Organic Process Research & Development

COMMUNICATION

pubs.acs.org/OPRD

Diarylketone Ketoreductase Screen and Synthesis Demonstration to Access mGlu2 Receptor Potentiators

Nicholas A. Magnus,* D. Scott Coffey, Amy C. DeBaillie, Chauncey D. Jones, Iwona A. Kaluzna,‡ Spiros Kambourakis,§ Yangwei J. Pu, Lin Wang, and James P. Wepsiec

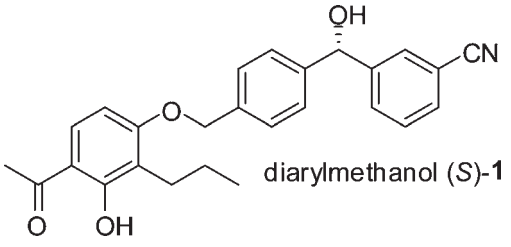
Eli Lilly and Company, Chemical Product Research and Development Division, Indianapolis, Indiana 46285, United States

Supporting Information

ABSTRACT: This communication describes proof of concept for an enantioselective enzyme-based synthesis of diarylmethanol (*S*)-**1** to access mGlu2 receptor potentiators. A ketoreductase (KRED) screen was applied to benzophenone **8** to afford chiral diarylmethanol (*S*)-**9**, which is a useful intermediate for the preparation of chiral diarylmethanol (*S*)-**1**. In addition, a more practical synthesis of benzophenone **8** was demonstrated utilizing Friedel−Crafts acylation and radical bromination chemistry.

INTRODUCTION

The excitatory amino acid L-glutamate mediates most of the excitatory neurotransmission within the central nervous system. 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 mGlu receptors (mGlu2 and mGlu3) being largely presynaptic and inhibitors of neurotransmission.[2] To access mGlu2 receptor potentiators to fund Lilly's research directed towards potential therapies for the treatment of migraine headaches, efficient syntheses were needed to prepare the ether-linked diarylmethanol (*S*)-**1**.



diarylmethanol (*S*)-**1**

The published syntheses of diarymethanols related to (*S*)-**1** initially utilized chiral chromatography which was improved upon through the development of an enantioselective aryl-transfer process.[3] This process involved using cryogenic conditions and pyrophoric reagents to convert arylbromide **2** into aryllithium **3**, which is converted to an arylboroxine **4** and then to an arylalkyl zinc species **5** to make the carbon−carbon bond of diarylmethanol **7** in the presence of a chiral ligand **6** (Scheme 1). The number of steps, conditions, and reagents required for the aryl-transfer process led us to investigate biocatalytic methods as an alternative. In particular, reports on the use of ketoreductases (KREDs) to prepare enantiomerically enriched diarylmethanols via reduction of benzophenones under ambient conditions in aqueous media indicated that such an approach would be more attractive.[4]

RESULTS AND DISCUSSION

The goal of this research was to achieve proof of concept for an enantioselective enzyme-based synthesis of diarylmethanol (*S*)-**1** with potential for scale-up. To that end, benzophenone **8** was identified as a suitable substrate for screening in KRED reductions to give chiral diarylmethanol (*S*)-**9** (Scheme 2), which could be further converted to (*S*)-**1** via selective activation of the primary alcohol. For the KRED screening study, benzophenone **8** was synthesized using a standard ketone synthesis, and a reference sample of diarylmethanol (*S*)-**9** was prepared by deprotecting **7** (see Supporting Information). The ketone **8** was reacted with KREDs from an enzyme kit supplied by Codexis (Table 1). Table 1 summarizes selected results from a screen of 60 KREDs for the conversion of **8** to **9**. Only those reductions giving the highest levels of enantioselectivity are reported.

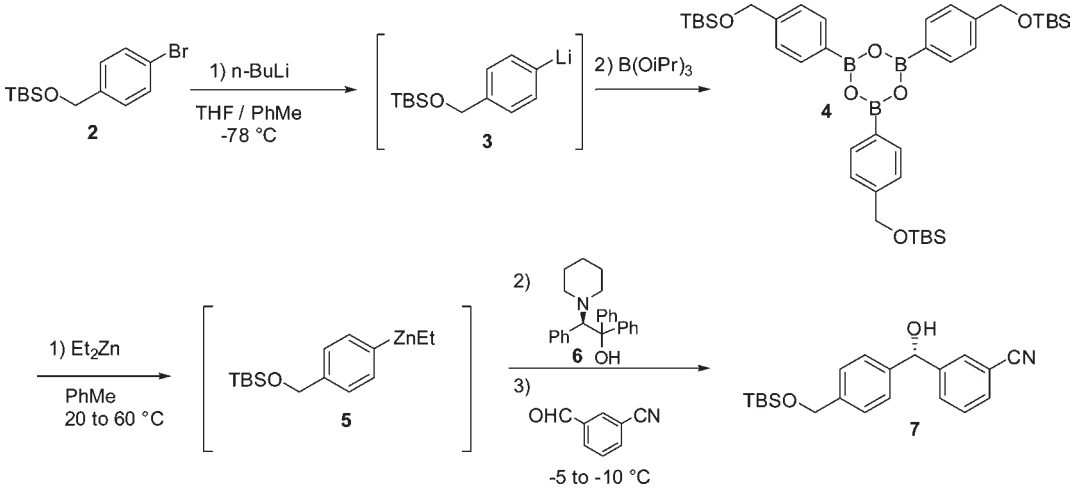
From the KRED screen for the reduction of ketone **8**, two enzymes were identified as highly *S*-selective, producing a ratio of 99:1 for *S*- to *R*-alcohols. These enzymes are KRED 111 and KRED 115. Both enzymes catalyzed reduction at moderate to good rates, with KRED 111 being the best at 0.62 U/mg, a rate that should be sufficient for scale-up.[5] In addition, eight KREDs were identified that were highly *R*-selective.

Synthesis of Enzymatic Substrate 8. Due to the utility of benzophenone **8** for the preparation of (*S*)-**1** and the positive screening results for the KRED-mediated enantioselective reduction of **8**, a synthesis of **8** was developed beginning with toluene (Scheme 3). 3-Cyanobenzoyl chloride **10** in toluene was treated with $AlCl_3$ to induce Friedel−Crafts acylation at the para position of toluene to afford benzophenone **11** in 80% yield.[6] The benzylic methyl group of **11** was subjected to radical bromination with AIBN and 1,3-dibromo-5,5-dimethylhydantoin in CH_3CN to give a mixture of mono- (**12**) and bis-bromination (**13**).[7] The bromination reaction mixture was treated with diisopropylethylamine and diethyl phosphite to selectively reduce **13** to **12** in 80% overall yield.[8] The bromine atom of **12** was replaced with actetate in a mixture of NaOAc and DMF to give **14** in 98% yield. Acetate **14** was subjected to methanolysis in a mixture of MeOH, water, and K_2CO_3 to afford **8** in 91% yield.[9]

Received: July 19, 2011
Published: October 08, 2011

dx.doi.org/10.1021/op2002479 | *Org. Process Res. Dev.* 2011, 15, 1377–1381

Scheme 1. Aryl-transfer process



Scheme 2. Enantioselective KRED reduction of benzophenone 8

Table 1. Results of screening KREDs for enantioselective reduction of ketone 8[a]

KRED[b]	U/mg[c]	yield[d] (%)	S^d (%)	R^d (%)
101	0.167	>98	97	3
108	0.012	>98	<2	>98
111	0.62	>98	99	1
112	0.072	>98	96	4
113	0.018	>98	95	5
114	0.66	>98	97	3
115	0.416	>98	99	1
116	0.014	>98	<2	>98
117	0.012	>98	<2	>98
118	0.096	>98	<2	>98
119	0.274	>98	<2	>98
120	0.007	>98	<3	>97
127	0.07	>98	<2	>98
128	0.72	>98	<2	>98

[a] See Experimental Section for screening conditions. [b] KRED number corresponds to the Codexis catalog number. [c] Unit definition: 1U = 1 μmol substrate conversion/mg of enzyme x min^{-1}. These activities were measured in cuvette assays where the rate of NADPH consumption (as measured by the rate of decrease at 340 nm) was measured after incubation of the enzyme with the substrate in the presence of NADPH. [d] Yield and percent for *S* or *R* by normal phase chiral HPLC.

To demonstrate the viability of diarylmethanol (*S*)-**9** for the preparation of (*S*)-**1**, diol (±)-**9** (prepared by standard conditions see Supporting Information) was exposed to Ms_2O in the presence of TEA in 2-butanone to give selective mesylation of the primary alcohol which was reacted with TBAB and KBr to generate the intermediate bromide (the bromide was observed to react more productively than the mesylate in ether couplings) (Scheme 4). The bromide was reacted with the potassium phenolate of resorcinol **17** to give (±)-**1** in 75% yield.[10]

CONCLUSIONS

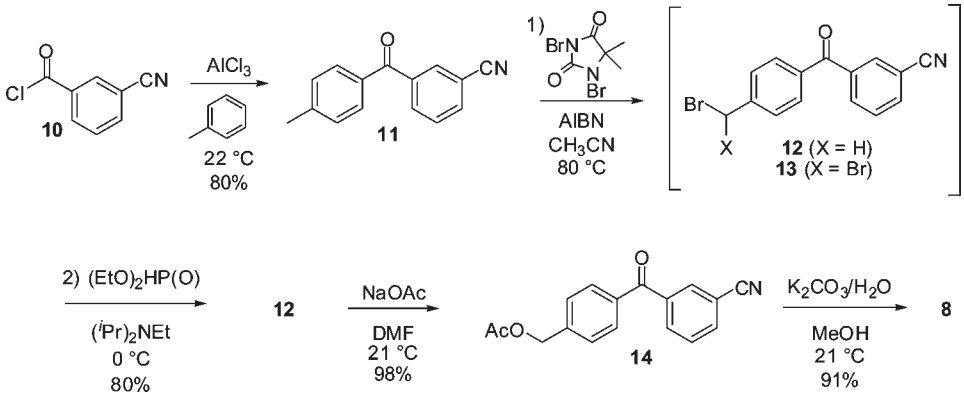
The KRED screen for the enantioselective reduction of benzophenone **8** demonstrated that chiral diol (*S*)-**9** could be generated in 98% ee from the prochiral ketone **8**, and the rate of conversion indicated utility for development to larger scale. Due to the potential of the enzyme chemistry, a scalable synthesis of benzophenone **8** was devised with four steps and 57% overall yield employing Friedel–Crafts acylation of toluene and radical bromination as key transformations. In addition, (*S*)-**9** was shown to be useful for the preparation of diarylmethanol (*S*)-**1** via activation and ether coupling of (±)-**9** to afford diarylmethanol (±)-**1** in 75% yield. Last, the goal of demonstrating proof of concept for an enantioselective enzyme-based synthesis of diarymethanol (*S*)-**1** with potential for scale-up was achieved.

EXPERIMENTAL SECTION

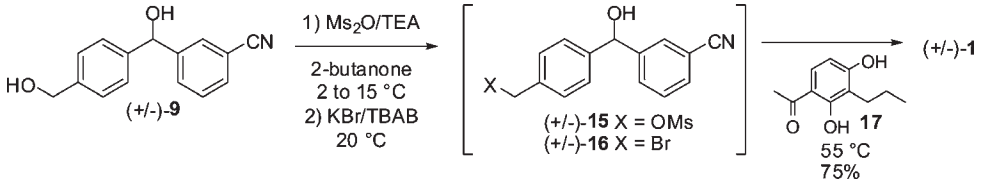
General. ^1H and ^{13}C NMR spectra were obtained on a Varian spectrometer at 400 and 101 MHz respectively. HPLC conditions: Instrument: Agilent 1100 series. Column: Zorbax SB-C8. Flow: 1.5 mL/min. A = 0.1% H_3PO_4, B = CH_3CN. Gradient: 95% A/5% B to 50% A over 10 min; change to 5% A over 5 min. Hold at 5% A for 5 min. Return to 95% A using a 3 min post time. Column temperature: 40 °C. Wavelength: 220 nm. HPLC method for chiral analysis of compound **9**: 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.

General KRED Screening Conditions for the Conversion of 3-(4-(Hydroxymethyl)benzoyl)benzonitrile (8) to (*S*) or (*R*)-3-(Hydroxy(4-(hydroxymethyl)phenyl)methyl)benzonitrile (9). Screening was carried out by incubating the diaryl ketone **8** (5 mg) in a reaction mixture under ambient conditions with individual KRED enzymes overnight (12–16 h). Reaction mixtures contained 10 mM ketone, 2 mg/mL KRED, 200 mM potassium phosphate buffer pH 6.9, 100 mM glucose, 0.5 mg/mL

Scheme 3. Friedel–Crafts/radical bromination-based synthesis of benzophenone 8



Scheme 4. Selective activation and ether synthesis to prepare (±)-1



glucose dehydrogenase (for recycling of the cofactor), and 1.5 mM NADPH cofactor. The diaryl ketone substrate was first dissolved in DMSO at 200 mM concentration and was subsequently added to the reaction mixture giving 5% (v/v) DMSO concentration and 10 mM final ketone concentration. The reactions were extracted with EtOAc (10 mL) and evaporated to afford the products for analysis. Note that the substrate did not completely dissolve and a heterogeneous mixture formed upon substrate addition, but this did not impede the screening. All reactions gave complete product formation (100% conversion to alcohol) after overnight reaction.

*3-(4-Methylbenzoyl)benzonitrile (**11**).* Under a nitrogen atmosphere, 3-cyanobenzoyl chloride **10** (5.00 g, 30.20 mmol) was dissolved in toluene (75 mL) at 22 °C to give a colorless solution. Aluminum trichloride (6.10 g, 45.30 mmol) was added to the reaction mixture. After 0.5 h, water (125 mL) was added over 0.5 h to the dark, greenish-yellow reaction mixture causing the color to change to amber and the temperature to rise to 31 °C. EtOAc (100 mL) was added to the mixture, giving clean phase separation. The organic phase was separated and dried with Na_2SO_4. Distillation to remove EtOAc at 40 °C in vacuo caused the product to crystallize. The resulting slurry was cooled to 0 °C, and the solids were filtered and washed with cold toluene (10 mL). The solids were dried in a vacuum oven at 46 °C to afford 4.54 g of crystalline product **11**. The mother liquor from the crystallization was concentrated to leave a solid which was dissolved in hot toluene (10 mL) to afford a second crop of crystals on cooling to 0 °C. The second crop of crystals was filtered, washed with cold toluene, and dried in a vacuum oven at 46 °C to afford a further 0.85 g of crystalline product **11**. A total of 5.39 g of product **11** was isolated as a colorless crystalline solid in 80% yield. Mp 139–140 °C. IR (neat) 3066, 2232, 1644, 1600, 1421 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 8.12–8.08 (m, 2 H), 7.98 (ddd, J = 7.9, 1.4, 1.5 Hz, 1 H), 7.74 (dd, J = 7.8, 7.8 Hz, 1 H), 7.66 (d, J = 8.2 Hz, 2 H), 7.38 (d, J = 8.2 Hz, 2 H), 2.40 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) 194.1, 144.4, 138.9, 136.0, 134.2, 133.8, 133.2, 130.5, 130.3, 129.8, 118.6, 112.4, 21.7. HRMS (ESI) calcd for $C_{15}H_{11}NO$ (M^+) 222.0913, found 222.0917.

*3-(4-(Bromomethyl)benzoyl)benzonitrile (**12**).* Under a nitrogen atmosphere at 20 °C, the ketone **11** (0.50 g, 2.26 mmol) was combined with 1,3-dibromo-5,5-dimethylhydantoin (0.58 g, 1.98 mmol), 2,2′-azo-bis-isobutyronitrile (0.02 g, 0.11 mmol), followed by CH_3CN (5 mL). The slurry was heated to 80 °C. After 2.0 h, an aliquot of reaction mixture was dissolved in CH_3CN for HPLC analysis which indicated a mixture of mono- and bis-bromination products, with <1% of the starting ketone remaining. The reaction mixture was cooled to 0 °C, and diisopropylethylamine (0.30 mL, 1.69 mmol) and diethyl phosphite (0.22 mL, 1.69 mmol) were added to the reaction mixture, followed by removal of the cooling bath. After 4.0 h at 21 °C, an aliquot of reaction mixture was dissolved in CH_3CN for HPLC analysis which indicated mainly the desired benzyl bromide **12**, with <1% of the bis-bromination product remaining. Water (3 mL) was added to the reaction mixture. A few seeds of **12** were added to the reaction mixture causing rapid nucleation of white solids. To the slurry was added a further amount of water (2 mL) over 0.5 h to further promote the crystallization. The solids were filtered and washed with a 1:1 mixture of CH_3CN and water (2 mL). After drying the resulting solids in a vacuum oven at 40 °C, 0.55 g of off-white crystals of **12** were isolated in 80% yield. Mp 94–96 °C. IR (neat) 3073, 3036, 2232, 1652, 1600, 1414 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 8.13–8.11 (m, 2 H), 8.01 (ddd, J = 8.0, 1.5, 1.5 Hz, 1 H), 7.77–7.73 (m, 3 H), 7.62 (d, J = 8.2 Hz, 2 H), 4.78 (s, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) 193.9, 143.8, 138.4, 136.2, 136.0, 134.3, 133.4, 130.8, 130.4, 130.0, 118.5, 112.3, 33.6. HRMS (ESI) calcd for $C_{15}H_{10}BrNO$ (M^+) 300.0019, found 300.0024.

*4-(3-Cyanobenzoyl)benzyl Acetate (**14**).* Under a nitrogen atmosphere at 21 °C, benzyl bromide **12** (1.00 g, 3.33 mmol) was

dx.doi.org/10.1021/op2002479 |*Org. Process Res. Dev.* 2011, 15, 1377–1381

dissolved in DMF (5 mL) followed by the addition of potassium acetate (0.65 g, 6.66 mmol). After 15.0 h, an aliquot of reaction mixture was diluted with CH_3CN for HPLC which indicated complete conversion of **12** to a slightly more polar product. EtOAc (10 mL) and water (5 mL) were added to the reaction to give two phases. The organic layer was separated and washed with water (2 × 5 mL) to remove DMF. The organic phase was dried with Na_2SO_4 and the solvent removed in vacuo to leave a yellow oil that crystallized under vacuum (0.92 mg) to afford a 98% yield of **14**. A sample of **14** (300 mg) was recrystallized from hot IPA (5 mL), and the following analytical data were collected: Mp 78−80 °C. IR (neat) 3073, 2940, 2232, 1727, 1652, 1451, 1421 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 8.13−8.11 (m, 2 H), 8.01 (ddd, J = 7.8, 1.5, 1.4 Hz, 1 H), 7.77−7.73 (m, 3 H), 7.54 (d, J = 8.0 Hz, 2 H), 5.18 (s, 2 H), 2.09 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) 194.1, 170.6, 142.2, 138.5, 136.2, 135.9, 134.3, 133.4, 130.5, 130.3, 128.2, 118.5, 112.3, 65.2, 21.1. HRMS (ESI) calcd for $C_{17}H_{13}NO_3$ (M^+) 280.0968, found 280.0972.

*3-(4-(Hydroxymethyl)benzoyl)benzonitrile (**8**) from Acetate (**14**).* Acetate **14** (0.25 g, 0.90 mmol) was suspended in MeOH (5 mL), heated to 45 °C to give a homogeneous solution, and cooled to 21 °C. At 21 °C, K_2CO_3 (0.27 g, 1.97 mmol) in water (0.5 mL) was added to the reaction mixture, giving an exotherm to 24 °C, a light-brown color, and precipitation of solids. After 0.5 h, a sample of the reaction mixture was dissolved in CH_3CN for HPLC that indicated complete conversion to the alcohol **8**. Water (0.5 mL) and saturated aqueous citric acid (2 mL) were added to the reaction mixture, causing further solids to precipitate. The solids were filtered, washed with water, and dried in a vacuum oven at 40 °C to afford **8** (0.19 g) in 91% yield. Mp 134−135 °C. IR (neat) 3426, 3068, 2235, 1644, 1599, 1577, 1421 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 8.12−8.09 (m, 2 H), 7.99 (ddd, J = 7.8, 1.4, 1.2 Hz, 1 H), 7.77−7.22 (m, 3 H), 7.50 (d, J = 8.2 Hz, 2 H), 5.40 (t, J = 5.7 Hz, 1 H), 4.6 (d, J = 5.7 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) 194.3, 149.0, 138.9, 136.1, 134.8, 134.2, 133.3, 130.4, 130.3, 126.8, 118.6, 112.3, 62.8. HRMS (ESI) calcd for formula $C_{15}H_{12}NO_2$ (M^+) 238.0863, found 238.0860.

*(±)-3-((4-((4-Acetyl-3-hydroxy-2-propylphenoxy)methyl)phenyl)(hydroxy)methyl)benzonitrile (**1**) from (±)-**9**. Mesylate Formation.* Under a nitrogen atmosphere at 20 °C, diol (±)-**9** (1.00 g, 4.18 mmol) was dissolved in 2-butanone (10 mL) and TEA (0.86 g, 8.50 mmol). The resulting mixture was cooled to 2−3 °C, and a solution of methanesulfonic anhydride (1.10 g, 6.31 mmol) in 2-butanone (5 mL) was added to the reaction mixture over 0.25 h. After 1.0 h at 2−3 °C, 2% citric acid in water (10 mL) and 2-butanone (10 mL) was added to the reaction mixture to give two phases. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and 5% NaCl in water (10 mL). The organic phase was transferred to an addition funnel with the aid of 2-butanone (5 mL), which was attached to a reactor.

Bromide Formation. Under a nitrogen atmosphere at 20 °C, the reactor was charged with KBr (0.60 g, 5.04 mmol) and TBAB (0.30 g, 0.93 mmol), and the mesylate/2-butanone solution was added and rinsed in with 2-butanone (5 mL). The resulting mixture was stirred for 21.0 h to complete the bromide formation.

Ether Formation. Under a nitrogen atmosphere at 20 °C, resorcinol **17** (0.85 g, 4.38 mmol) and K_2CO_3 (0.70 g, 5.06 mmol) were added to the bromide/2-butanone solution, and the resulting slurry was heated to 55 °C. After 5.0 h at 55 °C, the mixture was cooled to 20 °C, and a solution of 5% citric acid in water (15 mL) was added to the reaction (pH of the aqueous layer was 5). The reaction mixture was transferred to an addition funnel and rinsed in with 2-butanone (10 mL). The organic phase was separated, washed with 5% NaCl in water (15 mL), and concentrated on a roto-vap to give a yellow oil (2.25 g). The oil was dissolved in MeOH (10 mL) and seeded with (±)-**1** at 20 °C. After 0.5 h a thin slurry was produced which was stirred for 16.0 h to produce a thick slurry. The slurry was cooled to 0 °C, stirred for 1.0 h, filtered, and washed with cold MeOH (2 mL). The resulting off-white solids were dried under vacuum to afford (±)-**1** (1.31 g, 75%). Mp 138−139 °C. IR (neat) 3366, 3314, 2957, 2923, 2224, 1625, 1495, 1417, 1268 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 12.82 (s, 1H), 7.82 (bs, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 9.1 Hz, 1H), 6.15 (d, J = 4.0 Hz, 1H), 5.78 (d, J = 4.0 Hz, 1H), 5.19 (s, 2H), 2.56 (t, J = 7.4 Hz, 2H), 2.54 (s, 3H), 1.46 (sextet, J = 7.4 Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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, 131.6, 136.1, 144.9, 147.6, 161.5, 162.5, 204.4. HRMS (ESI) calcd for formula $C_{26}H_{25}NO_4$ (M^+) 416.1864, found 416.1856.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for compounds **8**, (*S*)-**9**, and (±)-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

Telephone: 317-651-1470. Fax: 317-276-4507. E-mail: magnus_nicholas_a@lilly.com.

Present Addresses

[‡]DSM Innovative Synthesis B.V., Poststraat 1, 6135 KR Sittard, the Netherlands.

[§]Synthetic Genomics, Inc., 11149 N. Torrey Pines Rd., La Jolla, CA 92037, U.S.A.

■ ACKNOWLEDGMENT

We are grateful to Dr. Rui Lin Gu for instruction on conducting enzyme reactions. Mr. Eric D. Crockett for performing all of the high-resolution mass spectrometer experiments, and Dr. Lars Magnusson, Mr. Keith Galyan, and Mr. John L. Bowers for analytical and chromatography support.

■ REFERENCES

(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.; 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) (a) 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. WO/2006/

057870 A1 20060601, 2006 (b) Magnus, N. A.; Anzeveno, P. B.; Coffey, D. S.; Hay, D. A.; Laurila, M. E.; Schkeryantz, J. M.; Shaw, B. W.; Staszak, M. A. *Org. Process Res. Dev.* **2007**, *11* (3), 560.

(4) (a) Truppo, M. D.; Pollard, D.; Devine, P. *Org. Lett.* **2007**, *9* (2), 335.(b) Truppo, M.; Morley, K.; Pollard, D.; Devine, P. *Practical Methods for Biocatalysis and Biotransformations*; Whittall, J., Sutton, P., Eds.; John Wiley & Sons Ltd.: Chichester, UK, 2010; pp 288−290.

(5) Kaluzna, I.; Rozzell, D.; Kambourakis, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3682.

(6) Wagner, G; Voigt, B; Steinbruck, K. *Pharmazie* **1976**, *31* (6), 354.

(7) Jones, P. B.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 2753.

(8) Starrett, J. E., Jr.; Gillman, K. W.; Olson, R. E. (Bristol-Myers Squibb Company, U.S.A.). U.S. Patent 2009111858 A1, 2009.

(9) The current synthesis is not desirable for scale-up as described in the Experimental Section with operations such as concentration to dryness and the use of drying agents. However, development of azeotropic solvent exchanges to afford drying and further development of the crystallizations would enable a fully scalable synthesis.

(10) While we demonstrated that (±)-**9** can be converted to (±)-**1**, and therefore (*S*)-**9** can be converted into (*S*)-**1**, the project was no longer funded to develop the single enantiomer process.