Supporting Information

Practical Asymmetric Synthesis of a Selective Endothelin A Receptor (ETA) Antagonist

Zhiguo J. Song*, Matthew Zhao, Lisa Frey, Jing Li, Lushi Tan, Cheng Y. Chen, David M. Tschaen, Richard Tillyer, Edward J. J. Grabowski, Ralph Volante, Paul J. Reider

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065.
zhiguo_song@merck.com

Yoshiaki Kato, Shigemitsu Okada, Takayuki Nemoto, Hiroki Sato, Atsushi Akao, Toshiaki Mase

Process R & D, Banyu Pharmaceutical Co. Ltd., Okazaki, Aichi 4440858, Japan

Experimental

General Moisture content in solvents and solutions were titrated on Karl Fisher coulometers and given as KF values (µg/ml or µg/g water). Purities by HPLC were reported as area percent (A%) of the desired peak based on integration of all signals or weight percent (Wt%) relative to a reference sample.

1,4-Dibromo-2-hydroxyethoxybenzene (7) Under nitrogen, to a three-necked flask was added ethylene glycol (350 mL), 1,4-dibromo-2-fluorobenzene (**6**, 68.6 g, 270 mmol), and 1-methyl-2-pyrrolidinone (35 mL). Solid potassium *t*-butoxide (112 g, 950 mmol) was added over 5 min. The batch was heated to 97-100 °C and aged at the same temperature for 8 h until HPLC indicated < 1.0% of starting material. The batch was homogeneous at the beginning but some solid precipitated out as the reaction proceeds. The batch was allowed to cool to 24 °C and water (137 mL) was added over 0.5 h. The mixture was filtered, and the solid was washed with ethylene glycol (2 x 15 mL). Water (1.2 L) was added to the combined filtrate and wash over 30 min. The mixture was cooled to 15 °C and aged for 1 h. The solid was collected by filtration, washed with water (2 x 20 mL), and dried by suction under nitrogen. Alcohol **7** was isolated as a light yellow solid (69.6 g, 87% yield, 100 A% pure). HPLC conditions: Zorbax RX-C18, 4.6 x 150; MeCN/0.1% H_3PO_4; 1.0 mL/min; Gradient: time 0, 50/50, 13 min 80/20; UV detector: 230 nm; Retention times (min): 1,4-dibromo-2-fluorobenzene **6**, 10 min, 1,4-dibromo-2-hydroxyethoxybenzene **7,** 6min.

2-Bromoethoxy-1,4-dibromobenzene (8) To a solution of 1,4-dibromo-2-hydroxyethoxybenzene (10.05 g, 33.9 mmol) in toluene (72 mL) was added PBr_3 (1.45 mL, 15.27 mmol) (5 min). The mixture was heated to 90 °C and aged for 2 h. The remainder of the PBr_3 was added followed by water (0.2 mL). The batch was heated at 90 °C for an additional 8 h and cooled to room temperature. The batch was quenched with 1 N NaOH (60 mL) slowly (30 min). The two layers were separated. The organic layer was washed with water and saved for the next step. HPLC conditions: Zorbax RX-C18, 4.6 x 150; MeCN/0.1% H_3PO_4 at 1.0 mL/min; Gradient: time 0, 50/50, 13 min 80/20; UV detector: 230 nm; Retention times (min): 2-bromoethoxy-1,4-dibromobenzene **8**, 10.5 min, intermediate ,11.0 min

A white crystalline solid resulted when all the solvent was removed under vacuum. mp. 57-59 ^oC. ^1H HMR (400 MHz, $CDCl_3$) 3.68 (t, J=6.3 Hz, 2H), 4.33 (t, J=6.3 Hz, 2H), 7.01-7.03 (m, 2H), 7.40 (d, J=9.9 Hz, 1H).

6-Bromo-2,3-dihydrobenzofuran (5) The tribromide solution from the previous step was concentrated to ~ 10 L and flushed with dry toluene (20 L). The final volume was about 8 L before the addition of THF (18 L). The batch was cooled to - 73 °C and *n*-butyllithium (1.6 M in hexane, 6.0 L) was added slowly, keeping the temperature < - 70 °C. The starting material was assayed by HPLC 15 min after the completion of the addition and more *n*-butyllithium was added (a total of 0.4 L) until no starting material was detected by HPLC. It took 5 h to complete the addition of *n*-butyllithium due to the poor cooling. Excess *n*-butyllithium was quenched with acetic acid (60 mL) before the batch was allowed to warm to 0 °C. Water (17 L) was added and the two layers were cut. The organic layer was washed with 0.5 N NaOH (2 x 9 L) and water (8 L). The batch was concentrated to ~ 8 L and flushed with methanol (2 x 10 L). The final volume was adjusted to ~ 8 L and the batch was cooled to 15-20 °C until some product crystallized, whereupon water (7 L) was added over 2 h (final methanol/water ~1:1). The batch was aged at 15 °C for 1h and filtered. The solid was washed with 2:3 methanol/water (2 x 4 L) and dried by suction under nitrogen for 6 h. Product (**5**) was isolated as a white solid (1.71 kg, KF = 7.3 µg/1 g, 95.07A%, 97 wt%, 85.5% corrected yield). There were 5 impurities in the product ranging from 0.5 to 1.6 A% which were not identified. HPLC conditions: Zorbax SB-C8 4.6x250; MeCN/0.1% H_3PO_4 at 1.5 mL/min; Gradient: time 0, 50/50, 10 min 90/10; UV detector: 220 nm; Retention time: 7.4 min .

6-Bromo-2-(N-isopropyl-N-benzylamino)pyridine (10) n-BuLi (1.27 L, 2.5 M, 3.18 mol) was added to a solution of *N*-isopropylbenzylamine (473g, 3.17 mol) in 0.67 L toluene and 0.72 L hexane at -15 to -10 °C in 1.75 h. The mixture was aged at -10 to 0 °C for 0.5 h to give the lithium amide. It was then transferred into a slurry of 2,6-dibromipyridine (500 g, 2.11 mol) and *N*-isopropylbenzylamine (317 g, 2.11 mol, 1.0 equiv.) in toluene (2.5 L) and hexane (2.5 L) at 5 to 10 °C in ~1 h. The mixture was stirred at 0 °C until the reaction was complete as monitored by HPLC. HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 40-90% in 15 min; 1.50 mL/min, 10mM Trizma buffer (pH = 7); 30 °C, UV detection at 220 nm; Retention times (min): 2,6-dibromopyridine 5.8, *N*-isopropylbenzylamine 5.1 (broad), product 12.6. The reaction was quenched by transferring the reaction mixture via a cannula into 2 *N* HCl (2.5 L) at 10-20 °C with vigorous stirring (some insoluble material was observed). The flask was rinsed with hexane (~250 mL x 2). DMF (1.5 L) was

added to dissolve most of the dark precipitate. The mixture was stirred for 20 minutes then settled. The layers were separated and the organic layer was washed with 3/1 DMF/water mixture (1.6 L) and then water (2.0 L x 2). It was concentrated under vacuum (100-40 mmHg, 40 °C bath) to a minimum volume then flushed with toluene (500mL x 2) (40-20 mmHg, 40-50 °C bath) then pumped for two hours to give the crude product **10** (596 g, 93.3wt%, 86% yield). ^{1}H NMR indicated 5.7wt% toluene. ^{13}C NMR (67 MHz, $CDCl_3$, ppm) 167.1, 140.0, 139.9, 139.1, 128.5, 126.7, 126.2, 114.7, 105.3, 46.4, 46.2, 20.1. HPLC indicated 2.7A% toluene, 0.8A% bis-amination product and 94.4A% of the desired product.

6-Bromo-3-formyl-2-(*N*-isopropyl-N-benzylamino)pyridine (11) A solution of 6-bromo-2-(*N*-isopropyl-N-benzylamino)pyridine (10) (550g, 93.3 wt%, 1.68 mol) was cooled to 10 °C then $POCl_3$ (670 mL, 1.10 Kg, 7.2 mol, 4.3 equiv.) was added with a addition funnel while maintaining the batch temperature below 30 °C (~1.2 h). The mixture was heated to 38-40 °C and aged overnight (15 hours). HPLC indicated the completion of the reaction. The reaction mixture was cooled to below 20 °C and then cannulated into a mixture of water (5.6 L) and toluene (3 L) with vigorous stirring and ice-water cooling to maintain <20 °C (~ 2 hours). After separating the layers, the aqueous DMF layer was extracted with more toluene (2 L). The combined toluene layer was washed with water (3 L x 2) and then treated with Darco-KB (50 g) for 0.5 hour. The mixture was filtered through a Solka-Floc pad and the filter pad was washed with toluene (0.5 L). The filtrate was concentrated under vacuum (40-50 °C bath, 30-50 mmHg) and the residue was pumped under high vacuum overnight to give the crude product **11** as a brown oil (570g). HPLC indicated 95% area purity.

Heck reaction to prepare 12 A 2-L, 3-neck round bottom flask equipped with a mechanical stirrer, temperature probe and nitrogen inlet was charged with a degassed solution of bromoaldehyde **11** (141 g, 0.423 mol based on HPLC assay) in N,N-dimethylacetamide (DMAC, 705 ml). The reaction was purged with N_2 (a 20 min subsurface sparge). The KF of the DMAC prior to degassing was 215 mcg/ml. Sodium acetate trihydrate (115 g, 0.846 mol) and t-butyl acrylate (65 ml, 0.444 mol) were added to the solution. Finally Pd (dppf) Cl_2 -CH_2Cl_2 (8.98 g, 0.011 mol) was added to the reaction vessel and the vessel flushed with N_2. The resulting mixture was stirred mechanically for 9h at 80 ^{o}C. When the reaction was complete, the solution was cooled to room temperature and diluted with toluene (1050 ml) and filtered through solka floc. The solka floc was then washed with 350 ml of toluene. A sample was then drawn from the homogeneous solution. A quantitative HPLC assay (compared to a chromatographed standard of Heck product) indicated 91% yield of the *trans* and *cis* (26:1) isomers. The solution was then washed once with water (700 ml). Upon layer separation a small amount of a dark emulsion appeared in the interface, but was easily removed into the water layer. The organic layer was azeotroped with toluene and the material was taken into the next step at a final volume of 620ml. HPLC conditions: Waters Symmetry C8, 4.6mmx250mm column at 45 ^{o}C, UV detector at 220 nm, eluent MeCN/water at 1.5 ml/min, time 0 50/50, 15 min 90/10, 17 min 90/10, 20 min 95/5. Retention time of bromoaldehyde **11**: 10.8 min, Heck reaction product **12** isomers: 11.2 min (*cis*) and 13.4min (*trans*).

2-Bromo-5-methoxybenzyl trityl ether (Ar_2Br): Under nitrogen, to a three-necked 12 L flask was added DMAC (3.14 L), Ph_3COH (573 g, 2.2 mol) and t-BuOK (236 g, 2.1 mol) sequentially. Then 2-bromo-5-methoxybenzyl chloride (**12**, 470 g, 2.0 mol) in DMAC (0.66 L) was added over 1 h. The reaction mixture was stirred at room temperature for another hour. Water (1.26 L) was slowly added

to the reaction mixture over 1 h to crystallize the product. The slurry was stirred at room temperature for another hour and filtered. The wet cake was washed with DMAC/H_2O (80:20, 3.0L) and water (3.5L). The cake was dried via vacuum suction under nitrogen for 12 h to give the product **Ar_2Br**, 800 g, (99.5WT%, 99.7A%) as a bright white crystalline solid. HPLC conditions: Column: Zorbax RX-C8, 4.6 x 150; Eluent: MeCN/H_2O at 1.5 mL/min; Gradient: t = 0 min, 50/50, 15 min, 90/10, 25 min, 90/10; UV detector: 220 nm; Retention times (min): Ph_3COH 8.5 min, trityl ether **Ar_2Br**, 16.4 min.

N,O-Acetal formation (13): A 3 L 3-neck round bottom flask equipped with a mechanical stirrer, N_2 line, Dean-Stark trap with condenser, and temperature probe were charged with toluene (0.93 L, KF=52 µg/mL) and the Heck reaction product **12** (185.8 g 0.573 mol, by HPLC assay). To the solution was added (S,S)-pseudoephedrine (104.1 g, 0.63 mol) and CSA (camphorsulfonic acid, 2.7 g). The reaction was refluxed overnight to ensure complete consumption of starting material **12** (monitored by HPLC and by ^{1}H NMR). Approx. 10.8 mL of water was collected in the Dean-Stark trap (10.3 mL was the expected amount, but the solvent or starting material may have contained some water). The mixture was cooled to rt, florisil (93 g) was added, and the slurry stirred for 30 min. The florisil was filtered off, and washed with toluene (0.93 L). The filtrate and wash were combined and washed two times with water (1.1 L each wash). After the second water wash, ^{1}H NMR confirmed that all of the DMAC (used in the Heck reaction) was removed. The organic layer was concentrated to 1.7 L. The solution was flushed with toluene until the KF was 250 µg/ml..

Preparation of 14: A 12 L 3-neck round bottom flask equipped with a mechanical stirrer, N_2 line, and temperature probe was charged with the aryl bromide **Ar_2Br** (395 g, 0.86 mol). The flask was purged with nitrogen. Degassed toluene (2.1 L, KF=84 µg/mL) and degassed THF (2.1 L, KF=278 µg/mL) were charged, and again the flask was purged with nitrogen. Both toluene and THF were degassed by a subsurface nitrogen sparge for 20 min. The solution was cooled to -70 ^{o}C (dry ice -acetone bath) and 1.6 M nBuLi (537 mL) was added (using a gas tight syringe) over 25 minutes. The solution was aged for 15 min and then checked by HPLC for residual **Ar_2Br**. The temperature increased to -68 ^{o}C during the nBuLi addition, but was easily controlled. To sample the reaction mixture, a small aliquot was quenched quickly into water-acetonitrile. HPLC indicated 10.9% **Ar_2Br** remaining. An extra 58.5 mL nBuLi was charged and the solution again aged for 15 min. HPLC indicated complete consumption of the **Ar_2Br**. A solution of **13** (from 0.573 mol **12**) in toluene (total volume 1.7 L) was added to the reaction mixture via canula over 20 minutes. During the addition, the temperature of the batch increased to -60 ^{o}C. After aging for 25 min, ^{1}H NMR and HPLC indicated that all of the starting material was consumed. The mixture was warmed to -50 ^{o}C and quenched by the addition of HOAc (179 mL). The reaction mixture was allowed to warm to 0 ^{o}C. Aqueous citric acid (333 g citric acid + 930 mL water) was added, and the biphasic mixture was stirred at rt for 16 h. The mixture was transferred to a separation funnel and the aqueous layer was removed. The organic layer was washed twice with saturated aqueous $NaHCO_3$ (1.6 L total), and once with water (800 mL). The organic layer was assayed and concentrated to approx. 1.3 L and solvent switched to toluene. HPLC assay yield (compared to a chromatographed standard of **14**) indicated 369.40 g **14** (84.8% yield from **12**). SFC assay indicated 92% ee (two sequential chiralcel AD columns, 300 bar pressure, 20-32% IPA over 12 min, UV detector at 250 nm). A large sintered glass funnel was packed with a slurry of florisil (2.58 kg) in 30% MTBE in toluene (approx. 2.5 L). The toluene solution of **14** was charged to the top of the florisil plug, and the material was eluted with

30% MTBE in toluene. The first 2.4 L of fitrate (not containing product) was discarded. An additional 10L of filtrate was collected and concentrated to afford an oil residue and HPLC assay indicated 350.26 g of **14** (95% recovery from the florisil treatment, 80% yield from **12**). The material was carried forward into the Grignard addition. HPLC Conditions: Column: Waters Symmetry C8, 4.6 x 250 mm, sample solvent: acetonitrile or 1:1 acetonitrile:water, flow rate: 1.0 mL/min, detector at 220 nm, eluent gradient MeCN/water: time 0-5 min, 50/50, 15-30 min 90/10, 35-50 min 95/5. Retention times: **12** 19.5 min, **13** 25.4 min, **Ar_2Br** 21.4 min, **Ar_2H** 20.5 min, **14** 27.0 min. Small amount of more pure **14** was prepared by column chromatography on silica gel.

^{13}C NMR (100 MHz, $CDCl_3$, ppm) 188.1, 171.3, 164.5, 159.0, 157.9, 144.0, 138.6, 136.4, 134.0, 129.4, 128.7, 128.5, 128.2, 128.0, 127.1, 126.7, 126.0, 119.4, 114.9, 113.1, 104.3, 87.8, 79.5, 65.2, 55.2, 47.3, 46.3, 41.6, 39.3, 27.8, 20.6, 20.3.

Grignard addition to prepare 15: Regular grade THF (with ~25ppm BHT) should be used since inhibitor free THF may contain significant amount of peroxide which retards the Grignard reaction. Grignard reagent preparation: To a 2-L three-neck round-bottom flask equipped with an efficient condenser, a thermocouple thermometer and a mechanical stirrer were added Mg (27.2 g, 1.12 mol) and THF (650 mL). The **Ar_2Br** solution in THF (635 mL, 322 g/L, 204.5 g, 1.03 mol) was charged into the addition funnel. The system was degassed by vacuum/N_2 cycle three times and then the mixture was heated to 50 °C. Part of the **Ar_2Br** solution (~ 50 mL) was added and mixture was stirred until the reaction was initiated (exothermic and color change). Caution: due to the induction period and very exothermic reaction, no more than 10% of the **Ar_2Br** should be added before the reaction was initiated! The remaining **Ar_2Br** solution was added at 50-60 °C in ~2 hours. The mixture was aged at 50 °C for 1 hour to give the Grignard reagent solution (~0.8 M). (The **Ar_2MgBr** may crystallize at higher concentration at rt). HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 40-90% in 15 min; 1.50 mL/min, 10mM Trizma buffer (pH = 7); 30 °C, UV detection at 220nm; Retention times: **Ar_2Br** 7.4 min, **Ar_2H** 5.3 min. Grignard addition: To a 5-L 4-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple thermometer and a nitrogen inlet, were charged dry crude conjugate addition product **15** (514 g) (assay 258 g, ~92% ee), NMP (1.25 L) and THF (0.75 L). The mixture was degassed by vacuum/N_2 cycle three times and then cooled to -50 °C. Approximately 1.1 L of the Grignard reagent was charged via a cannula in 1 hour at -45 to -50 °C. The mixture was aged for 1 hour at -50 °C. The completion of the reaction was confirmed by HPLC. More **Ar_2MgBr** may be added if necessary. The reaction was quenched by cannulating the reaction mixture into aqueous NH_4Cl (1.7 L 15wt%) with stirring (~40 min). Toluene (1 L) was added to aid the layer separation. The organic layer was washed with NH_4Cl (15wt%, 0.5 L x 2), brine (1 L) and then concentrated to a minimum volume (0.8 L). It was then flushed with more toluene (0.5 L) to dry the crude Grignard addition product (744g). HPLC assay indicates the presence of 294 g of the product **15** (98% yield) in the residue. The diastereoselectivity was ~96/4. HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 60-95% in 15 min; 1.50 mL/min, 10mM Trizma buffer (pH = 7); 30 °C, UV detection at 220nm. Retention time **14** 18.0 min, **15** 18.7 min. Normal phase HPLC conditions for diastereoselectivity measurement: YMC PVA 4.6 x 250 mm; hexane/IPA (95/5); 1.00 mL/min; UV detection at 220nm. Retention time major isomer 9.1 min, minor 7.4 min.

Cyclization to Prepare 17: To a 5-L four-neck round-bottom flask equipped with an addition funnel, a mechanical stirrer, a thermocouple thermometer and a N_2 inlet, were added the crude Grignard addition product **15** (780 g, 295 g assay) and THF (1.2 L). The system was degassed by vacuum/N_2 cycle and then cooled to -20 °C. Then $ClPO(NMe_2)_2$ (74 mL, 0.5 mol, 1.5 equiv.) was added followed by slow addition of 1.0 M (THF) NaHMDS (1.67 L, 2 hours) at –20 to 0 °C via a addition funnel (exothermic reaction during the addition of the 1st equivalent of NaHMDS). The mixture was aged for 3 hours at 0 °C and the completion of the reaction confirmed by HPLC (<1A% SM). More $ClPO(NMe_2)_2$ (0.1 equiv.) and NaHMDS (0.2 equiv.) may be added if necessary. The reaction was quenched by adding water (600 mL) slowly with a addition funnel (very exothermic during the addition of the first 50 mL of water!!!) followed by slow addition of 400mL of acetic acid (It was also very exothermic during the addition of the first 200mL of acetic acid!!!). The mixture was stirred for 0.5 h at 15-20 °C then the layers were separated. The pH of the aqueous layer was 6.3. The organic layer was washed with a 1/1 brine/water mixture (1.0 L) and then brine (1.0 L). It was concentrated under reduced pressure (30-60 mmHg, 40 °C bath) to 666 g and then flushed with MeCN (600 mL) (90-40 mmHg, 40 °C bath). To a 5-L three-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple thermometer and a addition funnel was charged MeCN (2.0 L). The mixture was cooled to 0 °C and concentrated HCl (900mL) was added with a addition funnel (<15 °C). The crude cyclization product (625 g crude, ~250 g by assay) was diluted with 400 mL of MeCN and then charged into the HCl in MeCN solution at 5-15 °C. The starting material flask was rinsed with more acetonitrile (100 mL) and the solution was added to the reaction mixture. The mixture was then allowed to warm to 20 °C and stirred overnight. The completion of the reaction was confirmed by HPLC (<2% t-butyl ester intermediate). HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 30-80% in 15 min; 1.50 mL/min, pH = 7, 10mM Trizma buffer; 30 °C, UV detection at 220nm; Retention times (min): t- intermediate **16** 17.9 min, product **17** acid 9.1 min. The mixture was then cooled to 0 °C and neutralized with NaOH (10 N, 1.16 L <25 °C) until the pH of the aqueous layer was between 5-7. Water (500 mL) was added to dissolve the inorganic salt precipitate after neutralization. MTBE (1 L) was added and the mixture was stirred for 15 minutes. The mixture was allowed to settle for 20 minutes and the layers were separated. The organic layer was extracted with NaOH (0.167 N, 4.0 L 2 equiv., then 0.1 N 1.0 L, 2x0.5 L). Assay of the organic layer indicated ~1-2% product loss. The combined aqueous layer was back extracted with MTBE (500 mL) and the back extract was then washed with NaOH (0.1 N 100 mL). Complete extraction of the product into the aqueous MeCN layer was quite difficult and has to be carried out repeatedly. A significant amount of the product (>2%) was extracted into the MTBE back extraction and has to be washed with some NaOH. To the combined NaOH extracts was added MTBE (1.5 L) and then the mixture was neutralized with HCl (2 N, 420 mL) to pH = 5-6 with stirring. The organic layer was separated and washed with brine (750 mL x 1 and 500 mL x 1). The brine washes were combined with the aqueous layer and then extracted with IPAc (1 L). The organic layer was washed with brine (0.5 L x 2). The combined organic layer was concentrated to a minimum volume (~0.4 L) and flushed with IPAc (1 L). The residue was diluted with IPAc (1.5 L) and treated with Darco-KB (~10g) for 2 hours. The mixture was filtered through a Solka-Floc pad. The pad was washed with IPAc (~300mL). Assay of the filtrate indicated the presence of 175 g (77% overall yield from **14**) of the product as its benzylamine salt equivalent. It was concentrated to 844g and then benzylamine (15 mL) and 1 g

of seed were added and the mixture was stirred under N_2 for 3 hours. The remaining benzylamine (29 mL) was added slowly (~1 hour) and the mixture was stirred overnight at rt. The mixture becomes very thick. The product was collected by filtration and the filter cake was washed with IPAc until the wash becomes almost colorless (600 mL). The product was dried by sucking air through it until constant weight (~3 hours) to give 158 g of the benzylamine salt **17** (97.3 A%, 70% overall yield from **14**). Mother liquor loss was 18 g (8.0%).
^{13}C NMR (100 MHz, CD_3OD, ppm) 180.6, 162.9, 160.4, 158.9, 158.1, 144.8, 141.2, 140.2, 134.1, 133.8, 133.1, 129.5, 128.7, 128.5, 128.4, 127.9, 126.2, 126.1, 126.0, 125.3, 124.3, 120.3, 113.3, 112.9, 108.6,105.6, 70.9, 66.1, 62.3, 54.2, 52.2, 46.4, 46.1, 42.9, 28.9, 19.2, 18.7.

Hydrogenation to prepare 2: To a slurry of the benzylamine salt **17** (70g, 96wt%, 0.10mol) in MTBE (750 mL) was added aqueous citric acid (500 mL 0.25 M). The mixture was stirred until all of the solid has dissolved. The pH of the aqueous layer should be 3-5. The layers were separated and the organic layer was the sequentially washed with aqueous citric acid (0.13 M, 250 mL), water (250 mL x 2) and brine (250 mL). The organic layer was concentrated under reduced pressure (~200mmHg, 30 °C bath) to 150 g and flushed with MeOH (400 mL). The residue was diluted with MeOH (600 mL) and submitted to the hydrogenolysis (5.64g 10% Pd/C, 40 psi, 40 °C, 3 h). The reaction mixture was diluted with THF (700 mL) to dissolve the product and then filtered through a Solka-Floc pad to remove the Pd catalyst. The pad was rinsed with a 2/1 THF/MeOH mixture (500 mL). The filtrate was concentrated to 230 g and then flushed with MeOH (500 mL x 2). The residue was diluted with MeOH (500 mL) and the slurry was stirred at 40 °C for 0.5 hour and aged at rt overnight. The product was collected by filtration and the filter cake was washed with MeOH (400 mL). It was dried by sucking air through it until a constant weight was achieved to give 45.2 g of the product as a white solid (95.3% yield, >98 A%). HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 10-70% in 15 min; 1.50 mL/min, 0.1% H_3PO_4; 30 °C, UV detection at 220nm. Retention times **2** 9.8 min.

^{13}C NMR (100 MHz, DMSO-d_6, ppm) 175.7, 162.0, 160.5, 159.2, 158.2, 144.3, 142.7, 134.0, 132.1, 129.8, 126.3, 125.4, 124.2, 120.4, 112.7, 112.6, 108.8, 106.8, 71.5, 62.1, 61.1, 55.4, 51.6, 42.3, 42.2, 29.3, 22.9, 22.7.