Notes

Synthesis of Racemic 6,7,8,9-Tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-diones as Antagonists of *N*-Methyl-D-aspartate (NMDA) and α-Amino-3-hydroxy-5-methylisoxazole-4-propionic Acid (AMPA) Receptors

Anthony P. Guzikowski,† Edward R. Whittemore,‡ Richard M. Woodward,‡ Eckard Weber,‡ and John F. W. Keana*,†

CoCensys, Inc., 213 Technology Drive, Irvine, California 92618, and Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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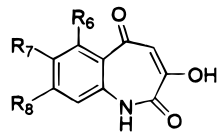
The synthesis and pharmacological properties of several racemic 6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-diones (THHBADs) are described. Synthesis was accomplished via a Schmidt reaction with 5,6,7,8-tetrahydro-2-methoxynaphthalene-1,4-diones (THMNDs) followed by demethylation. THMNDs were prepared via a Diels−Alder reaction with 2-methoxybenzoquinone (**5**) or 2-bromo-5-methoxybenzoquinone (**14**) and substituted 1,3-butadienes. The pharmacology of THHBADs was characterized by electrical recordings in *Xenopus* oocytes expressing rat brain NMDA and AMPA receptors. THHBADs are antagonists of NMDA and AMPA receptors with functional potency being dependent upon the substitution pattern on the tetrahydrobenzene moiety. The 7,8-dichloro-6-methyl (**18a**) and 7,8-dichloro-6-ethyl (**18b**) analogs are the most potent THHBADs prepared and have apparent antagonist dissociation constants (K_b values) of 0.0041 and 0.0028 μM, respectively, for NMDA receptors and 0.51 and 0.72 μM, respectively, for AMPA receptors.

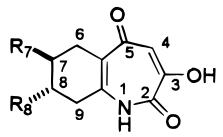
Introduction

N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors represent two major subtypes of ionotropic glutamate receptors found in the mammalian central nervous system.[1] Glutamate receptors have been associated with a variety of neurological disorders including the brain damage found in cerebral ischemia, epilepsy, Alzheimer's disease, and AIDS-related dementia.[2] NMDA and AMPA receptors are thought to contribute to the pathology of these diseases through glutamate-induced excitotoxicity.[3] This toxicity results from acute or chronic receptor overstimulation which promotes the influx of pathological levels of intracellular Ca^{2+}, resulting in eventual neuronal death. NMDA receptors possess strychnine insensitive glycine binding sites.[4] Occupation of these sites by glycine is necessary for receptor activation. On the basis of this observation, various antagonists of NMDA receptor glycine sites have been synthesized and characterized as potential therapeutic agents designed to limit the excitotoxic effects of glutamate.[5]

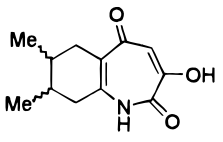
Previously, we investigated the pharmacology and structure−activity relationship (SAR) of 3-hydroxy-1*H*-1-benzazepine-2,5-diones (HBADs, e.g., **1a**−**c**),[6] a known class of NMDA receptor glycine site antagonists.[7,8] The synthetic methodology developed during this investigation[9] lent itself to the facile preparation of racemic 6,7,8,9-tetrahydro analogs of **1**. In a preliminary communication, we reported that the 6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-diones (THHBADs) **2a**,**b** and **3** are antagonists at NMDA receptor glycine sites with **2b** possessing moderate binding affinity ([^{3}H]-5,7-dichlorokynurenic acid (DCKA), see Table 1).[10] In this paper, we describe new, high-potency analogs. We also detail the synthetic methods employed and further delineate THHBAD pharmacology.



1a $R_6 = R_7 = H$; $R_8 = Cl$
1b $R_6 = H$; $R_7 = R_8 = Me$
1c $R_6 = R_8 = Me$; $R_7 = H$



2a $R_7 = R_8 = H$
2b $R_7 = R_8 = Cl$



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Chemistry

Synthesis. Racemic THHBADs were prepared via a Schmidt reaction of 5,6,7,8-tetrahydro-2-methoxynaphthalene-1,4-diones (THMNDs) followed by demethylation employing methods previously described for HBADs.[6] THMNDs were prepared via a Diels−Alder reaction with 2-methoxybenzoquinones and substituted 1,3-butadienes as described below.

The synthesis of THHBADs **2a**,**b** and **3** is shown in Scheme 1. A Diels−Alder reaction of diene **4a** or **4b** with dienophile **5**[11] followed by enolization of the resulting adducts (not shown) gave diol **6a** or **6b**, respec-

* Author to whom correspondence should be addressed. Present address: CoCensys, Inc.
† University of Oregon.
‡ CoCensys, Inc.
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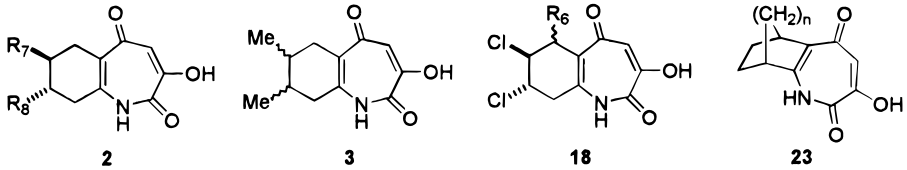
Table 1. Radioligand Binding Data and Functional Antagonist Potencies for Racemic THHBADs

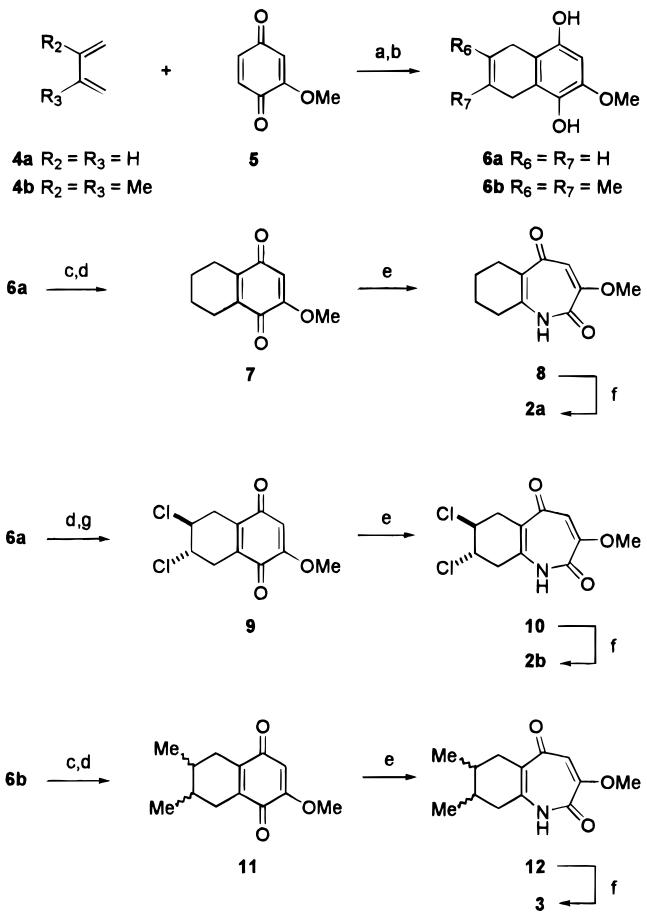


2 **3** **18** **23**

compd no.	R_6	R_7	R_8	n	IC_{50} (μM)[a] [^{3}H]DCKA	K_b (μM) NMDA (glycine)[b]	K_b (μM) AMPA (glutamate)[c]	K_b AMPA/ K_b NMDA[d]	n[e]
2a		H	H		3.2	0.74[f] (0.69−0.80)[g]	23 (20−27)	31	3,3
2b		Cl	Cl		0.13	0.042 (0.040−0.044)	0.78 (0.72−0.84)	19	4,4
3					0.23	0.12 (0.11−0.12)	5.3 (4.9−5.7)	44	4,3
18a	Me					0.0041 (0.0037−0.0045)	0.51 (0.46−0.57)	120	4,4
18b	Et					0.0028 (0.0027−0.0030)	0.72 (0.67−0.78)	260	4,4
23a				1		2.8 (2.5−3.0)	210 (130−350)	75	3,3
23b				2		0.26 (0.25−0.27)	79 (58−110)	300	4,3

[a] Data taken from ref 10. [b] Inhibition of NMDA receptors was measured in oocytes expressing cloned rat brain receptor subunits (NR1A/2C). Apparent antagonist dissociation constants (K_b values) were determined from inhibition of currents elicited by 1 μM glycine and 100 μM glutamate assuming simple competitive inhibition; mean response = 161 ± 5 nA (n = 26), holding potential = −70 mV (all experiments). [c] Inhibition of AMPA-preferring non-NMDA receptors was measured in oocytes expressing rat brain poly(A)$^+$ RNA isolated from the cerebral cortex. K_b values were determined from inhibition of currents elicited by 10 μM AMPA (a selective AMPA receptor agonist); mean response = 276 ± 35 nA (n = 24). [d] Steady-state selectivity index was estimated by dividing K_b AMPA by K_b NMDA. [e] Number of cells examined for NMDA and AMPA, respectively. [f] K_b values given to two significant figures. [g] 95% confidence intervals adjusted to the linear scale.

Scheme 1[a]



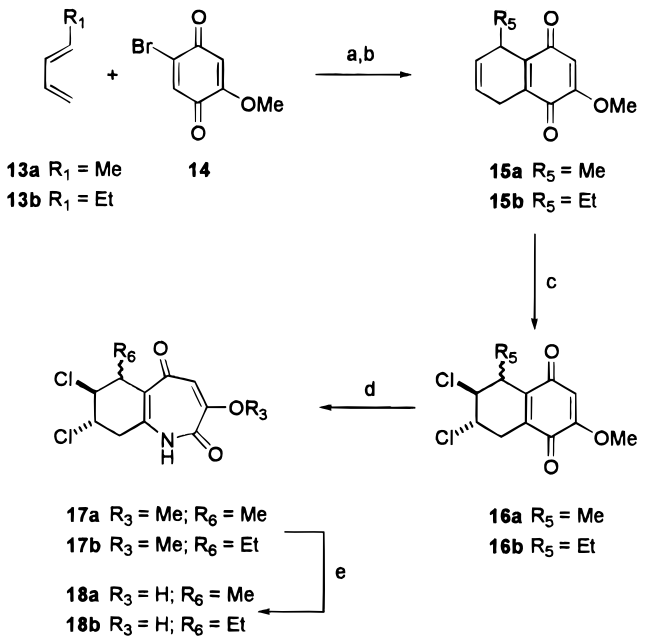
[a] (a) Toluene, hydroquinone, 65 °C; (b) K_2CO_3, MeOH, 25 °C then HCl/H_2O; (c) H_2, Pd/C, MeOH, 25 °C; (d) $NaIO_4$, $CHCl_3$/H_2O, 25 °C; (e) NaN_3, H_2SO_4, 0−25 °C; (f) BBr_3, CH_2Cl_2, 25 °C; (g) Cl_2, $CHCl_3$, 25 °C.

tively.[12,13] Hydrogenation of the 6,7-double bond of **6a** proceeded readily. The reduction product (not shown) underwent slow oxidation upon standing, and therefore, this product was immediately treated with periodate to give THMND **7**.[14] Alternatively, **6a** was oxidized with periodate, and the 6,7-double bond of the resulting 5,8-dihydronaphthalene-1,4-dione (not shown) was chlorinated to give racemic dichloro-THMND, **9**. Hydrogenation of the tetrasubstituted 6,7-double bond of **6b** proceeded slowly compared to the reduction of the disubstituted double bond of **6a**. Periodate oxidation of the crude hydrogenation reaction mixture gave **11** as a diastereomeric mixture (8:2, NMR). The presence of diastereomers indicates that the hydrogenation of **6b** does not proceed by exclusive *syn* addition.[15] A Schmidt reaction of THMNDs **7**, **9**, and **11** gave THHBAD methyl ethers **8**, **10**, and **12**, respectively. Treatment of **8**, **10**, and **12** with BBr_3 in CH_2Cl_2 followed by crystallization gave **2a**, racemic **2b**, and a diastereomeric mixture of **3** (8:2, NMR), respectively.[16] The structure of **2a** was confirmed by single-crystal X-ray analysis.[10]

Trisubstituted THHBADs **18a**,**b** were prepared as shown in Scheme 2. A Diels−Alder reaction of diene **13a** or **13b** with bromodienophile **14**[6] followed by *in situ* treatment of the resulting bromo adducts (not shown) with Et_3N gave dihydronaphthalene-1,4-dione **15a** or **15b**, respectively. The regiochemistry **15a** had been established earlier.[6] The regiochemistry of **15b** was based on analogy with that of **15a**. Chlorination of **15a** or **15b** gave dichloro-THMND **16a** or **16b**, respectively, each as a 6:4 mixture of diastereomers (by NMR). Ring expansion followed by demethylation gave THHBADs **18a**,**b** as diastereomeric mixtures after crystallization (9:1 and 8:2, respectively, NMR).[16] The stereochemistry for the predominant diastereomer of THHBAD **18a** is tentatively assigned as having a *cis* relationship between the C(6) methyl group and the C(7) chlorine atom employing ^{1}H NMR coupling constants.

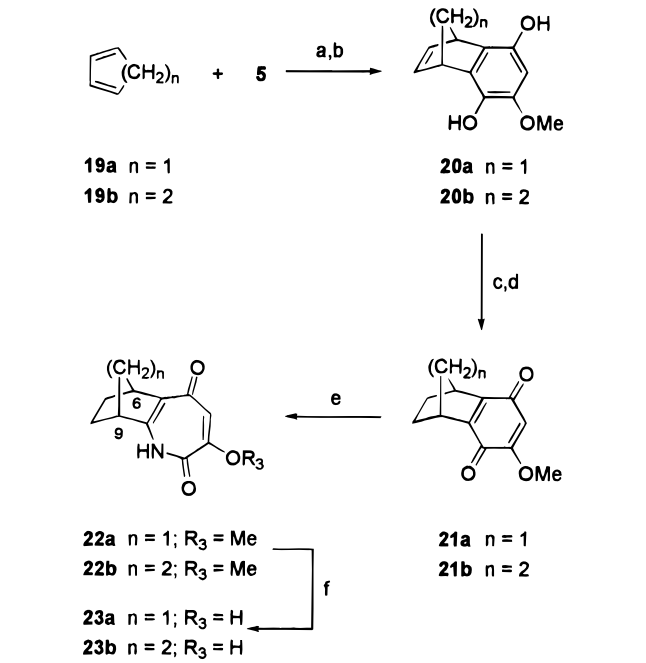
THHBADs with a methano (**23a**) or an ethano bridge (**23b**) linking C(6) and C(9) of the tetrahydrobenzene moiety were prepared as described for **2a** but starting with cyclic diene **19a** or **19b**, respectively (Scheme 3). The Schmidt reaction of **21a** proceeded vigorously compared to that of the other THMNDs, **21a** being consumed in one minute at 0 °C. For other THMNDs, the Schmidt reaction was allowed to warm to 25 °C, and the reaction mixture was stirred for several hours. The

Scheme 2[a]



[a] (a) Toluene, 80 °C; (b) Et_3N, MeOH/toluene, 25 °C; (c) Cl_2, $CHCl_3$, 25 °C; (d) NaN_3, CF_3SO_3H, 0−25 °C; (e) BBr_3, CH_2Cl_2, 25 °C.

Scheme 3[a]



[a] (a) Toluene, hydroquinone, 25 °C (**19a**) or 60 °C (**19b**); (b) K_2CO_3, MeOH, 25 °C then HCl/H_2O; (c) H_2, Pd/C, MeOH, 25 °C; (d) $NaIO_4$, $CHCl_3/H_2O$, 25 °C; (e) NaN_3, H_2SO_4, 0 °C (**21a**) or 0−25 °C (**21b**); (f) BBr_3, CH_2Cl_2, 25 °C.

yields of the Schmidt reactions ranged from 1.4% (**21a**) to 41% (**16b**).

Pharmacology

Functional antagonism of racemic THHBADs on NMDA receptors was assessed by measuring inhibition of membrane current responses in *Xenopus* oocytes expressing the cloned rat NMDA receptor subunit combination NR1A/2C as described in ref 6. Previous studies indicate that different diheteromeric NMDA receptor subunit combinations have only minor differences in apparent affinity for glycine site antagonists.[17] Moreover, site-directed mutagenesis indicates that the glycine site is located on the NR1 subunit.[18] In the present experiments, the NR1A/2C subunit combination was chosen because these responses have the lowest levels of variability and, therefore, give the most reliable values for SAR comparisons.

For THHBADs **2a**,**b** and **3**, the NMDA inhibition data obtained from the electrical assays on recombinant NMDA receptors (Table 1) parallels affinities obtained from [^{3}H]DCKA radioligand binding experiments on native receptors in rat neuronal membranes.[10] Furthermore, inhibition of NMDA receptors by THHBADs in the electrical assays was surmounted by increasing the glycine concentration in a manner consistent with competitive inhibition. Both results confirm that inhibition of NMDA receptors by THHBADs is the result of competitive antagonism at glycine sites.

With the exception of **23a**, the potency of THHBADs at NMDA receptors increases with increased substitution on the tetrahydrobenzene moiety. This is in contrast to the SAR observed for the HBAD series where only monosubstitution at C(8), e.g., **1a**, increases potency relative to the unsubstituted analog and potency is reduced by multiple substitution.[6] The hydrophobic region of THHBADs is nonplanar[10] and possesses conformational freedom not allowed in the HBAD series. These factors appear to contribute to more favorable substituent−receptor pocket interactions for the THHBAD series.

Compound **23a**, which has a methano bridge linking C(6) and C(9) of the tetrahydrobenzene moiety, is the least potent THHBAD assayed. It is 3−4 times less potent than the unsubstituted **2a** and about 10 times less potent than the analogous ethano-bridged compound **23b**. This reduced potency suggests that the methano-bridge constrains the tetrahydrobenzene portion of **23a** into a conformation that compromises interaction with the receptor pocket.

THHBAD **23b** possesses a methylene substituent at C(9). Even though this methylene substituent is *peri* to the amide hydrogen, compound **23b** retains moderate potency. For HBADs,[6] such *peri* substitution results in a total loss in activity. The *peri* substituent's steric bulk on the planar benzene portion of the HBAD molecule is believed to prevent effective hydrogen bonding of the amide hydrogen with the receptor pocket. In contrast, the nonplanar tetrahydrobenzene portion of **23b** apparently alleviates this adverse steric effect by allowing the substituent to be above or below the mean plane containing the amide hydrogen and the heterocyclic ring.

Substituents at C(7) and C(8) enhance THHBAD potency with the dimethyl analog **3** being about 6 times more potent than **2a** and the dichloro analog **2b** being about 18 times more potent. Higher potency analogs of **2b** are obtained by placing an additional substituent at C(6). The addition of a methyl group (**18a**) gives a 10-fold increase in potency relative to **2b** while an ethyl group (**18b**) increases the potency 15-fold. The increase in potency is presumably due to favorable hydrophobic interactions. Similar potency enhancement is observed for quinoxalinediones (QXs) possessing chloro and alkyl trisubstitution at C(5−7).[19]

Potency of AMPA receptor antagonism was assayed

in oocytes expressing rat brain poly(A)$^+$ RNA isolated from the cerebral cortex as described in ref 6 (Table 1). Inhibition of AMPA receptor responses by THHBADs was reversed by increasing the concentration of agonist (AMPA) as would be predicted for competitive antagonism. THHBADs antagonize AMPA receptors with lower potency than NMDA receptors. The rank ordering of potency for AMPA receptors generally parallels that for NMDA receptors. This trend is also observed for HBADs[6] and the majority of QXs.[19] The exception is the ethano-bridged compound **23b**, which is moderately active at NMDA receptors but is not well tolerated at AMPA receptors. The inhibition of both NMDA and AMPA receptors by THHBADs provides yet further evidence that structural similarities exist between the binding pockets that form NMDA receptor glycine sites and AMPA receptor glutamate sites.

Experimental Section

Chemistry. The Diels−Alder adducts resulting from the separate reactions of **4a, 4b, 19a**, and **19b** with **5** have been previously described.[12,13,20,21] Compound **15a** was prepared as previously described.[6] Reagents were used as received unless otherwise noted. Melting points were measured on a Thomas Hoover or a Mel-Temp melting point apparatus and are uncorrected. For compounds melting above 260 °C, a preheated block was employed. CH_2Cl_2 was distilled from CaH_2 immediately prior to use. Solvent removal was routinely performed on a rotoevaporator at 30−40 °C. All reactions were performed under N_2 unless otherwise noted. TLC analyses were performed on plastic backed F-254 silica gel plates. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer. Chemical shifts are reported in δ units referenced to the residual ^{1}H signal of the deuterated solvent ($CHCl_3$, δ 7.26; CD_3SOCD_2H, δ 2.49). Microanalyses were performed by Desert Analytics Laboratory, Tuscon, AZ.

5,8-Dihydro-2-methoxynaphthalene-1,4-diol (6a). A solution of 4a,5,8,8a-tetrahydro-2-methoxynaphthalene-1,4-dione[12] (6.40 g, 33.3 mmol) in MeOH (400 mL) was purged with N_2 for 10 min, and K_2CO_3 (4.60 g, 33.3 mmol) was added. The mixture was stirred at 25 °C for 20 min, and 10% aqueous HCl (150 mL) was added in one portion. The MeOH was removed to give a colorless suspension. The solid was collected and washed with dilute aqueous HCl. The collected solid was dried *in vacuo* to yield **6a** as a colorless solid (4.50 g, 70%): mp 143−144 °C (lit.[12] mp 123−124 °C); ^{1}H NMR ($CDCl_3$) δ 3.17−3.35 (m, 4H), 3.84 (s, 3H), 4.25 (s, 1H), 5.25 (s, 1H), 5.80−6.00 (m, 2H), 6.36 (s, 1H).

5,8-Dihydro-2-methoxy-6,7-dimethylnaphthalene-1,4-diol (6b). Diol **6b** was prepared as described for **6a** from 4a,5,8,8a-tetrahydro-2-methoxy-6,7-dimethylnaphthalene-1,4-dione[13] (4.00 g, 18.2 mmol) to yield **6b** as a colorless solid (3.90 g, 98%): mp 200−201 °C (lit.[13] mp 209−211 °C); ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 6H), 3.10−3.26 (m, 4H), 3.83 (s, 3H), 4.25 (s, 1H), 5.25 (s, 1H), 6.35 (s, 1H).

5,8-Dihydro-5,8-methano-2-methoxynaphthalene-1,4-diol (20a). Diol **20a** was prepared as described for **6a** from 4a,5,8,8a-tetrahydro-5,8-methano-2-methoxynaphthalene-1,4-dione[20] (3.10 g, 15.2 mmol) to yield **20a** as a colorless solid (3.00 g, 97%): mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (d, J = 6.9 Hz, 1H), 2.20 (d, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.99 (s, 1H), 4.17 (s, 1H), 4.33 (s, 1H), 5.21 (s, 1H), 6.03 (s, 1H), 6.70−6.80 (m, 2H).

5,8-Ethano-5,8-dihydro-2-methoxynaphthalene-1,4-diol (20b). Diol **20b** was prepared as described for **6a** from 5,8-ethano-4a,5,8,8a-tetrahydro-2-methoxynaphthalene-1,4-dione[21] (2.10 g, 9.62 mmol) to yield **20b** as a colorless solid (2.05 g, 98%): mp 112−115 °C; ^{1}H NMR ($CDCl_3$) δ 1.38−1.58 (m, 4H), 3.79 (s, 3H), 4.14 (s, 1H), 4.34 (s, 1H), 5.21 (b, 1H), 6.21 (s, 1H), 6.47−6.55 (m, 2H).

5,6,7,8-Tetrahydro-2-methoxynaphthalene-1,4-dione (7). A solution of **6a** (1.84 g, 9.57 mmol) in MeOH (50 mL) was hydrogenated over Pd/C (180 mg, 10%) at 20 psig for 30 min at 25 °C. The catalyst was removed by filtration (Celite), and the solvent was removed to yield a beige solid (1.80 g). Without purification, the solid was dissolved in $CHCl_3$ (100 mL) and the resulting solution was vigorously stirred with a solution of $NaIO_4$ (6.14 g, 28.7 mmol) in H_2O (150 mL) for 20 min at 25 °C. The layers were separated, and the aqueous portion was extracted with $CHCl_3$ (20 mL). The combined organic portion was washed with brine (20 mL), and the solvent was removed to yield a brown solid (1.80 g). The solid was crystallized from 95% EtOH to yield **7** as brilliant yellow plates (1.26 g, 68%): mp 167−168 °C (lit.[14] mp 172 °C); ^{1}H NMR ($CDCl_3$) δ 1.66−1.72 (m, 4H), 2.30−2.50 (m, 4H), 3.79 (s, 3H), 5.85 (s, 1H).

5,6,7,8-Tetrahydro-2-methoxy-6,7-dimethylnaphthalene-1,4-dione (11). Dione **11** was generally prepared as described for **7** from **6b** (2.00 g, 9.08 mmol). The hydrogenation of **6b** was performed at 30−40 psig for 24 h. Crude **11** was purified by chromatography (silica gel, $CHCl_3$) to yield a diastereomeric mixture (8:2, NMR) of **11** as an orange oil (787 mg, 39%): ^{1}H NMR ($CDCl_3$) δ 0.85−1.10 (m, 6H) 1.82−2.05 (m, 2H), 2.15−2.30 (m, 2H), 2.43−2.58 (m, 2H), 3.79 (s, 3H), 5.85 (s, 1H).

5,6,7,8-Tetrahydro-5,8-methano-2-methoxynaphthalene-1,4-dione (21a). Dione **21a** was generally prepared as described for **7** from **20a** (2.72 g, 13.3 mmol) to yield **21a** as a yellow powder (2.47 g, 91%): mp 107−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.10−1.22 (m, 2H), 1.40 (d, J = 9.3 Hz, 1H), 1.60−1.68 (m, 1H), 1.85−1.98 (m, 2H), 3.47−3.51 (m, 2H), 3.78 (s, 3H), 5.72 (s, 1H).

5,8-Ethano-5,6,7,8-tetrahydro-2-methoxynaphthalene-1,4-dione (21b). Dione **21b** was generally prepared as described for **7** from **20b** (2.05 g, 9.39 mmol) to yield **21b** as a yellow powder (1.71 g, 83%): mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 7.2 Hz, 4H), 1.71 (d, J = 7.5 Hz, 4H), 3.32−3.40 (m, 2H), 3.80 (s, 3H), 5.82 (s, 1H).

5-Ethyl-5,8-dihydro-2-methoxynaphthalene-1,4-dione (15b). Dione **15b** was prepared from 1,3-hexadiene (**13b**; 5.00 g, 61.0 mmol) and 2-bromo-5-methoxybenzoquinone (**14**; 8.70 g, 40.0 mmol) as previously described for **15a**[6] to yield **15b** as a yellow/green crystalline solid (4.12 g, 47%): mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H), 1.50−1.78 (m, 2H), 2.80−3.00 (m, 1H), 3.10−3.25 (m, 1H), 3.41−3.52 (m, 1H), 3.81 (s, 3H), 5.83−5.98 (m, 3H).

6,7-Dichloro-5,6,7,8-tetrahydro-2-methoxynaphthalene-1,4-dione (9). Diol **6a** (5.70 g, 29.7 mmol) was treated with $NaIO_4$ (12.7 g, 59.4 mmol) as described for the preparation of **7** to yield 5,8-dihydro-2-methoxynaphthalene-1,4-dione as a yellow powder (5.55 g, 97%): mp 171−172 °C; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 4H), 3.81 (s, 3H), 5.81 (s, 2H), 5.89 (s, 1H).

A solution Cl_2 (1.10 g, 15.5 mmol) in $CHCl_3$ (50 mL) was added to a solution of the above powder (2.75 g, 14.3 mmol) in $CHCl_3$ (60 mL) over 30 min. After addition, the solvent was removed to yield a yellow syrup. The addition of 95% EtOH (10 mL) followed by solvent evaporation (performed twice) yielded a yellow solid. The solid was crystallized twice from 95% EtOH to yield **9** as a yellow crystalline solid (1.89 g, 51%): mp 123−128 °C; ^{1}H NMR ($CDCl_3$) δ 2.98−3.25 (m, 4H), 3.83 (s, 3H), 4.47 (s, 2H), 5.94 (s, 1H).

6,7-Dichloro-5,6,7,8-tetrahydro-2-methoxy-5-methylnaphthalene-1,4-dione (16a). Dichloride **16a** was prepared by the chlorination of **15a** (950 mg, 4.65 mmol) as described for **9**. The crude reaction product was purified by chromatography (silica gel, 1:1 $CHCl_3$/hexanes) to yield a diastereomeric mixture of **16a** (6:4, NMR) as a yellow oil (425 mg, 33%): ^{1}H NMR ($CDCl_3$) δ 1.48−1.60 (m, 3H), 2.95−3.05 (m, 1H), 3.18−3.38 (m, 2H), 3.82 (s, 3H), 4.18−4.26 (m, 1H), 4.34−4.42 (m, 1H), 5.92 (s, 1H).

6,7-Dichloro-5-ethyl-5,6,7,8-tetrahydro-2-methoxynaphthalene-1,4-dione (16b). Dichloride **16b** was prepared by the chlorination of **15b** (2.00 g, 9.16 mmol) as described for **9** to yield a diastereomeric mixture of **16b** (6:4, NMR) as a yellow granular solid (1.37 g, 52%): mp 115−118 °C; ^{1}H NMR ($CDCl_3$) δ 0.98−1.07 (m, 3H), 1.75−2.08 (m, 2H), 2.86−3.00 (m, 1H), 3.19−3.40 (m, 2H), 3.78−3.88 (m, 3H), 4.30−4.51 (m, 2H), 5.85−5.93 (m, 1H).

6,7,8,9-Tetrahydro-3-methoxy-1*H*-1-benzazepine-2,5-dione (8). Solid **7** (600 mg, 3.12 mmol) was added in portions

to stirred, ice bath cold, concentrated H_2SO_4 (10 mL) to give a deep red solution. NaN_3 (406 mg, 6.24 mmol) was added in portions to the stirred, ice bath cold solution. After addition, the reaction mixture was allowed to warm to 25 °C. The reaction mixture was stirred for 16 h and added to crushed ice (100 mL) to give a yellow/brown solution. The solution was extracted with 30% MeOH/$CHCl_3$ (4 × 30 mL) and $CHCl_3$ (2 × 30 mL). The extract was washed with water (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL) and filtered. The solvent was removed to give a red solid (280 mg). An additional portion of crude **8** (350 mg) was obtained in exactly the same manner. The combined solids were purified by chromatography (silica gel, $CHCl_3$ followed by 2% EtOH/$CHCl_3$) to yield a pink solid. The solid was crystallized from 95% EtOH to yield **8** as a pale pink solid (242 mg, 19%): mp 227−228 °C; ^{1}H NMR (DMSO-d_6) δ 1.48−1.65 (m, 4H), 2.24−2.32 (m, 2H), 2.40−2.47 (m, 2H), 3.72 (s, 3H), 6.23 (s, 1H), 10.57 (s, 1H).

7,8-Dichloro-6,7,8,9-tetrahydro-3-methoxy-1*H*-1-benzazepine-2,5-dione (10). Benzazepine **10** was prepared via a Schmidt reaction of **9** (600 mg, 2.30 mmol) with NaN_3 (598 mg, 9.20 mmol) in concentrated H_2SO_4 (10 mL) as described for **8**. The reaction was performed three times, and the combined crude reaction product was purified by repeated crystallization from 95% EtOH to yield **9** as a colorless powder (112 mg, 6% for the three reactions): mp 229−230 °C; ^{1}H NMR (DMSO-d_6) δ 2.67 (dd, J = 18, 5.4 Hz, 1H), 2.87 (dd, J = 19, 5.1 Hz, 1H), 3.03 (dd, J = 18, 4.5 Hz, 1H), 3.22 (dd, J = 19, 4.8 Hz, 1H), 3.75 (s, 3H), 4.52−4.68 (m, 2H), 6.28 (s, 1H), 10.89 (s, 1H).

6,7,8,9-Tetrahydro-3-methoxy-7,8-dimethyl-1*H*-1-benzazepine-2,5-dione (12). A solution of **11** (560 mg, 2.54 mmol) in TFA (2 mL) was added in portions to stirred, ice bath cold, concentrated H_2SO_4 (10 mL) to give a deep red solution. NaN_3 (330 mg, 5.08 mmol) was added in portions to the stirred, ice bath cold solution. After addition, the reaction mixture was allowed to stir at 25 °C for 60 min. The reaction workup was as described for **8**. The crude reaction product was purified by chromatography (silica gel, $CHCl_3$) followed by crystallization from 95% EtOH to yield a diastereomeric mixture (8:2, NMR) of **12** as a brown granular solid (98 mg, 16%): mp 232−235 °C; ^{1}H NMR ($CDCl_3$) δ 0.88−1.07 (m, 6H), 1.80−2.65 (m, 6H), 3.84 (3H), 6.38 (s, 1H), 7.96 (b, 1H).

7,8-Dichloro-6,7,8,9-tetrahydro-3-methoxy-6-methyl-1*H*-1-benzazepine-2,5-dione (17a). A solution of **16a** (410 mg, 1.49 mmol) in TFA (2 mL) was added in portions to stirred, ice bath cold triflic acid (20 mL) to give a deep red solution. NaN_3 (387 mg, 5.96 mmol) was added in portions to the stirred, ice bath cold solution. After addition, the reaction mixture was allowed to stir at 25 °C for 2.5 h. The reaction workup was as described for **8**. The crude reaction product was purified by crystallization from 95% EtOH to yield a diastereomeric mixture (9:1, NMR) of **17a** as a brown solid (135 mg, 31%): mp 165 °C dec;[22] ^{1}H NMR (DMSO-d_6 and D_2O) δ 1.16−1.18 (m, 3H), 2.95 (dd, J = 18, 10 Hz, 1H), 3.07−3.28 (m, 2H), 3.70 (3H), 4.14 (dd, J = 10, 6.9 Hz, 1H), 4.35−4.45 (m, 1H), 6.24 (s, 1H).[23]

7,8-Dichloro-6-ethyl-6,7,8,9-tetrahydro-3-methoxy-1*H*-1-benzazepine-2,5-dione (17b). Benzazepine **17b** was prepared via a Schmidt reaction of **16b** (1.30 g, 4.50 mmol) with NaN_3 (585 mg, 9.00 mmol) in triflic acid (6 mL) as described for **8**. The reaction time was 4 h. The crude reaction product was purified by crystallization from 95% EtOH to yield a diastereomeric mixture (8:2, NMR) of **17b** as a yellow powder (563 mg, 41%): mp 196−200 °C; ^{1}H NMR (DMSO-d_6 and D_2O) δ 0.73−0.85 (m, 3H), 1.27−1.78 (m, 2H), 2.88−3.00 (m, 1H), 3.11 (dd, J = 17, 4.8 Hz, 1H), 3.38−3.45 (m, 1H), 3.74 (s, 3H), 4.22 (dd, J = 9.3, 6.0 Hz, 1H), 4.40−4.68 (m, 1H), 6.28 (s, 1H).[24]

6,7,8,9-Tetrahydro-6,9-methano-3-methoxy-1*H*-1-benzazepine-2,5-dione (22a). Solid **21a** (2.47 g, 12.1 mmol) was added in portions to stirred, ice bath cold, concentrated H_2SO_4 (40 mL) to give a deep purple solution. NaN_3 (3.15 g, 48.4 mmol) was added in portions over 1 min. Vigorous foaming occurred during the addition, which was controlled by rapid magnetic stirring. The reaction mixture was allowed to stir in the ice bath for 1 min after azide addition. The reaction workup was as described for **8**. The crude reaction product was triturated with acetone (2 mL) to give a yellow powder (78 mg). An additional portion of **21a** (1.64 g, 8.03 mmol) was treated in a similar manner to give a yellow powder (60 mg). The combined crude reaction product was crystallized from 95% EtOH to yield **22a** as a near colorless granular solid (64 mg, 1.4%): mp 285−287 °C; ^{1}H NMR ($CDCl_3$) δ 1.28−1.47 (m, 2H), 1.67−1.75 (m, 1H), 1.80−2.05 (m, 3H), 3.08 (s, 1H), 3.60 (s, 1H), 3.83 (s, 3H), 6.43 (s, 1H), 9.08 (s, 1H).

6,9-Ethano-6,7,8,9-tetrahydro-3-methoxy-1*H*-1-benzazepine-2,5-dione (22b). Benzazepine **22b** was prepared via a Schmidt reaction of **21b** (1.40 g, 6.41 mmol) with NaN_3 (833 mg, 12.8 mmol) in concentrated H_2SO_4 (22 mL) as described for **8**. The crude reaction product was purified by crystallization from 95% EtOH to yield **22b** as pale yellow flakes (471 mg, 31%): mp 276−278 °C; ^{1}H NMR ($CDCl_3$) δ 1.30−1.81 (m, 8H), 2.56−2.59 (m, 1H), 3.64 (s, 1H), 3.84 (s, 3H), 6.46 (s, 1H), 8.67 (s, 1H).

6,7,8,9-Tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-dione (2a). A solution of BBr_3 in CH_2Cl_2 (2.0 mL, 1 M) was added in one portion to a stirred suspension of **8** (207 mg, 1.00 mmol) in dry CH_2Cl_2 (2 mL) at 25 °C. A brown precipitate immediately formed. The reaction was stirred at 25 °C for 45 min. The reaction was added to saturated aqueous $NaHCO_3$ (15 mL), and the resulting orange solution was allowed to stir for 15 min. The solution was extracted with CH_2Cl_2 (1 × 4 mL). The aqueous portion was made acidic (pH 2) with concentrated HCl. The resulting precipitate was collected by filtration and washed with water (6 × 2 mL). The filter cake was crystallized from 95% EtOH to yield **2a** as beige flakes (115 mg, 60%): mp 237−238 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.46−1.65 (m, 4H), 2.23−2.31 (m, 2H), 2.40−2.50 (m, 2H), 6.30 (s, 1H), 10.14 (s, 1H), 10.84 (s, 1H). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

7,8-Dichloro-6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-dione (2b). THHBAD **2b** was prepared as described for **2a** from **10** (100 mg, 362 μmol) to yield **2b** as a beige solid (68 mg, 71%): mp 246−248 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.70 (dd, J = 18, 5.4 Hz, 1H), 2.91 (dd, J = 19, 5.4 Hz, 1H), 3.06 (dd, J = 18, 4.8 Hz, 1H), 3.26 (dd, J = 19, 4.8 Hz, 1H), 4.50−4.69 (m, 2H), 6.34 (s, 1H), 10.46 (s, 1H), 11.11 (s, 1H). Anal. ($C_{10}H_9Cl_2NO_3$) C, H, N.

6,7,8,9-Tetrahydro-3-hydroxy-7,8-dimethyl-l*H*-1-benzazepine-2,5-dione (3). THHBAD **3** was prepared as described for **2a** from **12** (90.0 mg, 367 μmol) to yield a diastereomeric mixture (8:2, NMR) of **3** as pale beige needles (56 mg, 67%): mp 242−243 °C dec; ^{1}H NMR (DMSO-d_6) 0.72−0.96 (m, 6H), 1.69−1.90 (m, 2H), 1.98−2.65 (m, 4H), 6.29 (s, 1H), 10.15 (b, 1H), 10.82 (s, 1H). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

7,8-Dichloro-6,7,8,9-tetrahydro-3-hydroxy-6-methyl-1*H*-1-benzazepine-2,5-dione (18a). THHBAD **18a** was prepared as described for **2a** from **17a** (120 mg, 413 μmol) to yield a diastereomeric mixture (9:1, NMR) of **18a** as a colorless solid (67 mg, 59%): mp 180−181 °C dec; ^{1}H NMR (DMSO-d_6 and D_2O) δ 1.00−1.25 (m, 3H), 2.97 (dd, J = 17, 9.6 Hz, 1H), 3.13 (dd, J = 17, 4.8 Hz, 1H), 3.22 (dq, J = 6.6, 6.6 Hz, 1H), 4.13 (dd, J = 9.3, 6.6 Hz, 1H), 4.37 (ddd, J = 9.6, 9.3, 4.8 Hz, 1H), 6.32 (s, 1H).[25] Anal. ($C_{11}H_{11}Cl_2NO_3$) C, H, N.

7,8-Dichloro-6-ethyl-6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-dione (18b). THHBAD **18b** was prepared as described for **2a** from **17b** (525 mg, 1.73 mmol) to yield a diastereomeric mixture (8:2, NMR) of **18b** as a beige solid (236 mg, 47%): mp 197 °C dec;[22] ^{1}H NMR (DMSO-d_6 and D_2O) δ 0.75−0.81 (m, 3H), 1.22−1.79 (m, 2H), 2.94 (dd, J = 17, 9.9 Hz 1H), 3.11 (dd, J = 17, 4.8 Hz, 1H), 3.25−3.45 (m, 1H), 4.20 (dd, J = 9.3, 5.7 Hz, 1H), 4.32−4.64 (m, 1H), 6.31−6.33 (m, 1H).[26] Anal. ($C_{12}H_{13}Cl_2NO_3$) C, H. N.

6,7,8,9-Tetrahydro-3-hydroxy-6,8-methano-1*H*-1-benzazepine-2,5-dione (23a). THHBAD **23a** was prepared as described for **2a** from **22a** (65.0 mg, 296 μmol) to yield **23a** as a near colorless granular solid (32 mg, 52%): mp 268−270 °C dec; ^{1}H NMR (DMSO-d_6 and D_2O) δ 0.97−1.10 (m, 1H), 1.15−1.28 (m, 2H), 1.44−1.53 (m, 1H), 1.68−1.90 (m, 2H), 3.21 (s, 1H), 3.31 (s, 1H), 6.27 (s, 1H).[27] Anal. ($C_{11}H_{11}NO_3$) C, H, N.

6,8-Ethano-6,7,8,9-tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-dione (23b). THHBAD **23b** was prepared as

described for **2a** from **22b** (350 mg, 1.50 mmol) to yield **23b** as colorless needles (169 mg, 51%): mp 252−254 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.08−1.23 (m, 2H), 1.29−1.45 (m, 2H), 1.47−1.67 (m, 4H), 2.96 (s, 1H), 3.46 (s, 1H), 6.35 (s, 1H), 10.04 (b, 1H), 11.46 (b, 1H). Anal. ($C_{12}H_{13}NO_3$) C, H, N.

Pharmacology. Methods employed were as described in ref 6.

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References

(1) Watkins, J. C. The NMDA Receptor Concept: Origins and Development. In *The NMDA Receptor*, 2nd ed.; Collingridge, G. L., Watkins, J. C., Eds.; Oxford University Press: Oxford, 1994; pp 1−30.

(2) (a) McCulloch, J. Excitatory Amino Acid Antagonists and Their Potential for the Treatment of Ischemic Brain Damage in Man. *Br. J. Clin. Pharmacol.* **1992**, *34*, 106−114. (b) Dodd, P. R.; Scott, H. L.; Westphalen, R. I. Excitotoxic Mechanisms in the Pathogenesis of Dementia. *Neurochem. Int.* **1994**, *25*, 203−219. (c) Lipton, S. A. Models of Neuronal Injury in AIDS: Another Role for the NMDA Receptor? *Trends Neurosci.* **1992**, *15*, 75−79.

(3) (a) Choi, D. W.; Rothman, S. M. The Role of Glutamate Neurotoxicity in Hypoxic-Ischemic Neuronal Death. *Annu. Rev. Neurosci.* **1990**, *13*, 171−182. (b) Meldrum, B.; Garthwaite, J. Excitatory Amino Acid Neurotoxicity and Neurodegenerative Disease. *Trends Pharmacol. Sci.* **1990**, *11*, 379−387.

(4) (a) Johnson, J. W.; Ascher, P. Glycine Potentiates the NMDA Response in Cultured Mouse Brain Neurons. *Nature (London)* **1987**, *325*, 529−531. (b) Kleckner, N. W.; Dingledine, R. Requirement for Glycine in Activation of NMDA-Receptors Expressed in *Xenopus* Oocytes. *Science (Washington, D.C.)* **1988**, *241*, 835−837.

(5) (a) Leeson, P. D. Glycine-Site *N*-Methyl-D-Aspartate Receptor Antagonists. In *Drug Design for Neuroscience;* Kozikowski, A. P., Ed.; Raven Press: New York, 1993; pp 339−381. (b) Leeson P. D.; Iversen, L. L. The Glycine Site on the NMDA Receptor: Structure-Activity Relationships and Therapeutic Potential. *J. Med. Chem.* **1994,** *37*, 4053−4067. (c) Iversen, L. L.; Kemp, J. A. Non-Competitive NMDA Antagonists as Drugs. In *The NMDA Receptor*, 2nd ed.; Collingridge, G. L., Watkins, J. C., Eds.; Oxford University Press: Oxford, 1994; pp 469−486.

(6) Guzikowski, A. P.; Cai, S. X.; Espitia, S. A.; Hawkinson, J. E.; Huettner, J. E.; Nogales, D. F.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. Analogs of 3-Hydroxy-1*H*-1-benzazepine-2,5-dione: Structure-Activity Relationship at *N*-Methyl-D-aspartate Receptor Glycine Sites. *J. Med Chem.* **1996,** *39*, 4643−4653.

(7) Swartz, K. J.; Koroshetz, W. J.; Rees, A. H.; Huettner, J. E. Competitive Antagonism of Glutamate Receptor Channels by Substituted Benzazepines in Cultured Cortical Neurons. *Mol. Pharmacol.* **1992,** *41*, 1130−1141.

(8) Chapdelaine, M. J.; McLaren, C. D. Therapeutic Benzazarine Compounds. U.S. Patent 5,254,683, Oct. 19, 1993.

(9) Keana, J. F. W.; Guzikowski, A. P.; Nogales, D. F.; Cai, S. X. Azepine Synthesis via a Diels−Alder Reaction. U.S. Patent 5,476,933, Dec. 19, 1995.

(10) Guzikowski, A. P.; Hawkinson, J.; Weber, E.; Keana, J. F. W. 6,7,8,9-Tetrahydro-3-hydroxy-1*H*-1-benzazepine-2,5-diones Via a Diels-Alder Reaction: Antagonists with a Non-Planar Hydrophobic Region for NMDA Receptor Glycine Sites. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2747−2748.

(11) Adler, E.; Magnusson, R. Periodate Oxidation of Phenols I. Monoethers of Pyrocatechol and Hydroquinone. *Acta Chem. Scand.* **1959,** *13*, 505−519.

(12) Cavill, G. W. K.; Quinn, R. J. Synthesis of *cis*-Bicyclo[4,4,0]deca-2,8-dien-4-one. *Aust. J. Chem.* **1973**, *26*, 595−601.

(13) Ansell, M. F.; Nash, B. W.; Wilson, D. A. The Diels-Alder Reaction of p-Benzoquinones. *J. Chem. Soc.* **1963,** 3012−3028.

(14) Cunningham, J.; Haslam, E.; Haworth, R. D. The Constitution of Piceatannol. *J. Chem. Soc.* **1963,** 2875−2883.

(15) The hydrogenation of substituted alkenes is known to give mixtures of *syn* and *anti* addition products. For examples, see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 2nd ed.; Plenum Press: New York, 1983; pp 193−198.

(16) In our hands, the diastereomeric mixtures present in **3** and **18a**,**b** could not be readily separated by chromatographic or crystallization techniques.

(17) Woodward, R. M.; Huettner, J. E.; Guastella, J.; Keana, J. F. W.; Weber, E. *In Vitro* Pharmacology of ACEA-1021 and ACEA-1031: Systemically Active Quinoxalinediones with High Affinity and Selectivity for *N*-Methyl-D-Aspartate Receptor Glycine Sites. *Mol. Pharmacol.* **1995**, *47*, 568−581.

(18) Kuryatov, A.; Laube, B.; Betz, H.; Kuhse, J. Mutational Analysis of the Glycine-Binding Site of the NMDA Receptor: Structural Similarity with Bacterial Amino Acid-Binding Proteins. *Neuron* **1994,** *12*, 1291−1300.

(19) Keana, J. F. W.; Kher, S. M.; Cai, S. X.; Dinsmore, C. M.; Glenn, A. G.; Guastella, J.; Huang, J.-C.; Ilyin, V.; Lü, Y.; Mouser, P. L.; Woodward, R. M.; Weber, E. Synthesis and Structure-Activity Relationships of Substituted 1,4-Dihydroquinoxaline-2,3-diones: Antagonists of *N*-Methyl-D-Aspartate (NMDA) Receptor Glycine Sites and of Non-NMDA Glutamate Receptors. *J. Med Chem.* **1995**, *38*, 4367−4379.

(20) Okamoto, Y.; Senokuchi, K.; Kenematsu, K. Lewis Acid Catalyzed [$2\sigma + 2\sigma$] Cycloreversion Reaction of Strained Caged Ketones to Triquinane Skeletons: Kinetic Evidence for a Large Acceleration of the Reaction Owing to Stereoelectronic Requirement. *Chem. Pharm. Bull.* **1984,** *32*, 4593−4599.

(21) Mehta, G.; Reddy, D. S.; Reddy, A. V. Lewis Acid Catalyzed [2 + 2] Cycloreversion of Cookson's Cage Ketones Under Ambient Conditions: Model System for Light Energy Conversion. *Tetrahedron Lett.* **1984,** *25*, 2275−2278.

(22) The compound decomposes without melting.

(23) The spectrum without D_2O shows an additional resonance (δ 10.77 (s, 1H)).

(24) The spectrum without D_2O shows an additional resonance (δ 10.75−10.84 (m, 1H)).

(25) The spectrum without D_2O shows additional resonances (δ 10.47 (b, 1H), 11.01 (s, 1H)).

(26) The spectrum without D_2O shows additional resonances (δ 10.49 (b, 1H), 11.06 (s, 1H)).

(27) The spectrum without D_2O shows additional resonances (δ 10.03 (b, 1H), 11.89 (b, 1H)).

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