SUPPORTING INFORMATION

N-Benzylhydroxylamine Addition to β-Aryl Enoates. Enantioselective Synthesis of β-aryl-β-Amino Acid Precursors

Mukund P. Sibi,* and Mei Liu
Department of Chemistry, North Dakota State University
Fargo, North Dakota 58105-5516
Mukund_Sibi@ndsu.nodak.edu

General Experimental. Methylene chloride was distilled from calcium hydride prior to use**.** Magnesium bromide-etherate was either purchased from Aldrich chemicals or freshly prepared from magnesium and dibromoethane (Pohmakotr, M.; Geiss, K.H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420). Flash chromatography were performed using EM Science silica gel 60 (230-400 mesh). Melting points were determined using the Fisher-Johns melting point apparatus. All glassware was oven and/or flame dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

^{1}H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), a Varian Mercury-300 (300 MHz) or a JEOL GSX-400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) down field 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, dd = doublets of doublets, m = multiplet, br = broad), coupling constant(s) and integration. ^{13}C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian Mercury-300 (75 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. HPLC analyses were carried out on either a Waters M-45 pump equipped with a ISCO V^4 variable wavelength UV detector connected to a Hewlett-Packard 3396 II integrator or a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with millennium^{32} workstation. Rotations were recorded on a JASCO-DIP-370 instrument. Elemental analyses were performed in house on a Perkin Elmer Series II CHNS/O Analyzer 2400.

Starting crotonamides 1a-1d. The synthesis of pyrazole crotonate (**1a**) has been described in the literature.[1]

General procedure for the acylation of 2-oxazolidinones or pyrrolidinones. To a stirred solution of the appropriate oxazolidinone or pyrrolidinone in anhydrous THF (0.3 M) at –78 °C was added 1.0 eq of n-BuLi. After 30 min, 1.1 eq of the *trans*-crotonyl chloride was added. The mixture was stirred at –78 °C for 2 to 3 h. The reaction was quenched with saturated aqueous ammonium chloride, and the slurry was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and then washed with saturated aqueous sodium bicarbonate. The combined organic extracts were washed with brine and dried over magnesium sulfate, then filtered, and solvent was removed under reduced pressure.

3-[(E)-2-Butenoyl]-2-oxazolidinone (1b) [2]**:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.94 (dd, *J* = 6.7, 1.3 Hz, 3H), 4.04 (t, *J* = 8.1 Hz, 2H), 4.40 (t, *J* = 8.0 Hz, 2H), 7.11-7.26 (m, 2H).

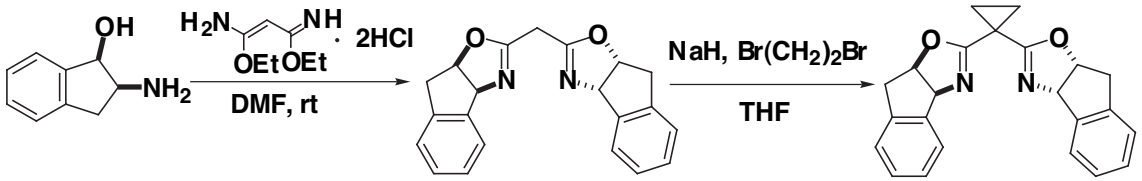
1-[(E)-2-Butenoyl]-2-pyrrolidinone (1c) [3]**:** ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.91 (dd, *J* = 9.6, 1.9 Hz, 3H), 1.95-2.08 (m, 2H), 2.58 (t, *J* = 11.8 Hz, 2H), 3.82 (t, *J* = 10.6 Hz, 2H), 7.05-7.25 (m, 2H).

1-[(*E*)-2-Butenoyl]-3,3-dimethyl-2-pyrrolidinone (1d): 3,3-dimethyl-2-pyrrolidinone was prepared according to the literature procedure.[4] The acylation of the 3,3-dimethyl-2-pyrrolidinone was then performed following the general procedure described above. The product was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) to afford an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (s, 6H), 1.86 (t, *J* = 7.0 Hz, 2H), 1.90 (dd, *J* = 6.7, 1.6 Hz, 3H), 3.71 (t, *J* = 7.0 Hz, 2H), 7.02-7.12 (m, 1H), 7.21-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 24.4, 32.5, 41.9, 43.2, 123.8, 145.7, 166.5, 180.6. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.89; H, 8.69; N, 7.82.

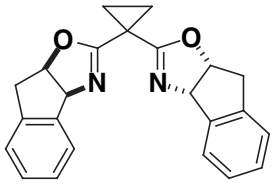
Preparation of Bisoxazoline Ligand 2: Under N_2, 2.5 equivalents of amino indanol was added to a rapidly stirred suspension of ethyl 3-amino-3-ethoxyprop-2-enimidate[5] in dry DMF (1g/10 mL) at 0°C. The white suspension was almost completely solubilized before new solid began to precipitate. The ice-bath was removed and the mixture was stirred at rt for 3 days. Most of the DMF was removed under vacuum at rt. The residue was then diluted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. The product was purified by recrystallization from ethanol, and used in the next step.

Preparation of Spirobisoxazoline Ligand: Under N_2, to a solution of dihydrobisoxazoline (0.2 M) in THF, was added 3 equivalents of NaH (60%) in portions at 0 °C. After complete addition, the mixture was stirred for 30 minutes at 0 °C. A solution of $Br(CH_2)_2Br$ (1.2 equivalents) in THF was then added dropwise at 0 °C over 10 minutes and the mixture was then heated to 50 °C and the reaction was completed within 0.5-2h. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The

extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by chromatography on silica gel (2% MeOH/EtOAc) followed by recrystallization using EtOAc/hexane.



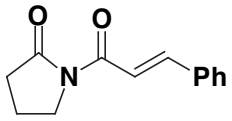
2



2

{3a*S*-[2(3'a*R, 8'a*S**), 3aα, 8aα]}-2,2'-(cyclopropylidene)-bis{3a, 8a-dihydro-8H-indeno[1,2-*d*]-oxazole} (2):** mp 163-164 °C; $[\alpha]^{20}_{D}$ = -349.3 (*c* 1.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.22 (m, 2H), 3.17 (d, *J* = 17.5 Hz, 1H), 3.36 (dd, *J* = 18.0, 7.0 Hz, 1H), 5.33-5.24 (m, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 7.25-7.19 (m, 3H), 7.45-7.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 18.4, 39.7, 76.5, 83.4, 125.2, 125.7, 127.4, 128.4, 139.8, 141.9, 165.9; R_f 0.20 (90% ethyl acetate/10%MeOH).

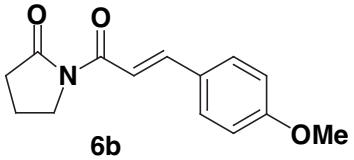
Preparation of starting materials for Table 3: Substrate 6a:



6a

Preparation of 1-(3-phenyl-propenoyl)-pyrrolidin-2-one 6a[6]: Under N_2, to a 250 mL flask containing 60 mL THF and 1.52 mL (20 mmol) of 2-pyrrolidinone, at –78 °C, was added dropwise 8 mL of *n*-BuLi (2.5 M in hexane, 20 mmol). The solution was stirred at –78 °C for 30 min, then 3.68 g (22 mmol) of cinnamoyl chloride in 20 mL THF was added. The reaction mixture was stirred for another 2-3 h at –78 °C, then slowly warmed up to room temperature. The resulting mixture was quenched with saturated ammonium chloride and concentrated under the reduced pressure. The slurry was redissolved in ether, and washed with sat. $NaHCO_3$ and brine. The organic layer was

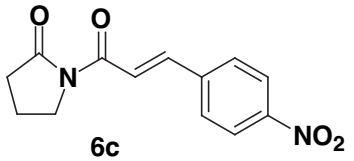
dried with $MgSO_4$ and concentrated to afford a solid. The product can be further purified by recrystallization in ether. mp 99-100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.04-2.11 (m, 2H), 2.65 (t, *J* = 8.1 Hz, 2H), 3.92 (t, *J* = 7.2 Hz, 2H), 7.38-7.39 (m, 3H), 7.61-7.62 (m, 2H), 7.84 (d, *J* = 15.8 Hz, 1H), 7.94 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 34.2, 46.1, 119.2, 128.8, 129.1, 130.6, 135.1, 145.8, 166.6, 176.0; R_f 0.40 (10% EtOAc/hexanes).



6b

Preparation of *p*-methoxycinnamoyl chloride: Under N_2, to a 100 mL round bottom flask containing 3.92 g (22 mmol) *p*-methoxycinnamic acid, was added 7 mL (80 mmol) oxalyl chloride. Reaction was initiated by one drop of DMF at 0 °C. The reaction mixture was kept stirring for 20 min at 0 °C, then slowly warmed up to room temperature. The excess oxalyl chloride was removed under reduced pressure, and the product was used without further purification.

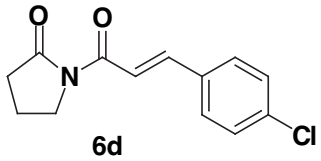
Substrate 1-(3-(4-methoxyphenyl)-propenoyl)-pyrrolidin-2-one 6b: Compound **6b** was prepared according to the methodology described for **6a**. mp 140-143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01-2.11 (m, 2H), 2.65 (t, *J* = 8.1 Hz, 2H), 3.84 (s, 1H), 3.92 (t, *J* = 7.3 Hz, 2H), 6.89-6.92 (m, 2H), 7.56-7.59 (m, 2H), 7.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 34.3, 46.1, 55.6, 114.5, 116.7, 127.9, 130.5, 145.6, 161.7, 166.8, 175.9; R_f 0.24 (40% EtOAc/hexanes); Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.12; H, 5.84; N, 5.50.



6c

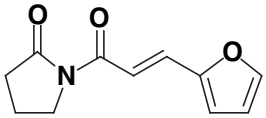
Substrate 1-(3-(4-nitrophenyl)-propenoyl)-pyrrolidin-2-one 6c: Compound **6c** was prepared according to the methodology described for **6b** using commercially available *p*-nitrocinnamic acid. The compound was purified by silica gel column chromatography and then recrystallized in ethanol. mp 175-177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06-2.16 (m, 2H), 2.68 (t, *J* = 8.1 Hz, 2H), 3.94 (t, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 15.7 Hz, 1H), 8.04 (d, *J* = 15.7 Hz, 1H), 8.24 (d, *J* = 8.9 Hz,

2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 34.1, 46.1, 123.4, 124.3, 129.2, 141.2, 142.2, 148.6, 165.6, 176.2; R_f 0.20 (40% EtOAc/hexanes); Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.56; H, 4.71; N, 10.49.



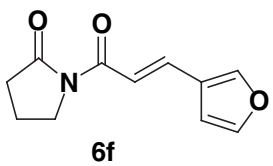
6d

Substrate 1-(3-(4-chlorophenyl)-propenoyl)-pyrrolidin-2-one 6d: Compound **6d** was prepared according to the methodology described for **6b** using commercially available *p*-chlorocinnamic acid. The compound was purified by silica gel column chromatography. mp 142-144 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.98-2.04 (m, 2H), 2.59 (t, *J* = 8.1 Hz, 2H), 3.58 (t, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 15.8 Hz, 1H), 7.83 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 34.2, 46.1, 119.7, 129.3, 129.9, 133.6, 136.4, 144.2, 166.3, 176.0; R_f 0.40 (40% EtOAc/hexanes); Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.53; H, 4.40; N, 5.62.



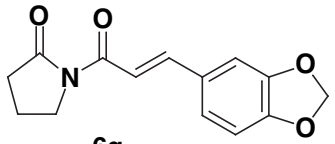
6e

Substrate 1-(3-(2-furyl)-propenoyl)-pyrrolidin-2-one 6e:. Compound **6e** was prepared according to the methodology described for **6b** using commercially available *trans*-2-furanacrylic acid. The compound was purified by silica gel column chromatography. mp 118-120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01-2.11 (m, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 3.90 (t, *J* = 7.3 Hz, 2H), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.66 (d, *J* = 3.2 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 15.3 Hz, 1H), 7.76 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 34.2, 46.1, 112.6, 115.7, 116.7, 131.9, 145.2, 151.8, 166.5, 175.7; R_f 0.30 (40% EtOAc/hexanes); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.16; H, 5.24; N, 6.78.



6f

Substrate 1-(3-(3-furyl)-propenoyl)-pyrrolidin-2-one 6f: Compound **6f** was prepared according to the methodology described for **6b** using commercially available furylacrylic acid. The compound was purified by silica gel column chromatography. mp 135-137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01-2.11 (m, 2H), 2.64 (t, *J* = 8.3 Hz, 2H), 3.91 (t, *J* = 7.3 Hz, 2H), 6.70 (d, *J* = 2.0 Hz, 1H), 7.42-7.43 (m, 1H), 7.64 (d,*J* = 15.7 Hz, 1H), 7.69 (s, 1H), 7.75 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 34.2, 46.1,108.1, 118.9, 123.5, 135.8, 144.6, 145.3, 175.9, 179.4; R_f 0.30 (40% EtOAc/hexanes); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.15; H, 5.46; N, 6.82.



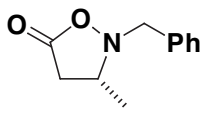
6g

Substrate 1-(3-(3,4-dimethoxyphenyl)-propenoyl)-pyrrolidin-2-one 6g: Compound **6g** was prepared according to the methodology described for **6b** using commercially 3,4-(methylenedioxy)cinnamic acid. The compound was purified by silica gel column chromatography. mp 141-144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01-2.11 (m, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 3.91 (t, *J* = 7.1 Hz, 2H), 6.00 (s, 2H), 6.80 (d, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.14 (d, *J* = 1.2 Hz, 1H), 7.75 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 34.3, 46.1,101.8, 107.2, 108.7, 117.2, 125.2, 129.6, 145.6, 148.5, 150.0, 166.7, 175.9. R_f 0.20 (40% EtOAc/hexanes); Anal. Calcd for $C_{14}H_{13}NO$: C, 66.86; H, 5.05; N, 5.40. Found: C, 64.66; H, 5.16; N, 5.09.

Preparation of BnNHOH: *N*-Benzylhydroxylamine hydrochloride was washed with 1 M NaOH then extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated to afford the desired solid product. *N*-Benzylhydroxylamine may also be prepared by sodium cyanoborohydride reduction of benzaldoxime according to a literature procedure.[7]

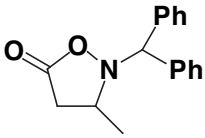
Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of hydroxylamines to crotonate. (Table 1, entry 1c): Under N_2, to a flask containing $MgBr_2{\cdot}Et_2O$ (0.05 mmol) and bisoxazoline **2** (0.05 mmol) was added CH_2Cl_2 (1 mL). Pyrrolidinone crotonate **1c** (0.167 mmol) (in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for 30 min at room temperature. The reaction was cooled to -60 °C, then BnNHOH (0.184 mmol) (in 1 mL CH_2Cl_2) was added. The

reaction was monitored by TLC and when judged complete was quenched with H_2O and extracted 2 x CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography. The enantiomeric purity was determined by HPLC.



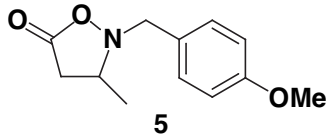
3

***N*-Benzyl-3-methylisoxazolidin-5-one 3[8]:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (d, *J* = 6.4, 3H), 2.57 (dd, *J* = 16.8, 11.1, 1H), 2.76 (dd, *J* = 16.5, 6.0, 1H), 3.43 (bs, 1H), 4.02 (d, *J* = 14.1 Hz, 1H), 4.21 (d, *J* = 14.1 Hz, 1H), 7.29-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 38.5, 61.7, 128.2, 128.8, 129.4, 135.6, 173.8; R_f 0.40 (30% EtOAc/70% hexanes); HPLC t_R 70.0 min (S-isomer); t_R 74.0 min (R-isomer) [Chiralcel OD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 85/15, 0.5mL/min].



4

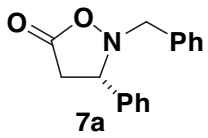
***N*-Benzhydrylhydroxyl-3-methylisoxazolidin-5-one 4:** The synthesis of *N*-benzhydrylhydroxylamine has been described in the literature.[7] The conjugate addition was then carried out according to the general procedure described above. mp 98-102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (d, *J* = 6.4, 3H), 2.46 (dd, *J* = 17.1, 7.4, 1H), 2.79 (bs, 1H), 3.59 (bs, 1H), 5.09 (s, 1H), 7.24-7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7, 37.3, 58.3, 74.8, 128.0, 128.1, 128.2, 128.7, 128.9, 139,4, 140.2, 143.7, 174.8; R_f 0.60 (40% EtOAc/60% hexanes); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 75.90; H, 6.07; N, 5.21; HPLC t_R 28.4 min; t_R 33.4 min [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/05, 0.6 mL/min].



5

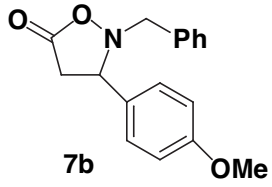
***N*-*p*-Methoxybenzyl-3-methylisoxazolidin-5-one 5:** The synthesis of *N*-*p*-Methoxybenzylhydroxylamine has been described in the literature.[9] The conjugate addition was then carried out according to the general procedure described above. mp 88-91°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.55 (dd, *J* = 16.9, 10.9 Hz, 1H), 2.74 (dd, *J* = 16.9, 6.4 Hz, 1H), 3.41-3.49 (m, 1H), 3.80 (s, 3H), 3.98 (d, *J* = 13.7 Hz, 1H), 4.15 (d, *J* = 14.1 Hz, 1H), 6.86-6.90 (m, 2H), 7.26-7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 38.5, 55.5, 61.1, 61.3, 114.2, 127.4, 130.8, 159.6, 173.9; R_f 0.25 (70% Et_2O/30% hexanes); Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.88; H, 6.77; N, 6.22; HPLC t_R 20.3 min; t_R 22.6 min [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min].

Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of BnNHOH to cinnamates. (Table 3, entry 6a): Under N_2, to a flask containing $MgClO_4$ or MgI_2 (0.05 mmol) and bisoxazoline **2** (0.05 mmol) was added CH_2Cl_2 (1 mL). Pyrrolidinone cinnamate **6a** (0.167 mmol) (in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for 30 min at room temperature. The reaction mixture was cooled to –60 °C, then BnNHOH (0.184 mmol) (in 1 mL CH_2Cl_2) was added. The reaction was monitored by TLC and when judged complete was quenched with H_2O and extracted 2 x CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford a white solid. The product was purified by silica gel chromatography. The enantiomeric purity was determined by HPLC.



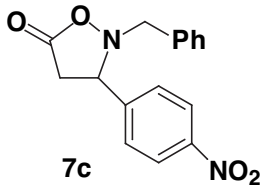
7a

***N*-Benzyl-3-phenylisoxazolidin-5-one 7a[8]:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.00 (d, *J* = 9.7, 2H), 3.96 (d, *J* = 14.8, 1H), 4.18 (d, *J* = 14.4, 1H), 4.37 (t, *J* = 9.6, 1H), 7.29-7.51 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ40.6, 61.1, 70.5, 127.9, 128.1, 128.7, 129.3, 129.4, 129.5, 135.6, 136.4, 172.7; HPLC t_R 21.7 min; t_R 25.4 min [Chiralcel AD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.5 mL/min].



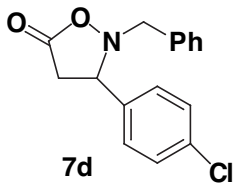
7b

***N*-Benzyl-3-(4-methoxyphenyl)isoxazolidin-5-one 7b[8]:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.96 (d, *J* = 11.1 Hz, 2H), 3.83 (s, 3H), 3.90 (d, *J* = 14.4 Hz, 1H), 4.16 (d, *J* = 14.8 Hz, 1H), 4.30 (t, *J* = 9.4 Hz, 1H), 6.93-6.96 (m, 2H), 7.26-7.34 (m, 5H), 7.40 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.6, 55.6, 60.8, 70.1, 114.7, 128.0, 128.1, 128.7, 129.1, 129.4, 135.7, 160.4, 172.8; HPLC t_R 39.7 min; t_R 46.1 min [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/05, 1.0 mL/min].



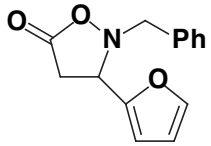
7c

***N*-Benzyl-3-(4-nitrophenyl)isoxazolidin-5-one 7c:** mp 121-125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.92 (dd, *J* = 17.1, 11.5 Hz, 1H), 3.08 (dd, *J* = 16.9, 7.3 Hz, 1H), 4.10 (dd, *J* = 21.2, 14.1 Hz, 2H), 4.48 (dd, *J* = 11.3, 7.3 Hz, 1H), 7.26-7.31 (m, 5H), 7.64 (d, *J* = 8.9 Hz, 2H), 8.25 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.2, 61.8, 68.9, 124.6, 128.5, 128.6, 128.8, 129.5, 134.5, 144.2, 148.4, 171.8; Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.81; H, 4.77; N, 9.43; HPLC t_R 58.2 min; t_R 70.7 min [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 85/15, 1.0 mL/min].



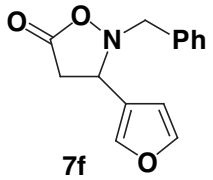
7d

***N*-Benzyl-3-(4-chlorophenyl)isoxazolidin-5-one 7d:** mp 63-66 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.92 (dd, *J* = 17.0, 11.9, 1H), 2.99 (dd, *J* = 17.1, 7.1, 1H), 3.96 (d, *J* = 14.8, 1H), 4.14 (d, *J* = 14.4, 1H), 4.34 (dd, *J* = 11.6, 7.2, 1H), 7.28-7.43 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.4, 61.2, 69.6, 128.2, 128.7, 129.2, 129.4, 129.6, 135.1, 135.2, 135.3, 172.4; R_f 0.6 (40% EtOAc/60% hexanes); Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.46; H, 4.93; N, 4.79; HPLC t_R 46.4 min; t_R 55.6 min [Chiralcel OJ (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 85/15, 1.0 mL/min].



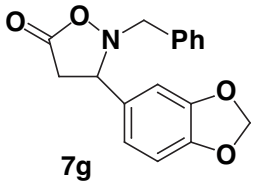
7e

***N*-Benzyl-3-(2-furyl)isoxazolidin-5-one 7d:** mp 63-65 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.94 (bs, 1H), 3.24 (bs, 1H), 4.04 (d, *J* = 10.7 Hz, 1H), 4.32 (bs, 1H), 4.46 (bs, 1H), 6.41 (d, *J* = 5.4 Hz, 2H), 7.29-7.34 (m, 5H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.2, 61.6, 62.9, 110.0, 110.9, 128.2, 128.6, 128.7, 129.5, 135.1, 143.8, 172.6; R_f 0.6 (40% EtOAc/60% hexanes); Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.77; H, 5.58; N, 5.79; HPLC t_R 33.0 min; t_R 37.4 min [Chiralcel AD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/05, 0.5 mL/min].



7f

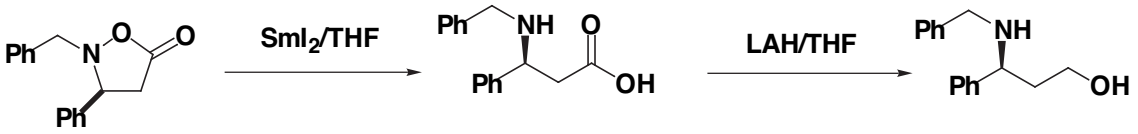
***N*-Benzyl-3-(3-furyl)isoxazolidin-5-one 7f:** mp 67-68 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.92 (d, *J* = 9.1 Hz, 1H), 3.94 (d, *J* = 14.4 Hz, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 4.34 (bs, 1H), 6.53 (s, 1H), 7.31-7.35 (m, 5H), 7.47-7.48 (m, 1H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.0, 61.0, 62.0, 109.0, 121.5, 128.2, 128.7, 129.4, 135.6, 141.3, 144.5, 172.9; R_f 0.6 (40% EtOAc/60% hexanes); Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.70; H, 5.49; N, 5.78; HPLC t_R 42.6 min; t_R 57.5 min [Chiralcel OJ (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min].



7g

***N*-Benzyl-3-(3,4-methylenedioxyphenyl)isoxazolidin-5-one 7g:** mp 61-63 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.93 (d, *J* = 10.5 Hz, 3H), 3.91 (d, *J* = 14.5 Hz, 1H), 4.17 (d, *J* = 14.9Hz, 1H), 4.26 (t, *J* = 9.5 Hz, 1H), 5.99 (s, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 7.28-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.5, 60.9, 70.3, 101.7, 107.7, 108.8, 121.8, 128.1, 128.7, 129.4, 130.0, 135.7, 148.4, 148.6, 172.6; R_f 0.5 (30% EtOAc/70% hexanes); Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.24; H, 4.92; N, 4.65; HPLC t_R 49.8 min; t_R 64.0 min [Chiralcel AS (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min].

Determination of absolute stereochemistry of 7a by conversion to a known amino alcohol 9.



7a **8** **9**

Preparation of Samarium (II) Iodide: A modified procedure was used for the synthesis of SmI_2.[10] Reaction was carried out in an ultrasonic bath. Under N_2, 180 mg (1.2 mmol) of Sm powder and 10 mL of dry THF was placed in an oven-dry reaction vial. After 30 min, 80 μL (1.0 mmol) of diiodomethane was added through a micro syringe, and a greenish-yellow color appeared. After an additional 2 hours, a deep blue color solution (0.1 M in THF) of SmI_2 was obtained.

(*S*)-3-Benzylamino-3-phenyl-propionic acid 8: In an ultrasonic bath, a solution of isoxazolidinone **7a** (80%ee) (0.38 mmol) in 2 mL THF was added to 15 mL of 0.1M SmI_2 in THF. After one hour, the reaction mixture was diluted with EtOAc and was washed with 15% sodium thiosulfate solution, followed by 1 M HCl. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 80 mg (84%) of the desired product.

(*S*)-3-Benzylamino-3-phenyl-propan-1-ol 9: The above crude product was dissolved in 3 mL of dry THF, and the resulting solution was added to a stirred suspension of 60 mg of lithium aluminum hydride in 1.5 mL THF. The mixture was stirred under N_2 overnight. The reaction was quenched with Na_2SO_4 decahydrate, and the slurry was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford the desired product **9**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82 (dq, *J* = 14.5, 3.6 Hz, 1H), 1.91-2.06 (m, 1H), 3.62 (AB, *J* = 12.7 Hz, 2H), 3.76-3.88 (m, 3H), 7.24-7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.9, 51.4, 63.1, 63.5, 126.8, 127.5, 127.7, 128.5, 128.8, 129.0, 139.6, 143.1; $[\alpha]^{25}_D$ = -33.6 (*c* 0.2, MeOH) {lit. $[\alpha]^{23}_D$ = -28.1 (*c* 0.06, MeOH) (75%ee); {lit.[11] $[\alpha]^{23}_D$ = -24.7 (*c* 0.93, MeOH) (66%ee) (*S*) enantiomer}. The sign of the rotation for the final compound indicates that it has the *S* configuration.

References

1. Kashima, C.; Harada, H.; Kita, I.; Fukuchi, I.; Hosomi, A. *Synthesis* **1994**, 61.
2. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340-5345.
3. Dieter, R. K.; Velu, S. E. *J. Org. Chem.* **1997**, *62*, 3798.
4. Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W. et. al. *J. Med. Chem.* **1996**, *39*, 1898

5. Hall, J.; Lehn, J-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.
6. Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701.
7. Gribble, G. W.; Leiby, R. W.; Sheehan, M. N. *Synthesis* **1977**, 856.
8. Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041.
9. Baldwin, J. E.; Cha, J. K.; Kruse, L. I. *Tetrahedron* **1985**, *41*, 5241.
10. Molander, G. A. *Organic Reactions;* Paquette, L. A. Ed.; John Wiley & Sons: New York, **1994**; Vol. 46, p 211
11. Shimizu, M.; Maruyama, S.; Suzuki, Y.; Fujisawa, T. *Heterocycles* **1997,** *45,* 1883.