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Synthesis of (+)-CP-99,994 via Pd(0)-Catalyzed Asymmetric Allylic and Homoallylic C-H Diamination of Terminal Olefin

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Abstract

This paper describes an asymmetric synthesis of the potent substance P receptor antagonist (+)-CP-99,994 from 4-phenyl-1-butene via Pd(0)-catalyzed asymmetric allylic and homoallylic C-H diamination.

(+)-CP-99,994 (**1**) is a potent and selective non-peptide substance P receptor antagonist (Figure 1).¹ Its biological activity has led to the development of various syntheses of this molecule and related analogues.^{2–5} Recently, we reported that terminal olefins can be enantioselectively diaminated at allylic and homoallylic carbons via C-H activation using di-*tert*-butyldiaziridinone (**3**) as nitrogen source with a catalyst derived from Pd₂(dba)₃ and the tetramethylpiperidine-based phosphorus amidite ligand **5** (Scheme 1).^{6,7} Herein, we wish to report the extension of this diamination process to the synthesis of (+)-CP-99,994.

The retrosynthetic plan for (+)-CP-99,994 is outlined in Scheme 2. Compound **1** can be obtained from diamino acid **7** via lactam **6**. Compound **7** can be derived from diamination of 4-phenyl-1-butene (**10**).

The synthesis of (+)-CP-99,994 is described in Scheme 3. Allylic and homoallylic C-H diamination of 4-phenyl-1-butene (**10**) with di-*tert*-butyldiaziridinone (**3**), Pd₂(dba)₃, and ligand *ent*-**5** gave imidazolidinone **9** in 78% yield and 90% ee. Compound **9** was oxidized to aldehyde **11** in 90% yield via dihydroxylation with OsO₄-NMO, followed by oxidative cleavage with NaIO₄.⁸ The olefination^{3b} of aldehyde **11**, followed by hydrogenation^{3b} gave ester **13** in high yields.

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Supporting Information Available: The synthetic procedure for ligand *ent*-**5**, the X-ray structure of (+)-CP-99,994 (**1**) (2HCl), and the data for the determination of the enantiomeric excess of compounds **9**, **17**, and **1** along with the NMR spectra for ligand *ent*-**5** and compounds **1**, **6**, **9**, **11–19** (38 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

One of the *tert*-butyl groups on the imidazolidinone of **13** was selectively removed with $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 to give compound **14** along with very small amounts of **15** in 98% yield.⁹ At this point, compounds **14** and **15** could not be separated by flash column chromatography. Treating compounds **14** and **15** with sodium bis(trimethylsilylamide) and subsequently with nosyl chloride¹⁰ gave compound **16** in 72% yield after recrystallization from hexanes and ethyl acetate. The remaining *tert*-butyl group of compound **16** was removed with methanesulfonic acid to give compound **17** in 95% yield and >99% ee. Cleavage of the imidazolidinone ring of **17** with potassium hydroxide solution,¹¹ followed by cyclization in refluxing AcOH ¹² led to lactam **18** in 72% yield in two steps. It was found that the nosyl group of **18** could not be removed with thiophenol under basic conditions. Compound **18** was then transformed to compound **19** in 94% yield by alkylation with 2-methoxybenzyl chloride. The removal of the nosyl group was realized by treating **19** with thiophenol and K_2CO_3 to give compound **6** in 79% yield.¹³ Based on a known procedure,^{1b,2a,b} reduction of compound **6** with borane dimethylsulfide (THF, reflux, 15 h) and subsequent treatment with saturated $\text{HCl-Et}_2\text{O}$ gave (+)-CP-99,994 (**1**) as its dihydrochloride salt in 80% yield and >99% ee. The spectroscopic data and optical rotation were consistent with literature data.^{1a,3c,3e,4b,4f} X-ray structure of (+)-CP-99,994 (**1**) dihydrochloride salt is shown in Supporting Information.^{1a}

In conclusion, (+)-CP-99,994 (2HCl) was synthesized from 4-phenyl-1-butene in overall 20% yield and >99% ee. The vicinal diamine moiety was introduced onto a readily available terminal olefin with our recently developed asymmetric allylic and homoallylic C-H amination process. The selective removal of one of the *tert*-butyl groups allows ready differentiation of the two nitrogens. Further application of the amination strategy to other biologically significant molecules is in progress.

Experimental Section

Synthesis of compound 9

A 50-mL flask containing $\text{Pd}_2(\text{dba})_3$ (0.345 g, 0.38 mmol) and ligand *ent*-**5** (0.769 g, 1.66 mmol) was evacuated and then filled with argon three times. Upon addition of benzene (2.0 mL, distilled from sodium), the resulting mixture was immersed in an oil bath (65 °C), stirred for 45 min, and then concentrated under vacuum at room temperature. 4-Phenyl-1-butene (1.0 g, 7.6 mmol) was then added. The resulting mixture was immersed in an oil bath (65 °C) with stirring. Then di-*tert*-butyldiaziridinone (3.21 g, 18.9 mmol) was added by syringe pump at a rate of 1.89 mmol/h. Upon completion of addition (10 h), the reaction mixture was stirred for additional 5 h and purified by flash chromatography (silica gel, hexane : ethyl acetate = 30:1, v/v) to give the amination product along with a small amount of dba, which was further purified by flash chromatography (silica gel, toluene then hexane:ethyl acetate = 30:1, v/v) to give amination product **9** as a colorless oil (1.75 g, 78% yield, 90% ee). The enantioselectivity was determined by HPLC (Chiralpak AD Column, NO. AD00CE-EA001, hexanes:*i*-propanol = 90:10, v/v). $[\alpha]_{\text{D}}^{20} = -29.2^\circ$ (c 1.0, CHCl_3) (90% ee); IR (KBr) 1689 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.26 (m, 5H), 6.04 (ddd, $J = 17.7, 10.2, 8.4\text{ Hz}$, 1H), 5.20 (d, $J = 17.7\text{ Hz}$, 1H), 4.16 (s, 1H), 3.65 (d, $J = 8.4\text{ Hz}$, 1H), 1.34 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 144.0, 140.9, 128.9, 127.8, 125.8, 115.7, 64.9, 63.3, 53.6, 53.4, 29.0, 28.8; HRMS Calcd for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$ ($M + 1$): 301.2274; Found: 301.2279.

Synthesis of compound 11

To a solution of compound **9** (2.33 g, 7.8 mmol) in 1,4-dioxane (140 mL) - H_2O (45 mL) was added $\text{Me}_3\text{NO}\cdot 2\text{H}_2\text{O}$ (1.73 g, 15.6 mmol) and aqueous OsO_4 (2.75 mL, 0.45 mmol, 4% w/w). Then the resulting mixture was stirred at rt for 14 h. Upon addition of NaIO_4 (5.81 g, 27.2 mmol), the reaction mixture was stirred at rt for 4 h, quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, and extracted with ethyl acetate (50 mL $\times$ 3), washed with brine, dried (MgSO_4),

filtered, concentrated, and recrystallized from hexane to give aldehyde **11** as a yellow crystal (2.12 g, 90% yield). mp. 120-122 °C; $[\alpha]_D^{20} = -10.0^\circ$ (c 1.0, CHCl₃); IR (KBr) 1728, 1674 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.77 (d, *J* = 3.3 Hz, 1H), 7.40-7.26 (m, 5H), 4.56 (d, *J* = 1.8 Hz, 1H), 3.66 (dd, *J* = 3.3, 1.8 Hz, 1H), 1.37 (s, 9H), 1.27 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 201.0, 159.0, 142.7, 129.1, 128.4, 125.8, 68.9, 57.6, 54.3, 53.8, 29.0, 28.8; Anal. Calcd for C₁₈H₂₆N₂O₂: C, 71.49; H, 8.67; N, 9.26; Found: C, 71.29; H, 8.54; N, 9.12.

Synthesis of compound 12

To a solution of aldehyde **11** (2.10 g, 6.9 mmol) in CH₂Cl₂ (40 mL) was added methyl (triphenylphosphoranylidene)acetate (2.55 g, 7.6 mmol). Upon stirring at rt for 4 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel, hexane:ethyl acetate = 8:1, v/v) to give compound **12** as a colorless oil (2.44 g, 99% yield). $[\alpha]_D^{20} = -66.9^\circ$ (c 1.0, CHCl₃); IR (KBr) 1728, 1690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.25 (m, 5H), 7.04 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.97 (d, *J* = 15.6 Hz, 1H), 4.18 (d, *J* = 1.5 Hz, 1H), 3.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H), 1.27 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 158.9, 149.1, 143.4, 129.1, 128.2, 125.8, 121.5, 62.7, 62.3, 53.9, 53.7, 52.0, 28.7; HRMS Calcd for C₂₁H₃₁N₂O₃ (M + 1): 359.2329; Found: 359.2332.

Synthesis of compound 13

A suspension of compound **12** (2.40 g, 6.7 mmol) and palladium on activated carbon (10 wt. %) (0.24 g) in MeOH (100 mL) was stirred under H₂ atmosphere (balloon) at rt for 2 h. The reaction mixture was filtered through Celite and concentrated to give compound **13** as a colorless oil (2.41 g, 99% yield). $[\alpha]_D^{20} = +6.0^\circ$ (c 1.0, CHCl₃); IR (KBr) 1739, 1686 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.21 (m, 5H), 4.18 (s, 1H), 3.69 (s, 3H), 3.21 (dd, *J* = 7.5, 2.4 Hz, 1H), 2.58-2.36 (m, 2H), 2.06-1.84 (m, 2H), 1.36 (s, 9H), 1.28 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 158.7, 144.2, 128.9, 127.8, 125.6, 61.1, 60.9, 53.5, 52.9, 52.0, 30.7, 29.0; HRMS Calcd for C₂₁H₃₃N₂O₃ (M + 1): 361.2486; Found: 361.2490.

Synthesis of compound 14 and compound 15

To a solution of compound **13** (2.30 g, 6.4 mmol) in CH₂Cl₂ (25 mL) at 0 °C was added CF₃CO₂H (25 mL) dropwise over 30 min. The reaction mixture was then warmed to room temperature slowly, stirred at room temperature for 10 h, and concentrated. The resulting residue was dissolved in CH₂Cl₂ (100 mL), washed with saturated aqueous Na₂CO₃ and brine, dried (MgSO₄), filtered, and concentrated to give a mixture of compounds **14** and **15** as a colorless oil (1.91 g, 98% yield) (the ratio of compound **14** to **15** is 15 to 1 based on ¹H NMR). $[\alpha]_D^{20} = -13.4^\circ$ (c 1.0, CHCl₃); IR (KBr) 1737, 1688 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 4.64 (brs, 1H), 4.37 (d, *J* = 3.3 Hz, 1H), 3.67 (s, 3H), 3.23-3.16 (m, 1H), 2.45-2.36 (m, 2H), 1.99-1.81 (m, 2H), 1.28 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.5, 161.7, 144.2, 128.9, 127.8, 125.9, 65.4, 58.2, 54.0, 51.8, 31.5, 29.7, 28.8; HRMS Calcd for C₁₇H₂₅N₂O₃ (M + 1): 305.1860; Found: 305.1861.

Synthesis of compound 16

To a stirred solution of compounds **14** and **15** (1.76 g, 5.8 mmol) in THF (12 mL) at -78 °C was added dropwise sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 6.1 mL, 6.1 mmol) over 10 min. After stirring at -78 °C for 15 min, a solution of 4-nitrobenzenesulfonyl chloride (1.54 g, 6.9 mmol) in THF (8 mL) was added dropwise at -78 °C over 10 min. The reaction mixture was stirred at -78 °C for another 2 h and allowed to warm to 0 °C slowly. Upon addition of water (30 mL), the mixture was extracted with ethyl acetate (50 mL × 3), washed with brine, dried (MgSO₄), filtered, concentrated, and purified by flash chromatography (silica gel, hexane:ethyl acetate = 6:1, v/v) to give a white solid (2.45 g, 86% yield) which was recrystallized from hexanes (15 mL) and ethyl acetate (10 mL) to give

compound **16** as a white crystal (2.05 g, 72%). mp. 131-132 °C; $[\alpha]_D^{20} = +37.6^\circ$ (*c* 1.0, CHCl₃); IR (KBr) 1727, 1532, 1397, 1350, 1174 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.34-7.22 (m, 3H), 6.92 (d, *J* = 6.9 Hz, 2H), 4.42 (s, 1H), 3.98-3.93 (m, 1H), 3.71 (s, 3H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.25-2.12 (m, 2H), 1.24 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 152.1, 150.6, 144.6, 141.3, 129.8, 129.4, 128.8, 125.1, 124.1, 62.6, 62.2, 55.6, 52.1, 30.6, 29.0, 28.2; Anal. Calcd for C₂₃H₂₇N₃O₇S: C, 56.43; H, 5.56; N, 8.58; Found: C, 56.66; H, 5.68; N, 8.72.

Synthesis of compound 17

To MeSO₃H (5 mL) was added compound **16** (1.69 g, 3.5 mmol) at rt. After stirring for 1 h, the reaction mixture was added dropwise to saturated aqueous Na₂CO₃ (30 mL) with vigorous stirring. The white precipitate was collected by suction filtration, dried under vacuum, and recrystallized from hexane and EtOAc to give compound **17** as a white solid (1.46 g, 95% yield, >99% ee) (the enantioselectivity was determined by HPLC, Chiralpak AD-H Column, NO. ADH0CE-FD069, hexanes:*i*-propanol = 85:15, v/v). mp. 123-125 °C; $[\alpha]_D^{20} = +47.9^\circ$ (*c* 1.0, CHCl₃); IR (KBr) 3314, 1730, 1532, 1351, 1175 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.25 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.36-7.22 (m, 3H), 6.94 (d, *J* = 7.5 Hz, 2H), 5.59 (s, 1H), 4.39 (s, 1H), 4.23-4.21 (m, 1H), 3.72 (s, 3H), 2.60-2.52 (m, 2H), 2.37-2.26 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 172.8, 155.1, 150.6, 143.6, 140.5, 129.4, 129.0, 125.0, 124.1, 65.7, 58.3, 52.1, 30.6, 29.0; Anal. Calcd for C₁₉H₁₉N₃O₇S: C, 52.65; H, 4.42; N, 9.69; Found: C, 52.42; H, 4.65; N, 9.68.

Synthesis of compound 18

A suspension of compound **17** (1.38 g, 3.2 mmol) in 60% (w/w) aqueous KOH (50 mL) was stirred at room temperature for 36 h. The resulting clear solution was diluted with water (20 mL) and adjusted to pH 5-6 with 12 N HCl. The yellow precipitate was collected by suction filtration, washed with water, and dried under vacuum to give a yellow solid (0.985 g, 79% yield). A suspension of the above yellow solid (0.860 g, 2.2 mmol) in AcOH (50 mL) was heated at reflux for 3 h. The resulting clear solution was concentrated under vacuum to give the crude product, which was recrystallized from EtOAc and MeOH to give compound **18** as a yellow solid (0.751 g, 91% yield) (72% yield for two steps). mp. 149-151 °C; $[\alpha]_D^{20} = -7.75^\circ$ (*c* 0.40, CH₃OH); IR (KBr) 3103, 1653, 1527, 1350, 1162 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.26-7.14 (m, 5H), 4.78 (d, *J* = 4.2 Hz, 1H), 3.93-3.87 (m, 1H), 2.64-2.37 (m, 2H), 2.04-1.78 (m, 2H); ¹³C NMR (75 MHz, CD₃OD) δ 174.5, 151.0, 148.2, 139.0, 129.3, 128.9, 128.8, 125.3, 60.6, 52.8, 28.5, 26.6; HRMS Calcd for C₁₇H₁₈N₃O₅S (M + 1): 376.0962; Found: 376.0964.

Synthesis of compound 19

A suspension of compound **18** (0.60 g, 1.6 mmol), 2-methoxybenzyl chloride (0.376 g, 2.4 mmol), sodium iodide (0.024 g, 0.16 mmol), and cesium carbonate (0.78 g, 2.4 mmol) in DMF (4 mL) was heated at 80 °C for 5 h. The resulting reaction mixture was diluted with water (50 mL), extracted with EtOAc (50 mL $\times$ 3), washed with brine, dried (MgSO₄), filtered, concentrated, and purified by flash chromatography (silica gel, CH₂Cl₂:MeOH = 100:1, v/v) to give compound **19** as a yellow solid (0.751 g, 94% yield). mp. 135-137 °C; $[\alpha]_D^{20} = -100.2^\circ$ (*c* 1.0, CHCl₃); IR (KBr) 3206, 1666 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.50-7.36 (m, 5H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 6.21 (s, 1H), 5.09-5.07 (m, 1H), 4.77-4.72 (m, 1H), 3.66 (d, *J* = 15.6 Hz, 1H), 3.46 (s, 3H), 3.26 (d, *J* = 15.6 Hz, 1H), 2.67-2.63 (m, 2H), 2.26-2.15 (m, 1H), 2.00-1.85 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 170.5, 156.8, 149.4, 147.2, 137.8, 131.3, 129.4, 128.9, 128.8, 127.9, 123.7, 123.0, 120.0, 109.6, 59.6, 58.6, 54.7, 44.4, 31.4, 20.4; HRMS Calcd for C₂₅H₂₆N₃O₆S (M + 1): 496.1537; Found: 496.1541.

Synthesis of compound **6**

A mixture of compound **19** (0.731 g, 1.5 mmol), PhSH (0.25 g, 2.3 mmol), K₂CO₃ (0.21 g, 1.5 mmol), and DMSO (4 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (30 mL × 3), washed with brine, dried (MgSO₄), filtered, concentrated, and purified by flash chromatography (silica gel, CH₂Cl₂:MeOH = 25:1, v/v) to give compound **6** as a yellow oil (0.368 g, 79% yield). $[\alpha]_D^{20} = +40.5^\circ$ (c 1.0, CHCl₃); IR (KBr) 3201, 3063, 1660 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.25 (m, 5H), 7.19 (td, *J* = 8.1, 1.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.90 (brs, 1H), 4.74 (d, *J* = 3.3 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.50 (s, 3H), 3.08-3.00 (m, 1H), 2.79-2.66 (m, 1H), 2.43-2.33 (m, 1H), 2.10-2.00 (m, 1H), 1.91-1.80 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.8, 157.5, 138.6, 129.5, 128.7, 128.3, 128.1, 127.6, 127.0, 120.3, 110.0, 60.7, 54.9, 52.9, 46.4, 27.5, 23.5; Anal. Calcd for C₁₉H₂₂N₂O₂: C, 73.52; H, 7.14; N, 9.03; Found: C, 73.80; H, 6.97; N, 9.19.

Synthesis of (+)-CP-99,994

To a solution of compound **6** (0.328 g, 1.06 mmol) in THF (3 mL) was added borane dimethylsulfide in THF (2.0 M, 2.8 mL, 5.6 mmol) under argon. The reaction mixture was heated at reflux for 18 h. After the reaction mixture was cooled to room temperature, MeOH (5 mL) was added dropwise (cautiously) to decompose the excess borane dimethylsulfide. The resulting mixture was then concentrated. EtOH (9 mL) and powdered K₂CO₃ (0.311 g, 2.25 mmole) were added. The resulting mixture was heated at reflux for 18 h, cooled, and concentrated. Water (20 mL) was added to the resulting residue. The mixture was extracted with CH₂Cl₂ (20 mL × 4), dried (MgSO₄), filtered, and concentrated. Then the residue was dissolved in a minimum amount of CH₂Cl₂ (2 mL), followed by addition of saturated HCl-ether (50 mL). After stirring for 2 h, white solids were collected by filtration, and recrystallized from a hot MeOH-EtOH (1:1, v/v) to give the 2HCl salt of (+)-CP-99,994 (**1**) as a white crystalline solid (0.31 g, 80% yield). mp. 253-255 °C; $[\alpha]_D^{20} = +77.3^\circ$ (c 11.0, MeOH); IR (KBr) 3461, 3386, 1603, 1491, 1440 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 7.76-7.68 (m, 2H), 7.62-7.52 (m, 3H), 7.40 (td, *J* = 7.8, 1.5 Hz, 1H), 7.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.98-6.92 (m, 2H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 4.06-3.98 (m, 1H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.70 (s, 3H), 3.72-3.62 (m, 1H), 3.38-3.28 (m, 1H), 2.55-2.40 (m, 2H), 2.34-2.22 (m, 1H), 2.06-1.94 (m, 1H); ¹³C NMR (75 MHz, CD₃OD) δ 159.0, 133.0, 132.84, 132.80, 131.2, 130.9, 128.4, 122.0, 119.0, 111.9, 60.4, 58.4, 56.1, 49.1, 45.6, 25.3, 17.8; Anal. Calcd for C₁₉H₂₆Cl₂N₂O: C, 61.79; H, 7.10; N, 7.58; Found: C, 61.53; H, 6.96; N, 7.74.

A suspension of the 2HCl salt of (+)-CP-99,994 (**1**) (0.105 g, 0.28 mmol) in CH₂Cl₂ (5 mL) and 1N NaOH (10 mL) was stirred at room temperature for 15 min. Then the mixture was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated to give (+)-CP-99,994 as yellow oil (0.075 g, 89% yield, >99% ee) (the enantioselectivity was determined by HPLC (Chiralcel OD-H Column, NO. ODHOCE-ME069, hexanes:*i*-propanol = 90:10). $[\alpha]_D^{20} = +69.8^\circ$ (c 1.0, CHCl₃); IR (KBr) 3329, 1492, 1461, 1241 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.18 (m, 5H), 7.15 (td, *J* = 8.1, 1.5 Hz, 1H), 6.97 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.87 (d, *J* = 2.1 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 1H), 3.43 (s, 3H), 3.41 (d, *J* = 13.8 Hz, 1H), 3.31-3.24 (m, 1H), 2.85-2.73 (m, 2H), 2.19-2.10 (m, 1H), 2.01-1.82 (m, 3H), 1.65-1.53 (m, 1H), 1.44-1.34 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 157.6, 142.3, 129.7, 128.2, 127.9, 126.6, 126.3, 120.0, 109.8, 64.0, 54.8, 54.6, 47.8, 46.8, 28.1, 20.3; HRMS Calcd for C₁₉H₂₅N₂O (M + 1): 297.1961; Found: 297.1965.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The Structure of (+)-CP-99,994

Scheme 1.

Scheme 2.

Scheme 3.