Supporting Information

Catalytic asymmetric synthesis of cyclic amino acids and alkaloid derivatives: Application to (+)-dihydropinidine and Selfotel synthesis

Taichi Kano, Takeshi Kumano, Ryu Sakamoto and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan

General Information: Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. 1H NMR spectra were measured on a JEOL JNM-FX400 (400MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane (in the case of CDCl3) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). 13C NMR spectra were recorded on a JEOL JNM-FX400 (100MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AD-H, AS-H and CHIRALCEL OD-H 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF and Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh). Glycine t-butyl ester-benzophenoneimine Shiff base 1,1 alanine t-buty-ester-p-chlorobenzaldimine Shiff base 6,2 chiral phase transfer catalysts (S)-2a, (S)-2b and (S)-2c were prepared according to literature procedure.3 Alkyl halides 3,4,68 and 137 were prepared according to literature procedure. Cyclic amino esters 5a,8 12b9 and 12c8 are known compounds. Selfotel (CGS-19755) was prepared by a similar method described in literature.10 Other simple chemicals were purchased and used as such.

General Procedure for Asymmetric Alkylation under Phase-Transfer Conditions

To a mixture of 1 (30 mg, 0.10 mmol), 3a (209 mg, 1.0 mmol) and (S)-2a (1.5 mg, 0.002 mmol) in toluene (1 mL) was added CsOH (42 mg, 0.25 mmol) at –40 °C, and the reaction mixture was vigorously stirred for 16 h. After the consumption of the starting material, the mixture was diluted with H2O, extracted with dichloromethane. The organic layer was dried over Na2SO4 and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford 4a (36 mg, 0.085 mmol, 85% yield) as an oil.
enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, \( \lambda = 254 \) nm, retention time: 6.3 min (major) and 10.0 min (minor)). \([\alpha]_D^{25} = 81.1 \) (c 1.0, CHCl\(_3\); 99% ee); \(^1\)H NMR \( \delta 1.27 \) (3H, s), 1.30-1.40 (2H, m), 1.44 (9H, s), 1.55-1.60 (2H, m), 1.87-1.93 (2H, m), 3.84-3.93 (5H, m), 7.17-7.19 (2H, m), 7.29-7.45 (2H, m); \(^1^3\)C NMR \( \delta 20.6, 23.8, 28.1, 33.8, 38.9, 64.6, 66.0, 80.8, 110.0, 127.88, 127.94, 128.4, 128.5, 128.8, 130.1, 136.7, 139.7, 169.9, 171.5; IR (neat) 1069, 1148, 1368, 1447, 1622, 1732, 2951 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{26}\)H\(_{34}\)NO\(_4\): 424.2482 ([M + H]\(^+\)), Found: 424.2491 ([M + H]\(^+\)).

(R)-tert-Butyl 2-(Diphenylmethyleneamino)-6-(2-methyl-1,3-dioxolan-2-yl)hexanoate 4b

Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, \( \lambda = 254 \) nm, retention time: 12.0 min (major) and 15.7 min (minor). \([\alpha]_D^{20} = 83.6 \) (c 0.5, CHCl\(_3\); 98% ee); \(^1\)H NMR \( \delta 1.20-1.37 \) (7H, m), 1.44 (9H, s), 1.57-1.61 (2H, m), 1.88 (2H, q, \( J = 7.6 \) Hz), 3.85-3.94 (5H, m), 7.15-7.18 (2H, m), 7.30-7.56 (6H, m), 7.63-7.65 (2H, m); \(^1^3\)C NMR \( \delta 23.7, 23.9, 26.3, 28.1, 33.6, 34.7, 39.1, 64.6, 66.0, 80.8, 110.0, 127.9, 128.0, 128.37, 128.42, 128.8, 130.1, 135.3, 136.8, 169.8, 171.6; IR (neat) 1152, 1368, 1622, 1732, 2359, 2978 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{27}\)H\(_{36}\)NO\(_4\): 438.2639 ([M + H]\(^+\)), Found: 438.2646 ([M + H]\(^+\)).

General Procedure for Diastereoselective Reductive Amination

![Diagram](https://example.com/diagram.png)

To a mixture of 4a (67 mg, 0.16 mmol), MeOH (3 mL) and H\(_2\)O (1.5 mL) was added TFA (36 \( \mu \)L, 0.48 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (34 mg) and the mixture was stirred at 40 °C for 24 h under hydrogen atmosphere. After filtration through celite, the filtrate was basified with aqueous NaHCO\(_3\) and extracted with dichloromethane. The organic layer was dried over Na\(_2\)SO\(_4\) and purified by chromatography on silica gel (dichloromethane/methanol = 50/1 as eluent) to afford 5a (28 mg, 0.14 mmol 88% yield) as an oil. \([\alpha]_D^{21} = 7.1 \) (c 0.7, CHCl\(_3\); 99% ee); \(^1\)H NMR \( \delta 0.98-1.08 \) (1H, m), 1.12 (3H, d, \( J = 6.4 \) Hz), 1.25-1.44 (2H, m), 1.46 (9H, s), 1.57-1.62 (1H, m), 1.77 (1H, br), 1.83-1.89 (1H, m), 1.94-1.99 (1H, m), 2.64 (1H, qdq, \( J = 11.0, 6.4, 2.7 \) Hz), 3.22 (1H, dd, \( J = 11.5, 2.7 \) Hz); \(^1^3\)C NMR \( \delta 22.8, 24.6, 28.0, 29.0, 33.8, 51.8, 59.8, 80.8, 172.6; IR (neat) 1153, 1368, 1726, 2359, 2978 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{11}\)H\(_{22}\)NO\(_2\): 200.1645 ([M + H]\(^+\)), Found: 200.1644 ([M + H]\(^+\)).

(2R,7R)-tert-Butyl 7-Methylazepane-2-carboxylate 5b

\([\alpha]_D^{22} = 15.0 \) (c 0.5, CHCl\(_3\); 98% ee); \(^1\)H NMR \( \delta 1.12 \) (3H, d, \( J = 6.6 \) Hz), 1.26-1.34 (1H, m), 1.40-1.44 (1H, m), 1.46 (9H, s), 1.61-1.76 (5H, m), 1.88 (1H, br), 1.98-2.07 (1H, m), 2.71-2.79 (1H, m), 3.39 (1H, dd, \( J = 9.8, 5.1 \) Hz); \(^1^3\)C NMR \( \delta 23.9, 25.0, 25.3, 28.0, 33.6, 39.6, 54.5, 61.0, 80.9, 174.1; IR (neat) 1157, 1368, 1726, 2359, 2926 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{12}\)H\(_{26}\)NO\(_2\): 214.1802 ([M + H]\(^+\)), Found: 214.1799 ([M + H]\(^+\)).
Synthesis of (2R,6R)-tert-Butyl 2,6-Dimethylpiperidine-2-carboxylate 7

To a mixture of 8 (161 mg, 0.60 mmol), 3a (254 mg, 6.0 mmol) and (S)-2a (9 mg, 0.012 mmol) in toluene (6 mL) was added CsOH (280 mg, 1.5 mmol) at –20 °C, and the reaction mixture was vigorously stirred for 20 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added EtOH (3 mL), H2O (3 mL), and TFA (245 μL, 3.3 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (80 mg) and the mixture was stirred at 40 °C for 36 h under hydrogen atmosphere. After filtration through celite, the result solution was basified with aqueous NaHCO3 and extracted with dichloromethane. The organic layer was dried over Na2SO4 and purified by chromatography on silica gel (dichloromethane/methanol = 30/1 as eluent) to afford 7 (79 mg, 0.37 mmol, 61% yield) as an oil. [α]21D = 18.3 (c 1.0, CHCl3; 96% ee); 1H NMR δ 0.91-1.02 (1H, m), 1.07 (3H, d, J = 6.4 Hz), 1.35 (3H, s), 1.46 (9H, s), 1.49-1.73 (6H, m), 2.86-2.91 (1H, m); 13C NMR δ 20.1, 20.6, 22.9, 27.8, 32.8, 34.0, 45.5, 58.1, 80.4, 175.7; IR (neat) 1145, 1284, 1368, 1454, 1724, 2932 cm−1; HRMS (ESI-TOF) Calcd. for C12H24NO2: 214.1802 ([M + H]+), Found: 214.1794 ([M + H]+).

Determination of the Enantiomeric Excess of (R)-tert-Butyl 2-Amino-2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate

To a mixture of 6 (54 mg, 0.20 mmol), 3a (418 mg, 2.0 mmol) and (S)-2a (3 mg, 0.004 mmol) in toluene (2 mL) was added CsOH (93 mg, 0.50 mmol) at –20 °C, and the reaction mixture was vigorously stirred for 24 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added MeOH (1 mL), H2O (1 mL), and TFA (53 μL, 0.7 mmol). After stirring for 0.5 h, the solution was basified with aqueous NaHCO3, extracted with dichloromethane, dried over Na2SO4 and concentrated. To a solution of the residue and triethylamine (56 μL, 0.40 mmol) in dichloromethane (2 mL) was added benzoyl chloride (34 μL, 0.24 mmol) at 0 °C. After stirring for 3 h at 0 °C, the mixture was quenched with H2O and extracted with dichloromethane. The organic layer was dried over Na2SO4 and purified by chromatography on silica gel (hexane/ethylacetate = 5/1 as eluent) to afford N-benzoylated...
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 19.2 min (major) and 30.2 min (minor)). [α]D = −12.6 (c 0.9, CHCl3; 96% ee); 1H NMR δ 1.26 (3H, s), 1.38-1.48 (2H, m), 1.51 (9H, s), 1.55-1.69 (2H, m), 1.71 (3H, s), 1.78-1.86 (1H, m), 2.52-2.60 (1H, m), 3.83-3.92 (4H, m), 7.41-7.51 (3H, m), 7.78-7.81 (2H, m); 13C NMR δ 19.1, 23.4, 23.7, 27.9, 36.0, 38.8, 61.2, 64.5, 64.6, 82.3, 109.8, 126.8, 128.5, 131.3, 135.2, 166.0, 174.2; IR (neat) 1152, 1663, 1728, 2980, 3408 cm⁻¹; HRMS (ESI-TOF) Calcd. for C21H32NO5: 378.2275 ([M + H]+), Found: 378.2271 ([M + H]+).

Asymmetric Synthesis of (+)-Dihydropinidine Hydrochloride

To a solution of 5a (123 mg, 0.64 mmol) in dioxane (2 mL) and H2O (2 mL) were added NaHCO3 (59 mg, 0.70 mmol) and Benzyl Chloroformate (101 μL, 0.70 mmol) at 0 °C. The resulting solution was stirred at room temperature overnight. The reaction mixture was evaporated to remove dioxane, extracted with dichloromethane and washed with 1 N HCl and H2O. The organic layer was dried over Na2SO4 and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford the (2R,6R)-1-benzyl 2-tert-butyl 6-methylpiperidine-1,2-dicarboxylate (193 mg, 91% yield). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 22.1 min (minor) and 24.0 min (major)). [α]D = 36.2 (c 1.0, CHCl3, 99% ee); 1H NMR δ 1.18 (3H, d, J = 7.1 Hz), 1.41 (9H, s), 1.47-1.71 (5H, m), 2.28 (1H, d, J = 6.6 Hz), 4.38-4.44 (1H, m), 4.73 (1H, br), 5.16 (2H, s), 7.26-7.36 (5H, m); 13C NMR δ 15.5, 18.7, 25.8, 27.8, 30.0, 46.7, 53.3, 67.0, 81.2, 127.78, 127.81, 128.4, 136.8, 156.1, 171.6; IR (neat) 1074, 1153, 1406, 1740, 2357 cm⁻¹; HRMS (ESI-TOF) Calcd. for C19H27NNaO4: 356.1832 ([M + Na]+), Found: 356.1827 ([M + Na]+).

To a solution of (2R,6R)-1-benzyl 2-tert-butyl 6-methylpiperidine-1,2-dicarboxylate (181 mg, 0.54 mmol) in toluene (9 mL) was added DIBAL-H (0.43 mL, 1.5 M in toluene) at –78 °C. After being stirred at the same temperature for 2 h, ethyl acetate (1 mL) was added dropwise. After stirring for 30 min, a few drops of H2O were then added. The resulting mixture was then warmed to room temperature and stirred vigorously for 1 h. The mixture was filtered through celite with dichloromethane as eluent. The filtrate was concentrated to afford crude aldehyde, which was used for the next reaction without further purification.

To a flask charged with Ph3PCH2CH3Br (301 mg, 0.81 mmol) in THF (8 mL) was added n-BuLi (0.50 mL, 1.6 M in hexane) at −78 °C. After being stirred for 1 h at room temperature, the crude aldehyde obtained above in THF (1 mL) was added at −78 °C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with 1 N HCl, extracted with dichloromethane, dried over Na2SO4 and purified by chromatography on silica gel (hexane/ethyl acetate = 20/1 as eluent) to afford E·Z mixture of (2R,6R)-benzyl 2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (81 mg, 55% yield, E (98% ee)/Z (95%)}
ee) = 1/5. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 40/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 15.5 min (Z: minor), 16.3 min (Z: major), 18.0 min (E: major), 19.5 min (E: minor)). I H NMR δ 1.17 (0.50H, d, J = 7.1 Hz), 1.24 (2.50H, d, J = 7.1 Hz), 1.45-1.50 (1H, m), 1.55-1.76 (8H, m), 4.40-4.44 (1H, m), 4.73 (0.17H, br), 5.03-5.07 (1H, m), 5.13 (1.67H, s), 5.14 (0.33H, d, J = 4.6 Hz), 5.44-5.48 (0.83H, m), 5.55-5.57 (0.17H, m), 5.72 (0.83H, ddq, J = 11.2, 9.5, 1.7 Hz), 7.28-7.36 (5H, m); 13C NMR δ (E isomer / Z isomer) 14.3/14.5, 17.8/12.7, 20.5/20.9, 28.8/30.0, 30.2/30.4, 46.4/46.3, 51.4/47.6, 66.8/66.9, 125.9/125.2, 127.71/127.75, 127.73/127.8, 128.4/128.3, 132.5/131.7, 137.2/137.1, 155.8/155.7; IR (neat) 1072, 1307, 1692, 2340, 2936 cm -1; HRMS (ESI-TOF) Calcd. for C17H24NO2: 274.1802 ([M + H]+), Found: 274.1800 ([M + H]+).

To a solution of (2R,6R)-benzyl 2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (45mg, 0.17 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The mixture was stirred under hydrogen atmosphere for 24 h at room temperature. The resulting mixture was filtered through celite with MeOH as eluent. To the filtrate was added HCl (3 mL, 1 M in MeOH) and the whole mixture was concentrated. The residue was recrystallized from ethyl acetate to yield (+)-dihydropinidine hydrochloride (20 mg, 67% yield): [α]26 D = 12.0 (c 0.2, EtOH); 1H NMR (CD3OD) δ 0.97 (3H, t, J = 4.0 Hz), 1.32-1.66 (10H, m), 1.87-1.93 (2H, m), 2.00 (1H, d, J = 12.0 Hz), 3.06 (1H, br), 3.18 (1H, br); 13C NMR δ 14.2, 19.5, 19.6, 23.5, 29.1, 31.7, 37.0, 55.0, 58.7; IR (neat) 1129, 1372, 1461, 2958 cm -1; HRMS (ESI-TOF) Calcd. for C9H20N: 142.1590 ([M + H]+), Found: 142.1596 ([M + H]+).

Synthesis of 6-(2-Bromoethyl)-1,4-dioxaspiro[4.4]nonane 8b
The title compound was prepared by a similar method described in literature. 1H NMR δ 1.31-1.36 (1H, m), 1.63-1.84 (5H, m), 1.91-1.95 (1H, m), 2.05-2.12 (2H, m), 3.35-3.40 (1H, m), 3.42-3.52 (1H, m), 3.87-3.95 (4H, m); 13C NMR δ 20.6, 28.9, 32.6, 32.8, 35.5, 44.6, 64.4, 64.5, 117.8; IR (neat) 1117, 1221, 1524, 1713, 2978, 3335 cm-1.

Synthesis of 6-(2-Bromoethyl)-1,4-dioxaspiro[4.5]decane 8c
The title compound was prepared by a similar method described in literature. 1H NMR δ 1.25-1.39 (3H, m), 1.43-1.49 (1H, m), 1.59-1.72 (3H, m), 1.76-1.81 (3H, m), 2.15-2.28 (1H, m), 3.38-3.45 (1H, m), 3.49-3.55 (1H, m), 3.91-3.99 (4H, m); 13C NMR δ 23.6, 24.5, 29.1, 32.3, 32.9, 34.5, 43.2, 64.5, 64.7, 110.4; IR (neat) 1117, 1221, 1524, 1713, 2978, 3335 cm-1.

Diastereo-mixture of (2R)-tert-Butyl 2-(Diphenylmethyleneamino)-5-(2-methyl-1,3-dioxolan-2-yl) hexanoate 9a
(2R,5S)/(2R,5S) = 1/1. 1H NMR δ 0.91 (1.5H, d, J = 6.8 Hz), 0.93 (1.5H, d, J = 7.1 Hz), 0.99-1.11 (1H, m), 1.19 (3H, s), 1.44 (4.5H, s), 1.45 (4.5H, s), 1.51-1.65 (2H, m), 1.69-1.88 (1H, m), 1.97-2.10 (1H, m), 3.79-3.93 (5H, m), 7.16-7.19 (2H, m), 7.3-7.46 (6H, m), 7.63-7.65 (2H, m); 13C NMR δ 14.5, 14.6, 20.2, 20.3, 28.06, 28.12, 31.4, 31.8, 32.0, 32.1, 41.3, 41.4, 47.5, 47.6, 48.8, 48.9, 64.49, 65.54, 66.3, 66.6, 80.76, 80.81, 112.29, 112.34, 127.89, 127.90, 127.94, 128.35, 128.37, 128.43, 128.77, 128.82, 129.9, 130.1, 136.78, 136.82, 139.80, 139.83, 169.7, 169.9, 171.5, 171.6; IR (neat) 1150, 1368, 1732, 2976 cm-1; HRMS
Diastereo-mixture of (2R,6R)-tert-Butyl 5,6-Dimethylpiperidine-2-carboxylate 12a

(2R,5R,6R)/(2R,5S,6R) = 2.5/1. ¹H NMR (toluene-d₈, 80 °C) δ 0.85 (0.86H, d, J = 6.1 Hz), 0.89 (2.14H, d, J = 7.1 Hz), 1.03 (2.14H, d, J = 6.6 Hz), 1.11 (0.86H, d, J = 6.4 Hz), 1.46 (9H, s), 1.47-1.71 (5.42H, m), 1.78-1.81 (0.29H, m), 1.95-2.00 (0.29H, m), 2.24 (0.29H, dq, J = 8.8, 6.4 Hz), 2.85 (0.71H, dq, J = 8.6, 2.9 Hz), 3.21-3.26 (1H, m); ¹³C NMR δ (2R,5R,6R/2R,5S,6R) 10.9/18.4, 20.0/20.3, 23.6/29.9, 28.01/28.00, 31.5/32.0, 33.8/37.7, 57.9/53.6, 60.2/59.7, 80.7/80.6, 172.9/172.6; IR (neat) 1155, 1233, 1368, 1730, 2930 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₂H₂₄NO₂: 214.1802 ([M + H]⁺), Found: 214.1807 ([M + H]⁺).

Determination of the Enantiomeric Excess of 12a

The enantiomeric excess of 12a was determined by HPLC analysis after conversion to the corresponding benzamide. (2R,5R,6R)/(2R,5S,6R) = 2.5 (99% ee)/1 (99% ee). Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: (2R,5R,6R: 9.8 min (minor), 10.9 min (major)), (2R,5S,6R: 12.1 min (major), 20.7 min (minor)). ¹H NMR (toluene-d₈, 80 °C) δ 0.38 (2.14H, d, J = 6.6 Hz), 0.61 (0.86H, d, J = 7.1 Hz), 0.77-0.79 (0.29H, m), 0.81 (2.14H, d, J = 7.1 Hz), 0.93 (0.71H, m), 0.95 (0.86H, d, J = 7.6 Hz), 1.09-1.49 (11H, m), 1.55-1.64 (0.29H, m), 1.74-1.80 (0.29H, m), 1.85-1.88 (0.71H, m), 1.96 (0.71H, d, J = 13.2 Hz), 3.76-4.69 (2H, m), 6.82-6.90 (3H, m), 7.13-7.19 (2H, m); ¹³C NMR δ (2R,5R,6R/2R,5S,6R) 15.6/23.1, 21.5/21.4, 27.3/26.1, 30.9/29.3, 36.17/36.15, 37.8/37.7, 56.1/55.1, 56.9/55.4, 84.0/83.8, 130.0/129.9, 131.2/131.9, 140.4/140.7, 141.4/141.5, 174.1/174.4, 174.8/175.5; IR (neat) 1155, 1412, 1641, 1726, 2361, 2976 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₉H₂₈NO₃: 318.2064 ([M + H]⁺), Found: 318.2048 ([M + H]⁺).

Diastereomixture of (2R)-tert-Butyl 2-(Diphenylmethylenecamino)-4-(1,4-dioxaspiro[4.4]nonan-6-yl) butanoate 9b

[α]ᵢ²⁰ = 91.6 (c 1.0, CHCl₃); ¹H NMR δ 1.21-1.42 (3H, m), 1.44 (9H, s), 1.57-1.74 (4H, m), 1.81-1.94 (4H, m), 3.81-3.91 (5H, m), 7.17-7.19 (2H, m), 7.29-7.44 (6H, m), 7.63-7.65 (2H, m); ¹³C NMR δ 20.6, 25.4, 28.1, 29.4, 31.6, 32.5, 35.8, 46.0, 64.4, 64.6, 66.3, 80.7, 118.2, 127.9, 128.3, 128.8, 129.1, 136.8, 169.8, 171.6; IR (neat) 1030, 1148, 1732, 2953 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₂₈H₃₆NO₄: 450.2639 ([M + H]⁺), Found: 450.2619 ([M + H]⁺).

Determination of the Enantiomeric Excess of 12b

The enantiomeric excess of 12b was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 16.4 min (major) and 22.3 min (minor). [α]ᵢ²⁰ = 41.6 (c 0.7, CHCl₃; 99% ee); ¹H NMR (toluene-d₈, 80 °C) δ 0.92-1.06 (4H, m), 1.12 (9H, s), 1.27 (3H, br), 1.51-1.57 (1H, m), 1.65-1.73 (2H, m), 1.84-1.88 (1H, m), 4.04 (1H, br), 4.68 (1H, br), 6.86-6.89 (3H, m), 7.13-7.15 (2H, m); ¹³C NMR δ 24.4, 27.7, 28.1, 30.9, 31.8, 33.1, 39.6, 57.2, 60.2, 83.8, 129.9, 131.2, 140.4, 141.6, 174.4, 174.6; IR (neat) 1153, 1368, 1414, 1603, 1726, 2972 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₂₆H₂₈NO₃: 330.2064 ([M + H]⁺), Found: 330.2069 ([M + H]⁺).
Diastereo-mixture of (2R)-2-(Diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.5]decan-6-yl) butanoate 9c

$([\alpha]_D^{22}) = 87.9 \, (c \, 1.0, \text{CHCl}_3) \); $^1$H NMR $\delta$ 1.18-1.34 (4H, m), 1.41-1.44 (2H, m), 1.44 (4.5H, s), 1.45 (4.5H, s), 1.47-1.50 (1H, m), 1.59-1.62 (2H, m), 1.65-1.81 (3H, m), 1.97-2.00 (1H, m), 3.81-3.93 (5H, m), 7.16-7.20 (2H, m), 7.29-7.44 (6H, m), 7.63-7.66 (2H, m),$ ^1$C NMR $\delta$ 21.8, 23.8, 23.9, 24.49, 24.52, 24.6, 24.7, 28.1, 29.0, 29.2, 31.8, 31.9, 34.8, 34.9, 44.39, 44.43, 64.61, 64.64, 64.7, 64.8, 66.3, 66.7, 80.7, 82.0, 110.80, 110.83, 127.89, 127.91, 127.93, 128.0, 128.26, 128.28, 128.36, 128.42, 128.75, 128.77, 130.01, 130.03, 136.8, 136.9, 139.8, 139.9, 141.4, 140.4, 141.4, 174.1, 174.2; IR (neat) 1150, 1368, 1732, 2932 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{29}$H$_{38}$NO$_4$: 464.2795 ([M + H]$^+$), Found: 464.2785 ([M + H]$^+$).

Determination of the Enantiomeric Excess of 12c

The enantiomeric excess of 12c was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, $\lambda$ = 254 nm, retention time: 13.6 min (major) and 16.5 min (minor). $([\alpha]_D^{19}) = 67.1 \, (c \, 1.0, \text{CHCl}_3; 99\% \text{ ee}) \); $^1$H NMR (toluene-d$_8$, 80 °C) $\delta$ 1.23-1.33 (4H, m), 1.51 (9H, s), 1.54-1.67 (2H, m), 1.73-1.88 (3H, m), 2.01-2.12 (2H, m), 2.27-2.28 (1H, m), 2.46 (1H, d, $J$ = 12.4 Hz), 4.45 (1H, br), 5.05 (1H, br), 7.15-7.17 (1H, m), 7.23-7.30 (3H, m), 7.57-7.59 (1H, m), $^1$C NMR $\delta$ 24.7, 29.3, 30.1, 30.9, 34.9, 35.8, 38.0, 39.3, 55.9, 58.0, 83.9, 83.9, 129.9, 131.2, 140.4, 141.4, 174.1, 174.2; IR (neat) 1153, 1325, 1368, 1411, 1638, 1724, 2930 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{21}$H$_{29}$NNaO$_3$: 366.2040 ([M + H]$^+$), Found: 366.2033 ([M + H]$^+$).

(R,Z)-2-(Diphenylmethyleneamino)-6,6-dimethoxy-4-methylhex-4-enoate 14a

Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, $\lambda$ = 254 nm, retention time: 17.2 min (minor) and 23.4 min (major). $([\alpha]_D^{19}) = 82.2 \, (c \, 0.9, \text{CHCl}_3; 92\% \text{ ee}) \); $^1$H NMR (toluene-d$_8$, 80 °C) $\delta$ 1.45 (9H, s), 1.52 (3H, d, $J$ = 1.2 Hz), 2.56-2.68 (2H, m), 3.15 (3H, s), 3.26 (3H, s), 4.07 (1H, dd, $J$ = 8.3, 5.1 Hz), 4.95 (1H, d, $J$ = 6.4 Hz), 5.30 (1H, dd, $J$ = 6.4, 0.8 Hz), 7.14-7.18 (2H, m), 7.28-7.46 (6H, m), 7.62-7.65 (2H, m); $^1$C NMR $\delta$ 17.1, 28.0, 43.4, 51.5, 52.6, 64.7, 81.2, 100.1, 124.9, 127.91, 127.94, 128.3, 128.5, 128.8, 130.1, 136.4, 138.1, 139.6, 172.6; IR (neat) 1053, 1150, 1368, 1411, 1638, 2367 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{26}$H$_{34}$NO$_4$: 424.2482 ([M + H]$^+$), Found: 424.2465 ([M + H]$^+$).

(2R,4S)-2-Methylpiperidine-2-carboxylate 15a

Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, $\lambda$ = 220 nm, retention time: 19.2 min (major) and 42.7 min (minor). $([\alpha]_D^{21}) = 8.8 \, (c \, 0.4, \text{CHCl}_3; 92\% \text{ ee}) \); $^1$H NMR $\delta$ 0.94 (3H, d, $J$ = 6.4 Hz), 0.95-1.05 (2H, m), 1.46 (9H, s), 1.48-1.63 (2H, m), 1.93-1.99 (1H, m), 2.60 (1H, dd, $J$ = 12.5, 2.7 Hz), 3.11-3.16 (1H, m), 3.18 (1H, dd, $J$ = 11.7, 2.7 Hz); $^1$C NMR $\delta$ 22.4, 28.0, 31.3, 34.7, 38.1, 45.8, 59.6, 80.8, 172.6; IR (neat) 1161, 1269, 1368, 1732, 2924, 2949 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{11}$H$_{24}$NO$_2$: 200.1645 ([M + H]$^+$), Found: 200.1641 ([M + H]$^+$).
Synthesis of (Z)-2-(3-(Benzzyloxy)-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane 13b

2-(3-Bromo-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane was prepared by a similar method described in literature.\textsuperscript{11, 12} \textsuperscript{1}H NMR $\delta$ 3.89-3.97 (2H, m), 3.99-4.07 (2H, m), 4.13 (2H, s), 4.27 (2H, d, $J = 1.6$ Hz), 5.55 (1H, dd, $J = 6.0, 1.6$ Hz), 5.77 (1H, dd, $J = 6.0, 0.8$ Hz); \textsuperscript{13}C NMR $\delta$ 26.4, 34.3, 65.1, 98.9, 130.4, 138.7; IR (neat) 939, 1051, 1117, 1207, 1396, 2887 cm$^{-1}$.

The title compound was prepared by a similar method described in literature\textsuperscript{13} starting from 2-(3-bromo-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane. \textsuperscript{1}H NMR $\delta$ 3.82-3.93 (2H, m), 3.95-4.05 (2H, m), 4.08 (2H, s), 4.52 (2H, s), 5.50 (1H, d, $J = 6.8$ Hz), 5.78 (1H, d, $J = 6.8$ Hz), 7.27-7.36 (5H, m); \textsuperscript{13}C NMR $\delta$ 34.1, 64.9, 65.0, 72.5, 98.8, 127.7, 127.8, 128.4, 129.6, 137.8, 139.9; IR (neat) 1055, 1246, 1396, 1703, 2884 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{14}$H$_{17}$BrNaO$_3$: 335.0253 ([M + Na]+), Found: 335.0247 ([M + Na]+).

(R,E)-tert-Butyl 4-(Benzyloxymethyl)-5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)pent-4-enoate 14b

Daicel Chiralpak AD-H, Hexane/EtOH = 50/1, flow rate 0.5 mL/min, $\lambda$ = 254nm, retention time: 19.6 min (minor) and 20.5 min (major). [$\alpha$]$_D$ = 62.6 (c 0.4, CHCl$_3$; 97% ee); \textsuperscript{1}H NMR $\delta$ 1.44 (9H, s), 2.67 (1H, dd, $J = 14.0, 8.8$), 2.87 (1H, dd, $J = 14.0, 4.4$ Hz), 3.75-3.83 (4H, m), 4.13 (1H, d, $J = 8.8, 4.4$ Hz), 4.29 (2H, d, $J = 31.2, 11.6$ Hz), 4.52 (2H, s), 7.16-7.19 (2H, m), 7.22-7.38 (11H, m), 7.60-7.64 (2H, m); \textsuperscript{13}C NMR $\delta$ 28.0, 38.3, 64.7, 64.8, 64.9, 67.1, 71.8, 81.1, 99.2, 127.45, 127.48, 127.6, 127.9, 128.1, 128.3, 128.5, 128.6, 128.9, 130.0, 136.5, 138.2, 139.8, 139.9, 170.3, 170.8; IR (neat) 959, 1069, 1148, 1730, 2884 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{33}$H$_{38}$NO$_5$: 528.2745 ([M + H]+), Found: 528.2752 ([M + H]+).

(2R,4S)-tert-Butyl 4-(Hydroxymethyl)piperidine-2-carboxylate 15b

[$\alpha$]$_D$ = 3.1 (c 1.4, CHCl$_3$); \textsuperscript{1}H NMR $\delta$ 1.08-1.21 (2H, m), 1.25 (1H, br), 1.46 (9H s), 1.62-1.72 (2H, m), 2.08 (1H, d, $J = 14.4$), 2.32 (1H, br), 2.67 (1H, td, $J = 12.4, 2.8$), 3.23-3.27 (2H, m), 3.48-3.55 (2H, m); \textsuperscript{13}C NMR $\delta$ 28.0, 28.8, 32.4, 38.9, 45.3, 59.0, 67.8, 81.3, 172.1; IR (neat) 1045, 1732, 2930 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{11}$H$_{22}$NO$_3$: 216.1594 ([M + H]+), Found: 216.1586 ([M + H]+).

Synthesis of Selfotel (CGS-19755)

Title compound was prepared by a similar method described in literature\textsuperscript{10} starting from 15b in 39% yield. 
overall yield. Spectrum data of obtained compound corresponded with literature.\textsuperscript{10}

(2R,4S)-Di-tert-butyl 4-(Hydroxymethyl)piperidine-1,2-dicarboxylate

95% yield. $[\alpha]_D^{26} = 39.4$ (c 1.5, CHCl$_3$); \textsuperscript{1}H NMR $\delta$ 1.45 (9H, s), 1.47 (9H, s), 1.70-1.80 (1H, m), 1.91-1.97 (2H, m), 2.03-2.08 (1H, m), 2.26 (1H, br), 3.08 (1H, br), 3.46 (1H, dd, $J = 11.2$, 7.6 Hz), 3.54 (1H, dd, $J = 11.2$, 6.8 Hz), 3.76 (1H, br), 4.41 (1H, br); \textsuperscript{13}C NMR $\delta$ 25.2, 26.7, 27.8, 28.0, 28.3, 53.7, 53.81, 63.6, 79.8, 81.5, 155.5, 172.4; IR (neat) 1152, 1366, 1697, 1734, 2976, 3435 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{16}$H$_{29}$NNaO$_5$ : 338.1938 ([M + Na]$^+$), Found: 338.1923 ([M + Na]$^+$).

(2R,4S)-tert-Butyl 4-(Bromomethyl)piperidine-2-carboxylate

71% yield. $[\alpha]_D^{23} = 7.8$ (c 0.9, CHCl$_3$); \textsuperscript{1}H NMR $\delta$ 1.45 (9H, s), 1.48 (9H, s), 1.66-1.68 (1H, m), 1.79-1.86 (1H, m), 2.03-2.10 (3H, m), 3.17 (1H, br), 3.33-3.41 (2H, m), 3.75 (1H, m), 4.35-4.38 (1H, m); \textsuperscript{13}C NMR $\delta$ 27.5, 27.9, 28.0, 28.3, 29.3, 33.9, 36.0, 53.7, 80.0, 81.5, 155.5, 171.8; IR (neat) 1150, 1366, 1697, 1732, 2976 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{16}$H$_{28}$BrNNaO$_4$ : 400.1094 ([M + Na]$^+$), Found: 400.1088 ([M + Na]$^+$).

(2R,4S)-Di-tert-butyl 4-((Diethoxyphosphoryl)methyl)piperidine-1,2-dicarboxylate

83% yield. $[\alpha]_D^{25} = 27.0$ (c 0.4, CHCl$_3$); \textsuperscript{1}H NMR $\delta$ 1.30 (6H, m), 1.44 (9H, s), 1.46 (9H, s), 1.63-1.84 (4H, m), 1.95-2.08 (2H, m), 2.16-2.24 (1H, m), 3.21 (1H, br), 3.72 (1H, br), 4.04-4.12 (4H, m), 4.35 (1H, dd, $J = 6.8$, 5.2 Hz); \textsuperscript{13}C NMR $\delta$ 14.1, 16.4 (d, $J = 2.7$ Hz), 16.5 (d, $J = 2.7$ Hz), 27.9, 28.27, 28.31, 29.1 (d, $J = 5.8$ Hz), 29.7, 32.1 (d, $J = 13.2$ Hz), 53.8, 61.4 (d, $J = 6.6$ Hz), 61.5 (d, $J = 6.6$ Hz), 79.9, 81.4, 155.7, 172.0; IR (neat) 1030, 1163, 1248, 1699, 2359, 2926, 2978 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{20}$H$_{38}$NNaO$_7$P : 458.2278 ([M + Na]$^+$), Found: 458.2285 ([M + Na]$^+$).

References


(9) Swarbrick, M. E.; Lubell, W. D. Chirality 2000, 12, 366.

Me

\text{Me}

\text{OMe}

\text{Ph}_2\text{C=N-N}=\text{CO}_2\text{Bu}^+ \quad \text{OMe}

\text{Me}

\text{OMe}

\text{Ph}_2\text{C=N-N}=\text{CO}_2\text{Bu}^+