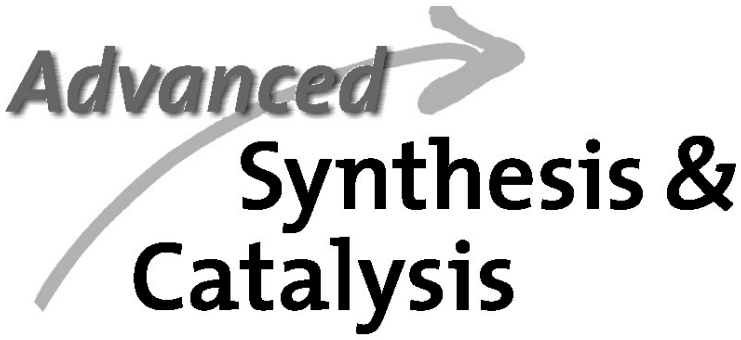

Supporting Information

Supporting Information

Enantioselective 1,3-Dipolar Cycloaddition of Nitrile Imines to a-Substituted- and a,b-Disubstituted-a,b-unsaturated Carbonyl Substrates: A Method for Generation of Dihydropyrazoles Bearing a Chiral Quaternary Center

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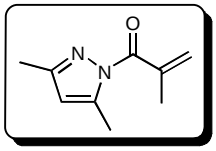
Department of Chemistry, North Dakota State University, Fargo, ND 58105

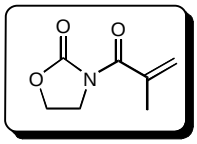
General: Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Magnesium perchlorate and magnesium iodide were purchased from Aldrich chemicals. Magnesium was prepared according to literature procedure. Cyclopropyl bisoxazoline ligand {3aR-[2(3'aS, 8'aR), 3aa, 8aa]}-2,2'-(cyclopropylidene)-bis{3a,8a-dihydro-8H-indeno[1,2d]-oxazole} was prepared according to literature procedure. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO^{TM} CombiFlash Companion with AnaLogix^{TM} RS-4 columns. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected. ^{1}H-NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C-NMR was recorded on Varian Unity/Inova-500 NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300 (75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.23) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a

2487 dual λ absorbance detector connected to a PC with Empower workstation. Rotations were recorded on a JASCO-DIP-370 instrument. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High Resolution Mass Spectra (HRMS) (ESI+) were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

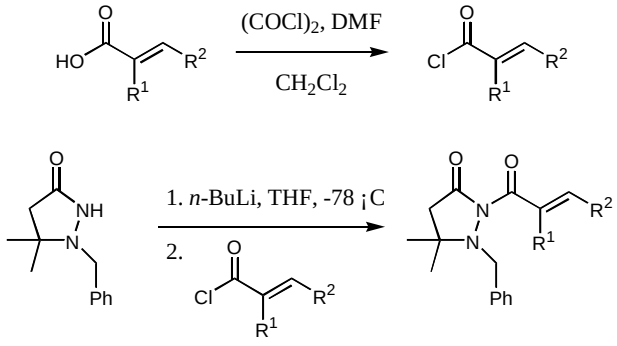


1-(2-Methylpropenoyl)-3,5-dimethylpyrazole (4a). This compound has been previously prepared.[1] Clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12-2.13 (m, 3H), 2.23 (s, 3H), 2.53 (s, 3H), 5.70—5.71 (m, 1H), 5.80-5.81 (m, 1H), 5.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 20.4, 111.3, 125.5, 129.3, 139.5, 144.8, 152.3; Anal. Calcd. for $C_9H_{12}N_2O$ C, 65.83; H, 7.37, N, 17.06; found: C, 65.71; N, 7.28:, H, 17.27.



3-(2-Methylpropenoyl)-oxazolidin-2-one (4b). This compound has been previously prepared.[1] White solid; mp 56-57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 4.00 (t, *J* = 7.9 Hz, 2H), 4.41 (t, *J* = 7.9 Hz, 2H), 5.39 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 43.1, 62.4, 121.0, 139.2, 152.9, 171.1; Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03; found: C, 54.11; H, 5.65; N, 9.20.

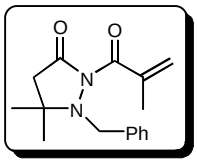
General procedure for *N*(2)-acylation of pyrazolidinones (Preparation of substrates 4c, 8a-e):



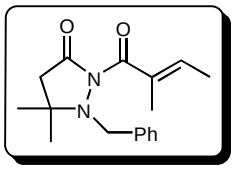
4e: R^1 = Me, R^2= H
8a: R^1 = Me, R^2 = Me
8b: R^1 = Me, R^2 = Et
8c: R^1 = Me, R^2 = Ph
8d: R^1, R^2 = -$(CH_2)_3$-
8e: R^1, R^2 = -$(CH_2)_4$-

To a solution of the appropriate α,β-unsaturated acid (11.0 mmol) in 15 mL of dichloromethane at 0 °C, under nitrogen, was added oxalyl chloride (12.1 mmol) followed by one drop of DMF. After 10 minutes the solution was allowed to warm to room temperature and stir for two hours. The solvent and excess oxalyl chloride were removed *in vacuo* to give crude acid chloride, which was used without further purification.

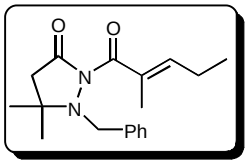
To a stirred solution of 1-benzyl-5,5-dimethyl-pyrazolidin-3-one (11.0 mmol) in anhydrous THF (45 mL) at –78 °C was added 1.0 eq. of *n*-BuLi. After 30 min 1.1 eq of crude acid chloride was then added dropwise and the mixture allowed to stir for 30 minutes at –78 °C and then allowed to warm to rt over two hours. The reaction was quenched with saturated aqueous ammonium chloride, and the slurry was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic layer was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography or recrystallization from 1:1 hexanes/EtOAc. Average yields were 80-90%.



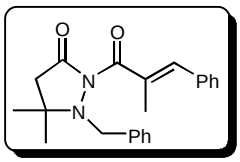
1-Benzyl-5,5-dimethyl-(2-methylpropenoyl)-pyrazolidin-3-one (4c). White solid; mp 103-105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.86 (s, 3H), 2.58 (s, 2H), 4.07 (s, 2H), 5.23 (d, *J* = 4 Hz, 2H), 7.22-7.29 (m, 3H), 7.39 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 26.3, 43.3, 57.7, 61.6, 120.3, 127.8, 128.4, 129.7, 137.0, 140.7, 168.4, 174.0; HRMS Exact mass calcd. for $C_{16}H_{20}N_2O_2Na^+$ 295.1417 found 295.1424.



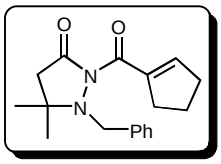
1-Benzyl-5,5-dimethyl-(*E*-2-methylbut-2-enoyl)-pyrazolidin-3-one (8a). White solid; mp 90-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 6H), 1.67 (dd, *J* = 7.0, 1.0 Hz, 3H), 1.71 (t, *J* = 1.5 Hz, 3H), 2.59 (s, 2H), 4.07 (s, 2H), 5.98 (dq, *J* = 1.5 Hz, 7.0 Hz, 1H), 7.21-7.29 (m, 3H), 7.37 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.1, 26.3, 43.5, 57.9, 61.6, 127.7, 128.4, 129.7, 132.8, 134.1, 137.1, 169.5, 174.0; HRMS Exact mass calcd. for $C_{17}H_{22}N_2O_2Na^+$ 309.1573 found 309.1589.



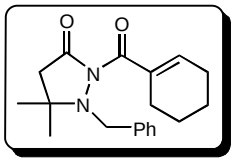
Substrate 8b. Tan solid; mp 76-78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.31 (s, 6H), 1.71 (s, 3H), 2.08 (app quintet, *J* = 7.5 Hz, 2.59 (s, 2H), 4.07 (s, 2H), 5.86 (dt, *J* = 1.5, 7.0 Hz, 1H), 7.20-7.28 (m, 3H), 7.38 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 13.5, 21.8, 26.4, 43.6, 57.9, 61.6, 127.8, 128.4, 129.7, 131.2, 141.1, 169.6, 174.0; HRMS Exact mass calcd. for $C_{18}H_{24}N_2O_2Na^+$ 323.1730 found 323.1737.



1-Benzyl-5,5-dimethyl-(*E*-2-methyl-3-phenylpropenoyl)-pyrazolidin-3-one (8c). White solid; mp 122-124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.96 (d, *J* = 1.5 Hz, 3H), 2.64 (s, 2H), 4.13 (s, 2H), 6.74 (s, 1H), 7.22-7.36 (m, 8H), 7.43 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 26.4, 43.4, 58.0, 61.8, 127.9, 128.1, 128.47, 128.53, 129.6, 129.9, 133.1, 135.5, 136.1, 137.0, 169.9, 174.1; HRMS Exact mass calcd. for $C_{22}H_{24}N_2O_2Na^+$ 371.1730 found 371.1736.

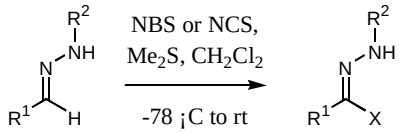


Substrate 8d. White solid; mp 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.81 (quintet, *J* = 7.5 Hz, 2H), 2.35-2.44 (m, 4H), 2.58 (s, 2H), 4.02 (s, 2H), 6.36 (t, *J* = 2.0 Hz, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 26.4, 32.9, 33.6, 43.3, 58.2, 61.7, 127.9, 128.5, 130.4, 136.5, 138.8, 142.3, 165.2, 174.0; HRMS Exact mass calcd. for $C_{18}H_{22}N_2O_2Na^+$ 321.1573 found 321.1587.



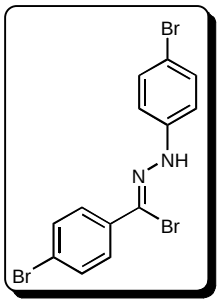
Substrate 8e. White solid; mp 133-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 6H), 1.54 (m, 4H), 2.06-2.09 (m, 4H), 2.58 (s, 2H), 4.05 (s, 2H), 6.15 (t, *J* = 1.5 Hz, 1H), 7.21-7.29 (m, 3H), 7.36 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.1, 25.1, 25.5, 26.4, 43.5, 58.0, 61.6, 127.8, 128.4, 129.9, 134.6, 136.2, 137.0, 168.9, 174.1; HRMS Exact mass calcd. for $C_{19}H_{24}N_2O_2Na^+$ 335.1730 found 335.1733.

General procedure for preparation of hydrazonoyl halides (5, 10a-c, 12a-d):

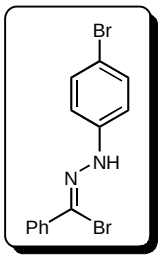


X = Br or Cl

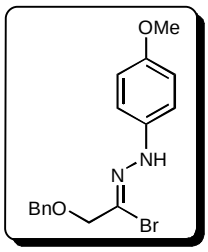
To NBS or NCS (73.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added methyl sulfide (147 mmol) over 5 minutes. After stirring for 15 minutes, the reaction was further cooled to –78 °C. Then the corresponding hydrazone (24.4 mmol) in CH_2Cl_2 (75 mL) was added. The reaction was allowed to stir at –78 °C for 1 h, then slowly allowed to warm to room temperature over 3 h. The reaction was quenched by addition of 200 mL of cold water. The organic layer was then washed with 200 mL cold water, 50 mL brine, 50 mL sat. aq. Na_2SO_3, and 100 mL water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Crude product was purified by flash column silica gel chromatography eluting first with 19:1 hexanes/EtOAc, then 9:1 hexanes/EtOAc to give the corresponding hydrazonoyl halides. Chromatography should be performed quickly as hydrazonoyl halides decompose over time on silica gel.



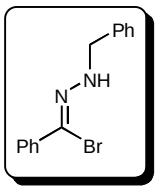
***N*-4-Bromophenyl-4-bromobenzohydrazonoyl bromide** (**5**). This compound has previously prepared.[2] Purple solid; m.p. = 143-146 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.7, 115.4, 119.2, 124.0, 129.1, 131.8, 132.5, 134.6, 142.1; HRMS Exact mass calcd. for $C_{26}H_{17}Br_2N_4^+$ (nitrile imine dimer + H^+) 700.8181 found 700.8146.



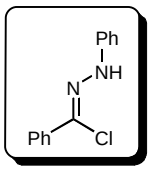
***N*-4-Bromophenylbenzohydrazonoyl bromide** (**10a**). This compound has previously prepared.[2] Red solid; m.p. = 94-96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (m, 2H), 7.35-7.43 (m, 5H), 7.89 (m, 2H), 8.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.5, 115.4, 120.5, 127.9, 128.6, 129.8, 132.5, 135.7, 142.4; HRMS Exact mass calcd. for $C_{26}H_{19}Br_2N_4^+$ (nitrile imine dimer + H^+) 544.9971 found 544.9995.



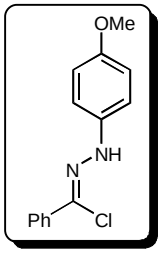
Hydrazonoyl Bromide 10b. Brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3H), 4.34 (s, 2H), 4.58 (s, 2H), 6.86 (d, J=8.9 Hz, 2H), 7.01 (d, J=8.9 Hz, 2H), 7.31-7.38 (m, 5 H), 7.60 (brs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.9, 71.9, 72.0, 72.8, 114.8, 114.5, 115.0, 128.1, 128.3, 128.4, 128.4, 128.7, 137.1, 137.4, 137.6, 154.9. HRMS Exact mass calcd for $C_{16}H_{17}BrN_2O_2Na^+$ 371.0371 found 373.0359.



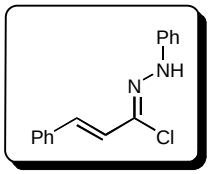
***N*-Benzylbenzohydrazonoyl bromide** (**10c**). This compound has been previously prepared.[2] Red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59 (s, 2H), 6.19 (br s, 1H), 7.30-7.42 (m, 4H), 7.84-7.87 (m, 2H) 7.30-7.42 (m, 4H).



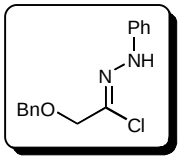
***N*-Phenylbenzohydrazonoyl chloride** (**12a**). This compound has been previously prepared.[3] Yellow-red solid; m.p. = 127-128 °C (lit. 129-131 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.30-7.42 (m, 5H), 7.92 (d, J = 7.2 Hz, 2H), 8.03 (br s, 1H); HRMS Exact mass calcd for $C_{26}H_{20}N_4^+$ (nitrile imine dimer) 388.1682 found 388.1688.



Hydrazonoyl Chloride 12b. Yellow-orange solid; mp 75-77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.35-7.43 (m, 3H), 7.92-7.94 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 114.9, 115.1, 126.5, 128.6, 128.8, 129.2, 134.8, 137.7, 154.8; HRMS Exact mass calcd for $C_{14}H_{13}N_2O^+$ (M^+-Cl) 225.1028 found 225.1022.

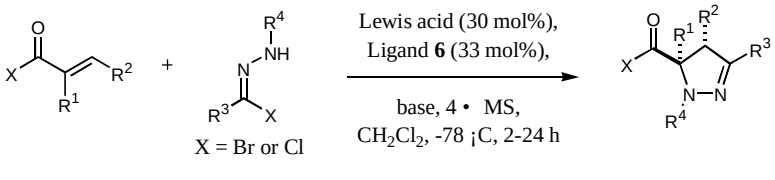


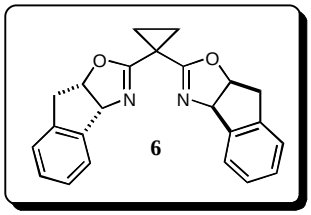
Hydrazonoyl Chloride 12c. This compound has been previously prepared.[3]



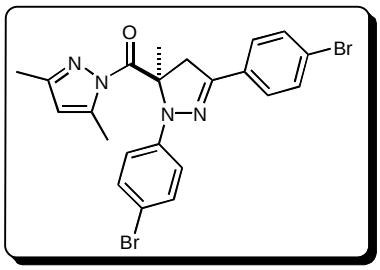
Hydrazonoyl Chloride 12d. Brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.41 (s, 2h), 4.62 (s, 2H), 6.97 (t, J=7.49, 1H), 7.11 (d, J=7.49 Hz, 2 H), 7.31-7.41 (m, 6H), 7.87 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.1, 72.8, 113.6, 121.5, 124.1, 128.1, 128.2, 128.4, 129.5, 129.6, 137.7, 143.4. HRMS Exact mass calcd for $C_{15}H_{15}N_2ONa^+$ 297.0771 found 297.0759.

Representative procedure for enantioselective nitrile imine cycloadditions (products 7a-c, 9a-e, 11a-d, 13a-d):



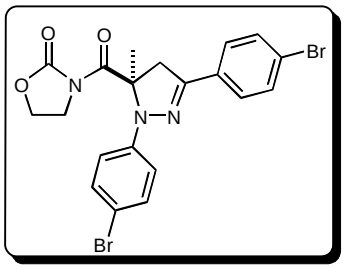


A flame-dried flask containing 4 Å molecular sieves (100 mg), Lewis acid (0.060 mmol), ligand **6** (0.066 mmol), and α,β-unsaturated substrate (0.2 mmol) in CH_2Cl_2 (2 mL) was stirred for 30 minutes at room temperature. The flask was then cooled to –78 °C and stirred for 5 minutes. Then hydrazonoyl halide (0.24 mmol) in CH_2Cl_2 (2 mL) was added to the reaction. After 5 minutes the appropriate base (0.24 mmol) was added to the reaction. The reaction was allowed to stir for 2-4 h or until starting material was consumed (TLC). Following completion of the reaction, 4Å molecular sieves were removed by filtration through a short pad of Celite. The reaction mixture was concentrated onto silica gel (2 g) and purified by column chromatography on an ISCO Combiflash system (100% hexanes to 40% EtOAc/hexanes gradient).

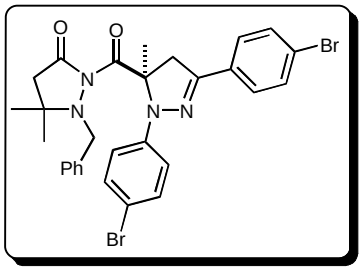


Product 7a. Yellow oil; The enantiomeric purity was determined by HPLC analysis after $LiAlH_4$ reduction to the corresponding alcohol **14** (254 nm, 25 °C) t_R 36.8 min; t_R 40.9 min [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min] as 0% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (s, 3H), 2.00 (s, 3H), 2.52 (s, 3H), 3.32 (d, *J* = 17.0 Hz, 1H), 4.11 (d, *J* = 17.0 Hz, 1H), 5.85 (s, 1H), 6.99 (m,

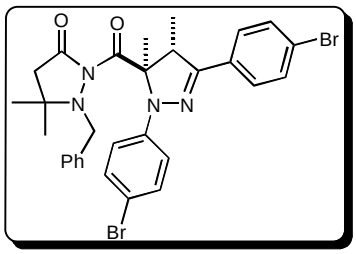
2H), 7.25 (m, 2H), 7.51 (m, 2H), 7.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.8, 24.0, 49.5, 71.5, 111.2, 111.9, 115.9, 120.9, 127.4, 131.4, 131.8, 131.89, 131.92, 132.1, 145.1, 152.4, 172.4; HRMS Exact mass calcd. for $C_{22}H_{21}Br_2N_4ONa^+$ 536.9896 found 536.9936.



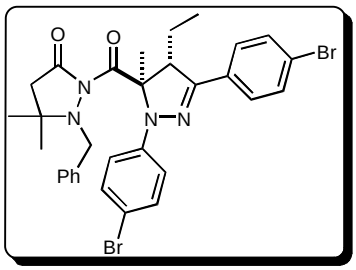
Product 7b. Clear oil; The enantiomeric purity was determined by HPLC analysis after $LiAlH_4$ reduction to the corresponding alcohol **14** (254 nm, 25 °C) t_R 36.8 min (major); t_R 40.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min] as 22% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H), 3.21 (d, *J* = 16.8 Hz, 1H), 3.93 (d, *J* = 16.8 Hz, 1H), 4.00-4.17 (m, 3H), 4.35-4.41 (m, 1H), 6.93 (m, 2H), 7.32 (m, 2H), 7.52 (m, 2H), 7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 44.9, 46.8, 62.7, 70.9, 112.3, 115.7, 123.2, 127.6, 131.2, 132.0, 132.1, 142.1, 146.0, 151.9, 172.8; Exact mass calcd. for $C_{20}H_{17}Br_2N_3O_3Na^+$ 527.9529found 527.9528.



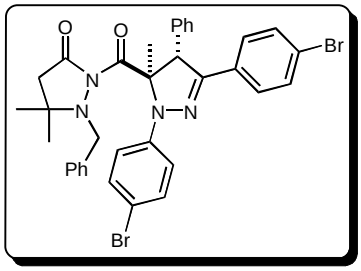
Product 7c. Yellow foam; mp 114-117 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 27.3 min (minor); t_R 36.8 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -150.00 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 3H), 1.18 (s, 3H), 1.58 (s, 3H), 2.31 (d, *J* = 17.5 Hz, 1H), 2.66 (d, *J* = 17.5 Hz, 1H), 3.08 (d, *J* = 16.0 Hz, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.26-7.34 (m, 5H), 7.49 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 24.8, 28.3, 43.7, 46.8, 57.0, 61.2, 70.9, 112.3, 116.0, 123.1, 127.5, 127.7, 128.6, 128.9, 131.4, 131.98, 132.05, 138.0, 142.3, 146.1, 169.9, 173.4; HRMS Exact mass calcd. for $C_{29}H_{29}Br_2N_4O_2^+$ 623.0652 found 623.0638.



Product 9a. Tan foam; mp 84-86 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 11.2 min (major); t_R 18.6 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -3.68 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 3H), 1.25 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 2.42 (d, *J* = 17.5 Hz, 1H), 2.69 (d, *J* = 17.5 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 1H), 4.19 (d, *J* = 14.0 Hz, 1H), 6.93 (d, *J* = 9.5 Hz, 2H), 7.25-7.30 (m, 5H), 7.41-7.43 (m, 2H), 7.50-7.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 15.6, 25.7, 27.6, 44.0, 47.8, 57.0, 61.3, 75.1, 112.6, 117.5, 122.7, 127.8, 128.1, 128.5, 129.2, 131.2, 131.8, 131.9, 137.5, 142.5, 150.2, 169.8, 173.9; Exact mass calcd. for $C_{30}H_{30}Br_2N_4O_2Na^+$ 659.0628 found 659.0622.

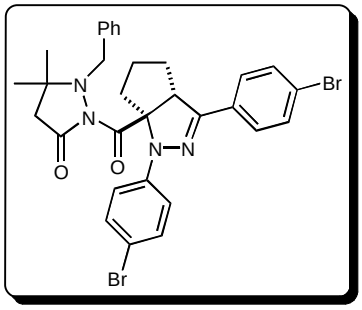


Product 9b. Pale yellow foam; mp 107-110 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 10.8 min (major); t_R 16.2 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -43.97 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, *J* = 7.6 Hz, 3H), 1.09. (s, 3H), 1.16 (s, 3H), 1.65 (s, 3H), 1.71-1.79 (m, 1H), 1.93-2.02 (m, 1H), 2.40 (d, *J* = 17.6 Hz, 1H), 2.69 (d, *J* = 17.6 Hz, 1H), 4.02 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.05 (d, *J* = 14.0 Hz, 1H), 4.15 (d, *J* = 14.0 Hz, 1H), 6.92 (m, 2H), 7.22-7.28 (m, 5H), 7.44-7.47 (m, 2H), 7.49 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 15.4, 20.2, 25.7, 27.7, 44.0, 54.4, 57.0, 61.3, 74.7, 112.6, 117.4, 122.7, 127.7, 128.2, 128.6, 128.9, 131.7, 131.8, 131.9, 138.1, 142.4, 149.4, 170.4, 173.7; Exact mass calcd. for $C_{31}H_{32}Br_2N_4O_2Na^+$ 673.0784 found 673.0780.

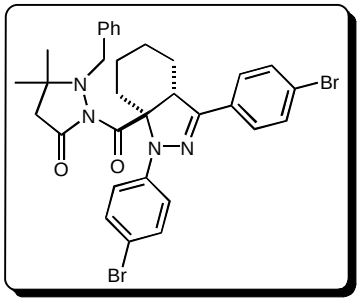


Product 9c. Characterized as an inseparable mixture (app. 2:1) of product and starting material as a thick oil. The

enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 20.0 min (minor); t_R 22.3 min (major) t_R 36.4 (substrate **8c**) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0 mL/min] as 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.13 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 2.46 (d, *J* = 17.5 Hz, 1H), 2.71 (d, *J* = 17.6 Hz, 1H), 4.16 (d, *J* = 14.0 Hz, 1H), 4.22 (d, *J* = 14.0 Hz, 1H), 7.01 (m, 2H), 7.22-7.51 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 25.9, 27.6, 43.9, 57.2, 59.9, 61.4, 76.1, 112.9, 117.5, 122.6, 127.7, 128.2, 128.3, 128.8, 129.0, 130.2, 131.1, 131.7, 131.9, 134.0, 137.0, 138.1, 142.3, 147.6, 169.7, 173.8; HRMS Exact mass calcd. for $C_{35}H_{33}Br_2N_4O_2^+$ 699.0965 found 699.1007.

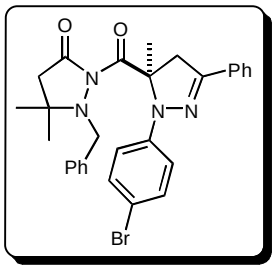


Product 9d. Tan solid; mp 235-237 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 11.6 min (major); t_R 18.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 98% ee. $[\alpha]_D^{25}$ = -106.79 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (s, 3H), 1.14 (s, 3H), 1.53-1.61 (m, 2H), 1.81-1.91 (m, 2H), 2.09 (m, 1H), 2.23 (d, *J* = 17.6 Hz, 1H), 2.59 (d, *J* = 17.6 Hz, 1H), 3.07 (m, Hz, 1H), 3.99 (d, *J* = 14.0 Hz, 1H), 4.16 (d, *J* = 14.0 Hz, 1H), 4.38 (dd, *J* = 4.4, 9.2 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 2H), 7.23-7.43 (m, 7H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.6, 28.1, 32.3, 37.2, 43.5, 57.1, 58.3, 61.3, 81.3, 112.0, 115.7, 122.8, 127.7, 128.0, 128.5, 129.2, 130.8, 132.0, 132.1, 137.7, 142.4, 150.2, 169.4, 173.6; Exact mass calcd. for $C_{31}H_{32}Br_2N_4O_2Na^+$ 671.0628 found 671.0632.

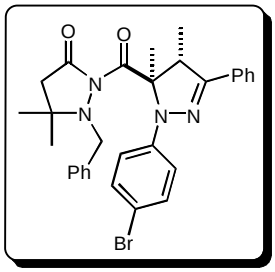


Product 9e. Tan foam; mp 99-102 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 11.9 min (major); t_R 15.1 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -93.23 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 3H), 1.20 (s, 3H), 1.23-1.59 (m, 4H), 1.79-1.88 (m, 3H), 2.34 (d, *J* = 17.5 Hz, 1H),

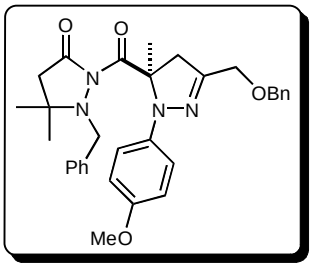
2.50-2.56 (m, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 4.18-4.22 (m, 2H), 6.97 (m, 2H), 7.25-7.30 (m, 5H), 7.44 (d, *J* = 6.5 Hz, 2H), 7.51-7.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 19.1, 22.4, 25.2, 25.5, 28.1, 44.0, 49.2, 57.1, 61.2, 74.3, 112.6, 117.3, 122.8, 127.7, 128.1, 128.5, 129.2, 131.4, 131.8, 131.9, 137.7, 142.6, 150.1, 170.3, 173.6; $C_{32}H_{33}Br_2N_4O_2^+$ 663.0965 found 663.0944.



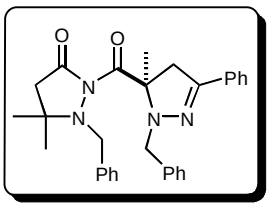
Product 11a. Tan foam; mp 105-108 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 12.7 min (minor); t_R 15.2 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -153.60 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 3H), 1.16 (s, 3H), 1.56 (s, 3H), 2.29 (d, *J* = 17.6 Hz, 1H), 2.63 (d, *J* = 17.6 Hz, 1H), 3.10 (d, *J* = 16.4 Hz, 1H), 3.84 (d, *J* = 16.4 Hz, 1H), 4.05 (d, *J* = 14.0 Hz, 1H), 4.21 (d, *J* = 14.0 Hz, 1H), 6.96 (m, 2H), 7.23-7.41 (m, 8H), 7.49 (m, 2H), 7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 24.9, 28.4, 43.7, 47.1, 57.0, 61.2, 70.7, 112.0, 116.0, 126.1, 127.7, 128.6, 128.8, 129.0, 129.2, 132.0, 132.5, 138.0, 142.5, 147.3, 170.3, 173.3; HRMS Exact mass calcd. for $C_{29}H_{29}BrN_4O_2Na^+$ 567.1366 found 567.1381.



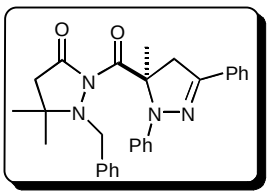
Product 11b. Tan foam; mp 91-94 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 8.5 min (major); t_R 10.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = -24.82 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 3H), 1.22 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.58 (s, 3H), 2.39 (d, *J* = 17.6 Hz, 1H), 2.66 (d, *J* = 17.6 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 4.18 (d, *J* = 14.0 Hz, 1H), 6.93 (m, 2H), 7.21-7.42 (m, 10H), 7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 15.6, 25.8, 27.7, 44.1, 48.1, 57.0, 61.3, 74.9, 112.3, 117.4, 126.8, 127.8, 128.6, 128.77, 128.83, 129.3, 131.8, 132.3, 137.7, 142.8, 151.4, 170.1, 173.8; HRMS Exact mass calcd. for $C_{30}H_{31}BrN_4O_2Na^+$ 581.1523 found 581.1553.



Product 11c. Pale yellow oil. The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 12.4 min (major); t_R 15.6 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 80% ee. $[\alpha]_D^{25}$ = -21.30 (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 3H), 1.20 (s, 3H), 1.47 (s, 3H), 2.32 (d, *J*=17.3 Hz, 1H), 2.66 (d, *J*=17.3 Hz, 1H), 2.84 (d, *J*=16.9 Hz, 1H), 3.62 (d, *J*=16.9 Hz, 1H), 3.74 (s, 3H), 4.07 (d, *J*=14.1 Hz, 1H), 4.25 (d, *J*=14.1 Hz, 1H), 4.45 (dd, *J*=15.6, 7.8 Hz, 2H), 4.60 (dd, *J*=18.5, 9.2 Hz, 2H), 6.75 (d, *J*=9.7 Hz, 2H), 9.7 (d, *J*=9.7 Hz), 7.25-7.50 (m, 14 H). ^{13}C NMR (125 MHz, $CDCl_3$) 22.3, 24.8, 28.6, 29.9, 43.9, 47.6, 55.8, 56.9, 61.1, 67.4, 71.0, 72.4, 114.6, 116.5, 127.7, 128.0, 128.2, 128.6, 128.7, 129.1, 138.1, 138.2, 147.4, 153.9, 171.1, 173.2. HRMS Exact mass calcd. for $C_{32}H_{36}N_4O_4Na^+$ 563.2634 found 563.2641.

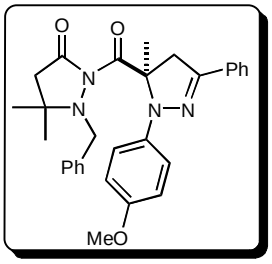


Product 11d. Colorless oil. The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 38.4 min (minor); t_R 31.4 min (major) [Chiralpak AD-H (1.00 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 67% ee. $[\alpha]_D^{25}$ = 86.29 (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) 1.12 (s, 3H), 1.31 (s, 3H), 1.53 (s, 3H), 2.57 (d, *J*=17.1 Hz, 1H), 2.72 (d, *J*=17.1 Hz, 1H), 3.28 (d, *J*=16.7 Hz, 1H), 3.51 (d, *J*=16.7 Hz, 1H), 3.97 (d, *J*=13.5 Hz, 1H), 4.07 (m, 2H), 4.25 (d, *J*=13.5 Hz, 1H), 7.23-7.62 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$) 19.5, 25.6, 26.4, 26.9, 44.2, 44.2, 53.5, 57.2, 61.4, 74.7, 125.7, 126.9, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7, 129.7, 133.4, 137.4, 140.2, 146.2, 170.8, 173.9. HRMS Exact mass calcd. for $C_{30}H_{32}BrN_4O_2H^+$ 481.2604 found 481.2612.

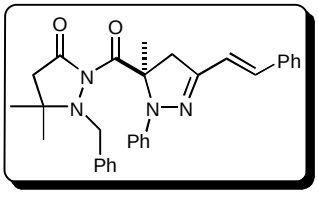


Product 13a. Yellow foam; mp 94-97 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 19.5 min (minor); t_R 21.9 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 97/3, 1.0 mL/min] as 96% ee. $[\alpha]_D^{25}$ = -209.77 (*c* 0.52, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01

(s, 3H), 1.16 (s, 3H), 1.61 (s, 3H), 2.28 (d, *J* = 17.5 Hz, 1H), 2.63 (d, *J* = 17.5 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 3.89 (d *J* = 16.0 Hz, 1H), 4.09 (d, *J* = 14.5 Hz, 1H), 4.24 (d, *J* = 14.5 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.30-7.36 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 24.9, 28.4, 43.7, 47.0, 57.0, 61.2, 70.7, 114.5, 119.9, 126.1, 127.6, 128.5, 128.8, 128.9, 129.0, 129.3, 132.8, 138.2, 143.5, 146.5, 170.7, 173.2; HRMS Exact mass calcd. for $C_{29}H_{30}N_4O_2Na^+$ 489.2261 found 489.2254.

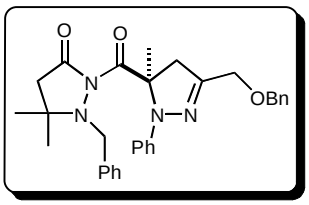


Product 13b. Tan foam; mp 91-94 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 23.4 min (minor); t_R 49.4 min (major) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 96% ee. $[\alpha]_D^{25}$ = -88.24 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 3H), 1.15 (s, 3H), 1.50 (s, 3H), 2.30 (d, *J* = 17.2 Hz, 1H), 2.63 (d, *J* = 17.2 Hz, 1H), 3.09 (d, *J* = 16.0 Hz, 1H), 3.73 (s, 3H), 3.86 (d, *J* = 16.0 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 4.22 (d, *J* = 14.0 Hz, 1H), 6.76 (d, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 7.28-7.39 (m, 6H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.9, 28.4, 43.7, 46.8, 55.8, 57.1, 61.2, 71.3, 114.6, 116.5, 125.9, 127.6, 128.5, 128.7, 128.8, 129.0, 132.9, 137.8, 138.2, 146.1, 154.0, 170.9, 173.2; HRMS Exact mass calcd. for $C_{30}H_{32}N_4O_3Na^+$ 519.2367 found 519.2361.



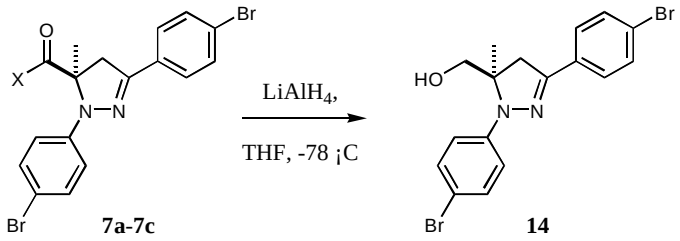
Product 13c. Yellow foam; mp 105-108 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 10.9 min (major); t_R 16.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 94% ee. $[\alpha]_D^{25}$ = -267.32 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.13 (s, 3H), 1.60 (s, 3H), 2.26 (d, *J* = 17.6 Hz, 1H), 2.63 (d, *J* = 17.6 Hz, 1H), 2.97 (d, *J* = 16.0 Hz, 1H), 3.72 (d, *J* = 16.0 Hz, 1H), 4.05 (d, *J* = 14.4, 1H), 4.20 (d, *J* = 14.4 Hz, 1H), 6.57 (d, *J* = 16.4 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.15-7.20 (m, 2H), 7.22-7.35 (m, 7H), 7.46 (d, *J* = 7.6

Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 25.0, 28.2, 43.7, 45.8, 57.0, 61.1, 70.6, 114.2, 120.1, 121.8, 126.9, 127.6, 128.3, 128.5, 128.9, 129.0, 129.3, 132.8, 136.9, 138.3, 142.8, 148.0, 170.3, 173.2; HRMS Exact mass calcd. for $C_{31}H_{32}N_4O_2Na^+$ 515.2417 found 515.2399.



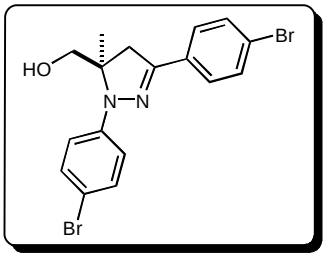
Product 13d. Yellow oil; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R 10.8 min (major); t_R 12.3 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min] as 91% ee. $[\alpha]_D^{25}$ = -108.42 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.16 (s, 3H), 1.49 (s, 3H), 2.25 (d, *J* = 17.6 Hz, 1H), 2.61 (d, *J* = 17.6 Hz, 1H), 2.82 (d, *J* = 16.8 Hz, 1H), 3.60 (d, *J* = 16.8 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.44 (d, *J* = 12.8 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 6.76 (tt, 7.2, 1.0 Hz, 1H), 6.96-6.99 (m, 2H), 7.12-7.17 (m 2H), 7.23-7.36 (m, 8H), 7.47 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 24.8, 28.5, 43.9, 47.7, 56.9, 61.1, 67.3, 70.4, 72.5, 114.3, 119.8, 127.6, 128.0, 128.2, 128.5, 128.7, 129.0, 129.2, 129.8, 138.2, 143.6, 147.8, 170.8, 173.1; HRMS Exact mass calcd. for $C_{31}H_{34}N_4O_3Na^+$ 533.2523 found 533.2533.

Procedure for reduction of products 7a-c to alcohol 14:



To a flask containing $LiAlH_4$ (0.8 mmol) in THF (3 mL) at –78 °C was added a solution of cycloadduct **7a-c** (0.2 mmol) in THF (2 mL). The reaction was allowed to stir until starting material had disappeared (TLC). The reaction was then carefully poured into a separatory funnel containing saturated aqueous ammonium chloride (10 mL). The slurry

was then extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated onto silica gel (2 g), and purified by column chromatography on an ISCO Combiflash system (100% hexanes to 50% EtOAc/hexanes gradient).



Alcohol 14. Yellow-green foam; mp 61-63 °C; The enantiomeric purity was determined by HPLC analysis after $LiAlH_4$ reduction of compound **7c** (Table 1, entry 9) to the corresponding alcohol **14** (254 nm, 25 °C) t_R 36.8 min; t_R 40.9 min [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min] as 99% ee. $[\alpha]_D^{25}$ = +142.99 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 3H), 2.00 (d, *J* = 10.0 Hz, 1H), 3.04 (d, *J* = 16.5 Hz, 1H), 3.59 (d, *J* = 16.5 Hz, 1H), 3.65 (dd, *J* = 12.0, 10.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 7.13-7.18 (m, 2H), 7.38-7.42 (m, 2H), 7.50-7.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 44.6, 67.0, 71.3, 115.2, 120.5, 123.2, 127.5, 131.7, 132.0, 132.1, 143.7, 148.7; HRMS Exact mass calcd. for $C_{17}H_{16}Br_2N_2ONa^+$ 444.9522 found 444.9517.

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[1] Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc*. **2002**, *124*, 984.
[2] Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.
[3] Patel, H. V.; Vyas, K. A.; Pandey, S. P.; Fernandes, P. S. *Tetrahedron* **1996**, *52*, 661-668.