Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams.

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Supporting Information

I. General Considerations.

Unless otherwise noted, THF, Et₂O, CH₂Cl₂ and toluene were purchased from J.T. Baker in CYCLE-TAINER[®] solvent-delivery kegs and vigorously purged with argon for 2h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et₂O) or through neutral alumina and copper (II) oxide (for toluene and CH₂Cl₂).¹ Dichloroethane and cyclohexane were purchased from EM Science in Drisolv[®] bottles and were used without further treatment. Fluorobenzene was purchased from Avacado and used as is. Starting materials for substrate synthesis were purchased from commercial sources and used as is. CuCl, CuCl₂, CuCl₂·H₂O and *t*-BuONa were purchased from Strem and used as is. PMHS (polymethylhydrosiloxane), ethyl alcohol, 2-propanol and *s*-BuOH were purchased from Aldrich and used as is. *t*-AmOH was purchased from Alfa Aesar and used as is. For rate studies, EtOH, *i*-PrOH, and *s*-BuOH from Aldrich Sure/Seal[™] bottles were used, and *t*-AmOH was distilled from CaH₂ under argon, and then degassed by three freeze/ pump/ thaw cycles. *t*-AmOD (degassed by three freeze/ pump/ thaw cycles) was prepared by quenching a pentane suspension of *t*-AmONa (purchased from Aldrich) with D₂O.

Unless otherwise noted, reactions for the preparation of starting materials were carried out in round bottom flasks under a positive pressure of nitrogen or argon. Unless otherwise noted, conjugate reductions were carried out under nitrogen or argon in Schlenk tubes sealed with Teflon screw caps. Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ¹H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are the average of two or more runs.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc). Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 or a Varian Unity 300 instrument. Infra Red spectra were recorded on an ASI Applied Systems ReactIR 1000 (liquids and solids were measured neat on a DiComp probe). All ^1H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuteriochloroform (77.23 ppm), and all were obtained with ^1H decoupling. Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were taken on a Perkin-Elmer 241 Polarimeter. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. Chiral High Pressure Liquid Chromatography analyses were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector, using the columns and wavelengths mentioned in section III.

II. Preparation of Substrates

General procedure for the esterification of alcohols with acryloyl chloride:

Acryloyl chloride (2 equiv) was added to a 0 °C solution of alcohol (1 equiv) and 2,6-Lutidine (2 equiv) in tetrahydrofuran (THF) (0.5M in alcohol). The mixture was then allowed to warm to ambient temperature and stirred until TLC analysis showed complete consumption of the alcohol. The reaction mixture was partitioned between diethyl ether and 10% HCl. The aqueous layer was separated and extracted two times with diethyl ether. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel.

General procedure for RCM of allylic and homoallylic acrylates:

¹ (a) Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P.J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Ed.* **2001**, *78*, 64.

A solution of the carbene complex (1 mol%) in dichloromethane (1 mL/ 100 μ mol Ru) was added via syringe pump to a refluxing solution of diene (1 equiv) in CH₂Cl₂ (4 mL/ mmol acrylate) over 10 h. The mixture was cooled to room temperature, concentrated to dryness, and the residue was purified by flash chromatography. Kugelrohr distillation was then performed to remove traces of Ru byproducts.

General procedure for the glyoxylic acid condensation/ borohydride reduction approach to β -substituted butenolides:

This procedure is as described in the literature, with the exception that commercially available piperidine hydrochloride was used in place of morpholine hydrochloride.² Glyoxylic acid monohydrate (1.05 equiv) and piperidine hydrochloride (1.1 equiv) were added to a solution of aldehyde (1 equiv) in 7/1 mixture of dioxane and water (2M in aldehyde) and the mixture was refluxed for 16 h. The mixture was cooled to ambient temperature and 10 % HCl was added. The solution was extracted four times with ethyl acetate, the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was dissolved in MeOH (1.5 mL/ mmol of aldehyde) and sodium borohydride (4 H⁺ equiv) was added portion-wise to the rapidly stirred solution. After 2h, the reaction mixture was treated with 10 % HCl and extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The residue was purified by flash chromatography.

4-Butyl-5H-furan-2-one (10a).

² (a) Bourguignon, J.J.; Wermuth, C.G. *J. Org. Chem.* **1981**, *46*, 4889. (b) Bourguignon, J.J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C.G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893.

Hexanal (6.0 mL, 49.9 mmol) was subjected to the glyoxylic acid condensation/ reduction protocol. The reaction mixture was purified by flash chromatography (30 % ethyl acetate/ hexanes) to afford the title compound as a colorless liquid (3.50 g, 50 %). The ¹H NMR spectra was in accord with a literature report.³

4-Isoropyl-5H-furan-2-one (10b).

Isovaleraldehyde (5.0 mL, 46.6 mmol) was subjected to the glyoxylic acid condensation/ reduction protocol. The reaction mixture was purified by flash chromatography (25 % ethyl acetate/ hexanes) to afford the title compound as a colorless liquid (1.50 g, 26%). The ¹H NMR spectra was in accord with a literature report.⁴

4-Benzyl-5H-furan-2-one (6b).

2-Benzyl-2-propen-1-ol⁵ (3.80 g, 25.6 mmol) was subjected to the general conditions for the esterification of allylic alcohols. The reaction mixture was purified by flash chromatography (5 % ether/ hexane) to afford **5b** as a colorless liquid (3.42 g, 66 %) which was used directly in the next step.

Acrylate **5b** (3.41 g, 16.9 mmol) was submitted to the general RCM procedure. The reaction mixture was purified by flash chromatography (35 % ethyl acetate/ hexanes) to yield a light purple oil. Kugelrohr distillation afforded the title compound as a colorless liquid (2.33 g, 79%). The ¹H NMR spectra was in accord with a literature report.⁶

4-(3,4-Dimethoxy-benzyl)-5H-furan-2-one (8c).

³ Pelletier, S.W.; Djarmati, Z.; Laj_i_, S.D.; Mi_ovi_, I.V.; Yang, D.T.C. *Tetrahedron* **1975**, *31*, 1659.

⁴ McMorris, T.C.; Chavez, R. G.; Patil, P. A., *J.Chem.Soc.,Perkin Trans.1* **1996**, 295.

⁵ Buboudin, J.G.; Jousseume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

⁶ Bella, M.; Piancatelli, G.; Pigro, M. C., *Tetrahedron* **1999**, *55*,12387.

4Å Molecular sieves (1.5 g) were added to a 23 °C solution of 3-(3,4-dimethoxyphenyl)-propan-1-ol (2.78 mL, 15.3 mmol) in CH₂Cl₂ (50 mL). After 30 min, pyridinium chlorochromate (4.94 g, 22.9 mmol) was added. After 1h, the mixture was filtered through a pad of celite and silica gel and concentrated to dryness to afford 2.46 g of **8c** as a pale yellow liquid (83 %). This material was used directly in the next step.

The glyoxylic acid condensation/ reduction protocol was applied to aldehyde **8c** (2.46 g, 12.7 mmol) to afford the title compound as a crystalline solid after purification by flash chromatography (60 % ethyl acetate/ hexanes) (2.35 g, 79%). Mp (CH₂Cl₂): 53-54 °C; ¹H NMR (300 MHz, CDCl₃) δ: 3.69 (s, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.71-4.74 (m, 2H), 4.72 (quint, *J* = 1Hz, 1H), 6.67 (AB, d, *J* = 1.5 Hz, 1H), 6.73 (ABX, dd, *J* = 8, 1.5 Hz, 1H), 6.84 (AB, d, *J* = 8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ: 34.98, 56.02 (two –OCH₃ carbons), 72.83, 111.59, 111.81, 116.43, 120.98, 128.04, 148.40, 149.37, 169.64, 173.90; IR (cm⁻¹): 1741, 1513, 1451; Anal. Calcd. for C₁₃H₁₄O₄: C, 66.66; H, 6.02. Found: C, 66.40; H, 5.99.

4-Phenyl-5H-furan-2-one (**6c**).

2-Phenyl-2-propen-1-ol⁵ (3.80 g, 25.6 mmol) was subjected to the general procedure for the esterification of allylic alcohols with acryloyl chloride except that toluene was used in place of THF as solvent. The reaction mixture was purified by flash chromatography (5 % ether/ hexanes) to afford acrylate **5c** as a colorless liquid (3.42 g, 66 %). This material was used directly in the next step.

The general RCM protocol was applied to **5c** (1.55 g, 8.23 mmol), except that 1.5 mol% of **7** was used instead of 1 mol%, and the reaction was conducted in refluxing ClCH₂CH₂Cl (10 mL) in stead of CH₂Cl₂. The residue obtained by concentration of the reaction mixture was stirred vigorously in ether and 700 mg of product was filtered off as a pale brown solid. Concentration of the mother liquors and purification by flash chromatography (30 % ethyl acetate/ hexanes) afforded a further 160 mg of product. This was combined with the material isolated by filtration and subjected to Kugelrohr distillation to afford the desired product as a white crystalline solid (850 mg, 64 %). Mp (Et₂O): 85-88 °C. The ¹H NMR spectra was in accord with a literature report.^{2b}

4-Methyl-5,6-dihydro-pyran-2-one (**6d**).

3-Methyl-3-buten-1-ol (5.9 mL, 58.1 mmol) was subjected to the conditions for the esterification of homoallylic alcohols except that ether was used in place of THF as solvent. The reaction mixture was purified by flash chromatography (5 % ether/ hexanes) to afford acrylate **5d** as a colorless liquid (3.64 g, 45 %).

The general conditions for RCM was applied to **5d** (2.00 g, 14.3 mmol). The reaction mixture was purified by flash chromatography (40 % ethyl acetate/ hexanes) to afford the title compound as a light purple oil which was subjected to Kugelrohr distillation to yield a colorless product (1.23 g, 76 %). The ^1H NMR spectra was in accord with a literature report.⁷

4-Propyl-5,6-dihydro-pyran-2-one (**12a**).

Triethoxyvinyl silane (11.5 mL, 54.5 mmol) and **11a** (3.87 g, 27.2 mmol) were added via syringe to a solution of $(\text{CO})\text{Ru}(\text{H})_2(\text{PPh}_3)_3$ (500 mg, 0.545 mmol) in toluene (25 mL). The reaction was warmed to 80 °C and stirred under an Ar atmosphere for 36 hours. GC analysis of the crude reaction mixture indicated the product was formed as a mixture of *Z* and *E* double bond isomers, present in a ratio of 4.9 : 1. The reaction mixture was concentrated to dryness and the residue was dissolved in a 1 : 1 mixture of MeOH/ THF (100 mL). Sodium bicarbonate (4.54 g, 54 mmol), sodium fluoride (11.3 g, 270 mmol) and hydrogen peroxide (34 mL, 540 mmol, 30 % aqueous) were added. After 24h, the reaction mixture was added to 10 % aqueous sodium sulfite (Caution! Mild exotherm observed). The aqueous layer was extracted four times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. Pyridinium *p*-toluenesulfonate (10 mg) was added and the mixture was placed in a 110 °C oil bath for 1h. The mixture was then purified by flash chromatography (30 % ethyl acetate/ hexanes) to afford the title compound as a colorless oil (828 mg, 22 %), along with non-lactonized material (646 mg, 14 %) as a 1.2 : 1 (*Z* : *E*) mixture of double bond isomers. The ^1H NMR spectra of **12a** was in accord with a literature report.⁸

4-Cyclohexyl-5,6-dihydro-pyran-2-one (**12b**).

⁷ Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, 10, 4349.

⁸ Kato, M.; Ouchi, A.; Yoshikoshi, A. *Bull.Chem.Soc.Jpn.* **1991**, 64, 1479.

Vinyl cyclohexane (3.7 mL, 27 mmol) and ethyl acrylate (5.9 mL, 54 mmol) were added to a solution of **7** (231 mg, 0.272 mmol) in CH_2Cl_2 (40 mL) and the mixture was refluxed for 3h. The mixture was concentrated to dryness and purified by flash chromatography (5 % ether/ hexanes) to yield **11b** as a colorless liquid (4.22g g, 85%). This material was used directly in the next step.

A solution of **11b** (497 mg, 2.72 mmol) in toluene (5 mL) was added to a solution of triethoxyvinylsilane (1.1 mL, 5.4 mmol) and $(\text{CO})\text{Ru}(\text{H})_2(\text{Ph}_3\text{P})_3$ (250 mg, 0.272 mmol) in toluene. The mixture was refluxed for 12 h, then cooled to room temperature and concentrated to dryness. The residue was purified by flash chromatography (5 % ether/ hexanes) to yield the silane as a pale yellow liquid (556 mg, 55 %). This material was used directly in the next step.

30 % Aqueous H_2O_2 (1.0 mL, 16.1 mmol) was added to a mixture of the silane prepared in the previous step (600 mg, 1.61 mmol), NaF (169 mg, 4.03 mmol) and NaHCO_3 (135 mg, 1.61 mmol) in a 1 : 1 (v/v) mixture of MeOH and THF (6 mL). After 24h, the mixture was partitioned between ethyl acetate and 10% HCl. The aqueous layer was extracted two times with ethyl acetate, the organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. PPTS (10 mg) was added and the residue was warmed to 115 °C for 30 min, then was purified by flash chromatography (30% ethyl acetate/ hexanes) to afford the title compound as a colorless oil (260 mg, 90%).
 ^1H NMR (300 MHz, CDCl_3) δ : 1.11-1.41 (m, 5H), 1.66-1.89 (m, 5H), 2.05-2.17 (m, 1H), 2.39 (tm, J = 6 Hz, 2H), 4.35 (tm, J = 6 Hz, 2H), 5.75-5.79 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ : 26.08, 26.18, 26.76, 30.66, 44.87, 66.32, 114.21, 165.45, 166.25, 202.31; Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.03; H, 9.04.

4-Butyl-1,5-dihydro-pyrrol-2-one (14a).

This substrate was prepared using a slight modification of a literature procedure.⁹ Propargyl bromide (16.1 mL of an 80% solution in toluene, 145 mmol) was added to a -30 °C suspension of LiHMDS (56.3 g, 336 mmol) in ether (Caution! Due to heat of solvation, ether will reflux on addition to LiHMDS and the solids should be cooled before

adding solvent). The mixture was allowed to warm to 23 °C over 4 h, then cooled to –30 °C. Ethylchloroformate (13.9 mL, 145 mmol) was added and the mixture was allowed to warm to 23 °C over 18 h. The reaction mixture was filtered through a pad of celite and concentrated to dryness. The residue was suspended in pentane and filtered through celite a second time. The filtrate was concentrated to dryness and the residue was purified by vacuum distillation (0.1 mm Hg) with the aid of a 10 cm Vigroux column. The material boiling above 90 °C was collected to afford 21.0 g (53 % yield) of a clear liquid which slowly turned brown on standing. GC analysis showed the material to be 97% pure.

n-BuLi (8.01 mL, 2.30 M in hexane, 18.4 mmol) was added to a –40 °C suspension of CuI (3.51 g, 18.4 mmol) in ether (80 mL). After 5 min, the resulting brown suspension was cooled to –78 °C and a solution of ethyl 4-(bistrimethylsilylamino)but-2-ynoate (5.20 g, 19.1 mmol) in ether (20 mL) was added. The mixture was allowed to warm to –50 °C for 3 h. The mixture was cooled back to –70 °C and MeOH (5 mL) was added. The mixture was warmed to ambient temperature and filtered through a pad of celite. The filtrate was concentrated to dryness and the residue was dissolved in acetone (30 mL). Saturated oxalic acid (30 mL) was added and the acetone was removed on a rotary evaporator. The residue was neutralized with saturated sodium carbonate and extracted three times with ether. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The residue was dissolved in 10% ether/ hexane and placed in a 0 °C fridge. After 16 h, the suspension was filtered to afford the desired product as a pale green solid (974 mg, 38%). A further 730 mg (28 %) was isolated after flash chromatography (5% MeOH/ CH₂Cl₂). The ¹H NMR spectra was in accord with a literature report.⁷

4-Butyl-1-(4-Methoxy-phenyl)-1,5-dihydro-pyrrol-2-one (14b).

Lactam **14a** (400 mg, 2.87 mmol), CuI (27.4 mg, 0.144 mmol), Cs₂CO₃ (1.22 g, 5.75 mmol), and 4-iodoanisole (1.01 g, 4.31 mmol) were added to a flask which was evacuated and charged with a nitrogen atmosphere. *N,N'*-Dimethylethylenediamine (61 µL, 0.575 mmol) and toluene (2.5 mL) were added and the mixture was warmed to 60 °C for 2 h. The reaction was cooled to ambient temperature and filtered through a plug of silica gel which was washed with ethyl acetate. The filtrate was concentrated to dryness and the residue was purified by flash chromatography (40% EtOAc/ Hexane) to afford the title compound as a crystalline solid (620 mg, 88%). Mp (Et₂O): 74-78 °C; ¹H NMR (300 MHz, CDCl₃) δ: 0.95 (t, *J* = 7 Hz, 3H), 1.40 (hexet, *J* = 7.5 Hz, 2H), 1.59 (quintet, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 4.26 (s, 2H), 5.91 (d, *J* = 1 Hz, 1H), 6.88 (AB, d, *J* = 9 Hz, 2H), 7.54 (AB, d, *J* = 9 Hz, 2H);

⁹ Corriu, R.J.P.; Bolin, G.; Iqbal, J.; Moreau, J.J.E; Vernhet, C. *Tetrahedron* **1993**, *49*, 4603.

^{13}C NMR (75 MHz, CDCl_3) δ : 14.13, 22.67, 29.56, 30.02, 55.50, 55.71, 114.31, 120.73, 122.92, 132.67, 156.07, 159.05, 170.58; IR (film, cm^{-1}): 1681, 1513, 1443, 1380, 1266; Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 9.81; N, 5.71. Found: C, 73.14; H, 7.76; N, 5.67.

4-Methyl-1-(4-Methoxy-phenyl)-1,5-dihydro-pyrrol-2-one (13).

Methodology used in the synthesis of the *N*-phenyl analogue analogue of **13** was employed.¹⁰ Methallyl chloride (50.3 mmol) was added to a mixture of *p*-anisidine (5.00 g, 40.6 mmol) and K_2CO_3 (2.80 g, 20.3 mmol) in water (35 mL) and the resulting mixture was refluxed for three hours open to the air. The mixture was cooled to ambient temperature and extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (10% ethyl acetate/ hexanes) to afford methallylated *p*-anisidine (3.79 g, 53%) as a pale yellow liquid. ^1H NMR (300 MHz, CDCl_3) δ : 1.77 (s, 3H), 3.62 (s, 3H (CH_2N and NH), 3.73 (s, 3H), 4.85 (s, 1H), 4.94 (s, 1H), 6.56 (AB, d, $J = 9\text{Hz}$, 2H), 6.75 (AB, d, $J = 9\text{ Hz}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 20.86, 51.06, 56.02, 110.95, 114.14, 114.89, 132.54, 143.15, 151.98; IR (film, cm^{-1}): 3409, 1511, 1441, 1231; Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.12; H, 8.49; N, 7.83.

n-BuLi (4.90ml, 2.30 M in hexanes, 11.3 mmol) was added to a $-30\text{ }^\circ\text{C}$ solution of *N*-methallylated *p*-anisidine prepared above (2.00g, 11.3 mmol) in diethyl ether (50 mL). After 5 min, the reaction mixture was warmed to ambient temperature. After 10 min, the reaction was cooled to $-30\text{ }^\circ\text{C}$ and *t*-BuLi (11.3 mL, 1.50M in pentane, 16.9 mmol) was added. After 10 min, the mixture was warmed to ambient temperature for 30 min, then cooled to $-30\text{ }^\circ\text{C}$. Dimethylcarbonate (951 μL , 11.3 mmol) was added and after 10 min the reaction mixture was warmed to ambient temperature. After 15 h, the mixture was treated with water and extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (70% ethyl acetate/ hexanes) to afford the title compound as a white crystalline solid (525 mg, 25 %). Mp (Et_2O): $100\text{--}102\text{ }^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ : 2.12 (d, $J = 2\text{ Hz}$, 3H), 3.79 (s, 3H), 4.25 (s, 2H), 5.93 (sextet, $J = 1.5\text{ Hz}$, 1H), 6.88 (AB, d, $J = 9\text{ Hz}$, 2H), 7.53 (AB, d, $J = 9\text{ Hz}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 15.52, 55.65, 56.54, 114.24, 120.68, 123.97, 132.56, 154.37, 156.00, 170.50; IR (film, cm^{-1}): 1671; Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.63; H, 6.40; N, 6.87.

4-Ethyl-1-(4-methoxy-phenyl)-5,6-dihydro-1*H*-pyridin-2-one (17).

Ethyl vinylketone (10.0 mL, 97.4 mmol) was added to a solution of *p*-anisidine (10g, 81.2 mmol) in THF (80 mL) and the mixture was warmed to reflux for 18 h. The solution was cooled to ambient temperature, equal parts water and brine were added, and the mixture was extracted two times with ethyl acetate. The organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was suspended in 15% Et_2O /hexanes (100 mL), stirred for 30 min, then filtered to afford the Michael addition product **16** as a pale grey solid (9.34 g, 55%). A second and third crop yielded a further 2.37 and 1.93 g respectively for a total isolated yield of 13.64 g (81%). Mp (Et_2O /hexanes): 41-43 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.05 (t, $J = 7.3$ Hz, 3H), 3.79 (q, $J = 7.3$ Hz, 2H), 2.69 (t, $J = 6.2$ Hz, 2H), 3.36 (t, $J = 6.2$ Hz, 2H), 3.74 (s, 3H), 6.58 (AB, d, $J = 9$ Hz, 2H), 6.77 (AB, d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 7.95, 36.52, 39.83, 41.52, 55.93, 114.61, 114.92, 136.16, 152.24, 210.83; IR (film, cm^{-1}): 3394, 1708, 1511, 1235, 1036; Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.69; H, 8.24; N, 6.66.

Saturated Na_2CO_3 (10 mL) was added to a solution of **16** (1.86 g, 8.97 mmol) and ethylmalonylchloride (1.40 mL (90% pure), 9.87 mmol) in CH_2Cl_2 (20 mL). After 30 min, water was added and the mixture was extracted two times with CH_2Cl_2 . The organic layers were washed with brine, filtered through cotton, and concentrated to dryness. The residue was dissolved in EtOH (30 mL). EtONa (1.22g, 17.9 mmol) was added and the mixture was stirred for 15 min at ambient temperature before powdered KOH (1.00 g, 17.9 mmol) was added and the mixture was heated to reflux for 18h. A 1:1 mixture of 10% hydrochloric acid and brine was added and the mixture was extracted four times with ethyl acetate. The organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was suspended in Et_2O (25 mL), stirred at 0°C for 30 min, then filtered to afford the title compound as a white solid (1.31 g, 70%). Mp (Et_2O): 96-98 °C; ^1H NMR (300 MHz, CDCl_3) δ : 1.14 (t, $J = 7.5$ Hz, 3H), 2.26 (q, $J = 7.5$ Hz, 2H), 2.44 (t, $J = 7$ Hz, 2H), 3.78 (t, $J = 7$ Hz, 2H), 3.80 (2, 3H), 5.85 (t, $J = 1.4$ Hz, 1H), 6.91 (AB, d, $J = 9$ Hz, 2H), 7.21 (AB, d, $J = 9$ Hz, 2H); ^{13}C (125 Hz, CDCl_3) δ : 11.34, 28.94, 29.60, 49.01, 55.62, 114.18, 119.24, 126.44, 135.75, 156.59, 157.42, 165.04; IR (neat film, cm^{-1}) 1667, 1623, 1511, 1239; Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.70; H, 7.41. Found: C, 72.58; H, 7.35.

III. Enantioselective Conjugate Reductions

General procedure for the reduction of 5-membered lactones:

¹⁰ Barluenga, J.; Fañanás, F.J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1988**, 29, 4859.

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (5 mol %), (*S*)-*p*-tolBINAP (5 mol %), and *t*-BuONa (20 mol %) were added to a Schlenk tube which was then evacuated and charged with an argon atmosphere. PMHS (4 equiv) and pentane (1.5 mL/ mmol of lactone) were added and the mixture was stirred for 2 h before being cooled to $-20\text{ }^\circ\text{C}$. A solution of lactone (1 equiv), dodecane as an internal standard (1 μL / mg of lactone), and *i*-PrOH (4 equiv) in toluene (1.5 mL/ mmol of lactone) was added via syringe. The mixture was stirred until GC analysis revealed >95% conversion of the substrate. The reaction mixture was partitioned between 10% hydrochloric acid and ethyl acetate. The aqueous layer was extracted two times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography.

General procedure for the reduction of 6-membered lactones:

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (5 mol %), (*S*)-BIPHEMP (5 mol%), and *t*-BuONa (20 mol%) were added to a Schlenk tube which was then evacuated and charged with an argon atmosphere. PMHS (2 equiv) and toluene (0.75 mL/ mmol of lactone) were added via syringe and the mixture was stirred for 30min. Pentane (1.5 mL/ mmol of lactone) was added and the mixture was cooled to $-40\text{ }^\circ\text{C}$. A solution of lactone (1 equiv) and dodecane as an internal standard (1 μL / mg of lactone) in toluene (0.75 mL/ mmol of lactone) was added via syringe, followed by *t*-AmOH (2 equiv). The mixture was stirred at $-40\text{ }^\circ\text{C}$ until GC analysis showed >95% conversion of the substrate. The reaction mixture was quenched by the addition of 10% hydrochloric acid. The aqueous layer was extracted three times with ether, the organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography.

General procedure for the reduction of unsaturated lactams:

A solution of lactam (1 equiv) and *i*-PrOH (4 equiv) in THF (0.75 mL/ mmol of lactam) was added to a $0\text{ }^\circ\text{C}$ slurry of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (5 mol%), (*S*)-*p*-tolBINAP (5 mol%), *t*-BuONa (20 mol%), and PMHS (4 equiv) in *c*-hexane (0.75 mL/

mmol of lactam) under nitrogen. The mixture was stirred at 0 °C until GC analysis showed >95% conversion of the substrate. The reaction mixture was quenched by the addition of 10% hydrochloric acid. The aqueous layer was extracted three times with ethyl acetate, the organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The residue was purified by flash chromatography.

4-Butyl-dihydro-furan-2-one.

The general conditions for the reduction of 5-membered lactones (3 h reaction time) were applied to **10a** (100 mg, 0.713 mmol). Purification by flash chromatography (15 → 20 % ethyl acetate/ hexanes) afforded the title compound as an oil (90 mg, 89 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 90 °C, 60 min, then 1 °C/ min to 120 °C, hold for 20 min, retention times: 93.9 min (major), 95.5 min (minor)) showed 86 % ee. α_D (589 nm, 38.5 mg/ mL CHCl₃) = +5. The ¹H NMR spectra and α_D were in accord with a literature report.¹¹

4-Isopropyl-dihydro-furan-2-one.

The general conditions for the reduction of 5-membered lactones (3 h reaction time) were applied to **10b** (100 mg, 0.793 mmol). Purification by flash chromatography (15 → 30 % ethyl acetate/ hexanes) afforded the title compound as an oil (89 mg, 88 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 90 °C, 60 min, then 1 °C/ min to 120 °C, hold for 20 min, retention times: 92.1 min (major), 93.9 min (minor)) showed 92 % ee. α_D (589 nm, 10.0 mg/ mL CHCl₃) = 12.7. The ¹H NMR spectra and α_D were in accord with a literature report.¹²

4-Benzyl-dihydro-furan-2-one.

¹¹ (a) Roeder, E.; Krauss, H. *Liebigs Ann. Chem.* **1992**, 177. (b) Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935.

¹² Koch, S. S. C.; Chamberlin, A. R., *J.Org.Chem.* **1993**, 58, 2725.

The general conditions for the reduction of 5-membered lactones (3 h reaction time) were applied to **6b** (100 mg, 0.574 mmol). Purification by flash chromatography (25 → 30 % ethyl acetate/ hexanes) afforded the title compound as an oil (93 mg, 92 % yield). Chiral HPLC analysis (Daicel Chiralpak® AD column (0.46cmØ x 25 cm), 1 mL/ min, 7% *i*-PrOH/ Hexane, retention times: 17.04 min (major), 18.62 min (minor)) showed 92 % ee. α_D (589 nm, 19.9 mg/ mL CHCl₃) = +5.9. The ¹H NMR spectra and α_D were in accord with a literature report.¹³

4-(3,4-Dimethoxy-benzyl)-dihydro-furan-2-one.

The general conditions for the reduction of 5-membered lactones (4.5 h reaction time), were applied to **10c** (200 mg, 0.854 mmol) except that dichloromethane (0.7 mL) was added to facilitate solvation of the starting material. Purification by flash chromatography (50 % ethyl acetate/ hexanes) afforded the title compound as a cloudy viscous oil (160 mg, 80 % yield). Chiral HPLC analysis (Daicel Chiralpak® OB-H column (0.46cmØ x 25 cm), 0.75 mL/ min, 35% *i*-PrOH/ Hexane, retention times: 72.6 min (major), 89.1 min (minor)) showed 92 % ee. α_D (589 nm, 26.4 mg/ mL CHCl₃) = +4.3. The ¹H NMR spectra and α_D were in accord with a literature report.¹⁴

4-Phenyl-dihydro-furan-2-one.

The general conditions for the reduction of 5-membered lactones were applied to **6c** (100, 0.624 mmol), except that CH₂Cl₂ (0.5 mL) was added to facilitate the solvation of the starting material (7 h reaction time). Purification by flash chromatography (35 % ethyl acetate/ hexanes) afforded the title compound as a crystalline solid (71 mg, 70 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 150 °C, 20 min, retention times: 15.4 min (major), 15.9 min (minor)) showed 71 % ee. Mp (ethyl acetate/ hexanes): 49-51 °C; α_D (589 nm, 19.9 mg/ mL CHCl₃) = +37.2. The ¹H NMR spectra, α_D , and melting point were in accord with a literature report.¹⁵

¹³ (a) Heerden, P. S. van; Bezuidenhout, B. C. B.; Ferreira, D., *Tetrahedron* **1996**, 52, 12313. (b) Caro, Y.; Masaguer, C. F.; Ravina, E., *Tetrahedron: Asymmetry* **2001**, 12, 1723.

¹⁴ Morimoto, T.; Chiba, M.; Achiwa, K., *Tetrahedron* **1993**, 49, 1793.

¹⁵ (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T., *Tetrahedron: Asymmetry* **1999**, 10, 4047. (b) Rizzacasa, M. A.; Sargent, M. V., *J.Chem.Soc.,Perkin Trans.1*, **1991**, 845.

4*S*-4-Methyl-tetrahydro-pyran-2-one.

The general conditions for the reduction of 6-membered lactones (3 h reaction time) were applied to **6d** (200 mg, 1.79 mmol). Purification by flash chromatography (5 % ethyl acetate/ dichloromethane) afforded a mixture of the title compound and an unidentified by product (160 mg, 5 : 1 mixture). A second flash chromatography (80 % ethyl acetate/ hexanes) afforded the title compound as a colorless liquid (135 mg, 66 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 120 °C, 20 min, retention times: 15.71 min (major), 17.48 min (minor)) showed 82 % ee. α_D (589 nm, 36.8 mg/ mL CHCl₃) = -23.6. The ¹H NMR spectra and α_D were in accord with a literature report.¹⁶

4*S*-4-Propyl-tetrahydro-pyran-2-one.

The general conditions for the reduction of 6-membered lactones (3 h reaction time) were applied to **12a** (100 mg, 0.713 mmol). Purification by flash chromatography (25 % ethyl acetate/ hexanes) afforded a mixture of the title compound and an unidentified by product (160 mg, 5 : 1 mixture). A second flash chromatography (80 % ether/ hexanes) afforded the title compound as a colorless liquid (71 mg, 70 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 120 °C, 50 min, retention times: 41.3 min (major), 46.2 min (minor)) showed 86 % ee. α_D (589 nm, 23.8 mg/ mL CHCl₃) = -21.4. The ¹H NMR spectra and α_D were in accord with a literature report.¹⁷

4*S*-4-Cyclohexyl-tetrahydro-pyran-2-one.

The general conditions for the reduction of 6-membered lactones (6 h reaction time) were applied to **12b** (80 mg, 0.44 mmol). Purification by flash chromatography (25 % ethyl acetate/ hexanes) afforded a mixture of the title compound and an unidentified by product (65 mg, 8 : 1 mixture). A second flash chromatography (80 % ether/ hexanes) afforded

¹⁶ Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E., *J.Org.Chem.* **1985**, 50, 4072.

¹⁷ (a) Kayser, M.M.; Chen, G.; Stewart, J.D. *J. Org. Chem.* **1998**, 63, 7103. (b) Jones, J.B.; Lok, K.P. *Can. J. Chem.* **1979**, 57, 1025.

the title compound as a colorless liquid (44 mg, 55 % yield). Chiral GC analysis (GTA column, 1 mL/ min, 150 °C, 50 min, retention times: 37.3 min (major), 40.0 min (minor)) showed 94 % ee. α_D (589 nm, 30.6 mg/ mL CHCl₃) = +6. The ¹H NMR spectra and α_D were in accord with a literature report.^{17b}

4*R*-4-Methyl-1-(4-methoxy-phenyl)-pyrrolidin-2-one.

The general reduction conditions for unsaturated lactams (1 hour reaction time) were applied to **13** (50 mg, 0.267 mmol). Purification of the residue by flash chromatography (70% ethyl acetate/ hexanes) afforded the title compound as a white crystalline solid (48 mg, 95%). Chiral HPLC analysis (Daicel Chiralpak® OB-H column (0.46cmØ x 25 cm), 0.5 mL/ min, 40% *i*-PrOH/ Hexane, 254, 280 nm, retention times: 18.4 min (major), 24.4 min (minor)) showed 93% ee. Mp (CH₂Cl₂): 49-51 °C; ¹H NMR (500 MHz, CDCl₃) δ : 1.20 (d, *J* = 6.8 Hz, 3H), 2.22 (ABX, dd, *J* = 16.7, 7.4 Hz, 1H), 2.55 (octet, *J* = 7.4 Hz, 1H), 2.72 (ABX, dd, *J* = 16.7, 8.4 Hz, 1H), 3.40 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.79 (s, 3H), 3.90 (dd, *J* = 9.5, 7.6 Hz, 1H), 6.89 (ABX, dm, *J* = 9.1 Hz, 2H), 7.47 (ABX, *J* = 9.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ : 19.42, 26.25, 40.61, 55.36, 56.26, 113.91, 121.72, 132.47, 156.43, 173.49; IR (film, cm⁻¹): 1688, 1513, 1397, 1266, 1034; Anal. Calcd. for C₁₂H₁₅NO₂: C, 70.22; H, 7.37. Found: C, 70.06; H, 7.31. α_D (589 nm, 23.8 mg/ mL CHCl₃) = -4.2.

4*R*-4-Butyl-1-(4-methoxy-phenyl)-pyrrolidin-2-one.

The general conditions for lactam reductions (three hour reaction time) were applied to **15** (78 mg, 0.318 mmol), except that toluene was used in place of THF. Purification by flash chromatography (10% ethyl acetate/ dichloromethane) afforded the title compound as a white crystalline solid (74 mg, 94%). Chiral HPLC analysis (Daicel Chiralpak® OB-H column (0.46cmØ x 25 cm), 0.5 mL/ min, 40% *i*-PrOH/ Hexane, 254 nm, retention times: 11.4 min (major), 14.4 min (minor)) showed 94% ee. Mp (diethyl ether): 54-56 °C; ¹H NMR (300 MHz, CDCl₃) δ : 0.92 (t, *J* = 7 Hz, 3H), 1.29-1.41 (m, 4H), 1.48-1.58 (m, 2H), 2.28 (ABX, dd, *J* = 16.5, 8 Hz, 1H), 2.46 (heptet, *J* = 8Hz, 1H), 2.70 (ABX, dd, *J* = 16.5, 8 Hz, 1H), 3.42 (ABX, dd, *J* = 9.5, 6.5 Hz, 1H), 3.80 (s, 3H), 3.86 (t, *J* = 9.5 Hz, 1H), 6.90 (AB, d, *J* = 9Hz, 2H), 7.48 (AB, d, *J* = 9Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ : 14.20, 22.86, 31.85, 34.44, 36.08, 39.37, 55.10, 55.63,

114.21, 121.93, 132.87, 156.68, 173.66; Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.58; H, 8.53. α_D (589 nm, 10.1 mg/ mL $CHCl_3$) = +5.

4*S*-4-Ethyl-1-(4-methoxy-phenyl)-piperidin-2-one.

The general conditions for lactam reduction (30 min reaction time) were applied to **17** (100 mg, 0.432 mmol). The residue was purified by flash chromatography (70% ethyl acetate/ hexanes) to afford the title compound as a white solid (90 mg, 89%). Chiral HPLC analysis (Daicel Chiralpak® OJ column (0.46cmØ x 25 cm), 1.0 mL/ min, 15% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 13.4 min (major), 15.4 min (minor)) showed 91% ee. Mp (diethyl ether): 58-60 °C; 1H NMR (300 MHz, $CDCl_3$) δ : 0.97 (t, J = 7.4 Hz, 3H), 1.42 (quintet, J = 7.2 Hz, 2H), 1.53-1.69 (m, 1H), 1.79-1.95 (m, 1H), 1.97-2.06 (m, 1H), 2.02 (ABX, dd, J = 17.3, 10.7 Hz, 1H), 2.68 (ABX, ddd, J = 17.6, 5.2, 2.2 Hz, 1H), 3.53-3.70 (m, 2H), 3.80 (s, 3H), 6.90 (AB, d, J = 9Hz, 2H), 7.14 (AB, d, J = 9Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 11.35, 28.67, 29.31, 34.94, 39.14, 51.24, 55.51, 114.40, 127.32, 135.97, 157.91, 169.92; IR (neat film, cm^{-1}): 1644, 1607, 1511, 1246; Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.10; H, 8.45; α_D (589 nm, 10.1 mg/ mL $CHCl_3$) = -39.4.

Reduction of **18** using low catalyst loading.

(*S*)-*p*-tolBINAP (5.0 mg, 0.00738 mmol), $CuCl_2$ (1.0 mg, 0.00738 mmol) and *t*-BuONa (1.7 mg, 0.0148 mmol) were added to a Schlenk tube which was evacuated and back filled with Ar. The mixture was suspended in *c*-hexane (1 mL) and transferred via canula to another Schlenk tube containing PMHS (1.77 mL, 29.5 mmol) and *c*-hexane (15 mL). **18** (1.35 mL, 7.38 mmol) and *t*-AmOH (3.23 mL, 29.5, mmol) were then added. After 36 h, the mixture was poured into 1N HCl, which was then extracted two times with ether. The organic layers were combined, washed with brine, and dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by flash chromatography (3% ether/ hexanes) to afford ethyl-(*S*)-phenylbutanoate as a colorless liquid (1.19 g, 90%) in 86% ee. HPLC analysis was performed as described by us previously.¹⁸ The 1H NMR spectra was in accord with our previous report.¹⁸

IV. Kinetic Studies

Study of Reduction rates with different alcohols.

A 15 mL Schlenk tube was charged with (*S*)-*p*-tolBINAP (10.0 mg, 0.015 mmol), CuCl₂ (2.0 mg, 0.015 mmol) and *t*-BuOK (3.3 mg, 0.030 mmol). The vessel was evacuated and purged with argon before PMHS (716 μ L, 12 mmol) and *c*-hexane (2 mL) were added. After stirring for 30 min, a solution of **18** (540 μ L, 3.0 mmol) and dodecane (300 μ L) in *c*-hexane (3 mL) was added. Each alcohol (12 mmol) was added via syringe pump over 60 min. Small aliquots were withdrawn periodically and the percent conversion was assessed by GC analysis.

V. Synthesis of (–)-Paroxetine

1-(4-Fluoro-phenyl)-3-(4-methoxy-phenylamino)-propan-1-one (**19**).

Triethyl amine (18.1 mL, 0.129 mmol) was added to a solution of *p*-anisidine (14.6 g, 0.119 mol) and 3-chloropropio-4'-fluorophenone (20 g, 0.108 mol) in THF (100 mL) and the mixture was warmed to reflux for 4 h. The mixture was cooled to ambient temperature and water was added. The mixture was extracted twice with ethyl acetate, the organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The residue was suspended in Et₂O (50 mL) and stirred for 30 min. Filtration afforded the title compound as a pale grey/ green solid (22.7 g, 77%). Mp (Et₂O): 107-108 °C; ¹H NMR (300 MHz, CDCl₃) δ : 3.23 (t, *J* = 6 Hz, 2H), 3.55 (t, *J* = 6 Hz, 2H), 3.73 (s, 3H), 3.83 (bs, 1H), 6.61 (ABX, dt, *J* = 9, 2.5 Hz, 2H), 6.76 (AB, d, *J* = 9, 2.5 Hz, 2H), 7.11 (tt, *J* = 8.5, 2 Hz, 2H), 7.95 (dd, *J* = 9, 5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ : 37.82, 40.01, 55.95, 114.05, 114.65, 115.82 (d, *J* = 22 Hz), 130.71 (d, *J* = 9 Hz), 133.21 (d, *J* = 3 Hz), 141.83, 152.30, 165.79 (d, 254 Hz), 197.69; IR (neat film, cm⁻¹): 3390, 1677, 1596, 1513; Anal. Calcd. for C₁₅H₁₄FNO₂: C, 70.58; H, 5.55; N, 5.14. Found: C, 70.32; H, 5.91; N, 5.20.

4-(4-Fluoro-phenyl)-1-(4-methoxy-phenyl)-5,6-dihydro-1*H*-pyridin-2-one (**21**).

Saturated sodium carbonate (50 mL) was added to a solution of **19** (10.00g, 36.6 mmol) and ethyl 3-chloro-3-oxopropionate (5.15 mL, 40.2 mmol, tech grade, ~90 pure) in CH₂Cl₂ (100 mL). After 30 min, water was added. The

¹⁸ Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*,

aqueous layer was extracted three times with CH_2Cl_2 , the organic layers were combined, washed with brine, filtered through cotton and concentrated to dryness. The residue was dissolved in EtOH (100 mL) and EtONa (9.96 g, 146 mmol) was added. After 15 min, the mixture was warmed to reflux for 30 min. The mixture was cooled to ambient temperature and poured into water. The resulting mixture was placed in an ice bath, stirred for 30 min and then filtered. The cake was suspended in toluene (100 mL), which was then concentrated to dryness to afford the title compound as a pale grey solid (8.36 g, 77%). ^1H NMR showed the material to be contaminated with ~5% of the β,γ -unsaturated isomer. Mp (toluene): 138-142 °C; ^1H NMR (300 MHz, CDCl_3) δ : 2.91 (t, J = 7 Hz, 2H), 3.82 (s, 3H), 3.94 (t, J = 7 Hz, 2H), 6.40 (s, 1H), 2.94 (AB, d, J = 9 Hz, 2H), 7.12 (t, J = 9 Hz, 2H), 7.26 (AB, d, J = 9 Hz, 2H), 7.55 (dd, J = 9, 5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 27.15, 48.56, 55.91, 114.18, 115.90 (d, 20 Hz), 122.03, 126.35, 128.09 (d, J = 8 Hz), 133.84 (d, J = 3 Hz), 135.55, 148.71, 157.79, 163.89 (d, J = 248 Hz), 165.34; IR (neat film, cm^{-1}): 1648, 1603, 1511, 1229; Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{FNO}_2$: C, 72.71; H, 5.42. Found: C, 72.72; H, 5.41.

4*R*-4-(4-Fluoro-phenyl)-1-(4-methoxy-phenyl)-piperidin-2-one (22).

CuCl_2 (13.3 mg, 0.0992 mmol) and $t\text{-BuONa}$ (19.1 mg, 0.198 mmol) were added to a mixture of **21** (1.18 g, 3.97 mmol), (*R*)-*p*-tolBINAP (13.5 mg, 0.0198 mmol), PMHS (3.81 mL, 63.5 mmol H^+) and $t\text{-AmOH}$ (6.95 mL, 63.5 mmol) in fluorobenzene (8 mL). After 45 min, 10% hydrochloric acid was added and the mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, and dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (60 $\rightarrow$ 100 % ethyl acetate/ hexanes) to afford the title compound as a crystalline solid (1.00 g, 89%, based on 95% pure starting material). Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cm ϕ x 25 cm), 1.0 mL/ min, 25% *i*-PrOH/ Hexane, retention times: 19.4 min (minor), 22.3 min (major)) showed 90 % ee. Mp (Et_2O): 183-186 °C; ^1H NMR (300 MHz, CDCl_3) δ : 2.02-2.27 (m, 2H), 2.64 (ABX, dd, J = 17, 11 Hz, 1H), 2.86 (ABX, ddd, J = 17, 5, 2 Hz, 1H), 3.18-3.30 (m, 1H), 6.62 (ABX, ddd, J = 12, 5, 4 Hz, 1H), 3.68-3.83 (m, 1H), 3.80 (s, 3H), 6.92 (ABX, dt, J = 9, 2 Hz, 2H), 7.03 (tt, J = 9, 2 Hz, 2H), 7.16 (AB, dt, J = 9, 2 Hz, 2H), 7.21 (ABX, dd, J = 9, 5.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 30.98, 38.31, 40.21, 51.06, 55.64, 114.61, 115.65 (d, J = 19 Hz), 127.41, 128.01 (d, J = 8 Hz), 135.74, 139.08 (d, J = 3 Hz), 158.19, 161.60 (d, J = 244 Hz), 169.16; IR (neat film, cm^{-1}): 1642, 1511, 1266; Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{FNO}_2$: C, 72.22; H, 6.06. Found: C, 72.22; H, 6.05. α_D (589 nm, 12.8 mg/ mL CHCl_3) = +8.

3*S*,4*R*-4-(4-Fluoro-phenyl)-1-(4-methoxy-phenyl)-2-oxo-piperidin-3-carboxylic acid methyl ester (23).

MeOH (889 μ L, 21.9 mmol) was added dropwise to a room temperature mixture of **22** (2.19 g, 7.32 mmol) and sodium hydride (1.76 g, 43.9 mmol, 60% suspension) in toluene (40 mL). Dimethyl carbonate (1.85 mL, 21.9 mmol) was then added and the mixture was warmed to reflux for 4h. The reaction mixture was poured slowly into water and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (40 $\rightarrow$ 50 % ethyl acetate/ hexanes) to afford the title compound as a white solid (2.07 g, 79%). Mp (CH_2Cl_2 / hexanes): 119-124 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ : 2.16 (m, 2H), 3.55-3.72 (m, 3H), 3.62 (s, 3H), 3.79-3.91 (m, 1H), 3.81 (s, 3H), 6.92 (AB, dt, $J = 9$, 2 Hz, 2H), 7.04 (tt, $J = 9$, 2 Hz, 2H), 7.20 (AB, dt, $J = 9$, 2 Hz, 2H), 7.23 (ABX, dd, $J = 9$, 5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 30.06, 41.08, 50.96, 52.36, 56.01, 57.74, 114.32, 116.02 (d, 24 Hz), 127.10, 128.19 ($J = 10$ Hz), 134.85, 136.94 (d, $J = 3$ Hz), 158.21, 162.03 (d, $J = 241$ Hz), 165.83, 170.23; IR (neat film, cm^{-1}): 1742, 1652; ; Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{FNO}_4$: C, 67.22; H, 5.64. Found: C, 67.50; H, 5.59. α_D (589 nm, 19.0 mg/ mL CHCl_3) = - 11.6.

[4*R*,3*S*-4-(4-fluoro-phenyl)-1-(4-methoxy-phenyl)-piperidin-3-yl]-methanol (24).

Borane (43.4 mL of a 1M THF solution, 43.4 mmol) was added to a flask containing **23** (1.94 g, 5.43 mmol). The resulting solution was refluxed for 18h, then cooled to ambient temperature and poured slowly into 1M NaOH. The mixture was extracted three times with ethyl acetate, the organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (50% ethyl acetate/ hexanes) to afford the title compound as a white solid (1.68 g, 98%). Mp (Et_2O): 94-98 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ : 1.10-1.20 (m, 1H), 1.84-2.04 (m, 2H), 2.05-2.19 (m, 1H), 2.43 (td, $J = 11$, 5 Hz, 1H), 2.59 (t, $J = 11$ Hz, 1H), 2.71 (td, $J = 11$, 3 Hz, 1H), 3.30 (dt, $J = 11$, 7 Hz, 1H), 3.46 (ABX, dt, $J = 11$, 4Hz, 1H), 3.59 (ABX, dm, $J = 11$ Hz, 1H); 3.77 (s, 3H), 3.81 (ABX, ddd, $J = 12$, 4, 2 Hz, 1H), 6.84 (ABX, dt, $J = 9$, 2 Hz, 2H), 6.97 (ABX, dt, $J = 9$, 2 Hz, 2H), 6.99 (hidden, 2H), 7.17 (ABX, ddt, $J = 9$, 5, 2 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 34.76, 44.30, 44.43, 52.41, 55.53, 55.76, 63.91, 114.47, 115.52 (d, $J = 21$ Hz), 119.15, 128.83 (d, $J = 8$ Hz), 139.83 (d, $J = 3$ Hz), 146.07, 153.90, 161.47

(d, $J = 244$ Hz); IR (neat film, cm^{-1}): 3361; ; Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{FNO}_2$: C, 72.36; H, 7.03. Found: C, 72.30; H, 7.07. α_D (589 nm, 9.8 mg/ mL CHCl_3) = -12.2.

(3*R*, 4*S*)-trans-*N*-tert-Butoxycarbonyl-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (26).

Ceric ammonium nitrate (2.45 g, 4.48 mmol) was added to a solution of **24** (353 mg, 1.12 mmol) in a 3:1 mixture of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (28 mL) at ambient temperature. After 30 min, NaOH (1M) was added and the mixture was extracted four times with CH_2Cl_2 . The organic layers were combined, washed with brine, filtered through cotton and concentrated to dryness. Di-*tert*-butyl carbonate (489 mg, 2.24 mmol) was added to the residue and the resulting mixture was dissolved in a 2:1 mixture of toluene/ H_2O (6 mL). Sodium hydroxide (270 μL , 25 wt%, 1.68 mmol) was added and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was diluted with H_2O and extracted twice with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The residue was purified by flash chromatography (50% ethyl acetate/ hexanes) to afford the title compound as a white solid (268 mg, 77%, two steps). The ^1H and ^{13}C NMR spectra and α_D ((589 nm, 11.6 mg/ mL CHCl_3) = -4) were consistent with a literature report.¹⁹

(-)-Paroxetine (4).

Primary alcohol **26** (195 mg, 0.629 mmol), **27** (239 mg, 0.818 mmol) and Cs_2CO_3 (308 mg, 0.944 mmol) were mixed in *o*-xylene (1 mL) in a 15 mL Schlenk tube under N_2 . The tube was sealed with a Teflon screw cap and warmed to 130 $^\circ\text{C}$. After 20 h, the mixture was cooled to ambient temperature, ethyl acetate was added and the mixture was filtered through a pad of celite. The filtrate was concentrated to dryness, dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL) was added. After 15 minutes, NaOH (1N) was added and the mixture was extracted four times with CH_2Cl_2 . The organic layers were washed with brine, filtered through cotton, and concentrated to dryness. The residue was purified by flash chromatography (5% diethyl amine/ ethyl acetate) to afford the title compound as an oil (99 mg, 48% over two

steps). ^1H NMR, ^{13}C NMR, IR and α_D ((589 nm, 16.1 mg/ mL CHCl_3) = -83) were found to be consistent with literature reports.¹⁹

¹⁹ Amat, M.; Boch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravittles, C.; Orozco, M.; Luque, J. *J.Org.Chem.* **2000**, *65*, 3074.