were homogeneous (except from the precipitation of NaCl) and in DME they were heterogeneous. At the end of the reactions the solids were filtered off, the solvent was evaporated, and the NMR spectrum of the products mixture was taken in $CDCl_3$. The NMR results were in good agreement (±3%) with the GC data.

Registry No. 1-TEG, 125331-78-4; 1-Cl, 23745-75-7; *cis*-**8**, 125331-76-2; *trans*-**8**, 125331-77-3; *cis*-**9**, 125331-80-8; *trans*-**9**, 125331-81-9; **10**, 125331-82-0; **11**, 125331-79-5; TEG^-, 37482-11-4.

Supplementary Material Available: ^{13}C NMR spectrum for compound **10** (1 page). Ordering information is given on any current masthead page.

Transannular Cyclizations of 5-(Hydroxyamino)dibenzo[*a*,*e*]cyclooctatrienes. Regioselective Synthesis of Dibenzohomotropane Analogues

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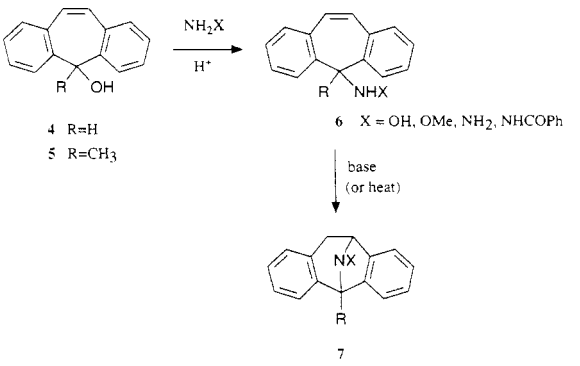
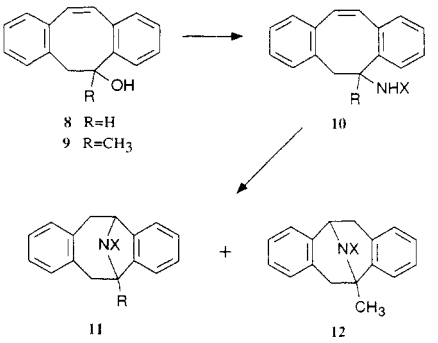
Solvolyses of 5-[(tosyloxy)methyl]dibenzo[*a*,*d*]cycloheptenes **18** provided substituted dibenzo[*a*,*e*]cyclooctatrien-5-ols **19** and **20**, the product distribution implicating the intermediacy of cyclopropyl phenonium ions **22** and **23**. Treatment of 5-methyl-5-hydroxydibenzo[*a*,*e*]cyclooctatrienes (e.g. **9**) with hydroxylamine under acidic conditions led to exclusive formation of N-hydroxy dibenzohomotropanes (e.g. **30**). Cyclizations of substituted derivatives, followed by reductive cleavage of the *N*-hydroxy groups, gave derivatives **2**, **35-42**, and **46**, which are ring homologues of the uncompetitive NMDA antagonist MK-801 (**1**). The more rapid rate of ring closure of 5-(hydroxyamino)dibenzo[*a*,*e*]cyclooctatrienes (e.g. **28**) relative to the corresponding cycloheptenes is rationalized by differences in strain energy in the transition states required for cyclization.

Tetracyclic analogues of the dibenzo[*a*,*d*]cycloheptenimine **1** (MK-801)[1] have potential therapeutic utility as anticonvulsant and neuroprotective agents. The biological effects of **1** are believed to result from specific antagonism of the *N*-methyl-D-aspartate (NMDA) preferring subtype of excitatory amino acid receptor.[2] The NMDA receptor, which is widespread in the mammalian central nervous system, is linked to a membrane-bound ionophore permeable to calcium ions and is believed to play a key role in learning and memory processes.[3] However, excessive stimulation of the receptor by the endogenous transmitter glutamic acid is thought to occur following cerebral ischaemic attacks (e.g. stroke), and the resulting increased cellular calcium influx probably contributes to subsequent cell death.[4] Compound **1** and other NMDA antagonists have been shown to possess neuroprotective activity in animal models of cerebral ischaemia.[5] Electrophysiological[2] and receptor binding[6] studies suggest that **1** acts by entering the open ion channel of the activated NMDA receptor and consequently blocking the cellular entry of calcium ions. MK-801 (**1**) is the most potent of a series of related analogues[1] and other structurally diverse molecules[6] that share this biological activity. As part of a study designed to define the structural and conformational properties necessary for ligand binding to the NMDA receptor, we required access to ring homologated analogues of **1**, including dibenzo[*a*,*e*]cyclooctanimines (**2** and **3**).

Scheme I



Scheme II



Routes developed for the synthesis of the bicyclo[3.2.1] ring system found in **1**[7,8] have made use of transannular

(1) Woodruff, G. N.; Wong, E. H. F.; Kemp, J. A. Eur. Pat. Appl. 0 230 370A2, 1987.
(2) Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104.
(3) Cotman, C. W.; Iversen, L. L. *Trends Neurosci.* **1987**, *10*, 263.
(4) Choi, D. W. *Trends Neurosci.* **1988**, *11*, 465.
(5) Ozyurt, E.; Graham, G. I.; Woodruff, G. N.; McCulloch, J. *J. Cereb. Blood Flow Metab.* **1988**, *8*, 138.
(6) Wong, E. H. F.; Knight, A. R.; Woodruff, G. N. *J. Neurochem.* **1988**, *50*, 274.

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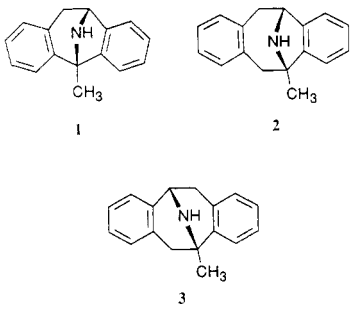
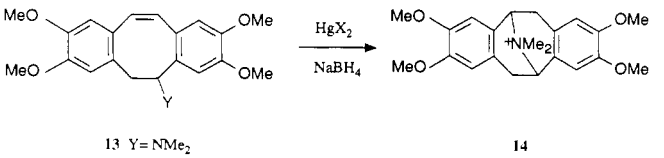


1 2 3

amino–olefin cyclization reactions (Scheme I). Optimal conditions for the formation of the intermediate **6** from the 5-hydroxydibenzo[*a*,*d*]cycloheptenes **4** and **5** were found to be capture of the carbonium ions derived from **4** and **5** by nucleophilic hydroxylamine and hydrazine derivatives (NH_2X).[8] Cyclization of the intermediate **6** was effected either thermally, or by treatment with base, and conversion of **7** (R = Me) to **1** was completed by reduction of the NX group. We anticipated that transannular ring closure reactions of 5-substituted dibenzo[*a*,*e*]cyclooctenes (**10**, Scheme II) might provide access to both the bicyclo-[4.2.1] (**11**) and bicyclo[3.3.1] (**12**) precursors of **2** and **3**, respectively. There have been two previous reports of attempts to effect similar ring closure reactions of 5-amino-substituted dibenzo[*a*,*e*]cyclooctenes.[9,10] Mercury(II)-mediated ring closure of the dimethylamino derivative **13** (Y = NMe_2, Scheme III) resulted in formation of the bicyclo[3.3.1] derivative **14** (the methyl quaternary salt of the pavine alkaloid argemonine).[9] However, attempts to prepare pavine alkaloids by cyclization of the 5-amino **13** (Y = NH_2) and 5-(acetylamino) **13** (Y = NHAc) derivatives were not successful.[10] Bicyclo[4.2.1] (dibenzohomotropane) derivatives were not reported to be products from the reactions of **13**, and only one incompletely characterized example of this ring system is known.[11] Transannular cyclizations of 5-aminocyclooct-1-enes lacking benzo substitution have been accomplished by aminomercuration[12] and by silver(I) ion catalyzed reactions of *N*-chloro amines,[13] but in both cases mixtures of 9-azabicyclo[3.3.1]- and -[4.2.1]nonanes were obtained.

In this paper[14] we describe a route for the synthesis of substituted derivatives of the cyclooctenecarbinol **9** and show that these compounds may be converted with complete regioselectivity to the [4.2.1]dibenzohomotropane ring structure **11** via labile hydroxylamine derivatives **10** (R = H and Me; X = OH and OMe). The relative rates of cyclization of cyclooctene derivatives **10** were found to be substantially greater than the corresponding cycloheptenes **6**, and this is rationalized by considerations of the geometries of the respective transition states required for transannular cyclization. An alternative approach was required for the synthesis of **3** and this is described in the accompanying paper.[15]

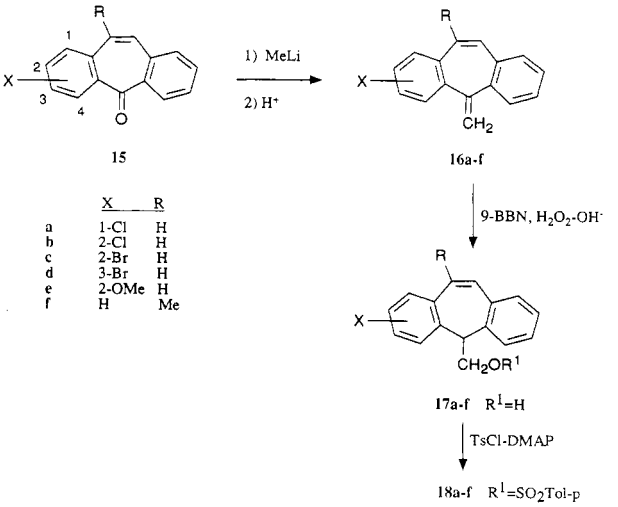
Scheme III[a]



13 Y = NMe_2 14

[a] Y = NH_2, NHAc did not cyclize.[10]

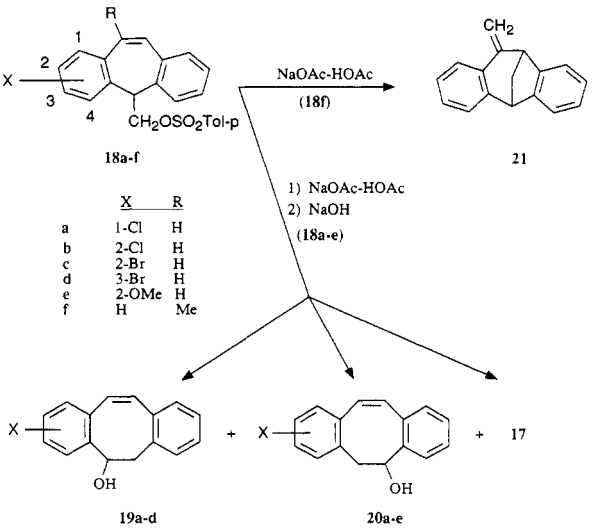
Scheme IV



	X	R
a	1-Cl	H
b	2-Cl	H
c	2-Br	H
d	3-Br	H
e	2-OMe	H
f	H	Me

15 16a-f 17a-f R^1=H 18a-f R^1=SO_2Tol-p

Scheme V[a]



18a-f 21

	X	R
a	1-Cl	H
b	2-Cl	H
c	2-Br	H
d	3-Br	H
e	2-OMe	H
f	H	Me

19a-d 20a-e

	X	19[a]	20[a]	17[a]
a	1-Cl	3.0	1	[b]
b	2-Cl	2.3	1	[b]
c	2-Br	2.0	1	[b]
d	3-Br	1.7	1	[b]
e	2-OMe	[c]	1	3.3

[a] Product ratios. [b] Trace quantities (<5%) formed. [c] Not detected.

Synthesis of Dibenzo[*a*,*e*]cycloocten-5-ols 19 and 20. The unsubstituted cycloocten-5-ol (**8**) was readily prepared from solvolytic rearrangement of the ditosylate of 9,10-bis(hydroxymethyl)-9,10-dihydroanthracene, a process that proceeds via the intermediate mono[(tosyloxy)methyl]cycloheptene.[16] Cycloocten-5-ols **19** and **20**

(7) (a) Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, D. C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117. (b) Evans, B. E.; Anderson, P. S.; Christy, M. E.; Colton, C. D.; Remy, D. C.; Rittle, K. E.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3127.

(8) Lamanec, T. R.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768.

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(10) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 1984.

(11) Ito, K.; Furukawa, H.; Iida, J.; Lee, K.-H.; Soine, T. O. *J. Chem. Soc., Chem. Commun.* **1974**, 1037.

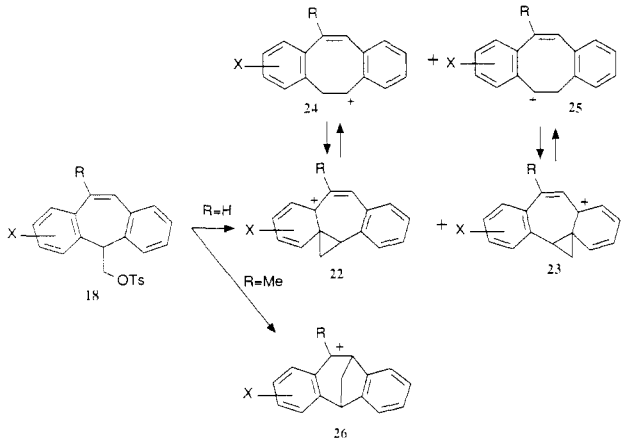
(12) Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. B.; Abood, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 7864.

(13) Bastable, J. W.; Hobson, J. D.; Riddell, W. D. *J. Chem. Soc., Perkin Trans. I* **1972**, 2205.

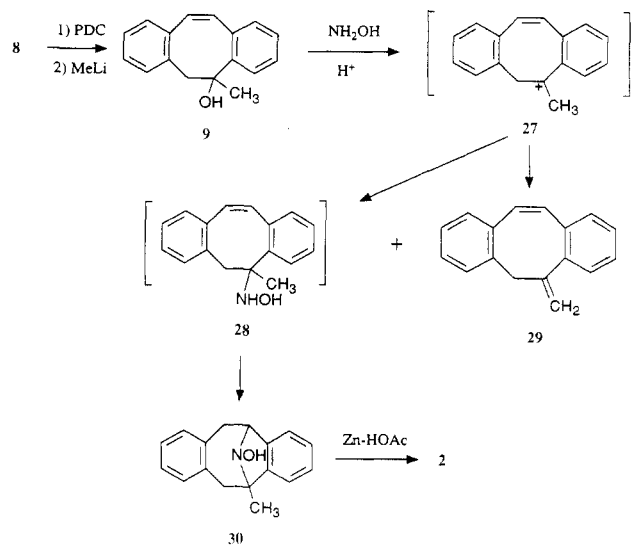
(14) Preliminary communication: Leeson, P. D.; James, K.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1989**, 433.

(15) Leeson, P. D.; et al. *J. Org. Chem.*, following paper in this issue.

Scheme VI



Scheme VII

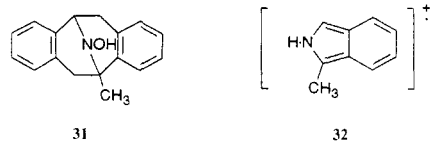


bearing substituents on the aromatic carbon atoms were required for the preparation of a wider group of analogues for structure–activity studies. Since the alternative route[10] to dibenzo[*a*,*e*]cycloocten-5-ols is not well suited for the preparation of monosubstituted derivatives, we explored solvolytic rearrangements (Scheme V) of tosylates **18a–f** of substituted 5-(hydroxymethyl)dibenzo[*a*,*d*]cycloheptenes **17a–f**. Substituted dibenzosuberenones **15a–f** (Scheme IV) were converted to the exocyclic olefins **16a–f** by treatment with methyllithium followed by dehydration of the resulting tertiary alcohols. This procedure proved to give better yields of **16a–f** than direct Wittig olefination reactions of **15a–f**. Hydroboration of **16a–f** with 9-BBN proceeded selectively at the exocyclic methylene, yielding alcohols **17a–f**, which were tosylated to form the required precursors **18a–f**.

Solvolytic ring expansions of the tosylates **18a–f** were performed by using the reported optimal conditions of refluxing acetic acid containing 2 equiv of sodium acetate.[17] The product mixtures were hydrolyzed and the resulting alcohols were separated by column chromatography. The product distribution is shown in Scheme V; the identities of the cyclooctenol regioisomers **19** and **20** are determined by using ^{1}H NMR spectroscopy by analysis of nuclear Overhauser effects (NOE's) in the subsequent imino-bridged cyclized derivatives (see below and Scheme VIII). Cyclooctenols were formed as the major products from acetolyses of the halogen-substituted tosylates **18a–d**, with the 5-substituted isomers **19a–d** being slightly preferred, and minor quantities (<5%) of the primary alcohols **17a–d** being produced. In contrast, the 2-methoxy derivative **18e** gave the 6-hydroxy regioisomer **20e** as the exclusive cyclooctene product (19% yield) together with the alcohol **17e** as the major product (62% yield). Substitution of the olefin by a methyl group (**18f**) led to an alternative solvolytic pathway, with the tetracyclic hydrocarbon **21** being formed as the major product.

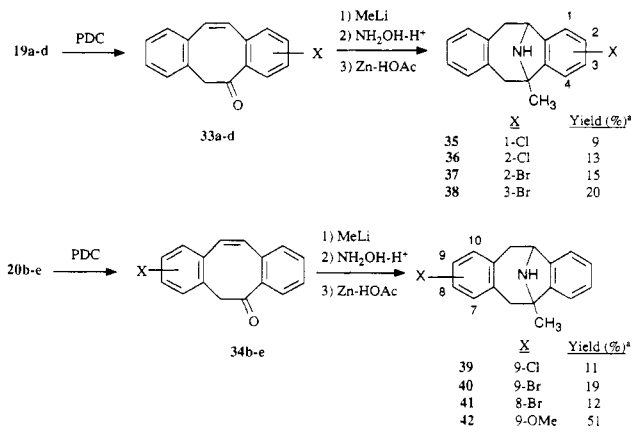
Several cationic species have been proposed as intermediates in the conversion of **18** (X = R = H) to **8**.[10,16–18] There is evidence that this process is reversible,[10,17] suggesting that product formation will be significantly influenced by the relative stabilities of intermediate carbonium ions. The results presented in Scheme V provide additional insight into the rearrangement mechanism. In particular, the regiochemical outcome of the reactions of the monosubstituted tosylates **18a–e** provides evidence, hitherto lacking, for the intermediacy of the ortho phenonium ions **22** and **23**, (Scheme VI). The major cyclooctene products obtained (**19a-d** and **20e**) are formally derived from the *least* stable of the two possible cyclooctene carbonium ions (**25** and **24**, respectively). The relative stabilities of the phenonium ions **22** and **23** are, however, in accord with the product distribution. With 2-methoxy substitution (**18e**), the isolation of **20e** and **17e** only (Scheme V) suggests that phenonium ion **22** is the exclusive cationic intermediate, with the high yield of the primary cycloheptenol **17e** presumably a consequence of direct nucleophilic attack of acetate at the unhindered methylene group of **22**. The formation of the exocyclic olefin **21** from the methyl derivative **18f** can be explained by an alternative solvolytic pathway, giving the bridged carbonium ion **26**. In this instance, the tertiary carbonium ion **26** must be stabilized relative to the alternative cationic species **22–25**.

Transannular Cyclization Reactions of 5-(Hydroxyamino)dibenzo[*a*,*e*]cyclooctenes. The required starting alcohol **9** (Scheme II) was prepared from **8** by oxidation to the corresponding ketone[16] followed by treatment with methyllithium (Scheme VII). The carbonium ion capture conditions developed by Lamanec and co-workers[8] for conversion of **5** to **6** (Scheme I) were used in attempts to prepare the hydroxylamine **28** from the alcohol **9**. Treatment of **9** with hydroxylamine hydrochloride in the presence of dichloroacetic acid and sodium acetate, however, gave the cyclized bicyclo[4.2.1] derivative **30** directly in 39% yield after basic workup. The alternative [3.3.1] isomer **31** was not detected and rearrangement of the intermediate carbonium ion **27** to form dibenzo[*a*,*d*]cycloheptene products[10,16] did not occur to any detectable extent. The only other product isolated from this reaction was the exocyclic olefin **29** (48% yield), which presumably arises from deprotonation of **27**. In common with the cycloheptenimine compounds **7** (X = OH)[8] the *N*-hydroxy derivative **30** was found by ^{1}H NMR spectroscopy to exist as approximately a 1:1 mixture of syn and anti atropisomers, which are a consequence of slow in-



(16) Cioranescu, E.; Bucur, A.; Banciu, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1965**, *10*, 141.
(17) Cioranescu, E.; Bucur, A.; Elian, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1965**, *10*, 149.
(18) Cioranescu, E.; Bucur, A.; Elian, M.; Banciu, M.; Voicu, J.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1965**, *10*, 161.

Scheme VIII[a]



	X	Yield (%)[a]
35	1-Cl	9
36	2-Cl	13
37	2-Br	15
38	3-Br	20
39	9-Cl	11
40	9-Br	19
41	8-Br	12
42	9-OMe	51

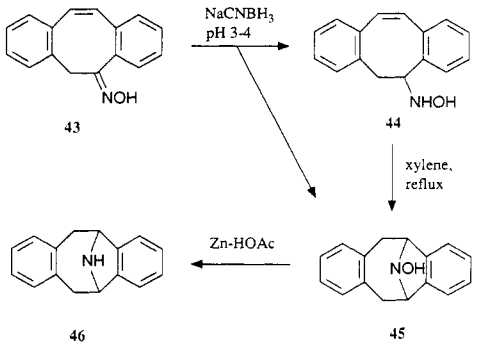
[a] Unoptimized overall yield for steps 1 and 2.

version at the tertiary nitrogen. Reductive cleavage of the *N*-hydroxy bond of **30** with zinc in acetic acid gave **2**. The structure of **2** was distinguished from the alternative bicyclo[3.3.1] isomer **3** by full assignment of the ^{1}H NMR spectrum and identification of specific NOE's. Irradiation of the signals assigned to the bridgehead methyl (δ 1.68) and methine (δ 4.61) protons gave NOE's to aromatic protons (at C-4 and C-1, respectively) in the same ring. The observation in the mass spectrum of the isoindole ion **32** (m/e = 131) was also diagnostic for the [4.2.1] ring structure,[13] since this ion would not be formed from **3**.[19] Finally, the structure was confirmed by single-crystal X-ray analysis and by a comparison of the spectral properties of **2** with authentic **3**.[15]

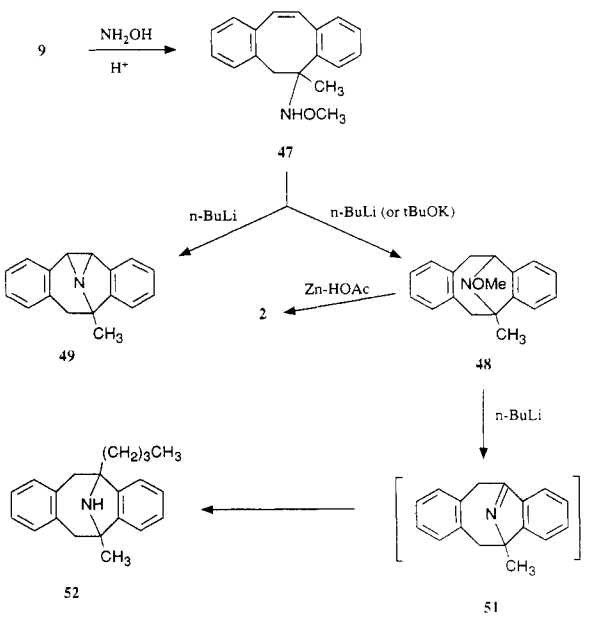
These results show that transannular cyclization of the presumed hydroxylamine intermediate **28** occurs rapidly and regioselectively at room temperature. In contrast, the corresponding 5-(hydroxyamino)cycloheptene **6** (R = Me; X = OH) is an isolable compound that requires refluxing overnight in toluene solution to effect cyclization.[8] The instability of **28** is shared by 5-(hydroxyamino)cyclopent-1-enes, which also readily cyclize at room temperature to form pyrrolidine products exclusively.[20] The [4.2.1] bicyclic hydroxylamine **30** appears to be the product of kinetic control, since the alternative [3.3.1] isomer **31** is predicted to be thermodynamically favored, as shown by studies of comparable 9-azabicyclo[4.2.1]- and -[3.3.1]nonanes.[21] This conclusion is supported by molecular mechanics calculations, which predict that **3** is 76 kJ·mol^{-1} more stable than **2**.[14]

Oxidation of the alcohols **19a–d** and **20b–e** gave the ketones **33a–d** and **34b–e**, which were converted to the monosubstituted dibenzohomotropanes **35–42**, (Scheme VIII). In these cases, the ketones were treated with methyllithium and the resulting crude alcohols were allowed to react with hydroxylamine under the same carbonium ion capture conditions used for the unsubstituted alcohol **9**. This resulted in formation of the cyclized [4.2.1] *N*-hydroxy compounds, which were converted to **35–42** by reduction with zinc in acetic acid. The structures of **35–42** were proven in each instance by ^{1}H NMR and NOE spectroscopy (see Experimental Section) and this allowed identification of the regiochemistries of the precursor alcohols **19a–d** and **20b–e**. The yields of the cyclization step

Scheme IX



Scheme X



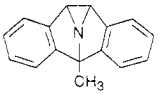
were variable (Scheme VIII) but conditions were not optimized. In most instances, the exocyclic olefin (i.e. substituted **29**) appeared to be the major byproduct. The benzene ring substitutions studied do not appear to influence the rate or regiochemical outcome of the cyclization, since the isomeric [3.3.1] products were not detected.

The presence of a methyl group at C-5 in **6** (R = CH$_3$, X = OH) facilitates ring closure, as illustrated by the lack of reactivity under thermal conditions of the desmethyl compound **6** (R = H; X = OH).[8] In contrast, the cyclooctene hydroxylamine lacking the 5-methyl group (**44**) readily cyclizes to form **45** (Scheme IX). Compound **44** could not be prepared directly from the alcohol **8** but reduction of the oxime **43**[16] with sodium cyanoborohydride under controlled conditions at pH 3–4 gave a 1:1 mixture of two products, which were shown to be the hydroxylamine **44** and the cyclized derivative **45**. Although compound **44** could not be obtained free from **45**, its isolation demonstrates improved stability relative to the methyl derivative **28**, which we were not able to isolate. Brief thermolysis of the mixture (refluxing xylene for 10 min) completed the conversion of **44** to **45**. Reduction of **45** gave the symmetrical derivative **46**, whose structure was proven by ^{1}H NMR and NOE studies. The observed slower rate of cyclization of **44** relative to **28** parallels the effect of 5-methyl substitution observed in the cycloheptene series (Scheme I).

Unlike the unsubstituted labile hydroxylamine **28**, the *O*-methyl derivative **47** could be isolated, in 83% yield, from treatment of the alcohol **9** with methoxylamine (Scheme X). Compound **47** was sufficiently stable to allow

(19) Gozler, B. In *The Alkaloids*, Vol. 31; Brossi, A., Ed.; Academic Press: New York, 1987; p 317.
(20) (a) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. (b) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317.
(21) Barluenga, J.; Perez-Prieto, J.; Bayon, A. M.; Asensio, S. *Tetrahedron* **1984**, *40*, 1199.

spectroscopic characterization, but decomposed on storage. Thermolysis of **47** failed to effect cyclization to **48**, which supports the intermediacy of nitroxyl radicals[22] in the cyclization of **28**. Attempts to effect cyclization of the methoxylamine **47** were explored by using basic conditions.[8,23,24] Treatment of **47** with potassium *tert*-butoxide in toluene–dimethyl sulfoxide[8] gave the bicyclo[4.2.1] derivative **48**, whose structure was confirmed by reduction to **2**. However, reaction of **47** with 1 molar equiv of *n*-butyllithium[23,24] in tetrahydrofuran, while giving **48** as the major product (56%), also resulted in the formation of the tricyclic aziridine **49** in low yield (9%). This result is in contrast with the reaction of the corresponding cycloheptene **6** (R = Me; X = OMe) with *n*-butyllithium, which results in exclusive conversion to the aziridine **50**.[23]



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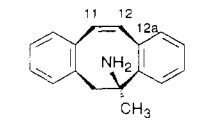
These findings are again consistent with the more rapid ring closure reactions of 5-(hydroxyamino)cyclooctenes **10** (X = OH) relative to the corresponding cycloheptenes **6** (X = OH). Thus transannular cyclization of the methoxylamine **47** in the presence of *n*-butyllithium proceeds at a faster rate than α-elimination of methanol to form the corresponding nitrene, and subsequently the aziridine **49**. In the case of the cycloheptene **6** (R = Me; X = OMe) α-elimination of methanol by *n*-butyllithium is the principal reaction pathway.

Treatment of the cyclized methoxylamine **48** with 1 molar equiv of *n*-butyllithium led to formation of the bridgehead *n*-butyl compound **52** in 31% yield. One plausible mechanism leading to **52** is initial β-elimination of methanol from **48**, giving a strained and highly reactive "anti-Bredt" imine (**51**), which would be rapidly quenched by further reagent. Attempts to perform the analogous conversion with the cycloheptenimine **7** (R = Me; X = OMe)[8] were without success.

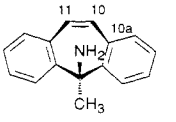
Conformational Effects on Rate of Cyclization. The foregoing studies have clearly demonstrated that transannular cyclization of 5-substituted dibenzo[*a*,*e*]cyclooctenes **10** provides a regiospecific synthesis of the dibenzohomotropane **11** ring system (Scheme II) and that the reaction proceeds at a significantly faster rate than the corresponding conversion of the homologous cycloheptenes **6** (Scheme I). The conformations of **6** and **10** (X = OH) that result in transannular ring closure must place the reacting hydroxylamine group in an axial position. A full comparative study of the solution conformations of the hydroxylamine derivatives was not possible because of the instability of these compounds. However, overall conformational trends were compared by variable-temperature ^{1}H NMR and NOE studies of the corresponding secondary (**4** and **8**) and tertiary (**5** and **9**) alcohols. The results (see Experimental Section) showed that in deuteriochloroform at room temperature, the cycloheptenols **4** and **5** and the cyclooctenols **8** and **9** undergo fast conformational interconversions. The cyclooctenols exist predominantly with the bulkier 5-substituent in the axial conformation, which is presumably favored because steric interference exists between the 5-substituent and neighboring peri aromatic protons. These studies show that the interconversions between possible conformers of the 5-substituted dibenzo[*a*,*d*]cycloheptenes and -[*a*,*e*]cyclooctenes are more rapid than the rates of ring closure of the hydroxylamine derivatives. Consequently the distribution of conformers in solution is not a determining factor governing the relative rates of the cyclization reactions of **6** and **10**.

Chart I. Interatomic Distances and Geometries of Cyclooctane and Cycloheptane Derivatives



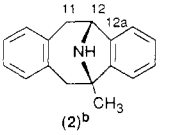
(I)[a]

N - C-12 3.11Å
N - C-11 3.76Å
N - C-12 - C-12a 74.2°
N - C-12 - C-11 108.2°



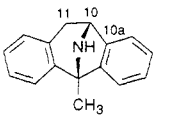
(II)[a]

N - C-10 2.97Å
N - C-10 - C-10a 78.8°
N - C-10 - C-11 77.0°



(2)[b]

N - C-12 - C-12a 102.3°
N - C-12 - C-11 112.5°



(1)[b]

N - C-10 - C-10a 100.3°
N - C-10 - C-11 106.1°

[a] Structures derived from molecular mechanics calculations using OPTIMOL.[30] Amines were used because molecular mechanics parameterization for hydroxylamines was not available. Compounds I and II have the amino group in the axial conformation. [b] Crystal structure geometry.

A rationalization for the rate difference appears from comparisons of the geometries of **10** and **6**, in the conformations (I and II, respectively, Chart I) that place the reacting 5-substituent in the required axial position for cyclization. The formation of the [4.2.1] ring system **11** instead of the thermodynamically favored [3.3.1] structure **12** can be explained by the closer proximity of the nitrogen atom in I to C-12 (3.11 Å) than to C-11 (3.76 Å). Thus N–C-12 bond formation is predictably kinetically favored relative to N–C-11 ring closure. The symmetrical cycloheptene conformer II places the nitrogen a similar distance from C-10, but the incipient N–C–C bond angles are different from those found in I. Comparisons of these incipient bond angles in I and II with the corresponding bond angles found in the products **2** and **1**, respectively, show that the angle N–C-12–C-11 in I is near optimal for product formation, but *both angles* N–C-10–C-10a and N–C-10–C-11 in II will have to increase in the product. Consequently, the transition state derived from II is likely to be more strained than the transition state obtained from I, and this could explain the observed slower rate of cyclization of II relative to I. The 5-methyl substituents in I and II may increase reactivity as a result of steric crowding leading to closer N–C distances in the transition state (Thorpe–Ingold effect[8]). This effect is reflected in the calculated geometry of the axial conformation of 5-desmethyl I, where the N–C-11 distance is increased to 3.61 Å from the value of 3.11 Å found in I.

Compounds **2** and **35–42** proved to possess high affinity for the ion channel binding site on the NMDA receptor,[25] with compound **2** being equipotent with MK-801 (**1**).

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Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as Nujol mulls. ^{1}H NMR spectra were measured at 360 or 250 MHz. Merck kieselgel 60 (230–400 mesh) was used for column chromatography. The starting dibenzosuberenones **15a–f** were prepared by application of established methodology, namely, via Wittig reaction of (2-carbomethoxybenzyl)triphenylphosphonium bromide with substituted benzaldehydes[26] and condensation of substituted phenylacetic acids with phthalic anhydride.[27]

2-Methoxy-5,6-dihydrodibenzo[a,e]cycloocten-6-ol (20e). To a cooled (0 °C) stirred solution of 2-methoxydibenzo[a,d]-cyclohepten-5-one (**15e**, 20 g, 0.09 mol) in anhydrous tetrahydrofuran, (THF, 200 mL) under a nitrogen atmosphere, was added dropwise a solution of methyllithium in diethyl ether (55.8 mL of a 1.6 M solution). After 45 min the mixture was quenched by the cautious addition of water (30 mL) and then extracted with diethyl ether (3 × 100 mL). The combined ethereal extracts were dried (Na_2SO_4), filtered, and evaporated to give a colorless oil (22.8 g). This crude alcohol was dissolved in dichloromethane (120 mL) and dichloroacetic acid (2.5 mL) was added. The solution was stirred at room temperature for 2 h, washed with saturated sodium hydrogen carbonate solution (100 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on flash silica using 5% ethyl acetate in hexane as eluent to give 2-methoxy-5-methylenedibenzo[a,d]cycloheptene (**16e**) (12.95 g, 65%) as a yellow solid, mp 131–133 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.8 (3 H, s, OCH_3), 5.21 (2 H, 2 d, J = 1.95 Hz, $=CH_2$), 6.75 (1 H, d, J = 11.8 Hz, 10-H or 11-H), 6.76 (1 H, d, J = 2.7 Hz, 1-H), 6.82 (1 H, d, J = 11.8 Hz, 11-H or 10-H), 6.90 (1 H, dd, J = 8.6 and 2.7 Hz, 3-H), and 7.23–7.40 (5 H, m, ArH); MS m/e 234 (M^+).

To a solution of **16e** (12.8 g, 0.055 mol) in anhydrous THF (50 mL), under an atmosphere of nitrogen, was added 9-borabicyclo[3.3.1]nonane (116 mL of a 0.5 M solution in THF), and the resulting mixture was heated under reflux for 3 h. After being cooled in an ice bath, the mixture was quenched by the slow addition of 2 N sodium hydroxide solution (150 mL) and 30% hydrogen peroxide (30 mL). The mixture was stirred vigorously at 0 °C for 45 min and then was allowed to warm to room temperature over a 2-h period and extracted with diethyl ether (3 × 200 mL). The combined ethereal extracts were washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on flash silica using 30% ethyl acetate in hexane as eluent to give 2-methoxy-5*H*-dibenzo[a,d]cycloheptene-5-methanol (**17e**) (10.9 g, 79%) as an oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.79 (2 H, d, J = 8.1 Hz, CH_2), 3.80 (3 H, s, OCH_3), 4.16 (1 H, t, J = 8.1 Hz, $CHCH_2$), 6.79 (1 H, d, J = 11.9 Hz, 10-H), 6.83 (1 H, d, J = 2.6 Hz, 1-H), 6.85 (1 H, d, J = 11.9 Hz, 11-H), 6.89 (1 H, dd, J = 8.3 and 2.6 Hz, 3-H), and 7.23–7.33 (5 H, m, Ar H); MS m/e (CI^+) 253 (M^+ + 1).

To a solution of **17e** (10.5 g, 0.042 mol) in dry dichloromethane (150 mL) were added *p*-toluenesulfonyl chloride (8.1 g, 0.042 mol), pyridine (6.6 g, 0.084 mol), and 4-(dimethylamino)pyridine (1 g). The reaction mixture was heated under reflux for 15 h, cooled, washed with water, then dried ($MgSO_4$), and evaporated. The residue was purified by flash silica chromatography using 15% ethyl acetate in hexane as eluent to give the corresponding tosylate **18e** (13.5 g, 79%) as an oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.44 (3 H, s, $ArCH_3$), 3.78 (3 H, s, OCH_3), 4.19–4.31 (3 H, *m*, $CHCH_2$), 6.58 (1 H, d, J = 11.9 Hz, 10-H or 11-H), 6.65 (1 H, d, J = 11.9 Hz, 11-H or 10-H), 6.68 (1 H, d, J = 2.7 Hz, 1-H), 6.85 (1 H, dd, J = 8.4 and 2.7 Hz, 3-H) and 7.16–7.42 (9 H, m, ArH); MS m/e 406 (M^+).

To a solution of **18e** (13.5 g, 0.033 mol) in glacial acetic acid (100 mL) was added anhydrous sodium acetate (5.6 g, 0.067 mol), and the mixture was heated under reflux for 15 h. The solvent was then removed under vacuum to leave a residue that was partitioned between water (120 mL) and dichloromethane (3 × 120 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated. The residue was dissolved in methanol (100 mL) and the vigorously stirred cooled (0 °C) solution treated with sufficient potassium hydroxide to give an apparent pH of 14. The mixture was warmed to room temperature, the solvent was removed, and the residue was partitioned between diethyl ether (3 × 100 mL) and water (100 mL). The ethereal layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography using flash silica with 10% ethyl acetate in hexane as eluent to give **20e** (1.6 g, 19%), mp 97–99 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.25 (1 H, dd, J = 13.8 and 10.0 Hz, $CH_AH_BCH_COH$), 3.39 (1 H, dd, J = 13.8 and 6.2 Hz, $CH_AH_BCH_COH$), 3.72 (3 H, s, OCH_3), 5.23 (1 H, dd, J = 10.0 and 6.2 Hz, $CH_AH_BCH_COH$), 6.61 (1 H, d, J = 2.7 Hz, 1-H), 6.70 (1 H, dd, J = 8.4 and 2.7 Hz, 3-H), 6.77 (1 H, d, J = 11.9 Hz, 11-H or 12-H), 6.87 (1 H, d, J = 11.9 Hz, 12-H or 11-H), 7.09–7.21 (3 H, m, ArH), 7.16 (1 H, dd, J = 8.5 and 2.7 Hz, 4-H), and 7.44 (1 H, dd, J = 8.6 and 2.6 Hz, 7-H); irradiation of H_B (δ 3.39) gave a NOE to the proton at δ 7.16, which is on the same ring as the methoxy group, and irradiation of H_C (δ 5.23) gave a NOE to the proton at δ 7.44, which is on the other aromatic ring; MS m/e 252 (M^+); IR ν_{max} 3400–3100 cm^{-1} (br, OH). Anal. Calcd for $C_{17}H_{16}O_2 \cdot 0.35H_2O$: C, 78.95; H, 6.51. Found: C, 78.77; H, 6.48. Further elution gave the primary alcohol **17e** (5.2 g, 62%).

The tosylates **18a–d,f** were synthesized from dibenzosuberenones **15a–d,f** by using the procedures described above for the preparation of **18e**. Compounds **18a–d** were solvolyzed as described for **18e** to give the following cyclooctenols **19** and **20** in the product ratios given in Scheme V.

1-Chloro-5,6-dihydrodibenzo[a,e]cycloocten-5-ol (19a), mp 158–160 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.12 (1 H, dd, J = 15.1 and 10.2 Hz, CH_AH_BCHOH), 3.63 (1 H, dd, J = 15.1 and 6.9 Hz, CH_AH_BCHOH), 5.57 (1 H, dd, J = 10.2 and 6.9 Hz, CH_AH_BCHOH), 6.74 and 7.03 (1 H, d, J = 11.9 Hz, ArCH=), and 7.07–7.46 (7 H, m, ArH); MS m/e 256 (M^+); IR ν_{max} 3350–3100 cm^{-1} (br, OH). Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.86; H, 5.10. Found: C, 74.53; H, 5.08.

1-Chloro-5,6-dihydrodibenzo[a,e]cycloocten-6-ol (20a), mp 144–146 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.39 (2 H, m, CH_2CHOH), 5.13 (1 H, m, CH_2CHOH), 6.77 and 7.02 (1 H, d, J = 11.9 Hz, ArCH=), and 7.07–7.38 (7 H, m, ArH); MS m/e 256 (M^+); IR ν_{max} 3180 cm^{-1} (br, OH). Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.86; H, 5.10. Found: C, 74.79; H, 5.20.

2-Chloro-5,6-dihydrodibenzo[a,e]cycloocten-5-ol (19b), mp 148–149 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.26 (1 H, dd, J = 14.0 and 9.9 Hz, CH_AH_BCHOH), 3.46 (1 H, dd, J = 14.0 and 6.3 Hz, CH_AH_BCHOH), 5.27 (1 H, dd, J = 9.9 and 6.3 Hz, CH_AH_BCHOH), 6.77 and 6.87 (1 H, d, J = 12.0 Hz, ArCH=), and 7.08–7.41 (7 H, m, ArH); MS m/e 258 and 256 (M^+); IR ν_{max} 3400–3100 cm^{-1} (br, OH). Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.86; H, 5.10. Found: C, 74.51; H, 5.14.

2-Chloro-5,6-dihydrodibenzo[a,e]cycloocten-6-ol (20b) (oil): ^{1}H NMR (360 mHz, $CDCl_3$) δ 3.27 (1 H, dd, J = 13.8 and 10.0 Hz, CH_AH_BCHOH), 3.41 (1 H, dd, J = 13.8 and 6.3 Hz, CH_AH_BCHOH), 5.25 (1 H, dd, J = 10.0 and 6.3 Hz, CH_AH_BCHOH), 6.75 and 6.90 (1 H, d, J = 12.0 Hz, ArCH=), and 7.07–7.44 (7 H, m, ArH); MS m/e 258 and 256 (M^+); IR ν_{max} 3400–3100 cm^{-1} (br, OH). Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.86, H, 5.10. Found: C, 74.65; H, 4.98.

2-Bromo-5,6-dihydrodibenzo[a,e]cycloocten-5-ol (19c), mp 148–151 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.26 (1 H, dd, J = 13.9 and 9.9 Hz, CH_AH_BCHOH), 3.46 (1 H, dd, J = 13.9 and 6.2 Hz, CH_AH_BCHOH), 5.24 (1 H, dd, J = 9.9 and 6.2 Hz, $CHOH$), 6.76 and 6.87 (1 H, d, J = 12.1 Hz, ArCH=), and 7.09–7.35 (7 H, m, ArH); MS m/e 302 and 300 (M^+); IR ν_{max} 3400–3100 cm^{-1} (OH). Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 63.71; H, 4.31.

2-Bromo-5,6-dihydrodibenzo[a,e]cycloocten-6-ol (20c) (oil): ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.25 (1 H, dd, J = 13.8 and 10.0 Hz, CH_AH_BCHOH), 3.40 (1 H, dd, J = 13.8 and 6.4 Hz, CH_AH_BCHOH), 5.26 (1 H, dd, J = 10.0 and 6.4 Hz, CH_AH_BCHOH), 6.75 and 6.90 (1 H, d, J = 12.1 Hz, ArCH=), and 7.08–7.45 (7 H, m, ArH); MS m/e 302 and 300 (M^+); IR ν_{max} 3475–3110 cm^{-1} (br, OH). Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 63.61; H, 4.29.

3-Bromo-5,6-dihydrodibenzo[a,e]cycloocten-5-ol (19d), mp 127–128 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.25 (1 H, dd, J =

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14.1 and 9.7 Hz, CH_AH_BCHOH), 3.48 (1 H, dd, J = 14.1 and 6.1 Hz, CH_AH_BCHOH), 5.26 (1 H, dd, J = 9.7 and 6.1 Hz, CH_AH_BCHOH), 6.75 and 6.85 (1 H, d, J = 12.3 Hz, ArCH=), 6.94–7.28 (6 H, m, ArH), and 7.63 (1 H, d, J = 2 Hz, 4-H); MS m/e 302 and 300 (M^+); IR ν_{max} 3420–3120 cm^{-1} (OH). Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 63.91; H, 4.31.

3-Bromo-5,6-dihydrodibenzo[*a*,*e*]cycloocten-6-ol (20d) (oil): ^1H NMR (360 MHz, $CDCl_3$) δ 3.26 (1 H, dd, J = 13.9 and 10.1 Hz, CH_AH_BCHOH), 3.42 (1 H, dd, J = 13.9 and 6.3 Hz, CH_AH_BCHOH), 5.27 (1 H, dd, J = 10.1 and 6.3 Hz, CH_AH_BCHOH), 6.73 and 6.89 (1 H, d, J = 12.3 Hz, ArCH=), and 6.93–7.41 (7 H, m, ArH); MS m/e 302 and 300 (M^+): IR ν_{max} 3400–3100 cm^{-1} (OH). Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 63.90; H, 4.39.

10-Methyl-5-methylene-5*H*-dibenzo[*a*,*d*]cycloheptene (16f). To a cooled (0 °C) solution of 10-methyl-5-oxodibenzo[*a*,*d*]cycloheptene (**15f**, 41 g, 0.187 mol) in anhydrous diethyl ether (400 mL) under an atmosphere of nitrogen was added a solution of methyllithium (160 mL of a 1.4 M solution in diethyl ether, 0.224 mol), and the resulting mixture was stirred at 0 °C for 0.75 h. Saturated ammonium sulfate solution (150 mL) was then added cautiously, and the organic layer was separated and washed successively with water (200 mL) and brine (200 mL), then dried (Na_2SO_4), and evaporated in vacuo to give crude tertiary alcohol (47 g) as an oil. To a solution of this alcohol (47 g) in dichloromethane (350 mL) was added dichloroacetic acid (2 mL), and the resulting mixture was heated at reflux for 72 h. The reaction mixture was cooled, then successively washed with saturated sodium bicarbonate solution (200 mL) and brine (200 mL), dried (Na_2SO_4), and evaporated in vacuo to give a residue, which was chromatographed on silica gel using petroleum ether (bp 60–80 °C) as eluent to give the title compound as colorless crystals (32.7 g, 80%), mp 59–60 °C: ^1H NMR (360 MHz, $CDCl_3$) δ 2.40 (3 H, d, J = 1.3 Hz, CH_3), 5.23 (1 H, d, J = 1.7 Hz, C=CH_AH_B), 5.24 (1 H, d, J = 1.7 Hz, C=CH_AH_B), 6.86 (1 H, br s, CH_3C=CH), 7.20–7.36 (7 H, m, ArH), and 7.45–7.48 (1 H, m, ArH); MS m/e 218 (M^+). Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.62; H, 6.50.

10-Methyl-5-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-5*H*-dibenzo[*a*,*e*]cycloheptene (18f). The olefin **16f** (32 g, 0.147 mol) was converted to the alcohol and tosylated [as described above for compound **16e**] to give the title compound (52 g, 91%), mp 95–97 °C: ^1H NMR (360 MHz, $CDCl_3$) δ 2.22 (3 H, d, J = 1.3 Hz, CH_3C=CH), 2.42 (3 H, s, $ArCH_3$), 4.24–4.31 (3 H, m, $CHCH_2OSO_2Ar$), 6.63 (1 H, br s, CH_3C=CH), and 7.10–7.45 (12 H, m, ArH); MS m/e 290 (M^+). Anal. Calcd for $C_{24}H_{22}O_3S$: C, 73.82; H, 5.68. Found: C, 73.78; H, 5.74.

10-Methylene-5,11-methano-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene (21). To a solution of the tosylate **18f** (51.3 g, 0.131 mol) in glacial acetic acid (500 mL) was added anhydrous sodium acetate (21.6 g, 0.263 mol), and the resulting mixture was heated at reflux for 5 h and then allowed to stand at room temperature for 60 h. The mixture was concentrated in vacuo and the residue was dissolved in methanol (500 mL) and then cooled in ice. Sufficient sodium hydroxide to give a pH of 14 was then added and the mixture was stirred at room temperature for 1 h. The methanol was removed under vacuum, and the residue was suspended in water (500 mL) and extracted with diethyl ether (2 × 300 mL). The combined extracts were washed with brine (200 mL), dried ($MgSO_4$), and evaporated to give an oil, which was purified by chromatography using dichloromethane as eluent to give the title compound as an oil (18 g, 63%): ^1H NMR (360 MHz, $CDCl_3$) δ 2.31 (1 H, d, J = 10.5 Hz, $CH_ACH_BH_CCH_D$), 2.57–2.63 (1 H, m, $CH_ACH_BH_CCH_D$), 3.99 (2 H, d, J = 4.5 Hz, $CH_ACH_BH_CCH_D$), 5.15 (1 H, s, CH_EH_F=C), 5.43 (1 H, s, CH_EH_F=C), 7.02–7.18 (6 H, m, ArH), 7.30 (1 H, dd, J = 7.3 and 1.4 Hz, ArH), and 7.57 (1 H, m, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 43.62 ($CHCH_2CH$), 48.39 ($CHCH_2CH$), 50.97 ($CHCH_2CH$), 105.05 (=CH_2), 121.81, 123.21, 124.63, 125.81, 126.52 (two carbons), 127.88 (non-fused ArC) and 130.56, 141.45, 143.92, 144.36, 148.99 (fused ArC and =C=); exact mass found 218.1076, $C_{17}H_{14}$ requires 218.1096.

5-Methyl-5,6-dihydrodibenzo[*a*,*e*]cycloocten-5-ol (9). Methyllithium (40 mL of a 1.4 M solution in hexane) was added to an ice-cooled solution of 5-oxo-5,6-dihydrodibenzo[*a*,*e*]cyclooctene[16] (10 g, 0.045 mol) in diethyl ether (300 mL) over a 5-min period. After the addition was completed, the reaction mixture was stirred for 10 min at room temperature, then cooled to 0 °C, and quenched by the cautious addition of water (100 mL). The aqueous layer was discarded and the organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was recrystallized from diethyl ether/hexane to give the alcohol **9** (6.2 g, 58%) as a colorless solid, mp 108–109 °C: ^1H NMR (360 MHz, $CDCl_3$) δ 1.50 (3 H, s, CH_3), 2.40 (1 H, br s, OH), 2.94 (1 H, d, J = 13.5 Hz, CH_AH_B), 3.81 (1 H, d, J = 13.5 Hz, CH_AH_B), 6.71 (2 H, d, J = 12.1 Hz, ArCH=), and 7.11–7.84 (8 H, m, ArH); MS m/e 236 (M^+). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.31; H, 6.88.

13-Hydroxy-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine (30). The carbinol **9** (0.9 g, 0.0038 mol) was added to a rapidly stirred suspension of hydroxylamine hydrochloride (2.64 g, 0.038 mol) and anhydrous sodium acetate (3.11 g, 0.038 mol) in dichloromethane (25 mL). The slurry was heated under reflux and dichloroacetic acid (8 mL) in dichloromethane (50 mL) was added over a 10-min period. The reaction mixture was heated under reflux for an additional 2 h and then allowed to cool, and sodium hydroxide solution (2 M, 60 mL) was added. The organic layer was separated and washed successively with water and brine, then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexane to give the title compound as a mixture of atropisomers (0.37 g, 39%), mp 159–163 °C: ^1H NMR (major atropisomer, 360 MHz, $CDCl_3$) δ 1.66 (3 H, s, CH_3), 2.41 (1 H, d, J = 15.8 Hz, 6-H_{eq}), 2.62 (1 H, dd, J = 16.0 and 5.5 Hz, 11-H_{eq}), 4.15 (1 H, d, J = 15.8 Hz, 6-H_{ax}), 4.24 (1 H, d, J = 16.0 Hz, 11-H_{ax}), 4.67 (1 H, d, J = 5.5 Hz, 12-H), and 6.73–7.06 (8 H, m, ArH); ^1H NMR (minor atropisomer) δ 1.78 (3 H, s, CH_3), 2.88 and 3.44 (2 H, d, J = 15.5 Hz, 6-H_{ax} and 6-H_{eq}), 3.10 (1 H, dd, J = 15.8 and 6.7 Hz, 11-H_{eq}), 3.58 (1 H, d, J = 15.8 Hz, 11-H_{ax}), and 4.77 (1 H, d, J = 6.7 Hz, 12-H); MS m/e 251 (M^+). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.06; H, 6.86; N, 5.54. The residue from the recrystallization was chromatographed on flash silica using 10% ethyl acetate in hexane as eluent to give **5-methylene-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten (29)** as a colorless oil (0.4 g, 48%): ^1H NMR (360 MHz, $CDCl_3$) δ 3.90 (2 H, br s, CH_2), 5.17 (2 H, m, C=CH_2), 6.73 and 6.84 (1 H, d, J = 12.5 Hz, ArCH=), and 7.05–7.38 (8 H, m, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 42.73 (CH_2), 115.14 (C=CH_2), 126.00, 126.94, 127.02, 127.41, 128.32, 128.83, 128.87, 130.42, 130.83, 133.29 (non-fused ArC and ArCH), 135.09, 137.35, 139.49 and 139.66 (fused ArC and C=CH_2); exact mass found 218.1091, $C_{17}H_{14}$ requires 218.1096. Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.61; H, 6.49.

5-Methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine (2). The hydroxylamine **30** (0.2 g, 0.8 mmol) was dissolved in glacial acetic acid (3 mL) and zinc dust (0.5 g) was added. The suspension was heated with stirring at 68 °C for 14 h; then the reaction mixture was filtered and the solvent was removed by evaporation. The residue was partitioned between diethyl ether (10 mL) and 1 N sodium hydroxide solution (10 mL) and the organic layer was washed successively with water and brine, dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized from *n*-hexane to give **2** (0.11 g, 58%) as a colorless solid, mp 125–126 °C: ^1H NMR (360 MHz, $CDCl_3$) δ 1.68 (3 H, s, CH_3), 2.43 (1 H, br s, NH), 2.95 (1 H, d, J = 15.5 Hz, 6-H_{eq}), 3.11 (1 H, dd, J = 15.8 and 5.3 Hz, 11-H_{eq}), 3.50 (1 H, d, J = 15.5 Hz, 6-H_{ax}), 3.53 (1 H, d, J = 15.8 Hz, 11-H_{ax}), 4.61 (1 H, d, J = 5.3 Hz, 12-H), and 6.79–7.25 (8 H, m, ArH); irradiation of the methyl group (δ 1.68) and 12-H (δ 4.61) gave NOE's to only one of the two aromatic 4 spin systems assigned previously by COSY analysis thereby identifying the [4.2.1] ring system; MS m/e 235 (M^+), 212, 144, 131 (100), 130, 103, 77. Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.59; H, 7.28; N, 6.05.

9-Methoxydibenzo[*a*,*e*]cycloocten-5(6*H*)-one (34e). To a solution of the alcohol **20e** (1.5 g, 0.006 mol) in dry dichloromethane was added crushed 4A molecular sieves (2.3 g), with rapid stirring. After 5 min pyridinium dichromate (4.5 g, 0.012 mol) was added to the suspension and stirring was continued at room temperature for 2 h. Diethyl ether (200 mL) was added and the reaction mixture was filtered through a plug of Celite. The solvent was removed under vacuum and the residue obtained was purified by chromatography on flash silica gel using 5% ethyl acetate in hexane as eluent to give the title compound (1.4 g, 94%) as

colorless needle-shaped crystals, mp 104–106 °C: ^{1}H NMR (360 MHz, $CDCl_3$) 3.75 (3 H, s, CH_3O), 3.99 (2 H, s, CH_2), 5.73 (1 H, d, J = 2.7 Hz, 1-H), 6.86 (1 H, dd, J = 8.5 and 2.7 Hz, 3-H), 7.01 (2 H, s, ArCH=), 7.29–7.51 (4 H, m, ArH), and 8.24 (1 H, dd, J = 8.0 and 1.4 Hz, 7-H); MS m/e 250 (M^+); IR ν_{max} (Nujol) 1665 cm^{-1} (CO). Anal. Calcd for $C_{17}H_{14}O_2 \cdot 0.1H_2O$: C, 80.99; H, 5.68. Found: C, 80.97; H, 5.78.

The alcohols **19a–d** and **20b–d** were oxidized as described for **20e** to give the following ketones.

1-Chlorodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (33a), mp 151–153 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.09 (2 H, s, CH_2), 7.06 and 7.20 (1 H, d, J = 11.9 Hz, ArCH=), 7.18–7.30 (5 H, m, ArH), 7.50 (1 H, dd, J = 7.8 and 1.4 Hz, 2-H), and 7.86 (1 H, dd, J = 8.0 and 1.3 Hz, 4-H); MS m/e 254 (M^+); IR ν_{max} (Nujol) 1670 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.10; H, 4.57.

2-Chlorodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (33b) (as an oil): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.04 (2 H, s, CH_2), 6.93 and 7.10 (1 H, d, J = 12.9 Hz, ArCH=), 7.22–7.42 (6 H, m, ArH), and 8.17 (1 H, d, J = 8.4 Hz, H-4); MS m/e 256 and 254 (M^+); IR ν_{max} (oil) 1680 cm^{-1} (br, CO). Anal. Calcd for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.19; H, 4.38.

2-Bromodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (33c), mp 121–123 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.03 (2 H, s, CH_2), 6.92 and 7.09 (H, d, J = 12.8 Hz, ArCH=), 7.20–7.56 (6 H, m, ArH), and 8.08 (1 H, d, J = 8.5 Hz, 4-H); MS m/e 300 and 298 (M^+); IR ν_{max} (Nujol) 1680 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.21; H, 3.69.

3-Bromodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (33d) (as an oil): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.04 (2 H, s, CH_2), 6.95 and 7.09 (H, d, J = 12.8 Hz, ArCH=), 7.22–7.59 (6 H, m, ArH), and 8.36 (1 H, d, J = 2.2 Hz, 4-H); MS m/e 300 and 298 (M^+); IR ν_{max} (oil) 1675 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.51; H, 4.01.

9-Chlorodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (34b) (as an oil): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.03 (2 H, s, CH_2), 6.96 and 7.06 (1 H, d, J = 12.8 Hz, ArCH=), 7.23–7.53 (6 H, m, ArH), and 8.22 (1 H, d, J = 7.9 Hz, 5-H); MS m/e 256 and 254 (M^+); IR ν_{max} (Nujol) 1675 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.21; H, 4.40.

9-Bromodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (34c), mp 147–150 °C: ^{1}H NMR (360 MHz, $CDCl_3$) 4.01 (2 H, s, CH_2), 6.96 and 7.06 (1 H, d, J = 17.7 Hz, ArCH=), 7.25–7.52 (6 H, m, ArH), and 8.21 (1 H, d, J = 8.0 Hz, 5-H); MS m/e 298 and 300 (M^+); IR ν_{max} (Nujol) 1680 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 63.98; H, 3.49.

8-Bromodibenzo[*a*,*e*]cycloocten-5(6*H*)-one (34d) (as an oil): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.04 (2 H, s, CH_2), 6.95 and 7.08 (1 H, d, J = 12.8 Hz, ArCH=), 7.23–7.53 (6 H, m, ArH), and 8.19 (1 H, d, J = 8.2 Hz, 5-H); MS m/e 300 and 298 (M^+); IR ν_{max} (oil) 1680 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.04; H, 3.51.

The following bicyclic imines **35–42** were prepared in the same way as described by **2**, by starting from the appropriate dibenzo[*a*,*e*]cycloocten-5-one (**33a–d** and **34b–d**).

1-Chloro-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (35), mp 196–198 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.91 (3 H, s, CH_3), 3.09 (1 H, d, J = 16.4 Hz, 6-H_{eq}), 3.35 (1 H, dd, J = 16.7 and 5.1 Hz, 11-H_{eq}), 3.78 (1 H, d, J = 16.7 Hz, 11-H_{ax}), 3.95 (1 H, d, J = 16.4 Hz, 6-H_{ax}), 5.26 (1 H, d, J = 5.1 Hz, 12-H), and 6.87–7.24 (7 H, m, ArH); irradiation of 12-H (δ 5.26) gave no NOE to the aromatic region but irradiation of 11-H_{eq} (δ 3.35) did give a NOE to the aromatic region; MS m/e 269 (M^+); exact mass found 269.0968, $C_{17}H_{16}ClN$ requires 269.0971. Anal. Calcd for $C_{17}H_{16}ClN \cdot HCl \cdot 0.6H_2O$: C, 64.40; H, 5.79; N, 4.42. Found: C, 64.34; H, 5.62; N, 4.34.

2-Chloro-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (36), mp 187–191 °C: ^{1}H NMR (360 MHz, DMSO) 1.89 (3 H, s, CH_3), 3.09 (1 H, d, J = 16.5 Hz, 6-H_{eq}), 3.27 (1 H, dd, J = 16.7 and 4.9 Hz, 11-H_{eq}), 3.73 (1 H, d, J = 16.7 Hz, 11-H_{ax}), 3.89 (1 H, d, J = 16.5 Hz, 6-H_{ax}), 5.22 (1 H, d, J = 4.9 Hz, 12-H), 6.90–6.97 (4 H, m, ArH), 7.23–7.27 (2 H, m, 3-H and 4-H), and 7.37 (1 H, s, H-1); NOE's were observed from 1-H to 12-H and from CH_3 to H-4; MS m/e 271 and 269 (M^+); exact mass found 269.0999, $C_{17}H_{16}NCl$ requires 269.09712. Anal. Calcd for $C_{17}H_{16}ClN \cdot 2HCl$: C, 59.58; H, 5.29; N, 4.09. Found: C, 59.90; H, 5.24; N, 4.00.

2-Bromo-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (37), mp 172–175 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.87 (3 H, s, CH_3), 3.11 (1 H, d, J = 16.4 Hz, 6-H_{eq}), 3.25 (1 H, dd, J = 16.7 and 5.0 Hz, 11-H_{eq}), 3.69 (1 H, d, J = 16.7 Hz, 11-H_{ax}), 3.84 (1 H, d, J = 16.4 Hz, 6-H_{ax}), 5.16 (1 H, d, J = 5.0 Hz, 12-H), 6.88–6.98 (4 H, m, ArH), 7.19 (1 H, d, J = 8.1 Hz, H-4), 7.37 (1 H, dd, J = 8.1 and 1.8 Hz, H-3), and 7.51 (1 H, d, J = 1.8 Hz, H-1); NOE's were observed from CH_3 to H-4 and from H-1 to H-12; MS m/e 313 (M^+); exact mass found 313.0427, $C_{17}H_{16}NBr$ requires 313.04661. Anal. Calcd for $C_{17}H_{16}BrN \cdot 2HCl$: C, 52.74; H, 4.69; N, 3.62. Found: C, 52.89; H, 4.49; N, 3.56.

3-Bromo-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (38), mp 186–189 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.89 (3 H, s, CH_3), 3.13 (1 H, d, J = 16.5 Hz, 6-H_{eq}), 3.30 (1 H, dd, J = 16.6 and 5.0 Hz, 11-H_{eq}), 3.68 (1 H, d, J = 16.6 Hz, 11-H_{ax}), 3.82 (1 H, d, J = 16.5 Hz, 6-H_{ax}), 5.19 (1 H, d, J = 5.0 Hz, 12-H), 6.90–7.00 (4 H, m, ArH), 7.22 (1 H, d, J = 8.0 Hz, 1-H), 7.36 (1 H, dd, J = 8.0 and 1.7 Hz, 2-H), and 7.51 (1 H, d, J = 1.7 Hz, 4-H); NOE's were observed from CH_3 to 4-H and from 1-H to 12-H; MS m/e 313 (M^+); exact mass found 313.0464, $C_{17}H_{16}BrN$ requires 313.04661. Anal. Calcd for $C_{17}H_{16}BrN \cdot 2.3HCl$: C, 51.29; H, 4.63; N, 3.52. Found: C, 51.03; H, 4.57; N. 3.5.

9-Chloro-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (39), mp 174–176 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.89 (3 H, s, CH_3), 3.14 (1 H, d, J = 16.5 Hz, 6-H_{eq}), 3.34 (1 H, dd, J = 16.8 and 6.1 Hz, 11-H_{eq}), 3.70 (1 H, d, J = 16.8 Hz, 11-H_{ax}), 3.84 (1 H, d, J = 16.5 Hz, 6-H_{ax}), 5.20 (1 H, d, J = 6.1 Hz, 12-H), 6.90 (1 H, d, J = 8.2 Hz, H-7), 6.99 (1H, dd, J = 8.1 and 2.1 Hz, H-8), 7.04 (1 H, d, J = 2.1 Hz, H-10), and 7.17–7.27 (4 H, m, ArH); NOE's were observed from CH_3 and from 12-H to the aromatic protons on the unsubstituted ring; MS m/e 269 (M^+); exact mass found 269.0987, $C_{17}H_{16}NCl$ requires 269.09712. Anal. Calcd for $C_{17}H_{16}ClN \cdot HCl \cdot 0.5H_2O$: C, 64.77; H, 5.76; N, 4.44. Found: C, 64.72; H, 5.69; N, 4.41.

9-Bromo-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (40), mp 189–191 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.88 (3 H, s, CH_3), 3.12 (1 H, d, J = 16.5 Hz, 6-H_{eq}), 3.36 (1 H, dd, J = 16.7 and 5.9 Hz, 11-H_{eq}), 3.72 (1 H, d, J = 16.7 Hz, 11-H_{ax}), 3.83 (1 H, d, J = 16.5 Hz, 6-H_{ax}), 5.19 (1 H, d, J = 5.9 Hz, 12-H), 6.84 (1 H, d, J = 8.1 Hz, 7-H), 7.12 (1 H, dd, J = 8.1 and 2.0 Hz, 8-H), and 7.17–7.42 (5 H, m, ArH); NOE's were observed from CH_3 and from 12-H to the aromatic protons on the unsubstituted ring and from 7-H to 6-H_{eq}; MS m/e 313 (M^+); exact mass found 313.0454, $C_{17}H_{16}NBr$ requires 313.04661. Anal. Calcd for $C_{17}H_{16}BrN \cdot 2.7HCl$: C, 49.48; H, 4.57; N, 3.39. Found: C, 49.50; H, 4.26; N, 3.36.

8-Bromo-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (41), mp 274 °C: ^{1}H NMR (360 MHz, DMSO) δ 2.15 (3 H, s, CH_3), 2.86 (1 H, d, J = 16.5 Hz, 6-H_{eq}), 3.16 (1 H, dd, J = 16.8 and 5.2 Hz, 11-H_{eq}), 4.12 (1 H, d, J = 16.8 Hz, 11-H_{ax}), 4.32 (1 H, d, J = 16.5 Hz, 6-H_{ax}), 5.30 (1 H, d, J = 5.2 Hz, 12-H), 6.73 (1 H, d, J = 8.1 Hz, H-10), 6.96 (1 H, d, J = 1.9 Hz, H-7), and 7.03–7.21 (5 H, m, ArH); irradiation of 11-H_{ax} gave a NOE to H-10 and irradiation of 6-H_{ax} gave a NOE to H-7; MS m/e 313 (M^+); exact mass found 313.0442, $C_{17}H_{16}NBr$ requires 313.04661. Anal. Calcd for $C_{17}H_{16}BrN \cdot HCl \cdot 0.5H_2O$: C, 56.77; H, 5.04; N, 3.89. Found: C, 56.91; H, 5.03; H, 3.88.

9-Methoxy-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine hydrochloride (42), mp 229–231 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.87 (3 H, s, CH_3), 3.04 (1 H, d, J = 16.4 Hz, 6-H_{eq}), 3.24 (1 H, dd, J = 16.8 and 5.2 Hz, 11-H_{eq}), 3.60 (3 H, s, OCH_3), 3.68 (1 H, d, J = 16.8 Hz, 11-H_{ax}), 3.76 (1 H, d, J = 16.4 Hz, 6-H_{ax}), 5.15 (1 H, d, J = 5.2 Hz, 12-H), 6.49 (2 H, m, 8-H and 10-H), 6.79 (1 H, d, J = 8.7 Hz, 7-H), and 7.16–7.26 (4 H, m, ArH); irradiation of 7-H gave a NOE to 6-H_{eq} and irradiation of the 8-H and 10-H multiplet gave a NOE to 11-H_{eq}; MS m/e 265 (M^+); exact mass found 265.1444, $C_{18}H_{19}NO$ requires 265.1466. Anal. Calcd for $C_{18}H_{19}NO \cdot HCl \cdot 0.3H_2O$: C, 70.37; H, 6.76; N, 4.56. Found: C, 70.31; H, 6.70; N, 4.50.

5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine Hydrochloride (46). To a solution of the oxime **43**[16] (0.25 g) and methyl orange (0.003 g) in dry methanol (20 mL) was added sodium cyanoborohydride (0.132 g). A solution of concentrated

hydrochloric acid (250 μL) in methanol (3 mL) was added dropwise, with the pH of the reaction mixture being maintained between 3 and 4. After the addition was complete, stirring was continued for a further 2 h at room temperature. This addition procedure was repeated three times, using a total of 0.53 g of sodium cyanoborohydride and 1 mL of concentrated hydrochloric acid in methanol (12 mL). After being stirred for 14 h at room temperature following the final addition, the reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL) and then a 1 N sodium hydroxide solution was added until a pH of 14 was attained. The organic layer was separated and the aqueous solution was extracted with a further portion of ethyl acetate (150 mL). The organic layers were combined, washed with water (100 mL) and brine (100 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo to leave a residue, which by NMR spectroscopy (360 MHz, $CDCl_3$) was a 1:1 mixture of the hydroxylamine **44** and the hydroxy imine **45**; signals for **44** were identified at δ 3.31 (2 H, apparent d, J = 8.9 Hz, CH_2) and 4.55 (1 H, apparent t, J = 8.9 Hz, CH). The mixture was heated in *m*-xylene (10 mL) at 130 °C for 10 min and the solvent removed by evaporation to leave a residue, which was partially purified by chromatography on silica gel using 30% ethyl acetate in hexane as eluant to give the hydroxy imine **45** (0.165 g, 66%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.09 (2 H, dd, J = 16.0 and 6.9 Hz, 6- and 11-H_{eq}), 3.53 (2 H, d, J = 16.0 Hz, 6- and 11-H_{ax}), 4.75 (2 H, d, J = 6.9 Hz, 5- and 12-H), 6.82–6.90 (4 H, m, ArH), and 7.02–7.13 (4 H, m, ArH). This hydroxy imine was dissolved in glacial acetic acid (5 mL), zinc dust (0.165 g) was added, and the suspension was heated at 60 °C for 8 h. After being cooled to room temperature, the reaction mixture was filtered, then adjusted to pH 12 by the addition of 1 N sodium hydroxide solution, and extracted into ethyl acetate (2 × 75 mL). The combined organic layers were washed with water (1 × 100 mL) and brine (1 × 100 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using 10% methanol in dichloromethane as eluant to give an oil, which was treated with a solution of saturated hydrochloric acid in ethyl acetate (1 mL) to yield the title compound **46** as a colorless solid (0.045 g, 25%), mp >290 °C: ^{1}H NMR (360 MHz, DMSO) δ 3.25 (2 H, dd, J = 16.8 and 5.5 Hz, 6- and 11-H_{eq}), 3.82 (2 H, d, J = 16.8 Hz, 6- and 11-H_{ax}), 5.22 (2 H, d, J = 5.5 Hz, 5- and 12-H), 6.92 (4 H, s, ArH), 7.13–7.17 (2 H, dd, J = 5.5 and 3.2 Hz, 2-H and 3-H), and 7.25–7.28 (2 H, dd, J = 5.5 and 3.2 Hz, 1-H and 4-H); irradiation of 1-H and 4-H gave a NOE to 5-H and 12-H and to 2-H and 3-H; irradiation of 2-H and 3-H gave a NOE to 1-H and 4-H; MS m/e (CI^+) 222 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{15}N\cdot HCl\cdot 0.35H_2O$: C, 72.77; H, 6.37; N, 5.30. Found: C, 72.85; H, 6.35; N, 5.20.

***N*-Methoxy-5-methyl-5,6-dihydrodibenzo[*a*,*e*]cyclooctene-5-amine (47).** To a stirred, cooled (0 °C) solution of dichloroacetic acid (19.4 g, 0.15 mol) in dry dichloromethane (25 mL) was added anhydrous sodium acetate (8.2 g, 0.10 mol). The mixture was stirred until a clear solution was obtained; then further dichloromethane (15 mL) and methoxyamine hydrochloride (8.35 g, 0.10 mol) were added. After 0.5 h, the alcohol **9** (2.36 g, 0.010 mol) was added and the mixture stirred at room temperature for 4 h. The mixture was cooled (0 °C) and aqueous sodium hydroxide (2 M) added until an apparent pH of 12 was obtained. The organic layer was separated, washed with water, dried, and evaporated to leave a residue, which was chromatographed on silica gel using 20% ethyl acetate in hexane as eluant to give the title compound (2.21 g, 83%), mp 48–50 °C: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.50 (3 H, s, CH_3), 3.35 (2 H, d, CH_2), 3.60 (3 H, s, OCH_3), 5.60 (1 H, br s, NH), and 6.60–8.0 (10 H, m, CH and ArH); MS m/e 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO\cdot 0.1H_2O$: C, 80.92; H, 7.24; N, 5.24. Found: C, 80.80; H, 7.27; N, 4.98.

13-Methoxy-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene-5,12-imine (48). To a solution of the methoxyamine **47** (1.90 g, 0.0072 mol) in toluene containing 10% dimethyl sulfoxide (20 mL) was added potassium *tert*-butoxide (0.805 g, 0.0071 mol). The stirred suspension was warmed to 55 °C under an atmosphere of nitrogen and after 3 min was cooled to 0 °C and diluted with an equal volume of diethyl ether. The solution was washed with water (3 × 20 mL), dried, and evaporated to leave a residue, which crystallized from diethyl ether/hexane to give the title compound as a mixture of atropisomers (1.28 g, 67%), mp 85–88 °C: ^{1}H NMR (atropisomer A, 360 MHz, $CDCl_3$) δ 1.65 (3 H, s, CH_3), 2.42 (1 H, d, J = 15.8 Hz, 6-H_{eq}), 2.59 (1 H, dd, J = 15.8 and 5.2 Hz, 11-H_{eq}), 3.75 (3 H, s, OCH_3), 4.08 (1 H, d, J = 15.8 Hz, 6-H_{ax}), 4.10 (1 H, d, J = 15.8 Hz, 11-H_{ax}), 4.78 (1 H, d, J = 5.2 Hz, 12-H), and 6.7–7.1 (8 H, m, ArH); ^{1}H NMR (atropisomer B) δ 1.76 (3 H, s, CH_3), 2.84 (1 H, d, J = 15.4 Hz, 6-H_{eq}), 3.10 (1 H, dd, J = 15.4 and 7.3 Hz, 11-H_{eq}), 3.43 (1 H, d, J = 15.3 Hz, 6-H_{ax}), 3.52 (1 H, d, J = 15.4, 11-H_{ax}), 3.65 (3 H, s, OCH_3), and 4.71 (1 H, d, J = 7.3 Hz, 12-H); MS m/e 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.27; H, 7.21; N, 5.31. Reduction of **48** using zinc in acetic acid as described above gave compound **2**, identical in all respects with the sample obtained from **30**.

2,3:6,7-Dibenzo-1-methyl-9-azatricyclo[3.3.1.0^{8,9}]nona-2,6-diene (49). To a solution of the methoxyamine **47** (0.5 g, 0.0019 mol) in dry tetrahydrofuran (15 mL) at −78 °C under an atmosphere of nitrogen was added, dropwise, *n*-butyllithium (1.18 mL of a 1.6 M solution of hexane, 0.0019 mol). After the addition was complete the reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to ambient temperature over a period of 1 h. The reaction mixture was quenched with water (15 mL) and the separated organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue obtained was purified by chromatography on silica gel with 10% ethyl acetate in hexane as eluant to give the methoxy imine **48** (0.28 g, 56%) and the title compound **49** (0.04 g, 9%), mp 132 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.64 (3 H, s, CH_3), 2.69 (1 H, d, J = 15.6 Hz, 8-H_{eq}), 3.36 (1 H, d, J = 15.6 Hz, 8-H_{ax}), 3.43 (1 H, d, J = 5.3 Hz, 4-H or 5-H), 3.75 (1 H, d, J = 5.3 Hz, 5-H or 4-H), and 6.86–7.17 (8 H, m, ArH); MS m/e 233 (M^+); exact mass found 233.1189, $C_{17}H_{15}N$ requires 233.1204. Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.72; H, 6.28; N, 5.90.

12-Butyl-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,12-imine (52). To a stirred cooled (−78 °C) solution of the methoxy imine **48** (0.132 g, 0.50 mmol) in anhydrous diethyl ether (3 mL) under a nitrogen atmosphere was added a solution of *n*-butyllithium in hexane (0.33 mL of a 1.47 M solution, 0.50 mmol). The solution was warmed to room temperature, after 4 h water (2 mL) was added cautiously, and the organic layer was removed, dried, and evaporated. The residue was chromatographed on silica gel using 20% ethyl acetate in hexane as eluant to give the title compound as a colorless oil (46 mg, 31%). The oil was dissolved in ethyl acetate and a 5 M solution of hydrogen chloride in ethyl acetate (0.5 mL) was added. The solution was evaporated and the residue crystallized from ether to give the hydrochloride salt (45 mg), mp 230–4 °C: ^{1}H NMR (360 MHz, DMSO) δ 1.00 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.44 (2 H, q, J = 7.3 Hz, CH_2CH_3), 1.67 (2 H, m, $CH_2CH_2CH_3$), 1.91 (3 H, s, CH_3), 2.00 (1 H, m, $CH_AH_BCH_2CH_2CH_3$), 2.46 (1 H, m, $CH_AH_BCH_2CH_2CH_3$), 3.04 (2 H, d, J = 16.2 Hz, 6-H_{eq} and 11-H_{eq}), 3.79 (1 H, d, J = 16.2 Hz, 6-H_{ax}), 3.91 (1 H, d, J = 16.2 Hz, 11-H_{ax}), and 6.83–7.2 (8 H, m, ArH); MS m/e 291 (M^+). Anal. Calcd for $C_{21}H_{25}N\cdot HCl$: C, 76.92; H, 7.99; N, 4.27. Found: C, 76.75; H, 7.98; N, 4.17.

Conformational Study of Alcohols 4, 5, 8, and 9. NMR spectra were acquired with a Bruker AM360 instrument fitted with a BVT1000 variable temperature unit and measured temperatures are uncorrected. Internuclear distance ratios for the substituted cyclooctene **9** were obtained from transient NOE measurements by using a selective inversion–recovery technique.[28] The double-bond protons were assigned by using COSY and NOE methods. Coupling constants were measured between H5 and both H6 (anti) and H6 (syn) for the hydroxycyclooctene **8** and NOE used to assign the proton spectrum.

The coalescence temperatures for the cycloheptenes **4** and **5** were found to be 260 K and 300 K, respectively. Line widths gave rate constants of 133 s^{-1} and 8.9 s^{-1} and thus ΔG_c of 13.03 and 16.04 kcal/mol.[29] Coalescence temperatures for the cyclooctenes **8** and **9** were estimated as 165 K (by extrapolation) and ≪160 K, respectively.

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The conformers of all four compounds were modeled by using Moledit/Optimol.[30] The interatomic distances obtained for the conformers of cyclooctene **9** by modeling were compared to experimental distances derived from transient NOE methods and were found to be in good agreement for the equatorial hydroxy conformer (R = 0.957) but much less so for the axial hydroxy conformer (R = 0.482). This indicates that the equatorial hydroxy, axial methyl conformer of cyclooctene **9** predominates in solution, which is consistent with calculated energies of 29.9 kcal/mol (equatorial OH) and 33 kcal/mol (axial OH), although variable temperature studies show that interconversion between conformers is very facile (fast exchange regime at 300 K). The axial hydroxy conformer of cyclooctene 8 was indicated as the major conformer by the observation of a strong NOE between H5 and H4, and comparison of calculated and measured coupling constants for this conformer [$J_{H5,H6(syn)}$ = 10.1 Hz (obsd), 9.2 (calcd); $J_{H5,H6(anti)}$ = 6.2 Hz (obsd), 7.3 (calcd)]. This is in agreement with the energies calculated for the axial OH and the two possible skewed equatorial OH conformers of 8, which are 28.04, 29.41, and 30.1 kcal/mol, respectively, but interconversion between conformers is again rapid at 300 K. Interconversion between the conformers of the cycloheptenes **4** and **5** was also rapid at 300 K, and no conformational preference was observed. In dibenzo[a,d]cycloheptenes possessing bulkier 5-substituents, the axial conformer is favored.[31]

In conclusion, it is unlikely that conformation plays a significant role in determining the relative reactivities of the hydroxylamines **6** (X = OH), **28**, and **44** since, despite the strong bias observed in the conformational populations of the corresponding cyclooctenes **8** and **9**, conformational interconversion is not a rate limiting factor at relevant temperatures.

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Registry No. **1**, 70449-94-4; **2**, 124812-64-2; **4**, 10354-00-4; **5**, 18259-45-5; **9**, 124813-06-5; **15a**, 4189-17-7; **15b**, 3973-55-5; **15c**, 124853-22-1; **15d**, 3979-65-5; **15e**, 42982-04-7; **15f**, 22046-29-3; **16e**, 124813-48-5; **16f**, 125303-39-1; **17e**, 124813-50-9; **18a**, 124813-45-2; **18b**, 124813-21-4; **18c**, 124813-10-1; **18d**, 124813-30-5; **18e**, 124813-51-0; **18f**, 117374-57-9; **19a**, 124813-43-0; **19b**, 124813-22-5; **19c**, 124813-11-2; **19d**, 124813-28-1; **20a**, 124813-44-1; **20b**, 124813-20-3; **20c**, 124813-12-3; **20d**, 124813-29-2; **20e**, 124813-53-2; **21**, 38240-87-8; **29**, 125299-78-7; **30** (isomer 1), 125409-20-3; **30** (isomer 2), 125409-22-5; **33a**, 124813-46-3; **33b**, 124813-23-6; **33c**, 124813-13-4; **33d**, 124813-31-6; **34b**, 124813-25-8; **34c**, 124813-15-6; **34d**, 124813-39-4; **34e**, 124813-54-3; **35**, 124812-98-2; **36**, 124812-90-4; **37**, 124813-60-1; **38**, 124812-92-6; **39**, 124812-91-5; **40**, 124812-89-1; **41**, 124812-97-1; **42**, 124812-99-3; **43**, 2975-65-7; **44**, 125303-41-5; **45**, 124813-57-6; **46**, 124813-01-0; **47**, 124813-37-2; **48** (isomer 1), 125409-21-4; **48** (isomer 2), 125409-23-6; **49**, 125303-40-4; **52**, 124812-96-0; I, 125303-42-6; II, 89442-08-0; 5-oxo-5,6-dihydrodibenzo[a,e]cyclooctene, 3111-86-2.

Supplementary Material Available: Tables of crystal data, fractional coordinates, bond distances, and bond angles of structure **2** (6 pages). Ordering information is given on any current masthead page.

(30) MSDRL Molecular Modelling Package, written by the Molecular Systems Group, MSDRL Rahway.

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Transannular Reactions of 5-Azido- and 5-Nitronodibenzo[*a*,*e*]cyclooctatrienes and -dibenzo[*a*,*d*]cycloheptatrienes. Syntheses of Pavine and Homoisopavine Analogues

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Transannular cycloaddition reactions of substituted dibenzocyclooctenes and dibenzocycloheptenes have been used to prepare ring homologues of the uncompetitive *N*-methyl-D-aspartate receptor antagonist MK-801 (1) and its major hydroxylated metabolite. Controlled thermolysis of the 5-azidodibenzo[*a*,*e*]cyclooctene **5** yields the pentacyclic aziridine **14**. In contrast, thermolysis of the corresponding cycloheptene azide **8** results in ring expansion, forming the imine **17**. Aziridine ring opening reactions of **14** provide a regiospecific route to the 12-endo-substituted pavine alkaloid analogues **3** and **23–25**. Treatment of the dibenzo[*a*,*e*]cyclooctene-5-ol **13** and the corresponding cyclohepten-5-ol **32** with formaldoxime under acidic conditions gave isoxazolidines **27**, **28**, and **33**, probably via intramolecular cycloaddition of the lable nitrones **6** and **9**. Ring cleavage reactions of the isoxazolidines formed the exo-hydroxy-substituted homoisopavines **29** and **30** and the iminomethanocycloheptane **34**. The more facile transannular reactions of the cyclooctenes relative to the cycloheptene derivatives can be explained by the formation of less strained transition states in the cyclooctene cases.

The discovery that antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamic acid receptor can prevent neuronal damage in animal models of cerebral ischemia[1] has stimulated attempts to identify novel ligands that interact with this receptor. In the accompanying paper, we described the synthesis of the dibenzocyclooctanimine **1**,[2] a ring homologue of the prototype non-competitive NMDA antagonist MK-801 (**2**).[3] Compound **1** was obtained from spontaneous ring closure of the unstable hydroxylamine **4**, a process that proceeded regioselectively, affording the bicyclo[4.2.1] system exclusively (Chart I).

The isomeric bicyclo[3.3.1] compound **3** possesses the ring system found in pavine alkaloids, and several routes to this structural class have been developed.[4] However,

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