# 2-Substituted (2*SR*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)glycines as Potent and Selective Antagonists of Group II Metabotropic Glutamate Receptors. 2. Effects of Aromatic Substitution, Pharmacological Characterization, and Bioavailability

Paul L. Ornstein,* Thomas J. Bleisch, M. Brian Arnold, Joseph H. Kennedy, Rebecca A. Wright, Bryan G. Johnson, Joseph P. Tizzano, David R. Helton, Mary Jeanne Kallman, and Darryle D. Schoepp

*Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285*

Marc Hérin

*Lilly Development Centre S.A., Parc Scientifique de Louvain-la-Neuve, Rue Granbonpre, 11, 1348 Mont Saint-Guibert, Belgium*

*Received July 30, 1997*

In this paper we describe the synthesis of a series of α-substituted analogues of the potent and selective group II metabotropic glutamate receptor (mGluR) agonist (1S,1′S,2′S)-carboxycyclopropylglycine (**2**, L-CCG 1). Incorporation of a substituent on the amino acid carbon converted the agonist **2** into an antagonist. All of the compounds were prepared and tested as a series of four isomers, i.e., two racemic diastereomers. On the basis of the improvement in affinity realized for the α-phenylethyl analogue **3**, in this paper we explored the effects of substitution on the aromatic ring as a strategy to increase the affinity of these compounds for group II mGluRs. Affinity for group II mGluRs was measured using [$^3$H]glutamic acid (Glu) binding in rat forebrain membranes. Antagonist activity was confirmed for these compounds by measuring their ability to antagonize (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid-induced inhibition of forskolin stimulated cyclic-AMP in RGT cells transfected with human mGluR2 and mGluR3. Meta substitution on the aromatic ring of **3** with a variety of substituents, both electron donating (e.g., methyl, hydroxy, amino, methoxy, phenyl, phenoxy) and electron withdrawing (e.g., fluorine, chlorine, bromine, carboxy, trifluoromethyl) gave from 1.5- to 4.5-fold increases in affinity. Substitution with *p*-fluorine, as in **97** ($IC_{50} = 0.022 \pm 0.002$), was the exception. Here, a greater increase in affinity was realized than for either the ortho- or meta-substituted analogues; **97** was the most potent compound resulting from monosubstitution of the aromatic. At best, only modest increases in affinity were realized for certain compounds bearing either two chlorines or two fluorines, and two methoxy groups gave no improvement in affinity (all examined in a variety of substitution patterns). Three amino acids, **4**, **5**, and **104**, were resolved into their four constituent isomers, and affinity and functional activity for group II mGluRs was found to reside solely in the *S*,*S*,*S*-isomers of each, consistent with **1**. With an $IC_{50} = 2.9 \pm 0.6$ nM, the resolved xanthylmethyl compound **168** was the most potent compound from this SAR. Amino acid **168** demonstrated high plasma levels following intraperitoneal (ip) administration and readily penetrated into the brain. This compound, however, had only limited (∼5%) oral bioavailability. Systemic administration of **168** protected mice from limbic seizures produced by the mGluR agonist 3,5-dihydroxyphenylglycine, with an $ED_{50} = 31$ mg/kg (ip, 60 min preinjection). Thus, **168** represents a valuable tool to study the role of group II mGluRs in disease.

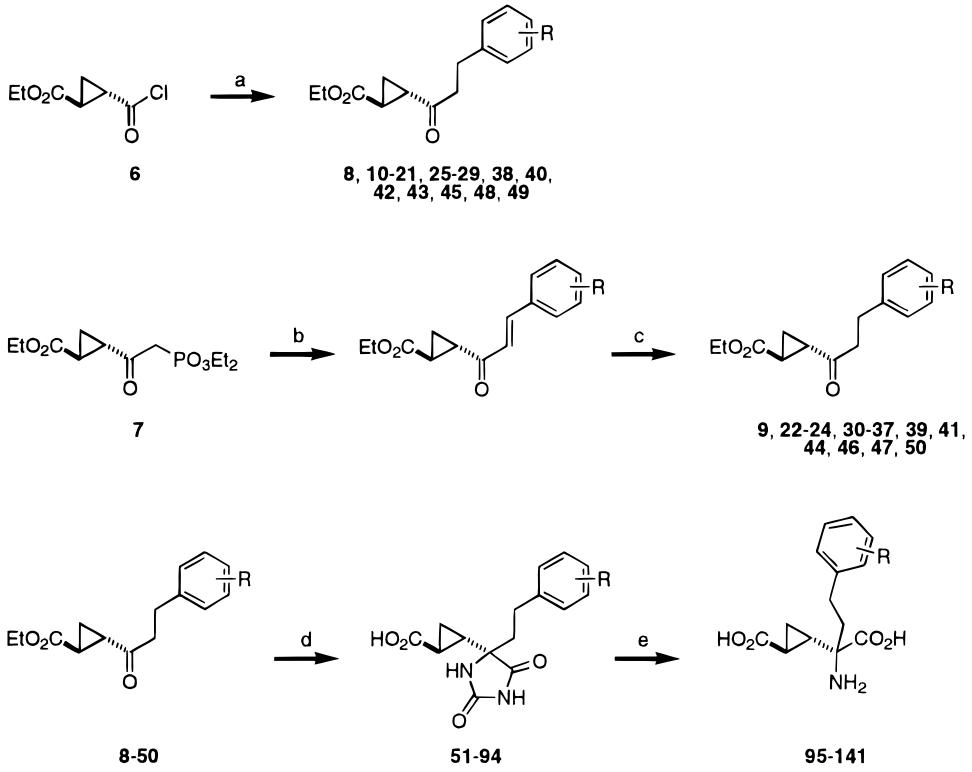
Metabotropic glutamate receptors (mGluRs) are a type of excitatory amino acid receptor that are coupled through G-proteins to enzyme systems which liberate second messengers to transduce signals.[1] Three types of mGluR receptors, group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8) have been identified; each is distinguished on the basis of on pharmacology and sequence homology. We have vigorously pursued the synthesis of compounds which function as antagonists of these receptors. The dearth of potent agonists and antagonists for mGluRs has impeded our understanding of the physiological role these receptors play in the central nervous system and their potential utilities as therapeutic agents.[2]

In the preceding paper,[3] we detailed the preparation of a series of amino acids related to **1** (more commonly referred to as L-CCG 1, CCG refers to carboxycyclopropylglycine; Chart 1), a potent and somewhat selective agonist for group II mGluRs.[4] We determined affinity of these compounds for group II mGluRs using [$^3$H]-glutamic acid binding in rat forebrain membranes, which under the conditions employed was very selective for binding to mGluRs (vis á vis ionotropic glutamate

* Address correspondence to: Paul L. Ornstein, Lilly Research Laboratories, Lilly Corporate Center, DC 0510, Indianapolis, IN 46285. Phone: 317-276-3226. Fax: 317-276-7600. E-mail: ornstein_paul@lilly.com.

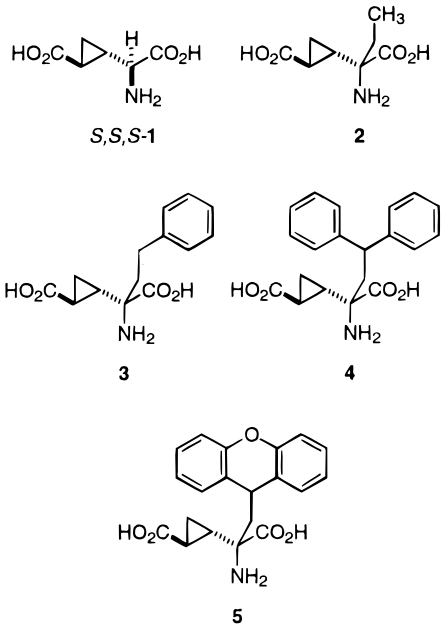
S0022-2623(97)00498-6 CCC: $15.00 
Published on Web 01/14/1998

**Scheme 1**[a]




[a] (a) RI, Zn(Cu), PhH, *N*,*N*-dimethylacetamide, 60 °C; $Pd(Ph_3P)_4$, room temperature; (b) NaH, THF, ArCHO, room temperature to reflux; (c) $H_2$, 5% Pd/C, EtOH, room temperature, 15 psi; (d) NaOH, $H_2O$, EtOH, 70 °C; add KCN and $(NH_4)_2CO_3$, 55 °C; (e) see Table 1 for hydrolysis conditions used for each substrate; Dowex 50-X8, 10% pyridine/water.

**Chart 1**




receptors−iGluRs).[5−7] We found that appending a substituent such as ethyl (**2**) onto the amino acid carbon converted an agonist to an antagonist, although with a significant loss in potency. Affinity was increased relative to **1** ($IC_{50}$ = 0.47 $\mu$M) and **2** ($IC_{50}$ = 2.2 $\mu$M) when a phenyl ring was attached at the ethyl terminus, leading to **3** ($IC_{50}$ = 0.32 $\mu$M). 2,2-Diphenylethyl substitution (**4**; $IC_{50} = 0.24 \pm 0.08$ $\mu$M)) gave a further increase in potency, and linking those two aromatic rings with, for example, an oxygen atom as in the xanthyl compound **5** ($IC_{50} = 0.010 \pm 0.001$ $\mu$M), significantly enhanced potency. In this paper, we examine the effects of substitution on the aromatic ring of **3** with either one or two substituents, the resolution of three compounds into their constituent isomers to determine in which isomer the mGluR antagonist activity resides, some preliminary in vivo effects of these compounds, and some data relating to the bioavailability of **5** in rats.

## Chemistry

**Synthesis of Racemic Amino Acids.** As in the preceding paper,[3] we prepared keto−esters **8**−**50** (Table 1) either by coupling **6** with an organozincate (prepared from the corresponding iodide with zinc−copper couple) in the presence of palladium(0) (Scheme 1; **8, 10**−**21, 25**−**29, 38, 40, 42, 43, 45, 48**, and **49**) or by reaction of the sodium salt of **7** with an aldehyde followed by hydrogenation of the enone (Scheme 1; **9, 22**−**24, 30**−**37, 39, 41, 44, 46, 47**, and **50**). We prepared the requisite iodides as described before from the corresponding substituted phenylethyl alcohol, which was either commercially available or prepared by reduction of the commercially available substituted phenylacetic acid. For ketone **25**, methyl 3-hydroxyphenylacetate was converted to triflate **149**, followed by Stille coupling with phenyl tri-*n*-butylstannane to afford the ester **150**, which after reduction afforded the alcohol **151** (Scheme 2). For ketones **22** and **23**, we prepared the aldehydes needed for Horner−Emmons condensation by palladium-mediated coupling of either cyclopropylmagnesium bromide or cyclopentylmagnesium chloride with **142** to afford **143** and **145**, respectively, which upon hydrolysis gave **144** and **146**, respectively (Scheme 2).[8] Hydroge-

**Table 1.** Experimental Information for the Synthesis of Keto−Esters, Hydantoin Acids, and Amino Acids[a]

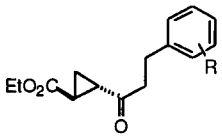
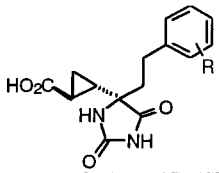
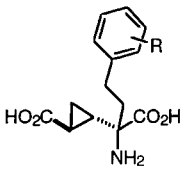
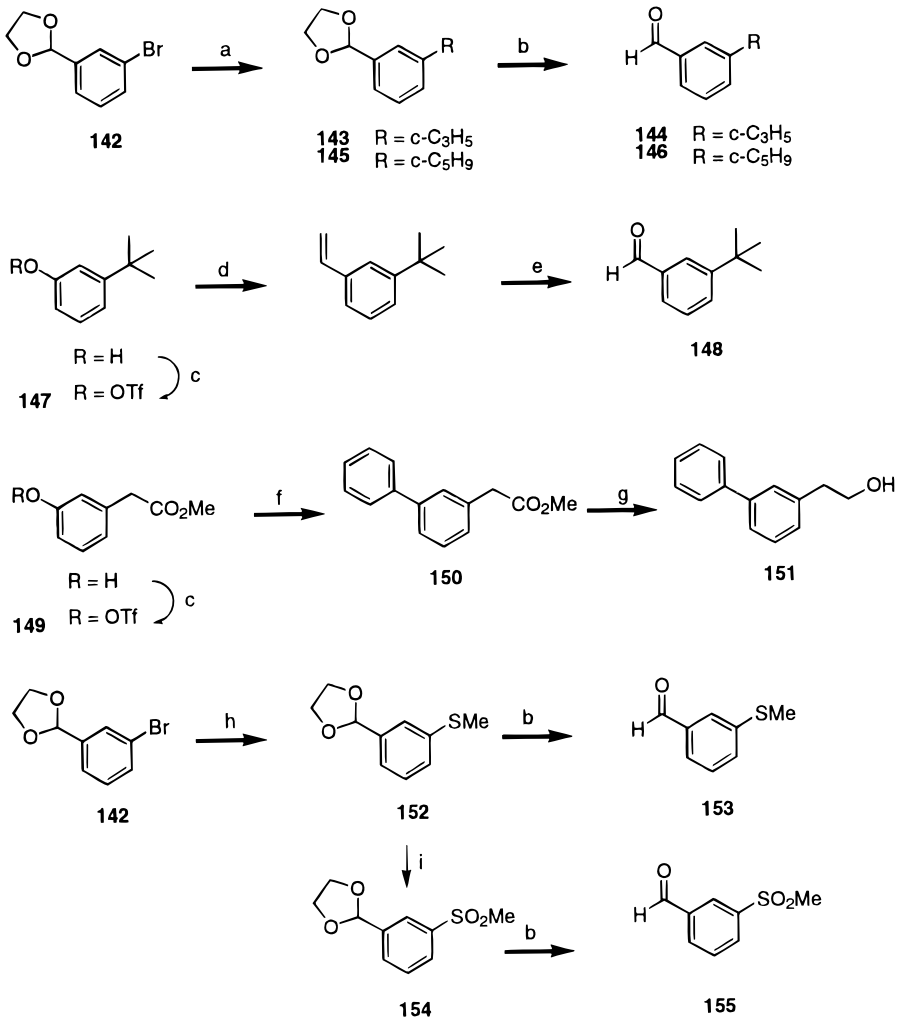
| |  | | | |  | |  | | |
|---|---|---|---|---|---|---|---|---|---|
| R | Source of Iodide[b] | Ketone Synthetic Method[c] | Ketone (%Yield)[d] | Ketone Analysis | Synthesis of Hydantoin[e] | Hydantoin (% Yield)[f] | Hydantoin Hydrolysis[g] | Amino Acid (% Yield)[f] | Amino Acid Analysis[h] |
| 2-F | OH | Zincate | **8** (29) | C,H•0.25 $H_2O$ | B | **51** (48) | G (250) | **95** (8) | C,H,N•0.3 $H_2O$ |
| 3-F | NA[i] | H-E | **9** (76) | C,H,N•0.25 $H_2O$[j] | B | **52** (69) | G (200) | **96** (40) | C,H,N |
| 4-F | OH | Zincate | **10** (36) | C,H | B | **53** (72) | G (250) | **97** (25) | C,H,N•0.25 $H_2O$ |
| 2- Cl | OH | Zincate | **11** (73) | C,H | A (120 °C) | **54** (86) | E | **98** (35) | C,H,N |
| 3- Cl | OH | Zincate | **12** (75) | C,H | A (120 °C) | **55** (79) | E | **99** (41) | C,H,N |
| 4- Cl | OH | Zincate | **13** (60) | C,H | A (120 °C) | **56** (79) | E | **100** (35) | C,H,N |
| 3-Br | $CO_2H$ | Zincate | **14** (65) | C,H | B | **57** (74) | G (250) | **101** (19) | C,H,N•0.25 $H_2O$ |
| 4-Br | OH | Zincate | **15** (38) | C,H,N[k] | B | **58** (78) | G (250) | **102** (2) | C,H,N•0.25 $H_2O$ |
| 2-Me | OH | Zincate | **16** (97) | C,H | A (120 °C) | **59** (69) | E | **103** (10) | C,H,N |
| 3-Me | OH | Zincate | **17** (31) | C,H | A (120 °C) | **60** (33) | E | **104** (41) | C,H,N•0.9 $H_2O$ |
| 4-Me | OH | Zincate | **18** (91) | C,H | A (120 °C) | **61** (48) | *N*-BOC | **105** (32) | C,H,N |
| 2-$CF_3$ | OH | Zincate | **19** (27) | C,H | B | **62** (63) | G (250) | **106** (30) | C,H,N |
| 3-$CF_3$ | OH | Zincate | **20** (65) | - - | B | **63** (100) | G (250) | **107** (30) | C,H,N•0.5 $H_2O$ |
| 4-$CF_3$ | $CO_2H$ | Zincate | **21** (39) | C,H | B | **64** (72) | G (250) | **108** (8) | C,H,N•$C_3H_6O$[l] |
| 3-*n*-Propyl | NA | H-E | **22** (43) | C,H | B (alt) | **65** (73) | H | **109** (47) | C,H,N |
| 3-*c*-Pentyl | NA | H-E | **23** (60) | C,H | B (alt) | **66** (88) | H | **110** (60) | C,H,N |
| 3-*t*-Butyl | NA | H-E | **24** (65) | C,H | B (alt) | **67** (85) | H | **111** (60) | C,H,N•0.25 $H_2O$ |
| 3-Ph | See Text | Zincate | **25** (41) | C,H | B (alt) | **68** (100) | G (200) | **112** (2) | C,H,N•0.5 $H_2O$ |
| 4-Ph | $CO_2H$ | Zincate | **26** (36) | C,H | B | **69** (61) | G (250) | **113** (2) | C,H,N•0.65 $H_2O$ •0.25$C_5H_5N$[l] |
| 2-OMe | OH | Zincate | **27** (30) | C,H•0.25 $H_2O$ | A (125 °C) | **70** (58) | E | **114** (40) | C,H,N•0.25 $H_2O$ |
| 3-OMe | OH | Zincate | **28** (70) | C,H | A (125 °C) | **71** (58) | F | **115** (14) | C,H,N•0.25 $H_2O$ |
| 4-OMe | OH | Zincate | **29** (78) | C,H | A (125 °C) | **72** (64) | E | **116** (52) | C,H,N |
| 2-OH | NA | NA | NA | NA | NA | NA | 48% HBr | **117** (47) | C,H,N•0.75 $H_2O$[l] |
| 3-OH | NA | NA | NA | NA | NA | NA | 48% HBr | **118** (46) | C,H,N•0.5 $H_2O$ |
| 4-OH | NA | NA | NA | NA | NA | NA | 48% HBr | **119** (52) | C,H,N•0.75 $H_2O$[l] |
| 2-OPh | NA | H-E | **30** (54) | C,H | B (alt) | **73** (86) | G (200) | **120** (41) | C,H,N |
| 3-OPh | NA | H-E | **31** (79) | C,H | B | **74** (82) | G (200) | **121** (35) | C,H,N•0.25 $H_2O$ |
| 3-SMe | NA | H-E | **32** (44) | C,H,N | B (alt) | **75** (81) | H | **122** (42) | C,H,N |

**Table 1** (Continued)

| R | Source of Iodide[b] | Ketone Synthetic Method[c] | Ketone (%Yield)[d] | Ketone Analysis | Synthesis of Hydantoin[e] | Hydantoin (% Yield)[f] | Hydantoin Hydrolysis[g] | Amino Acid (% Yield)[f] | Amino Acid Analysis[h] |
|---|---|---|---|---|---|---|---|---|---|
| 3-$SO_2Me$ | NA | H-E | **33** (60) | C,H | B (alt) | **76** (37) | H | **123** (7) | C,H,N |
| | | | | | | **77** (33) | H | **124** (33) | C,H,N•0.5 $H_2O$ |
| 3-$CO_2H$ | NA | H-E | **34** (78)[m] | C,H,N | B (alt) | **78** (69)[l] | G (200) | **125** (33) | C,H,N•0.3 $H_2O$ |
| 4-$CO_2H$ | NA | H-E | **35** (46)[m] | C,H,N | B (alt) | **79** (72)[l] | G (200) | **126** (26) | C,H,N |
| 3-$NH_2$ | NA | H-E | **36** (92)[m] | C,H,N[l] | B (alt) | **80** (86) | H | **127** (54) | C,H,N•0.25 $H_2O$•0.25 $NH_3$ |
| 2,3-di-F | NA | H-E | **37** (66) | C,H | B (alt) | **81** (80) | H | **128** (25) | C,H,N |
| 2,4-di-F | $CO_2H$ | Zincate | **38** (62) | C,H | B (alt) | **82** (76) | G (200) | **129** (10) | C,H,N |
| 2,5-di-F | NA | H-E | **39** (72) | C,H | B (alt) | **83** (70) | G (200) | **130** (75) | C,H,N |
| 3,4-di-F | $CO_2H$ | Zincate | **40** (41) | C,H | B (alt) | **84** (78) | G (200) | **131** (39) | C,H,N |
| 3,5-di-F | NA | H-E | **41** (60) | C,H•0.35 $H_2O$ | B (alt) | **85** (80) | H | **132** (9) | C,H,N•0.25 $H_2O$ |
| 2,3,4,5,6-F | $CO_2H$ | Zincate | **42** (55) | C,H•0.5 $CH_2Cl_2$ | B | **86** (56) | G (250) | **133** (31) | C,H,N |
| 2,4-di-Cl | $CO_2H$ | Zincate | **43** (45) | C,H | B | **87** (57) | G (250) | **134** (41) | C,H,N |
| 2,6-di-Cl | NA | H-E | **44** (23) | C,H | B (alt) | **88** (71) | H | **135** (38) | C,H,N |
| 3,4-di-Cl | $CO_2H$ | Zincate | **45** (57) | C,H | B | **89** (52) | G (250) | **136** (41) | C,H,N•0.25 $H_2O$ |
| 3,5-di-Cl | NA | H-E | **46** (50) | C,H[n] | B | **90** (47)[o] | G (200) | **137** (14)[o] | C,H,N[l] |
| 2,3-di-OMe | NA | H-E | **47** (59) | C,H | B | **91** (40) | G (250) | **138** (24) | C,H,N |
| 2,5-di-OMe | $CO_2H$ | Zincate | **48** (41) | C,H | B | **92** (56) | E | **139** (30) | C,H,N |
| 3,4-di-OMe | $CO_2H$ | Zincate | **49** (65) | C,H[l] | B | **93** (59) | E | **140** (46) | C,H,N•0.25 $H_2O$ |
| 3,5-di-OMe | NA | H-E | **50** (52) | C,H | B | **94** (71) | G (150) | **141** (19) | C,H,N |

[a] See Experimental Section for full detail. [b] "OH" indicates that the 2-arylethyl alcohol was commercially available. "$CO_2H$" indicates that the 2-aryl acetic acid was commercially available, and was reduced to the alcohol with borane methyl sulfide. Alcohols were converted to the iodide with iodine, triphenylphosphine, and imidazole in dichloromethane. [c] "Zincate" refers to formation of the ketone by palladium-mediated coupling of an organozincate (formed from the iodide and zinc/copper couple) with acid chloride 6. "H-E" refers to Horner−Emmons condensation of the sodium salt of **7** with the corresponding aldehyde to form an enone, which is then hydrogenated to give the ketone. [d] All ketones are racemic. One isomer is shown for clarity. [e] For either method of hydantoin formation, the keto−ester was hydrolyzed to the keto−acid prior to reaction, except where indicated. Method A: reaction in a sealed tube at the temperature indicated in parentheses; 2.5 equiv of sodium cyanide and 4.5 equiv of ammonium carbonate; 1:1 ethanol/water. Method B: reaction in an open system; 5 equiv of sodium cyanide and 9 equiv of ammonium carbonate; 1:1 ethanol/water; 55−60 °C. Method B (alt): the same as method A, except that the ester was hydrolyzed to the acid without isolation prior to the addition of sodium cyanide and ammonium carbonate. [f] All hydantoins and amino acids are a mixture of two racemic diastereomers (except for **76**, **77**, **123**, and **124**, which are single racemic diastereomers). One isomer of the cyclopropane is shown for clarity. [g] Method C: hydrolysis with 5 N sodium hydroxide in an open system at reflux. Method D: hydrolysis with 5 N sodium hydroxide in a sealed tube at the temperature indicated in parentheses for 24 h. Method E: hydrolysis with 5 N sodium hydroxide in a stainless steel high-pressure reactor at 250 °C overnight. Method F: hydrolysis with 1.5 N barium hydroxide in an open system at reflux. Method G: hydrolysis with 1.5 N barium hydroxide in a stainless steel high-pressure reactor overnight at the temperature inidicated in parentheses. Method H: hydrolysis with 1 N sodium hydroxide in a stainless steel high-pressure reactor at 200 °C overnight. *N*-BOC: Refers to conversion of 61 to the bis-BOCed hydantion with di-*tert*-butyl dicarbonate, triethylamine, and DMAP in acetonitrile, followed by attempted hydrolysis to 105 with 1 N aqueous NaOH in THF at reflux. When this failed, the material was then hydrolyzed by method D. See text and Experimental Section for explicit conditions. 48% HBr: Refers to demethylation of the corresponding *O*-methyl amino acid with refluxing 48% aqueous HBr. [h] All amino acids were isolated by cation exchange chromatography (see experimental) except for **109** and **130**, which were isolated by isoelectric precipitation. Amino acids **102** and **132** were recrystallized from acetic acid following ion exchange chromatography. [i] Not applicable. [j] The elemental analysis for this compound is actually for hydantoin **52**. [k] The elemental analysis for this compound is actually for hydantoin **58**. [l] 16. Anal. C: calcd, 73.82; found, 76.06. **36**. Anal. C: calcd, 68.94; found, 69.88. **49**. Anal. C: calcd, 66.65; found, 67.17. **108**. Anal. N: calcd, 3.60; found, 3.15. **113**. Anal. H: calcd, 6.40; found, 5.89. **117**. Anal. H: calcd, 6.37; found, 5.87. **119**. Anal. H: calcd, 6.37; found, 5.85. 137. Anal. C: calcd, 50.62; found, 52.43. Anal. H: calcd, 4.55; found, 5.19. [m] The functional group on ketones **34/35** and hydantoins **78/79** was a nitrile, which was then hydrolyzed to the carboxylate in the final hydrolysis. The amino group of ketone **36** is protected as the *N*-*tert*-butoxycarbonyl (*N*-BOC) group prior to hydantoin formation; it is then removed in the final hydrolysis. [n] The elemental analysis for this compound is actually for the enone, not the saturated ketone **46**. The enone was recrystallized from ethylacetate/hexane. [o] Hydantoin **90** was converted to the *N*-benzenesulfonimide (on the imide nitrogen of the hydantoin) prior to hydrolysis.

**Scheme 2**[a]




[a] (a) c-$C_3H_5MgBr$ for **143**, c-$C_5H_9MgBr$ for **145**, $Pd(Ph_3P)_4$, THF, reflux; (b) 4:1 $CH_3CN$/1 N HCl, room temperature; (c) *N*-phenyltriflimide, *i*-$Pr_2NEt$, $CH_2Cl_2$, room temperature; (d) $CH_2$═$CHSn$-*n*-$Bu_3$, $Pd(Ph_3P)_4$, LiCl, dioxane, 100 °C; (e) 2.5% $OsO_4$ in 2-propanol, dioxane, water; $NaIO_4$; (f) $PhSn$-*n*-$Bu_3$, $Pd(Ph_3P)_4$, LiCl, toluene, reflux; (g) LAH, THF, room temperature; (h) *n*-BuLi, THF, −78 °C; MeSSMe, warm to room temperature; (i) *m*-CPBA, $CH_2Cl_2$, −78 °C to room temperature.

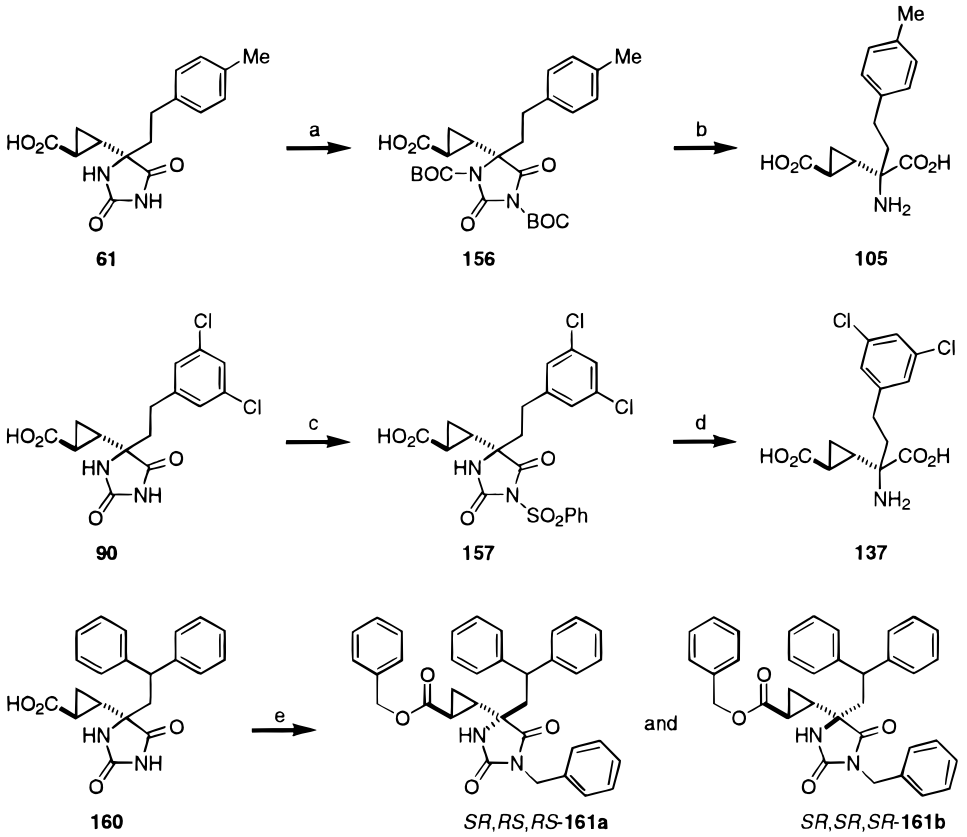
nation of the enone leading to **22** was accompanied by cleavage of the cyclopropane introduced into **144** on the aromatic ring, leading to the *n*-propyl substituent. For ketone **24**, we prepared aldehyde **148** by conversion of 3-*tert*-butylphenol to the corresponding triflate **147**, followed by Stille coupling with vinyl tri-*n*-butylstannane and then oxidative cleavage with osmium tetroxide and sodium metaperiodate (Scheme 2). Metal−halogen exchange of **142** with *n*-butyllithium followed by quench with dimethyl disulfide afforded **152**, and hydrolysis then afforded **153**, the aldehyde required for synthesis of ketone **32** (Scheme 2). Alternatively, we oxidized **152** to the sulfone **154**, which upon hydrolysis yielded **155**, the aldehyde required for synthesis of ketone **33** (Scheme 2). The substituent on the aromatic ring of ketones **34** and **35** is a nitrile, which is hydrolyzed in the last step to yield a carboxylate. For ketone **36**, the 3-amino substituent is introduced through reaction of 3-nitrobenzaldehyde with the sodium salt of **7**, which upon reduction of the enone yields the corresponding 3-amino compound; this is then protected as the *N*-BOC prior to hydantoin formation and ultimately regenerated again as an amine following the subsequent hydantoin hydrolysis.

As described in the previous paper,[3] we prepared hydantoins **51**−**94** by condensation of the keto−acids derived from **8**−**50** (by hydrolysis prior to hydantoin formation) with sodium cyanide and ammonium carbonate either in a sealed tube (Table 1, method A, **54**−**56, 59**−**61**, and **70**−**72**) or an open system (Table 1, method B, **51**−**53, 57, 58, 62**−**69**, and **73**−**94**). In certain cases, the keto−ester was hydrolyzed to the keto−acid in situ, and this is indicated as method B (alt) in Table 1.[9]

Hydrolysis to the amino acids **95**−**141** was effected by the method indicated in Table 1. These methods were described in detail in the preceding paper.[3] In nearly all cases, the amino acid was isolated as the inner salt following cation-exchange chromatography.[3] In a few instances, we were able to facilitate isolation and obviate ion-exchange chromatography using isoelectric precipitation (amino acids **109** and **130**). We prepared the hydroxy-substituted compounds **117**, **118**, and **119** by demethylation of the methoxy-substituted amino acids **114**, **115**, and **116**, respectively, with refluxing 48% aqueous hydrobromic acid.

Because of the difficulties encountered in the hydrolyses of these hydantoins, in a few cases we explored

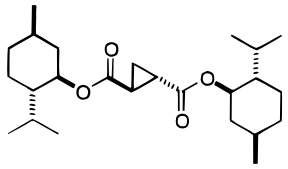
**Scheme 3**[a]



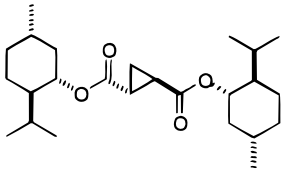

[a] (a) $(BOC)_2O$, $Et_3N$, DMAP, $CH_3CN$, room temperature; (b) 1 N NaOH, reflux; concentrated HCl, pressure tube, 150 °C; Dowex 50-X8, 10% pyridine/water; (c) $NaN(SiMe_3)_2$, THF, room temperature; $PhSO_2Cl$; (d) 1.5 N $Ba(OH)_2$, 200 °C (see method G, Table 1); Dowex 50-X8, 10% pyridine/water; (e) BnBr, $KHCO_3$, DMF, 130 °C.

alternative methods that activated the hydantoin prior to hydrolysis. For example, **61** was converted to the bis-*tert*-butoxycarbonyl derivative **156** (Scheme 3). It was reported by Rebek that this technique allows for hydantoin hydrolysis under relatively mild conditions (1 N sodium hydroxide at room temperature).[10] In our hands, this technique did not work particularly well, and we found that hydrolysis required reflux in 1 N sodium hydroxide followed by heating with concentrated hydrochloric acid at 150 °C to afford amino acid **105**. For hydantoin **90**, we examined activation as the *N*-benzenesulfonylimide (prepared from **90** with sodium bis(trimethylsilyl)amide, diisopropyl-*N*-ethylamine and benzenesulfonyl chloride); however, we found no significant improvement in yield to amino acid **137** following hydrolysis of the proposed product **157** with 1.5 N barium hydroxide at 200 °C in a sealed system (Scheme 3).

**Synthesis of Nonracemic Amino Acids.** We decided to prepare the four constituent isomers of the amino acids with (xanth-9-yl)methyl (**5**), (3-methylphenyl)ethyl (**104**), and 2,2-diphenylethyl (**4**) side chains to determine in which isomer or isomers the mGluR antagonist activity resided. We believed this was a representative sample of what was found to be active in this SAR. We had ready access to both antipodes of nonracemic cyclopropanedicarboxylate (*S,S*-**158** and *R,R*-**159**; the designators refer to the stereochemistry of the cyclopropane carbons) using a known procedure that prepared this compound by diastereoselective alkylation/cyclopropanation of dimenthyl succinate with LTMP and bromochloromethane.[11] We thus required a strategy to separate the hydantoin diastereomers.



*S,S*-**158**



*R,R*-**159**

We found that it was very difficult to separate hydantoin diastereomers by either normal or reverse phase preparative chromatography, and the techniques that worked modestly well were impractical for large-scale synthesis. Hydantoins **76** and **77** were the only ones which readily separated by fractional crystallization. Thus we believed that our best strategy was to introduce a group onto these compounds that would modulate their polarity and enhance opportunities for chromatographic separation. We hoped, for example, that we could introduce a benzyl group onto the imide nitrogen of the hydantoin (with concomitant esterifica-

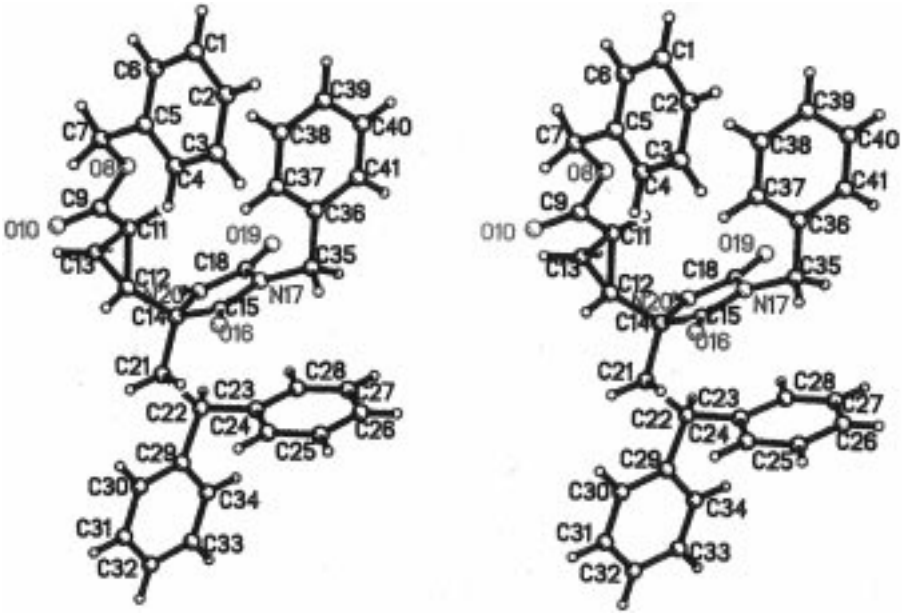



**Figure 1.** Stereoview of *SR,SR,SR*-**161** from the X-ray crystallograph.

tion), separate the diastereomers, and then remove the benzyl group prior to hydrolysis. To this end, alkylation of the racemic hydantoin−acid mixture **160** with benzyl bromide and potassium bicarbonate in dimethylformamide cleanly afforded the N,O-bisalkylated compound, whose diastereomers **161a** (first to elute on chromatography) and **161b** separated readily by flash chromatography on silica gel (Scheme 3). That we obtained **161b** as an X-ray suitable crystal was a distinct advantage of this exercise (Figure 1). It allowed us to unambiguously assign the relative stereochemistry of the two diastereomers: **161b** is *SR,SR,SR* (by X-ray) and **161a** is *SR,RS,RS* (by default).

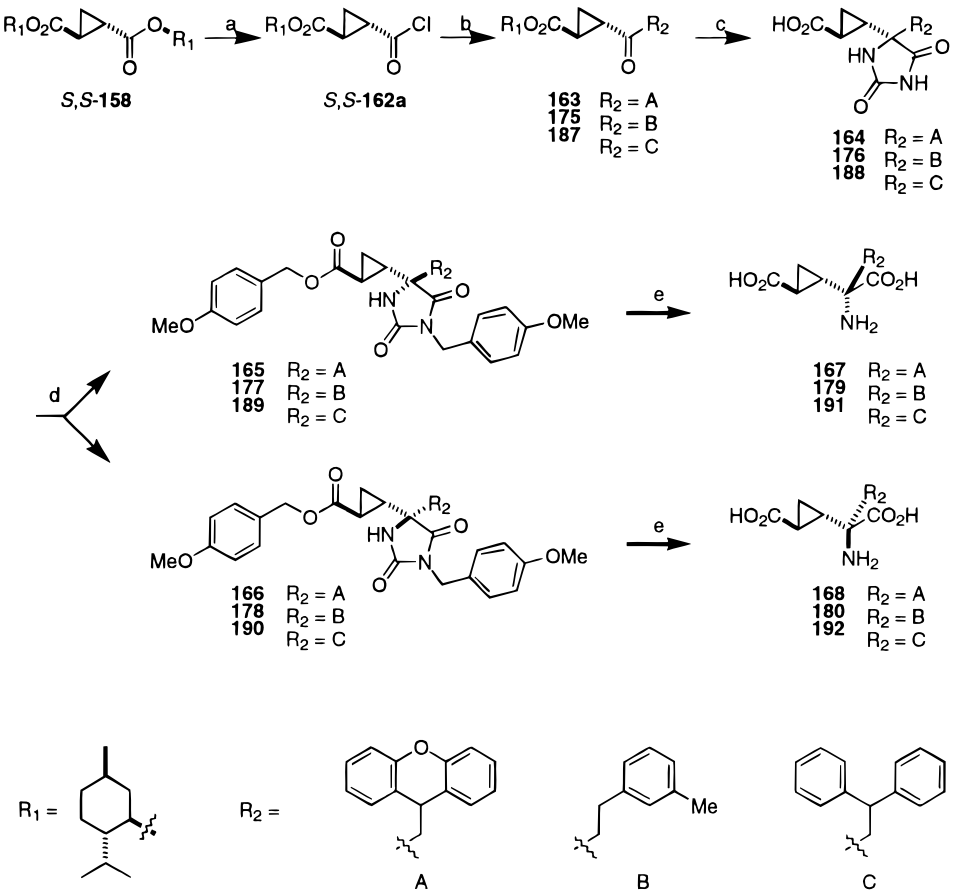
Since we were unable to remove the *N*-benzyl group of **160** or **161** by either hydrogenation or strong acid solvolysis, we switched to the *p*-methoxybenzyl group. These compounds still separated quite easily, and the group was removed using ceric ammonium nitrate oxidation (vide infra).

Selective hydrolysis of either *S,S*-**158** or *R,R*-**159** to the acid−ester with 1 equiv of sodium hydroxide in aqueous 2-propanol, followed by acid chloride formation with neat thionyl chloride, afforded *S,S*-**162a** or *R,R*-**162b**, respectively, (Scheme 4 for **162a**, Scheme 5 for **162b**). We found it necessary to use 2-propanol as the cosolvent instead of ethanol (which was used in the preparation of **6**) to suppress transesterification. Palladium-mediated coupling of *S,S*-**162a** with the organozincate from 9-xanthylmethyl iodide and zinc/copper couple afforded the nonracemic ketone **163** (Scheme 4), which was transformed to a mixture of hydantoin−acids **164** using method B (alt). We found that reaction of this mixture with *p*-methoxybenzyl bromide and potassium bicarbonate in dimethylformamide afforded N-alkylation of the imide nitrogen along with esterification of the cyclopropanecarboxylate. The two diastereomeric products from this reaction were easily separable by chromatography, affording **165** and **166**.[12] Our intention in using the *p*-methoxybenzyl group was that it could be removed oxidatively prior to hydrolysis. However, we believed that the xanthyl group would not be stable to ceric ammonium nitrate (a fact which we verified experimentally), and so we decided to attempt hydrolysis on the N-substituted hydantoin. We were thus gratified to find that hydrolysis of **165** with barium hydroxide in a sealed system (method G) or hydrolysis of **166** with sodium hydroxide in a sealed system (method H) gave the *R,S,S*-amino acid **167** and the *S,S,S*-amino acid **168**, respectively. Removal of the benzyl group was unnecessary. Using the same sequence of reactions (Scheme 5), condensation of *R,R*-**162b** with the above organozincate afforded **169**, which was converted to the mixture of hydantoin−acids **170** using the two-pot method B. N,O-Di-*p*-methoxybenzylation afforded the readily separated **171** and **172**, which were each hydrolyzed with method G to afford the *S,R,R*-amino acid **173** and the *R,R,R*-amino acid **174**, respectively.

Schemes 4 and 5 show the preparation of the (3-methylphenyl)ethyl-substituted compounds. Condensation of either *S,S*-**162a** (Scheme 4) or *R,R*-**162b** (Scheme 5) with the organozincate from (3-methylphenyl)ethyl iodide afforded the ketones **175** and **181**, respectively. N,O-Di-*p*-methoxybenzylation of each afforded two separable diastereomers: **177** and **178** from **176** (Scheme 4); **183** and **184** from **182** (Scheme 5). Oxidative cleavage with ceric ammonium nitrate on **177**, **183**, and **184**, cleanly afforded the diastereomerically pure hydantoins without the *p*-methoxybenzyl groups; each was then hydrolyzed with barium hydroxide in a sealed system to afford amino acids **179**, **185**, and **186**, respectively. As for the xanthyl compounds, we found that the N,O-di-*p*-methoxybenzylated hydantoin **178** could be hydrolyzed to the amino acid **180** without difficulty, using conditions that we found to be optimal for these hydrolyses (1 N sodium hydroxide in a sealed system at 200 °C, Scheme 4).

Schemes 4−6 show the preparation of the 2,2-diphenylethyl-substituted compounds. Reaction of the organozincate from 2,2-diphenylethyl iodide with either *S,S*-**162a** (Scheme 4) or *R,R*-**162b** (Scheme 5) gave ketones **187** and **193**, respectively. Hydantoin formation with **187** afforded **188**, which was converted to the *N,O*-bis(*p*-methoxybenzyl)hydantoins **189** and **190** (Scheme 4).

**Scheme 4**[a]



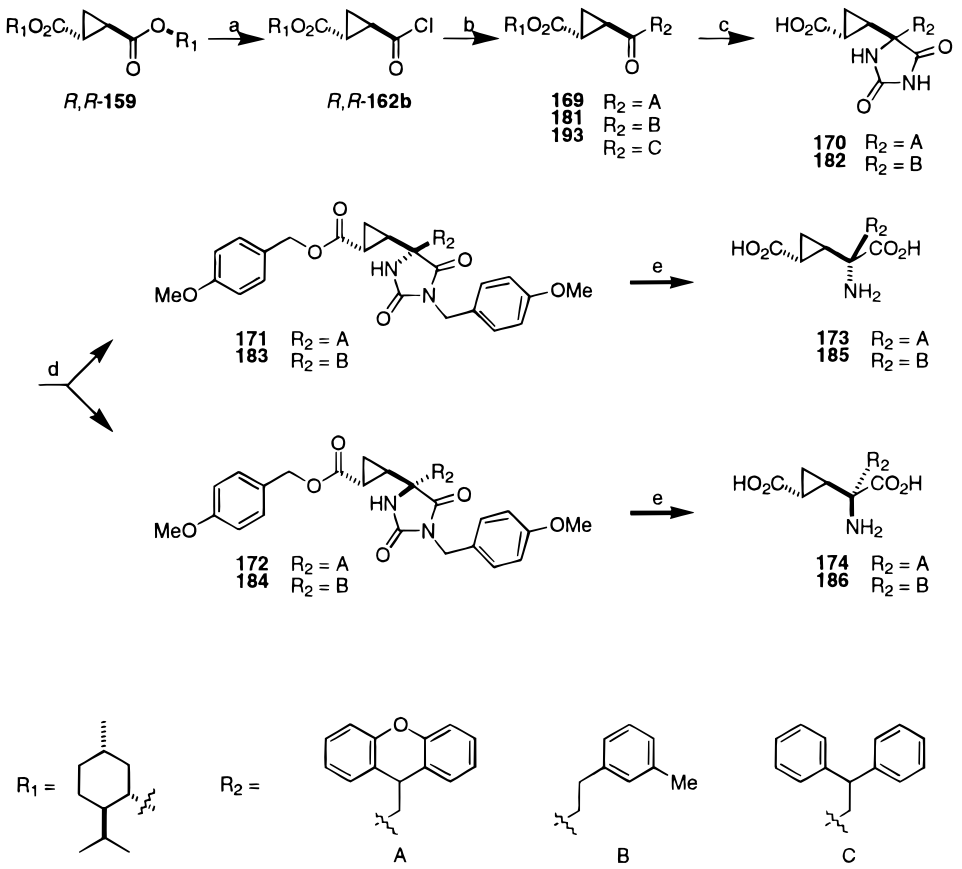

[a] (a) 5 N NaOH, 2-propanol, 70 °C; $SOCl_2$, room temperature; (b) RI, Zn(Cu), PhH, *N*,*N*-dimethylacetamide, 60 °C; $Pd(Ph_3P)_4$, room temperature; (c) NaOH, $H_2O$, EtOH, 55 °C; add KCN and $(NH_4)_2CO_3$, 55 °C; (d) *p*-$MeOPhCH_2Br$, $KHCO_3$, DMF, 125 °C; flash chromatography, 30% EtOAc/hexane; (e) for **177** and **189**, prior to hydrolysis: ceric ammonium nitrate, $CH_3CN$, $H_2O$, room temperature; see Table 1 for hydrolysis conditions; **167**, **179**, and **191**, method G; **168**, **180**, and **192**, method H.

The *p*-methoxybenzyl groups of **189** were removed with ceric ammonium nitrate followed by exhaustive hydrolysis to afford **191**. As for other amino acids, we found that it was not necessary to remove the *p*-methoxybenzyl groups prior to hydrolysis, and thus **190** afforded **192**. To our surprise, conversion of **193** to the hydantoin afforded a small amount of diastereomerically pure compound **195**, along with the typical mixture of hydantoins **194** and **195** (Scheme 6). With this compound, we wanted to explore if derivatization of the hydantoin with the benzenesulfonyl group on the imide nitrogen would allow for hydrolysis to the amino acid under much milder conditions, while still providing ease of diastereomer separation. To this end, reaction of the mixture of hydantoins **194** and **195** with sodium bis(trimethylsilyl)amide followed by benzenesulfonyl chloride afforded a not so readily separable mixture of compounds **196** and **197**. Hydrolysis of **196** with barium hydroxide at reflux in an open system gave the desired amino acid **198**, albeit in very low yield. The diastereomerically pure hydantoin **195** was also converted to the *N*-benzenesulfonyl compound **197**, but in this case hydrolysis was carried out with 1 N sodium hydroxide at reflux. This yielded a small amount of amino acid **199**, along with a product that was distinct from the hydantoin but still appeared to contain an *N*-benzenesulfonyl group. This material was exhaustively hydrolyzed with 6 N hydrochloric acid to afford an additional small quantity of **199**. Our overall results with the *N*-benzenesulfonyl group were disappointing, and it was not used for any subsequent compound.

All of the nonracemic amino acids were evaluated for optical purity using a chiral HPLC column, Chiracel-OD. All of the amino acids (**167, 168, 173, 174, 179, 180, 181, 185, 186, 191, 198**, and **199**) were found to have enantiomeric excesses (ee's) of greater than 98%, except for **192**, which was found to have an ee of 93%.[13]

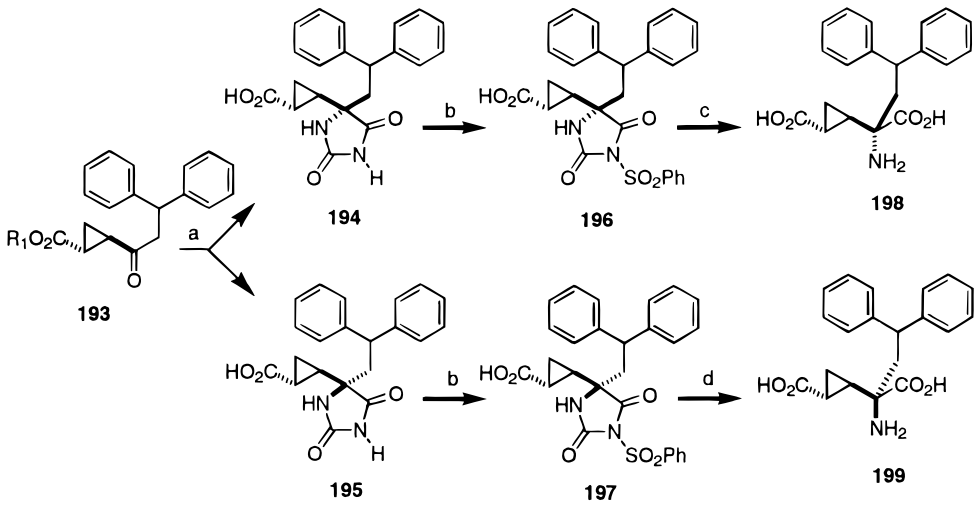
The TLC and flash chromatography elution profiles of the diastereomeric pairs of dibenzylated hydantoin–acids were consistent across the different pairs, with the *R*,*S*,*S*- or *S*,*R*,*R*-isomers eluting first and the *S*,*S*,*S*- or *R*,*R*,*R*-isomers eluting second. This was true for all three side chains ((3-methylphenyl)ethyl, 2,2-diphenylethyl, or xanthylmethyl), whether substituted with benzyl or *p*-methoxybenzyl. As was mentioned above, an X-ray crystallograph of **161b** (which is racemic) confirmed the relative stereochemistry of the first- and second-eluting isomers. The absolute stereochemistry of these compounds then follows because we know the absolute stereochemistry of the dimenthyl cyclopropanedicarboxylates from which they are derived. $^1H$ NMR chemical shifts and coupling patterns were very similar for the benzylic and cyclopropane protons of the racemic *N*,*O*-dibenzyl hydantoins **161a** and **161b** and the corresponding nonracemic *N*,*O*-bis(*p*-methoxybenzyl)hydantoins **189** and **190**, respectively. Consistent patterns were observed in the $^1H$ NMR spectra of the cyclopropane protons for each pair of derivatized hy-

**Scheme 5**[a]




[a] (a) 5 N NaOH, 2-propanol, 70 °C; $SOCl_2$, room temperature; (b) RI, Zn(Cu), PhH, *N*,*N*-dimethylacetamide, 60 °C; $Pd(Ph_3P)_4$, room temperature; (c) NaOH, $H_2O$, EtOH, 55 °C; add KCN and $(NH_4)_2CO_3$, 55 °C; (d) *p*-MeOPhCH$_2$Br, $KHCO_3$, DMF, 125 °C; flash chromatography, 30% EtOAc/hexane; (e) for **183** and **184**, prior to hydrolysis: ceric ammonium nitrate, $CH_3CN$, $H_2O$, room temperature; **173**, **174**, **185**, and **186** hydrolyzed by method G (see Table 1).

**Scheme 6**[a]




[a] (a) NaOH, $H_2O$, EtOH, 55 °C; KCN, $(NH_4)_2CO_3$, $H_2O$, EtOH, 55 °C; (b) $NaN(SiMe_3)_2$, THF, room temperature; $PhSO_2Cl$, reflux; (c) $Ba(OH)_2$, $H_2O$, reflux; isoelectric precipitation; (d) 1 N NaOH, reflux; Dowex 50-X8, 10% pyridine/water; forerun from ion exchange: 6 N HCl, reflux.

dantoins, independent of the α-substituent.[14] For example, the relative spacing of the cyclopropane protons for the first-eluted *R*,*S*,*S*- (**165**, **177**, and **189**) or *S*,*R*,*R*-isomers (**171** and **183**) was very consistent, although the absolute chemical shifts varied slightly. This was also true for the second-eluted *S*,*S*,*S*- (**166**, **178**, and **190**) or *R*,*R*,*R*- (**172** and **184**) isomers. The pattern of cyclopropane protons for the first-eluted isomers was, however, distinct from that of the second-eluted isomers. Consistent patterns amongst these two sets of isomers were also seen for the *N*- and *O*-benzylmethylenes.[10] Thus we feel confident in our absolute stereochemical assignments for the various nonracemic amino acids prepared herein.

**Structure−Activity Studies: Substituted Phenylethyl Amino Acids.** All of the amino acids pre-

pared in this study were evaluated for their ability to inhibit binding of [$^3$H]glutamic acid to rat forebrain membranes,[5−7] and these data are shown in Table 2 (data for the unsubstituted analogue **1** is provided for comparison). Most of the novel compounds were evaluated as a mixture of four stereoisomers; however, the non racemic amino acids **167, 168, 173, 174, 179, 180, 185, 186, 191, 192, 198**, and **199** were the exceptions.

Selected analogues in this series were also evaluated for functional agonist or antagonist activity in nonneuronal cell lines (RGT for rat glutamate transporter) expressing either cloned human mGluR2 or mGluR3 (Table 2) receptors.[15,16] No agonist activity was observed with the compounds alone (data not shown). Antagonist activity was assessed in these cell lines by looking at the ability of these compounds to block 1*S*,3*R*-ACPD-induced inhibition of forskolin-stimulated cyclic-AMP.

On the basis of the significant improvement in affinity realized with amino acid **3** (phenylethyl substitution), we focused a significant portion of the SAR on exploring the effects of substitution on the aromatic ring. We looked at both mono- and disubstituted compounds. It was our hope that minor structural changes, such as substitution on the aromatic ring, would afford significant increases in affinity and functional potency. In fact, these goals were realized.

We explored a variety of substituents, both electron donating and withdrawing, oriented ortho, meta, and para on the aromatic ring. The results of these efforts are shown in Table 2. In a comprehensive fashion, we looked at halogens, such as fluorine (**95, 96**, and **97**), chlorine (**98, 99**, and **100**) and bromine (**101** and **102**); alkyls such as methyl (**103, 104**, and **105**) and trifluoromethyl (**106, 107**, and **108**); hydroxy (**117, 118**, and **119**), methoxy (**114, 115**, and **116**), and phenoxy (**120** and **121**); phenyl (**112** and **113**); and carboxy (**125** and **126**). We also looked at some other substituents, such as thiomethyl (**122**), sulfonylmethyl (**124**), and amino (**127**) only in the meta position. We found that meta substitution of a variety of functional groups consistently provided a significant increase in affinity for mGluRs, ranging from 1.4- to 14-fold over the unsubstituted compound. Ortho substitution was either much less effective or deleterious to affinity, while para substitution was in general deleterious. Fluorine was the only substituent that showed an increase in affinity when substituted in the para position (**97**), and **97** was more potent than its meta-substituted counterpart **96**. It is interesting to note that both electron-donating (e.g., hydroxy (**118**), amino (**127**), methoxy (**115**), and methyl (**104**)) and electron-withdrawing (e.g., trifluoromethyl (**107**), carboxy (**125**), and chloro (**99**)) substituents gave increases in affinity. We also observed that both positively (**127**) and negatively (**125**) charged substituents increased affinity, the latter better than the former. On the basis of these observations, we suspected that the increase in affinity for meta-substitution in large part reflected the benefit of a small increase in steric bulk. To explore the scope of this steric change, we prepared larger alkyls such as *n*-propyl (**109**), cyclopentyl (**110**), and *tert*-butyl (**111**), along with phenyl (**112**) and phenoxy (**121**). Most of these substitutions either decreased activity (**109** and **112** were 6-fold less potent than **104**) or eliminated it entirely. The unusual exception was the phenoxy analogue **121**, which was about 1.5-fold more potent than **3**. Methoxy (**115**) was a beneficial substitution, but the isosteric thiomethoxy **122** was less active than **3**, and oxidation of **122** to the sulfone (**124**) increased activity.

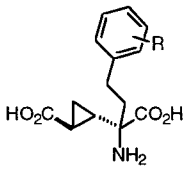
When selected analogues from this part of the SAR were evaluated in functional assays, they were found to be antagonists at both mGluR2 and mGluR3. In general, compounds were not selective for either mGluR, except for the carboxy (**125**) and amino (**127**) analogues, which were 15−20-fold more potent at mGluR3. Increases in receptor affinity for **97, 99, 107, 115, 118**, and **124** led to increases in functional antagonist potency relative to the unsubstituted compound **3**.

In the next aspect of the SAR, we explored whether an additional substituent on the aromatic ring might further enhance affinity. We looked at two fluorines (**128**−**132**), two chlorines (**134**−**137**), and two methoxys (**138**−**141**). We also prepared the perfluorophenyl compound **133**, and this change gave a slight decrease in affinity. An additional chlorine provided some benefit, an additional fluorine was neither beneficial nor deleterious, and an additional methoxy was deleterious to affinity. In general, 3,5-disubstitution was best, as in **132, 137**, and **141**. The difluoro analogue **132** was equipotent to the 4-fluoro compound **97**, and the dichloro analogue **137** was about 3-fold more potent than the 3-chloro compound **99** and nearly as potent as **97**. The dimethoxy analogue **141** was slightly less potent than the 3-methoxy compound **115**. One might conclude from these data that along with a steric component there may also be an electronic component that in the right cases leads to increased affinity.

**Structure−Activity Studies: Resolved Amino Acids.** We chose three compounds, **104**, **4**, and **5**, from the SAR reported herein and in the previous paper, to be resolved into their four constituent isomers. We felt that this would represent the scope of structural changes made (e.g., meta-substituted phenylethyl, diphenylethyl, and constrained diphenylethyl) which offered significant increases in affinity. Of the four diastereomers possible for the CCGs, the greatest potency for mGluRs was seen with CCG-1. Of that diastereomer, activity resided in the *S*,*S*,*S*-isomer **1**. The nature of our preparation of these amino acids afforded us racemic mixtures of two of the four CCG diastereomers, corresponding to CCG-1 and CCG-2. It was our hope that the same pattern of stereoselectivity for CCGs vis-á-vis agonist activity would also be realized for the antagonists, i.e., one isomer bearing the bulk of the activity.

We found that as for **1**, affinity for group II mGluRs resided in the *S*,*S*,*S*-isomers **168** (xanthyl), **180** ((3-methylphenyl)ethyl), and **192** (diphenylethyl). These compounds were also found to be potent functional antagonists of both mGluR2 and -3, with no significant differences in selectivity observed between those two mGluRs. All of the other isomers were either marginally active or inactive. The xanthylmethyl compound **168** (LY341495) binds with very high affinity to rat brain mGluRs, with an $IC_{50}$ of 2.9 ± 0.6 nM, and is a very potent functional antagonist, with $IC_{50}$s at human mGluR2 and mGluR3 of 23 ± 4 and 10 ± 8 nM, respectively. Thus, the addition of this substituent to

**Table 2.** Affinities of Novel Compounds for Group II Metabotropic Glutamate Receptors in Rat Forebrain Membranes and Functional Antagonist Activity in Cloned (RGT) Cells Expressing Human Group II MGluRs




| Amino Acid[a] | R | ACPD-Sensitive [$^3$H]Glutamate Binding $IC_{50}$ (μM)[b] | Antagonist activity at human mGluR2 $IC_{50}$ (μM)[c] | Antagonist activity at human mGluR3 $IC_{50}$ (μM)[c] |
|---|---|---|---|---|
| **1** | -- | 0.47 | agonist | agonist |
| **3** | H | 0.32 | 0.85 | 0.65 |
| **95** | 2-F | 0.31 ± 0.11[e] | | |
| **96** | 3-F | 0.16 ± 0.06[e] | | |
| **97** | 4-F | 0.022 ± 0.002[e] | 0.18 | 0.21 |
| **98** | 2- Cl | 0.26 | | |
| **99** | 3- Cl | 0.10 ± 0.003[e] | 0.18 | 0.18 |
| **100** | 4- Cl | 0.41 | | |
| **101** | 3-Br | 0.069 ± 0.012[e] | | |
| **102** | 4-Br | 0.68 | | |
| **103** | 2-Me | 0.57 | | |
| **104** | 3-Me | 0.089 ± 0.036[e] | | |
| **105** | 4-Me | 0.59 | | |
| **106** | 2-$CF_3$ | 0.48 | | |
| **107** | 3-$CF_3$ | 0.14 ± 0.05[e] | 0.22 | 0.42 |
| **108** | 4-$CF_3$ | | | |
| **109** | 3-*n*-Propyl | 0.57 | | |
| **110** | 3-*c*-Pentyl | >10 | | |
| **111** | 3-*t*-Butyl | >10 | | |
| **112** | 3-Ph | 0.51 | | |
| **113** | 4-Ph | 1.5 | | |
| **114** | 2-OMe | 0.17[d] | | |
| **115** | 3-OMe | 0.094 ± 0.033[e] | 0.43[d] | 0.16[d] |
| **116** | 4-OMe | 1.4 | | |
| **117** | 2-OH | 0.22 ± 0.07[e] | | |
| **118** | 3-OH | 0.15 ± 0.04[e] | 1.0 | 0.26 |
| **119** | 4-OH | 0.30 | | |
| **120** | 2-OPh | 0.36 | | |
| **121** | 3-OPh | 0.22[d] | | |

**Table 2** (Continued)

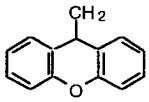
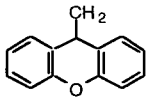
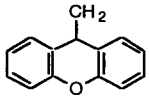
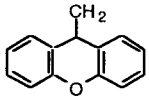
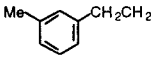
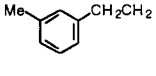
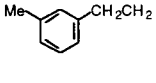
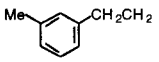
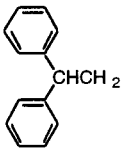
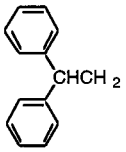
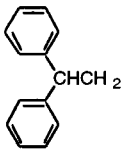
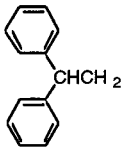
| Amino Acid[a] | R | ACPD-Sensitive [$^3$H]Glutamate Binding $IC_{50}$ (μM)[b] | Antagonist activity at human mGluR2 $IC_{50}$ (μM)[c] | Antagonist activity at human mGluR3 $IC_{50}$ (μM)[c] |
|---|---|---|---|---|
| **122** | 3-SMe | 0.41 | | |
| **123** | 3-$SO_2$Me | 2.4 | | |
| **124** | 3-$SO_2$Me | 0.11 ± 0.06′ | 0.19 | 0.18 |
| **125** | 3-$CO_2$H | 0.077 ± 0.024′ | 1.8 | 0.08 |
| **126** | 4-$CO_2$H | 0.37 | | |
| **127** | 3-$NH_2$ | 0.20 | 3.1 | 0.20 |
| **128** | 2,3-di-F | 0.13 ± 0.06′ | | |
| **129** | 2,4-di-F | 0.063 ± 0.001′ | | |
| **130** | 2,5-di-F | 0.29 | | |
| **131** | 3,4-di-F | 0.034 ± 0.008′ | | |
| **132** | 3,5-di-F | 0.021 ± 0.004′ | | |
| **133** | 2,3,4,5,6-F | 0.37 | | |
| **134** | 2,4-di-Cl | 0.22 | | |
| **135** | 2,6-di-Cl | 0.71 | | |
| **136** | 3,4-di-Cl | 0.067 ± 0.015′ | | |
| **137** | 3,5-di-Cl | 0.029 ± 0.004′ | | |
| **138** | 2,3-di-OMe | 4.9 | | |
| **139** | 2,5-di-OMe | 0.17 | | |
| **140** | 3,4-di-OMe | 0.46 | | |
| **141** | 3,5-di-OMe | 0.11 ± 0.02′ | | |
| *R,S,S*-**167** |  | 0.53 | | |
| *S,S,S*-**168** |  | 0.0029 ± 0.0006′ | 0.023 ± 0.004 | 0.010 ± 0.008 |
| *S,R,R*-**173** |  | 0.86[d] | | |
| *R,R,R*-**174** |  | 4.2 | | |
| *R,S,S*-**179** |  | (4%) | | |
| *S,S,S*-**180** |  | 0.012 ± 0.003′ | 0.18 | 0.08 |
| *S,R,R*- |  | 8.1 | | |

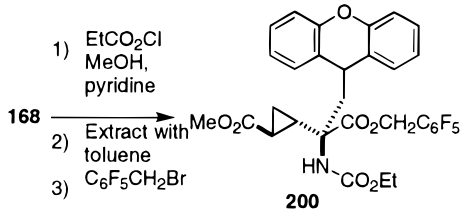
**Table 2** (Continued)

| Amino Acid[a] | R | ACPD-Sensitive [$^3$H]Glutamate Binding $IC_{50}$ (μM)[b] | Antagonist activity at human mGluR2 $IC_{50}$ (μM)[c] | Antagonist activity at human mGluR3 $IC_{50}$ (μM)[c] |
|---|---|---|---|---|
| **185** *R,R,R-* |  | (0%) | | |
| *R,S,S-* **191** |  | 2.0[d] | | |
| *S,S,S-* **192** |  | 0.035 ± 0.005[e] | 0.22 | 0.17 |
| *S,R,R-* **198** |  | (0%) | | |
| *R,R,R-* **199** |  | (8%) | | |

[a] All compounds are a mixture of four stereoisomers (*S,S,S; R,S,S; S,R,R; R,R,R;* the first letter denotes stereochemistry at the amino acid carbon, and the next two letters denote stererochemistry at the cyclopropane carbons), unless otherwise noted. [b] See refs 5 and 6. All experiments are single-point determinations, except as noted. Numbers in parentheses refer to percent displacement of radioligand at 1 μM. [c] See refs 15 and 16. All experiments are single-point determinations, except as noted. [d] Average of two determinations. [e] Average of three determinations.

the amino acid carbon of **1** imparts a 162-fold increase in receptor affinity.

**Pharmacokinetic Evaluation of 168 following Systemic Administration in Rats.** We evaluated **168** in rats following intravenous (iv), intraperitoneal (ip), and oral (po) administration to determine its oral and systemic bioavailability. We looked at both plasma and brain concentrations, measured over time, following all three routes of administration (Table 4). Isolation and detection of the compound was made possible from plasma and brain by first derivatization with ethyl chloroformate and methanol, which yielded the monomethyl ester/ethyl carbamate. This material was extracted from plasma and brain with toluene and then alkylatively esterified with perfluorobenzyl bromide to afford derivative **200** (eq 1), which could be detected using GC/MS.



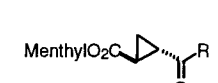
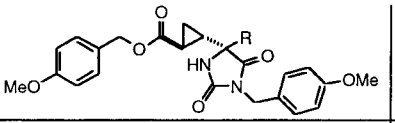
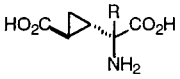
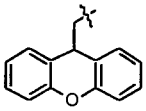
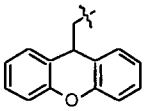
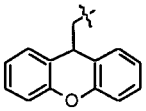
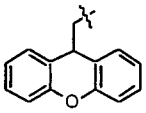
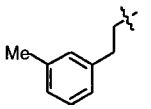
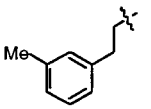
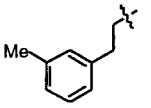
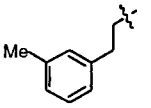
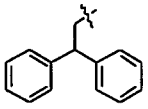
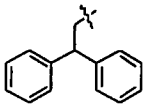
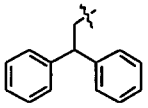
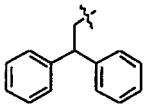

**200**

We found that, following either an iv or ip dose of 10 mg/kg, peak plasma concentrations ($C_{max}$) were observed for **168** at 15 min, the first time point at which measurements were taken. By 4 h, **168** is nearly cleared from plasma. The half-life by both routes is nearly identical, about 45 min. Peak brain concentrations are achieved somewhere between 15 and 30 min after either iv or ip administration, indicating that the compound rapidly crosses the blood−brain barrier in rats. It appears that about 10% of the iv and ip dose gets into the brain.

Oral administration of either a 10 or 100 mg/kg dose of **168** gave peak plasma concentrations at 30 min for the low dose and 60 min for the high dose; however, oral plasma concentrations were significantly lower than those observed by the parenteral routes of administration. Oral absorption was much more consistent over time, indicating that the compound may be more slowly absorbed by this route. Peak brain levels were achieved at a much later time (4−6 h) than was observed following parenteral administration. We found that **168** was less than 5% bioavailable following oral administration. Thus, while the bioavailability of **168** is excellent following parenteral administration, oral bioavailability was low.

**In Vivo Antagonist Effects of 168.** Amino acid **201** (LY354740) is a very potent and highly selective group II mGluR agonist which is active following parenteral

**Table 3.** Physical Chemical Data for Resolved Amino Acids and Intermediates: Optical Rotations and Elemental Analyses

| |  | | |  | | |  | | |
|---|---|---|---|---|---|---|---|---|---|
| R | Ketone[a] | $[\alpha]_D$[b] | Analysis | Hydantoin[c] | $[\alpha]_D$[b] | Analysis | Amino Acid[c] | $[\alpha]_D$[b] | Analysis |
|  | *S,S*-**163** | +64.2° | C,H | *R,S,S*-**165** | +60.4° | C,H,N | *R,S,S*-**167** | +46.0° (c = 0.5) | C,H,N |
|  | | | | *S,S,S*-**166** | +85.2° | C,H,N | *S,S,S*-**168** | +36.0° (c = 0.5) | C,H,N •0.5 $H_2O$ |
|  | *R,R*-**169** | −85.0° | C,H[e] | *S,R,R*-**171** | −87.8° | C,H,N | *S,R,R*-**173** | −24.0° (c = 0.25) | C,H,N •$H_2O$ |
|  | | | | *R,R,R*-**172** | −66.0° | C,H,N | *R,R,R*-**174** | −27.0° (c = 1) | C,H,N •0.5 $H_2O$•0.05 $C_5H_5N$ |
|  | *S,S*-**175** | +105° | C,H | *R,S,S*-**177** | +48.4° | C,H,N | *R,S,S*-**179** | +46.0° (c = 0.5) | C,H,N |
|  | | | | *S,S,S*-**178** | +67.4° | C,H,N | *S,S,S*-**180** | +62.0° (c = 0.5) | C,H,N •0.25 $H_20$ |
|  | *R,R*-**181** | −98.3° | C,H | *S,R,R*-**183** | −51.8° | C,H,N | *S,R,R*-**185** | −56.0° (c = 0.5) | C,H,N •0.75 $H_2O$ |
|  | | | | *R,R,R*-**184** | −67.8° | C,H,N | *R,R,R*-**186** | −28.3° (c = 0.5) | C,H,N |
|  | *S,S*-**187** | +28.4° | C,H | *R,S,S*-**189** | +47.8° | C,H,N | *R,S,S*-**191** | +44.0° (c = 0.5) | C,H,N •0.25 $H_2O$ |
|  | | | | *S,S,S*-**190** | +63.8° | C,H,N | *S,S,S*-**192** | +42.8° (c = 0.5) | C,H,N •0.25 $H_2O$ |
|  | *R,R*-**193** | −95.5° | C,H | *S,R,R*-**194**[f] | +3.6° | C,H,N[f] | *S,R,R*-**198** | −18.9° (c = 0.3) | C,H,N •0.75 $H_2O$ |
|  | | | | *R,R,R*-**197**[f] | | C,H,N[f] | *R,R,R*-**199** | −40.0° (c = 0.25) | C,H,N •1.5 NaCl |

[a] The stereochemical designators for the ketone refer to the stereochemistry of the cyclopropane carbons. Although not shown, these compounds are either the (1*R*,2*S*,5*R*)-menthyl (**163**, **175**, **187**) or the (1*S*,2*R*,5*S*)-menthyl (**169**, **181**, **193**) esters. The stereochemical designators for the hydantoins and amino acids are given in an order where the first letter refers to C-5 of the hydantoin or the amino acid carbon and the second and third letters refer to the stereochemistry of the cyclopropane carbons. [b] All rotations on the ketones and *N*,*O*-bis(*p*-methoxybenzyl)hydantoins were done at $c = 1$ in dichloromethane, except for **187**, which was $c = 1$ in methanol. All rotations on the amino acids were done in 1 N sodium hydroxide at the concentration indicated in parentheses. [c] 169. Anal. C: calcd, 78.00; found, 78.51. H: calcd, 7.67; found, 7.01. [d] All of the amino acids, with the exception of 192, were found to have an optical purity (enatiomeric excess) ≥98%, as determined by HPLC on a Chiracel OD-R column. See footnote 13 for conditions. [e] The optical rotation and elemental analysis for **194** are for the parent hydantoin diastereomer, containing no *p*-methoxybenzyl groups. The elemental analysis for **197** is for the *N*-(phenylsulfonyl)hydantoin, which also contains no *p*-methoxybenzyl groups. See Scheme 6 for structures.

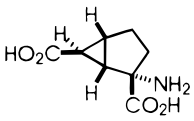
**Table 4.** Plasma and Brain Concentrations and Pharmacokinetic Parameters of **168** following Intravenous (iv), Intraperitoneal (ip), and Oral (po) Administration in Rats

| time (h) | 10 mg/kg iv | 10 mg/kg ip | 10 mg/kg po | 100 mg/kg po |
|---|---|---|---|---|
| Plasma Concentrations (ng/mL) | | | | |
| 0.25 | 12020 | 14270 | | |
| 0.5 | 5968 | 10690 | 64.1 | 197.2 |
| 1 | 2436 | 4572 | 48.3 | 475.3 |
| 2 | 845.2 | 1121 | 50.0 | 419.6 |
| 4 | 35.9 | 39.9 | 28.3 | 95.5 |
| 6 | | | 17.5 | 102.2 |
| Brain Concentrations (ng/g) | | | | |
| 0.25 | 233.8 | 210.9 | | |
| 0.5 | 243.4 | 245.5 | 1.7 | 5.1 |
| 1 | 187.9 | 235.1 | 2.1 | 16.4 |
| 2 | 177.3 | 202.3 | 3.0 | 23.9 |
| 4 | 144.8 | 148.9 | 7.4 | 20.1 |
| 6 | | | 4.8 | 29.6 |

| parameters[a] | 10 mg/kg iv | 10 mg/kg ip | 10 mg/kg po | 100 mg/kg po |
|---|---|---|---|---|
| Plasma Pharmacokinetic Parameters | | | | |
| $t_{1/2}$ (h) | 0.48 | 0.44 | 2.64 | 1.94 |
| Cl (p) (L/h/kg) | 1.19 | 0.78 | | |
| $V_d$ (area) (L/kg) | 0.83 | 0.49 | | |
| $C_{max}$ (ng/mL) | 12020 | 14270 | 64.1 | 475.3 |
| $T_{max}$ (h) | 0.25 | 0.25 | 0.5 | 1 |
| AUC (4 or 6) (ng/mL) h | 8374 | 12727 | 217.4 | 1378 |
| AUC (infinity) (ng/mL) h | 8399 | 12752 | 283.9 | 1663 |
| % bioavailability | <Tr> | 152 | 3.4 | 2.0 |
| Brain Pharmacokinetic Parameters | | | | |
| $t_{1/2}$ (h) | 5.43 | 4.75 | NC | NC |
| $C_{max}$ (ng/g) | 243.4 | 245.5 | 7.4 | 30.0 |
| $T_{max}$ (h) | 0.5 | 0.5 | 4 | 6 |
| AUC (4 or 6) (ng/mL) h | 701.4 | 773.5 | 26.5 | 120.4 |
| AUC (infinity) (ng/mL) h | 1837 | 1794 | NC | NC |

[a] $t_{1/2}$, half-life; Cl, clearance rate; $V_d$, volume of distribution; $C_{max}$, maximum concentration achieved in plasma or brain; $T_{max}$, time of maximum concentration; AUC, area under the curve.

and oral administration in animals. For example, ip administration of a 10 mg/kg dose of **201** (20 min prior



201

to evaluation) significantly increased the time that male NIH Swiss mice spent exploring the open zone of an elevated plus maze (Figure 2), which indicated an anxiolytic profile for this compound.[12] We felt that the use of **201** in this assay might allow us to demonstrate in vivo group II mGluR antagonist activity with a compound, from this SAR, e.g., **168**. We looked at doses of 0.03, 0.1, and 0.3 mg/kg of **168**, administered ip 20 min prior to administration of **201** (Figure 2). We found that the dose of 0.3 mg/kg was effective in antagonizing the effects of **201**, as indicated by a decrease in time spent exploring the open zone of the elevated plus maze, without altering closed arm performance or nose pokes. Thus, we demonstrated that this in vivo pharmacological effect of **201**, a highly selective group II mGluR agonist, can be blocked by in vivo administration of the group II mGluR antagonist, **168**.

**In Vivo Activity of 168 in a Mouse Limbic Seizure Model.** The lack of very potent and selective antagonists for mGluRs has hampered our ability to understand the therapeutic potential of these compounds. We hope that these potent and systemically active group II mGluR antagonists will be useful research tools to define what value these compounds may have as therapeutic agents.

It has been shown that intracerebral (ic) injection of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid ACPD (1*S*,3*R*-ACPD) or (3,5-dihydroxyphenyl)glycine (3,5-DHPG; **202**) produces a characteristic limbic seizure in CD-1 mice.[17] The former compound is a nonselective group I and II mGluR agonist,[18] while the latter is a selective group I mGluR agonist.[19,20] Confident that **168** demonstrated very good bioavailability following parenteral administration, we evaluated this amino acid for its ability to block limbic seizures induced by **202**. Given intraperitoneally 60 min prior to 400 nmol (ic) of **202**, we saw a dose-dependent protection from limbic seizures at doses ranging from 10 to 100 mg/kg, with an $ED_{50}$ of 31 mg/kg.

## Conclusions

In this and the preceding paper, we showed that by appending a lipophilic group onto the amino acid carbon of the potent and selective mGluR agonist **1**, we obtained a very potent series of group II mGluR antagonists. Incorporation of a substituent onto the aromatic ring of **3** provided in many cases a significant increase in potency. Except for fluorine, activity was optimized when the substituent was meta on the aromatic ring. In many cases, activity was increased regardless of whether the substituent was electron donating or withdrawing, leading us to believe that the improvement in activity was mostly a result of a favorable steric interaction with the receptor protein. When three amino acids were resolved into their constituent isomers, activity for each was found to reside in the *S*,*S*,*S*-isomer.

One compound, the *S*,*S*,*S*-xanthylmethyl compound **168** (the most potent analogue from this SAR), was evaluated for oral and systemic bioavailability. We found that while good plasma and brain levels were achieved following iv and ip administration, oral bioavailability for this compound was disappointingly low (≤5%). A low dose of amino acid **168** was able to block anxiolytic effects of an mGluR agonist in the elevated plus maze in mice, and higher doses were effective in blocking agonist-induced limbic seizures in mice, both following ip administration. Thus, these compounds should serve as a useful systemically active tools to explore the nature of group II mGluRs in CNS disorders, possibly beginning to define the therapeutic potential for this class of compounds.

## Experimental Section

**General.** See the preceding paper.[3]

**2-(3-Cyclopropylphenyl)-1,3-dioxolane (143).** A solution of 5.0 g (21.8 mmol) of 2-(3-bromophenyl)-1,3-dioxolane (**142**), 0.64 g (0.55 mmol) of tetrakis(triphenylphosphine)palladium-(0), and cyclopropylmagnesium bromide (prepared from 4.2 g (34.9 mmol) of cyclopropyl bromide and 0.79 g (32.7 mmol) of magnesium filings in 18 mL of THF) in 120 mL of THF was heated to reflux for 5 h, then cooled, and treated with 50 mL

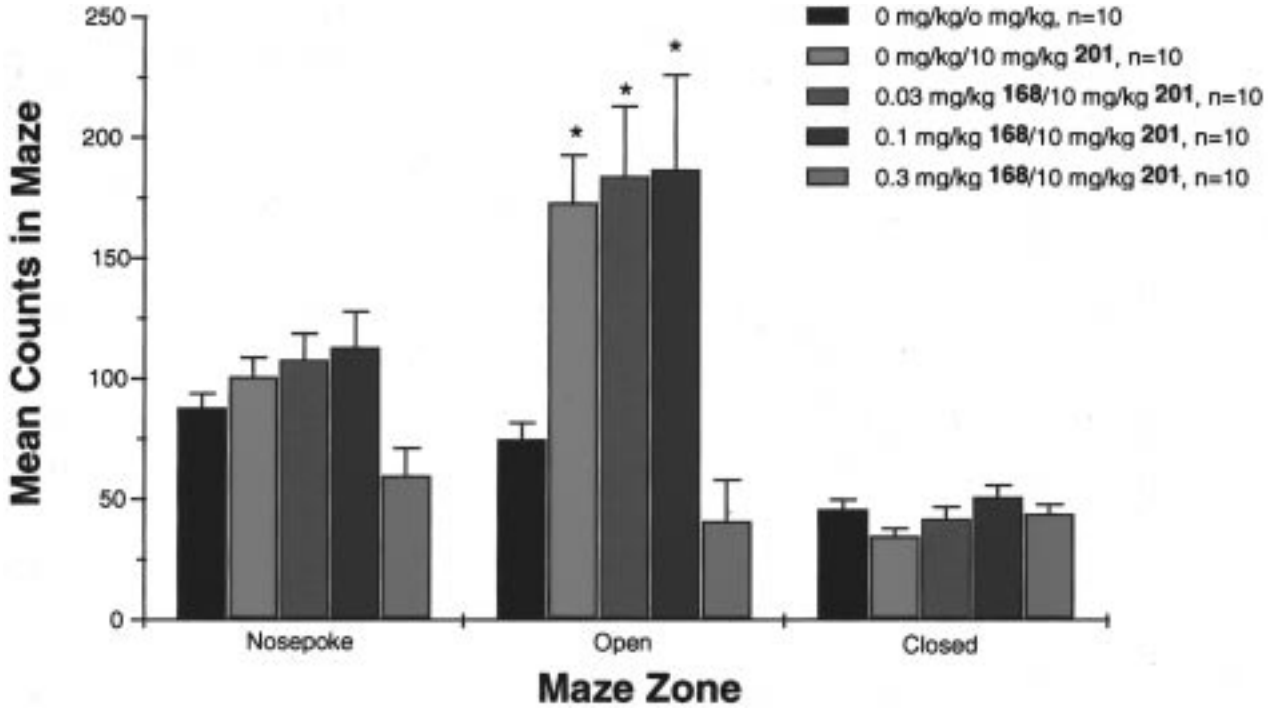



**Figure 2.** Effects of a group II mGluR antagonist (**168**) on a group II mGluR agonist (**201**)-induced increases on the elevated plus maze in male NIH Swiss mice. Amino acid **168** was administered 20 min prior to administration of **201**, which was administered 20 min before evaluation in the maze.

of water. The mixture was extracted three times with 100 mL each of ether, and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (250 g silica gel, 10% ethyl acetate/hexane) afforded 2.3 g (56%) of **143**.

**3-Cyclopropylbenzaldehyde (144).** A solution of 2.3 g (12.1 mmol) of **143** in 70 mL of acetonitrile and 18 mL of 1 N hydrochloric acid were stirred overnight at room temperature and then concentrated in vacuo to remove most of the acetonitrile. The mixture was diluted with 25 mL of water and extracted three times with 25 mL each of ether. The combined organic extracts were washed once with 25 mL of saturated aqueous sodium bicarbonate, then dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.6 g (91%) of **144**.

**2-(3-Cyclopentylphenyl)-1,3-dioxolane (145).** As for **143**, 5.0 g (21.8 mmol) of **142**, 0.64 g (0.55 mmol) of tetrakis(triphenylphosphine)palladium(0), and 27.2 mL (54.5 mmol) of cyclopentylmagnesium chloride in 120 mL of THF afforded 2.2 g (47%) of **145**.

**3-Cyclopentylbenzaldehyde (146).** As for **144**, 2.2 g (10.2 mmol) of **145** afforded 1.6 g (91%) of **146**.

**3-*tert*-Butyl-1-(((trifluoromethyl)sulfonyl)oxy)benzene (147).** A room-temperature solution of 7.4 g (46.6 mmol) of 3-*tert*-butylphenol, 20.8 g (58.3 mmol) of *N*-phenyltriflimide, and 6.0 g (46.6 mmol) of diisopropyl-*N*-ethylamine in 130 mL of dichloromethane was stirred overnight and then concentrated in vacuo. The residue was partitioned between 200 mL of ethyl acetate and 50 mL of water, the organic layer was separated, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (600 g of silica gel, 25% ethyl acetate/hexane) afforded 12.3 g (93%) of **147**.

**3-*tert*-Butylbenzaldehyde (148).** A solution of 12.3 g (43.5 mmol) of **147**, 14.2 g (44.8 mmol) of vinyl tri-*n*-butylstannane, 5.5 g (131 mmol) of lithium chloride, and 2.5 g (2.2 mmol) of tetrakis(triphenylphosphine)palladium(0) in 170 mL of dioxane was heated to 100 °C for 3 h, then cooled, diluted with 200 mL of ether, filtered through diatomaceous earth and concentrated in vacuo. The residue was dissolved in 150 mL of hexane and washed once with 100 mL of water and once with 100 mL of saturated aqueous potassium fluoride. Ether (150 mL) was added to break the emulsion, the aqueous layer was separated, and the organic layer was washed once with 50 mL of water. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue (3-*tert*-butyl-1-vinylbenzene) was dissolved in 200 mL of dioxane and 65 mL of water and then treated with 7.2 mL of a 2.5% solution of osmium tetroxide in 2-propanol (0.57 mmol). After 10 min at room temperature, 18.6 g (87.0 mmol) of sodium metaperiodate was added and the mixture stirred for 1 h at room temperature. Water (200 mL) and 100 mL of ether were added, the organic layer was separated, and the aqueous layer was extracted twice with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (400 g silica gel, 5% ethyl acetate/hexane) afforded 3.2 g (45%, three steps) of **148**.

**Methyl 3-(((Trifluoromethyl)sulfonyl)oxy)phenylacetate (149).** As for **147**, 24.2 g (146 mmol) of methyl 3-hydroxyphenylacetate, 65 g (182 mmol) of *N*-phenyltriflimide, and 18.8 g (146 mmol) of diisopropyl-*N*-ethylamine in 500 mL of dichloromethane gave 43.5 g (100%) of **149**.

**Methyl 3-Biphenylacetate (150).** A solution of 15.3 g (51.2 mmol) of **149**, 18.8 g (51.2 mmol) of phenyltri-*n*-butylstannane, and 6.4 g (153.6 mmol) of lithium chloride in 173 mL of toluene was degassed by evacuating with a vacuum and then purging with nitrogen (three times), the 2.3 g (2.0 mmol) of tetrakis(triphenylphosphine)palladium(0) was added, and the mixture was heated to reflux for 6 h, then cooled, diluted with 170 mL of ether and filtered, through diatomaceous earth. This solution was washed three times with 100 mL each of saturated aqueous potassium fluoride, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (500 g of silica gel, 10% ethyl acetate/hexane) afforded 3.9 g (33%) of **150**.

**2-(3-Biphenylyl)ethanol (151).** A solution of 3.8 g (16.8 mmol) of **150** in 10 mL of THF was added slowly to a room temperature suspension of 0.2 g (5.0 mmol) of lithium aluminum hydride in 50 mL of THF. An additional 0.2 g (5.0 mmol) of lithium aluminum hydride was added and the mixture stirred for 1 h more, wherein another 0.2 g (5.0 mmol) of lithium aluminum hydride was added. After an additional 1 h, the reaction was quenched slowly with 50 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer extracted four times with 20 mL each

of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 3.7 g (100%) of **151**.

**2-(3-(Methylthio)phenyl)-1,3-dioxolane (152).** To a −78 °C solution of 60.0 g (201 mmoL) of **142** in 450 mL of THF was added 132 mL (211 mmoL; 1.6 M in hexane) of *n*-butyllithium, and the mixture was stirred for 10 min at −78 °C. Then 18.9 g (201 mmol) of dimethyl disulfide was added, and the mixture was stirred for 1 h and then warmed to room temperature over 1 h. The mixture was quenched with 300 mL of water and extracted three times with 200 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (750 g of silica gel, 5% EtOAc/toluene) afforded 31.8 g (81%) of **152**.

**3-(Methylthio)benzaldehyde (153).** As for **144**, 2.3 g (11.8 mmol) of **152** afforded 1.4 g (77%) of **153**.

**2-(3-(Methylsulfonyl)phenyl)-1,3-dioxolane (154).** To a −78 °C solution of 31.8 g (162 mmoL) of **152** in 500 mL of dichloromethane was added a slurry of 102 g (324 mmol) of 55% *m*-CPBA in 200 mL of dichloromethane. The mixture was stirred for 30 min at −78 °C and for 1 h while warming to room temperature. Then 250 mL of 1 N sodium thiosulfate was added, and the mixture was stirred for 15 min. Then 500 mL of saturated aqueous sodium bicarbonate was added, the organic layer was separated, and the aqueous layer was extracted twice with 250 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 36 g (99%) of **154**.

**3-(Methylsulfonyl)benzaldehyde (155).** A solution of 36 g (159 mmol) of **154** in 750 mL of acetonitrile and 200 mL of 1 N hydrochloric acid was stirred overnight at room temperature, then concentrated in vacuo to about 400 mL. 500 mL of ether and 100 mL of brine were added, the organic layer separated and the aqueous layer extracted twice with 150 mL of ether. The combined organic extracts were washed once with 250 mL of saturated aqueous sodium bicarbonate, then dried ($MgSO_4$), filtered and concentrated in vacuo to afford 25 g (84%) of **155**.

**(2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-4-(4-hydroxyphenyl)butanoic Acid (119).** A solution of 0.36 g (1.2 mmol) of **116** in 5 mL of 48% aqueous hydrobromic acid was heated to 110 °C for 24 h, then cooled, and concentrated in vacuo. The residue was dissolved in 5 mL of water and concentrated in vacuo, and this procedure was then repeated. Cation-exchange chromatography of the residue gave a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.17 g (52%) of **119**.

**(5*SR*)- and (5*RS*)-2,4-Bis-(*tert*-butoxycarbonyl)-5-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-5-(2-(4-methylphenyl)ethyl)imidazolidine-2,4-dione (156).** A solution of 0.8 g (2.6 mmol) of **61**, 0.5 g (5.2 mmol) of triethylamine, 1.7 g (7.7 mmol) of di-*tert*-butyl dicarbonate, and 0.025 g (0.2 mmol) of 4-(*N*,*N*-dimethylamino)pyridine in 10 mL of acetonitrile was stirred at room temperature for 3 h. The mixture was washed with 20 mL of 10% aqueous sodium bisulfate, the organic layer was separated, and the aqueous layer was extracted three times with 25 mL of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.2 g (100%) of **156**.

**(2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-4-(4-methylphenyl)butanoic Acid (105).** A solution of 1.2 g (2.6 mmol) of **156** in 25 mL of 1 N sodium hydroxide was heated to reflux for 24 h, then cooled, and dissolved in 25 mL of concentrated hydrochloric acid. The resulting solution was placed in a 3.5 × 20 cm pressure tube, sealed with a no. 15 Teflon screw plug, and heated to 150 °C for 8 h. The solution was cooled, extracted once with 50 mL of ether, and then concentrated in vacuo. Cation-exchange chromatography of the residue afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.23 g (32%) of **105**.

**(2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-4-(3,5-dichlorophenyl)butanoic Acid (137).** A 5 mL (5.0 mmol) portion of 1 N sodium bis(trimethylsilyl)-amide was added to a solution containing 0.9 g (2.5 mmol) of **90** and 0.7 g (5.0 mmol) of *N*,*N*-diisopropylethylamine in 8 mL of tetrahydrofuran. The mixture was stirred 20 min, then 1.0 g (5.0 mmol) of *p*-toluenesulfonyl chloride was added, and stirring was continued overnight. The mixture was added to 10 mL of 10% aqueous sodium bisulfate and then extracted three times with 5 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue and 4.0 g (12.5 mmol) of barium hydroxide in 20 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 7 with 0.7 mL (12.5 mmol) of concentrated sulfuric acid. The resulting solid was filtered and washed three times with 10 mL each of 0.25 N sodium hydroxide. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.11 g (14%) of **137**.

**Nonracemic Amino Acids. (1*S*,2*S*)-2-((1*R*,2*S*,5*R*)-Carbomenthyloxy)cyclopropane-1-carbonyl Chloride (162a).** A solution of 35 g (86.1 mmol) of di-(1*R*,2*S*,5*R*)-menthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate (**158**)[9] and 18.9 mL (94.7 mmol) of 5 N aqueous sodium hydroxide in 260 mL of isopropyl alcohol was stirred overnight at 70 °C and then concentrated in vacuo. The residue was dissolved in 300 mL of water and washed two times with 100 mL each of ether, and then the aqueous layer was acidified to pH 1 by the addition of 1 N hydrochloric acid. This solution was extracted four times with 100 mL each of ethyl acetate, and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 19.7 g (86%) of the acid−ester. This residue was dissolved in 70 mL (114.0 g, 0.96 mol) of thionyl chloride, stirred overnight at room temperature, and then concentrated in vacuo to afford 20.1 g (82% overall) of **162a**.

**(1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cyclopropane-1-carbonyl Chloride (162b).** As for **162a**, 18 g (44.3 mmol) of di-(1*S*,2*R*,5*S*)-menthyl (1*R*,2*R*)-cyclopropane-1,2-dicarboxylate (**159**)[9] and 9.8 mL (48.7 mmol) of 5 N aqueous sodium hydroxide in 135 mL of isopropyl alcohol afforded the acid−ester, which with 36 mL (58.7 g, 0.49 mol) of thionyl chloride gave 10.1 g (80%) of **162b**.

**(1*S*,2*S*)-2-((1*R*,2*S*,5*R*)-Carbomenthyloxy)cycloprop-1-yl (9-Xanthyl)methyl Ketone (163).** A solution of 11.3 g (35 mmol) of (9-xanthyl)methyl iodide and 5.5 g (84 mmol) of zinc/copper couple in 115 mL of benzene and 16 mL of *N*,*N*-dimethylacetamide was stirred for 3 h at 60 °C, then treated with 1.6 g (1.4 mmol) of tetrakis(triphenylphosphine)palladium-(0), and heated for 5 min more. The heating bath was removed, 10 g (35 mmol) of **162a** was added, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with 115 mL of ethyl acetate and filtered through diatomaceous earth. The filtrate was washed with 200 mL of 10% aqueous sodium bisulfate, 200 mL of saturated aqueous sodium bicarbonate, and 200 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (500 g of silica gel, 10% ethyl acetate/hexane) of the residue afforded 9.6 g (61%) of **163**.

**(5*SR*)-5-((1*SR*,2*SR*)-2-Carboxycycloprop-1-yl)-5-((9-xanthyl)methyl)imidazolidine-2,4-dione (164).** A solution of 26.6 g (59.6 mmol) of **163** in 135 mL of ethanol and 65.5 mL of 1 N sodium hydroxide was stirred 24 h at 55 °C. Then 19.4 g (298.0 mmol) of potassium cyanide, 41.8 g (536 mmol) of ammonium carbonate, and 65 mL of water were added; then this mixture was heated to 55 °C for 48 h. The mixture was cooled, extracted once with 100 mL of ether then added to 300 mL of 5 N hydrochloric acid. The resulting mixture was allowed to stand at room temperature, then the solid was filtered, and recrystallization from acetone and water afforded 11.5 g (51%) of **164**.

**(5*R*)-5-(1*S*,2*S*-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-5-((9-xanthyl)methyl)-3-(4-methoxybenzyl)-imidazolidine-2,4-dione (165) and (5*S*)-5-((1*S*,2*S*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-5-((9-xanthyl)methyl)-3-(4-methoxybenzyl)imidazolidine-2,4-dione (166).** A solution of 3.8 g (10 mmol) of **164** and 2.8 g (28 mmol) of potassium bicarbonate in 30 mL of DMF was treated with 3.6 g (23 mmol) of 4-methoxybenzyl chloride and heated to 125 °C for 2 h. The mixture was diluted with 30 mL of ether and 60 mL of water. The organic layer was removed, the aqueous layer was extracted three times with 20 mL each of ether, of then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (600 g of silica gel, 30% ethyl acetate/hexane) of the residue afforded 2.3 g (38%) of **165** (higher $R_f$ material) and 2.2 g (36%) of **166** (lower $R_f$ material).

**(2*R*)-2 Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-3-(9-xanthyl)propanoic Acid (167).** A solution of 2.3 g (3.7 mmol) of **165** and 5.9 g (18.6 mmol) of barium hydroxide in 25 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 7 with 1.0 mL (18.6 mmol) of concentrated sulfuric acid. The resulting solution was heated at 100 °C for 1 h, and then the solid was filtered and washed three times with 10 mL each of water. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.15 g (11%) of **167**.

**(2*S*)-2-Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-3-(9-xanthyl)propanoic Acid (168).** A solution of 5.2 g (8.4 mmol) of **166** in 100 mL of 1 N sodium hydroxide was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled, extracted three times with 30 mL each of ether, and then acidified to pH 7 with concentrated hydrochloric acid. Cation-exchange chromatography of this solution afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 1.5 g (52%) of **168**.

**(1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl (9-Xanthyl)methyl Ketone (169).** As for **163**, 6.7 g (20.7 mmol) of (9-xanthyl)methyl iodide, 2.6 g (39.6 mmol) of zinc/copper couple, and then 0.4 g (0.34 mmol) of tetrakis(triphenylphosphine)palladium(0) and 4.9 g (17.2 mmol) of **162b** in 60 mL of benzene and 6 mL of *N*,*N*-dimethylacetamide afforded 5.0 g (65%) of **169**.

**(1*R*,2*R*)-2-Carboxycycloprop-1-yl (9-Xanthyl)methyl Ketone.** A solution of 4.7 g (10.5 mmol) of **169** in 30 mL of ethanol and 11.5 mL of 1 N sodium hydroxide was stirred 7 h at 65 °C, then 5.2 mL (5.2 mmol) more 1 N sodium hydroxide was added. The reaction mixture was stirred for an additional 16 h at 60 °C. The mixture was concentrated in vacuo, and the residue was dissolved in 50 mL of water, extracted three times with 50 mL each of ether, and then brought to pH 1 with 10% aqueous sodium bisulfate. The resulting solution was extracted three times with 50 mL each of ethyl acetate, and the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 3.1 g (95%) of (1*R*,2*R*)-2-carboxycycloprop-1-yl (9-xanthyl)methyl ketone.

**(5*SR*)-5-((1*R*,2*R*)-2-Carboxycycloprop-1-yl)-5-((9-xanthyl)methyl)imidazolidine-2,4-dione (170).** A solution of 7.1 g (23.1 mmol) of (1*R*,2*R*)-2-carboxycycloprop-1-yl (9-xanthyl)-methyl ketone in 40 mL of ethanol was added to a solution of 7.5 g (115.5 mmol) of potassium cyanide and 20.0 g (207.4 mmol) of ammonium carbonate in 40 mL of water, and then this mixture was heated to 55 °C for 120 h. The mixture was cooled and added to 400 mL of 10% aqueous sodium bisulfate. The resulting mixture was allowed to stand at room temperature, the solid was filtered, and recrystallization from acetone and water afforded 6.8 g (78%) of **170**.

**(5*S*)-5-((1*R*,2*R*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-5-((9-xanthyl)methyl)-3-(4-methoxybenzyl)-imidazolidine-2,4-dione (171) and (5*R*)-5-((1*R*,2*R*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-5-((9-xanthyl)methyl)-3-(4-methoxybenzyl)imidazolidine-2,4-dione (172).** As for **165/166**, 5.8 g (15.3 mmol) of **170**, 4.3 g (42.8 mmol) of potassium bicarbonate, and 5.5 g (35.2 mmol) of 4-methoxybenzyl chloride in 60 mL of DMF afforded 4.0 g (43%) of **171** (higher $R_f$ material) and 4.2 g (44%) of **172** (lower $R_f$ material).

**(2*S*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-3-(9-xanthyl)propanoic Acid (173).** A mixture of 3.7 g (6.1 mmol) of **171** and 9.5 g (30.3 mmol) of barium hydroxide in 40 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 2 with 4 N sulfuric acid. The resulting solution was heated at 100 °C for 1 h, and then the solid was filtered and washed three times with 50 mL each of 0.2 N sodium hydroxide. Cation-exchange chromatography of the filtrate afforded 80 mg of a solid that was soluble in acetone. The filter cake from filtration after acidification was washed two times with 0.25 N sodium hydroxide and once with 30 mL of water. After the pH was adjusted 2 with 5 N hydrochloric acid, cation-exchange chromatography afforded a solid which was suspended in acetone, filtered, rinsed with acetone and ether, and then dried in vacuo at 60 °C to afford 41 mg (2%) of **173**.

**(2*R*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-3-(9-xanthyl)propanoic Acid (174).** A solution of 4.0 g (6.5 mmol) of **172** and 10.2 g (32.3 mmol) of barium hydroxide in 40 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 2 with 4 N sulfuric acid. The resulting solution was filtered through diatomaceous earth and washed two times with 25 mL each of 0.25 N sodium hydroxide. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 1.0 g (43%) of **174**.

**(1*S*,2*S*)-2-((1*R*,2*S*,5*R*)-Carbomenthyloxy)cycloprop-1-yl 2-(3-Methylphenyl)ethyl Ketone (175).** As for **163**, 5.4 g (22 mmol) of 1-iodo-2-(3-methylphenyl)ethane and 3.4 g (52 mmol) of zinc/copper couple, then 0.9 g (0.8 mmol) of tetrakis-(triphenylphosphine)palladium(0) and 5.7 g (20 mmol) of **162a** in 66 mL of benzene and 8 mL of *N*,*N*-dimethylacetamide, afforded 4.6 g (61%) of **175**.

**(5*SR*)-5-((1*S*,2*S*)-2-Carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione (176).** As for **164**, 25.5 g (69.0 mmol) of **175** and 76 mL of 1 N sodium hydroxide in 150 mL of ethanol and then 22.4 g (344.0 mmol) of potassium cyanide, 48.3 g (619.0 mmol) of ammonium carbonate, and 75 mL of water afforded 18.1 g (90%) of **176**.

**(5*R*)-5-((1*S*,2*S*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-3-(4-methoxybenzyl)-5-(2-(3-methylphenyl)-ethyl)imidazolidine-2,4-dione (177) and (5*S*)-5-(1*S*,2*S*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-3-(4-methoxybenzyl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione (178).** As for **165/166**, 2.6 g (8.9 mmol) of **176**, 2.5 g (25.1 mmol) of potassium bicarbonate, and 3.2 g (20.6 mmol) of 4-methoxybenzyl chloride in 30 mL of DMF afforded 1.6 g (33%) of **177** (higher $R_f$ material) and 1.6 g (33%) of **178** (lower $R_f$ material).

**(5*R*)-5-((1*S*,2*S*)-Carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione.** A solution of 1.5 g (2.8 mmol) of **177** in 90 mL of acetonitrile was added to a solution of 12.3 g (22.4 mmol) of ceric ammonium nitrate in 30 mL of water, and then this mixture was stirred at room temperature for 2.5 h. The mixture was diluted with 90 mL of brine, the organic layer was separated, the aqueous layer extracted four times with 30 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (150 g of silica gel, 2% glacial acetic acid/50% ethyl acetate/48%hexane) of the residue afforded 0.49 g (60%) of (5*R*)-5-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione.

**(2*R*)-2-Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-4-(3-methylphenyl)butanoic Acid (179).** A solution of 0.49 g (1.7 mmol) of (5*R*)-5-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-5-(2-(3-

methylphenyl)ethyl)imidazolidine-2,4-dione and 2.7 g (8.5 mmol) of barium hydroxide in 10 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 7 with 0.5 mL (8.5 mmol) of concentrated sulfuric acid. The resulting solution was heated at 100 °C for 1 h, and then the solid was filtered and washed three times with 10 mL each of water. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water and filtered, washed, water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.21 g (44%) of **179**.

**(2*S*)-2-Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-4-(3-methylphenyl)butanoic Acid (180).** A solution of 7.3 g (13.4 mmol) of **178** in 100 mL of 1 N sodium hydroxide was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled, washed three times with 30 mL each of ether, and then acidified to pH 7 with concentrated hydrochloric acid. Cation-exchange chromatography of this solution afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 1.9 g (50%) of **180**.

**(1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl 2-(3-Methylphenyl)ethyl Ketone (181).** As for **163**, 5.7 g (23.0 mmol) of 1-iodo-2-(3-methylphenyl)ethane and 2.9 g (44.2 mmol) of zinc/copper couple then with 0.44 g (0.38 mmol) of tetrakis(triphenylphosphine)palladium(0) and 5.5 g (19.2 mmol) of **162b** in 65 mL of benzene and 6.5 mL of *N*,*N*-dimethylacetamide afforded 4.7 g (65%) of **181**.

**(1*R*,2*R*)-2-(Carboxycycloprop-1-yl) 2-(3-Methylphenyl)-ethyl Ketone.** A solution of 4.4 g (11.8 mmol) of **181** in 35 mL of ethanol and 14.3 mL of 1 N sodium hydroxide was stirred 18 h at 65 °C and then concentrated in vacuo. The residue was dissolved in 30 mL of water, extracted three times with 10 mL each of ether, and then brought to pH 2 with 10% aqueous sodium bisulfate. The resulting solution was extracted four times with 15 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo at 60 °C to afford 2.3 g (95%) of (1*R*,2*R*)-2-carboxycycloprop-1-yl 2-(3-methylphenyl)ethyl ketone.

**(5*SR*)-5-((1*R*,2*R*)-2-Carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione (182).** A solution of 2.4 g (10.3 mmol) of (1*R*,2*R*)-2-carboxycycloprop-1-yl 2-(3-methylphenyl)ethyl ketone in 16 mL of ethanol was added to a solution of 3.4 g (51.7 mmol) of potassium cyanide and 8.9 g (93.0 mmol) of ammonium carbonate in 16 mL of water, and then this mixture was heated to 55 °C for 24 h. The mixture was cooled and added to 200 mL of 10% aqueous sodium bisulfate. The resulting mixture was allowed to stand at room temperature, the solid thus obtained was filtered, and recrystallization from acetone and water afforded 2.0 g (63%) of **182**.

**(5*S*)-5-((1*R*,2*R*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-3-(4-methoxybenzyl)-5-(2-(3-methylphenyl)-ethyl)imidazolidine-2,4-dione (183) and (5*R*)-5-((1*R*,2*R*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-3-(4-methoxybenzyl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione (184).** As for **165/166**, 2.0 g (6.5 mmol) of **182**, 1.8 g (18.3 mmol) of potassium bicarbonate, and 2.4 g (15.0 mmol) of 4-methoxybenzyl chloride in 25 mL of DMF afforded 1.7 g (48%) of **183** (higher $R_f$ material) and 1.2 g (34%) of **184** (lower $R_f$ material).

**(5*S*)-5-((1*R*,2*R*)-2-Carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione.** A solution of 1.6 g (2.9 mmol) of **183** in 90 mL of acetonitrile was added to a solution of 12.5 g (22.9 mmol) of ceric ammonium nitrate in 30 mL of water, and then this mixture was stirred at room temperature for 2.5 h. The mixture was diluted with 60 mL of brine and extracted four times with 40 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (200 g of silica gel, 2% glacial acetic acid/50% ethyl acetate/48% hexane) of the residue afforded a solid which was recrystallized from water/acetone. The crystals were filtered, rinsed with water, and dried in vacuo at 60 °C to afford 0.44 g (50%) of (5*S*)-5-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)-ethyl)imidazolidine-2,4-dione.

**(2*S*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-4-(3-methylphenyl)butanoic Acid (185).** A solution of 0.44 g (1.4 mmol) of (5*S*)-5-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione and 2.3 g (7.2 mmol) of barium hydroxide in 12 mL of water was heated to 250 °C for 16 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 2 with concentrated sulfuric acid. The resulting solution was heated at 90 °C for 1 h, and then the solid was filtered and washed three times with 10 mL each of water. The filtrate was concentrated in vacuo to a volume of 10 mL. Cation-exchange chromatography of the filtrate afforded a solid that was dissolved in water and concentrated in vacuo. The resulting solid was suspended in acetone, filtered, washed with acetone and ether, and then dried in vacuo at 60 °C to afford 21 mg (5%) of **185**.

**(5*R*)-5-((1*R*,2*R*)-2-Carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione.** A solution of 1.0 g (1.9 mmol) of **184** in 60 mL of acetonitrile was added to a solution of 8.3 g (15.2 mmol) of ceric ammonium nitrate in 20 mL of water, and then this mixture was stirred at room temperature for 2.5 h. The mixture was diluted with 60 mL of brine and extracted four times with 20 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (50 g of silica gel, 2% glacial acetic acid/50% ethyl acetate/48% hexane) of the residue afforded a solid which was recrystallized from water/acetone. The crystals were filtered, rinsed with water, and dried in vacuo at 60 °C to afford 0.25 g (42%) of (5*R*)-5-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)-imidazolidine-2,4-dione.

**(2*R*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-4-(3-methylphenyl)butanoic Acid (186).** A solution of 0.53 g (1.75 mmol) of (5*R*)-5-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-5-(2-(3-methylphenyl)ethyl)imidazolidine-2,4-dione and 2.8 g (8.8 mmol) of barium hydroxide in 15 mL of water was heated to 250 °C for 16 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 2 with concentrated sulfuric acid. The resulting solution was heated at 90 °C for 1 h, and then the solid was filtered through Celite, washed three times with 10 mL each of water and three times with 10 mL each of 0.33 N sodium hydroxide, and concentrated in vacuo to about 10 mL. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.09 g (19%) of **186**.

**(1*S*,2*S*)-2-((1*R*,2*S*,5*R*)-Carbomenthyloxy)cycloprop-1-yl 2,2-Diphenylethyl Ketone (187).** As for **163**, 5.5 g (18 mmol) of 2,2-diphenyl-1-iodoethane and 2.8 g (42.9 mmol) of zinc/copper couple and then 0.8 g (0.7 mmol) of tetrakis-(triphenylphosphine)palladium(0) and 4.7 g (16.4 mmol) of **162a** in 60 mL of benzene and 8 mL of *N*,*N*-dimethylacetamide afforded 5.2 g (73%) of **187**.

**(5*SR*)-5-((1*S*,2*S*)-2-Carboxycycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione (188).** As for **164**, 9.4 g (21.7 mmol) of **187** and 24 mL of 1 N sodium hydroxide in 50 mL of ethanol and then 7.7 g (119.0 mmol) of potassium cyanide, 19.5 g (195.0 mmol) of ammonium carbonate, and 24 mL of water afforded 4.0 g (50%) of **188**.

**(5R)-5-((1*S*,2*S*)-2-(((4-Methoxybenzyl)oxy)carbonyl)cycloprop-1-yl)-5-(2,2-diphenylethyl)-3-(4-methoxybenzyl)-imidazolidine-2,4-dione (189) and (5*S*)-5-((1*S*,2*S*)-2-((4-Methoxy)benzyloxy)cycloprop-1-yl)-5-(2,2-diphenylethyl)-3-(4-methoxybenzyl)imidazolidine-2,4-dione (190).** As for **165/166**, 4.0 g (11.0 mmol) of **187**, 3.1 g (30.7 mmol) of potassium bicarbonate, and 3.9 g (25.2 mmol) of 4-methoxybenzyl chloride in 40 mL of DMF afforded 2.0 g (30%) of **189** (higher $R_f$ material) and 2.7 g (41%) of **190** (lower $R_f$ material).

**(5*R*)-5-((1*S*,2*S*)-2-Carboxycycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione.** A solution of 1.0 g (1.6 mmol) of **189** in 50 mL of acetonitrile was added to a solution of 7.2 g (13.2 mmol) of ceric ammonium nitrate in 15 mL of water, and then this mixture was stirred at room temperature

for 5 h. The mixture was diluted with 50 mL of brine. The organic layer was separated, the aqueous layer was extracted four times with 50 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (150 g of silica gel, 2% glacial acetic acid/50% ethyl acetate/48% hexane) of the residue afforded 0.37 g (63%) of (5*R*)-5-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione.

**(2*R*)-2-Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-4,4-diphenylbutanoic Acid (191).** A solution of 0.37 g (1.0 mmol) of (5*R*)-5-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione and 1.6 g (5 mmol) of barium hydroxide in 10 mL of water was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 7 with 0.27 mL (5 mmol) of concentrated sulfuric acid. The resulting solid was filtered and washed three times with 10 mL each of water. Cation-exchange chromatography of the filtrate afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.028 g (8%) of **191**.

**(2*S*)-2-Amino-2-((1*S*,2*S*)-2-carboxycycloprop-1-yl)-4,4-diphenylbutanoic Acid (192).** A solution of 2.7 g (4.5 mmol) of **190** in 100 mL of 1 N sodium hydroxide was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled, washed three times with 30 mL each of ether, and then acidified to pH 7 with concentrated hydrochloric acid. This solution was concentrated to half its volume, and then cation-exchange chromatography afforded a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.91 g (59%) of **192**.

**(1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl 2,2-Diphenylethyl Ketone (193).** As for **163**, 7.1 g (23.0 mmol) of 2,2-diphenyl-1-iodoethane and 2.9 g (44.2 mmol) of zinc/copper couple and then 0.44 g (0.38 mmol) of tetrakis(triphenylphosphine)palladium(0) and 5.5 g (19.2 mmol) of **162b** in 65 mL of benzene and 6.5 mL of *N*,*N*-dimethylacetamide afforded 4.5 g (54%) of **193**.

**(5*S*)-5-((1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione (194) and (5*R*)-5-((1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)-cycloprop-1-yl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione (195).** A solution of 6.3 g (14.5 mmol) of **193** in 35 mL of ethanol was added to a solution of 4.7 g (72.3 mmol) of potassium cyanide and 12.5 g (130.1 mmol) of ammonium carbonate in 20 mL of water, and then this mixture was heated to 55 °C for 24 h. The mixture was cooled, and 25 mL of water was added. The mixture was extracted four times with 30 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (400 g of silica gel, 25% ethyl acetate/hexane) of the residue afforded 4.3 g of **193** and 2.3 g of a mixture of **194** and **195**. Trituration with ethyl acetate afforded 0.54 g (7%) of **195** (two crops). The mother liquors were concentrated in vacuo to afford 1.2 g (16%) of a mixture of **194** and **195** (undetermined ratio).

**(5*S*)-5-((1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl)-3-(phenylsulfonyl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione (196).** A solution of 1.1 g (2.1 mmol) of the mixture of **194** and **195** in 15 mL of THF was treated with 2.3 mL (2.3 mmol) of sodium bis(trimethylsilyl)amide (1 M in THF) and stirred at room temperature for 20 min. To the mixture was added 0.4 g (2.2 mmol) of benzenesulfonyl chloride, and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled, diluted with 15 mL of water, and extracted three times with 20 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (150 g of silica gel, 25% ethyl acetate/hexane) of the residue afforded 0.55 g (43%) of **196**, 0.21 g (16%) of a mixture of **196** and **197**, and 0.05 g (4%) of **197**.

**(2*S*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-4,4-diphenylbutanoic Acid (198).** A mixture of 0.51 g (0.8 mmol) of **196** and 1.3 g (4.0 mmol) of barium hydroxide in 10 mL of water was heated to reflux for 18 h. The mixture was cooled and acidified to pH 3 with 4 N sulfuric acid and heated to reflux for 1 h. While hot, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The resulting solid was suspended in 0.5 mL of water, and 10 drops of 1 N sodium hydroxide were added. The mixture was then filtered, and the filtrate was acidified to pH 2 with 1 N hydrochloric acid, whereupon a precipitate formed. The precipitate was filtered, washed with water, acetone, and ether, and then dried in vacuo at 60 °C to afford 0.02 g (7%) of **198**.

**(5*R*)-5-((1*R*,2*R*)-2-((1*S*,2*R*,5*S*)-Carbomenthyloxy)cycloprop-1-yl)-3-(phenylsulfonyl)-5-(2,2-diphenylethyl)imidazolidine-2,4-dione (197).** A solution of 0.51 g (1.0 mmol) of **195** in 12 mL THF was treated with 1.1 mL (1.1 mmol) of a 1 M THF solution of sodium bis(trimethylsilyl)amide. The mixture was stirred at room temperature for 30 min, 0.19 g (1.1 mmol) of benzenesulfonyl chloride was added, and the mixture was heated to reflux for 16 h. The mixture was cooled, diluted with 15 mL of water, and then extracted three times with ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (75 g of silica gel, 30% ethyl acetate/hexane) of the residue afforded 0.41 g (63%) of **197**.

**(2*R*)-2-Amino-2-((1*R*,2*R*)-2-carboxycycloprop-1-yl)-4,4-diphenylbutanoic Acid (199).** A solution of 0.41 g (0.64 mmol) of **197** in 25 mL of 1 N aqueous sodium hydroxide was heated to reflux for 18 h. The mixture was cooled and extracted twice with 20 mL each of ether. The aqueous portion was acidified to pH 2 with 5 N hydrochloric acid, and the resulting precipitate was filtered, washed two times with 5 mL each of water, and then with acetone, whereupon the solid dissolved. Cation-exchange chromatography of the filtrate afforded a solid which was dissolved in acetone and concentrated in vacuo. The solid was suspended in ether, filtered, and dried in vacuo at 60 °C to afford 7 mg (3%) of **199**. The forerun from the cation-exchange column was concentrated in vacuo and heated to reflux for 18 h in 6 N aqueous hydrochloric acid. The mixture was cooled and concentrated in vacuo. Water was added, and the mixture was concentrated in vacuo again. The resulting solid was suspended in 10 mL of water, filtered, rinsed once with water, twice with acetone, and twice with ether, and then dried in vacuo at 60 °C to afford another 24 mg (10%) of **199**.

**Pharmacokinetic Studies with 168. Methods. 168** was administered to male Fischer 344 rats either intravenously (iv) at a dose of 10 mg/kg, intraperitoneally (ip) at a dose of 10 mg/kg, or orally (po) at a dose of 10 or 100 mg/kg. Five rats were used per route and dose level. Blood and brain were taken from one rat at 0.25, 0.5, 1, 2, and 4 h following iv or ip administration, and at 0.5, 1, 2, 4, and 6 h following po administration. Plasma and brain tissue homogenates were prepared and analyzed by GCMS, using negative ion chemical ionization, following derivatization and extraction as described hereunder (LOQ 100 pg/mL plasma or 1 ng/g brain tissue).

**Acknowledgment.** The authors thank the Physical Chemistry Department of Lilly Research Laboratories for spectral data and elemental analyses. The authors also especially thank Jack Campbell for the liberal use of his high pressure hydrogenation equipment and Joe Kennedy for the chiral HPLC analysis.

**Supporting Information Available:** A list of all of the names of the amino acids prepared in this paper and $^1H$ NMR spectra for compounds **165, 166, 177, 178, 189**, and **190** (11 pages). Ordering information is given on any current masthead page.

## References

(1) Pin, J.-P.; Duvosin, R. The metabotropic glutamate receptors: structure and functions. *Neuropharmacology* **1995**, *34*, 1−26.

(2) Ornstein, P. L.; Monn, J. A.; Schoepp, D. D. Agonists and antagonists for metabotropic glutamate receptors. *Curr. Pharm. Des.* **1995**, *1*, 355−362.
(3) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. 2-Substituted (2*SR*)-2-amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)glycines as potent and selective antagonists of group II metabotropic glutamate receptors. 1. Effects of alkyl, arylalkyl, and diarylalkyl substitution. *J. Med. Chem.* **1998**, *41*, 346−357.
(4) Hayashi, Y.; Tanabe, Y.; Aramori, I.; Masu, M.; Shimamoto, K.; Ohfune, Y.; Nakanishi, S. Agonist analysis of 2-(carboxycyclopropyl)glycine isomers for cloned metabotropic glutamate receptor subtypes expressed in Chinese hamster ovary cells. *Br. J. Pharmacol.* **1992**, *107*, 539−543.
(5) Schoepp, D. D.; True, R. A. 1*S*,3*R*-ACPD-Sensitive (metabotropic) [$^3$H]glutamate binding in membranes. *Neurosci. Lett.* **1992**, *145*, 100−104.
(6) Wright, R. A.; McDonald, J. W.; Schoepp, D. D. Distribution and ontogeny of 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid-sensitive and quisqualate-insensitive [$^3$H]glutamate binding sites in the rat brain. *J. Neurochem.* **1994**, *63*, 938−945.
(7) Schoepp, D. D.; Johnson, B. G.; Salhoff, C. R.; Wright, R. A.; Goldsworthy, J. S.; Baker, S. R. Second-messenger responses in brain slices to elucidate novel glutamate receptors. *J. Neurosci. Methods* **1995**, *59*, 105−110.
(8) Hayashi, T.; Konishi, M.; Kumanad, M. Dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II): an effective catalyst for cross-coupling reaction of a secondary alkyl Grignard reagent with organic halides. *Tetrahedron Lett.* **1979**, 1871−1874.
(9) Unexpectedly, crystallization of the product formed from ketone **33** gave fractionation into two hydantoin diastereomers **76** (the first to crystallize) and **77**. Of all the examples prepared in this and the preceding paper, this was the only compound to demonstrate such behavior. We isolated all other hydantoins as an approximate 1:1 mixture of two racemic hydantoin diastereomers. This was easily seen in the $^{13}$C NMR of the hydantoin amino acids.
(10) Kubik, S.; Meissner, R. S.; Rebek, J., Jr. Synthesis of α,α-dialkylated amino acids with adenine or thymine residues. A new mild and facile hydrolysis of hydantoins. *Tetrahedron Lett.* **1994**, *35*, 6635−6638.
(11) Furuta, K.; Iwanga, K.; Yamamoto, H. Condensation of (−)-diementhyl succinate dianion with 1,ω-dihalides: (+)-(1S,2S)-cyclopropane-1,2-dicarboxylic acid. *Org. Synth.* **1988**, *67*, 76−85.
(12) Our convention is to use the first letter of this stereochemical designator to indicate the stereochemistry at C-5 of the hydantoin (what becomes the amino acid carbon) and the second and third letters to indicate the stereochemistry of the cyclopropane carbons.
(13) All compounds were evaluated on a 0.46 × 25 cm Chiracel-OD HPLC column, using UV detection at 210 nm, and at a column temperature of 35 °C. Amino acids **167** ($t_R$ = 5.71 min) and **168** ($t_R$ = 4.47 min) were eluted with 20% acetonitrile/80% water with 0.1% trifluroacetic acid at a flow rate of 1.5 mL/min; amino acids **173** ($t_R$ = 9.89 min) and **174** ($t_R$ = 10.41 min) were eluted with 15% acetonitrile/85% water with 0.1% trifluroacetic acid at a flow rate of 1.5 mL/min; amino acids **179** ($t_R$ = 8.97 min), **180** ($t_R$ = 7.47 min), **185** ($t_R$ = 6.48 min), and **186** ($t_R$ = 6.29 min) were eluted with 10% acetonitrile/90% water with 0.1% trifluroacetic acid at a flow rate of 1.5 mL/min; amino acids **191** ($t_R$ = 11.15 min), **192** ($t_R$ = 8.70 min), **198** ($t_R$ = 10.50 min), and 199 ($t_R$ = 7.53 min) were eluted with 20% acetonitrile/80% water with 0.1% trifluroacetic acid at a flow rate of 1.0 mL/min.
(14) Actual photoreproductions of $^1$H NMR spectra for selected dibenzylated compounds are included in the Supporting Information for reference.
(15) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. Design, synthesis and pharmacological characterization of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740): A potent, selective, and orally active group 2 metabotropic glutamate receptor antagonist possessing anticonvulsant and anxiolytic properties. *J. Med. Chem.* **1997**, *40*, 528−537.
(16) Schoepp, D. D. Johnson, B. G.; Wright, R. A.; Salhoff, C. R.; Mayne, N. G.; Wu, S.; Cockerham, S. L.; Burnett, J. P.; Belagaje, R.; Bleakman, D.; Monn, J. A. LY354740 Is a potent and highly selective group II metabotropic glutamate receptor agonist in cells expressing human glutamate receptors. *Neuropharmacology* **1997**, *36*, 1−11.
(17) Tizzano, J. P.; Griffey, K. I.; Schoepp, D. D. Induction or protection of limbic siezures in mice by mGluR subtype selective agonists. *Neuropharmacology* **1995**, *34*, 1063−1067.
(18) Desai, M. A.; Conn, P. J. Selective activation of phosphoinositide hydrolysis by a rigid analogue of glutamate. *Neurosci. Lett.* **1990**, *109*, 157−162. Palmer, E.; Monoghan, D. T.; Cotman, C. W. Trans-ACPD, a selective agonist to the PI-coupled excitatory amino acid receptor. *Eur. J. Pharmacol.* **1989**, *166*, 585−587.
(19) Ito, I.; Kohda, A.; Tanabe, S.; Hirose, E.; Hayashi, M.; Mitsunaga, S.; Sugiyama, H. 3,5-Dihydroxyphenylglycine: a potent agonist of metabotropic glutamate receptors. *NeuroReport* **1992**, *3*, 1013−1016.
(20) Schoepp, D. D.; Goldsworthy, J.; Johnson, B. G.; Salhoff, C. R.; Baker, S. R. *J. Neurochem.* **1994**, *63*, 769−772.

JM970498O