DOI: 10.1002/adsc.201600329
Advanced Synthesis & Catalysis

Enantioselective Synthesis of a Positive Allosteric Modulator of the Metabotropic Glutamate Receptor 5 (mGluR5) Receptor *via* Dynamic Kinetic Resolution of α-Amino Ketones

Francisco González-Bobes,[a,*] Ronald Hanson,[a] Neil Strotman,[a] Zhiwei Guo,[a] and Animesh Goswami[a]

[a] Chemical & Synthetic Development, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, NJ 08903, USA
Fax: (+1)-732-227-3932; phone: (+1)-732-227-7926; e-mail: francisco.gonzalezbobes@bms.com

Received: March 25, 2016; Revised: April 25, 2016; Published online: ■■ ■■, 0000

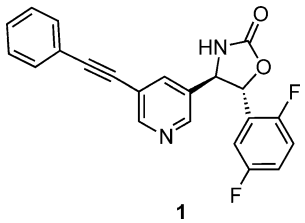
Dedicated to Professor José Barluenga.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600329.

Abstract: The concise synthesis of a pharmaceutical candidate is described. The chiral core of the molecule is assembled using an aza-benzoin condensation and a dynamic kinetic resolution (DKR) as the key reactions. This enables superb control of the regio-, diastereo- and enantioselectivity of the synthesis. Both biocatalysts and transition metal catalysts are remarkably effective in the key asymmetric reduction step. Similar approaches could be considered in the synthesis of other 1,2-amino alcohols where traditional approaches based on functionalization of alkenes, epoxides or aziridines may suffer from selectivity issues.

Keywords: asymmetric synthesis; biotransformations; homogenous catalysis; regioselectivity; umpolung

Glutamate is the major excitatory neurotransmitter in the mammalian brain, playing an important role in a wide variety of physiological process.[1] Glutamatergic neurotransmission is predominantly mediated through activation of cell surface receptors including ligand-gated ion channels (ionotropic receptors) and metabotropic glutamate G protein coupled receptors (mGluRs).[2] Within this family, the mGluR5 receptor is expressed broadly throughout the central nervous system (CNS) and has attracted interest for a number of therapeutic indications with implications in different behavioral and cognitive processes.[3] During the course of a program directed to the discovery of mGluR5 modulators, oxazolidinone **1** was identified as a potential candidate for pre-clinical development (Figure 1).[4]



1

Figure 1. mGluR5 modulator **1**.

The initial route to **1** relied on the osmium-catalyzed aminohydroxylation of *trans* alkene **3** (Figure 2) to set both the absolute and relative configuration of the chiral centers on the target molecule.[5] This reaction occurred with modest regioselectivity (3:1) and ~90% *ee*, negatively impacting the overall yield and throughput of the synthesis. Herein, we report a stereoselective synthesis of **1** avoiding the use of the toxic osmium catalyst and precluding the formation of undesired regioisomers (Scheme 1). These results may prove useful towards the asymmetric synthesis of the popular 1,2-amino alcohol motif where approaches based on the functionalization of alkenes, epoxides or aziridines often are challenged with selectivity issues.

Two major strategic challenges to accomplish a selective synthesis of **1** were recognized. The first was to identify a highly enantioselective method to set the vicinal stereocenters with the desired relative stereochemistry. The second was to devise an approach that would not form regioisomers, thus preventing undesired yield losses. To address the enantioselectivity challenge, we were drawn to explore the asymmetric

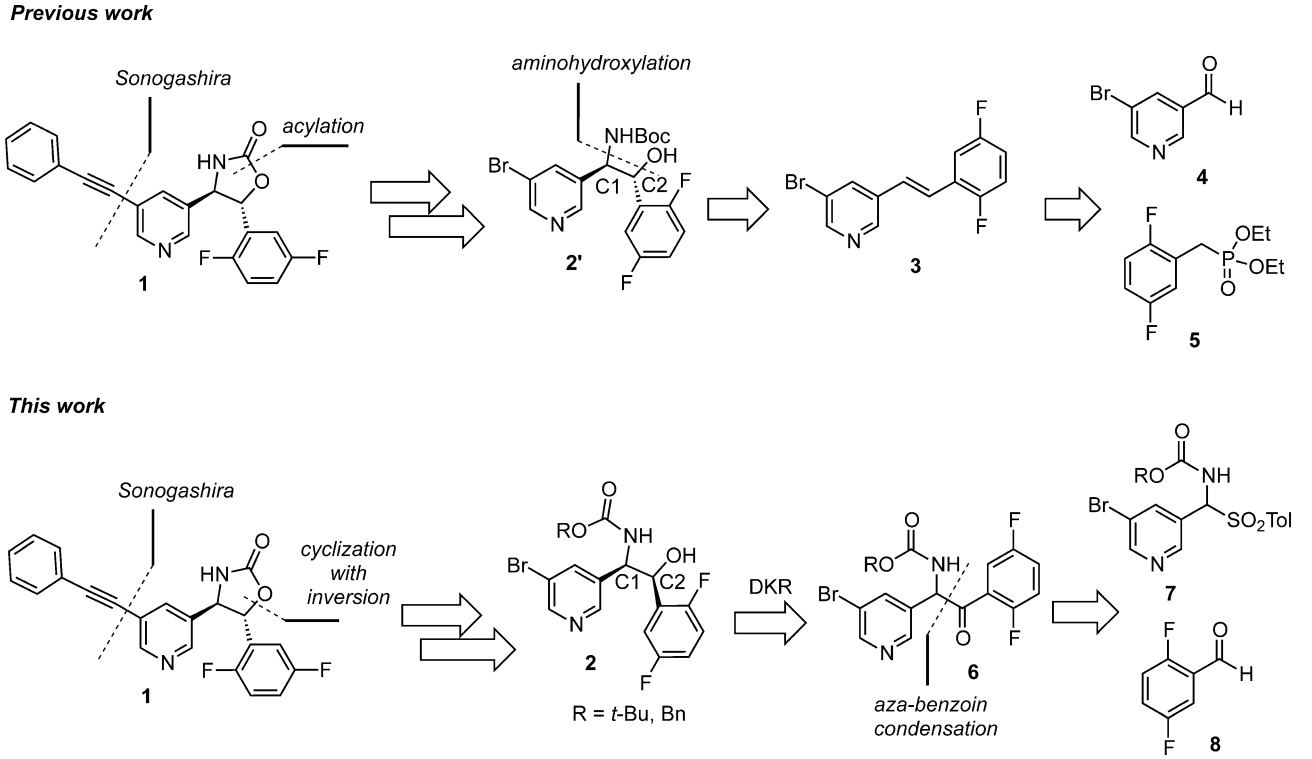
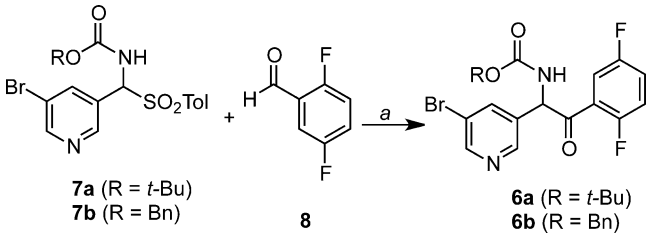


Figure 2. Synthetic approaches for the preparation of **1**.



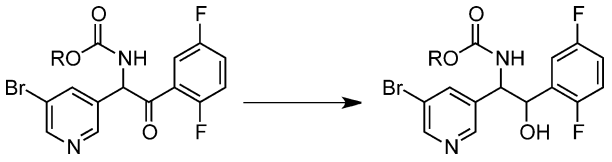
Scheme 1. Synthesis of protected α-amino ketones *via* aza-benzoin condensation. *Conditions:* (a) **7** (1 equiv.), **8** (1.05 equiv.), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium chloride (5–7 mol%), NEt_3 (5 equiv.), CH_2Cl_2, 0 °C, 78% yield of **6a**, 75% yield of **6b**.

reduction of an adequately protected α-amino ketone.[6] This approach would need to both overcome the potential formation of *syn* and *anti* isomers,[7] and be amenable to a dynamic kinetic resolution (DKR) that theoretically could generate a single enantiomer of the desired amino alcohol from racemic amino or amido ketone.[8] To test the feasibility of this idea, an efficient synthesis of protected α-amino ketone **6** was required. The convergent disconnection of C-1–C-2 was particularly attractive as it would prevent the formation of any undesired regioisomer. To this end, the aza-benzoin condensation was chosen due to its operational simplicity, avoidance of oxidation state adjustments, and the easy access to all the required precursors and catalysts.[9] After minimal reaction optimization, **6** was prepared in two steps using pyridine **7** as bench-stable surrogate for the reactive intermediate Boc- and Cbz-imines and the readily available aldehyde **8** under thioazolium-based catalysis (Scheme 1).

With the α-amino ketone derivatives in hand, the asymmetric reduction of **6** was then explored. Table 1 summarizes the results obtained when exploring a range of commercially available enzymatic catalysts such as ketoreductases and selected yeast strains.[10] We hypothesized that either the *syn* or the *anti* amino alcohol, resulting from the respective *syn* or *anti* hydride additions,[11] could be productively cyclized to make the oxazolidinone with retention[12] or inversion[13] at the C-2 stereocenter.

A number of catalysts, including isolated ketoreductases and yeast strains, proved highly selective to prepare either enantiomer of the *syn* **2a′** and *anti* isomers **2a** (Table 1, entries 1–4 and 5–9, respectively). Importantly, the Cbz-protected amino ketone **6b** could also be transformed in excellent stereoselectivities (entry 10).[15] Collectively, these results represent a breakthrough in the area. Attaining of high enantioselectivities with concomitant modulation of *syn/anti* selectivities in protected substrates using other reduction methods has remained an unsolved synthetic challenge. In general, mixtures of *syn* and *anti* adducts are formed and stereochemical outcomes are difficult to predict.[16]

Table 1. Enzymatic reduction of protected amino ketones.



6a (R = *t*-Bu)
6b (R = Bn)

2a (*anti*, R = *t*-Bu)
2a' (*syn*, R = *t*-Bu)
2b (*anti*, R = Bn)
2b' (*syn*, R = Bn)

Entry	Substrate	Catalyst (wt%)[a]	*dr* (**2**:**2′**)[b]	*ee* [%][b]
1	**6a**	KRED-NADH-107 (100)	9:91	97 (1*R*,2*R*)
2	**6a**	KRED-148 (500)	11:89	97 (1*R*,2*R*)
3	**6a**	*Pichia anomala*	29:71	>99 (1*R*,2*R*)
4	**6a**	*Rhodococcus* sp.	4:96	97 (1*S*,2*S*)
5	**6a**	ES-KRED-112 (100)	96:4	>99 (1*R*,2*S*)
6	**6a**	KRED-145 (500)	98:2	>99 (1*R*,2*S*)
7	**6a**	CRED-A131 (100)	98:2	>99 (1*S*,2*R*)
8	**6a**	*Pichia methanolica*	>200:1	>99 (1*R*,2*S*)
9	**6a**	*Actinosynnema pretiosum*	>200:1	>99 (1*S*,2*R*)
10	**6b**	KRED-145 (40)	>200:1	>99 (1*R*,2*S*)[c]

[a] Screening conditions for commercial ketoreductase enzymes: 1 mg ketone dissolved in 0.02 mL DMSO, 1 mM NADP or NAD, 5 mg glucose, 0.05 mg glucose dehydrogenase,1 mM dithiothreitol and 0.98 mL 0.1 M KPi pH 7, 20–87 h, 30 °C. For microbial screening 2 mg ketone in 0.02 mL DMSO was added to 1-day-old 2 mL cultures and incubated for 2 days. Conversion and enzyme loading for each case are shown in the Supporting Information.

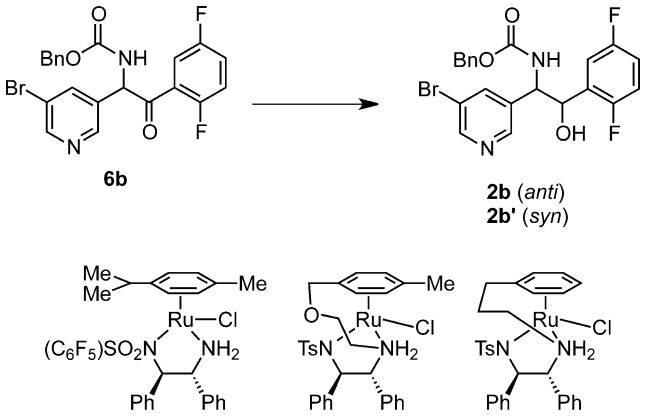
[b] Diastereomeric ratios and enantiomeric excess were determined by HPLC.[14]

[c] Experiment run on a 1-g scale.

Despite the high selectivities observed, the relatively low catalyst turnovers of the ketoreductases[14,17] prompted us to consider the use of a stereoselective hydrogenation *via* DKR. We evaluated a series of organometallic catalysts under typical transfer hydrogenation conditions using formic acid as the hydrogen donor and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base (Table 2).[18]

Derivatives of Noyori's ruthenium transfer hydrogenation catalysts were employed,[19] since these were expected to provide high *anti*-selectivity in the DKR.[20] A survey of several commercial variants of this catalyst revealed three that offered high enantio- and diastereoselectivities in different solvents (entries 1–7, Table 2). In addition to obtaining high selectivity with a pentafluorophenyl variant of Noyori's RuCl(*p*-cymene)Ts-DPEN catalyst (catalyst **A**, entries 1–3), variants with the diamine ligand tethered

Table 2. Ru-catalyzed DKR of protected amino ketone **6b**.[a]



6b

2b (*anti*)
2b' (*syn*)

A **B** **C**

Entry	Solvent	Catalyst	*dr* (**2b**:**2b′**)[b]	*ee* [%][b]
1	THF	**A**	120:1	−94
2	DCM	**A**	>200:1	−95
3	MeCN	**A**	164:1	−94
4	THF	**B**	>200:1	−98
5	DCM	**B**	>200:1	−91
6	MeCN	**B**	>200:1	−92
7	MeCN	**C**	>200:1	−97

[a] Screening conducted with 3 mol% (*R*,*R*)-catalyst, HCO_2H (3 equiv.) and DABCO (5 equiv.) at room temperature.

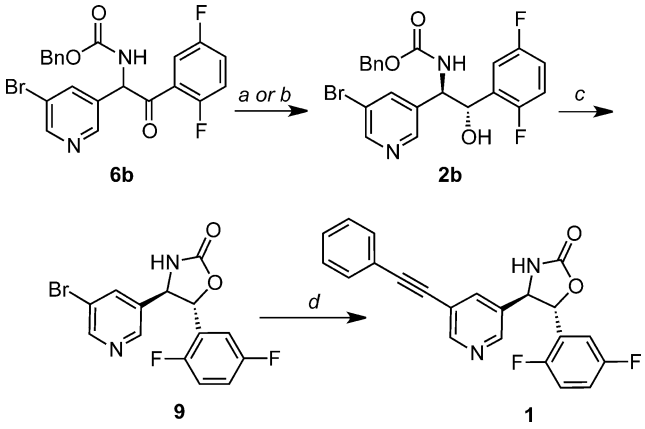
[b] Determined by HPLC. 100% conversion observed in all cases in <48 h.

to the ancillary η^6 arene ligand, developed by Ikariya (**B**) and Wills (**C**), also provided excellent selectivity (entries 4–7).[21]

We prepared **2b** with high diastereo- and enantiomeric purity using the (*S*,*S*)-isomer of catalyst **B**. As anticipated, the *anti* isomer could be easily converted to the desired oxazolidinone intermediate **9** *via* cyclization with inversion of configuration at the C-2 center[13] thus intercepting a known intermediate in the previous synthesis. The synthesis of **1** was completed *via* a palladium-catalyzed Sonogashira[22] coupling reaction (Scheme 2).[5] Overall, the target compound was obtained in 5 steps and 35% overall yield.

In conclusion, we have reported the concise enantioselective synthesis of a pharmaceutical candidate *via* the asymmetric reduction of an α-amino ketone derivative. The use of an aza-benzoin condensation to rapidly build the key carbon-carbon bond enabled an efficient convergent synthesis that precluded the formation of undesired regioisomers.

Both transition metal and biocatalysis-based routes provided exceptional diastereo- and enantiocontrol in the preparation of the key amino alcohol intermediate and circumvented the limitations of the original aminohydroxylation-based approach.



Scheme 2. Synthesis of **1** from α-amino ketone derivative **6b**. *Conditions:* (a) **6b**, DMSO, H_2O, 1 M potassium phosphate buffer pH 8, glucose, DTT (1 mM), NADP (0.5 mM), glucose dehydrogenase, and 40 wt% KRED-145, 30 °C. 80% yield, >99% *ee*, >200:1 **2b**:**2b′**. (b) Transfer hydrogenation: 1.5 mol% catalyst (*S*,*S*)-Ts-DENEB, THF, DABCO (5 equiv.), HCO_2H (3 equiv.), room temperature, 80%, 98.5% *ee* and >200:1 **2b**:**2b′**. (c) Ms_2O (3 equiv.), pyridine, 65–70 °C, 78%. (d) $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), PPh_3 (19 mol%), MeCN, NEt_3, 80 °C, 93%.

Experimental Section

General Information

Experiments were run under a positive nitrogen atmosphere. All reagents were used as received without further purification. Reaction progress and final product purity were monitored using HPLC. KRED-NADH-107, KRED-148 and KRED-145 were purchased from Codexis. ES-KRED-112 was purchased from Enzysource and CRED-A131 was purchased from Almac. Determinations of *ee* and *dr* were done by reverse phase HPLC. Specific conditions of analysis are provided in the Supporting Information.

Preparation of Benzyl [(5-Bromopyridin-3-yl)(tosyl)-methyl]carbamate (7b)

5-Bromonicotinaldehyde (10.00 g, 1.0 equiv.) was dissolved in acetonitrile (300 mL). Sodium-*p*-toluenesulfinate (14.37 g, 1.5 equiv.), benzyl carbamate (12.19 g, 1.5 equiv.) and chlorotrimethylsilane (13.7 mL, 2.0 equiv.) were sequentially added and the resulting mixture was stirred at room temperature for 18 h. Water (500 mL) was then added and the resulting slurry was aged for 6 h, then filtered and washed twice with acetonitrile:water (3:5 v/v, 150 mL) then water (2×150 mL). The resulting solid was dried under vacuum at room temperature and then at 60 °C. Carbamate **7b** was obtained as a white solid; yield: 21.3 g (83%); mp (from acetonitrile:H_2O): 180 °C (decomposition). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.17 (d, J = 10.6 Hz, 1 H), 8.82–8.70 (m, 3 H), 8.41–8.38 (m, H), 8.1 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 8.1 Hz, 2 H), 7.39–7.30 (m, 3 H), 7.20 (d, J = 6.2 Hz, 2 H), 6.31 (d, J = 10.6 Hz, 1 H), 4.92 (d, J = 12.5 Hz, 1 H), 4.87 (d, J = 12.5 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 155.2, 151.1, 149.0, 145.4, 139.4, 136.3, 133.0, 129.8, 129.3, 128.5, 127.8, 120.0, 72.0, 66.4, 21.3; HR-MS: m/z = 475.0311, calculated for $C_{21}H_{20}O_4N_2Br$: 475.0322.

Preparation of Benzyl [1-(5-Bromopyridin-3-yl)-2-(2,5-difluorophenyl)-2-oxoethyl]carbamate (6b)

Dichloromethane (225 mL) was added to a vessel containing **7b** (15 g, 1 equiv.) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium chloride (0.6 g, 0.07 equiv.). 2,5-Difluorobenzaldehyde (**8**, 3.61 mL,1.05 equiv.) was then added and the resulting mixture was cooled in an ice-water bath. Triethylamine (22 mL, 5 equiv.) was then added drop-wise leading to the formation of a deep yellow solution. The mixture was held at 0 °C for 12 h and then warmed up to room temperature. The reaction was then quenched with aqueous sodium chloride (200 mL, 10%), the phases were split and the organic layer was dried over anhydrous sodium sulfate. After concentration **6b** was isolated as a white solid by ISCO column chromatography (gradient from 5% to 20% ethyl acetate in *n*-hexane); yield: 11.4 g (78%); mp (from *n*-hexane/ethyl acetate): 155–160 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.65 (d, J = 2.2 Hz, 1 H), 8.57 (d, J = 8.3 Hz, 1 H), 8.56 (t, J = 1.5 Hz, 1 H), 8.02 (br s, 1 H), 7.65 (m, 1 H), 7.52 (m, 1 H), 7.39 (dt, J = 9.5, 4.1 Hz, 1 H), 7.31 (m, 3 H), 7.24 (d, J = 6.9 Hz, 2 H), 6.17 (d, J = 8.3 Hz, 1 H), 5.06 (d, J = 12.0 Hz, 1 H), 5.03 (d, J = 12.0 Hz, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 193.2 (d, $J_{C,F}$ = 2.8 Hz), 158.0 (d, $J_{C,F}$ = 179.6 Hz), 156.0 (d, $J_{C,F}$ = 190.6 Hz), 155.8, 149.9, 148.2, 138.6, 134.1, 136.7, 128.3, 127.9, 127.5, 125.2 (dd, $J_{C,F}$ = 15.1, 6.9 Hz), 119.9, 118.7 (dd, $J_{C,F}$ = 25.7, 8.2 Hz), 116.6 (dd, $J_{C,F}$ = 25.7, 1.8 Hz), 65.9, 60.1 (d, $J_{C,F}$ = 4.6 Hz); HR-MS: m/z = 461.0304, calculated for $C_{21}H_{16}O_3N_2BrF_2$: 461.0307.

Preparation of Benzyl [(1*R*,2*S*)-1-(5-Bromopyridin-3-yl)-2-(2,5-difluorophenyl)-2-hydroxyethyl]carbamate (2b)

Biotransformation: Carbamate **6b** (1 g, 1 equiv.), 100 mL DMSO, 350 mL water, 50 mL of 1 M KPi pH 8, 5 g of glucose, 77 mg of DTT (1 mM), 191 mg of NADP (0.5 mM), 20 mg of glucose dehydrogenase and 400 mg of KRED-145 were stirred for 41 h at 30 °C. After extractive work-up with EtOAc, crude **2b** was obtained in quantitative yield. The product was recrystallized from ethyl acetate/*n*-hexane mixtures to afford **2b** as a white solid; yield: 0.8 g (80%).

Transfer hydrogenation: In a 25-mL vessel, **6b** (165 mg, 1 equiv.) and DABCO (195 mg, 5 equiv.) were dissolved in THF (2.5 mL). (*S*,*S*)-Ts-DENEB (3.5 mg, 0.015 equiv.) was then added followed by formic acid (40 μL, 3 equiv.). The resulting mixture was stirred at room temperature for 24 h. The solution was then purified by ISCO column chromatography (gradient from 10% to 35% EtOAc in *n*-hexanes) yielding **2b** an off-white solid; yield: 132 mg (82%); mp (from EtOAc/hexane): 150–155 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.57 (d, J = 2.2 Hz, 1 H), 8.35 (d, J = 1.6 Hz, 1 H), 8.28 (t, J = 2.2 Hz, 1 H), 8.01 (d, J = 9.4 Hz, 1 H), 7.35–7.25 (m, 3 H), 7.21 (dt, J = 8.8, 2.2 Hz, 1 H), 7.19 (d, J = 7.5 Hz, 2 H), 7.15 (dddd, J = 8.8, 8.5, 4.5, 3.3 1 H), 7.01 (ddd, J = 8.5, 5.6, 3.3 Hz, 1 H), 5.91 (d, J = 5.5 Hz, 1 H), 4.99 (dd, J = 7.4, 5.5 Hz, 1 H), 4.97 (dd, J = 12.8, 1.6 Hz, 1 H), 4.90 (d, J = 12.8 Hz, 1 H), 4.87 (dd, J = 9.4, 7.4 Hz, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 158.0 (d, $J_{C,F}$ = 240 Hz), 155.6 (d,

$J_{C,F}$ = 240 Hz), 155.4, 149.0, 147.9, 138.0, 137.5, 136.9, 131.3 (d, $J_{C,F}$ = 17.7 Hz), 128.3, 127.8, 127.4, 119.7, 116.6 (dd, $J_{C,F}$ = 25.0, 8.0 Hz), 115.7 (dd, $J_{C,F}$ = 25.0, 8.0 Hz), 114.7 ($J_{C,F}$ = 25.0, 5.0 Hz), 68.2, 65.4, 56.7; $[\alpha]_D^{20}$: +27.7 (c = 0.0072 g mL^{-1}, MeOH); HR-MS: m/z = 463.0459, calculated for $C_{21}H_{18}O_3N_2BrF_2$: 463.0463.

The chiral purity was determined with the following HPLC method: Phenomenex Lux u Cellulose (3 μm × 4.6 × 150 mm). Mobile phase A: 0.05 TFA in H_2O/MeCN (95v/5v), mobile phase B 0.05% TFA in H_2O/MeCN 5v/95v). Gradient: 0 min, 35% B; 25 min 50% B, 30 min 100% B, 35 min, 100% B. Wavelength: 271 nm. Injection volume: 10 μL, Flow: 1 mL min^{-1}. Oven temperature: 40 °C. Retention times **2b′** 10.19 min, **2b** 11.44 min.

Preparation of (4*R*,5*R*)-4-(5-Bromopyridin-3-yl)-5-(2,5-difluorophenyl)oxazolidin-2-one (9)[5]

Carbamate **2b** (210 mg, 1 equiv.) was dissolved in pyridine (3.1 mL). Ms_2O (240 mg, 3 equiv.) was then added and the resulting mixture was heated to 65–70 °C. After 18 h, the mixture was diluted with water (10 mL) and EtOAc (10 mL). The aqueous layer was back-extracted with EtOAc (10 mL) and the combined organic phases were sequentially washed with aqueous citric acid (10 mL, 10%), and brine (10 mL, 15%) and then dried over anhydrous sodium sulfate. After filtration and solvent evaporation the product was purified by ISCO column chromatography (gradient from 10% to 35% EtOAc in *n*-hexanes) affording **9** as an off-white solid; yield: 125 mg (78%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 (d, J = 2.3 Hz, 1H), 8.55–8.53 (m, 2H), 8.15 (t, J = 2.3 Hz, 1H), 7.43–7.28 (m, 3H), 5.65 (d, J = 5.3 Hz, 1H), 5.01 (d, J = 5.3 Hz, 1H).

The chiral purity was determined with the following HPLC method: Chiralpak AS-3R (3 μm × 4.6 × 150 mm). Mobile phase: 0.01 M NH_4OAc in MeOH:H_2O (20v/80v), mobile phase B: 0.01 M NH_4OAc in MeOH:H_2O:MeCN (20v/5v/75v). Gradient: 0 min, 0% B; 30 min 100% B, 35 min 100% B. Wavelength: 220 nm. Injection volume: 10 μL, flow: 1 mL min^{-1}. Oven temperature: 25 °C. Retention times **9** 18.41 min; undesired enantiomer 17.26 min.

Preparation of (4*R*,5*R*)-5-(2,5-Difluorophenyl)-4-[5-(phenylethynyl)pyridin-3-yl]oxazolidin-2-one (1)[5]

Oxazolidinone **9** (0.97 g, 1 equiv.) was added to a vessel containing acetonitrile (8.7 mL) and NEt_3 (0.98 mL). Phenylacetylene (0.415 g, 1.5 equiv.), triphenylphosphine (0.135 g, 0.19 equiv.), $PdCl_2(PPh_3)_2$ (0.092 g, 0.05 equiv.) and CuI (0.025 g, 0.05 equiv.) were sequentially added. The resulting solution was sparged with nitrogen for ~5 min and was then heated to 80 °C. After 5 h the dark solution was cooled to room temperature and then concentrated to a semi-solid residue under reduced pressure. Ethyl acetate (5 mL) was added and the solution was concentrated to dryness yielding a dark brown solid. The solid was then treated with ethyl acetate (10 mL) and the resulting mixture was stirred for 10 min at room temperature and then filtered. The filtrate was sequentially washed with aqueous ammonia (3 × 10 mL, 10%), brine (10 mL, 10%), sodium bisulfite (2 × 10 mL, 10%) and brine (10 mL, 10%). The organic layer was then treated with charcoal (~250 mg) at room temperature overnight. The mixture was filtered through celite and the ethyl acetate solution was solvent switched into *n*-heptane. The resulting solid was filtered and crystallized from acetone and water to afford **1** as a light brown solid; yield: 0.96 g (93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.76 (d, J = 2 Hz, 1H), 8.58–8.53 (m, 2H), 8.06 (t, J = 2 Hz, 1H), 7.68–7.55 (m, 2H), 7.50–7.30 (m, 6H), 5.66 (d, J = 6.6 Hz, 1H), 5.03 (d, J = 6.6 Hz, 1H).

The chiral purity was determined with the following HPLC method: Phenomenex Lux Cellulose-1 (3 μm × 4.6 × 250 mm). Mobile phase : 0.1% diethylamine in 20 mM aqueous ammonium carbonate (pH 8.8)/MeCN (40v/60v). Isocratic. Wavelength: 281 nm. Injection volume: 10 μL, flow: 1 mL min^{-1}. Oven temperature: 40 °C. Retention times **1** 10.30 min, undesired enantiomer 12.73 min.

Acknowledgements

We thank Dr. Charles Pathirana for NMR spectroscopy experiments and Mr. Jonathan Marshall for HR-MS data. Professor Phil Baran and Drs. Rodney L. Parsons, Antonio Ramirez, Ian Young, David A. Conlon and Robert E. Waltermire are acknowledged for helpful discussions.

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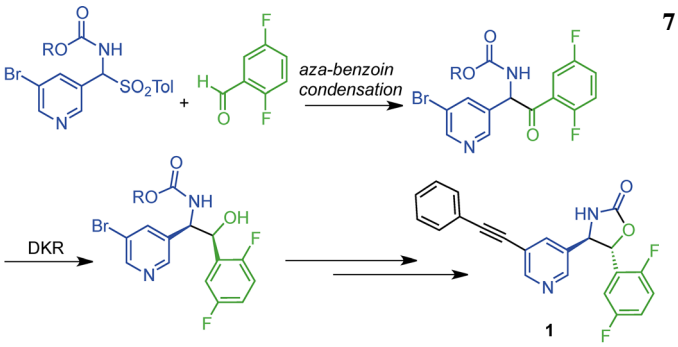

- Five-step synthesis of the Metabotropic Glutamate Receptor 5 (mGluR5) positive allosteric modulator **1**
- 35 % overall yield, >200:1 *dr*, > 99% *ee*
- Single regioisomer obtained by using aza-benzoin condensation as key carbon-carbon bond forming reaction
- Highly modular dynamic kinetic resolution (DKR) using both transition metal and biocatalysts