SUPPORTING INFORMATION

Self-disproportionation of Enantiomers of Thalidomide and its Fluorinated Analogue via Gravity-driven Achiral Chromatography: Mechanistic Rationale and Implications

Mayaka Maeno, Etsuko Tokunaga, Takeshi Yamamoto, Toshiya Suzuki, Yoshiyuki Ogino, Emi Ito, Motoo Shiro, Toru Asahi* and Norio Shibata*
General information

Silica-gel chromatographies were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualized with UV light (302 nm). The \(^1\)H-NMR (300 MHz), \(^{19}\)F-NMR (282 MHz) spectra for solution in CDCl\(_3\) were recorded on a Varian Mercury 300. Chemical shifts (\(\delta\)) are expressed in ppm downfield from TMS or CFCl\(_3\). Mass spectra were recorded on a SHIMADZU LCMS-2010EV. HPLC analyses were performed on a JASCO U-2080 Plus using 4.6 x 250 mm CHIRALCEL OJ-H column. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. \((\pm\)-1\[^{1}\], \((\pm\)-2\[^{2}\,^{2a,\,^{2b}}\), \((R\)-1\[^{3}\], and \((R\)-2\[^{4}\] were prepared according to previously reported procedures. Their enantiomeric mixtures were prepared using \((\pm\)-1 100 mg and \((R\)-1 50 mg or \((\pm\)-2 100 mg and \((R\)-2 50 mg.

\((\pm\)-Thalidomide (1)

\[
\begin{align*}
\text{A white solid. } &\quad \text{\(^1\)H NMR (300 MHz, CDCl\(_3\)): } \delta 7.97 \text{ (bs, 1H), 7.91-7.87 (m, 2H), 7.80-7.76 (m, 2H), } \\
&\quad \text{5.00 (dd, } J = 12.2, 5.1 \text{ MHz, 1H), 2.95-2.75 (m, 3H), 2.19-2.14 (m, 1H); IR (KBr): 3195, 3098, 1772, } \\
&\quad 1710, 1387, 1327, 1259, 1209, 1114, 1091, 1019, 1001, 890, 859, 7278, 607 \text{ cm}^{-1}; \text{MS (ESI, m/z) calculated for } C_{13}H_{10}N_2NaO_4 ([M + Na]^+) 281.05, \text{found 280.90} \\
\end{align*}
\]

\((R\)-Thalidomide (1)

\[
\begin{align*}
\text{A white solid. Spectral data for } (R\)-1 (\(^1\)H NMR, IR, MS) corresponded to \((\pm\)-1. HPLC (DAICEL CHIRALCEL OJ-H, 4.6x250 mm, EtOH=100, flow rate 0.5 mL/min, } \lambda =254 \text{ nm) } t_R = 12.75 \text{ min (major).} \\
\end{align*}
\]

\((\pm\)-3’-Fluorothalidomide (2)

\[
\begin{align*}
\text{A white solid. } &\quad \text{\(^1\)H NMR (300 MHz, CDCl\(_3\)): } \delta 8.07 \text{ (bs, 1H), 7.96-7.90 (m, 2H), 7.87-7.83 (m, 2H), } \\
&\quad 3.64-3.56 (m, 1H), 2.93-2.86 (m, 1H), 2.67-2.48 (m, 2H); \quad \text{\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): } \delta -131.51 \text{ (s, 1F); IR (KBr): 3317, 3175, 3100, 1798, 1738, 1699, 1365, 1331, 1205, 1117, 1042, 873, 837, 715, \text{cm}^{-1}; } \\
&\quad \text{MS (ESI, m/z) calculated for } C_{13}H_{9}FN_2NaO_4 ([M + Na]^+) 299.04, \text{found 298.95} \\
\end{align*}
\]
(R)-3’-Fluorothalidomide (2)
A white solid. Spectral data for (R)-2 (1H NMR, 19F NMR, IR, MS) corresponded to (±)-2. HPLC (DAICEL CHIRALCEL OJ-H, 4.6×250 mm, EtOH=100, flow rate 0.5 mL/min, λ=254 nm) t_R = 12.49 min (major).

Typical purification experiment using a column chromatography with an achiral phase
3 g of silica-gel (60N spherical neutral size 63-210 μm or 40-50μm) was packed in a 10 mm x 50 mm glass column with hexane and ethyl acetate as the eluent under atmospheric pressure at room temperature. In general, a solution of 10.0 mg of 1 or 2 dissolved in 0.15 mL of DMSO was loaded on this packed column following which this column was pressurized at the abovementioned pressure and 50-60 (each 2.0 mL) fractions were collected until no more 1 or 2 were detected by TLC analysis. Each fraction was then subjected to high-performance liquid chromatography (HPLC) analysis to determine enantiomeric excess (ee).

References
HPLC chromatograms of (±)-1 and (R)-1
DAICEL CHIRALCEL OJ-H, 4.6×250 mm, EtOH=100, flow rate 0.5 ml/min, λ=254 nm

<table>
<thead>
<tr>
<th>PK No</th>
<th>Time</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.750</td>
<td>100</td>
</tr>
</tbody>
</table>

(R)-1: 99% ee

<table>
<thead>
<tr>
<th>PK No</th>
<th>Time</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.767</td>
<td>50.762</td>
</tr>
<tr>
<td>2</td>
<td>17.675</td>
<td>49.238</td>
</tr>
</tbody>
</table>

(±)-1
HPLC chromatograms of (±)-2 and (R)-2
DAICEL CHIRALCEL OJ-H, 4.6×250 mm, EtOH=100, flow rate 0.5 ml/min, λ=254 nm

PK No | Time | Area%
--- | --- | ---
1 | 12.492 | 100

(R)-2: 99% ee

PK No | Time | Area%
--- | --- | ---
1 | 12.475 | 50.719
2 | 13.908 | 49.281

(±)-2
(±)-1

$^1$H NMR CDCl$_3$
(±)-2

$^{19}$F NMR CDCl$_3$
IR (KBr) spectra of (±)-1

calculated for C_{13}H_{10}N_{2}NaO_{4} ([M + Na]^+) 281.05, found 280.90

ESI MS spectra of (±)-1
IR (KBr) spectra of (±)-2

calculated for C_{13}H_9FN_2NaO_4 ([M + Na]^+) 299.04, found 298.95

ESI MS spectra of (±)-2

calculated for C_{13}H_9FN_2NaO_4 ([M + Na]^+) 299.04, found 298.95