(2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-Carboxy-3′-hydroxymethylcyclopropyl) Glycine Is a Highly Potent Group 2 and 3 Metabotropic Glutamate Receptor Agonist with Oral Activity

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Received July 22, 2003

The asymmetric synthesis and biological activity of (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-carboxy-3′-hydroxymethylcyclopropyl) glycine ((+)-**3**) is described. This novel C-3′ substituted carboxy cyclopropyl glycine is a highly potent group 2 and group 3 mGluR agonist that has proven to be orally active in both fear potentiated startle (animal model for anxiety) and PCP-induced motor activation (animal model for psychosis) assays in rats.

Introduction

It has been over 45 years since the excitatory and neurotoxic actions of L-glutamate (Glu) were initially described. Glu is the major excitatory neurotransmitter in the mammalian central nervous system (CNS).[1,2] Glu receptors are subdivided into ionotropic (GluRs) and metabotropic receptors (mGluRs).[3,4] The mGluRs are members of the type 3 G protein coupled receptors (GPCRs), which also include $GABA_B$, calcium-sensing, and certain pheromone receptors.[5] There are currently eight distinct mGluR proteins (mGluR1−8) which 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. With the cloning of mGluR subtypes, the pharmacology of mGluRs began to progress more rapidly. Previously discovered and newly discovered mGluR active agents can be fully characterized for their affinity and/or functional activity across the cloned mGluRs. A number of potent and selective compounds for subtypes as well as subgroups of mGluRs have been discovered as useful radioligands or pharmacological tools to explore the biochemical and behavioral consequences of mGluR modulation.[6]

Among the several classes of Glu analogues, carboxycyclopropylglycines (CCGs) represent a valuable source of both potent and selective agonist and antagonist ligands for the various members of the Glu receptor family. (2*S*,1′*S*,2′*S*)-2-(2′-Carboxycyclopropyl) glycine (L-CCG-I) (Chart 1 and Table 1) is a selective and nanomolar potent agonist for group 2 mGluRs and some group 3 mGluRs (mGluR6 and mGluR8 subtypes) with micromolar potency at group 1 mGluRs and the rest of group 3 mGluRs (mGluR4 and mGluR7 subtypes).[7,8] The corresponding *gem*-difluoro-substituted L-F_2CCG-I is a more potent agonist at mGluR2; however, its activity at other mGluR subtypes has not been reported.[9] 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 equal potency but with improved selectivity. Thus, both (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-carboxy-3′-methoxymethylcyclopropyl) glycine (*cis*-MCG-I) (Chart 1) and *trans*-MCG-I maintain the agonist activity at mGluR2 compared to L-CCG-I but have increased selectivity versus group 1 mGluR subtypes.[10] (2*S*,2′*R*,3′*R*)-2-(2′,3′-Dicarboxycyclopropyl) glycine (DCG-IV) also displays potent group 2 activity. However, it has agonist activity at the NMDA receptor and unexpectedly mGluR antagonist activity at group 3 (Table 1).[11,12] We have very recently reported that compound (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-methylcyclopropyl) glycine **(1)**, in which a methyl group in the 3′-position is on the same face to the α-amino acid, is the most potent and selective group 2 mGluR agonist belonging to the carboxycyclopropyl glycine family known to date.[13]

On the other hand, Pellicciari et al. have demonstrated that the stereoselective introduction of a bulky, hydrophobic group such as a phenyl ring in the 3′-position confers antagonism to the corresponding CCG analogue, (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-phenylcyclopropyl) glycine (PCCG-4, Chart 1).[14] Furthermore, the same authors have also shown that compounds with other tethered bulky substituents at the same position like 9-xanthenylmethyl-CCG (XM-CCG-I) and 9-xanthenylethyl-CCG (XE-CCG-I) have the same antagonistic effect.[15]

Finally, it should be pointed out that our laboratories have reported that a substituent α to the amino acid

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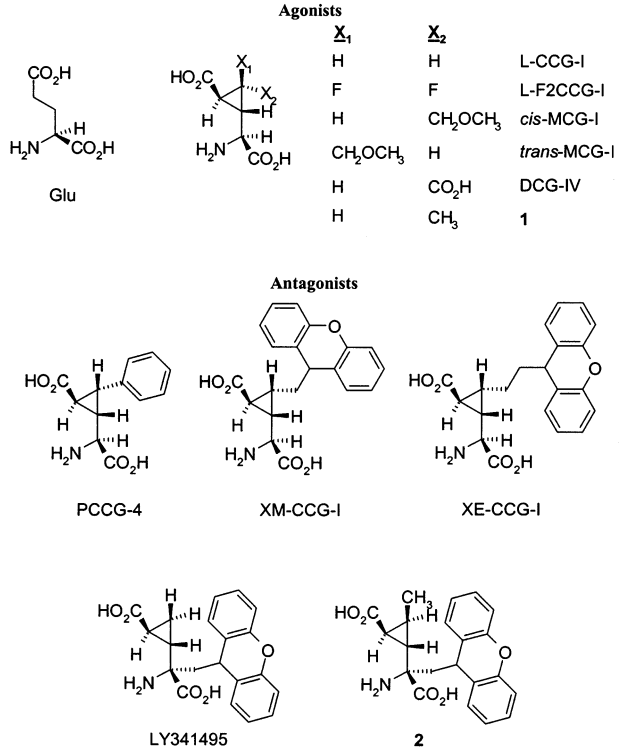
10.1021/jm030967o CCC: $27.50
Published on Web 12/09/2003

Chart 1



center (2 position) converts an agonist into an antagonist (LY341495, Chart 1).[16] Interesting enough, we have also demonstrated some time ago that the combination of both effects, α (C-2) and C-3′ disubstitution, retains the antagonist effect,[17] indicating that, at least in **2**, the C-2 and not the C-3′ substitution drives the pharmacology of the compound.

We felt that substituted CCGs are a very versatile platform that has not been widely enough explored, and therefore, it is still not well understood what structural features are driving the agonism−antagonism profile as well as the activity across all mGluRs. In the aim to further explore the effect of substituents on the C-3′ position of the L-CCG-I and to develop novel, potent, and selective agonists for mGluRs, we designed and prepared the 3′-*cis*-hydroxymethyl analogue **3**, which has the additional possibility of acting as both hydrogen bond donor and acceptor.

On the basis of absolute stereochemistry of the highly potent and selective group 2 mGluR agonist **1** determined by us (2*S*,1′*S*,2′*S*,3′*R*) and taking into account that of the 16 possible isomers for MCGs the highest agonist activity for mGluR2 was that observed for the *cis*-MCG-I, with the same stereochemistry pattern (2*S*,1′*S*,2′*R*,3′*R*), we decided to synthesize the corresponding enantiomerically pure analogue of **3**, (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-carboxy-3′-hydroxymethylcyclopropyl) glycine. Herein, we describe the asymmetric synthesis and biological activity of (+)-**3** (Chart 2, Table 1).

Chemistry

As a first goal, we decided to develop a racemic diastereoselective synthesis for **3**. In a retrosynthetic analysis, lactol **(**±**)-6** was envisioned as its plausible precursor (Scheme 1). Since this lactol would exist in equilibrium with its aldehyde form **(**±**)-6a**, classical methods of amino acid synthesis techniques would convert **(**±**)-6** to the desired product. The only limitation of this approach was that the amino acid would be presumably obtained as a mixture of diastereoisomers. The synthesis of **(**±**)-6** was straightforward in two steps starting from butenolide **4** after cyclopropanation reaction with ethyl(dimethylsulfuranylidene)acetate (EDSA), generated in situ by treatment of ethyl dimethylsulfonium acetate bromide and a base, and further chemoselective reduction of the lactone. Unfortunately, under the best reaction conditions for the cyclopropanation of **4** ($EtO_2CCH_2SMe_2Br$, Cs_2CO_3, DMF, rt), lactone **(**±**)-5** was obtained with a poor 22% yield (Scheme 1). This limitation prompted the development of an alternative approach for the synthesis of **(**±**)-6** from cycloadduct **8**. Thus, **8** was obtained as a single diastereoisomer by rhodium-catalyzed cyclopropanation of ethyl diazoacetate with *cis*-4,7-dihydro-1,3-dioxepin **(7)**. Cleavage of the acetal provided diol **9**, which was isolated with a 63% combined yield from **7**. Conversion of diol **9** to the corresponding lactol **(**±**)-6** was possible by oxidation with a variety of common oxidizing reagents (TPAP, TEMPO, Swern conditions). However, it has to be noted that overoxidation of **(**±**)-6** to the lactone **(**±**)-5** was the major side product in these cases. Fortunately, partial oxidation of **9** with MnO_2 afforded exclusively hemiketal **(**±**)-6** as only one of the two possible epimers in a very high yield.

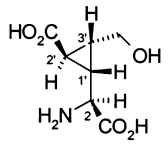
Conversion of lactol **(**±**)-6** to the amino acid using the Strecker reaction was initially investigated. As predicted, poor stereoselectivity was observed. Treatment of **(**±**)-6** with potassium cyanide and ammonium chloride in the presence of alumina under sonication gave a 2:1 mixture of the two possible racemic aminonitriles **(**±**)-10** (Scheme 2). Further transformation of this mixture to their corresponding *N*-Boc-aminodiesters by treatment with a saturated solution of HCl in EtOH and subsequent protection of the nitrogen afforded a 2:1 mixture of isomers **(**±**)-11** and **(**±**)-12**, respectively, in good yield. The isomers were separated by column chromatography, and their relative configurations were assigned based on nuclear Overhauser effect (NOE) measurements on their corresponding pyroglutamate derivatives **(**±**)-13** and **(**±**)-14**, obtained by Jones oxidation of **(**±**)-11** and **(**±**)-12**, respectively. The corresponding relative configurations (1*SR*,5*RS*,6*RS*) in both **(**±**)-13** and **(**±**)-14** at the three cyclopropyl carbons were assigned through coupling constant analysis. All the proton and carbon resonances were assigned through the combination of 1D and 2D experiments (^{1}H, COSY, HSQC, 1D-NOESY). Since it is well-known that for cyclopropane derivatives $J_{cis} > J_{trans}$,[18] the coupling constant values ($J_{H5-H6} = 3.2$ Hz for **(**±**)-13** and 3.3 Hz for **(**±**)-14**, $J_{H1-H6} = 2.9$ Hz for **(**±**)-13** and 2.8 Hz for **(**±**)-14**, $J_{H1-H5} = 6.4$ Hz for **(**±**)-13** and 6.5 Hz for **(**±**)-14**) indicate that H^1 is cis to H^5 and trans to H^6 in both cases. To elucidate the relative stereochemistry of the substituent at the C-2 position in both **(**±**)-13** and **(**±**)-14**, ROESY-2D experiments were performed (Figure 1). For **(**±**)-13**, the ROESY-2D spectrum showed a cross-peak between H^2 and H^6, whereas for **(**±**)-14** it was not detected and instead a relevant NOE effect was present between H^2 and H^1 and H^2 and H.[5] These NOE patterns

Table 1. Potency and Subtype Selectivity of Human MGluR Agonists Reported in NM Values

	group 1[a]		group 2[b]		group 3[b]			
compd	mGluR1	mGluR5	mGluR2	mGluR3	mGluR4	mGluR6	mGluR7	mGluR8
L-CCG-I	23000	17000	300[c]	600	4,000	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	>100000	>100000	100	NT[e]	NT[e]	NT[e]	NT[e]	NT[e]
trans-MCG-I	>100000	>100000	300	NT[e]	NT[e]	NT[e]	NT[e]	NT[e]
DCG-IV	>100000[c]	389000[c]	300[c]	200[c]	*23000*[c,f]	*40000*[c,f]	*40000*[c,f]	*32000*[c,f]
1	>100000	>100000	8	38	>100000	1198	>100000	1320
S-AP4	>100000	>100000[c]	448000	>100000	320	55	175000	60
(*RS*)-PPG	>500000	>500000	>300000	>200000	5200	4700	185000	210
(*S*)−3,4-DCPG	32000	>100000	>100000	>100000	8800	3600	>100000	31
(±)-3	>100000	>100000	5	11	NT[e]	NT[e]	NT[e]	NT[e]
(−)-3	NT[e]	NT[e]	>100000	>100000	NT[e]	NT[e]	NT[e]	>100000
(+)-3	>100000	>100000	4	7	1800	147	>100000	10

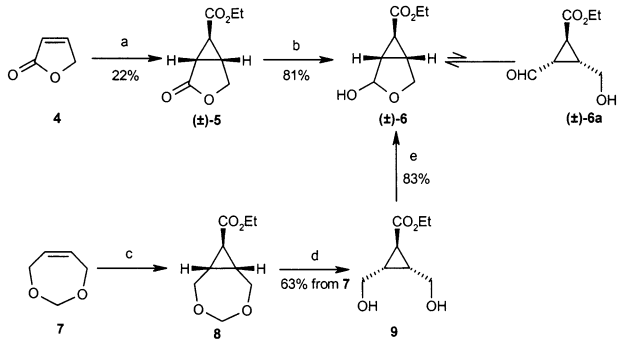
[a] Assay used: EC50/PI hydrolysis in nonneuronal cells. [b] Assay used: EC50/inhibition of forskolin c-AMP in nonneuronal cells. [c] For rat subreceptors. [d] Reference 11. [e] NT: not tested. [f] Antagonist.

Chart 2



(+)-3

Scheme 1[a]



[a] (a) $EtO_2OCH_2SMe_2Br$, Cs_2CO_3, DMF, room temperature; (b) DIBAL-H, THF, −78 °C; (c) N_2CHCO_2Et, $Rh_2(OAc)_4$, CH_2Cl_2, reflux; (d) 0.5 N HCl/EtOH, reflux; (e) MnO_2, CH_3CN, room temperature.

confirmed a relative stereochemistry of (2*RS*, 1′*SR*, 2′*RS*, 3′*RS*) for alcohol **(±)-11** and (2*SR*, 1′*SR*, 2′*RS*, 3′*RS*) for alcohol **(±)-12**.

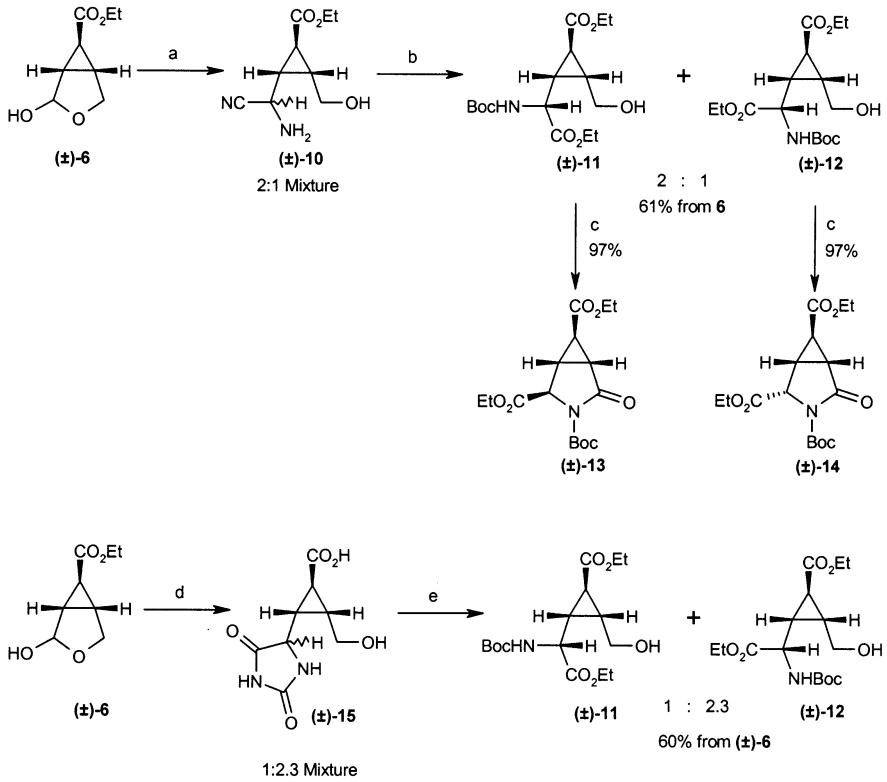
Comparison of the relative stereochemistry of **(±)-11** (2*RS*,1′*SR*,2′*RS*,3*RS*) and **(±)-12** (2*SR*,1′*SR*,2′*RS*,3*RS*) to that of *cis*-MCG-I and **1** allowed us to believe that **(±)-12** was the direct precursor of **(±)-3**. Considering that **(±)-12** was the minor isomer in the Strecker reaction, we decided to investigate other methods for the installation of the amino acid moiety that might enhance the steroselectivity of the desired isomer. Toward this end, we next ran a Bucherer−Bergs reaction for the generation of the amino acid center, which is generally known to produce the opposite stereochemical effect of a Strecker reaction.[19] Thus, hydrolysis of lactol **(±)-6** followed by treatment with an excess of sodium cyanide and ammonium carbonate afforded a 1:2.3 mixture of hydantoins **(±)-15**. Further hydrolysis of hydantoins with 1 N sodium hydroxide to the amino acids and their subsequent esterification and nitrogen protection furnished a mixture of **(±)-11** and **(±)-12** in a 1:2.3 ratio that was separated by column chromatography. ^{1}H NMR analysis of the mixture proved that its major component was the desired isomer **(±)-12**.

The racemic *N*-Boc diester **(±)-12** was then subjected to basic hydrolysis followed by treatment with 2 N HCl to afford the corresponding hydrochloride salt. The zwitterion of the final amino acid **(±)-3** was obtained by treatment of the hydrochloride with propylene oxide in methanol (Scheme 3).

To identify the active enantiomer of **(±)-3**, chiral HPLC separation of the racemate **(±)-12** was performed prior to its hydrolysis to the final zwitterions. Each antipode was then separately submitted to a sequential treatment with TFA and further hydrolysis with 3 N sodium hydroxide. Finally, both isomers were isolated after precipitation with concentrated HCl. Affinity of **(+)-3** and **(−)-3** for group 2 mGluR was then evaluated.[20] As a result, the binding assay showed that isomer **(+)-3** had a very high affinity for both mGluR2 and mGluR3 (mGluR2, Ki = 23 nM; mGluR3, Ki = 3nM) whereas **(−)-3** demonstrated to be inactive in the same assay (mGluR2, Ki > 10000 nM; mGluR3, Ki > 10000 nM). Thus, it was concluded that the affinity for group 2 mGluRs resided in the **(+)-3** isomer and it was profiled for agonist and antagonist activity at all of the known mGluR subtypes (vide infra).

To determine the absolute stereochemistry of **(+)-3**, we developed a new enantioselective synthesis based on the asymmetric intramolecular cyclopropanation of allylic and homoallylic diazoacetates using Doyle catalysts.[21] This new synthesis started with the commercially available *cis*-4-benzyloxy-2-buten-1-ol **(16)** as starting material (Scheme 4). By use of a general procedure for preparing diazoacetates, **16** was transformed into the corresponding acetoacetic ester **17** using diketene. Subsequent diazo transfer followed by base-induced deacylation of the intermediate α-diazo acetoacetic ester afforded diazoacetate **18**. Enantioselective intramolecular cyclopropanation of **18** catalyzed by Rh_2(4*S*-MPPIM)$_4$,[22] followed by alkaline hydrolysis and further esterification with diazomethane of the (1*R*,5*S*,6*R*)-cyclopropyl lactone **(−)-19** (ee >95%)[23] afforded the intermediate (1*S*,2*R*,3*S*)-hydroxyester **(−)-20**. Subsequent protection of the hydroxyl group, and further epimerization of the methoxycarbonyl moiety of **(−)-21** afforded epimer **(−)-22** upon removal of the TBS group. After oxidation of alcohol **(−)-22** to (1*S*,2*S*,3*R*)-aldehyde **(+)-23** by treatment with tetra-*n*-propylammonium perruthenate (TPAP) in the presence of *N*-me-

Scheme 2[a]



[a] (a) KCN, NH_4Cl, CH_3CN, ultrasound; (b) i. HCl/EtOH (satd), H_2O, room temperature, ii. Boc_2O, $NaHCO_3$ (satd), dioxane, room temperature; (c) Jones reagent, acetone, 0 °C to room temperature; (d) i. 1 N NaOH, EtOH, 60 °C, ii. NaCN, $(NH_4)_2CO_3$, H_2O, reflux; (e) i, 1 N NaOH, reflux, ii. 1 N HCl/EtOH, iii. Boc_2O, $NaHCO_3$ (satd), dioxane, room temperature.

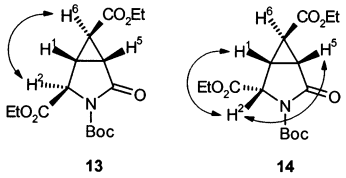
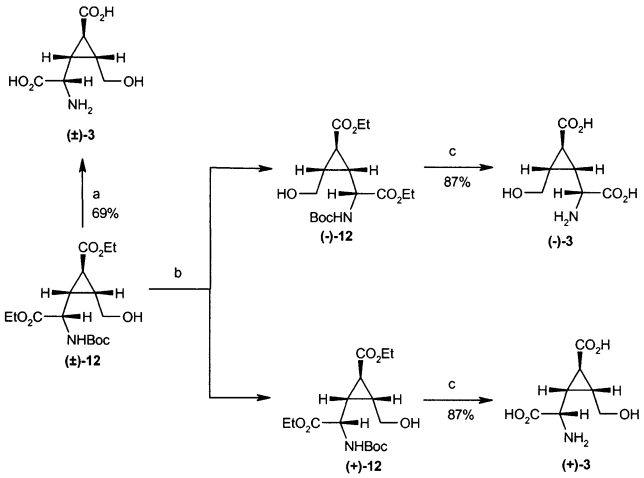


Figure 1. NOE correlations for compounds **13** and **14**.

Scheme 3[a]



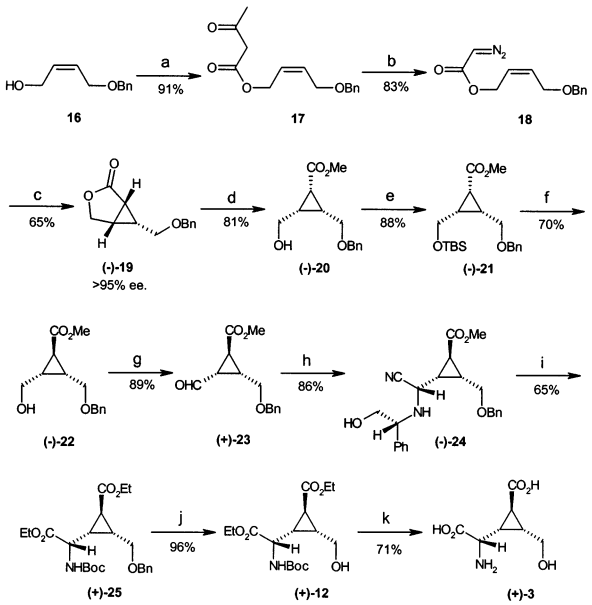
[a] (a) i. 2.5 N LiOH, THF, room temperature, ii. 2 N HCl, room temperature, iii. propylene oxide. MeOH, room temperature; (b) chiral HPLC separation; (c) i. TFA, CH_2Cl_2, room temperature, ii. 3 N NaOH, room temperature.

thylmorpholine *N*-oxide (NMO), a diastereoselective Strecker synthesis was performed.[24] Condensation of (+)-**23** with optically active *R*-(−)-α-phenylglycinol (99% ee), followed by nucleophilic addition of cyanide to the Schiff base, afforded the expected mixture of the two possible α-amino nitrile derivatives in a 9:1 ratio, in which the major component (−)-**24** was separated by medium-pressure chromatography in 86% isolated yield. Since *R*-(−)-α-phenylglycinol preferentially induces opposite chirality in the newly formed asymmetric center,[24] the absolute configuration of the more abundant constituent of the mixture of glycinonitriles was assigned as (2*S*,1′*S*,2′*R*,3′*R*)-[(*R*)-(phenylglycinyl)])-aminonitrile ((−)-**24**). After oxidative cleavage of (−)-**24** with lead tetraacetate and further acidic hydrolysis, *N*-Boc-aminodiester (+)-**25** was obtained by treatment of the corresponding amino diacid with a saturated solution of HCl in EtOH and subsequent protection of the nitrogen. Deprotection of the hydroxyl group afforded (+)-**12** in 8% overall yield. Further basic hydrolysis of (+)-**12** followed by hydrolysis with 2 N HCl and subsequent treatment of the hydrochloride salt with propylene oxide in methanol afforded the zwitterion of the final amino acid (+)-**3,** which possesses identical physicochemical properties to the one synthesized through the first method reported herein (Scheme 3).

Pharmacology

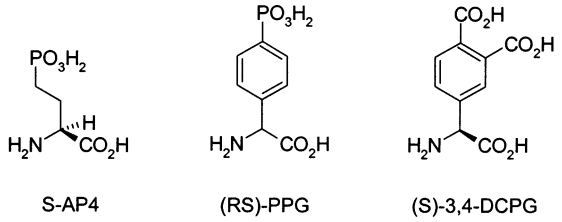
Racemic and enantiomerically purecompounds (±)-3 and (+)-**3** were evaluated in adult rat cerebral cortical slices for their ability to influence forskolin-stimulated c-AMP formation (group 2 and 3 mGluRs)[25] or basal [^{3}H]-IP formation (group 1 mGluR).[26] The data (EC_{50}) are shown in Table 1 along with other known CCG agonists and some representative group 3 mGluR selective agonists: L-1-amino-4-phosphonobutyric acid (L-AP4),

Scheme 4[a]



[a] (a) Diketene, AcONa, THF, reflux; (b) i. *p*-$AcNHC_6H_4SO_2N_3$, Et_3N, CH_3CN, room temperature, ii. LiOH, H_2O, room temperature; (c) $Rh_2(4S\text{-MPPIM})_4$, CH_2Cl_2, reflux; (d) i. 2.5 N LiOH, THF, room temperature, ii. CH_2N_2, Et_2O, 0 °C; (e) TBSCl, imidazole, DMF; room temperature; (f) i. KHMDS, THF, −78 to −10 °C, ii. TBAF, THF, 0 °C; (g) TPAP, NMO, mol sieves (4A), CH_2Cl_2; room temperature; (h) i. (*R*)-phenylglycinol, MeOH, room temperature, ii. TMSCN, room temperature; (i) i. $Pb(AcO)_4$, CH_2Cl_2, MeOH, 0 °C, ii. HCl/EtOH satd, H_2O, room temperature, iii. Boc_2O, $NaHCO_3$ satd, dioxane, room temperature; (j) H_2, 5% Pd/C, MeOH, room temperature; (k) i. 2.5 N LiOH, THF, room temperature, iii. 2 N HCl, room temperature, iii. propylene oxide, MeOH, room temperature.

Chart 3



(*RS*)-4-phosponophenylglycine ((*RS*)-PPG), and (*S*)-dicarboxyphenylglycine ((*S*)-3,4-DCPG) (see Chart 3).[27] The molecular pharmacology of group 3 mGluR is not as developed as that for groups 1 and 2. This is partially due to the greater diversity of receptor subtypes within this class and partially to the paucity of pharmacological tools developed to study these targets.

As shown in Table 1, compound (+)-**3** was identical to L-CCG-I in its biological profile through all mGluRs although 90-fold more potent for mGluR2/3 and 4- and 40-fold for mGluR6 and mGluR8, respectively. Therefore, the presence of the hydroxymethyl group in the same face as the amino acid center could be enhancing the population of the active conformation needed for effective interaction with the binding site of mGluR2, 3, 6, and 8, and/or providing an additional direct (e.g., H-bond) interaction with the receptor. Lack of data for group 3 mGluR for the methoxy analogue *cis*-MCG-1 precludes defining the role of a hydrogen bond interaction of the hydroxy functionality of compound (+)-**3**. The pure enantiomer (+)-**3** is the most potent cyclopropyl glycine thus far known for these mGluRs (2, 3, 6, and 8).

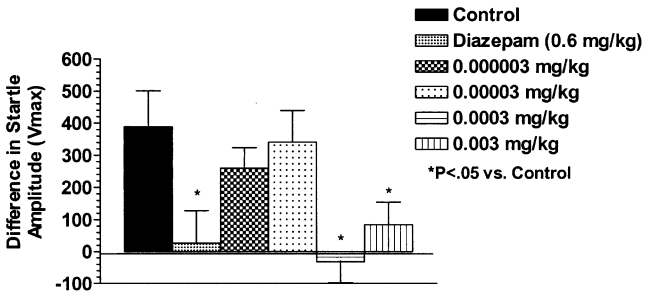


Figure 2. Effect of mGlu 2/3 and mGlu8 agonist (+)-**3** on fear potentiated startle. Diazepam (0.6 mg/kg) was given ip 30 min prior to testing. (+)-**3** was administered orally 60 min prior to testing. $*P < 0.05$.

Behavioral Pharmacology Studies

The recent years have seen a growing interest in the field of mGluR agonists, due to the intriguing therapeutic opportunities offered by their modulation. It is hoped that drugs targeted at mGluRs hold new promise to safely and effectively treat a wide range of psychiatric and neurological disorders. In particular, there is an accumulation of experimental evidence which implicates both groups 2 and 3 mGluRs in the treatment of schizophrenia,[28] anxiety,[29] drug withdrawal,[30] depression,[31] neuroprotection,[32] pain,[33] Alzheimer's disease,[34] epilepsy,[35] and Parkinson's disease.[36]

We studied the oral potencies of (+)-**3** in two mGluR2 linked therapeutic animal models: the fear-potentiated startle and PCP-induced hyperactivity assays in rats.

The rat fear-potentiated startle was specifically chosen, as it is highly sensitive to mGluR2 agonists and served as the basis for developing therapeutic agents for anxiety disorders in humans.[29] Diazepam (0.6 mg/kg i.p.) was used as a positive control in each experiment, and all experiments were performed in fed rats. As shown in Figure 2, (+)-**3** dose dependently blocked the fear-potentiated startle response in rats with a MED of 0.0003 mg/kg.

Drugs such as phencyclidine (PCP) and ketamine produce schizophrenia-like symptoms in humans.[28i] It was reported that group 2 agonists suppressed PCP-induced excitatory behaviors (hyperlocomotion, ambulations, stereotypy) in rats.[28a] As shown in Figure 3, oral administration of (+)-**3** attenuated PCP-induced ambulations (ED_{50} = 1.82 mg/kg), fine motor movements (MED = 3 mg/kg), and decreased time at rest (MED = 3 mg/kg) in rats. Similarly observed with previous ligands, the difference in potency detected for (+)-**3** in the fear-potentiated startle and the PCP in vivo animal models is due to their different sensitivity to group 2 mGluR selective agonists.[29a,28c]

In conclusion, we have shown that enantiomerically pure (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-carboxy-3′-hydroxymethylcyclopropyl) glycine **((**+)-**3)** is a highly potent agonist at mGluR2, 3, 6, and 8. Furthermore, (+)-**3** has been demonstrated to possess potent oral activity in animal models of anxiety and psychosis. Further studies directed at expanding the structure−activity relationship for this novel mGluR agonist platform will be reported in due course.

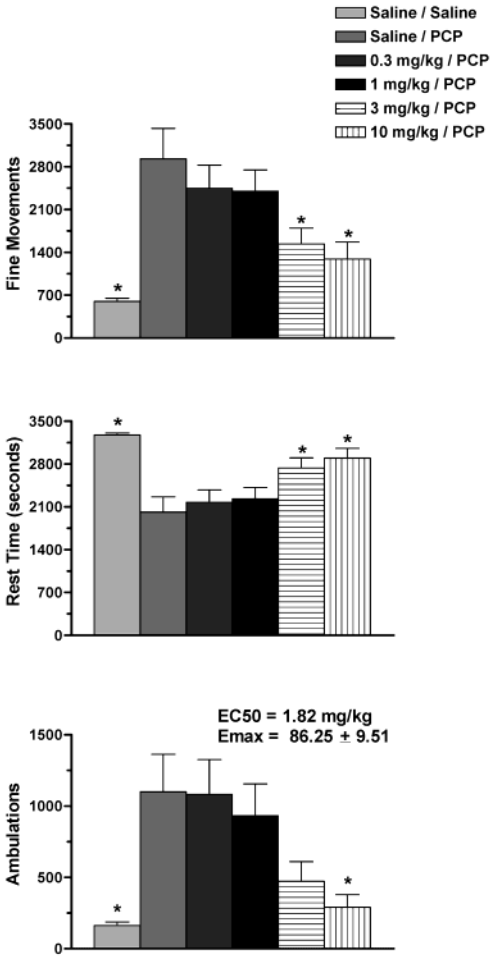


Figure 3. Effect of mGlu 2/3 and mGlu8 agonist (+)-**3** on PCP (5 mg/kg) evoked behaviors. (+)-**3** or vehicle was administered orally 2 h prior to PCP or vehicle s.c. injection. Behaviors were monitored over a 60 min time period immediately after injection of PCP. Data (mean + S.E.) are presented as total number of behaviors expressed during 60 min; $n = 8$ rats. *$P < 0.05$. When compared to saline/PCP control EC_{50} calculated (nonlinear regression sigmoidal dose response variable slope) is amount of drug to inhibit the PCP-evoked response of ambulations by 50%. E_{max} is the maximum percent effect of the compound.

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-DRX (500 MHz) spectrometer. Chemical shifts are reported as ppm (δ) relative to 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 and with a Bellingham Stanley ADP-220. Analytical 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 in the Universidad Complutense Analytical Centre (Facultad de Farmacia), Madrid. PCP was obtained from Sigma (St. Louis, MO).

Animals. All experiments were performed in accordance with Eli Lilly and Company animal care and use policies, each animal being used on only one occasion. Male Sprague Dawley rats (225−274 g) were obtained from Harlan Industries, Indianapolis, IN. Animals were group housed (maximum eight rats per cage) under standard laboratory conditions (12 h light/dark cycle) with ad libitum access to water and feed for at least 1 day prior to overnight fasting for use in oral dosing studies.

Ethyl (2*SR*,3*RS*)-2,3-Dihydroxymethylcyclopropane Carboxylate (9). To a solution of *cis*-4,7-dihydro-1,3-dioxepin (10.0 g, 99.9 mmol) in CH_2Cl_2 (50 mL) was added $Rh_2(OAc)_4$ (442 mg, 1.0 mmol). The resulting suspension was allowed to stir vigorously at reflux while a solution of ethyl diazoacetate (22.0 mL, 209.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise over a period of 5−6 h. After the addition was completed, the reaction was allowed to stir for 15 min followed by cooling to room temperature and filtering through a plug of silica gel. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (AcOEt/hexane 1:10 and then 1:5) to afford 17.5 g of an inseparable mixture of cyclopropanated product **8** and both isomers of $EtO_2CCH{=}CHCO_2Et$. This mixture was taken into 0.5 N HCl/EtOH (400 mL, 200 mmol) and allowed to stir under reflux for 2−3 h (until TLC showed no starting material) at which time the solvent was removed in vacuo. The residue was dissolved in EtOH (200 mL) and concentrated to dryness in vacuo. The residue was taken up again in EtOH (200 mL), and the resulting solution was neutralized with $NaHCO_3$ (solid). The mixture was allowed to stir for 30 min, filtered, and concentrated. The resulting residue was purified by column chromatography (AcOEt/hexane 1:1 and then 3:1) to give diol **9** (11.0 g, 63%) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 1.23 (t, $J = 7.1$ Hz, 3H), 1.49 (t, $J = 3.5$, 1H), 1.89−2.00 (m, 2H), 2.72 (br s, 2H), 3.31−3.42 (m, 2H),4.05−4.16 (m, 2H) and 4.10 ppm (c, $J = 7.1$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.0, 23.8, 27.1 (2C), 60.3 (2C), 60.8 and 172.8 ppm. Anal. ($C_8H_{14}O_4$) C; H.

Ethyl (1*RS*,5*SR*,6*RS*)-2-Hydroxy-3-oxabicyclo[3.1.0]-hexane-6-carboxylate ((±)-6). To a solution of ethyl (2*SR*,3*RS*)-2,3-dihydroxymethylcyclopropane carboxylate **(9)** (10.5 g, 60.3 mmol) in CH_3CN (150 mL) at room temperature was added activated MnO_2 (29.1 g mL, 301.5 mmol) followed by stirring for 24 h at which time additional MnO_2 (29.1 g, 301.5 mmol) was added followed by stirring an additional 24 h. The mixture was poured onto a stirring suspension of silica gel (20 g) in AcOEt (450 mL), and the resulting mixture was filtered through a plug of Celite. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (AcOEt/hexane 1:2 and then 1:1) to afford lactol **(**±**)-6** (8.7 g, 83%). ^{1}H NMR (200 MHz, $CDCl_3$): 1.23 (t, $J = 7.1$ Hz, 3H), 1.43 (t, $J = 3.3$ Hz, 1H), 2.21−2.23 (m, 2H), 2.76 (d, $J = 3.0$ Hz, 1H), 3.85 (d, $J = 8.7$ Hz, 1H), 4.06 (d, $J = 8.7$ Hz, 1H), 4.10 (c, $J = 7.1$ Hz, 2H), and 5.32 (d, $J = 3.0$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 22.1, 25.0, 31.2, 60.8, 67.3, 97.8, and 171.9 ppm.

Ethyl (2*RS*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) Glycinate (11); and Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) Glycinate ((±)-12). Method A. A suspension of NH_4Cl (2.42 g, 45.3 mmol) and neutral aluminum oxide (1.4 g) in CH_3CN (50 mL) was ultrasonicated for 1 h. A solution of ethyl (1*RS*,5*SR*,6*RS*)-2-hydroxy-3-oxabicyclo[3.1.0]-hexane-6-carboxylate **(**±**)-6**) (780 mg, 4.53 mmol) in CH_3CN (20 mL) was added to the mixture, and the reaction was ultrasonicated for 1 h at which time finely powdered KCN (3.54 g, 54.36 mmol) was added and the mixture was allowed to react for 15 h. Additional aluminum oxide (3.2 g) was added to the reaction mixture, and it was ultrasonicated for an additional 4 days. The mixture was then filtered through a plug of Celite, and the inorganics were washed with CH_3CN to give 710 mg of a 2:1 mixture of the two possible racemic aminonitriles **(**±**)-10** as a yellow oil that was used without further purification. A solution of **(**±**)-10** (380 mg, 1.92 mmol) in HCl/EtOH (saturated) (20 mL) and H_2O (0.10 mL, 5.75 mmol) was stirred for 1 h at 0 °C and for 48 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in absolute EtOH (25 mL). The resulting solution was evaporated under reduced pressure, and the residue was taken up again

in absolute EtOH (25 mL). This procedure was repeated three times followed by neutralization with $NaHCO_3$ (solid), stirring for 1 h, filtering through a plug of Celite, and concentration to dryness. A dioxane (20 mL) solution of the resulting residue was treated with a saturated aqueous solution of $NaHCO_3$ (5 mL) followed by a solution of di-*tert*-butyl dicarbonate (500 mg, 2.3 mmol) in dioxane (5 mL). The mixture was allowed to stir overnight, at which time the layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography (AcOEt/hexane 1:2) to give 400 mg (61% overall yield) of a 2:1 mixture of racemic diastereoisomers **(±)-11** and **(±)-12**. After separation of both isomers by column chromatography (Et_2O/hexane 1:1), the more abundant constituent of the mixture was determined to be racemic ethyl (2*RS*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-11)** whereas the minor diastereoisomer (with lower R_f) was assigned as the desired racemic ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-12)**.

Method B. A solution of ethyl (1*RS*,5*SR*,6*RS*)-2-hydroxy-3-oxabicyclo[3.1.0]-hexane-6-carboxylate **((±)-6)** (6.8 g, 39.5 mmol) in EtOH (95 mL) and 1 N NaOH (47.4 mL, 47.4 mmol) was allowed to stir at 60 °C for 2 h. To the resulting solution was added a suspension of $(NH_4)_2CO_3$ (34.3 g, 355.5 mmol) and NaCN (9.7 g, 197.5 mmol) in H_2O (50 mL). The mixture was allowed to stir under reflux for 3 days and then cooled to room temperature. The EtOH was removed in vacuo and the resulting aqueous solution was cooled to 0 °C while the pH was adjusted to ∼6 by the addition of 1 N $KHSO_4$. The solution was evaporated to dryness in vacuo to give a residue that was dissolved in 1 N NaOH (400 mL, 400 mmol) followed by stirring under reflux for 48 h. Upon cooling to 0 °C the pH was adjusted to 1−2 by addition of 1 N HCl followed by removal of the solvent in vacuo. The resulting residue was dissolved in a 1 N HCl/EtOH (400 mL, 400 mmol), and the mixture was stirred for 2 days at room temperature. The solvent was removed in vacuo and residue taken into EtOH (200 mL). After solvent was removed in vacuo, the residue was again taken into EtOH (200 mL) and the solution was neutralized with $NaHCO_3$ (solid) and stirred for 1 h. The inorganics were filtered off and the solvent was removed in vacuo. The residue was dissolved in dioxane (300 mL) at room temperature, and a saturated aqueous solution of $NaHCO_3$ (∼100 mL) was added (until pH was adjusted to ∼8). The mixture was treated with a dioxane (100 mL) solution of di-*tert*-butyl dicarbonate (10.4 g, 47.4 mmol) dropwise followed by vigorous stirring at room temperature overnight. The mixture was diluted with AcOEt, and the layers were separated. The aqueous layer was extracted with AcOEt (2×), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography (AcOEt/hexane 1:2) to give 8.1 g (60% overall yield) of a 1:2.3 mixture of racemic diastereoisomers **(±)-11** and **(±)-12**, respectively. After separation of both isomers by column chromatography (Et_2O/hexane 1:1), the more abundant constituent of the mixture (with lower R_f) was determined to be the desired racemic ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-12)** whereas the minor diastereoisomer was the racemic ethyl (2*RS*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-11)**.

(±)-11: Ethyl (2*RS*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) Glycinate. ^{1}H NMR (300 MHz, $CDCl_3$): 1.18 (t, J = 7.1 Hz), 3H, 1.25 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H), 1.57−1.65 (m, 1H), 1.70 (t, J = 4.9 Hz, 1H), 1.84−1.92 (m, 1H), 3.49 (t, J = 10.4 Hz, 1H), 3.97−4.30 (m, 6H), 5.60 (br d, J = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 14.1, 21.6, 28.2 (3C), 28.4, 29.6, 50.9, 59.4, 60.7, 61.9, 81.1, 155.9, 171.1, 172.3. Mp <50 °C. Anal. ($C_{16}H_{27}NO_7$) C, H, N.

(±)-12: Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) Glycinate. ^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.70−1.81 (m, 2H), 1.91−2.11 (m, 1H), 3.17 (dd, J = 3.1, 10.1 Hz, 1H), 3.54−3.67 (m, 1H), 3.95−4.33 (m, 5H), and 5.20 (br d, J = 7.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.0, 14.1, 22.5, 28.2 (3C), 28.9, 29.2, 52.3, 60.8, 61.0, 62.5, 80.4, 155.3, 171.8, and 172.4 ppm. Anal. ($C_{16}H_{27}NO_7$) C, H, N.

Ethyl (1*SR*,2*RS*,5*RS*,6*RS*)-3-(*tert*-Butoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2,6-dicarboxylate ((±)-13). To a solution of ethyl (2*RS*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-11)** (74 mg, 0.21 mmol) in acetone (2 mL) at 0 °C was added Jones reagent (0.63 mL, previously cooled to 0 °C) dropwise. The reaction mixture was stirred for 1 h at 0 °C and 2 h at room temperature after which time H_2O (2 mL) and ^{i}PrOH (2 mL) were added followed by extraction with AcOEt (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (AcOEt) to give **(±)-13** (68 mg, 97%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz), 1.46 (s, 9H), 1.95 (dd, 1H, J_1 = 3.2 Hz, J_2 = 2.9 Hz), 2.42 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.9 Hz), 2.53 (dd, 1H, J_1 = 6.4 Hz, J_2 = 3.2 Hz), 4.16 (q, 2H, J = 7.1 Hz), 4.21−4.32 (m, 2H), and 4.57 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.4, 14.5, 22.6, 25.7, 28.2 (3C), 29.0, 60.3, 62.1, 62.6, 84.4, 149.4, 169.3, 169.4, and 169.9 ppm. Mp 78−81 °C. Anal. ($C_{16}H_{23}NO_7$) C, H, N.

Ethyl (1*SR*,2*SR*,5*RS*,6*RS*)-3-(*tert*-Butoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2,6-dicarboxylate ((±)-14). To a solution of ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-12)** (100 mg, 0.29 mmol) in acetone (2 mL) at 0 °C was added Jones reagent (0.87 mL, previously cooled to 0 °C) dropwise. The reaction mixture was stirred for 1 h at 0 °C and 2 h at room temperature after which time H_2O (2 mL) and ^{i}PrOH (2 mL) were added followed by extraction with AcOEt (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (AcOEt) to give **(±)-14** (92 mg, 97%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (t, 3H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz), 1.49 (s, 9H), 2.36 (dd, 1H, J_1 = 3.3 Hz, J_2 = 2.8 Hz), 2.56 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.8 Hz) 2.65 (dt, 1H, J_1 = 6.5 Hz, J_2 = 3.3 Hz), 4.13−4.21 (m, 2H), 4.26−4.34 (m, 2H), and 4.76 (d, 1H, J = 6.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5, 13.6, 21.5, 21.7, 27.3 (3C), 28.6, 58.1, 61.4, 61.7, 83.3, 148.1, 168.1, 168.7, and 168.9 ppm. Mp 78−80 °C. Anal. ($C_{16}H_{23}NO_7$) C, H, N.

(2*SR*,1′*SR*,2′*RS*,3′*RS*)-2-(2′-Carboxy-3′-hydroxymethylcyclopropyl) Glycine ((±)−3). To a solution of ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-12)** (145 mg, 0.42 mmol) in THF (3.5 mL) was added 2.5 N LiOH (6.7 mL, 16.8 mmol). The mixture was vigorously stirred overnight. The organic layer was separated and discarded, and the aqueous layer was 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) and evaporated under reduced pressure. A solution of the residue in 2 N HCl (3.5 mL) was stirred overnight. The solvent was then removed in vacuo, and the resulting solid was washed with Et_2O. The resulting hydrochloride salt was dissolved in MeOH (3 mL), and propylene oxide (10 mL) was added. The mixture was stirred overnight and the resulting insoluble solid was filtered and washed with Et_2O to give **(±)-3** (55 mg, 69% overall yield) as a white solid. ^{1}H NMR (200 MHz, D_2O): 1.77−2.11 (m, 3H), 3.62 (d, J = 11.0 Hz, 1H), 3.66 (dd, J = 8.6, 12.5 Hz, 1H), and 3.90 ppm (dd, J = 6.0, 12.5 Hz, 1H). ^{13}C NMR (50 MHz, D_2O): 25.0, 27.7, 29.1, 54.8, 61.0, 173.9, and 177.9 ppm. Mp 154−156 °C. Anal. ($C_7H_{11}NO_5$) C, H, N.

(2*R*,1′*R*,2′*S*,3′*S*)-2-(2′-Carboxy-3′-hydroxymethylcyclopropyl) Glycine ((−)-3) and (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-Carboxy-

3′-hydroxymethylcyclopropyl) Glycine ((+)-3). The corresponding enantiomers of ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-(2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl) glycinate **((±)-12)** were separated by chiral HPLC using the following analytical method: Chiralpak AD 4.6 × 250 mm column; eluent, 10% MeOH, 10% IPA in heptane; flow, 1.0 mL/min; UV, 220 nm. Retention time for (−)-**12**: 5.5 min. Retention time for (+)-**12**: 7.0 min. Once both isomers were separated, they were further purified by silica gel chromatography (AcOEt/hexane 1:1).

To a stirred solution of either (−)-**12** or (+)-**12** (1 equiv) in CH_2Cl_2 (2 mL/mmol) at 2 °C was added TFA (10 equiv) over a few minutes, maintaining the temperature below 5 °C. The mixture was allowed to warm to room temperature with stirring for 2.5 h. The mixture was evaporated under reduced pressure to give a faint yellow oil. The oil was dissolved in CH_2Cl_2 (1.2 mL/mmol), and the volatiles were evaporated (3×). This process was repeated using EtOH (3 × 1.3 mL/mmol) to afford a faint yellow oil which was dissolved in 3 N NaOH (5 equiv) using a water bath to maintain the temperature slightly above ambient temperature. The faint yellow homogeneous mixture was stirred for 1.25 h before the pH was slowly lowered to 3.5 using concentrated HCl. Once crystallization initiated, the pH was adjusted to 2.55 over 10 min using concentrated HCl. The suspension was cooled to 2 °C and allowed to stir for 2.25 h before the white solid was collected and washed with cold water (1 × 12 mL, 2 × 5 mL). The material was dried in vacuo for several hours at 38 °C and for 2.5 days at room temperature, affording (−)-**3** from (−)-**12** or (+)-**3** from (+)-**12** (87% yield). (−)-**3**: $[\alpha]^{20}_D$ −4.1 (*c* 1.1, 1 N NaOH). (+)-**3**: $[\alpha]^{20}_D$ +3.3 (*c* 1.1, 1 N NaOH).

***cis*-4-Benzyloxy-2-buten-1-yl Acetoacetate (17).** To a solution of *cis*-4-benzyloxy-2-buten-1-ol **(16)** (5.0 g, 28.1 mmol) in anhydrous THF (20 mL) was added sodium acetate (0.14 g, 1.7 mmol). The mixture was heated at reflux, and a solution of freshly distilled diketene (2.4 mL, 31.5 mmol) in anhydrous THF (10 mL) was added dropwise over 1 h. The reaction mixture was refluxed for an additional 30 min upon completion of the addition. The mixture was cooled and Et_2O (30 mL) and saturated aqueous sodium chloride (50 mL) were added. The organic layer was extracted, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column of chromatography (AcOEt/hexane 1:4) to afford product **17** (6.70 g, 91% overall yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 2.24 (s, 3H), 3.44 (s, 2H), 4.12 (d, 2H, J = 5.5 Hz), 4.51 (s, 2H), 4.69 (d, 2H, J = 6.6 Hz), 5.66−5.74 (m, 1H), 5.80−5.88 (m, 1H), and 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 30.0, 49.7, 60.9, 65.4, 72.3, 125.8, 127.5, 127.6, 128.3, 131.2, 137.8, 166.7, and 200.2. Anal. ($C_{15}H_{18}O_4$) C, H.

***cis*-4-Benzyloxy-2-buten-1-yl diazoacetate (18).** To a solution of *cis*-4-benzyloxy-2-buten-1-yl acetoacetate **(17)** (4.78 g, 18.2 mmol) in anhydrous CH_3CN (50 mL) was added Et_3N (3.2 mL, 23.5 mmol). The reaction mixture was treated with a solution of *p*-acetamidobezenesulfonyl azide (5.7 g, 23.7 mmol) in anhydrous CH_3CN (50 mL) dropwise over 30 min. After the mixture was stirred for 2.5 h at room temperature, 3 N LiOH (19.8 mL, 59.4 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with Et_2O/AcOEt 2:1 (2 × 60 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (AcOEt/hexane 1:10) to afford product **18** (3.73 g, 83% overall yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 4.12 (d, 2H, J = 6.0 Hz), 4.51 (s, 2H), 4.71 (d, 2H, J = 6.6 Hz), 4.74 (s, 1H), 5.66−5.74 (m, 1H), 5.79−5.87 (m, 1H), 7.73 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 46.1, 60.5, 65.5, 72.4, 126.5, 127.6, 127.7, 128.3, 130.9, 137.9, 160.5.

(1*R*,5*S*,6*R*)-6-Benzyloxymethyl-3-oxabicyclo[3.1.0]hexan-2-one ((−)-19). To a suspension of Rh_2(4*S*-MPPIM)$_4$ (47.8 mg, 0.034 mmol) in anhydrous CH_2Cl_2 (50 mL) under reflux was added a solution of *cis*-4-benzyloxy-2-buten-1-yl diazoacetate **(18)** (1.8 g, 7.3 mmol) in anhydrous CH_2Cl_2 (100 mL) dropwise overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane 1:5) to afford (−)-**19** (1.03 g, 65% overall yield, 86% conversion, ee >95%) as a colorless oil. $[\alpha]^{20}_D$ = −24.2° (*c* 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.77−1.87 (m,1H), 2.27 (dd, 1H, J_1 = 8.8 Hz, J_2 = 6.0 Hz), 2.38 (dd, 1H, J_1 = 12.6 Hz, J_2 = 6.0 Hz), 3.42 (dd, 1H, J_1 = 10.4 Hz, J_2 = 8.8 Hz), 3.69 (dd, 1H, J_1 = 10.4 Hz, J_2 = 6.6 Hz), 4.20 (d, 1H, J = 9.9 Hz), 4.39 (dd, 1H, J_1 = 9.9 Hz, J_2 = 4.9 Hz), 4.49 (d, 1H, J = 11.5 Hz), 4.56 (d, 1H, J = 11.5 Hz), 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 22.2, 22.3, 64.6, 66.3, 73.2, 127.7, 127.8,. 128.4, 137.6, 174.2. Anal. ($C_{13}H_{14}O_3$) C, H.

Methyl (1*S*,2*R*,3*S*)-2-benzyloxymethyl-3-hydroxymethylcyclopropane Carboxylate ((−)-20). To a solution of (1*R*,5*S*,6*R*)-6-benzyloxymethyl-3-oxabicyclo[3.1.0]hexan-2-one **((−)-19)** (0.70 g, 3.2 mmol) in anhydrous THF (20 mL) was added 2.5 N LiOH (51.1 mL, 127.7 mmol). After being stirred at room temperature for 2 h, the mixture was neutralized with 5% citric acid and extracted with AcOEt. The organic layer was then dried ($MgSO_4$), filtered, and concentrated in vacuo. A solution of the residue in Et_2O (30 mL) at 0 °C was treated with a recently prepared CH_2N_2 solution in Et_2O at 0 °C (until the yellow color is retained). The mixture was stirred for 1 h and concentrated in vacuo. Purification of the crude residue by column chromatography (AcOEt/hexane 1:5) afforded (−)-**20** (0.65 g, 81%) as coloroless oil. $[\alpha]^{20}_D$ = −14.3° (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.75−1.83 (m, 2H), 1.90−1.96 (m, 1H), 3.65 (s, 3H), 3.76−3.89 (m, 2H), 3.94−4.05 (m, 2H), 4.53 (s, 2H), 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 20.7, 22.6, 25.3, 51.5, 56.9, 64.2, 73.0, 127.6, 127.7, 128.3, 137.5, 171.6. Anal. ($C_{14}H_{18}O_4$) C, H.

Methyl(1*R*,2*R*,3*S*)-2-Benzyloxymethyl-3-(*tert*-butyldimethylsilyl)oxymethylcyclopropane Carboxylate ((−)-21). To a solution of methyl (1*S*,2*R*,3*S*)-2-benzyloxymethyl-3-hydroxymethylcyclopropane carboxylate **((−)-20)** (0.65 g, 2.6 mmol) in DMF (20 mL) was added imidazole (0.44 g, 6.5 mmol) and *tert*-butyldimethylsilil chloride (1.42 g, 9.0 mmol). The mixture was stirred at room temperature for 2 h, and a mixture of ice−water and Et_2O (30 mL) was then added. The organic layer was washed with H_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude residue by column chromatography (AcOEt/hexane 1:99) afforded (−)-**21** (0.83 g, 88%) as coloroless oil. $[\alpha]^{20}_D$ = −7.0° (*c* 0.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.20 (s, 3H), 0.21 (s, 3H), 1.04 (s, 9H), 1.85−1.94 (m, 2H), 2.03−2.09 (m, 1H), 3.80 (s,3H), 3.98 (dd, 1H, J_1 = 10.4 Hz, J_2 = 7.1 Hz), 4.08 (dd, 2H, J_1 = 9.3 Hz, J_2 = 6.0 Hz), 4.18 (dd, 1H, J_1 = 10.4 Hz, J_2 = 6.0 Hz), 4.66 (dd, 2H, J_1 = 15.4 Hz, J_2 = 11.5 Hz), 7.43−7.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): −5.4, 18.1, 19.8, 23.6, 25.7, 26.1, 51.3, 57.1, 64.2, 72.8, 127.4, 127.6, 128.2, 138.3, 171.6.

Methyl (1*R*,2*R*,3*S*)-2-Benzyloxymethyl-3-hydroxymethylcyclopropane Carboxylate ((−)-22). To a solution of methyl (1*R*,2*R*,3*S*)-2-benzyloxymethyl-3-(*tert*-butyldimethylsilil)oxymethylcyclopropane carboxylate **((−)-21)** (0.45 g, 1.22 mmol) in anhydrous THF (40 mL) at −78 °C under nitrogen was added a 0.5 M KHMDS solution in toluene (2.8 mL, 1.4 mmol). The mixture was stirred for 2.5 h and then allowed to react by warming to −10 °C. After 10 min at −10 °C, the reaction was cooled again to −78 °C and quenched with a saturated aqueous solution of NH_4Cl (25 mL). The aqueous layer was extracted twice with AcOEt, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The resulting residue was dissolved in anhydrous THF (25 mL), and tetrabuthylamonium fluoride (2.5 mL, 1 M) was added at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. After hexane (10 mL), Et_2O (20 mL), and H_2O (50 mL) were added, the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (AcOEt/hexane 1:4) to afford (−)-**22** (0.22 g, 70%) as a colorless oil. $[\alpha]^{20}_D$ = −23.2° (*c* 0.44, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.51 (t, 1H, J = 4.4 Hz), 1.95−1.98 (m, 2H), 3.24−3.35 (m, 2H), 3.65 (s, 3H), 3.85−3.93 (m, 2H), 4.49 (d, 1H, J = 11.5 Hz), 4.58 (d, 1H, J = 11.5 Hz), and 7.29−7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$):

23.8, 24.4, 27.7, 51.8, 60.6, 67.9, 73.0, 127.8, 127.9, 128.4, 136.9, 172.7. Anal. ($C_{14}H_{18}O_4$) C, H.

Methyl (1*S*,2*S*,3*R*)-3-Benzyloxymethyl-2-formylcyclopropane Carboxylate ((+)-23). To a solution of methyl (1*R*,2*R*,3*S*)-2-benzyloxymethyl-3-hydroxymethylcyclopropane carboxylate ((−)-**22**) (0.22 g, 0.86 mmol) in CH_2Cl_2 (10 mL) at room temperature and under argon was added molecular sieves (4 Å) (0.4 g). After the mixture was stirred for 5 min, NMO (0.15 g, 1.3 mmol) and TPAP (0.006 g, 0.02 mmol) were added and the mixture stirred overnight at which time the reaction was filtered through a plug of Celite and the solvent was removed in vacuo. The residue was purified by column chromatography (AcOEt/hexane 1:4) to afford (+)-**23** (0.19 g, 89%) as coloroless oil. $[\alpha]^{20}_D = +58.9°$ (*c* 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 2.27−2.36 (m, 1H), 1.51 (t, 1H, *J* = 6.0 Hz), 2.56−2.62 (m, 1H), 3.47 (dd, 1H, J_1 = 10.4 Hz, J_2 = 7.7 Hz), 3.70 (s, 3H), 3.78 (dd, 1H, J_1 = 10.4 Hz, J_2 = 5.5 Hz), 4.45 (t, 2H, *J* = 12.6 Hz), 7.26−7.32 (m, 5H), 9,58 (d, 1H, *J* = 2.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 25.4, 30.0, 34.3, 52.1, 65.4, 72.9, 127.6, 127.7, 128.3, 137.4, 171.0, 196.9.

(2*S*,1′*S*,2′*R*,3′*R*,1″*R*)-*N*-[(2″-Hydroxy-1″-phenyl)ethyl]-2-[3′-benzyloxymethyl-2′-(methoxycarbonyl)cyclopropyl] Glycinonitrile ((−)-24). To a solution of methyl (1*S*,2*S*,3*R*)-3-benzyloxymethyl-2-formylcyclopropane carboxylate **(**(+)-**23)** (0.15 g, 0.6 mmol) in MeOH (5 mL) was added (*R*)-α-phenylglycinol (0.08 g, 0.62 mmol). The resulting solution was stirred at room temperature for 2 h and then cooled to 0 °C. Trimethylsilylcyanide (0.12 g, 1.2 mmol) was added, and the resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo to afford a mixture of diastereomeric aminonitriles (0.20 g, 91%). The major diastereoisomer (−)-**24** was separated and purified by column chromatography (AcOEt/hexane 1:2) to give 0.18 g as colorless oil. $[\alpha]^{20}_D = -70.5°$ (*c* 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.86 (t, 1H, *J* = 4.9 Hz), 1.95−2.00 (m, 2H), 3.45−3.60 (m, 3H), 3.63−3.69 (m, 4H), 3.69−3.80 (m, 1H), 4.04 (dd, 1H, J_1 = 8.8 Hz, J_2 = 3.8 Hz), 4.42 (s, 2H), 7.22−7.54 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): 23.5, 24.9, 27.3, 46.1, 52.0, 62.7, 66.2, 67.0, 72.7, 118.7, 127.4, 127.7, 127.8, 128.1, 128.3, 128.7, 137.2, 137.9, 172.5. Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

Ethyl (2*S*,1′*S*,2′*R*,3′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[3′-benzyloxymethyl-2′-(ethoxycarbonyl)cyclopropyl] Glycinate ((+)-25). Lead tetraacetate (0.18 g, 0.42 mmol) was added to a solution of the (2*S*,1′*S*,2′*R*,3′*R*,1″*R*)-*N*-[(2″-hydroxy-1″-phenyl)ethyl]-2-[3′-benzyloxymethyl-2′-(methoxycarbonyl)-cyclopropyl] glycinonitrile **(**(−)-**24)** (0.15 g, 0.39 mmol) in a 1:1 mixture of CH_2Cl_2−MeOH (10 mL) at 0 °C followed by stirring for 10 min. The mixture was treated with H_2O (10 mL) and passed through Celite. The filtrate was concentrated in vacuo, and the residue was dissolved in HCl/EtOH (saturated) (15 mL) at 0 °C followed by treatment with H_2O (0.21 mL, 1.17 mmol). After the mixture was stirred at room temperature for 18 h, the solvents were evaporated under reduced pressure leaving behind a residue that was taken into EtOH. The solution was neutralized with $NaHCO_3$ (solid) and concetrated in vacuo to give a residue which was taken into dioxane (15 mL) at room temperature and treated with a saturated aqueous solution of $NaHCO_3$ (until pH was adjusted to ∼8). A solution of di-*tert*-butyl dicarbonate (0.1 g, 0.47 mmol) in dioxane (3 mL) was added dropwise, and the mixture was vigorously stirred at room temperature overnight followed by dilution with AcOEt and layer separation. The aqueous layer was extracted with AcOEt (2×), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography (AcOEt/hexane 1:4) to give 0.11 g (65% overall yield) of product (+)-**25** as a yellow oil. $[\alpha]^{20}_D = +28.7°$ (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.21−1.28 (m, 6H), 1.42 (s, 9H), 1.71−1.94 (m, 3H), 3.60 (dd, 1H, J_1 = 10.4 Hz, J_2 = 6.6 Hz), 3.80 (dd, 1H, J_1 = 9.9 Hz, J_2 = 4.9 Hz), 4.09−4.22 (m, 5H), 4.51−4.55 (m, 2H), 5.31 (d, 1H, *J* = 8.2 Hz), 7.29−7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 14.1, 23.7, 26.3, 28.2, 28.5, 52.2, 60.8, 61.4, 61.6, 72.9, 80.1, 127.7, 127.8, 128.4, 137.8, 155.2, 172.2, 172.7. Anal. ($C_{23}H_{33}NO_7$) C, H, N.

Ethyl (2*S*,1′*S*,2′*R*,3′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[2′-ethoxycarbonyl-3′-hydroxymethylcyclopropyl] Glycinate ((+)-12). To a solution of ethyl (2*S*,1′*S*,2′*R*,3′*R*)-*N*-(*tert*-butoxycarbonyl)-2-[3′-benzyloxymethyl-2′-(ethoxycarbonyl)-cyclopropyl] glycinate **(**(+)-**25)** (0.030 g, 0.07 mmol) in MeOH (3 mL) was added Pd (C) 5% (0.006 g, 20 wt %). The mixture was stirred under hydrogen (balloon) at room temperature for 6 h and filtered through Celite, and the solvent was evaporated in vacuo to afford (+)-**12** (0.023 g, 96%) as a colorless oil. $[\alpha]^{20}_D = +32.6°$ (*c* 0.46, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (t, 3H, *J* = 7.1 Hz), 1.32 (t, 3H, *J* = 7.1 Hz), 1.45 (s, 9H), 1.70−1.81 (m, 2H), 1.91−2.11 (m, 1H), 3.17 (dd, 1H, J_1 = 10.1 Hz, J_2 = 3.1 Hz), 3.54−3.67 (m, 1H), 3.95−4.33 (m, 6H), 5.20 (br d, 1H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 14.1, 22.5, 28.2, 28.9, 29.2, 52.3, 60.8, 61.0, 62.5, 80.4, 155.3, 171.8, 172.4.

(2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-Carboxy-3′-hydroxymethylcyclopropyl) Glycine ((+)-3). Isolated as a white solid in 71% yield from (+)-**12** according to the same procedure described for preparing **(**±)-3. $[\alpha]^{20}_D$ +3.4 (*c* 1.1, 1 N NaOH). ^{1}H NMR (200 MHz, D_2O): 1.77−2.11 (m, 3H), 3.62 (d, *J* = 11.0 Hz, 1H), 3.66 (dd, *J* = 8.6, 12.5 Hz, 1H), and 3.90 ppm (dd, *J* = 6.0, 12.5 Hz, 1H). ^{13}C NMR (50 MHz, D_2O): 25.0, 27.7, 29.1, 54.8, 61.0, 173.9, and 177.9 ppm. Mp 155−156 °C. Anal. ($C_7H_{11}NO_5$) C, H, N.

Biological Assay. 1. Receptor Functional Assay.[13] **2. Fear Potentiated Startle Assay.**[13] **3. PCP-Induced Motor Activation Assay.** Compound (+)-**3** was tested against PCP-induced motor activation (ambulations) in rats. Behavioral parameters were monitored in transparent, shoebox cages that measured 45 × 25 × 20 cm, with a 1 cm depth of wood chips on the cage floor and a metal grill on top of the cage. Rectangular photocell monitors (Hamilton Kinder, Poway, CA) with a bank of 12 photocell beams (8 × 4 formation) surrounded each test cage. A lower rack of photocell beams was positioned 5 cm above the cage floor to enable detection of the location of the animals body, while an upper bank positioned 10 cm above the first tabulated rearing activity. Ambulations (locomotor activity) and rearing were recorded by the computer and stored for each test session. Male Sprague−Dawley rats were generally food-fasted 12−18 h prior to the experiment. In some experiments, rats were allowed food and water ad libitum prior to the experiment. On the test day animals were placed in the test cage for a 30-min habituation period before testing to allow for acclimation to the test cage environment. Following this habituation period, animals were administered challenges of PCP (5 mg/kg s.c.) or 0.9% NaCl vehicle (1 mL/kg) and behavioral assessment began immediately following their administration. Animals were monitored over a 60 min period in all instances. Compound (+)-**3** or vehicle were administered at various pretreatment times prior to the PCP challenge.[37] Statistical analysis was carried out using the GraphPad PRISM statistical/graphing package (GraphPad, San Diego, CA). Data were analyzed using a one-way analysis of variance (ANOVA) and post-hoc comparisons were performed using Dunnett's multiple comparisons test. Significance from PCP control is indicated by an asterisk, $*p < 0.05$.

Acknowledgment. We thank Dr. James A. Monn and Dr. Juan F. Espinosa for their helpful collaboration.

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JM030967O