Dual Catalyst Control in the Amino Acid-Peptide-Catalyzed Enantioselective Baylis-Hillman Reaction

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Supporting Information

General Procedures. Proton NMR spectra were recorded on a Varian 400 spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm), or with the solvent reference relative to TMS employed as an internal standard (CDCl_3 , δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on a Varian 400 (100 MHz) or 500 (125 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl_3 , δ 77.0 ppm). All NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with KMnO_4 , cerium ammonium molybdenate (CAM), or ninhydrin solutions. Flash column chromatography was performed using Silica Gel 60Å (32-63 micron). Optical rotations were recorded on a Rudolph Research Analytical Autopol IV Automatic polarimeter at the sodium D line (path length 50 mm). The reported optical rotations are for material of the optical purity (enantiomeric excess) reported in the Tables of the text. High resolution mass spectra were acquired in the Mass Spectrometry facility at Boston College (Chestnut Hill, MA) or at the University of Illinois (Urbana-Champaign, IL). The method of ionization is indicated in parenthesis.

Analytical and preparative reverse phase HPLC were performed on a Rainin SD-200 chromatograph equipped with a single wavelength UV detector (214 nm or 254 nm). Analytical normal phase HPLC was performed on a Hewlett-Packard 1100 Series chromatograph equipped with a diode array detector (214 nm and 254 nm).

All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Benzaldehyde and 2-furaldehyde were freshly distilled while all other aldehydes were used as received. Methyl vinyl ketone was used as received (Aldrich Chemical Company, 99%). HPLC grade chloroform was purified by the method of Perrin [Chloroform was washed with concentrated sulfuric acid (5 x 5 mL) followed by washing with water (5 x 5 mL), dried over potassium carbonate and distilled under nitrogen.].¹ In all solid phase syntheses, unless otherwise specified, the term “wash” refers to the following sequence of rinses: DMF (4X), MeOH (4X), CH₂Cl₂ (4X). Stereochemical proofs were conducted as previously reported.²

Peptide Synthesis.

Peptides **3-7** were synthesized using standard solution phase protocols. Peptides **8-12** were synthesized on solid support using commercially available Fmoc-Phe-Wang polystyrene resin. Couplings were performed using 4 equiv. of amino acid, 4 equiv. of HBTU, and 8 equiv. Hünig's base in DMF, for 3h. Deprotections were performed using 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation; dipeptides were deprotected using 50% piperidine in DMF for 5 min.). Peptides were cleaved from solid support using a mixture of MeOH : DMF : Et₃N (9:1:1) for 3 d. The peptides were characterized by electrospray mass spectrometry (ESI⁺) and used in reaction screens without further purification. A representative procedure for the solid-phase synthesis of peptide **10** is given below.

Synthesis of BOC-(β -Me)His-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Phe-OMe (10): Into a 5 mL Bio-Rad chromatography column was placed Fmoc-Phe-Wang resin (44 mg, 0.80 mmol/g). To the reaction vessel was added 2.0 mL of 20% piperidine/DMF and the reaction was agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-L-Cha-OH (55 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), and DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 50% piperidine/DMF solution (2.0 mL) was added to the reaction vessel and the mixture was agitated for 5 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-D-Pip-OH (49 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 4:1:1 DMF : pyridine : acetic anhydride solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-D-Phe-OH (54 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-L-(trt)Gln-OH (85 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-L-Chg-OH (53 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), Fmoc-Aib-OH (45 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 20 minutes. The resin was then washed.

To the reaction vessel was then added DMF (2.0 mL), BOC-(β -Me)L-His-OH (28 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol), DIPEA (49 μ L, 0.28 mmol). The reaction was agitated for 3 h. The resin was then washed.

A 20% piperidine/DMF solution (2.0 mL) was added to the reaction vessel. The mixture was then agitated for 1 minute. The resin was then washed.

The resin was transferred to a 20 mL Bio-Rad chromatography column. The peptide was cleaved from the resin with a 9:1:1 MeOH : DMF : Et₃N solution (10 mL). The reaction mixture was agitated for 3 days. The cleavage solution was drained and concentrated in vacuo. The resulting white solid was used without purification.

Data for Peptides 3-12.

BOC-Pmh-OMe (3). ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 1H), 6.78 (s, 1H), 5.22 (bd, J = 7.6 Hz, 1H), 4.54 (m, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.09 (m, 2H), 1.43 (s, 9H); **TLC** R_f 0.51 (8% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₁₃H₂₁N₃O₄ + H]⁺ requires *m/z* 284.1610. Found 284.1609 (FAB⁺). **HPLC retention time** 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

BOC-Pmh-Aib-OMe (4). ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 5.17 (s, 1H), 4.27 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.03 (d, J = 6.4 Hz, 2H), 1.50 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H); **TLC** R_f 0.40 (8% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₁₇H₂₈N₄O₅ + H]⁺ requires *m/z* 369.2138. Found 369.2138 (FAB⁺). **HPLC retention time** 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

BOC-Pmh-Aib-Phe-OMe (5). ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 1H), 7.30-7.11 (m, 5H), 6.81 (s, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 5.25 (d, J = 6.4 Hz, 1H), 4.82 (dd, J = 13.6, 6.4 Hz, 1H), 4.19 (m, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.06 (m, 4H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 9H); **TLC** R_f 0.43 (8% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₂₆H₃₇N₅O₆ + H]⁺ requires *m/z* 516.2822. Found 516.2823

(FAB⁺). **HPLC retention time** 2.0 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Phe-D-Phe-OMe (6). ¹H NMR (400 MHz, CDCl₃) δ 7.43 (s, 1H), 7.33-7.15 (m, 10H), 6.86 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.58 (s, 1H), 5.10 (d, J = 6.0 Hz, 1H), 4.80-4.69 (m, 2H), 4.25-4.20 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.39 (m, 2H), 3.16-3.04 (m, 3H), 2.98-2.88 (m, 2H), 1.44-1.40 (m, 15H); **TLC** R_f 0.44 (8% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₃₅H₄₆N₆O₇ + Na]⁺ requires *m/z* 685.3326. Found 685.3322 (ESI⁺). **HPLC retention time** 2.5 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Cha-hPhe-D-Phe-OMe (7). ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 8.8 Hz, 1H), 7.37 (s, 1H), 7.30-7.13 (m, 7H), 6.87 (s, 1H), 6.79 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 4.64 (m, 1H), 4.41 (m, 1H), 4.33 (m, 1H), 4.01 (m, 1H), 3.61 (s, 3H), 3.27 (s, 3H), 3.17-3.07 (m, 2H), 3.05 (d, J = 4.4 Hz, 1H), 3.01 (d, J = 4.0 Hz, 1H), 2.81 (dd, J = 16, 9.6 Hz, 2H), 2.68 (m, 2H), 2.40-2.30 (m, 2H), 2.13-1.90 (m, 4H), 1.80-1.64 (m, 8H), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 9H), 1.25-0.94 (m, 4H); **TLC** R_f 0.53 (10% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₄₅H₆₃N₇O₈ + H]⁺ requires *m/z* 830.4816. Found 830.4817 (FAB⁺). **HPLC retention time** 2.6 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Chg-(trt)Gln-D-Phe-Phe-OMe (8). ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 8.0 Hz, 2H), 7.31-7.07 (m, 27H), 7.03-6.91 (m, 2H), 6.84 (s, 1H), 5.47 (s, 1H), 4.74-4.67 (m, 1H), 4.51-4.45 (m, 1H), 4.41-4.25 (m, 1H), 4.20-4.16 (m, 1H), 4.07-4.05 (m, 1H), 3.50 (s, 3H), 3.26-3.21 (m, 1H), 3.18 (s, 3H), 2.99-2.94 (m, 2H), 2.72-2.66 (m, 2H), 2.36-2.06 (m, 5H), 1.80-1.09 (m, 27H); **TLC** R_f 0.43 (8% MeOH/CH₂Cl₂); **Exact mass** calcd. for [C₆₇H₈₁N₉O₁₀ + Na]⁺ requires *m/z* 1194.6004. Found 1194.6016 (ESI⁺). **HPLC retention time** 9.7 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Chg-(trt)Gln-D-Phe-(BOC)Trp-Phe-OMe (9). ^1H NMR (400 MHz, CDCl_3) δ 8.07 (bd, J = 7.8 Hz, 1H), 7.58-7.48 (m, 4H), 7.27-7.11 (m, 30H), 7.00 (s, 1H), 6.83 (s, 1H), 6.69 (bd, J = 8.0 Hz, 1H), 5.54 (s, 1H), 4.67-4.55 (m, 2H), 4.10-3.97 (m, 3H), 3.42 (s, 3H), 3.30-3.20 (m, 2H), 3.18 (s, 3H), 3.13-2.97 (m, 2H), 2.92-2.86 (m, 3H), 2.76-2.70 (m, 2H), 2.39-2.29 (m, 3H), 2.18-2.10 (m, 5H), 1.85-1.50 (m, 14H), 1.49-1.36 (m, 6H), 1.30-1.00 (m, 12H); **TLC** R_f 0.48 (8% MeOH/ CH_2Cl_2); **Exact mass** calcd. for $[\text{C}_{83}\text{H}_{99}\text{N}_{11}\text{O}_{13} + \text{H}]^+$ requires m/z 1458.7502. Found 1458.7506 (FAB $^+$). **HPLC retention time** 5.1 min on a RP-18 X Terra (Waters) column eluting with 90% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Phe-OMe (10). ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 4.0 Hz, 1H), 7.38-7.06 (m, 24H), 6.90 (s, 1H), 6.78-6.77 (m, 2H), 5.99 (d, J = 4.8 Hz, 1H), 4.60-4.52 (m, 2H), 4.35-4.32 (m, 2H), 4.15-4.10 (m, 3H), 3.54 (s, 3H), 3.27-3.12 (m, 3H), 2.97-2.94 (m, 4H), 2.85-2.78 (m, 2H), 2.62-2.57 (m, 2H), 2.48-2.41 (m, 2H), 2.25-2.19 (m, 5H), 2.11-2.04 (m, 2H), 1.75-1.12 (m, 44H); **TLC** R_f 0.47 (8% MeOH/ CH_2Cl_2); **Exact mass** calcd. for $[\text{C}_{82}\text{H}_{105}\text{N}_{11}\text{O}_{12} + \text{H}]^+$ requires m/z 1436.8022. Found 1436.8035 (ESI $^+$). **HPLC retention time** 3.4 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

BOC-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-L-Phe-Phe-OMe (11). ^1H NMR (400 MHz, CDCl_3) δ 8.31 (bs, 1H), 7.85 (bs, 1H), 7.59 (bs, 1H), 7.47 (bs, 1H), 7.26-7.08 (m, 27H), 6.99 (bs, 1H), 6.86 (m, 2H), 6.76 (s, 1H), 6.41 (s, 1H), 5.88 (s, 1H), 4.62-4.54 (m, 2H), 4.36-4.26 (m, 4H), 4.13 (m, 2H), 3.59 (s, 3H), 3.17 (s, 3H), 2.98-2.90 (m, 2H), 2.84-2.79 (m, 2H), 2.62-2.54 (m, 2H), 2.48-2.40 (m, 2H), 2.25-2.20 (m, 2H), 2.09-2.03 (m, 2H), 1.74-0.87 (m, 51H); **TLC** R_f 0.40 (8% MeOH/ CH_2Cl_2); **Exact mass** calcd. for $[\text{C}_{91}\text{H}_{114}\text{N}_{12}\text{O}_{13} + \text{H}]^+$ requires m/z 1583.8706. Found 1583.8703 (ESI $^+$). **HPLC retention time** 6.2 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at 0.2 mL/min.

BOC-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Val-(BOC)Trp-Phe-OMe (12). ^1H NMR (400 MHz, CDCl_3) δ 8.74 (bs, 1H), 8.17 (bs, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.40-6.91 (m, 30H), 6.75 (s, 2H), 6.71-6.89 (m, 1H), 5.98 (s, 1H), 4.74-4.70 (m, 5H), 4.48-4.08 (m, 6H), 3.64 (s, 3H), 3.23-2.84 (m, 15H), 2.25-2.09 (m, 4H), 1.69-0.76 (60H); **TLC** R_f 0.33 (8% MeOH/ CH_2Cl_2); **Exact mass**

calcd. for $[\text{C}_{103}\text{H}_{132}\text{N}_{14}\text{O}_{16} + \text{Na}]^+$ requires m/z 1843.9843. Found 1843.9840 (ESI⁺). **HPLC retention time** 45.4 min on a RP-18 X Terra (Waters) column eluting with 55% MeOH/water at 0.2 mL/min.

General Procedure for the Baylis-Hillman reaction:

Enantioselective Baylis-Hillman Reaction Employing **10**.

To a 10 mL round bottom flask, flame dried and equipped with a stir bar, was added peptide **10** (0.0015 mmol), dissolved in CHCl_3/THF (1:2, 0.5M), L-proline (0.0015 mmol), aldehyde **1** (0.015 mmol), and methyl vinyl ketone (0.029 mmol). The resulting mixture was stirred until complete loss of starting material was observed by TLC (2:1 hexanes/ethyl acetate). The reaction was diluted with chloroform and purification via flash chromatography (SiO_2 , CHCl_3) afforded 2.7 mg (81%) of **2** as a pale yellow oil.

3-[Hydroxy-(2-nitro-phenyl)-methyl]-but-3-en-2-one (2**).**

¹H NMR (CDCl_3 , 400 MHz) δ 7.98 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 6.22 (s, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 3.49 (bs, 1H), 2.37 (s, 3H); ¹³C NMR (CDCl_3 , 100 MHz) δ 199.5, 149.0, 147.8, 136.7, 133.5, 128.8, 128.5, 126.6, 124.5, 67.1, 26.2; IR (film, cm^{-1}) 3414, 1675, 1525, 1351; TLC R_f 0.52 (40% ethyl acetate/hexanes); $[\alpha]_D^{25}$ -114 (1.0, CHCl_3 , 78% ee); **Exact mass** calcd. for $[\text{C}_{11}\text{H}_{11}\text{NO}_4 + \text{Na}]^+$ requires m/z 244.0586. Found 244.0585 (ESI⁺). **Assay of enantiomeric purity:** Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: 95:5 hexanes: 2-propanol; Flow rate 0.75 mL/min; 29.8 min (minor ent), 32.5 min (major ent).

3-[Hydroxy-(1-nitro-naphthalen-2-yl)-methyl]-but-3-en-2-one (21**).** ¹H NMR (CDCl_3 , 400 MHz) δ 7.99 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.77 (d, J =

8.1 Hz, 1H), 7.66-7.58 (m, 3H), 6.29 (s, 1H), 6.00 (s, 1H), 5.89 (d, J = 4.4 Hz, 1H), 3.51 (d, J = 4.7 Hz, 1H), 2.36 (s, 3H); ¹³C NMR (CDCl_3 , 100 MHz) δ 199.3, 147.5, 146.2, 132.9, 130.8, 130.6, 128.5, 127.8, 127.7, 127.3, 124.0, 123.9, 121.5, 67.9, 26.2; IR (film, cm^{-1}) 3414, 2363, 2332, 1675, 1527, 1361; TLC R_f

0.45 (40% ethyl acetate/hexanes); $[\alpha]_D^{25}$ -196 (1.0, CHCl₃, 73% ee); **Exact mass** calcd for [C₁₅H₁₃N₁O₄ + Na]⁺ requires m/z 294.0742. Found 294.0741 (ESI⁺). **Assay of enantiomeric purity:** Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: 93:7 hexanes: 2-propanol; Flow rate 0.75 mL/min; 34.1 min (minor ent), 38.1 min (major ent).

Proof of absolute stereochemistry. The absolute stereochemistry of the major adduct **22** was determined by comparing the sign of the specific rotation with reported literature data² using the partial kinetic resolution of the racemic compound **22** by Sharpless epoxidation using L-(+)-diethyl tartrate, which should react preferentially with compound (*S*)-**22**. Measurement of the optical rotation and comparison to the literature showed the sample to be of the (*R*)-configuration: $[\alpha]_D^{25}$ -3.8 (0.53, CHCl₃); Literature for (3*R*)-3-[Hydroxy-(4-nitro-phenyl)-methyl]-but-3-en-2-one: $[\alpha]_D^{25}$ -12.1 (0.53, CHCl₃)

3-[(2,4-Dinitro-phenyl)-hydroxy-methyl]-but-3-en-2-one (25). ^1H NMR (CDCl₃, 400 MHz) δ 8.80 (d, *J* = 2.2 Hz, 1H), 8.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.05

(d, *J* = 8.8 Hz, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 5.85 (s, 1H), 3.55 (bs, 1H), 2.38 (s, 3H); ^{13}C NMR (CDCl₃, 100 MHz) δ 199.5, 148.1, 147.9, 147.2, 143.2, 130.6, 127.3, 127.1, 120.1, 67.4, 25.9; **IR** (film, cm⁻¹) 3408, 3106, 2357, 1673, 1606, 1536, 1347; **TLC** *R*_f 0.43 (40% ethyl acetate/hexanes); $[\alpha]_{\text{D}}^{25}$ -135 (*l.o.*, CHCl₃, 63% ee); **Exact mass** calcd for [C₁₁H₁₀N₂O₆ + Na]⁺ requires *m/z* 289.0437. Found 289.0430 (ESI⁺). **Assay of enantiomeric purity:** Enantiomers of product were separated by chiral HPLC employing a Chiralcel OJ column (Diacel). Conditions: 90:10 hexanes:ethanol; Flow rate 0.75 mL/min; 54.3 min (major ent), 63.1 min (minor ent).

3-(Hydroxy-(3-methoxy-2-nitro-phenyl)-methyl)-but-3-en-2-one (26). ^1H NMR (CDCl₃, 400 MHz) δ 7.43 (t, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* =

8.4 Hz, 1H), 6.24 (s, 1H), 5.96 (s, 1H), 5.66 (d, *J* = 5.5 Hz, 1H), 3.89 (s, 3H), 3.46 (d, *J* = 5.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (CDCl₃, 100 MHz) δ 199.7, 150.9, 147.8, 140.2, 134.7, 131.4, 128.1, 119.6, 112.4, 68.1, 56.8, 26.5; **IR** (film, cm⁻¹) 3414, 1674, 1531; **TLC** *R*_f 0.30 (30% ethyl acetate/hexanes); $[\alpha]_{\text{D}}^{25}$ -112 (*l.o.*, CHCl₃, 81% ee); **Exact mass** calcd for [C₁₂H₁₀N₂O₄ + Na]⁺ requires *m/z* 274.0691. Found 274.0699 (ESI⁺). **Assay of enantiomeric purity:** Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: 90:10 hexanes:2-propanol; Flow rate 0.75 mL/min; 30.7 min (minor ent), 33.7 min (major ent).

3-[Hydroxy-(2-trifluoromethyl-phenyl)-methyl]-but-3-en-2-one (27). ^1H NMR (CDCl₃, 400 MHz) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.59 (m, 1H),

7.42 (t, *J* = 7.7 Hz, 1H), 6.19 (s, 1H), 6.06 (bs, 1H), 5.54 (s, 1H), 3.42 (d, *J* = 3.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (CDCl₃, 100 MHz) δ 199.9, 149.7, 139.2, 131.9, 127.7, 127.6, 127.3, 125.7, 122.6, 119.9, 67.3, 26.4; **IR** (film, cm⁻¹) 3420, 1678, 1312, 771; **TLC** *R*_f 0.48 (30% ethyl acetate/hexanes); $[\alpha]_{\text{D}}^{25}$ -31 (0.83,

CHCl₃, 71% ee); **Exact mass** calcd for [C₁₂H₁₁O₂F₃+ Na]⁺ requires *m/z* 267.0609. Found 267.0605 (ESI⁺).

Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: 95:5 hexanes:2-propanol; Flow rate 0.75 mL/min; 13.2 min (minor ent), 15.5 min (major ent).

References and Notes

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