2-propanol = 90 : 10
Flow Speed: 1.0 cm³ / min
Conc. 3 mg / mL
Vol. 3 mL
UV: 254 nm

<table>
<thead>
<tr>
<th>NO.</th>
<th>RT</th>
<th>AREA</th>
<th>CONC</th>
</tr>
</thead>
<tbody>
<tr>
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S-75