Organocatalytic Enantioselective Friedel-Crafts Alkylation of the Sterically Encumbered α-Alkyl Enal: One-pot Biomimetic Total Synthesis of Yuehchukene.

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SUPPORTING INFORMATION:
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General Procedure. All solvents were reagent grade. L-proline (99+%) was purchased from Bachem. Other chemicals were purchased from Aldrich or Acros Chemical Co. Reactions were normally carried out under argon atmosphere in glassware. Silica gel 60 (Merck Geduran Si 60, particle size 0.063 – 0.200 nm) was employed for flash chromatography. Melting points are uncorrected. $^1$H NMR spectra were obtained in CDCl₃ unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500). $^{13}$C NMR spectra were obtained at 100 MHz or 125 MHz. $E_e$ values were measured by HITACHI L-2130 HPLC with HITACHI Diode Array detector L-2455 on a chiral column (chiralpak IC, 0.46 cm ID x 25 cm, particle size 5 μ; or chiralpak IA 0.46 cm ID x 25 cm, particle size 5 μ) by elution with IPA-hexane. The flow rate of the indicated elution solvent is maintained at 1.0 mL/min, and the retention time of a compound is recorded accordingly. Focused microwave irradiation was carried out at atmospheric pressure with a CEM Discover microwave reactor (5 mL reactors). The melting point was recorded on a melting point apparatus (MPA100 – Automated melting point system, Stanford Research Systems, Inc.) and is uncorrected. The optical rotation values were recorded with a Jasco-P-2000 digital polarimeter.
Preparation of 4a

To a solution of aldehyde 2 (102 mg, 0.68 mmol, 2 equiv), catalyst-IV (22.1 mg, 0.068 mmol, 0.2 equiv) and additive-(S)-A11 (47.3 mg, 0.14 mmol, 0.4 equiv) in CHCl₃–EtOAc (1:1, 1 mL) was added indole 3a (40 mg, 0.34 mmol, 1 equiv) at ~25 °C. The resulting solution was stirred at ambient temperature for 15 days. To the reaction mixture was added Et₃N (34 mg, 0.34 mmol, 1 equiv) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give the residue. The crude product was purified by flash column chromatography with 8% EtOAc-hexane ($R_f = 0.54$ for trans-4a after developing three times in 15% EtOAc-hexane and $R_f = 0.51$ for cis-4a after developing three times in 15% EtOAc-hexane) to afford product 4a as mixture of diastereomers (23 mg, 25% yield) as a yellow oil. Further purification of 4a provided the pure trans-4a for spectra analysis. Selected spectroscopic data for trans-4a: $[\alpha]_D^{26} -95.5$ (c 1, CHCl₃) for 88% ee of trans-4a; IR (neat): 3417, 2963, 2825, 1712, 1457, 1260, 1096, 1011, 803, 1742 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 9.70 (d, $J = 4.5$ Hz, 1 H), 7.96 (bs, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.31 (d, $J = 8.0$ Hz, 1 H), 7.18 – 7.14 (m, 1 H), 7.09 – 7.05 (m, 1 H), 6.93 (d, $J = 2.5$ Hz, 1 H), 5.50 (s, 1 H), 4.08 – 4.05 (m, 1 H), 2.63 (dd, $J = 11.0$, 4.0 Hz, 1 H), 2.18 (d, $J = 17.0$ Hz, 1 H), 1.71 (s, 3 H), 1.69 (d, $J = 17$ Hz, 1 H), 1.12 (s, 3 H), 1.11 (s, 3 H), $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 206.5 (CH), 136.7 (C), 131.7 (C), 126.4 (C), 123.0 (CH), 122.0 (CH), 121.9 (CH), 119.4 (CH), 119.2 (CH), 117.5 (C), 111.3 (CH), 60.8 (CH), 46.5 (CH₂), 33.8 (C), 32.2 (CH), 29.3 (CH₃), 23.4 (CH₃), 21.5 (CH₃); MS ($m/z$, relative intensity): 268 ($M^+$ + 1, 20) 267 ($M^+$, 100), 238 (80), 222 (39), 182 (76), 168 (77), 130 (26), 117 (44), exact mass calculated for $C_{18}H_{21}NO (M^+)$: 267.1623; found: 267.1624.
Preparation of 4b

To a solution of aldehyde 2 (81.6 mg, 0.54 mmol, 2 equiv), catalyst-IV (17.7 mg, 0.05 mmol, 0.2 equiv) and additive-(S)-A11 (37.8 mg, 0.11 mmol, 0.4 equiv) in CHCl3–EtOAc (1:1, 0.77 mL) was added indole 3b (40 mg, 0.27 mmol, 1 equiv) at ~25 °C. The resulting solution was stirred at ambient temperature for 15 days. To the reaction mixture was added Et3N (27 mg, 0.27 mmol, 1 equiv) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give the residue. The crude product was purified by flash column chromatography with 10 % EtOAc-hexane ($R_f = 0.49$ for trans-4b after developing three times in 15 % EtOAc-hexane and $R_f = 0.46$ for cis-4b after developing three times in 15 % EtOAc-hexane) to afford product 4b as mixture of diastereomers (24 mg, 30 % yield) as yellow oil; Selected spectroscopic data for trans-4b: $[\alpha]_D^{26} = -59.2$ (c 1, CHCl3) for 58% ee of trans-4b; IR (neat): 3414, 2964, 2828, 1716, 1486, 1457, 1439, 1260, 1217, 1027, 800, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3): $\delta$ 9.70 (d, $J = 4.5$ Hz, 1 H), 7.84 (bs, 1 H), 7.21 (d, $J = 8.5$ Hz, 1 H), 7.03 (d, $J = 2.0$ Hz, 1 H), 6.91 (d, $J = 2.5$ Hz, 1 H), 6.82 (dd, $J = 8.5$, 2.5 Hz, 1 H), 5.49 (s, 1 H), 4.04 – 4.00 (m, 1 H), 3.83 (s, 3 H), 2.60 (dd, $J = 11$, 4 Hz, 1 H), 2.16 (d, $J = 17$ Hz, 1 H), 1.78 –1.68 (m, 1 H), 1.71 (s, 3 H), 1.11 (s, 3 H), 1.10 (s, 3 H), 13C NMR (125 MHz, CDCl3): $\delta$ 206.5 (CH), 153.6 (C), 131.82 (C), 131.76 (C), 126.8 (C), 122.9 (CH), 122.7 (CH), 117.2 (C), 111.9 (CH), 111.8 (CH), 101.6 (CH), 60.6 (CH), 55.9 (CH3), 46.5 (CH2), 33.8 (C), 32.1 (CH), 29.3 (CH3), 23.4 (CH3), 21.5 (CH3); MS ($m/z$, relative intensity): 298 (M$^+$ + 1, 21), 297 (M$^+$, 100), 268 (76), 252 (26), 212 (74), 198 (52), 147 (40), 101 (39), exact mass calculated for C19H23NO2 (M$^+$): 297.1729; found : 297.1728.
Preparation of 4c

To a solution of aldehyde 2 (91.5 mg, 0.61 mmol, 2 equiv), catalyst-IV (19.8 mg, 0.06 mmol, 0.2 equiv) and additive-(S)-A11 (42.4 mg, 0.12 mmol, 0.4 equiv) in CHCl3–EtOAc (1:1, 0.87 mL) was added indole 3c (40 mg, 0.30 mmol, 1 equiv) at ~25 °C. The resulting solution was stirred at ambient temperature for 15 days. To the reaction mixture was added Et3N (31 mg, 0.305 mmol, 1 equiv) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give the residue. The crude product was purified by flash column chromatography with 8 % EtOAc-hexane ($R_f = 0.35$ for trans-4c after developing two times in 15 % EtOAc-hexane and $R_f = 0.32$ for cis-4c after developing two times in 15 % EtOAc-hexane) to afford product 4c as mixture of diastereomers (23 mg, 27 % yield) as yellow oil; Selected spectroscopic data for trans-4c: $[\alpha]_D^{26} = -72.1$ (c 0.8, CHCl3) for 72% ee of trans-4c; IR (neat): 3375, 3012, 2963, 2825, 1719, 1543, 1484, 1466, 1369, 1317, 1205, 1157, 1021, 990, 858, 752 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3): $\delta$ 9.68 (d, $J = 4.5$ Hz, 1 H), 7.84 (bs, 1 H), 7.34 (s, 1 H), 7.20 (d, $J = 8.0$ Hz, 1 H), 6.98 (dd, $J = 8.5$, 1.5 Hz, 1 H), 6.89 (d, $J = 2.5$ Hz, 1 H), 5.49 (s, 1 H), 4.06 – 4.02 (m, 1 H), 2.60 (dd, $J = 11.0$, 4.0 Hz, 1 H), 2.43 (s, 3 H) 2.17 – 2.14 (m, 1 H), 1.78 – 1.67 (m, 1 H), 1.70 (s, 3 H), 1.11 (s, 6 H), $^{13}$C NMR (125 MHz, CDCl3): $\delta$ 206.6 (CH), 135.0 (C), 131.6 (C), 128.4 (C), 126.6 (C), 123.7 (CH), 123.0 (CH), 122.0 (CH), 118.9 (CH), 117.0 (C), 110.9 (CH), 60.6 (CH), 46.5 (CH2), 33.8 (C), 32.1 (CH), 29.3 (CH3), 23.4 (CH3), 21.62 (CH3), 21.57 (CH3); MS ($m/z$, relative intensity): 282 (M$^+$ + 1, 22), 281 (M$^+$, 100), 252 (92), 236 (33), 196 (75), 182 (58), 131 (35), 59 (55), exact mass calculated for C19H23NO (M$^+$): 281.1780; found : 281.1782.
Preparation of 4d

![Chemical structure](image)

To a solution of aldehyde 2 (81.6 mg, 0.54 mmol, 2 equiv), catalyst-IV (17.7 mg, 0.05 mmol, 0.2 equiv) and additive-(S)-A11 (37.8 mg, 0.11 mmol, 0.4 equiv) in CHCl₃–EtOAc (1:1, 0.77 mL) was added indole 3d (40 mg, 0.27 mmol, 1 equiv) at ~25 °C. The resulting solution was stirred at ambient temperature for 15 days. To the reaction mixture was added Et₃N (27 mg, 0.27 mmol, 1 equiv) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give the residue. The crude product was purified by flash column chromatography with 10 % EtOAc-hexane ($R_f = 0.47$ for trans-4d after developing two times in 15 % EtOAc-hexane and $R_f = 0.44$ for cis-4d after developing two times in 15 % EtOAc-hexane) to afford product 4d as mixture of diastereomers (19 mg, 23 % yield) as yellow oil; Selected spectroscopic data for trans-4d: [α]₀²⁶ –83.3 (c 1, CHCl₃) for 78% ee of trans-4d; IR (neat): 3369, 3015, 2963, 2825, 1718, 1484, 1466, 1317, 1205, 1156, 1021, 857, 752, 666 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.69 (d, $J = 4.0$ Hz, 1 H), 7.80 (bs, 1 H), 7.43 (d, $J = 9.0$ Hz, 1 H), 6.81 (dd, $J = 6.5$, 2.0 Hz, 2 H), 6.74 (dd, $J = 8.5$, 2.0 Hz, 1 H), 5.48 (s, 1 H), 4.02 – 3.99 (m, 1 H), 3.81 (s, 3 H), 2.58 (dd, $J = 11.0$, 4.0 Hz, 1 H), 2.17 – 2.14 (m, 1 H), 1.77 – 1.66 (m, 1 H), 1.70 (s, 3 H), 1.10 (s, 3 H), 1.09 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃): δ 206.5 (CH), 156.5 (C), 137.4 (C), 131.7 (C), 123.0 (CH), 120.7 (C), 120.5 (CH), 120.0 (CH), 117.5 (C), 109.3 (CH), 94.8 (CH), 60.7 (CH), 55.7 (CH₃), 46.5 (CH₂), 33.8 (C), 32.3 (CH), 29.3 (CH₃), 23.5 (CH₃), 21.5 (CH₃), MS (m/z, relative intensity): 298 (M⁺ + 1, 21), 297 (M⁺, 100), 268 (100), 212 (61), 198 (39), 147 (38), 59 (44), exact mass calculated for C₁₉H₂₃NO₂ (M⁺): 297.1729; found: 297.1731.
Preparation of 4e

To a solution of aldehyde 2 (68 mg, 0.45 mmol, 2 equiv), catalyst-IV (14.3 mg, 0.04 mmol, 0.2 equiv) and additive-(S)-A11 (30.6 mg, 0.09 mmol, 0.4 equiv) in CHCl₃–EtOAc (1:1, 0.60 mL) was added indole 3e (40 mg, 0.23 mmol, 1 equiv) at ~25 °C. The resulting solution was stirred at ambient temperature for 15 days. To the reaction mixture was added Et₃N (23 mg, 0.23 mmol, 1 equiv) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give the residue. The crude product was purified by flash column chromatography with 15 % EtOAc-hexane ($R_f$ = 0.30 for trans-4e after developing two times in 30 % EtOAc-hexane and $R_f$ = 0.27 for cis-4e after developing two times in 30 % EtOAc-hexane) to afford product 4e as mixture of diastereomers (18 mg, 24 % yield) as yellow oil. For purified trans-4e, darkkhaki solid, m.p. decomposed at 185 °C. Selected spectroscopic data for trans-4e: $[\alpha]_D^{26} = -78.2$ (c 1.2, CHCl₃) for 79% ee of trans-4e; IR (neat): 3372, 2960, 1718, 1484, 1466, 1317, 1205, 1157, 1022, 755 cm⁻¹; $^1$H NMR (500 MHz, CDCl₃): δ 9.70 (d, $J$ = 4 Hz, 1 H), 7.80 (bs, 1 H), 7.01 (s, 1 H), 6.82 (s, 1 H), 6.79 (d, $J$ = 2.5 Hz, 1 H), 5.50 (s, 1 H), 4.02 – 3.99 (m, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.56 (dd, $J$ = 11.0, 4.5 Hz, 1 H), 2.15 – 2.02 (m, 1 H), 1.79 – 1.70 (m, 1 H), 1.71 (s, 3 H), 1.11 (s, 3 H), 1.10 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl₃): δ 206.5 (CH), 147.2 (C), 144.6 (C), 131.7 (C), 130.9 (C), 123.0 (CH), 120.2 (CH), 119.1 (C), 117.4 (C), 101.2 (CH), 94.7 (CH), 60.8 (CH), 56.4 (CH₃), 56.2 (CH₃), 46.5 (CH₂), 33.8 (C), 32.1 (CH), 29.3 (CH₃), 23.4 (CH₃), 21.5 (CH₃); MS ($m/z$, relative intensity): 328 (M⁺ + 1, 22), 327 (M⁺, 100), 298 (99), 284 (19), 282 (16), 242 (41), 228 (28), 177 (36), 71 (32), exact mass calculated for C₂₀H₂₅NO₃ (M⁺): 327.1834; found : 327.1834.
**Figure S1.** ORTEP and Stereo plots for X-ray crystal structures of (–)-trans-4e.

CCDC-1011541 contains the supplementary crystallographic data for (–)-trans-4e. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Preparation of 1a

To a solution of aldehyde 4a (15 mg, 0.06 mmol) and indole 3a (7.9 mg, 0.07 mmol, 1.2 equiv) in CH$_2$Cl$_2$ (0.1M, 0.56 mL) was added (S)-CSA (2.6 mg, 0.01 mmol, 0.2 equiv) at room temperature. The resulting solution was stirred at ambient temperature for 7 days until the completion of reaction, as monitored by TLC. To the reaction mixture was added Et$_3$N (6 mg, 0.06 mmol) and the corresponding reaction mixture was stirred for 30 min. The reaction solution was concentrated in vacuo to give a crude residue. The crude product was purified by flash column chromatography with 8 % EtOAc-hexane ($R_f = 0.40$ for 1a) after developing three times in 15 % EtOAc-hexane to afford product 1 (15 mg, 73 % yield) as amorphous white powder; m.p. 125-127 °C (decomp.) Lit. 128 °C; 1, 127; 2 Selected spectroscopic data for 1a:

IR (neat): 3410, 2963, 2906, 1454, 1415, 1260, 1114, 1008, 865, 797, 701 cm$^{-1}$; 1H NMR (500 MHz, CDCl$_3$): δ 8.00 (bs, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 7.48 (bs, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.18 (dd, J = 7.5, 7.5 Hz, 1 H), 7.15 – 6.99 (m, 5 H), 7.18 (d, J = 6.0 Hz, 1 H), 3.15 (dd, J = 8.5, 7.0 Hz, 1 H), 2.25 (d, J = 17.0 Hz, 1 H), 1.64 (s, 3 H), 1.61 (d, J = 17.0 Hz, 1 H), 1.07 (s, 3 H), 0.85 (s, 3 H), 13C NMR (125 MHz, CDCl$_3$): δ 145.1 (C), 140.2 (C), 136.5 (C), 130.2 (C), 126.8 (C), 124.2 (C), 122.9 (CH), 122.3 (CH), 122.0 (CH), 120.52 (CH), 120.48 (CH), 119.50 (CH), 119.48 (CH), 119.4 (C), 118.4 (C), 118.2 (CH), 111.7 (CH), 111.2 (CH), 60.7 (CH), 41.0 (CH$_2$), 38.3 (CH), 37.6 (CH), 33.5 (C), 29.1 (CH$_3$), 28.9 (CH$_3$), 24.1 (CH$_3$); MS (m/z, relative intensity): 366 (M$^+$, 17), 351 (8), 284 (12), 267 (82), 245 (25), 238 (58), 222 (35), 182 (91), 168 (94), 117 (62), 97 (47), 85 (82), 71 (100), 57 (100); exact mass calculated for C$_{26}$H$_{26}$N$_2$(M$^+$): 366.2096; found : 366.2093.

3 In a separate reaction, starting from 84% ee of trans-4a with (S)-A12 in CH$_2$Cl$_2$ at ~35 °C for 15 days provided 73% yield of 1a with 21% ee. For the yuehchukene (1a) obtained (21% ee): [α]$_D^{26}$ = -16.6 (c 1.4, CHCl$_3$).
### $^1$H NMR Data for Yuehchukene (1a)

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\(^a\)Spectrum recorded at 500 MHz (Varian Unity INOVA 500) in CDCl₃
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\(^a\)Spectrum recorded at 125 MHz (Varian Unity INOVA 500) in CDCl\(_3\)

---


\(^6\) Imaizumi, Katsuaki; Ishikura, Minoru; Katagiri, Nobuya Heterocycles, 2000, 53, 2201 – 2220.


One-pot synthesis of (±)-yuechukene (1a) from aldehyde 2 and indole (3a)

\[
\begin{array}{c}
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\end{array}
\begin{array}{c}
+ \\
\text{TFA (50 mol %)} \\
\text{toluene, 60 °C, 24h} \\
\end{array}
\begin{array}{c}
\text{NH} \\
3a \\
\end{array}
\begin{array}{c}
\text{TFA} \\
\text{H} \\
1a \\
\end{array}
\]

To a solution of aldehyde 2 (100 mg, 0.67 mmol) and indole 3a (156 mg, 1.33 mmol, 2 equiv) in toluene (0.2 M, 3.3 mL) was added TFA (38 mg, 0.33 mmol, 0.5 equiv) at room temperature. The resulting solution was heated to 60 °C and stirred at the same temperature for 24 h until the completion of reaction, as monitored by TLC. The solution was cooled to 0 °C, followed by the addition of Et3N (67 mg, 0.66 mmol), and the corresponding reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with H2O (10 mL). The organic reaction solution was concentrated in vacuo to give a crude residue. The crude product was purified by flash column chromatography with 8 % EtOAc-hexane (Rf = 0.40 for 1a after developing three times in 15 % EtOAc-hexane) to afford product 1 (40 mg, 16 % yield) as white solid.

One-pot synthesis of (±)-1b from aldehyde 2 and indole 3b

\[
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\end{array}
\begin{array}{c}
+ \\
\text{TFA (50 mol %)} \\
\text{toluene, 60 °C, 24h} \\
\end{array}
\begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{NH} \\
3b \\
\end{array}
\begin{array}{c}
\text{MeO} \\
1b \\
\end{array}
\]

To a solution of aldehyde 2 (100 mg, 0.67 mmol) and indole 3b (196 mg, 1.33 mmol, 2 equiv) in toluene (0.2 M, 3.3 mL) was added TFA (38 mg, 0.33 mmol, 0.5 equiv) at room temperature. The resulting solution was heated to 60 °C and stirred at the same temperature for 24 h until the completion of reaction, as monitored by TLC. The solution was cooled to 0 °C, followed by the addition of Et3N (67 mg, 0.66 mmol), and the corresponding reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with H2O (10 mL). The organic solution was concentrated in vacuo to give a crude residue. The crude product was purified by flash column chromatography with 10 %
EtOAc-hexane ($R_f = 0.50$ for 1b after developing two times in $20\%$ EtOAc-hexane) to afford product 1b (30 mg, 13 % yield) as yellow solid. m.p. 160 °C (decomp). Selected spectroscopic data for 1b: IR (neat): 3403, 2947, 1586, 1484, 1211, 1034, 799, 760 cm$^{-1}$; $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.26 (d, $J = 2.5$ Hz, 1 H), 7.07 (dd, $J = 9.0$, 2.5 Hz, 1 H), 6.95 – 7.01 (m, 3 H), 6.77 (d, $J = 9.0$ Hz, 1 H), 6.67 (bs, 1 H), 6.48 (d, $J = 2.0$ Hz, 2 H), 5.87 (s, 1 H), 4.50 (d, $J = 8.0$ Hz, 1 H), 4.05 – 4.10 (m, 1 H), 3.59 (s, 3 H), 3.39 (s, 3 H), 3.17 (dd, $J = 8.0$, 8.0 Hz, 1 H), 2.29 (d, $J = 17.0$ Hz, 1 H), 1.66 (s, 3 H), 1.59 (d, $J = 17.0$ Hz, 1 H), 1.15 (s, 3 H), 0.95 (s, 3 H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 155.3 (2 C), 146.7 (C), 136.2 (C), 132.2 (C), 130.2 (2 C), 125.5 (C), 124.3 (CH), 123.2 (CH), 120.8 (C), 119.0 (C), 113.3 (CH), 113.0 (CH), 112.6 (CH), 111.0 (CH), 101.6 (CH), 101.4 (CH), 62.2 (CH), 55.8 (CH$_3$), 55.7 (CH$_3$), 41.8 (CH$_2$), 39.1 (CH), 38.2 (CH), 34.0 (C), 29.7 (CH$_3$), 29.6 (CH$_3$), 24.5 (CH); MS (m/z, relative intensity): 427 (M$^+$ +1, 31), 426 (M$^+$, 100), 411 (43), 359 (56), 264 (35), 185 (45), 160 (38), 57 (54); exact mass calculated for C$_{28}$H$_{30}$N$_2$O$_2$ (M$^+$): 426.2307; found: 426.2310.

One-pot synthesis of (±)-1c from aldehyde 2 and indole 3c

To a solution of aldehyde 2 (100 mg, 0.67 mmol) and indole 3c (175 mg, 1.33 mmol, 2 equiv) in toluene (0.2 M, 3.3 mL) was added TFA (38 mg, 0.33 mmol, 0.5 equiv) at room temperature. The resulting solution was heated to 60 °C and stirred at the same temperature for 24 h until the completion of reaction, as monitored by TLC. The solution was cooled to 0 °C, followed by the addition of Et$_3$N (67 mg, 0.66 mmol), and the corresponding reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with H$_2$O (10 mL). The organic solution was concentrated in vacuo to give a crude residue. The crude product was purified by flash column chromatography with 8 % EtOAc-hexane ($R_f = 0.60$ for 1c after developing two times in 15 % EtOAc-hexane) to afford product 1c (40 mg, 15 % yield) as yellow oil. Selected spectroscopic data for 1c: IR (neat): 3404, 2917, 1716, 1620, 1454, 1297, 1096, 798 cm$^{-1}$; $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.54 (s, 1 H), 7.41 (s, 1 H), 6.98 – 7.16 (m, 3 H), 6.81 (d, $J = 8.5$ Hz, 1 H), 6.68 (bs, 1 H), 6.51 (bs, 1 H), 6.40 (d, $J = 8.0$ Hz, 2 H), 4.57 (d, $J = 8.0$ Hz, 1 H), 3.90 (s, 3 H), 3.39 (s, 3 H), 3.18 (dd, $J = 8.0$, 8.0 Hz, 1 H), 2.30 (d, $J = 17.0$ Hz, 1 H), 1.66 (s, 3 H), 1.59 (d, $J = 17.0$ Hz, 1 H), 1.15 (s, 3 H), 0.95 (s, 3 H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 155.3 (2 C), 146.7 (C), 136.2 (C), 132.2 (C), 130.2 (2 C), 125.5 (C), 124.3 (CH), 123.2 (CH), 120.8 (C), 119.0 (C), 113.3 (CH), 113.0 (CH), 112.6 (CH), 111.0 (CH), 101.6 (CH), 101.4 (CH), 62.2 (CH), 55.8 (CH$_3$), 55.7 (CH$_3$), 41.8 (CH$_2$), 39.1 (CH), 38.2 (CH), 34.0 (C), 29.7 (CH$_3$), 29.6 (CH$_3$), 24.5 (CH); MS (m/z, relative intensity): 427 (M$^+$, 100), 411 (43), 359 (56), 264 (35), 185 (45), 160 (38), 57 (54)
6.45 (d, J = 2.5 Hz, 1 H), 5.88 (s, 1 H), 4.52 (d, J = 8.5 Hz, 1 H), 4.05 – 4.11 (m, 1 H), 3.20 (dd, J = 8.0, 8.0 Hz, 1 H), 2.48 (s, 3 H), 2.31 (s, 3 H), 2.26 – 2.28 (m, 1 H), 1.65 (s, 3 H), 1.56 (d, J = 16.5 Hz, 1 H), 1.14 (s, 3 H), 1.01 (s, 3 H); 1H NMR (125 MHz, CD6D6): δ 146.1 (C), 139.6 (C), 135.5 (C), 130.1 (C), 129.2 (C), 128.9 (C), 128.7 (C), 125.6 (C), 124.5 (CH), 124.4 (CH), 122.64 (CH), 122.63 (CH), 120.3 (C), 119.4 (CH), 119.1 (CH), 118.9 (C), 112.1 (CH), 111.6 (CH), 62.3 (CH), 41.8 (CH2), 39.1 (CH), 38.1 (CH), 34.0 (C), 29.8 (CH3), 29.5 (CH3), 24.5 (CH3), 22.2 (CH3), 22.1 (CH3); MS (m/z, relative intensity): 395 (M+ +1, 12), 394 (M+, 34), 379 (17), 248 (15), 221 (18), 207 (13), 198 (13), 149 (34), 85 (42), 71 (62), 58 (100); exact mass calculated for C28H30N2 (M+): 394.2409; found : 394.2407.
Fig S14. 1H NMR (CDCl3, 500 MHz) of compound 4a.
Fig S15. 13C NMR (CDCl₃, 125 MHz) of compound 4a.
Fig S17. HSQC of compound 4a.

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**F1 (ppm)**

**F2 (ppm)**
Fig S18. COSY of compound 4a.
Fig S19. NOESY of compound 4a.
Fig S20. 1H NMR (CDCl3, 500 MHz) of compound 4b.
Fig S21. 13C NMR (CDCl3, 125 MHz) of compound 4b.
Fig S22. DEPT of compound 4b.
Fig S23. HMQC of compound 4b.
Fig S24. COSY of compound 4b.
Fig S25. NOESY of compound 4b.
Fig S26. 1H NMR (CDCl₃, 500 MHz) of compound 4c.
Fig S27. 13C NMR (CDCl3, 125 MHz) of compound 4c.
Fig S28. DEPT of compound 4c.
Fig S29. HSQC of compound 4c.
Fig S30. COSY of compound 4c.
Fig S31. NOESY of compound 4c.
Fig S32. 1H NMR (CDCl3, 500 MHz) of compound 4d.
Fig S33. 13C NMR (CDCl3, 125 MHz) of compound 4d.
Fig S34. DEPT of compound 4d.
Fig S35. HSQC of compound 4d.

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**Diagram**
- F1 (ppm): 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20
- F2 (ppm): 2, 3, 4, 5, 6, 7
Fig S37. NOESY of compound 4d.
Fig S38. $^1$H NMR (CDCl$_3$, 500 MHz) of compound 4e.
Fig S39. 13C NMR (CDCl₃, 125 MHz) of compound 4e.
Fig S40. DEPT of compound 4e.
Fig S41. HMQC of compound 4e.
Fig S42. COSY of compound 4e.
Fig S43. NOESY of compound 4e.
Fig S44. 1H NMR (CDCl3, 500 MHz) of compound 1a.
Fig S45. 13C NMR (CDCl3, 125 MHz) of compound 1a.
Fig S46. DEPT of compound 1a.

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**Diagram:**

- X-axis: 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 ppm
- Y-axis: Various peaks and intensities

**Note:** The diagram illustrates the DEPT spectrum of compound 1a, showing the peaks at different ppm values.
Fig S47. HSQC of compound 1a.
Fig S48. COSY of compound 1a.
Fig S49. NOESY of compound 1a.
Fig S50. 1H NMR (C6D6, 500 MHz) of compound 1b.
Fig S51. 13C NMR (C6D6, 125 MHz) of compound 1b.
Fig S52. DEPT of compound 1b.
Fig S54. COSY of compound 1b.
Fig S55. NOESY of compound 1b.
Fig S56. 1H NMR (C6D6, 500 MHz) of compound 1c.
Fig S57. 13C NMR (C6D6, 125 MHz) of compound 1c.
**Fig S58. DEPT of compound 1c.**

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**Spectrum**

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**REFERENCE**

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Fig S59. HSQC of compound 1c.
Fig S60. COSY of compound 1c.
Fig S61. NOESY of compound 1c.
D-2000 Elite HPLC System Manager Report

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Processed Date and Time: 2014/03/05 06:45 下午

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Application (data): NITIN Vial Number: 1
Sample Name: NSD-09-183 (Racemic) Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
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Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

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Fig S62. HPLC analysis of the racemic compound 4a, for comparison in Table 1.
D-2000 Elite HPLC System Manager Report

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Processed Date and Time: 2013/09/17 02:52 下午
Reported Date and Time: 2013/09/17 02:54 下午

Data Path: D:\NITIN\DATA\0016\ 
Processing Method: Test-IPA/Hx-1
System (acquisition): Sys 1 Series: 0016
Application (data): NITIN Vial Number: 1
Sample Name: NSD-09-96 (Take moto-NH2) Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC Method Developer: NSD
Method Description:
Chrom Type: Fixed WL Chromatogram, 275 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 100000

Fig S63. HPLC analysis of the compound 4a (Table 1, entry 1)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/09/19 02:34 下午
Processed Date and Time: 2013/09/19 03:25 下午
Reported Date and Time: 2013/09/19 03:26 下午

Data Path: D:\NITIN\DATA\0017\n
Processing Method: Test-IPA/Hx-1
System (acquisition): Sys 1 Series: 0017
Application(data): NITIN Vial Number: 1
Sample Name: NSD-09-97 (Quinidine-NH2) Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC Method Developer: NSD
Method Description:

Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA Calculation Method: EXT-STD
Scale Factor 1: 1.000

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743358  33985  100.000

Peak rejection level: 200000

Fig S64. HPLC analysis of the compound 4a (Table 1, entry 3)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/09/13 11:37 上午
Reported Date and Time: 2013/09/13 01:51 下午
Processed Date and Time: 2013/09/13 01:50 下午

Data Path: D:\NITIN\DATA\0015\n
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Series: 0015
Application(data): NITIN
Vial Number: 1
Sample Name: NSD-09-94 (Hydroquinine-NH2)
Vial Type: UNK
Volume: 20.0 ul

Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC
Method Developer: NSD
Method Description:

Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S65. HPLC analysis of the compound 4a (Table 1, entry 4)
**D-2000 Elite HPLC System Manager Report**

Analyzed Date and Time: 2013/11/19 10:44 上午
Reported Date and Time: 2013/11/19 11:18 上午

Processed Date and Time: 2013/11/19 11:16 上午

Data Path: D:\NITIN\DATA\0038\
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1  Series: 0038
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-09-128(DHQ-TCA-CH2Cl2)  Vial Type: UNK
Injection from this vial: 1 of 1  Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

![Chromatogram Image]

Processing Method: Test-IPA/Hx-1
Column Type: IC  Method Developer: NSD
Method Description:

Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

**Fig S66. HPLC analysis of the compound 4a (Table 1, entry 6)**
Fig S67. HPLC analysis of the compound 4a (Table 1, entry 10)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/11/06 12:47 午
Processed Date and Time: 2013/11/06 12:47 午
Data Path: D:\NITIN\DATA\0034\ 
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Application(data): NITIN
Sample Name: NSD-09-118(DHQ-2-NBA-CH2Cl2)
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

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Peak rejection level: 100000

Fig S68. HPLC analysis of the compound 4a (Table 1, entry 11)
Fig S69. HPLC analysis of the compound 4a (Table 1, entry 14)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/10/23 11:07 上午
Reported Date and Time: 2013/10/23 11:57 上午

Processed Date and Time: 2013/10/23 11:57 上午

Data Path: D:\NITIN\DATA\0028\ 
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Application(data): NITIN
Sample Name: NSD-09-114(DHQ-NH2-R-PACH2Cl2)
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

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1277211  78083  100.000

Peak rejection level: 200000

Fig S70. HPLC analysis of the compound 4a (Table 1, entry 15)
**D-2000 Elite HPLC System Manager Report**

**Analyzed Date and Time:** 2013/10/23 10:38 上午  
**Reported Date and Time:** 2013/10/23 11:54 上午  
**Processed Date and Time:** 2013/10/23 11:52 上午  

**Data Path:** D:\NITIN\DATA\0027\  
**Processing Method:** Test-IPA/Hx-1

**System (acquisition):** Sys 1  
**Series:** 0027  
**Application(data):** NITIN  
**Sample Name:** NSD-09-113(DHQ-NH2-S-PACH2Cl2)  
**Vial Number:** 1  
**Volume:** 20.0 ul  
**Series:** 0027  
**Vial Type:** UNK

**Injection from this vial:** 1 of 1  
**Sample Description:** 5%IPA+HX 1mL/MIN COL-IC

**Chrom Type:** Fixed WL Chromatogram, 275 nm

![Chromatogram Image]

**Processing Method:** Test-IPA/Hx-1  
**Column Type:** IC  
**Method Developer:** NSD

**Method Description:**  
**Chrom Type:** Fixed WL Chromatogram, 275 nm

**Peak Quantitation:** AREA  
**Calculation Method:** EXT-STD  
**Scale Factor 1:** 1.000

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**Peak rejection level:** 200000

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**Fig S71.** HPLC analysis of the compound 4a (Table 1, entry 16)
Fig S72. HPLC analysis of the compound 4a (Table 1, entry 19)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/09/26 11:49 上午
Processed Date and Time: 2013/09/26 12:23 下午
Reported Date and Time: 2013/09/26 12:25 下午

Data Path: D:\NITIN\DATA\0019\Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1  Series: 0019
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-09-103 (Quinine-NH2-CHCl3)  Vial Type: UNK
Volume: 20.0 ul
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC  Method Developer: NSD
Method Description:

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Peak rejection level: 200000

Fig S73. HPLC analysis of the compound 4a (Table 1, entry 20)
Fig S74. HPLC analysis of the compound 4a (Table 1, entry 21)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/10/10 11:04 上午
Processed Date and Time: 2013/10/10 12:10 下午
Data Path: D:\NITIN\DATA\0025\ 
System (acquisition): Sys 1 
Application(data): NITIN 
Sample Name: NSD-09-105(QuinineNH2- Dioxane) 
Injection from this vial: 1 of 1 
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

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1047245  49526  100.000

Peak rejection level: 200000

Fig S75. HPLC analysis of the compound 4a (Table 1, entry 22)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/10/04 04:52 下午  
Reported Date and Time: 2013/10/04 05:23 下午

Processed Date and Time: 2013/10/04 05:22 下午

Data Path: D:\NITIN\DATA\0022\  
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1  
Series: 0022

Application(data): NITIN  
Vial Number: 1

Sample Name: NSD-09-106 (Quinine-NH2-THF)  
Vial Type: UNK

Volume: 20.0 ul

Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC  
Method Developer: NSD
Method Description:

Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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522417 30411 100.000

Peak rejection level: 100000

Fig S76. HPLC analysis of the compound 4a (Table 1, entry 23)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/10/10 11:32 上午
Processed Date and Time: 2013/10/10 12:12 下午

Data Path: D:\NITIN\DATA\0026\nProcessing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Application(data): NITIN
Sample Name: NSD-09-110 (QuinineNH2-DCE)
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC
Method Developer: NSD
Method Description:

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S77. HPLC analysis of the compound 4a (Table 1, entry 24)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/12/06 11:04 上午
Processed Date and Time: 2013/12/06 01:38 下午

Report Name: modified
System: Sys 1

Data Path: D:\NITIN\DATA\0044\
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1    Series: 0044
Application (data): NITIN    Vial Number: 1
Sample Name: NSD-09-131 (DHQ-DCM-EtOAc)    Vial Type: UNK
Injection from this vial: 1 of 1    Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC    Method Developer: NSD
Method Description:
Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 50000

Fig S78. HPLC analysis of the compound 4a (Table 1, entry 26)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/02/28 06:01 下午
Processed Date and Time: 2014/03/05 06:49 下午
Reported Date and Time: 2014/03/05 06:50 下午
Data Path: D:\NITIN\DATA\0081\nProcessing Method: test-IPA/Hx-3

System (acquisition): Sys 1  Series: 0081
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-09-172-F1 (Chiral)  Vial Type: UNK
Injection from this vial: 1 of 1  Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/Min Col=IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC  Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 50000

Fig S79. HPLC analysis of the compound 4a (Table 1, entry 27)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/12/06 01:34 下午
Processed Date and Time: 2013/12/06 02:47 下午
Reported Date and Time: 2013/12/06 02:48 下午

Data Path: D:\NITIN\DATA\0045\-
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Application (data): NITIN
Sample Name: NSD-09-132(DHQ-CHCl3-EtOAc)
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC
Method Developer: NSD
Method Description:

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 10000

Fig S80. HPLC analysis of the compound 4a (Table 1, entry 28)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2013/12/31 02:15 下午
Processed Date and Time: 2013/12/31 04:44 下午
Reported Date and Time: 2013/12/31 04:45 下午

Data Path: D:\NITIN\DATA\0058\n
Processing Method: Test-IPA/Hx-1
System (acquisition): Sys 1  Series: 0058
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-09-145(DHQ-CHCl3-EtOAc)  Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC  Method Developer: NSD
Method Description:
Chrom Type: Fixed WL Chromatogram, 275 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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478145  25275  100.000

Peak rejection level: 5000

Fig S81. HPLC analysis of the compound 4a (Table 1, entry 29)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/01/09 02:16 下午
Reported Date and Time: 2014/01/16 02:21 下午
Processed Date and Time: 2014/01/16 02:20 下午

Data Path: D:\NITIN\DATA\0064\ 
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1 
Application(data): NITIN 
Sample Name: NSD-09-160(MicroW-CHCl3-EtOAc) 
Injection from this vial: 1 of 1 
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC 
Method Developer: NSD
Method Description:

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663835   34772   100.000

Peak rejection level: 100000

Fig S82. HPLC analysis of the compound 4a (Table 1, entry 30)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/02/28 05:28 下午
Reported Date and Time: 2014/03/05 06:46 下午
Processed Date and Time: 2014/03/05 06:45 下午
Data Path: D:\NITIN\DATA\0079\
Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1
Series: 0079
Application(data): NITIN
Vial Number: 1
Sample Name: NSD-09-183 (Racemic)
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC
Method Developer: NITIN

Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S83. HPLC analysis of the racemic compound 4a, as a standard for comparison (Scheme 2)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/02/28 06:01 上午
Processed Date and Time: 2014/03/05 06:49 下午

Data Path: D:\NITIN\DATA\0081\ Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1 Series: 0081
Application (data): NITIN Vial Number: 1
Sample Name: NSD-09-172-F1 (Chiral) Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/Min Col-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 50000

Fig S84. HPLC analysis of the compound 4a (Scheme 2, Method A)
Fig S85. HPLC analysis of the mixture of chiral compound 4a and the racemic 4a, for comparison (Scheme 2, Method A)
Fig S86. HPLC analysis of the compound 4a (Scheme 2, Method B)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/02/17 10:22 上午
Processed Date and Time: 2014/02/17 11:47 上午
Reported Date and Time: 2014/02/17 11:48 上午

Data Path: D:\NITIN\DATA\0073\ 
Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1
Application (data): NITIN
Sample Name: NSD-09-171 (Racemic)
Injection from this vial: 1 of 1
Volume: 20.0 µl

Sample Description: 8%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

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Peak rejection level: 200000

Fig S87. HPLC analysis of the racemic compound 4b, as a standard for comparison (Scheme 2)
**D-2000 Elite HPLC System Manager Report**

*Analyzed Date and Time:* 2014/02/17 10:49 上午  
*Reported Date and Time:* 2014/02/17 11:51 上午

*Data Path: D:\NITIN\DATA\0074\  
*Processing Method: test-IPA/Hx-3*

**System (acquisition):** Sys 1  
**Series:** 0074

**Application (data):** NITIN  
**Vial Number:** 1

**Sample Name:** NSD-09-169-F1 (Chiral)  
**Vial Type:** UNK

**Injection from this vial:** 1 of 1  
**Volume:** 20.0 ul

**Sample Description:** 8%IPA+HX 1mL/Min Col-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

---

**Processing Method:** test-IPA/Hx-3  
**Column Type:** IC  
**Method Developer:** NITIN

**Method Description:**

Chrom Type: Fixed WL Chromatogram, 280 nm

**Peak Quantitation:** AREA  
**Calculation Method:** EXT-STD

**Scale Factor 1:** 1.000

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Peak rejection level: 50000

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*Fig S88. HPLC analysis of the compound 4b (Scheme 2, Method A)*
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/02/17 11:15 上午
Reported Date and Time: 2014/02/17 11:53 上午
Processed Date and Time: 2014/02/17 11:52 上午
Data Path: D:\NITIN\DATA\0075\nProcessing Method: test-IPA/Hx-3
System (acquisition): Sys 1  Series: 0075
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-09-169-F1 (CO)  Vial Type: UNK
Injection from this vial: 1 of 1  Volume: 20.0 ul
Sample Description: 8%IPA+HX 1mL/Min Col-IC

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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738819  32047  100.000

Peak rejection level: 50000

Fig S89. HPLC analysis of the mixture of chiral compound 4b and the racemic 4b, for comparison (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/03/07 10:37 上午  
Reported Date and Time: 2014/03/07 11:09 上午

Processed Date and Time: 2014/03/07 11:07 上午

Data Path: D:\NITIN\DATA\0085\  
Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1  
Series: 0085

Application(data): NITIN  
Vial Number: 1

Sample Name: NSD-09-178(cat+acid-1:1-5-OMe)  
Vial Type: UNK  
Volume: 20.0 ul

Injection from this vial: 1 of 1
Sample Description: 8%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC  
Method Developer: NITIN
Method Description:
Chrom Type: Fixed WL Chromatogram, 280 nm
Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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2072153  99989  100.000

Peak rejection level: 50000

Fig S90. HPLC analysis of the compound 4b (Scheme 2, Method B)
Fig S91. HPLC analysis of the racemic compound 4c, as a standard for comparison (Scheme 2)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/03/11 10:59 上午
Processed Date and Time: 2014/03/11 12:07 下午
Data Path: D:\NITIN\DATA\0088\nProcessing Method: test-IPA/Hx-3

System (acquisition): Sys 1
Application (data): NITIN
Sample Name: NSD-09-175-F1 (Chiral)
Injection from this vial: 1 of 1
Series: 0088
Vial Number: 1
Vial Type: UNK
Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/Min Col=IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC
Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S92. HPLC analysis of the compound 4c (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/03/11 11:27 上午
Processed Date and Time: 2014/03/11 12:09 下午
Data Path: D:\NITIN\DATA\0089\ 
Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1
Application(data): NITIN
Sample Name: NSD-09-175-F1 (CO)
Injection from this vial: 1 of 1
Volume: 20.0 ul

Sample Description: 5%IPA+HX 1mL/Min Col=IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC
Method Developer: NITIN
Method Description:

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S93. HPLC analysis of the mixture of chiral compound 4c and the racemic 4c, for comparison (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/06/25 01:17 下午
Processed Date and Time: 2014/06/25 02:16 下午
Data Path: D:\NITIN\DATA\0140\Processing Method: test-IPA/Hx-3
System (acquisition): Sys 1 Series: 0140
Application(data): NITIN Vial Number: 1
Sample Name: NSD-10-27-F1 cat-acid(1:1) Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 5000

Fig S94. HPLC analysis of the compound 4c (Scheme 2, Method B)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/03/27 11:00 上午
Reported Date and Time: 2014/03/27 12:50 下午
Processed Date and Time: 2014/03/27 12:48 下午

Data Path: D:\NITIN\DATA\0093\nProcessing Method: test-IPA/Hx-3

System (acquisition): Sys 1
Series: 0093

Application (data): NITIN
Vial Number: 1
Sample Name: NSD-10-06-F1 (Racemic)
Injection from this vial: 1 of 1
Injection Volume: 20.0 ul
Sample Description: 8%IPA+HX 1mL/MIN COL-IC

Retention Time (min)

Intensity (mV)

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-3
Column Type: IC
Method Developer: NITIN
Method Description:

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 50000

Fig S95. HPLC analysis of the racemic compound 4d, as a standard for comparison (Scheme 2)
Fig S96. HPLC analysis of the compound 4d (Scheme 2, Method A)
Fig S97. HPLC analysis of the mixture of chiral compound 4d and the racemic 4d, for comparison (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/04/04 04:23 下午
Processed Date and Time: 2014/04/04 05:03 下午
Reported Date and Time: 2014/04/04 05:04 下午

Data Path: D:\NITIN\DATA\0104\ 
Processing Method: test-IPA/Hx-3

System (acquisition): Sys 1  
Application(data): NITIN  
Sample Name: NSD-10-04-F1 (acid-cat-1:1)  
Injection from this vial: 1 of 1  
Sample Description: 8%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 280 nm

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Scale Factor 1: 1.000

Peak Quantitation: AREA
Calculation Method: EXT-STD

Peak rejection level: 5000

Fig S98. HPLC analysis of the compound 4d (Scheme 2, Method B)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/19 11:24 上午
Processed Date and Time: 2014/05/19 01:45 下午

Sample Name: NSD-10-02-F1 (Racemic)
Injection from this vial: 1 of 1
Volume: 20.0 ul
Sample Description: 10%IPA+HX 1mL/MIN COL-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

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Peak rejection level: 5000

Fig S99. HPLC analysis of the racemic compound 4e, as a standard for comparison (Scheme 2)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/19 11:54 上午
Processed Date and Time: 2014/05/19 01:46 下午
Reported Date and Time: 2014/05/19 01:47 下午

Data Path: D:\NITIN\DATA\0125\ 
Processing Method: Test-IPA/Hx-2

System (acquisition): Sys 1  
Application(data): NITIN  
Sample Name: NSD-09-184-F1 (Chiral)  
Injection from this vial: 1 of 1  
Volume: 20.0 ul  
Sample Description: 10%IPA+HX 1mL/Min Col-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: Test-IPA/Hx-2
Column Type: IA  
Method Developer: NSD

Method Description:
Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 5000

Fig S100. HPLC analysis of the compound 4e (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/19 12:18 下午
Processed Date and Time: 2014/05/19 01:48 下午
Data Path: D:\NITIN\DATA\0126\Processing Method: Test-IPA/Hx-2

System (acquisition): Sys 1 Series: 0126
Application(data): NITIN Vial Number: 1 Sample Name: NSD-09-184-F1 (CO) Vial Type: UNK Injection from this vial: 1 of 1 Volume: 20.0 ul Sample Description: 10%IPA+HX 1mL/Min Col-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: Test-IPA/Hx-2 Column Type: IA Method Developer: NSD Method Description: Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA Calculation Method: EXT-STD Scale Factor 1: 1.000

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176022 7493 100.000

Peak rejection level: 5000

Fig S101. HPLC analysis of the mixture of chiral compound 4e and the racemic 4e, for comparison (Scheme 2, Method A)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/19 01:06 下午
Reported Date and Time: 2014/05/19 02:13 下午
Processed Date and Time: 2014/05/19 02:12 下午

Data Path: D:\NITIN\DATA\0127\n
System (acquisition): Sys 1  Series: 0127
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-10-03-F1 (Chiral-C-A- 1:1)  Vial Type: UNK
Volume: 20.0 ul

Injection from this vial: 1 of 1
Sample Description: 10%IPA+HX 1mL/Min Col-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: Test-IPA/Hx-2
Column Type: IA  Method Developer: NSD
Method Description:

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<td>93.036</td>
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Peak rejection level: 5000

Fig S102. HPLC analysis of the compound 4e (Scheme 2, Method B)
D-200 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/30 02:54 下午  
Reported Date and Time: 2014/05/30 03:38 下午  
Processed Date and Time: 2014/05/30 03:38 下午  
Data Path: D:\NITIN\DATA\0130\  
Processing Method: test-IPA/Hx-2 (Final Compound)  
System (acquisition): Sys 1  
Application (data): NITIN  
Sample Name: NSD-09-147 (Final-CSA)  
Injection from this vial: 1 of 1  
Series: 0130  
Vial Number: 1  
Vial Type: UNK  
Volume: 20.0 ul  
Sample Description: 10%IPA+HX 1mL/MIN COL-IA  
Chrom Type: Fixed WL Chromatogram, 280 nm  
Processing Method: test-IPA/Hx-2 (Final Compound)  
Column Type: IA  
Method Developer: NITIN  
Method Description:  
Chrom Type: Fixed WL Chromatogram, 280 nm  
Peak Quantitation: AREA  
Calculation Method: EXT-STD  
Scale Factor 1: 1.000  
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Peak rejection level: 200000

Fig S103. HPLC analysis of the compound 1a (Table 2, entry 1).
Fig S104. HPLC analysis of the recovered compound 4a, (Table 2, entry 1)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/01/28 11:59 上午
Processed Date and Time: 2014/06/20 11:04 上午
Reported Date and Time: 2014/06/20 11:05 上午

Data Path: D:\NITIN\DATA\0070\%
Processing Method: Test-IPA/Hx-1

System (acquisition): Sys 1
Application(data): NITIN
Sample Name: NSD-09-168 (MichaelP-CSA- 6day)
Injection from this vial: 1 of 1
Sample Description: 5%IPA+HX 1mL/MIN COL-IC

Chrom Type: Fixed WL Chromatogram, 275 nm

Processing Method: Test-IPA/Hx-1
Column Type: IC
Method Developer: NSD
Method Description:

Chrom Type: Fixed WL Chromatogram, 275 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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<tr>
<td>1</td>
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<td>255937</td>
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<tr>
<td>2</td>
<td>18.47</td>
<td>71631</td>
<td>2505</td>
<td>21.868</td>
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Total Area: 327568
Area % Total: 100.000

Peak rejection level: 5000

Fig S105. HPLC analysis of the recovered compound 4a, (Table 2, entry 2)
D-2000 Elite HPLC System Manager Report

Analyzed Date and Time: 2014/05/30 02:14 下午
Processed Date and Time: 2014/05/30 03:39 下午
Reported Date and Time: 2014/05/30 03:40 下午

Data Path: D:\NITIN\DATA\0129\Processing Method: test-IPA/Hx-2 (Final Compound)

System (acquisition): Sys 1 Series: 0129
Application (data): NITIN Vial Number: 1
Sample Name: NSD-10-15 Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 20.0 ul
Sample Description: 10%IPA+HX 1mL/MIN COL-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-2 (Final Compound)
Column Type: IA Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

No. | RT  | Area  | Height | Area %
---|-----|-------|--------|------
 1 | 17.25 | 607459 | 22992 | 39.575
 2 | 21.78 | 927482 | 27934 | 60.425

Peak rejection level: 200000

Fig S106. HPLC analysis of compound 1a, (Table 2, entry 3)
Processed Date and Time: 2014/05/30 12:28 下午

Processed Data and Time: 2014/05/30 12:28 下午

Data Path: D:\NITIN\DATA\0128\test-IPA/Hx-2 (Final Compound)

System (acquisition): Sys 1  Series: 0128
Application(data): NITIN  Vial Number: 1
Sample Name: NSD-10-21  Vial Type: UNK
Injection from this vial: 1 of 1  Volume: 20.0 ul
Sample Description: 10%IPA+HX 1mL/MIN COL-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: test-IPA/Hx-2 (Final Compound)
Column Type: IA  Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S107. HPLC analysis of compound 1a, (Table 2, entry 4)
**D-2000 Elite HPLC System Manager Report**

**Analyzed Date and Time:** 2013/11/14 10:18 上午  
**Reported Date and Time:** 2013/11/14 11:47 上午

**Processed Date and Time:** 2013/11/14 11:45 上午

**Data Path:** D:\NITIN\DATA\0036\  
**Processing Method:** test-IPA/Hx-2 (Final Compound)

**System (acquisition):** Sys 1  
**Series:** 0036

**Application (data):** NITIN  
**Vial Number:** 1

**Sample Name:** NSD-09-124 (AKA-DCM)  
**Vial Type:** UNK

**Injection from this vial:** 1 of 1  
**Volume:** 20.0 ul

**Sample Description:** 10%IPA+HX 1mL/MIN COL-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

---

**Processing Method:** test-IPA/Hx-2 (Final Compound)

**Column Type:** IA  
**Method Developer:** NITIN

**Method Description:**

Chrom Type: Fixed WL Chromatogram, 280 nm

**Peak Quantitation:** AREA

**Calculation Method:** EXT-STD

**Scale Factor 1:** 1.000

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</thead>
<tbody>
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<td>39478</td>
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<td>2</td>
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<td>1293857</td>
<td>36107</td>
<td>52.815</td>
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</tbody>
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**Peak rejection level:** 200000

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**Fig S108. HPLC analysis of compound 1a, (Table 3, entry 1)**
D-2000 ELITE HPLC SYSTEM MANAGER REPORT

Analyzed Date and Time: 2013/11/14 11:06 上午
Reported Date and Time: 2013/11/14 11:50 上午
Processed Date and Time: 2013/11/14 11:49 上午

Data Path: D:\NITIN\DATA\0037\\
Processing Method: Test-IPA/Hx-2 (Final Compound)

System (acquisition): Sys 1  Series: 0037
Application (data): NITIN  Vial Number: 1
Sample Name: NSD-09-125 (AKA-toluene)  Vial Type: UNK
Injection from this vial: 1 of 1  Volume: 20.0 ul
Sample Description: 10%IPA+HX 1mL/MIN COL-IA

Chrom Type: Fixed WL Chromatogram, 280 nm

Processing Method: Test-IPA/Hx-2 (Final Compound)
Column Type: IA  Method Developer: NITIN
Method Description:

Chrom Type: Fixed WL Chromatogram, 280 nm

Peak Quantitation: AREA
Calculation Method: EXT-STD
Scale Factor 1: 1.000

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Peak rejection level: 200000

Fig S109. HPLC analysis of compound 1a, (Table 3, entry 2)