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

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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 (1*S*,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. We explored alkyl substitution, both normal and terminally branched; phenylalkyl and diphenylalkyl substitution; and a variety of aromatic and carbocyclic surrogates for phenyl. 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. We found that while alkyl substitution provided no increase in affinity relative to **2**, phenylethyl and diphenylethyl substitution, as in **105** and **109**, respectively, were quite beneficial. The affinity of **109** was further enhanced when the two aromatic rings were joined by an oxygen or sulfur atom to form the tricyclic xanthylmethyl and thioxanthylmethyl amino acids **113** and **114**, respectively. Amino acid **113**, with an IC_{50} of 0.010 μM in the [^{3}H]Glu binding assay, was 52-fold more potent than **2**, whose IC_{50} was 0.47 μM.

Glutamic acid, the major excitatory neurotransmitter in the central nervous system (CNS), exerts its actions at both ionotropic and metabotropic excitatory amino acid (EAA) receptors. Characteristic of the superfamily of ligand-gated ion channel receptors, ionotropic EAA receptors are composed of multiple protein subunits; when embedded in the cell membrane, these subunits form a ligand-gated pore through which calcium and sodium ions can enter the cell and transduce signals. The three subclasses of ionotropic EAA receptors are *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA), and kainic acid. Each subclass is distinguished in terms of its pharmacology and molecular biology.[1] Metabotropic glutamate receptors (mGluRs) are also similar to other G-protein-coupled receptors in that a single protein subunit forms the receptor.[2] mGluRs are distinguished from other G-protein-coupled receptors by their very large N-terminal extracellular domain. Signals are transduced at mGluRs by coupling through G-proteins to effector systems such as phospholipase C or adenylate cyclase, which liberate the second messengers inositol trisphosphate and diacylglycerol or cyclic adenosine monophosphate, respectively. To date, three subclasses of mGluRs have been distinguished on the basis of similarities in pharmacology and sequence homology of the receptor proteins. Group I mGluRs are coupled to phospholipase C, and include mGluR1 and mGluR5; group II mGluRs are negatively coupled to adenylate cyclase and include mGluR2 and mGluR3; and group III mGluRs are also are negatively coupled to adenylate cyclase and include mGluR4, mGluR6, mGluR7, and mGluR8.

Chart 1 shows the known potent and selective agonist ligands for mGluRs.[3] **1** (1*S*,3*R*-ACPD),[4] **2** (L-CCG-1, CCG referring to carboxycyclopropylglycine)[5] and **3** (L-AP4)[6] were among the first relatively potent agonists identified for mGluRs, and they were instrumental in expanding our understanding of the functional consequences of activation of these receptors. One limitation of compound **1** was its relative lack of selectivity, having activity at both group I and group II mGluRs. Amino acid **2**, while more potent at group II mGluRs, is still able to activate group I mGluRs. **3** (L-AP4), however, is relatively selective for group III mGluRs. Recently described are amino acid **4** (3,5-DHPG),[7] which is a selective agonist for group I mGluRs. Incorporation of nitrogen into the ring of **1** afforded **5** (2*R*,4*R*-APDC).[8] While this change did not improve potency, it greatly improved the selectivity of **5** for group II mGluRs. The constrained glutamate analogue **6** (LY354740) is a highly selective and potent agonist for group II mGluRs.[9,10] Addition of a carboxy group to **2**, as in **7** (DCG-IV),[11] yielded a compound that is more potent than **2**, but also possesses agonist activity at NMDA receptors, and **8** (*cis*-MCG-I),[12] with an additional methoxymethyl group on the cyclopropane ring, is more selective but less potent than **2**. The availability of

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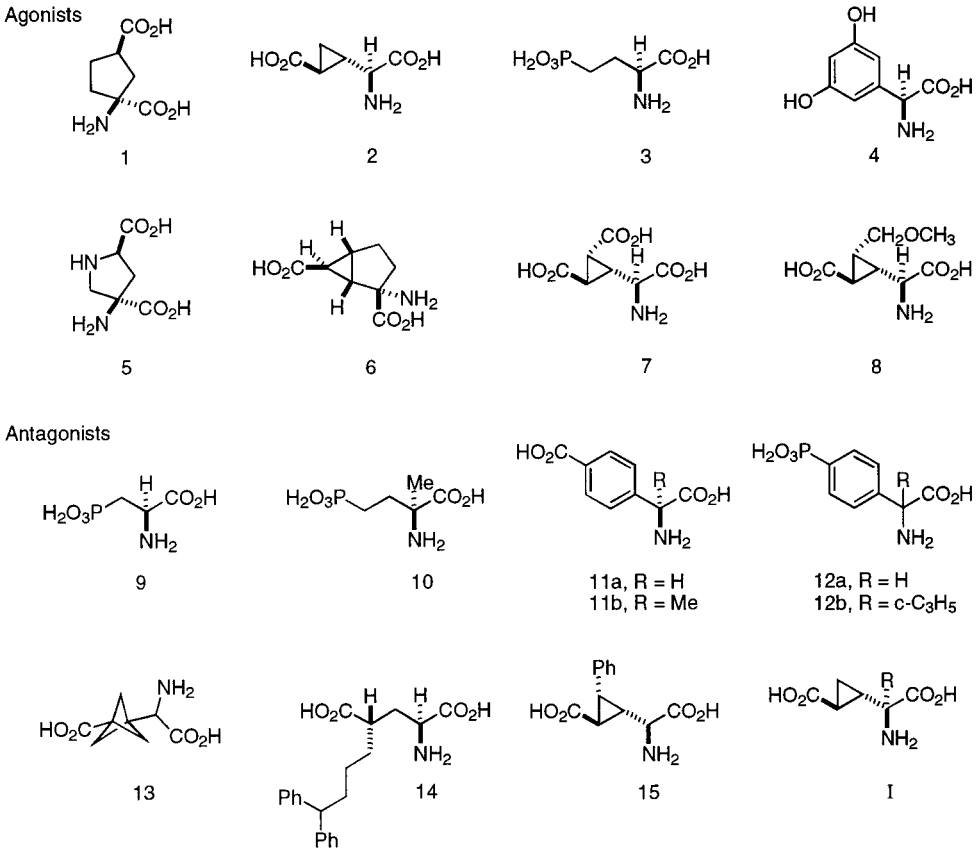
Chart 1



these selective agonists has enabled pharmacologists to better understand the physiological role of group II mGluRs in the CNS and thus better define their therapeutic potential.[13]

There currently exists a lack of potent and selective antagonists for mGluRs.[3] The identification of potent and selective antagonists for NMDA and AMPA receptors was instrumental in defining the therapeutic potential of these compounds. Amino acids such as those shown in Chart 1 represent the best compounds yet described as antagonists for this class of glutamate receptors. Compound **9** (L-AP3) was the first antagonist described for mGluRs and was neither potent nor selective.[14] The α-methyl derivative of **3** (**10**, MAP-4) is a selective antagonist for group III mGluRs, but is relatively nonpotent.[15] Recent studies have shown that the *S*-isomers of certain carboxy-substituted phenylglycines, e.g., **11a** and **11b**, are antagonists selective for mGluRs over ionotropic glutamate receptors, but not particularly potent or selective at mGluRs.[16] Conversion of the carboxylate of **11b** to a phosphonic acid afforded **12a**, which was more selective for group III over group I and II mGluRs.[17] Greater potency was achieved with **12b**, where a cyclopropane replaced the methyl that was appended to the amino acid carbon.[18] It was recently shown that the addition of a diphenylbutyl group to the 4-position of glutamic acid, as in **14**, yielded a much more potent and relatively selective antagonist for group II mGluRs.[19] This was the first example where an agonist such as glutamic acid was converted to an mGluR antagonist. During the course of our work on analogues of **2**, Pelliciari reported that incorporation of a phenyl ring at C-3′ of the cyclopropane converted **2** into the modestly potent antagonist **15**.[20]

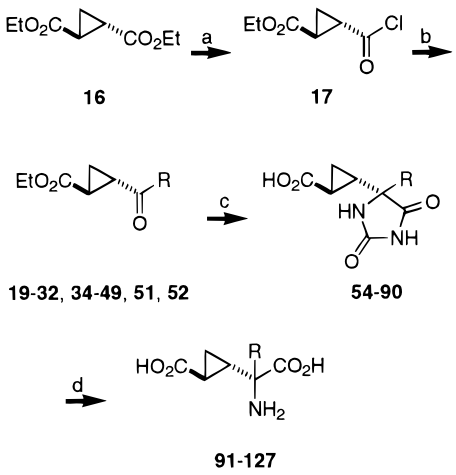
It was our goal to develop novel, potent, and selective antagonists for mGluRs. We hoped that incorporation of a lipophilic side chain, such as the diphenylbutyl group in **14**, would convert the agonist **2** to a potent and relatively selective mGluR antagonist. In this paper and the accompanying paper,[21] we report the synthesis and pharmacological characterization of a series of compounds, e.g. **I** (Chart 1), where a lipophilic side-chain R is incorporated onto the α-amino acid carbon of **2**.

Chemistry

Our general approach to the desired cyclopropane amino acids (see Scheme 1) envisioned desymmetryzing commercially available C-2 symmetric diethyl cyclopropanedicarboxylate **16** to the corresponding acid chloride **17**, followed by coupling with a Knochel-type organozincate to afford a ketone.[22] Then using classical amino acid synthesis techniques, we would convert the ketones to the desired products. The only limitation of this approach was that the amino acids would likely be obtained as a mixture of diastereomers, a problem we believed we could deal with later in the synthesis if compounds were active.

To this end (Scheme 1), treatment of **16** with 1 equiv of sodium hydroxide in aqueous ethanol afforded the corresponding acid−ester, which after treatment with thionyl chloride then afforded the acid chloride **17**. Treatment of the appropriate iodide (Table 1) with zinc−copper couple gave the necessary organozincate, and palladium-mediated coupling with **17** then yielded the desired ketones **19**−**32**, **34**−**49**, and **51**−**52**. The iodides necessary for this reaction were either commercially available or prepared by iodination of the corresponding commercially available alcohol with triphenylphosphine

Scheme 1[a]



[a] (a) NaOH, H_2O, EtOH, 0 °C; $SOCl_2$; (b) RI, Zn(Cu), PhH, *N*,*N*-dimethylacetamide, 60 °C; $Pd(Ph_3P)_4$, room temperature; (c) NaOH, H_2O, EtOH, 70 °C; add KCN and $(NH_4)_2CO_3$, 55 °C; (d) see Table 1 for hydrolysis conditions used for each substrate; Dowex 50-X8, 10% pyridine/water.

diiodide (in a few cases, the iodide was prepared by mesylation of the alcohol followed by displacement with sodium iodide (ketones **28** and **35**), or by treatment of the alcohol with iodotrimethylsilane (ketones **26**, **27**, and **30**)). If the alcohol was not commercially available, it was prepared by borane reduction of the corresponding commercially available carboxylic acid. Scheme 2 shows the synthetic routes used to prepare the alcohols necessary for ketones **41**, **42**, and **44**. Treatment of either 1-tetralone or 9-xanthone with the ylide derived from (methoxymethyl)triphenylphosphonium chloride and sodium bis(trimethylsilyl)amide afforded the corresponding enol ethers **128** and **129**, respectively; hydrolysis and reduction then gave the alcohols **130** and **131**, respectively. Conversion of 4-chromanone to the cyanohydrin **132**, followed by hydrolysis in the presence of tin(II) chloride, yielded the carboxylic acid **133**,[23] which after borane reduction gave alcohol **134**. Iodination of **130**, **131**, and **134**, followed by reaction as in Scheme 1, then afforded ketones **41**, **42**, and **44**. We prepared ketone **18** by coupling lithium dimethyl cuprate with **17**, and ketone **33** by the palladium-mediated coupling of (phenoxymethyl)tri-*n*-butylstannane with **17** (Scheme 2).

We investigated an alternative approach to these ketones that would take advantage of the abundance of aldehydes, especially aromatic aldehydes, that are commercially available (Scheme 3). To this end, we condensed **17** with the Cu(I) salt of dimethyl lithiomethylphosphonate to yield the β-keto phosphonate **135**. Reaction of the sodium salt (from NaH) of **135** with 1-methylindole-3-carboxaldehyde gave enone **136** that was hydrogenated to afford the desired ketone **50**. We converted 2-adamantanone to 2-adamantanecarboxaldehyde much as for **128** and **129**, with the ylide from (methoxymethyl)triphenylphosphonium chloride and sodium bis(trimethylsilyl)amide followed by hydrolysis (Scheme 3). Reaction of this aldehyde with the sodium salt of **135** afforded enone **137**, and hydrogenation gave ketone **53**. While this methodology was only useful for a limited number of examples in this paper, it is more extensively applied in the following paper.[21]

We initially investigated conversion of these ketones to the amino acids using the Strecker reaction with sodium cyanide and ammonium chloride; however, even with sonication in the presence of alumina, the Strecker reaction failed. We next turned our attention to using the Bucherer–Berg reaction, which offers the advantage of nonreversibility through formation of a hydantoin. We found that partial hydrolysis of the ethyl ester to the acid was occurring under the conditions of the Bucherer–Berg reaction, and this was complicating analysis of this reaction. Therefore we found it was more expedient to first hydrolyze the ester to the corresponding acid. We then formed the hydantoin from the keto–acids corresponding to **18**–**53**. One of the problems in this reaction was the relatively sluggish reactivity of the keto–acids derived from **18**–**53**, which we believe in part reflects the sterically crowded environment around the carbonyl group. At the reflux point of the solvent (1:1 ethanol/water), these reactions were slow. To enhance the rate, we carried out these reactions in a sealed tube to allow for higher reaction temperatures (method A, Table 1). This strategy was successful for the synthesis of many of the requisite hydantoins (**55**–**62**, **65**–**68**, **70**–**74**, **79**, **82**, **83**, **88**, and **89**). However, the best solution that we found for forming the hydantoins under Bucherer–Berg conditions was to run the reaction in an open flask at 55–60 °C in aqueous ethanol using a greater amount of sodium cyanide and ammonium carbonate (method B, Table 1; which uses 5 and 9 equiv, respectively, i.e., twice the usual amount for this reaction). We later found that we could do the ester hydrolysis in situ prior to the addition of sodium cyanide and ammonium carbonate, obviating an isolation step and thus improving our reaction yield (method B (alt), Table 1). As we predicted, there was no stereoselectivity in the formation of these hydantoins, and all were obtained as an approximately 1:1 inseparable mixture of two racemic diastereomers (four total compounds in the mixture).[24]

The most difficult step in this synthetic strategy was the hydrolysis of the hydantoin to the amino acid. The inherent stability of the hydantoin coupled with the significant steric hindrance of the 5,5-disubstitution on the hydantoin ring made these reactions very difficult to perform. The exact conditions used for each amino acid are given in Table 1. We first looked at hydrolysis using 1 N sodium hydroxide in an open flask, and these reactions failed. With a few substrates, we were able to get hydrolysis with 5 N sodium hydroxide at reflux (method C, Table 1, amino acids **97** and **110**), but the conversion and isolated yields were very low and it was clear this would not be a generally applicable procedure. Heating in a sealed tube with 5 N sodium hydroxide (method D, Table 1, acid amino acids **92**–**94**, **96**, **98**, **104**, **105**, **109**, and **111**) allowed for higher temperatures, but glass leached into the solution during the long reaction time required for hydrolysis, and this complicated isolation of the amino acid. Using a hydrogenation bomb allowed for higher temperatures without etching, and at 250 °C with 5 N sodium hydroxide (method E, Table 1, amino acids **95**, **99**, **102**, **103**, **107**, **108**, **116**, **119**, **120**, and **126**), the reaction was improved. However, the use of 5 N sodium hydroxide greatly complicated isolation of the desired products. These

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

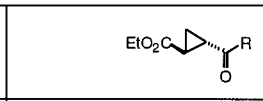
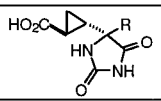
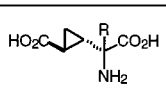
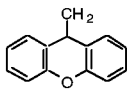
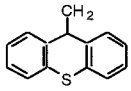
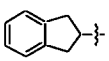
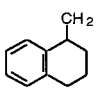
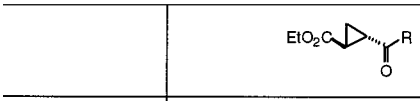
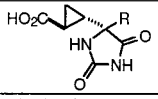
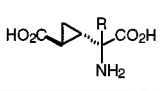
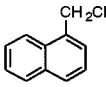
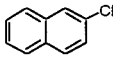
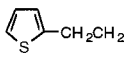
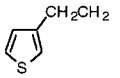
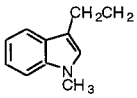
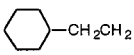
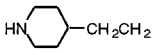
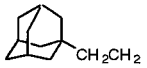
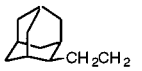
								
R	Source of Iodide[b]	Ketone[c] (% Yield)	Ketone Analysis	Synthesis of Hydantoin[d]	Hydantoin (% Yield)[e]	Hydantoin Hydrolysis[f]	Amino Acid (% Yield)[e,g]	Amino Acid Analysis
CH_3	NA[h]	**18** (46)	C,H•0.25 H_2O	B	**54** (50)	G	**91** (35)	C,H,N
CH_3CH_2	R-I	**19** (53)	C,H•0.25 H_2O	A (100 °C)	**55** (48)	D (160 °C)	**92** (18)	C,H,N
$CH_3(CH_2)_2$	R-I	**20** (73)	C,H[i]	A (100 °C)	**56** (70)	D (130 °C)	**93** (61)	C,H,N
$CH_3(CH_2)_3$	R-I	**21** (73)	C,H	A (100 °C)	**57** (60)	D (130 °C)	**94** (59)	C,H,N[i]
$CH_3(CH_2)_4$	R-I	**22** (86)		A (100 °C)	**58** (65)	E	**95** (13)	C,H,N•0.3 H_2O[i]
$CH_3(CH_2)_7$	R-I	**23** (88)	C,H	A (100 °C)	**59** (60)	D (150 °C)	**96** (12)	C,H,N
$(CH_3)_2CH$	R-I	**24** (73)	C,H	A (90 °C)	**60** (71)	C	**97** (12)	C,H,N•0.75 NH_4OH[i]
$(CH_3)_2CHCH_2$	R-I	**25** (83)	C,H•0.25 H_2O	A (90 °C)	**61** (56)	D (100 °C)	**98** (19)	C,H,N
	R-OH	**26** (71)	C,H	A (150 °C)	**62** (20)	E	**99** (10)	C,H,N
	R-OH	**27** (49)	C,H[i]	B	**63** (35)	F	**100** (18)	C,H,N
	R-OH	**28** (43)	C,H	B	**64** (41)	G	**101** (66)	C,H,N•0.25 H_2O
$(CH_3)_2CH(CH_2)_2$	R-OH	**29** (79)	C,H	A (150 °C)	**65** (71)	E	**102** (13)	C,H,N
$(CH_3)_2CH(CH_2)_3$	R-OH	**30** (58)	C,H•0.25 H_2O	A (150 °C)	**66** (74)	E	**103** (58)	C,H,N•0.5 H_2O
$PhCH_2$	R-Br	**31** (68)	C,H	A (90 °C)	**67** (100)	D (125 °C)	**104** (16)	C,H,N•0.5 H_2O
$Ph(CH_2)_2$	R-I	**32** (68)	C,H	A (90 °C)	**68** (94)	D (125 °C)	**105** (48)	C,H,N
$PhCH_2O$	NA	**33** (92)		B	**69** (26)	G	**106** (28)	C,H,N
$Ph(CH_2)_3$	R-Br	**34** (86)	C,H[i]	A (100 °C)	**70** (54)	E	**107** (33)	C,H,N
$Ph(CH_2)_4$	R-OH	**35** (64)	C,H	A (100 °C)	**71** (76)	E	**108** (45)	C,H,N
$(Ph)_2CHCH_2$	R-OH	**36** (88)	C,H	A (90 °C)	**72** (56)	D (125 °C)	**109** (35)	C,H,N•0.5 H_2O
$(Ph)_2CH(CH_2)_2$	R-OH	**37** (77)	C,H	A (80 °C)	**73** (34)	C	**110** (8)	C,H,N•0.75 H_2O
$(Ph)_2CH(CH_2)_3$	R-OH	**38** (73)	C,H•0.35H_2O	A (90 °C)	**74** (83)	D (150 °C)	**111** (48)	C,H,N•0.5 H_2O
$(PhCH_2)_2CHCH_2$	$R(CH_2)_{n-1}CO_2H$	**39** (42)	C,H	B	**75** (75)	G	**112** (10)	C,H,N•0.75 H_2O
	$R(CH_2)_{n-1}CO_2H$	**40** (64)	C,H	B	**76** (31)	F	**113** (3)	C,H,N•0.4 H_2O
	See Scheme 2	**41** (9)	C,H	B (alt)	**77** (20)	H	**114** (5)	C,H,N•HCl[i]
	See Scheme 2	**42** (66)		B (alt)	**78** (36)	H	**115** (19)	C,H,N
	R-OH	**43** (81)		A (150 °C)	**79** (79)	E	**116** (21)	C,H,N
	See Scheme 2	**44** (62)		B (alt)	**80** (81)	H	**117** (43)	C,H,N

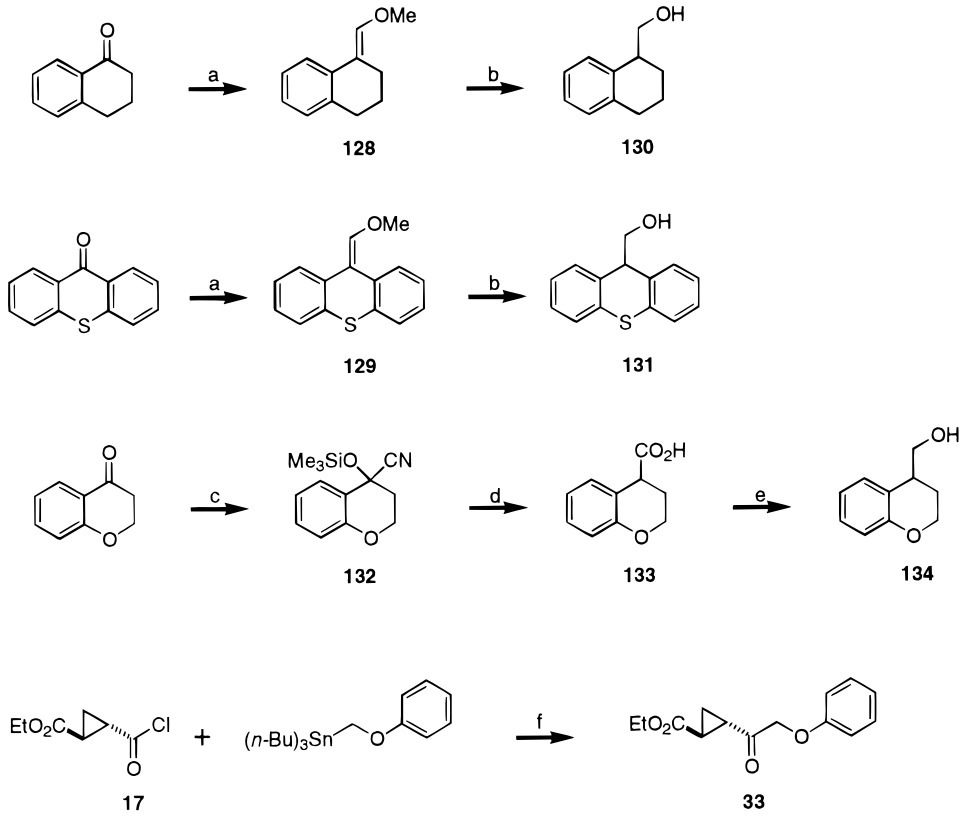
Table 1 (Continued)

								
R	Source of Iodide[b]	Ketone[c] (% Yield)	Ketone Analysis	Synthesis of Hydantoin[d]	Hydantoin (% Yield)[e]	Hydantoin Hydrolysis[f]	Amino Acid (% Yield)[e,g]	Amino Acid Analysis
$PhCH(CH_3)CH_2$	R-OH	**45** (94)	C,H	B	**81** (47)	F	**118** (17)	C,H,N
	R-OH	**46** (75)	C,H	A (150 °C)	**82** (42)	E	**119** (51)	C,H,N
	R-OH	**47** (80)	C,H	A (120 °C)	**83** (81)	E	**120** (54)	C,H,N
	$R(CH_2)_{n-1}CO_2H$	**48** (60)	C,H	B	**84** (63)	G	**121** (39)	C,H,N
	R-OH	**49** (35)	C,H	B	**85** (72)	G	**122** (51)	C,H,N
	See Scheme 3	**50** (60)	C,H,N	B	**86** (77)	G	**123** (11)	C,H,N•H_2O
	---	---	---	NA	**87** (82)[j]	G	**124** (44)	C,H,N•0.25 H_2O
	R-OH*	**51** (21)[k]		A (120 °C)	**88** (52)[k]	F	**125** (61)	C,H,N
	R-OH	**52** (77)		A (125 °C)	**89** (56)	E	**126** (35)	C,H,N•0.75 H_2O
	See Scheme 3	**53** (42)	C,H•0.25 H_2O	B (alt)	**90** (85)	H	**127** (23)	C,H,N•0.65 HCl

[a] See Experimental Section for full detail. [b] As a source of the iodide, the substrate shown was commercially available. All iodides prepared from the alcohol and triphenylphosphine diiodide unless otherwise indicated. Iodides for ketones **26**, **27**, and **30** prepared from the corresponding alcohol with iodotrimethylsilane in chloroform. Iodides for ketones **28** and **35** were prepared from the corresponding alcohol by conversion to the mesylate with mesyl chloride and triethylamine in dichloromethane, followed by treatment with sodium iodide in acetone. Iodide for ketone **34** prepared from the corresponding bromide by treatment with sodium iodide in 2-butanone. [c] All ketones are racemic. One isomer is shown for clarity. [d] All hydantoins and amino acids are a mixture of two racemic diastereomers. One isomer of the cyclopropane 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] 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 at 250 °C overnight. Method H: hydrolysis with 1 N sodium hydroxide in a stainless steel high-pressure reactor at 200 °C overnight. [g] All amino acids were isolated by cation-exchange chromatography, except where noted. Amino Acid **106** was isolated by isoelectric precipitation and then recrystallized from water. Amino acid **110** was isolated by anion-exchange chromatography and then recrystallized from water and acetone. Amino acids **115** and **117** were isolated by isoelectric precipitation. Amino acid **123** was isolated by cation-exchange chromatography, followed by recrystallization from water/acetone. Amino acid **124** was isolated by cation-exchange chromatography, followed by recrystallization from water. [h] NA = not applicable. For ketones **18**, **33**, **50**, and **53**, see the Experimental Section for preparation. [i] **94**. Anal. C: calcd, 55.80; found, 56.96. **95**. Anal. N: calcd, 5.97; found, 6.52. **97**. Anal. H: calcd, 8.31; found 7.82. **20**. Anal. C: calcd, 65.19; found, 66.22. **27**. Anal. C: calcd, 69.61; found, 70.06. **34**. Anal. C: calcd, 73.82; found, 77.73. **114**. Anal. C: calcd, 59.18; found, 59.64. [j] Hydantoin **87** was prepared by hydrogenation of the aromatic ring of hydantoin **68**; see the Experimental Section. [k] Ketone **51** has an *N*-*tert*-butoxycarbonyl (*N*-BOC) protecting group, which is carried forward to hydantoin **88** and then removed in the final hydrolysis to amino acid **125**. See ref 26 for the preparation of 1-(*tert*-butoxycarbonyl)-4-(2-hydroxyethyl)piperidine.

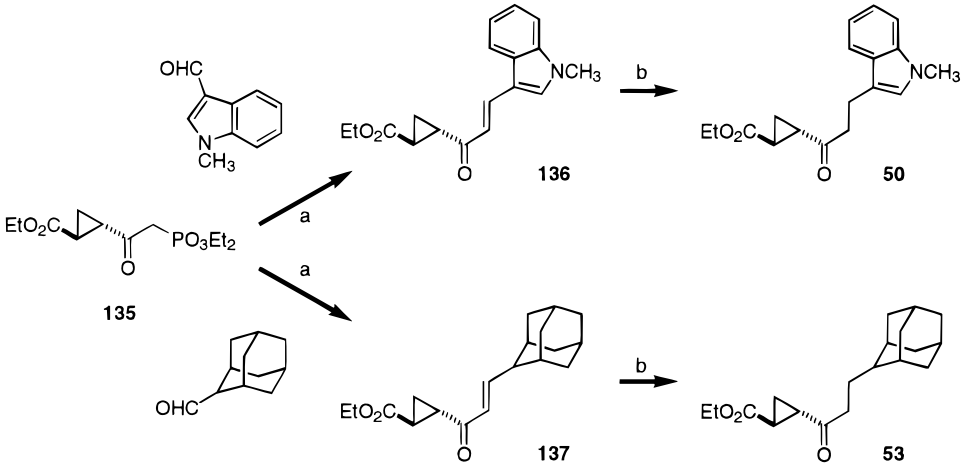
amino acids were purified by cation exchange chromatography and isolated as their inner salts. This necessitated a low pH solution for loading on the resin. The high concentration of sodium hydroxide in these hydrolyses creates a significant amount of salt upon acidification that greatly complicated the ion exchange chromatography. The use of barium hydroxide (about 1.5 N), which is one of the bases of choice for hydantoin

Scheme 2[a]



[a] (a) $Ph_3PCH_2OCH_3^+Cl^-$, $NaN(TMS)_2$, dioxane, 0 °C; (b) Et_2O, 70% aqueous $HClO_4$, room temperature; $NaBH_4$, EtOH, 0 °C; (c) TMSCN, ZnI_2, CH_2Cl_2, 0 °C to room temperature; (d) $SnCl_2{\cdot}(H_2O)_2$, AcOH, concentrated HCl, reflux; (e) $BH_3{\cdot}SMe_2$, THF, 0 °C; (f) $(Ph_3P)_4Pd(0)$, THF, reflux.

Scheme 3[a]

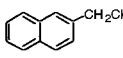
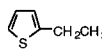
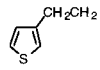
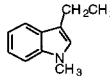
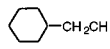
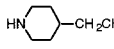
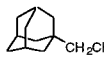
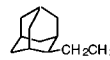
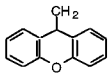
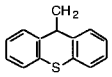


[a] (a) NaH, THF, RCHO, room temperature to reflux; (b) H_2, 5% Pd/C, EtOH, room temperature, 15 psi.

hydrolysis, allows for more facile removal of salts after hydrolysis. Acidification with a quantitative amount of sulfuric acid creates insoluble barium sulfate, which can be more readily removed prior to cation exchange chromatography. As with sodium hydroxide in an open flask at reflux, barium hydroxide was not particularly effective (method F, Table 1, amino acids **100**, **113**, **118**, and **125**). The hydrolysis with barium hydroxide was best performed in a hydrogenation bomb at 250 °C (method G, Table 1, amino acids **91**, **101**, **106**, **112**, and **121**−**124**), and this procedure was used with many examples in this and the following study.

Troubled by the difficulty in this hydrolysis, and unsatisfied with the highly variable yields and the difficult isolation, we decided to evaluate this reaction in more detail. We compared lithium, sodium, potassium, and barium hydroxide, at various concentrations, at temperatures ranging from 150 to 250 °C, with all reactions performed in a hydrogenation bomb. From this experimentation, we found that the best conditions for hydrolysis were 1 N sodium hydroxide at 200 °C (method H, Table 1, amino acids **114**, **115**, **117**, and **127**). With these conditions we found that conversion was usually quantitative, that the amount of extraneous salts was diminished to the point where ion exchange was not compromised, and that we could isolate many

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]	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]
2	H	0.47	agonist	agonist	**115**		0.63		
91	CH_3	6.2							
92	CH_3CH_2	2.2	6.5	2.5	**116**		>10		
93	$CH_3(CH_2)_2$	2.1							
94	$CH_3(CH_2)_3$	1.4			**117**		0.23[d]		
95	$CH_3(CH_2)_4$	1.8							
96	$CH_3(CH_2)_7$	1.7							
97	$(CH_3)_2CH$	>10			**118**	$PhCH(CH_3)CH_2$	0.20 ± 0.06[e]		
98	$(CH_3)_2CHCH_2$	0.70	1.6	1.8	**119**		0.24 ± 0.06[e]	0.24	0.47
99		29.5	>10	>10					
100		1.4			**120**		2.8		
101		0.23	1.1	1.4	**121**		0.58		
102	$(CH_3)_2CH(CH_2)_2$	1.1			**122**		0.21	1.0	0.57
103	$(CH_3)_2CH(CH_2)_3$	0.85							
104	$PhCH_2$	>10	>10	>10	**123**		0.28	1.4	1.2
105	$Ph(CH_2)_2$	0.32	0.85	0.65					
106	$PhCH_2O$	11.2[d]			**124**		0.38		
107	$Ph(CH_2)_3$	0.63	1.0	0.55					
108	$Ph(CH_2)_4$	2.3	0.45	2.8	**125**		>10		
109	$(Ph)_2CHCH_2$	0.24 ± 0.08[e]	4.36	0.28					
110	$(Ph)_2CH(CH_2)_2$	7.1	>10	>10	**126**		0.20	0.24	0.76
111	$(Ph)_2CH(CH_2)_3$	7.0							
112	$(PhCH_2)_2CHCH_2$	>10			**127**		0.55		
113		0.010 ± 0.001[e]	0.20	0.016					
114		0.019 ± 0.003[e]							

[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 stereochemistry at the cyclopropane carbons), unless otherwise noted. [b] See refs 24 and 25. All experiments are single-point determinations, except as noted. [c] See refs 8 and 9. All experiments are single-point determinations, except as noted. [d] Average of two determinations. [e] Average of three determinations.

of these amino acids directly from the hydrolysis mixture by isoelectric precipitation.

Structure−Activity Studies

All of the amino acids prepared in this study were evaluated for their ability to inhibit binding of [^{3}H]-glutamic acid to rat forebrain membranes.[25,26] This is the only binding assay yet described in whole brain that will identify affinity for metabotropic glutamate receptors, and pharmacological studies with this assay indicated that it is selective for group II mGluRs. For example, binding of [^{3}H]glutamic acid is insensitive to compounds **3** and **4** (Chart 1).[27] Since glutamic acid is rather promiscuous in its binding profile, this assay is run in the presence of a cocktail of other agents to block binding to ionotropic glutamate receptors. All compounds, except for **2**, were evaluated as a mixture of four stereoisomers. Data for these compounds is given in Table 2, with data for the unsubstituted analogue **2** provided for comparison.

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 mGluR 2 or mGluR3 (Table 2).[8,9] 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.[18]

We first looked at alkyl substitution, both normal and terminally branched, adjacent to the amino acid center. Modest differences in activity were seen among the group of *n*-alkyl compounds, where methyl (**91**), ethyl (**92**), propyl (**93**), butyl (**94**), pentyl (**95**), and octyl (**96**)

substitution all lowered affinity relative to the unsubstituted compound. Among the branched alkyl compounds, the isobutyl analogue **98** was about 2-fold less active than **2**, and this was the most potent compound among the group of alkyl-substituted compounds. The isopropyl analogue **97** was significantly less active than **2**, and the isopentyl and isohexyl compounds **102** and **103**, respectively, were modestly potent, like the normal alkyl compounds. Consistent with the binding data, **92** was less potent functionally as an antagonist at mGluR2 and mGluR3 than **98**.

To further explore if we could enhance the potency of **98**, we prepared the cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl compounds **99**, **100**, and **101**, respectively. Amino acid **99** was 42-fold lower and **100** was about 2-fold lower in affinity than **98**; however, the cyclohexylmethyl compound **101** was 3-fold higher in affinity than **98** and more potent than **2**. Amino acid **101** was also found to be a functional antagonist at mGluR2 and mGluR3, while the relatively low potency of **99** did not manifest itself as an antagonist, with little inhibition seen at the highest dose tested. We do not yet understand the dramatic difference in potency among these three analogues but postulate that it may reflect the positive effects of an appropriate amount of added steric bulk, which increases going from cyclobutyl to cyclopentyl to cyclohexyl. This was one of our first results which indicated that α-substitution of **2** would increase affinity for this series at group II mGluRs.

We next turned our attention to phenylalkyl substitution, hoping that we might identify an adventitious aromatic recognition site. We observed relatively low affinity for the benzyl compound **104**, indicative that substitution with a aromatic group in close proximity to the amino acid carbon is detrimental to activity. This may reflect an unfavorable steric interaction, and is consistent with the poor activity of **97**. The phenylethyl compound **105** was very potent (slightly better than **2**), while the phenylpropyl and phenylbutyl compounds **107** and **108** were less potent than **105**. The series of phenylalkyl derivatives **104**, **105**, **107**, and **108** were evaluated for functional antagonist activity at mGluR2 and mGluR3, and the relative potency observed for these compounds in the functional assays reflects their relative potency in the binding assay. Amino acid **104** was inactive, and **105** was more potent than **107** and **108**, except that **108** was more potent than **105** at mGluR2. The indanyl analogue **116**, a conformationally constrained analogue of **105**, was less potent than **105**. This may reflect an intolerance for aromatic substitution adjacent to the amino acid center, as we observed for **104**. Replacement of the ethylene of **105** with an oxymethylene group, as in **106**, caused a 35-fold decrease in affinity relative to **105**. Substitution on the carbon adjacent to the phenyl as in **117** (a carbocyclic ring that attaches to the phenyl) or **118** (methyl; a mixture of four diastereomers) increased affinity relative to **105**.

Very gratifying was that addition of another phenyl to the terminal carbon of **105**, as in the diphenylethyl compound **109**, gave a 4-fold increase in affinity relative to **105** and a 6-fold increase relative to **2**. The diphenylpropyl and diphenylbutyl analogues **110** and **111** and the 2-benzylphenylpropyl analogue **112** were all less potent than **109**; **110** and **111** were much less potent than their phenylalkyl counterparts. The diphenylethyl compound **109** proved to be a functional antagonist at group II mGluRs; however it was about 16-fold more potent at mGluR3 than at mGluR2; the diphenylpropyl compound **110** was inactive at both mGluR 2 and mGluR3.

An even greater increase in potency was observed when the two phenyl rings of **109** were bound together by an oxygen or sulfur atom. The tricyclic xanthyl and thioxanthyl analogues **113** and **114** were 52- and 39-fold more potent than **2**, with affinities at group II mGluRs of 0.010 and 0.019 μM, respectively. The importance of the tricyclic system is evident when we compare the activity of the chromylmethyl derivative **115** with that of **113**. In **115**, one of the aromatic rings of the xanthyl compound is excised, leading to a 70-fold decrease in affinity. Amino acid **113** was a potent functional antagonist at mGluR2 and mGluR3, and like **109**, it was more potent at mGluR3 than mGluR2 (about a 13-fold difference).

We investigated substitution of phenyl with other aromatics such as naphthyl, thienyl, and indolyl. The 1-naphthylethyl compound **119** was about 2-fold more potent than **105**, while the 2-naphthylethyl compound **120** was much less active. The 3-thienyl and 3-indolyl analogues **122** and **123** were slightly more active than **105**, while the 2-thienyl compound **121** was less active. **119**, **122**, and **123** were also potent functional antagonists at mGluR2 and mGluR3. Reduction of the phenyl of **105** to the cyclohexylethyl compound **124** was tolerated, with only a slight decrease in potency; however, inclusion of a nitrogen atom into this ring, as in the 4-piperidylethyl compound **125**, was deleterious to activity. Even a bulky carbocyclic substituent was well tolerated, as in the 1- and 2-adamantylethyl compounds **126** and **127**, respectively. Amino acid **126** was slightly more potent than **105** and **124**, while **127** was slightly less active; **126** was also a potent functional antagonist at mGluR2 and mGluR3.

Conclusions

We prepared a series of carboxycyclopropylglycine compounds **15**, in which a substituent was incorporated onto the α-amino acid carbon. In this paper, we looked at the effects of alkyl, arylalkyl, and diarylalkyl substitution. We found that affinity for group II mGluRs was optimal when the α substituent was phenylethyl (**105**), diphenylethyl (**109**), or xanthylmethyl (**113** and **114**). The phenyl ring of **105** could be replaced with a saturated carbocyclic ring such as cyclohexyl (**124**) or 1-adamantyl (**126**) or an aromatic surrogate such as naphthyl (**119**), thienyl (**122**), or indolyl (**123**). In most cases where functional antagonist activity was assessed at the human group II metabotropic glutamate receptors mGluR2 and mGluR3, little difference was seen when comparing activity between these two receptors. However, the diarylethyl compounds **109** and **113** were 13−16-fold more potent at mGluR3 versus mGluR2.

Experimental Section

General. Benzene was dried by azeotropic distillation. Tetrahydrofuran was dried by distillation from sodium. All other solvents and reagents were used as obtained. Field desorption mass spectroscopy (FDMS) was performed using

either a VG 70SE or a Varian MAT 731 instrument. The reactions were generally monitored for completion using thin-layer chromatography (TLC). Thin-layer chromatography was performed using E. Merck Kieselgel 60 F_{254} plates, 5 cm × 10 cm, 0.25 mm thickness. Spots were detected using a combination of UV and chemical detection [plates dipped in a ceric ammonium molybdate solution (75 g of ammonium molybdate and 4 g of cerium(IV) sulfate in 500 mL of 10% aqueous sulfuric acid) and then heated on a hot plate]. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Control Equipment Corporation 440 elemental analyzer. "Chromatography" refers to flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923) on 230−400 mesh silica gel 60, using the amount of silica gel and solvent of elution referred to parenthetically in the text. "Cation-exchange chromatography" refers to ion exchange with Dowex 50X-8 (100−200) resin (H^+ form). The resin was prepared by washing (in a coarse porosity sintered glass funnel) sequentially with water, methanol, water, 3 N NH_4OH, water, 1 N HCl, and water until the pH is neutral. The compound in water was slowly eluted onto the resin, and then the column was washed sequentially with water, 50% aqueous THF, and water. The compound is eluted off the resin with 10% aqueous pyridine, and the product-containing fractions (which are detected with ninhydrin stain on a TLC plate) are combined and concentrated in vacuo. To remove pyridine, the mixture is diluted with water and concentrated in vacuo three times. The compound thus obtained is suspended in water, filtered, washed with water, acetone, and ether, and then dried in vacuo at 60 °C. "Anion-exchange chromatography" refers to anion exchange with Bio-Rad AG1-X8 anion-exchange resin (hydroxide form). The resin (obtained in acetate form) was prepared by washing (in a coarse porosity sintered glass funnel) sequentially with water, methanol, water, twice with 1 N sodium hydroxide (converts to the hydroxide form), and water until pH 7. The compound in water was slowly eluted onto the resin, and then the column was washed sequentially with water, 50% aqueous THF, and water. The compound is eluted off the resin with 3 N aqueous acetic acid, and the product-containing fractions (which are detected with ninhydrin stain on a TLC plate) were combined and concentrated in vacuo.

(1*SR*,2*SR*)-2-Carbethoxycyclopropane-1-carbonyl Chloride (17). A 0 °C solution of 50 g (268 mmol) of diethyl (1*SR*,2*SR*)-*trans*-cyclopropane-1,2-dicarboxylate (**16**) and 54 mL (268 mmol) of 5 N aqueous sodium hydroxide in 500 mL of ethanol was stirred 6 h and then concentrated in vacuo. The residue was dissolved in 300 mL of water and washed twice with 200 mL each of ether and then the aqueous layer was acidified to pH 1 by the addition of concentrated hydrochloric acid. This solution was extracted four times with 200 mL each of ether, and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. This residue was dissolved in 170 mL (277 g, 170 mmol) of thionyl chloride, stirred overnight at room temperature, and then concentrated in vacuo to afford 32.5 g (69%) of **17**.

Typical Procedure for the Preparation of an Alcohol from the Corresponding Carboxylic Acid, 2-(2-Thienyl)-ethanol. A 0 °C solution of 10.0 g (70.3 mmol) of (2-thienyl)-acetic acid in 200 mL of tetrahydrofuran was treated dropwise with 14.1 mL of 10.0 M borane methyl sulfide. After addition was complete, the mixture was stirred for 2 h at 0 °C and for 4 h while warming to room temperature. The reaction was quenched with 200 mL of saturated sodium bicarbonate, the organic layer was separated, and the aqueous layer was extracted three times with 70 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 8.8 g (97%) of the title compound.

Typical Procedure for the Preparation of an Iodide from the Corresponding Alcohol, 2-(2-Thienyl)ethyl Iodide. A solution of 29.6 g (102.6 mmol) of triphenylphosphine and 26.0 g (102.6 mmol) of iodine in 210 mL of dichloromethane was stirred 10 min at room temperature, then treated with 11.6 g (171.0 mmol) of imidazole, stirred an additional 10 min, and then treated with 8.8 g (68.4 mmol) of 2-(2-thienyl)ethanol in 40 mL of dichloromethane. After being left to stand overnight at room temperature, the mixture was washed with 200 mL of 10% aqueous sodium bisulfate, the organic layer was separated, and the aqueous layer was extracted three times with 100 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue (400 g of silica gel, 10% ethyl acetate/hexane) afforded 7.6 g (46%) of the title compound.

Representative Procedure for Palladium-Mediated Coupling of an Organozincate Prepared from an Iodide and 17. Preparation of (1*SR*,2*SR*)-2-Carbethoxycyclo-prop-1-yl 2-(2-Thienyl)ethyl Ketone (48). A solution of 5.1 g (21.3 mmol) of 2-(2-thienyl)ethyl iodide and 2.1 g (32.7 mmol) of zinc/copper couple in 47 mL of benzene and 4.7 mL of *N*,*N*-dimethylacetamide was stirred for 2 h at 60 °C. The heating bath was removed and then the mixture treated with 0.32 g (0.28 mmol) of tetrakis(triphenylphosphine)palladium(0). After 5 min, 2.5 g (14.2 mmol) of **17** was added and the mixture stirred at room temperature for 1.5 h. The mixture was diluted with 50 mL of ethyl acetate and filtered through diatomaceous earth. The filtrate was washed with 50 mL of 1 N hydrochloric acid, 50 mL of saturated aqueous sodium bicarbonate, and 50 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (200 g of silica gel, 20% ethyl acetate/hexane) of the residue afforded 2.2 g (60%) of **48**.

Representative Procedure for Hydrolysis of Keto−Ester to Keto−Acid. Preparation of (1*SR*,2*SR*)-2-Carboxycycloprop-1-yl 2-(2-Thienyl)ethyl Ketone. A solution of 2.1 g (8.1 mmol) of **48** in 25 mL of ethanol and 8.9 mL of 1 N sodium hydroxide was stirred 24 h at room temperature and then concentrated in vacuo. The residue was dissolved in 50 mL of 10% sodium bisulfate and extracted four times with 25 mL each of ethyl acetate, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.6 g (88%) of the title compound.

Method A: Formation of Hydantoin from Keto−Acid in a Sealed Tube. Preparation of (5*SR*)- and (5*RS*)-5-((1*SR*,2*SR*)-2-Carboxycycloprop-1-yl)-5-*n*-pentylimidazolidine-2,4-dione (58). A solution of 2.6 g (14.1 mmol) of (1*SR*,2*SR*)-2-carboxycycloprop-1-yl *n*-pentyl ketone in 20 mL of ethanol was added to a solution of 2.3 g (35.1 mmol) of potassium cyanide and 5.0 g (63.2 mmol) of ammonium carbonate in 20 mL of water, and then this mixture was placed in a 3.5 × 20 cm pressure tube, sealed with a no. 15 Teflon screw plug, and heated to 100 °C for 24 h. The mixture was cooled, vented, added to 100 mL of 10% aqueous sodium bisulfate, and then extracted four times with 75 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 3.0 g (84% for this step; 65% for combination of keto-ester to keto-acid hydrolysis and then hydantoin formation) of **58**.

Method B: Conversion of Keto−Acid to Hydantoin in an Open Flask. (5*SR*)- and (5*RS*)-5-((1*SR*,2*SR*)-2-Carboxycycloprop-1-yl)-5-(2-(2-thienyl)ethyl)imidazolidine-2,4-dione (84). A solution of 1.6 g (7.1 mmol) of (1*SR*,2*SR*)-2-carboxycycloprop-1-yl 2-(2-thienyl)ethyl ketone in 7.5 mL of ethanol was added to a solution of 2.3 g (35.7 mmol) of potassium cyanide and 6.2 g (64.2 mmol) of ammonium carbonate in 7.5 mL of water, and then this mixture was heated to 55 °C for 24 h. The mixture was cooled and added to 150 mL of 10% sodium bisulfate, and the resulting precipitate was filtered, washed three times with water, and then recrystallized from water and acetone. Drying in vacuo at 60 °C afforded 1.5 g (72%) of **84**.

Method B (alt): One-Pot Ester Hydrolysis and Subsequent Hydantoin Formation in an Open Flask. Preparation of (5*SR*)- and (5*RS*)-5-((1*SR*,2*SR*)-2-Carboxycyclo-prop-1-yl)-5-((1-tetralyl)methyl)imidazolidine-2,4-dione (80). A solution of 2.5 g (8.1 mmol) of **44** in 65 mL of ethanol and 9.6 mL of 1 N sodium hydroxide was stirred 4 h

at 70 °C and then concentrated in vacuo. The residue was dissolved in 40 mL of 1:1 ethanol/water and treated with 2.8 g (43.5 mmol) of potassium cyanide and 7.5 g (78.3 mmol) of ammonium carbonate; then this mixture was heated to 55 °C for 72 h. The mixture was cooled and added to 250 mL of 10% sodium bisulfate, and the resulting precipitate was filtered, washed three times with water, and then recrystallized from water and acetone. Drying in vacuo at 60 °C afforded 2.3 g (81%) of **80**.

Method C: Hydrolysis of Hydantoin to Amino Acid with 5 N Sodium Hydroxide in an Open Flask. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-3-methylbutanoic Acid (97). A solution of 2.2 g (9.7 mmol) of **60** in 50 mL of 1 N sodium hydroxide was heated to reflux for 24 h, and then 25 mL of 5 N sodium hydroxide was added and reflux continued for another 24 h. The mixture was cooled and acidified to pH 7 with concentrated hydrochloric acid. The resulting solid was filtered and washed three times with 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 0.37 g (12%) of **97**.

Method D: Hydrolysis of Hydantoin to Amino Acid in a Sealed Tube. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-6,6-diphenylhexanoic Acid (111). A solution of 2.7 g (6.9 mmol) of **74** in 25 mL of 5 N sodium hydroxide was placed in a 3.5 × 20 cm pressure tube, sealed with a no. 15 Teflon screw plug, and heated to 150 °C for 24 h. The mixture was cooled and acidified to pH 4 with concentrated hydrochloric acid. The resulting solid was filtered and washed three times with 10 mL each of water, once with 10% pyridine/water, and once again with water, and then the filtrate was concentrated in vacuo. Cation-exchange chromatography of the residue afforded a solid that was suspended in water, filtered, and washed with water, acetone, and ether to afford 0.95 g (37%) of **111**. A second crop was isolated from the filtrate and afforded 0.28 g (11%) of **111**.

Method E: Hydrolysis of Hydantoin to Amino Acid with 5 N Sodium Hydroxide in a Hydrogenation Bomb. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)heptanoic Acid. A solution of 3.0 g (11.8 mmol) of **58** in 30 mL of 5 N sodium hydroxide was heated to 250 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 7 with concentrated hydrochloric acid. The resulting solid was filtered and washed three times with 10% pyridine/water, and then the filtrate was concentrated in vacuo. Cation-exchange chromatography of the residue afforded a solid that was suspended in water and filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.39 g (13%) of **95**.

Method F: Hydrolysis of Hydantoin to Amino Acid Using Barium Hydroxide in an Open Flask. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-3-cyclopentylpropanoic Acid (100). A solution of 1.0 g (3.8 mmol) of **63** and 5.9 g (18.8 mmol) of barium hydroxide in 13 mL of water was heated to reflux for 72 h. The mixture was cooled and treated with 1 mL (18 mmol) of concentrated sulfuric acid. The resulting solid was filtered and washed three times with water. Cation-exchange chromatography of the filtrate gave a solid that was suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo at 60 °C to afford 0.16 g (18%) of **100**.

Method G: Hydrolysis of Hydantoin to Amino Acid Using Barium Hydroxide in a Hydrogenation Bomb. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-carboxycycloprop-1-yl)-4-(2-thienyl)butanoic Acid (121). A solution of 1.5 g (4.9 mmol) of **84** and 7.8 g (24.7 mmol) of barium hydroxide in 37 mL of water was heated to 250 °C for 24 h in a stainless steel high-pressure reactor. The mixture was cooled and acidified to pH 2 with concentrated sulfuric acid, affording a solid that was filtered and rinsed with water. The solid was suspended in 20 mL of hot 10% aqueous pyridine then filtered and rinsed with 10 mL of hot 10% aqueous pyridine. The filtrates were combined and concentrated in vacuo to remove most of the pyridine. 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 0.52 g (39%) of **121**.

Method H: Hydrolysis of Hydantoin to Amino Acid with 1 N Sodium Hydroxide in a Sealed Tube. Preparation of (2*SR*)- and (2*RS*)-2-Amino-2-((1*SR*,2*SR*)-2-Carboxycycloprop-1-yl)-3-(1-tetralyl)propanoic Acid (117). A solution of 2.3 g (7.0 mmol) of **80** in 75 mL of 1 N sodium hydroxide was heated to 200 °C for 24 h in a stainless steel high-pressure reactor. After cooling, the pH was adjusted to 8 with 5 N hydrochloric acid, and then the mixture was extracted with 50 mL each of ethyl acetate and ether. The pH of the aqueous layer was then adjusted to 2 with 5 N hydrochloric acid, and the resulting precipitate was filtered, washed with water, acetone, and ether, and then dried in vacuo at 60 °C to afford 0.9 g (43%) of **117**.

(1*SR*,2*SR*)-2-Carbethoxycycloprop-1-yl Methyl Ketone (18). To a 0 °C suspension of 4.7 g (24.8 mmol) of copper(I) iodide in 75 mL of THF was added 35.5 mL (49.7 mmol, 1.4 M in ether) of methyllithium. The mixture was cooled to −78 °C, stirred for 30 min at that temperature, then treated with 4.0 g (22.6 mmol) of **17**, and stirred for an additional 1 h. The reaction was quenched with 100 mL of saturated aqueous ammonium chloride, the organic layer separated, and the aqueous layer extracted three times with 40 mL of ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (200 g of silica gel, 35% ethyl acetate/hexane) afforded 1.6 g (46%) of **18**.

(Phenoxymethyl)tri-*n*-butylstannane. A solution of 11.4 g (26.5 mmol) of (iodomethyl)tri-*n*-butylstannane, 2.5 g (26.5 mmol) of phenol, and 4.4 g (31.7 mmol) of potassium carbonate in 75 mL of THF was stirred 24 h at room temperature, then an additional 3.5 g (25.3 mmol) of potassium carbonate and 1 g (10.6 mmol) of phenol were added, and the mixture was then heated to reflux for 24 h. The mixture was cooled, diluted with 150 mL of ether, and washed once with 75 mL of water. The organic layer was separated, the aqueous layer was extracted three times with 25 mL each of ether, and then the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (400 g of silica gel, hexane) of the residue afforded 4.7 g (44%) of the title compound.

(1*SR*,2*SR*)-2-Carbethoxycycloprop-1-yl Phenoxymethyl Ketone (33). A solution of 2.1 g (11.8 mmol) of **17**, 4.7 g (11.8 mmol) of (phenoxymethyl)tri-*n*-butylstannane, and 0.05 g (0.04 mmol) of tetrakis(triphenylphosphine)palladium(0) in 35 mL of THF was heated to reflux for 4.5 h and then treated with 50 mg (0.07 mmol) of bis(triphenylphosphine)palladium-(II) dichloride, and the mixture was heated at reflux overnight. Another 50 mg (0.07 mmol) of bis(triphenylphosphine)palladium(II) dichloride and 0.6 g (3.4 mmol) of **17** were added, and the mixture was refluxed for 5 h. The mixture was cooled, diluted with 80 mL of ether, and washed with 50 mL of 10% aqueous sodium bisulfate, 50 mL of saturated aqueous sodium bicarbonate, and 50 mL of 50% aqueous potassium fluoride. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (125 g of silica gel, 20% ethyl acetate/hexane) of the residue afforded 2.7 g (92%) of **33**.

1-(Methoxymethylidene)tetralin (128). To a 0 °C solution of the ylide generated from 32.8 g (95.8 mmol) of (methoxymethyl)triphenylphosphonium chloride and 95 mL (95 mmol) of sodium bis(trimethylsilyl)amide in 150 mL of dioxane was added 10.0 g (68.4 mmol) of 1-tetralone in 50 mL of dioxane, and the mixture was stirred 1 h at 0 °C. The reaction was quenched with 125 mL of water, and then the mixture was extracted three times with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (750 g of silica gel, 35% ethyl acetate/hexane) afforded 12.4 g (100%) of **128**.

Tetralin-1-carboxaldehyde. To a room-temperature solution of **128** in 300 mL of ether was added dropwise over 25

min 110 mL of 70% perchloric acid. After an additional hour of stirring, 150 mL of brine was added; the organic layer was separated and then washed with 400 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer extracted twice with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 9.9 g (90%, two steps) of tetralin-1-carboxaldehyde.

1-Tetralylmethanol (130). To a 0 °C solution of 9.9 g (60.7 mmol) of tetralin-1-carboxaldehyde in 160 mL of ethanol was added 1.2 g (30.4 mmol) of sodium borohydride. After 1 h at 0 °C, the mixture was partitioned between 300 mL of ethyl acetate and 200 mL of water. The organic layer was separated and the aqueous layer extracted twice with 100 mL each of ethyl acetate and 100 mL of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (500 g of silica gel, 30% ethyl acetate/hexane) afforded 7.0 g (71%) of **130**.

4-Cyano-4-((trimethylsilyl)oxy)chromane (132). To a 0 °C solution of 10.0 g (67.5 mmol) of 4-chromanone and 0.4 g of zinc iodide in 200 mL of dichloromethane was added 13.5 mL (10.0 g, 101.8 mmol) of cyanotrimethylsilane. After being stirred overnight while warming to room temperature, the mixture was washed with 200 mL of saturated aqueous sodium bicarbonate, and then the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 16.2 g (97%) of **132**.

4-Carboxychromane (133). A mixture of 16.2 g (65.5 mmol) **132** and 56.0 g (248.3 mmol) of tin(II) chloride dihydrate in 60 mL each of acetic acid and concentrated hydrochloric acid was heated to reflux for 3 days, then cooled to room temperature, and extracted three times with 150 mL each of dichloromethane. The combined organics were washed three times with 130 mL each of 2 N sodium hydroxide, and then the combined basic washes were extracted twice with 100 mL each of ether and subsequently acidified to pH 2 with 5 N hydrochloric acid (in an ice bath). The acidic aqueous mixture was extracted three times with 150 mL each of ethyl acetate, and the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 11.3 g (97%) of **133**.

Dimethyl [(1*SR*,2*SR*)-2-(Carbethoxycycloprop-1-yl)-2-oxoethyl]phosphonate (135). To a −78 °C solution of 36.1 g (290.9 mmol) of dimethyl methylphosphonate in 560 mL of THF was added via cannulus 200 mL (320 mmol, 1.6 M in hexane) of butyllithium. After 30 min at −78 °C, 60.9 g (320 mmol) of copper(I) iodide was added, the mixture was stirred for 1 h at −45 °C, and then 56.5 g (320 mmol) of **17** in 200 mL of THF was added at a moderate rate. After 2 h of stirring at −45 °C, and at room temperature overnight, the reaction was quenched with 250 mL of 0.5 M (in water) ethylenediaminetetraacetic acid (precipitate) followed by 250 mL of water and 600 mL of dichloromethane. The mixture was filtered through diatomaceous earth (0.75 in. layer in a 2 L sintered-glass funnel), then the organic layer was separated, and the aqueous layer was extracted twice with 300 mL each of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Preparative HPLC afforded 33.1 g (39%) of **135**.

(1*SR*,2*SR*)-2-Carbethoxycycloprop-1-yl 2-(1-Methylindol-3-yl)ethenyl Ketone (136). A solution of 2.0 g (7.6 mmol) of **135** in 10 mL of tetrahydrofuran was added to a suspension of 0.3 g (7.6 mmol) of sodium hydride in 15 mL of tetrahydrofuran, and the mixture was stirred for 20 min at room temperature. A solution of 1.3 g (7.6 mmol) of 1-methylindole-3-carboxaldehyde in 10 mL of tetrahydrofuran was added and the mixture stirred for 16 h at reflux. The mixture was cooled to room temperature, diluted with 30 mL of water, and extracted three times with 15 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 2.2 g (96%) of **136**.

(1*SR*,2*SR*)-2-Carbethoxycycloprop-1-yl 2-(1-Methylindol-3-yl)ethyl Ketone (50). A solution of 2.2 g (7.2 mmol) of **136** in 50 mL of ethanol and 0.1 g of 5% palladium on carbon was degassed (brief evacuation under vacuum for about 30 s followed by venting to nitrogen the first time and then to hydrogen the subsequent two times) and then stirred for 3.5 h at room temperature under hydrogen (in a balloon). The mixture was filtered through diatomaceous earth and concentrated in vacuo. Chromatography (100 g of silica gel, 20% ethyl acetate/hexane) of the residue afforded 1.4 g (63%) of **50**.

2-Adamantanecarboxaldehdye. To a 0 °C solution of the ylide generated from 16.0 g (46.6 mmol) of (methoxymethyl)-triphenylphosphonium chloride and 46 mL (46 mmol) of sodium bis(trimethylsilyl)amide in 75 mL of THF was added 5.0 g (33.3 mmol) of 2-adamantanone in 20 mL of THF, and the mixture was stirred for 1.5 h at 0 °C. The reaction was quenched with 100 mL of water, and then the mixture was extracted three times with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was stirred for 4 h at room temperature in 200 mL of acetonitrile and 50 mL of 1 N hydrochloric acid and then concentrated in vacuo to remove most of the acetonitrile. Brine (50 mL) of was added and the mixture extracted three times with 100 mL each of ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo, and chromatography (4″ of silica gel in a 600 mL sintered-glass funnel, 10% ethyl acetate/hexane) of the residue afforded 4.9 g (89%, two steps) of the title compound.

(1*SR*,2*SR*)-2-Carbethoxycycloprop-1-yl 2-(2-Adamantyl)ethyl Ketone (53). As for **50**, 2.0 g (7.6 mmol) of **135**, 0.32 g (8.0 mmol) of sodium hydride, and 1.4 g (8.3 mmol) of 2-adamantanecarboxaldehdye afforded **137**, which was hydrogenated with 1.6 g of 5% Pd/C in 50 mL of ethanol at 40 °C and 60 psi overnight. The mixture was filtered through diatomaceous earth and concentrated in vacuo. Chromatography (65 g of silica gel, 10% ethyl acetate/hexane) of the residue afforded 0.7 g (42%) of **53**.

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Supporting Information Available: A list of all of the names of the amino acids prepared in this paper along with representative ^1H NMR spectra for key intermediates and products are included (7 pages). Ordering information is given on any current masthead page.

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