

SUPPORTING INFORMATION

Optimized Catalytic Enantioselective Aryl Transfer Process Gives Access to mGlu2 Receptor Potentiators

Nicholas A. Magnus,* Peter B. Anzeveno, D. Scott Coffey, David A. Hay, Michael E. Laurila, Jeffrey
M. Schkeryantz, Bruce W. Shaw, and Michael A. Staszak

*Eli Lilly and Company, Chemical Product Research and Development Division, Indianapolis, Indiana
46285, U.S.A.*

Table of Contents

1. Analytical methods	S2
2. Procedure and spectra for 4	S2-S3
3. Procedure and spectra for 6 and 7	S3-S5
4. Procedure and spectra for 8	S6
5. Procedure and spectra for 9	S6-7
6. Procedure and spectra for pyrrole 12	S7-S9
7. Procedure and spectra for pyrrole 1	S9

Experimental Procedures

Analytical Methods: Steps 1 and 2 are monitored using the following GC conditions: Instrument: HP model 6890. Column: J & W Scientific DB-1, 30m, 250 μ m. Starting oven temperature: 60 °C. Initial integration time: 2 min. Maximum temperature: 300 °C. Rate: 18 °C/min. to 300 °C. Hold time: 15 min.

Detector: Flame-ionization. Sample preparation: See the experimental write-up for steps 1 & 2.

Steps 3-6 are monitored using the following HPLC conditions: Instrument: Agilent 1100 Series. Column: Zorbax® SB-C8. Flow: 1.5 mL/min. A = 0.1% H₃PO₄, B = CH₃CN. Gradient: 95% A/5% B to 50% A over 10 min; Change to 5% A over 5 min. Hold at 5% A for 5 min. Return to 95% A using a 3 min. Post Time. Column Temperature: 40 °C. Wavelength: 220 nm.

(4-Bromo-benzyloxy)-tert-butyl-dimethyl-silane (4)⁴: Under a nitrogen atmosphere, a reactor was charged with 4-bromobenzyl alcohol (500.0 g, 2.67 moles) and CH₂Cl₂ (3000 mL). The mixture was stirred at 22.2 °C for 5 minutes to dissolve all solids (an endotherm ensued from 22.2 °C to 12.1 °C). Triethylamine (324.6 g, 447.1 mL, 3.21 moles, 1.20 equivalents) was added in one portion and rinsed in with CH₂Cl₂ (500 mL) (an exotherm from 12.1 °C to 19.4 °C was associated with this addition). 4-Dimethylaminopyridine (DMAP) (13.1 g, 0.11 mol, 0.04 equiv) was added and the resulting mixture stirred for 5 minutes. TBS-Cl (443.2 g, 2.94 moles, 1.1 equivalents) was added in 3 portions over 30 minutes, with the portions being rinsed in with CH₂Cl₂ (500 mL). An exotherm from 19.1 °C to 29.9 °C was observed with the first portion of TBS-Cl, after which cool tap water was added to the bath. The pot temperature was maintained between 24 to 27 °C for the remaining additions. After 2 hours of stirring at ~25 °C, a sample of the reaction mixture was obtained and syringe-tip filtered to remove salts. The filtrate (100 μ L in 1.2 mL CH₂Cl₂) was assayed by GC, which indicated ~1.2% starting material remained. The reaction mixture was quenched with D.I. H₂O (2000 mL) and stirred for 10 minutes to dissolve all solids. The bottom (organic) layer was washed with saturated ammonium chloride (4 x 2500 mL, washes checked by pH paper to insure the final wash layer was not basic). The organics were washed with D.I. H₂O (2500 mL), dried over Na₂SO₄, and concentrated in vacuo (32 °C bath). Compound **4** (824.2 g) was afforded as a clear oil (theory = 805.4 g). GC assay (area %) = 97.0%. ¹H

NMR (CDCl₃, 500 MHz) δ 0.13 (s, 6H), 0.98 (s, 9H), 4.72 (s, 2H), 7.23 (d, 2H, $J=8$ Hz), 7.48 (d, 2H, $J=8$ Hz). ¹³C NMR (75.4 MHz, DMSO) δ 5.42, 17.89, 25.69, 63.50, 119.74, 128.10, 130.95, 140.52.

3-{[4-(tert-Butyl-dimethyl-silyloxymethyl)-phenyl]-hydroxy-methyl}-benzonitrile (6) and (S)-

(7): Part A: Formation of Grignard Reagent: Under a nitrogen atmosphere, a flask was charged with magnesium turnings (48.4 g, 1.99 moles, 1.2 equivalents, see note 1) and THF (2500 mL). 1,2-Dibromoethane (1.5 mL, see note 2 below) was added and stirring was started. Neat, crude **4** (500.0 g, 1.66 moles) was charged to the addition funnel. The contents of the reaction vessel were heated to 50 °C. Approximately 10% of the volume of the addition funnel was added to the reaction flask and stirring was continued at 50 °C for 5 minutes. No initiation was noted. The set-point for heating was raised to 60 °C. Within minutes, initiation was observed, and the mixture began to reflux. The remaining bromide was added in a constant slow stream over 1.3 hours while maintaining a gentle reflux (see note 3 below). The addition funnel was rinsed in with THF (50 mL), replaced with a stopper, and the reaction mixture allowed to continue refluxing. After 1.5 hours at reflux, GC assay showed ~1.2% starting bromide remained (see note 4 below). The mixture was refluxed for a total of 2 hours and the heating mantle was removed, allowing the mixture to cool to ~50 °C. A cool tap water bath was put in place to further lower pot temperature to ~30 °C.

Part B: Reaction of Grignard Reagent with 3-Cyanobenzaldehyde **5**. Under a nitrogen atmosphere, a flask was charged with 3-cyanobenzaldehyde **5** (196.9 g, 1.50 moles, 0.90 equiv) and THF (2500 mL). The resulting solution was cooled to ~ -70 °C using a dry-ice/acetone bath (see note 5 below). Using a large bore cannula needle, the Grignard mixture from part A was transferred to an addition funnel and added to the mixture of **5** in THF over 1.3 hours, keeping the pot temperature below -60 °C (see note 6 below). The resulting mixture was stirred at -60 to -70 °C for 1 hour, then warmed to ~ -35 °C over 30 minutes. After stirring at -30 °C for an additional 30 minutes, the mixture was assayed by GC (see note 7 below) which showed the reaction to be complete. A 22 L bottom outlet flask was charged with cold D.I. H₂O (5260 mL) and cold 5M HCl (400 mL). With stirring, the cold reaction mixture was transferred via a large bore cannula needle using a slight positive pressure on the flask. The resulting mixture was

stirred for 5 minutes and then diluted with MTBE (2630 mL). After stirring for 10 minutes, the layers were allowed to separate. The upper layer (organic) was washed with D.I. H₂O (2600 mL), saturated sodium bisulfite solution (2 x 2600 mL, 880.6 g NaHSO₃ in 5200 mL H₂O), D.I. H₂O (2600 mL) and saturated NaHCO₃ solution (2600 mL). The organics were dried over Na₂SO₄, transferred to a 10 L Büchi flask and concentrated *in vacuo* (40 °C bath) for 2.5 hours. After allowing the resulting oil to pull overnight under full house vacuum at ambient temperature, a total of 548.6 g of off-white solids were recovered. Theory = 530.8 g. GC assay ~84.8 area %.

Part C: Reslurry of Crude Solids with Ligroin: The crude solids of **6** were scraped free of the walls of the Büchi flask and crushed into a fine powder with a spatula. Ligroin (5L) was added and the flask was spun (no heat, no vacuum) at moderate speed for 3 hours. The solids were filtered across a polypropylene pad, rinsed with Ligroin (2 x 500 mL) and pulled dry. The material was vacuum-dried overnight at 25 °C to afford 445.6 g (83.9% overall yield) of white solids. GC assay ~95 area %.

Part D: Silica Gel Plug Purification of diarylmethanol **6** Prior to Chiral Chromatography: A 30 cm sintered glass funnel was set up using a large filter flask and KieselGel 60 silica (7 kg, 240-400 mesh). The silica was wetted with a solvent mixture (50/45/5 CH₂Cl₂/heptane/EtOAc) using a slight vacuum pull on the filter. 390.6 grams of **6** were dissolved in CH₂Cl₂ (450 mL) and EtOAc (52 mL). This solution was diluted with heptane (470 mL) and poured onto the top of the silica plug. After rinsing the flask out with 100 mL of the eluent, the material was eluted from the silica gel plug. A total of 21 fractions (4L) were collected, allowing 3-4 minutes per fraction. The fractions were analyzed by TLC (using the eluent as developing solvent, *R_f* of product = 0.25). Fractions 8-18 were combined and concentrated *in vacuo* to afford 346.6 g of white solids (88.8%). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.08 (s, 6H), 0.91 (s, 9H), 4.68 (s, 2H), 5.78 (d, 1H, *J* = 4 Hz), 6.13 (d, 1H, *J* = 4 Hz), 7.26 (d, 2H, *J* = 8 Hz), 7.37 (d, 2H, *J* = 8 Hz), 7.53 (t, 1H, *J* = 8 Hz), 7.69 (t, m, 2H, *J* = 8 Hz), 7.82 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 5.36, 17.92, 25.74, 64.00, 73.06, 110.99, 118.78, 125.94, 126.05, 129.34, 129.44, 130.47, 131.01, 139.96, 143.32, 147.32; IR (KBr) 3439, 2949, 2921, 2886, 2859, 2225, and 1470 cm⁻¹. Anal. Calcd for C₂₁H₂₇NO₂Si: C, 71.35; H, 7.70; N, 3.96; O, 9.05. Found: C, 71.89; H, 7.71; N, 4.00.

Notes for the Grignard Procedure: 1) Development work had indicated that the 99.98% small magnesium turnings from Aldrich were easier to initiate than the lower purity reagent grade turnings. 2) The 1,2 dibromoethane was used in catalytic amount to aid Grignard initiation. In this case, the 1.5 mL employed calculates to a 0.01 equivalent load. 3) During the slow addition of the neat **4**, the heat source was shut and the reflux was addition rate controlled. Heating was restarted after the addition was complete and the associated exotherm subsided. 4) Based on earlier experience with these reactions, completion was considered achieved at $\leq 3\%$ starting bromide using the GC assay developed for this step. The samples for this analysis were prepared by removing 100 μL of the reaction mixture and quenching into 1 mL 1M HCl in a 7 mL vial. The sample was shaken, diluted with 2.5 mL MTBE and shaken again. After separation, 1 mL of the upper (MTBE) layer was carefully removed and analyzed directly by GC. 5) Although dissolved at rt., the cyanobenzaldehyde precipitates at $\sim -50\text{ }^\circ\text{C}$ to form a slurry. 6) The cyanobenzaldehyde re-dissolves within the first 1/10th of the addition of the Grignard reagent, producing a homogeneous mixture. 7) The same sample preparation recipe as described in note 4 was employed for the second portion of the reaction. Samples were analyzed by GC.

Part E: Chiral Chromatography to Separate Enantiomers: Chiral Chromatography Conditions: Column Chiralpak AD 11 x 33 cm. Eluent 1/4/95 ratio of 3A EtOH/MeOH/heptane. Flow Rate 680 mL/min. Detector UV 235 nm. Loading 2.0 g substrate/cycle. Injection 30 mL. Cycle Time 11.1 min.. Productivity 10.8 g/h. Solvent Usage 26 L/h. Retention Times Isomer I (not desired) = 8.6 min.. Isomer **7** (desired) = 10.0 min..

A total of 1666 g of purified racemic mixture **6** were resolved by this chromatography system. After combining fractions and concentrating *in vacuo*, 829 grams of the desired isomer **7** were afforded with >98% enantiomeric excess. This represented a 48.5% material recovery.

3-[[4-(tert-Butyl-dimethyl-silyloxy)methyl]-phenyl]-(tetrahydro-pyran-2-yloxy)-methyl]

benzotrile (8): Under a nitrogen atmosphere, a flask was charged with 3,4-dihydro-2H-pyran (134.45 g, 1.82 moles, 1.5 equivalents), pyridinium *p*-toluene sulfonate (PPTS) (27.3 g, 0.12 mol, 0.10 equiv), and CH_2Cl_2 (3.5 L). To this mixture was added the **7** (376.4 g, 1.22 moles), and the resulting solution

was stirred for 18 h at 23 °C. The reaction mixture was transferred to a separatory funnel and washed with saturated NaHCO₃ solution (866 mL) and brine (866 mL). The solution was dried over MgSO₄ and concentrated *in vacuo* to afford 469 grams of diastereomers of **8** as a yellow oil (theory = 469 g). ¹H NMR (CDCl₃, 500 MHz) (Note: diastereomeric mixture) δ 0.09 (s, 6H), 0.11 (s, 6H), 0.95 (s, 9H), 0.96 (s, 9H), 1.53-1.62 (bm, 10 H), 1.69-1.75 (bm, 4H), 1.90-1.93 (bm, 2H), 3.48-3.53 (m, 2H), 3.78-3.86 (m, 2H), 4.63-4.65 (m, 2H), 4.71-4.74 (d, 4H), 5.80-5.81 (d, 2H), 7.26-7.33 (m, 8H), 7.37-7.44 (m, 2H), 7.50-59 (m, 4H), 7.68-7.72 (d, 2H).

3-[(4-Hydroxymethyl-phenyl)-(tetrahydro-pyran-2-yloxy)-methyl]-benzotrile (9): Under a nitrogen atmosphere, a flask was charged with **8** (469.4 g, 1.07 moles) and THF (1.8 L). To this solution was added 1M tetrabutylammonium fluoride (TBAF) in THF (1.35 L, 1.35 moles, 1.26 equivalents). The resulting mixture was stirred for 18 h at 23 °C. After transferring to a separatory funnel, the reaction mixture was diluted with water (3.6 L). The mixture was extracted with EtOAc (2 x 3.6 L). The combined organic extracts were washed with water (1.8 L), brine (1.8 L) and dried over MgSO₄. After filtration of the drying agent, the filtrate was concentrated *in vacuo* to afford a yellow oil (413.2 g, theory = 346.9 g). The crude oil was purified using a silica gel plug. A sintered glass funnel was charged with KeiselGel 60 (2066 g). The silica was wetted with heptane containing 2.5 % v/v EtOAc. The crude oil was dissolved in CH₂Cl₂ (620 mL) and charged to the top of the silica plug. The material was eluted with heptane (12.4 L) followed by EtOAc (12.4 L). The EtOAc fractions were collected, concentrated *in vacuo*, and re-dissolved in toluene (2.3 L). This solution was concentrated *in vacuo* using a 65 °C bath to afford 343.3 grams (98%) of diastereomers of **9** as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) (diastereomeric mixture) δ 1.49-1.67 (m, 4H), 1.70-1.75 (m, 2H), 1.81 (bs, 1H), 1.87-1.97 (m, 1H), 3.46-3.54 (m, 1H), 3.76-3.87 (m, 1H), 4.62-4.65 (m, 1H), 4.67 (d, 2H), 5.81 (s, 1H), 7.32-7.44 (m, 5H), 7.50-7.59 (m, 2H), 7.67 (d, 1H).

3-[[4-(4-Acetyl-3-hydroxy-2-propyl-phenoxy)methyl]-phenyl]-methyl]-benzotrile (12): Part A: Mesylation/Chlorination of diastereomers of **9**. Under a nitrogen atmosphere, **9** (130.8 g, 0.40 mol) was dissolved in CH₂Cl₂ (1.31 L) and charged to the reaction vessel.

The mixture was cooled to 0 to -5 °C (see note 1). Methanesulfonyl chloride (34.4 mL, 0.44 mol, 1.1 equiv) was added in one portion to the reaction vessel (see note 2). Triethylamine (67.7 mL, 0.49 mol, 1.2 equiv) was charged to an addition funnel and subsequently added to the reaction vessel over 30 minutes (see note 3). The resulting mixture was stirred at 0 °C for 15 minutes. The cooling bath was removed and the reaction mixture allowed to warm to 23 °C. Stirring was continued for 20 hours (see note 4). The reaction mixture was quenched with water (650 mL), the layers were separated, and the organic portion was washed with saturated NaHCO₃ (650 mL) and water (650 mL). The organics were dried (Na₂SO₄), and concentrated in vacuo to afford 138.5 g (100 %) of diastereomers of a crude mixture of mesylates/chlorides **10a/10b** as a pale yellow oil (see note 5). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.40-1.55 (bm, 3H), 1.58-70 (bm, 2H), 1.73-1.82 (bm, 1H), 3.37-3.42 (bm, 1 H), 3.62-71 (bm, 1H), 4.58 (d, 1H), 4.72 (d, 2H), 5.87 (d, 1H), 7.39 (m, 4H), 7.55 (m, 1H), 7.70 (m, 2H), 7.86 (d, 1H).

Notes for the Mesylation/Chlorination of diastereomers of **9**: 1) An ice bath which included low levels of acetone was employed to cool the mixture to slightly below 0 °C. 2) There was no exotherm noted with this addition, only a slight 0.7 °C rise caused by the addition of the room temperature reagent. 3) This portion of the reaction is exothermic and is controlled by the addition rate. The maximum pot temperature attained was 2.5 °C. 4) After the overnight stir, the mixture was analyzed by HPLC (220nm). This analysis indicated no remaining starting material. The product is actually a mixture of chlorides and mesylates, which are both present as diastereomers and are visualized in both the HPLC and ¹H NMR spectra. 5) The HPLC analysis indicated a total of 96.7% (uncorrected, area percent) products for the reaction.

Part B: Coupling with 1-(2,4-Dihydroxy-3-propyl-phenyl)-ethanone **11** to form the diastereomers of **12**. Under a nitrogen atmosphere, a crude mixture of mesylates/chlorides **10a/10b** from Part A of this procedure (138.2 g, 0.40 mol) were dissolved in acetone (1000 mL). To this mixture was added 1-(2,4-dihydroxy-3-propyl-phenyl)-ethanone **11** (70.7 g, 0.36 mol, 0.90 equiv, see note 1), NaI (57.6 g, 0.38 mol) and K₂CO₃ (55.9 g, 0.40 mol). The resulting mixture was heated to reflux. After 6.25 h at reflux (see note 2), the reaction mixture was slowly cooled to 23 °C, and filtered. The filter cake was rinsed

with acetone (50 mL) and the filtrate was concentrated *in vacuo* (40 °C bath) to remove the acetone. The resulting residue (213.1 g of yellow solids) was treated with EtOAc (1300 mL) and H₂O (650 mL) and stirred at room temperature until all of the solids dissolved (see note 3). The organic layer was separated, washed with water (3 x 650 mL) and brine (500 mL), then dried (Na₂SO₄). After concentrating the organics *in vacuo* (45 °C bath), 207.4 g (100%, see notes 4, 5 & 6) of diastereomers of **12** were afforded as yellow/tan solids. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.82 (m, 3H), 1.41-52 (bm, 5H), 1.57-1.61 (bm, 2H), 1.63-1.72 (bm, 1H), 2.48 (m, 1H), 2.54 (s, 3H), 2.55 (m, 1H), 3.40 (bm, 1H), 3.67 (m, 1H), 4.58 (m, 1H), 5.21 (d, 2H), 5.86 (d, 1H), 6.69 (dd, 1H), 7.45 (m, 4H), 7.55 (m, 1H), 7.68-7.70 (m, 3H), 7.86 (d, 1H).

Notes for the Coupling Reaction: 1) Since we are using crude material, we assumed a potency of 90% for stoichiometry purposes, and all equivalents are based upon 90% of 0.40 mol. 2) The reaction was monitored by HPLC during its course. The HPLC spectrum is quite complex, as it shows diastereomeric mixes of the starting materials, the intermediate iodides, and the products. The HPLC analysis at 5.5 hours of reflux had indicated that ~3% of the starting materials remained. Previous experience with this reaction had shown that 6-6.5 hours of heating were needed for completion, which is set to be ≤ 2% starting materials. At the end of the heating period, the mantle was removed and the reaction allowed to self cool in order to allow for final conversion of starting materials to occur. 3) The filtration of the reaction mixture removed excess K₂CO₃ and a good portion of the KI salts present. However, KI has some solubility in acetone and is carried along with the product during this filtration. Consequently, the crude solids will not completely dissolve in the EtOAc without the addition of water. 4) A yield calculation here is not realistic, since the starting material was crude and the product is also very crude. A viable yield will be calculated after the *O*-THP deprotection over the three steps from **9**. 5) The HPLC analysis of the crude product (220nm) shows a diastereomeric mixture with a total area percent for products of ~87%. 6) The shift listing for the ¹H NMR signals is for product peaks only. There are several extraneous peaks present which can be attributed to both solvents and residual reagents.

(S)-3-[[4-(4-Acetyl-3-hydroxy-2-propyl-phenoxy)methyl]-phenyl]-hydroxy-methyl-benzonitrile

(1): Under a nitrogen atmosphere, a flask was charged with crude **12** (544.6 g, 1.08 moles) and EtOH (4.9 L). The resulting solution was treated with pyridinium *p*-toluene sulfonate (PPTS) (28.1 g, 0.11 mol), and heated to 55 °C. After 18 h at 55 °C, the heating mantle was replaced with a cooling bath and the condenser was replaced with an addition funnel. The reaction solution was cooled to 37 °C. Water (2.6 L) was charged to an addition funnel and added to the reaction mixture over 30 minutes. The mixture was further cooled to 0 to 5 °C and stirred for 3.5 h. The resulting crystals were filtered, washed with cold water (1 L), and vacuum-dried at 45 °C. A total of 375.6 grams (82.9% from **9**) of **1** was recovered as pale yellow crystals. mp (DSC) (10°C/min.) onset 138.82 °C, peak 142.40 °C; IR (KBr pellet) 3314, 3229, 2959, 2928, 2869, 2228, 1633, 1497, and 1418 cm⁻¹. ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.84 (t, 3H, *J* = 7 Hz), 1.46 (q, 2H, *J* = 7 Hz), 2.54 (s, 3H), 2.52-2.58 (m, 2H), 5.19 (s, 2H), 5.78 (d, 1H), 6.14 (d, 1H), 6.69 (d, 1H), 7.37 (d, 2H, *J* = 8 Hz), 7.41 (d, 2H, *J* = 8 Hz), 7.50 (t, 1H, *J* = 8 Hz), 7.65 (dt, 1H, *J* = 8 Hz), 7.71 (d, 1H, *J* = 8 Hz), 7.82 (s, 1H), 12.82 (s, 1H). ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 14.5, 21.9, 24.4, 26.8, 69.8, 73.5, 104.4, 111.6, 114.2, 117.3, 119.3, 126.9, 127.6, 129.9, 130.0, 131.1, 131.5, 136.1, 144.9, 147.6, 161.5, 162.6, 204.4; HRMS (AP+ TOF) calcd for C₂₆H₂₅NO₄ 415.1784, found 415.1783. Anal. Calcd. for C₂₆H₂₅NO₄: C, 75.16; H, 6.03; N, 3.37. Found C, 74.96; H, 6.17; N, 3.40.