Articles

10,5-(Iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and Derivatives. Potent PCP Receptor Ligands

Kyle R. Gee,† Peter Barmettler,† Michael R. Rhodes,† Robert N. McBurney,‡ N. Laxma Reddy,‡ Lain-Yen Hu,‡ Ronald E. Cotter,‡ Philip N. Hamilton,‡ Eckard Weber,§ and John F. W. Keana*,†

Department of Chemistry, University of Oregon, Eugene, Oregon 97403, Cambridge NeuroScience, Inc., Cambridge, Massachusetts 02139, and Department of Pharmacology, University of California, Irvine, California 92717

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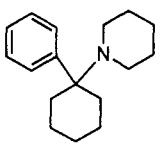
IDDC (**3**, 10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene) and a series of substituted derivatives were synthesized and evaluated in vitro for their ability to displace tritiated MK-801 ([^{3}H]-**2**) from its specific binding site in guinea pig brain homogenate. Substitution at the 3-position of **3** with bromine, chlorine, and fluorine led to increased binding affinity. In contrast, substitution of donor groups at the 3-position gave decreased binding affinities, as did all substitutions at the 7-position and on nitrogen. Where racemic mixtures were resolved, the (+)-optical antipodes were more active than their enantiomers or racemates. The most active ligand found in this study was (+)-**13e** (IC_{50} = 15.5 ± 4.5 nM). The affinity of (+)-**13e** for the PCP receptor makes it among the most potent ligands known. In vitro neuroprotection was demonstrated by **3**, (+)-**3**, and (+)-**6** (*N*-Me-IDDC) against glutamate-induced cell death in rat hippocampal cells.

Introduction

The amino acid L-glutamate is an important neurotransmitter at excitatory synapses within the central nervous system.[1] Neuronal responses to glutamate are complex and appear to be mediated by at least three different receptor types, one of which is the NMDA subtype, named for its specific ligand *N*-methyl-D-aspartic acid.[2] Excessive stimulation by glutamate of the NMDA receptor has been strongly implicated in nerve cell death following ischemic or hypoxic insults to the brain, as well as during the course of neurodegenerative desease.[3] Excessive influx of calcium ions through an ion channel associated with the NMDA receptor during ischemic events plays a key role in neuronal death.[4] Within the NMDA receptor ion channel exists a receptor site known as the PCP (phencyclidine, **1**) receptor.[5] Compounds that bind



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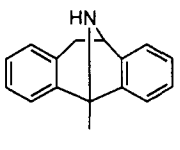

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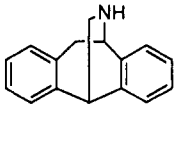

(+)-**3**

to the PCP receptor interrupt ion flow, reducing the agonist action of glutamate at the NMDA receptor. Thus, ligands for the PCP receptor have potential as neuroprotective agents in the treatment of ischemia.[3] Efforts in several laboratories have been made to develop new potent, highly specific ligands for the PCP receptor. (5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10-imine (MK-801, **2**)[6] is among the most potent PCP receptor ligands known.

Structural comparisons of **2** with other rigid molecules using molecular modeling techniques[7] suggested to us that IDDC (**3**, 10,15-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene) and **2** shared similar structural features. Herein we report on the chemistry and pharmacology of **3** and several substituted analogs. Pharmacological results include the ligands' affinities for the PCP receptor as measured by their ability to displace [^{3}H]-**2** from rat brain membrane suspensions. In vitro neuroprotection experiments against glutamate-induced cell death are also described.

Chemistry

IDDC (**3**)[8] was synthesized according to Scheme I. Alkylation of racemic, 1,2-diphenylethylamine (**4**) with bromoacetaldehyde diethyl acetal in DMF afforded **5**, which was cyclized with perchloric acid to **3** according to the method of Suzuki et al.[9]

Optically active (+)-**3** [$[\alpha]^{25}_D$ = +165°, (*c* = 1, EtOH)] was prepared beginning with *R*-(−)-**4**, which was resolved from its racemate with L-(+)-tartaric acid in water following the general method of Potapov et al.,[10] to afford *R*-(−)-**4** in 98% enantiomeric excess (ee); the absolute configuration and maximum specific rotation had been previously determined by Nakazaki et al.[11] The absolute configuration at C-5 of (+)-**3** was constrained by the geometry of the molecule to be *S*, since the *R* configuration of C-10 was carried through the synthesis from the starting *R*-(−)-**4**. The ee (98%) of (+)-**3** was assumed to be the same as for the starting material.

Optically active (+)-**6**[12] was synthesized by reductive amination of formaldehyde with (+)-**3** according to the general method of Borch and Hassid.[13] The 5-methyl analog **8**[14] was prepared by alkylation of **4** with propargyl bromide to give **7**, followed by cyclization with triflic acid (Scheme I).

Several analogs of **3** were prepared with substitution at C-3 and C-7 of the aromatic rings (Scheme II). A similar

† University of Oregon.
‡ Cambridge NeuroScience, Inc.
§ University of California, Irvine.

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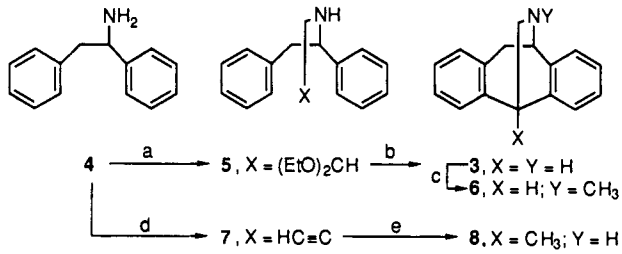
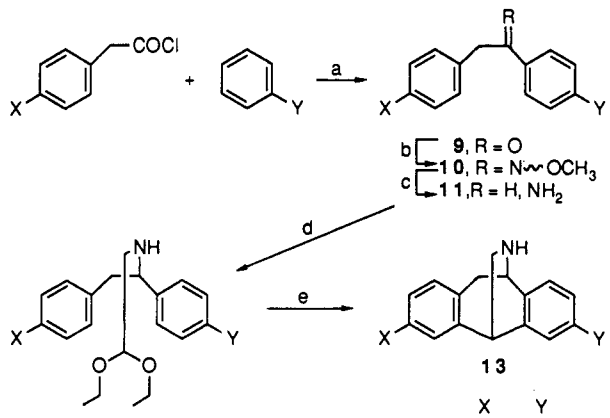
Scheme I[a]



[a] (a) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF; (b) $HClO_4$; (c) HCHO, $NaBH_3CN$; (d) $BrCH_2CCH$, K_2CO_3, EtOH; (e) CF_3SO_3H.

Scheme II[a]



	X	Y
a,	H	OMe
b,	H	Cl
c,	Cl	H
d,	Br	H
e,	F	H
f,	OMe	H
g,	Me	H
h,	Ph	H
i,	Cl	OMe
j,	Br	OMe
k,	F	F

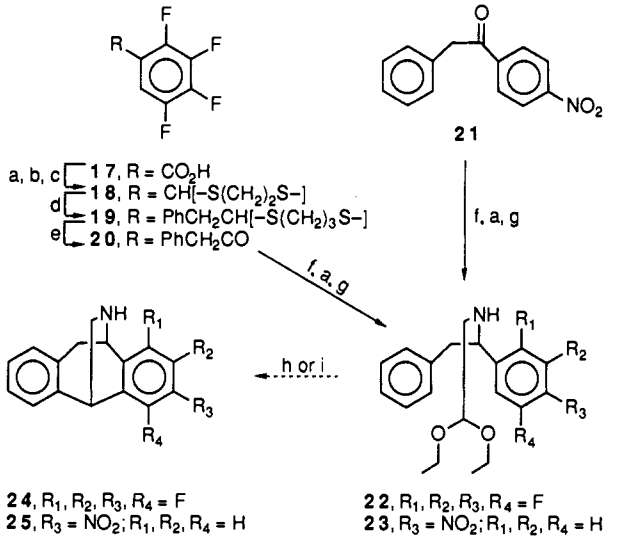
[a] (a) $AlCl_3$; (b) CH_3ONH_2·HCl, pyridine; (c) BH_3·THF; (d) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF; (e) $HClO_4$ or H_2SO_4.

series of 3- and 7-substituted derivatives of **2** was recently reported by the Merck group.[15] The first step toward analogs of **3** was the synthesis of appropriately substituted desoxybenzoins (**9**) using standard Friedel–Crafts chemistry. Surprisingly, reductive amination of these desoxybenzoins with sodium cyanoborohydride and ammonia or aminoacetaldehyde dimethyl acetal consistently failed to form the corresponding amines **11** or amino acetals **12**, respectively, in acceptable yield. Therefore, amination of the desoxybenzoins was achieved by a two-step route by forming the oxime methyl ethers **10** according to the general method of Singh,[16] followed by borane–THF reduction[17] of the mixture of *E*- and *Z*-oxime isomers thus formed. The resulting 1,2-diphenylethylamines **11** were alkylated and cyclized as described in Scheme I to afford **13**.

N-Methyl-3-bromo-IDDC (**14**) and N-methyl-3-bromo-7-methoxy-IDDC (**15**) were prepared from **13d** and **13j**, respectively, by amination of formaldehyde. 3-Iodo-IDDC (**16**) was prepared from **13d** by reaction with potassium iodide in the presence of nickel powder.[15,18]

The limitations of the method shown in Scheme II to prepare substituted analogs of **3** were demonstrated by the failure of tetrafluoro- and nitro-substituted acetals **22** and **23**, respectively (Scheme III), to undergo double cyclization to **24** and **25** upon treatment with perchloric or triflic acid. Acetals **22** and **23** were prepared without

Scheme III[a]



[a] (a) BH_3·THF; (b) PCC; (c) $HS(CH_2)_3SH$, BF_3-Et_2O; (d) (i) n-BuLi; (ii) $PhCH_2Br$; (e) NBS, acetone/H_2O; (f) CH_3ONH_2·HCl, pyr; (g) $BrCH_2CH(OEt)_2$, DMF, K_2CO_3; (h) $HClO_4$; (i) CF_3SO_3H.

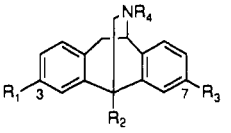
difficulty according to the methodology of Scheme II from the ketones **20** and **21**,[19] respectively. The double cyclization reaction is apparently prevented by the strong electron-withdrawing ability of the substituents.

The 3-halogenated derivatives **13c** and **13e** showed relatively high affinities for the PCP receptor (Table I). Given the higher affinity of (+)-**3** for the PCP receptor over its racemate (Table I), we sought to resolve racemates **13c** and **13e** in order to assess the binding affinities of the enantiomers separately. Preparative HPLC separation afforded the resolved enantiomers (+)-**13c**, (−)-**13c**, (+)-**13e**, and (−)-**13e** in >97% ee.[20] Dechlorination of a sample of **13c** enriched in the (−)-isomer (prepared by repeated cycles of precipitation of the product from racemic **13c** and (+)-di-*p*-toluoyl-D-tartaric acid from 2-butanone, followed by conversion into the free base) via sodium in THF–*tert*–butyl alcohol afforded (−)-**3** in 61% ee, establishing the absolute configuration of (−)-**13c** as 5(*R*),10(*S*). Thus the absolute configuration of (+)-**13c** is 5(*S*),10(*R*), analogous to that of **2**.

With an eye toward synthesizing an azido-IDDC for use in potential photolabeling experiments of the PCP receptor,[21] the amino group of **3** was protected as an acetamide to give **26**. Nitration afforded several mononitro products that were difficult to separate, the easiest to isolate being the 3-nitro derivative **27** in 20% yield by trituration with acetone (Scheme IV). Treatment of **27** with hydrazine and KOH in hot ethylene glycol gave diamine **29**, which was then treated with nitrous acid and sodium azide to give azide **30**. Attachment at the 3 position was confirmed by conversion of **29** into the previously prepared chloride **13c** by the method of Doyle et al.[22] Acidic hydrolysis of **27** afforded the deacetylated nitro compound **28**.

In addition to the *N*-methyl derivative **6**, more complex N-substituted derivatives of **3** were prepared. *N*-[3-(Dimethylamino)-1-propyl]-IDDC (**31**) was obtained from the reaction of **3** with 3-(dimethylamino)propyl chloride hydrochloride in DMF in the presence of triethylamine. Similarly, *N*-(2-pyridinylmethyl)-IDDC (**32**) was prepared from **3** and 2-picolyl chloride hydrochloride in DMF in the presence of diisopropylethylamine. *N*-Isopropyl-

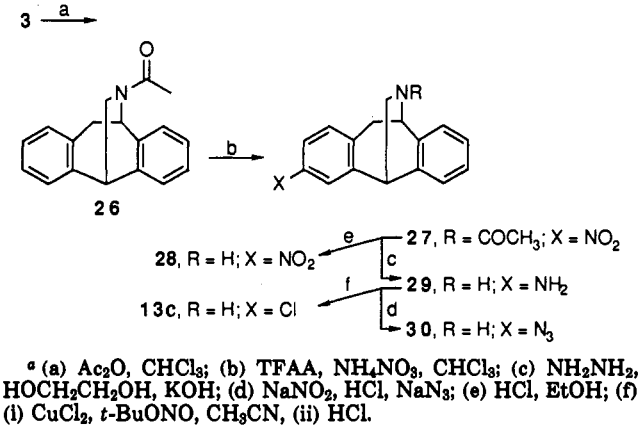
Table I. Inhibition of [^{3}H]-2 Binding to the PCP Receptor by Substituted 10,5-(Iminomethano)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptenes and 2



compd[a]	R_1	R_2	R_3	R_4	IC_{50}[b]	SEM[c]	*n*
(+)-13e	F	H	H	H	15.5	4.5	3
13e	F	H	H	H	29.4	0.8	3
(+)-13c	Cl	H	H	H	32.1	12.9	3
(+)-3	H	H	H	H	37.6	5.7	4
13k	F	H	F	H	51.2	13.4	3
13d	Br	H	H	H	51.7	6.5	6
3	H	H	H	H	59.4	5.8	6
13c	Cl	H	H	H	71.3	6.4	6
13g	CH_3	H	H	H	108	4.5	2
13i	Cl	H	OCH_3	H	113	26	4
13j	Br	H	OCH_3	H	114	24	3
8	H	CH_3	H	H	119	17	5
16	I	H	H	H	160	16	2
13f	OCH_3	H	H	H	168	2	2
13a	H	H	OCH_3	H	332	60	2
13h	Ph	H	H	H	421	47	2
29	NH_2	H	H	H	486	86	3
30	N_3	H	H	H	500		1
(−)-13e	F	H	H	H	531	38	3
15	Br	H	OCH_3	CH_3	643	256	2
13b	H	H	Cl	H	690	108	3
(+)-6	H	H	H	CH_3	826	68	11
(−)-13c	Cl	H	H	H	931	3	3
14	Br	H	H	CH_3	1044	146	3
33	H	H	H	$CHMe_2$	1879	248	2
28	NO_2	H	H	H	4300	490	2
31	H	H	H	$(CH_2)_3NMe_2$	12000	4000	4
26	H	H	H	$COCH_3$	>10000		4
27	NO_2	H	H	$COCH_3$	>10000		4
32	H	H	H	CH_2(2-pyridyl)	>10000		4
2					4.2	0.5	5

[a] Racemic unless otherwise indicated. [b] nM, against [^{3}H]-2. [c] Not given when only one determination is made.

Scheme IV[a]

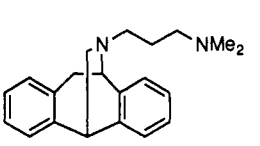


[a] (a) Ac_2O, $CHCl_3$; (b) TFAA, NH_4NO_3, $CHCl_3$; (c) NH_2NH_2, $HOCH_2CH_2OH$, KOH; (d) $NaNO_2$, HCl, NaN_3; (e) HCl, EtOH; (f) (i) $CuCl_2$, *t*-BuONO, CH_3CN, (ii) HCl.

IDDC (**33**) was prepared by the reaction of **3** with 2-bromopropane in DMSO in the presence of potassium carbonate.

Results and Discussion

The PCP receptor affinities of **3** and analogs relative to [^{3}H]-**2** were determined as described previously.[23] The results are shown in Table I. Substitution of the electron-withdrawing halogens Br, Cl, and F (**13d**, **13c**, and **13e**, respectively) at C-3 increased the affinity of the IDDC ligand for the receptor in the racemic series. However, with electron-withdrawing substituents at C-3, size apparently becomes the predominant factor in influencing affinity when substituents are larger than bromine. Thus, even though the nitro group is a substantially more powerful withdrawing substituent than the halogens, at C-3 it results in quite a low binding affinity (compound **28**). The larger withdrawing substituents iodine and phenyl (**16** and **13h**) also cause lower affinities, though not as dramatically as that induced by the C-3 nitro group. Among IDDC ligands with small substituents at C-3, the importance of electronic character of the substituent is further demonstrated by the decreased binding affinities of ligands with donors of increasing power (Me, OMe, and NH_2 in compounds **13g**, **13f**, and **29**, respectively). Among these three compounds there is an inverse relationship between donating power and binding affinity. By contrast, substitution of either a donor group (OMe, compounds **13i**, **13j**, and **13a**) or a withdrawing group (Cl in **13b**, F in **13k**) at C-7 led to a decrease in binding affinity, relative to hydrogen. The higher affinities of **13i** and **13j** over **13a** demonstrate the generality of the receptor's preference for halogen-induced electron withdrawal at C-3. In all cases examined, N-substitution led to substantially lower binding affinities. A rough correlation between increasing size and lower affinity (compounds (+)-**6**, **33**, **31**, **26**, and **32**) was observed.



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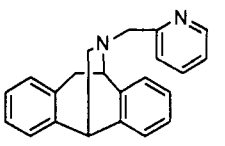

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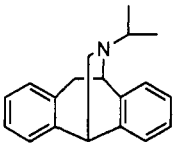

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The higher affinity of (+)-**3** for the PCP receptor, relative to the racemate, led us to resolve the more potent ligands **13c** and **13e** into their enantiomers for a more thorough evaluation of the stereochemical requirements of the receptor for IDDC-type ligands. A significant preference for the (+)-optical antipodes was found, as was the case in the MK-801 series.[15] Thus, affinities of (+)-**13c** and (+)-**13e** were about 30 times higher than those of the (−)-isomers.

The in vitro neuroprotective properties of (±)-**3**, (+)-**3**, and (+)-**6** were determined using rat hippocampal cell cultures and various concentrations of glutamate (Table II). Enhanced cell survival was observed with all three compounds, with values for (+)-**6** (10 μM) approaching those of **2** (5 μM) for glutamate concentrations <100 μM. Interestingly, while (+)-**3** and (+)-**6** were essentially equipotent neuroprotectants, (+)-**3** was 2200% more potent than (+)-**6** in the binding assay (Table I). Thus, (+)-**6** was a much better neuroprotectant in the cell cultures than predicted by the binding assay. This may be because the *N*-methyl group in (+)-**6** renders the molecule more lipophilic than (+)-**3**, allowing the ligand better access to membrane-bound receptors in the cultured cells. It is also possible that unidentified neuroprotective mechanisms may be operating in the case of (+)-**6**.

Table II. Percent in Vitro Neuroprotection of (±)-3, (+)-3, (+)-6, and 2 against Glutamate-Induced Toxicity

glutamate μM	control	SEM (n)	(±)-3 (5 μM)	SEM (n)	(+)-3 (5 μM)	SEM (n)	(+)-6 (5 μM)	SEM (n)	(+)-6 (10 μM)	SEM (n)	2 (5 μM)	SEM (n)
0	94.9	3.9 (8)	99.1	0.9 (3)	93.6	4.3 (5)	91.0	9.0 (2)	97.8	2.1 (2)	97.5	1.1 (4)
3	82.0	6.7 (7)	85.3	11.3 (3)	68.8	6.3 (4)	74.7	15.8 (2)	93.6	6.3 (2)	98.3	0.7 (4)
10	63.6	7.9 (8)	76.6	19.4 (3)	76.3	8.3 (5)	65.0	39.9 (2)	90.0	4.9 (2)	94.7	1.0 (4)
30	55.3	8.9 (8)	71.5	27.0 (3)	73.3	13.3 (4)	62.7	37.3 (2)	92.1	6.9 (2)	95.5	3.5 (4)
100	43.5	10.8 (8)	61.3	25.6 (3)	73.9	15.1 (5)	59.9	34.4 (2)	84.0	10.0 (2)	93.9	2.2 (4)
300	30.5	12.5 (7)	39.9	20.4 (3)	57.2	7.2 (5)	58.7	38.8 (2)	56.6	2.0 (2)	90.3	3.4 (4)
1000	09.5	3.4 (8)	25.5	20.8 (3)	40.5	11.2 (5)	23.3	13.0 (2)	53.3	2.7 (2)	88.4	5.4 (4)

Summary

Racemic **3** showed strong affinity for the PCP receptor, and the (+)-optical antipode was more active than the racemate. The receptor's selective affinity for the (+)-isomer of the parent IDDC structure was demonstrated in the three cases (**3**, **13c**, **13e**) in which the enantiomers were resolved. Substitution at C-3 of **3** with the electron-withdrawing halogen atoms Br, Cl, and F led to increased affinity. However, the non-halogen electron-withdrawing substituents NO_2 and Ph significantly decreased binding affinity, relative to **3**. Electron-donating substituents (Me, OMe, NH_2) at C-3 caused a decrease in binding affinity as well. Both electron-withdrawing and -donating substituents at C-7 caused decreased binding affinity without exception. In every case, N-substitution (alkyl and acyl) led to decreased binding affinity, relative to **3**. In vitro neuroprotection against lethal glutamate concentrations was demonstrated by (+)-**3** and (+)-**6**. The study presented here demonstrates that **3** and several of its derivatives are potent PCP receptor ligands, and that the binding affinity of (+)-**13e** places it among the most potent PCP receptor ligands known.

Experimental Section

General. Except where noted, solvents and reagents were used as received. Melting and boiling points are uncorrected. All reactions were run under a nitrogen atmosphere. NMR spectra were obtained on a General Electric QE 300 instrument, and the chemical shifts are reported in δ units using residual solvent proton signals as the reference. Infrared spectra were obtained on a Nicolet 5DXB FT-IR spectrometer as 5% solutions in the indicated solvent; absorptions are indicated by wavenumber (cm^{-1}), and classified as strong (s), medium (m), or weak (w). Mass spectroscopy was carried out in the electron ionization mode with a VG ZAB-2-HF mass spectrometer using a VG-H-250 data system. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. "Flash" chromatography was performed under a positive air pressure with Davisil silica gel (grade 643, 200–425 mesh, 150 Å). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 F_{254} plates with a fluorescent indicator, and visualization was effected with an ultraviolet lamp. Preparative TLC was performed on Analtech GF precoated silica gel (1000 μm) glass-backed plates (20 × 20 cm). Tetrahydrofuran and ether were distilled from blue sodium benzophenone ketyl, methylene chloride was distilled from calcium hydride, and DMF was dried over molecular sieves. All other reagents were used as received, unless otherwise indicated.

The general method of Allen and Barker[24] was followed in the preparation of 4-substituted phenylacetyl chlorides from their respective acids.

(+)-10(*R*),5(*S*)-(Iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene ((+)-3). A mixture of *R*-(−)-**4**[10] [249.5 mg, 1.3 mmol, $[\alpha]^{19}_D = -50.1°$ ($c = 3.7$), EtOH, ee = 98%], anhydrous potassium carbonate (193.6 mg, 1.4 mmol), and bromoacetaldehyde diethyl acetal (distilled, 284.1 mg, 1.4 mmol) in DMF (2.4 mL) was stirred at 90 °C for 12 h. Sodium hydroxide (10%, 10 mL) was added and the resulting mixture extracted with methylene chloride. The extract was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography on 10 g silica gel using an elution gradient of ether to ether/THF (2:1) to give (*R*)-**5** as 283.3 mg of a clear, light yellow liquid (71% yield): ^1H NMR ($CDCl_3$) 7.34–7.16 (m, 10H), 4.53 (dd, J = 6.3, 5.0 Hz, 1H), 3.86 (dd, J = 8.5, 5.9 Hz, 1H), 3.55 (dt, J = 9.3, 6.9 Hz, 2H), 3.40 (dt, J = 9.3, 7.2 Hz, 2H), 2.98 (dd, J = 13.2, 5.9 Hz, 1H), 2.91 (dd, J = 13.2, 8.5 Hz, 1H), 2.57 (dd, J = 12.0, 5.0 Hz, 1H), 2.51 (dd, J = 12.0, 6.3 Hz, 1H), 1.76 (br s, 1H), 1.10 (t, J = 6.9 Hz, 6H).

A mixture of perchloric acid (70%, 6 mL) and *R*-**5** (280 mg, 8.9 mmol) was stirred at room temperature for 24 h, and basified with 2 N NaOH. The resulting mixture was extracted with methylene chloride (2 × 10 mL), and the extract was concentrated. The residue was purified by flash chromatography followed by vacuum distillation (170 °C/0.5 mmHg) to give (+)-**3** as 153.4 mg of a clear light yellow oil that solidified on standing (78% yield). The ee (98%) is assumed to be the same as for *R*-(−)-**4**: $[\alpha]^{25}_D$ = +165° (c = 1, EtOH); R_f 0.22 (THF); mp 79–85 °C; ^1H NMR ($CDCl_3$) 7.30–7.05 (m, 8H), 4.34 (t, J = 3.6 Hz, 1H), 3.93 (d, J = 4.2 Hz, 1H), 3.67 (d, J = 11.1 Hz, 1H), 3.51 (dd, J = 17.5, 3.7 Hz, 1H), 3.33 (dd, J = 11.1, 4.6 Hz, 1H), 3.23 (dd, J = 17.5, 3.2 Hz, 1H), 2.10 (br s, 1H); ^{13}C NMR ($CDCl_3$) 143.0 (s), 141.6 (s), 140.4 (s), 135.4 (s), 131.5 (d), 128.0 (d), 127.3 (d), 126.9 (d), 126.8 (d), 126.0 (d), 125.6 (d), 125.0 (d), 55.1 (d), 50.8 (t), 46.9 (d), 41.7 (t); *m/e* (rel intensity) 221 (M^+, 47), 192 (100), 131 (62); HRMS 221.1218 (221.1204 calcd for $C_{16}H_{15}N$).

The maleate salt was prepared by reaction with maleic acid in ethanol to give (+)-**3**·$C_4H_4O_4$ as a white powder: mp 160–163 °C. Anal. ($C_{20}H_{19}NO_4 \cdot 0.1H_2O$) C, H, N.

(+)-*N*-Methyl-10(*R*),5(*S*)-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene ((+)-6). To a stirred solution of (+)-**3** [206.3 mg, 0.93 mmol, $[\alpha]_D$ = +165° (c = 1, EtOH)] in acetonitrile (3 mL) and 37% aqueous formaldehyde (0.40 mL) at room temperature was added sodium cyanoborohydride (109.2 mg, 1.73 mmol). The resulting mixture was stirred for 15 min, and 10 drops of glacial acetic acid were added to lower the pH to 7. The mixture was stirred for 20 h and treated with 2 N NaOH (5 mL). This mixture was extracted with ether (4 × 4 mL). The combined organic portions were dried over potassium carbonate, and the solvent was evaporated to give 229 mg of a clear oil, which was purified by flash chromatography (chloroform/ether) followed by Kugelrohr distillation (180 °C, 0.05 mmHg) to give (+)-**6** as 122.1 mg of a clear colorless oil (56% yield): R_f 0.41 (THF); $[\alpha]^{25}_D$ = +189° (c = 1, EtOH); ^1H NMR ($CDCl_3$) 7.34–7.03 (m, 8H), 3.94 (dd, J = 3.9, 3.0 Hz, 1H), 3.83 (dd, J = 4.7, 1.1 Hz, 1H), 3.62 (dd, J = 17.7, 3.9 Hz, 1H), 3.58 (dd, J = 10.5, 1.1 Hz, 1H), 3.00 (dd, J = 17.7, 3.3 Hz, 1H), 2.92 (dd, J = 10.5, 4.8 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$) 142.5 (s), 141.4 (s), 138.6 (s), 135.2 (s), 131.3 (d), 127.8 (d), 127.3 (d), 126.8 (d), 126.7 (d), 126.0 (d), 125.9 (d), 125.1 (d), 62.7 (d), 59.8 (t), 47.0 (d), 45.2 (q), 36.6 (t).

The hydrochloride salt of (+)-6 was prepared in ethanol by adding ethanolic HCl: mp 122–126 °C dec. Anal. ($C_{17}H_{18}NCl·1.5H_2O$) C, H, N.

General Procedure A for Converting Substituted Desoxybenzoins (9) into Substituted 1,2-Diphenylethanone *O*-Methyloximes (10). To a solution of the desoxybenzoin (9, 5.0 mmol) in pyridine (15 mL, dried over molecular sieves) was added methoxylamine hydrochloride (8.0 mmol) in one portion at room temperature. The resulting solution was stirred under nitrogen overnight. The pyridine was removed in vacuo, and the residual solids were extracted with ether (75 mL). Filtration and evaporation of the solvent afforded a mixture of geometrical oxime isomers (10) as colorless syrups, which were either used without further purification or purified by column chromatography on neutral alumina (I) using benzene or toluene as eluant. The mixture of isomers was not usually separated; they were reacted together in the next (reduction) step.

General Procedure B for Converting Substituted 1,2-Diphenylethanone *O*-Methyloximes (10) into Substituted 1,2-Diphenylethylamines (11). To a solution of a mixture of syn- and anti-oxime isomers (10, 5 mmol) in 50 mL of THF was added borane–tetrahydrofuran complex (1.0 M, 25 mmol) via syringe at room temperature. The resulting colorless solution was refluxed under nitrogen for 3 h, and cooled in an ice/water bath. Water (40 mL) was carefully added, followed by 20% NaOH (40 mL). The resulting colorless biphasic mixture was refluxed overnight with vigorous magnetic stirring, and allowed to cool to room temperature. Hexanes (50 mL) were added, and the layers were separated. The aqueous portion was extracted with hexanes (1 × 50 mL), and the organic portions were combined and dried over potassium carbonate. Evaporation of the solvent afforded the crude amines as cloudy syrups, which were purified by chromatography on neutral alumina (I) using chloroform/ethyl acetate (1:1 to 0:1) to give the pure amines (11) as clear, colorless syrups.

General Procedure C for Converting Substituted 1,2-Diphenylethylamines (11) into Substituted *N*-(2,2-Diethoxyethyl)-1,2-diphenylethylamines (12). To a solution of the amine (11, 5 mmol) in DMF (20 mL) was added bromoacetaldehyde diethyl acetal (distilled, 10 mmol) and potassium carbonate (10 mmol) at room temperature. The resulting mixture was heated at 100 °C for 16 h and cooled to 10 °C. Sodium hydroxide (10%, 100 mL) was added, and the resulting mixture was extracted with methylene chloride (3 × 40 mL). The combined organic portions were washed with water (2 × 40 mL) and brine (1 × 40 mL) and dried over potassium carbonate. The solvent was evaporated, and the residue was purified by flash chromatography using 3:1 hexanes/EtOAc as eluant, giving the acetals 12 as clear, pale yellow or colorless syrups.

General Procedure D for Converting Aryl-Substituted *N*-(2,2-Diethoxyethyl)-1,2-diphenylethylamines (12) into Aryl-Substituted IDDC's (13). To the neat acetal 12 (1.0 mmol) was added perchloric acid (70%, 15 mmol) or sulfuric acid (96%, 15 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 h. Ice (1 g) was added, followed by 10% sodium hydroxide until the pH > 10. The resulting mixture was extracted with methylene chloride (3 × 8 mL). The combined extracts were washed with brine (1 × 10 mL) and dried over sodium sulfate. The solvent was evaporated and the residue purified by flash chromatography or preparative thin-layer chromatography using 15% methanol/EtOAc as eluant, affording pure substituted IDDC's (13).

7-Methoxy-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (13a). According to general methods A-D (using perchloric acid in method D) 13a was formed as a clear, colorless syrup in 26% yield from 9a: R_f 0.10 (EtOAc/MeOH 4:1); IR ($CDCl_3$) 3352 (w), 3063 (w), 3019 (w), 2916 (m), 2831 (w), 1490 (s), 1450 (m), 1283 (m), 1249 (s), 1134 (m); ^{1}H NMR ($CDCl_3$) 7.33–7.01 (m, 5H), 6.80 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 2.7 Hz), 6.73 (d, J = 2.7 Hz, 1H over 6.76–6.73), 4.32 (t, J = 3.6 Hz, 1H), 3.87 (d, J = 4.1 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, J = 11.7, 1.1 Hz, 1H), 3.47 (dd, J = 17.5, 3.8 Hz), 3.32 (dd, J = 11.5, 4.6 Hz), 3.21 (dd, J = 17.5, 3.3 Hz, 1H), 2.2 (br s, 1H); ^{13}C NMR ($CDCl_3$) 159.1, 142.8, 135.5, 132.6, 131.5, 128.0, 126.8, 126.0, 111.9, 111.6, 55.4, 54.5, 50.6, 47.5, 42.3; HRMS 251.1313 (251.1311 calcd for $C_{17}H_{17}NO$).

The hydrochloride salt was formed by bubbling HCl gas into an ethereal solution of 13a to give 13a·HCl as a white powder: mp 269–272 °C dec. Anal. ($C_{17}H_{18}NOCl$) H, N; C: calcd, 70.95; found, 70.47.

7-Chloro-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (13b). According to general methods A–D (using sulfuric acid in method D), 13b was formed in 19% yield as a clear, pale yellow syrup from 9b: R_f 0.19 (EtOAc/MeOH 4:1); IR ($CDCl_3$) 3352 (w), 3062 (w), 3019 (m), 2922 (s), 1874 (m), 1602 (m), 1578 (w), 1499 (m), 1481 (s), 1451 (m), 1415 (m), 1269 (w), 1179 (w), 1082 (m); ^{1}H NMR 7.25–7.04 (m, 7H), 4.33 (t, J = 3.6 Hz, 1H), 3.88 (d, J = 4.4 Hz, 1H), 3.66 (dd, J = 11.4, 1.0 Hz, 1H), 3.49 (dd, J = 17.6, 3.8 Hz, 1H), 3.31 (dd, J = 11.4, 4.7 Hz, 1H), 3.20 (dd, J = 17.6, 3.4 Hz, 1H), 2.06 (s, 1H),; ^{13}C NMR ($CDCl_3$) 143.2, 142.3, 138.8, 135.1, 132.7, 131.4, 128.0, 127.0, 126.8, 126.3, 126.1, 125.7, 54.6, 50.5, 46.9, 41.7; HRMS 255.0800 (255.0816 calcd for $C_{16}H_{14}NCl$).

The hydrochloride salt was formed from 13b and hydrogen chloride in ether as a white powder: mp 290–292 °C dec. Anal. ($C_{16}H_{15}NCl_2·0.25H_2O$) C, H, N.

3-Chloro-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (13c). According to general methods A–D (using perchloric acid in method D), 13c was isolated as a clear, colorless syrup in 34% yield from 9c: R_f 0.22 (20% MeOH/EtOAc); IR ($CDCl_3$) 3352 (m), 3074 (m), 3025 (m), 2922 (s), 2874 (m), 1596 (s), 1487 (s), 1457 (m), 1421 (m), 1372 (m), 1251 (m), 1179 (m), 1106 (s); ^{1}H NMR ($CDCl_3$) 7.27–7.19 (m, 5H), 7.09 (dd, J = 8.2, 2.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 4.31 (t, J = 3.7 Hz, 1H), 3.86 (d, J = 4.1 Hz, 1H), 3.64 (dd, J = 11.7, 1.1 Hz, 1H), 3.45 (dd, J = 17.6, 3.85 Hz, 1H), 3.31 (dd, J = 11.5, 4.85 Hz, 1H), 3.17 (dd, J = 17.6, 3.4 Hz, 1H), 2.40 (s, 1H); ^{13}C NMR ($CDCl_3$) 144.6, 140.8, 140.1, 133.8, 132.8, 131.3, 127.7, 127.4, 127.2, 126.7, 125.6, 125.0, 54.8, 50.5, 46.6, 41.2; HRMS 255.0825 (255.0816 calcd for $C_{16}H_{14}NCl$).

The maleate salt was prepared by reaction in ethanol with maleic acid to give 13c·$C_4H_4O_4$ as a white powder: mp 153.7–156.0 °C. Anal. ($C_{20}H_{18}NO_4Cl$) C, H, N.

Preparative chiral HPLC[20] of the free base afforded (+)-13c and (−)-13c as semisolid oils. For (+)-13c: $[\alpha]^{25}_D$ = +260° (c = 1, EtOH). For (−)-13c: $[\alpha]^{25}_D$ = −270° (c = 0.5, EtOH).

3-Bromo-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (13d). According to general methods A–D (using perchloric acid in method D), 13d was formed in 33% yield from 9d as a clear, pale brown syrup that solidified upon standing: mp 87.5–90.0 °C; R_f 0.26 (EtOAc/MeOH 4:1); IR ($CDCl_3$) 3352 (w), 3080 (w), 3025 (w), 2922 (m), 2874 (w), 1590 (m), 1481 (s), 1457 (m), 1421 (m), 1372 (w), 1251 (m), 1179 (m), 1112 (m); ^{1}H NMR 7.37 (d, J = 2.0 Hz, 1H), 7.30–7.15 (m, 5H), 6.90 (d, J = 8.2 Hz, 1H), 4.30 (t, J = 3.7 Hz, 1H), 3.84 (d, J = 4.5 Hz, 1H), 3.62 (d, J = 11.2, 1H), 3.43 (dd, J = 17.6, 3.8 Hz, 1H), 3.28 (dd, J = 11.5, 4.8 Hz, 1H), 3.14 (dd, J = 17.6, 3.4 Hz, 1H), 2.10 (s, 1H); ^{13}C NMR ($CDCl_3$) 145.4, 141.1, 140.5, 134.8, 133.4, 130.9, 129.9, 127.7, 127.5, 126.0, 125.3, 119.6, 55.1, 51.9, 46.8, 41.6; m/e (rel intensity) 301 (M^+, 15), 300 (16), 299 (M^+, 15), 299 (15), 299 (15), 298 (16), 273 (7), 272 (37), 271 (13), 270 (37), 269 (8), 191 (22), 189 (23), 130 (100); HRMS 299.0302 (299.0310 calcd for $C_{16}H_{14}NBr$).

The maleate salt was prepared by reaction with maleic acid in ethanol to give 13d·$C_4H_4O_4$ as a white powder: mp 165.0–165.7 °C. Anal. ($C_{20}H_{18}NO_4Br$) C, H, N.

***N*-Methyl-3-bromo-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (14).** As for (+)-6, 13d (68.1 mg, 0.227 mmol), acetonitrile (0.50 mL), aqueous formaldehyde (37% solution, 0.065 mL, 0.87 mmol), and sodium cyanoborohydride (20.0 mg, 0.318 mmol) afforded 14 as 49 mg of a clear colorless syrup (69% yield): R_f 0.36 (EtOAc/MeOH 4:1); ^{1}H ($CDCl_3$) 7.33 (d, J = 1.9 Hz, 1H), 7.24–7.15 (m, 5H), 6.91 (d, J = 8.2 Hz, 1H), 3.96 (t, J = 3.6 Hz, 1H), 3.60 (d, J = 3.8 Hz, 1H), 3.60 (dd, J = 10.8, 1.1 Hz, 1H), 3.57 (dd, J = 17.4, 4.0 Hz, 1H), 2.94 (dd, J = 17.5, 3.0 Hz, 1H), 2.91 (dd, J = 10.7, 4.6 Hz, 1H), 2.50 (s, 3H); HRMS 313.0442 (313.0467 calcd for $C_{17}H_{16}NBr$).

The hydrochloride salt was prepared with hydrogen chloride in ether as a pale yellow powder: mp 174–176 °C dec. Anal. ($C_{17}H_{17}NBrCl·0.5H_2O$) C, H, N.

3-Iodo-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (16). The methods of Thompson et al.[15] and

Takagi et al.[18] were adapted. A mixture of **13d** (75 mg, 0.25 mmol), nickel powder (73 mg, 1.3 mmol, 3 μm), potassium iodide (83 mg, 0.50 mmol), iodine (3 mg, 0.01 mmol), and DMF (0.50 mL) was degassed by bubbling nitrogen through for 20 min. A septum was placed on the flask with a nitrogen inlet, and the flask was immersed in an oil bath at 150 °C. After 5 h of stirring, the heat was removed and the reaction mixture allowed to achieve room temperature. Water (5 mL) and ethyl acetate (5 mL) were added with stirring. The liquid portion was removed by pipet, and the residual solids were rinsed with ethyl acetate (3 × 5 mL). All the liquids were combined and hexanes (10 mL) were added. The layers were separated, and the organic portion was dried over sodium sulfate. The solvent was evaporated to afford a clear brown syrup, which was purified by flash chromatography using an elution gradient of EtOAc/MeOH (1:0 to 9:1, the methanol containing 1% NH_4OH). A pale yellow, cloudy syrup (46.6 mg) was obtained (46% yield); no **13d** was observed in the mass spectrum: R_f 0.23 (20% methanol/EtOAc); ^1H NMR (acetone-d_6) 7.62 (d, J = 1.5 Hz, 1H), 7.40 (dd, J = 8.2, 1.6 Hz, 1H), 7.29–7.10 (m, 4H), 6.81 (d, J = 8.1 Hz, 1H), 4.35 (t, J = 3.5 Hz, 1H), 3.97 (d, J = 3.7 Hz, 1H), 3.51 (dd, J = 10.7, 0.9 Hz, 1H), 3.36 (dd, J = 17.7, 3.6 Hz, 1H), 3.23 (dd, J = 11.3, 4.7 Hz, 1H), 3.03 (dd, J = 17.7, 3.2 Hz, 1H); 1.26 (s, 1H); *m/e* (rel intensity) 347 (M+, 21), 318 (55), 191 (19), 189 (20), 165 (13), 132 (32), 130 (100), 117 (26); HRMS 347.0199 (347.0172 calcd for $C_{16}H_{14}NI$).

3-Fluoro-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13e). According to general methods A–D (perchloric acid used in method D), **13e** was prepared in 28% overall yield, beginning with **9e**, as a yellow syrup: R_f 0.37 ($CHCl_3$/MeOH 9;1); ^1H NMR ($CDCl_3$) 7.25–7.17 (m, 4H), 6.98 (dd, J = 8.4, 5.8 Hz, 1H), 6.88 (dd, J = 9.3, 2.7 Hz, 1H), 6.80 (td, J = 8.4, 2.7 Hz, 1H), 4.47 (t, J = 3.7 Hz, 1H), 3.87 (d, J = 4.0 Hz, 1H), 3.69 (dd, J = 11.6, 1.0 Hz, 1H), 3.60 (dd, J = 17.4, 3.6 Hz, 1H), 3.48 (br s, 1H), 3.37 (dd, J = 11.6, 4.8 Hz, 1H), 3.16 (dd, J = 17.4, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) 161.0 (d, J_{C-F} = 245.0 Hz), 144.2, 140.7, 137.6, 132.9, 130.5, 127.5, 127.2, 125.6, 125.5, 114.5 (d, J_{C-C-F} = 21.1 Hz), 113.6 (d, J_{C-C-F} = 20.8 Hz), 54.9, 50.3, 46.6, 40.7; HRMS 239.1132 (239.1110 calcd for $C_{16}H_{14}NF$).

The hydrochloride salt was prepared with hydrogen chloride in ether: mp 274–276 °C dec. Anal. ($C_{16}H_{15}ClFN \cdot 0.33H_2O$) C, H, N.

Preparative chiral HPLC[20] of the free base afforded (+)-**13e** and (−)-**13e** as semisolid oils. For (+)-**13e**: $[\alpha]^{25}_D$ = +126° (*c* = 1, EtOH); the hydrochloride salt was prepared from hydrogen chloride in ether: mp 287–288 °C dec. Anal. ($C_{16}H_{15}ClFN \cdot 0.33H_2O$) C, H, N. For (−)-**13e**: $[\alpha]^{25}_D$ = −134° (*c* = 0.5, EtOH).

3-Methoxy-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13f). According to general methods A–D (using perchloric acid in method D), **13f** was formed in 5% yield from **9f** as a clear, colorless syrup: R_f 0.17 (ethyl acetate/methanol 4:1); ^1H NMR ($CDCl_3$) 7.2 (br s, 4H), 6.97 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.4 Hz), 6.70 (d, J = 2.5 Hz), 6.67 (d, J = 2.6 Hz, 2H over 6.75–6.67), 4.33 (t, J = 3.6 Hz, 1H), 3.86 (d, J = 4.2 Hz, 1H), 3.79 (s, 3H), 3.66 (d, J = 11.8 Hz, 1H), 3.43 (dd, J = 17.2, 3.7 Hz, 1H), 3.32 (dd, J = 11.5, 4.7 Hz, 1H), 3.16 (dd, J = 17.2, 3.3 Hz, 1H), 2.12 (s, 1H); ^{13}C NMR ($CDCl_3$) 157.8, 144.1, 141.3, 140.4, 132.4, 127.2, 127.1, 126.8, 125.5, 124.9, 113.6, 112.2, 55.3, 55.2, 50.7, 47.3, 41.0; *m/e* (rel intensity) 251 (M^+, 31), 250 (23), 222 (66), 179 (34), 178 (31), 130 (100); HRMS 251.1330 (251.1311 calcd for $C_{17}H_{17}NO$).

The hydrochloride salt was prepared as off-white microcrystals by reaction in ether of **13f** with HCl(g), followed by crystallization from ethanol. Anal. ($C_{17}H_{18}NOCl$) C, H, N.

3-Methyl-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13g). Beginning with **9g**, **13g** was prepared in 48% overall yield via general methods A–D (perchloric acid used in method D) as a pale brown syrup: ^1H NMR ($CDCl_3$) 7.21–6.94 (m, 7H), 4.37 (t, J = 3.6 Hz, 1H), 3.87 (d, J = 4.2 Hz, 1H), 3.68 (d, J = 10.7 Hz, 1H), 3.49 (dd, J = 17.5, 3.8 Hz, 1H), 3.33 (dd, J = 11.5, 4.7 Hz, 1H), 3.19 (dd, J = 17.5, 3.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) 142.4, 141.4, 135.4, 131.6, 128.5, 127.4, 127.2, 126.7, 125.4, 124.9, 55.0, 50.4, 46.7, 40.9, 20.7; HRMS 235.1330 (235.1357 calcd for $C_{17}H_{17}N$).

3-Phenyl-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13h). Beginning with **9h**, **13h** was prepared by general methods A–D (perchloric acid used in method D) in 18% overall yield as a white powder: R_f 0.40 ($CHCl_3$/MeOH 9:1); mp 107–108 °C; ^1H NMR ($CDCl_3$) 7.61–7.12 (m, 12H), 4.42 (t, J = 3.6 Hz, 1H), 4.01 (d, J = 4.2 Hz, 1H), 3.73 (d, J = 12.7 Hz, 1H), 3.58 (dd, J = 17.8, 3.5 Hz, 1H), 3.37 (dd, J = 11.5, 4.7 Hz, 1H), 3.18 (dd, J = 17.8, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) 143.4, 141.6, 141.3, 140.0, 139.4, 134.5, 132.2, 129.1, 129.1, 127.8, 127.5, 127.4, 127.4, 127.4, 127.0, 125.9, 125.8, 125.5, 55.3, 50.8, 47.3, 41.4; HRMS 297.1492 (297.1517 calcd for $C_{22}H_{19}N$). Anal. ($C_{22}H_{18}N \cdot 1.5H_2O$) C, N; H: calcd, 6.83; found, 6.22.

3-Chloro-7-methoxy-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13i). Beginning with **9i**, **13i** was prepared according to general methods A–D (perchloric acid used in method D) in 62% overall yield as a clear yellow syrup that solidified upon standing: mp 103–104 °C; R_f 0.36 (10% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) 7.30–6.79 (m, 6H), 5.04 (br s, 1H), 4.44 (t, J = 3.5 Hz, 1H), 3.86 (d, 1H), 3.85 (s, 3H), 3.69 (dd, J = 12.2 Hz, 1H), 3.56 (dd, J = 17.0, 3.3 Hz, 1H), 3.37 (dd, J = 13.7, 4.4 Hz, 1H), 3.18 (dd, J = 18.5, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 151.7, 143.4, 141.6, 136.1, 132.8, 128.4, 127.8, 126.9, 126.3, 125.6, 112.5, 111.7, 55.4, 54.1, 50.0, 47.0, 41.0; HRMS 285.0910 (285.0920 calcd for $C_{17}H_{18}NOCl$). Anal. ($C_{16}H_{17}ClNO \cdot 1.5H_2O$) N; C: calcd, 65.27; found, 64.84 H: calcd, 6.12; found, 5.21.

3-Bromo-7-methoxy-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (13j). Beginning with **9j**, **13j** was prepared in 55% overall yield according to general methods A–D (perchloric acid in method D) as a shiny white solid: ^1H NMR ($CDCl_3$) 7.34–6.73 (m, 6H), 4.33 (t, J = 3.4 Hz, 1H), 3.79 (d, 1H), 3.79 (s, 3H), 3.61 (d, J = 11.7 Hz, 1H), 3.43 (dd, J = 17.7, 3.6 Hz, 1H), 3.28 (dd, J = 11.5, 4.6 Hz, 1H), 3.11 (dd, J = 17.7, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 159.1, 144.7, 141.9, 134.4, 133.2, 131.9, 130.7, 129.8, 126.2, 119.4, 112.3, 111.6, 55.4, 54.0, 50.1, 46.8, 41.4; HRMS 329.0428 (329.0415 calcd for $C_{17}H_{18}NOBr$).

N-Methyl-3-bromo-7-methoxy-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (15). To a solution of **13j** (50 mg, 0.15 mmol) in formic acid (1.1 mL) was added formaldehyde (37% aqueous solution, 0.061 mL, 0.76 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 3 h, followed by reflux for 2 h. The reaction mixture was basified with 1 N NaOH to pH 12 and extracted with methylene chloride (2 × 40 mL). The combined extracts were dried over magnesium sulfate, and the solvent evaporated to yield a crude product, which was purified by preparative TLC using $CHCl_3$/MeOH (9:1) to give the title compound as 42 mg of a yellow syrup (78% yield): ^1H NMR ($CDCl_3$) 7.31–6.75 (m, 6H), 3.93–3.74 (m, 2H), 3.79 (s, 3H), 3.60–3.53 (m, 2H), 2.94–2.85 (m, 2H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$) 159.2, 144.2, 141.9, 134.4, 133.0, 130.5, 130.3, 129.8, 127.1, 119.2, 112.2, 111.2, 61.8, 59.3, 55.4, 46.9, 45.3, 38.6; HRMS 343.0564 (343.0571 calcd for $C_{16}H_{18}NOBr$).

3,7-Difluoro-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (13k). Beginning with **9k**, **13k** was prepared in 16% overall yield via general methods A–D (perchloric acid used in method D) as a yellow syrup: R_f 0.24 ($CHCl_3$/MeOH 9:1); ^1H NMR ($CDCl_3$) 7.19–6.80 (m, 6H), 4.37 (t, J = 3.5 Hz, 1H), 3.83 (d, J = 4.3 Hz, 1H), 3.65 (dd, J = 11.6 Hz, 1H), 3.47 (dd, J = 17.4, 3.3 Hz, 1H), 3.30 (dd, J = 11.6, 4.7 Hz, 1H), 3.15 (dd, J = 17.4, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 162.4 (d, J_{C-F} = 245.5 Hz), 160.8 (d, J_{C-F} = 245.2 Hz), 143.7, 142.4, 135.3, 132.8, 130.4, 126.5, 114.4 (d, J_{C-C-F} = 21.3 Hz), 113.7 (d, J_{C-C-F} = 20.8 Hz), 113.5 (d, J_{C-C-F} = 21.2 Hz), 112.7 (d, J_{C-C-F} = 21.8 Hz), 54.0, 49.8, 46.4, 40.7; HRMS 257.1038 (257.1016 cald for $C_{16}H_{13}NF_2$).

Reduction of (−)-13c to (−)-3. The method of Gassman and Pape[25] was adapted. To a solution of (−)-**13c** [33.7 mg, 0.132 mmol, $[\alpha]^{25}_D$ = −187° (c = 1, EtOH)] in THF (1.25 mL, freshly distilled from sodium/benzophenone ketyl) under nitrogen was added sodium metal (110 mg, 4.78 mmol). *tert*-Butyl alcohol (0.175 mL, 1.86 mmol, dried over molecular sieves) was added at room temperature. The resulting colorless reaction mixture was refluxed overnight. After cooling in an ice bath, the excess sodium was consumed by careful methanol addition, followed by water (5 mL) and ether (5 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 5 mL). The extract was dried over potassium carbonate, and the solvent was evaporated to afford a colorless syrup, which was purified by preparative TLC using 9:1 EtOAc/MeOH as eluant, giving (−)-**3** as 21.5 mg of a colorless syrup (74% yield): $[\alpha]^{25}_D$

= −100° (c = 1, EtOH); R_f 0.20 (4:1 EtOAc/MeOH); ^{1}H NMR ($CDCl_3$) 7.26–7.02 (m, 8H), 4.37 (t, J = 3.7 Hz, 1H), 3.93 (d, J = 4.4 Hz, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.51 (dd, J = 17.6, 3.8 Hz, 1H), 3.34 (dd, J = 11.4, 4.7 Hz, 1H), 3.24 (dd, J = 17.6, 3.4 Hz, 1H), 2.67 (s, 1H); HRMS 221.1199 (221.1204 calcd for $C_{16}H_{17}N$).

***N*-Acetyl-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (26).** To a stirred solution of **3** (1.18 g, 5.34 mmol) in chloroform (10 mL) was added acetic anhydride (1.05 mL, 11.1 mmol, distilled) at room temperature. The resulting tan solution was stirred overnight at room temperature, and the volatile materials were evaporated, leaving a tan oil. Crystallization from acetonitrile (3 mL) afforded **26** as 1.10 g of amorphous white granules (79% yield). A second crystallization from acetonitrile gave an analytically pure sample: mp 198.5–200.5 °C; IR ($CHCl_3$) 1630 (s, C=O); ^{1}H NMR ($CDCl_3$) (resonance peaks for geometrical isomers *syn* and anti to the A ring appear in a 1:3 ratio) 7.02–7.31 (m, 8H), *5.12* and 5.91 (m, 1H), 4.05 (m, 2H), 3.79 (dd, J = 10, 3 Hz, 1H), *3.56* and 3.64 (dd, J = 17, 4 Hz, 1H), 3.06 and *3.20* (d, J = 17 Hz, 1H), 2.08 and *2.34* (s, 3H). Anal. ($C_{16}H_{17}NO$) C, H, N.

Nitration of 26. To a stirred solution of **26** (3.47 g, 13.2 mmol) in chloroform (10 mL) was added in one portion trifluoroacetic anhydride (6 mL, distilled) at room temperature. The resulting yellow two-phase mixture was cooled in an ice bath to 5 °C, followed by portionwise addition of ammonium nitrate (1.12 g, 13.9 mmol) over 30 min. Stirring was continued at 5 °C for 30 min; the ice bath was removed and the reaction temperature rose to 40 °C. Stirring was continued for another 2 h, during which the reaction mixture became a yellow solution. The solvent was evaporated, leaving a thick oil which was diluted with methylene chloride (25 mL) and poured into 1 N NaOH (50 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried over potassium carbonate and concentrated to a thick oil. Acetone (30 mL) was added, causing a white precipitate to form overnight. Two more crops of white powder were subsequently collected from the mother liquors. Combination of all the solids (874 mg) and crystallization from boiling methanol (50 mL) afforded **27** as 810 mg of white plates (20% yield): mp 217.5–218.5 °C; ^{1}H NMR ($CDCl_3$, resonance peaks for syn and anti isomers appear in a 1:5 ratio) 8.16 (d, J = 2.1 Hz, 1H), 8.01 (dd, J = 8.4, 2.1 Hz, 1H), 7.31–7.19 (m, 5H), 5.93 and 5.18 (m, 1H), 4.09 (d, J = 10.6 Hz, 1H), 3.82 (dd, J = 10.6, 3.5 Hz, 1H), 3.71 (dd, J = 18.5, 4.5 Hz, 1H), 3.28 and 3.13 (dd, J = 18.5, 1.5 Hz, 1H), 2.34 and 2.10 (s, 3H). Anal. ($C_{18}H_{18}N_2O)_3 \cdot 0.25H_2O$) C, H, N.

A solution of **27** (103 mg, 0.333 mmol) in ethanol (2 mL) and concentrated HCl (2 mL) was refluxed overnight. The mixture was neutralized with sodium bicarbonate and basified (pH > 10) with 10% NaOH. Extraction with methylene chloride and evaporation of the solvent left a brown oil, which was purified by preparative TLC ($CHCl_3$/MeOH 9:1) to give **28** as 61 mg of a pale brown oil (68% yield): R_f 0.12 (5% MeOH/$CHCl_3$); IR ($CDCl_3$) 1521 (s), 1351 (s); ^{1}H NMR ($CDCl_3$) 8.07 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 8.4, 2.1 Hz, 1H), 7.27–7.15 (m, 5H), 4.35 (t, J = 3.6 Hz, 1H), 4.04 (d, J = 4.5 Hz, 1H), 3.66 (d, J = 11.5 Hz, 1H), 3.58 (dd, J = 18.4, 3.8 Hz, 1H), 3.35 (dd, J = 11.6, 4.8 Hz, 1H), 3.27 (dd, J = 18.4, 3.4 Hz, 1H), 2.20 (br s, 1H). The hydrochloride salt was formed from hydrogen chloride in anhydrous ether/methanol as a white powder: mp 314–316 °C dec. Anal. ($C_{16}H_{15}N_2O_2Cl$) C, H, N.

3-Azido-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (30). A solution of **27** (52 mg, 0.17 mmol) in ethylene glycol (2 mL) and hydrazine hydrate (1.5 mL) was heated at reflux for 1 h. Potassium hydroxide (56 mg, 0.99 mmol) was added and refluxed resumed for 20 h. The resulting light brown solution was cooled, poured into 1 N NaOH, and extracted with methylene chloride. The combined organic portions were washed with water, and dried over potassium carbonate, and the solvent was evaporated to give 47.6 mg of an off white oil. This oil was purified by preparative TLC (methanol as eluant) to afford the diamine **29** as 39.7 mg of an oil: R_f 0.17 (MeOH); ^{1}H NMR ($CDCl_3$) 7.23 (m, 4H), 6.83 (d, J = 8.0 Hz, 1H), 6.53 (unresolved d, 1H), 6.45 (dd, J = 8.0, 1.6 Hz, 1H), 4.30 (m, 1H), 3.76 (d, J = 4.0 Hz, 1H), 3.63 (d, J = 11.4 Hz, 1H), 3.39 (dd, J = 17.1, 3.5 Hz, 1H), 3.27 (dd, J = 11.4, 4.6 Hz, 1H), 3.11 (dd, J = 17.1, 2.6 Hz, 1H).

To a solution of **29** (39 mg, 0.17 mmol) in 2 N HCl (8 mL) at 0–5 °C was added sodium nitrite (59 mg, 0.86 mmol). The resulting yellow solution was stirred for 20 min at 0–5 °C. Sodium azide (116 mg, 1.78 mmol) was slowly added. Stirring was continued for 1 h at room temperature. The reaction mixture was extracted with ether (2 × 5 mL). The aqueous layer was basified to pH 11 using solid KOH and extracted with methylene chloride. The combined extracts were dried over potassium carbonate, and the solvent was evaporated to give 29 mg of a brown oil. Preparative TLC (THF) afforded **30** as 18 mg of a brown oil (40% from **27**): R_f 0.36 (THF); IR ($CHCl_3$) 2113 (N_3); ^{1}H NMR ($CDCl_3$) 7.2 (m, 4H), 7.00 (d, J = 8 Hz, 1H), 6.83 (d, J = 2 Hz, 1H), 6.77 (dd, J = 8, 2 Hz, 1H), 4.32 (t, J = 3 Hz, 1H), 3.86 (d, J = 4 Hz, 1H), 3.63 (d, J = 12 Hz, 1H), 3.46 (dd, J = 17, 3 Hz, 1H), 3.29 (dd, J = 12, 5 Hz, 1H), 3.15 (dd, J = 17, 3 Hz, 1H), 2.63 (bs, 1H).

***N*-[3-(Dimethylamino)-1-propyl]-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (31).** To a solution of **3** (103 mg, 0.465 mmol) in DMF (4.0 mL, dried over molecular sieves) under nitrogen at room temperature was added triethylamine (188 mg, 1.86 mmol, distilled from calcium hydride) and 3-(dimethylamino)propyl chloride hydrochloride (111 mg, 0.700 mmol). The resulting pale yellow mixture was stirred at 75 °C for 24 h, and partitioned between 10% NaOH (20 mL) and methylene chloride (20 mL). The layer were separated, and the aqueous portion was extracted with methylene chloride (2 × 15 mL). The combined organic portions were washed with water (3 × 20 mL) and brine (1 × 25 mL) and dried over sodium sulfate. Concentration in vacuo afforded a pale brown liquid, which was purified by flash chromatography using $CHCl_3$/MeOH/NH_4OH (5:1:0.01) as eluant. The diamine **31** was obtained as 70.0 mg of a clear pale yellow oil (49% yield): R_f 0.07 ($CHCl_3$/MeOH/NH_4-OH 9:1:0.01); ^{1}H NMR ($CDCl_3$) 7.22–7.00 (m, 8H), 4.06 (t, J = 3.5 Hz, 1H), 3.85 (d, J = 3.4 Hz, 1H), 3.59 (dd, J = 21.9, 4.0 Hz, 1H), 3.53 (d, J = 10.1 Hz, 1H), 3.06–2.96 (m, 2H), 2.75–2.53 (m, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.23 (s, 6H), 1.71 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) 142.4, 141.6, 138.8, 135.5, 131.1, 127.7, 126.6 (br), 125.7, 125.6, 124.9, 60.9, 58.1, 57.7, 56.0, 47.0, 45.4, 39.2, 26.7; HRMS 306.2094 (306.2096 calcd for $C_{21}H_{26}N_2$).

The dihydrochloride salt was prepared from **31** and hydrogen chloride in dry ether, as a hygroscopic white powder: mp 156–160 °C dec. Anal. ($C_{21}H_{26}N_2Cl_2 \cdot 0.2H_2O$) C, H; N: calcd, 7.31; found 7.76.

***N*-(2-Pyridinylmethyl)-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (32).** As for **31**, **32** was prepared from **3** (112.3 mg, 0.5075 mmol), 2-picolyl chloride hydrochloride (83.2 mg, 0.508 mmol, and diisopropylethylamine (332 mg, 2.57 mmol, distilled) in dry DMF (5.0 mL). Flash chromatography using EtOAc/hexanes (1:1) afforded pure **35** as 117.2 mg of a pale brown oil (74% yield). Trituration with dry ether afforded analytically pure **32** as a white microcrystalline solid: mp 126–127 °C; R_f 0.38 (EtOAc); ^{1}H NMR ($CDCl_3$) 8.57 (d, J = 4.5 Hz, 1H), 7.64 (dt, J = 7.5, 1.4 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.24–7.03 (m, 9H), 4.09 (t, J = 3.5 Hz, 1H), 4.03–3.88 (m, 3H), 3.72–3.60 (m, 2H), 3.11–2.98 (m, 2H); ^{13}C NMR ($CDCl_3$) 160.5, 149.4, 142.7, 141.9, 138.7, 136.6, 135.9, 131.4, 128.1, 127.5, 127.0 (br), 126.2, 126.1, 125.3, 123.2, 122.2, 64.0, 60.9, 58.7, 47.4, 39.8. Anal. ($C_{22}H_{20}N_2$) C, H, N.

***N*-(2-Propyl)-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (33).** A mixture of **3** (300 mg, 1.36 mmol), 2-bromopropane (201 mg, 1.63 mmol), and potassium carbonate (282 mg, 2.04 mmol) in DMSO (5.0 mL, distilled from CaH_2) was heated at 50 °C for 18 h. The reaction mixture was partitioned between methylene chloride (25 mL) and aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous portion was extracted with methylene chloride (1 × 15 mL). The combined organic portions were washed with water (2 × 15 mL) and brine (1 × 20 mL) and dried over potassium carbonate. Concentration in vacuo afforded an orange syrup, which was purified by flash chromatography (hexane/EtOAc 3:1 to 1:1), giving 190 mg of a pale orange syrup. This syrup was further purified by preparative TLC (two plates, chloroform/MeOH 50:1); the polar band at R_f 0.3 was the desired product **33**, which was isolated as 101 mg (28% yield) of a clear colorless syrup that solidified upon standing into white granules: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) 7.20–7.00 (m, 8H), 4.18 (dd, J = 4.3, 2.9 Hz, 1H), 3.87 (t, J = 3.3 Hz, 1H),

3.54 (dd, J = 9.9, 1.8 Hz, 1H), 3.45 (dd, J = 17.1, 4.6 Hz, 1H), 3.08–2.92 (m, 3H), 1.11 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H).

The perchlorate salt was prepared from **33** and perchloric acid in ethanol/water as ivory microcrystals: mp 202–203 °C. Anal. ($C_{19}H_{22}NO_4Cl$) C, H, N.

Pharmacology. PCP Receptor Binding Assays. See ref 23 for experimental details.

In Vitro Neurotoxicity Assay. Dissociated rat hippocampal cultures were prepared using a modification of the method of Huettner and Baughman.[26] The cortices were removed from 1–3 day postnatal rats (Sprague–Dawley) that had been anesthetized with chloral hydrate, and hippocampi were dissected out and placed in a chloride-free dissociation medium supplemented with 1 mM kynurenic acid and 10 mM magnesium sulfate.[27] The hippocampi were washed in the dissociation medium and then incubated for 2 × 20 min at 37 °C in dissociation medium containing 10 units/mL of Papain (Worthington). After the enzyme treatment, the tissue was incubated for three 5-min periods at 37 °C with 10 mg/mL trypsin inhibitor (Sigma type II-0).

The cells were dissociated by trituration in growth medium and plated as 0.15-mL droplets of cell suspension onto the center of 35-mm Primaria (Falcon) dishes that had been stamped with a labeled 26 × 26 grid of approximately 0.64 cm^2 total area using a Mecanex BB form (WPI, New Haven) and coated with poly-(D-lysine) and laminin (Collaborative Research). The cell density was 2.5–4.0 × 10^5 cells per dish. The growth medium was Eagles minimum essential media (MEM, Earle's salts) supplemented with 5% fetal bovine serum (Cell Culture Laboratories), 5% defined supplemented calf serum (HyClone), 50 mM glucose, 50 units/mL penicillin/streptomycin and MITO+ serum extender (Collaborative Research). The cells were maintained at 37 °C in a humidified 4.5% CO_2 atmosphere. Cells were left for 12–14 h to attach to the plate surface, then 1.5 mL of growth medium was added to each dish, and 1 mL was removed and replaced with a further 1 mL of fresh medium. This process removed most of the cell debris and unattached cells. The area of cell attachment and proliferation did not significantly extend beyond the treated central area. After 2–4 days in culture, non-neuronal cell division was arrested by a 2–3 day exposure to 5 μM cytosine arabinoside.

The cells were maintained in a medium that was similar to the growth medium but without the fetal bovine serum. The medium was changed on a weekly schedule, replacing two-thirds the volume with fresh medium. The only glutamate present in the media was that contained in the calf serum which gave a final concentration of 12 μM.

Before treatment, sister cultures were examined under phase-contrast microscopy to ensure that the cultures were of a similar density. Exposure to glutamate was carried out at 32–34 °C in a HEPES-buffered "controlled salt solution" (CSS) similar to that reported by others,[28] but with 10 mM HEPES substituted for Tris-HCl and buffered for pH 7.4 at 34 °C. The cultures were washed twice with CSS and then incubated for 5 min with a solution containing 1 μM glycine and the compound to be tested (the controls had 1 μM glycine only). The drug and control solutions were coded so that the assay was performed blind; only after the cells were counted was the code revealed. Glycine was included since it has been shown to potentiate the effects of glutamate at the NMDA site,[29] and the preincubation with the test drugs enhances the neuroprotection activity.[30] CSS containing 1 μM glycine plus drug and a known concentration of glutamate (0–1000 mM) were added by triple exchange and the cultures were incubated for 5 min. The cultures were washed four times with CSS and then with medium before being placed in the incubator overnight. Cultures were removed from the incubator the next day, washed twice with CSS, and treated for 5 min with 0.4% Trypan Blue, a dye that is only taken up by dead and dying cells. The cultures were washed three times and the surviving cells counted in the grid area using phase-contrast microscopy. Cell survival was normalized as a percentage of the highest cell count, and the results were plotted against glutamate concentration. Cultures not exposed to glutamate generally had between 4500 and 5500 surviving cells in the grid area.

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Supplementary Material Available: Yields and spectral data for compounds **10a–d,f**, **11a–d,f**, **12a–d,f**, **22**, **23** and intermediates in the conversion of **20** and **21** into **22** and **23** and experimental details for the synthesis of **18–20** and conversion of **29** into **13c** (11 pages). Ordering information is given on any current masthead page.

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