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ASYMMETRIC SYNTHESIS OF THE ANTIEPILEPTIC DRUG LEVETIRACETAM

Tatsushi Imahori, Keisuke Omoto, Yumi Hirose, and Hiroki Takahata*

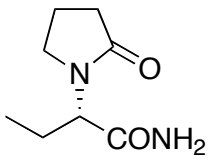
Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, Sendai 981-8558, Japan
E-mail:takahata@tohoku-pharm.ac.jp

Dedicated to Professor Ryoji Noyori on his 70th birthday.

Abstract – Palladium-catalyzed asymmetric synthesis of levetiracetam of antiepileptic drug was expediently accomplished.

INTRODUCTION

Levetiracetam, [(*S*)-**1**] (Keppra®, 38), was approved by the FDA, at the end of 1999 as an antiepileptic drug for an add-on therapy for partial onset seizures in adults with epilepsy. Epilepsy is a common medical disorder with a prevalence of around 1% in the general population and requires prolonged and sometimes lifelong drug therapy.[1] Many procedures for chiral synthesis of **1** have been developed.[2] However, there have been few reports on its asymmetric synthesis.[3] As a part of our ongoing interest in synthesis of biologically important compounds based on palladium-catalyzed asymmetric allylic alkylation,[4] we describe an asymmetric synthesis of **1** through a dynamic kinetic asymmetric transformation (DYKAT) reaction with butadiene monoepoxide (**2**) of succinimide (**3**) using the Trost naphthyl ligand (**4**).[5]

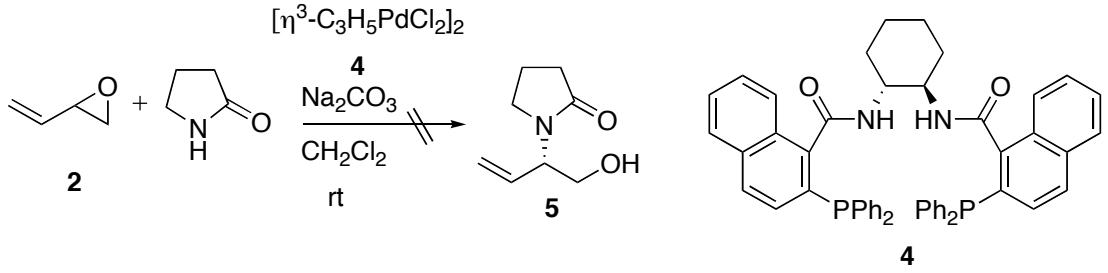


1 Levetiracetam
Keppra®, 38

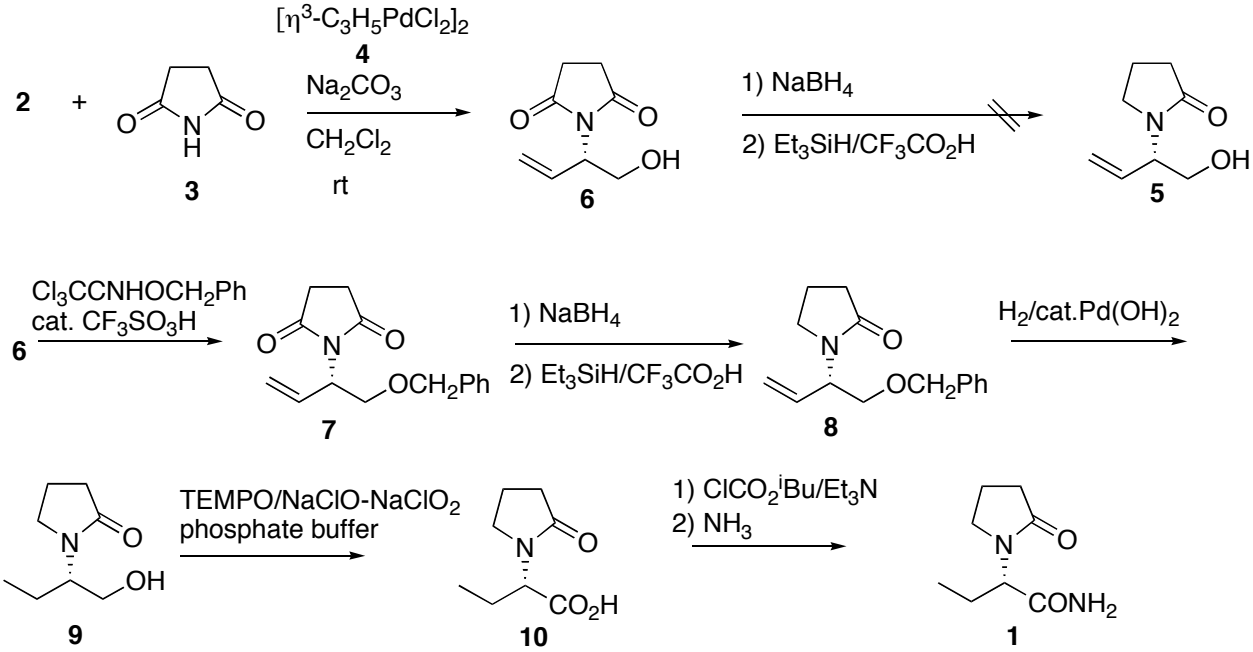
Figure1

RESULTS AND DISCUSSION

First, although a DYKAT reaction between **2** and pyrrolidone as a nucleophile under Trost's condition was examined, this reaction unfortunately afforded no desired product (**5**), resulting in recovery of pyrrolidone. On the other hand, Figueredo very recently reported that the use of succinimide (**3**) as a nucleophile was particularly successful. [6]



Scheme 1



Scheme 2

DYKAT reaction with **2** of **3** using a π-allyl palladium chloride dimer in the presence of (*R,R*)- Trost naphthyl ligand (**4**) provided the imide **6** in 85% yield. Half reduction of **6** with $NaBH_4$ in methanol at –4 °C followed by treatment with a combination of triethylsilane and TFA gave no amide **5**. After protection of hydroxyl, a similar transformation of imide to amide was examined. Benzylation of **6** with benzyl bromide in the presence of NaH as a base afforded the benzyl-protected imide **7** in 57% yield. The use of benzyl 2,2,2-trichloroacetimidate in the presence of CF_3SO_3H resulted in a higher yield (91%).[7] The enantiomeric excess of **7** is 93%.[8] A two-step sequence of imide **7** provided the amide **8** in 78%

yield. Both hydrogenation and hydrogenolysis were simultaneously performed with cat. $Pd(OH)_2$ under hydrogen to give hydroxyl **9** in 92% yield. Oxidation of **9** with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in the presence of sodium hypochlorite-sodium chlorite in acetonitrile buffer (pH 6.7)[9] gave carboxylic acid **10** and subsequent treatment with iso-butyl chloroformate and ammonium hydroxide afforded **1** in 60% yield, the spectral data for which were found to be in good agreement with reported values in the literature.[10]

In summary, an asymmetric synthesis of **1** has been performed in eight steps (34% overall yield) starting from a DYKAT reaction with butadiene monoepoxide (**2**) of succinimide (**3**) under Trost's condition.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin-Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-AL 400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh) or KANTO Silica Gel 60N (40-50 mm) for flash chromatography.

1-((*S*)-1-Hydroxybut-3-en-2-yl)pyrrolidin-2,5-dione [(*S*)-6]

To a mixture of (1*R*,2*R*)-(+)-1,2-diaminocyclohexan-*N*,*N*'-bis(2-diphenylphosphino-1-naphthoyl) *(R,R)*-Trost ligand) (38 mg, 0.048 mmol), π-allyl palladium chloride dimer (5.9 mg, 0.016 mmol), sodium carbonate (21 mg, 0.2 mmol), and succinimide (404 mg, 4 mmol) in CH_2Cl_2 (32 mL) was added butadien monoepoxide (0.322 mL, 4 mmol) and then the mixture was stirred at rt for 23 h. After addition of H_2O, the mixture was successively extracted with Et_2O (three times) and CH_2Cl_2 (nine times). The extracts were dried over and Na_2SO_4 and evaporated. The residue was chromatographed on silica gel using (hexane : EtOAc = 1 : 3) as eluant to give **6** (734 mg, 85 %) as an oil; $[\alpha]_D^{27}$ -28.6 ($CHCl_3$, *c* 1.0). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.62-2.63 (m, 1H), 2.70-2.75 (m, 4H), 3.85 (dt, *J*= 3.9, 11.7 Hz, 1H), 4.02-4.09 (m, 1H), 4.78 (dd, *J*= 7.8, 11.7 Hz, 1H), 5.23-5.30 (m, 2H), 6.10 (ddd, *J*= 7.3, 10.2, 17.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.06, 56.62, 61.89, 119.20, 131.20, 177.67. IR (neat) cm^{-1}: 1694, 1771, 3444. EI-MS (m/z): 170 (M^++1). HRMS Calcd for $C_8H_{12}NO_3$: 170.0817, Found: 170.0816

1-((*S*)-1-(Benzyloxy)but-3-en-2-yl)pyrrolidine-2,5-dione (7)

To a solution of **6** (907 mg, 4.2 mmol) in hexane / CH_2Cl_2 (36 mL / 18 mL) were successively added

benzyl 2,2,2-trichloroacetimidate (1.0 mL, 5.5 mmol) and CF_3SO_3H (0.040 mL, 0.45 mmol) and then the whole was stirred at rt for 3.5 h. sat. aq. $NaHCO_3$ (140 mL) was added to the solution and the mixture was extracted with CH_2Cl_2 (180 mL x 3). The extracts were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel using (hexane : EtOAc = 3 : 1) as eluant to give **7** (987 mg, 91 %) as an oil; $[\alpha]_D^{27}$ +16.9 ($CHCl_3$, *c* 1.1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.65 (s, 4H) 3.62 (dd, *J*= 5.8, 10.1 Hz, 1H), 4.07 (t, *J*= 10.1 Hz, 1H), 4.45 (d, *J*= 12.7, 1H), 4.55 (d, *J*= 12.7, 1H), 4.91-4.97 (m, 1H), 5.22-5.30 (m, 2H). 6.08 (ddd, *J*= 7.7, 10.1, 17.4 Hz, 1H), 7.26-7.38 (m, 7H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.04, 53.89, 68.20, 72.76, 119.56, 127.62, 127.70, 128.38, 131.48, 137.90, 176.97. IR (neat) cm^{-1}: 1702, 1774. EI-MS (m/z): 259 (M^+). HRMS Calcd for $C_{14}H_{15}NO_3$: 259.1208, Found: 259.1202

1-((*S*)-1-(Benzyloxy)but-3-en-2-yl)pyrrolidin-2-one (8)

To a solution of **7** (160 mg, 0.62 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.137 mg, 3.26 mol) at –4 °C and the whole was stirred at the same temperature for 2 h. After addition of sat. aq. $NaHCO_3$ (20 mL), the mixture was extracted with CH_2Cl_2 (30 mL x 3). The extracts were dried over Na_2SO_4 and evaporated. To the residue was added CH_2Cl_2 (15 mL). TFA (2 mL, 26.4 mmol) and Et_3SiH (2 mL, 12.6 mmol) were successively added to the solution and the whole was stirred at rt for 1.5 h. After addition of H_2O (15 mL), the mixture was extracted with CH_2Cl_2 (30 mL x 2). The extracts were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel using (hexane: EtOAc = 5 : 1) as eluant to give **8** (118 mg, 78%) as an oil; $[\alpha]_D^{27}$ +19.2 ($CHCl_3$, *c* 1.0). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.60 (br s, 5H), 1.95-2.03 (m, 2H), 2.40-2.44 (m, 2H), 3.37 (t, *J*= 7.2 Hz, 2H). 3.58-3.66 (m, 2H), 4.47 (d, *J*= 12.1 Hz, 1H), 4.58 (d, *J*= 12.1 Hz, 1H), 4.90-4.94 (m, 1H), 5.18-5.24 (m, 2H), 5.79 (ddd, *J*= 5.8, 10.6, 16.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.22, 31.13, 43.74, 52.60, 69.44, 72.75, 117.87, 127.63, 127.66, 128.35, 132.57, 137.89, 175.42. IR (neat) cm^{-1}: 1103, 1683. EI-MS (m/z): 245 (M^+) HRMS Calcd for $C_{15}H_{19}NO_2$: 245.1416, Found: 245.1426.

1-((*S*)-1-Hydroxybutan-2-yl)pyrrolidin-2-one (9)

A mixture of **8** (190 mg, 0.77 mmol) and $Pd(OH)_2$ (81.1 mg, 0.12 mmol) in MeOH (2.6 mL) under hydrogen atmosphere for 1 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was chromatographed on silica gel using (Et_2O : MeOH = 5 : 1) as eluant to give **9** (113 mg, 92%) as an oil. $[\alpha]_D^{28}$ -11.8 ($CHCl_3$, *c* 0.9). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, *J*= 7.7 Hz, 3H), 1.43-1.67 (m, 3H), 2.00-2.09 (m, 2H), 2.43-2.47 (m, 2H), 2.74 (br s, 1H), 3.31-3.45 (m, 2H), 3.61 (dd, *J*= 8.7, 11.6 Hz, 1H), 3.75 (dd, *J*= 3.9, 11.6 Hz, 1H), 3.86-3.93 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.54, 18.11, 21.02, 31.45, 43.43, 55.64, 62.62, 176.58. IR (neat) cm^{-1}: 1668, 3384. EI-MS (m/z): 157 (M^+). HRMS Calcd for $C_8H_{15}NO_2$: 157.1103, Found: 157.1096.

(*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid (10)

Alcohol **9** (59 mg, 0.38 mmol) was dissolved in MeCN (1.9 mL) and pH 6.7 NaH_2PO_4 aq. buffer (0.67M

phosphate) (1.4 mL) and warmed to 40 °C. TEMPO (4.2 mg, 0.027 mmol) and a solution of sodium chlorite (68.7 mg, 0.76 mmol) in H_2O (0.35 mL) were successively added to the reaction mixture. A diluted solution of bleach (9.8 mL) was added to the mixture and the whole was stirred at 40 °C for 91 h. The reaction was cooled to rt and quenched with sat. aq. Na_2SO_3. The mixture was basified with 2N NaOH and the whole was extracted with CH_2Cl_2. The aqueous layer was acidified with 2N HCl and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated to give **10** (54 mg, 84%) as a solid. mp 124-125 ˚C [lit.,[2b] mp 124-6 ˚C]; $[\alpha]^{19}_D$ -23.0 (*c* 1, acetone) [lit.,[2d] $[\alpha]^{25}_D$ -24.32 (*c* 1, acetone)]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, *J* = 7.7 Hz, 3H), 1.67-1.76 (m, 1H), 1.99-2.13 (m, 3H), 2.49 (t, *J* = 7.7 Hz, 2H), 3.37 (td, *J* = 8.7, 5.8 Hz, 1H), 3.52-3.58 (m, 1H), 4.64 (dd, *J* = 10.6, 4.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.8, 18.2, 21.9, 30.9, 44.1, 55.6, 174.2, 177.1; IR (neat): 2880, 1719 cm^{-1}; EI-Ms (m/z): 171 (M^+); HRMS: Calcd for $C_8H_{13}NO_3$: 171.0895, Found: 171.0903.

(*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide (levetiracetam) (1)

Isobutyl chloroformate (0.43 mL, 0.328 mmol) was added to a solution of **10** (54 mg, 0.315 mmol) and triethylamine (0.046 mL, 0.33 mmol) in THF (0.2 mL) at 0 °C and the whole was stirred for 0.5 h. 28% NH_4OH (0.1 mL, 1.45 mmol) was added to reaction mixture at 0 °C and the whole was stirred at rt for 11 h. K_2CO_3 (44.8 mg, 0.324 mmol) was added to the reaction. The mixture was filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel using (Et_2O : MeOH = 10 : 1) as eluant to give **1** (39 mg, 72%) as a solid. mp 114-115°C [lit.,[2b] mp 115-117 ˚C]; $[\alpha]^{24}_D$ -95.3 (*c* 1, acetone) [lit.,[2b] $[\alpha]^{25}_D$ -90.5 (*c* 0.99, acetone)]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 7.7 Hz, 3H), 1.62-1.73 (m, 1H), 1.90-2.08 (m, 3H), 2.34-2.48 (m, 2H), 3.35-3.48 (m, 2H), 4.46 (dd, *J* = 8.7, 6.8 Hz, 1H), 5.77 (br s, 1H), 6.45 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.5, 18.1, 21.0, 31.0, 43.8, 56.0, 172.3, 176.0; IR (neat): 3359, 3188, 1675, 1653, 1432 cm^{-1}; EI-Ms (m/z): 170 (M^+); HRMS: Calcd for $C_8H_{14}N_2O_2$: 170.1055, Found: 170.1052.

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