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

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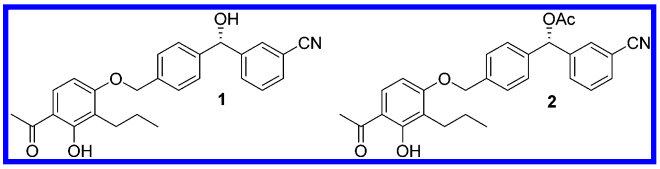
Abstract:

An asymmetric enantioselective aryl transfer reaction was developed to give access to the diarylmethanol 7 and ultimately acetate 2 which is useful for the preparation of mGlu2 receptor potentiators (Scheme 3). The aryl transfer chemistry involved the preparation of a proposed arylalkylzinc species 14 from boroxine 16 and diethylzinc (DEZ), and reacting this mixture with aldehyde 5 in the presence of chiral ligand 15. During the course of optimizing the preparations of proposed intermediate 14 and diarylmethanol 7, an understanding of optimal stoichiometry and reaction times was gained through empirical observation, the use of solution IR, and analyzing off-gases via real time gas analysis/mass spectroscopy. The preparation of diarylmethanol 7 and subsequent conversion into acetate 2 required carefully selected workups, selective extractions, and azeotropic distillations to generate a series of stock solutions to accommodate oil intermediates that finally gave acetate 2 as a crystalline solid with >99% ee.

Introduction

The excitatory amino acid L-glutamate mediates most of the excitatory neurotransmission within the central nervous system (CNS). Glutamate receptors are classified into two main types, ionotropic (iGlu), which are glutamate-mediated ion channels, and metabotropic (mGlu), which are a class of G-protein-coupled receptors.[1] The mGlu receptors have been divided into three main groups (I−III) with the group II (mGlu2 and -3) mGlu receptors being largely presynaptic and generally inhibiting neurotransmission.[2] To access multikilogram quantities of mGlu2 receptor potentiators to fund Lilly's research directed towards potential therapies for the acute treatment of migraine headaches, processes needed to be developed to synthesize the ether-linked diarylmethanols **1** and **2**.[3]



Results and Discussion

In order to fund toxicological evaluations, 500 g of diarylmethanol **1** was synthesized using the chemistry outlined in Scheme 1.

The Scheme 1 synthesis began with the protection of 4-bromobenzyl alcohol **3** as *tert*-butyldimethylsilyl (TBS) ether **4** by exposure to *tert*-butyldimethylsilyl chloride (TBS-Cl) in the presence of triethylamine (TEA) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2.[4] The corresponding Grignard reagent of ether **4** was prepared by reaction of **4** with magnesium turnings in refluxing THF,[5] which was subsequently reacted with 3-cyanobenzaldehyde **5** to afford an 80% yield of diarylmethanol **6** as a racemic mixture. The racemic diarylmethanol **6** was subjected to an arduous chiral chromatography to give a 47% yield of the desired diarylmethanol enantiomer **7**. In order to differentiate the alcohols of **7**, the secondary alcohol was protected as a tetrahydropyran (THP) acetal by reaction with 3,4-dihydro-2H-pyran and catalytic pyridinium *p*-toluene sulfonate (PPTS) in CH_2Cl_2 to afford **8**.[6] Reaction of **8** with tetrabutylammonium fluoride (TBAF) in THF afforded good yields of primary alcohol **9**. Reaction of **9** with methanesulfonyl chloride (MsCl) and TEA in CH_2Cl_2 gave mixtures of mesylate **10a** and chloride **10b**. The chloride **10b** is a major product formed in the mesylation, because the TEA-hydrochloride that is generated has good solubility in the reaction media and can supply chloride ion to displace the mesylate from **10a**. Due to the sluggish reactivity of chloride **10b**, the **10a**/**10b** mixture was reacted with sodium iodide under Finkelstein halogen, halogen exchange conditions to give the intermediate iodide **10c** which reacted with the phenolate of **11** in a Williamson ether synthesis to afford ether **12**. Standard THP cleavage conditions (PPTS in wet EtOH) gave the chiral diarylmethanol **1** in 80% overall yield from **9**.[7]

In order to rapidly prepare multikilogram amounts of **1** in "fixed" pilot-plant reactors, the plan was to develop the

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(1) For reviews on the pharmacology of Metabotropic Glutamate Receptors, see: (a) Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **1997**, *32*, 1. (b) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.

(2) (a) Lam, A. G. M.; Soriano, M. A.; Monn, J. A.; Schoepp, D. D.; Lodge, D.; McCulloch, J. *Neurosci. Lett.* **1998**, *254*, 121. (b) Kingston, A. E.; O'Neill, M. J.; Lam, A.; Bales, K. R.; Monn, J. A.; Schoepp, D. D. *Eur. J. Pharmacol.* **1999**, *377*, 155. (c) Helton, D. R.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D.; Kallman, M. J. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 651.

(3) Aicher, T. D.; Cortez, G. S.; Groendyke, T. M.; Khilevich, A.; Knobelsdorf, J. A.; Magnus, N. A.; Marmsater, F. P.; Schkeryantz, J. M.; Tang, T. P. (Eli Lilly and Company, U.S.A.). PCT Int. Appl. 2006, WO 2006057870 A1 20060601.

(4) Boaz, N. W.; Fox, K. M. *J. Org. Chem.* **1993**, *58*, 3042.

(5) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871.

(6) Parham, W. E.; Anderson, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 4187.

(7) (a) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942. (b) Gala, D.; Steinman, M.; Jaret, R. S. *J. Org. Chem.* **1986**, *51*, 4488. (c) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

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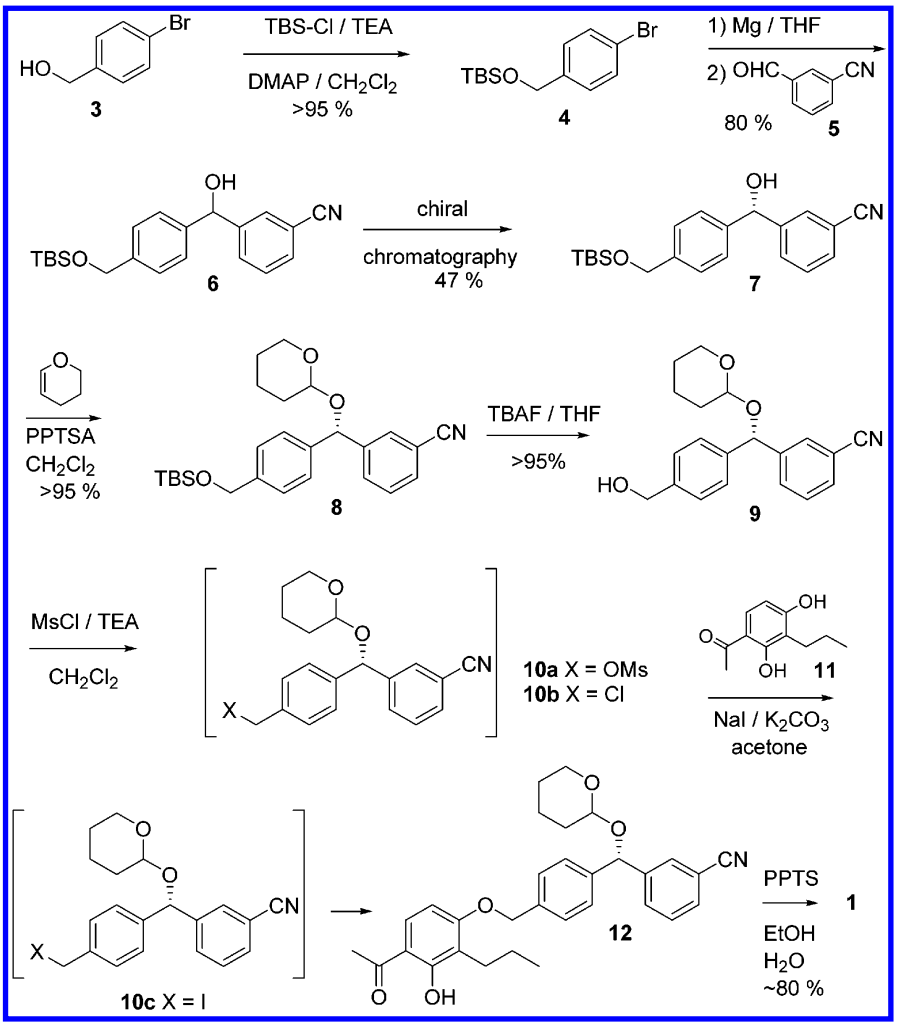
Scheme 1



Scheme 1 chemistry for scale-up and replace the chiral chromatography with an asymmetric synthesis method. The initial goal was an asymmetric preparation of diarylmethanol **7** (Scheme 1). To achieve this goal, asymmetric reduction of the appropriate ketone and resolution of **6** via enzymatic methods were pursued as the highest probability solutions for preparations of **7**. In addition to these approaches, the recent advances in asymmetric aryl transfer chemistry of aryl zinc species to aromatic aldehydes was difficult to discount as a possible solution.[8] The work of Bolm's group involving arylboronic acids as precursors to aryl zinc species was particularly attractive since it permitted the use of the Scheme 1 aryl bromide **4** as the precursor to the requisite, known boronic acid **13** (Scheme 2).[9] The Bolm methodology of converting arylboronic acids to aryl zinc species uses about 130 mol % excess of arylboronic acid; therefore, reduction of this amount would be a focus for process development.[8] The recent work of the Pericàs group also appeared to have important information relevant to the development of an efficient asymmetric aryl transfer process.[10] The Pericàs group employed solution IR to monitor the rate of phenyl transfer from diphenylzinc (DPZ), relative to the phenyl transfer rate from mixtures of DPZ and diethylzinc (DEZ), with and without an amino alcohol catalyst present, using *p*-tolualdehyde as the electrophile. The kinetic study showed that DPZ transferred phenyl to the aldehyde at 0 °C with no ligand present, mixtures of DPZ and DEZ did not transfer phenyl or ethyl to the aldehyde at 0 °C until an amino alcohol catalyst was present (i.e., no background reaction), and in the mixed zinc species experiments the phenyl group transferred preferentially. The optimal ratio of DPZ to DEZ to ensure high conversion of the aldehyde and selective phenyl transfer was determined to be 1.32 equiv of DEZ to 0.64 equiv of DPZ (i.e., 2 to 1), which equates to about a 28 mol % excess of phenyl groups. In order to answer the question of whether this more desirable aryl group stoichiometry from the Pericàs work could extrapolate to the Bolm arylboronic acid technique of generating aryl zinc species, the following research was conducted.

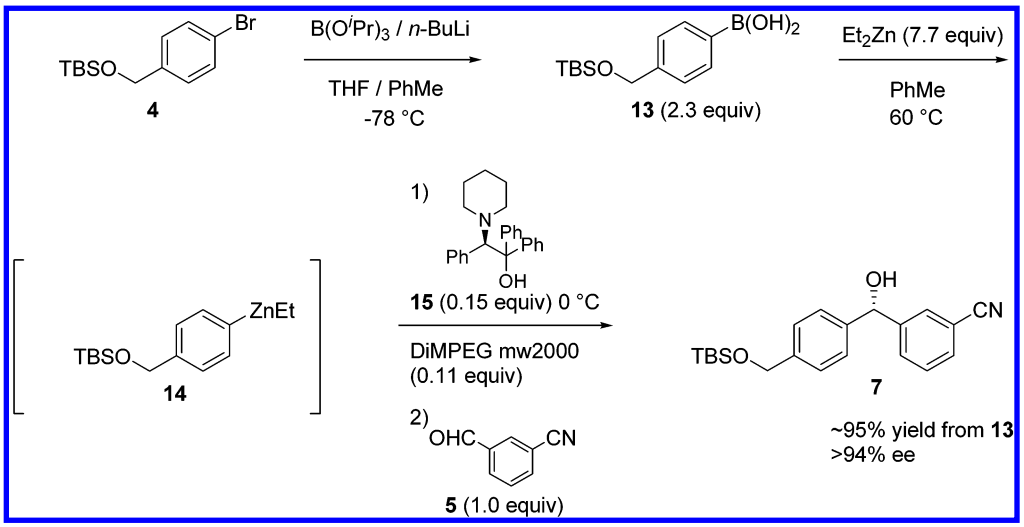
The arylboronic acid **13** was prepared according to the literature procedure (Scheme 2).[9] The reports from Bolm and

(8) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454 and references therein.

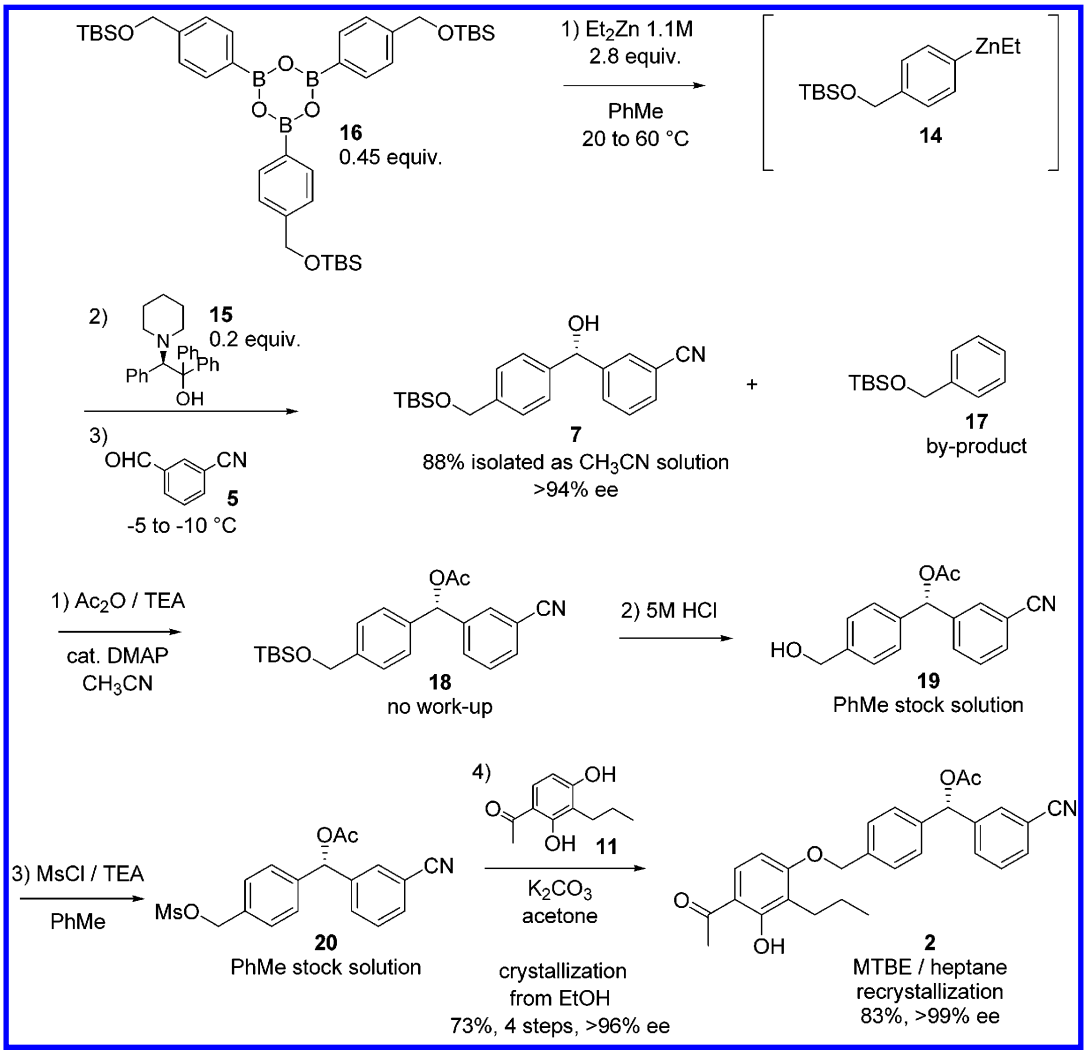
(9) Zheng, N.; Armstrong, J. D., III; Kan K. E.; Keller, J.; Liu, T.; Purick, R.; Lynch, J.; Hartner, F. W.; Volante, R. P. *Tetrahedron Asymmetry* **2003**, *14*, 3435.

(10) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532.

Scheme 2



Scheme 3



Pericàs led us to the design of this initial reaction: a toluene mixture of arylboronic acid **13**, DEZ, the polymer additive dimethoxypolyethyleneglycol-m2000 (DiMPEG), and the relatively simple amino alcohol ligand (*R*)-(−)-2-piperidino-1,1,2-triphenylethanol, **15**,[8,11] was reacted with 3-cyanobenzaldehyde **5** (Scheme 2). The result of this first attempt was

(11) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1998**, *63*, 7078.

to produce the diarylmethanol **7** in about 95% yield with >94% ee.

While the Scheme 2 chemistry had given a desirable yield and enantioselectivity in the production of **7**, there were some potential areas for development to make it more useful for the preparation of kilogram amounts: (1) improve efficiency by reducing or removing the poorly soluble DiMPEG polymer additive; (2) reduce the equivalents of ligand **15**; (3) reduce the equivalents of arylboronic acid **13**; (4) reduce the equivalents of DEZ; (5) reduce the reaction volumes which were 300 mL/g of aldehyde **5**, and reduce the workup volume which was 700 mL/g of aldehyde **5**; (6) remove the chromatography that had been required to purify **7** due to the excesses of reagents present (crystallization of **7** was not an option due to its being an oil).

To address these development needs, a multigram preparation of arylboronic acid **13** was conducted with the slight modification of using *n*-hexyllithium instead of *n*-butyllithium to avoid the dangers of butane release during processing. During the proton NMR characterization of this multigram batch of arylboronic acid **13**, the integration of the −OH group protons did not add up to the required amount of 2 when run in deuterated DMSO as had been reported in the literature characterization.[9] The proton NMR spectrum of **13** was next collected in deuterated chloroform, and the −OH group protons were completely absent. Since toluene was the reaction solvent that **13** was to be reacted in, the proton NMR was also gathered in deuterated toluene which also indicated the absence of −OH protons. In addition, the literature preparation of **13** reported an IR spectrum with no bands beyond 3000 cm^{-1} which was not in keeping with a typical IR spectrum for a boronic acid.[12] After reviewing the spectroscopic data associated with **13**, it became apparent that the structure of arylboronic acid **13** was not correct and that the actual structure was the boroxine **16** (Scheme 3). This structural understanding was critical for the pending stoichiometry optimization due to the significant molecular weight differences between **13** and **16**.

The DiMPEG polymer was removed from the Scheme 2 aryl transfer reaction, and at the original ligand **15** loading of 15 mol % the enantioselectivity dropped from >94% to 91%. However, if the ligand **15** loading was increased to 20%, the enantioselectivity of the aryl transfer returned to >94%. A ligand **15** loading of 30% gave 96% enantioselectivity, and a ligand **15** loading of 40% gave a modest gain in enantioselectivity to 96.8% which indicated that increases in ligand **15** loading did not have a linear relationship with respect to increases in enantioselectivity. Removal of the DiMPEG polymer led to a substantial reduction in reaction volume, and afforded clean layer separations during the workup which had proven problematic previously. In addition, the piperidine-based ligand **15** could now be removed easily from the crude reaction mixtures with aqueous HCl washes, an event that had been complicated by the presence of the DiMPEG polymer. Those acidic extracts were essentially pure ligand **15**-hydrochloride, and neutralization

(12) Siverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th Ed.; John Wiley & Sons: New York, 1981; pp 112−120.

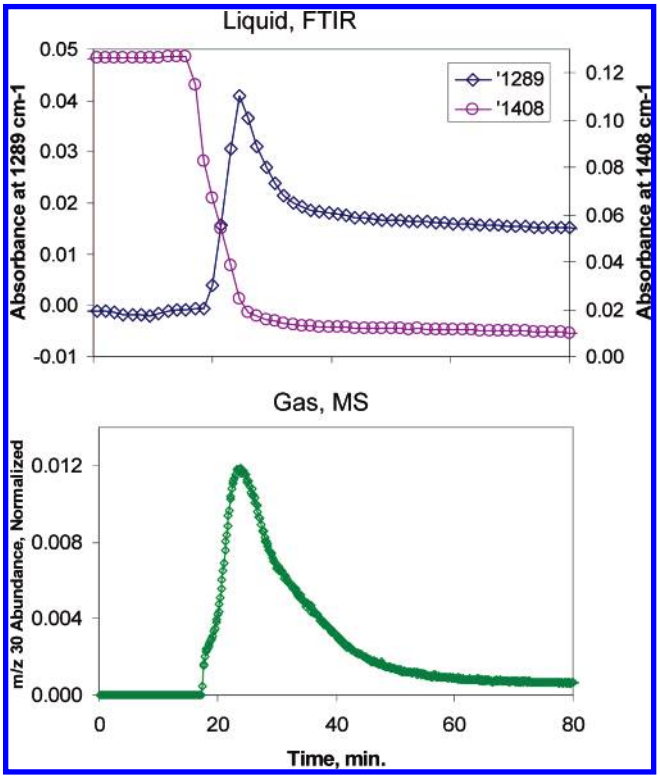


Figure 1. **Liquid IR absorbance changes and ethane gas evolution observed during the addition of DEZ to boroxine 16 in toluene.**

with caustic, followed by filtration, afforded an unoptimized 70% recovery of the ligand **15**. Subsequent chiral HPLC analysis and subjection of the recovered ligand **15** to the aryl transfer reaction protocol conclusively proved it to be recyclable.

Optimization of the equivalents of boroxine **16** and DEZ began with an attempt to analyze the reaction between these components in toluene. Initially, the boron−zinc exchange reactions between boroxine **16** and DEZ were performed per the literature references, with a 15−20 h stir period at 60 °C with no method of analysis. In an attempt to ensure reproducibility, solution IR (ReactIR 4000 instrument with DiComp probe) and a real-time gas analyzer−mass spectrometer (RTGA−MS) were used to better understand the reaction between boroxine **16** and DEZ in toluene. During the DEZ addition to the boroxine **16** in toluene, the temperature rose from 20 to 26 °C, and the IR scans showed consumption of a band at 1408 cm^{-1} and production of a band at 1289 cm^{-1} with little or no change within minutes after the addition was complete. In addition, the RTGA−MS data indicated a rapid decay in the evolution of ethane from the system after the DEZ addition was complete. The top half of Figure 1 illustrates the absorbance changes observed by IR as a result of the DEZ addition. The bottom half of Figure 1 illustrates the monitoring of ethane evolution and decay as a result of the DEZ addition, and mass spectra shown in Figure 2 confirm that the gas monitored was ethane and not ethylene. Subsequent heating of the reaction mixture to 60 °C caused the new band at 1289 cm^{-1} to be consumed within 0.5 h (Figure 3), and the resulting mixture was found

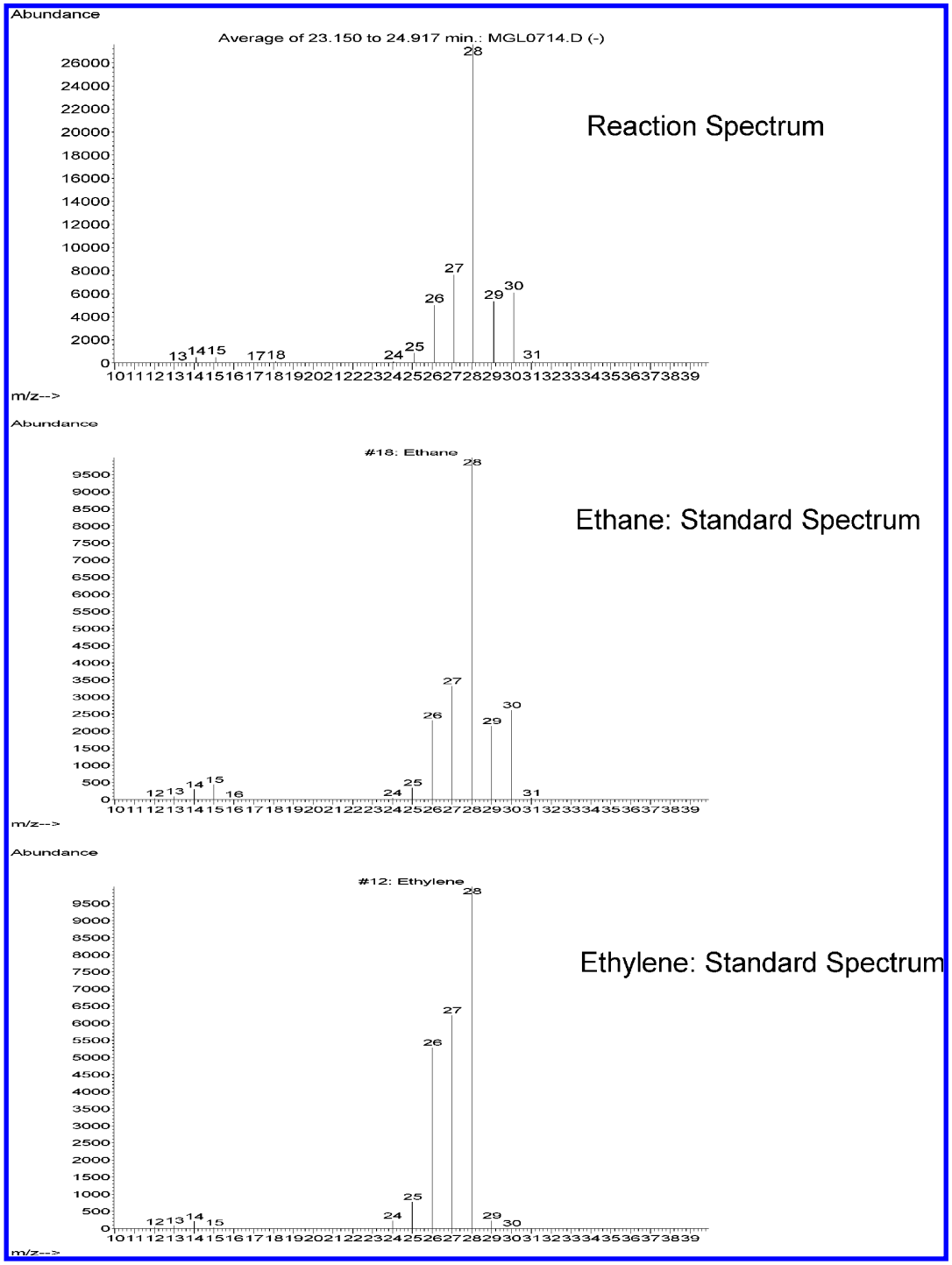


Figure 2. **Mass spectrum of gas evolved during the addition of DEZ to boroxine 16 in toluene, and comparison to standards of ethane and ethylene to confirm the identity.**

to be proficient in the aryl transfer chemistry. Based on the results of these experiments, the current 15−20 h period at 60 °C after the DEZ addition could be reduced to a 2 h period at 60 °C to affect the boron−zinc exchange with no concerns of reproducibility due to an incomplete reaction.

In order to optimize the amount of boroxine **16** used for the preparation of diarylmethanol **7**, reactions were set up essentially as depicted in Scheme 2 with 0.78 equiv of boroxine **16** (130 mol % excess of aryl equivalents) relative to aldehyde **5**, but without the DiMPEG polymer. After HPLC analysis confirmed that all of the starting aldehyde **5** had been consumed, additional small aliquots of aldehyde **5** were added to the reactions over time, allowing each to be consumed. The HPLC analysis after each aldehyde **5** addition revealed that the boroxine **16** equivalents could be reduced to 0.45 (35 mol % excess of aryl equivalents) with good production of diarylmethanol **7** and enantioselectivties maintained at >94%. These results were comparable to the optimal DPZ stoichiometry described by the Pericàs group.[10] Attempts to reduce the boroxine **16** equivalents to lower than 0.45 led to undesired ethyl transfer to the aldehyde **5**. In addition, it was found that the amount of DEZ could not be

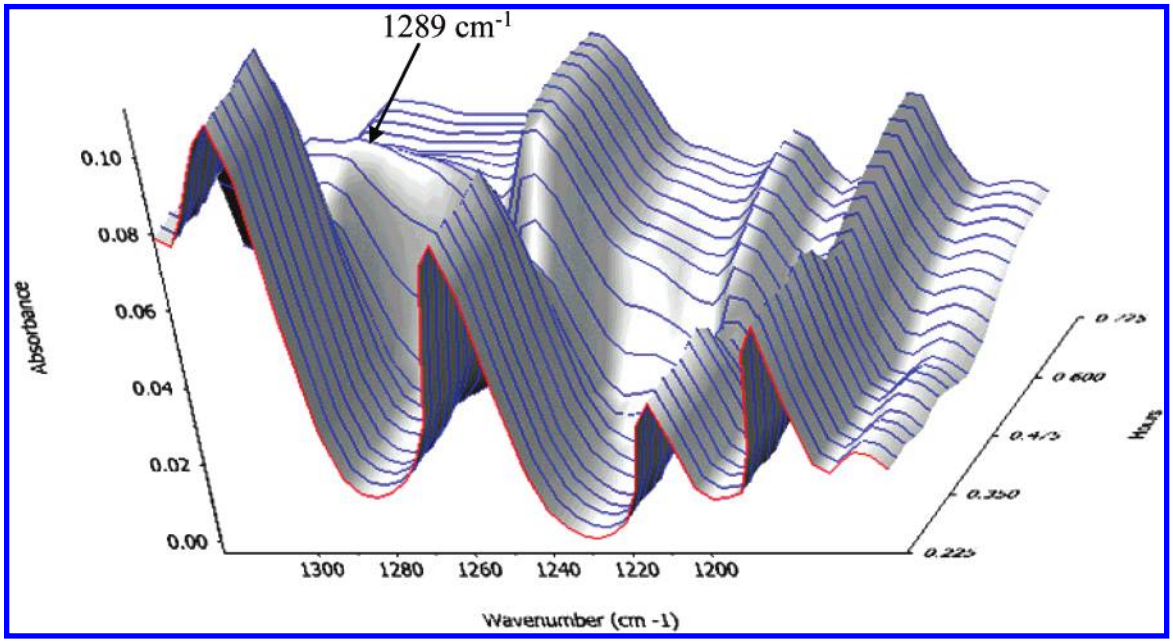


Figure 3. **IR waterfall plots correspond to the addition of diethyl zinc solution to the boroxine 16 in toluene between 20 °C to 26 °C, and the subsequent heatup to 60 °C. The band at 1289 cm^{-1} that is produced during the DEZ addition is consumed at 60 °C.**

reduced to much lower than 2.8 equiv (relative to the boroxine **16**), from the original 7.7 equiv, without deleterious affects to the conversion of aldehyde **5**. The effect of temperature was also examined in the production of diarylmethanol **7**, and it was found that no improvements in conversion or enantioselectivity were observed below −10 °C, and that temperatures of 10 °C or above led to undesired ethyl transfer to the aldehyde **5** and slightly lower enantioselectivities.

With the reagent stoichiometry optimized, the workup of the enantioselective aryl transfer reaction to produce a stock solution of the oil diarylmethanol **7** was pursued. To cope with the zinc waste produced in this chemistry, the reaction mixture was treated with wet acetic acid to directly precipitate $Zn(OAc)_2 \cdot 2H_2O$ (mp 237 °C) which is a readily filtered granular solid (dry acetic acid as the quench produced slimy $Zn(OAc)_2$ which was difficult to remove). After removal of the zinc waste, the ligand **15** could be extracted into aqueous HCl for subsequent recycling, and this operation further removed salts. After salt and ligand **15** removal, the remaining impurity in the primarily toluene organic phase was the benzyloxy-*tert*-butyl-dimethyl-silane "proteo-derivative" **17** (Scheme 3). The silane **17** was not tolerated well in the subsequent chemistry; thus, it was necessary to remove it from the toluene solution containing **7**. This was achieved by employing azeotropic distillation to replace the toluene with CH_3CN followed by selectively extracting **17** from the CH_3CN with heptane (CH_3CN and heptane are essentially immiscible). The result of these workup operations was to produce a solution of **7** in 88% yield with >94% ee. As a result of the optimizations to the aryl transfer reaction and the workup, the maximum reaction volumes which were 300 mL/g of aldehyde **5** went down to 37 mL/g, and the maximum workup volume which was 700 mL/g of aldehyde **5** went down to 60 mL/g. This reaction was run in a pilot plant using 17.6 kg of aldehyde **5** and 47.6 kg of boroxine **16** with results comparable to those observed in the laboratory.

To simplify the stereochemistry and improve functional group compatibility, acetate was chosen as a replacement for the previous THP protecting group for **7**. The CH_3CN stock solution of **7** was reacted with acetic anhydride in the presence of TEA and catalytic DMAP (DMAP was necessary for good conversion) to afford the acetate **18** (Scheme 3). It was found that the reaction mixture of **18** could be treated with aqueous HCl directly to effect removal of the TBS group and give the oil primary alcohol **19** (Scheme 3). Once again, taking advantage of the immiscibility of heptane with CH_3CN, the TBS-OH that was generated in the production of **19** was extracted with heptane. After the extraction, the CH_3CN was replaced via azeotropic distillation for toluene, and ammonium salts generated from the prior chemistry were removed by water washing. The toluene solution of **19** was reacted with MsCl in the presence of TEA to form the mesylate **20** and precipitate TEA-hydrochloride. Due to the insolubility of TEA-hydrochloride in the primarily toluene reaction media, the chloride derivative of **20** was negligible, and this obviated the need for the Finkelstein halogen, halogen exchange that had been used in the Scheme 1 chemistry. The TEA-hydrochloride was washed away with water to give a toluene solution of **20** which was diluted with acetone and reacted with the phenolic compound **11** in the presence of potassium carbonate to give acetate **2** (Scheme 3). The acetate **2** was afforded in 73% yield over four steps after crystallization from EtOH in >96% ee. Recrystallization of acetate **2** from a mixture of MTBE and heptane increased the ee to >99% with an 83% yield. With procedures developed to prepare kilograms of acetate **2** a more complete assessment of potential mGlu2 receptor potentiator therapeutics can now be realized.

Conclusions

In short, the mGlu2 receptor potentiator precursor molecule **1** was prepared via a racemic synthesis combined with a chiral chromatography as outlined in Scheme 1. In addition, an asymmetric enantioselective aryl transfer reaction was developed to give ready access to kilograms of the chiral diarylmethanol **7** and ultimately acetate **2** which is also useful for the preparation of mGlu2 receptor potentiators (Scheme 3).

Experimental Section

HPLC Method for Analyzing the Scheme 3 Synthesis of Acetate 2. Column: Zorbax Rapid Resolution SB-C8, 4.6 mm × 75 mm, 3.5 μm. Flow rate: 2 mL/min. Column temperature: 30 °C. Wavelength: 220 nm. A = 0.1% H_3PO_4 in Milli-Q water. B = acetonitrile. Gradient: 80% A at 0 min to 10% A at 7 min. Hold at 10% A for 1 min. Return to 80% A over 0.5 min and hold at 80% A for 0.5 min prior to next injection. HPLC method for chiral analysis: Column: Chiralpak AD 250 mm × 4.6 mm, 10 μm particle size. Flow rate: 1 mL/min. Column temperature: ambient. Wavelength: 280 nm. Mobile phase: heptane/2-propanol/TFA (60:40:0.01 v/v/v). Gradient: isocratic.

2,4,6-Tris-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-cyclotriboroxine (16).[9] Under a nitrogen atmosphere at 23 °C, (4-bromobenzyloxy)-*tert*-butyldimethylsilane **4** (390.0 g, 1.29 mol), anhydrous THF (3.90 L), anhydrous toluene (0.83 L), and trisopropylborate (117.7 g, 0.625 mol) were combined. The resulting mixture was stirred at ambient temperature for 30 min, then cooled to −78 °C using a dry ice/acetone bath. A 2.3 M hexane solution of *n*-hexyllithium (195.2 g, 0.634 mol) was transferred to an addition funnel, then added dropwise to the above mixture over 2.5 h. The reaction mixture was allowed to warm to −20 °C and quenched by the addition of 2 M HCl (1.32 L). After stirring at 0 °C for 0.5 h, EtOAc (2.1 L) was added, and the mixture was stirred for an additional 0.5 h. Stirring was stopped, and the layers were separated. The organic portion was washed with 5% aqueous $NaHCO_3$ and then concentrated in vacuo to a volume of 3 L. This solution was treated with CH_3CN (3 L) and was reconcentrated to 3 L volume. This process was repeated 2 more times, resulting in a white suspension. The mixture was filtered, and the resulting solids were washed with CH_3CN (0.5 L). After vacuum drying the solids (45 °C, 48 h), 245 g of **16** was recovered as a white powder (76.0%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 18H), 0.98 (s, 27H), 4.85 (s, 6H), 7.46 (d, 6H, J = 8 Hz), 8.20 (d, 6H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.23, 18.43, 25.96, 64.95, 125.42, 128.76, 135.67, 146.27. IR (KBr) 1611, 1410, 1369, 1347, 1300, 1250, 1087, and 836 cm^{-1}.

(*S*)-3-{[4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-phenyl]-hydroxy-methyl}-benzonitrile (7). The boroxine **16** (30.1 g, 40.4 mmol) was charged to a reactor and subjected to five alternating vacuum/nitrogen purges via a Firestone apparatus and was finally purged under a nitrogen flow. Diethylzinc (DEZ) (1.1 M) in toluene (312.3 mL, 343.5 mmol) was transferred to an addition funnel via cannula and was added to **16**. After 5 min, heating was initiated with a set point of 60 °C. After 17 h at 60 °C, the mantle was removed, and the mixture was cooled to −10 °C using an ice/acetone bath. (*R*)-(−)-2-Piperidino-1,1,2-triphenylethanol **15** (6.7 g, 18.7 mmol) was dissolved in toluene (70 mL) and added to the reaction mixture via syringe. Stirring was continued for 30 min. 3-Cyanobenzaldehyde **5** (12.2 g, 93.3 mmol) was dissolved in toluene (40 mL) and transferred to the addition funnel. This solution was added dropwise to the reaction mixture while maintaining the pot temperature below −5 °C. After 4 h at −10 to −5 °C, the reaction mixture was quenched by the dropwise addition of a mixture of AcOH (59.0 mL, 1003 mmol) and H_2O (14 mL). The resulting slurry was filtered, and the solids (zinc acetate dihydrate) were rinsed with toluene (50 mL). The filtrate was transferred to a separatory funnel and washed sequentially with 0.5 M HCl (2 × 200 mL), H_2O (2 × 100 mL), 0.5 M NaOH (100 mL), and H_2O (100 mL). The organic portion was concentrated in vacuo using a 45 °C bath. Crude chiral diarylmethanol **7** (40.4 g) was recovered (theory = 33.0 g). Crude **7** (40.4 g gross, 33.0 g theory, 93.3 mmol) was dissolved in CH_3CN (330 mL) and transferred to a 1-L separatory funnel. Heptane (66 mL) was added, the mixture was shaken, and the layers were allowed to separate. This extractive process was repeated with 5 × 33 mL of heptane, allowing ∼15 min separation time per extract. The CH_3CN (lower) layer was weighed (314.3 g) and held for assay and direct carry-thru to the next step. HPLC analysis employing a standard curve based upon purified oil **7** indicated that the CH_3CN solution contained 29.1 g of the desired product (88.3% yield). Chiral HPLC assay results: 95.5% ee. ^{1}H NMR (DMSO-d_6, 500.0 MHz): δ 0.04 (s, 6H), 0.87 (s, 9H), 4.64 (s, 2H), 5.75 (d, 1H, J = 3.8 Hz), 6.08 (d, 1H J = 3.8 Hz), 7.22 (d, 2H, J = 7.2 Hz), 7.33 (d, 2H, J = 7.2 Hz), 7.48 (t, 1H, J = 7.2 Hz), 7.65 (m, 2H), 7.78 (s, 2H).

(*S*)-Acetic Acid [4-(*tert*-butyl-dimethyl-silanyloxymethyl)-phenyl]-(3-cyano-phenyl)-methyl Ester (18). Under a nitrogen atmosphere, a flask was charged with a CH_3CN solution of **7** (28.35 g, 80.2 mmol). Acetic anhydride (10.6 g, 104.2 mmol), triethylamine (11.4 g, 112.4 mmol), and DMAP (0.23 g, 1.8 mmol) were added to the reaction mixture, and stirring was continued for 1 h. This reaction mixture of **18** was used directly in the next step without workup. ^{1}H NMR ($CDCl_3$, 500.0 MHz) δ 0.10 (s, 6H), 0.94 (s, 9H), 2.18 (s, 3H), 4.73 (s, 2H), 6.85 (s, 1H), 7.27 (d, 2H, J = 8 Hz), 7.32 (d, 2H, J = 8 Hz), 7.44 (t, 1H, J = 8 Hz), 7.56 (m, 2H), 7.64 (s, 1H).

(*S*)-Acetic Acid (3-cyano-phenyl)-(4-hydroxymethyl-phenyl)-methyl Ester (19). To a flask containing a CH_3CN solution of **18** (31.7 g, 80.2 mmol) was added 5 M HCl (28 mL, 140 mmol). The resulting mixture was stirred at 23 °C for 2.75 h, transferred to a separatory funnel, and extracted with heptane (3 × 320 mL). The *tert*-butyl-dimethyl-silanol-containing heptane extracts were discarded. Toluene (476 mL) and D.I. water (320 mL) were added to the remaining (CH_3CN) layer, and after shaking, the layers were allowed to separate. The aqueous layer was back extracted with toluene (320 mL). The organic phases were combined and washed with saturated $NaHCO_3$ (320 mL) followed by D.I. water (320 mL). The solution was concentrated by vacuum

distillation to a volume of 40 mL and then was diluted with toluene (286 mL). The resulting mixture of **19** was held for transfer to the next step. ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 2.17 (s, 3H), 4.68 (s, 2H), 6.85 (s, 1H), 7.30 (d, 2H, J = 8 Hz), 7.37 (d, 2H, J = 8 Hz), 7.46 (t, 1H, J = 8 Hz), 7.56 (m, 2H), 7.63 (s, 1H).

(*S*)-Acetic Acid (3-Cyano-phenyl)-(4-methanesulfonyloxymethyl-phenyl)-methyl Ester (20). Under a nitrogen atmosphere, a flask was charged with a toluene solution of alcohol **19** (20.7 g, 73.6 mmol) followed by triethylamine (12.3 mL, 88.4 mmol), and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (6.6 mL, 84.6 mmol) was charged to an addition funnel and added dropwise to the above mixture over 30 min. The reaction mixture was stirred at 0 °C for 1 h and transferred to a separatory funnel. After washing with D.I. water (2 × 50 mL), the toluene solution of mesylate **19** was held for transfer to the next step. ^{1}H NMR ($CDCl_3$, 500.0 MHz) δ 2.19 (s, 3H), 2.97 (s, 3H), 5.22 (s, 2H), 6.85 (s, 1H), 7.36 (d, 2H, J = 8 Hz), 7.42 (d, 2H, J = 8 Hz), 7.46 (t, 1H, J = 8 Hz), 7.55 (d, 1H, J = 8 Hz), 7.59 (d, 2H, J = 8 Hz), 7.63 (s, 1H).

(*S*)-Acetic Acid [4-(4-Acetyl-3-hydroxy-2-propyl-phenoxymethyl)-phenyl]-(3-cyano-phenyl)-methyl Ester (2). Under a nitrogen atmosphere, a flask was charged with a toluene solution of mesylate **19** (26.4 g, 73.6 mmol). Acetone (344 mL), 2′4′-dihydroxy-3′-propyl-acetophenone **11** (12.9 g, 66.5 mmol), and K_2CO_3 (10.2 g, 73.9 mmol) were charged to the reaction flask, and the resulting mixture was heated to 60 °C and stirred for 6.5 h. An additional charge of 2′4′-dihydroxy-3′-propyl-acetophenone (0.67 g, 3.4 mmol) was made to the reaction mixture, and stirring was continued for 5.5 h. Heating was stopped, and the flask contents were allowed to cool to 23 °C and then were filtered. The solids were rinsed with toluene (75 mL), and the resulting filtrate was concentrated in vacuo to a total volume of 132 mL. The solution was transferred to a separatory funnel and washed with D.I. water (2 × 132 mL). The organic portion was further concentrated in vacuo to 60 mL. To the still warm solution (70 °C), absolute EtOH (240 mL) was added and the mixture again concentrated to 234 mL. To the still warm solution (70 °C), absolute EtOH (66 mL) was added and the resulting solution concentrated to 100 mL. To the still warm solution (70 °C), absolute EtOH (190 mL) was added and the mixture allowed to cool slowly to 23 °C. The resulting suspension was stirred for 15 h and filtered. The solids were washed with cold absolute EtOH (0 °C, 34 mL) and further dried in a vacuum oven at 45 °C. Compound **2** (24.5 g) was isolated as an off-white solid (72.9% from **7**). Chiral assay: 96.7% ee.

Procedure for ee Upgrade of 2. Under a nitrogen atmosphere, a flask was charged with crude **7** (24.5 g, 53.6 mmol) and MTBE (123 mL). The suspension was heated to reflux, held for 10 min, and then allowed to cool to 27 °C. Heptane (50 mL) was charged to an addition funnel and then added to the above mixture over 20 min. The resulting mixture was stirred at 23 °C for 2 h and filtered. The crystals were washed with 1:1 MTBE/heptane (50 mL), and vacuum-dried at 45 °C to afford 20.4 g (83.1%) of off-white crystals of **2**. Chiral assay: 99.4% ee. mp (DSC) (10 °C/min) onset 96.18 °C, peak 100.05 °C; $[\alpha]^{21}_D$ 20.1 (c = 1.0 DMSO); IR (KBr pellet) 3466, 3085, 3065, 2967, 2933, 2867, 2225, 1740, 1620, 1497, and 1417 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500.0 MHz): δ 0.84 (t, 3H, J = 7 Hz), 1.42−1.49 (m, 2H), 2.15 (s, 3H), 2.54 (s, 3H), 2.55−2.58 (m, 2H), 5.21 (s, 2H), 6.68 (d, 1H, J = 8 Hz), 6.83 (s, 1H), 7.42 (d, 2H, J = 8 Hz), 7.45 (d, 2H, J = 8 Hz), 7.55 (t, 1H, J = 7 Hz), 7.72−7.77 (m, 3H), 7.91 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.4, 21.3, 21.9, 24.4, 26.8, 69.5, 75.6, 104.4, 112.1, 114.3, 117.3, 118.9, 127.3, 127.8, 130.3, 130.4, 131.6, 131.7, 132.1, 137.2, 139.8, 142.6, 161.5, 162.5, 169.9, 204.4; HRMS (AP^+; accurate mass) calcd for $C_{28}H_{27}NO_5$ 457.1889, found 457.1892. Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.39; H, 5.95; N, 3.00.

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Supporting Information Available

Experimental procedures and spectral data for the Scheme 1 chemistry to prepare **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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