Supporting information

Synthesis of All Four Stereoisomers of Reboxetine via Diastereoselective Henry Reaction

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Lists of contents

I. Preparations of aldehydes (S)- and (R)-3  2
II. Copies of HPLC spectra  4
III. Copies of NMR spectra  8
I. Preparations of aldehydes (S)- and (R)-3

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\begin{align*}
\text{(S)-mandelic acid} & \quad \text{AcCl, MeOH} \\
\text{(R)-mandelic acid} & \quad \text{TBSCl, imi, DCM, 40 °C} \\
\text{(S)-2, 95%} & \quad \text{DIBAL-H, DCM, -78 °C, 10 h} \\
\text{(R)-3, 96%} & \quad \text{94%}
\end{align*}
\]

Methyl (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetate [(S)-2]

To a solution of (S)-mandelic acid (30.40 g, 200 mol) in dry methanol (150 mL) was added 1.4 mL of acetyl chloride (20 mmol) via syringe. The mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL), washed with water (60 mL), saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in dry DCM (200 mL), and then sequentially added imidazole (20.40 g, 300 mmol) and tert-butyldimethylsilyl chloride (36.40 g, 240 mmol). The reaction mixture was stirred at 40 °C for 5 hours (as monitored by TLC), quenched with saturated ammonium chloride and extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (50:1, v/v), which afforded the product as a colorless liquid (53.24 g, 95% yield). \([\alpha]_{D}^{20} +50.0 (c \ 1.0 \text{ in CHCl}_3)\); \(1^H\) NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.49-7.45 (m, 2H), 7.36-7.26 (m, 3H), 5.24 (s, 1H), 3.68 (s, 3 H), 0.92 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); \(13^C\) NMR (CDCl\(_3\), 126 MHz) \(\delta\) 172.6, 139.2, 128.4, 128.1, 126.4, 74.4, 52.2, 25.7, 18.4, -5.0(8), -5.1(4); HRMS (ESI): \(m/z\) calcd for C\(_{13}\)H\(_{24}\)O\(_3\)Si [M+Na]\(^+\) 303.1392, found 303.1397.

(R)-Methyl 2-(tert-butyldimethylsilyloxy)-2-phenylacetate [(R)-2]

Following the same procedure for \((S)-2\), the title product was obtained starting from \((R)-mandelic acid in 93% yield. \([\alpha]_{D}^{20} -51.2 (c \ 1.0 \text{ in CHCl}_3)\); \(1^H\) and \(13^C\) NMR data are
identical to that of (S)-2.

(S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde [(S)-3]

To a solution of (S)-2 (22.40 g, 80.0 mmol) in dry DCM (240 mL) was dropwise added a solution of DIBAL-H in hexane (1M, 88 mL, 88 mmol) at -78 °C under nitrogen. The reaction mixture was stirred at -78 °C for additional 10 hours before being quenched with MeOH (10 mL). A saturated Rochelle salt solution (30 mL) was then added to the reaction, stirred rapidly at room temperature for 30 min and then extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (50:1, v/v) afforded the product as a colorless liquid (19.21 g, 76.8 mmol, 96%). $[\alpha]_D^{20} -14.2$ (c 1.0, CHCl$_3$); 1H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.51 (d, $J = 2.15$ Hz, 1H), 7.41-7.36 (m, 4H), 7.34-7.30 (m, 1H), 5.00 (d, $J = 2.07$ Hz, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); 13C NMR (CDCl$_3$, 126 MHz) $\delta$ 199.6, 136.6, 128.7, 128.4, 126.4, 80.0, 25.8, 18.3, -4.8; HRMS (ESI): m/z calcd for C$_{14}$H$_{22}$O$_2$Si $[M+Na]^+$ 273.1287, found 273.1285.

(R)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde [(R)-3]

Following the same procedure for (S)-3, the title product was obtained starting from (R)-mandelic acid in 94% yield. $[\alpha]_D^{20} +10.6$ (c 1.0 in CHCl$_3$); 1H and 13C NMR data are identical to that of (S)-3.
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Flow Rate: 1.0 mL/min
CT: 20°C
Sample Name: (1S,2S)-4

![Chemical Structure]

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Flow Rate: 1.0mL/min
CT: 20°C
Sample Name: (1S,2R)-4

PDA Ch1 208nm

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CT: 20°C
Sample Name: (1\text{R},2\text{R})-4

![Chemical Structure](image)

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Flow Rate: 1.0mL/min
CT: 20°C
Sample Name: (1R,2S)-4

PDA Ch1 208nm

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(2S,3S)-6

\[
\begin{align*}
\text{f1 (ppm)} & = 167.28 \\
& = 140.31 \\
& = 128.66 \\
& = 128.28 \\
& = 128.66 \\
& = 140.31 \\
& = 167.29
\end{align*}
\]