Asymmetric Syntheses, Opioid Receptor Affinities, and Antinociceptive Effects of 8-Amino-5,9-methanobenzocyclooctenes, a New Class of Structural Analogues of the Morphine Alkaloids

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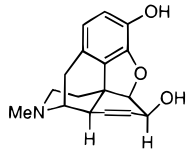
Several 8-amino-5,9-methanobenzocyclooctenes have been prepared by asymmetric organic synthesis techniques. Opioid receptor affinity studies have revealed the virtual absence of enantioselectivity for receptor binding, particularly at the μ-receptor, for the (+)-**3a**−**f** and the (−)-**3a**−**f** series. It is noteworthy that inversion of configuration at the nitrogen-bearing carbon atom [(5*S*,8*S*,9*S*)-8-amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene, (+)-**3a** vs (5*S*,8*S*,9*R*)-8-amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene, (*dl*)-**22**] resulted in a >10-fold increase in κ-receptor affinity. Antinociceptive studies demonstrated that (*dl*)-**22** was a full κ-agonist while (+)-**3a** and (−)-**3a** did not possess κ-activity. Although both (*dl*)-**22** and (+)-**3a**/(−)-**3a** had high affinity for the μ-receptor, these compounds did not act as high-affinity agonists or antagonists at this receptor.

Introduction

Morphine (**1**) is the prototype μ-receptor agonist.[2] The affinities of morphine for the κ- and δ-receptors are substantially less than that for the μ-receptor. Metazocine **2**, an *N*-methyl derivative within the benzomorphan series, is an effective analgesic agent in mice.[2c]



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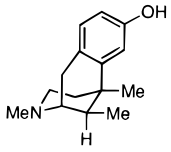

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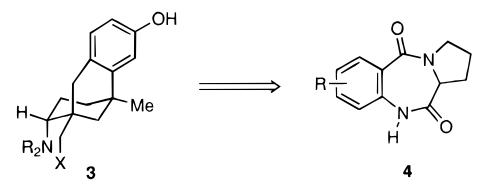
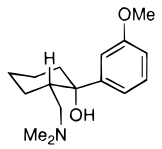
We became interested in the possible opioid receptor affinities of **3**, in which the amino group is exocyclic and one additional atom distant from the phenolic ring characteristic of morphine (**1**) and the benzomorphan **2**. It was expected that this structure would be available in both enantiomeric modifications via Birch reduction−alkylation of the pyrrolobenzodiazepine-5,11-dione **4**, a ring system that had already provided efficient asymmetric synthesis of (+)-pumiliotoxin-C[3] and related poison frog alkaloids.[4] Chemical modifications would enable a range of substituents R and X to be incorporated in preliminary structure−opioid receptor affinity studies, and it seemed likely that the effect of inverting configuration at the nitrogen bearing carbon atom in **3** could be addressed.



3 **4**

There is considerable precedence for high levels of analgesic activity from structures that contain exocyclic amino substituents. The methadones[5] and the arylcyclohexylamines[6] are among the structurally least complex yet highly potent synthetic analgetics available. Aryl-substituted 2-(dimethylamino)-1-cyclohexanols such as (−)-ciramadol[7] and tramadol (**5**)[8] exhibit potencies comparable to morphine and codeine as do the aminotetralins that incorporate a bridging hydrocarbon unit.[9] Dezocine (**6**), an aminotetralin with mixed agonist/antagonist activity, shows high affinity for the μ- and δ-receptors, but low affinity for the κ-receptor.[9,10] The 1-amido-2-aminocyclohexanes such as U-50488 are highly κ-selective opioid agonists.[11]



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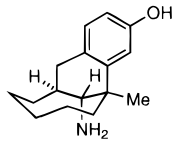

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Results and Discussion

Synthesis. The enantioselective synthesis of (−)-**3a**, a primary amine with high affinity and selectivity for the μ-receptor, is shown in Scheme 1. The starting material 7-methylpyrrolobenzodiazepine-5,11-dione (**4a**) is prepared in one step from D-proline and the corresponding isatoic anhydride by literature procedures.[3] Birch reduction of **4a** with 4.4 equiv of potassium in a solution of NH_3 and THF in the presence of 2 equiv of *tert*-butyl alcohol, followed by alkylation with *p*-methoxybenzyl bromide gave **7** in 73% isolated yield on a 60 g reaction scale. Treatment of **7** with trifluoromethanesulfonic acid in CH_2Cl_2 provided the annelated 5,9-methanobenzocyclooctene **8** in 88% yield. Stereochemical assignments for **8** are based on X-ray data collected for an analogue of **8** lacking the 3-methoxy substituent.[12]

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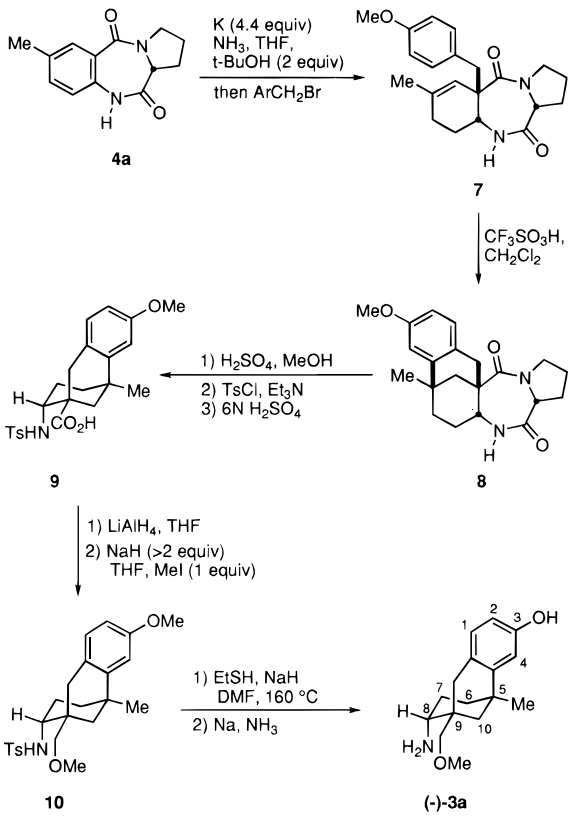
Scheme 1



The chiral auxiliary was removed by a protocol involving sequential amide bond cleavages. Treatment of **8** with methanol−sulfuric acid gave an amino ester, which was converted to a tosylamide with tosyl chloride−triethylamine. The tosylamide carboxylic acid **9** was obtained by hydrolysis of the tosylamide in 6 N H_2SO_4 (80% overall yield).

Reduction of the carboxylic acid group in **9** with lithium aluminum hydride in THF gave a primary alcohol that was converted to the tosyl amide methyl ether **10** by reaction with >2 equiv of NaH in THF followed by the addition 1.1 equiv of MeI (75% overall yield from **9**). The desired chemoselectivity for *O*- vs *N*-alkylation was anticipated from consideration of relative pK_a values for the tosylamide (model: $PhSO_2$-NH_2 in DMSO at 25 °C, 16.1) and primary alcohol (MeOH, 29.0).[13] The dianion forms on treatment with 2 equiv of base and alkylation occurs selectively at the more nucleophilic alkoxide ion.

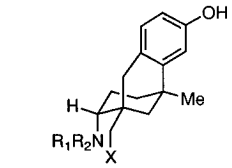
Selective demethylation of the C(3) methoxy group was accomplished by treatment with sodium thioethoxide in DMF solution at 160 °C.[14] The phenolic amine (−)-**3a** was obtained in 70% overall yield from **10** by reductive cleavage of the tosylamide group with sodium in ammonia.

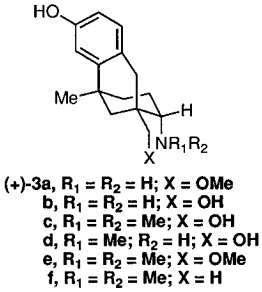
Modifications to the chemistry outlined in Scheme 1 enabled the synthesis of analogues of (−)-**3a**. The primary amino alcohol (−)-**3b** was prepared as were the monomethyl- and dimethyl-substituted amino alcohols (−)-**3c** and (−)-**3d**, the dimethylamino methyl ether (−)-**3e**, and the side chain deoxygenated analogue (−)-**3f**. The enantiomer of 7-methylpyrrolobenzo-diazepine-5,-11-dione (**4a**) prepared from L-proline provided the enantiomeric series (+)-**3a**−(+)-**3f**. The novel azetidine

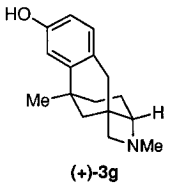
Table 1. Affinities of Synthetic Alkaloids for the Opioid Receptors[a]

	K_i (nM)		
compound	μ	δ	κ
(+)-**3a**	1.99	1,830	80.8
(−)-**3a**	2.29	467	53.1
(+)-**3b**	41.2	$>10^6$	$>10^4$
(−)-**3b**	40.6	$>10^4$	109
(+)-**3c**	830	$>10^6$	2,900
(−)-**3c**	870	$>10^6$	3,800
(+)-**3d**	42	$>10^6$	440
(−)-**3d**	380	$>10^6$	650
(+)-**3e**	25.2	1,400	123
(−)-**3e**	19.3	6,740	60.9
(+)-**3f**	2,020	$>10^4$	5,960
(−)-**3f**	297	$>10^5$	409
(+)-**3g**	179	$>10^4$	215
(*dl*)-**15**	27.7	863	17.2
(*dl*)-**16**	91.6	459	51.9
(*dl*)-**22**	1.99	170	6.62
(*dl*)-**29**	102	>5,000	795
(*dl*)-**31**	3,800	$>10^4$	$>10^4$
morphine	0.9	132	330

[a] The K_i values of all the compounds were determined by the inhibition of the binding of 0.8 nM [^{3}H]DAMGO, 1 nM [^{3}H]DPDPE, and 1 nM [^{3}H]U69,593 for μ-, δ-, and κ-binding sites respectively. The K_i values were calculated using the computer program EBDA. The K_i value is calculated using the following formula: $K_i = [IC_{50}]/[1 + (D/K_D)]$ (Cheng and Prusoff equation); IC_{50} is the concentration of the cold drug that inhibits 50% of the radioactive drug binding; D is the concentration of the radioactive drug; K_D is the equilibrium dissociation constant of the radioactive drug for the binding site; [^{3}H]DAMGO $K_D = 1$ nM; [^{3}H]U69,593 $K_D = 1.35$ nM; [^{3}H]DPDPE $K_D = 4.7$ nM.





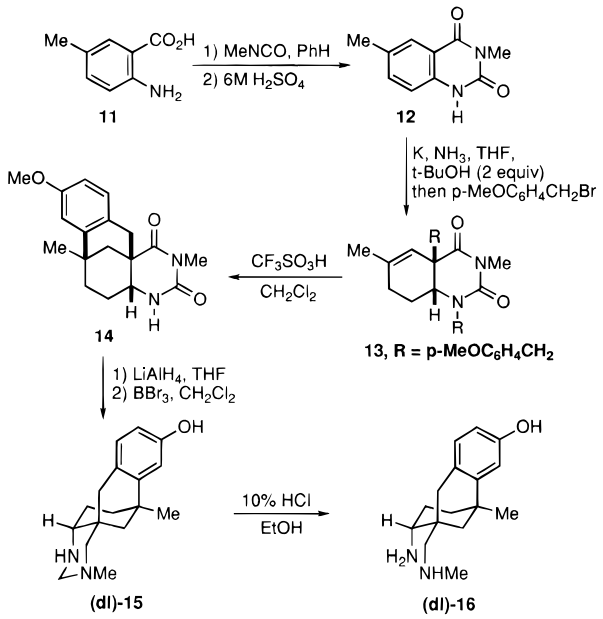


(+)-**3g** also was prepared.

A major discovery resulting from the receptor pharmacology of (+)-**3a**−**f** and (−)-**3a**−**f** was the observation of little if any stereoselectivity of receptor binding (Table 1). Consequently, a modified synthesis plan was formulated that was expected to provide new and more easily obtainable structures as racemates. Recognizing the importance of a primary amino substituent and a heteroatom on the side chain in **3** (X = OMe), we decided to prepare the racemic phenolic diamines (*dl*)-**15** and (*dl*)-**16** (Scheme 2).

Quinazoline-2,4-dione **12** was prepared in 75% yield from the reaction of 2-amino-5-methylbenzoic acid **11** with methyl isocyanate, followed by acid-catalyzed intramolecular condensation.[15] The Birch reduction−alkylation of **12**, carried out as described for **4a**, resulted in the production of several products. However, reaction

Scheme 2

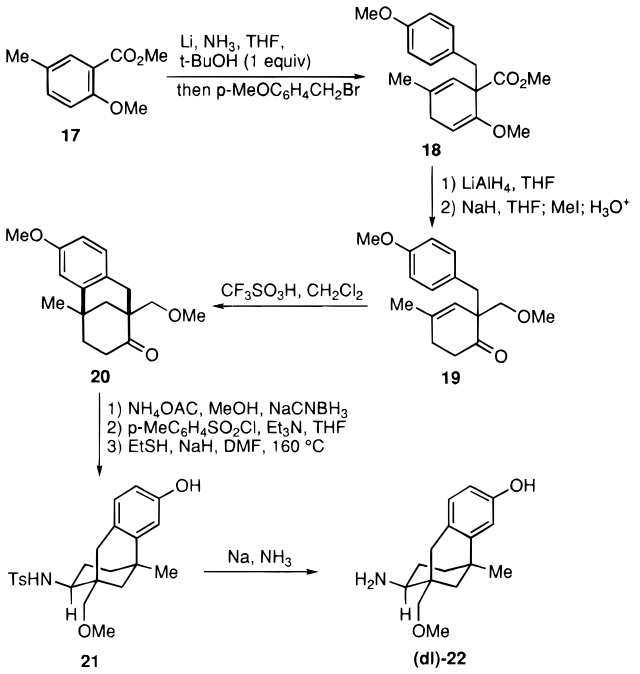


conditions were found which gave sufficient quantities of the racemic *C,N*-dialkylated, tetrahydroquinazoline-2,4-dione **13** to complete a synthesis of **16**; the presence of a small amount of the corresponding trans isomer was observed in ^{1}H NMR spectra of **13**. Treatment of **13** with trifluoromethanesulfonic acid gave cyclized product in 92% yield, from which pure **14** could be obtained by fractional crystallization. It should be noted that the superfluous *N*-substituent in **13** was cleaved under the acidic conditions required for cyclization. Reduction of **14** with lithium aluminum hydride, followed by demethylation of the C(3) methoxy group with BBr_3 in methylene chloride, afforded the phenolic hexahydropyrimidine **15**. Although somewhat resistant to the usual conditions[16] for acid-catalyzed hydrolysis of the methylenediamine group in **15**, racemic diamine **16** was obtained in 81% yield by refluxing a solution of **15** in 10% hydrochloric acid in ethanol.

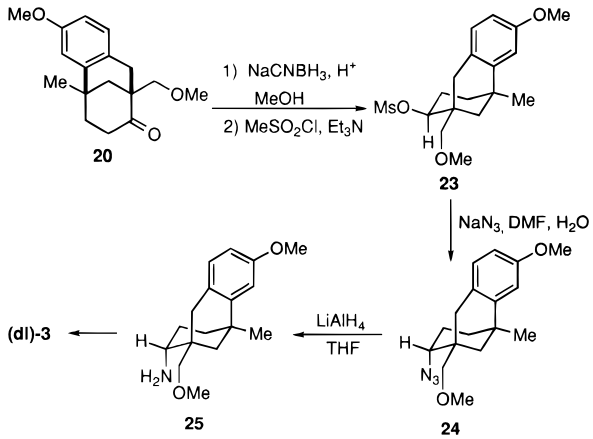
The next goal was the preparation of an analogue of **3a** with an equatorial rather than an axial primary amino group on the cyclohexane ring, *e.g.*, (*dl*)-**22**. Birch reduction−alkylation of methyl 2-methoxy-5-methylbenzoate (**17**) gave the diene carboxylic ester **18**. The ester group in **18** was reduced with lithium aluminum hydride to give a diene alcohol that was methylated with attendant hydrolysis of the enol ether to give the ketone methyl ether **19** in 76% overall yield from **17**. Cyclization of **19** gave the bridged ketone **20** (75% yield) with little if any competing cyclization involving the ketone carbonyl group.

Reductive amination of **20** with 10 equiv of ammonium acetate and 1.1 equiv of sodium cyanoborohdride in methanol in the presence of 4 Å molecular sieves gave the equatorial amine in 86% isolated yield. It is noteworthy that application of the Borch procedure[17] for reductive amination has been reported[18] to produce "impractical mixtures of stereoisomeric amines"; however, the Borch reductive amination of **20** produced the equatorial isomer with ~12:1 diastereoselectivity (as judged by HPLC analysis of the intermediate tosylamide, prepared by treatment of the amine with toluenesulfonyl chloride in THF).[19] Cleavage of the C(3) methyl ether in the intermediate tosylamide with

Scheme 3



Scheme 4

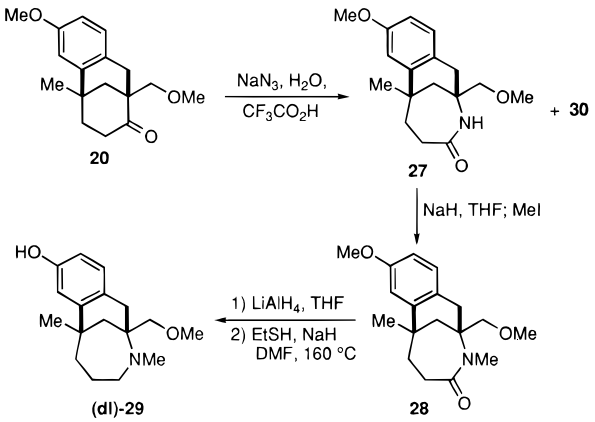


sodium thioethoxide in DMF gave phenol **21** in 71% overall yield from **20**. The tosylamide group in **21** was reduced with sodium in ammonia to give (*dl*)-**22** in 58% yield.

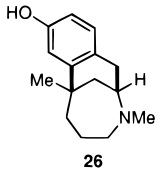
With racemic bicyclic ketone **20** available, we developed a synthesis of (*dl*)-**3** that avoided the utilization of chiral auxiliaries, *e.g.*, racemic prolinol. Reduction of **20** with sodium cyanoborohydride gave an equatorial alcohol that was converted to mesylate **23** (Scheme 4). Substitution of the mesylate group in **23** with sodium azide gave the axial azide **24**. Reduction of **24** with lithium aluminum hydride afforded **25** which was converted to (*dl*)-**3** by methods developed for the conversion of the equatorial primary amine to (*dl*)-**22** as shown in Scheme 3.

The discovery of an enhancement of receptor affinity by the methoxymethyl substituent (*vide infra*) suggested that this group might have a similar effect on the receptor pharmacology of other analgesic agents. We decided to prepare **29**, which is a derivative of **26**, a seven-membered ring homologue of the 6,7-benzomorphans; compound **26** is analgetically as potent (hot plate

Scheme 5

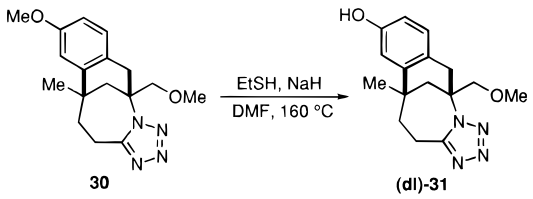


method) but has a higher level of toxicity than morphine.[20]



The synthesis of **29** is shown in Scheme 5. Schmidt rearrangement of ketone **20** with hydrazoic acid in trifluoroacetic acid gave lactam **27** in 88% yield along with a small amount of tetrazole **30**. Treatment of **27** with sodium hydride and methyl iodide gave the *N*-methyl lactam **28** (72%); reduction of **28** with lithium aluminum hydride provided the seven-membered ring amine (82%) and selective demethylation gave the desired (*dl*)-**29**.

Tetrazoles have been found to possess CNS activity. For example, pentylenetetrazole, obtained from caprolactam, is a narcotic antagonist.[21] Reaction conditions that afforded a somewhat higher yield of tetrazole **30** were found, and selective demethylation of **30** gave the phenolic tetrazole **31**.



Opioid Receptor Pharmacology. Several important relationships between structure and opioid receptor affinity are apparent from an inspection of binding constants listed in Table 1. Most noteworthy is the virtual absence of enantioselectivity for receptor binding, particularly at the μ-receptor, for the (+)-**3** and (−)-**3** series. In a classic demonstration of opioid stereospecificity, levorphanol and its inactive enantiomer dextrorphan showed 4 orders of magnitude difference in their ability to displace a ^{3}H-labeled ligand.[22] Furthermore, the unnatural enantiomers of codeine, morphine and heroin showed no antinociceptive activity on subcutaneous injection in mice.[23] Like the opioid alkaloids, (+)-**3** and (−)-**3** contain a rigid ring system; however, the nitrogen atom in **3** is exocyclic and free to assume orientations inaccessible to the nitrogen atom

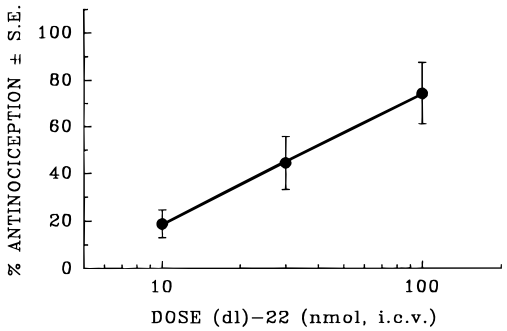


Figure 1. Dose−response line for (*dl*)-**22** given by icv injection 20 min before testing in the mouse tail-flick assay.

in morphine, etc. With respect to molecular rigidity and the presence of an exocyclic amino group, the structure of **3** is similar to dezocine **6**. However, dezocine is a considerably more potent analgesic agent than its enantiomer.[9,10]

Increasing substitution at the nitrogen atom in the series **3a**, **3e** or **3b**, **3d**, **3c** was found to result in decreased affinities for the μ-receptor. The presence of an oxygen atom on the side chain at C(9) was found to be more important than a nitrogen atom (cf. **3a** and **16**) although **15** with the more rigid methylenediamine group did exhibit better μ- and κ-receptor affinities compared to **16**. A methyl ether provided better receptor affinities than the hydroxyl substituent (cf. **3a** and **3b**; **3e** and **3c**). The novel azetidine **3g** and tetrazole **31** did not display enhanced receptor affinities. Addition of the methoxymethyl substituent to **26** (*i.e.*, **29**) did not result in encouraging receptor pharmacology. Perhaps the most remarkable discovery was that inversion of configuration at the nitrogen bearing carbon atom (**3a** vs **22**) resulted in a >10-fold increase in κ-receptor affinity.

Antinociceptive Studies. The racemic compound (*dl*)-**22** was tested in the mouse 55 °C warm-water tail flick to determine if this compound acted as an opioid agonist or antagonist. All drugs were administered as 5 μL icv injections with testing taking place 20 min later. As shown in Figure 1, (*dl*)-**22** produced antinociception in a dose-dependent manner. The D_{50} value, the dose required for 50% antinociception, was 37.0 nmol (95% confidence limits, 30−45 nmol). Since (*dl*)-**22** displayed high affinity for both μ- and κ-opioid receptors in the binding assays, the mouse acetic acid writhing test was used to determine whether (*dl*)-**22** produced antinociception through the μ- or κ-opioid receptors. While a sensitive test for measuring antinociception mediated by μ-opioid receptors, the warm-water tail flick test is less effective at detecting antinociception mediated by κ-opioid receptors.[24] As shown in Figure 2, an icv dose of 10 nmol of (*dl*)-**22** produced 76% antinociception in the writhing assay. This same dose produced only 19% antinociception in the tail flick test.

To determine the receptor selectivity of (*dl*)-**22**, opioid antagonists selective for either the μ-, δ-, or κ-receptors were used. The μ-selective antagonist β-funaltrexamine (β-FNA)[25] was administered as an icv injection of 20 nmol at 24 h before testing. The δ-selective antagonist ICI 174,864[26] (4 nmol) and the κ-selective antagonist norbinaltorphimine (nor-BNI)[27] (1 nmol) were coinjected with 10 nmol of (*dl*)-**22**. As shown in Figure 2, nor-BNI antagonized the antinociception produced by

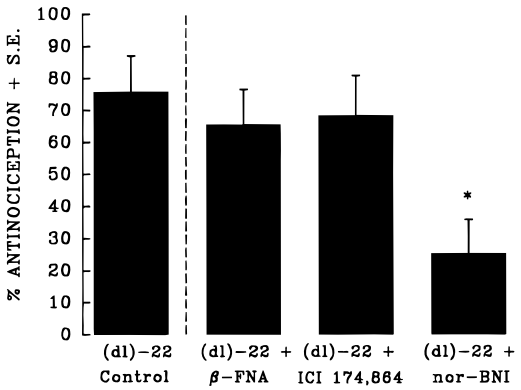


Figure 2. Antinociceptive effects of icv (*dl*)-**22** (10 nmol, −10 min) in mice with or without pretreatment with icv β-FNA (20 nmol, −24 h) or co-administered with either ICI 174,864 (4 nmol, −10 min) or nor-BNI (1 nmol, −10 min) in the mouse acetic acid writhing assay. Data are the mean ± SE from 10 mice in each group. *$P \leq 0.05$, significantly different from (*dl*)-**22** alone.

Table 2. Mouse Tail-Flick Test

drug	dose, nmol	% antinociception	no. of mice
morphine	3	65 ± 12	9
	10	100 ± 0	5
(+)-**3a**	300	13 ± 7.4	5
(+)-**3a** + morphine	100 + 3	58 ± 17	5
(−)-**3a**	100	37 ± 13	10
(*dl*)-**22**	100	74 ± 13	9

(*dl*)-**22**, while the μ- and δ-selective antagonists did not reduce antinociception.

Experiments were performed to determine that the doses of the δ-selective antagonist ICI 174,864 and the κ-selective antagonist nor-BNI were effective at the doses used in the experiments with (*dl*)-**22**. When the δ-selective peptide [D-Pen,[2] D-Pen[5]]enkephalin (DPDPE)[28] was given by icv injection at a dose of 10 nmol, 20 min before testing, 55 ± 13% antinociception was obtained. When 10-nmol DPDPE and 4-nmol ICI 174,864 were co-injected into mice 20 min before testing, antinociception was reduced to 5 ± 2%. Likewise, U50,488 at an icv dose of 30 nmol administered 20 min before testing produced 57 ± 11% antinociception in the mouse tail flick test. In the presence of nor-BNI, the antinociception was reduced to 1 ± 0.3%. These results demonstrate that the selective antagonists were tested at the appropriate doses and antinociception produced by (*dl*)-**22** was mediated by the κ receptor.

While the racemic compound (*dl*)-**22** had high affinity for both μ- and κ-receptors, the C(8) epimeric enantiomers, (+)-**3a** and (−)-**3a**, had high affinity only for the μ-opioid receptor as determined in the radioreceptor binding assays (Table 1). In the mouse tail flick test, a 300-nmol icv injection of (+)-**3a** produced minimal antinociception as shown in Table 2. When (+)-**3a** was co-injected with 3 nmol of morphinesulfate, the antinociception induced by morphine was not significantly altered, demonstrating that (+)-**3a** did not act as an agonist or antagonist at the μ-opioid receptor, as measured by the warm-water tail flick test. The enantiomer (−)-**3a** produced 37 ± 13% antinociception when given as a 100-nmol icv injection at 20 min before testing, demonstrating that it acted as a weak opioid agonist in the tail flick test. This antinociception was blocked by co-administration of the opioid antagonist naloxone.

The racemic compound (*dl*)-**22** bound to the μ- and κ-opioid receptors with high affinity and acted as a κ-agonist. The C(8) epimeric enantiomers (+)-**3a** and (−)-**3a** retained high affinity for the μ-receptor, but did not bind to the κ-receptor with comparable affinity. While (*dl*)-**22** was a full κ-agonist, (+)-**3a** and (−)-**3a** did not possess κ-activity. This finding is not surprising since (+)-**3a** and (−)-**3a** bound to the κ-receptor with low affinity.

Both (*dl*)-**22** and (+)-**3a**/(−)-**3a** had high affinity for the μ-opioid receptor, but did not act as high affinity agonists or antagonists at this receptor in the mouse tail flick test. (−)-**3a** produced mild antinociception at a dose of 100 nmol, suggesting weak agonist activity at the μ-receptor. These findings suggest that either these compounds bind to the μ-receptor at a site that is distinct from the agonist or antagonist binding site(s) or they have low efficacy at the μ-receptor. The fact that (−)-**3a** produced 37% antinociception at a dose of 100 nmol suggests that the compound is an agonist with low efficacy. In membrane-binding experiments, **3a** may inhibit [^{3}H]DAMGO binding by acting as a noncompetitive inhibitor, probably introducing a conformational change in the receptor. The binding site for these compounds on the μ-receptor may be less accessible in vivo, resulting in a diminished pharmacological response at this receptor.

Experimental Section

Opioid Receptor Pharmacology. Affinities of the synthetic alkaloids for μ-, δ-, and κ-opioid receptors were determined for the hydrochloride salts and are shown in Table 1. Neuronal homogenates used in all assays were prepared by the following procedure. Calf frontal cortex or calf caudate tissue was obtained by dissection and immediately homogenized in 50 mM Tris-HCl buffer (pH 7.7 at 25 °C) containing 10 mM $MgSO_4$ and 0.5 mM EDTA. Following centrifugation at 14000*g* for 15 min at 4 °C the membranes were resuspended in buffer and incubated at 37 °C for 15 min to degrade endogenous opioid peptides. The homogenates were centrifuged for 10 min at 14000*g*, resuspended in buffer, recentrifuged, and stored as a pellet at −30 °C until use. Protein determinations were performed using Pierce BCA protein assay.

[^{3}H]Radioligands used are commercially available from NEN DuPont, Wilmington, DE. Opioid specific radioligands used were [^{3}H]Tyr-D-Ala-Gly-*N*-methyl-Phe-Gly-ol (41.6 Ci/mmol) (DAMGO) for μ-selective receptors; [^{3}H](2,5-D-penicillamine)-enkephalin (DPDPE) for δ-selective receptors; and [^{3}H]U69,593 (43.6 Ci/mmol) for κ-selective receptors. Naloxone hydrochloride was purchased from Sigma Chemical Co., St. Louis, MO, and was used for all assays to determine nonspecific binding.

Radioligand binding assays were performed in triplicate in a final volume of 2 mL containing 800−900 μL of tissue buffer, 100 μL of 1 μM naloxone as nonspecific determinant, 100 mL of [^{3}H]DAMGO, 1 nM each of [^{3}H]DPDPE and [^{3}H]U69,593, and 1 μL of tissue homogenate. The tissue concentrations used were 10 mg wet weight of calf frontal cortex for μ- and κ-binding sites and 12 mg wet weight of calf caudate for the δ-binding site; tissue was added last. Incubation times used were 30 min for the μ-selective ligand [^{3}H]DAMGO and the κ-selective ligand [^{3}H]U69,593 at 37 °C and 4 h for the δ-selective ligand [^{3}H]DPDPE at 25 °C. The apparent K_i values for all the compounds were determined by incubating membranes with eight concentrations of the ligands in the presence of either 0.8 nM [^{3}H]DAMGO,[29] 1 nM [^{3}H]DPDPE,[30] or 1 nM [^{3}H]U69,593[31] to measure their affinity for μ-, δ-, and κ-receptor sites, respectively. The binding was terminated by rapid filtration through Whatman GF/B glass filters presoaked in 0.1% polyethyleneimine for 30 min and rinsed with two 2

mL aliquots of cold 50 mM Tris-HCl buffer, pH 7.5. The filters were placed in vials containing 5 mL of Ecosint A scintillation fluid and allowed to equilibrate for 3 h before counting. The membrane bound radioactivity on the filters was counted by liquid scintillation spectrometry. The apparent K_i values of the compounds (Table 1) were calculated using EBDA.

Animals. Male, ICR mice (20−25 g, Harlan Sprague Dawley, Inc., Indianapolis, IN) were used for all experiments. Mice were kept in groups of six in a temperature-controlled room with a 12 h light−dark cycle (lights on 7:00 a.m. to 7:00 p.m.) Food and water were available ad libitum until the time of the experiment. Each subject was tested only once.

Injection Techniques. Intracerebroventricular injections were made directly into the lateral ventricle according to the modified method of Haley and McCormick.[32] The mouse was lightly anesthetized with ether, an incision was made in the scalp, and the injection was made 2 mm lateral and 2 mm caudal to bregma at a depth of 3 mm using a 10 μL Hamilton syringe. The volume of all icv injections was 5 μL.

Tail-Flick Assay. The thermal nociceptive stimulus was 55 °C water with the latency to tail flick or withdrawal taken as the endpoint.[33] After determining control latencies, the mice received graded icv doses of opioid agonists or antagonists at various times. The compounds were given as a single icv injection with testing taking place 20 min after the injection. In the antagonistic study, (−)-**3a** and (+)-**3a** were given as a single injection either alone or with 3 nmol of morphine at 20 min before testing. A cutoff time of 15 s was used; if the mouse failed to display a tail flick, the tail was removed from the water and that animal was assigned a maximal antinociceptive score of 100%. Mice showing no response within 5 s in the initial control test were eliminated from the experiment. Antinociception at each time point was calculated according to the following formula: % antinociception = 100 × (test latency − control latency)/(15 − control latency).

Mouse Acetic Acid Writhing Assay. (*dl*)-**22** was given as a single 5 μL icv injection to mice 5 min before an ip injection of 0.6% acetic acid (10 mL/kg) was administered to each mouse. Five minutes after administration, the number of writhing signs displayed by each mouse was counted for an additional 5 min. Antinociception for each tested mouse was calculated by comparing the test group to a control group in which mice were treated with icv saline. Data were calculated according to the formula: % antinociception = [100 × (mean number of writhes in control group − number of writhes by each mouse)]/(mean number of writhes in control group).

Synthesis. NMR spectra were obtained with a Varian Unity 500 spectrometer for solutions in deuteriochloroform with tetramethylsilane as an internal standard. Chemical ionization mass spectra (isobutane) were determined with a Hewlett-Packard 5987A GC−MS system. High-resolution mass spectra were provided by Schering-Plough Research Institute. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer and calibrated with a polystyrene film (1601 cm^{-1} band). Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Melting points were obtained from samples in open capillary tubes and are uncorrected. When appropriate, reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was distilled over sodium and benzophenone under nitrogen. Although the preparation of (−)-**3a** is shown in Scheme 1, the preparation of (+)-**3a** is given in the Experimental Section so that a large-scale Birch reduction−alkylation, the focal point of the synthetic pathway, could be described.

(5a*R*,9a*S*,11a*S*)-5a-Benzyl-(4-methoxy)-7-methyl-1,2,3,8,9,9a,10,11a-octahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione [(+)-7]. A 5 L three-necked round-bottomed flask, equipped with a mechanical stirrer, a 200 mL dropping funnel sealed with a rubber septum, and a dry ice/acetone cooled cold-finger condenser bearing a nitrogen inlet/outlet valve vented through a mineral oil bubbler was charged with a solution of (+)-**4a**[3] (57.57 g, 0.25 mol), *tert*-butyl alcohol (37.06 g, 0.50 mol), and dry tetrahydrofuran (200 mL). The mixture was cooled to −78 °C (dry ice/acetone bath), and 3 L of dry ammonia was distilled into the reaction flask. After stirring was initiated, a total of 43.01 g (1.1 mol, 4.4 equiv) of potassium metal was added in small chunks at −78 °C. The resulting blue solution was stirred vigorously for 2 h, after which piperylene was added dropwise until the blue coloration disappeared. Next, 4-methoxybenzyl bromide (100.53 g, 0.50 mol) was added via the dropping funnel. The reaction mixture slowly turned pink and then yellow-orange. After an additional 3 h of stirring, solid ammonium chloride (70 g) was added, ammonia was allowed to evaporate overnight, and the mixture was partitioned between water and chloroform. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel and crystallized from methylene chloride/hexane to give (+)-**7** (63.80 g, 0.18 mol, 73%): mp 173.2−174.4 °C; ^{1}H NMR ($CDCl_3$) δ 7.06 (dfs, 2 H, J = 6.7 Hz), 6.81 (dfs, 2 H, J = 6.7 Hz), 6.40 (d, exchangeable with D_2O, NH, J = 5.3 Hz), 5.98 (s, 1 H), 4.14 (m, 1 H), 3.79 (s, 3 H), 3.4−3.6 (m, 2 H), 3.30 (d, 1 H, J = 14.0 Hz), 2.58 (d, 1 H, J = 13.9 Hz), 1.73 (s, 3 H), 1.5−2.4 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.09, 171.8, 158.7, 132.4, 130.8, 128.7, 125.3, 113.5, 55.3, 55.1, 54.0, 48.6, 46.3, 45.6, 27.1, 23.8, 23.7, 23.1, 22.1; IR (film) 3400 (sharp), 1680, 1605, 1510, 1440, 1410, 1210 cm^{-1}; CIMS, m/z (relative intensity) 355 (M^+ + 1, 100), 121 (93); $[\alpha]^{22}_D$ +65° (c 2.1, $CHCl_3$); (−)-**7a**: $[\alpha]^{22}_D$ −56° (c 2.5, $CHCl_3$). Anal. ($C_{21}H_{26}N_2O_3$) C, H.

(5*S*,7a*S*,9a*S*,14a*S*)-5,14a-Methano-3-methoxy-5-methyl-7a,8,9a,10,11,12-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-diazepine[3,4-*i*]benzocyclooctene-9,14-dione [(+)-8]. A solution of (+)-**7** (19.39 g, 55 mmol) in dry methylene chloride (45 mL) was added to freshly distilled trifluoromethanesulfonic acid (250 mL) at 0 °C. The solution was stirred at ambient temperature for 15 min. Cooled water (5 mL) was added dropwise to the cooled reaction mixture, and then aqueous sodium bicarbonate was added until the solution was weakly alkaline. The mixture was extracted with methylene chloride, dried (K_2CO_3), and evaporated. The residue was chromatographed on silica gel to give (+)-**8** (15.43 g, 43.5 mmol, 79%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 1 H, J = 8.3 Hz), 6.82 (d, 1 H, J = 2.6 Hz), 6.72 (dd, 1 H, J = 2.7, 8.4 Hz), 6.08 (d, exchangeable with D_2O, NH, J = 5.8 Hz), 4.68 (t, 1 H, J = 6.8 Hz), 4.08 (m, 1 H), 3.79 (s, 3 H), 3.65 (d, 1 H, J = 17.1 Hz), 3.60 (m, 2 H), 2.70 (d, 1 H, J = 16.9 Hz), 2.63 (m, 1 H), 2.25 (d, 1 H, J = 13.3 Hz), 1.4−2.1 (m, 8 H), 1.38 (s, 3 H); ^{13}C ($CDCl_3$) δ 174.6, 171.7, 158.0, 143.20, 128.4, 127.9, 111.6, 110.2, 56.2, 55.2, 52.6, 49.8, 48.2, 38.0, 37.6, 34.9, 34.6, 28.0, 27.8, 25.2, 20.1; IR (5% solution in $CHCl_3$) 3410 (s), 1675, 1608 cm^{-1}; CIMS, m/z (relative intensity) 355 (M^+ + 1, 100); $[\alpha]^{22}_D$ +130° (c 2.5, $CHCl_3$); (−)-**8** $[\alpha]^{21}_D$ −120° (c 2.5, $CHCl_3$). Anal. ($C_{21}H_{26}N_2O_3$) C, H.

(5*S*,8*S*,9*S*)-9-Carboxy-5,9-methano-3-methoxy-5-methyl-8-(*N*-tosylamino)benzocyclooctene [(+)-9]. A solution of (+)-**8** (28.80 g, 81 mmol) in anhydrous methanol (130 mL) and concentrated sulfuric acid (16.56 g, 162 mmol) was refluxed under nitrogen until TLC analysis indicated the disappearance of (+)-**8** (2−3 days). The solution was concentrated, and saturated sodium bicarbonate was added until the aqueous layer was basic. Then saturated ammonium hydroxide was added until a pH of 10 was obtained. The solution was extracted with methylene chloride, and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in dry THF (100 mL) and cooled to 0 °C. Triethylamine (12.35 g, 122 mmol) was added followed by a solution of *p*-toluenesulfonyl chloride (16.97 g, 89 mmol) in THF (50 mL). The resulting solution was stirred for 60 h at ambient temperature and then partitioned between saturated sodium chloride and ethyl acetate. The combined organic layers were dried, concentrated, and chromatographed on silica gel to give the tosyl amide (26.12 g, 47 mmol, 80% based on 7.97 g of recovered starting material) as a colorless foam. A suspension of the tosylamide (13.52 g, 25 mmol) in sulfuric acid (6 N, 100 mL) was heated at 100 °C for 2 days. After cooling, the heterogeneous aqueous solution was saturated with sodium chloride and extracted with methylene chloride until the aqueous layer became clear. The combined organic layers were dried, concentrated, and filtered through a short silica gel column to give (+)-**9** (12.48 g, 23 mmol, 92%)

as a light brown solid: ^{1}H NMR ($CDCl_3$) δ 10.56 (bs, exchangeable with D_2O, COOH), 7.81 (d, 1 H, J = 8.5 Hz), 7.29 (d, 1 H, J = 8.5 Hz), 6.94 (d, 1 H, J = 8.0 Hz), 6.76 (d, 1 H, J = 2.5 Hz), 6.68 (dd, 1 H, J = 2.5, 8.0 Hz), 6.21 (d, exchangeable with D_2O, NH), 3.76 (s, 3 H), ~3.7 (m, 1 H), 3.10 (d, 1 H, J = 17.5 Hz), 2.86 (d, 1 H, J = 17.5 Hz), 2.38 (s, 3 H), 1.94 (d, 1 H, J = 13.5 Hz), 1.80 (d, 1 H, J = 13.5 Hz), 1.63 (m, 1 H), 1.48 (d, 1 H, J = 12.5 Hz), 1.35 (s, 3 H), 1.13−1.25 (m, 2 H); ^{13}C ($CDCl_3$) δ 179.7, 158.1, 143.8, 143.3, 137.5, 129.6, 128.4, 127.1, 126.5, 111.6, 110.0, 55.8, 55.1, 45.6, 37.0, 35.2, 34.5, 34.4, 27.7, 25.0, 21.5; CIMS, m/z (relative intensity) 430 (M^+ + 1, 68), 276 (73), 157 (100).

(5*S*,8*S*,9*S*)-5,9-Methano-3-methoxy-9-(methoxymethyl)-5-methyl-8-(*N*-tosylamino)benzocyclooctene [(+)-10]. Lithium aluminum hydride (0.210 g, 5.53 mmol) was added to a solution of (+)-**9** (1.509 g, 3.52 mmol) in 45 mL of THF at 4 °C. The solution was refluxed overnight, brine was then added at 4 °C, and solid material was filtered. The filtrate was extracted with CH_2Cl_2, and the organic layers were dried over Na_2SO_4 and concentrated to give the alcohol as a white foam (1.353 g, 93%). To a solution of the alcohol (1.108 g, 2.67 mmol) in 20 mL of THF was added sodium hydride (0.285 g, 11.9 mmol). The mixture was stirred at room temperature for 1 h, 170 μL of methyl iodide (2.73 mmol) was then introduced, and stirring was continued for 1 h. Additional addition of methyl iodide was added (20 μL, total 0.19 mL, 3.05 mmol). After 4 h, excess NaH was quenched with water cooled to 4 °C, and the resulting solution was acidified with concentrated HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (Et_2O−hexane, 3:7) provided (+)-**10** (0.974 g, 85%): mp 181.5−182.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2 H, J = 8.3 Hz), 7.30 (d, 2 H, J = 8.3 Hz), 6.90 (d, 1 H, J = 8.6 Hz), 6.76 (d, 1 H, J = 2.7 Hz), 6.66 (dd, 1 H, J = 2.7, 8.3 Hz), 6.06 (m, 1 H), 3.75 (s, 3 H), 3.25 (m, 1 H), 3.19 (s, 3 H), 3.16 (d, 1 H, J = 9.0 Hz), 3.01 (d, 1 H, J = 9.0 Hz), 2.74 (d, 1 H, J = 17.8 Hz), 2.44 (d, 1 H, J = 17.8 Hz), 2.42 (s, 3 H), 1.72−1.65 (m, 1 H), 1.61 (d, 1 H, J = 13.2 Hz), 1.47 (d, 1 H, J = 13.4 Hz), 1.39 (d, 1 H, J = 13.2 Hz), 1.33 (s, 3 H), 1.21−1.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.8, 144.6, 143.0, 137.7, 129.5, 128.2, 127.8, 127.1, 111.2, 109.9, 81.2, 59.1, 57.1, 55.1, 37.5, 37.4, 36.7, 34.9, 34.4, 27.9, 25.4, 21.4; IR (CH_2Cl_2) 3236, 2934, 1610, 1496, 1333, 1160 cm^{-1}; HRMS calcd for $C_{24}H_{32}NO_4S$ $(M + H)^+$ 430.2052, found 430.2058.

(5*S*,8*S*,9*S*)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene [(+)-3a]. To a stirred solution of (+)-**10** (0.312 g, 0.727 mmol) and ethanethiol (0.30 mL, 4.1 mmol) in 4 mL of DMF at 4 °C was added sodium hydride (0.145 g, 6.04 mmol). The mixture was refluxed overnight. A few drops of concentrated HCl was added to the reaction mixture cooled (4 °C), and DMF was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and water. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed on silica gel to give the phenol as a yellow foam (0.271 g, 90%). To a solution of the phenol (0.271 g, 0.653 mmol) in 6 mL of THF and ~30 mL of NH_3 at −78 °C was added small pieces of sodium until a dark blue coloration persisted. The solution was stirred at −78 °C for 30 min then quenched with solid NH_4Cl. NH_3 was allowed to evaporate and the remaining mixture was diluted with brine and extracted with CH_2Cl_2. Chromatography on two alumina preparative TLC plates (1.5 mm, EtOAc−hexane, 1:1). The band at the baseline was removed and extracted with 30% MeOH in CH_2Cl_2. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed with water. Evaporation of solvent afforded (+)-**3a** as a yellow foam (0.127 g, 75%): ^{1}H NMR ($CDCl_3$) δ 6.92 (d, 1 H, J = 8.0 Hz), 6.73 (d, 1 H, J = 2.5 Hz), 6.60 (dd, 1 H, J = 2.7, 8.3 Hz), 3.43 (d, 1 H, J = 8.8 Hz), 3.37 (s, 3 H), 3.10 (d, 1 H, J = 8.8 Hz), 3.06 (m, 1 H), 2.89 (d, 1 H, J = 17.6 Hz), 2.65 (d, 1 H, J = 17.8 Hz), 1.69 (dt, 1 H, J = 4.4, 13.2 Hz), 1.58 (d, 1 H, J = 12.9 Hz), 1.42−1.30 (m, 2 H), 1.33 (s, 3 H), 1.28 (d, 1 H, J = 12.7 Hz), 1.22−1.19 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.8, 144.3, 128.4, 127.5, 113.5, 111.3, 81.9, 59.3, 52.4, 38.8, 37.8, 36.2, 35.0, 34.6, 28.1, 27.1; IR (CH_2Cl_2) 3584, 2924 (overlap with a broad peak), 1609, 1110 cm^{-1}; $[\alpha]^{27}_D$ +62° (c 1.0, EtOH); HRMS calcd for $C_{16}H_{24}NO_2$ $(M + H)^+$ 262.1807, found 262.1803; (−)-**3a** $[\alpha]^{30}_D$ −64° (c 1.0, EtOH). Anal. ($C_{16}H_{23}NO_2 \cdot {}^1/_2H_2O$) C, H.

(5*S*,8*S*,9*S*)-8-Amino-3-hydroxy-5,9-methano-9-(hydroxymethyl)-5-methylbenzocyclooctene [(+)-3b]: ^{1}H NMR ($CDCl_3$) δ 6.91 (d, 1 H, J = 8.1 Hz), 6.72 (d, 1 H, J = 2.6 Hz), 6.60 (dd, 1 H, J = 2.6, 8.2 Hz), 3.69 (d, 1 H, J = 11.7 Hz), 3.26 (d, 1 H, J = 11.5 Hz), 3.03 (bs, 1 H), 2.36 (s, 2 H), 2.06 (d, 1 H, J = 13.6 Hz), 1.45 (s, 3 H), 1.3−1.5 (m, 9 H).

(5*S*,8*S*,9*S*)-3-Hydroxy-5,9-methano-9-(hydroxymethyl)-5-methyl-8-(*N*,*N*-dimethylamino)benzocyclooctene [(+)-3c]: ^{1}H NMR ($CDCl_3$) δ 6.82 (d, 1 H, J = 8.1 Hz), 6.77 (d, 1 H, J = 2.3 Hz), ~6.7 (b, exchangeable with D_2O, 1 H), 6.63 (dd, 1 H, J = 2.5, 8.2 Hz), 3.82 (d, 1 H, J = 11.1 Hz), 3.50 (d, 1 H, J = 11.0 Hz), 2.70 (d, 1 H, J = 5.7 Hz), 2.43 (s, 3 H), 2.40 (s, 2 H), 2.09 (d, 1 H, J = ~14 Hz), 1.36 (s, 3 H), 1.2−1.8 (m, 6 H); ^{13}C ($CDCl_3$) δ 154.6, 144.9, 128.5, 127.4, 113.3, 111.2, 73.9, 67.8, 44.5, 41.3, 38.7, 38.1, 37.9, 34.8, 28.8, 18.2; IR (film) ~3200 (broad) cm^{-1}; CIMS, m/z (relative intensity) 276 (M^+ + 1, 100); $[\alpha]^{24}_D$ +83° (c 2.2, EtOH); (−)-**3c**: $[\alpha]^{23}_D$ −80° (c 2.0, EtOH). Anal. ($C_{17}H_{25}NO_2 \cdot HCl$) C, H.

(5*S*,8*S*,9*S*)-3-Hydroxy-5,9-methano-9-(hydroxymethyl)-5-methyl-8-(*N*-methylamino)benzocyclooctene [(+)-3d]: ^{1}H NMR ($CDCl_3$) δ 6.86 (d, 1 H, J = 8.2 Hz), 6.76 (d, 1 H, J = 2.5 Hz), 6.23 (dd, 1 H, J = 2.6, 8.2 Hz), ~4.4 (bs, exchangeable with D_2O, 3 H), 3.83 (d, 1 H, J = 10.7 Hz), 3.39 (d, 1 H, J = 10.7 Hz), 2.56 (bs, 1 H), 2.43 (s, NCH_3), 2.34 (s, 2 H), 1.95 (d, 1 H, J = 13.5 Hz), 1.35 (s, 3 H), 1.1−1.6 (m, 5 H); IR (film) 3200 (broad) cm^{-1}; CIMS, m/z (relative intensity) 262 (M^++1, 100); $[\alpha]^{25}_D$ +63° (c 1.5, $CHCl_3$); (−)-**3d**: $[\alpha]^{28}_D$ −66° (c 1.4, $CHCl_3$).

(5*S*,8*S*,9*S*)-3-Hydroxy-5,9-methano-9-(methoxymethyl)-5-methyl-8-(*N*,*N*-dimethylamino)benzocyclooctene [(+)-3e]: ^{1}H NMR ($CDCl_3$) δ 6.88 (d, 1 H, J = 8.1 Hz), 6.74 (d, 1 H, J = 2.0 Hz), 6.60 (dd, 1 H, J = 2.2, 8.1 Hz), ~ 5.65 (b, exchangeable with D_2O, OH), 3.58 (d, 1 H, J = 8.9 Hz), 3.36 (s, 3 H), 3.22 (d, 1 H, J = 8.8 Hz), 3.06 (d, 1 H, J = 17.6 Hz), 2.93 (d, 1 H, J = 12.8 Hz), 2.37 (s, 6 H), 2.34−2.53 (m, 1 H), 1.31 (s, 3 H), 1.10−1.79 (m, 6 H); ^{13}C ($CDCl_3$) δ 154.1, 144.6, 128.8, 128.5, 113.2, 111.1, 80.7, 64.2, 59.0, 58.3, 44.7, 40.3, 39.1, 38.9, 38.6, 34.4, 28.6, 18.6, 18.2; IR (film) 3310 (b), 3000−2800, 2760, 1600, 1450, 1230, 1100 cm^{-1}; CIMS, m/z (relative intensity) 290 (M^+ + 1, 100), 258 (94).

(5*S*,8*S*,9*R*)-3-Hydroxy-5,9-methano-5,9-dimethyl-8-(*N*,*N*-dimethylamino)benzocyclooctene [(+)-3f]: ^{1}H NMR ($CDCl_3$) δ 6.87 (d, 1 H, J = 8.3 Hz), 6.73 (d, 1 H, J = 2.7 Hz), 6.59 (dd, 1 H, J = 2.7, 8.2 Hz), ~5.90 (b, exchangeable with D_2O, OH), 2.75 (d, 1 H, J = 17.5 Hz), 2.50 (dd, 1 H, J = 1.7, 17.1 Hz), 2.36 (s, 6 H), 2.30 (m, 1 H), 1.33 (s, 3 H), 1.14 (s, 3 H), 0.95−1.84 (m, 6 H); ^{13}C ($CDCl_3$) δ 153.8, 144.8, 129.7, 128.3, 112.9, 111.2, 66.9, 46.6, 44.5, 44.2, 39.1, 35.4, 28.9, 28.6, 18.7, 18.4; IR (film) 3300 (b), 3000−2800 cm^{-1}; CIMS, m/z (relative intensity) 260 (M^+ + 1, 100); $[\alpha]^{30}_D$ +110° (c 0.30, EtOH); (−)-**3f**: $[\alpha]^{32}_D$ −66° (c 0.47, EtOH).

(5*S*,8*S*,9*R*)-3-Hydroxy-5,9-methano-*N*,5-dimethylazetidino[2,3-*i*]benzocyclooctene [(+)-3g]: ^{1}H NMR ($CDCl_3$) δ ~8.9 (bs, exchangeable with D_2O, OH), 6.86 (d, 1 H, J = 8.1 Hz), 6.72 (d, 1 H, J = 2.0 Hz), 6.58 (dd, 1 H, J = 2.2, 8.1 Hz), 3.31 (d, 1 H, J = 6.5 Hz), 2.49−2.85 (m, 4 H), 2.33 (s, NCH_3), 2.05 (dfs, 1 H, J = 12.4 Hz), 1.26 (s, 3 H), 1.11−1.73 (m, 5 H); ^{13}C ($CDCl_3$) δ 155.3, 144.8, 130.0, 127.1, 113.5, 113.2, 72.3, 64.7, 44.2, 43.0, 41.0, 37.7, 36.6, 35.8, 29.4, 22.9; IR (film) 3300 (b), 3100−2750 (b) cm^{-1}; CIMS, m/z (relative intensity) 244 (M^+ + 1, 100).

3,6-Dimethylquinazoline-2,4-dione (12). A solution of 2-amino-5-methylbenzoic acid (15.08 g, 99.9 mmol) and methyl isocyanate (7.0 mL, 120 mmol) in 450 mL of dry benzene was refluxed for 2 h. Benzene was evaporated, and the resulting brown solid was treated with 200 mL of 6 M H_2SO_4 and heated under reflux for 1 h. After standing overnight, the solid was filtered and washed with water until the pH of the filtrate was 6−7. After drying in an oven at 80−85 °C overnight, **12** was obtained as a white solid (14.16 g, 75%): mp 258−259 °C; ^{1}H NMR ($CDCl_3$) δ 9.91 (br) (s, 1 H), 7.94 (m, 1 H, J = 1.2 Hz), 7.43 (dd, 1 H, J = 1.5, 8.3 Hz), 7.03 (d, 1 H, J = 8.3 Hz), 3.49 (s, 3 H), 2.41 (s, 3 H); ^{13}C (DMSO-d_6) δ 162.4, 150.5, 137.4, 136.1, 131.8, 126.9, 115.2, 113.7, 27.2, 20.5; IR (DMSO-d_6) 3445

(br), 2874, 1713, 1665, 1520, 1453, 1298 cm^{-1}; CIMS, *m/z* (relative intensity), 191 ($M^+ + 1$, 100). Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

(±)-(4a*S*,8a*R*)-1-(4′-Methoxybenzyl)-4a-(4′-methoxybenzyl)-3,6-dimethyl-7,8,8a-trihydroquinazoline-2,4-dione (13). A three-necked reaction flask containing **12** (5.491 g, 28.9 mmol) and *tert*-butyl alcohol (5.5 mL, 58 mmol) in 45 mL of THF at −78 °C was charged with approximately 400 mL of NH_3. Small pieces of potassium were added until a blue coloration persisted. The solution was stirred at −78 °C for 1.5 h, and then a few drops of piperylene were added. 4-Methoxybenzyl bromide (16.96 g, 84.4 mmol) was added, and the solution was stirred at −78 °C for 1.75 h and then at −33 °C for 2 h. Solid NH_4Cl was added, and NH_3 was allowed to evaporate. The resulting residue was partitioned between CH_2Cl_2 and water. The organic layers were combined, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel provided an inseparable mixture of **13** and the trans-fused diastereomer (∼4:1) as a yellow oil (4.547 g, 36%). **13**: ^1H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J = 8.8 Hz), 6.89 (d, 2 H, J = 8.5 Hz), 6.68 (d, 2 H, J = 8.5 Hz), 6.60 (d, 2 H, J = 8.8 Hz), 5.56 (br) (s, 1 H), 4.88 (d, 1 H, J = 14.6 Hz), 4.27 (d, 1 H, J = 14.6 Hz), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.24 (s, 3 H), 3.01 (dd, 1 H, J = 3.2, 12.7 Hz), 2.79 (d, 1 H, J = 13.6 Hz), 2.53 (d, 1 H, J = 13.7 Hz), 1.86−1.79 (m, 2 H), 1.74−1.69 (m, 1 H), 1.65 (s, 3 H), 1.53−1.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 159.4, 158.4, 152.8, 136.0, 131.2, 130.4, 129.3, 127.2, 121.8, 114.1, 113.3, 55.21, 55.16, 55.05, 49.6, 48.0, 41.1, 28.9, 27.9, 24.5, 23.2; IR (film) 2932, 1665, 1615, 1515, 1466, 1253, 1182, 1038 cm^{-1}; CIMS, *m/z* (relative intensity) 435 ($M^+ + 1$, 25), 315 (7), 121 (100).

(±)-(5*S*,7a*S*,11a*S*)-5,11a-Methano-3-methoxy-5,10-dimethyl-7a,8-dihydropyrimidino[5,6-*i*]benzocyclooctene-9,-11-dione (14). To a stirred solution of **13** and the minor trans-fused diastereomer (4.547 g, 10.5 mmol) in 5 mL of CH_2Cl_2 at 4 °C was added 12 mL of trifluoromethanesulfonic acid. The solution was stirred at room temperature for 20 min, and then ice−water followed by saturated potassium carbonate was added cautiously at 4 °C until the solution was basic to pH paper. Extraction with CH_2Cl_2 and flash chromatography provided a 4:1 mixture of **14** and the trans-fused diastereomer (3.011 g, 92%). Crystallization of the mixture from CH_2Cl_2 and pentane afforded **14** as a white foam: ^1H NMR δ 7.07 (d, 1 H, J = 8.5 Hz), 6.80 (d, 1 H, J = 2.5 Hz), 6.75 (dd, 1 H, J = 2.6, 8.5 Hz), 6.46−6.34 (m, 1 H), 4.01 (d, 1 H, J = 17.6 Hz), 3.80 (s, 3 H), 3.57 (m, 1 H), 3.20 (s, 3 H), 2.50 (d, 1 H, J = 17.9 Hz), 1.85 (d, 1 H, J = 12.7 Hz), 1.76 (dt, 1 H, J = 3.9, 13.2 Hz), 1.63 (d, 1 H, J = 12.5 Hz), 1.55 (d, 1 H, J = 14.9 Hz), 1.45 (m, 1 H), 1.37 (s, 3 H), 1.36−1.33 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 157.9, 155.1, 142.7, 128.7, 127.3, 111.5, 110.2, 55.1, 51.3, 41.6, 36.5, 34.4, 34.3, 33.7, 27.8, 27.7, 24.3; IR (CH_2Cl_2) 3420, 2935, 1721, 1675, 1454, 1293 cm^{-1}; CIMS, *m/z* (relative intensity) 315 ($M^+ + 1$, 100).

(±)-(5*S*,7a*S*,11a*R*)-3-Hydroxy-5,11a-methano-5,10-dimethyl-7a,8, 9,11-tetrahydropyrimidino[5,6-*i*]benzocyclooctene [(*dl*)-15]. A mixture of **14** (0.380 g, 1.21 mmol) and lithium aluminum hydride (0.237 g, 6.24 mmol) in 25 mL of THF was refluxed overnight. Water was added at 4 °C followed by a few drops of 5% NaOH to make the solution slightly basic. Solid material was removed by filtration and was washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography on Florisil (MeOH−Et_2O, 1:4) gave the diamine as a yellow foam (0.280 g, 81%). To a solution of the diamine (0.168 g, 0.587 mmol) in 2.5 mL of dry CH_2Cl_2 was added 1.2 mL of 1.0 M boron tribromide in CH_2Cl_2 at −78 °C. The resulting solution was stirred at −78 °C for 1 h. After warming to room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ and brine. The pH was adjusted to >8 with 30% NaOH. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on Florisil (MeOH−Et_2O, 1:3) gave (*dl*)-**15** as a white foam (80 mg, 50%): ^1H NMR ($CDCl_3$) δ 6.88 (d, 1 H, J = 8.3 Hz), 6.67 (d, 1 H, J = 2.2 Hz), 6.57 (dd, 1 H, J = 2.3, 8.2 Hz), 3.90 (d, 1 H, J = 10.8 Hz), 2.89 (d, 1 H, J = 11.0 Hz), 2.56 (d, 1 H, J = 11.5 Hz), 2.53 (m, 1 H), 2.47 (d, 1 H, J = 17.3 Hz), 2.38 (d, 1 H, J = 17.1 Hz), 2.17 (s, 3 H), 2.11 (d, 1 H, J = 13.2 Hz), 1.93 (d, 1 H, J = 11.5 Hz), 1.45−1.39 (m, 3 H), 1.34 (d, 1 H, J = 13.2 Hz), 1.26 (s, 3 H), 1.23−1.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.8, 144.6, 128.6, 127.6, 113.6, 111.6, 70.5, 67.3, 58.7, 42.4, 40.2, 39.2, 35.6, 35.3, 33.0, 28.2, 25.9; IR (CH_2Cl_2) 2930 (br, overlap), 1610, 1464, 1240 cm^{-1}; CIMS, *m/z* (relative intensity) 273 ($M^+ + 1$, 100).

(±)-(5*S*,8*S*,9*S*)-8-Amino-3-hydroxy-5,9-methano-5-methyl-9-[(methylamino)methyl]benzocyclooctene [(*dl*)-16]. A solution of (*dl*)-**15** (57 mg) in 1 mL of 10% HCl and 3 mL of EtOH was heated under reflux for ∼36 h. The solution was diluted with brine and made basic (pH >8) with 30% NaOH, then extracted with THF. Evaporation of solvent afforded (*dl*)-**16** as a yellow solid (44 mg, 81%): ^1H NMR ($CDCl_3$) δ 6.86 (d, 1 H, J = 8.1 Hz), 6.72 (d, 1 H, J = 2.2 Hz), 6.59 (dd, 1 H, J = 2.5, 8.3 Hz), 3.00 (m, 1 H), 2.91 (br) (m, 3 H), 2.83 (d, 1 H, J = 17.3 Hz), 2.71 (d, 1 H, J = 11.5 Hz), 2.64 (d, 1 H, J = 17.6 Hz), 2.46 (s, 3 H), 2.33 (d, 1 H, J = 11.7 Hz), 1.68−1.63 (m, 1 H), 1.56 (d, 1 H, J = 12.9 Hz), 1.41−1.35 (m, 2 H), 1.31−1.26 (m, 1 H), 1.30 (s, 3 H), 1.20−1.17 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.6, 144.7, 128.5, 128.1, 113.4, 111.3, 63.1, 52.6, 39.9, 38.3, 37.4, 37.1, 35.1, 35.0, 28.3, 28.2; IR (film) 3367 (br), 2929, 1576, 1469 cm^{-1}; HRMS calcd for $C_{16}H_{25}N_2O$ ($M + H)^+$ 261.1967, found 261.1965.

6-Carbomethoxy-1-methoxy-6-(4′-methoxybenzyl)-4-methyl-1,4-cyclohexadiene (18). To a solution of methyl 2-methoxy-5-methylbenzoate (4.956 g, 27.5 mmol) and *tert*-butyl alcohol (2.6 mL, 28 mmol) in 30 mL of THF at −78 °C was condensed approximately 400 mL of NH_3. Small pieces of lithium metal were added until a blue coloration persisted. After stirring at −78 °C for 40 min, a few drops of piperylene were added. 4-Methoxybenzyl bromide (12.00 g, 59.7 mmol) was added, and the resulting solution was stirred at −78 °C for 30 min, then −33 °C for an additional hour. Solid NH_4Cl was added, and NH_3 was allowed to evaporate. The residue was partitioned between CH_2Cl_2 and water. The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (Et_2O-Hexane 1:5.5) afforded **18** as clear crystals (7.136 g, 86%): mp 109−110 °C; ^1H NMR ($CDCl_3$) δ 6.92 (d, 2 H, J = 8.5 Hz), 6.70 (d, 2 H, J = 8.7 Hz), 5.18 (m, 1 H), 4.58 (t, 1 H, J = 3.7 Hz), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.52 (s, 3 H), 3.25 (d, 1 H, J = 13.4 Hz), 2.90 (d, 1 H, J = 13.4 Hz), 2.46 (dd, 1 H, J = 3.9, 21.8 Hz), 2.01 (d, 1 H, J = 21.5 Hz), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 157.6, 151.5, 134.4, 131.1, 129.1, 121.0, 112.2, 93.9, 54.6, 53.7, 53.6, 52.0, 39.7, 30.4, 22.0; IR (CH_2Cl_2) 2951, 2911, 1725, 1665, 1611, 1512, 1233, 1175, 1039 cm^{-1}; CIMS, *m/z* (relative intensity) 303 ($M^+ + 1$, 100). Anal. ($C_{18}H_{22}O_4$) C, H.

2-(4′-Methoxybenzyl)-2-(methoxymethyl)-4-methylcyclohex-3-en-1-one (19). Lithium aluminum hydride (0.965 g, 25.4 mmol) was slowly added to a solution of **18** (4.967 g, 16.4 mmol) in 70 mL of THF at 4 °C. The mixture was refluxed overnight, water was added dropwise at 4 °C, and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_2 and concentrated. Flash chromatography on silica gel provided the alcohol as a yellow oil (4.345 g, 96%). Sodium hydride (0.549 g, 22.9 mmol) was added to a solution of the alcohol (3.06 g, 11.2 mmol) in 35 mL of THF at 4 °C. Methyl iodide (1.4 mL, 22.5 mmol) was added, and the resulting solution was stirred overnight at room temperature. Then 10% HCl was added dropwise until the solution was acidic to pH paper. The solution was diluted with brine and extracted with Et_2O. The organic layers were combined, dried, and evaporated. Chromatography on silica gel provided **19** (2.82 g, 92%): ^1H NMR ($CDCl_3$) δ 6.95 (d, 2 H, J = 8.7 Hz), 6.75 (d, 2 H, J = 8.8 Hz), 5.33 (m, 1 H), 3.76 (s, 3 H), 3.59 (d, 1 H, J = 8.6 Hz), 3.29 (s, 3 H), 3.27 (d, 1 H, J = 8.6 Hz), 2.92 (d, 1 H, J = 12.9 Hz), 2.50 (d, 1 H, J = 13.2 Hz), 2.35−2.28 (m, 1 H), 2.10−2.03 (m, 2 H), 1.76 (s, 3 H), 1.66−1.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 213.9, 158.0, 136.8, 131.2, 128.6, 124.8, 113.0, 78.7, 59.3, 55.0, 54.4, 40.7, 38.9, 28.2, 23.4; IR (film) 2914, 2836, 1708, 1612, 1512, 1443, 1248, 1180, 1113 cm^{-1}; CIMS, *m/z* (relative intensity) 275 ($M^+ + 1$, 100). Anal. ($C_{17}H_{22}O_3$) C, H.

5,9-Methano-3-methoxy-9-(methoxymethyl)-5-methylbenzocycloocten-8-one (20). A solution of **19** (3.537 g, 12.9 mmol) in 15 mL of CH_2Cl_2 and 18 mL of trifluoromethanesulfonic acid was stirred at 4 °C for 15 min. Ice−water and then saturated potassium carbonate were added cautiously until the solution tested basic to pH paper. The solution was extracted with CH_2Cl_2. After drying and removal of solvent, chromatography on silica gel afforded **20** as a yellow oil (2.666 g, 75%): ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 1 H, J = 8.3 Hz), 6.93 (d, 1 H, J = 2.7 Hz), 6.74 (dd, 1 H, J = 2.7, 8.3 Hz), 3.81 (s, 3 H), 3.64 (d, 1 H, J = 9.3 Hz), 3.38 (s, 3 H), 3.35 (d, 1 H, J = 9.3 Hz), 3.01 (d, 1 H, J = 17.1 Hz), 2.57 (dd, 1 H, J = 1.1, 17.2 Hz), 2.24 (m, 1 H), 2.00 (dd, 1 H, J = 3.6, 13.1 Hz), 1.96−1.87 (m, 3 H), 1.82−1.78 (m, 1 H), 1.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.6, 158.3, 143.5, 129.3, 126.7, 111.8, 110.8, 76.5, 59.4, 55.2, 48.5, 42.2, 42.0, 37.6, 35.5, 35.0, 27.5; IR (film) 2925, 1700, 1610, 1495, 1464, 1235, 1111 cm^{-1}; CIMS, m/z (relative intensity) 275 (M^+ + 1, 100). Anal. ($C_{17}H_{22}O_3$) C, H.

(±)-(5*S*,8*S*,9*R*)-3-Hydroxy-5,9-methano-9-(methoxymethyl)-5-methyl-8-(*N*-tosylamino)benzocyclooctene (21). A mixture of **20** (0.894 g, 3.26 mmol), sodium cyanoborohydride (0.228 g, 3.62 mmol), ammonium acetate (2.56 g, 33.2 mmol), and 4 Å molecular sieves (1.25 g) in 35 mL of anhydrous MeOH was stirred at room temperature for 76 h. The solid was removed by filtration and was rinsed with MeOH. The filtrate was concentrated, and then water and 5% NaOH were added to make the solution basic. Extraction with CH_2Cl_2, drying, and removal of solvent, followed by chromatography on neutral alumina (MeOH-CH_2Cl_2, 1:4), provided the amine (0.774 g, 86%). A solution containing the amine (0.332 g, 1.21 mmol), triethylamine (0.3 mL, 2.16 mmol), and *p*-toluenesulfonyl chloride (0.364 g, 1.91 mmol) in 8 mL of THF was stirred at room temperature until all the starting material was consumed (≤38 h). The solution was diluted with water and extracted with CH_2Cl_2. The organic phases were combined, washed with saturated NH_4Cl, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel gave the tosylamide (0.512 g, 99%). The diastereomeric composition of the tosylamide was determined by HPLC with a variable-wavelength detector. Separation was performed on a CHIRALCEL OD column with the detection wavelength setting at 254 nm. The eluent system was 2.5% (v/v) 2-propanol in hexane with a flow rate of 1.0 mL/min and pressure of 30 bar. The ratio of the axial and equatorial tosylamide diastereomers was ∼1:12. To a stirred solution of the tosylamide (0.415 g, 0.967 mmol) and ethanethiol (0.4 mL, 5.41 mmol) in 4 mL of DMF at 4 °C was added sodium hydride (0.167 g, 6.96 mmol). The solution was refluxed overnight, and then a few drops of concentrated HCl were added. DMF was evaporated under reduced pressure, and the resulting residue was partitioned between CH_2Cl_2 and water. The organic layers were dried, concentrated, and flash chromatographed on silica gel to give **21** as a white solid (0.330 g, 82%): ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.1 Hz), 6.85 (d, 1 H, J = 8.3 Hz), 6.67 (s, 1 H), 6.58 (d, 1 H, J = 8.1 Hz), 5.34 (d, 1 H, J = 5.9 Hz), 3.20 (s, 3 H), 3.17 (m, 1 H), 3.14 (d, 1 H, J = 8.8 Hz), 2.94 (d, 1 H, J = 8.8 Hz), 2.73 (d, 1 H, J = 17.9 Hz), 2.54 (d, 1 H, J = 17.6 Hz), 2.40 (s, 3 H), 1.57 (d, 1 H, J = 13.0 Hz), 1.47 (br) (d, 1 H, J = 11.5 Hz), 1.32−1.26 (m, 4 H), 1.22 (s, 3 H), 0.97−0.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 153.9, 144.3, 143.2, 137.6, 129.5, 128.7, 127.8, 127.1, 113.3, 111.2, 81.2, 59.0, 58.6, 42.4, 40.4, 37.9, 34.3, 31.7, 27.8, 27.6, 21.5; IR (THF) 3290 (br), 1608, 1440, 1325, 1153 cm^{-1}; CIMS, m/z (relative intensity) 416 (M^+ + 1, 67), 262 (27), 172 (54), 157 (100). Anal. ($C_{23}H_{29}NO_4S$) C, H, N.

(±)-(5*S*,8*S*,9*R*)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene [(*dl*)-22]. To a three-necked flask containing **21** (0.314 g, 0.757 mmol), 5 mL of dry THF, and ∼30 mL of NH_3 at −78 °C was added small pieces of sodium until a blue coloration persisted for 30 min. Solid NH_4Cl was added, and NH_3 was allowed to evaporate. Brine was added, and the mixture was extracted with CH_2Cl_2. After combining extracts, drying and removal of solvent in vacuo, chromatography on neutral alumina (MeOH−CH_2Cl_2, 1:4) afforded (*dl*)-**22** as a yellow foam (0.114 g, 58%): ^{1}H NMR ($CDCl_3$) δ 6.89 (d, 1 H, J = 8.3 Hz), 6.70 (d, 1 H, J = 2.6 Hz), 6.57 (dd, 1 H, J = 2.6, 8.3 Hz), 3.94 (br) (s, 3 H), 3.35 (s, 3 H), 3.27 (d, 1 H, J = 9.1 Hz), 3.18 (d, 1 H, J = 9.0 Hz), 2.93 (d, 1 H, J = 18.1 Hz), 2.92 (dd, 1 H, J = 4.6, 12.0 Hz), 2.44 (d, 1 H, J = 17.6 Hz), 1.57 (dd, 1 H, J = 2.7, 12.8 Hz), 1.56−1.53 (m, 1 H), 1.47−1.37 (m, 2 H), 1.35 (d, 1 H, J = 12.7 Hz), 1.28 (s, 3 H), 0.94−0.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.9, 144.7, 128.6, 127.4, 113.5, 111.6, 83.4, 59.4, 56.1, 42.7, 41.0, 38.2, 34.7, 30.9, 29.3, 27.9; IR (CH_2Cl_2) 3355, 2929 (br, overlap), 1608, 1493, 1463, 1109 cm^{-1}; HRMS calcd for $C_{16}H_{24}NO_2$ ($M + H)^+$ 262.1807, found 262.1800. Anal. ($C_{16}H_{23}NO_2 \cdot {}^1/_3H_2O$) C, H.

8-Mesyl-5,9-methano-3-methoxy-9-(methoxymethyl)-5-methylbenzocyclooctene (23). To a solution of **20** (0.221 g, 0.807 mmol) in 3 mL of anhydrous CH_3OH and 1 mL of 1 M HCl in Et_2O was added sodium cyanoborohydride (0.062 g, 0.99 mmol). The resulting solution was stirred at room temperature for 3 h. Solvents were evaporated, and the resulting residue was partitioned between Et_2O and water. The organic layer was dried, concentrated, and flash chromatographed on silica gel to afford the alcohol as a clear oil (0.205 g, 92%) which solidified upon standing. To the alcohol (0.114 g, 0.413 mmol) in 5 mL of CH_2Cl_2 was added triethylamine (0.6 mL) at 4 °C, followed by methanesulfonyl chloride (0.1 mL, 1.29 mmol). After stirring at room temperature for 17 h, water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel provided **23** as a clear oil (0.108 g, 74%), which solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 7.01 (d, 1 H, J = 8.3 Hz), 6.81 (d, 1 H, J = 2.6 Hz), 6.71 (dd, 1 H, J = 2.7, 8.3 Hz), 4.86 (dd, 1 H, J = 5.5, 11.6 Hz), 3.79 (s, 3 H), 3.42 (d, 1 H, J = 9.0 Hz), 3.36 (s, 3 H), 3.01 (s, 3 H), 3.00 (d, 1 H, J = 9.3 Hz), 2.94 (d, 1 H, J = 17.1 Hz), 2.40 (d, 1 H, J = 17.6 Hz), 2.00−1.96 (m, 1 H), 1.76 (dd, 1 H, J = 1.4, 13.2 Hz), 1.67 (dd, 1 H, J = 2.9, 13.3 Hz), 1.55 (dd, 1 H, J = 3.6, 13.4 Hz), 1.53−1.51 (m, 1 H), 1.46 (td, 1 H, J = 12.4, 4.7 Hz), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.9, 144.2, 128.7, 127.9, 111.4, 110.3, 84.0, 77.8, 58.9, 55.2, 42.1, 40.2, 38.8, 38.0, 34.5, 30.7, 27.3, 27.0; IR (film) 2925, 1607, 1572, 1495, 1460, 1352, 1293, 1242, 1178, 1110 cm^{-1}; CIMS, m/z (relative intensity) 355 (M^+ + 1, 18), 259 (100).

8-Azido-5,9-methano-3-methoxy-9-(methoxymethyl)-5-methylbenzocyclooctene (24). A homogeneous solution of **23** (0.081 g, 0.23 mmol) and sodium azide (0.340 g, 5.23 mmol) in 2.5 mL of DMF and 0.5 mL of water was heated at 92 °C for 118 h. After removal of DMF at reduced pressure, the residue was partitioned between CH_2Cl_2 and water. The combined organic layers were dried, concentrated, and chromatographed on silica gel to give **24** as a clear oil (0.036 g, 52%): ^{1}H NMR ($CDCl_3$) δ 6.99 (d, 1 H, J = 8.6 Hz), 6.80 (d, 1 H, J = 2.7 Hz), 6.70 (dd, 1 H, J = 2.6, 8.5 Hz), 3.80 (m, 1 H), 3.78 (s, 3 H), 3.45 (d, 1 H, J = 8.7 Hz), 3.38 (s, 3 H), 3.05 (d, 1 H, J = 8.8 Hz), 2.97 (d, 1 H, J = 18.1 Hz), 2.71 (d, 1 H, J = 18.0 Hz), 1.69−1.64 (m, 2 H), 1.45 (d, 1 H, J = 13.0 Hz), 1.39−1.36 (m, 1 H), 1.34 (s, 3 H), 1.30 (d, 1 H, J = 12.5 Hz), 1.28−1.26 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.9, 144.5, 128.6, 128.3, 111.3, 110.1, 80.7, 63.7, 59.1, 55.2, 38.3, 37.6, 36.6, 36.0, 34.5, 28.0, 24.4; IR (film) 2915, 2093, 1606, 1496, 1452, 1240, 1113 cm^{-1}; CIMS, m/z (relative intensity) 302 (M^+ + 1, 91), 274 (100), 259 (77).

(±)-(5*S*,8*S*,9*S*)-8-Amino-5,9-methano-3-methoxy-9-(methoxymethyl)-5-methylbenzocyclooctene (25). A mixture of **24** (5 mg) and excess lithium aluminum hydride in 1 mL of THF was refluxed for 2.5 h. The reaction mixture was quenched with water at 4 °C and filtered. The filtrate was extracted with CH_2Cl_2. Drying and removal of solvent provided (±)-**25** (5 mg) in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 1 H, J = 8.3 Hz), 6.81 (d, 1 H, J = 2.7 Hz), 6.71 (dd, 1 H, J = 2.7, 8.3 Hz), 3.79 (s, 3 H), 3.47 (d, 1 H, J = 9.3 Hz), 3.42 (s, 3 H), 3.41−3.36 (m, 1 H), 3.20 (d, 1 H, J = 9.3 Hz), 2.87 (d, 1 H, J = 18.1 Hz), 2.70 (d, 1 H, J = 17.8 Hz), 2.04−1.94 (m, 2 H), 1.77 (d, 1 H, J = 14.4 Hz), 1.43−1.36 (m, 2 H), 1.41 (s, 3 H), 1.28−1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.8, 144.5, 128.4, 128.3, 111.2, 109.9, 80.6, 59.3, 55.1, 52.9, 38.5, 37.3, 35.6, 34.7, 27.6, 25.3 (2C); IR (CH_2Cl_2) 2925 (b), 1610, 1500 cm^{-1}.

5,10-Methano-3-methoxy-10-(methoxymethyl)-5-methyl-5,6,7,9,10,11-hexahydro-9-benzazonin-8-one (27). An aqueous solution of NaN_3 was first prepared by dissolving

0.105 g of NaN_3 in 0.53 mL of water. A portion of this solution (0.457 mmol) was added dropwise at room temperature to a solution of **20** (0.109 g, 0.398 mmol) in 4 mL of CF_3CO_2H. After 30 min, the resulting dark brown solution was heated at ~65 °C for 4 h. Some CF_3CO_2H was removed under reduced pressure, and then water and aqueous NaOH were added to make the solution basic. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were then dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel gave **27** as a brown oil (0.101 g, 88%): ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 1 H, J = 8.3 Hz), 6.84 (d, 1 H, J = 2.6 Hz), 6.75 (dd, 1 H, J = 2.7, 8.5 Hz), 6.43 (br) (s, 1 H, D_2O exchangeable), 3.80 (s, 3 H), 3.41 (s, 3 H), 3.27 (dd, 2 H, J = 8.6, 13.2 Hz), 3.06 (d, 1 H, J = 18.1 Hz), 2.99 (d, 1 H, J = 18.1 Hz), 2.25−2.20 (m, 1 H), 2.02 (td, 1 H, J = 16.1, 2.9 Hz), 1.83−1.77 (m, 3 H), 1.69−1.64 (m, 1 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.6, 158.4, 142.7, 129.5, 126.8, 112.0, 110.7, 82.6, 59.3, 55.2, 53.0, 44.5, 39.5, 39.2, 36.7, 33.7, 30.2; IR (film) 3363, 3210, 2920, 1640, 1494, 1435, 1293, 1240 cm^{-1}; CIMS, *m*/*z* (relative intensity) 290 (M^+ + 1, 100).

5,10-Methano-3-methoxy-10-(methoxymethyl)-5,9-dimethyl-5,6,7,9,10,11-hexahydro-9-benzazonin-8-one (28). To a stirred solution of **27** (0.037 g, 0.13 mmol) in 3 mL of dry THF was added NaH (0.060 g, 2.5 mmol), and the resulting mixture was refluxed for 8 h. After cooling to room temperature, CH_3I (0.2 mL, 3.2 mmol) was added and the solution was refluxed for another 18 h. Water was added, and the solution was extracted with CH_2Cl_2. The combined organic layers were dried, concentrated, and flash chromatographed to give **28** as a yellow oil (0.028 g, 72%): ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1 H, J = 8.5 Hz), 6.86 (d, 1 H, J = 2.7 Hz), 6.67 (dd, 1 H, J = 2.7, 8.3 Hz), 3.79 (s, 3 H), 3.63 (d, 1 H, J = 9.8 Hz), 3.39 (s, 3 H), 3.27 (d, 1 H, J = 9.8 Hz), 2.94 (dd, 1 H, J = 2.3, 16.5 Hz), 2.86 (m, 1 H), 2.79 (s, 3 H), 2.72 (dd, 1 H, J = 2.4, 14.9 Hz), 2.71 (d, 1 H, J = 16.6 Hz), 2.42 (dt, 1 H, J = 15.1, 4.4 Hz), 2.15 (td, 1 H, J = 13.6, 3.7 Hz), 1.83 (dt, 1 H, J = 14.1, 4.9 Hz), 1.75 (d, 1 H, J = 14.9 Hz), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.7, 158.6, 147.2, 129.7, 124.5, 111.8, 111.4, 78.3, 59.6, 59.2, 55.2, 43.2, 38.9, 38.5, 35.2, 34.5, 32.2, 30.4; IR (film) 2921, 1610, 1450, 1388, 1290, 1240 cm^{-1}; CIMS, *m*/*z* (relative intensity) 304 (M^+ + 1, 100).

3-Hydroxy-5,10-methano-10-(methoxymethyl)-5,9-dimethyl-5,6,7,8,10,11-hexahydro-9-benzazonine [(*dl*)-29]. A mixture of **28** (0.090 g, 0.30 mmol) and $LiAlH_4$ (0.048 g, 1.3 mmol) in 7 mL of THF was refluxed overnight. Excess $LiAlH_4$ was quenched with water at 4 °C, and the solid was filtered. The filtrate was extracted with CH_2Cl_2. After drying and removal of solvent, flash chromatography on neutral alumina afforded the amine as a clear oil (0.070 g, 82%). To a solution of the amine (0.070 g, 0.24 mmol) in 3 mL of DMF was added ethanethiol (0.2 mL, 2.7 mmol), followed by sodium hydride (0.085 g, 3.5 mmol). The resulting solution was refluxed for 72 h. A few drops of concentrated HCl was added at room temperature, and DMF was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and water. The combined organic extracts were dried and concentrated; chromatography on silica gel afforded (*dl*)-**29** as a yellow oil (0.046 g, 69%): ^{1}H NMR ($CDCl_3$) δ 6.87 (d, 1 H, J = 8.0 Hz), 6.76 (d, 1 H, J = 2.5 Hz), 6.59 (dd, 1 H, J = 2.6, 8.1 Hz), 5.13 (br) (s, 1 H), 3.45 (d, 1 H, J = 9.3 Hz), 3.37 (s, 3 H), 3.25 (d, 1 H, J = 9.2 Hz), 3.20 (dd, 1 H, J = 11.0, 14.7 Hz), 2.67 (dd, 1 H, J = 3.2, 15.7 Hz), 2.49 (d, 1 H, J = 15.7 Hz), 2.46 (dd, 1 H, J = 5.5, 14.4 Hz), 2.33 (s, 3 H), 2.23 (dd, 1 H, J = 3.4, 14.6 Hz), 1.92 (m, 1 H), 1.69 (d, 1 H, J = 14.4 Hz), 1.38−1.31 (m, 2 H), 1.22 (s, 3 H), 1.17−1.11 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.0, 145.2, 130.1, 127.9, 113.1, 112.3, 79.4, 59.2, 57.1, 52.2, 44.9, 44.5, 38.1, 38.0, 36.9, 34.4, 27.2; IR (film) 3315 (br), 2913, 1608, 1445, 1232 cm^{-1}; CIMS, *m*/*z* (relative intensity) 276 (M^+ + 1, 100).

5,10-Methano-3-methoxy-10-(methoxymethyl)-5-methyl-5,6,7,9,10,11-hexahydrotetrazolo[1,2-*i*]-9-benzazonine (30). In the Schmidt rearrangement to prepare **27**, a small amount of tetrazole **30** also was obtained: ^{1}H NMR ($CDCl_3$) δ 6.91 (d, 1 H, J = 8.6 Hz), 6.87 (d, 1 H, J = 2.7 Hz), 6.71 (dd, 1 H, J = 2.7, 8.6 Hz), 4.23 (d, 1 H, J = 9.6 Hz), 3.96 (d, 1 H, J = 9.6 Hz), 3.80 (s, 3 H), 3.45 (s, 3 H), 3.26−3.21 (m, 1 H), 3.24 (d, 1 H, J = 17.1 Hz), 2.90 (d, 1 H, J = 17.1 Hz), 2.30−2.24 (m, 3 H), 2.08−2.03 (m, 1 H), 1.88−1.82 (m, 1 H), 1.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.0, 155.3, 141.7, 130.4, 124.0, 112.3, 111.4, 77.8, 62.8, 59.3, 55.2, 42.2, 40.2, 37.5, 36.7, 31.9, 21.5; IR (film) 2920, 1606, 1495, 1460, 1287, 1240, 1115 cm^{-1}; CIMS, *m*/*z* (relative intensity) 315 (M^+ + 1, 100).

3-Hydroxy-5,10-methano-10-(methoxymethyl)-5-methyl-5,6,7,9,10,11-hexahydrotetrazolo[1,2-*i*]-9-benzazonine [(*dl*)-31]. To a solution of **30** (0.033 g, 0.11 mmol) in 3 mL of DMF was added EtSH (0.10 mL, 1.4 mmol), followed by NaH (0.040 g, 1.7 mmol). The resulting solution was refluxed for 50 h. A few drops of concentrated HCl was added at room temperature, and DMF was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and water. The combined organic extracts were dried, concentrated, and chromatographed on silica gel to give (*dl*)-**31** as a brown solid (0.010 g, 32%): ^{1}H NMR ($CDCl_3$) δ 6.87 (d, 1 H, J = 2.5 Hz), 6.81 (d, 1 H, J = 8.3 Hz), 6.66 (dd, 1 H, J = 2.4, 8.3 Hz), 4.26 (d, 1 H, J = 9.5 Hz), 3.93 (d, 1 H, J = 9.5 Hz), 3.44 (s, 3 H), 3.22−3.17 (m, 1 H), 3.20 (d, 1 H, J = 17.1 Hz), 2.87 (dd, 1 H, J = 1.7, 17.1 Hz), 2.33−2.22 (m, 3 H), 2.03−1.99 (m, 1 H), 1.84−1.78 (m, 1 H), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.7, 155.5, 141.7, 130.5, 123.2, 114.8, 112.4, 77.8, 63.3, 59.3, 42.3, 40.0, 37.6, 36.6, 31.9, 21.4; IR (film) 3246 (br), 2925, 1610, 1500, 1440, 1290, 1230, 1114 cm^{-1}; CIMS, *m*/*z* (relative intensity) 301 (M^+ + 1, 100).

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