Supporting Information

A new synthesis of L-hydroxypipecolic acid

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General
All commercially available reagents were used without purification unless otherwise noted. Column chromatography was performed using silica gel (200-300 mesh). Reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC). TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of potassium permanganate (KMnO$_4$), an acidic solution of vanillin or a solution of ninhydrin in ethanol followed by heating with a heat gun. $^1$H NMR and $^{13}$C NMR spectra were recorded in CDCl$_3$ operating at 400 MHz and 100 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent CDCl$_3$ (7.28 ppm) or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl$_3$ (77.10 ppm). Chemical shifts are reported in $\delta$ (parts per million) values. Coupling constants J are reported in Hz. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiple (m). High-resolution mass spectra were recorded on a Liquid Chromatograph Mass Spectrometer (LCMS - IT - TOF).
Synthetic procedures

(R, E)-3-(2, 2-dimethyl-1, 3-dioxolan-4-yl)acrylaldehyde (1)

60.0g (0.46 mol) of (S)-2, 2-dimethyl-1, 3-dioxolane-4-carbaldehyde was added into 1L toluene, 174.8g (0.51mol) of (methoxymethyl)triphenylphosphonium chloride was added under nitrogen, then 78 mL of Et₃N was added dropwise slowly into the mixture. The reaction was stirred at room temperature for 4 h. The reaction solution was concentrated in a rotary evaporator. The obtained crude product of 1 was purified by silica gel column chromatography (PE: EA = 8:1). 61.2g, 85% yield, yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.58 (d, J = 7.8 Hz, 1H), 6.76 (dd, J = 15.7, 5.4 Hz, 1H), 6.37 – 6.34 (m, 1H), 4.78 (dd, J = 5.4, 1.3 Hz, 1H), 4.23 (dd, J = 8.3, 6.8 Hz, 1H), 3.72 (dd, J = 8.3, 6.8 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 192.87, 152.99, 132.33, 110.49, 74.82, 68.68, 26.39, 25.58.

(R)-3-(2, 2-dimethyl-1, 3-dioxolan-4-yl)propanal (2)

61.2g (0.39mol) of 1 was added into 800ml THF, then 3.3g of (0.03mol) of Pd/C was added. The reaction was stirred at room temperature in a hydrogen atmosphere for 2 h. The reaction solution was concentrated in a rotary evaporator. The crude 2 without further purified. 62g, 98% yield, orange oil; ¹H NMR (400 MHz, CDCl₃) δ 9.79 (d, J = 0.6 Hz, 1H), 4.16 – 4.08 (m, 1H), 4.04 (dd, J = 7.6, 6.4 Hz, 1H), 3.59 – 3.48 (m, 1H), 2.67 – 2.49 (m, 2H), 1.97 – 1.76 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 201.5, 109.1, 74.8, 69.0, 40.0, 26.8, 26.0, 25.5.
(R)-3-(2, 2-dimethyl-1, 3-dioxolan-4-yl)propanal (3)

62g (0.39mol) of 2 was added into 1L dry THF, then 52g (0.43mol) of 2-methylpropane-2-sulfinamide and 156g (0.975mol) of CuSO₄ was added. The reaction was stirred at 40°C for 12 h and filtrated, filtrate was concentrated in a rotary evaporator. The crude 3 without further purified. 62g, 99% yield, orange oil, [α]²⁵D = -24.7 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (t, J = 4.1 Hz, 1H), 4.20 – 4.08 (m, 1H), 4.06 – 4.03 (m, 1H), 3.57 – 3.47 (m, 1H), 2.71 – 2.51 (m, 2H), 1.93 – 1.80 (m, 2H), 1.38 (d, J = 3.9 Hz, 3H), 1.31 (d, J = 4.0 Hz, 3H), 1.17 (d, J = 4.1 Hz, 9H).¹³C NMR (101 MHz, CDCl₃) δ 168.6, 109.0, 75.0, 69.1, 56.6, 32.3, 29.1, 26.9, 25.6, 22.3. HRMS (ESI) m/z calcd for C₁₂H₂₃NO₃S [M + H]⁺ 262.1471, found 262.1470.

(R)-N-((R)-1-cyano-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-2-methylpropane-2-sulfinamide (4)

52.2g (0.2 mol) of 3 was added into 1L THF, then 76g (0.675mol) of Na₂CO₃ was added, the mixture was cooled to -10°C and TMS-CN (990mg, 4.75mmol) in THF (10 mL) was added. The reaction was stirred at -10°C-15°C for 24 h. The reaction solution was concentrated in a rotary evaporator. The obtained crude product of 4 was purified by recrystallization with EA. 51.3g, 99% yield, white soild, [α]²⁵D = 31.4 (c = 1.0, CHCl₃), m.p. 97.3 – 97.6 °C, Dr = (83%); HPLC: Enantiomeric excess was determined by HPLC with a YMC-Pack ODS-A column (5 mm particle size, 4.6 mm x 150 mm), (water/methanol = 10/90, 1 mL/min, 210 nm, 25°C); tr1 = 8.944 min, tr2 = 9.390 min.
$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.35 (dd, $J = 14.2$, 7.4 Hz, 1H), 4.19 (d, $J = 7.8$ Hz, 1H), 4.12 – 4.08 (m, 2H), 3.58 (q, $J = 6.4$ Hz, 1H), 2.08 – 2.04 (m, 2H), 1.85 – 1.81 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.26 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 119.0, 110.7, 75.2, 70.5, 57.5, 45.8, 31.8, 29.3, 26.7, 25.6, 22.5. HRMS (ESI) m/z calcd for C$_{13}$H$_{24}$N$_2$O$_3$S [M + H]$^+$ 289.1580, found 289.1582.

(R)-N-((1R, 4R)-1-cyano-4, 5-dihydroxypentyl)-2-methylpropane-2-sulfinamide (5)

51.3g (0.178mol) of 4 was added into 600ml MeOH, then 2.37g (0.125mol) of PTSA was added. The reaction was stirred at room temperature for 2 h. The reaction solution was concentrated in a rotary evaporator. The obtained crude product of 5 was purified by silica gel column chromatography (DCM: MeOH = 4:1). 34.4g, 78% yield, white solid, $[\alpha]^2_{D} = -24.5$ (c = 1.0, CHCl$_3$), m.p 84.8-88.6 °C; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.14 (d, $J = 8.0$ Hz, 1H), 4.37 – 4.27 (m, 1H), 4.04 (s, 1H), 3.82 – 3.62 (m, 3H), 3.53 (dd, $J = 10.6$, 6.9 Hz, 1H), 2.09 (dd, $J = 14.5$, 7.1 Hz, 2H), 1.71 (dd, $J = 14.1$, 6.7 Hz, 2H), 1.26 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 119.8, 71.6, 66.2, 57.5, 46.1, 31.3, 28.7, 22.7. HRMS (ESI) m/z calcd for C$_{10}$H$_{20}$N$_2$O$_3$S [M + H]$^+$ 249.1267, found 249.1266.

(R)-N-((R)-1-cyano-3-((R)-oxiran-2-yl)propyl)-2-methylpropane-2-sulfinamide (6)

34.4g (0.139mol) of 5 was added into 300ml CHCl$_3$, then 43.7g (0.167mol) of Ph$_3$P was added under nitrogen, the mixture was cooled to 0°C and 33.6g (0.167mol) of DIAD was added dropwise slowly. The reaction was stirred at 55°C for 4 h. The
reaction solution was concentrated in a rotary evaporator. The obtained crude product of 6 was purified by silica gel column chromatography (PE: EA = 1:1). 26.8 g, 84% yield, orange oil, \([\alpha]^{25}_D = 27.9\) (c = 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta 4.39\) (d, \(J = 8.0\) Hz, 1H), 4.34 – 4.25 (m, 1H), 2.97 (d, \(J = 3.6\) Hz, 1H), 2.82 (t, \(J = 4.0\) Hz, 1H), 2.57 (s, 1H), 2.19 – 2.06 (m, 2H), 2.03 (d, \(J = 10.8\) Hz, 1H), 1.62 (dd, \(J = 14.2, 7.1\) Hz, 1H), 1.25 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta 119.0, 57.2, 51.3, 47.2, 46.1, 31.5, 28.0, 22.5\). HRMS (ESI) m/z calcd for C₁₀H₁₈N₂O₂S [M + H]⁺ 231.1162, found 231.1161.

\(2S, 5S\)-1-((R)-tert-butylsulfinyl)-5-hydroxypiperidine-2-carbonitrile (7)

11.5 g (0.05 mol) of 6 was added into 200 ml toluene, then 15.9 g (0.15 mol) of Na₂CO₃ was added under nitrogen. The reaction was stirred at 80°C for 24 h. The reaction solution was concentrated in a rotary evaporator. The obtained crude product of 7 was purified by silica gel column chromatography (PE: EA = 1:1). 3.45 g, 67% yield, orange oil, \([\alpha]^{25}_D = 34.3\) (c = 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta 4.39\) (d, \(J = 6.2\) Hz, 1H), 4.03 (d, \(J = 5.5\) Hz, 1H), 3.03 (s, 1H), 2.84 (s, 1H), 2.62 (s, 1H), 2.13 (s, 3H), 1.77 (s, 1H), 1.27 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta 118.6, 56.9, 51.19, 47.7, 47.0, 31.4, 28.1, 22.4\). HRMS (ESI) m/z calcd for C₁₀H₁₈N₂O₂S [M + H]⁺ 231.1162, found 231.1161.

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Table S1 Optimization of Reaction Conditions for Synthesis of Compound 7

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(2S, 5S)-5-hydroxypiperidine-2-carboxylic hydrochloride (8)

2.3g (0.01 mol) of 7 was added into 20 mL of concentrated HCl and heated to 75°C in a sealed vial for 20 h. The reaction mixture was allowed to cool and was concentrated. The obtained crude product of 8 was purified by trituration with Et₂O. 1.66g, 92% yield, white solid; ¹H NMR (400 MHz, D₂O) δ 4.22 (s, 1H), 4.01 – 3.97 (dd, J = 3.6, 4Hz, 1H), 3.40 – 3.36 (m, 1H), 3.26 –3.22 (dd, J = 1.6, 1.6 Hz, 1H), 2.21 – 2.04 (m, 2H), 2.00 – 1.82(m, 2H).
Optical purity characterization of compound 4

Racemic characterization of compound 4
Chiral representation of compound 4

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面积百分比报告

排序 信号
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稀释因子  1.0000
内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=210 nm

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$^1$H NMR, $^{13}$C NMR

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

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

$^{13}$C NMR (400 MHz, CDCl$_3$) of 2
$^1$H NMR (400 MHz, CDCl$_3$) of 3

$^{13}$C NMR (400 MHz, CDCl$_3$) of 3
$^1$H NMR (400 MHz, CDCl$_3$) of 4

$^{13}$C NMR (400 MHz, CDCl$_3$) of 4
$^1$H NMR (400 MHz, CDCl$_3$) of 5

$^{13}$C NMR (400 MHz, CDCl$_3$) of 5
$^1$H NMR (400 MHz, CDCl$_3$) of 6

$^{13}$C NMR (400 MHz, CDCl$_3$) of 6
$^{1}H$ NMR (400 MHz, CDCl$_3$) of 7

$^{13}C$ NMR (400 MHz, CDCl$_3$) of 7
$^1$H NMR (400 MHz, D$_2$O) of 8
Notes and references


