

Supporting Information

General. Microanalyses were performed by Galbraith Laboratories or Atlantic Microlab. The actual charges of substrates and reagents are given below. The molar amounts are calculated based on the assays of the materials. Similarly, yields are calculated based on assay corrected moles of substrates and products. Proton (¹H) nuclear magnetic resonance (NMR) spectra were recorded on either a Unity Inova Varian 300 MHz or Unity Inova Varian 400 MHz spectrometer. ¹H NMR descriptions are reported as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Carbon (¹³C) nuclear magnetic resonance (NMR) spectra were recorded on either a Unity Inova Varian 300 or Unity Inova Varian 400 spectrometer at 75 MHz and 100 MHz, respectively.

Melting points were determined using a Laboratory Devises Mel-Temp Instrument equipped with a Fluke 51 Thermocouple. Thin-layer chromatography was performed on EM Science 0.25 nm Silica Gel 60, glass-backed plates with F₂₅₄ indicator. UV light was employed for visualization. Flash chromatography was performed on Universal Scientific 0-63 mesh Silica Gel. Liquid chromatography and mass spectrum analysis were performed on an Agilent 1100 Series LC/MSD model number G1946D equipped with an APCI ionization source and photodiode array. Chiral HPLC method for separation of enantiomers of **3** utilized a Chiralpak AD column with the hexane:IPA 90:10 + 0.1% TEA as eluting solvent at a flow rate of 1mL/min monitored at 254 nm. The (S)-isomer: retention time was 7.6 min. and the (R)-isomer was 8.4 min.

For pilot plant operations, operators generally employed standard safety precautions including the use of a full-face respirator when charging all materials. Operators were

fitted with either a Tyvek suit or smock and chemical resistant gloves when charging highly hazardous materials. Special equipment needs are noted in the experimental description. All equipment was cleaned and dried to specification prior to use.

Asymmetric Michael Reaction

1,1-Dimethylethyl (E)-3-[3-bromo-5-chloro-2-(methoxymethoxy)phenyl]-2-propenoate (6). To a rapidly stirred suspension of anhydrous LiCl (1.6 g, 0.038 mol) in anhydrous acetonitrile (308 mL) under nitrogen at room temperature was added t-butyl diethylphosphonoacetate (8.35 g, 7.8 mL, 0.033 mol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.04 g, 5.0 mL, 0.033 mol) and **5** (8.8 g, 0.031 mol). The mixture was stirred until complete by TLC (typically 2-3 hours) by which time all of the lithium salt had dissolved. The mixture was then poured into water (200 mL) and the product removed by filtration. The solid was washed with water (4 x 50 mL) then dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with brine (50 mL), dried (MgSO_4), filtered and concentrated. The product was an off-white solid (9.7 g, 82%): mp. 83.0 °C; IR (nujol mull) 1713, 1294, 1276, 1255, 1221, 1161, 1042, 994, 960, 914, 880, 863, 754, 721, 697 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.87 (d, 1H, J = 16.5 Hz, trans alkene CH), 7.59 (d, 1H, ArH), 7.51 (d, 1H, ArH), 7.36 (d, 1H, J = 16.5 Hz, trans alkene CH), 5.00 (s, 2H, CH_2), 3.61 (s, 3H, CH_3), 1.47 (s, 9H, tBu); ^{13}C (CDCl_3) δ 165.8 (CO), 152.6 (C), 137.2 (CH), 134.3 (CH), 132.4 (C), 130.9 (C), 126.5 (CH), 123.8 (CH), 119.1 (C), 101.0 (CH_2), 81.3 (C), 58.7 (CH_3), 28.6 (CH_3).

Salt release of N-allyl- α -methylbenzylamine HCl. A solution of sodium hydroxide (2.24 g, 0.056 mol) in water (60 mL) cooled to 0-5 °C was added in aliquots (S)-N-allyl-

α -methylbenzylamine hydrochloride (10 g, 0.051 mol) while maintaining the temperature between 0-5 °C. The mixture was stirred for 10 min. then extracted with TBME (3 x 20 mL). The combined extracts were washed with brine, dried (MgSO_4), filtered and concentrated. The amine was isolated as a pale yellow oil (7.0 g, 86%): ^1H NMR (CDCl_3) δ 7.25-7.11 (m, 5H, ArH), 5.81 (m, 1H, Allyl CH), 5.05 (m, 2H, Allyl CH_2), 3.72 (q, 1H, CH), 3.00 (d, 2H, Allyl NCH_2), 1.29 (d, 3H, CH_3).

1,1-Dimethylethyl (3R)-3-{allyl[(1S)-1-phenylethyl]amino}-3-[3-bromo-5-chloro-2-(methoxymethoxy)phenyl]propanoate (7). To a solution of N-allyl- α -methylbenzylamine (469 mg, 2.91 mmol) in anhydrous THF (9.6 mL) at 0-5 °C was added dropwise n-butyllithium (1.6M hexanes solution, 1.82 mL, 2.91 mmol). The solution was stirred for 30 min. then cooled to -30 °C. A solution of **6** (1.0 g, 2.649 mmol) in anhydrous THF (2.5 mL) was then added dropwise and the reaction stirred at -30 °C for 2 hours. Saturated NH_4Cl solution (2 mL) was added and the mixture diluted with TBME (10 mL). The aqueous phase was extracted with TBME (3 x 2 mL) and the combined organics washed with 1M citric acid (3 x 5 mL), saturated NaCO_3 (2 x 5 mL) and brine (5 mL). The organic phase was dried (MgSO_4), filtered and concentrated. The residue was purified on silica gel eluting with 0-5 % ethyl acetate/hexane. The product was obtained as a colorless oil (1.06 g, 75%): IR (thin film) 3077, 2977, 2931, 1727, 1450, 1433, 1392, 1368, 1297, 1250, 1203, 1158, 1076, 946, 760, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.33-7.05 (m, 7H, ArH), 5.71 (m, 1H, allyl CH), 5.12-4.85 (m, 4H, allyl CH_2 and MOM CH_2), 4.81 (dd, 1H, NCH), 3.97 (q, 1H, NCHCH_3), 3.51 (s, 3H, CH_3), 3.20 (br d, 2H, allyl CH_2), 2.75 (dd, 1H, CH_2OtBu), 2.43 (dd, 1H, CH_2OtBu), 1.28 (s, 9H, tBu),

1.09 (d, 3H, CH₃); ¹³C NMR (CDCl₃) δ 170.8 (CO), 151.9 (C), 144.7 (C), 140.0 (C), 139.2 (CH), 132.1 (CH), 130.3 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.0 (CH), 118.7 (C), 116.0 (CH₂), 100.7 (CH₂), 80.9 (C), 58.7 (CH), 56.7 (CH), 54.0 (CH₃), 49.7 (CH₂), 40.7 (CH₂), 28.3 (CH₃), 15.5 (CH₃).

1,1-Dimethylethyl (3R)-3-[3-bromo-5-chloro-2-(methoxymethoxy)phenyl]-3-[(1S)-1-phenylethyl]amino}propanoate (8). A solution of **7** (0.5 g, 0.929 mmol) in anhydrous CH₂Cl₂ (2.5 mL) was degassed. This was added catalytic tetrakis(triphenylphosphine)palladium (10.7 mg) and N,N-dimethylbarbituric acid (435 mg, 2.787 mmol). The solution was stirred at 30-35 °C for 2 h. After cooling to room temperature the CH₂Cl₂ was removed *in vacuo* and replaced by TBME (10 mL). The ethereal solution was extracted with saturated K₂CO₃ (2 x 2 mL) then filtered to aid separation of an emulsion. The TBME solution was dried (MgSO₄), filtered and concentrated to give a pale-yellow oil (480 mg) that contained 13% diallyldimethyl barbituric acid. The corrected yield of product was 91%: IR (thin film) 3081, 2977, 2932, 2830, 1726, 1681, 1451, 1433, 1381, 1369, 1312, 1295, 1256, 1199, 1158, 1073, 996, 949, 862, 846, 824, 758, 701 cm⁻¹; ¹H NMR (CDCl₃) δ 7.05-7.35 (m, 7H, ArH), 5.25 (dd, 2H, MOM CH₂), 4.62 (dd, 1H, NCH), 3.60 (q, 1H, NCHCH₃), 3.45 (s, 3H, CH₃), 2.59 (dd, 1H, CH₂OtBu), 2.38 (dd, 1H, CH₂OtBu), 1.35 (s, 9H, tBu), 1.31 (d, 3H, CH₃); ¹³C NMR (CDCl₃) δ 171.1 (CO), 152.0 (C), 146.0 (C), 140.5 (C), 131.8 (CH), 131.2 (C), 130.7 (C), 128.7 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 100.7 (CH₂), 81.2 (C), 58.2 (CH₃), 56.0 (CH), 52.1 (CH), 43.1 (CH₂), 28.5 (CH₃), 23.3 (CH₃); mass spectrum (m/z, ES+) 502 (11), 500 (100), 498 (75).

1,1-Dimethylethyl (3R)-3-amino-3-[2-(methoxymethoxy)phenyl]propanoate (9).

To a solution of **8** (100 mg, 0.2 mmol) in methanol/water/acetic acid (3.5 mL, 85:12:3) was added palladium on carbon (40 mg, 10%, 50% Degussa wet paste). The mixture was degassed thoroughly with nitrogen, then hydrogen and stirred at ambient for 18 hours. The catalyst was removed by filtration through Celite® and the solution concentrated. The residue was dissolved in TBME (20 mL) and extracted with 1M hydrochloric acid (3 x 5 mL). The pH of the combined aqueous extracts was adjusted to pH 8 with potassium carbonate. This was extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried (MgSO_4), filtered and concentrated to give the amine **9** as a pale-yellow oil (44 mg, 79%). The loss of both halogens was confirmed by ^{13}C NMR and mass spectrum analysis: IR (thin film) 3380, 2977, 1725, 1601, 1489, 1368, 1233, 1199, 1154, 1079, 1000, 757 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.31-6.85 (m, 4H, ArH), 5.16 (s, 2H, MOM CH_2), 4.58 (dd, 1H, CHNH_2), 3.42 (s, 3H, CH_3), 2.64 (dd, 1H, CH_2), 2.52 (dd, 1H, CH_2), 1.55 (brs, 2H, $\text{NH}_2 + \text{H}_2\text{O}$), 1.37 (s, 9H, tBu); ^{13}C NMR (CDCl_3) δ 172.0 (CO), 154.8 (C), 128.6 (CH), 127.5 (CH), 122.3 (CH), 114.4 (CH), 94.8 (CH_2), 81.0 (C), 56.6 (CH_3), 55.5 (CH), 44.1 (CH_2), 28.5 (CH_3); mass spectrum (m/z, ES+) 282 (100), 226 (38), 209 (11) ($\text{C}_{15}\text{H}_{24}\text{NO}_4 = 282$).

Asymmetric Enamine Reduction

Synthesis of Ethyl 3-(3-bromo-5-chloro-2-hydroxyphenyl)-3-oxopropanoate (11).

To a solution of **10** (20.0 g, 0.117 mol) in DMF (200 mL) was charged solid N-bromosuccinimide (22.95 g, 0.129 mol). After stirring for 3 h at room temperature a further charge (4.16 g) of N-bromosuccinimide was added. After stirring for 1 h, the reaction was quenched with water (500 mL) and cooled in an ice bath for 30 min. The resulting solid was collected by filtration and washed with water (2 x 100 mL). The crude product (28.2 g) was slurried in methanol (40 mL) for 2 hours, then cooled to < 10 °C, filtered and the solid washed with methanol (2 x 10 mL) to give 22.8 g (78% yield) of **11** as a beige solid. ¹H NMR (CDCl₃) δ 12.75 (s, 1H, OH), 7.65 (d, 1H, ArH), 7.60 (d, 1H, ArH), 2.60 (s, 3H COCH₃).

A solution of **11** (13.0 g, 0.052 mol) and diethyl carbonate (24.6 g, 0.21 mol) in toluene (104 mL) was added dropwise *via* dropping funnel to sodium hydride (60% dispersion in mineral oil, 4.59g, 0.115 mol) in toluene (26 mL) under a nitrogen atmosphere, keeping the temperature below 30 °C. After the addition was complete the reaction was heated to reflux for 2 h. *Caution: Vigorous gases evolution occurs at 85-90 °C.* After 2 h the reaction was cooled to room temperature and quenched by the addition of 3M HCl (260 mL). To this was added ethyl acetate (200 mL), the layers separated and the aqueous layer extracted with ethyl acetate (50 mL). The combined organic layers were washed with saturated NaHCO₃ (130 mL) and water (50 mL), dried (MgSO₄) and concentrated to a yellow solid (17.6 g): mp. 75 °C; IR (nujol mull) 1715, 1633 cm⁻¹; ¹H NMR (CDCl₃) δ 12.35.(s, 1H, OH), 7.7 (s, 1H, ArH), 7.6 (s, 1H, ArH), 4.15 (q, 2H, OCH₂), 3.9.(s, 2H, CH₂), 1.2.(t, 3H, CH₃); ¹³C NMR (CDCl₃) δ 197.9 (ketone CO), 166.4

(ester CO), 158.3, 139.9, 129.2, 124.6, 120.2, 113.6, 62.49 (CH₂), 46.2 (OCH₂), 14.4 (CH₃).

Ethyl 3-(acetylamino)-3-[2-(acetyloxy)-3-bromo-5-chlorophenyl]-2-propenoate (12). To a clear stirred solution of **11** (4.0 g, 12.5mmol) in DMF (80 mL) was added ammonium acetate (12 g). The resultant suspension was stirred overnight (16 h) at room temperature to afford a deep yellow suspension. The solvent were removed *in vacuo* at 30 °C, the residue poured onto water (100 mL), extracted with ethyl acetate (4 x 50 mL), washed with water (50 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo*. The residue was dissolved in TBME (50 mL) and hexanes added (50 mL). This was concentrated *in vacuo* to approximately 60 mL, and allowed to stand for 30 min. prior to filtration and isolation of the first crop of corresponding enamine (2.1 g). The mother liquors were then removed *in vacuo* to afford a crude reaction product that was purified by silica gel column chromatography using hexanes: ethyl acetate (3:7). Concentration *in vacuo* afforded a second crop of the enamine, ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)-2-propenoate (0.8 g, 73% combined): mp 89-91 °C (dec); IR (nujol mull) 1712, 1616, 1524 cm⁻¹; ¹H NMR (DMSO) δ 10.10-9.50 (br, 1H, NH/OH), 7.70 (d, 1H, ArH), 7.50-7.70 (br, 2H, NH/OH), 4.52 (s, 1H, CHCO₂Et), 4.05 (q, 2H, OCH₂CH₃), 1.20 (t, 3H, OCH₂CH₃); ¹³C NMR (DMSO) δ 1169.5, 157.8, 132.8, 129.0, 128.4, 123.8, 113.3, 84.5, 58.3, 14.9. A duplication of signals was observed when using CDCl₃ as NMR solvent. ¹H NMR (CDCl₃) δ 10.25-10.45 (br, 0.99H, NH/OH), 7.66 (d, 0.33H, ArH), 7.56 (d, 0.67H, ArH), 7.37 (d, 0.33H, ArH), 7.34 (d, 0.67H, ArH), 6.45-6.65 (br, 2.01H, NH/OH), 4.92 (s, 0.67H, CHCO₂Et), 4.30 (q, 0.66H, OCH₂CH₃), 4.20 (q, 1.34H, OCH₂CH₃), 1.33 (t, 3H, OCH₂CH₃).

To an equivolume mixture of acetic anhydride and pyridine (1.8 mL) was added ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)-2-propenoate (198 mg, 0.617 mmol). The yellow solution was left stir overnight (16 h) at room temperature prior to being poured onto saturated aqueous ammonium chloride (50 mL). This was extracted with ethyl acetate (3 x 25 mL), the organic layer dried (MgSO_4) and filtered. Removal of the solvents *in vacuo* afforded a pale colored solid that was purified by silica gel column chromatography (hexanes:ethyl acetate 5:1) to afford **12** as pale colored crystals. Recrystallization from ethyl acetate:hexanes gave rise to 234 mg of **12** (94%) as clear transparent crystals: mp 131-133 °C; IR (nujol mull) 1778, 1703, 1663, 1629, 1583, 1294, 1170 cm^{-1} ; ^1H NMR (CDCl_3) δ 10.89-10.82 (br, 1H, NH), 7.62 (d, 1H, ArH), 7.25 (d, 1H, ArH), 5.11 (s, 1H, CHCO_2Et), 4.22 (q, 2H, OCH_2CH_3), 2.30 (s, 3H, Ac), 2.14 (s, 3H, Ac), 1.32 (t, 3H, t, OCH_2CH_3); ^{13}C NMR (CDCl_3) δ 168.8, 168.0, 148.5, 144.5, 133.6, 133.5, 133.4, 132.3, 128.3(3), 128.3(1), 117.8, 101.6, 61.6, 24.7, 20.8, 14.5.

(\pm)-Ethyl 3-(acetylamino)-3-[2-(acetoxyl)-3-bromo-5-chlorophenyl]-2-propenoate (\pm **3).** A 4-dram pressure vial containing **12** (50 mg, 0.124 mmol) and methylene chloride (2 mL) was degassed with argon. To this was added Rh-DUPHOS catalyst (5-7 mg, *ca* 7 nmol, *ca* 5-7 mol%). A small stirring bar was added and the reactor sealed inside a high-pressure reaction vessel. An atmosphere of AR hydrogen was then introduced and the pressure maintained at 8 bar for *ca* 2 minutes prior to venting. This procedure was repeated 5 times. The high-pressure reaction vessel was then repressurized with hydrogen (5 bar) and the contents left to stir at room temperature overnight (15-17 h). The vessel was vented and the contents filtered through a short plug of silica gel using ethyl acetate. The fractions were combined and concentrated *in vacuo*. The product was dissolved in

CDCl₃ and the reaction product composition analyzed by 360 MHz ¹NMR spectroscopy and by chiral HPLC.

Resolution of (±)-3 via diastereomeric salt formation.

8-Bromo-6-chloro-2H-1-benzopyran-2-one (13). To an inerted, 378 L (100 gal) reactor equipped with a reflux condenser was charged **4** (20 kg, 85 mol) and acetic anhydride (46.7 kg, 457 mol). Triethylamine (8.59 kg, 85 mol) was charged while maintaining 25 °C cooling on the jacket. A 20 °C temperature rise was observed and all starting material was dissolved giving rise to a dark, reddish-brown solution. The reaction mass was heated to 135 °C. Reflux began at 120 °C and the reaction mixture turned completely brown. This temperature was maintained for 14 h. The solution was then cooled to 70 °C (*note the reaction mass solidifies if cooled to 65 °C*) and 100 % ethanol (8.58 kg, 186 mol) charged while maintaining 70 °C ± 5 °C. Water (143 kg, 7.96 kmol) was added again while maintaining a temperature of 70 °C ± 5 °C. The contents were cooled over a 4 h period to 20 °C and the product mixture transferred to a 0.2 m² Hastelloy C, jacketed, agitating Nutsche filter. The product cake was deliquored and dried *in vacuo* to afford **13** (17.28 kg) in 79% yield: mp. 151-154 °C.

(±)-Ethyl β-amino-3-bromo-5-chloro-2-hydroxybenzenepropanoate, monohydrochloride (±)-(3). To a 378 L (100 gal) pressure reactor equipped for distillation was charged **13** (16.6 kg, 63.8 mol) and 2B ethanol (50 kg). The reactor was sealed and anhydrous ammonia (109 kg) charged. The batch was heated to 80 °C with agitation attaining an internal pressure of 581 psig. After 24 h, the batch was cooled to 25-30 °C and carefully vented to another reactor configured with an acid scrubber. The reaction

mixture was allowed to sit overnight for further venting. The next morning heat was applied to the jacket to drive off the remaining ammonia. At one point vacuum was applied to assist with the ammonia purge. Following this procedure, the ammonia/ethanol solution was distilled to minimum stir volume, and ethanol 2B (52 kg) charged back to the reactor. After stirring for 0.5 h, HCl (23 kg) was carefully charged to the reaction mixture over a 2.5 h period. An exotherm from ambient to reflux was observed during the addition. Upon completion, the temperature of the system was increased to reflux (79 °C), maintained for 1 h. and then distillation *in vacuo* completed affording approximately 190 L of distillate. Toluene (67 kg) followed by hexane (67 kg) was added to the mixture to yield a thin, light-brown slurry. The batch was dropped employing a 24" centrifuge, the cake washed with hexanes and then transferred to a tray dryer where the product was dried at 40 °C for approximately 60 h to afford 17.8 kg of **(±)-3** as the monohydrochloride salt.

Formation of ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt. Solid (R)-(-)-mandelic acid (943 mg, 6.2 mmol) was added to a stirred solution of racemic **3** free base (2.0 g, 6.2 mmol) in ethyl acetate (30 mL) and the mixture was heated to reflux with stirring. The yellow solution was cooled to ambient temperature to precipitate an off-white solid. After 1 hour the solid was filtered, washed by displacement with ethyl acetate (2 x 4 mL) and dried to give ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt as an off-white solid (1.33g, 45%, 63.2% ee). ^1H NMR (DMSO) δ 7.60-7.00 (m, 7H, ArH), 4.95 (s, 1H, CH(OH)CO₂H), 4.58 (t, 1H, CH₂CHNH), 4.03 (q, 2H, CH₃CH₂O), 2.85 (m, 2H, CH₂CHNH), 1.15 (t, 3H, CH₃CH₂O).

Recrystallization of ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt. Ethyl acetate (19 mL) was added to ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt (1.25 g, 2.6 mmol) and the mixture was heated to reflux with stirring. The pale yellow solution was cooled to ambient temperature, precipitating a white solid. After a 1 h the solid was filtered, washed by displacement with ethyl acetate (2 x 2.5 mL) and dried to give purified ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt as a white solid (0.71 g, 57%, 92.2% *ee*).

A second recrystallization (0.55g mandelic acid salt) from ethyl acetate (8.25 mL), following the method described above, gave ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate mandelic acid salt as a white solid (0.39g, 71%, 99% *ee*).

Formation of ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt. Solid (1R)-(-)-10-camphor sulfonic acid (1.44 g, 6.2 mmol) was added to a stirred solution of racemic ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate free base (2.0 g, 6.2 mmol) in isopropanol (10 mL) and the mixture was heated to reflux with stirring. The yellow solution was cooled to ambient temperature to precipitate an off-white solid. After a 1 h the solid was filtered, washed by displacement with isopropanol (2 x 4ml) and dried to give ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt as an off-white solid (1.4 g, 41%, 53% *ee*). ^1H NMR (DMSO) δ 7.70 (d, 1H, ArH), 7.52 (d, 1H, ArH), 4.90 (bt, 1H, CH_2CHNH), 4.02 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 3.02 (m, 2H, CH_2CHNH), 2.90 (d, 1H, CSA), 2.65 (m, 1H, CSA), 2.45 (d, 1H, CSA), 2.25 (m, 1H, CSA), 2.10-1.70 (m, 1H, CSA), 1.30 (m, 2H, CSA), 1.15 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.05 (s, 3H, CSA), 0.80 (s, 3H, CSA).

Recrystallization of ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt. Isopropanol (19 mL) was added to ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt (1.31 g, 2.4 mmol) and the mixture was heated to reflux with stirring. The pale yellow solution was cooled to ambient temperature to precipitate a white solid. After a 1 h the solid was filtered, washed by displacement with isopropanol (2 x 2.5 mL) and dried to give purified ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt as a white solid (0.79g, 60%, 93% *ee*).

A second recrystallization (0.70 g camphorsulfonic acid salt) from isopropanol (10.5 mL) following the method described above, gave ethyl 3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate camphorsulfonic acid salt as a white solid (0.50 g, 71%, >98% *ee*).

Imino-Reformatsky Approach.

3-Bromo-5-chloro-2-[(2-methoxyethoxy)methoxy]benzaldehyde (14). To a clean, dry 378 L (100 gal) was charged with deadhead vacuum DMF (81 kg). Aldehyde **4** (24.5 kg 104 mol) and potassium carbonate (14.4 kg, 104 mol) were charged via the manway. The reactor was sealed and capped with nitrogen. After 20 min of agitation, methoxyethoxymethyl chloride (13.7 kg, 110 mol) was charged *via* a small pump and nalgene addition line while maintaining an internal temperature of 20-25 °C. *Caution, MEM chloride is clear, flammable, toxic lachrymator and may cause heritable genetic damage. Avoid inhalation and contact.* The reaction mixture was agitated for 3.5 h.

To a clean 757 L (200 gal) reactor was charged 397 L (105 gal) of water. The reaction mixture was transfer to the reactor containing the water. The product begins to precipitate from solution. After complete addition, the slurry was stirred for 1-2 h. The precipitated product was isolated by filtration on a 24-inch centrifuge. This required 1 or 2 loads. Each cake was washed twice with water (23 L) and spin dry as much as possible. The wet cake was dried in a vacuum tray dryer at 15-20 °C for 16 h. *Note – do not heat the dryer since the product melts at 31-33 °C.* Isolated was 31.1 Kg (92%) of **14**: m.p. 32.5-33 °C.

Preparation of t-butoxycarbonylmethyl zinc bromide (Reformatsky reagent). To a clean, dry, inerted 757 L (200 gal) jacketed reactor equipped with reflux condenser was charged zinc (45.6 kg), THF (327 kg), and 1,2-dibromoethane (4.0 kg). Agitation was initiated, the reaction contents heated to reflux (ca. 67 °C) and held at reflux for at least 1 h. The contents were cooled to 50 °C, then t-butyl bromoacetate charged in the following sequence – 15.5 kg, 15.5 kg, 31.0 kg, 31.0 kg, and 31.0 kg. An exotherm was

observed with each charged and that exotherm allowed to subside before addition of the next aliquot. *Caution. Failure to follow this charge protocol may result in an uncontrollable exotherm.* After complete addition of the t-butyl bromoacetate, the batch was held at 50 °C for at least 1 h, cooled to 0 °C and no more than 45% by weight (ca. 147 kg) removed *in vacuo*. *Note removal of too much solvent may result in aggressive precipitation and stop the agitator.* NMP (123 kg) was added to the resulting concentrate and the reagent solution cooled to –15 °C. *Note the reagent is not stable in NMP at ambient temperature for extended period of time.*

β-(S)-β-[(E)-[3-bromo-5-chloro-2-[(2-methoxyethoxy)methoxy]phenyl]methyl-ene]amino]phenylethanol (15). To a clean, dry and inerted 2839 L (750 gal) glass-lined reactor was charged **14** (240 kg, 742 mol) and NMP (221 kg). The contents were stirred for 15 min and batch temperature maintained at 25 °C. *Note the dissolution is endothermic.* In a separate vessel was charged (S)-(+)-Phenylglycinol (102.3 kg, 746 mol) and NMP (221 kg). The contents were stirred for 15 min and batch temperature maintained at 25 °C. *Note the dissolution is endothermic.* The phenylglycinol containing solution was transferred to the **14** solution and the mixture stirred for at least 24 h. Once complete, the product solution was dried employing a column of molecular sieves (180 kg) giving rise to a product solution with ≤ 0.4 wt. % moisture. The solution was placed in a glass-lined reactor and cooled to –15 °C.

1,1-Dimethylethyl (S)-3-bromo-5-chloro-2-[(2-methoxyethoxy)methoxy]-β-[(1S)-2-hydroxy-1-phenylethyl]amino]benzenepropanoate (16). The NMP solution of **15** was transferred to the Reformatsky reagent solution over 4 h period while maintaining a temperature below –5 °C. *Note there is a delayed exotherm observed upon initial*

addition. This was held at -5 °C for at least 3 h and then cooled to -15 °C. Filter the solution to remove excess Zinc.

In a separate vessel was prepared the quench solution by charging water (1090 Kg), NH₄Cl (266 Kg) and 37% HCl (62 kg). This mixture was stirred until the ammonium chloride dissolved and then precooled to 5 °C. *Note this was a temperature adjustment to aid in controlling the exotherm of the subsequent quench. Be mindful that cooling does cause some precipitation of NH₄Cl.* Transfer the quench solution slowly into the solution containing **15** while maintaining the internal temperature below 10 °C. After the addition was complete, the contents were warmed the contents to 20 °C. Charge MTBE (800 kg) and stir for 30 minutes. The agitation was stopped and the contents allowed to settle for 1 hour. *Note the organic and aqueous layers are similar in color.* Transfer the aqueous layer to another vessel and charge MTBE (425 kg) to the vessel containing this aqueous layer. This was stirred for 20 min. and allowed to settle for 20 min. The aqueous layer was separated and disposed of.

The combined organic extracts were washed with 19 wt. % aqueous NH₄Cl (562 kg), water (600 L) and 23 wt. % aqueous NaCl (630 kg). The resulting product solution was vacuum distill until an internal of 45 °C was reached. *NOTE the vacuum was approximately 2 psia.* The contents were allowed to cool to 25 °C and methanol (411 kg) charged. The methanol solution of **15** was cooled to 0-5 °C and used without further purification.

1,1-Dimethylethyl (3S)-3-[3-bromo-5-chloro-2-(methoxyethoxy)phenyl]-3-[[1-phenylmethylidene]amino]propanoate (17). To separate vessel was charged sodium periodate (319 kg, 1490 mol) and methanol (686 kg). Stirring was initiated and the

contents heated to 30 °C. To this was charged 33 wt. % methylamine in ethanol (84.8 kg, 900 mol). The aforementioned methanol solution of **15** was charged and held at 30 °C for 12 h. *Note the **15** charge needs to occur within 1 hour of the methylamine charge; otherwise loss of conversion is observed.* After the 12 h hold, ethyl acetate (2622 kg) was added and this agitated for 15 minutes.

The filter was pre-coated with Celite (34 kg), then the inorganics filtered off. The filter cake was washed with ethyl acetate (379 kg) and the organic extracts combined. The solids were disposed of. The system was vacuum distilled until minimum stir volume or until batch temperature 40 °C was reached. *Note potential excess methylamine may need to be scrubbed from the distillate.* To this was charged ethyl acetate (2622 kg) and vacuum distilled again until minimum stir volume or until a batch temperature 40 °C was reached until the methanol content was 2.5 wt. % by GC. *Note the methanol content is important to maximize the yield of product in the following operations.*

To the reaction mixture was charged ethyl acetate (1880 kg). The solution was stirred for 10 min, then water (1487 kg) added. This mixture was stirred for 30 min., agitation halted and allowed to settle for 30 min. The aqueous phase was transferred to a separate vessel and back extracted with ethyl acetate (540 kg). The aqueous phase was disposed of and the organic phases combined.

To a separate vessel was prepared a 20 wt. % aqueous sodium thiosulfate pentahydrate (596 kg) solution. This was charged to the organic phase, stirred for 20 min., allowed to settle for 60 min and the aqueous phase disposed of. The organic phase was then washed with 24 wt. % brine solution (625 kg) and the aqueous wash disposed

of. The organic phase was distilled *in vacuo* to a minimum stir volume or until the batch temperature reached 40 °C. Following this distillation ethanol (743 kg) was charged to the reaction mixture and this distilled to a minimum stir volume or until the batch temperature reached 40 °C. Finally, ethanol (1390 kg) was charged giving rise to a solution of **17**, which was used without further purification. *Note the ethyl acetate content should be ≤ 0.7% and the water ≤ 0.2%.* Isolated sample: IR (thin film): 2977, 2930, 2882, 1726, 1642 cm⁻¹; ¹H NMR (CDCl₃) δ 8.35 (s, 1H, ArH), 7.70 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.20 (m, 4H, ArH), 5.17 (m, 3H, OCH₂CH₂O and CH₂CHN), 4.00 (m, 2H), 3.55 (m, 2H), 2.80 (dd, 1H, CH₂CHN), 2.72 (dd, 1H, CH₂CHN), 1.27 (s, 9H, tBu); ¹³C NMR (CDCl₃) δ 177.4 (C, CO), 170.2 (CH, ArCHN), 158.2 (C, Aryl), 147.7 (C, Aryl), 143.6 (C, Aryl), 139.2 (CH, Aryl), 138.6 (CH, Aryl), 138.2 (C, Aryl), 136.2 (CH, Aryl), 134.8 (CH, Aryl), 125.2 (C, Aryl), 107.1 (CH₂, OCH₂O), 88.3 (C, tBu), 79.4 (CH₂, OCH₂CH₂O), 77.5 (CH₂, OCH₂CH₂O), 72.4 (CH, CH₂CHN), 66.7 (CH₃, OMe), 51.3 (CH₂, CH₂CHN), 35.7 (CH₃, tBu).

Ethyl (3S)-3-amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)propanoate 4-methylbenzenesulfonate (3). To a clean, dry reactor was added p-toluenesulfonic acid monohydrate (184 kg, 967 mol). The ethanol solution of **17** was transferred to this vessel and agitation initiated. The reaction mixture was heated to reflux (70-78 °C) and held at reflux for 8 h. The contents were cooled to 10 °C and then vacuum distilled to minimum stir volume or until the batch temperature reached 40 °C. *Note removing too much solvent will give rise to an extremely viscous/solids slurry.* Once the distillation was complete, THF (642 kg) was charged, the contents cooled to 10 °C and vacuum distillation resumed to either a minimum stir volume or until batch temperature reached 40 °C. After this

distillation was complete, THF (658 kg) was charged and the contents heated to 65 °C. Once the product was dissolved, heptane (1015 kg) was charged at such a rate as to maintain 65 °C. *Note product will precipitate during heptane addition.* The contents were then cooled to 5 °C and held that this temperature for 2 h.

To a separate vessel was charged acetone (932 kg). The acetone was cooled to 0 °C. The (S)-3 ethyl ester, p-TsOH salt was filtered and the product cake washed with the cold acetone in 3 equal portions. The wet cake of (S)-3 ethyl ester, p-TsOH was dried *in vacuo* in a tumble dryer at 25 °C until a LOD of less than 1.0% was achieved affording 100 kg (51%) of (S)-3 ethyl ester, p-TsOH: m.p. 118.1 °C; IR (nujol mull) 1724, 1598, 1327 cm⁻¹; ¹H NMR (DMSO) δ 7.73 (s, 1H, ArH), 7.50 (d, 3H, ArH), 7.10 (d, 2H, ArH), 4.90 (m, 1H, CH₂CHN), 4.06 (q, 2H, CH₃CH₂O), 3.00 (m, 2H, CH₂CHN), 2.30 (s, 3H, CH₃-Ar), 1.15 (t, 3H, CH₃CH₂O); ¹³C NMR (DMSO) δ 169.4 (C, CO), 151.1 (C, Aryl), 146.1 (C, Aryl), 137.9 (C, Aryl), 132.6 (CH, Aryl), 128.4 (CH, Aryl), 127.6 (CH, Aryl), 125.8 (CH, Aryl), 124.5 (C, Aryl), 112.8 (C, Aryl), 61.0 (CH₂, CH₃CH₂O), 46.2 (CH, CH₂CHN), 37.5 (CH₂, CH₂CHN), 21.1 (CH₃, Me-Ar), 14.2 (CH₃, CH₃CH₂O). *ee* >98% (chiral HPLC). Anal. Calcd for C₁₈H₂₁BrClNO₆S: C, 43.69; H, 4.27%; N, 2.83; Br, 16.15; Cl, 7.16; S, 6.48. Found: C, 44.47; H, 4.46; N, 2.66; Br, 15.15; Cl, 7.05%, S, 6.52.