Pd-Catalyzed Carboamination of Oxazolidin-2-Ones. A Stereoselective Route to *trans*-2,5-Disubstituted Pyrrolidines.

Georgia S. Lemen and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109-1055

Supporting Information

Experimental procedures, characterization data for new compounds, and complete descriptions of stereochemical assignments.

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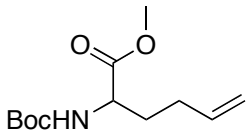
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $[(allyl)PdCl]_2$, and all phosphine ligands were purchased from Strem Chemical Co. or Aldrich Chemical Co. and used without further purification. All aryl bromides and common reagents were obtained from commercial sources and were used as obtained, with the exception of 4-bromo-1,2-(methylenedioxybenzene), which was filtered through a plug of silica gel plug prior to use. Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate[1] (**S1**), (±)-

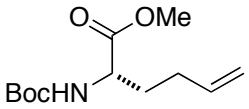
2-[(*tert*-butoxycarbonyl)amino]hex-5-enoic acid[2] and (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[3] (**14**) were synthesized according to literature procedures. Toluene, diethyl ether, methylene chloride, and THF were purified using a GlassContour solvent purification system. Benzene was freshly distilled from calcium hydride. Ethanol was distilled from magnesium turnings activated with iodine and stored over activated molecular sieves. $[(allyl)PdCl]_2$ and NaO^tBu were stored in a nitrogen-filled glovebox, removed just prior to use, and were weighed outside of the glovebox. Ratios of diastereomers were determined by ^1H NMR analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^1H NMR analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Table 2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 2.

Preparation and Characterization of Substrates

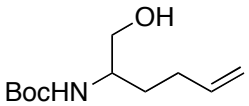


(±)-Methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (13).[4] An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with zinc dust (11.9 g, 182 mmol). The flask was purged with nitrogen, then DMF (20 mL) and 1,2-dibromoethane (0.79 mL, 9.1 mmol) were added. The resulting mixture was heated to 90 ºC for 20 min, then cooled to rt and stirred for 5 min. Chlorotrimethylsilane (0.24 mL, 1.9 mmol) was added, and the reaction mixture was stirred at rt for 30 min. A solution of methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (**S1**) (10.0 g, 30.4 mmol) in DMF (20 mL) was added, and the mixture was stirred at rt until the iodide had been completely consumed as determine by TLC analysis (ca 25 min). The reaction mixture was cooled to –60 ºC and a solution of anhydrous lithium chloride (2.58 g, 60.8 mmol) and copper (I) cyanide (2.72 g, 30.4 mmol) in DMF (40 mL) was added via cannula over 15 min. The resulting mixture was warmed to 0 ºC and stirred for 20 min. The mixture was then cooled to –60 °C and allyl chloride (5.0 mL, 60.8 mmol) was added in one portion. The resulting mixture was warmed to –10 ºC and stirred for 3 h. The reaction was then quenched slowly with saturated aqueous ammonium chloride (80 mL).

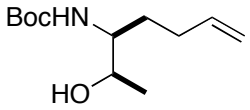
The mixture was transferred to a separatory funnel an extracted with 1:1 ethyl acetate/hexanes (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a clear oil (5.76 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.74 (m, 1 H), 5.08–4.98 (m, 3 H), 4.36–4.28 (m, 1 H), 3.74 (s, 3 H), 2.18–2.04 (m, 2 H), 1.95–1.86 (m, 1 H), 1.76–1.66 (m, 1 H), 1.45 (s, 9 H).



(–)-(*S*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (13). (–)-(*S*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (5.383 g, 16.35 mmol) was converted to the title compound using a procedure analogous to that described above. This procedure afforded the title compound as a clear oil (2.71 g, 68%), $[\alpha]^{20}_D$ –20.7 (*c* 0.97, MeOH). [lit.[5] $[\alpha]^{23}_D$ –22.43 (*c* 1.0, MeOH)]. ^{1}H NMR data were identical to those reported above for (±)-**13**.



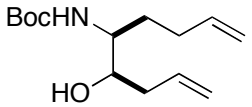
(±)-*tert*-Butyl 1-hydroxyhex-5-en-2-ylcarbamate (15a).[6] An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (**13**) (4.95g, 20.3 mmol). The flask was purged with nitrogen, then THF (200 mL) was added and the resulting solution was cooled to 0 °C. Lithium borohydride (665 mg, 30.5 mmol) was added in one portion, the reaction mixture was stirred at 0 ºC for 5 min, then warmed to rt and stirred for 11.5 h. Saturated aqueous ammonium chloride (150 mL) was added slowly and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a clear oil (3.70 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.77 (m, 1 H), 5.07–4.97 (m, 2 H), 4.62 (s, br, 1 H), 3.72–3.61 (m, 2 H), 3.59–3.53 (m, 1 H), 2.26–2.07 (m, 3 H), 1.66–1.48 (m, 2 H), 1.45 (s, 9 H).



(±)-(2*R,3*S**)-*tert*-Butyl 2-hydroxyhept-6-en-3-ylcarbamate (15b).** An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[3] (**14**) (2.0 g, 7.34 mmol). The flask was purged with nitrogen, THF (49 mL) was added, and the resulting solution was cooled to 0 °C. Methylmagnesium bromide (6 mL, 18 mmol, 3 M in Et_2O) was added via syringe over 2 min, and the reaction mixture was stirred at 0 ºC for 4.5 h. The reaction mixture was carefully poured into saturated aqueous ammonium chloride (50 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (**S2**) as a clear oil (1.37 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.73 (m, 1 H), 5.24–5.14 (m, 1 H), 5.09–4.98 (m, 2 H), 4.38–4.30 (m, 1 H), 2.21 (s, 3 H), 2.20–1.90 (m, 3 H), 1.66–1.55 (m, 1 H), 1.45 (s, 9 H).

A portion of the (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (**S2**) was converted to the title compound using the following procedure. An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with anhydrous ethanol (20 mL). The flask was cooled to –78 °C and stirred for 1 h, then solid lithium tri-*tert*-butoxyaluminum hydride (1.526 g, 6.0 mmol) was added, the flask was purged with nitrogen, and the resulting ethanolic solution of $LiAl(O\textit{t}Bu)_3H$ was maintained at –78 °C. A separate oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (682 mg, 3.0 mmol, 1 equiv) and anhydrous ethanol (10 mL) then cooled to –78 ºC and stirred for 1 h. The solution of (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate was added to the solution of $LiAl(O\textit{t}Bu)_3H$ dropwise via cannula over 30 min. The resulting mixture was stirred at –78 ºC for 1.5 h, then 10% aqueous citric acid (20 mL) was added, the mixture was warmed to rt, and stirred for 1 h. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Benzene (x mL) was added, and the mixture was again concentrated *in vacuo* to facilitate removal of

ethanol. The resulting crude product was purified by flash chromatography on silica gel to afford 649 mg (93%) of the title compound as white solid, mp 77–79 ºC. This material was obtained with >20:1 dr as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.76 (m, 1 H), 5.07–4.97 (m, 2 H), 4.60–4.50 (m, 1 H), 3.90–3.81 (m, 1 H), 3.66–3.58 (m, 1 H), 2.56 (d, J = 4.5 Hz, 1 H), 2.24–2.14 (m, 1 H), 2.14–2.04 (m, 1 H), 1.65–1.56 (m, 1 H), 1.49–1.39 (m, 10 H), 1.14 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 137.8, 115.1, 79.6, 70.4, 55.6, 30.4, 29.0, 28.3, 18.3; IR (film) 3352, 2978, 1689 cm^{-1}. MS (ESI) 252.1579 (252.1576 calcd for $C_{12}H_{23}NO_3$, M + Na^+).



(±)-(4*R,5*S**)-*tert*-Butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (15c).** An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate **14** (1.0 g, 3.67 mmol). The flask was purged with nitrogen, THF (26 mL) was added, and the resulting solution was cooled to –78 ºC. Allylmagnesium bromide (11 mL, 11 mmol, 1 M in Et_2O) was added dropwise over 40 min, and the resulting mixture was stirred at –78 ºC for 4 h. The reaction mixture was carefully poured into saturated aqueous ammonium chloride (25 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford (±)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (**S3**) as a clear oil (792 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97–5.86 (m, 1 H), 5.85–5.73 (m, 1 H), 5.24–5.10 (m, 3 H), 5.08–4.99 (m, 2 H), 4.42–4.34 (m, 1 H), 3.35–3.21 (m, 2 H), 2.18–1.90 (m, 3 H), 1.65–1.54 (m, 1 H), 1.44 (s, 9 H).

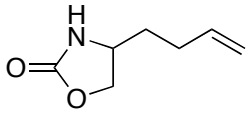
A portion of (±)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (**S3**) (792 mg, 3.1 mmol) was converted to the title compound using a procedure analogous to that described above for the conversion of (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate to (±)-(2*R**,3*S**)-*tert*-butyl 2-hydroxyhept-6-en-3-ylcarbamate. This procedure afforded 739 mg (92%) of the title compound as a white solid, mp 99–101 ºC. This product was obtained with >20:1 dr as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.76 (m, 2 H), 5.18–5.11 (m, 2 H), 5.08–5.01 (m, 1

H), 5.01–4.96 (m, 1 H), 5.68 (d, J = 8.4 Hz, 1 H), 3.73–3.55 (m, 2 H), 2.46 (d, J = 4.0 Hz, 1 H), 2.34-2.00 (m, 4 H), 1.74–1.62 (m, 1 H), 1.54–1.38 (m, 10 H); ^{13}C NMR 156.2, 137.9, 134.8, 118.1, 115.1, 79.5, 73.5, 54.4, 38.2, 30.3, 28.6, 28.4; IR (film) 3352, 3079, 1684 cm^{-1}; MS 278.1740 (278.1732 calcd for $C_{14}H_{25}NO_3$, M + Na^+).

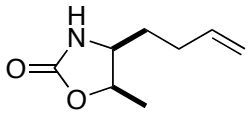
(–)-(4*R*,5*S*)-*tert*-Butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (15c). (+)-(*S*)-*tert*-Butyl (1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[3] (**14**) (2.00g, 7.34 mmol) was converted to (+)-(S)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (1.478 g, 79%, clear oil, 90% purity) using a procedure analogous to that employed above for the synthesis of the racemic compound. $[\alpha]^{20}_D$ +54.5 (*c* 0.99, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for the racemic compound.

(+)-(*S*)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (1.458g mg, 5.76 mmol) was converted to the title compound using a procedure analogous to that employed above for the synthesis of the racemic compound. This procedure afforded 1.216 g (83%) of the title compound as a white solid, mp 115–117 ºC. This product was obtained with >20:1 dr as judged by ^{1}H NMR analysis. $[\alpha]^{20}_D$ –21.7 (*c* 1.07, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**15c**.

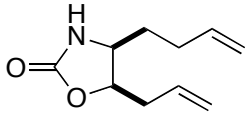
General Procedure 1: Synthesis of 4-(but-3-en-1-yl)oxazolidin-2-one derivatives. An oven-dried round bottom flask was cooled under a stream of nitrogen and charged with the appropriate Boc-protected amino alcohol (1 equiv), THF (10 mL/mmol), and sodium hydride (60% dispersion in mineral oil, 1.2 equiv). The flask was equipped with a reflux condenser and purged with nitrogen. The reaction mixture was then heated to reflux with stirring until the starting material had been completely consumed as judged by TLC analysis. The mixture was cooled to rt, quenched with saturated aqueous ammonium chloride, and transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3x), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.



(±)-4-(But-3-en-1-yl)oxazolidin-2-one (9).[7] The reaction of (±)-*tert*-butyl 1-hydroxyhex-5-en-2-ylcarbamate (**13a**) (1.50 g, 6.97 mmol) was conducted according to General Procedure 1 for 2.75 h to afford 957 mg (97%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1 H), 5.38 (s, br, 1 H), 5.11–5.02 (m, 2 H), 4.50 (t, J = 8.5 Hz, 1 H), 4.04 (dd, J = 6.5, 8.5 Hz, 1 H), 3.93–3.86 (m, 1 H), 2.16–2.10 (m, 2 H), 1.77–1.65 (m, 2 H).

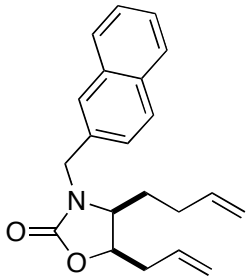


(±)-(4*S,5*R**)-4-(But-3-en-1-yl)-5-methyloxazolidin-2-one (16a).** The reaction of (±)-(2*R**,3*S**)-*tert*-butyl 2-hydroxyhept-6-en-3-ylcarbamate (**15b**) (649 mg, 2.83 mmol) was conducted according to General Procedure 1 for 1 h to afford 424 mg (97%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.75 (m, 1 H), 5.40 (s, br, 1 H), 5.12–5.03 (m, 2 H), 4.81–4.75 (m, 1 H), 3.82–3.76 (m, 1 H), 2.21–2.04 (m, 2 H), 1.64–1.59 (m, 2 H), 1.36 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 136.9, 115.9, 76.1, 55.1, 30.2, 29.0, 14.8; IR (film) 3267, 2942, 1748 cm^{-1}. MS (ESI) 178.0847 (178.0844 calcd for $C_8H_{13}NO_2$, M + Na^+).



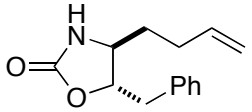
(±)-(4*S,5*R**)-5-Allyl-4-(but-3-en-1-yl)oxazolidin-2-one (16b)**. The reaction of (±)-(4*R**,5*S**)-*tert*-butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (**15c**) (670 mg, 2.62 mmol) was conducted according to General Procedure 1 for 2 h to afford 440 mg (93%) of the title compound as a white solid, mp 40–42 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.74 (m, 2 H), 5.34 (s, br, 1 H), 5.21–5.14 (m, 2 H), 5.12–5.04 (m, 2 H), 4.66 (ddd, J = 5.5, 8.0, 8.5 Hz, 1 H), 3.80 (dt, J = 5.0, 8.0 Hz, 1 H), 2.59–2.51 (m, 1 H), 2.41–2.34 (m, 1 H), 2.22–2.04 (m, 2 H), 1.67–1.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.8, 132.7, 118.3, 116.1, 79.3, 55.0, 33.6, 30.1, 28.9; IR (film) 3265, 2932, 1748 cm^{-1}. MS (ESI) 204.1002 (204.1000 calcd for $C_{10}H_{15}NO_2$, M + Na^+).

(+)-(4*S*,5*R*)-5-Allyl-4-(but-3-en-1-yl)oxazolidin-2-one (16b). The reaction of (–)-(4*R*,5*S*)-*tert*-butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (1.017 mg, 3.98 mmol) was conducted according to General Procedure 1 for 7 h to afford 629 mg (87%) of the title compound as a white solid, mp 34–35 ºC. $[\alpha]^{23}_{D}$ +5.48 (*c* 10.2, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**16b**. The enantiomeric purity of this compound was determined to be 99% ee by conversion to **S4** and analysis by chiral HPLC as described below.



(+)-(4*S*,5*R*)-5-Allyl-4-(but-3-en-1-yl)-3-(naphthalen-2-ylmethyl)oxazolidin-2-one (S4). An oven dried test tube equipped with a stirbar was cooled under a stream of nitrogen and charged with (+)-**16b** (50 mg, 0.28 mmol) and sodium hydride (12 mg, 0.30 mmol). The tube was purged with nitrogen and anhydrous DMF (0.40 mL) was added. The resulting mixture was stirred at rt for 25 min, then a solution of 2-(bromomethyl)naphthalene (62 mg, 0.28 mmol) in DMF (0.15 mL) was added in one portion. The reaction mixture was stirred at rt for 24.5 h, then was quenched with saturated aqueous ammonium chloride (2 mL). The resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate (5 x 2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a clear oil (49 mg, 55 %). The enantiopurity was determined to be 99% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O-1 5100, 0.46 cm x 25 cm, 13% isopropanol/ hexanes, 2.0 mL/min, RT= 23.8 and 33.3 min]. $[\alpha]^{23}_{D}$ +36.8 (*c* 2.27, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 3 H), 7.72–7.70 (m, 1 H), 7.53–7.46 (m, 2 H), 7.43–7.39 (m, 1 H), 5.90–5.79 (m, 1 H), 5.75–5.63 (m, 1 H), 5.20–5.12 (m, 2 H), 5.03–4.93 (m, 2 H), 4.49 (ddd, *J* = 4.8, 7.6, 8.8 Hz, 1 H), 4.22 (d, *J* = 15.6 Hz, 1 H), 3.60 (dt, *J* = 4.4, 7.2 Hz, 1 H), 2.59–2.49 (m, 1 H), 2.40–2.31 (m, 1 H), 2.08–2.00 (m, 2 H), 1.80–1.65 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 136.6, 133.6, 133.3, 132.9, 132.7, 128.8, 127.7, 126.9, 126.4, 126.2, 125.7, 118.5, 115.7,

77.1, 56.5, 46.5, 33.6, 29.4, 26.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3056, 2936, 1749 cm^{-1}. MS (ESI) 344.1614 (244.1626 calcd for $C_{21}H_{23}NO_2$, M + Na^+).

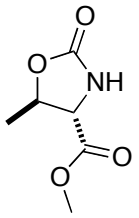


(±)-(4*S,5*S**)-5-Benzyl-4-(but-3-en-1-yl)oxazolidin-2-one (18b).** An oven-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate **14** (1.91 g, 7.00 mmol). The flask was purged with nitrogen, THF (19 mL) was added, and the resulting solution was cooled to 0 ºC. Benzylmagnesium bromide (14 mL, 21 mmol, 1.5 M in THF) was added dropwise over 3 min, and the resulting mixture was slowly warmed from 0 ºC to rt over 4 h. The reaction was then quenched slowly with 1 M HCl (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.89 g (89%) of (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate (**S5**) as a white solid, mp 61–65 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 3 H), 7.22–7.18 (m, 2 H), 5.80–5.67 (m, 1 H), 5.20–5.10 (m, 1 H), 5.04–4.96 (m, 2 H), 4.48–4.40 (m, 1 H), 3.86–3.74 (m, 2 H), 2.13–1.85 (m, 3 H), 1.65–1.53 (m, 1 H), 1.44 (s, 9 H).

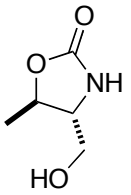
A flame-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with anhydrous ethanol (40 mL). The flask was cooled to –78 °C and stirred for 1 h, then solid lithium tri-*tert*-butoxyaluminum hydride (3.06 g, 12.0 mmol) was added, the flask was purged with nitrogen, and the resulting ethanolic solution of $LiAl(OtBu)_3H$ was maintained at –78 °C. A separate flame-dried round bottom flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate (**S5**) (1.83 g, 6.0 mmol, 1 equiv) and anhydrous ethanol (20 mL). The resulting mixture was cooled to 0 ºC and stirred for 30 min. The solution of (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate was then added to the solution of $LiAl(OtBu)_3H$ dropwise via cannula over 15 min. The resulting mixture was stirred at –78 ºC for 3 h, then 10% aqueous citric acid (20 mL) was added, the mixture was warmed to rt, and stirred for 1 h. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL).

The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. To remove ethanol, the product was dissolved in benzene (40 mL), and the resulting solution was concentrated *in vacuo*. This was repeated three additional times to afford 1.58 g (86%) of *tert*-butyl [(2*S**,3*R**)-2-hydroxy-1-phenylhept-6-en-3-yl]carbamate (**15d**) as a white solid, mp 120–124 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2 H), 7.26–7.21 (m, 3 H), 5.88–5.79 (m, 1 H), 5.08–5.03 (m, 1 H), 5.02–4.98 (m, 1 H), 4.68 (d, *J* = 9.0 Hz, 1 H), 3.91–3.85 (m, 1 H), 3.71–3.63 (m, 1 H), 2.85–2.80 (m, 1 H), 2.67 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.27–2.17 (m, 2 H), 2.15–2.06 (m, 1 H), 1.79–1.70 (m, 1 H), 1.59–1.50 (m, 1 H), 1.45 (s, 9 H).

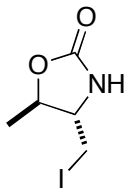
A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with *tert*-butyl [(2*R**,3*S**)-2-hydroxy-1-phenylhept-6-en-3-yl]carbamate (**15d)** (1.58 g, 1.6 mmol, 1 equiv). The flask was purged with nitrogen, 1,2-dichloroethane (26 mL, 5 mL/mmol) was added, and the resulting mixture was cooled to 0 ºC. Methane sulfonylchloride (0.60 mL, 888 mg, 7.8 mmol) and N,N-diisopropylethylamine (2.7 mL, 2.0 g, 15.5 mmol) were added, and the mixture was warmed to rt and stirred for 1 h. The mixture was heated to 75 ºC for 30 h, then cooled to rt. Saturated aqueous ammonium chloride (20 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.701 g (59%) of the title compound as a brown solid, mp 48–51 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5 H), 6.13 (s, br, 1 H), 5.73–5.61 (m, 1 H), 5.01–4.94 (m, 2 H), 4.44–4.38 (m, 1 H), 3.54 (td, *J* = 5.2, 7.6 Hz, 1 H), 3.10 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.91 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.03–1.96 (m, 2 H), 1.60–1.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.7, 135.2, 129.5, 128.7, 127.1, 116.0, 82.5, 56.4, 40.5, 34.2, 29.5; IR (film) 3260, 2925, 1750 cm^{-1}. MS (ESI) 254.1160 (254.1157 calcd for $C_{14}H_{17}NO_2$, M + Na^+).



(+)-(4*S*,5*R*)-Methyl 5-methyl-2-oxooxazolidine-4-carboxylate (S6).[8] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with triphosgene (3.50 g, 11.8 mmol) and L-threonine methyl ester hydrochloride (2.00 g, 11.8 mmol). The flask was equipped with a reflux condenser and purged with nitrogen. THF was added and the resulting mixture was heated to reflux for 1 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.85 g (98%) of the title compound as a clear oil. $[\alpha]^{23}_{D}$ +27.5 (*c* 1.18, CH_2Cl_2) [lit.[8] $[\alpha]^{20}_{D}$ +30.5 (*c* 0.12, CH_2Cl_2)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, br, 1 H), 4.80–4.72 (m, 1 H), 3.99 (d, *J* = 5.2 Hz, 1 H), 3.82 (s, 3 H), 1.57 (d, *J* = 6.4 Hz, 3 H).



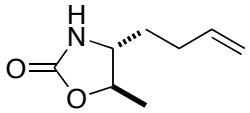
(+)-(4*R*,5*R*)-4-(Hydroxymethyl)-5-methyloxazolidin-2-one (S7).[9] An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged dry flask was charged with **(+)-**(4*S*,5*R*)-methyl 5-methyl-2-oxooxazolidine-4-carboxylate (**S6**) (1.85g, 11.6 mmol). The flask was purged with nitrogen, anhydrous ethanol (23 mL) was added, and the resulting mixture was cooled to 0 °C. Sodium borohydride (461 mg, 12.2 mmol) was added, the mixture was stirred at 0 ºC for 5 min, then warmed to rt and stirred for 1.5 h. Saturated aqueous ammonium chloride (2 mL) was added and the resulting mixture was stirred at rt for 45 min. The reaction mixture was then filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the 1.32 g (87%) of title compound as a white solid, mp 81–84 ºC, $[\alpha]^{23}_{D}$ +65.4 (*c* 1.14, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, br, 1 H), 4.52–4.45 (m, 1 H), 3.76–3.70 (m, 1 H), 3.66–3.59 (m, 1 H), 3.58–3.53 (m, 1 H), 2.00 (s, br, 1 H), 1.47 (d, *J* = 6.5 Hz, 3 H).



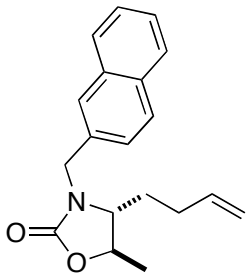
(+)-(4*S*,5*R*)-4-(Iodomethyl)-5-methyloxazolidin-2-one (17). An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (+)-(4*R*,5*R*)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (**S7**) (1.29 g, 9.8 mmol). The flask was purged with nitrogen, pyridine (3.6 mL) was added, and the mixture was cooled to 0 ºC. Tosyl chloride (2.81 g, 14.7 mmol) was added, the flask was purged with nitrogen, and the reaction mixture was warmed to rt and stirred for 18 h. The mixture was diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and washed with 1 M hydrochloric acid (3 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 2.23 g (80%) of (4*R*,5*R*)-5-methyl-2-oxooxazolidin-4-ylmethyl 4-methylbenzenesulfonate (**S8**) as a white solid, mp 105–106 ºC. $[\alpha]^{23}_D$ +31.9 (*c* 1.65, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 H), 7.41–7.37 (m, 2 H), 5.17 (s, br, 1 H), 4.39–4.33 (m, 1 H), 4.04 (dd, *J* = 5.0, 10.5 Hz, 1 H), 3.97 (dd, *J* = 6.5, 10.5 Hz, 1 H), 3.73–3.68 (m, 1 H), 2.48 (s, 3 H), 1.45 (d, *J* = 6.5 Hz, 3 H).

A portion of the (+)-(4*R*,5*R*)-(5-methyl-2-oxooxazolidin-4-yl)methyl 4-methylbenzenesulfonate (**S8**) was converted to the title compound using the following procedure. An oven-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (4*R*,5*R*)-5-methyl-2-oxooxazolidin-4-ylmethyl 4-methylbenzenesulfonate (2.22 g, 7.8 mmol), sodium iodide (5.47 g, 36.5 mmol), and anhydrous acetone (32 mL). The flask was equipped with reflux condenser, purged with nitrogen, and the reaction mixture was heated to reflux for 6 h. The mixture was then cooled to rt, filtered, and concentrated *in vacuo*. The crude product was dissolved in ethyl acetate (15 mL) and washed with saturated sodium sulfite (2 x 15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.51 g (59%) of the title compound as a pale yellow solid, mp 45–47 ºC, $[\alpha]^{23}_D$ +3.70 (*c* 1.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.55 (s, br, 1 H), 4.41–4.36 (m, 1 H), 3.65–3.61 (m, 1 H), 3.23–3.18 (m, 2 H), 1.49 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 78.9, 60.0, 20.8, 7.3; IR (film) 3288, 2926, 1744 cm^{-1}. MS (ESI) 263.9498 (263.9494 calcd for $C_5H_8INO_2$, M +

Na^+).



(+)-(4*R*,5*R*)-4-(But-3-en-1-yl)-5-methyloxazolidin-2-one (18a). The conversion of (+)-(4*S*,5*R*)-4-(iodomethyl)-5-methyloxazolidin-2-one (**17**) (1.45 g, 6.02 mmol) to the title compound was accomplished using a procedure identical to that described above for the preparation of (±)-methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (**13**). This procedure afforded 748 mg (80%) of the title compound as a clear oil, $[\alpha]^{23}_D$ +70.5 (*c* 1.12, CH_2Cl_2). The enantiomeric purity of this compound was determined to be 99% ee by conversion to **S9** and analysis by chiral HPLC as described below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, br, 1 H), 5.84–5.72 (m, 1 H), 5.11–5.00 (m, 2 H), 4.29 (app quint, *J* = 6.0 Hz, 1 H), 3.45–3.39 (m, 1 H), 2.22–2.06 (m, 2 H), 1.65 (q, *J* = 7.2 Hz, 2 H), 1.42 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 136.8, 115.9, 78.9, 59.2, 33.9, 29.7, 20.1; IR (film) 3275, 2932, 1751 cm^{-1}. MS (EI): 155.0946 (155.0946 calcd for $C_8H_{13}NO_2$, M^+).



(+)-(4*R*,5*R*)-4-(But-3-en-1-yl)-5-methyl-3-(naphthalen-2-ylmethyl)oxazolidin-2-one (S9)

The conversion of (+)-**16a** (43 mg, 0.28 mmol) to the title compound was accomplished using a procedure analogous to that described above for the preparation of **S4**. This procedure afforded the title compound as a clear oil (57 mg, 70 %). The enantiopurity was determined to be 99% ee by chiral HPLC analysis [Chiracel OJ-H, 0.46 cm x 25 cm, 15% isopropanol/ hexanes, 2.0 mL/min, RT= 8.5 and 17.0 min]. $[\alpha]^{23}_D$ +30.0 (*c* 1.07, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.80 (m, 3 H), 7.72–7.69 (m, 1 H), 7.53–7.46 (m, 2 H), 7.43–7.39 (m, 1 H), 5.75–5.63 (m, 1 H), 5.01–4.93 (m, 3 H), 4.34–4.26 (m, 1 H), 4.21 (d, *J* = 15.2 Hz, 1 H), 3.13 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H), 2.10–1.89 (m, 2 H), 1.82–1.72 (m, 1 H), 1.66–1.55 (m, 1 H), 1.30 (d, *J* = 6.4 Hz, 3

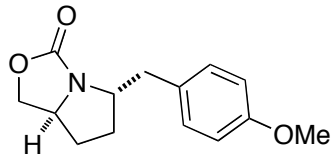
H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 136.6, 133.5, 133.2, 132.9, 128.8, 127.7, 126.9, 126.4, 126.2, 125.8, 115.8, 75.1, 60.5, 46.1, 30.4, 28.0, 20.9 (one carbon signal is absent due to incidental equivalence); IR (film) 3053, 2926, 1744 cm^{-1}. MS (ESI) 318.1458 (318.1470 calcd for $C_{19}H_{21}NO_2$, M + Na^+).

Preparation and Characterization of Products

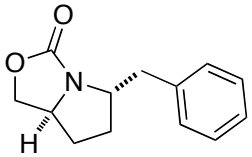
General Procedure 2: Pd-catalyzed Synthesis of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivatives Using $Pd(OAc)_2$ as the Precatalyst. An oven dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol %) and RuPhos (4 mol %). The tube was evacuated and refilled with nitrogen three times, then benzene (1 mL/mmol, substrate) was added and the resulting yellow solution was stirred at rt for 20 min to provide a red solution. Solid NaO^{t}Bu (1.2 equiv) was added, the tube was purged with nitrogen, then a solution of the substrate (1 equiv) and the aryl bromide (1.2 equiv) in benzene (2 mL/mmol substrate) was added. The sides of the Schlenk tube were rinsed with additional benzene (1 mL/mmol substrate), then the reaction mixture was immersed in an 80 ºC oil bath and stirred until the starting material was consumed as determined by ^{1}H NMR analysis of a small aliquot removed from the mixture. The reaction mixture was cooled to rt and saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

General Procedure 3: Pd-catalyzed Synthesis of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivatives Using $[(allyl)Pd(Cl)]_2$ as the Precatalyst. An oven dried Schlenk tube was cooled under a stream of nitrogen and charged with $[(allyl)Pd(Cl)]_2$ (1 mol % complex, 2 mol % Pd), RuPhos (4 mol %), and NaO^{t}Bu (1.2 equiv). The tube was evacuated and refilled with nitrogen three times, then a solution of the substrate (1 equiv) and the aryl halide (1.2 equiv) in benzene (4 mL/mmol substrate) was added. The reaction mixture was immersed in an 80 ºC oil bath and stirred until the starting material was consumed as determined by ^{1}H NMR analysis of a small aliquot removed from the mixture. The reaction mixture was cooled to rt and saturated aqueous

ammonium chloride (2 mL) and ethyl acetate (5 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

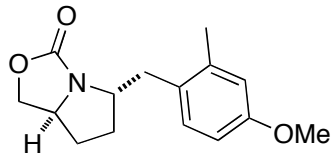


(±)-(5*S,7a*S**)-5-(4-Methoxybenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (19).** The reaction of **9** (71 mg, 0.50 mmol) with 4-bromoanisole (75 µL, 0.60 mmol) was conducted at 80 ºC for 20.5 h according to general procedure 3. This procedure afforded 102 mg (82%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.14 (m, 2 H), 6.86–6.82 (m, 2 H), 4.50 (dd, *J* = 7.5, 8.5 Hz, 1 H), 4.16–4.09 (m, 2 H), 3.79 (s, 3 H), 3.77–3.70 (m, 1 H), 2.92 (dd, *J* = 5.5, 14.0, 1 H), 2.76 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.11 (dtd, *J* = 1.5, 8.0, 13.0 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.68 (tdd, *J* = 7.0, 11.5, 13.5 Hz, 1 H), 1.52–1.40 (m, 1 H); ^{13}C NMR δ 161.4, 158.2, 130.5, 129.6, 113.8, 67.6, 59.5, 59.0, 55.2, 40.6, 31.6, 31.4; IR (film) 2932, 1748 cm^{-1}. MS (ESI) 270.1108 (270.1106 calcd for $C_{14}H_{17}NO_3$, M + Na^+).

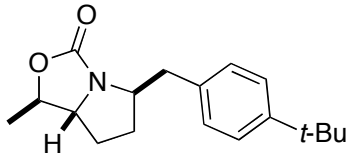


(±)-(5*S,7a*S**)-5-Benzyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (21).** The reaction of **9** (71 mg, 0.50 mmol) with bromobenzene (63 µL, 0.60 mmol) was conducted at 80 ºC for 21 h according to general procedure 3. This procedure afforded 87 mg (80%) of the title compound as a pale yellow amorphous solid, mp 39–41 °C. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 3 H), 4.46 (dd, *J* = 8.0, 8.5 Hz, 1 H), 4.20–4.10 (m, 2 H), 3.79–3.72 (m, 1 H), 3.00 (dd, *J* = 5.5, 13.5 Hz, 1 H), 2.80 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.12 (dtd, *J* = 1.2, 8.0, 13.0 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.69 (tdd, *J* = 7.5, 11.5, 13.0 Hz, 1 H), 1.52–1.40 (m, 1 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 161.4, 137.5, 129.5, 128.3, 126.4, 67.5, 59.4, 58.9, 41.5, 31.7, 31.4; IR (film) 2967, 1749 cm^{-1}. MS (ESI) 240.1008 (240.1000 calcd for $C_{13}H_{15}NO_2$, M + Na^+).



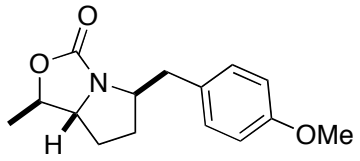
(±)-(5*S,7a*S**)-5-(4-Methoxy-2-methylbenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (22)**. The reaction of **9** (71 mg, 0.50 mmol) with 2-bromo-5-methoxytoluene (85 μL, 0.60 mmol) was conducted at 80 ºC for 4 h according to general procedure 2. This procedure afforded 83 mg (64%) of the title compound as a pale yellow solid, mp 65–69 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 3.0 Hz, 1 H), 6.68 (dd, *J* = 2.5, 8.5 Hz, 1 H), 4.47 (dd, *J* = 8.0, 9.0 Hz, 1 H), 4.15–4.08 (m, 2 H), 3.89–3.82 (m, 1 H), 3.78 (s, 3 H), 3.00 (dd, *J* = 6.0, 14.5 Hz, 1 H), 2.69 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.35 (s, 3 H), 2.13 (dtd, *J* = 2.0, 8.0, 13.5 Hz, 1 H), 2.05–1.98 (m, 1 H), 1.69 (tdd, *J* = 7.5, 11.5, 13.0 Hz, 1 H), 1.52–1.42 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.1, 138.0, 130.9, 128.2, 115.9, 111.0, 67.6, 59.0, 58.9, 55.1, 38.2, 32.1, 31.5, 20.0; IR (film) 2926, 1750 cm^{-1}. MS (ESI) 284.1261 (284.1263 calcd for $C_{14}H_{17}NO_3$, M + Na^+).



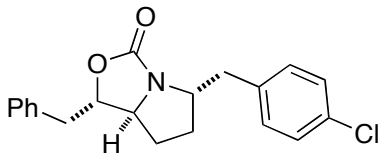
(±)-(1*R,5*R**,7a*R**)-5-[4-(*tert*-Butyl)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (23).** The reaction of **(±)-18a** (78 mg, 0.50 mmol) with 4-bromo-1-*tert*-butylbenzene (105 μL, 0.60 mmol) was conducted at 80 ºC for 27 h according to general procedure 3. This procedure afforded 88 mg (61%) of the title compound as a tan solid, mp 89–94 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) 7.33–7.29 (m, 2 H), 7.18–7.15 (m, 2 H), 4.38 (dq, *J* = 4.0, 6.5 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.36 (ddd, *J* = 2.5, 5.5, 9.5 Hz, 1 H), 3.01 (dd, *J* = 5.0, 13.5 Hz, 1 H), 2.71 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.09 (dtd, *J* = 2.0, 5.0, 13.0 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.67 (tdd, *J* = 7.5, 11.0, 13.0 Hz, 1 H), 1.49–1.38 (m, 4 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$)

160.9, 149.3, 134.5, 129.2, 125.2, 65.8, 59.1, 41.0, 34.4, 31.8, 31.4, 31.0, 21.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2963, 1750 cm^{-1}. MS (ESI) 310.1785 (310.1783 calcd for $C_{18}H_{25}NO_2$, M + Na^+).

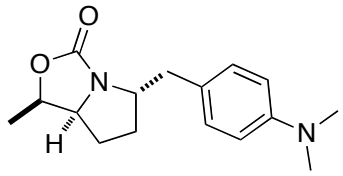
(+)-(1*R*,5*R*,7a*R*)-5-[4-(*tert*-Butyl)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (23). The reaction of **(+)-18a** (78 mg, 0.50 mmol) with 4-bromo-1-*tert*-butylbenzene (105 µL, 0.60 mmol) was conducted at 80 ºC for 27 h according to general procedure 3. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. This procedure afforded 102 mg (71%) of the title compound as a tan solid, mp 81–84 ºC. The enantiopurity was determined to be 99% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O-1 5100 0.46 cm x 25 cm, 7% isopropanol/ hexanes, 1.0 mL/min, RT= 26.8 and 31.7 min]. $[\alpha]^{23}_D$ +52.2 (*c* 1.06, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**23**.



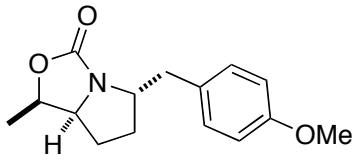
(±)-(1*R,5*R**,7a*R**)-5-(4-Methoxybenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (24).** The reaction of **(±)-18a** (78 mg, 0.50 mmol) with 4-bromoanisole (75 µL, 0.60 mmol) was conducted at 80 ºC for 6.5 h according to general procedure 3. This procedure afforded 106 mg (81%) of the title compound as a pale yellow solid, mp 87–89 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.12 (m, 2 H), 6.86–6.81 (m, 2 H), 4.36 (dq, *J* = 4.0, 6.4 Hz, 1 H), 4.08 (dt, *J* = 4.8, 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.30 (ddd, *J* = 4.0, 5.2, 9.6 Hz, 1 H), 2.92 (dd, *J* = 4.4, 13.6 Hz, 1 H), 2.73 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.08 (dtd, *J* = 2.4, 8.4, 12.8 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.65 (tdd, 7.6, 10.8, 12.8 Hz, 1 H), 1.48–1.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.2, 130.6, 129.6, 113.7, 76.6, 65.8, 59.2, 55.2, 40.4, 31.5, 31.0, 21.2; IR (film) 2930, 1749 cm^{-1}. MS (ESI) 284.1259 (284.1263 calcd for $C_{15}H_{19}NO_3$, M + Na^+).



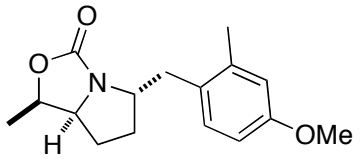
(±)-(1*S,5*S**,7a*S**)-1-Benzyl-5-(4-chlorobenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (25).** The reaction of **18b** (58 mg, 0.25 mmol) with 4-bromochlorobenzene (57 mg, 0.30 mmol) was conducted at 80 ºC for 15 h according to general procedure 3 except using 2.5 mol % $[Pd(allyl)(Cl)]_2$ and 10 mol % 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 58 mg (68%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 7 H), 7.07–7.02 (m, 2 H), 4.49 (ddd, *J* = 3.6, 6.4, 6.8 Hz, 1 H), 4.10–4.02 (m, 1 H), 3.39 (ddd, *J* = 4.0, 5.6, 10.0 Hz, 1 H), 3.11 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.94 (dd, *J* = 7.2, 14.0 Hz, 1 H), 2.85–2.73 (m, 2 H), 2.08 (dtd, *J* = 1.6, 8.0, 12.8 Hz, 1 H), 1.83–1.75 (m, 1 H), 1.62–1.51 (m, 1 H), 1.45–1.33 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 135.9, 135.3, 132.4, 131.0, 129.5, 128.7, 128.4, 127.1, 80.4, 63.2, 58.9, 40.9, 40.5, 31.5, 31.3; IR (film) 3029, 1750 cm^{-1}. MS (ESI) 364.1065 (364.1080 calcd for $C_{20}H_{20}ClNO_2$, M + Na^+).



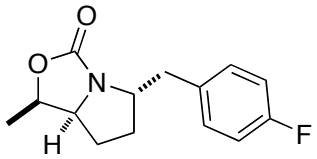
(±)-(1*R,5*S**,7a*S**)-5-[4-(Dimethylamino)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (26).** The reaction of **16a** (78 mg, 0.50 mmol) with 4-bromo-*N,N*-dimethylaniline (120 mg, 0.60 mmol) was conducted at 80 ºC for 7 h according to general procedure 2. This procedure afforded 96 mg (70%) of the title compound as an orange solid, mp 97–100 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2 H), 6.70–6.66 (m, 2 H), 4.75 (app quint, *J* = 6.8 Hz, 1 H), 4.17–4.09 (m, 1 H), 3.63 (ddd, *J* = 4.4, 7.2, 10.8 Hz, 1 H), 2.93–2.86 (m, 7 H), 2.70 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.12–2.04 (m, 1 H), 1.68–1.57 (m, 2 H), 1.55–1.41 (m, 1 H), 1.34 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 149.3, 130.2, 125.4, 112.6, 72.1, 63.0, 59.8, 40.7, 31.0, 25.8, 15.6 (one carbon signal is absent due to incidental equivalence); IR (film) 2926, 1749 cm^{-1}. MS (ESI) 297.1572 (297.1579 calcd for $C_{16}H_{22}N_2O_2$, M + Na^+).



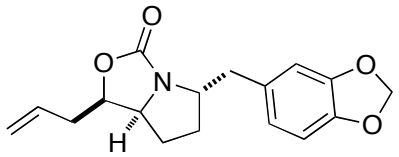
(±)-(1*R,5*S**,7a*S**)-5-(4-Methoxybenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (27).** The reaction of **16a** (78 mg, 0.50 mmol) with 4-bromoanisole (75 μL, 0.60 mmol) was conducted at 80 ºC for 22 h according to general procedure 3. This procedure afforded 111 mg (85%) of the title compound as peach colored solid, mp 91–93 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2 H), 6.86–6.80 (m, 2 H), 4.76 (app quint, *J* = 6.8 Hz, 1 H), 4.13 (dq, *J* = 5.6, 7.2 Hz, 1 H), 3.71 (s, 3 H), 3.67–3.60 (m, 1 H), 2.90 (dd, *J* = 5.2, 14.0 Hz, 1 H), 2.75 (dd, *J* = 7.6, 13.6 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.67–1.55 (m, 2 H), 1.54–1.42 (m, 1 H), 1.34 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 158.2, 130.6, 129.6, 113.7, 72.1, 63.1, 59.7, 55.2, 40.8, 31.1, 25.8, 15.6; IR (film) 2926, 1749 cm^{-1}. MS (ESI) 284.1266 (284.1263 calcd for $C_{15}H_{19}NO_3$, M + Na^+).



(±)-(1*R,5*S**,7a*S**)-5-(4-Methoxy-2-methylbenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (28).** The reaction of **16a** (78 mg, 0.50 mmol) with 2-bromo-5-methoxytoluene (85 μL, 0.60 mmol) was conducted at 80 ºC for 4 h according to general procedure 3. This procedure afforded 85 mg (61%) of the title compound as a pale yellow solid, mp 85–88 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 1 H), 6.73–6.66 (m, 2 H), 4.78 (app quint, *J* = 7.0 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.80–3.73 (m, 4 H), 2.98 (dd, *J* = 5.5, 14.0 Hz, 1 H), 2.69 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.35 (s, 3 H), 2.16–2.09 (m, 1 H), 1.71–1.57 (m, 2 H), 1.55–1.46 (m, 1 H), 1.35 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.1, 138.0, 130.8, 128.2, 115.8, 110.9, 72.2, 63.0, 59.2, 55.1, 38.4, 31.6, 25.9, 20.0, 15.7; IR (film) 2932, 1749 cm^{-1}. MS (ESI) 298.1421 (298.1419 calcd for $C_{16}H_{21}NO_3$, M + Na^+).

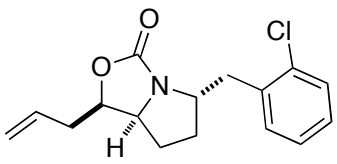


(±)-(1*R,5*S**,7a*S**)-5-(4-Fluorobenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (29).** The reaction of **16a** (78 mg, 0.50 mmol) with 4-bromofluorobenzene (70 μL, 0.60 mmol) was conducted at 80 ºC for 17 h according to general procedure 3 except using 2.5 mol % $[Pd(allyl)(Cl)]_2$ and 10 mol % 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 97 mg (78%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2 H), 7.01–6.96 (m, 2 H), 4.80–4.73 (m, 1 H), 4.17–4.10 (m, 1 H), 3.64 (ddd, *J* = 5.5, 8.0, 11.0 Hz, 1 H), 2.91 (dd, *J* = 5.5, 13.5 Hz, 1 H), 2.79 (dd, *J* = 7.5, 14.0 Hz, 1 H), 2.16–2.10 (m, 1 H), 1.69–1.62 (m, 1 H), 1.62–1.45 (m, 2 H), 1.35 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 134.5 Hz), 160.5, 133.3 (d, *J* = 3.9 Hz), 130.9 (d, *J* = 7.8), 115.1 (d, *J* = 21.6 Hz), 72.1, 63.1, 59.7, 41.0, 31.3, 25.9, 15.6. IR (film) 2980, 2939, 1748 cm^{-1}. MS (ESI) 272.1071 (272.1063 calcd for $C_{14}H_{16}FNO_2$, M + Na^+).

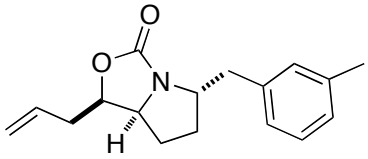


(±)-(1*R,5*S**,7a*S**)-1-Allyl-5-(benzo[*d*][1,3]dioxol-5-ylmethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (30).** The reaction of **(±)-16b** (91 mg, 0.50 mmol) with 4-bromo-1,2-(methylenedioxy)benzene (121 mg, 0.60 mmol) was conducted at 80 ºC for 8 h according to general procedure 2. This procedure afforded 96 mg (70%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75–6.72 (m, 2 H), 6.69–6.66 (m, 1 H), 5.93 (s, 2 H), 5.84–5.72 (m, 1 H), 5.20–5.12 (m, 2 H), 4.66 (q, *J* = 9.0 Hz, 1 H), 4.13–4.05 (m, 1 H), 3.69 (ddd, *J* = 4.8, 7.2, 10.8 Hz, 1 H), 2.87 (dd, *J* = 7.0, 17.5 Hz, 1 H), 2.71 (dd, *J* = 9.5, 17.5 Hz, 1 H), 2.61–2.52 (m, 1 H), 2.37–2.28 (m, 1 H), 2.16–2.07 (m, 1 H), 1.76–1.69 (m, 1 H), 1.65–1.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 147.5, 146.1, 132.2, 131.3, 122.5, 118.6, 109.9, 108.1, 100.8, 75.2, 62.5, 59.6, 41.5, 34.7, 31.1, 25.9; IR (film) 2939, 1750 cm^{-1}. MS (ESI) 324.1200 (324.1212

calcd for $C_{17}H_{19}NO_4$, M + Na^+).



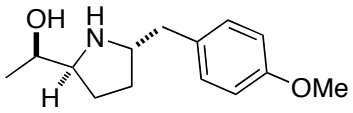
(±)-(1*R,5*S**,7a*S**)-1-Allyl-5-(2-chlorobenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (31)** The reaction of **(±)-16b** (91 mg, 0.50 mmol) with 2-bromochlorobenzene (70 μL, 0.60 mmol) was conducted at 80 ºC for 17 h according to general procedure 3 except using 2.5 mol % $[Pd(allyl)(Cl)]_2$ and 10 mol % 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 77 mg (53%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2 H), 7.23–7.14 (m, 2 H), 5.84–5.72 (m, 1 H), 5.21–5.12 (m, 2 H), 4.67 (dd, *J* = 7.6, 14.4 Hz, 1 H), 4.24 (app quint, *J* = 7.2 Hz, 1 H), 3.79 (ddd, *J* = 5.2, 7.2, 11.2 Hz, 1 H), 3.07 (dd, *J* = 7.2, 14.0 Hz, 1 H), 2.95 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.63–2.53 (m, 1 H), 2.38–2.30 (m, 1 H), 2.23–2.14 (m, 1 H), 1.81–1.74 (m, 1 H), 1.71–1.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 135.7, 134.4, 132.2, 131.3, 129.4, 127.9, 126.7, 118.6, 75.2, 62.2, 58.7, 38.9, 34.7, 31.4, 25.8; IR (film) 3073, 2938, 1752 cm^{-1}. MS (ESI) 314.0923 (314.0924 calcd for $C_{16}H_{18}ClNO_2$, M + Na^+).



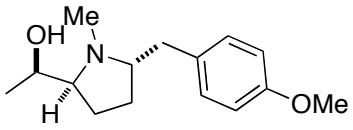
(–)-(1*R,5*S**,*7aS**)-1-Allyl-5-(3-methylbenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (32).** The reaction of **(+)-16b** (91 mg, 0.50 mmol) with 3-bromotoluene (73μL, 0.60 mmol) was conducted at 80 ºC for 7 h according to general procedure 3. This procedure afforded 108 mg (80%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr, $[\alpha]^{23}_D$ –10.6 (*c* 1.23, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 1 H), 7.07–7.01 (m, 3 H), 5.84–5.72 (m, 1 H), 5.20–5.11 (m, 2 H), 4.65 (q, *J* = 7.2 Hz, 1 H), 4.19–4.10 (m, 1 H), 3.70 (ddd, *J* = 5.2, 7.2, 11.2 Hz, 1 H), 2.98 (dd, *J* = 5.6, 13.6 Hz, 1 H), 2.72 (dd, *J* = 8.4, 13.6 Hz, 1 H), 2.61–2.51 (m, 1 H), 2.38–2.28 (m, 4

H), 2.14–2.05 (m, 1 H), 1.75–1.68 (m, 1 H), 1.66–1.44 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 137.9, 137.5, 132.2, 130.4, 128.2, 127.2, 126.5, 118.6, 75.2, 62.4, 59.4, 41.9, 34.8, 31.3, 25.9, 21.4; IR (film) 2940, 1753 cm^{-1}. MS (ESI) 294.1460 (294.1470 calcd for $C_{17}H_{21}NO_2$, M + Na^+).

Conversion of Oxazolidinone Products to *trans*-2,5-Disubstituted Pyrrolidines



(1'*R,2*S**,5*S**)-1-[5-(4-Methoxybenzyl)pyrrolidin-2-yl]ethanol (33).** An oven-dried test tube equipped with a stirbar was cooled under a stream of nitrogen and charged with **27** (50 mg, 0.19 mmol) and freshly ground sodium hydroxide (56 mg, 1.4 mmol). The tube was capped with a rubber septum and purged with nitrogen. Dry ethanol (0.55 mL) was added and the resulting mixture was heated in a 75 ºC oil bath for 17 h. The mixture was then cooled to rt and 1M HCl was added slowly until the solution had reached pH = 8. The mixture transferred to a separatory funnel and extracted with methylene chloride (4 x 2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 43 mg (96%) of the title compound as a white solid, mp 114–116 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2 H), 6.87–6.83 (m, 2 H), 3.79 (s, 3 H), 3.70–3.64 (m, 1 H), 3.41 (app quint, *J* = 7.0 Hz, 1 H), 3.25 (dt, *J* = 2.8, 6.4 Hz, 1 H), 2.68–2.60 (m, 2 H), 2.20 (s, br, 2 H), 1.93–1.85 (m, 1 H), 1.81–1.73 (m, 1 H), 1.72–1.62 (m, 1 H), 1.49–1.41 (m, 1 H), 1.11 (d, *J* = 5.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 131.5, 129.9, 113.9, 68.1, 61.8, 59.9, 55.2, 41.6, 31.8, 23.8, 18.7; IR (film) 3415, 3260, 2925 cm^{-1}. MS (ESI) 236.1651 (236.1651 calcd for $C_{14}H_{21}NO_2$, M + Na^+).



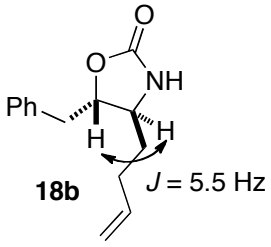
(1'*R,2*S**,5*S**)-1-[5-(4-Methoxybenzyl)-1-methylpyrrolidin-2-yl]ethanol (34).**
A flame dried flask equipped with a stirbar was cooled under a stream of nitrogen and charged with **27** (50 mg, 0.19 mmol) and ether (3.2 mL). The resulting suspension was cooled to 0 °C and $LiAlH_4$ (0.57 mL, 0.57 mmol, 1 M in Et_2O) was added. The resulting mixture was warmed

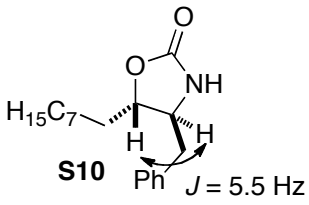
to rt and stirred for 14 h. The mixture was then diluted with ether (4 mL) and cooled to 0 °C. Water (0.04 mL) was added, followed by a solution of 10 M NaOH (0.02 mL), and additional water (0.04 mL). The flask was warmed to rt stirred for 2 h. The solution was then decanted, dried over anhydrous sodium sulfate, filtered through Celite, and concentrated *in vacuo* to afford 45 mg (95%) of the title compound as white solid, mp 80–83 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 7.07–7.02 (m, 2 H), 6.86–6.81 (m, 2 H), 3.88 (dq, *J* = 2.4, 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.39–3.31 (m, 1 H), 3.05–2.93 (m, 2 H), 2.57 (ddd, *J* = 2.4, 6.0, 8.8 Hz, 1 H), 2.47 (s, 3 H), 2.17 (dd, *J* = 11.2, 13.2 Hz, 1 H), 1.88–1.72 (m, 2 H), 1.59–1.49 (m, 2 H), 1.13 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 132.2, 130.0, 113.8, 66.8, 66.5, 64.0, 55.2, 34.7, 31.8, 27.3, 21.6, 18.3; IR (film) 3404, 2927 cm^{-1}. MS (ESI) 250.1811 (250.1807 calcd for $C_{15}H_{23}NO_2$, M + Na^+).

Assignment of Stereochemistry

Stereochemistry of 4,5-Disubstituted Oxazolidin-2-ones

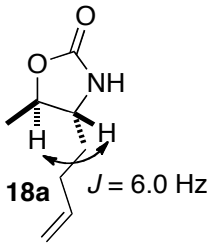
The stereochemistry of **18b** was assigned based on a vicinal coupling constant of 5.5 Hz between the protons on C4 and C5, which was determined by ^{1}H NMR decoupling experiments. This coupling constant is identical to that previously reported for oxazolidin-2-one **S10**.[10]

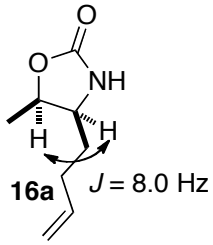




From Ref. 10

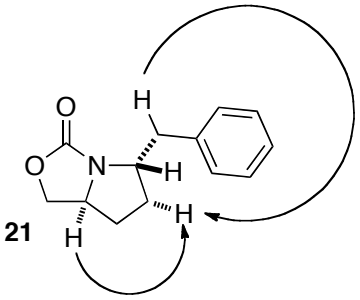
The threonine derived *trans*-4,5-disubstituted oxazolidin-2-one (**18a**) displayed a vicinal coupling constant of 6.0 Hz between the C4 and C5 hydrogen atoms. In contrast, the *cis*-4,5-disubstituted analog (**16a**) exhibited a vicinal coupling constant of 8.0 Hz (the coupling constants were determined via ^{1}H NMR decoupling experiments). The stereochemistry of the threonine substrate was assigned based on both the stereochemistry of threonine and by coupling constant comparison.[10] Substrate **16b** was assigned based on analogy to **16a**.



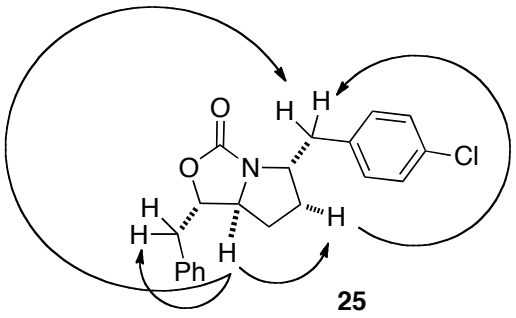


Stereochemistry of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-ones

The stereochemistry of **21** was assigned through a ^{1}H NMR 2D-NOESY experiment as depicted below. The stereochemistry of **19** and **22** were assigned based on analogy to **21**.

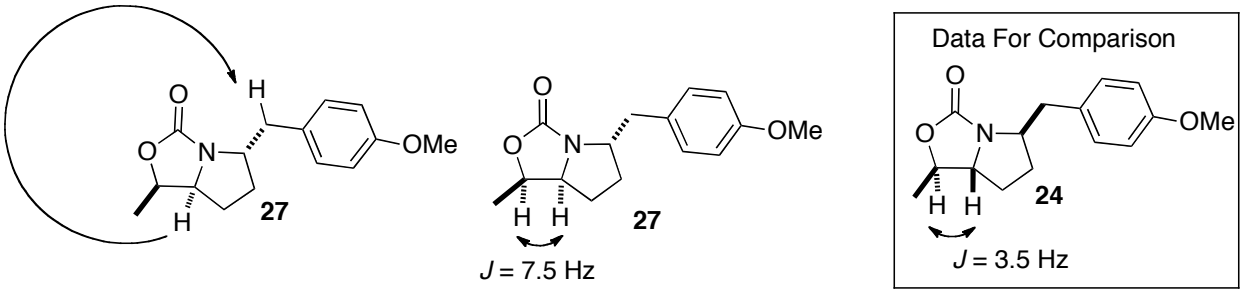


The stereochemistry of **25** was assigned through a ^{1}H NMR 2D-NOESY experiment as depicted below. The stereochemistry of **23** and **24** were assigned based on analogy to **25**.



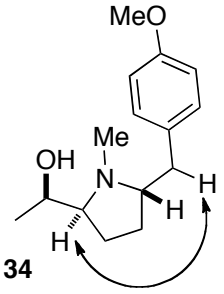
The stereochemistry of **27** was assigned through a combination of a ^{1}H NMR 2D-NOESY experiment and analysis of coupling constants (obtained by ^{1}H NMR decoupling experiments). As shown below, nOe data indicated that the substituents on C2 and C5 of the pyrrolidine ring are in a *trans*-orientation. The vicinal coupling constant between C4 and C5 of the oxazolidin-2-one ring was measured to be 7.5 Hz, which is considerably larger than the 3.5 Hz coupling of the C4 and C5 hydrogen atoms on isomer **24** (characterized as noted above). The stereochemistry of

26, **28**, **29**, **30**, **31** and **32** were assigned based on analogy to **27**.



Stereochemistry of *trans*-Disubstituted Pyrrolidines

The stereochemistry around the pyrrolidine ring in **34** was assigned through a ^{1}H NMR nOe experiment as depicted below, and the stereochemistry hydroxyl-bearing carbon atom was assigned based on the configuration of the oxazolidinone starting material (**27**). The stereochemistry of **33** was assigned based on analogy to **34**.



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