(2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-Carboxy-3′-methylcyclopropyl) Glycine Is a Potent and Selective Metabotropic Group 2 Receptor Agonist with Anxiolytic Properties

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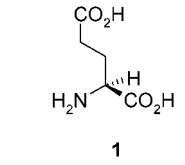
The asymmetric synthesis and biological activity of (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methylcyclopropyl) glycine **7** and its epimer at the C3′ center **6** are described. Compound **7** is a highly potent and selective agonist for group 2 metabotropic glutamate receptors (mGluRs). It is also systemically 4 orders of magnitude more active in the fear-potentiated startle model of anxiety in rats than the rigid constrained bicyclic system LY354740. Therefore, we have shown that high molecular complexity of conformationally constrained bicyclic systems is not a requirement to achieve highly selective and potent group 2 mGluRs agonists.

Introduction

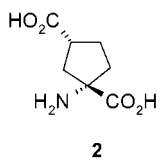
Excitatory amino acids (EAA) are present in abundance in the brain: it is estimated that around 50% of neurons in the brain may utilize glutamate (**1**) as a neurotransmitter. L-Glutamate (Glu) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate receptors are subdivided into ionotropic (GluRs)[1,2] and metabotropic receptors (mGluRs).[3,4] The ionotropic receptors mediate fast synaptic transmission through ligand-gated ion channels while metabotropic receptors are G protein-coupled and have a modulatory role in the CNS. Ionotropic receptors have been subdivided into three classes on the basis of their sensitivity to the following ligands: NMDA (*N*-methyl-D-aspartate), KA (kainate), and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) from which they take their names.[5] On the other hand, there are currently eight distinct mGluR proteins (mGluR1−8) that have been pharmacologically distinguished into three groups based on amino acid sequence homology, signal transduction mechanisms, and agonist pharmacology. Group 1 mGluRs (mGluR1 and 5) are positively coupled to phospholipase C activation and groups 2 (mGluR2 and 3) and 3 (mGluR4 and 6−8) are negatively coupled to adenylate cyclase. In recent years, significant progress has been made in the identification of selective agents for each of the main groups of mGluR subtypes. Thus, in Charts 1 and 2, some of the more potent and selective known group 2 agonists are represented.[6]

(1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD, **2**, Chart 1) was the first glutamate analogue found to activate mGluRs expressed in the rat brain. However, this ligand has little subtype selectivity, with similar potency observed across all mGluRs.[7,8] In Table 1, the pharmacological profiles for the most potent known group 2 agonists are shown across all of the metabotropic receptor subtypes. Conformational constraint of the glutamate pharmacophore into a fused bicyclic [3.1.0] ring system resulted in LY354740 (Chart 1, Table 1).[9] This compound is among the most potent and selective agonists for group 2 receptors described to date. Also, the oxygen- and sulfur-containing heterocyclic compounds LY379268 and LY389795 (Chart 1) have been described.[10] These heterobicyclic amino acids are also among the most potent agonists for group 2 mGluRs thus far described (Table 1). Like LY354740, neither of these analogues showed affinity for native GluRs nor did they produce agonist or antagonist effects at group 1 mGluRs. Moreover, these compounds show

Chart 1



1



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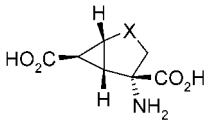
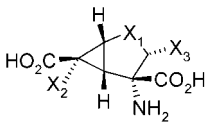
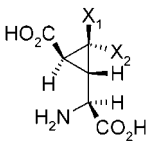


X=	
CH_2	LY354740
O	LY379268
S	LY389795



X_1	X_2	X_3	
CH_2	H	F	**3**
CH_2	F	H	**4**
CO	F	H	**5**

Chart 2



X_1	X_2	
H	H	L-CCG-I
F	F	L-F2CCG-I
H	CO_2H	DCG-IV
H	CH_2OCH_3	*cis*-MCG-I
CH_2OCH_3	H	*trans*-MCG-I

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Table 1. Potency and Subtype Selectivity of Human mGluR Agonists Reported in Nanomolar Values

	group 1a		group 2b		group 3b			
compd	mGluR1	mGluR5	mGluR2	mGluR3	mGluR4	mGluR6	mGluR7	mGluR8
Glu, **1**	10 000[c]	4000[c]	4000[c]	9000[c]	12 000[c]	20 000[c]	5 400 000[c]	NT
ACPD, **2**	42 000	15 000[c]	12 000	860 000	90 000	18 000	1 000 000	45 000
LY354740	>100 000	>100 000	7.9	21	>100 000	3000	>100 000	11 500
LY379268	>100 000	>100 000	3	5	21 000	400	>100 000	2000
LY389795	>100 000	>100 000	4	8	>100 000	2000	>100 000	7000
3	>100 000[d]	>100 000[d]	29.4	45.4	>100 000[d]	>100[d]	>100 000[d]	>100 000[d]
4	>100 000[d]	>100 000[d]	16.6	89	>100 000[d]	>100[d]	>100 000[d]	NT[e]
5	>100 000[d]	>100 000[d]	0.57	2.7	>100 000[d]	>100[d]	>100 000[d]	NT[e]
L-CCG-I	23 000	17 000	300[c]	600	4000	600[c]	47 000	400
L-F2CCG-I	NT[e]	NT[e]	90[c]	NT[e]	NT[e]	NT[e]	NT[e]	NT[e]
cis-MCG-I	>100 000	>100 000	100	NT[e]	NT[e]	NT[e]	NT[e]	NT[e]
trans-MCG-I	>100 000	>100 000	300	NT[e]	NT[e]	NT[e]	NT[e]	NT[e]
DCG-IV	>100 000[c]	389 000[c]	300[c]	200[c]	*23 000*[c,f]	*40 000*[c,f]	*40 000*[c,f]	*32 000*[c,f]
6	>100 000	>100 000	188	2000	NT[e]	NT[e]	NT[e]	2800
7	>100 000	>100 000	8	38	>100 000	1198	>100 000	1320

[a] Assay used, EC_{50}/PI hydrolysis in nonneuronal cells. [b] Assay used, EC_{50}/inhibition of forskolin c-AMP in nonneuronal cells. [c] For rat subreceptors. [d] Ref 11. [e] NT, not tested. [f] Antagonist.

efficacy in a number of experimental animal models following systemic administration.[9,10]

Recently, Nakazato et al.[11] have reported that other substituted fused bicyclic [3.1.0] ring systems, which are closely related analogues of LY354740 (**3**−**5**), have a similar profile at recombinant human mGluR2 and 3 (Table 1).

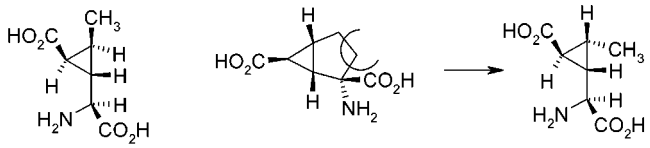
On the other hand, (2*S*,1′*S*,2′*S*)-2-(2′-carboxycyclopropyl)glycine (L-CCG-I) (Chart 2 and Table 1) shows nanomolar potency for group 2 and some group 3 (mGluR6 and mGluR8) subtypes and micromolar potency at the remaining mGluR subtypes.[12,13] The corresponding geminal fluoro-substituted L-F_2CCG-I is a more potent agonist at mGluR2; however, activity at other mGluR subtypes has not been reported.[14] Further investigation of the effect of substitution at the 3′-position of L-CCG-I has led to the identification of additional potent group 2 mGluR agonists with improved selectivity but reduced potency. Thus, introduction of a methoxymethyl substituent on the same face of the cyclopropane ring as the α-amino acid functionality afforded (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methoxymethylcyclopropyl) glycine (*cis*-MCG-I) (Chart 2), while incorporation of the methoxymethyl on the face opposite to the α-amino acid gave *trans*-MCG-I.[15] Unfortunately, activities for these two compounds at other mGluR subtypes have not been reported. (2*S*,2′*R*,3′*R*)-2-(2′,3′-Dicarboxycyclopropyl) glycine (DCG-IV) displays potent group 2 activity but has agonist activity at the NMDA receptors and antagonist effects at all of the group 3 mGluR subtypes (Table 1).[16,17]

Those data suggest that the cyclopropyl glycine moiety does not produce as great a potency and selectivity as the corresponding fused bicyclic [3.1.0] ring system counterparts. This may be due to the conformational freedom of these cyclopropyl systems as compared to the rigid bicyclic form, which imparts a superior potency and selectivity at group 2 mGluRs.

Despite this, we felt that 2′-carboxy-3′-substituted cyclopropyl glycine compounds have not been widely enough explored since only a limited number of compounds are known and their pharmacological characterization is lacking.

In this study, it was our goal to develop novel, potent, and selective group 2 mGluR agonists. To accomplish this goal, the C3′-methyl C2′-carboxycyclopropyl glycine **7** was designed as a ring-opened version of LY354740. The asymmetric synthesis and biological activity of this molecule is described. In addition, the biological activity of the epimer at the C3′ center **6** is described to demonstrate the stereochemical requirement at this center for affinity at the group 2 mGluRs (Chart 3).

Chart 3



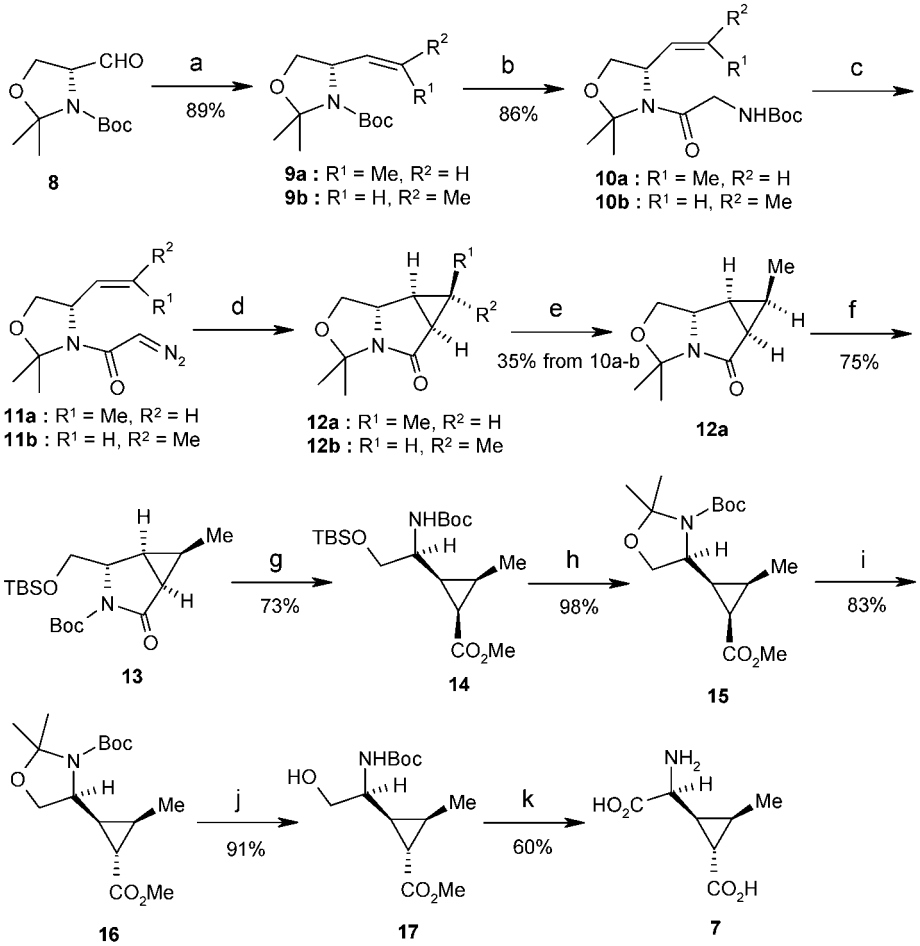
6 LY354740 **7**

Chemistry

We have already published the stereoselective synthesis of **6**.[18] In a first approach directed toward the asymmetric synthesis of **7**, we explored either the rhodium- or the palladium-catalyzed cyclopropanation of olefins **9a**,**b** (obtained as a 6:1 mixture by a Wittig reaction of Garner's aldehyde **8**, prepared from D-serine,[19] with methyltriphenyl phosphonium bromide) with ethyl diazoacetate (Scheme 1). Although a similar approach has been recently published for the synthesis of the group 2 antagonist (2*R*,1′*S*,2′*R*,3′*S*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine (PCCG-13)[20] and despite a variety of attempts under different conditions, we were unable to obtain the corresponding cyclopropane derivatives. Therefore, a more entropically favored intramolecular cyclopropanation was tried as reported by Ohfune et al.[21] The mixture of olefins **9a**,**b** was converted to *N*-Boc-glycyl olefins **10a**,**b** by removal of the *N*-Boc protecting group, followed by condensation of the free amino group with *N*-Boc-glycine and further acetonide formation. Subsequent removal of the *N*-Boc in the presence of the acetonide, followed by diazotization, gave **11a**,**b**, which underwent intramolecular palladium-catalyzed cyclopropanation to stereoselectively give the *exo*-adducts **12a**,**b**.[22]

Both isomers were easily separated by flash chromatography, and the structure of the major compound was established by ^{1}H nuclear magnetic resonance (NMR).

Scheme 1[a]



[a] (a) $Ph_3PCH_2CH_3$, Br, KHMDS, dioxane, room temperature. (b) (i) 1 N HCl/MeOH; (ii) Boc-Gly-Osu, Et_3N, MeOH/THF, room temperature; (iii) $Me_2(OMe)_2$, PTSA, PhH, reflux. (c) (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, room temperature; (ii) $NaNO_2$, 5% citric acid, Et_2O, room temperature. (d) $Pd(OAc)_2$, PhH, 70 °C. (e) Separation: column chromatography, AcOEt/Hexane 1:2. (f) (i) Dowex 50WX8-100, MeOH, room temperature; (ii) TBSCl, imidazole, DMF, room temperature; (iii) Boc_2O, Et_3N, DMAP, THF, room temperature. (g) (i) 1 N LiOH, THF, room temperature; (ii) CH_2N_2, Et_2O, 0 °C. (h) (i) CSA, MeOH, room temperature; (ii) $Me_2(OMe)_2$, CSA, acetone, 60 °C. (i) KHMDS, THF, −78 °C to room temperature. (j) CSA, MeOH, room temperature. (k) (i) Jones reagent, acetone, 0 °C to room temperature; (ii) 2.5 N LiOH, THF, room temperature; (iii) 1 N HCl/AcOEt; (iv) propylene oxide, MeOH, room temperature.

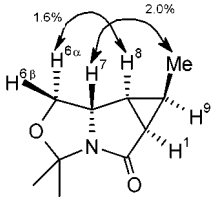
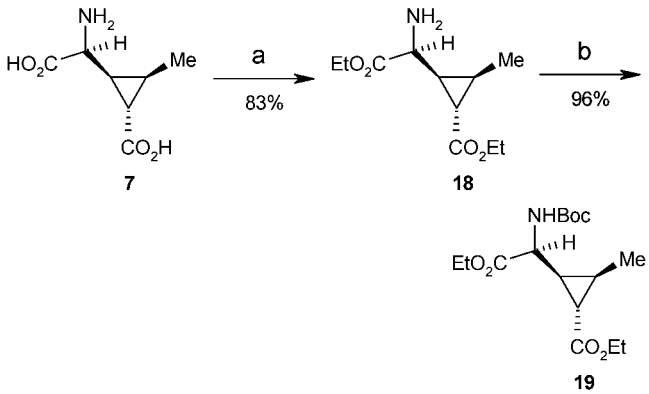


Figure 1. NOE correlations of compound **12a**.

The results of nuclear Overhauser effect (NOE) experiments showed it to be the desired isomer **12a**, which possessed 1*R*,7*S*,8*S*,9*R* stereochemistry (Figure 1). Removal of the acetonide and reprotection of the amide and the hydroxyl groups gave the *N*-Boc-γ-lactam **13**, which was cleaved by treatment with LiOH to afford **14** after esterification with diazomethane. Once the TBS group was removed and the acetonide was reintroduced, the C2′ carbon atom was epimerized to isomer **16** upon treatment with base. Acetonide hydrolysis of **16** followed by sequential Jones oxidation, ester hydrolysis with LiOH, removal of the *N*-Boc, and final treatment with propylene oxide in methanol afforded **7** with a 6.5% overall yield from aldehyde **8**. Its relative configuration (1′*S*,2′*S*,3′*R*) at the three cyclopropyl carbons was assigned through coupling constant analysis in its *N*-Boc-diethyl derivative **19** (Scheme 2). All of the proton and carbon resonances were assigned through the combination of one-dimensional (1D) and two-dimensional (2D) experiments (1H, correlation spectroscopy (COSY), HSQC, 1D nuclear Overhauser enhancement spectroscopy (NOESY)). Because it is well-known that for

Scheme 2[a]



[a] (a) Cl_2SO_2, EtOH, reflux. (b) Boc_2O, $NaHCO_3$ (saturated), THF, room temperature.

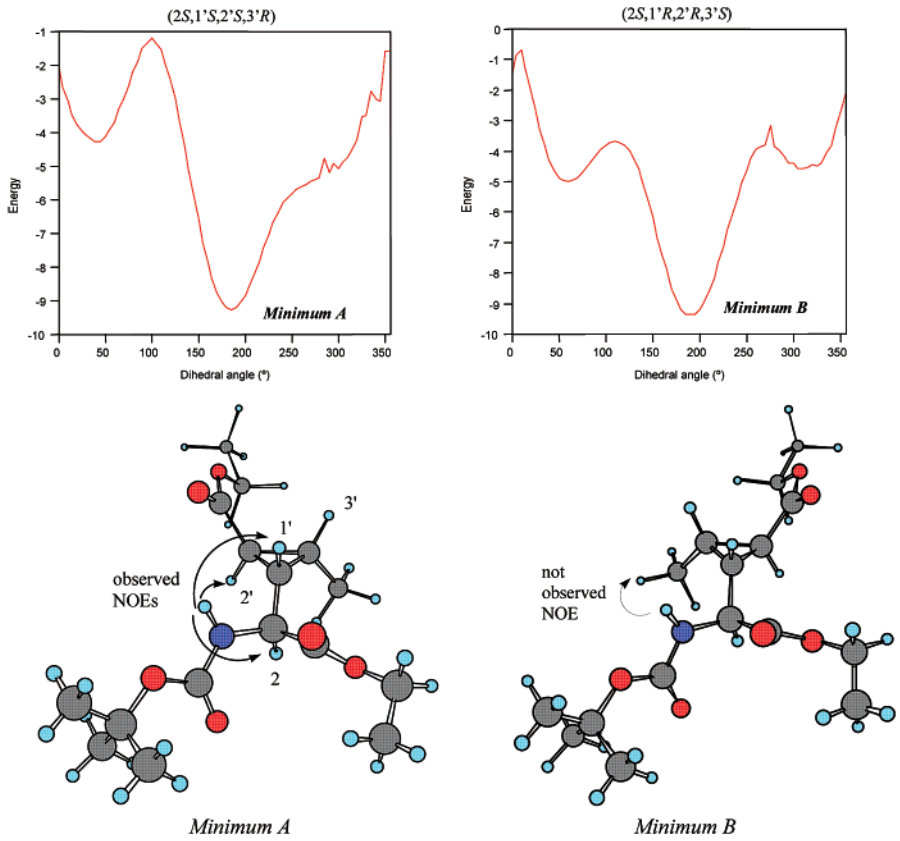
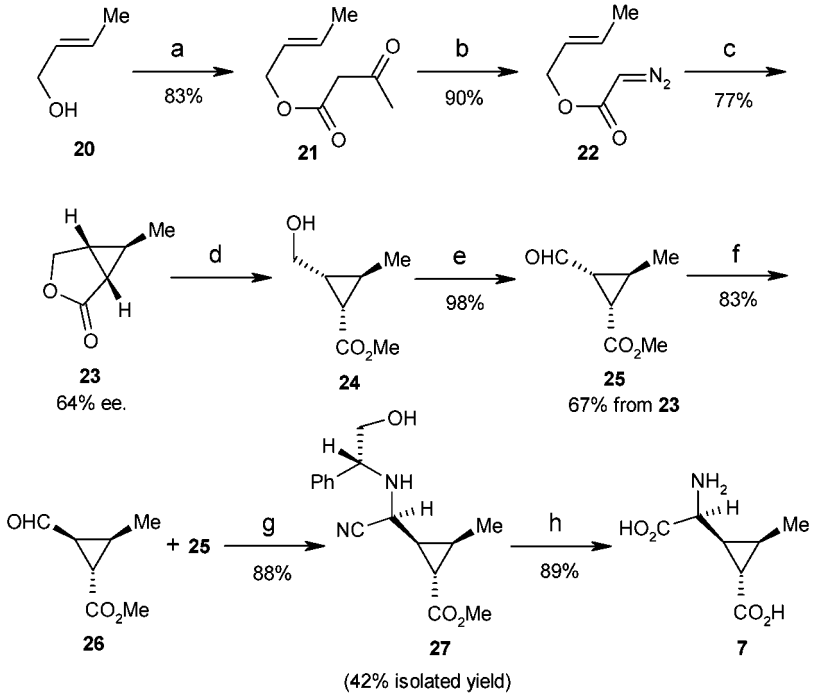


Figure 2. Plot of energy (kcal/mol) vs H2−C2−C1′−H1′ dihedral angle (°) for (2*S*,1′*S*,2′*S*,3′*R*) and (2*S*,1′*R*,2′*R*,3′*S*) isomers and conformation of their global minima.

cyclopropane derivatives $J_{cis} > J_{trans}$,[23] the coupling constant values ($J_{H1'-H3'} = 9.1$ Hz, $J_{H1'-H2'} = 4.4$ Hz, and $J_{H2'-H3'} = 4.7$ Hz) indicate that H1′ is cis to H3′ and trans to H2′. Furthermore, absolute stereochemistry of **7** was confirmed based on combination of molecular modeling calculations and NOE data. Because the absolute stereochemistry at the amino acid center is fixed to 1*S* due to the use of D-serine as starting material, the two possible absolute configurations (2*S*,1′*S*,2′*S*,3′*R*) and (2*S*,1′*R*,2′*R*,3′*S*) were subjected to a conformational search around the C1−C1′ bond using the MMFF94s force field within SYBYL software. From those, minimum A is the most stable conformer for (2*S*,1′*S*,2′*S*,3′*R*) isomer by 5.0 kcal/mol and minimum B is the most stable conformer for (2*S*,1′*R*,2′*R*,3′*S*) by 4.3 kcal/mol (Figure 2). It should be noted that both configurations show a strong preference for an approximately 180° H2−C2−C1′-H1′ torsion. Indeed, a large $J_{H2-H1'}$ value (10.7 Hz) was measured for **19** in the proton spectrum, indicating that H2 is anti to H1′ as predicted by the calculations. Selective inversion of the amide proton in a 1D NOESY experiment produced NOEs to H2, H1′, and H2′, whereas no NOE to the methyl protons was detected. Because the NH proton is close to H2′ in minimum A but close to the methyl group in minimum B (Figure 2), this NOE pattern was consistent with absolute configuration (2*S*,1′*S*,2′*S*,3′*R*).

However, because of the difficulties in scaling-up the intramolecular cyclopropanation step (step d, Scheme 1), this reaction sequence was not suitable for the preparation of large quantities of **7**. Thus, we developed a new enantioselective synthesis based in the asymmetric intramolecular cyclopropanation of allylic and homoallylic diazoacetates using Doyle catalysts.[24] The new synthesis started with the cheap and readily available crotyl alcohol **20** as starting material (Scheme 3). Using a general procedure for preparing diazoacetates, **20** was transformed into its corresponding acetoacetic ester **21** with diketene. Subsequent diazo transfer followed by base-induced deacylation of the intermediate α-diazo acetoacetic ester afforded diazoacetate **22**. Slow addition of a solution of **22** to a solution of Rh_2(5*R*-MEPY)$_4$ in refluxing dichloromethane gave the (−)-cyclopropyl lactone **23**[25] in very good yield. The enantiomeric excess of **23** was determined to be 64% by titration with the chiral shift reagent Eu(tfc)$_3$ in C_6D_6 and integration of suitable diastereotopic protons in the ^{1}H NMR spectrum (±2%), and its absolute configuration (1*S*,5*R*,6*R*) was assigned based on the opposite one reported for its antipode, obtained through the same method using Rh_2(5*S*-MEPY)$_4$[25] and upon analogy to other reported cyclopropyl lactones.[26] Alkaline hydrolysis of the lactone, followed by treatment of the acidified product with diazomethane, afforded an intermediate hydroxy ester **24**, which was immediately oxidized to (+)-aldehyde **25** by treatment with tetra-*n*-propylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO). The epimerization of aldehyde **25** to *epi*-aldehyde **26** was studied under a variety of reaction conditions. The most favorable conditions were found to be the treatment of **25** with strong base, followed by reesterification with diazomethane to provide **26** as the major isomer in a c.a. 5:1 (^{1}H NMR) inseparable mixture. With this mixture of aldehydes (**25** and **26**) in hand, a diastereoselective Strecker synthesis was performed.[27] Condensation of this mixture with

Scheme 3[a]



[a] (a) Diketene, AcONa, THF, reflux. (b) (i) *p*-AcNHC$_6$H$_4$SO$_2$N$_3$, Et$_3$N, CH$_3$CN, room temperature; (ii) LiOH, H$_2$O, room temperature. (c) Rh$_2$(5*R*-MEPY)$_4$, CH$_2$Cl$_2$, reflux. (d) (i) 2.8 N LiOH, THF, room temperature; (ii) CH$_2$N$_2$, Et$_2$O, 0 °C. (e) TPAP, NMO, mol sieves (4 Å), CH$_2$Cl$_2$, room temperature. (f) (i) 10% NaOH, MeOH, room temperature; (ii) CH$_2$N$_2$, Et$_2$O, 0 °C. (g) (i) (*R*)-Phenylglycinol, MeOH, room temperature; (ii) TMSCN, room temperature. (h) (i) Pb(Ac)$_4$, CH$_2$Cl$_2$, MeOH, 0 °C; (ii) 6 N HCl; (iii) Dowex 50 × 8-100.

optically active *R*-(−)-α-phenylglycinol (99% ee), followed by nucleophilic addition of a cyanide to the Schiff base, gave an expected mixture of eight α-amino nitrile derivatives, in which a major component was detected and separated from the minor amount of the other possible diastereoisomers by medium-pressure chromatography in 42% isolated yield (de > 98% high-performance liquid chromatography (HPLC)). Because two new contiguous chiral centers are present, each aldehyde was expected to yield the four corresponding diastereomeric-substituted α-amino nitriles. Because *R*-(−)-α-phenylglycinol preferentially induces opposite chirality in the newly formed asymmetric center,[27] the absolute configuration of the more abundant constituent of the mixture of glycinonitriles was assigned as (2*S*,1′*S*,2′*S*,3′*R*)-[(*R*)-(phenylglycinyl)]amino nitrile **27**. After oxidative cleavage of **27** with lead tetraacetate and further acidic hydrolysis and ion exchange chromatography (Dowex 50 × 8-100, 10% Py), (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methylcyclopropyl)glycine **7** was isolated in 12% overall yield from crotyl alcohol and its physicochemical properties were identical to the one synthesized through the first method reported herein (Scheme 1). To determine the enantiomeric purity of **7**, Mosher amides derived from both *R*-(+)-α-methoxy-(trifluoromethyl)phenylacetyl chloride (*R*-(+)-MPTA) and *S*-(−)-α-methoxy-(trifluoromethyl) phenylacetyl chloride (*S*-(−)-MPTA) of its diethyl ester derivative **18** (Scheme 2) were prepared.[28] Comparison of NMR spectra (Brucker Avance 500) of the resulting derivatives revealed an enantiomeric excess >96%.

Pharmacology

Compounds **6** and **7** were evaluated in cloned mGluRs for their ability to influence forskolin-stimulated adenosine cyclic 3′,5′-phosphate (c-AMP) formation (groups 2 and 3 mGluRs) or basal [^{3}H]IP formation (group 1 mGluRs) (see Experimental Section). These data are shown in Table 1 together with other known agonists. It should be pointed out that a substituent α to the amino acid center would convert an agonist into an antagonist.[29] As shown in Table 1, compound **7** was similar to LY354740 in its biological profile on all mGluRs. On the other hand, **6**, the C3′ epimer, was much less active than predicted. Therefore, the presence of the methyl group on the same face as the amino acid center is enough to confer a molecular conformation that permits effective interaction with the binding site of the receptor as seen for LY354740.

Behavioral Pharmacology

The advent of selective and potent group 2 mGluR agonists has provided an accumulation of experimental evidence that implicates group 2 mGluRs as targets for the treatment of schizophrenia,[30] anxiety,[31] drug withdrawal,[32] depression,[33] neuroprotection,[34] pain,[35] Alzheimer's disease,[36] epilepsy,[37] and Parkinsons disease.[38]

In this study, the effects of the novel CCG derivative **7** were investigated in the rat fear-potentiated startle assay31a, [39] in which LY354740 had been previously shown to be active. This model was specifically chosen, as it is highly sensitive to mGluR2 agonists and served as the basis for developing LY354740 for anxiety disorders in humans. As a positive control in each experiment, diazepam (0.6 mg/kg ip) was used. All experiments were performed in fed rats. While LY354740 significantly blocked fear-potentiated startle with an mean effective dose (MED) of 3 mg/kg (po), **7** was 4 orders of magnitude more potent with an MED of 0.0003 mg/kg (po). Given that the in vitro potencies of LY354740

and **7** are similar across all of the mGluR clones, it is likely that the increased potency of **7** may be due to a better bioavailability in rats following oral administration than for LY354740.

In conclusion, we have shown that enantiomerically pure (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methylcyclopropyl) glycine **7** is a highly potent and selective agonist for group 2 mGluRs. It has also proven to be systemically active in the fear-potentiated startle model of anxiety in rats. Therefore, we have shown that the high molecular complexity of conformationally constrained bicyclic systems is not a requirement to achieve highly selective and potent group 2 mGluR agonists. Further studies on the expanded structure−activity relationship of other C3′-substituted C2′ carboxy cyclopropyl glycine compounds and their evaluation in additional experimental animal models will be reported in due course.

Experimental Section

General. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a positive pressure of nitrogen. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AC-200P (200 MHz), Brucker AM-300 (300 MHz), or Brucker Avance 500 (500 MHz) spectrometer. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (TMS) as internal standard. Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical thin-layer chromatography (TLC) was performed on Merck TLC glass plates precoated with F_{254}silica gel 60 (UV, 254 nm and phosphomolibdic acid). Chromatographic separations were performed by using 230−400 mesh silica gel (Merck). Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

(1′*Z*) and (1′*E*) *tert*-Butyl (4*S*)-2,2-Dimethyl-4-(1′-propenyl)-3-oxazolidinecarboxylates (9a,b). To a suspension of Ph_3PEtBr (4.86 g, 13.9 mmol) in anhydrous dioxane (100 mL) under nitrogen at room temperature, a 0.5 M solution of KHMDS in toluene (22.3 mL, 11.7 mmol) was added. After it was stirred for 1 h, the mixture was added dropwise via cannula to a solution of the *tert*-butyl (4*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate **8** (2.0 g, 8.7 mmol) in anhydrous dioxane (40 mL) under nitrogen at room temperature. After the addition was completed, the reaction mixture was stirred for 30 min and then poured onto a (1:1) mixture of H_2O−Et_2O (500 mL). Layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give a residue, which was purified by chromatography using AcOEt/Hexane (1:10) as eluent to give 1.8 g (89% yield) of a 6:1 mixture of **9a**,**b** respectively. **9a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.52 (s, 3H), 1.60 (s, 3H), 1.70 (d, J = 1.1 Hz, 3H), 3.65 (dd, J = 3.3, 8.8 Hz, 1H), 4.06 (dd, J = 6.0, 8.8 Hz, 1H), 4.72−4.62 (m, 1H) and 5.61−5.39 ppm (m, 2H).

(1′*Z*) and (1′*E*)-3-[*N*-(*tert*-Butoxycarbonyl)glycyl]-(4*S*)-2,2-dimethyl-4-(1′-propenyl)-1,3-oxazolidine (10a,b). To a solution of the mixture **9a**,**b** (1.77 g, 4.48 mmol) in MeOH (10 mL) at 0 °C was added 1 N HCl/MeOH (30 mL). The reaction mixture was stirred for 1 h and at room temperature overnight. The solvent was removed in vacuo, and the residue was taken into H_2O (10 mL). This solution was adjusted to pH 7 by addition of 1 N NaOH and then to pH 9 by Et_3N. The solvent was removed in vacuo, and the residue was dissolved in MeOH (20 mL) and THF (30 mL) (additional Et_3N was added until the solution became pH 9). To this solution at 0 °C was added *N*-hydroxysuccinimide *N*-(*tert*-butoxy-carbonyl)glycinate (2.2 g, 8.06 mmol) and then warmed to room temperature. After the mixture was stirred for 1 h, the solvent was removed in vacuo and the oily residue was dissolved in AcOEt. The insoluble material was filtered off, and the filtrate was concentrated in vacuo to give a residue that was subjected to column chromatography on silica gel (AcOEt). The resulting Boc-glycyl compound was dissolved in benzene (25 mL), and *p*-toluensulfonic acid (21 mg, 0.11 mmol) and 2,2-dimethoxypropane (1.9 mL, 15.4 mmol) were added. The mixture was stirred under reflux for 24 h. To this solution at room temperature, MeOH (5 mL) was added and the mixture was stirred for 30 min. Then, $NaHCO_3$ (1−2 g) was added, and after it was stirred for 15 min, the insoluble material was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (AcOEt/Hexane 1:5 and then 1:3) to give a 6:1 mixture of **10a**,**b**, respectively (1.89 g, 86%). **10a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.56 (s, 3H), 1.66 (s, 3H), 1.76 (dd, J = 1.6, 7.2 Hz, 3H), 3.86−3.78 (m, 3H), 4.15 (dd, J = 6.1, 8.8 Hz, 1H), 4.61−4.57 (m, 1H), 5.50−5.39 (m, 2H), 5.74−5.63 ppm (m, 1H).

(1*R*,7*S*,8*S*,9*R*)-3-Aza-9-methyl-4,4-dimethyl-5-oxatricyclo[6.1.0.03,7]nonan-2-one (12a). To a solution of the mixture **10a**,**b** (2.7 g, 9.05 mmol) and 2,6-lutidine (3.27 mL, 28.06 mmol) in anhydrous CH_2Cl_2 (30 mL) at room temperature under nitrogen was added TMSOTf (3.44 mL, 19.0 mmol). The mixture was stirred for 15 min, cooled to 0 °C, and quenched with a saturated aqueous solution of NH_4Cl (15 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was taken into Et_2O (75 mL) at room temperature, and a $NaNO_2$ (3.12 g, 45.25 mmol) solution in H_2O (35 mL) was added with stirring. To this suspension, a 5% solution of citric acid in H_2O was added until the pH was adjusted to ∼3. The mixture was vigorously stirred for 30 min at room temperature and then extracted three times with Et_2O. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting diazoacetamides **11a**,**b** were dissolved in benzene (200 mL) without further purification, and $Pd(OAc)_2$ (100 mg, 0.45 mmol) was added. The mixture was heated at 70 °C for 30 min, and then, the solvent was removed in vacuo. The residue was purified by flash chromatography using AcOEt/Hexane (1:1) as eluent to give the corresponding exo-adducts **12a**,**b**. The major and desired isomer **12a** was separated by column chromatography using AcOEt/Hexane (1:2) as eluent (570 mg, 35% overall yield); $[\alpha]_D$ = +57.0° (c = 0.105, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, J = 6.6 Hz, 1H), 1.39 (s, 3H), 1.52−1.40(m, 1H), 1.74 (s, 3H), 1.89 (dd, J = 6.1, 8.2 Hz, 1H), 2.18−2.07 (m, 1H), 3.51 (dd, J = 7.1, 9.9 Hz, 1H), 3.82−3.77 (m, 1H), 4.02 ppm (dd, J = 5.5, 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.8, 17.3, 21.6, 23.8, 28.6, 28.9, 58.4, 67.9, 93.7, 172.8 ppm. Anal. ($C_{10}H_{15}NO_2$): C, H, N.

(1*R*,4*S*,5*S*,6*R*)-3-Aza-3-*N*-(*tert*-butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxymethyl]-6-methyl Bicyclo[3.1.0]-hexane-2-one (13). A mixture of **12a** (440 mg, 2.42 mmol) and Dowex 50W × 8 resin (H^+ form, 200 mg) in MeOH (20 mL) was stirred overnight at room temperature. The resin was then filtered off, and the filtrate was concentrated in vacuo. To a solution of the residue and imidazole (660 mg, 9.68 mmol) in DMF (10 mL) was added a solution of *tert*-butyldimethylsilyl chloride (1.10 g, 7.26 mmol) in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then poured onto cold water and extracted three times with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure (DMF was removed by azeotropic distillation with toluene). A solution of the resulting residue, Et_3N (0.68 mL, 4.48 mmol), Boc_2O (790 mg, 3.63 mmol), and DMAP (60 mg, 0.48 mmol) in THF (15 mL) was stirred overnight at room temperature and then poured onto water and extracted three times with AcOEt. The combined organic layers were washed successively with 5% aqueous citric acid and H_2O, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo, and the resulting residue was purified by column chromatography (AcOEt/Hexane 1:6) to give the

bicyclic lactam **13** (640 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 1.42−1.34(m, 1H), 1.49 (s, 9H), 1.87 (dd, J = 6.6, 7.7 Hz, 1H), 2.05−1.99 (m, 1H), 3.91−3.76 ppm (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5 (2C), 7.6, 16.0, 18.1, 19.5, 25.7 (3C), 25.8, 28.0 (3C), 56.7, 63.7, 82.6, 149.5, 172.4 ppm.

Methyl (1*R*,2*S*,3*R*,1′*S*)-2-[1′-[*N*-(*tert*-Butoxycarbonyl)-amino]-2′-(*tert*-butyldimethylsilyl)oxy-ethyl]-3-methyl-1-cyclopropanecarboxylate (14). To a solution of **13** (480 mg, 1.35 mmol) in THF (13.5 mL), 1 N LiOH (13.5 mL) was added. The mixture was vigorously stirred overnight and then adjusted to pH ∼3 by addition of 5% aqueous citric acid. The aqueous layer was extracted three times with AcOEt, and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. A solution of the residue in Et_2O (25 mL) at 0 °C was treated with a recently prepared CH_2N_2 solution in Et_2O (until the yellow color is retained) at 0 °C. After 30 min, the solvent was removed and the residue was purified by column chromatography (AcOEt/Hexane 1:6) to afford **14** (380 mg, 73%). $[\alpha]_D = -45.0°$ (c = 0.132, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.26−1.18 (m, 1H), 1.31 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H), 1.52−1.44 (m, 1H), 1.75−1.70 (m, 1H), 3.64 (s, 3H), 3.78−3.62 (m, 2H), 3.98−3.89 (m, 1H), 4.75 ppm (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5 (2C), 7.8, 18.3, 19.1, 20.2, 25.7, 25.8 (3C), 28.0 (3C), 47.4, 51.2, 65.1, 78.7, 154.8, 171.8 ppm.

(4*S*,1′*S*,2′*R*,3′*R*)-3-[*N*-(*tert*-Butoxycarbonyl)]-2,2-dimethyl-4-[2′-(methoxycarbonyl)-3′-methyl cyclopropyl]-1,3-oxazolidine (15). A mixture of **14** (380 mg, 1.0 mmol) and camphorsulfonic acid (11.4 mg, 0.05 mmol) in MeOH (50 mL) was stirred at room temperature for 4 h. The solvent was then removed in vacuo, and the residue was taken into acetone. To this solution under nitrogen atmosphere, 2,2-dimethoxypropane (1.2 mL, 9.8 mmol) was added, and the mixture was stirred for 2 h at 60 °C. Then, the reaction mixture was cooled to room temperature and $NaHCO_3$ (50 mg) was added. The mixture was then filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (AcOEt/Hexane 1:6) to give **15** (300 mg, 98%); $[\alpha]_D = -38.0°$ (c = 0.105, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (br s, 2H), 1.45 (br s, 15H), 1.60 (s, 3H), 1.87−1.81 (m, 1H), 3.71 (s, 3H), 3.85 (dd, J = 2.2, 8.8 Hz, 1H), 4.07 (dd, J = 6.0, 8.8 Hz, 1H), 4.37 ppm (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.9, 16.6, 21.1, 24.5, 27.8, 27.9, 28.3 (3C), 51.0, 51.9, 68.6, 79.5, 93.4, 151.8, 171.9 ppm. Anal. ($C_{16}H_{27}NO_5$): C, H, N.

(4*S*,1′*S*,2′*S*,3′*R*)-3-[*N*-(*tert*-Butoxycarbonyl)]-2,2-dimethyl-4-[2′-(methoxycarbonyl)-3′-methylcy-clopropyl]-1,3-oxazolidine (16). To a solution of **15** (300 mg, 0.96 mmol) in anhydrous THF at −78 °C under nitrogen, 0.5 M KHMDS solution in toluene (5.75 mL, 2.87 mmol) was added. The mixture was slowly allowed to react at room temperature (over a period of 4 h) and then stirred at room temperature for 15 min. The reaction mixture was cooled again to −78 °C and then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted twice with Et_2O and AcOEt, and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting residue was purified by column chromatography (AcOEt/Hexane 1:6) to give the epimerized product **16** (250 mg, 83%); $[\alpha]_D = -15.4°$ (c = 0.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, J = 6.1 Hz, 3H), 1.50 (br s, 15H), 1.75−1.57 (m, 3H), 3.66−3.57 (br s, 1H), 3.67 (s, 3H), 3.85 (d, J = 8.2 Hz, 1H), 4.05−3.97 ppm (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5, 19.8, 23.2, 27.0, 27.8, 28.3 (3C), 31.5, 51.4, 56.3, 68.6, 80.1, 94.0, 152.1, 174.2 ppm. Anal. ($C_{16}H_{27}NO_5$): C, H, N.

Methyl (1*S*,2*S*,3*R*,1′*S*)-2-[1′-[*N*-(*tert*-Butoxycarbonyl)-amino]-2′-hydroxyethyl]-3-methyl-1-cyclo-propanecarboxylate (17). A mixture of **16** (250 mg, 0.8 mmol) and camphorsulfonic acid (9.2 mg, 0.04 mmol) in MeOH (40 mL) was stirred at room temperature overnight. The following day, additional camphorsulfonic acid (11.0 mg, 0.047 mmol) was added and the mixture was stirred for 48 h. Then, $NaHCO_3$ (50 mg) was added and the mixture was filtered off. The filtered mixture was concentrated in vacuo, and the residue was purified by column chromatography (AcOEt/Hexane 1:1) to give the corresponding alcohol **17** (200 mg, 91%).

(2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-Carboxy-3′-methylcyclopropyl)-glycine (7). To a solution of **17** (200 mg, 0.73 mmol) in acetone (5 mL) at 0 °C, Jones Reagent (1.12 mL) previously cooled to 0 °C was added. The mixture was stirred for 2 and 3 h at room temperature. Then, the reaction was quenched with 2-propanol (5 mL) and H_2O (5 mL), stirred for 15 min, and poured onto AcOEt (75 mL). The organic layer was washed several times with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was dissolved in THF (5 mL), and 2.5 N LiOH (10 mL) was added. The mixture was vigorously stirred overnight. The organic layer was separated and discarded, and the aqueous layer washed with Et_2O. After the aqueous solution was adjusted to pH ∼1 by addition of 1 N HCl at 0 °C, it was extracted four times with AcOEt, and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. A solution of the residue in 1 N HCl/AcOEt (5 mL) was stirred overnight. The solvent was removed in vacuo, and the resulting solid was washed with Et_2O. The hydrochloride salt was dissolved in MeOH (3 mL), and propylene oxide (5 mL) was added. The mixture was stirred overnight, and the resulting insoluble solid was filtered and washed with Et_2O to give **7** (75 mg, 60%) as a white solid; $[\alpha]_D = +22°$ (c = 0.23, H_2O); mp 178−180 °C. ^{1}H NMR (200 MHz, D_2O/KOD): δ 1.20−1.07 (m, 4H), 1.44−1.38(m, 2H), 2.90 ppm (d, J = 9.8 Hz, 1H). ^{13}C NMR (50 MHz, D_2O/KOD): δ 13.7, 21.9, 30.9, 32.8, 56.7, 183.4, 184.5 ppm. Anal. ($C_7H_{11}NO_4$): C, H, N.

Ethyl *N*-(*tert*-Butoxycarbonyl) (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-(Ethoxycarbonyl)-3′-methylcyclopropyl)glycinate (19). To a solution of **7** (49 mg, 0.28 mmol) in anhydrous EtOH (3.0 mL) at 0 °C, thionyl chloride (62.0 μL, 0.85 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h and then heated at reflux for 3 h. The reaction was cooled to room temperature, the solvent was removed in vacuo, and the resulting white solid was taken into CH_2Cl_2 (10 mL). The resulting solution was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL), and the organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give **18** (53 mg, 83%) as a colorless oil. To a solution of **18** (50 mg, 0.22 mmol) in THF (3.0 mL), a saturated aqueous solution of $NaHCO_3$ (1.5 mL) was added and the mixture was vigorously stirred for 5 min. To this mixture, a solution of Boc_2O (58 mg, 0.26 mmol) in THF (1.5 mL) was added and the reaction was stirred overnight. Layers were separated, and the aqueous phase was extracted three times with AcOEt. The combined organic layers were washed with a saturated aqueous solution of NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (AcOEt/Hexane 1:10) to give **19** (70 mg, 96%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13−1.22 (m, 9H), 1.38 (s, 9H), 1.40 (dd, J = 4.4, 4.7 Hz, 1H), 1.46 (m, 1H), 1.59 (ddd, J = 4.4, 9.1, 10.7 Hz, 1H), 3.64 (dd, J = 6.9, 10.7 Hz, 1H), 3.98−4.16 (m, 4H), 7.65 (d, J = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.4, 13.9, 14.0, 21.2, 25.5, 28.0, 28.1 (3C), 52.3, 59.9, 60.5, 78.3, 155.4, 171.3, 172.4 ppm. Anal. ($C_7H_{12}O_3$): C, H, N.

***trans*-2-Buten-1-yl Acetoacetate (21).** To a refluxing solution of crotyl alcohol **20** (21.5 mL, 252 mmol) and sodium acetate (1.24 g, 15.12 mmol) in anhydrous THF (70 mL) under nitrogen, a solution of diketene (21.34 mL, 277.1 mmol) in anhydrous THF (30 mL) was added dropwise over a period of 1 h. The reaction mixture was heated at reflux for 30 min upon completion of the addition and then cooled to room temperature and diluted with Et_2O (300 mL). The resulting solution was washed with a saturated aqueous solution of NaCl (2 × 50 mL), and the organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The brown residue was purified by column chromatography (Hexane/Et_2O 5:1) to afford **21** (33.0 g, 83%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (dd, J = 6.5 and 0.9 Hz, 3H), 2.27 (s, 3H), 3.46 (s, 2H), 4.56 (d, J = 6.5 Hz, 2H), 5.65−5.50 (m, 1H), 5.88−

5.74 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.9, 29.2, 49.2, 65.0, 124.2, 130.8, 166.3, 199.7 ppm.

***trans*-2-Buten-1-yl Diazoacetate (22).** To a solution of **21** (40.0 g, 256 mmol) and Et_3N (46.0 mL, 330 mmol) in anhydrous CH_3CN (250 mL) at room temperature, a solution of *p*-acetamidobenzenesulfonyl azide (80.0 g, 333 mmol) in anhydrous CH_3CN (250 mL) was added dropwise over a period of 30 min. A white precipitate was observed after 15−20 min and additional CH_3CN (300 mL) was added to facilitate stirring. The resulting mixture was stirred at room temperature for 1 h, and a solution of LiOH (35.5 g, 845 mmol) in H_2O (300 mL) was added. After it was stirred for one additional hour, the resulting mixture was poured onto 2:1 Et_2O:AcOEt (500 mL) and the layers were separated. The aqueous layer was extracted with 2:1 Et_2O:AcOEt (500 mL), and the combined organic layers were washed with a saturated aqueous solution of NaCl (200 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (Hexane/AcOEt 9:1) to afford **22** (32.2 g, 90%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (dd, J = 6.3 and 1.3 Hz, 3H), 4.58 (dt, J = 5.7 and 1.0 Hz, 2H), 5.09 (s, 1H), 5.66−5.50 (m, 1H), 5.89−5.72 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.1, 45.5, 64.8, 124.8, 130.8, 166.1 ppm.

(1*S*,5*R*,6*R*)-(−)-6-Methyl-3-oxabicyclo[3.1.0]hexan-2-one (23). To a solution of Rh_2(5*R*-MEPY)$_4$ (63.5 mg, 0.082 mmol) in anhydrous CH_2Cl_2 (250 mL) heated at reflux, a solution of *trans*-2-buten-1-yl diazoacetate **22** (5.0 g, 35.7 mmol) in anhydrous CH_2Cl_2 (500 mL) was added dropwise over a period of 30 h. After the addition was completed, the mixture was allowed to react under reflux overnight and then cooled to room temperature. The solvent was removed in vacuo, and the residue was purified by column chromatography (Hexane/AcOEt 5:1 and then 2:1) to give **23** (3.1 g, 77%) as a pale yellow oil with an enantiomeric excess of 64%; $[\alpha]_D = -68.5$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (d, J = 4.8 Hz, 3H), 1.29−1.18 (m, 1H), 1.80−1.84 (m, 1H), 1.96−2.04 (m, 1H), 4.34−4.20 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 19.9, 24.0, 24.2, 68.6, 174.9 ppm.

Methyl (1*S*,2*R*,3*R*)-2-Hydroxymethyl-3-methylcyclopropropane-1-carboxylate (24). To a solution of **23** (3.9 g, 34.7 mmol) in THF (350 mL) at room temperature, a solution of LiOH (7.29 g, 174 mmol) in H_2O (174 mL) was added. The mixture was stirred overnight at room temperature. The organic phase was removed in vacuo, and the resulting aqueous solution was washed with Et_2O (2 × 50 mL), cooled to 0 °C, and adjusted to pH ∼2−3 by addition of 1 N HCl. The aqueous layer was extracted with AcOEt (6 × 200 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting (1*S*,2*R*,3*R*)-2-hydroxymethyl-3-methylcyclopropropane-1-carboxylic acid was taken into Et_2O (150 mL) and cooled to 0 °C, and a solution of diazomethane in Et_2O was added in small portions until TLC showed that no starting material remained. The solvent was removed in vacuo to afford 22 (5.0 g). This crude was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (d, J = 6.5 Hz, 3H), 1.60−1.38 (m, 3H), 3.69 (s, 3H), 3.78 (dd, J = 7.5 and 12.0 Hz, 1H), 3.96 (dd, J = 5.5 and 12.0 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.8, 20.3, 24.7, 31.5, 50.9, 58.8, 172.8 ppm. Anal. ($C_7H_{12}O_3$): C, H, N.

Methyl (1*S*,2*R*,3*R*)-2-Formyl-3-methylcyclopropropane-1-carboxylate (25). To a solution of **24** (5.0 g) in anhydrous CH_2Cl_2 (350 mL) at room temperature under nitrogen, molecular sieves (4 Å) (3.5 g) were added. After it was stirred for 15 min, the mixture was cooled to 0 °C and *N*-methylmorholine-*N*-oxide (6.1 g, 52.1 mmol) was added. After 10 min, tetrapropylammonium perruthenate (490 mg, 1.39 mmol) was added in small portions and the mixture was allowed to react at room temperature. The solvent was removed in vacuo, and the residue was taken into AcOEt (200 mL). The resulting suspension was filtered through a plug of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (Hexane/AcOEt 6:1 and then 4:1) to give **25** (3.3 g, 67% yield) as an oil; $[\alpha]_D = +22.0°$ (c = 0.75, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, J = 6.1 Hz, 3H), 1.89−1.78 (m, 1H), 2.00 (dd, J = 6.1 and 8.7 Hz, 1H), 2.27 (sx, J = 6.1 Hz, 1H), 3.69 (s, 3H), 9.32 (d, J = 6.6 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.3, 22.3, 30.2, 38.4, 52.0, 170.8, 199.0 ppm. Anal. ($C_7H_{10}O_3$): C, H, N.

Methyl (1*S*,2*S*,3*R*)-2-Formyl-3-methylcyclopropropane-1-carboxylate (26). A solution of NaOH (27.0 g, 675 mmol) in H_2O (270 mL) was added to a solution of **25** (3.3 g, 23.5 mmol) in MeOH (330 mL), and the mixture was stirred at room temperature for 4 days. MeOH was removed under reduced pressure, and the resulting aqueous layer was washed with Et_2O (2 × 50 mL), cooled to 0 °C, and adjusted to pH ∼2−3 by addition of an aqueous solution of citric acid (10−25%). The aqueous layer was extracted with AcOEt (6 × 250 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting carboxylic acid was taken into Et_2O (150 mL) and cooled to 0 °C, and a solution of diazomethane in Et_2O was added in small portions until TLC showed no starting material left. The solvent was removed in vacuo, and the residue was purified by column chromatography (Hexane/AcOEt 4:1) to afford an inseparable 5:1 mixture of **26** and starting material **25** (2.77 g, 83%). This mixture was used in the next step without any other further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (d, J = 6.4 Hz, 3H), 2.06−1.97 (m, 1H), 2.31 (dd, J = 4.6 and 5.0 Hz, 1H), 2.53 (ddd, J = 9.4, 4.6 and 3.6 Hz, 1H), 3.69 (s, 3H), 9.60 (d, J = 3.7 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.0, 24.3, 27.6, 28.7, 52.2, 175.5, 198.0 ppm.

(2*S*,1′*S*,2′*S*,3′*R*,1″*R*)-*N*-[(2″-Hydroxy-1″-phenyl)ethyl]2-(2′-methoxycarbonyl-3′-methylcyclo-propyl)glycinonitrile (27). To a solution of a 5:1 mixture of **26** and epimer **25** (2.7 g, 19.0 mmol) in MeOH (190 mL), (*R*)-(−)-2-phenylglycinol (99% ee) (2.9 g, 20.9 mmol) was added. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Trimethylsilylcyanide (5.1 mL, 38.0 mmol) was added to the mixture and allowed to react at room temperature overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography (Hexane/AcOEt 2:1 and then 1:1) to afford a mixture of aminonitriles (4.8 g, 88%). The major diastereoisomer **27** was separated and purified by medium-pressure chromatography (Hexane/Acetone 7:2) to give 2.3 g (42% isolated yied) as a colorless oil; $[\alpha]_D = -60.5°$ (c = 0.39, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (d, J = 6.4 Hz, 3H), 1.35 (t, J = 4.7 Hz, 1H), 1.70−1.56 (m, 1H), 1.88 (dt, J = 4.4 and 9.4 Hz, 1H), 2.99 (br d, J = 9.1 Hz, 1H), 3.58 (dd, J = 9.3 and 10.8 Hz, 1H), 3.70 (s, 3H), 3.79 (dd, J = 4.0 and 10.8 Hz, 1H), 4.10 (dd, J = 4.0 and 9.3 Hz, 1H), 7.38−7.24 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.5, 21.3, 27.5, 29.3, 46.9, 52.5, 63.3, 67.6, 119.3, 127.9 (2C), 128.8 (2C), 129.4, 138.4, 173.7 ppm. Anal. ($C_{16}H_{20}N_2O_3$): C, H, N.

(2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-Carboxy-3′-methylcyclopropyl)-glycine (7). Lead tetraacetate (5.16 g, 11.6 mmol) was added to a solution of **27** (2.8 g, 9.7 mmol) in a 1:1 mixture of MeOH and CH_2Cl_2 (100 mL) at 0 °C. After 10 min, H_2O (60 mL) was added and the mixture was filtered off through Celite. The filtrate was concentrated in vacuo, and the residue was taken into 6 N HCl (50 mL) and refluxed overnight. The solvent was removed in vacuo to afford the corresponding hydrochloride salt of **7**. After purification by ion exchange chromatography (Dowex 50 × 8-100), **7** (1.5 g, 89%) was obtained as a white solid; $[\alpha]_D = +28°$ (c = 0.28, H_2O); mp 179−181 °C. ^{1}H NMR (200 MHz, D_2O/KOD): δ 1.20−1.07 (m, 4H), 1.44−1.38 (m, 2H), 2.90 ppm (d, J = 9.8 Hz, 1H). ^{13}C NMR (50 MHz, D_2O/KOD): δ 13.7, 21.9, 30.9, 32.8, 56.7, 183.4, 184.5 ppm. Anal. ($C_7H_{11}NO_4$): C, H, N.

Modeling Calculations for Compound 19. The computational studies were performed using the molecular modeling program SYBYL running on a Silicon Graphics Octane workstation. After energy minimization of the structures with MMFF94s force field, a systematic conformational search was carried using the grid search module of the software. The conformations were generated by rotating the C2−C1′ dihedral from 0 to 355° by 5° increments, after which each structure was optimized and its energy was computed.

NMR Spectroscopy. NMR spectra for compound **19** and for the Mosher's amides derived from **18** were acquired on a Bruker Avance 500 spectrometer in DMSO-d_6 at 25 °C with an inverse probe. Proton and carbon chemical shifts were referenced to residual solvent signal. Absolute value COSY, phase sensitive HSQC, and HMBC spectra were acquired using gradient selection techniques. One-dimensional NOESY experiments were carried out with the selective 1D double-pulse field-gradient spin−echo module using a mixing time of 500 ms. Data were processed using XWINNMR Bruker program on a Silicon Graphics computer.

Biological Assay. 1. Receptor Functional Assay. Compounds **6** and **7** were profiled for agonist and antagonist activity at all of the known mGluR subtypes using clonal nonneuronal cell lines derived as previously described.[40] In vitro phosphoinositide hydrolysis assays were carried out for transfected cells expressing mGlu1 and mGlu5 receptors. Briefly, cells were seeded into 24 well culture plates at 2.5 × 105 cells per well in medium containing no added glutamine and cultured at 37 °C in a humidified atmosphere of 5% CO_2 in air. After 24 h, cultures were labeled with [^{3}H]myo-inositol (4 μCi/mL) for a further 20 h. Cells were washed in assay medium containing HEPES (10 mM), inositol (10 mM), and LiCl (10 mM). Compounds were added to the cultures either alone or 20 min prior to the addition of agonist quisqualate (0.3 μM) and then incubated for 60 min at 37 °C. The reaction was terminated by replacing the medium with acetone:MeOH (1:1), and the cultures were incubated on ice for 20 min. Separation of the [^{3}H]inositol phosphates was carried out by Sep-Pak Accell Plus QMA ion exchange chromatography (Waters, Millipore Ltd., U.K.) according to previously described methods.[41] The [^{3}H]inositol monophosphate (INS P1) fraction was eluted with 0.1 M triethylammonium bicarbonate buffer, and radioactivity was measured by liquid scintillation counting. Cyclic AMP assays were carried out for cells expressing mGlu2, mGlu3, mGlu4, mGlu6, mGlu7, and mGlu8. Cells were washed with Dulbecco's phosphate-buffered saline (PBS) plus 3 mM glucose and 500 μM isobutylmethylxanthine (IBMX) and preincubated for 30 min at 37 °C. Each well was then washed, and compound was added together with forskolin (15 μM final concentration). Antagonist effects of compounds were evaluated by preincubation with compound for 15 min followed by agonist and forskolin addition. Cells were incubated for 20 min at 37 °C and then terminated by adding 6 mM EDTA solution to each well and placing the plate in a boiling water bath. Concentrations of cAMP were determined by an Amersham [^{3}H]cAMP SPA kit. Protein content in each well was determined using the modified Bradford−Pierce assay (Pierce Chemicals, U.S.A.).

2. Fear-Potentiated Startle Assay. This paradigm was conducted over three consecutive days. SR-LAB (San Diego Instruments, San Diego, CA) chambers were used for conditioning sessions and for producing and recording startle responses. All 3 days began with a 5 min adaptation period before the trial started. On day one (baseline startle) after the adaptation period, the animals received 30 trials of 120 dB auditory noise. Startle responding was measured through transducers located under the startle platforms. Recorded values represent a maximum change in voltage (V_{max}). The mean startle amplitude (V_{max}) was used to assign animals to groups ($n = 8$) with similar means before conditioning began. Day two consisted of conditioning the animals. Each animal received 0.5 mA of shock for 500 ms preceded by a 5 s presentation of light (15 W), which remained on for the duration of the shock. Ten presentations of the light and shock were administered. Animals tested in the postconditioning paradigm were administered compound prior to testing on day 3. Excluding the first 10 trials, the startle response amplitudes for each trial type were averaged for each animal. Data were presented as the difference between light + noise and noise alone. Differences in startle response amplitudes were analyzed by JMP statistical software using a one way ANOVA (analysis of variance, *t*-test). Group differences were considered to be significant at $p < 0.05$.

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Supporting Information Available: ^{1}H NMR spectra of Mosher amide derivatives of compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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