Design and Synthesis of a Novel Series of 1,2-Disubstituted Cyclopentanes as Small, Potent Potentiators of 2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic Acid (AMPA) Receptors

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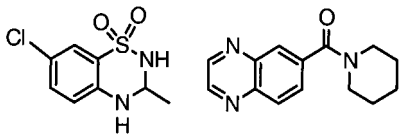
2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) potentiators are ligands that act as positive allosteric modulators at the AMPA receptors. We recently disclosed a novel series of 2-arylpropylsulfonamides that were potent potentiators of responses mediated through AMPA receptors. To further define the structural requirements for activity in this series, new ring-constrained analogues were prepared and a new stereocenter was introduced. The potentiating activity was highly dependent on the stereochemistry at the 2-position of the disubstituted cyclopentane and was independent of the relative stereochemistry at the 1-position. Compound (*R*,*R*)-**10** represents a potent, novel potentiator of iGluR4 flip receptors (EC_{50} = 22.6 nM).

Introduction

The neurotransmitter glutamate is the principal mediator of fast excitatory transmission in the central nervous system (CNS). It is believed that defects in glutamatergic neurotransmission are associated with many human neurological and psychiatric disorders. AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)-propanoic acid) receptors are a subset of ionotropic glutamate receptors. Activation of AMPA receptors is critical for expression and maintenance of long-term potentiation, an enduring form of synaptic plasticity that may be associated with certain forms of learning and memory.[1] AMPA receptor protein subunits have been cloned and identified as GluR1−4.[2] These subunits are thought to form tetrameric or pentameric ion channel complexes. In addition, there are also amino acid sequence variants of the subunit, the two splice variant isoforms, flip and flop.[3,4]

Several molecules known as AMPA receptor potentiators such as **1** (IDRA-21) and **2** (CX-516)[5,6] (Figure 1) have been shown to positively modulate ion influx through recombinant and neuronal AMPA receptors via an allosteric mechanism of action. We have recently described a novel class of 2-arylpropylsulfonamides (Figure 2, **3a**−**d**) as AMPA receptor potentiators.[7,8] In an effort to further expand our understanding of the structural requirements for activity within this series, we proposed new ring-constrained analogues. By bridging the methyl group with the methylene unit, we introduced an additional stereocenter in the form of a 1-amino-2-aryl-cyclopentane, allowing the possibility of four diastereomers. In this article, we will detail the



1 **2**

Figure 1.

controlled synthesis of a set of substituted monoaryl cis and trans cyclopentanes and examine the effects on AMPA potentiator activity by varying the phenyl ring substituents and cyclopentane ring stereochemistry. When compared to our previously reported series,[7,8] these compounds are significantly more potent.

Chemistry

Two general approaches have been reported for the synthesis of 2-phenylcyclopentylamines. Early efforts focused on the preparation of 2-phenylcyclopentanone, formation of the oxime, and reduction, typically giving mixtures of difficult to separate cis and trans 2-phenylcyclopentylamines. One noted exception is the work of Wiehl, who was able to make enantiomerically pure cis amines by using a chiral amine for oxime formation.[9] The second approach involved the opening of cyclopentene oxide with an aryl Grignard reagent and subsequent conversion of the alcohol to an amine.[10] This method has the advantage of producing only the trans aryl adduct, and subsequent manipulation to either the cis or the trans amine is possible. We chose the latter method for both its simplicity and the current commercial availability of many substituted aryl Grignard reagents.

Scheme 1 outlines the synthesis of *cis*-2-aryl-1-aminocyclopentanes. Reaction of commercially available aryl Grignard reagents (**4a**−**h**) with cyclopentene oxide

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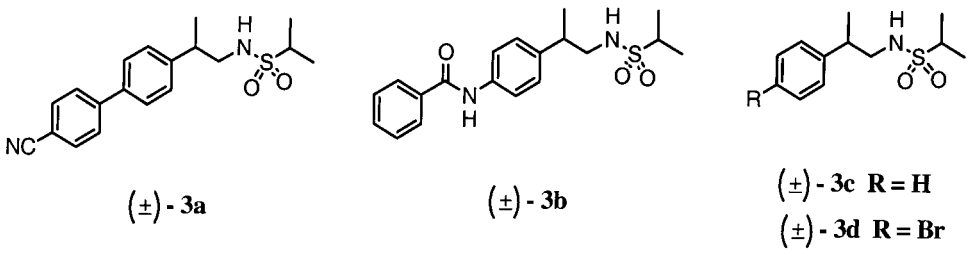
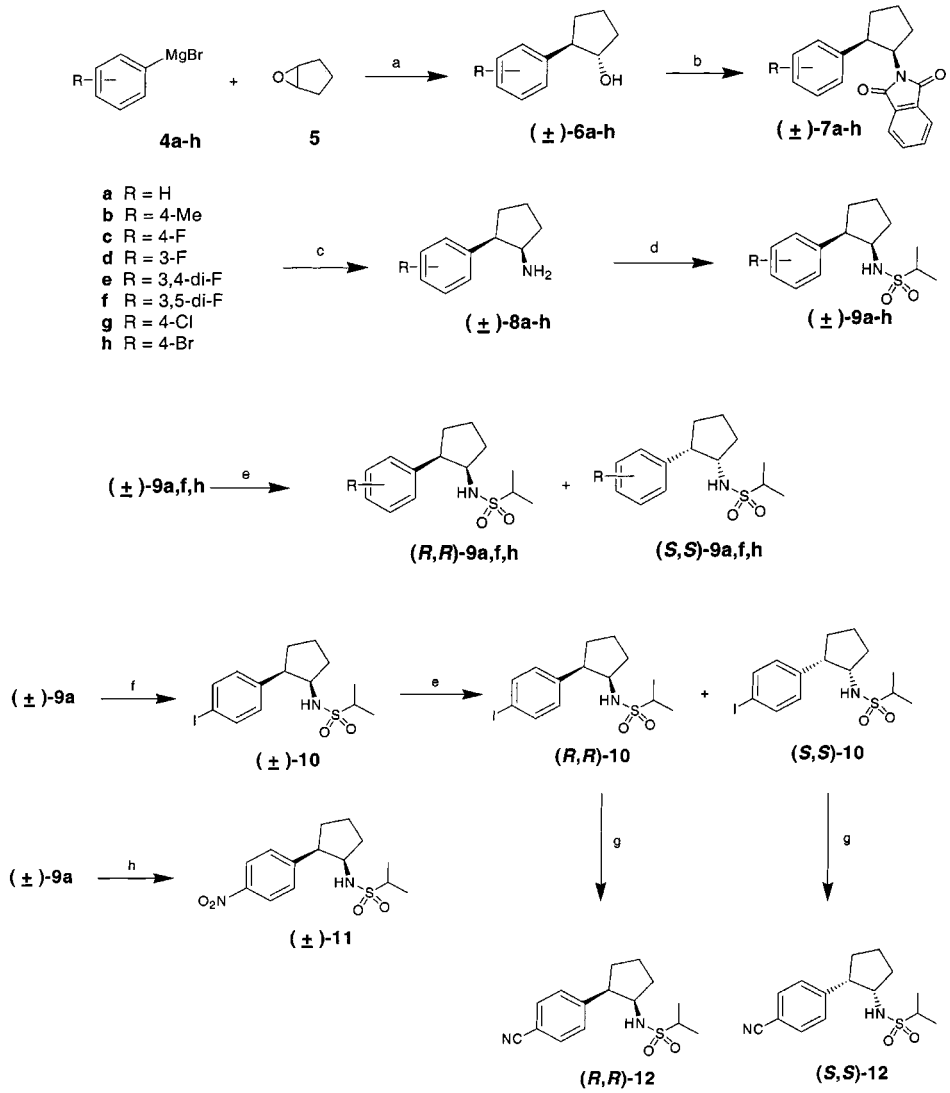


Figure 2.

Scheme 1. Synthesis of *cis*-2-Phenyl-1-Amino-Cyclopentanes[a]



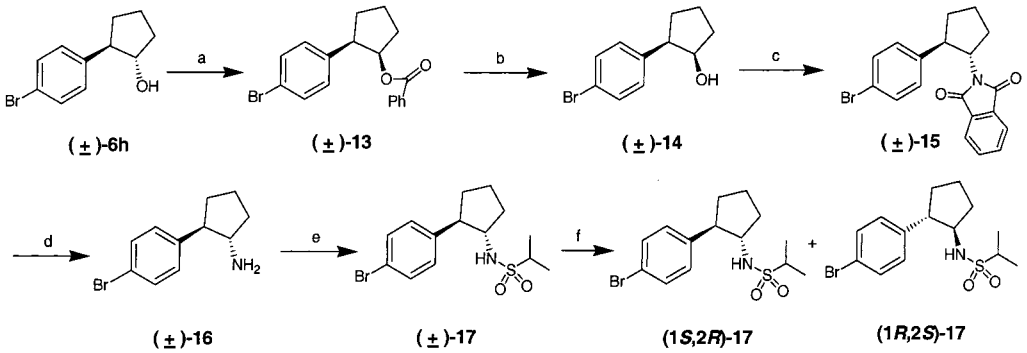
[a] Reagents: (a) CuI, THF, 2 h. (b) Phthalimide, DIAD, Ph_3P, THF. (c) Hydrazine or 2-aminoethanol. (d) *i*-Pr-SO_2Cl, DBU, CH_2Cl_2. (e) Chiral chromatography using Chiralcel AD column. (f) HOAc, H_2SO_4, I_2, I_2O_5. (g) $Zn(CN)_2$, $PdCl_2$(dppf), DMF. (h) $NaNO_3$, TFA.

provides the trans cyclopentanols **6a**−**h** exclusively. The Mitsunobu reaction with phthalimide proceeds with complete inversion to give cis compounds **7a**−**h**. Aminolysis with hydrazine or hydroxyethylamine afforded the amines **8a**−**h** in good yield. Substitution of the amine as the isopropylsulfonamide was found to be optimal in our previously published series and so was also exclusively retained throughout this series.

To have a versatile intermediate for further chemical manipulations, the selective para iodination of the phenyl derivative **9a** was examined. We found moderate success using periodic acid and iodine but later found the method of Brazdil (diiodine pentoxide, iodine) to give the cleanest, highest yield of compound **10**.[11] The cis enantiomers were separated by chiral chromatography using a Chiralcel AD column to give compounds (*R*,*R*)-**10** and (*S*,*S*)-**10**. The iodo-containing intermediates were converted to the cyano-containing compounds using zinc cyanide and palladium catalysis to yield compounds (*R*,*R*)-**12** and (*S*,*S*)-**12**.[12] Alternatively, para nitration of **9a** was accomplished with sodium nitrate and trifluoroacetic acid to yield compound **11**. For three of these cis analogues (**9a**,**f**,**h**), we chose to separate enantiomers by chiral chromatography using a Chiralcel OD column.

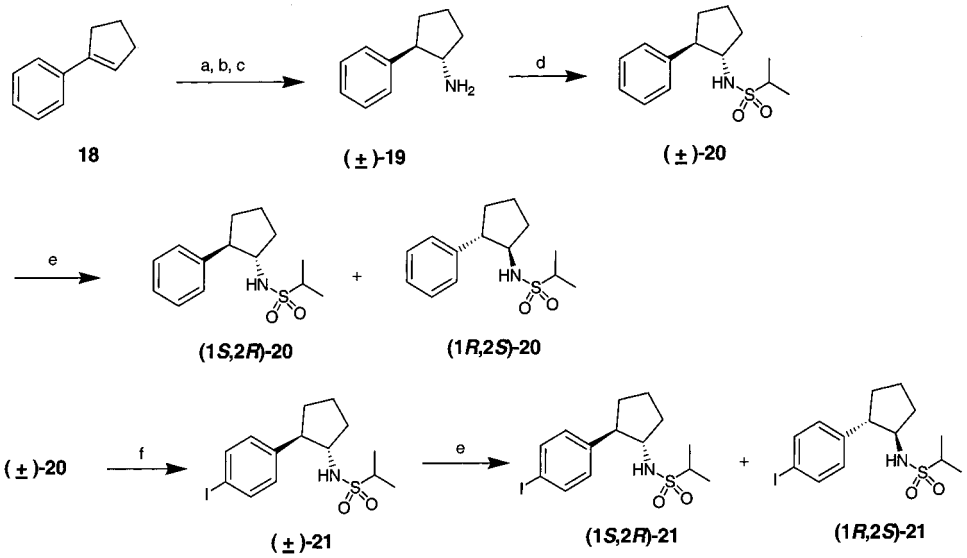
A smaller set of compounds was made in the trans series by two approaches that are outlined in Schemes

Scheme 2. Synthesis of *trans*-2-Phenyl-1-Amino-Cyclopentanes[a]



[a] Reagents: (a) Benzoic acid, DEAD, Ph_3P, THF. (b) NaOH, MeOH, 3 h. (c) Phthalimide, DEAD, THF. (d) Hydrazine, toluene. (e) *i*-Pr-SO_2Cl, DBU, CH_2Cl_2. (f) Chiral chromatography using Chiralcel OD column.

Scheme 3. Alternate Synthesis of *trans*-2-Phenyl-1-Amino-Cyclopentanes[a]



[a] Reagents: (a) $BH_2Cl{\cdot}SMe_2$, CH_2Cl_2. (b) Me_3Al, hexanes. (c) NH_2OSO_3H, THF. (d) *i*-Pr-SO_2Cl, DBU, CH_2Cl_2. (e) Chiral chromatography using Chiralcel OD column. (f) HOAc, H_2SO_4, I_2, I_2O_5, 90 °C, 22 h.

2 and 3. The route in Scheme 2 follows the same general approach as for the cis analogues but with the addition of an inversion step for the secondary alcohol. The inversion of the alcohol in **6h** was accomplished with benzoic acid by a Mitsunobu reaction. The ester **13** was hydrolyzed to the cis alcohol **14** using sodium hydroxide. The remainder of the synthesis is analogous to that described above for the cis series.

An interesting alternate approach to the *trans*-2-phenyl-1-amino-cyclopentanes is shown in Scheme 3. Following the pioneering work of H. C. Brown, the selective hydroboration of commercially available 1-phenylcyclopentene **18** yielded exclusively the trans amine **19**.[13] The overall transformation for the synthesis of **19** is shown in Scheme 4 involving three air-sensitive steps. Beginning with the addition of monochloroborane dimethyl sulfide complex across the double bond, a dimeric product has been proposed. Replacement of the chlorine with a methyl group using trimethylaluminum facilitates the replacement of boron for amine using commercially available hydroxylamine-O-sulfonic acid (HSA). The overall yield is moderate, and the procedure is labor intensive, but because no intermediates must be isolated, the sequence can be executed much more rapidly than a stepwise one. Sulfonylation and selective iodination were carried out as previously described. Chiral chromatographic separation was achieved for all three trans analogues prepared (**17**, **20**, and **21**). Assignment of the absolute configuration was based on an X-ray structure determination of (1*S*,2*R*)-**20**[14] and made possible by anomalous dispersion techniques using the heavy atom sulfur. In all cases, the later-eluting chromatographic peak, including (1*S*,2*R*)-**20** (see Experimental Section), was the more active isomer; therefore, the assignment of the *R* configuration at the 2-position of the remaining enantiomeric pairs was made.

Pharmacology

All new compounds were evaluated for their ability to potentiate responses mediated by 100 μM L-glutamate in HEK293 cells expressing homomeric iGluR4 flip receptors.[15] The activities at various concentrations were expressed as a percentage of responses evoked by 100 μM cyclothiazide, and EC_{50} values were then calculated (Tables 1 and 2). This report will only show results on the cloned human form of $GluR4_{flip}$. Data are shown for both racemates and individual enantiomeric pairs in selected cases.

It was quickly recognized that this series of compounds was more potent than our previously disclosed

Scheme 4. Hydroboration of 1-Phenylcyclopentene

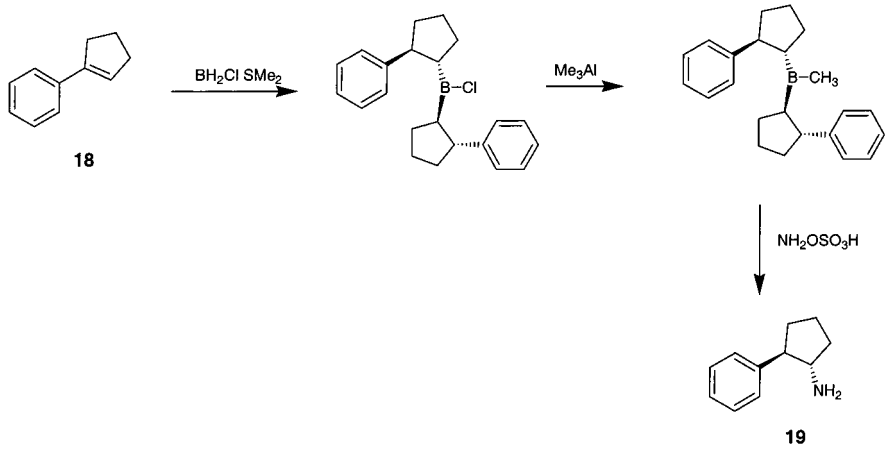
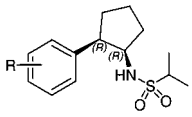


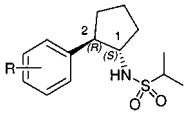
Table 1. Summary of EC_{50} Values for AMPA Receptor Potentiators: Cis Derivatives



compd[a]	R	$GluR4_{flip}$ EC_{50} ± SEM (nM)[b,c]
(±)-**3a**		290 ± 100
(±)-**3b**		520
(±)-**3c**		0%
(±)-**3d**		26%
(±)-**9a**	4-H	48% ± 5 (n = 6)
(*S*,*S*)-**9a**	4-H	2%
(*R*,*R*)-**9a**	4-H	1740 ± 880
(±)-**9b**	4-Me	434 ± 109
(±)-**9c**	4-F	57% ± 4 (n = 4)
(±)-**9d**	3-F	621 ± 56
(±)-**9e**	3,4-di-F	1100 ± 550
(±)-**9f**	3,5-di-F	281 ± 97
(*S*,*S*)-**9f**	3,5-di-F	5%
(*R*,*R*)-**9f**	3,5-di-F	118 ± 20
(±)-**9g**	4-Cl	247 ± 26
(±)-**9h**	4-Br	147 ± 37
(*S*,*S*)-**9h**	4-Br	27%
(*R*,*R*)-**9h**	4-Br	68 ± 11
(±)-**10**	4-I	45.8 ± 2.8
(*S*,*S*)-**10**	4-I	34%
(*R*,*R*)-**10**	4-I	22.6 ± 2.5
(±)-**11**	4-NO_2	190 ± 11
(*S*,*S*)-**12**	4-CN	17%
(*R*,*R*)-**12**	4-CN	403 ± 84

[a] See Figure 2 for the structures of **3a**−**d**. [b] Human transfected HEK293 cells. Values represent mean EC_{50} values determined from at least three separate experiments.[15] [c] Those compounds not achieving an EC_{50} are represented as a percent potentiation (n = 1) at the highest dose tested (3 μM).

Table 2. Summary of EC_{50} Values for AMPA Receptor Potentiators: Trans Derivatives



compd	R	$GluR4_{flip}$ EC_{50} ± SEM (nM)[a,b]
(±)-**20**	4-H	70% ± 11 (n = 4)
(1*R*,2*S*)-**20**	4-H	6%
(1*S*,2*R*)-**20**	4-H	551 ± 13
(±)-**17**	4-Br	130 ± 16
(1*R*,2*S*)-**17**	4-Br	2%
(1*S*,2*R*)-**17**	4-Br	82.1 ± 18.8
(±)-**21**	4-I	93.1 ± 15.4
(1*R*,2*S*)-**21**	4-I	12%
(1*S*,2*R*)-**21**	4-I	32.8 ± 1.9

[a] Human transfected HEK293 cells. Values represent mean EC_{50} values determined from at least three separate experiments.[15] [b] Those compounds not achieving an EC_{50} are represented as a percent potentiation (n = 1) at the highest dose tested (3 μM).

potentiators. For comparison purposes, we have included in Table 1 results for four compounds from our earlier structure−activity relationship studies. For instance, the unsubstituted phenyl compound **3c** in the 2-arylpropylsulfonamide series was inactive at the highest concentration tested (0% at 3 μM), whereas compound (±)-**9a** was measurably more active (48% at 3 μM). Likewise, the 4-bromo derivative in the 2-arylpropylsulfonamide series (±)-**3d** (26% at 3 μM) was significantly less active than the cyclopentane derivative (±)-**9h** (EC_{50} = 147 nM). The effect of various fluorine substituents was particularly interesting. The 3-F-substituted compound **9d** was a more potent AMPA potentiator than the 4-F-substituted compound **9c**. A further enhancement in potency was seen with the 3,5-difluorinated compound **9f** (EC_{50} = 281 nM). The most potent racemic compound disclosed to date in the 2-arylpropylsulfonamide series is (±)-**3a**, with an EC_{50} = 290 nM. In Table 1, we show four racemic compounds that are more potent, including 4-chloro, 4-bromo, and 4-iodo. We observe a preference for large halogens in the para position over unsubstituted, methyl, nitro, or cyano substituents. Five pairs of cis enantiomers were separated, and the data were reported in Table 1. The vast majority of the potentiating activity of these compounds was in a single enantiomer. The most potent enantiomer was the 4-iodo (*R*,*R*)-**10** with an EC_{50} = 22.6 nM.

In Table 2, a smaller set of trans compounds is reported. It is interesting that the activity of the trans isomers is essentially indistinguishable from the cis. For instance, the 4-Br cis compound (±)-**9h** and trans compound (±)-**17** had EC_{50} values of 147 and 130 nM, respectively. The results indicate that either the *R* or *S* isomer can be tolerated at the 1-position of the cyclopentane ring, but the *R* isomer is required at the 2-position. Until we know more about the receptor

binding site for these molecules, the significance of these observations will be open to speculation.

Conclusion

We have reported new syntheses of 2-phenylcyclopentylamines with complete control of cis vs trans stereochemistry. These compounds have allowed us to examine the effect of constraining our previously published 2-arylpropylsulfonamide series (Figure 2). Where direct comparisons can be made, these cyclopentyl analogues are more potent AMPA potentiators than our previous series. The activities of the cis vs trans cyclopentyl isomers are equipotent within the limited set shown here. However, for the enantiomers, a clear preference for the *R* configuration at position 2 is seen (Tables 1 and 2). The most potent potentiators were those with halogen substituents, for example, (*R*,*R*)-**10** (EC_{50} = 22.6 nM); the potent activity of the 3,5-difluoro analogue (*R*,*R*)-**9f** (EC_{50} = 118 nM) is also noteworthy. These compounds are the most potent small molecule AMPA potentiators that have been reported to date. The expansion of this series will be reported in due course.

Experimental Section

General. All reactions were performed under a positive N_2 flow with commercially available solvents. All Grignard reagents were from commercial sources (Rieke Metals) with the exception of *p*-Br-phenylmagnesium bromide, which can be made from 1,4-dibromobenzene according to literature methods. 1-Phenylcyclopentene was purchased from Chemsampco, Trenton, NJ. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on either a Varian Mercury-400 or General Electric QE-300 spectrometer. Fast atom bombardment high-resolution mass spectra (FAB-HRMS) were obtained on a VG Analytical VGZAB-2SE mass spectrometer. Field desorption mass spectra (FDMS) were obtained on a VG Analytical VG70SE mass spectrometer. Combustion analyses were performed on a Control Equipment Corporation 440 elemental analyzer and were within 0.4% of the calculated values unless otherwise noted. Electrospray mass spectra were obtained on a Micromass Platform LCZ mass spectrometer using a Gilson 215 flatbed autosampler and HP1100 pump system. Medium-pressure liquid chromatography (MPLC) was performed using PrepPak silica gel cartridges on a Waters Prep LC/System 500A. Flash chromatography was performed over silica gel 60 (230−400 mesh ASTM). Preparative centrifugal thin-layer chromatography (TLC) was performed on a Harrison model 7924 chromatotron with Merck silica gel 60 PF254 containing $CaSO_4 \cdot 0.5H_2O$ binder.

Assay Method. Calcium measurements in iGluR4 transfected HEK293 cells were performed as described in Miu et al.[15] Briefly, 96 well plates containing confluent monolayers of HEK293 cells stably expressing human AMPA receptors were prepared. Cells were incubated in buffer solution (10 mM glucose, 138 mM sodium chloride, 1 mM magnesium chloride, 5 mM potassium chloride, 5 mM calcium chloride, and 10 mM *N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid, adjusted to pH 7.1−7.3) containing 20 μM Fluo3-AM dye (obtained from Molecular Probes Inc.) for 60 min. Cells were washed with buffer solution, and fluorescence measurements were made using a FLUOROSKAN II fluorometer (Labsystems) that indicated changes in fluorescence upon influx of calcium into cells upon stimulation by glutamate (100 μM) in the presence of cyclothiazide (100 μM) or compound. Compound applications preceded glutamate additions by 5 min, and fluorescent measurements were made immediately prior to the addition of glutamate and 3 min following glutamate addition.

(±)-*trans*-2-Phenyl-cyclopentanol (6a). A 1 L three-necked round-bottom flask equipped with a mechanical stirrer, addition funnel, and thermometer was charged with 1 M tetrahydrofuran (THF) solution of phenylmagnesium bromide (300 mL, 300.0 mmol) and copper iodide (3.8 g, 20.0 mmol). To this reaction mixture was then added cyclopentene oxide (25.23 g, 300.0 mmol) dissolved in THF (50.0 mL) dropwise over a period of 60 min (reaction was quite exothermic, reaching THF reflux by the end of addition). The reaction mixture was then stirred to room temperature and quenched with a 25% solution of ammonium chloride (200.0 mL). Ether was added (80.0 mL), and the upper organic layer was separated. The organic layer was washed with 25% ammonium chloride solution, dried with anhydrous magnesium sulfate, filtered, and concentrated to a filtrate to provide **6a** (47.7 g, 98%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 7.4−7.2 (aromatic, 5H), 4.16−4.13 (m, 1H), 2.88−2.80 (m, 1H), 2.2−2.0 (m, 2H), 1.8−1.6 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 144.05, 129.25, 128.11, 127.10, 81.11, 55.13, 34.64, 32.57, 22.46.

(±)-*trans*-2-*p*-Tolyl-cyclopentanol (6b). The title compound was prepared in a manner analogous to the procedure for **6a**, starting with 10.0 mL of a 1 M ethereal solution of *p*-tolylphenylmagnesium bromide (100 mmol). The same work-up gave 1.7 g of a crude yellow oil. The title compound was purified by radial chromatography eluting with 25:75 EtOAc: hexanes to give 1.48 g of **6b** (84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.17−7.09 (aromatic, 4H), 4.13−4.07 (m, 1H), 2.85−2.78 (m, 1H), 2.30 (s, 3H), 2.2−2.0 (m, 2H), 1.84−1.6 (m, 4H).

(±)-*trans*-2-(4-Fluoro-phenyl)cyclopentanol (6c). The title compound was prepared from 4-fluorophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 26% yield. ^{1}H NMR ($CDCl_3$): δ 7.31 (m, 2H), 7.10 (m, 2H), 4.21 (m, 1H), 2.96 (m, 1H), 2.30−2.18 (m, 2H), 2.00−1.75 (m, 4H).

(±)-*trans*-2-(3-Fluoro-phenyl)cyclopentanol (6d). The title compound was prepared from 3-fluorophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 73% yield. ^{1}H NMR ($CDCl_3$): δ 7.22 (m, 1H), 7.00 (m, 1H), 6.90 (m, 2H), 4.12 (m, 1H), 2.86 (m, 1H), 2.20−2.00 (m, 2H), 1.90−1.60 (m, 4H).

(±)-*trans*-2-(3,4-Difluoro-phenyl)cyclopentanol (6e). The title compound was prepared from 3,4-difluorophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 70% yield. ^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H), 7.00 (m, 2H), 4.04 (m, 1H), 2.79 (m, 1H), 2.15−2.00 (m, 2H), 1.83−1.50 (m, 4H).

(±)-*trans*-2-(3,5-Difluoro-phenyl)cyclopentanol (6f). The title compound was prepared from 3,5-difluorophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 30% yield. ^{1}H NMR ($CDCl_3$): δ 6.72 (m, 2H), 6.60 (m, 1H), 4.05 (m, 1H), 2.81 (m, 1H), 2.15−2.00 (m, 2H), 1.82−1.56 (m, 4H). FDMS = 198.

(±)-*trans*-2-(4-Chlorophenyl)cyclopentanol (6g). The title compound was prepared from *p*-chlorophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 31% yield. ^{1}H NMR ($CDCl_3$): δ 7.27 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.2 Hz), 4.12 (m, 1H), 3.70 (m, 1H), 2.05 (m, 2H), 1.90−1.63 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 143.00, 132.25, 129.86, 121.00, 80.98, 54.40, 32.45, 22.38.

(±)-*trans*-2-(*p*-Bromo-phenyl)cyclopentanol (6h). The title compound was prepared from *p*-bromophenylmagnesium bromide and cyclopentene oxide in a manner analogous to the procedure described above for **6a** in 26% yield. ^{1}H NMR ($CDCl_3$): δ 7.31 (m, 2H), 7.10 (m, 2H), 4.21 (m, 1H), 2.96 (m, 1H), 2.30−2.18 (m, 2H), 2.00−1.75 (m, 4H).^{13}C NMR ($CDCl_3$): δ 143.00, 132.25, 129.86, 121.00, 80.98, 54.40, 32.45, 22.38.

(±)-*cis*-2-(2-Phenyl-cyclopentyl)isoindole-1,3-dione (7a). A 500 mL three-necked round-bottom flask equipped with a mechanical stirrer, thermometer, reflux condenser, addition funnel, and a nitrogen blanket is charged with triphenylphosphine (16.19 g, 61.73 mmol) and THF (200 mL). To the solution at 0 °C was added dropwise a solution of diisopropyl azodicarboxylate (12.15 mL, 61.73 mmol) dissolved in THF (30 mL) over a period of 10 min. A massive precipitate formed immediately after addition. To the slurry was then added solid phthalimide (9.08 g, 61.7 mmol), followed by a solution of **6a** (10.0 g, 61.7 mmol) dissolved in THF (30 mL) over a period of

20 min, maintaining temperature at 0−5 °C (the reaction mixture went into solution by the end of alcoholic substrate addition). The reaction was then stirred at 0 °C for 4 h and brought to room temperature overnight for convenience. The reaction was quenched with water (200 mL), and the organics were extracted with chloroform (200 mL). The organic layer was washed with water (100 mL) and dried with anhydrous magnesium sulfate. Subsequent filtration and concentration under reduced pressure afforded an oil that solidified on equilibrating to room temperature. To the precipitate was then added hexane (250 mL) with vigorous stirring. The triphenylphosphine oxide precipitate was filtered off, and the filtrate was concentrated to an oil. Silica gel plug filtration of the oil with 1:1 ethyl acetate:hexanes and subsequent concentration of product fractions afforded **7a** (12.5 g, 70%) as an off-white precipitate. ^{1}H NMR ($CDCl_3$): δ 7.64−7.52 (aromatic, 4H), 7.15−6.9 (aromatic, 5H), 5.1−5.0 (m, 1H), 3.50−3.39 (m, 1H), 2.68−2.40 (m, 2H), 2.35−2.20 (m, 2H), 2.1−2.0 (m, 1H), 1.8−1.6 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 168.86, 139.68, 131.67, 128.41, 128.01, 126.44, 122.89, 54.60, 50.34, 30.56, 28.89, 25.4. Anal. ($C_{19}H_{17}NO_2$) C, H, N.

(±)-*cis*-2-(2-*p*-Tolyl-cyclopentyl)isoindole-1,3-dione (7b). The title compound was prepared in a manner analogous to the procedure for **7a** from **6b** (1.48 g, 8.4 mmol). The title compound was purified by radial chromatography eluting with ethyl acetate and then again eluting with methylene chloride to give 0.69 g (27%) of **7b** as an oil, which solidified under vacuum. ^{1}H NMR ($CDCl_3$): δ 7.62−7.52 (m, 4H), 7.00 (d, 2H, J = 9 Hz), 6.82 (d, 2H, J = 9 Hz), 5.01−4.95 (m, 1H), 3.41−3.32 (m, 1H), 2.6−2.4 (m, 2H), 2.22−2.15 (m, 2H), 2.10 (s, 3H), 2.03−1.88 (m, 1H), 1.73−1.6 (m, 1H). Anal. ($C_{20}H_{19}NO_2 \cdot 0.2H_2O$) C, H, N.

(±)-*cis*-2-(2-*p*-Fluorophenyl-cyclopentyl)isoindole-1,3-dione (7c). The title compound was prepared in a manner analogous to the procedure for **7a** from **6c** to give 47% of **7c** as an oil. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 4H), 7.08 (m, 2H), 6.74 (m, 2H), 4.98 (m, 1H), 3.39 (m, 1H), 2.50 (m, 2H), 2.20 (m, 2H), 2.03 (m, 1H), 1.69 (m, 1H).

(±)-*cis*-2-(2-*m*-Fluorophenyl-cyclopentyl)isoindole-1,3-dione (7d). The title compound was prepared in a manner analogous to the procedure for **7a** from **6d** to give 43% of **7d** as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 4H), 6.99 (m, 1H), 6.88 (d, 1H, J = 7 Hz), 6.82 (d, 1H, J = 9 Hz), 6.63 (m, 1H), 5.00 (m, 1H), 3.40 (m, 1H), 2.48 (m, 2H), 2.20 (m, 2H), 2.05 (m, 1H), 1.68 (m, 1H). FDMS = 309. Anal. ($C_{19}H_{16}FNO_2 \cdot 0.3H_2O$) C, H, N.

(±)-*cis*-2-(2-(3,4-Difluorophenyl)cyclopentyl)isoindole-1,3-dione (7e). The title compound was prepared in a manner analogous to the procedure for **7a** from **6e** to give 94% of **7e** as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 4H), 6.90 (m, 1H), 6.78 (m, 2H), 4.94 (m, 1H), 3.33 (m, 1H), 2.43 (m, 2H), 2.17 (m, 2H), 1.98 (m, 1H), 1.68 (m, 1H).

(±)-*cis*-2-(2-(3,5-Difluorophenyl)cyclopentyl)isoindole-1,3-dione (7f). The title compound was prepared in a manner analogous to the procedure for **7a** from **6f** to give 53% of **7f** as an oil. ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 4H), 6.64 (m, 2H), 6.39 (m, 1H), 5.00 (m, 1H), 3.37 (m, 1H), 2.43 (m, 2H), 2.20 (m, 2H), 2.04 (m, 1H), 1.68 (m, 1H). FDMS = 327. Anal. ($C_{19}H_{15}F_2NO_2 \cdot 0.3H_2O$) C, H, N.

(±)-*cis*-2-(2-(4-Chlorophenyl)isoindole-1,3-dione (7g). The title compound was prepared in a manner analogous to the procedure for **7a** from **6g** to give 19% of **7g** as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 4H), 7.08 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.7 Hz), 5.05 (m, 1H), 3.19 (m, 1H), 2.50 (m, 2H), 2.24 (m, 2H), 2.07 (m, 1H), 1.75−1.61 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 169.31, 138.75, 134.46, 132.56, 132.03, 130.23, 128.63, 123.55, 54.70, 50.17, 31.21, 29.50, 25.79.

(±)-*cis*-2-(2-(4-Bromophenyl)cyclopentyl)isoindole-1,3-dione (7h). The title compound was prepared in a manner analogous to the procedure for **7a** from **6h** to give 27% of **7h** as an oil that solidified. ^{1}H NMR ($CDCl_3$): δ 7.67−7.57 (m, 4H), 7.2 (d, 2H), 7.00 (d, 2H), 3.32−2.35 (m, 2H), 2.27−2.16 (m, 2H), 2.09−2.00 (m, 1H), 1.77−1.03 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 168.43, 138.48, 133.67, 131.23, 130.79, 129.83, 122.78, 119.96, 54.00, 49.59, 30.58, 28.93, 25.17.

(±)-*cis*-2-Phenyl-cyclopentylamine (8a). A 1000 mL three-necked flask equipped with a mechanical stirrer, thermometer, addition funnel, and a reflux condenser was charged with **7a** (27.3 g, 93.9 mmol) and toluene (400 mL). To this solution was added anhydrous hydrazine (29.48 mL, 939.1 mmol) dropwise over a period of 15 min. The reaction was stirred at room temperature for 60 min, and then, it was heated at 90−95 °C for 6 h. The reaction was cooled to room temperature, the precipitates were filtered, the cake was washed with toluene (50.0 mL), and the filtrate was concentrated to provide **8a** (15.1 g, 100%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.35−7.19 (aromatic, 5H), 3.7−3.4 (m, 1H), 3.10−3.05 (m, 1H), 2.1−2.0 (m, 2H), 2.0−1.9 (m, 2H), 1.69−1.63 (m, 1H), 1.6−1.5 (m, 1H), 0.8−0.6 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 142.00, 129.20, 128.96, 126.86, 56.68, 51.75, 34.98, 27.96, 23.05.

(±)-*cis*-2-*p*-Tolyl-cyclopentylamine (8b). To **7b** (582 mg, 1.91 mmol) was added ethanolamine (5 mL), and the solution was heated to 80 °C and stirred for 30 min. ES-MS indicated that the reaction was not complete, and the reaction was heated to 90 °C for 30 min. The reaction was diluted with ethyl ether and washed with dilute sodium hydroxide and brine, and the organic layer was dried over sodium sulfate. The filtrate was concentrated to provide 313 mg (94%) of **8b** as a colorless oil. The oil was used directly without further characterization. Mass spectrum (ES-MS): M + 1 = 176.

(±)-*cis*-2-*p*-Fluorophenyl-cyclopentylamine (8c). The title compound was prepared in a manner analogous to the procedure for **8b** from **7c** to give 61% of **8c** as a colorless oil. Mass spectrum (ES-MS): M + 1 = 180.

(±)-*cis*-2-*m*-Fluorophenyl-cyclopentylamine (8d). The title compound was prepared in a manner analogous to the procedure for **8b** from **7d** to give 92% of **8d** as a colorless oil. Mass spectrum (ES-MS): M + 1 = 180. ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 1H), 7.02−6.85 (m, 3H), 3.52 (m, 1H), 3.05 (m, 1H), 2.00 (m, 4H), 1.69 (m, 1H), 1.55 (m, 1H), 1.25 (brs, 2H).

(±)-*cis*-2-(3,4-Difluorophenyl)cyclopentylamine (8e). The title compound was prepared in a manner analogous to the procedure for **8b** from **7e** to give 80% of **8e** as an oil. Mass spectrum (ES-MS): M + 1 = 198.

(±)-*cis*-2-(3,5-Difluorophenyl)cyclopentylamine (8f). The title compound was prepared in a manner analogous to the procedure for **8b** from **7f** to give 100% of **8f** as an oil. Mass spectrum (ES-MS): M + 1 = 198.

(±)-*cis*-2-(4-Chlorophenyl)cyclopentylamine Oxalate (8g). The title compound was prepared in a manner analogous to the procedure for **8a** from **7g** to give 75% of **8g** as an oil. The free base was dissolved in ethyl acetate and treated with oxalic acid (1.0 eq). The slurry was stirred for 60 min and filtered, and the off-white precipitate was dried under house vacuum at 35 °C to provide **8g**. ^{1}H NMR (DMSO): δ 7.90 (m, 4H), 7.39 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.5 Hz), 3.72 (m, 1H), 3.18 (m, 1H), 2.12 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H). Anal. ($C_{11}H_{14}ClN \cdot 1.1C_2H_2O_4$) C, H, N.

(±)-*cis*-2-(4-Bromophenyl)cyclopentylamine (8h). The title compound was prepared in a manner analogous to the procedure for **8b** from **7h** to give 27% of **8h** as an oil. ^{1}H NMR ($CDCl_3$): δ 7.4 (d, 2H), 7.10 (d, 2H), 3.5 (m, 1H), 3.00 (m, 1H), 2.0−1.8 (m, 4H), 1.79−1.60 (m, 1H), 1.60−1.50 (m, 1H), 0.86 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 141.00, 132.00, 131.00, 128.00, 120.00, 36.20, 31.00, 28.00, 21.3. The free base was dissolved in ethyl acetate and treated with oxalic acid (1.0 equiv). The slurry was stirred for 60 min and filtered, and the off-white precipitate was dried under house vacuum at 35 °C to provide **8g**. Anal. ($C_{11}H_{14}ClN \cdot 1.1C_2H_2O_4$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)amide (9a). A 250 mL three-necked round-bottom flask equipped with a magnetic stirrer is charged with **8a** (8.72 g, 54.2 mmol), methylene chloride (80 mL), triethylamine (14.8 mL, 106 mmol), and (dimethylamino)pyridine (0.33 g, 2.71 mmol) with stirring. The reaction solution was then cooled to 0 °C (ice/water bath), and then, isopropylsulfonyl chloride (5.96

mL, 53.07 mmol) dissolved in methylene chloride (20 mL) was added dropwise over a period of 30 min. The reaction was then stirred at 0 °C for 60 min and brought to room temperature. It was then stirred for 1.5 h and quenched with 1 N HCl (150 mL). The lower organic layer was separated, and the aqueous layer was back-extracted with methylene chloride (50 mL). The combined organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated to **9a** (9.06 g, 64%) as a tan solid. ^{1}H NMR ($CDCl_3$): δ 7.31 (m, 2H), 7.21 (m, 3H), 3.95 (m, 1H), 3.71 (d, 1H, J = 8 Hz), 3.29 (m, 1H), 2.82 (m, 1H), 2.15−1.70 (m, 6H), 1.18 (d, 3H, J = 7 Hz), 0.98 (d, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): δ 140.28, 128.90, 128.81, 127.23, 59.10, 53.78, 48.70, 33.76, 28.62, 21.79, 16.56. Anal. ($C_{14}H_{21}NO_2S$) C, H, N.

(*S*,*S*)-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)-amide ((*S*,*S*)-9a). The racemic cis compound **9a** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at UV of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 1.0 mL/min monitoring at UV of 250 nm. The early-eluting compound had a retention time of 7.03 min. Enantiomeric excess was estimated to be 99% by high-performance liquid chromatography (HPLC). Anal. ($C_{14}H_{21}NO_2S$) C, H, N.

(*R*,*R*)-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)-amide ((*R*,*R*)-9a). The racemic cis compound **9a** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at UV of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow of 1.0 mL/min monitoring at UV of 250 nm. The later-eluting compound had a retention time of 7.84 min. Enantiomeric excess was estimated to be 98% by HPLC. Anal. ($C_{14}H_{21}NO_2S$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid (2-*p*-Tolyl-cyclopentyl)amide (9b). A 100 mL round-bottom flask equipped with a magnetic stirrer was charged with **8b** (313 mg, 1.79 mmol) and methylene chloride (5.0 mL), and the solution was cooled to 0 °C. DBU (0.32 mL, 2.14 mmol) and isopropylsulfonyl chloride (0.24 mL, 2.14 mmol) were added. The reaction was then stirred at 0 °C for 60 min and brought to room temperature with stirring overnight. The reaction was diluted with methylene chloride and washed with aqueous ammonium chloride and brine, and the organic layer was dried over sodium sulfate. The title compound was purified by radial chromatography eluting with methylene chloride to give 250 mg (50%) of **9b**. ^{1}H NMR ($CDCl_3$): δ 7.13−7.05 (m, 4H), 3.90 (m, 1H), 3.50 (d, 1H, J = 8 Hz), 3.30−3.25 (m, 1H), 2.95−2.83 (m, 1H), 2.30 (s, 3H), 2.1−1.7 (m, 6H), 1.20 (d, 3H, J = 8 Hz), 1.02 (d, 3H, J = 8 Hz). Anal. ($C_{15}H_{23}NO_2S$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid [2-(4-Fluoro-phenyl)-cyclopentyl]amide (9c). The title compound was prepared in a manner analogous to the procedure for **9b** from **8c** to give 65% of **9c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 2H), 7.00 (m, 2H), 3.93 (m, 1H), 3.44 (m, 1H), 3.29 (m, 1H), 2.88 (m, 1H), 2.08 (m, 2H), 1.92 (m, 2H), 1.75 (m, 2H), 1.20 (d, 3H, J = 7 Hz), 1.07 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M + 1 = 286. Anal. ($C_{14}H_{20}FNO_2S\cdot 0.1H_2O$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid [2-(3-Fluoro-phenyl)-cyclopentyl]amide (9d). The title compound was prepared in a manner analogous to the procedure for **9b** from **8d** to give 55% of **9d** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.31 (m, 1H), 7.03 (d, 1H, J = 8 Hz), 6.95 (m, 2H), 3.99 (m, 1H), 3.51 (d, 1H, J = 8 Hz), 3.31 (m, 1H), 2.91 (m, 1H), 2.12 (m, 2H), 1.96 (m, 2H), 1.80 (m, 2H), 1.22 (d, 3H, J = 7 Hz), 1.09 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M + 1 = 286. Anal. ($C_{14}H_{20}FNO_2S$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid [2-(3,4-Difluoro-phenyl)cyclopentyl]amide (9e). The title compound was prepared in a manner analogous to the procedure for **9b** from **8e** to give 42% of **9e** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.20−6.93 (m, 5H), 3.98 (m, 1H), 3.50 (m, 1H), 3.28 (m, 1H), 2.92 (m, 1H), 2.11 (m, 2H), 1.92 (m, 2H), 1.77 (m, 2H), 1.22 (d, 3H, J = 7 Hz), 1.12 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 302. Anal. ($C_{14}H_{19}F_2NO_2S$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid (2-(3,5-Difluorophenyl)cyclopentyl)amide (9f). The title compound was prepared in a manner analogous to the procedure for **9b** from **8f** to give 65% of **9f** as a white solid. ^{1}H NMR ($CDCl_3$): δ 6.80−6.66 (m, 5H), 3.98 (m, 1H), 3.51 (d, 1H, J = 8 Hz), 3.28 (m, 1H), 2.93 (m, 1H), 2.10 (m, 2H), 1.91 (m, 2H), 1.78 (m, 2H), 1.23 (d, 3H, J = 7 Hz), 1.12 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 302. Anal. ($C_{14}H_{19}F_2NO_2S$) C, H, N.

(*S*,*S*)-*cis*-Propane-2-sulfonic Acid (2-(3,5-Difluorophenyl)cyclopentyl)amide ((*S*,*S*)-9f). The racemic cis compound (570 mg) **9f** was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 27 cm Chiralcel OD eluting with 90% heptane/10% IPA at a flow rate of 330 mL/min monitoring at a UV wavelength of 255 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD-H eluting with 90% heptane/10% IPA at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The early-eluting compound had a retention time of 6.9 min. The yield was 263 mg. Enantiomeric excess was estimated to be 99% by HPLC.

(*R*,*R*)-*cis*-Propane-2-sulfonic Acid (2-(3,5-Difluorophenyl)cyclopentyl)amide ((*R*,*R*)-9f). The racemic cis compound (570 mg) **9f** was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 27 cm Chiralcel OD eluting with 90% heptane/10% IPA at a flow rate of 330 mL/min monitoring at a UV wavelength of 255 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD-H eluting with 90% heptane/10% IPA at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The late-eluting compound had a retention time of 11.1 min. The yield was 265 mg. Enantiomeric excess was estimated to be 99% by HPLC.

(±)-*cis*-Propane-2-sulfonic Acid (2-*p*-Chlorophenyl-cyclopentyl)amide (9g). The title compound was prepared in a manner analogous to the procedure for **9b** from **8g** to give 55% of **9g** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 2H, J = 8 Hz), 7.14 (d, 2H, J = 8 Hz), 3.93 (m, 1H), 3.42 (d, 1H, J = 8 Hz), 3.28 (m, 1H), 2.90 (m, 1H), 2.08 (m, 2H), 1.90 (m, 2H), 1.75 (m, 2H), 1.20 (d, 3H, J = 7 Hz), 1.09 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 300. Anal. ($C_{14}H_{20}ClNO_2S$) C, H, N.

(±)-*cis*-Propane-2-sulfonic Acid (2-*p*-Bromophenyl-cyclopentyl)amide (9h). The title compound was prepared in a manner analogous to the procedure for **9b** from **8h** to give 45% of **9h** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J = 8 Hz), 7.08 (d, 2H, J = 8 Hz), 3.93 (m, 1H), 3.58 (d, 1H, J = 8 Hz), 3.25 (m, 1H), 2.88 (m, 1H), 2.05 (m, 2H), 1.90 (m, 2H), 1.72 (m, 2H), 1.19 (d, 3H, J = 7 Hz), 1.08 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 344, 346. Anal. ($C_{14}H_{20}BrNO_2S$) C, H, N. Exact mass calcd for (M + H) $C_{14}H_{21}BrNO_2S$, 346.0476; found, 346.0486.

(*S*,*S*)-*cis*-Propane-2-sulfonic Acid (2-*p*-Bromophenyl-cyclopentyl)amide ((*S*,*S*)-9h). The racemic cis compound (233 mg) **9h** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel AD eluting with a gradient of 5−50% IPA/heptane over 30 min at a flow rate of 5.0 mL/min monitoring at a UV wavelength of 260 nm. The analytical column was 0.46 cm × 25 cm Chiralcel AD eluting with a gradient of 5−50% IPA/heptane over 30 min at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The early-eluting compound had a retention time of 9.1 min. The yield was 109 mg. Enantiomeric excess was estimated to be 97% by HPLC.

(*R*,*R*)-*cis*-Propane-2-sulfonic Acid (2-*p*-Bromophenyl-cyclopentyl)amide ((*R*,*R*)-9h). The racemic cis compound (233 mg) **9h** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel AD eluting with a gradient of 5−50% IPA/

heptane over 30 min at a flow rate of 5.0 mL/min monitoring at a UV wavelength of 260 nm. The analytical column was 0.46 cm × 25 cm Chiralcel AD eluting with a gradient of 5−50% IPA/heptane over 30 min at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The late-eluting compound had a retention time of 10.4 min. The yield was 109 mg. Enantiomeric excess was estimated to be 88% by HPLC.

(±)-*cis*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)-cyclopentyl]amide (10). Compound **9a** (1.8 g, 6.7 mmol) was dissolved in 20 mL of glacial acetic acid, and 0.7 mL (7.1 mmol) of concentrated sulfuric acid was added followed by 2 mL of water. To this solution were added periodic acid (0.35 g, 1.6 mmol) and iodine (0.77 g, 3.0 mmol). The resulting mixture was heated to 60 °C for 3 h. The reaction was cooled to room temperature, and 20 mL of a 10% aqueous solution of sodium bisulfite was added. The product was extracted into ethyl acetate and then washed with water and dilute sodium bicarbonate and dried over magnesium sulfate. This was then filtered and concentrated in vacuo to 2.2 g of crude yellow oil. This oil was purified by reverse phase chromatography to give 341 mg (13%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 3.97 (m, 1H), 3.45 (d, 1H, J = 8 Hz), 3.28 (m, 1H), 2.92 (m, 1H), 2.10 (m, 2H), 1.93 (m, 2H), 1.77 (m, 2H), 1.22 (d, 3H, J = 7 Hz), 1.11 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 392. Anal. ($C_{14}H_{20}INO_2S$) C: calcd, 42.76; found, 43.23. H, N.

(*S*,*S*)-*cis*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)-cyclopentyl]amide ((*S*,*S*)-10). The racemic cis compound **10** was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 28 cm Chiralcel AD eluting with 100% 3A alcohol at a flow rate of 300.0 mL/min monitoring at a UV wavelength of 275 nm. The analytical column was 0.46 cm × 25 cm Chiralcel AD eluting with 100% 3A alcohol at a flow rate of 1.0 mL/min monitoring at UV of 220 nm. The early-eluting compound had a retention time of 4.69 min. Enantiomeric excess was estimated to be 99% by HPLC.

(*R*,*R*)-*cis*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)-cyclopentyl]amide ((*R*,*R*)-10). The racemic cis compound **10** was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 28 cm Chiralcel AD eluting with 100% 3A alcohol at a flow rate of 300.0 mL/min monitoring at a UV wavelength of 275 nm. The analytical column was 0.46 cm × 25 cm Chiralcel AD eluting with 100% 3A alcohol at a flow rate of 1.0 mL/min monitoring at UV of 220 nm. The late-eluting compound had a retention time of 5.91 min. Enantiomeric excess was estimated to be 99% by HPLC.

(±)-*cis*-Propane-2-sulfonic Acid [2-(4-Nitro-phenyl)-cyclopentyl]amide (11). Compound **9a** (560 mg, 2.1 mmol) was dissolved in 10 mL of trifluoroacetic acid, and 534 mg (6.3 mmol) of sodium nitrate was added. The reaction was stirred for 5 h at room temperature. The reaction was diluted with methylene chloride and washed with water and dilute sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated in vacuo to 620 mg of a crude yellow oil. This oil was purified by radial chromatography eluting with 98:2 methylene chloride:ethyl acetate to give 120 mg (18%) of **11** as a white solid and also 400 mg (62%), which contained a small amount of ortho nitrated product. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8 Hz), 4.01 (m, 2H), 3.35 (m, 1H), 2.82 (m, 1H), 2.13 (m, 2H), 1.96 (m, 2H), 1.77 (m, 2H), 1.13 (d, 3H, J = 7 Hz), 1.03 (d, 3H, J = 7 Hz). Anal. ($C_{14}H_{20}N_2O_4S$) C, H, N. Mass spectrum (ES-MS): M − 1 = 311.

(*S*,*S*)-*cis*-Propane-2-sulfonic Acid [2-(4-Cyano-phenyl)-cyclopentyl]amide ((*S*,*S*)-12). Compound **(*S*,*S*)-10** (128 mg, 0.33 mmol) was dissolved in 4 mL of dimethylformamide (DMF) and degassed. Zinc cyanide (23 mg, 0.20 mmol) and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane 1:1 (21 mg, 0.03 mmol) were added, and the reaction was heated to 125 °C with stirring overnight. The reaction had not progressed far, and so, 0.5 mL of water, Tris(dibenzylideneacetone)dipalladium(0) (8 mg), and zinc cyanide (20 mg) were added, and the reaction was heated to 130 °C with stirring overnight. The reaction was diluted with methylene chloride and washed with dilute sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated to a crude brown oil. The title compound was purified by radial chromatography eluting with methylene chloride to 2% MeOH/methylene chloride to give 21 mg (22%) of **(*S*,*S*)-12** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8 Hz), 4.05 (m, 1H), 3.58 (d, 1H, J = 8 Hz), 3.37 (m, 1H), 2.90 (m, 1H), 2.15 (m, 2H), 1.95 (m, 2H), 1.78 (m, 2H), 1.20 (d, 3H, J = 7 Hz), 1.11 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 291. Exact mass calcd for (M + Na) $C_{15}H_{20}N_2O_2S$, 315.1143; found, 315.1146.

(*R*,*R*)-*cis*-Propane-2-sulfonic Acid [2-(4-Cyano-phenyl)-cyclopentyl]amide ((*R*,*R*)-12). Compound **(*R*,*R*)-10** (131 mg, 0.33 mmol) was dissolved in 4 mL of DMF and 0.5 mL of water and degassed. Zinc cyanide (70 mg, 0.60 mmol), Tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.02 mmol), and 1,1′-Bis(diphenylphosphino)ferrocene (22 mg, 0.04 mmol) were added, and the reaction was heated to 135 °C with stirring overnight. The reaction was diluted with methylene chloride and washed with dilute sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated to a crude brown oil. The title compound was purified by radial chromatography eluting with 0.2% MeOH/methylene chloride to 2% MeOH/methylene chloride to give 75 mg (77%) of **(*R*,*R*)-12** as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8 Hz), 4.05 (m, 1H), 3.58 (d, 1H, J = 8 Hz), 3.37 (m, 1H), 2.90 (m, 1H), 2.15 (m, 2H), 1.95 (m, 2H), 1.78 (m, 2H), 1.20 (d, 3H, J = 7 Hz), 1.11 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M − 1 = 291. Exact mass calcd for (M + Na) $C_{15}H_{20}N_2O_2S$, 315.1143; found, 315.1138.

(±)-*cis*-Benzoic Acid 2-(4-Bromo-phenyl)cyclopentyl Ester (13). Into a 250 mL three-necked flask fitted with a stirrer and thermometer were placed 5.00 g (24.7 mmol) of DEAD and 3.50 g (28.7 mmol) of benzoic acid in THF (50 mL). A total of 5.78 g (24.0 mmol) of the alcohol **(±)-6h** and 7.50 g (28.6 mmol) of triphenylphosphine in THF (50 mL) were added dropwise while stirring at 0 °C under a nitrogen atmosphere. After 2 h at this temperature, the TLC showed that the reaction was complete. The solution was allowed to warm to room temperature and then concentrated under reduced vacuum to yield 9.14 g of an oil. This material was purified via silica gel chromatography employing the Water's prep. 2000 and eluting with an isocratic solvent of hexane/methylene chloride 1:1 to yield 3.74 g (45%) of **13** as a slowly crystallizing oil. ^{1}H NMR ($CDCl_3$): δ 7.80 (d, 2H, J = 8 Hz), 7.50 (m, 2H), 7.37 (m, 3H), 7.18 (d, 2H, J = 8 Hz), 5.58 (m, 1H), 3.22 (m, 1H), 2.25−1.60 (m, 6H). Mass spectrum (ES-MS): M − 1 = 344. Anal. ($C_{18}H_{17}BrO_2$) C, H.

(±)-*cis*-2-(4-Bromo-phenyl)cyclopentanol (14). To compound **13** (3.70 g, 10.7 mmol) was added 5% NaOH/MeOH (75 mL, excess) in a 250 mL single-necked flask and stirred at room temperature for 3 h. The reaction mixture was then concentrated under reduced pressure to yield a semisolid. This material was taken into ether and washed once with water, dried over potassium carbonate, and concentrated under reduced vacuum to yield 3.01 g of an oil. This material was purified via silica gel chromatography employing the Water's prep. 2000 and eluting with an isocratic solvent of hexane/methylene chloride 1:1 to yield 2.31 g (90%) of **14** as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J = 8 Hz), 7.18 (d, 2H, J = 8 Hz), 4.28 (m, 1H), 2.98 (m, 1H), 2.10−1.67 (m, 6H), 1.18 (brs, 1H). Mass spectrum (ES-MS): M + 1 = 241. Anal. ($C_{11}H_{13}BrO$) C, H.

(±)-*trans*-2-[2-(4-Bromo-phenyl)cyclopentyl]isoindole-1,3-Dione (15). Into a 500 mL 3 N flask fitted with a stirrer and thermometer, 8.49 g (42.0 mmol) of DEAD in THF (25 mL) was added dropwise to 10.4 g (42.0 mmol) of triphenylphosphine in THF (175 mL) while stirring at 0 °C under a nitrogen atmosphere. A white precipitate formed. At this same temperature, 6.18 g (42.0 mmol) of phthalimide in THF (25 mL) was added dropwise followed by 10.2 g (42.0 mmol) of

14 in THF (25 mL) added dropwise at 0 °C. The reaction was then stirred at this temperature for 4 h and then allowed to warm to room temperature. The mixture was poured into water, and the desired material was extracted with ethyl acetate. The organic layer was washed once with water, dried over potassium carbonate, and concentrated under reduced vacuum to yield 27.3 g of a semisolid. This material was extracted with 3−500 mL portions of hexanes and filtered. The filtrate was concentrated under reduced vacuum to yield 14.7 g of a yellow solid. This material was purified via silica gel chromatography employing the Water's prep. 2000 and eluting with an isocratic solvent of hexane/ethyl acetate 9:1 to yield 5.20 g (34%) of **15** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 2H), 7.65 (m, 2H), 7.32 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 4.70 (m, 1H), 3.90 (m, 1H), 2.40−1.70 (m, 6H). Mass spectrum (ES-MS): M + 2 = 372. Anal. ($C_{19}H_{16}BrNO_2$) C, H, N.

(±)-*trans*-2-(4-Bromo-phenyl)cyclopentylamine (16). Into a 250 mL 3 N flask fitted with a stirrer, thermometer, and condenser was placed 5.10 g (14.0 mmol) of **15** in toluene (60 mL). To this mixture was added dropwise 4.50 g (140 mmol) of hydrazine in toluene (20 mL) while it was stirred at room temperature under a nitrogen atmosphere. The reaction was then heated at 95 °C for 6 h. The reaction was cooled to room temperature and stirred overnight. The precipitate that had formed was filtered, and the filtrate was dried over potassium carbonate and then concentrated under reduced vacuum to yield 3.41 g of an oil. This material was purified via silica gel chromatography employing the Water's prep. 2000 and eluting with an isocratic solvent of methylene chloride/methanol 9:1 to yield **16** (3.30 g, 98%) as a light oil. ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 3.15 (m, 1H), 2.52 (m, 1H), 2.11 (m, 2H), 1.77 (m, 6H), 1.44 (m, 1H). Mass spectrum (ES-MS): M − 1 = 239. Anal. ($C_{11}H_{14}NBr\cdot 0.4H_2O$) C, N, H calcd, 6.03; found, 5.50.

(±)-*trans*-Propane-2-sulfonic Acid [2-(4-Bromo-phenyl)cyclopentyl]amide (17). Into a 250 mL three-necked flask fitted with a stirrer and thermometer, 3.73 g (15.4 mmol) of 2-propanesulfonyl chloride was added dropwise to 3.30 g (14.0 mmol) of **16** and 4.23 g (16.8 mmol) DBU in methylene chloride (90 mL) while it was stirred at 0 °C under a nitrogen atmosphere. The reaction was then allowed to warm to room temperature and stirred overnight. The mixture was diluted with methylene chloride (100 mL), washed once with water, dried over potassium carbonate, and concentrated under reduced vacuum to yield 5.63 g of a solid. This material was purified via silica gel chromatography employing the Water's prep. 2000 and eluting with an isocratic solvent of hexane/ethyl acetate 7:3 to yield 3.54 g (73%) of **17** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J = 8 Hz), 7.14 (d, 2H, J = 8 Hz), 4.15 (d, 1H, J = 8 Hz), 3.62 (m, 1H), 2.70 (m, 2H), 2.32 (m, 1H), 2.13 (m, 1H), 1.80 (m, 2H), 1.62 (m, 2H), 1.18 (d, 3H, J = 7 Hz), 1.01 (d, 3H, J = 7 Hz). Mass spectrum (ES-MS): M + = 346. mp 128°−130 °C. Anal. ($C_{14}H_{20}BrNO_2S$) C, H, N.

(1*R*,2*S*)-*trans*-Propane-2-sulfonic Acid [2-(4-Bromo-phenyl)cyclopentyl]amide ((1*R*,2*S*)-17). The racemic trans compound **17** (11.2 g) was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 29 cm Chiralcel OD eluting with 90% heptane/10% IPA at a flow rate of 330 mL/min monitoring at a UV wavelength of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD-H eluting with 90% heptane/10% IPA at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 240 nm. The early-eluting compound had a retention time of 6.7 min. The yield was 4.6 g. Enantiomeric excess was estimated to be 99% by HPLC. Anal. ($C_{14}H_{20}BrNO_2S$) C, H, N.

(1*S*,2*R*)-*trans*-Propane-2-sulfonic Acid [2-(4-Bromo-phenyl)cyclopentyl]amide ((1*S*,2*R*)-17). The racemic trans compound **17** (11.2 g) was separated into individual enantiomers by chiral chromatography. The prep column used was 8 cm × 29 cm Chiralcel OD eluting with 90% heptane/10% IPA at a flow rate of 330 mL/min monitoring at a UV wavelength of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD-H eluting with 90% heptane/10% IPA at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 240 nm. The late-eluting compound had a retention time of 8.5 min. The yield was 4.9 g. Enantiomeric excess was estimated to be 98% by HPLC.

Chloro-bis-(2-phenyl-cyclopentyl)borane. This used a modification of H. C. Brown et al.[13] 1-Phenylcyclopentene (commercial 96%) (10.0 g, 69.4 mmol) was placed in an oven-dried flask under nitrogen and diluted with 60 mL of dry methylene chloride. The solution was cooled to 0 °C and monochloroborane−methyl sulfide complex (3.6 mL, 35 mmoL) was added dropwise via syringe. The solution was allowed to warm to room temperature and stirred overnight. The solvent was removed by aspirator vacuum under a nitrogen atmosphere to provide a crude colorless oil. This oil was used directly in the next step without further characterization.

Methyl-bis-(2-phenyl-cyclopentyl)borane. Chloro-bis-(2-phenyl-cyclopentyl)borane from above was diluted with 60 mL of dry hexanes under nitrogen. The solution was cooled to 0 °C, and a 2 M solution of trimethylaluminum in hexanes (5.8 mL) was added dropwise causing the reaction to turn orange. The reaction was allowed to warm to room temperature and stirred for 1.5 h. During this time, a red-brown mass precipitated out of solution, leaving a yellow supernatant. The hexanes supernatant was transferred via cannula to a nitrogen-flushed separatory funnel containing 50 mL of saturated aqueous ammonium chloride. The organic phase became colorless and was transferred via cannula to a dry flask containing sodium sulfate for drying. The solution was then transferred via cannula to a dry, nitrogen-flushed flask, and the solvent was removed under aspirator vacuum and nitrogen. The clear oil was used directly without further characterization.

(±)-*trans*-2-Phenyl-cyclopentylamine (19). Methyl-bis-(2-phenyl-cyclopentyl)borane (theoretical 34.7 mmoL) from above was diluted with 40 mL of dry THF. A 8.3 g (73 mmol) amount of HSA was slurried in a separate dry flask in 60 mL of THF, and small portions were transferred via cannula to control the exothermic reaction. The cloudy white solution was stirred at room temperature for 24 h. The reaction mixture was filtered, and the THF was removed in vacuo. The residue was treated with 30 mL of concentrated HCl, 15 mL of methanol, 20 mL of water, and 60 mL of diethyl ether and stirred at room temperature for 30 min. The aqueous phase was collected, and the organic phase was washed with water and combined with the aqueous phase. The aqueous phase was cooled to 0 °C, layered with diethyl ether, and made strongly basic with sodium hydroxide pellets. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2×) and ethyl acetate (1×). The organic phases were combined and dried over sodium sulfate. The filtrate was concentrated to 5.96 (53%) of **19** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.31−7.15 (m, 5H), 3.19 (m, 1H), 2.57 (m, 1H), 2.08 (m, 2H), 1.80 (m, 6H), 1.49 (m, 1H). Mass spectrum (ES-MS): M + 1 = 162.

(±)-*trans*-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)amide (20). Compound **19** (5.95 g, 37.0 mmol) was dissolved in dry methylene chloride and cooled to 0 °C under a nitrogen atmosphere. A 6.1 mL (41 mmol) amount of DBU was added followed by dropwise addition of 2-propanesulfonyl chloride (4.6 mL, 41 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was judged incomplete by TLC, and an additional 20% of DBU and 2-propanesulfonyl chloride were added. Stirring at room temperature was continued for 3 days. The reaction was diluted with methylene chloride and washed (1 × 100 mL) with 1 N HCl. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to 9.3 g. The product was purified on silica by Chromatotron eluting with 99:1 methylene chloride:ethyl acetate to yield 5.7 g (31%) of **20** as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.29 (m, 2H), 7.22 (m, 3H), 3.99 (d, 1H, J = 8 Hz), 3.67 (m, 1H), 2.72 (m, 1H), 2.60 (m, 1H), 2.35 (m, 1H), 2.12 (m, 1H), 1.80 (m, 3H), 1.61 (m, 1H), 1.12 (d, 3H, J = 7 Hz), 0.90 (d, 3H, J = 7 Hz). Anal. ($C_{14}H_{21}NO_2S$) C: calcd,

62.89; found, 62.38. H, N. Exact mass calcd for (M + NH_4) $C_{14}H_{25}N_2O_2S$, 285.1637; found, 285.1629.

(1*S*,2*R*)-*trans*-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)amide ((1*S*,2*R*)-20). The racemic trans compound **20** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at UV of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 1.0 mL/min monitoring at UV of 250 nm. The later-eluting compound had a retention time of 8.97 min. Enantiomeric excess was estimated to be 99% by HPLC. Mass spectrum (ES-MS): M − 1 = 266. Anal. ($C_{14}H_{21}NO_2S$) C, H, N.

(1*R*,2*S*)-*trans*-Propane-2-sulfonic Acid (2-Phenyl-cyclopentyl)amide ((1*R*,2*S*)-20). The racemic trans compound **20** was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at UV of 250 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 10% IPA in heptane containing 0.2% dimethylethylamine at a flow rate of 1.0 mL/min monitoring at UV of 250 nm. The early-eluting compound had a retention time of 6.82 min. Enantiomeric excess was estimated to be 99% by HPLC. Anal. ($C_{14}H_{21}NO_2S$) C: calcd, 62.89; found, 62.46. H, N. Mass spectrum (ES-MS): M − 1 = 266.

(±)-*trans*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)-cyclopentyl]amide (21). Racemic **20** (0.52 g, 1.5 mmol) was dissolved in 30 mL of glacial acetic acid. To this solution was added concentrated sulfuric acid (0.16 mL, 1.6 mmol) at room temperature followed by iodine (0.19 g, 0.74 mmol) and diiodine pentoxide (0.20 g, 0.59 mmol). The reaction was then protected from light and heated to 90 °C and stirred for 22 h. To the dark brown reaction mixture was slowly added 10% aqueous sodium bisulfite. The mixture was cooled to 0 °C for 1 h, and a light brown solid was collected by filtration. The solid was dissolved in warm diethyl ether and washed with water (2×) and then saturated sodium bicarbonate (1×). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo to give 435 mg (75%) of **21**. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 4.05 (d, 1H, J = 8 Hz), 3.62 (m, 1H), 2.70 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), 1.80 (m, 2H), 1.62 (m, 2H), 1.15 (d, 3H, J = 7 Hz), 0.98 (d, 3H, J = 7 Hz). Anal. ($C_{14}H_{20}INO_2S$) C, H, N. Mass spectrum (ES-MS): M − 1 = 392. Exact mass calcd for (M + NH_4) $C_{14}H_{24}IN_2O_2S$, 411.0603; found, 411.0611.

(1*R*,2*S*)-*trans*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)cyclopentyl]amide ((1*R*,2*S*)-21). The racemic trans compound **21** (400 mg) was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 90% heptane/10% IPA containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at a UV wavelength of 260 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 90% heptane/10% IPA containing 0.2% dimethylethylamine at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The early-eluting compound had a retention time of 9.32 min. The yield was 200 mg. Enantiomeric excess was estimated to be 99% by HPLC. Mass spectrum (ES-MS): M − 1 = 392.

(1*S*,2*R*)-*trans*-Propane-2-sulfonic Acid [2-(4-Iodo-phenyl)cyclopentyl]amide ((1*S*,2*R*)-21). The racemic trans compound **21** (400 mg) was separated into individual enantiomers by chiral chromatography. The semiprep column used was 1 cm × 25 cm Chiralcel OD eluting with 90% heptane/10% IPA containing 0.2% dimethylethylamine at a flow rate of 4.0 mL/min monitoring at a UV wavelength of 260 nm. The analytical column was 0.46 cm × 25 cm Chiralcel OD eluting with 90% heptane/10% IPA containing 0.2% dimethylethylamine at a flow rate of 1.0 mL/min monitoring at a UV wavelength of 220 nm. The late-eluting compound had a retention time of 12.28 min. The yield was 172 mg. Enantiomeric excess was estimated to be 98% by HPLC. Mass spectrum (ES-MS): M − 1 = 392.

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Supporting Information Available: X-ray crystallographic data for (1*S*,2*R*)-**20**. This material is available free of charge at http://pubs.acs.org.

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(15) Miu, P.; Jarvie, K. R.; Radhakrishnan, V.; Gates, M. R.; Ogden, A.; Ornstein, P. L.; Zarrinmayeh, H.; Ho, K.; Peters, D.; Grabell, J.; Gupta, A.; Zimmerman, D. M.; Bleakman, D. Novel AMPA receptor potentiators LY392098 and LY404187: effects on recombinant human AMPA receptors in vitro. *Neuropharmacology* **2001**, *40*, 976−983. Calcium influx measurements: 96 well plates containing confluent monolayers of HEK293 cells stably expressing human AMPA receptors were prepared. Cells were incubated in buffer solution (10 mM glucose, 138 mM sodium chloride, 1 mM magnesium chloride, 5 mM potassium chloride, 5 mM calcium chloride, and 10 mM *N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid, adjusted to pH 7.1−7.3) containing 20 μM Fluo3-AM dye (obtained from Molecular Probes Inc., Eugene, OR) for 60 min. Cells were washed with

buffer solution, and fluorescence measurements were made using a FLUOROSKAN II fluorometer (Labsystems, Needham Heights, MA) that indicated changes in fluorescence upon influx of calcium into cells upon stimulation by glutamate (100 μM) in the presence of cyclothiazide (100 μM) or compound. Compound applications preceded glutamate additions by 5 min, and fluorescent measurements were made immediately prior to addition of glutamate and 3 min following glutamate addition.

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