

twice with CHCl_3 , and the combined CHCl_3 extracts were dried (Na_2SO_4) and concentrated. The residue was recrystallized from EtOH to give 3.2 g (32%) of **23a** (Table II).

1-(3-Fluorobenzyl)-1,2-dihydropyrimidine-2-thione hydrochloride (23b) was prepared from *N*-(3-fluorobenzyl)thiourea¹⁵ in 13% yield by the method used to prepare **23a**.

1-(3,5-Difluorobenzyl)-1,2-dihydropyrimidine-2-thione hydrochloride (23c) was prepared from *N*-(3,5-difluorobenzyl)thiourea¹⁵ in 10% yield by the same method used for the preparation of **23a**.

pK_a Determinations were obtained by titration of the compounds in 2:1 MeOH-H₂O (to overcome solubility constraints).

Enzymology. In vitro IC₅₀ determinations were made as previously reported.⁴ The IC₅₀ is defined as the concentration of compound that produces 50% inhibition of product formation when compared to uninhibited control.

Registry No. 1, 23269-10-5; 2, 95333-64-5; 3, 95333-65-6; 4, 95333-56-5; 4-HCl, 95359-66-3; 5, 16042-26-5; 5-HCl, 123566-30-3; 6, 95460-25-6; 6-HCl, 123566-31-4; 7, 26163-58-6; 7-2HCl, 22600-75-5; 8, 95460-13-2; 8-2HCl, 123593-05-5; 9, 123593-06-6; 9-HCl, 123566-32-5; 10, 5376-10-3; 10-HCl, 5272-57-1; 11, 41833-17-4; 12, 10045-64-4; 13, 123566-33-6; 14, 123566-34-7; 15b, 95333-80-5; 15c, 95333-81-6; 15d, 95333-60-1; 16a, 123566-44-9; 16b, 123566-45-0; 16c, 123566-46-1; 17a, 23289-13-6; 17b, 107186-77-6; 17c, 107186-78-7; 17d, 107186-80-1; 18a, 29983-31-1; 18b, 112961-33-8; 18c, 112961-34-9; 19a, 68700-73-2; 20a, 33898-72-5; 20c, 105219-26-9; 21a, 31493-51-3; 21c, 105968-95-4; 21d, 105968-97-6; 22a, 123566-55-2; 22b, 123566-56-3; 22c, 123566-57-4; 23a, 123566-58-5; 23b, 123566-63-2; 23b-HCl, 123566-60-9; 23c, 123566-64-3; 23c-HCl,

123566-62-1; 28, 56643-95-9; 29, 10045-65-5; 30, 95460-12-1; 31, 95460-14-3; 32, 95460-15-4; 33, 123566-35-8; 34, 95460-23-4; 35, 123566-36-9; 36, 123566-37-0; 37, 123566-39-2; 38, 123566-42-7; 39, 90390-27-5; 40, 105969-16-2; 41, 107186-81-2; 42, 63351-94-0; 43, 107186-82-3; 44, 107186-83-4; 45, 93114-14-8; 46, 107186-84-5; 47, 107186-85-6; 48, 107186-79-8; 49, 112961-36-1; 50, 112961-39-4; 51, 112961-37-2; 52, 123566-47-2; 53, 123566-48-3; 54, 123566-49-4; 55, 105219-25-8; 56, 5729-06-6; 57, 105969-13-9; 58, 105969-11-7; 59, 105968-93-2; 60, 79568-07-3; 61, 123566-50-7; 62, 123566-51-8; 63, 123566-52-9; 64, 32967-14-9; 65, 123566-53-0; 66, 123566-54-1; *p*-MeOC₆H₄CH₂NHCH₂CH(OMe)₂, 54879-77-5; NH₂CN, 420-04-2; PhCHO, 100-52-7; *m*-FC₆H₄CHO, 456-48-4; 3,5-F₂C₆H₃CHO, 32085-88-4; NH₂CH₂CH₂NH₂, 107-15-3; PhCH₂NHCH₂CH₂NH₂, 4152-09-4; 3,5-F₂C₆H₃CH₂NHCH₂CH₂NH₂, 123566-40-5; PhCH₂NHCH₂CH₂NHC(=S)SH, 123566-41-6; 3,5-F₂C₆H₃CH₂NHCH₂CH₂NHC(=S)SH, 123566-43-8; 3,5-F₂C₆H₃CN, 64248-63-1; *m*-FC₆H₄CH₂NH₂, 100-82-3; PhCH₂NCS, 622-78-6; *t*-BuOCONHNH₂, 870-46-2; *o*-NO₂C₆H₄Cl, 88-73-3; PhCH₂NH₂, 100-46-9; *m*-BrC₆H₄F, 1073-06-9; 3,5-F₂C₆H₃Br, 461-96-1; *m*-FC₆H₄CH₂NHC(=S)NH₂, 123566-59-6; 3,5-F₂C₆H₃CH₂NHC(=S)NH₂, 123566-61-0; 1-[3-(4-methoxyphenyl)propyl]imidazole-2-thione, 95333-89-4; 1-(4-methoxybenzyl)imidazole-2-thione, 95460-09-6; 1-benzylimidazole, 4238-71-5; 1-benzyl-2-methylimidazole, 13750-62-4; 1-[4-(benzyloxy)benzyl]-2-methylimidazole, 123566-38-1; 3,5-difluoro-4-methoxybenzonitrile, 104197-15-1; 1-benzyl-1,2,3-triazole, 4368-68-7; 3-pyridinecarbonitrile, 100-54-9; 3-benzylpyridine, 620-95-1; *N*-benzylthiourea, 621-83-0; malonaldehyde tetramethyl acetal, 102-52-3; dopamine β -hydroxylase, 9013-38-1; 3-benzylpyridine *N*-oxide, 32361-74-3.

Synthesis and Pharmacological Evaluation of a Series of Dibenzo[*a,d*]cycloalkenimines as *N*-Methyl-D-aspartate Antagonists

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Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065, and Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR, United Kingdom. Received April 10, 1989

A series of 73 dibenzo[*a,d*]cycloalkenimines were synthesized and evaluated for their ability to displace (+)-10,11-dihydro-5-methyl-5H-dibenzo[*a,d*]cyclohepten-5,10-imine ([³H]-(+)-10) from its specific binding site on rat cortical membranes. A number of the more active compounds (*K_i* ranging from 0.006 to 0.21 μM) were evaluated for *N*-methyl-D-aspartate (NMDA) antagonist activity in the rat cortical slice (*K_i* ranging from 0.08 to 0.9 μM) and anticonvulsant activity in the mouse against NMDA induced convulsions. The ED₅₀ values ranged from 0.22 to 7.76 mg/kg and correlated reasonably well with the *K_i* determination. In the dibenzo[*a,d*]cyclohepten-5,10-imine series, the (+)-5*S*,10*R* enantiomer displayed consistently higher levels of biological activity. While substitution at the 3-position of (+)-10 with electronegative atoms generally increased in vitro activity, a loss of potency relative to (+)-10 (MK-801) was observed in vivo for all of the compounds tested.

Sometime ago a number of 1,4-dihydronaphthalen-1,4-imines were synthesized in our laboratory to explore the biologic properties of these molecules.¹ Interest in these rigid heterocycles had been stimulated by the observation that 9-methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (**1**) displayed modest antiseizure and apparent anxiolytic activity when orally administered to rodents. In the course of pursuing this study, the structurally related 9,10-dihydroanthracen-9,10-imines² were found to have similar biological properties. Placement of methyl groups on the bridgehead positions of this construction

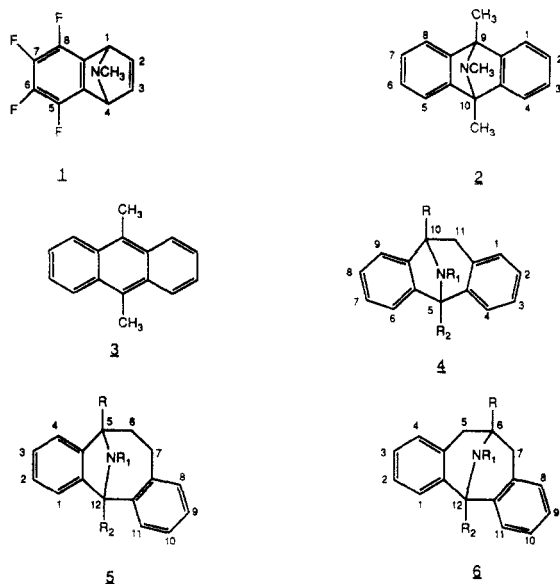
gave rise to compounds which were surprisingly more potent than the lead structure **1**, and also exhibited a high level of central sympathomimetic activity.³

Sedation is a frequently encountered side effect of available anticonvulsant drugs. The spectrum of phar-

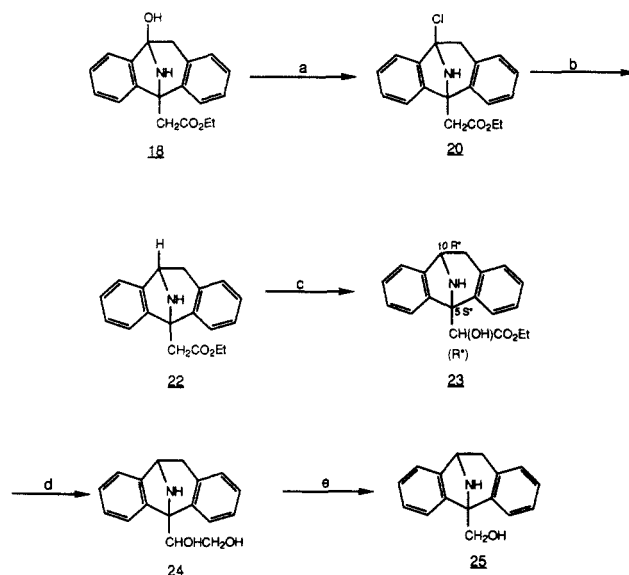
[†]Rahway, NJ.

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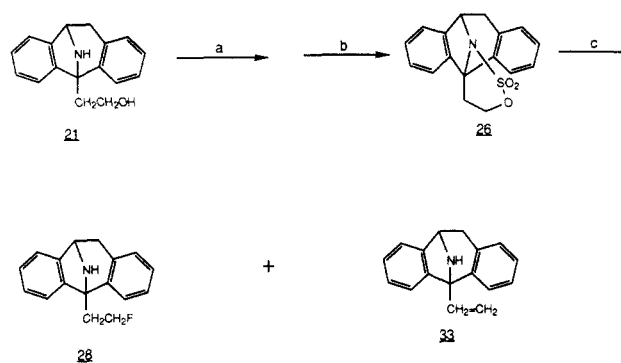
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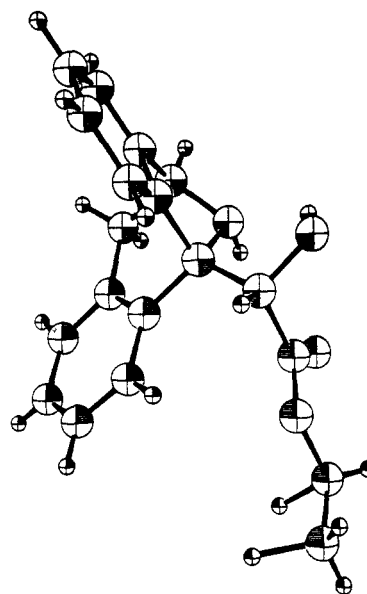
macological actions displayed by the parent 9,10,11-trimethyl-9,10-dihydroanthracen-9,10-imine (**2**) suggested potential for a clinically useful, non-sedating antiepileptic agent. Before this possibility could be explored, it was discovered that the compound was susceptible to chemical and enzymatic oxidative deamination. Initially, formation of 9,10-dimethylanthracene (**3**), a potent mutagen, was observed upon exposure of **2** to methanolic hydrogen peroxide.⁴ Subsequently it was demonstrated that non-specific liver oxidases could perform this transformation.⁵ The metabolic fate of **2** into the known mutagen **3** obviously precluded clinical evaluation of this class of compounds. Further experimental work revealed the chemical instability of *N*-oxides of anthracen-9,10-imines toward deamination by a cheletropic mechanism.⁴ Presumably, the enzyme-mediated deamination proceeds along a similar pathway. Several tactics were considered for circumventing this metabolic problem. The simplest and most attractive maneuver was to reorganize the carbon skeleton of **2** by moving one of the two symmetrical bridgehead methyl groups into the central ring of the hydrocarbon backbone as a methylene unit.³ Achiral anthracenimine **2** is formally converted by this operation into chiral dibenzo[*a,d*]cycloheptenimine **4**. Much of the molecular topography is retained, however, as can be seen with the aid of computer graphics. A key feature of this design was that the bridgehead methyl groups, which were deemed crucial for the biological actions of the anthracenimines, could be retained (**4** where *R* or *R*₂ = methyl). Two further ring expansions of **4** were conceived (**5** and **6**) which retained the benzhydryl bridgehead carbon. We have reported efficient syntheses of these three classes of compounds previously.^{6,7} Subsequently it was determined that

Scheme I^a

^a (a) SOCl₂; (b) Zn, AcOH; (c) KNTMS₂/2-(phenylsulfonyl)-3-phenyloxaziridine; (d) LiAlH₄; (e) NaIO₄/NaBH₄.

Scheme II^a

^a (a) (CF₃SO₂)₂O; (b) Bu₄NF, 20 °C; (c) Bu₄NF, 70 °C.

Figure 1. ORTEP plot of hydroxy ester **23**.

dibenzo[*a,d*]cycloheptenimine **4**, where *R* and *R*₁ are hydrogen and *R*₂ is a methyl group (MK-801) was indeed a potent anticonvulsant agent without sedative properties.⁸

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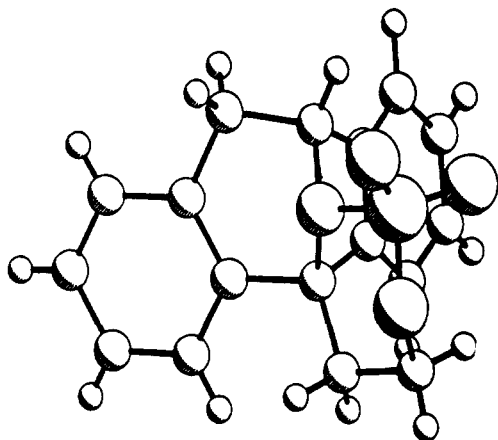


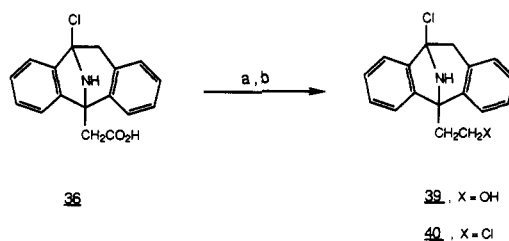
Figure 2. ORTEP plot of cyclic sulfonate 26.

Insight into the underlying mechanism of the anticonvulsant action was provided by the discovery that (+)-10 is a selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) subclass of receptors for the excitatory amino acid L-glutamic acid in brain tissue.⁹ Furthermore, a high affinity binding site in the rat brain was also identified using [³H]-(+)-10 as radioligand.⁹⁻¹¹ Other noncompetitive antagonists of the phencyclidine class were found to compete with 10 for this binding site.⁹ These key discoveries generated a more sensitive in vitro bioassay for evaluating and selecting compounds for further development as anticonvulsants¹² or neuroprotective agents for brain ischemia.¹³ We report here the results of an investigation into the structure-activity relationships of a series of compounds which possess the dibenzo[*a,d*]-cycloalkenimine framework (4-6).

Chemistry

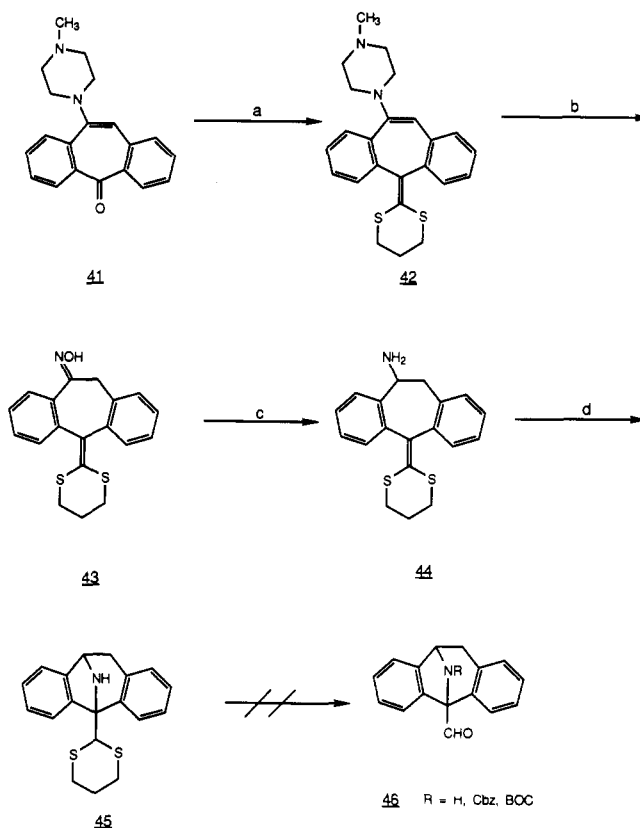
Syntheses of the dibenzocyclohepten- and -octenimines 7-32 and 46-58 have been described elsewhere.^{6,7,14-20} The remarkably stable hydroxy ester 18 proved to be a valuable starting material for the synthesis of compounds substituted at the 5- and 10-positions (via 19-21) and was prepared in four steps from 10-(4'-methylpiperazin-1-yl)-5*H*-dibenzo[*a,d*]cyclohepten-5-one⁶ by using the methods reported earlier.¹⁴ Oxidation of the potassium enolate derived from ester 22 with 3-phenyl-2-(phenylsulfonyl)oxa-

Scheme III^a



^a (a) BH₃·THF, (b) SOCl₂.

Scheme IV^a



^a (a) 2-(trimethylsilyl)-1,3-dithiane, nBuLi; (b) NH₂OH·HCl, MeOH; (c) Zn, AcOH; (d) nBuLi.

ziridine²¹ afforded a single diastereomer of hydroxy ester 23 (Scheme I). Single-crystal X-ray diffraction analysis revealed that the relative stereochemistry of the newly formed asymmetric center was of the *R** configuration relative to the 5*S**,10*R** carbons of the dibenzocycloheptenimine ring system (Figure 1).²²

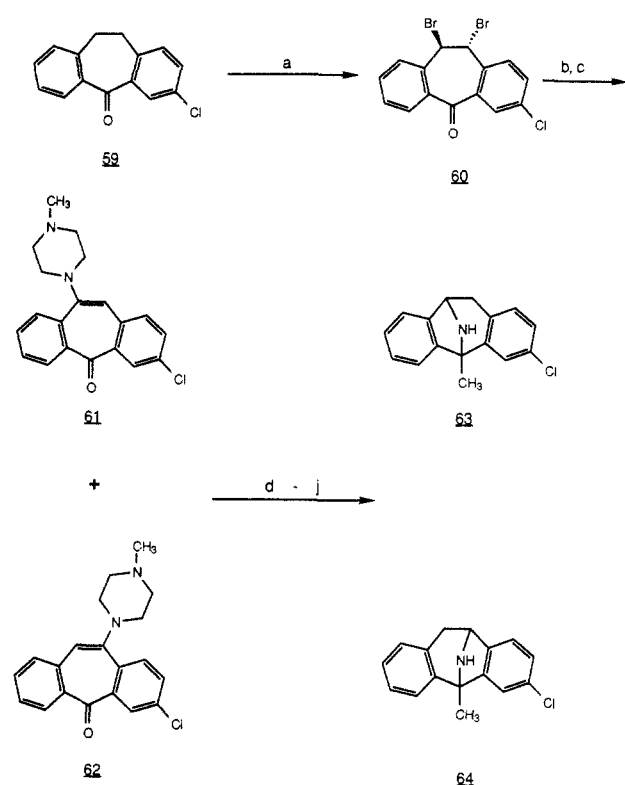
Hydroxy ester 23 was converted into 5-hydroxymethyl derivative 25 via diol 24.¹⁷ The cyclic sulfamate derivatives (i.e. 26, Scheme II and Figure 2) of both 25 and 5-hydroxyethyl analogue 21 were found to be useful intermediates for the introduction of a fluorine atom¹⁸ and thereby provided 27 and 28. When the fluoride displacement reaction of 26 was conducted at high pH, 5-vinyl

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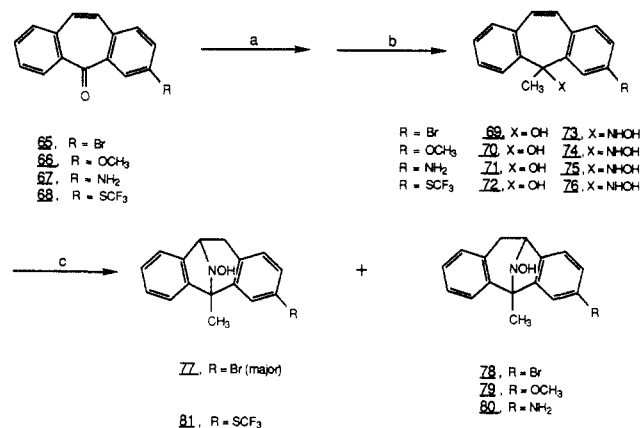
(22) On examination of the ORTEP of 23 (Figure 1), it is tempting to speculate that the 2-sulfonyloxaziridine reagent is delivered to the *si* face of an *E*-enolate by coordination to a potassium counterion which is internally chelated to the nitrogen ring atom. Assuming the nitrogen lone pair is oriented in the enolate as in the crystal of 23, the potassium ion would be in closer proximity to the *si* face.

Scheme V^a



^a (a) NBS; (b) KOH; (c) *N*-methylpiperazine, KOTBu; (d) fractional crystallization; (e) MeLi; (f) HCl; (g) NH₂OH·HCl, NaOAc; (h) NaCNBH₃, pH = 2.0; (i) xylene, reflux; (j) Zn, HOAc.

Scheme VI^a



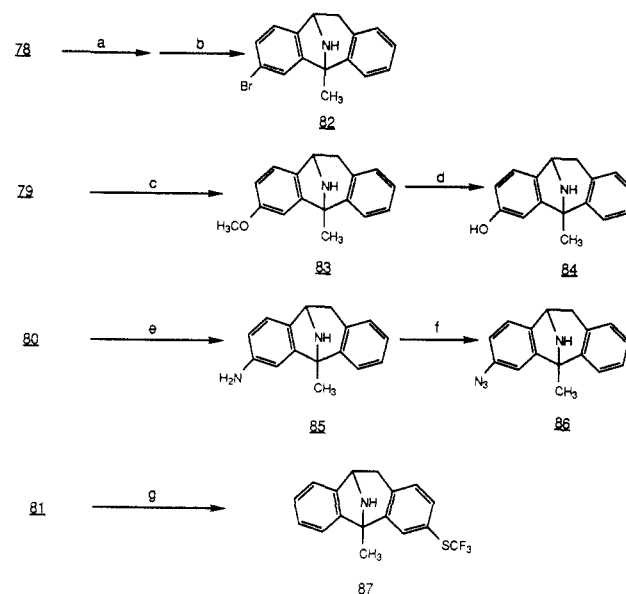
^a(a) CH_3MgBr ; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{Cl}_2\text{CHCO}_2\text{H}$; (c) KOtBu , PhCH_3 , DMSO .

33 was formed as a byproduct (Scheme II).²³ Esters **18** and **20** were converted into the carboxylic acids **34** and **36** in the usual manner. 10-Chloro derivatives **39** and **40** were obtained from carboxylic acid **36** as shown in Scheme III.

1,3-Dithiane **45** was prepared from enamino **41** by a route similar to that used for **10⁶** as shown in Scheme IV. In this case, however, the hydroxylamine equivalent of **44** would not undergo thermal cyclization.²⁴

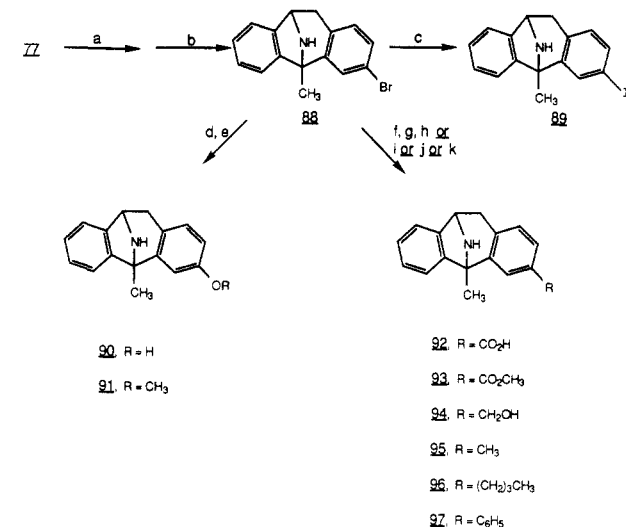
3- and 7-chloro compounds **63** and **64** were prepared in a manner similar to that first described for 3- and 7-bromo

Scheme VII^a



^a (a) Ac_2O ; (b) $\text{BH}_3\cdot\text{THF}$; (c) Zn , AcOH ; (d) $\text{Pyr}\cdot\text{HCl}$, Δ ; (e) Zn , AcOH ; (f) HONO/NaN_3 , (g) Zn , AcOH .

Scheme VIII^a

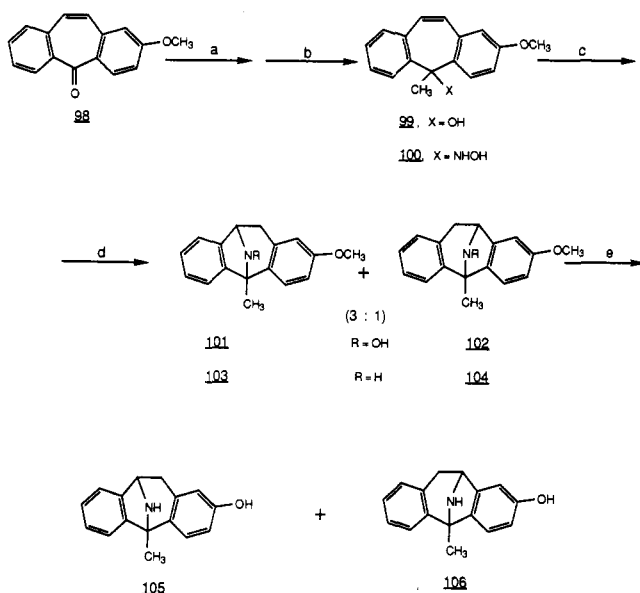


^a (a) Ac_2O ; (b) $\text{BH}_3\cdot\text{THF}$; (c) Ni , KI ; (d) $\text{tBuLi}/\text{MeO}_3\text{B}/\text{H}_2\text{O}_2$; (e) $(\text{BOC})_2\text{O}$, $\text{Et}_3\text{N}/\text{NaOH}$, $\text{CH}_3\text{I}/\text{TFA}$; (f) $\text{tBuLi}/\text{CO}_2/\text{AcOH}$; (g) BF_3OEt_2 , CH_3OH ; (h) LiAlH_4 ; (i) CH_3MgBr , ZnCl_2 , dppNiCl_2 (cat); (j) $n\text{BuLi}$; (k) $(\text{BOC})_2\text{O}/\text{PhZnCl}$, $\text{dppTPd}(\text{OAc})_2$ (cat)/ TFA .

analogues **88** and **82**, as shown in Scheme V, by utilizing the large solubility difference of enaminones **61** and **62** for separating the isomers early in the synthetic scheme.

A more convenient and efficient process for the preparation of the racemic 3-bromo **88** employed the cyclization of 5-(hydroxyamino)dibenzocycloheptene **73** derived from tertiary alcohol **69** (Scheme VI).¹⁶ 3-Bromo isomer **77** was formed preferentially during the base-induced cyclization of hydroxyamine **73** (4:1, **77**:**78**). A similar result was observed for 3-(trifluoromethyl)thio-substituted hydroxyamine **76**, which afforded the 3-SCF₃-substituted **81** regioselectively. Interestingly, 3-methoxy and 3-amino derivatives **74** and **75** gave 7-methoxy- and 7-amino-substituted cyclized products **79** and **80** with essentially complete regioselectivity.

While reduction with zinc dust in acetic acid provided the 7-methoxy-, 7-amino-, and 3-[(trifluoromethyl)thio]-dibenzocycloheptenimines 83, 85, and 87, the bromo de-

Scheme IX^a

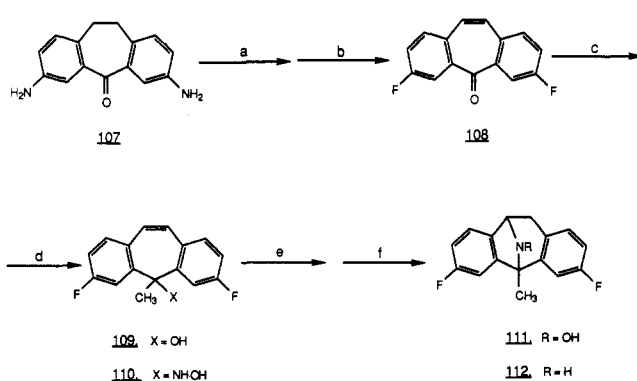
^a (a) CH_3MgBr ; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{Cl}_2\text{CHCO}_2\text{H}$, NaOAc ; (c) KOT-Bu , PhCH_3 , DMSO ; (d) Zn , AcOH ; (e) BBr_3 .

derivatives required more selective conditions. Thus, 3-bromo 88 and 7-bromo 82 were formed by borane reduction of the acetylated *N*-hydroxy derivatives (Scheme VII and VIII). 7-Hydroxy 84 and 7-azido 86 were derived from 7-methoxy 83 and 7-amino 85, respectively, as shown in Scheme VII.

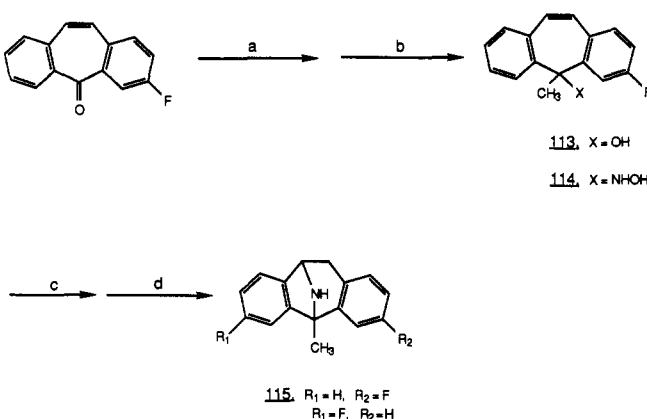
With racemic 3-bromo 88 accessible in larger quantities, substitution of the 3-position with a variety of substituents became possible. Thus, 3-iodo 89 was prepared by exchange with iodide in the presence of nickel powder.²⁵ 3-Hydroxy 90 was formed by lithiation of the 3-bromo 88 with *tert*-butyllithium, conversion to the arylboronic acid, and in situ oxidation with aqueous hydrogen peroxide.²⁶ Selective methylation of 90 gave 3-methoxy analogue 91. Lithiation of the 3-bromo derivative also proved useful for regioselective conversion into the 3-carboxy-, 3-carbomethoxy-, and 3-hydroxymethyl-substituted analogues 92, 93 and 94 by a sequence of carboxylation, esterification, and subsequent reduction. 3-Methyl and 3-phenyl derivatives 95 and 97 were obtained directly from the 3-bromo 88 by either nickel- or palladium-catalyzed coupling with methyl or phenylzinc chloride.²⁷ Attempted lithiation of 3-bromo 88 with *n*-butyllithium provided 3-*n*-butyl derivative 96 as the major product.

Application of the intramolecular cyclization approach to 5-(hydroxyamino)dibenzocycloheptene 100 derived from ketone 98 via carbinol 99 generated a new synthesis of 2- and 8-methoxy analogues 103 and 104 as a 3:1 mixture, respectively (Scheme IX). While this route is shorter than the previously reported method,¹⁴ we were unable to separate the isomers by conventional chromatography or crystallization techniques. The regioisomers could be separated, however, after demethylation by a combination of chromatography and fractional crystallization into 2- and 8-hydroxy derivatives 105 and 106.

The symmetrical 3,7-difluoro derivative 112 was accessible from 3,7-diamino ketone 107 via 3,7-difluoro ketone

Scheme X^a

^a (a) HONO , HBF_4 ; (b) NBS , Δ ; (c) CH_3MgBr ; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{Cl}_2\text{CHCO}_2\text{H}$; (e) KOTBu , Δ ; (f) Zn , HOAc .

Scheme XI^a

^a (a) CH_3MgBr ; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{Cl}_2\text{CHCO}_2\text{H}$; (c) KOTBu ; (d) Zn , HOAc .

108, likewise by the 5-hydroxyamino cyclization (108 \rightarrow 111, Scheme X). Application of this method to the monofluorinated derivative led to an inseparable mixture of 3- and 7-fluoro 115 in which the 3-fluoro isomer predominated (Scheme XI).

Although thermal ring closures of alkenylhydroxylamines have been postulated to proceed via a radical chain mechanism,²⁸ the observed product ratios (formation of compounds 77-81, 101, 102 and *N*-OH derivative of 115) are qualitatively²⁹ more consistent with formation of an intermediate benzylic carbanion. Electron releasing, or -E, substituents at the 3-position should destabilize an intermediate benzylic anion para to the -E substituent and thus favor formation of the 7-isomer, whereas electron withdrawing, or +I, substituents should favor the 3-isomer through stabilizing the carbanion. If an intermediate benzylic radical were involved, -E substituents should favor the 3-isomer and +I substituents should have little or no preference. Semiempirical molecular orbital (MNDO) calculations were performed in an attempt to confirm these qualitative arguments and provide a more quantitative correlation of mechanism with observed product ratios. The calculated heats of formation of the radical and anion intermediates are shown in Tables I and II. The differences in the heats of formation between the 3- and 7-positions, $\Delta\Delta H_f$ 3-7, or 2- and 8-positions, $\Delta\Delta H_f$

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Table I. MNDO Heats of Formation (kcal/mol) of Radical Intermediates^a

	ΔH_f 3(2)-isomer		ΔH_f 7(8)-isomer		$\Delta\Delta H_f$ 3(2)-7(8)	$\Delta\Delta G^{*b}$	3(2):7(8) product ratio
	syn	anti	syn	anti			
3-NH ₂	80.22	81.09	80.13	80.87	0.09	>3.00	0:100
3-OCH ₃ ^c	40.43	41.22	40.35	40.88	0.08	1.43	10:90
3-H	79.24	79.95	79.24	79.95	0.00	0.00	50:50
2-OCH ₃ ^c	40.49	41.24	40.26	41.06	0.23	-0.65	73:27
3-F	32.85	38.55	32.93	33.55	-0.08	-0.90	80:20
3-Br	82.02	82.69	82.00	82.76	0.02	-0.90	80:20
3-SCF ₃	-66.18	-65.52	-66.23	-65.22	0.05	>-3.00	100:0

^a The two values listed for each isomer correspond to the syn and anti conformers of the hydroxylamine bridge. In addition, these values correspond to the lower energy orientation ("up" or "down") of the hydroxyl hydrogen; in all cases, "up" was preferred. ^b Calculated from the experimental 3:7 product ratios with the relationship: 3:7 ratio = $e^{-\Delta\Delta G^*/RT}$; $T = 55^\circ\text{C}$. ^c Cited values refer to calculations in which the OCH₃ group was held coplanar with the aromatic ring. The OCH₃ group is twisted in the fully optimized MNDO geometry, contrary to experimental evidence³¹ which suggests that anisole has a planar heavy-atom skeleton.

Table II. MNDO Heats of Formation (kcal/mol) of Anion Intermediates^a

	ΔH_f 3(2)-isomer		ΔH_f 7(8)-isomer		$\Delta\Delta H_f$ 3(2)-7(8)	$\Delta\Delta G^{*b}$	3(2):7(8) product ratio
	syn	anti	syn	anti			
3-NH ₂ ^c	119.95 (37.76)	127.08 (41.04)	89.76 (37.45)	93.35 (40.94)	30.19 (0.31)	>3.00	0:100
3-OCH ₃ ^d	-1.58	1.91	-2.20	1.29	0.62	1.43	10:90
3-H	37.04	40.55	37.04	40.55	0.00	0.00	50:50
2-OCH ₃ ^d	-3.99	3.94	-2.14	5.93	-1.85	-0.65	73:27
3-F	-15.04	-11.97	-12.52	-9.05	-2.52	-0.90	80:20
3-Br	31.92	34.87	36.73	40.24	-4.81	-0.90	80:20
3-SCF ₃	-129.02	-127.15	-115.53	-106.90	-13.49	>-3.00	100:0

^a The two values listed for each isomer correspond to the syn and anti conformers of the hydroxylamine bridge. In addition, these values correspond to the lower energy orientation ("up" or "down") of the hydroxyl hydrogen: in the syn isomer, "down" was preferred, in the anti isomer "up" was preferred. ^b Calculated from the experimental 3:7 product ratios with the relationship: 3:7 ratio = $e^{-\Delta\Delta G^*/RT}$; $T = 55^\circ\text{C}$. ^c Cited values refer to the dianion produced by deprotonation of both the 3-NH₂ substituent and the NH of the hydroxylamine bridge; values in parentheses refer to the monoanion produced by deprotonation only at the NH of the hydroxylamine bridge. ^d Cited values refer to calculations in which the OCH₃ group was held coplanar with the aromatic ring. The OCH₃ group is twisted in the fully optimized MNDO geometry, contrary to experimental evidence³¹ which suggests that anisole has a planar heavy-atom skeleton.

Table III. MNDO Deprotonation Enthalpies (kcal/mol)^a

	ΔH_f RNHOH	ΔH_f RN ⁻ -OH	DPE RN-HOH	ΔH_f RNHO ⁻	DPE RNHO-H	ΔDPE^b
3-H	74.93	67.15	359.42	73.37	365.64	6.22
3-NH ₂ ^c	70.13	67.38 (51.60)	364.45 (348.67)	73.55	370.62	6.17 (15.78)
2-OCH ₃	36.23	28.08	359.05	34.43	365.40	6.35
3-OCH ₃	36.85	27.74	358.09	33.97	364.32	6.23
3-F	28.68	17.35	355.87	23.83	362.35	6.48
3-SCF ₃	-76.56	-85.92	357.84	-79.23	364.53	6.69
3-Br	77.57	66.52	356.15	73.21	362.84	6.69

^a The deprotonation enthalpy (DPE) of a species BH is defined as the heat of reaction for loss of a proton to form the conjugate base: $\text{BH} \rightarrow \text{B}^- + \text{H}^+$; $\text{DPE BH} = \Delta H_f \text{B}^- + \Delta H_f \text{H}^+ - \Delta H_f \text{BH}$. The DPE of a compound is thus equal to the proton affinity of its conjugate base. Since MNDO is known to give a very poor estimate of the heat of formation of H⁺ (calcd 326.7 kcal/mol; obsd 367.2 kcal/mol), the experimental value³² was used in calculating DPE's. ^b Difference in enthalpy between N and O deprotonation. In all cases, deprotonation at N was calculated to be more favorable than deprotonation at O. ^c Values in parentheses refer to deprotonation of the 3-NH₂ substituent, rather than the NH of the 5-NHOH group.

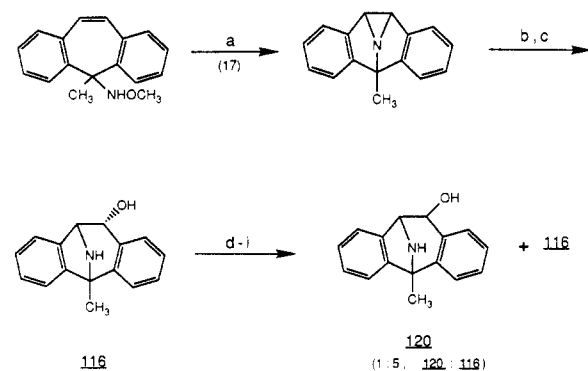
2-8, should give an upper bound to the enthalpies of activation, $\Delta\Delta H^\ddagger$, for the regioisomeric reactions. Since $\Delta\Delta S^\ddagger$ should be small and constant for an intramolecular rearrangement at equilibrium, the calculated $\Delta\Delta H^\ddagger$ values should correlate with the $\Delta\Delta G^\ddagger$ values derived from the observed product ratios. No such correlation exists with the radical intermediates in Table I, while the carbanion results in Table II are in excellent agreement.³⁰

An anionic mechanism requires preferential deprotonation of nitrogen rather than oxygen, since only 1 equiv of base was generally employed in the reaction. Indeed,

(30) In further support of these MNDO calculations, it was determined that the syn and anti NOH conformers were calculated to have $\Delta H_f = 0.47$ kcal/mol for the 3-H entry. The observed ratio by ¹H NMR integration is 2:1 syn:anti ($\Delta G_f = 0.42$ kcal/mol).

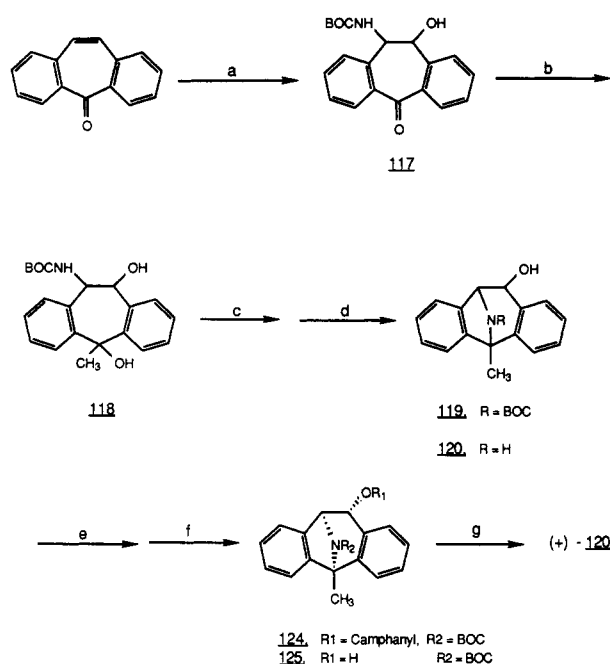
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Scheme XII^a

^a (a) nBuLi; (b) HOAc, NaOAc; (c) KOH; (d) (BOC)₂O; (e) MsCl, Et₃N; (f) nBu₄NOAc; (g) KOH; (h) HCl, EtOH; (i) NH₄OH.

the calculated deprotonation enthalpies given in Table III consistently favor deprotonation at nitrogen. Only the

Scheme XIII^a

^a (a) OsO₄(cat.), tBuO₂CNCl(Na), AgNO₃; (b) CH₃Li; (c) *p*-TsOH; (d) TFA; (e) camphanyl chloride/crystallization; (f) LiOH; (g) HCl.

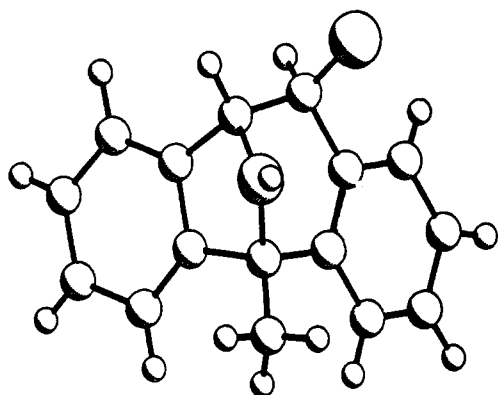


Figure 3. ORTEP plot of 11-*exo*-hydroxy 120.

3-NH₂ group is predicted to be more acidic than the 5-NHOH group, in agreement with the experimentally observed requirement for 2 equiv of base in this example. These calculations, therefore, strongly support an anionic mediated reaction mechanism for the ring-closure reaction.

After exploring a number of synthetic routes to the 11-*exo*-hydroxylated derivative 120 involving stereochemical inversion of the readily accessible 11-*endo*-hydroxy 116¹⁷ (Scheme XII), a four-step synthesis was developed starting from dibenzosuberone (Scheme XIII). The Sharpless procedure for oxyamination³³ provided the *N*-protected hydroxyketone 117 in 40% conversion. Carbinol 118 obtained by methyl lithium addition underwent acid-catalyzed cyclization to form 119 contaminated with approximately equal amounts of the analogous product resulting from transannular cyclization of the hydroxyl group. Chromatography and deprotection gave

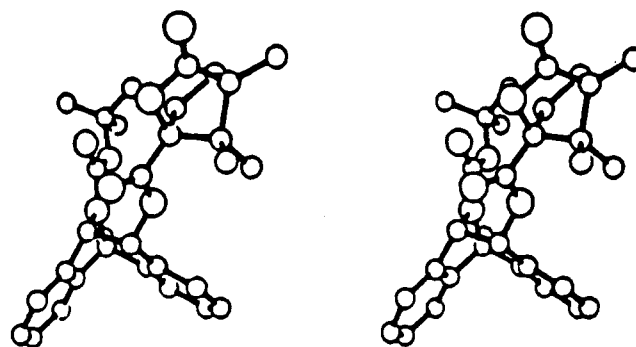
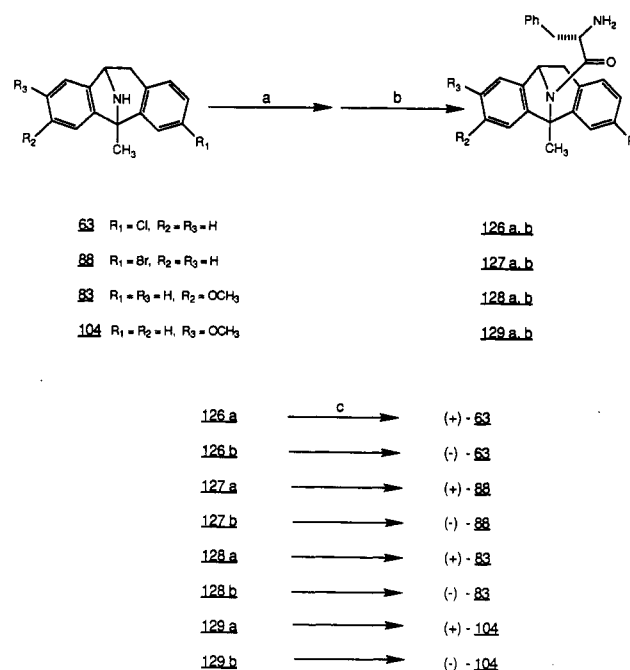


Figure 4. ORTEP plot of camphanate 124.

Scheme XIV^a

^a (a) BOC-Phe-OH, BOP-Cl; (b) TFA; (c) PhNCS, Δ.

racemic 11-*exo*-hydroxy 120. Resolution was achieved by fractional crystallization of the diastereomeric camphanyl esters 124. Sequential deprotection gave 125 and the pure (+)- and (-)-enantiomers of 120. The relative and absolute stereochemistry of 120 were established unambiguously by single-crystal X-ray diffraction analysis of 120 and 124 (Figures 3 and 4).

Resolution of 3-chloro 63, 3-bromo 88, 7-methoxy 83, and 8-methoxy 104 was accomplished through chromatographic separation of the diastereomeric *L*-phenylalanine derivatives^{3,4} 126-129 (Scheme XIV). Edman degradation afforded the pure (+)- and (-)-enantiomers.

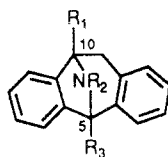
Due to the utility of 3-bromo analogue 88 for obtaining the generally potent 3-substituted analogues, a more direct synthesis of the (+)-enantiomer was subsequently developed. Direct bromination of (+)-10 with *N*-bromosuccinimide in aqueous sulfuric acid provided (+)-3-bromo 88, together with small amounts of another unidentified isomer, in moderate yield.

Biological Results and Discussion

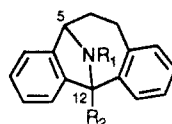
Relative affinity for the *N*-methyl-D-aspartate receptor ion channel complex was assessed in vitro in homogenized rat brain membranes using the K_i (μM) for displacement of the radioligand [³H]-(+)-10.^{9,11} The binding affinities for the dibenzo[a,d]cycloheptenimines substituted at the

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Table IV. Inhibition of [³H]-(+)-10 Binding to Rat Brain Membranes by Bridgehead-Substituted Dibenzo[*a,d*]cyclohepten-5,10-imines

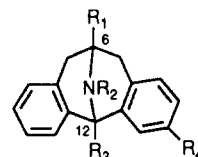
compd (ref)	R ₁	R ₂	R ₃	K _i , μM	n
7 (20)	H	H	H	22.60	1
8 (1)	H	CH ₃	H	12.00	1
9 (6)	H	CH ₃	CH ₃	0.610	1
10 (6, 16)	H	H	CH ₃	0.056	1
11 (7)	CH ₃	CH ₃	CH ₃	0.710	1
12 (6, 16)	H	OH	CH ₃	19.00	2
13 (6)	H	H	CH ₂ CH ₃	0.045	2
14 (14)	H	CH ₂ CH ₃	H	24.00	1
15 (14)	H	CH ₂ CH ₂ -OH	H	71.00	1
16 (6)	H	H	CH ₂ CH ₂ CH ₃	8.60	2
17 (14)	OH	OH	CH ₂ CO ₂ Et	>4500	1
18 (14)	OH	H	CH ₂ CO ₂ Et	3.60	1
19 (17)	OH	H	CH ₂ CH ₂ OH	0.074	1
21 (14)	H	H	CH ₂ CH ₂ OH	0.260	1
22	H	H	CH ₂ CO ₂ Et	0.550	1
23	H	H	(S)-CH(OH)CO ₂ Et	0.390	1
24 (17)	H	H	(S)-CH(OH)CH ₂ OH	0.320	1
25 (17)	H	H	CH ₂ OH	0.350 ± 0.047	3
27 (17, 18)	H	H	CH ₂ F	0.160 ± 0.028	3
28 (18)	H	H	CH ₂ CH ₂ F	0.174 ± 0.093	5
29 (17)	H	H	CH ₂ SC ₆ H ₅	73.00	1
30 (17)	H	H	CH ₂ S(O)C ₆ H ₅	>160	1
31 (17)	OH	H	CH ₃	0.077	2
32 (17)	F	H	CH ₃	0.930	1
33	H	H	CH=CH ₂	0.087 ± 0.021	3
34	OH	H	CH ₂ CO ₂ H	280	1
35	OH	H	CH ₂ CONH ₂	6.40	1
36	Cl	H	CH ₂ CO ₂ H	>4500	1
37	Cl	H	CH ₂ CONH ₂	>90	1
38	H	H	(S)-CH(OH)CO ₂ H	>1000	1
39	Cl	H	CH ₂ CH ₂ OH	0.280	1
40	Cl	H	CH ₂ CH ₂ Cl	53.00	1
45	H	H	2-(1,3-dithianyl)	>10	1

Table V. Inhibition of [³H]-(+)-10 Binding by Dibenzo[*a,d*]cycloocten-5,12-imines

compd (ref)	R ₁	R ₂	K _i , μM	n
46 (7)	CH ₃	CH ₃	8.80	1
47 (7)	CH ₃	H	2.60	1
48 (7)	CH ₃	OH	>100	1

5 and 10 bridgehead positions are summarized in Table IV, while the 2-, 3-, 7-, 8-, and 11-substituted dibenzo[*a,d*]cycloheptenimines are compared in Tables VII and VIII, respectively. The effect of substitutions in the dibenzo[*a,d*]cyclooctenimines is summarized in Tables V and VI. The binding affinities of the resolved enantiomers of (+)-10 and derivatives 63, 83, 88, 106, and 120 are compared in Table IX.

The potencies of the high affinity analogues as NMDA antagonists were determined *in vitro* in a rat cortical slice preparation and expressed as apparent "K_b" (μM) values calculated from the shift to the right of the NMDA concentration-response curve.⁹ These data are compared with the corresponding K_i values from the radioligand displacement assay in Table X. Inhibition of convulsions induced by *N*-methyl-D,L-aspartate (NMDLA) in the

Table VI. Inhibition of [³H]-(+)-10 Binding by Dibenzo[*a,d*]cycloocten-6,12-imines

compd (ref)	R ₁	R ₂	R ₃	R ₄	K _b , μM	n
49 (7)	CH ₃	CH ₃	CH ₃	H	8.70	1
50 (7)	H	CH ₃	CH ₃	H	1.20	1
51 (6)	H	H	CH ₃	H	0.139	2
52 (6)	H	H	H	H	5.10	1
53 (6)	H	H	OH	H	57.00	1
55 (6)	H	CH ₃	H	H	57.00	1
55 (6)	H	CH ₃	OH	H	290.00	1
56 (15)	H	H	CH ₃	Cl	0.110	1
57 (6)	H	H	CH ₂ CH ₃	H	0.120	1
58 (15)	H	CH ₃	CH ₂ CH ₃	H	2.04	1

mouse was used as an *in vivo* model.³⁵ The ED₅₀ (mg/kg) was determined for the more potent analogues and is compared to the apparent K_b for NMDA antagonism in Table XI.

The weak activity of dibenzo[*a,d*]cyclooctenimines 46 and 50 relative to the analogous dibenzo[*a,d*]cycloheptenimine 9 may be related to molecular geometry. Inspection of molecular models reveals considerable differences in the molecular topography upon ring expansion of the cycloheptenimine ring. The increased affinity afforded by the C-5 bridgehead methyl group in all ring systems becomes evident on comparison of 9, 46, and 50 with 8, 47, and 54, respectively (Tables IV–VI). All of the compounds tested which lacked the C-5 methyl (i.e. 7, 14, 15, 122, and 123) were greater than 10-fold less active in the displacement binding assay. A marked decrease in affinity for the (+)-10 binding site was displayed by all compounds alkylated (8, 9, 11, 14, 15, 46, 47, 48, 49, 50, 54, 55, 58) or hydroxylated (12 and 17) on the ring nitrogen.

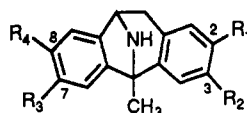
Substitution on the seven-membered ring (C-5, C-10, and C-11) was generally better tolerated than on nitrogen, with only modest decreases in potency observed. With the exception of special enhancement engendered by the C-5 methyl group, introduction of alkyl, hydroxyl, or halogen substituents generally resulted in decreased K_i, apparent K_b, and anticonvulsant activity (ED₅₀). No simple correlation of nitrogen basicity (pK_b) or steric factors could be determined, although both of these seem to exert an influence on the activity. The relatively high level of potency retained by the 11-*exo*-hydroxy derivative 120 was particularly interesting since the glucuronide of 120 was identified as a major urinary human metabolite of the parent drug.³⁶

Aromatic substitution in all series gave compounds with high affinity for the (+)-10 binding site. In particular, compounds with halogen substitution at the 3-position or hydroxylation at the 7- or 8-positions were more active than (+)-10 in the displacement assay. 3-Chloro compound 64 is noteworthy as the only derivative in this study that displayed greater potency than (+)-10 as an NMDA antagonist in the cortical slice.

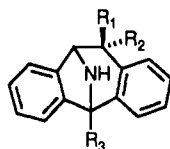
In all cases examined, resolution lead to increased biological activity for the (+)-enantiomer. The moderately

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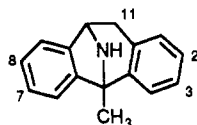
(36) A personal communication from Dr. Howard B. Hucker.

Table VII. Inhibition of [³H]-(+)-10 Binding by Aryl-Substituted 5-Methyldibenzo[*a,d*]cyclohepten-5,10-imines

compd (ref)	R ₁	R ₂	R ₃	R ₄	K _i , μM	n
10 (6, 16)	H	H	H	H	0.056	2
63	H	H	Cl	H	0.084 ± 0.010	5
64	H	Cl	H	H	0.011 ± 0.004	4
82	H	H	Br	H	0.180	1
83	H	H	OCH ₃	H	0.036	1
84	H	H	OH	H	0.023 ± 0.007	3
85	H	NH ₂	H	H	0.027	1
86	H	N ₃	H	H	0.140	2
87	H	SCF ₃	H	H	17.00	1
88	H	Br	H	H	0.080	1
89	H	I	H	H	0.011 ± 0.007	5
90	H	OCH ₃	H	H	0.046	1
91	H	OH	H	H	0.018 ± 0.010	4
94	H	CH ₂ OH	H	H	0.137 ± 0.005	3
95	H	CH ₃	H	H	0.034 ± 0.007	4
96	H	(CH ₂) ₃ CH ₃	H	H	1.25	2
97	H	C ₆ H ₅	H	H	0.032 ± 0.010	3
103 (14)	OCH ₃	H	H	H	0.610	1
104 (14)	H	H	H	OCH ₃	0.033 ± 0.006	3
105	OH	H	H	H	0.277 ± 0.104	3
106	H	H	H	OH	0.049 ± 0.002	3
112	H	F	F	H	0.031 ± 0.013	4
115	H	F	H	H	0.030 ± 0.010	5

Table VIII. Effect of C-11 Substitution of Dibenzo[*a,d*]cyclohepten-5,10-imine on the Inhibition of [³H]-(+)-10 Binding to Rat Brain Membranes

compd (ref)	R ₁	R ₂	R ₃	K _i , μM	n
10 (6, 16)	H	H	CH ₃	0.056	2
116 (17)	H	OH	CH ₃	2.70	2
120	OH	H	CH ₃	0.210	2
121 (17)	F	H	CH ₃	0.011 ± 0.004	5
122 (20)	OH	H	H	7.75	2
123 (20)	H	OH	H	110.0	2

Table IX. Inhibition of [³H]-(+)-10 Binding by Optical Antipodes of 5-Methyldibenzo[*a,d*]cyclohepten-5,12-imines

compd (ref)	substituent	K _i , μM	n
(+)-10 (14)	MK-801	0.031 ± 0.002	12
(-)-10 (14)		0.211 ± 0.025	5
(+)-63	3-chloro	0.006 ± 0.002	4
(-)-63		0.300	2
(+)-83	7-methoxy	0.025 ± 0.014	3
(-)-83		0.102	2
(+)-88	3-bromo	0.006 ± 0.003	4
(-)-88		0.113	2
(+)-106	8-hydroxy	0.023 ± 0.002	3
(-)-106		0.761 ± 0.195	3
(+)-120	11-exo-hydroxy	0.092 ± 0.027	3
(-)-120		0.302	1

high level of activity retained by the (-)-optical antipode is somewhat intriguing. When the near symmetry of the molecular framework is taken into consideration, however,

Table X. Antagonism of Responses to NMDA in the Cortical Slice by Dibenzo[*a,d*]cycloalkenimines Compared to K_i of Membrane Binding

compd ^a	apparent K _b , ^b μM	K _i , ^c μM
(+)-63	0.080 ± 0.010	0.006 ± 0.002
63	0.067 ± 0.018	0.011 ± 0.004
(+)-10	0.080 ^d	0.031 ± 0.002
10	0.120 ± 0.040	0.056
84	0.130 ± 0.004	0.023 ± 0.007
104	0.130 ± 0.008	0.033 ± 0.006
(+)-106	0.140 ± 0.022	0.023 ± 0.002
121	0.230 ± 0.077	0.011 ± 0.004
83	0.230 ± 0.064	0.036
28	0.230 ± 0.053	0.174 ± 0.093
91	0.240 ± 0.032	0.018 ± 0.010
106	0.240 ± 0.124	0.049 ± 0.002
(+)-120	0.250 ± 0.039	0.092 ± 0.027
97	0.260 ± 0.012	0.032 ± 0.010
120	0.280 ± 0.091	0.210
57	0.290 ± 0.113	0.120
94	0.270 ± 0.035	0.137 ± 0.005
51	0.310 ± 0.005	0.139
112	0.320 ± 0.119	0.031 ± 0.013
33	0.320 ± 0.142	0.087 ± 0.021
(-)-10	0.380 ± 0.062	0.211 ± 0.025
115	0.380 ± 0.101	0.030 ± 0.010
95	0.380 ± 0.017	0.034 ± 0.007
82	0.460 ± 0.017	0.180
(+)-88	0.500 ^d	0.006 ± 0.003
89	0.510 ± 0.245	0.011 ± 0.007
105	0.510 ± 0.166	0.277 ± 0.104
(-)-63	0.560 ± 0.058	0.300
13	0.590 (n = 2)	0.045
31	0.660 ± 0.294	0.077
56	0.680 ± 0.180	0.110
27	0.720 ± 0.132	0.160 ± 0.028
88	0.900 ± 0.154	0.080
63	1.66 ± 0.52	0.084 ± 0.010
19	2.10 ± 0.26	0.074
122	2.79 ± 0.40	7.75
123	9.60 ± 0.47	110.00
12	45.60 ± 8.30	19.00

^a All compounds were racemic unless otherwise indicated. ^b n = 3 unless specified. ^c For n values, see Tables I-IV. ^d See footnote e Table XI.

Table XI. Anticonvulsant Activity. Inhibition of Convulsions in Mice Induced by *N*-Methyl-D,L-aspartate (NMDLA)

compd ^a	ED ₅₀ , ^b mg/kg	95% confidence limits	K _b , ^c μM
(+)-10	0.22 ^e	0.15–0.34	0.080
(+)-120	0.35	0.26–0.48	0.250 ± 0.039
28	0.29	0.17–0.40	0.230 ± 0.053
84	(0.43)	0.24–0.61	0.130 ± 0.004
(+)-64	0.53	0.37–0.60	0.080 ± 0.010
95	0.53	0.30–0.84	0.380 ± 0.017
64	1.15 (0.67)	0.84–2.06 (0.45–0.93)	0.067 ± 0.018
91	(0.75)	0.34–1.20	0.240 ± 0.032
83	(0.77)	0.62–1.17	0.230 ± 0.064
(+)-106	(0.97)	0.75–2.55	0.140 ± 0.022
106	1.15	0.95–1.60	0.240 ± 0.124
94	1.19	0.75–1.87	0.270 ± 0.035
88	1.42 ^d (1.25)	0.89–2.24	0.900 ± 0.154
(-)-10	1.44	0.93–1.82	0.380 ± 0.062
121	(1.27)	0.06–1.85	0.230 ± 0.077
27	(2.55)	1.29–3.87	0.720 ± 0.132
(-)-64	1.92	1.19–2.81	0.560 ± 0.058
91	(2.12)	1.38–3.84	0.510 ± 0.166
97	7.76	6.03–9.56	0.260 ± 0.012

^a All compounds were racemic unless otherwise indicated. ^b All compounds were given iv 15 min before the convulsant (NMDLA). The ED₅₀ values in parentheses were obtained when the NMDLA was administered ip (500 mg/kg). All other results were after sc administration of NMDLA (500 mg/kg). ^c For *n* values, see Table X. ^d Following sc administration of NMDA at 400 mg/kg. ^e For (+)-10 and (+)-88, the potency value was taken as the threshold dose that produced a significant reduction in the NMDA responses, as it was impossible to estimate a dose ratio because of the marked flattening of the dose-response relationship.³⁵

this result may not be too surprising. The modest 2-fold decrease in binding and NMDA antagonism resulting from exo-hydroxylation ((+)-120) of the 11-position is of interest in light of the metabolic fate of the parent drug.

The general discrepancy observed between the data obtained in the displacement binding assay (*K_i*) and NMDA antagonism determination (apparent *K_b*) summarized in Table X indicates that a subtle yet important disruption of the channel-receptor complex upon homogenization of the intact membranes is likely. Correlation between the apparent *K_b* for NMDA antagonism and anticonvulsant activity in the rat is reasonably good, considering potential differences in metabolism and bioavailability (Table XI).

The results of this study indicate that the *in vitro* radioligand displacement assay coupled with apparent *K_b* determination for NMDA antagonism is a useful means of designing and selecting clinical candidates with this mechanism of action for anticonvulsant therapy. The pharmacology of (+)-10, which was reported previously,⁸ is consistent with this mechanism of action. While the utility of this approach for the development of a neuroprotective agent for brain ischemia remains to be demonstrated, the most potent compound of this investigation, (+)-10, has recently been shown to prevent ischemia-induced neuronal degradation in the gerbil,³⁷ mouse,³⁵ rabbit,³⁸ and chick³⁹ by blocking glutamate toxicity.^{40a} Issues related to the suitability of noncompetitive NMDA an-

tagonists for clinical use in preventing brain ischemia have been elaborated in other publications.^{40a-c}

Experimental Section

Synthesis. All reactions were run under dry nitrogen atmosphere at room temperature with appropriate stirring unless otherwise specified. During workup, organic extracts were routinely dried over anhydrous magnesium sulfate or sodium sulfate and concentrated with a rotary evaporator under reduced pressure. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained on either a Varian XL-300, Nicolet 360, or Varian EM-390 (90 MHz) spectrometer. Unless otherwise indicated, the NMR spectra were taken in CDCl₃ solution with TMS as an internal standard. Chemical shifts are reported in ppm downfield from TMS. Infrared spectra were recorded on a Perkin-Elmer 1420 infrared spectrometer in chloroform solution unless otherwise specified. Specific rotations were determined on a Perkin-Elmer Model 241 polarimeter. Column chromatography was performed with E. Merck 240–400 mesh silica gel by either gravity or low nitrogen pressure (5 psi). Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates. Reversed-phase preparative HPLC was carried out on a Waters Prep-500 with a C-18 Prep-PakTM cartridge. Analyses for C, H, and N were performed by John P. Moreau at Merck in West Point, PA and were within ±0.4% of the theoretical values. Potassium hexamethyldisilazane in toluene was obtained as a 15 wt% solution from the Callery Chemical Co., Callery, PA 16024.

5-[(Ethoxycarbonyl)methyl]-10-hydroxy-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (18). To a slurry of 0.138 mol of sodium hydride, free from mineral oil by washing, in 60 mL of toluene was added dropwise 34.5 g (0.155 mol) of triethyl phosphonoacetate while the temperature was maintained at 30–35 °C by cooling as necessary. After 1 h, a solution of 35 g (0.115 mol) of 10-(4'-methylpiperazin-1-yl)-5H-dibenzo[*a,d*]cyclohepten-5-one⁶ in 275 mL of toluene was added dropwise, and the temperature was maintained at 25–30 °C by cooling. After the gelatinous mixture was stirred for 3 h, the solution was decanted and the precipitate was washed with 3 × 75 mL of toluene at 65 °C. The combined extracts were stirred with 50 mL of 0.5 N HCl at 0–5 °C for 15 min, diluted with 500 mL of ether, separated, and washed with water. After drying, the product, 5-[(ethoxycarbonyl)methylene]-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-10-one, weighed 23.4 g (69%): mp 56–62 °C; TLC (5% EtOH/toluene) *R_f* = 0.54; ¹H NMR 1.1 (t, 3 H, CH₃, *J* = 6 Hz), 3.8 (d, 1 H, benzylic, *J* = 14 Hz), 4.05 (q, 2 H, CH₂, *J* = 6 Hz), 4.45 (d, 1 H, benzylic, *J* = 14 Hz), 6.45 (s, 1 H, vinyl), 7.4 (m, 7 H, aromatic), 8.1 (m, 1 H, H-9); IR (Nujol) 1720 (ester C=O), 1680 (ketone C=O) cm⁻¹. This crude product was dissolved in 300 mL of wet ether and stirred with 6.0 g (0.086 mol) of NH₂OH·HCl and 12.0 g (0.088 mol) of NaOAc·3H₂O for 48 h. The solid product was collected, washed with ether, and stirred in 300 mL of H₂O for 1 h. The product was again collected and dried to yield 21.6 g (83%) of 5-[(ethoxycarbonyl)methyl]-10,12-dihydroxy-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine: mp 195–197 °C dec; TLC (10% EtOH/toluene) *R_f* = 0.42; IR (KBr) 3375 (OH), 1710 (C=O) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.0 (t, 3 H, CH₃, *J* = 6 Hz), 2.45 (d, 1 H, CH₂ at C-5, *J* = 15 Hz), 3.1 (d, 1 H, benzylic, *J* = 1.3 Hz), 3.35 (d, 1 H, CH₂ at C-5, *J* = 15 Hz), 3.65 (d, 1 H, benzylic, *J* = 1.3 Hz), 3.95 (q, 2 H, ester CH₂, *J* = 15 Hz), 6.25 (s, 1 H, OH, exchanged by D₂O), 7.1 (m, 8 H, aromatic), 7.7 (s, 1 H, OH, exchanged by D₂O). This product was slurried in 125 mL of AcOH and to it was added portionwise 16 g of zinc dust. The mixture was stirred and heated at 65 °C for 3 h, filtered, and concentrated. The residue was dissolved in 500 mL of water and the pH was adjusted to 12 with 10% NaOH. The solid was collected and washed with water. After drying, 15 g (75%) of 18 was obtained: mp 195–197 °C; TLC (10% EtOH/toluene) *R_f* = 0.5; IR (KBr) 3310 (OH), 1740 (C=O) cm⁻¹; ¹H NMR δ 1.3 (t, 3 H, CH₃, *J* = 6 Hz), 2.9 (d, 1 H, CH₂ at C-5, *J* = 17 Hz), 3.2 (d, 1 H, benzylic, *J* = 18 Hz), 3.3 (d, 1 H, CH₂ at C-5, *J* = 17 Hz), 3.85 (d, 1 H, benzylic, *J* = 18 Hz), 4.2 (q, 2 H, ester CH₂, *J* = 6 Hz), 7.1 (m, aromatic and OH, 1 H exchanged by D₂O). The hydrochloride salt of 18 was prepared by dissolving the free base in 350 mL of hot acetone, mixing it with 7 mL of

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7 N ethanolic HCl, filtering, and drying. The yield of 18-HCl was 14.3 g; mp 247–250 °C dec.

10-Chloro-5-[(ethoxycarbonyl)methyl]-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine Hydrochloride (20). A slurry of 18-HCl (17.8 g, 0.052 mol) in thionyl chloride (250 mL) was warmed to reflux. Heating was stopped until the exothermic reaction subsided and then continued at reflux until a clear solution was obtained (ca. 20 min). The solution was concentrated and the residue was dried by repeated coevaporation with toluene and then suspended in acetone and filtered. After drying, the yield of white solid (20) was 15.4 g (81%); mp 223–227 °C dec; TLC (CHCl₃ saturated with concentrated aqueous NH₃) *R_f* = 0.87.

5-[(Ethoxycarbonyl)methyl]-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (22). A solution of 1.19 g of the hydrochloride of 20 in 150 mL of 5% ethanol in water was made basic by the addition of saturated NaHCO₃ and was extracted with CH₂Cl₂ (4 × 40 mL). Combined organics were washed with saturated NaHCO₃ (2 × 50 mL) dried, filtered, and concentrated to give 1.02 g of the free base as a light yellow solid.

The solid was dissolved in 14 mL of glacial acetic acid and to it was added portionwise 4.35 g of zinc dust. After heating at 60 °C for 16 h, the reaction mixture was filtered (rinsed in with 150 mL of CH₂Cl₂). The filtrate was concentrated to dryness, diluted with 50 mL of water, made basic with saturated NaHCO₃, and extracted with CH₂Cl₂ (4 × 50 mL). Combined organics were washed with water (2 × 50 mL) and brine (1 × 50 mL), dried, filtered, and concentrated to give a glassy solid. Column chromatography (3% MeOH/CHCl₃) gave 0.869 g (88%) of 22 as a white glassy solid: mp 83–85 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.20 (t, 3 H, *J* = 7.1 Hz), 2.72 (d, 1 H, *J* = 17.1 Hz), 3.30 (d, 1 H, *J* = 16.4 Hz), 3.44 (dd, 1 H, *J*₁ = 17.2 Hz, *J*₂ = 5.7 Hz), 3.58 (d, 1 H, *J* = 16.1 Hz), 4.12 (q, 2 H, *J* = 7.1 Hz), 4.75 (d, 1 H, *J* = 5.6 Hz), 6.93–7.35 (m, 8 H). Anal. (C₁₉H₁₉NO₂) C, H, N.

5(S*)-[1(R*)-(Ethoxycarbonyl)-1-hydroxymethyl]-10-(R*)-11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (23). A stirred solution of 30 mL of potassium hexamethyldisilazane (15 wt % or ca. 0.69 M in toluene) and 80 mL of dry THF was cooled to –78 °C and a solution of 2.3 g (7.8 mmol) of 22 in 25 mL of dry THF was added dropwise at a rate to maintain the internal temperature at –70 ± 8 °C. A solution of 5.1 g (20 mmol) of 3-phenyl-2-(phenylsulfonyl)oxaziridine⁴¹ in 20 mL of dry THF was added dropwise over 5 min. After an additional 15 min in the cold, the reaction was quenched with 10 mL of 6 N HCl. The mixture was concentrated to remove THF and then extracted 2× with 50 mL of ether. The aqueous layer was made basic with saturated NaHCO₃ and extracted with 3 × 50 mL of ethyl acetate. The combined organic extracts were dried and concentrated. The residue was recrystallized from 10 mL of 1:10 EtOAc/Et₂O in two crops. The combined yield was 2.06 g (85%) of a white crystalline solid: mp 145–146 °C; ¹H NMR δ 1.2 (t, 3 H, *J* = 7 Hz), 2.85 (d, 1 H, *J* = 18 Hz), 3.4 (dd, 1 H, *J* = 6 and 18 Hz), 4.15 (dq, 2 H, *J* = 7 and 1 Hz), 4.85 (d, 1 H, *J* = 6 Hz), 5.3 (s, 1 H), 7.2 (m, 8 H, aromatic). Anal. (C₁₉H₁₉NO₃) C, H, N.

5-Vinyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (33). This compound was isolated as a minor product of the reaction of cyclic sulfamate 26 with tetra-*n*-butylammonium fluoride in CH₃CN in the manner described earlier.¹⁸ With use of preparative HPLC to purify the products, 5-fluoroethyl product 28 eluted first, followed by 5-vinyl compound 33: ¹H NMR δ 2.7 (d, 1 H, *J* = 18 Hz), 3.5 (dd, 1 H, *J* = 6 and 18 Hz), 4.75 (d, 1 H, *J* = 6 Hz), 5.58 (d, 1 H, *J* = 10 Hz), 5.7 (d, 1 H, *J* = 18 Hz), 6.85 (dd, 1 H, *J* = 10 and 18 Hz). The hydrochloride of 33 had mp >206 dec. Anal. (C₁₇H₁₅N·HCl·0.6H₂O) C, H, N.

5-(Carboxymethyl)-10-hydroxy-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (34). A solution of 18 (15.5 g, 50 mmol) in 400 mL of THF and 250 mL of 1 N LiOH was stirred overnight and then concentrated. The pH of the aqueous solution was adjusted to 5.5 with 6 N HCl and the precipitate collected by filtration and washed with H₂O. Drying the solid at 65 °C for 2 h (0.1 mm) gave 15.2 g of 34: ¹H NMR (DMSO-*d*₆) δ 2.95 (d, 1 H, *J* = 18 Hz), 3.25 (d, 1 H, *J* = 18 Hz), 3.45 (d, 1 H, *J* = 18 Hz), 3.55 (d, 1 H, *J* = 18 Hz), 7.0–7.4 (m, 8 H). Anal.

(C₁₇H₁₅NO₃) C, H, N. Addition of 2.34 mL of 8.6 N ethanolic HCl to a solution of 5.65 g of 34 in 100 mL of acetone gave 5.40 g of 34 HCl.

5-[(Aminocarbonyl)methyl]-10-hydroxy-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (35). A pressure bottle was charged with 18 (0.62 g, 2 mmol), 1 N CH₃ONa in CH₃OH (10 mL), and anhydrous NH₃ (ca. 7 mL). After 4 h the mixture was concentrated, and the residue was dissolved in H₂O (50 mL), extracted into EtOAc (3 × 50 mL), and dried. Recrystallization from CH₃CN gave 0.250 g (45%) of 35: mp 242–243 °C; ¹H NMR (DMSO-*d*₆) δ 2.82 (d, 1 H, *J* = 18 Hz), 3.15 (d, 1 H, *J* = 18 Hz), 3.22 (d, 1 H, *J* = 18 Hz), 3.28 (d, 1 H, *J* = 18 Hz), 6.45 (s, 1 H), 6.9–7.3 (m, 8 H), 7.85 (s, 1 H). Anal. (C₁₇H₁₈N₂O₂) C, H, N.

5-(Carboxymethyl)-10-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (36). A solution of 20 (13.0 g, 35.7 mmol) in 725 mL of DME and 215 mL of 1 N LiOH was stirred overnight and then concentrated. The pH of the aqueous solution was adjusted to 6.5 with 3 N HCl and the precipitate was collected by filtration and washed with H₂O. Drying the solid at 65 °C for 2 h (0.1 mm) gave 6.8 g (68%) of 36: ¹H NMR (DMSO-*d*₆) δ 3.34 (d, 1 H, *J* = 18 Hz), 3.38 (d, 1 H, *J* = 18 Hz), 3.86 (d, 1 H, *J* = 18 Hz), 3.92 (d, 1 H, *J* = 18 Hz), 7.0–7.50 (m, 8 H). Anal. (C₁₇H₁₄ClNO₂) C, H, N.

5-[(Aminocarbonyl)methyl]-10-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (37). A solution of 34-HCl (1.9 g, 6 mmol) and SOCl₂ (30 mL) was heated to reflux for 15 min and then 60 mL of toluene was added and concentrated to dryness. The residue was dissolved in THF (40 mL) and concentrated NH₄OH (2 mL) was added. After concentration, the residue was dissolved in CHCl₃ (100 mL), washed 2 × 75 mL of H₂O, and dried. The residue, after purification by column chromatography (gradient elution of CHCl₃, 95:5:0.5 CHCl₃/CH₃OH/NH₄OH, then 90:10:1 CHCl₃/CH₃OH/NH₄OH) and recrystallization from EtOAc, gave 0.740 g of 37: mp 229–230 °C; ¹H NMR (DMSO-*d*₆) δ 3.32 (d, 1 H, *J* = 18 Hz), 3.38 (d, 1 H, *J* = 18 Hz), 3.48 (d, 1 H, *J* = 18 Hz), 3.88 (d, 1 H, *J* = 18 Hz), 5.35 (s, 1 H), 6.9–7.3 (m, 8 H), 7.7 (s, 1 H). Anal. (C₁₇H₁₅ClN₂O) C, H, N.

10,11-Dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine-5-α-hydroxyacetic Acid (38). To a solution containing 0.080 g (2.6 mmol) of hydroxy ester 23 in 25 mL of 1,2-dimethoxyethane was added a solution of lithium hydroxide hydrate (0.330 g, 8.0 mmol) in 5 mL of water. The mixture was stirred under nitrogen at 25 °C for 4 h, during which time a thick suspension formed. The pH was adjusted to 6.9 with 1 N HCl before removing most of the solvent in vacuo. The residue was taken up in a minimum volume of water and the resulting solution was stirred until the product crystallized to give 0.590 g (80%). Recrystallization from 2-propanol gave an analytical sample: mp 269–271 °C; ¹H NMR (DMSO-*d*₆) δ 2.86 (d, 1 H, *endo*-CH₂, *J* = 17 Hz), 3.52 (dd, 1 H, *exo*-CH₂, *J* = 5 and 17 Hz), 4.54 (s, 1 H, CH), 5.34 (d, 1 H, CH, *J* = 5 Hz), 7.08–7.32 (m, 5 H, Ar), 7.51 (dd, 2 H, *J* = 7 and 15 Hz, Ar), 8.20 (d, 1 H, Ar, *J* = 7 Hz). Anal. (C₁₇H₁₅NO₃) C, H, N.

5-(Hydroxyethyl)-10-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (39). To a stirred suspension of 36 (3.0 g, 10 mmol) in dry THF (20 mL) was added 25 mL of 1 M BH₃ in THF slowly. After warming to room temperature and stirring overnight, 6 N HCl (4 mL) was added cautiously. After 5 h, the mixture was concentrated, the residue was dissolved in H₂O (50 mL), and the pH was adjusted to 11 with 40% NaOH. The mixture was extracted into CHCl₃ (2 × 50 mL) and dried. Recrystallization from CH₃CN gave 2.5 g (87%) of 39: mp 144–147 °C; ¹H NMR δ 2.55 (complex m, 1 H), 2.8 (complex m, 1 H), 3.35 (d, 1 H, *J* = 18 Hz), 3.5 (br s, 1 H), 3.72 (d, 1 H, *J* = 18 Hz), 3.9 (complex m, 2 H), 4.2 (br s, 1 H), 6.9–7.5 (m, 8 H). Anal. (C₁₇H₁₆ClNO) C, H, N. Addition of 0.40 mL of 8.6 N ethanolic HCl to a solution of 0.857 g of 39 in 10 mL of acetone gave 0.810 g of 39-HCl.

5-(2-Chloroethyl)-10-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (40). A solution of 39-HCl (0.438 g, 1.5 mmol) and SOCl₂ (5 mL) was heated to reflux for 15 min then 60 mL of CHCl₃ was added and concentrated to dryness. The residue was dissolved in CHCl₃ (20 mL), washed with saturated Na₂CO₃ (15 mL) and H₂O (2 × 15 mL), and dried. The residue was dissolved in acetone, treated with 0.15 mL of 8.6 N

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ethanolic HCl, and filtered. Drying at 65 °C (0.1 mm) gave 0.360 g (70%) of 40-HCl: mp 247 °C dec; ¹H NMR (DMSO-*d*₆) δ 2.9 (dt, 1 H, *J* = 9 and 18 Hz), 3.5 (d, 2 H, *J* = 18 Hz), 3.8 (t, 2 H, *J* = 9 Hz), 3.9 (d, 1 H, *J* = 18 Hz), 7.0–7.6 (m, 8 H). Anal. (C₁₇H₁₅Cl₂N·HCl) C, H, N.

10-(4-Methyl-1-piperazinyl)-5-[2-(1,3-dithiylidene)]-5H-dibenzo[*a,d*]cycloheptene (42). A stirred solution of 2.3 mL (12.0 mmol) of 2-trimethylsilyl-1,3-dithiane in 10 mL of THF under N₂ was cooled in an ice/brine cold bath, and 7.8 mL (12.5 mL (12.5 mmol) of 1.6 M *n*-butyllithium in hexane was added over a 5-min period via a syringe. After stirring for 40 min at 0 °C, a solution of 3.04 g (10 mmol) of 10-(4-methyl-1-piperazinyl)-5H-dibenzo[*a,d*]cyclohepten-5-one (41)⁶ in 8 mL of THF was added rapidly dropwise. The solution was stirred in the cold for 1.5 h, quenched by pouring into saturated NH₄Cl, and worked up by extracting with two portions of CH₂Cl₂. The combined organic layers were washed with water and brine, dried over Na₂SO₄, and concentrated at reduced pressure. The residue was crystallized from EtOAc in two portions to afford 3.09 g (76%) of 42 as a yellow solid, which was used directly in the following reaction.

10,11-Dihydro-10-oximido-5-[2-(1,3-dithiylidene)]-5H-dibenzo[*a,d*]cycloheptene (43). A mixture of 10.0 g (24.6 mmol) of 42, 20.0 g (288 mmol) of NH₂OH·HCl, and 500 mL of methanol was heated at reflux for 1 h. The mixture was concentrated to approximately 200 mL, poured into H₂O, and extracted with three portions of CHCl₃. The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated to afford a yellow residue which was triturated with 1:9 (v/v) EtOAc/hexanes to give 8.73 g (100%) of 43 as a pale yellow solid. An analytical sample was obtained by crystallization from EtOAc/hexanes, mp 187–189 °C. Anal. (C₁₉H₁₇NOS₂) C, H, N.

10,11-Dihydro-10-amino-5-[2-(1,3-dithiylidene)]-5H-dibenzo[*a,d*]cycloheptene (44). To a stirred solution of 8.0 g (23.6 mmol) of 43 in 500 mL of acetic acid was added 32 g of Zn dust in one portion. The mixture was stirred in a 65 °C oil bath for 1.25 h, cooled briefly, filtered through a sintered-glass funnel, and concentrated to a small volume. The residue was dissolved in water, brought to pH 10 with aqueous NaOH, and extracted with two 300-mL portions of CHCl₃, and the combined organic layers were washed with water. After drying over MgSO₄, the solvents were removed by evaporation at reduced pressure to give 5.10 g (66%) of 44 as a yellow solid. An analytical sample was afforded by trituration with EtOAc/hexanes to give a pale yellow solid. Anal. (C₁₉H₁₉NS₂) C, H, N.

10,11-Dihydro-5-[2-(1,3-dithiyl)]-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (45). To a stirred solution of 5.66 g (17.4 mmol) of 44 in 500 mL of THF was added 12.0 mL (19.2 mmol) of 1.6 M *n*-butyllithium in hexane dropwise. After 40 min, the reaction was quenched by the addition of 3.0 mL of 1:1 MeOH–5% NaHCO₃. Evaporation at reduced pressure gave a residue which was diluted with water and extracted with two portions of CHCl₃. The combined organic layers were washed with water and dried over MgSO₄, and the solvents were removed at reduced pressure. The residue was crystallized from 175 mL of EtOAc to afford 3.09 g of 45 as a yellow solid. An additional 0.55 g was obtained by chromatography of the mother liquor on 250 g of silica gel with 1:1 EtOAc/hexanes, followed by crystallization to give a total of 3.64 g (64%). An analytical sample was provided by crystallization from EtOAc to give a colorless solid, mp 223–225 °C. Anal. (C₁₉H₁₉NS₂) C, H, N.

3-Chloro-10-(4'-methylpiperazin-1-yl)-5H-dibenzo[*a,d*]cyclohepten-5-one (61) and 7-Chloro-10-(4'-methylpiperazin-1-yl)-5H-dibenzo[*a,d*]cyclohepten-5-one (62). A solution of 20 g (0.0824 mol) of 3-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one^{19,42} (59), 0.2 g of dibenzoyl peroxide, and 32.3 g (0.018 mol) of *N*-bromosuccinimide in 400 mL of CCl₄ was heated to reflux (exothermic) for 6 h. The mixture was filtered, diluted with CHCl₃ (300 mL), washed with H₂O (3 × 250 mL), and dried. The residue after concentration was triturated with ether and filtered to yield 27.3 g (83%) of 3-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one (60): TLC (toluene) *R*_f = 0.68; ¹H NMR δ 5.7 (s, 2 H), 7.37 (m, 6 H, aromatic), 8.03 (m, 2 H, aromatic).

Dibromide 60 (27.3 g) was added to a solution of KOH (6 g) in methanol (750 mL). The mixture was heated to reflux for 1

h, cooled, and filtered. The precipitate was partitioned between CHCl₃ and H₂O. The organic phase was dried and concentrated, affording 20.1 g (90%) of a mixture of 10-bromo-3-chloro-5H-dibenzo[*a,d*]cyclohepten-5-one and 11-bromo-3-chloro-5H-dibenzo[*a,d*]cyclohepten-5-one: mp 155–165 °C; ¹H NMR 6.97–8.17 (overlapping signals, aromatic and vinyl); TLC (toluene) *R*_f = 0.58. The mixture of 10- and 11-bromo ketones (31.9 g, 0.1 mol) was dissolved in a solution of butyl alcohol (300 mL) containing 20 g of *N*-methylpiperazine and to it was added 14.3 g of potassium *tert*-butoxide. The reaction was stirred and heated under reflux for 4 h and concentrated. The residue was slurried with H₂O (225 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined extracts were concentrated, and the residue was triturated with ether. The crystalline solids that formed were recrystallized twice from CH₃CN and yielded 11.6 g (34%) of 61: mp 158–162 °C; ¹H NMR δ 2.3 (s, 3 H, CH₃), 2.57 (m, 4 H, CH₂), 2.93 (m, 4 H, CH₂), 6.3 (s, 1 H, H-11), 7.7 (m, 7 H, aromatic); TLC (10% MeOH/CHCl₃) *R*_f = 0.7.

The ether mother liquor from crystallization of 61 was concentrated and the residue purified by column chromatography (5% MeOH/CH₂Cl₂) to yield 62 (10.7 g, 42%) as a glass: ¹H NMR δ 2.3 (s, 3 H, CH₃), 2.6 (m, 4 H, CH₂), 2.93 (m, 4 H, CH₂), 6.4 (s, 1 H, H-10), 7.6 (m, 7 H, aromatic); TLC (5% MeOH/CH₂Cl₂) *R*_f = 0.4.

3-Chloro-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (63). To a solution of the enamino ketone 61 (23 g) in 100 mL of dry THF was added with stirring methylolithium in ether (1.4 M, 62 mL) and the reaction temperature was maintained at 0–5 °C. After 4 h, the mixture was concentrated and the residue was stirred with ice/water (100 mL) and the solid collected by filtration (22.5 g, 92%), mp 175–192 °C. The carbinol was stirred in EtOH (45 mL) with 43 mL of 7.3 N HCl and 20 mL of 6 N aqueous HCl for 45 min and then heated to reflux for 3 h, concentrated, diluted with H₂O (100 mL), and extracted into ether (3 × 60 mL). The extracts were dried, concentrated, and recrystallized from cyclohexane to yield 8.0 g (50%) of solid 3-chloro-5-methylene-10-oxo-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene: mp 86–93 °C; TLC (toluene) *R*_f = 0.5; ¹H NMR δ 4.07 (s, 2 H), 5.5 (d, 1 H, *J* = 1 Hz), 5.87 (d, 1 H, *J* = 1 Hz), 7.4 (m, 6 H), 8.2 (m, 1 H). The solid (7.65 g) was dissolved in 140 mL of MeOH containing NH₂OH·HCl (2.65 g) and NaOAc·3H₂O (5.35) and warmed to reflux for 3 h. After cooling, ether (150 mL) was added; the mixture was filtered and concentrated to dryness. The residue was partitioned between ether and H₂O; the organic phase was separated and dried. The residue on evaporation was recrystallized from ethanol and gave 7.1 g (87%) of the 10-oxime in two crops: mp 179–183 °C; ¹H NMR 4.1 (s, 2 H), 5.4 (d, 1 H, *J* = 1 Hz), 5.8 (d, 1 H, *J* = 1 Hz), 7.4 (m, 6 H), 7.85 (m, 1 H), 8.6 (br s, 1 H). Anal. (C₁₆H₁₂ClNO) C, H, N. The oxime (6.1 g) was dissolved in 200 mL of MeOH containing NaCNBH₃ (6 g). Ethanolic HCl was added dropwise to maintain the pH at 2–3. After 5 h the reaction was complete by TLC (3% MeOH/CHCl₃) and the mixture was concentrated. The residue was slurried with 1 N HCl, the pH was adjusted to 8 with concentrated NH₄OH, and the mixture was extracted with ether (3 × 100 mL). The extracts were dried and concentrated, and the residue was recrystallized from MeOH (6.1 g, 99%): mp 155–156 °C; ¹H NMR δ 3.35 (d, 2 H, *J* = 4 Hz), 4.43 (t, 1 H, *J* = 4 Hz), 5.35 (d, 1 H, *J* = 1 Hz), 5.57 (d, 1 H, *J* = 1 Hz), 7.3 (m, 8 H). Anal. (C₁₆H₁₄ClNO) C, H, N. The hydroxylamine (7.9 g) was heated as a slurry in *n*-octane to reflux. After 4 h, the crystalline product was collected (5.7 g, 72%): mp 173–176 °C; ¹H NMR δ 2.0 (s, 3 H), 2.5 (d, 1 H, *J* = 17 Hz), 3.65 (dd, 1 H, *J* = 17 and 6 Hz), 4.65 (d, 1 H, *J* = 6 Hz), 6.8–7.4 (m, 8 H). The cyclized product (5 g) was dissolved in AcOH (50 mL) and Zn dust (3.2 g) was added portionwise. The mixture was heated to 65 °C for 3.5 h, filtered, and concentrated. The residue was slurried with cold 5% NaOH and extracted with CH₂Cl₂ (3 × 150 mL). The extracts were dried and concentrated to yield 3.8 g (82%) of 62: ¹H NMR δ 1.87 (s, 3 H), 2.67 (d, 1 H, *J* = 17 Hz), 3.4 (m, 2 H), 4.7 (d, 1 H, *J* = 6 Hz), 6.8–7.4 (m, 7 H). The hydrochloride of 63, from ethanolic HCl/ether, and mp >300 °C. Anal. (C₁₆H₁₄ClN·HCl) C, H, N.

7-Chloro-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine (64). To a solution of enamino ketone 62 (28.5 g, 0.084 mol) in 100 mL of dry THF was added methylolithium in ether (1.4 M, 77 mL) and the temperature was maintained at

0–5 °C. After 4 h, the mixture was concentrated and the residue was slurried with ice/H₂O (100 mL) and the solid was collected by filtration (18.75 g, 63%), mp 132–154 °C. The carbinol (13.45 g) was stirred in EtOH (27 mL) and ethanolic HCl (27 mL, 7.3 N) at room temperature for 1 h and then 4 N HCl was added (12 mL) and the mixture was heated at reflux for 2 h. After cooling, the crystalline product was collected (6.4 g, 66%): mp 147–151 °C; IR 1670 cm⁻¹; ¹H NMR δ 4.05 (s, 2 H), 5.5 (d, 1 H, *J* = 1 Hz), 5.8 (d, 1 H, *J* = 1 Hz), 7.3 (m, 6 H), 8.05 (d, 1 H, *J* = 8 Hz). Anal. (C₁₆H₁₁ClO) C, H, N. The 5-methylene 11-ketone (6.4 g) was converted into 64 with an identical procedure as that described above for the conversion of the 5-methylene 10-ketone into 63. The intermediates had the following physical characteristics: 3-chloro-5-methylene-11-(hydroxyimino)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (91%), mp 167–170 °C; 3-chloro-5-methylene-11-(hydroxyamino)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (99%), mp 137–140 °C; 7-chloro-*N*-hydroxy-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (63%), mp 171–174 °C. Reduction of the 7-chloro-*N*-hydroxy intermediate (3.3 g) with zinc dust (2.3 g) for 3 h at 65 °C followed by workup as described for 63 gave 2.9 g (93%) of 64, mp 127–130 °C. The hydrochloride was obtained from 1.8 mL of 7 N EtOH HCl and 20 mL of ether (2.3 g): mp >300 °C; ¹H NMR δ 2.0 (s, 3 H), 7.8 (d, 1 H, *J* = 18 Hz), 3.6 (m, 1 H), 5.2 (d, 1 H, *J* = 3 Hz), 6.6–7.4 (m, 7 H). Anal. (C₁₆H₁₄ClN HCl) C, H, N.

3-Bromo-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5-ol (69). To 35 mL of dry THF was added 48 mL of methylmagnesium bromide solution (2.85 M in ether, 0.14 mol). The resulting solution was stirred in an ice bath and a solution of 28.5 g (0.10 mol) of 3-bromo-5*H*-dibenzo[a,d]cyclohepten-5-one⁴² (65) in 125 mL of dry THF was added over 20 min. When the addition was complete, the cooling bath was removed and the mixture was allowed to stir at ambient temperature for 6 h. The mixture was again cooled to 0 °C and an aqueous solution of 5 M ammonium chloride (100 mL) was added slowly until the foaming had subsided. The organic phase was separated and the aqueous layer, to which NaCl was added, was extracted with 2 × 100 mL of EtOAc. The combined organic layers were rotavaporated to remove THF, and the residue was taken up in 500 mL of EtOAc. The resulting solution was washed with dilute aqueous ammonium chloride and then with brine, and dried over MgSO₄. Removal of the solvent left an oil which crystallized from a mixture of EtOAc/pentane and gave 20.5 g (68%) of 69: mp 86–90 °C; ¹H NMR δ 1.56 (s, 3 H), 2.27 (s, 1 H), 6.95 (dd, 2 H, *J* = 12 and 30 Hz), 7.15–7.50 (m, 5 H), 7.93 (d, 1 H, 8 Hz), 8.14 (s, 1 H).

3-Methoxy-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5-ol (70). With use of the procedure described for 69, 3-methoxy-5*H*-dibenzo[a,d]cyclohepten-5-one⁴³ (66) gave 70 (100%): ¹H NMR δ 1.72 (s, 3 H), 2.35 (s, 1 H), 4.05 (s, 3 H).

3-Amino-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5-ol (71). With use of the procedure described for 69, 3-amino-5*H*-dibenzo[a,d]cyclohepten-5-one⁴⁴ (67) gave 71 (52%), which was not characterized due to its instability but used directly for the preparation of 75.

3-[(Trifluoromethyl)thio]-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5-ol (72). With use of the procedure described for 69, 3-(trifluoromethyl)-5*H*-dibenzo[a,d]cyclohepten-5-one⁴⁴ (68) gave 72 (83%): ¹H NMR δ 1.59 (s, 3 H), 2.29 (s, 1 H).

3-Bromo-5-methyl-5-(hydroxyamino)-5*H*-dibenzo[a,d]cycloheptane (73). A suspension of 13.8 g (0.199 mol) hydroxylamine hydrochloride and 18.0 g (0.220 mol) of NaOAc in 60 mL of CH₂Cl₂ was mixed with an efficient stirrer while 17.0 mL (0.206 mol) of dichloroacetic acid was added in a thin stream. The reaction, mildly exothermic during the addition, was allowed to continue in a 50 °C bath for 1 h, after which time a solution of

69 (3-bromo-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5-ol; 12.0 g, 0.040 mol), in 120 mL of CH₂Cl₂ was added over 5 min. The mixture was heated at reflux for 2 days until all of the carbinol had reacted, at which time it was poured onto crushed ice and basified with dilute NH₄OH. The layers were separated, and the aqueous phase was extracted two more times with CH₂Cl₂. The combined CH₂Cl₂ layers were washed with water and brine and then dried (Na₂SO₄). Removal of the solvent left an oil, which was purified by flash chromatography (1% CH₃OH in CHCl₃, saturated with NH₃). Trituration of the resulting oil with hexane afforded 8.0 g (63%) of 73: mp 150.5–154 °C; ¹H NMR δ 2.22 (s, 3 H, OH), 5.10 (br s, 2 H, exchangeable), 6.40 (br s, 1 H, exchangeable), 7.12 (dd, 2 H, vinyl, *J* = 12, 28 Hz), 7.22–7.80 (m, 7 H, Ar).

3-Methoxy-5-methyl-5-(hydroxyamino)-5*H*-dibenzo[a,d]cycloheptene (74). With use of the procedure described for the preparation of 73 (reaction period at reflux 1 h), from 70 there was obtained 88% of 74: ¹H NMR δ 2.23 (s, 3 H), 3.82 (s, 3 H).

3-Amino-5-methyl-5-(hydroxyamino)-5*H*-dibenzo[a,d]cycloheptene (75). With use of the procedure described for the preparation of 73 (reaction period at reflux 2 h), from 71 there was obtained 84% of 75: ¹H NMR δ 1.42 (minor) and 1.98 (major) (br s, 3 H).

3-[(Trifluoromethyl)thio]-5-methyl-5-(hydroxyamino)-5*H*-dibenzo[a,d]cycloheptene (76). With use of the procedure described for the preparation of 73 (reaction period at reflux 48 h), from 72 there was obtained 72% of 76: ¹H NMR δ 2.24 (s, 3 H).

12-Hydroxy-(3- and 7-bromo)-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (77 and 78). To a solution of 0.710 g (6.3 mmol) of potassium *tert*-butoxide in 20 mL of toluene containing 10% DMSO was added the solid hydroxylamine 73 (2.0 g, 6.3 mmol) over several minutes. The reaction flask was immersed in a 55 °C oil bath and the mixture was stirred for 15 min. The reaction, complete by TLC (toluene/ether 1:1), was quenched by dropwise addition of water and the product mixture was extracted into EtOAc. The combined EtOAc extracts were washed with brine and concentrated to a foam. This was taken up in 30 mL of toluene and the solution was then extracted with 3 × 25 mL of a 1:1 mixture of 1 N HCl/HOAc. The combined acidic aqueous extracts were chilled and treated with NH₄OH to pH 8. Three extractions with CH₂Cl₂, followed by washes with dilute NaHCO₃ solution and brine and then drying (Na₂SO₄), led to isolation of 1.7 g (85%) of a foam which was an 80/20 mixture, respectively, of 3- and 7-bromo-*N*-hydroxy-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imines by ¹H NMR analysis. The spectrum observed was a composite of the following resonances observed for each regioisomer prepared by a method that was unequivocal insofar as regiochemistry is concerned.¹⁴ For 3-bromo-*N*-hydroxy-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine: ¹H NMR δ 1.93 (major) and 1.99 (minor) (s, 3 H, CH₃), 2.51 (major) and 2.80 (minor) (d, 1 H, endo-CH₂, *J* = 17 Hz), 3.50–3.65 (m, 1 H, exo-CH₂), 4.66 (major) and 4.78 (minor) (d, 1 H, CH, *J* = 5 Hz), 6.76–7.45 (m, 8 H, Ar). For the 7-bromo isomer: ¹H NMR δ 1.93 (major) and 1.99 (minor) (s, 3 H, CH₃), 2.54 (major) and 2.83 (minor) (d, 1 H, endo-CH₂, *J* = 17 Hz), 3.55–3.71 (overlapping dd, 1 H, exo-CH₂, *J* = 5 and 17 Hz), 4.61 (major) and 4.73 (minor) (d, 1 H, CH, *J* = 5 Hz), 6.89–7.33 (m, 8 H, Ar).

Trituration of the foam with 10 mL of ether afforded 1.047 g of isomerically pure 3-isomer in two crops, mp 182–183 °C.

12-Hydroxy-7-methoxy-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (79). With use of the procedure described for 77 and 78, from 74 there was obtained 79 (96%) as a mixture of isomers. The ¹H NMR of 79 suggested a 9:1 preference of the 7-regioisomers: ¹H NMR δ 1.95 (major) and 2.00 (minor) (s, 3 H), 2.55 (major) and 2.83 (minor) (d, 1 H), 3.53–3.85 (m, 1 H), 3.70 (major) and 3.71 (minor) (s, 3 H), 4.60 (major) and 4.72 (minor) (d, 1 H), 6.55–7.33 (m, 7 H), 7.68 (major) and 7.87 (minor) (br s, 1 H).

12-Hydroxy-7-amino-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (80). With use of the procedure described for 77 and 78 but employing 2 equiv of potassium *tert*-butoxide, from 75 there was obtained 80 (90%) as a mixture of conformational isomers: ¹H NMR δ 1.90 (major) and 1.96 (minor) (s, 3 H), 2.52 (major) and 2.80 (minor) (d, 1 H), 3.45–3.67

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(m, 3 H), 4.55 (major) and 4.67 (minor) (d, 1 H), 6.35–7.35 (m, 8 H).

12-Hydroxy-3-[(trifluoromethyl)thio]-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (81). With use of the procedure described for 77 and 78, from 76 there was obtained 81 (57%) as a mixture of conformational isomers: ^1H NMR δ 1.96 (major) and 2.03 (minor) (s, 3 H), 2.60 (major) and 2.80 (minor) (d, 1 H), 3.57–3.71 (overlapping dd, 1 H), 4.64 (major) and 4.78 (minor) (d, 1 H), 6.92–7.68 (m, 8 H).

7-Bromo-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (82). A solution of 1.6 g (0.005 mol) of 78 in 3 mL of acetic anhydride was stirred for 1 h and concentrated to dryness. The residue was dissolved in dry THF and cooled to 0 °C. A solution of BH_3 in THF (60 mL of 1.0 M) was added and the solution was heated to reflux for 2 days. The reaction was cooled to 0 °C, quenched by the addition of H_2O (2 mL), and concentrated. The mixture was diluted with 150 mL of 0.5 N HCl and heated under reflux for 1.5 h. After cooling, the mixture was extracted with ether. The aqueous layer was made basic with concentrated NH_4OH and extracted with three portions of ether. The combined ether extracts were dried and concentrated to give 1.15 g of 82 as a white solid, mp 130–134 °C. The solid was dissolved in hot ethanol and converted to the hydrochloride with 0.6 mL of 7 N ethanolic HCl. After recrystallization from CH_3CN , there was obtained 0.900 g (53%) of 82-HCl: mp >300 °C; ^1H NMR δ 2.20 (s, 3 H), 3.05 (d, 1 H, J = 18 Hz), 3.75 (dd, 1 H, J = 6 and 18 Hz), 5.35 (d, 1 H, J = 6 Hz), 7.0–7.6 (m, 7 H). Anal. ($\text{C}_{16}\text{H}_{14}\text{BrN}\cdot\text{HCl}$) C, H, N.

7-Methoxy-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (83). With use of the zinc-acetic acid reduction procedure described for the preparation of 63, from 79 there was obtained 83 (99%): ^1H NMR δ 1.90 (s, 3 H), 2.72 (d, 1 H, J = 18 Hz), 3.43 (dd, 1 H, J = 6 and 18 Hz), 3.73 (s, 3 H), 4.65 (d, 1 H, J = 6 Hz), 6.61–7.28 (m, 7 H). The regiochemical assignment of the 7- OCH_3 substituent was verified by ^1H NMR experiments: irradiation of the benzylic methine proton produced a nuclear Overhauser enhancement (NOE) in the aromatic four-spin system whereas irradiation of either of the benzylic methylene resonances gave a NOE in the aromatic three-spin system. These results are in contrast to a similar study on 3-methoxy derivative 91, prepared from 3-bromo compound 88. Anal. ($\text{C}_{17}\text{H}_{17}\text{NO}\cdot\text{HCl}$) C, H, N.

7-Hydroxy-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (84). A mixture of 83-HCl (0.760, 2.6 mmol) and pyridine hydrochloride (3.9 g) was stirred at 200 °C for 90 min. The melt was cooled to ca. 50 °C, diluted with 25 mL of H_2O , basified with saturated NaHCO_3 , and extracted with ethyl acetate (3 \times 50 mL). After drying, the residue (0.500 g, 81%) was recrystallized from ethyl acetate and afforded 0.400 g of 84: mp 249–250 °C; ^1H NMR ($\text{DMSO}-d_6$) δ 1.75 (s, 3 H), 2.53 (d, 1 H), 3.26 (dd, 1 H, J = 5 and 16 Hz), 4.45 (d, 1 H, J = 5 Hz), 6.45 (m, 2 H), 6.89–7.27 (m, 5 H), 9.14 (s, 1 H, OH). Anal. ($\text{C}_{15}\text{H}_{15}\text{NO}$) C, H, N.

7-Amino-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (85). With use of the zinc-acetic acid reduction procedure described for the preparation of 63, from 80 there was obtained 85 (95%): ^1H NMR ($\text{CD}_3\text{CN}/\text{D}_2\text{O}$) δ 1.79 (s, 3 H), 2.60 (d, 1 H), 2.89 (s, 3 H, exchangeable with D_2O), 3.34 (dd, 1 H), 6.39 (m, 2 H), 6.92–7.30 (m, 5 H). The regiochemical assignment of the 7- NH_2 substituent was verified by ^1H NMR spin decoupling experiments which produced NOE's similar to those described for the 7-methoxy compound 83. The hydrogen fumarate salt of 85 was prepared in the usual manner, mp 251–253 °C dec. Anal. ($\text{C}_{16}\text{H}_{16}\text{N}_2\cdot\text{C}_4\text{H}_4\text{O}_4$) C, H, N.

7-Azido-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (86). To a mixture of H_2SO_4 (1.0 mL) and HOAc (5.0 mL) stirred in an ice bath was added 355 mg (1.0 mmol) of 7-amino-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen fumarate (85), followed by 0.147 mL of isoamyl nitrite (1.1 mmol). After stirring at –5 to 0 °C for 1 h, the mixture was diluted to 10 mL with cold water and stirring was continued for another 30 min. A small amount of Norit was added and after 10 min the mixture was filtered into an ice-cold flask. The yellow filtrate was treated with a solution of 130 mg (2.0 mmol) of sodium azide dissolved in 2 mL of water and soon thereafter nitrogen evolution was observed. Stirring was continued

at 0 °C for 2 h and then the mixture was basified with 40% NaOH, and a temperature of ≤ 25 °C was maintained. The mixture was extracted with 3 \times 15 mL of EtOAc, and the combined EtOAc extracts were washed with water, saturated aqueous Na_2CO_3 , water, and brine and dried (Na_2SO_4). The crude mixture was purified by column chromatography to remove some unreacted amino compound ($\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$, 95:5:0.5–90:10:1). 7-Azido compound 86 eluted as the less polar component: MS m/e M^+ = 262, $M - 28$ = 234; IR (CHCl_3) ν_{max} 2120, 1300 cm^{-1} , ^1H NMR δ 1.91 (s, 3 H), 2.72 (d, 1 H, J = 17 Hz), 3.45 (dd, 1 H, J = 5 and 17 Hz), 4.68 (d, 1 H, J = 5 Hz), 6.68–7.38 (m, 7 H). The free base was converted to its hydrochloride salt with ethanolic HCl. Anal. ($\text{C}_{16}\text{H}_{14}\text{N}_4\cdot\text{HCl}$) C, H, N.

3-[(Trifluoromethyl)thio]-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (87). With use of the zinc-acetic acid reduction procedure described for the preparation of 63, but increasing the reaction time to >6 h, from 81 there was obtained 87 (28%) after column chromatography to separate unreacted N-hydroxy starting material from the product: ^1H NMR δ 1.93 (s, 3 H), 2.54 (br s, 1 H), 2.76 (d, 1 H), 3.47 (dd, 1 H), 4.71 (d, 1 H), 6.95–7.57 (m, 7 H). The regiochemical assignment of the 3- SCF_3 substituent was verified by ^1H NMR spin decoupling experiments which produced NOE's opposite to those described for 7-methoxy compound 83. The hydrogen chloride salt of 87 was prepared in the usual manner. Anal. ($\text{C}_{17}\text{H}_{14}\text{F}_3\cdot\text{NS}\cdot\text{HCl}$) C, H, N.

3-Bromo-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (88). A solution of 3.8 g (0.012 mol) of 77 in 8 mL of acetic anhydride was stirred under nitrogen for 2 h. The solution was concentrated to dryness and the residue was dissolved in 90 mL of dry THF. A solution of borane in THF (135 mL of 1.0 M) was added under a nitrogen atmosphere at 0 °C and when the addition was complete the mixture was stirred at reflux for 3 days, until, following a miniworkup, the reaction was complete by TLC (98:2, $\text{CHCl}_3/\text{CH}_3\text{OH}$). Chilled in an ice bath, the reaction was quenched by dropwise addition of water and when the gas evolution had ceased the THF was removed in vacuo. The residue was suspended in 80 mL of 1 N HCl and stirred at 90 °C for 2 h. Upon cooling, the mixture was filtered and the filtrate was made alkaline with 10% NaOH. Extractions with toluene/EtOAc mixtures resulted in isolation of 4.1 g of a solid (88) which was taken up in ether and treated with ethanolic HCl to precipitate 3-bromo-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrochloride (88-HCl) as a white solid: 3.45 g (86%); mp >310 °C; ^1H NMR δ 2.22 (s, 3 H, CH_3), 3.05 (d, 1 H, endo- CH_2 , J = 17 Hz), 3.64 (dd, 1 H, exo- CH_2 , J = 5 and 17 Hz), 5.37 (d, 1 H, CH, J = 5 Hz), 7.08 (d, 1 H, Ar, J = 8 Hz), 7.35–7.58 (m, 5 H, Ar), 7.68 (d, 1 H, Ar, J = 2 Hz). Anal. ($\text{C}_{16}\text{H}_{14}\text{BrN}\cdot\text{HCl}$) C, H, N.

3-Iodo-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (89). A mixture of 88 (600 mg, 2.0 mmol), nickel powder (585 mg, 10.0 mmol, 5 μm from Strem Chemical Co.), potassium iodide (665 mg, 4.0 mmol), and iodine (25 mg, 0.1 mmol) in 3 mL of dry dimethylformamide was degassed with nitrogen for 10 min and then immersed in a preheated 150 °C oil bath. After stirring under nitrogen for 6 h, the mixture was cooled, diluted with 50 mL of water, and extracted with EtOAc, the liquid mixture was decanted from the metallic solids and the latter was washed several times with fresh solvent. The combined organic layers were further diluted with 30 mL of hexane, washed (aqueous NaHCO_3), and dried. Evaporation of the solvents left 600 mg (86%) of (89) as an oil. Trituration with ether/hexane gave a pale yellow solid (310 mg), mp 135–138 °C. Column chromatography of the mother liquors (EtOAc/acetone, 2:1) provided another 100 mg of product. An analytical sample was prepared by recrystallization from ether/hexane: mp 138.5–140 °C; ^1H NMR δ 1.89 (s, 3 H, CH_3), 2.60 (br s, 1 H, NH), 2.66 (d, 1 H, endo- CH_2 , J = 17 Hz), 3.38 (dd, 1 H, exo- CH_2 , J = 5 and 17 Hz), 4.70 (d, 1 H, CH, J = 5 Hz), 6.68 (d, 1 H, Ar, J = 8 Hz), 7.10–7.34 (m, 4 H, Ar), 7.41 (dd, 1 H, Ar, J = 2 and 8 Hz), 7.57 (d, 1 H, Ar, J = 2 Hz). Anal. ($\text{C}_{16}\text{H}_{14}\text{IN}$) C, H, N.

3-Hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (90). A solution containing 0.600 g (2.0 mmol) of 88 in 12 mL of freshly distilled THF was stirred under nitrogen at –78 °C; a 1.7 M solution of *tert*-butyllithium in pentane (2.9 mL, 5.0 mmol) was added dropwise. After 15 min at –78 °C,

the solution was warmed to -20°C and, after 30 min at that temperature, was again chilled to -78°C . A solution of trimethyl borate (0.62 mL, 5.5 mmol) in 3 mL of dry THF was added and the reaction mixture was warmed to and stirred at 25°C for 1 h. After cooling to 0°C , the mixture was treated with 0.37 mL (6.2 mmol) of acetic acid dissolved in 2 mL of THF. The cooling bath was removed, and after 15 min, a solution containing 2.0 mL of 30% hydrogen peroxide in 5 mL of THF was added. After 18 h at 0°C , the mixture was allowed to warm to 25°C prior to workup: Saturated aqueous NaHCO_3 (30 mL) was added and the mixture was extracted three times with ether. After washing and drying of the combined ether extracts, the solvent was removed to give an oil residue. The latter was purified by column chromatography (EtOAc, gradient of CH_3OH , from 10% to 20%). The product fractions were combined to give an oil which was recrystallized from EtOAc: mp $269\text{--}269.5^{\circ}\text{C}$; $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 1.74 (s, 3 H), 2.45 (d, 1 H), 3.18 (dd, 1 H), 3.40 (br d, 1 H, exchangeable), 4.51 (d, 1 H), 6.41–7.35 (m, 7 H), 9.08 (s, 1 H, CH, exchangeable). Anal. ($\text{C}_{16}\text{H}_{15}\text{NO}$) C, H, N.

3-Methoxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine (91). A suspension of **90** (0.195 g, 0.82 mmol) in 5 mL of CHCl_3 , stirred in an ice bath, was treated with 0.114 mL (0.82 mmol) of triethylamine, followed by the dropwise addition of di-*tert*-butyl dicarbonate dissolved in 3 mL of CHCl_3 . The mixture was stirred for 18 h at 25°C , during which time complete solution was obtained. The solution was diluted with CHCl_3 and washed twice with aqueous NaHCO_3 and dried. The residue after evaporation was purified by chromatography (CHCl_3 , gradient 5–10% CH_3OH) to afford 0.200 g (72%) of the *N*-BOC protected compound: $^1\text{H NMR}$ δ 2.11 (s, 9 H), 2.18 (s, 3 H), 2.54 (d, 1 H, $J = 17$ Hz), 3.58 (dd, 1 H, $J = 5$ and 17 Hz), 5.35 (d, 1 H, $J = 5$ Hz), 6.10 (br s, 1 H, exchangeable), 6.52 (dd, 1 H, $J = 2.5$ and 8 Hz), 6.73 (d, 1 H, $J = 8$ Hz), 6.81 (d, 1 H, $J = 2.5$ Hz), 6.97–7.33 (m, 4 H).

A mixture of 0.180 g (0.53 mmol) of the *N*-BOC protected tricyclic phenol, 0.166 g (0.53 mmol) of benzyltributylammonium chloride, 0.083 mL (1.33 mmol) of iodomethane, and 0.80 mL (0.80 meq) of 1.0 N NaOH was vigorously stirred in a mixture of 4 mL of CH_2Cl_2 and 3 mL of water under nitrogen for 18 h. The reaction mixture was partitioned between 30 mL each of CH_2Cl_2 and water. Extraction of the aqueous phase with additional CH_2Cl_2 led to isolation of a dark yellow oil which was then partitioned between ether and water. The layers were separated, the aqueous layer was extracted twice more with ether, and the combined ether layers were washed twice with 2 N NaOH and dried. Evaporation of the solvent left 0.150 g of an oil: $^1\text{H NMR}$ δ 1.40 (s, 9 H), 2.23 (s, 3 H), 2.55 (d, 1 H, $J = 17$ Hz), 3.60 (m, 1 H), 3.76 (s, 3 H), 5.34 (d, 1 H, $J = 5$ Hz), 6.62 (dd, 1 H, 2.5, $J = 8$ Hz), 6.82 (d, 1 H, $J = 8$ Hz), 6.87 (s, 1 H, 2.5 $J = \text{Hz}$), 7.05–7.33 (m, 4 H).

Amine deprotection was accomplished by treating a CH_2Cl_2 solution of the crude *N*-BOC 3-methoxy compound at 0°C with 1 mL of trifluoroacetic acid. The cooling bath was removed and the mixture was stirred for 45 min and then concentrated to dryness. The residue was washed twice with CH_2Cl_2 and ether, leaving an oil which was basified with saturated aqueous NaHCO_3 and extracted into ether. After drying and removal of solvents, there was obtained 0.100 g of **91** (75%): $^1\text{H NMR}$ δ 1.91 (s, 3 H), 2.60 (br s, 1 H, exchangeable), 2.68 (d, 1 H, $J = 17$ Hz), 3.40 (dd, 1 H, $J = 5$ and 17 Hz), 3.76 (s, 3 H), 4.70 (d, 1 H, $J = 5$ Hz), 6.60–7.33 (m, 7 H). The hydrochloride salt was prepared by addition of ethanolic HCl and precipitation from ether. Recrystallization from CH_3CN /EtOH gave **91**·HCl: Anal. ($\text{C}_{17}\text{H}_{17}\text{NO}\cdot\text{HCl}\cdot 0.125\text{CH}_3\text{CN}$) C, H, N.

3-Carboxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine (92). In a three-neck flask fitted with a thermometer, magnetic stirrer, rubber septum, and a gas inlet tube connected to a bubbler was dissolved 0.500 g (1.66 mmol) of **88** in 10 mL of freshly distilled THF. The solution, stirred at -78°C under nitrogen, was treated with 2.45 mL (4.15 mmol) of a 1.7 M solution of *tert*-butyllithium in pentane. After stirring at -78°C for 30 min, the nitrogen was replaced by dry CO_2 (generated from dry ice by sublimation through a CaSO_4 drying tube connected with tubing to the reaction vessel). After several minutes a copious white precipitate had formed and the cooling bath was removed. Stirring under CO_2 was continued at ambient temperature for 2 h and then 1 mL of H_2O was added and the

THF was evaporated in vacuo. The residue was slurried in 20 mL of H_2O for 1 h and then filtered. The clear filtrate was carefully adjusted to pH 6.5 by addition of AcOH. The white solid which precipitated was washed with H_2O and then ether/ CH_3CN and dried to yield 0.280 g (64%) of **92**: $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 1.87 (s, 3 H), 2.66 (d, 1 H, $J = 17$ Hz), 3.39 (dd, 1 H, $J = 5$ and 17 Hz), 4.61 (d, 1 H, $J = 5$ Hz), 7.00–7.17 (m, 4 H), 7.33 (d, 1 H, $J = 8$ Hz), 7.64 (dd, 1 H, 2 and 8 Hz), 7.83 (s, 1 H). Anal. ($\text{C}_{17}\text{H}_{15}\text{NO}_2\cdot 0.5\text{H}_2\text{O}$) C, H, N.

3-(Hydroxymethyl)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (94). 3-Carboxy compound **92** (0.265 g, 1 mmol) was suspended in 25 mL of absolute CH_3OH and boron trifluoride etherate (0.6 mL, 5 mmol) was added. The mixture was stirred at reflux for 18 h, after which the solvent was removed in vacuo. The residue was basified with dilute aqueous NaHCO_3 and the methyl ester was extracted into ether. From the combined ether extracts was obtained 0.240 g (86%) of 3-(methoxycarbonyl)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (**93**): $^1\text{H NMR}$ δ 1.99 (s, 3 H), 2.63 (br s, 1 H, exchangeable), 2.80 (d, 1 H, $J = 17$ Hz), 3.50 (dd, 1 H, $J = 5$ and 17 Hz), 3.90 (s, 3 H), 4.72 (d, 1 H, $J = 5$ Hz), 7.01–7.33 (m, 5 H), 7.77 (dd, 1 H, $J = 2$ and 8 Hz), 7.95 (d, 1 H, $J = 2$ Hz). A solution of the methyl ester in a mixture of ether (20 mL) and dry THF (10 mL) was added dropwise with stirring to a suspension containing 0.087 g (2.3 mmol) of lithium aluminum hydride in 25 mL of dry ether at 40°C under an inert atmosphere. When the addition was complete the mixture was heated at 55°C for 2 h and then stirred at 25°C for 18 h. The mixture was chilled in an ice bath and the reaction was quenched by the dropwise addition of 10 mL of saturated aqueous sodium potassium tartrate. After stirring for several hours, the mixture was filtered and the white solid was washed with H_2O , and the ether was then dried to give 0.185 g (74%) of **94**, mp $215\text{--}217^{\circ}\text{C}$. Additional product was obtained from the ether washings: $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 1.80 (s, 3 H), 2.55 (d, 1 H, $J = 17$ Hz), 3.28 (dd, 1 H, $J = 5$ and 17 Hz), 3.35 (br s, 1 H, exchangeable), 4.39 (s, 2 H), 4.54 (d, 1 H, $J = 5$ Hz), 5.06 (s, 1 H, exchangeable), 6.85 (d, 1 H, $J = 8$ Hz), 6.96–7.34 (m, 6 H). Anal. ($\text{C}_{17}\text{H}_{17}\text{NO}\cdot 0.5\text{H}_2\text{O}$) C, H, N.

3,5-Dimethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (95). To a mixture of 76.5 mg (0.14 mmol) of 1,3-bis(diphenylphosphino)propane nickel(II) chloride in 40 mL of dry THF was added methylmagnesium bromide in ether (4.5 mL of 3.0 M). The solution was cooled to 0°C and a solution of zinc chloride in ether (13.5 mL of 1.0 M) was added. To this mixture was added 0.412 g (1.37 mmol) of **88**. The mixture was warmed to reflux for 26 h. After cooling the reaction was quenched by addition of 400 mL of H_2O and diluted with 100 mL of ether and 200 mL of concentrated NH_4OH . The aqueous layer was extracted 2×100 mL of ether, and the combined extracts were dried and concentrated. The residue was purified by column chromatography (EtOAc) to give 315 mg (95%) of **95**, which was contaminated with ca. 10% of reduced product **10**. Preparative HPLC (0.1% TFA- H_2O / CH_3CN gradient elution) gave a sample of the TFA salt of **95**, uncontaminated with **10**. Conversion to the free base with dilute NaOH, extraction into ether, drying, and addition of ethanolic HCl gave **95**·HCl (99.1% pure by HPLC): $^1\text{H NMR}$ (CD_3OD) δ 2.22 (s, 3 H), 2.33 (s, 3 H), 3.05 (d, 1 H, $J = 17$ Hz), 3.66 (dd, 1 H, $J = 5$ and 17 Hz), 5.33 (d, 1 H, $J = 5$ Hz), 6.99–7.57 (m, 7 H). Anal. ($\text{C}_{17}\text{H}_{17}\text{N}\cdot\text{HCl}\cdot 0.4\text{H}_2\text{O}$) C, H, N.

3-(1-Butyl)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (96). To a solution of *n*-butyllithium (13.3 mL, 1.6 M in hexane, 0.021 mol) in THF (20 mL) at -65°C was added over 5 min a solution containing 2.56 g (0.085 mol) of **88** in 15 mL of THF. The mixture was stirred at 0°C for 1 h and then at 25°C for 18 h. The mixture was diluted with 200 mL of ether, washed with dilute aqueous NaHCO_3 , and dried. Column chromatography (CHCl_3 / CH_3OH / NH_4OH 95:5:0.5) of the oil remaining after evaporation of the solvents afforded 1.5 g of an oil which solidified upon trituration with EtOAc/ether. This material was shown to have a minor amount of reduction product **10** which was not removable by recrystallization. Preparative HPLC (Delta Pak, C-18 100 Å; $f = 100$ mL/min; gradient, solvent A = water, solvent B = CH_3CN , 1 mL TFA/liter of each solvent, 0–60% B over 1 h) afforded **96** which was 99.7% pure; $^1\text{H NMR}$ δ 0.93 (t, 3 H, 7 Hz), 1.28–1.58 (m, 4 H), 1.92 (s, 3 H), 2.52 (t, 2 H, $J = 7$ Hz), 2.71 (d, 1 H, $J = 17$ Hz), 3.42 (dd,

1 H, $J = 5$ and 17 Hz), 4.68 (d, 1 H, $J = 5$ Hz), 6.82–7.33 (m, 7 H). The hydrochloride salt was prepared in the usual manner. Anal. ($C_{20}H_{23}N \cdot HCl$) C, H, N.

3-Phenyl-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (97). A solution of 0.300 g (1 mmol) of 88 and 0.35 g (1.6 mmol) of di-*tert*-butyl dicarbonate in 50 mL of $CHCl_3$ was heated to reflux for 5 h and then concentrated to dryness. The residue was triturated with hexanes to give 0.400 g of the *N*-BOC protected 3-bromo compound which was homogeneous by TLC (5% EtOAc/hexanes): 1H NMR δ 1.40 (s, 9 H), 2.2 (s, 3 H), 2.55 (d, 1 H, $J = 18$ Hz), 3.58 (br dd, 1 H, $J = 6$ and 18 Hz), 5.35 (d, 1 H, $J = 6$ Hz), 3.8 (d, 1 H, $J = 9$ Hz), 7.05–7.45 (m, 6 H). A stirred solution of 1,1'-bis(diphenylphosphino)ferrocene⁴⁵ (26 mg) and $Pd(OAc)_2$ (15 mg) in 20 mL of dry THF was warmed to reflux for 10 min and then cooled to 0 °C. To this cold solution was added, in sequence, 2 mL of 1 M phenyllithium in ether, 2 mL of 1 M $ZnCl_2$ in ether, and the *N*-BOC-3-bromo-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (0.400 g, 1 mmol) in 5 mL of THF. After stirring at ambient temperature for 24 h, the reaction was quenched with 100 mL of dilute aqueous NH_3 and extracted into 3 \times 50 mL of ether. The residue was purified by column chromatography (5% EtOAc/hexanes) to give 0.38 g (95%) of *N*-BOC 97, which was homogeneous by TLC: 1H NMR δ 1.40 (s, 9 H), 2.30 (s, 3 H), 2.65 (d, 1 H, $J = 18$ Hz), 3.70 (dd, 1 H, $J = 6$ and 18 Hz), 5.4 (d, 1 H, $J = 6$ Hz), 7.2–7.85 (m, 12 H). *N*-BOC 97 was taken up in 5 mL of anhydrous CF_3CO_2H , kept at 25 °C for 1 h, and then concentrated to dryness. The residue was partitioned between dilute aqueous NH_3 and $CHCl_3$ (100 mL of each) and the organic layer was concentrated to dryness. The residue was dissolved in ether and converted to the hydrochloride by addition of ethanolic HCl. The product (97-HCl) obtained in this manner (0.25 g, 76%) was 99.95% pure by analytical HPLC (210 nm): mp >190 °C dec; 1H NMR ($DMSO-d_6$) δ 2.25 (s, 3 H), 3.0 (d, 1 H, $J = 18$ Hz), 3.65 (dd, 1 H, $J = 6$ and 18 Hz), 5.4 (d, 1 H, $J = 6$ Hz), 7.2–7.85 (m, 12 H). Anal. ($C_{22}H_{19}N \cdot HCl \cdot 0.5H_2O$) C, H, N.

2-Methoxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5-ol (99). With use of the procedure described for 69, from 2-methoxy-5H-dibenzo[a,d]cyclohepten-5-one⁴³ (98) there was obtained 99 (77%): 1H NMR δ 1.72 (s, 3 H), 2.35 (s, 1 H), 3.78 (s, 3 H).

2-Methoxy-5-methyl-5-(hydroxyamino)-5H-dibenzo[a,d]cycloheptene (100). With use of the procedure described for 73 (reaction period at reflux 1 h), from 99 there was obtained 100 (65%): 1H NMR δ 1.72 (s, 3 H), 2.35 (s, 1 H), 3.78 (s, 3 H).

12-Hydroxy-(2- and 8-methoxy)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (101 and 102). With use of the procedure described for 77 and 78, from 100 there was obtained 72% of 101 and 102, as a mixture of isomers (2-methoxy isomers were major): 1H NMR δ 1.99 and 2.05 (s, 3 H, CH_3), 2.57 and 2.84 (d, 1 H, endo- CH_2 , 17 Hz), 3.44–3.78 (m, 1 H, exo- CH_2), 3.66 and 3.68 and 3.72 and 3.74 (s, 3 H, OCH_3), 4.60 and 4.72 (d, 1 H, CH, 5 Hz), 6.38–7.30 (m, 7 H, Ar).

(2- and 8-Methoxy)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (103 and 104). To a solution of 101 and 102 (2.78 g, 0.01 mol) in glacial HOAc (50 mL) was added 2.6 g of zinc dust portionwise. The mixture was stirred and heated at 65 °C for 90 min, cooled, and filtered. The filtrate was poured onto 50 mL of crushed ice, basified with $(NH_4)_2SO_4$, and concentrated to a foam to give 2.3 g (92%) of 103 and 104: 1H NMR 1.91 and 1.92 (s, 3 H, CH_3), 2.73 and 2.76 (d, 1 H, endo- CH_2 , $J = 17$ Hz), 3.45 (dd, 1 H, exo- CH_2 , $J = 5$ and 17 Hz), 3.72 and 3.77 (s, 3 H, OCH_3 , ratio = 3:1), 4.69 and 4.70 (d, 1 H, CH, $J = 5$ Hz).

2-Hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (105) and 8-Hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (106). A solution of the regioisomeric mixture of 2- and 8-methoxy compounds 103 and 104 (1.7 g, 6.9 mmol, isomer ratio ca. 3:1) in 75 mL of CH_2Cl_2 , stirred under argon at –78 °C, was treated with a 1.0 M solution of boron tribromide in CH_2Cl_2 (1.4 mL, 14.0 mmol) over 5 min. After 30 min, the cooling bath was removed and the mixture was stirred at ambient temperature for 2 h, until

the reaction was complete by TLC (CH_2Cl_2 /acetone/ CH_3OH , 65:20:15). The mixture was cooled to 10 °C, treated with brine and with NH_4OH to pH 7.0 and then with saturated aqueous $NaHCO_3$. The alkaline mixture was filtered, the layers of the filtrate were separated, and the CH_2Cl_2 phase was set aside. The solids and the aqueous phase were recombined and extracted with 3 \times 75 mL of *n*-butanol, after which the combined butanol extracts were twice washed with brine. The residue left after evaporation of the butanol was dissolved in CH_2Cl_2 and the solution was added to the previously isolated CH_2Cl_2 solution. Upon washing with $NaHCO_3$ and brine, the solution was dried (Na_2SO_4) and purified by column chromatography elution with $CHCl_3$ saturated with NH_3 , 5% CH_3OH . The early homogeneous fractions ($R_f = 0.36$) were combined and concentrated to an oil (1.0 g). Trituration with EtOAc afforded 0.56 g of the isomerically pure 2-hydroxy isomer 105 as a solid, mp 208–212 °C.¹⁴

The remaining mixed fractions were combined to give 0.66 g of the 2- and 8-hydroxy isomers ($R_f = 0.36$ and 0.32, respectively). Conversion to the hydrogen fumarate salts in acetone/ethanol led to preferential crystallization of the 2-isomer (0.46 g). The mother liquors, enriched in the 8-isomer, were converted back to the free base with $NaHCO_3$, and trituration of the oil residue with EtOAc afforded the pure 8-hydroxy compound 106, mp 245–247 °C.¹⁴

3,7-Diamino-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (107). A mixture of 3,7-dinitro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one⁴⁶ (36 g), 10% palladium on carbon (2.0 g), and ethanol (1.4 L) were shaken under 50 psi of hydrogen for 4 h at 23 °C. The catalyst was filtered off and the filtrate concentrated to dryness. The solid remaining (28 g) was sufficiently pure to be used for diazotization: mp 167.5–169 °C; TLC (15% EtOAc/ $CHCl_3$) $R_f = 0.14$.

3,7-Difluoro-5H-dibenzo[a,d]cyclohepten-5-one (108). A suspension of 10.0 g (0.042 mol) of 107 in 18 mL of a 48% aqueous solution of fluoboric acid was stirred mechanically in an ice/salt bath as a solution containing 6.2 g (0.089 mol) of sodium nitrite in 10 mL of cold water was added over 30 min. The mixture was stirred at 0 °C for 2 h and filtered, and the red-brown solid washed with 10-mL portions of ice water, cold CH_3OH , and ether. The air-dried material (15.26 g, 84%) contained no starting material by TLC (EtOAc/ CH_3CH 80:20). The crude diazonium salt was decomposed by adding the solid portionwise to 1100 mL of xylene at 125 °C, the gaseous byproducts being swept out of the reaction flask under a stream of nitrogen into a trap of crushed ice. After the addition was complete (30 min) stirring was continued at reflux for 2 h. Upon cooling, the tarry byproducts were removed by filtration, and the filtrate was washed with water and 5% NaOH and dried. Removal of the solvents left 11.4 g of a red, oily solid. Recrystallization from ethanol gave pure 3,7-difluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one: mp 99–105 °C; 1H NMR δ 3.16 (s, 4 H, CH_2), 7.10–7.28 (m, 4 H, Ar), 7.72 (dd, 2 H, Ar, $J = 3$ and 9.5 Hz).

A mixture containing 4.3 g (0.017 mol) of 3,7-difluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one, 6.6 g (0.037 mol) of *N*-bromosuccinimide, and 200 mg of dibenzoyl peroxide in 140 mL of CCl_4 was stirred at reflux for 24 h by which time the bromine color in the refluxate had disappeared. The mixture was cooled to 25 °C and filtered to remove succinimide. The filtrate was washed with 2% NaOH and H_2O and dried.

Evaporation gave a sticky yellow solid (7.1 g, 100%): 1H NMR δ 5.78 (s, 2 H, CH), 7.15–7.55 (m, 4 H, Ar), 7.80 (dd, 2 H, Ar, $J = 3$ and 9.5 Hz). This crude 10,11-dibromo compound (7.1 g, 0.017 mol) was dissolved in 75 mL of acetone and treated with a solution of sodium iodide (12.5 g, 0.083 mol) in 35 mL of acetone. The mixture, which had turned red-brown on mixing, was stirred at reflux for 15 min and then concentrated to dryness. The residue was partitioned between EtOAc and dilute aqueous sodium bisulfite. The organic phase was washed once more with bisulfite solution and water and dried. Evaporation gave a yellow solid, which was purified by column chromatography ($CHCl_3$ /hexane 2:1) to give 4.0 g of pure 3,7-difluoro-5H-dibenzo[a,d]cyclohepten-5-one (108): mp 163–164 °C; 1H NMR δ 7.01 (s, 2 H, vinyl),

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7.36 (ddd, 2 H, H-2 and H-8, $J = 3_{\text{(HH)}}, 8_{\text{(HH)}}, \text{ and } 10_{\text{(HF)}} \text{ Hz}$), 7.58 (dd, 2 H, H-1 and H-9, $J = 4.5_{\text{(HF)}} \text{ and } 8_{\text{(HH)}} \text{ Hz}$), 7.96 (dd, 2 H, H-4 and H-6, $J = 3_{\text{(HH)}} \text{ and } 10_{\text{(HF)}} \text{ Hz}$). Anal. ($\text{C}_{15}\text{H}_{18}\text{F}_2\text{O}$) C, H, N.

3,7-Difluoro-5-methyl-5H-dibenzo[a,d]cyclohepten-5-ol (109). With use of the procedure described for 69, from 3,7-difluoro-5H-dibenzo[a,d]cyclohepten-5-one (108) there was obtained 109 (89%): $^1\text{H NMR } \delta$ 1.58 (s, 3 H), 2.30 (s, 1 H).

3,7-Difluoro-5-methyl-5-(hydroxyamino)-5H-dibenzo[a,d]cycloheptene (110). With use of the procedure described for 73 (reaction period at reflux 72 h), from 109 there was obtained 110 (65%): $^1\text{H NMR } \delta$ 2.16 (s, 1 H).

12-Hydroxy-3,7-difluoro-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (111). A mixture of 110 (0.90 g, 0.033 mol), 0.50 g (0.045 mol) potassium *tert*-butoxide, and 10 mL of a DMSO/toluene (1:9) was heated to 65 °C. After 1 h, the reaction mixture was poured onto crushed ice and extracted with EtOAc. The combined organic phases were concentrated to dryness, and the residue was taken up in toluene. The resulting solution was then extracted twice with 1:1 HOAc/1 N HCl mixtures. The combined aqueous acidic extracts were made alkaline (pH 8.5) with NH_4OH and extracted with CH_2Cl_2 . The combined CH_2Cl_2 extracts were concentrated and purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ 9:1) to afford 0.274 g of an oil which was 55:45 mixture of uncyclized starting material (110) and cyclized product (111) by $^1\text{H NMR}$. The mixture was not separable by TLC or HPLC: $^1\text{H NMR}$ 1.87 (major) and 1.92 (minor) (s, 1.35 H, CH_3 of cyclized material), 2.19 (s, 1.65 H, CH_3 of starting material), 2.49 (major) and 2.78 (minor) (d, 0.45 H, endo- CH_2 , $J = 17 \text{ Hz}$), 3.48–3.63 (m, 0.45 H, exo- CH_2), 4.59 (major) and 4.72 (minor) (d, 0.45 H, CH, $J = 5 \text{ Hz}$), 6.70–7.45 (m, 6.5 Ar).

3,7-Difluoro-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (112). A stirred solution of 111 (0.25 g) and 0.32 g of zinc dust in 5 mL of HOAc was heated to 65 °C for 30 h. The mixture was cooled to 25 °C, filtered, diluted with crushed ice, and made alkaline with NH_4OH . The mixture was then extracted three times with CH_2Cl_2 , and the combined organic layers were washed with dilute aqueous NaHCO_3 and dried. The oil residue was purified by repeated column chromatography ($\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 95:5:0.5 EtOAc). The more polar product was an oil which upon trituration with ether gave 112 (0.09 g) as a solid: mp 152–153 °C; $^1\text{H NMR } \delta$ 1.87 (s, 3 H), 2.50 (br s, 1 H, exchangeable), 2.68 (d, 1 H, $J = 17 \text{ Hz}$), 3.49 (dd, 1 H, $J = 5$ and 17 Hz), 4.67 (d, 1 H, $J = 5 \text{ Hz}$), 6.70–7.00 (m, 5 H), 7.18–7.26 (m, 1 H). Anal. ($\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}$) C, H, N.

3-(and 7-)Fluoro-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclopenten-5,10-imines (115). With use of the procedure described for 77 and 78, from 114 there was obtained in 73% yield the cyclized products, 12-hydroxy-3-(and 7-)fluoro-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imines. Proton NMR evidence suggested a regioisomer mixture of 4:1 as determined by the ratios of the endo- CH_2 doublets: $^1\text{H NMR } \delta$ 1.94 (major) and 1.99 (minor) (s, 3 H, CH_3), 2.54:2.55 (1:4) (major) and 2.82:2.84 (1:4) (minor) (d, 1 H, endo- CH_2 , $J = 17 \text{ Hz}$), 3.56–3.72 (m, 1 H, exo- CH_2), 4.62 (major) and 4.75 (minor) (d, 1 H, CH, $J = 5 \text{ Hz}$), 6.70–7.44 (m, Ar). A solution of 1.2 g (4.7 mmol) of *N*-hydroxy 115 in 8 mL of HOAc was treated with 1.0 g of zinc dust and the mixture was stirred under nitrogen at 65 °C for 20 h. The mixture was cooled and filtered. The combined filtrates were concentrated to a yellow oil, which was taken up in ice water, basified with NH_4OH , and extracted three times with ether. The combined ether extracts were dried, and the oily residue was purified by column chromatography (EtOAc). The solid product (0.87 g, 77%) was a 3:1 mixture of regioisomers by $^1\text{H NMR}$ as determined by integration of the endo- CH_2 doublets. Two recrystallizations from ether/hexane afforded an 84:16 isomer ratio of 115: mp 112–115 °C; $^1\text{H NMR}$ ($\text{CDCl}_3 + \text{C}_6\text{D}_6$) δ 1.89 (s, 3 H), 2.55 (br s, 1 H), 2.69 (d, 0.16 H, $J = 17 \text{ Hz}$), 2.71 (d, 0.84 H, $J = 17 \text{ Hz}$), 3.36 (dd, 0.16 H, $J = 17 \text{ Hz}$), 3.40 (dd, 0.84 H, $J = 5$ and 17 Hz), 4.62 (d, 0.84 H, $J = 5 \text{ Hz}$), 4.65 (d, 0.16 H, $J = 5 \text{ Hz}$), 6.69–7.28 (m, 7 H). A spin decoupling experiment as described for 87 produced NOE's consistent with the assignment of the 3-substituted isomer as the major one. Anal. ($\text{C}_{16}\text{H}_{14}\text{FN}$) C, H, N.

3-Fluoro-5-methyl-5H-dibenzo[a,d]cyclohepten-5-ol (113). With use of the procedure described for 69, from 3-fluoro-5H-

dibenzo[a,d]cyclohepten-5-one¹⁹ there was obtained 113 (100%): $^1\text{H NMR } \delta$ 1.58 (s, 3 H), 2.27 (s, 1 H).

3-Fluoro-5-methyl-5-(hydroxyamino)-5H-dibenzo[a,d]cycloheptene (114). With use of the procedure described for 73 (reaction period, at reflux for 5 h), from 113 there was obtained 114 (62%): $^1\text{H NMR } \delta$ 2.21 (s, 3 H).

(5R,10R*,11R*)-(±)-5-Methyl-10,11-dihydro-11-hydroxy-5H-dibenzo[a,d]cyclohepten-5,10-imine (116). A stirred solution of 24 g of 5-methyl-5-(methoxyamino)-5H-dibenzo[a,d]cycloheptene in 230 mL of dry THF cooled to –78 °C was treated dropwise with 65 mL of 1.47 M *n*-butyllithium in hexane. After stirring at –78 °C for 30 min, the solution was allowed to warm to 25 °C, where it was stirred for 1 h. The resultant dark green solution was added to 100 mL of water and the organic phase was dried and concentrated. The residue was triturated with hexane and chilled to give 13.6 g (66%) of 8b,8c-dihydro-4b-methyl-4bH-azirino[2,1,3-*c,d*]dibenzo[a,d]pyrrolizine¹⁷ as a white solid: mp 112–114 °C; $^1\text{H NMR } \delta$ 1.95 (s, 3 H), 4.05 (s, 2 H), 7.01–7.37 (m, 8 H). Anal. ($\text{C}_{16}\text{H}_{13}\text{N}$) C, H, N. The aziridine (8.6 g) was added to a warm solution of 40 g of sodium acetate in 100 mL of acetic acid and the mixture was stirred under reflux for 30 min. The reaction mixture was cooled in an ice bath, neutralized with concentrated NH_4OH , and extracted with Et_2O (4 × 200 mL). The combined organic extracts were washed with water (2 × 100 mL), dried, and concentrated. The resultant crude product was purified by column chromatography (CH_2Cl_2 (80%)/acetone (8%)/MeOH (2%)) to give 7.9 g (76%) of the acetate of 116: mp 172–174 °C; $^1\text{H NMR } \delta$ 1.92 (s, 3 H), 2.15 (s, 3 H), 4.93 (d, 1 H, $J = 6.0 \text{ Hz}$), 6.30 (d, 1 H, $J = 6.1 \text{ Hz}$), 7.11–7.26 (m, 8 H). A solution of the acetate (10.6 g) and 56 g of KOH in 200 mL of dry MeOH was stirred at 25 °C for 3 h. Concentration of the reaction mixture and trituration of the residue with 150 mL of water afforded 9.0 g of crude product, which was recrystallized from 2-propanol to give 7.7 g (85%) of 116 as a white solid: mp 189.5–190.5 °C; $^1\text{H NMR } \delta$ 1.90 (s, 3 H), 2.87 (br s, 1 H), 4.69 (d, 1 H, $J = 5.8 \text{ Hz}$), 5.15 (m, 1 H), 7.10–7.41 (m, 8 H). Anal. ($\text{C}_{16}\text{H}_{15}\text{NO}$) C, H, N.

(5R*,10R*,11S*)-(±)-5-Methyl-10,11-dihydro-11-exo-hydroxy-5H-dibenzo[a,d]cyclohepten-5,10-imine (120). To a stirred solution of 2.2 g of 116 in 60 mL of THF was added 60 mL of 1 N aqueous NaOH followed by 6.0 g of di-*tert*-butyl dicarbonate. The mixture was heated under reflux for 1.5 h and allowed to cool to room temperature. The organic phase was collected and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organics were washed with water (2 × 50 mL), dried, and concentrated to give 3.6 g of crude product, which, after recrystallization from 2-propanol, yielded 2.7 g (86%) of the *N*-BOC-protected 116 as a white solid: mp 177–178 °C; $^1\text{H NMR } \delta$ 1.41 (s, 9 H), 2.25 (s, 3 H), 5.25 (dd, 1 H, $J_1 = 10 \text{ Hz}$, $J_2 = 5.4 \text{ Hz}$), 5.41 (d, 1 H, $J = 5.4 \text{ Hz}$), 7.11–7.39 (m, 8 H). To a solution of 2.7 g of *N*-BOC 116 in 30 mL of dry CH_2Cl_2 cooled to 0 °C was added 1.6 mL of Et_3N followed by 0.67 mL of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 1 h and then filtered. The filtrate was washed with water (2 × 25 mL), dried, and concentrated to give 3.3 g (99%) of crude *N*-BOC-11-*O*-mesylate as a white solid: mp 137 °C darkens, 143 °C dec; $^1\text{H NMR } \delta$ 7.07–7.50 (m, 8 H). A mixture of 3.4 g of the mesylate and 12.4 g of tetrabutylammonium acetate in 30 mL of dry 1-methyl-2-pyrrolidinone was heated at 140 °C for 2.5 h. The mixture was added to 150 mL of water and the solution was extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were washed with water (2 × 50 mL), dried, and concentrated to give 3.9 g of an oil. Column chromatography (10% ethyl acetate/hexanes) afforded 2.1 g (76%) of a mixture of the *N*-BOC 11R* and 11S* acetates in a ratio of 3:2. 11R* acetate: $^1\text{H NMR } \delta$ 1.47 (s, 9 H), 2.16 (s, 3 H), 2.27 (s, 3 H), 5.57 (d, 1 H, $J = 5.4 \text{ Hz}$), 6.42 (d, 1 H, $J = 5.4 \text{ Hz}$), 7.0–7.5 (m, 8 H). 11S* acetate: $^1\text{H NMR } \delta$ 1.35 (s, 9 H), 1.94 (s, 3 H), 2.61 (s, 3 H), 4.58 (d, 1 H, $J = 3.7 \text{ Hz}$), 6.35 (d, 1 H, $J = 3.7 \text{ Hz}$), 7.0–7.5 (m, 8 H). A mixture of 1.4 g of the *N*-BOC 11R* and 11S* acetates in 40 mL of MeOH and 5.3 mL of 1 N aqueous KOH was stirred at 25 °C for 2 h and concentrated to dryness. The residue was taken up in 50 mL of water and the mixture was extracted with CH_2Cl_2 (4 × 25 mL). The combined organics were washed with water (2 × 25 mL), dried, and concentrated to give 1.2 g of crude product as an oil. To a stirred solution of the oil in 40 mL of absolute EtOH cooled

to 0 °C in an ice/water bath was added ethanolic HCl (14 mL, 6.2 M). The reaction mixture was stirred at 25 °C for 18 h and then was concentrated. The resultant residue was dissolved in 50 mL of water and the solution was made slightly basic by the addition of dilute NH₄OH then was extracted with CH₂Cl₂ (4 × 25 mL). The combined organics were washed with water (2 × 25 mL), dried, and concentrated to give 0.6 g of crude product as an oil. The product was purified by column chromatography (5% MeOH/CHCl₃) followed by preparative HPLC [Spectra-Physics system; Whatman Partisil M20 10/25 ODS3; CH₃CN (10%)/MeOH (10%) water (80%)] to give 320 mg of 116 and 42 mg of 120, which was further purified by recrystallization from ethyl acetate/hexane: mp 190 °C dec; ¹H NMR δ 2.12 (s, 3 H), 4.63 (s, 1 H), 5.02 (s, 1 H), 7.07–7.39 (m, 8 H). Anal. (C₁₆H₁₅NO) C, H, N.

(10S*,11R*)-11-(tert-Butylcarboxamido)-10,11-dihydro-10-hydroxy-5H-dibenzo[a,d]cyclohepten-5-one (117). To a stirred slurry of 4.91 g (28.3 mmol) of *tert*-butyl *N*-chloro-*N*-sodiocarbamate in 75 mL of acetonitrile under N₂ was added 9.63 g (56.7 mmol) of AgNO₃ in one portion. After stirring at room temperature for 10 min, 3.90 g (18.9 mmol) of dibenzosubarenone was added in one portion as a solid, followed by the addition of 3.8 mL of 2.5% OsO₄ in *tert*-butyl alcohol and 1.53 mL of water. The stirred mixture was heated in an oil bath maintained at 50 °C for 14 h. After the addition of 3 mL of brine, the mixture was filtered through a glassine filter paper, and the filter was washed with 35 mL of acetonitrile. The filtrate was diluted with 38 mL of aqueous 5% Na₂SO₃ and the mixture was heated at reflux for 4.0 h. After cooling to ca. 50 °C, the mixture was filtered through a glassine filter paper and concentrated. The residue was partitioned between 250 mL of CHCl₃ and 300 mL of water, and the aqueous layer was extracted with 50 mL of CHCl₃. The combined organic layers were washed three times with water, dried, and concentrated to give 7.0 g of a dark green oil. This oil was purified by column chromatography (700 g silica gel, 8.0 cm diameter, 25% EtOAc/hexanes; the sample was loaded in CHCl₃) to give 3.15 g of a light brown solid. Recrystallization from EtOAc/hexanes gave 2.60 g (40%) of 117 as pale yellow crystals in two crops: mp 188–191 °C gas evol; ¹H NMR δ 1.35 (s, 9 H), 5.25 (d, 1 H, *J* = 6 Hz), 5.36 (d, 1 H, *J* = 9 Hz).

(5S*,10S*,11S*)- and (5S*,10S*,11S*)-11-(tert-Butylcarboxamido)-10,11-dihydro-10-hydroxy-5-methyl-5H-dibenzo[a,d]cycloheptene (118). To a stirred solution of 4.0 g (11.8 mmol) of 117 in 100 mL of THF at –5 °C was added 34.0 mL of a solution of methyllithium (1.4 M in ether) dropwise over a 5-min period. The reddish solution was stirred in the cold for 2.2 h, poured into ice water and extracted with three portions of CHCl₃. The combined organic layers were washed with water, dried, and concentrated to give 4.2 g (100%) of 118 as a colorless solid. An analytical sample was obtained by crystallization from 25% EtOAc/cyclohexane: ¹H NMR δ 1.35 (s, 9 H), 1.67 (s, 3 H), 5.25 (d, 1 H, *J* = 5 Hz), 5.38 (d, 1 H, *J* = 9 Hz). Anal. (C₂₁H₂₅NO₄) C, H, N.

(5R*,10S*,11S*)-N-(tert-Butoxycarbonyl)-10,11-dihydro-11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (119). To a stirred mixture of 4.2 g (11.8 mmol) of 118 in 400 mL of benzene heated to reflux was added 114 mg of *p*-toluenesulfonic acid hydrate. Refluxing was continued while allowing the benzene to distill off for 10 min. The solution was cooled in an ice bath and washed with cold 5% HCl. The organic layer was washed with 5% NaHCO₃ and water, dried, and concentrated to give a yellow oil. Column chromatography (1% CH₃OH/CHCl₃) gave 1.76 g (44%) of 119 as a colorless solid. A sample was purified further by further chromatography (25% EtOAc/hexanes) and crystallization from cyclohexane: mp 128–131 °C; ¹H NMR δ 1.34 (s, 9 H), 2.24 (s, 3 H), 4.48 (d, 1 H, *J* = 10 Hz), 5.58 (s, 1 H).

(5R*,10S*,11S*)-10,11-Dihydro-11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (120). A solution of 1.2 g of 119 in 60 mL of CHCl₃ was cooled to 0 °C and 30 mL of trifluoroacetic acid was added in one portion. After stirring for 2.0 h in the cold, the mixture was concentrated to dryness. The residue was partitioned between 5% NaHCO₃ and 2 × 100 mL of CHCl₃. The combined organic layers were washed with water, dried, and concentrated. The brown oily residue was purified by column chromatography (95:5:0.5 CHCl₃/CH₃OH/NH₄OH)

and recrystallization from 1:1 ethyl acetate/hexanes to give 0.80 g of racemic 120: mp 215–218 °C; ¹H NMR δ 1.91 (s, 3 H), 4.45 (m, 1 H), 4.58 (m, 1 H). Anal. (C₁₆H₁₅NO) C, H, N.

(5R,10S,11S)- and (5S,10R,11R)-N-(tert-Butoxycarbonyl)-10,11-dihydro-11-[(–)-camphanoyloxy]-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (124). A solution of 1.28 g (3.79 mmol) of 119, 3.0 mL of pyridine, and 1.07 g (4.93 mmol) of (–)-camphanic acid chloride in 40 mL of CH₂Cl₂ was allowed to stir overnight. The solution was poured into ice-cold 5% HCl, and the aqueous layer was extracted with two portions of CHCl₃. The combined organic layers were washed with water and 5% NaHCO₃ and dried. The residue (2.15 g of a colorless foam) was dissolved in 1:5 EtOAc/hexanes (20 mL/g), seeded with pure (5R,10R,11S)-124, and filtered after ca. 4 h to give 0.3 g of (5R,10S,11S)-124 of >99% diastereomeric purity. The diastereomers were conveniently analyzed by analytical HPLC using an IBM CN 26 × 0.4 cm reversed-phase column (part no. 8635796) with 1:7 2-propanol/hexanes, flow rate = 2.0 mL/min, 230 nm. The 5R,10S,11S diastereomer elutes at 4.0 min and the 5S,10R,11R diastereomer elutes at 3.1 min: ¹H NMR δ 0.95 (s, 3 H), 1.25 (s, 3 H), 1.10 (s, 3 H), 1.40 (s, 9 H), 2.25 (s, 3 H), 5.73 (s, 1 H), 5.83 (s, 1 H). The pure 5S,10R,11R diastereomer was obtained by preparative HPLC, on a Waters custom CN column (prep 500) using a 150 mL/min flow rate, from the mother liquors of the crystallization (gradient elution from 100% hexanes to 25% 2-propanol/hexanes over 1 h). By combining appropriate fractions, there was obtained an additional 0.7 g of (5R,10S,11S)-124 and 1.0 g of (5S,10R,11R)-124.

(5R,10S,11S)-N-(tert-Butoxycarbonyl)-10,11-dihydro-11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (125). To a stirred solution of 255 mg (0.49 mmol) of (5R,10S,11S)-124 in 24 mL of DME was added a solution of 215 mg (5.12 mmol) of LiOH·H₂O in 4.0 mL of water. After stirring for 18 h at room temperature, the mixture was poured into 5% NaHCO₃ and extracted twice with CHCl₃. The combined organic layers were washed with water, dried, and concentrated to give 162 mg (97%) of 125 as a colorless oil.

(5R,10S,11S)-(+)-10,11-Dihydro-11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine [(+)-120]. To a stirred solution of 162 mg (0.49 mmol) of 125 in 20 mL of CH₃CN under N₂ was added 223 μL of 8.5 M ethanolic HCl dropwise at room temperature. After stirring for 1.5 h, a second portion of 223 μL of the HCl solution was added, and the stirring was continued for 1.25 h. The reaction solution was poured into cold 10% Na₂CO₃ and extracted with two portions of CHCl₃, and the combined organic layers were washed with water and dried over Na₂SO₄. Evaporation of the solvents at reduced pressure provided 107 mg of a colorless solid which was crystallized from 4.5 mL of acetonitrile to give 74 mg (65%) of 120 as colorless crystals, [α]_D²³ = +136° (c = 0.98, CH₃OH). Anal. (C₁₆H₁₅NO) C, H, N.

To a stirred solution of 1.51 g (0.61 mmol) of 120 in 150 mL of CH₃CN under N₂ at 80 °C was added 751 mg (6.47 mmol) of maleic acid as a solid. The stirred solution was immediately cooled in a 22 °C water bath, followed by cooling in an ice water bath for 20 min. The resulting precipitate was collected and washed with a minimum volume of CH₃CN and dried at 0.01 mm, 50 °C, to give 1.97 g of a colorless solid: mp 209–210 °C dec; [α] = +115.5° (c = 0.695, methanol). Anal. (C₁₆H₁₅NO·C₄H₄O₄) C, H, N.

(5S,10R,11R)-(–)-10,11-Dihydro-11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine [(–)-120]. In a manner similar to that described for the preparation of (+)-120 from 186 mg of (5S,10R,11R)-124, there was obtained 120 mg (89%) of the 5S,10R,11R enantiomer of 125. Deprotection of (5S,10R,11R)-125 (129 mg as described above gave 65 mg (75%) of a colorless solid, (–)-120: [α]_D²³ = –138° (c = 0.97, CH₃OH). Anal. (C₁₆H₁₅N·O·0.2H₂O) C, H, N.

Resolution of the 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cycloheptenimines: The method of Rittle and Evans,³⁴ modified in the manner described in the following procedure, was found to be generally reliable for the resolution of this class of compounds.

(5S,10R)-L-Phenylalanyl-3-bromo-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (127a) and (5R,10S)-L-Phenylalanyl-3-bromo-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (127b). To a stirred

solution of 88 (2.27 g, 6.7 mmol) in 70 mL of CH_2Cl_2 cooled to 0–5 °C was added diisopropylethylamine (DIPEA; 2.57 mL, 14.75 mmol), BOC-L-phenylalanine (1.96 g, 7.37 mmol), and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl; 1.88 g, 7.37 mmol). The reaction mixture was kept in a refrigerator at 0–5 °C for 5 days, adding additional portions of BOC-L-Phe (0.5 g), BOP-Cl (0.5 g), and DIPEA (1.0 mL) daily and monitoring the reaction progress by TLC (95:5:0.5 $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$). The mixture was diluted with EtOAc (750 mL), washed with ice-cold 5% HCl (500 mL) and 5% NaHCO_3 , and dried. After purification by column chromatography (50% EtOAc/hexanes), the residue (4 g) afforded 2.9 g of the BOC-L-Phe amides of 88 as a colorless foam, TLC (1:2 EtOAc/hexanes) R_f = 0.47. Deprotection of the BOC was effected by dissolving the diastereomeric mixture of BOC-L-Phe amides (2.9 g) in CH_2Cl_2 (60 mL), cooling to 0 °C, and adding anhydrous trifluoroacetic acid (15 mL). After 30 min at 0 °C, the mixture was concentrated to dryness, dissolved in CHCl_3 (100 mL), and washed with 10% Na_2CO_3 (500 mL). The aqueous layer was extracted with CHCl_3 (2 × 100 mL), and the combined organic extracts were dried. Column chromatography of the residue (2.34 g) on 400 g of silica gel (gradient elution of 5% $\text{CH}_3\text{OH}/\text{EtOAc}$ (1 L), 10% $\text{CH}_3\text{OH}/\text{EtOAc}$ (1 L), then 15% $\text{CH}_3\text{OH}/\text{EtOAc}$ 0.5 L) gave first (5*R*,10*S*)-L-Phe amide 127b (0.735 g) and then in the latter fractions (5*S*,10*R*)-L-Phe amide 127a (1.23 g).

(5*S*,10*R*)-(+)-3-Bromo-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-88]. A mixture of (5*S*,10*R*)-L-Phe amide 127a (1.23 g, 2.75 mmol) and phenyl isothiocyanate (0.362 mL, 3.02 mmol) in CH_2Cl_2 was heated on a steam bath until the solvents were gone. The residue was redissolved in CH_2Cl_2 (25 mL) and the evaporation process was repeated until the starting material (127a) was consumed as evidence by TLC (15% $\text{CH}_3\text{OH}/\text{EtOAc}$). The residue was then dissolved in anhydrous trifluoroacetic acid (20 mL), stirred at 50 °C for 20 min, and then concentrated to dryness. The residue was dissolved in CHCl_3 (200 mL), washed with 10% Na_2CO_3 and water, and dried. After column chromatography (8% $\text{CH}_3\text{OH}/\text{EtOAc}$) of the residue there was obtained 0.638 g of (+)-88 as a viscous oil. Addition of 8.6 M ethanolic HCl (0.250 mL) to a solution of (+)-88 (0.638 g) in ether (20 mL) gave 0.630 g of (+)-88-HCl, $[\alpha]_D^{25}$ = +196° (c = 0.57, CH_3OH). Anal. ($\text{C}_{16}\text{H}_{14}\text{BrN}\cdot\text{HCl}\cdot 0.2\text{H}_2\text{O}$) C, H, N.

(5*R*,10*S*)-(–)-3-Bromo-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(–)-88]. With use of the procedure described for the (+)-88 enantiomer, from 0.735 g of (5*R*,10*S*)-127b there was obtained 0.300 g of (–)-88-HCl, $[\alpha]_D^{25}$ = –227.2° (c = 1.07, CH_3OH). Anal. ($\text{C}_{16}\text{H}_{14}\text{BrN}\cdot\text{HCl}\cdot 0.3\text{H}_2\text{O}$).

(5*S*,10*R*)-L-Phenylalanyl-3-chloro-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (126a) and (5*R*,10*S*)-L-Phenylalanyl-3-chloro-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (126b). From 2.28 g of racemic 63, there was obtained 0.864 g of (5*R*,10*S*)-126b (high R_f) and 1.345 g of (5*S*,10*R*)-126a (low R_f) as a foam.

(5*S*,10*R*)-(+)-3-Chloro-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-63]. From (5*S*,10*R*)-126 (1.345 g) there was obtained 0.647 g of (+)-63-HCl: mp 193–195 °C dec; $[\alpha]_D^{25}$ = +277° (c = 0.45, CHCl_3). Anal. ($\text{C}_{16}\text{H}_{14}\text{ClN}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$) C, H, N.

(5*R*,10*S*)-(–)-3-Chloro-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(–)-63]. From (5*R*,10*S*)-126b (0.864 g) there was obtained 0.341 g of (–)-63-HCl: mp 190–192 °C dec; $[\alpha]_D^{25}$ = –285° (c = 0.445, CHCl_3). Anal. ($\text{C}_{16}\text{H}_{14}\text{ClN}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$) C, H, N.

(5*S*,10*R*)-L-Phenylalanyl-7-methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (128a) and (5*R*,10*S*)-L-Phenylalanyl-7-methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (128b). From 3.52 g of racemic 83, there was obtained 1.13 g of (5*R*,10*S*)-128b (R_f = 0.42, 8:2:1 EtOAc/ $\text{CHCl}_3/\text{CH}_3\text{OH}$) and 1.80 g of (5*S*,10*R*)-128a (R_f = 0.27) as a foam.

(5*S*,10*R*)-(+)-7-Methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-83]. From (5*S*,10*R*)-128a (1.80 g) there was obtained 0.72 g of (+)-83-HCl (HPLC on a chiral Pirkle column detected 11% of the (–)-enantiomer: mp 262–264 °C dec; $[\alpha]_D^{25}$ = +48.6° (c = 1.8, CH_3OH). Anal. ($\text{C}_{17}\text{H}_{17}\text{NO}\cdot\text{HCl}\cdot 0.25\text{H}_2\text{O}$) C, H, N.

(5*R*,10*S*)-(–)-7-Methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(–)-83]. From (5*R*,10*S*)-128b (1.1 g) there was obtained 0.23 g of (–)-83-HCl (HPLC on a chiral Pirkle column detected 2.5% of the (+)-enantiomer): mp 264 °C dec; $[\alpha]_D^{25}$ = –57.9° (c = 1.3, CH_3OH). Anal. ($\text{C}_{17}\text{H}_{17}\text{NO}\cdot\text{HCl}\cdot 0.25\text{H}_2\text{O}$) C, H, N.

(5*S*,10*R*)-L-Phenylalanyl-8-methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (129a) and (5*R*,10*S*)-L-Phenylalanyl-8-methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine (129b). From 1.5 g of racemic 104, there was obtained 0.68 g of (5*R*,10*S*)-129b (R_f = 0.47, 20% $\text{CH}_3\text{OH}/\text{EtOAc}$) and 0.82 g of (5*S*,10*R*)-129a (R_f = 0.35) as a foam.

(5*S*,10*R*)-(+)-8-Methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-104]. From (5*S*,10*R*)-129a (0.82 g) there was obtained 0.35 g of (+)-104, $[\alpha]_D^{25}$ = +170° (c = 1.0, CH_3OH).

(5*R*,10*S*)-(–)-8-Methoxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(–)-104]. From (5*R*,10*S*)-129b (0.68 g) there was obtained 0.35 g of (–)-104: $[\alpha]_D^{25}$ = –191° (c = 1.5, CH_3OH).

(5*S*,10*R*)-(+)-8-Hydroxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-106]. With use of the demethylation procedure described for the preparation of 84, from (+)-104 (0.35 g) there was obtained 0.13 g of (+)-106: mp 236–238 °C; $[\alpha]_D^{25}$ = +216° (c = 1.2, CH_3OH). Anal. ($\text{C}_{16}\text{H}_{15}\text{NO}$) C, H, N.

(5*R*,10*S*)-(–)-8-Hydroxy-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(–)-106]. With use of the demethylation procedure described for the preparation of 84, from (–)-104 (0.35 g) there was obtained 0.17 g of (–)-106: mp 237–239 °C; $[\alpha]_D^{25}$ = –226° (c = 1.3, CH_3OH). Anal. ($\text{C}_{16}\text{H}_{15}\text{NO}$) C, H, N.

(5*S*,10*R*)-(+)-3-Bromo-10,11-dihydro-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine [(+)-88]. To a stirred solution of 200 mL of 85:15 (v/v) $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ at 40 °C was added 10 g (45.2 mmol) of (+)-10 free base. When the solid was dissolved, the solution was allowed to cool to room temperature, and 8.45 g (47.5 mmol) of *N*-bromosuccinimide was added. The mixture was allowed to stir overnight and then diluted with 200 mL of ice water and carefully basified with concentrated NH_4OH (ca. 500 mL). This solution was cooled to ca. 15 °C and extracted with two portions of ether. The combined ether layers were washed with water and brine and dried.

The residue (89% area by HPLC) was purified by column chromatography on 500 g of silica gel (5% $\text{CH}_3\text{OH}/\text{EtOAc}$). The desired product eluted after a close moving impurity. By combining appropriate fractions, there was obtained in 45% yield (+)-88: ^1H NMR 1.90 (s, CH_3), 2.05 (br s, NH), 2.68 (d, J = 16 Hz, H-11a), 3.38 (dd, J = 16 and 5 Hz, H-11), 4.70 (d, J = 5 Hz, H-10), 6.82 (d, J = 8 Hz, H-arom), 7.02–7.32 (m, 5 H, H-arom), 7.40 (d, J = 1 Hz, H-arom).

Addition of 0.36 mL of 8.5 N ethanolic HCl to a solution of (+)-88 (0.910 g) in ether (30 mL) gave, after drying at 65 °C (0.1 mm), 0.947 g of (+)-88-HCl as a colorless solid, $[\alpha]_D^{25}$ = +231° (c = 0.6, CH_3OH). Anal. ($\text{C}_{16}\text{H}_{15}\text{BrClN}$) C, H, N.

Computational Methodology. All molecular geometries were created and initially optimized by using the Merck molecular modeling system MOLEDT,⁴⁷ which includes a modified MM2 force field.⁴⁸ Molecular orbital calculations were carried out using the MNDO⁴⁹ semiempirical molecular orbital method as implemented in the AMPAC package of programs.⁵⁰ Choice of the MNDO, rather

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than the AM1,⁵¹ method was mediated by the presence of an SCF₃ substituent, since AM1 is not currently parameterized for sulfur.⁵² Calculations on neutral and anionic species were performed by using the RHF closed-shell method; calculations on radical species were performed by using the RHF half-electron (RHF/HE) method.⁵³ Since MNDO is known to give a very poor estimate of the heat of formation of H⁺ (calcd 326.7 kcal/mol; obsd 367.2 kcal/mol), the experimental value³² was used in calculating deprotonation enthalpies (DPE's).

In Vitro Binding Studies. Cerebral cortices from Male Sprague-Dawley rats (200–300 g) were homogenized in 9 volumes of ice-cold 0.32 M sucrose by eight strokes with a Teflon/glass homogenizer at 500 rpm. The homogenate was centrifuged for 10 min at 1000g, and the supernatant was recentrifuged at 10000g for 20 min at 4 °C. The pellet was suspended in 5 mM Tris-HCl (pH 7.4) and incubated at 23 °C for 20 min prior to final centrifugation at 50000g for 20 min at 4 °C. The pellet was resuspended in assay buffer (HEPES Krebs composition: 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO₄, 5 mM NaHCO₃, HEPES, 1.2 mM KH₂PO₄, 2.5 mM CaCl₂, 11 mM D-glucose, pH 7.4) at 70 mL per gram of original tissue. Binding of [³H]-(+)-10 was measured by incubating 750-μL duplicates aliquots of this membrane suspension (ca. 0.75 mg of protein) with 100 μL of buffer containing displacer/analogue or of buffer alone (total binding), 100 μL of 50 nM [³H]-(+)-10, and 50 μL of buffer for 60 min at 23 °C. Nonspecific binding was defined by 10 μL of unlabeled (+)-10 (10 μM (thienylcyclohexyl)piperidine gave the same result).

Incubation was terminated by rapid filtration through Whatman GF/B filters, which were washed immediately with two 5-mL portions of ice-cold 0.9% NaCl in a Brandel M24-R cell harvester. Radioactivity on the filters was determined by liquid-scintillation counting in standard vials with 10 mL of Ready Gel scintillant (Beckman) with 50% efficiency. Protein concentrations were determined according to the method of Lowry et al.⁵⁴

NMDA Antagonism in the Rat Cortical Slice. Population depolarizations of rat cortical tissue induced by excitatory amino acids were recorded by using a greased-gap technique in a manner similar to that first described by Harrison and Simmonds.⁵⁵ Male Sprague-Dawley rats, weighing approximately 100 g, were killed by decapitation and their brains were rapidly removed. A 3–4 mm thick coronal slice was cut by hand from an area delineated

rostrally by the olfactory tubercle and caudally by the optic chiasm. The rostral surface of the section was fixed, with cyanoacrylic glue, to a glass slide attached to an aluminum block and mounted on the stage of an Oxford vibratome. The section was completely immersed in continuously gassed (95% O₂/5% CO₂) artificial cerebrospinal fluid (aCSF), at room temperature, of the following composition (in mM): NaCl, 124; MgSO₄, 2; KCl, 2; KH₂PO₄, 1.25; NaHCO₃, 25; CaCl₂, 2; glucose, 11.

Coronal sections, 500 μm thick, were cut with the vibratome and further dissected into 1 mm wide wedges consisting of cortex, white matter, and underlying striatal tissue. The wedges were mounted in a two-compartment chamber with the ventral margin of the cortical tissue traversing a greased slot in such a way that the cortical tissue lay almost entirely in one compartment and the white matter and striatal tissue within the other.

The chamber containing the cortical tissue (vol ≤ 0.3 mL) was continuously gravity-perfused with aCSF at a rate of 1.5–2 mL min⁻¹. At this stage, Mg²⁺ was omitted from the aCSF to prevent the voltage-dependent block of NMDA responses by this cation, and tetrodotoxin (10⁻⁷ M) was included to prevent spontaneous paroxysmal potentials induced by the removal of Mg²⁺. The dc potential between the two compartments was monitored on a potentiometric recorder via conventional Ag/AgCl electrodes. The chamber containing the cortical tissue was always electrically grounded.

Excitatory amino acid agonists, made up in aCSF, were applied for periods of 1 min with a separating interval of not less than 10 min. Control responses were obtained to test applications of NMDA (5, 10, and 20 μM). Compound (+)-10, or one of its analogues, was then continuously perfused, and after 15–20 min, three applications of 20 μM NMDA were made at 15-min intervals in order to develop agonist-dependent block produced by this class of compounds. Following this a concentration–response curve to NMDA in the presence of the antagonist was obtained.

The potency of the analogues as NMDA antagonists was expressed as an apparent “K_b” value calculated from the shift to the right of the NMDA concentration–response curve, with the relationship $D_b = \text{antagonist concentration}/\text{CR}1$. The concentration ratio (CR) was calculated from the midpoint of the control concentration–response curve. If the antagonist produced a profound flattening of the NMDA concentration–response curve and no concentration ratio could be obtained, then the experiment was repeated with a lower antagonist concentration. If this failed to produce a measurable concentration ratio, then the potency value was taken as the threshold concentration that produced a significant NMDA antagonism.^{9,35}

In Vivo Anticonvulsant Evaluation. The protocol for this assay has been described earlier.³⁵

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