Asymmetric Synthesis of 9-Alkyl-2-benzyl-6,7-benzomorphans: Characterization as Novel σ Receptor Ligands

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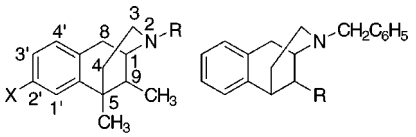
A convenient enantioselective synthesis of (1*R*,5*R*,9*R*)- and (1*S*,5*S*,9*S*)-9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**) which starts with naphthaldehyde is described. These compounds were designed to gain additional information on the structure−σ binding relationship of the 6,7-benzomorphan class of σ ligands. In contrast to pentazocine and most 6,7-benzomorphans, the (1*R*,5*R*,9*R*)-isomers of **2a**−**c** showed greater affinity for the σ_1 receptor than the (1*S*,5*S*,9*S*)-isomers. Despite reversal of enantioselectivity at the σ_1 sites, moderate affinity and enantioselectivity at the σ_2 sites [greater affinity for (1*R*,5*R*,9*R*)-isomers than (1*S*,5*S*,9*S*)-isomers] were maintained. A comparison of the binding affinities of **2a**−**c** to the more conformationally flexible *trans*-2-alkyl-1-benzaminoethyl-1,2-dihydronaphthalenes (**10a**−**c**) suggested that the relatively rigid structure of **2a**−**c** played an important part in their σ_1 binding properties. These compounds, particularly (1*R*,5*R*,9*R*)-2-benzyl-9-methyl-6,7-benzomorphan [(−)-**2a**], which has a K_i value of 0.96 nM, will be useful in further characterization of the σ_1 receptor.

Introduction

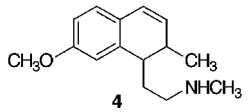
σ Receptors bind various classes of psychoactive agents, including opiate-related compounds, phencyclidine-related compounds, typical neuroleptics, and some antidepressants.[1,2] However, σ receptors are unique binding sites, having pharmacological profiles distinct from other neurotransmitter receptors. Two classes of σ receptors are now widely accepted,[3] and various biochemical, physiological, and behavioral processes have been attributed to them. σ_1 Receptors have been implicated in modulation of NMDA-stimulated neurotransmitter release and electrophysiological activity,[4,5] modulation of muscarinic receptor-stimulated phosphoinositide turnover,[6] modulation of opiate analgesia,[7] and regulation of learning and memory processes.[8,9] σ_2 Receptors have been implicated in regulation of movement and posture,[10,11] modulation of potassium channel conductances,[12,13] contraction of the electrically stimulated guinea pig ileum,[14] modulation of intracellular calcium levels,[15,16] and induction of cell morphology changes and apoptosis.[17−19] The σ_1 receptor has been cloned from guinea pig liver,[20] rat brain,[21] and human placenta.[22] The sequence revealed a unique protein, unrelated to any known receptor. Although there was some sequence homology to an enzyme of fungal sterol metabolism,[20] the significance of this is not yet clear since the protein has no known enzymatic activity.

σ Receptor binding ligands consist of a variety of structurally unrelated compounds. 2-Substituted 5,9α-dimethyl-2′-hydroxy-6,7-benzomorphans were the first structural class of σ ligands with the 2-allyl analogue **1a**, referred to as *N*-allyl-*N*-normetazocine, NANM, or SKF 10,047 by various investigators, being the first σ ligand.[1,2] The well-known analgesic pentazocine (**1b**), which is *N*-dimethylallyl-*N*-normetazocine, was found to have a much higher affinity than **1a** for the receptor.[1] The (1*R*,5*R*,9*R*)-(−)-isomers of these racemic drugs are responsible for their analgesic activity.[23,24] The (1*S*,5*S*,9*S*)-(+)-isomer is responsible for the σ receptor activity. Usually, it has been concluded that (+)-benzomorphans have comparable affinities for the two subtypes.[1,25−29] The reduction in affinity of (+)-benzomorphans at σ_2 sites leads to a reversal of enantioselectivity, whereby (−)-isomers have higher affinity than (+)-isomers. In fact, the opposite enantioselectivity of the benzomorphans such as **1a**,**b** played an important part in defining the σ_1 and σ_2 receptors.[1,30]



1a, R = CH_2=$CHCH_2$, X = OH
b, R = $(CH_3)_2C$=$CHCH_2$, X = OH
c, R = $C_6H_5CH_2$, X = OH
d, R = $C_6H_5CH_2$, X = H

2a, R = CH_3
b, R = C_2H_5
c, R = $(CH_3)_2CH$



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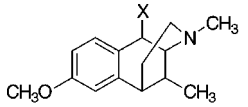

5a, X = H
b, X = OH
c, X = OAc

Our search for high-affinity, specific σ receptor ligands has focused on the benzomorphan class of compounds. The benzomorphan ring system provides a convenient rigid backbone for probing the pharmacophoric requirements of σ receptor sites. For the purposes of such SAR

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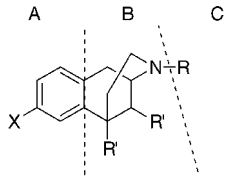

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Figure 1. Structure−activity relationship zones for the benzomorphan structure.

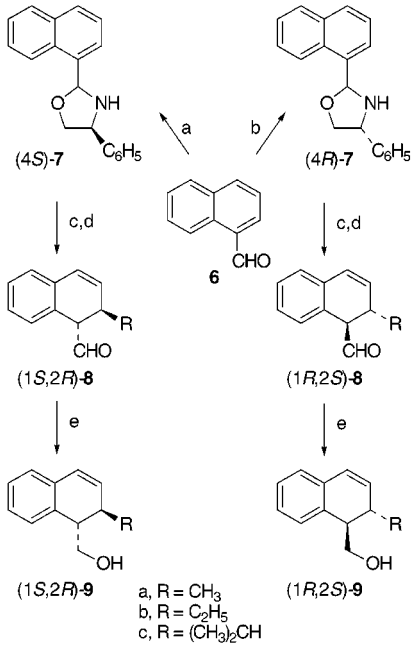
studies, the benzomorphan nucleus can be conceptually divided into three zones: the aromatic ring (A), the saturated or morphan segment (B), and the nitrogen substituent (C) (see structure **3** in Figure 1). In previous studies from our laboratory, we reported the effects of changes in zones A and C on σ_1 and σ_2 binding affinity and selectivity.[25−29] To gain information concerning the effects of zone B on σ receptor binding properties, we designed a SAR study to synthesize and evaluate a series of compounds that involves changes in the 5- and 9α-methyl groups present in the *N*-normetazocine class of compounds. In this report, we present novel asymmetric syntheses of (+)- and (−)-9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**) and show that in contrast to all previously reported *N*-substituted *N*-normetazocine analogues and their 2′-deoxy analogues, the (1*R*,5*R*,9*R*)-isomers of **2a**−**c** have higher affinity for the σ_1 receptor than the (1*S*,5*S*,9*S*)-isomers. A part of this study has been reported in a preliminary communication.[31]

Chemistry

Inoue and May reported that mercury(II) acetate−sodium borohydride cyclization of the dihydronaphthalene **4** gave a mixture of **5b**,**c**.[32] Compound **5c** could be converted to **5b**, and reduction of **5b** with palladium in acetic acid containing perchloric acid gave the desired (2*RS*,6*RS*,11*RS*)-(±)-2,9-dimethyl-2′-methoxy-6,7-benzomorphan (**5a**). The synthesis of Inoue and May suffers the disadvantage of providing racemic material and requiring several steps to prepare the key intermediate **4**.[32] In 1992, Pridgen et al.[33] reported that either optical antipode of *trans*-1-hydroxymethyl-2-alkyl-1,2-dihydronaphthalene [(1*S*,2*R*)- or (1*R*,2*S*)-**9**] could be prepared in high chemical and optical purity via the aldehyde (1*S*,2*R*)- or (1*R*,2*S*)-**8** by the route shown in Scheme 1. Thus, the addition of the appropriate alkylmagnesium halide to the oxazolidine **7**, derived from (*R*)- or (*S*)-phenylglycinol and naphthaldehyde **6**, followed by acid-catalyzed cleavage of the chiral auxiliary and reduction of the resulting aldehyde **8**, provided the required optically active alcohols **9** in either optical form depending on the phenylglycinol used.

Scheme 2 outlines how either (1*S*,2*R*)-**8a**−**c** or (1*S*,2*R*)-**9a**−**c** were converted to the common intermediate (1*S*,2*R*)-**10**, which was cyclized to give the desired 6,7-benzomorphans (1*S*,5*S*,9*S*)-**2a**−**c**. The (1*R*,5*R*,9*R*)-**2a**−**c** isomers were prepared in a similar fashion starting with (1*R*,2*S*)-**8a**−**c** or (1*R*,2*S*)-**9a**−**c**. Thus, subjecting (1*S*,2*R*)-**8a**−**c** to the Wittig reaction using the ylid prepared from (methoxymethyl)triphenylphosphonium chloride in tetrahydrofuran at −78 °C gave the methoxy vinyl ether (1*S*,2*R*)-**11a**−**c**. Acid hydrolysis of vinyl ethers **11a**−**c** resulted in the formation of aldehydes (1*S*,2*R*)-**12a**−**c**. Reductive amination of **12a**−**c** with benzylamine hydrochloride in methanol using sodium cyanoborohydride provided the desired intermediates (1*S*,2*R*)-**10a**−**c**. These intermediates also were prepared from (1*S*,2*R*)-**9a**−**c**. Thus, tosylation of (1*S*,2*R*)-**9a**−**c** with toluene-*p*-sulfonyl chloride followed by treatment of the resulting tosylate with potassium cyanide in dimethyl sulfoxide at 105 °C yielded nitriles (1*S*,2*R*)-**13a**−**c**. Lithium aluminum hydride reduction of **13a**−**c** in diethyl ether afforded amines (1*S*,2*R*)-**14a**−**c** which were benzoylated with benzoyl chloride to give the amides (1*S*,2*R*)-**15a**−**c**. Reduction of **15a**−**c** with lithium aluminum hydride in tetrahydrofuran gave benzylamines (1*S*,2*R*)-**10a**−**c**. Mercuric acetate-assisted cyclization of (1*S*,2*R*)-**10a**−**c** in THF at 25 °C followed by reduction with lithium aluminum hydride or sodium borohydride afforded the desired 6,7-benzomorphans (1*S*,5*S*,9*S*)-**2a**−**c**. The use of lithium aluminum hydride provided cleaner reactions and higher yields than sodium borohydride. ^{1}H NMR spectra of the unpurified products obtained using the sodium borohydride procedure suggested that small amounts of (1*R*,5*S*,9*S*)-**16** were present. The structural assignment of benzomorphans **2a**−**c** is based on the elemental analysis of the hydrochloride salts and ^{1}H NMR, ^{13}C NMR, 2D ^{1}H−^{1}H correlation NMR, and 2D ^{1}H−^{13}C correlation NMR data of the free bases.

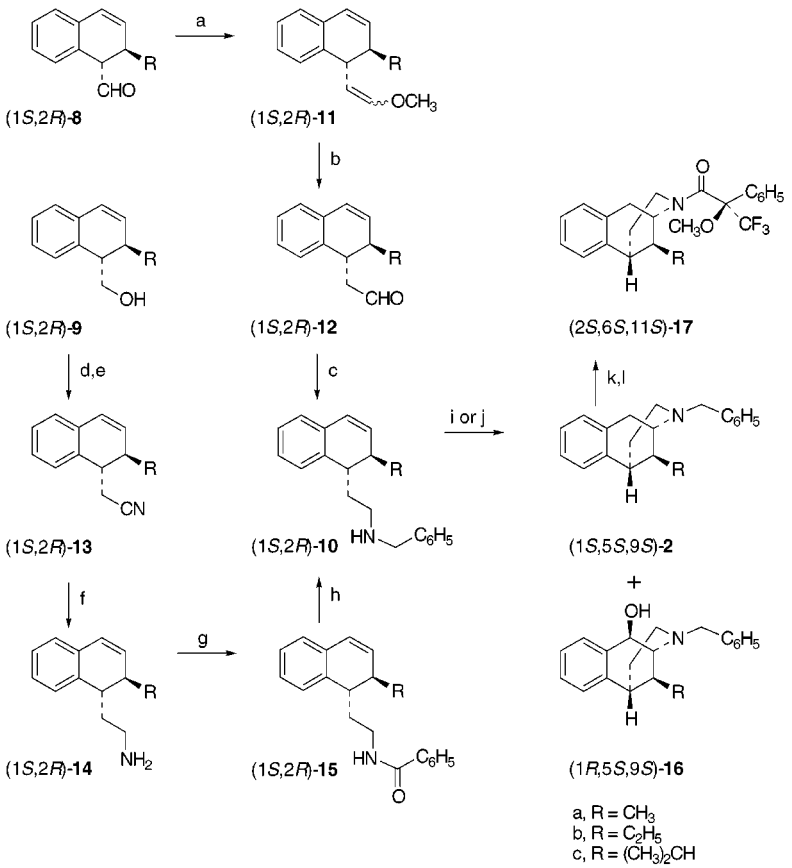
Scheme 1[a]



[a] (a) (*S*)-Phenylglycinol, $MgSO_4$, $CHCl_3$, reflux; (b) (*R*)-phenylglycinol, $MgSO_4$, $CHCl_3$, reflux; (c) RMgCl; (d) 3 M HCl; (e) $NaBH_4$, MeOH, 0 °C.

The absolute configurations of starting alcohols **9** produced by the method shown in Scheme 1 are known[34,35] and were verified by comparison with the published optical rotation for each enantiomer.[33,36] As the stereochemistry of all three stereogenic centers in the product is determined by the stereochemistry of the alcohol starting material, the absolute stereochemistry of the benzomorphans **2a**−**c** was established. Optical purities of **2a**,**c** were determined to be ≥99% by HPLC analysis using a Sumichiral OA-4900 column (Rainin Instrument, Inc.). Optical purities of **2b**,**c** were also shown to be ≥96% by gas chromatography−mass spectral analysis of the (*R*)-2-methoxy-2-trifluoromethylphen-

Scheme 2[a]



[a] (a) $CH_3OCH_2P^+(C_6H_5)_3Cl^-$, NaHMDS, THF; (b) 3 N HCl, 25 °C; (c) $C_6H_5CH_2NH_3^+Cl$, $NaBH_3CN$, CH_3OH; (d) TsCl-pyridine, 0 °C; (e) KCN−DMS), 105 °C; (f) $LiAlH_4-Et_2O$; (g) PhCOCl, triethanolamine-CH_2Cl_2; (h) $LiAlH_4$−THF, reflux; (i) $Hg(OAc)_2$, Et_3N, THF, followed by $LiAlH_4$; (j) $Hg(OAc)_2$−THF, 50 °C, followed by $NaBH_4$, NaOH (aq); (k) H_2, 10% Pd/C, CH_3OH; (l) (*R*)MTPACl, (j) $(C_2H_5)_3N$, CH_2Cl_2.

ylacetyl amides **17b**,**c**. The amides **17a**−**c** were prepared by catalytic debenzylation of **2b**,**c** followed by acylation of the unpurified intermediate *N*-nor analogue with (*R*)-2-methoxy-2-trifluoromethylphenylacetyl chloride [(*R*)MTPACl]. The report that the optical purity of intermediate **9b** was ≥96%[33] also shows the optical purity of **2b** must be at least 96%.

Ligand Binding Studies

σ_1 Binding sites were labeled using the σ_1-selective ligand [^{3}H]-(+)-pentazocine[37] and guinea pig brain membranes, as described previously.[38] Rat liver membranes have been shown previously to be a rich source of σ_2 sites and are labeled using [^{3}H]DTG in the presence of dextrallorphan to mask σ_1 sites.[39]

Various concentrations of the test ligand ranging from 0.005 to 1000 nM or from 0.05 to 10000 nM were incubated with guinea pig brain membranes (σ_1) or rat liver membranes (σ_2) and radioligand. Assays were carried out using the conditions described below: σ_1, 3 nM [^{3}H]-(+)-pentazocine; σ_2, 5 nM [^{3}H]DTG + 1 μM dextrallorphan. IC_{50} values were derived using the computerized iterative curve-fitting program GraphPAD InPlot (San Diego, CA). K_i values were calculated from IC_{50} values using the Cheng−Prusoff equation[40] and K_d values that were predetermined in independent experiments.

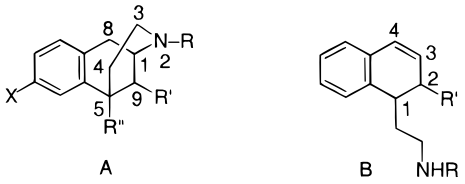
The results expressed as K_i values of the 9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**), 2-alkyl-1-benzylaminoethyl-1,2-dihydronaphthalene (**10a**−**c**), and reference compounds are shown in Table 1.

Results and Discussion

(+)- and (−)-Pentazocine have K_i values of 3.1 and 83.1 nM, respectively, for the σ_1 receptor (see Table 1). In sharp contrast, (+)- and (−)-pentazocines have K_i values of 1540 and 36.5 nM for the σ_2 receptor. Studies of several other *N*-normetazocine analogues showed that the (+)-(1*S*,5*S*,9*S*)-isomer always possessed higher affinity for the σ_1 receptor than the (−)-(1*R*,5*R*,9*R*)-isomer.[25] One of the bases for defining two types of σ receptors (σ_1 and σ_2) was the opposite enantioselectivity for the *N*-normetazocine class of compounds.[1,3,30] The fact that (+)- and (−)-pentazocines as well as several other benzomorphans bind to the σ receptor with enantioselectivity suggested that the rigid framework of this class of compounds imparted directionality to the lone-pair nitrogen electrons and/or that the steric bulk of the tricyclic system contributes to the enantioselectivity.[26]

Additional studies from our laboratory showed that the rigid *cis*-5,9-dimethyl-6,7-benzomorphan (*cis*-*N*-normetazocine) could be used as a structural template to provide useful SAR data for helping establish a pharmacophore for σ receptors.[25−29,31] These SAR studies involved changes in the *N*-substituent and the aromatic ring, zones C and A, respectively, in Figure 1. The zone C studies revealed that (1*S*,5*S*,9*S*)-*N*-benzyl-*N*-normetazocine [(+)-**1c**] possessed a 0.67 nM K_i value

Table 1. σ Binding Data for 6,7-Benzomorphans and Related Compounds



compd	structure	stereochemistry	R	R′	R″	X	K_i (nM)[a] σ_1, [^{3}H](+)-pentazocine	K_i (nM)[a] σ_2, DTG	σ_2,σ_1 ratio[b]
(+)-pentazocine [(+)-**1b**]	A	1*S*,5*S*,9*S*	$(CH_3)_2$=$CHCH_2$	CH_3	CH_3	OH	3.1 ± 0.3[c]	1540 ± 313[d]	500
(−)-pentazocine [(−)-**1b**]	A	1*R*,5*R*,9*R*	$(CH_3)_2C$=$CHCH_2$	CH_3	CH_3	OH	83.1 ± 6.2[c]	36.5 ± 5.76[d]	0.44
(+)-**1c**	A	1*S*,5*S*,9*S*	$C_6H_5CH_2$	CH_3	CH_3	OH	0.67 ± 0.10[c]	1710 ± 407	2600
(−)-**1c**	A	1*R*,5*R*,9*R*	$C_6H_5CH_2$	CH_3	CH_3	OH	36.5 ± 6.3[c]	192 ± 36	5
(+)-**1d**	A	1*S*,5*S*,9*S*	$C_6H_5CH_2$	CH_3	CH_3	H	18.4 ± 2.13[d]	487 ± 65.6	26
(−)-**1d**	A	1*R*,5*R*,9*R*	$C_6H_5CH_2$	CH_3	CH_3	H	82.9 ± 4.6	149 ± 9	1.8
(+)-**2a**	A	1*S*,5*S*,9*S*	$C_6H_5CH_2$	CH_3	H	H	5.74 ± 0.17	587 ± 57	102
(−)-**2a**	A	1*R*,5*R*,9*R*	$C_6H_5CH_2$	CH_3	H	H	0.96 ± 0.02	131 ± 19	136
(+)-**2b**	A	1*S*,5*S*,9*S*	$C_6H_5CH_2$	C_2H_5	H	H	26.7 ± 3.47	478 ± 76.1	18
(−)-**2b**	A	1*R*,5*R*,9*R*	$C_6H_5CH_2$	C_2H_5	H	H	3.36 ± 0.11	115 ± 10.7	34
(+)-**2c**	A	1*S*,5*S*,9*S*	$C_6H_5CH_2$	$(CH_3)_2CH$	H	H	167 ± 11.5	944 ± 99	6
(−)-**2c**	A	1*R*,5*R*,9*R*	$C_6H_5CH_2$	$(CH_3)_2CH$	H	H	31.7 ± 3.36	133 ± 4.75	4
(+)-**10a**	B	1*S*,2*R*	$C_6H_5CH_2$	CH_3			19.6 ± 1.73	607 ± 38	31
(−)-**10a**	B	1*R*,2*S*	$C_6H_5CH_2$	CH_3			17.3 ± 0.18	371 ± 11	22
(+)-**10b**	B	1*S*,2*R*	$C_6H_5CH_2$	C_2H_5			16.6 ± 0.27	759 ± 34	46
(−)-**10b**	B	1*R*,2*S*	$C_6H_5CH_2$	C_2H_5			14.8 ± 1.8	850 ± 52	57
(+)-**10c**	B	1*S*,2*R*	$C_6H_5CH_2$	$(CH_3)_2CH$			12 ± 0.33	854 ± 13	71
(−)-**10c**	B	1*R*,2*S*	$C_6H_5CH_2$	$(CH_3)_2CH$			11.7 ± 0.65	785 ± 37	67

[a] Values are the average ± SEM of two to three experiments. Each experiment was carried out in duplicate. [b] σ_2/σ_1 are ratios of K_i values. [c] K_i values taken from ref 15. [d] These K_i values are slightly different from those in ref 29 due to the fact that they contain data from additional experiments.

for the σ_1 receptor and was highly selective for the σ_1 site relative to the σ_2 site (σ_2/σ_1 ratio = 2600) (see Table 1). In a SAR study of zone A (Figure 1), we found that replacement of the 2′-hydroxyl group with a hydrogen to give (1*S*,5*S*,9*S*)-*cis*-5,9-dimethyl-6,7-benzomorphan [(+)-**1d**] resulted in a 28-fold loss in affinity for the σ_1 receptor (0.67 nM compared to 18.4 nM). There was also a 4-fold increase in affinity at the σ_2 receptor.

As a continuation of the SAR study of the 6,7-benzomorphan class of σ ligands, we have synthesized the (1*S*,5*S*,9*S*)- and (1*R*,5*R*,9*R*)-isomers of several 9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**) and evaluated their binding affinities at σ_1 and σ_2 receptors. The goal of this study was to gain information involving changes in zone B (Figure 1) of the 6,7-benzomorphans on σ_1 binding properties. Since the 9-methyl analogue **2a** can be viewed as an analogue of **1d** where the 5-methyl group has been removed, the binding results from this compound allowed the determination of the effect of this group on σ_1 and σ_2 binding affinity and selectivity. Compounds **2b**,**c**, which possess a 9-ethyl and 9-isopropyl substituent, respectively, provided information on the effect of larger and more lipophilic groups in this position. Most importantly, a comparison of the σ binding affinities of the (+)- and (−)-isomers in each case allowed the determination of the enantioselectivity of these changes to zone B (Figure 1) of the 6,7-benzomorphans. The σ_1 binding affinities for the 9-alkyl-6,7-benzomorphans **2a**−**c** range between 0.96 and 167 nM. The (1*R*,5*R*,9*R*)-9-methyl analogue (−)-**2a** has the highest affinity, while the (1*S*,5*S*,9*S*)-9-isopropyl analogue (+)-**2c** has the lowest affinity. The affinities for **2a**−**c** at the σ_2 site are lower than those for the σ_1 site with K_i values ranging from 115 to 944 nM. Compound (1*R*,5*R*,9*R*)-**2a** shows the greatest selectivity for the σ_1 site relative to the σ_2 site (σ_2/σ_1 = 136). Unexpectedly and in sharp contrast to pentazocine (**1b**) and *cis*-*N*-benzyl-*N*-normetazocine (**1d**), each of the 9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**) showed enantioselectivity toward the (−)-(1*R*,5*R*,9*R*)-isomers at σ_1 sites. In the case of **2a** where a direct comparison to **1d** is possible, this reverse in enantioselectivity is due to a 38-fold increase in affinity of (−)-**2a** relative to (−)-**1d** and only a 3-fold increase in affinity of (+)-**2a** relative to (+)-**1d**. Even though the binding affinity at the σ_2 site for all three compounds is much weaker than binding to the σ_1 site, the (1*R*,5*R*,9*R*)-isomer in each case has the higher affinity for the σ_2 receptor.

Compounds **10a**−**c** are the intermediates used to prepare compounds **2a**−**c** and thus possess many of the structural features present in **2a**−**c**. However, since compounds **2a**−**c** are tricyclic and **10a**−**c** bicyclic, the latter compounds possess a larger degree of conformational freedom. The σ_1 K_i values for these compounds are particularly informative. Note that there is essentially no difference in the K_i values at the σ_1 receptor regardless of the stereochemistry or the size of the 9-substituent. The σ_1 K_i values range from 11.7 nM for the (1*R*,2*S*)-9-isopropyl analogue (−)-**10c** to 19.6 nM for the (1*S*,2*R*)-9-methyl analogue (+)-**10a**. Note that cyclization of (1*R*,2*S*)-**10a** and (1*R*,2*S*)-**10b** to (1*R*,5*R*,9*R*)-**2a** and (1*R*,5*R*,9*R*)-**2b** results in an 18- and 4.4-fold increase in σ_1 affinity, whereas cyclization of (1*R*,2*S*)-**10c** to (1*R*,5*R*,9*R*)-**2c** results in a 2.7-fold loss in σ_1 affinity. These results strongly suggest that the unique σ_1 binding properties of **2a**−**c** are due at least in part to the rigid framework of the 6,7-benzomorphan structure. These results are also consistent with our previous hypothesis that the rigid framework and directionality imparted to the lone-pair nitrogen electrons are impor-

tant to the σ_1 binding properties of 6,7-benzomorphans.[26] It is also interesting to note that the stereochemical factors governing enantioselectivity at σ_1 sites are separate from those for σ_2 sites since the B-zone alteration which reversed enantioselectivity at σ_1 sites did not change enantioselectivity at σ_2 sites.

In summary, we have reported results which show that 9-alkyl-2-benzyl-6,7-benzomorphans (**2a**−**c**) have a reversed enantioselectivity [i.e. (1*R*,5*R*,9*S*) better than (1*S*,5*S*,9*S*)] for the σ_1 receptor when compared with pentazocine (**1b**), 2-benzyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (**1c**, *cis*-*N*-benzyl-*N*-normetazocine), and *cis*-2-benzyl-5,9-dimethyl-6,7-benzomorphan (**1d**). These compounds will be valuable for the further characterization of the σ receptors.

Experimental Section

General. All reactions were performed in oven-dried glassware under an argon atmosphere and were magnetically stirred. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium benzophenone ketyl prior to use. Methylene chloride was dried by distillation from P_2O_5. Other anhydrous solvents and reagents were purchased from Aldrich Chemical Co., Inc. and were used without further purification. Melting points were determined in open capillary tubes with a Meltemp melting point apparatus and are uncorrected. Optical rotations were determined with an Autopol III automatic polarimeter (Rudolph Research, Flanders, NJ). Radial preparative-layer chromatography (radial PLC) was performed on a chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1-, 2-, or 4-mm thicknesses of Kieselgel 60 PF_{254} coating gypsum. When optical purity was determined using chiral HPLC, a Sumichiral OA-4900 column (Rainin Instrument, Inc.) was used. Nuclear magnetic resonance spectra were recorded on a Bruker AM-250 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (δ) downfield from tetramethylsilane (0 ppm). ^{13}C NMR chemical shifts are reported in parts per million (δ) relative to $CDCl_3$ (77.0 ppm). IR spectra were recorded on a Shimadzu infrared spectrometer (IR-460). Elemental analysis was performed by Atlantic Microlabs Inc., Norcross, GA.

[^{3}H]-(+)-Pentazocine (51.7 Ci/mmol) was supplied by Dr. K. C. Rice (Laboratory of Medicinal Chemistry, NIDDK, NIH). [^{3}H]DTG (39.1 Ci/mmol) was purchased from DuPont/New England Nuclear (Boston, MA). Haloperidol, Tris-HCl, and poly(ethylenimine) were purchased from Sigma Chemicals (St. Louis, MO).

(1*S*,2*R*)-*trans*-2-Methyl-1,2-dihydronaphthalene-1-carboxaldehyde (8a). To a stirred solution of oxazolidine (4*S*)-**7**[33] (1.90 g, 6.95 mmol) in THF (60 mL) at −78 °C was added methylmagnesuim chloride (3 M in THF, 9.3 mL, 27.3 mmol) dropwise. After 30 min, the solution was allowed to warm to room temperature and refluxed for 17 h, then cooled to 0 °C. Aqueous HCl (3 N, 25 mL, 75 mmol) was added, and the reaction mixture was stirred for an additional 2 h. The layers were separated, and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, 1% Et_2O−hexanes) afforded 0.85 g (71%) of (1*S*,2*R*)-**8a** as a pale yellow oil: $[\alpha]^{23}_D$ −212° (*c* 0.575, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.57−9.56 (m, 1H), 7.31−7.11 (m, 4H), 6.39 (d, 1H, J = 10 Hz), 5.96 (dd, 1H, J = 5.0, 10.0 Hz), 3.33 (s, 1H), 3.01−2.96 (m, 1H), 1.07 (d, 3H, J = 7.15 Hz); ^{13}C NMR ($CDCl_3$) δ 200.8, 132.3, 129.6, 128.3, 128.2, 127.8, 126.7, 125.9, 58.3, 28.7, 18.6; IR (neat) 3015, 2860, 2700, 1726, 1688, 1484, 1452, 1121, 1034, 788 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Methyl-1,2-dihydronaphthalene-1-carboxaldehyde (8a). The title compound was prepared by a procedure analogous to that used for (1*S*,2*R*)-**8a**. The oxazolidine (4*R*)-**7** (2.97 g, 10.9 mmol) afforded 1.31 g (70%) of (1*R*,2*S*)-**8a** as a pale yellow oil: $[\alpha]^{23}_D$ +212° (*c* 0.415, $CHCl_3$).

(1*S*,2*R*)-*trans*-2-Ethyl-1,2-dihydronaphthalene-1-carboxaldehyde (8b). To a stirred solution of oxazolidine (4*R*)-**7** (3.53 g, 12.8 mmol) in THF (75 mL) at −78 °C was added ethylmagnesuim chloride (2 M in THF, 19.5 mL, 39 mmol) dropwise. After 3 h, the solution was allowed to warm to room temperature and stirred overnight, then cooled to 0 °C. Aqueous HCl (3 N, 25 mL, 75 mmol) was added, and the reaction mixture was stirred for an additional 1 h. The layers were separated, and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, 1% Et_2O−hexanes) afforded 1.87 g (78%) of (1*S*,2*R*)-**8b** as a pale yellow oil: $[\alpha]^{23}_D$ −252° (*c* 0.370, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.28−7.09 (m, 4H), 6.41 (d, 1H, J = 9.7 Hz), 6.01 (dd, 1H, J = 5.7, 9.7 Hz), 3.41 (s, 1H), 2.81−2.73 (m, 1H), 1.56−1.29 (m, 2H), 0.93 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 204.1, 135.1, 133.6, 129.9, 128.4, 128.2, 127.1, 126.6, 52.6, 44.4, 27.6, 23.0, 19.4, 12.1; IR (neat) 3015, 2865, 2705, 1724, 1677, 1481, 1452, 1372, 1052 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Ethyl-1,2-dihydronaphthalene-1-carboxaldehyde (8b). The title compound was prepared by a procedure analogous to that used for (1*S*,2*R*)-**8b**. Oxazolidine (4*R*)-**7** (2.58 g, 9.4 4 mmol) afforded 1.35 g (77%) of (1*R*,2*S*)-**8b** as a colorless oil: $[\alpha]^{23}_D$ +253° (*c* 0.320, $CHCl_3$).

(1*S*,2*R*)-*trans*-2-Isopropyl-1,2-dihydronaphthalene-1-carboxaldehyde (8c). Using a procedure analogous to the one described for the preparation of **8b**, 2.10 g (81%) of (1*S*,2*R*)-**8c** was obtained from 3.59 g (13 mmol) of oxazolidine (4*S*)-**7**: $[\alpha]^{22}_D$ −271° (*c* 0.745, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 7.26−6.99 (m, 4H), 6.62 (d, 1H, J = 9.9 Hz), 5.90 (dd, 1H, J = 5.1, 9.9 Hz), 2.54−2.51 (m, 1H), 2.08−2.01 (m, 1H), 1.36 (s, 3H), 0.96 (d, 3H, J = 6.88 Hz), 0.68 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 205.4, 136.6, 133.0, 128.5, 128.2, 127.2, 127.1, 126.0, 125.8, 52.1, 50.0, 29.7, 22.5, 21.7, 17.2; IR (neat) 3055, 2935, 2820, 1719, 1682, 1484, 1463, 1384, 1105, 1034, 928, 824 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Isopropyl-1,2-dihydronaphthalene-1-carboxaldehyde (8c). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**8c**, 1.78 g (80%) of (1*R*,2*S*)-**8c** was obtained from 3.06 g (11.2 mmol) of oxazolidine (4*S*)-**7**: $[\alpha]^{22}_D$ +269° (*c* 0.495, $CHCl_3$).

(1*S*,2*R*)-*trans*-2-Methyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11a). A solution of NaHMDS in THF (1 M, 4.0 mL, 4.0 mmol) was added dropwise to a mixture of (methoxymethyl)triphenylphosphonium chloride (1.44 g, 4.20 mmol) in THF (13 mL) at −78 °C. After 1 h, aldehyde (1*S*,2*R*)-**8a** (0.392 g, 2.28 mmol) in THF (10 mL) was added dropwise and the mixture was stirred at −78 °C for 4 h, then quenched with water (10 mL). The separated aqueous layer was extracted with ether (4 × 10 mL) and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, 1% EtOAc−hexanes) afforded 0.350 g (77%) of (1*S*,2*R*)-**11a** as a colorless oil: $[\alpha]^{23}_D$ −231° (*c* 0.610, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.28−7.00 (m, 4H), 6.43−6.30 (m, 2H), 5.90−5.81 (m, 1H), 4.78 (dd, 1H, J = 10.0, 12.5 Hz), 3.56 (s, 3H), 3.02 (t, 3H, J = 9.25 Hz), 1.11−1.07 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 148.5, 147.2, 137.9, 137.5, 134.2, 134.0, 127.6, 127.2, 126.6, 126.4, 126.0, 108.8, 105.2, 59.6, 56.1, 44.9, 40.4, 35.3, 32.7, 19.6, 19.4; IR (neat) 3050, 2950, 2820, 1648, 1480, 1451, 1385, 1279, 1204, 1146, 1104, 939, 782 cm^{-1}. Anal. ($C_{14}H_{16}O$) C, H.

(1*R*,2*S*)-*trans*-2-Methyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11a). Using a procedure analogous to that described for (1*S*,2*R*)-**11a**, aldehyde (1*R*,2*S*)-**8** (0.479 g, 2.78 mmol) afforded 0.471 g (77%) of (1*R*,2*S*)-**11a** as a colorless oil: $[\alpha]^{23}_D$ +212° (*c* 0.805, $CHCl_3$). Anal. ($C_{14}H_{16}O$) C, H.

(1*S*,2*R*)-*trans*-2-Ethyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11b). Using a procedure analogous to the one described for the preparation of **11a**, 1.29 g (75%) of

(1*S*,2*R*)-**11b** was obtained from the Wittig reaction of 1.50 g (8.10 mmol) of aldehyde (1*S*,2*R*)-**8b**: $[\alpha]^{23}_D$ −210° (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.17−7.02 (m, 4H), 6.44 (dd, 1H, *J* = 1.5, 9.7 Hz), 6.32 (d, 1H, *J* = 12.6 Hz), 5.96 (dd, 1H, *J* = 4.3, 9.7 Hz), 4.83 (dd, 1H, *J* = 9.1, 12.6 Hz), 3.52 (s, 3H), 3.21−3.14 (m, 1H), 2.20−2.16 (m, 1H), 1.57−1.31 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 147.7, 137.6, 132.8, 131.6, 127.7, 126.9, 126.5, 126.3, 125.7, 105.4, 55.7, 41.8, 41.7, 25.7, 10.9; IR (neat) 3010, 2870, 1650, 1478, 1450, 1373, 1230, 1210, 1146, 1119, 945 cm^{-1}. Anal. ($C_{15}H_{18}O$) C, H.

(1*R*,2*S*)-*trans*-2-Ethyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11b). Using a procedure analogous to the one described for the preparation of **11a**, 0.795 g (80%) of (1*R*,2*S*)-**11b** was obtained from the Wittig reaction of 0.863 g (4.64 mmol) of aldehyde (1*R*,2*S*)-**8b**: $[\alpha]^{23}_D$ +280° (*c* 0.900, $CHCl_3$). Anal. ($C_{15}H_{18}O$) C, H.

(1*S*,2*R*)-*trans*-2-Isopropyl-1-methyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11c). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**11a**, 1.21 g (80%) of (1*S*,2*R*)-**11a** was obtained from the Wittig reaction of 1.34 g (6.70 mmol) of aldehyde (1*S*,2*R*)-**18c**: $[\alpha]^{22}_D$ −304° (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31−6.96 (m, 4H), 6.52 (d, 1H, *J* = 9.89 Hz), 6.05 (d, 1H, *J* = 7.16 Hz) 5.87 (dd, 1H, *J* = 6.0, 9.89 Hz), 4.72 (d, lH, *J* = 7.18 Hz), 2.54−2.49 (m, 1H), 2.26−2.13 (m, 1H), 1.49 (s, 3H), 0.90 (d, 3H, *J* = 7.07 Hz), 0.39 (d, 3H, *J* = 7.07 Hz); ^{13}C NMR ($CDCl_3$) δ 147.7, 145.0, 132.5, 127.9, 127.7, 127.5, 126.5, 125.8, 124.7, 109.8, 59.8, 49.7, 42.3, 30.5, 29.6, 21.6, 16.4; IR (neat) 3055, 2935, 1658, 1474, 1446, 1380, 1281, 1208, 1107, 1073, 1035, 818, 787 cm^{-1}. Anal. ($C_{16}H_{20}O$) C, H.

(1*R*,2*S*)-*trans*-2-Isopropyl-1-methyl-1-(2-methoxyvinyl)-1,2-dihydronaphthalene (11c). Using a procedure analogous to the one described for the preparation of **11a**, 1.03 g (76%) of (1*R*,2*S*)-**11c** was obtained from the Wittig reaction of 1.19 g (5.93 mmol) of aldehyde (1*R*,2*S*)-**8c**: $[\alpha]^{23}_D$ +262° (*c* 0.865, $CHCl_3$). Anal. ($C_{16}H_{20}O$) C, H.

(1*S*,2*R*)-*trans*-2-Methyl-1,2-dihydronaphthalene-1-acetaldehyde (12a). A solution of vinyl ether (1*S*,2*R*)-**11a** (0.158 g, 0.789 mmol) in THF (7 mL) and 3 N HCl (5 mL) was stirred at room temperature overnight. The layers were separated and the aqueous layer was extracted with ether (4 × 5 mL). The combined organic extracts were washed with saturated K_2CO_3 solution and brine, dried over anhydrous K_2CO_3, and filtered through Celite. Removal of the solvent in vacuo yielded the crude aldehyde. Purification by radial PLC (silica gel, 5−10% EtOAc−hexanes) provided 0.112 g (77%) of aldehyde (1*S*,2*R*)-**12a** as a colorless oil: $[\alpha]^{23}_D$ −361° (*c* 0.740, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.52−9.48 (m, 1H), 7.32−7.07 (m, 4H), 6.47 (dd, 1H, *J* = 2.25, 9.63 Hz), 5.77 (dd, 1H, *J* = 3.3, 9.59 Hz), 2.79(dd, 1H, *J* = 2.91, 14.23 Hz), 2.54−2.45 (m, 1H), 2.32 (dd, 1H, *J* = 3.6, 14.17 Hz), 1.49 (s, 3H), 1.10 (d, 3H, *J* = 7.33 Hz); ^{13}C NMR ($CDCl_3$) δ 203.6, 140.4, 133.9, 132.9, 127.8, 127.0, 126.5, 126.2, 124.7; IR (neat) 3015, 2865, 2725, 1718, 1479, 1444, 1368, 1096, 1038, 786 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Methyl-1,2-dihydronaphthalene-1-acetaldehyde (12a). Using a procedure analogous to that used to prepare (1*S*,2*R*)-**12a**, the vinyl ether (1*R*,2*S*)-**11a** (0.20 g, 1.0 mmol) provided 0.148 g (80%) of aldehyde (1*R*,2*S*)-**12** as a colorless oil: $[\alpha]^{23}_D$ +368° (*c* 1.10, $CHCl_3$).

(1*S*,2*R*)-*trans*-2-Ethyl-1,2-dihydronaphthalene-1-acetaldehyde (12b). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**12a**, acid hydrolysis of 0.456 g (2.13 mmol) of vinyl ether (1*S*,2*R*)-**11b** gave 0.341 g (80%) of (1*S*,2*R*)-**12b** as a colorless oil: $[\alpha]^{24}_D$ −358° (*c* 0.670, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.54−9.52 (m, 1H), 7.29−7.05 (m, 4H), 6.5 (dd, 1H, *J* = 2.57, 9.66 Hz) 5.93 (dd, 1H, *J* = 3.50, 9.66 Hz), 2.75 (dd 1H, *J* = 2.78, 14.29 Hz), 2.33 (dd, 1H, *J* = 3.57, 14.29 Hz), 2.22−2.16 (m, 1H), 1.75−1.66 (m, 1H), 1.50 (s, 3H), 1.34−1.21 (m, 1H), 0.98 (t, 3H, *J* = 7.33 Hz); ^{13}C NMR ($CDCl_3$) δ 203.6, 140.7, 133.0, 131.4, 127.7, 127.5, 127.0, 126.9, 124.5, 48.7, 45.8, 40.0, 24.8, 21.5, 12.2; IR (neat) 3055, 2925, 2820, 1718, 1480, 1446, 1371, 1101, 1071, 1040, 789 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Ethyl-1,2-dihydronaphthalene-1-acetaldehyde (12b). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**12b**, acid hydrolysis of 0.563 g (2.63 mmol) of vinyl ether (1*R*,2*S*)-**11a** gave 0.436 g (83%) of (1*R*,2*S*)-**11b** as a colorless oil: $[\alpha]^{24}_D$ +375° (*c* 0.635, $CHCl_3$).

(1*S*,2*R*)-*trans*-2-Isopropyl-1,2-dihydronaphthalene-1-acetaldehyde (12c). Using a procedure analogous to the one described for the preparation of **12a**, acid hydrolysis of 0.506 g (2.24 mmol) of vinyl ether (1*S*,2*R*)-**11c** gave 0.385 g (80%) of (1*S*,2*R*)-**12c** as a colorless oil: $[\alpha]^{23}_D$ −353° (*c* 0.710, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.0−9.96 (m, 12H), 7.22−7.02 (m, 4H), 6.61 (dd, 1H, *J* = 9.83 Hz), 5.90 (dd, 1H, *J* = 5.73, 9.83 Hz), 2.99 (dd, 1H, *J* = 2.2, 15.63 Hz), 2.79 (dd, 1H, *J* = 2.95, 15.63 Hz), 2.47−2.43 (m, 1H), 2.05−1.93 (m, 1H), 1.43 (s, 3H), 0.93 (d, 3H, *J* = 6.9 Hz), 0.46 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4, 142.8, 133.0, 129.0, 128.2, 127.5, 127.2, 126.8, 123.0, 52.9, 49.5, 48.8, 39.7, 29.5, 29.2, 22.3, 16.7; IR (neat) 3055, 2930, 2730, 1719, 1479, 1449, 1381, 1072, 1040, 809, 788 cm^{-1}.

(1*R*,2*S*)-*trans*-2-Isopropyl-1,2-dihydronaphthalene-1-acetaldehyde (12c). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**12c**, acid hydrolysis of 0.722 g (3.16 mmol) of vinyl ether (1*R*,2*S*)-**11c** gave 0.585 g (86%) of (1*R*,2*S*)-**12c** as a colorless oil: $[\alpha]^{23}_D$ +345° (*c* 1.03, $CHCl_3$).

(1*S*,2*R*)-*trans*-1-[2-(Benzylamino)ethyl]-2-methyl-1,2-dihydronaphthalene (10a). A mixture of aldehyde (1*S*,2*R*)-**12a** (0.083 g, 0.44 mmol), benzylamine hydrochloride (0.128 g, 0.89 mmol), and $NaBH_3CN$ (0.028 g, 0.44 mmol) in MeOH (6 mL) was stirred at room temperature overnight. The separated aqueous layer was extracted with ether (4 × 5 mL), and the combined organic extracts were washed with brine, dried over anhydrous K_2CO_3, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, MeOH−EtOAc−hexanes, 0.1:0.9:4) afforded 0.099 g (80%) of (1*S*,2*R*)-**10a** as a colorless oil: $[\alpha]^{22}_D$ −280° (*c* 0.325, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.00 (m, 9H), 6.34 (d, 1H, *J* = 9.5 Hz), 5.91 (dd, 1H, *J* = 5.0, 9.5 Hz), 3.73 (s, 2H), 2.63−2.55 (m, 2H), 2.37−2.27 (m, 2H), 1.75−1.66 (m, 2H), 1.25 (m, 1H), 0.93 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 140.6, 137.5, 132.7, 132.3, 129.2, 128.4, 128.2, 126.9, 126.5, 126.2, 125.4, 54.1, 47.2, 42.8, 35.6, 34.1; IR (neat) 3300, 3010, 2865, 1467, 1447, 1358, 1119, 1027, 846 cm^{-1}. The free base was converted to the tartrate salt: $[\alpha]^{22}_D$ 143° (*c* 0.275, $CHCl_3$); mp 57.2−60.8 °C. Anal. ($C_{24}H_{29}NO_6 \cdot 0.25H_2O$) C, H.

(1*R*,2*S*)-*trans*-1-[2-(Benzylamino)ethyl]-2-methyl-1,2-dihydronaphthalene (10a). Using a procedure analogous to that used to prepare (1*S*,2*R*)-**10a**, the aldehyde (1*R*,2*S*)-**12a** (0.125 g, 0.67 mmol) afforded 0.142 g (76%) of (1*R*,2*S*)-**10a** as a colorless oil: $[\alpha]^{22}_D$ +271° (*c* 0.465, $CHCl_3$). The free base was converted to the tartrate salt: $[\alpha]^{22}_D$ +106° (*c* 0.120, $CHCl_3$); mp 46.5−49.0 °C. Anal. ($C_{24}H_{29}NO_6 \cdot 1.25H_2O$) C, H.

(1*S*,2*R*)-*trans*-1-[2-(Benzylamino)ethyl]-2-ethyl-1,2-dihydronaphthalene (10b). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**10a**, reductive amination of 0.308 g (1.54 mmol) of aldehyde **5b** afforded 0.398 g (89%) of amine (1*S*,2*R*)-**10b** as a colorless oil: $[\alpha]^{24}_D$ −265° (*c* 0.470, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−6.99 (m, 9H), 6.37 (d, 1H, *J* = 9.6 Hz), 5.95 (dd, 1H, *J* = 6.0, 9.6 Hz), 3.73 (s, 3H), 2.76 (t, 1H, *J* = 7.2 Hz), 2.64−2.56 (m, 2H), 2.10 (q, 1H, *J* = 6.8, 13.6 Hz), 1.76−1.66 (m, 2H), 1.41−1.20 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 140.6, 138.1, 132.6, 131.6, 129.0, 128.4, 128.2, 126.9, 126.5, 126.2, 125.9, 54.1, 47.3, 40.6, 35.7, 26.8, 11.8; IR (neat) 3300, 3010, 2865, 1486, 1448, 1367, 1119, 1026, 903 cm^{-1}. The free base was converted to the tartrate salt: $[\alpha]^{22}_D$ −146° (*c* 0.165, $CHCl_3$); mp 43.6−47.0 °C. Anal. ($C_{25}H_{31}NO_6 \cdot 0.5H_2O$) C, H, N.

(1*R*,2*S*)-*trans*-1-[2-(Benzylamino)ethyl]-2-ethyl-1,2-dihydronaphthalene (10b). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**10b**, reductive amination of 0.430 g (2.15 mmol) of aldehyde (1*R*,2*S*)-**12b** afforded 0.491 g (78%) of amine (1*R*,2*S*)-**10b** as a colorless oil: $[\alpha]^{24}_D$ +281° (*c* 0.895, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−6.99 (m, 9H), 6.37 (d, 1H, *J* = 9.6 Hz), 5.95 (dd, 1H, *J* = 6.0, 9.6 Hz), 3.73 (s, 3H), 2.76 (t, 1H, *J* = 7.2 Hz), 2.64−2.56 (m, 2H),

2.10 (q, 1H, J = 6.8, 13.6 Hz), 1.76−1.66 (m, 2H), 1.41−1.20 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 140.6, 138.1, 132. 6, 131.6, 129.0, 128.4, 128.2, 126.9, 126.5, 126.2, 125.9, 54.1, 47.3, 40.6, 35.7, 26.8, 11.8; IR (neat) 3300, 3010, 2865, 1486, 1448, 1367, 1119, 1026, 903 cm^{-1}. The free base was converted to the tartrate salt: $[\alpha]^{22}_D$ +183° (*c* 0.230, $CHCl_3$); mp 54.8−57.2 °C. Anal. ($C_{25}H_{31}NO_6$) C, H, N.

(1*S*,2*R*)-*trans*-1-[2-(Benzylamino)ethyl]-2-isopropyl-1,2-dihydronaphthalene (10c). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**10b**, reductive amination of 0.940 g (2.29 mmol) of aldehyde afforded 0.586 g (84%) of amine (1*S*,2*R*)-**10c** as a colorless oil: $[\alpha]^{23}_D$ −279° (*c* 0.435, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−6.98 (m, 9H), 6.42 (d, 1H, J = 9.6 Hz), 5.90 (dd, 1H, J = 6.0, 9.7 Hz), 3.73 (s, 2H), 2.86 (t, 1H, J = 7.2, Hz), 2.63−2.56 (m, 2H), 1.94 (t, 1H, J = 6.7 Hz), 1.75−1.48 (m, 2H), 1.38−1.0 (m, 1H), 0.82 (d, 3H, J = 6.75 Hz); ^{13}C NMR ($CDCl_3$) δ 140.7, 138.8, 132.9, 130.2, 128.4, 128.2, 126.9, 126.5, 126.4, 126.1, 554.2, 47.2, 46.1, 38.6, 36.5, 32.2, 20.5, 20.3; IR (neat) 3305, 3050, 2920, 2810, 1487, 1452, 1378, 1179, 1116, 1027, 816 cm^{-1}. The free base was converted to the tartrate salt: $[\alpha]^{23}_D$ −152° (*c* 0.630, $CHCl_3$); mp 47.6−50.1 °C. Anal. ($C_{26}H_{33}NO_6 \cdot 0.25H_2O$) C, H, N.

(1*R*,2*S*)-*trans*-1-[2-(Benzylamino)ethyl]-2-isopropyl-1,2-dihydronaphthalene (10c). Using a procedure analogous to the one described for the preparation of (1*S*,2*R*)-**10c**, reductive amination of 0.553 g (2.58 mmol) of aldehyde (1*R*,2*S*)-**12c** afforded 0.577 g (73%) of amine (1*R*,2*S*)-**10c** as a colorless oil: $[\alpha]^{22}_D$ +269° (*c* 0.745, $CHCl_3$). The free base was converted to the tartrate salt: $[\alpha]^{22}_D$ +181° (*c* 0.335, $CHCl_3$); mp 57.4−60.2 °C. Anal. ($C_{26}H_{33}NO_6$) C, H, N.

(1*S*,2*R*)-*trans*-1-(Cyanomethyl)-2-ethyl-1,2-dihydronaphthalene (13b). To a solution of 7.0 g (0.04 mol) in 17 mL of anhydrous pyridine was added 6.34 g (0.02 mol) of (1*S*,2*R*)-**9b**[33] in 25 mL of pyridine for 30 min at 0 °C, then kept at 10 °C overnight. The reaction mixture was diluted with water and extracted with ethyl ether. The ether extracts were washed three times with 1 N hydrochloric acid and brine and dried ($MgSO_4$). Concentration of the extracts gave the tosylate. A mixture of the tosylate and 2.75 g (0.04 mol) of potassium cyanide in 63 mL of DMSO was stirred for 2 h at 105 °C. The cooled reaction mixture was diluted with ethyl ether, washed twice with water, and dried ($MgSO_4$). The residue obtained on concentration was purified by flash chromatography on silica gel using hexanes−EtOAc (95:5) as the eluent to give 3.65 g (67%) of (1*S*,2*R*)-**13b** as an oil: $[\alpha]^{24}_D$ −280° (*c* 0.125, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 7.04−7.25 (m, 4H), 6.45 (d, J = 9.6 Hz, 1H), 5.97 (dd, J = 6.1, 9.6 Hz, 1H), 3.02 (t, J = 7.8 Hz, 1H), 2.39−2.57 (m, 2H), 2.32 (q, J = 6.9 Hz, 1H), 1.22−1.57 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). Anal. ($C_{14}H_{15}N$) C, H, N.

(1*R*,2*S*)-*trans*-1-(Cyanomethyl)-2-ethyl-1,2-dihydronaphthalene (13b). Using a procedure analogous to that described for (1*S*,2*R*)-**13b**, 590 mg (3.1 mmol) of (1*R*,2*S*)-**9b**[33] afforded 380 mg (64%) of (1*R*,2*S*)-**13b**: $[\alpha]^{24}_D$ +273 (*c* 0.16, $CHCl_3$). Anal. ($C_{14}H_{15}N$) C, H, N.

(1*S*,2*R*)-*trans*-1-(Cyanomethyl)-2-isopropyl-1,2-dihydronaphthalene (13c). Using a procedure analogous to that described for (1*S*,2*R*)-**13b**, 0.665 g (56%) of (1*S*,2*R*)-**13c** was obtained from 1.14 g (0.01 mol) of (1*S*,2*R*)-**9c**: $[\alpha]^{21}_D$ −319 (*c* 0.17, $CHCl_3$); ^{1}H NMR δ 7.04−7.25 (m, 4H), 6.51 (d, J = 9.6 Hz, 1H), 5.95 (ddd, J = 1.2, 6.1, 9.6 Hz, 1H), 3.16 (t, J = 7.7 Hz, 1H), 2.39−2.56 (m, 2H), 2.15 (t, J = 6.8 Hz, 1H),1.62 (m, J = 6.8 Hz, 1H),0.87 (dd, J = 2.2, 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 134.7, 132.2, 128.5, 128.3, 127.7, 126.7, 126.5, 118.8, 45.0, 37.9, 31.7, 24.0, 20.2, 20.0. Anal. ($C_{14}H_{15}N$) C, H, N.

(1*R*,2*S*)-*trans*-1-(Cyanomethyl)-2-isopropyl-1,2-dihydronaphthalene (13c). Using a procedure analogous to that described for (1*S*,2*R*)-**13c**, 1.22 g (0.0063 mol) of (1*R*,2*S*)-**9c**[33] was converted to 0.584 g (43%) of (1*R*,2*S*)-**13c**: $[\alpha]^{22}_D$ +315 (*c* 0.17, $CHCl_3$).

(1*R*,2*S*)-*trans*-1-[2-(Benzoylamino)ethyl]-2-ethyl-1,2-dihydronaphthalene (15b). A solution of 313 g (1.59 mmol) of (1*R*,2*S*)-**13b** in 6 mL of anhydrous ethyl ether was added to 1.6 mL of 1.0 M $LiAlH_4$ in THF in 15 mL of ethyl ether, and the mixture was stirred under argon at 25 °C for 1.5 h. The cooled reaction mixture was treated with 15% sodium hydroxide solution, the ether layer separated, and the aqueous layer extracted with ether. The dried ($MgSO_4$) ether extracts were concentrated to give the amine (1*R*,2*S*)-**14b**. The amine was dissolved in 8 mL of CH_2Cl_2 containing 0.5 mL of triethylamine, and 0.25 mL of benzoyl chloride was added. The reaction mixture was concentrated, and the resulting residue was purified by flash chromatography with silica gel using hexanes−EtOAc (75:25) as the eluent to give 301 mg (62%) of (1*R*,2*S*)-**15b**: $[\alpha]^{22}_D$ 212° (*c* 0.125, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.05−7.63 (m, 9H), 6.39 (d, J = 9.6 Hz, 1H), 6.00 (dd, J = 6.2, 9.6 Hz, 1H), 5.88 (bs, 1H), 3.22−3.66 (m, 2H), 2.74 (t, J = 7.2 Hz, 1H), 2.16 (q, J = 6.8 Hz, 1H), 1.03−1.44 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). Anal. ($C_{21}H_{23}NO$) C, H, N.

(1*S*,2*R*)-*trans*-1-[2-(Benzoylamino)ethyl]-2-ethyl-1,2-dihydronaphthalene (15b). Using a procedure analogous to that described for (1*R*,2*S*)-**15b**, 299 mg (62%) of (1*S*,2*R*)-**15b** was obtained from 313 mg (1.59 mmol) of (1*S*,2*R*)-**13**.

(1*R*,2*S*)-*trans*-1-[2-(Benzoylamino)ethyl]-2-isopropyl-1,2-dihydronaphthalene (15c). Using a procedure analogous to that described for (1*R*,2*S*)-**15b**, 530 mg (70%) of (1*S*,2*R*)-**15c** was obtained from 500 mg (2.33 mmol) of (1*R*,2*S*)-**13c**: $[\alpha]^{22}_D$ 319 (*c* 0.215, C_2H_5OH); ^{13}C NMR ($CDCl_3$) δ 167.2, 138.0, 134.7, 132.9, 131.1, 130.2, 128.4, 127.2, 126.7, 126.6, 126.5, 126.2, 46.1, 38.9, 38.7, 36.1, 32.0, 20.7, 20.0. Anal. ($C_{22}H_{25}NO$) C, H, N.

(1*S*,2*R*)-*trans*-1-[2-(Benzoylamino)ethyl]-2-isopropyl-1,2-dihydronaphthalene (15c). Using a procedure analogous to that described for (1*R*,2*S*)-**15c**, 601 mg (69%) of (1*S*,2*R*)-**15c** was obtained from 572 mg (2.71 mmol) of (1*S*,2*R*)-**13c**.

General Procedure for the Reduction of 15b,c to 10b,c. A solution of 1.56 mmol of **15** in 7 mL of THF was added to 3.1 mL of 1 M $LiAlH_4$ in THF in 8 mL of THF, and the mixture was refluxed for 4 h. The cooled reaction mixture was treated with 15% sodium hydroxide and sufficient water to form a solid that could be separated by filtration. Concentration of the filtrate gave the desired **15b** or **15c** isomer. The ^{1}H NMR spectra were identical to the products prepared from **12b**,**c**.

(1*S*,5*S*,9*S*)-2-Benzyl-9-methyl-6,7-benzomorphan (2a). To a mixture of $Hg(OAc)_2$ (0.351 g, 1.1 mmol) and Et_3N (0.24 mL, 1.727 mmol) in THF (30 mL) at room temperature was added amine (1*S*,2*R*)-**10a** (0.203 g, 0.73 mmol) in THF (10 mL) dropwise, and the reaction mixture was stirred at room temperature overnight. A solution of $LiAlH_4$ (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise, and the mixture was stirred for an additional 2 h, then quenched with saturated K_2CO_3 solution (10 mL). The separated aqueous layer was extracted with ether (5 × 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous K_2CO_3, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, MeOH/EtOAc/hexanes, 0.1:0.6:1.3) provided 0.112 g (55%) of (1*S*,5*S*,9*S*)-**2a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61−7.01 (m, 9H), 3.71, 3.61 (AB, 2H, J = 13.5 Hz), 3.06 (d, 1H, J = 18.5 Hz), 2.94−2.91 (m, 1H), 2.82 (bs, 1H), 2.63 (dd, 1H, J = 5.9, 18.5 Hz), 2.44−2.39 (m, 1H), 2.24−2.20 (m, 1H), 2.11−2.03 (m, 2H), 1.51−145 (m, 1H), 0.84 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 139.7, 139.0, 137.0, 129.3, 128.8, 128.2, 127.3, 126.8, 125.8, 125.7, 59.7, 56.6, 43.2, 39.7, 35.7, 34.3, 23.7, 17.4. The free base was converted to the hydrochloride salt: $[\alpha]^{24}_D$ +98° (*c* 0.145, EtOH); mp >210 °C dec. Anal. ($C_{20}H_{24}ClN \cdot 0.25H_2O$) C, H, N.

(1*R*,5*R*,9*R*)-2-Benzyl-9-methyl-6,7-benzomorphan (2a). To a mixture of $Hg(OAc)_2$ (0.510 g, 1.60 mmol) and Et_3N (0.4 mL, 2.87 mmol) in THF (60 mL) at room temperature was added amine (1*R*,2*S*)-**10a** (0.340 g, 1.23 mmol) in THF (25 mL) dropwise, and the reaction mixture was stirred at room temperature for 64 h. A solution of $LiAlH_4$ (1 M in THF, 3.0 mL, 3.0 mmol) was added dropwise, and the mixture was stirred for an additional 2 h, then quenched with saturated K_2CO_3 solution (15 mL). The separated aqueous layer was extracted with ether (5 × 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous K_2-

CO_3, and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (silica gel, MeOH/EtOAc/hexanes, 0.1:0.6:1.3) provided 0.176 g (52%) of (1*R*,5*R*,9*R*)-**10a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61−7.01 (m, 9H), 3.71, 3.61 (AB, 2H, J = 13.5 Hz), 3.06 (d, 1H, J = 18.5 Hz), 2.94−2.91 (m, 1H), 2.82 (bs, 1H), 2.63 (dd, 1H, J = 5.9, 18.5 Hz), 2.44−2.39 (m, 1H), 2.24−2.20 (m, 1H), 2.11−2.03 (m, 2H), 1.51−145 (m, 1H), 0.84 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 139.7, 139.0, 137.0, 129.3, 128.8, 128.2, 127.3, 126.8, 125.8, 125.7, 59.7, 56.6, 43.2, 39.7, 35.7, 34.3, 23.7, 17.4. The free base was converted to the hydrochloride salt: $[\alpha]^{24}_D$ −97° (*c* 0.165, EtOH); mp >210 °C dec. Anal. ($C_{20}H_{24}ClN\cdot 0.25H_2O$) C, H, N.

(1*S*,5*S*,9*S*)-2-Benzyl-9-ethyl-6,7-benzomorphan (2b). A solution of 152 mg (0.52 mmol) of (1*S*,2*R*)-**10b** and 352 mg (1.1 mmol) of mercuric acetate in 20 mL of THF was stirred for 24 h at 25 °C. A solution of 120 mg (3.2 mmol) of sodium borohydride in 5 mL of 1 N sodium hydroxide was added to the reaction mixture, and stirring continued for an additional 5 h. The mixture was extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was purified by silica gel chromatography using hexanes/EtOAc (9:1) as the eluent to give 68 mg (43%) of (1*S*,5*S*,9*S*)-**2b**: ^{1}H NMR ($CDCl_3$) δ 6.93−7.31 (m, 9H), 3.64 (AB, J = 13.5 Hz, 2H), 3.54, 2.98 (d, J = 18.6 Hz, 1H), 2.96 (d, J = 6.4 Hz, 1H), 2.87 (d, J = 2.6 Hz, 1H), 2.52 (dd, J = 6.0, 18.6 Hz, 1H), 2.32−2.36 (m, 1H), 1.87−2.10 (m, 3H), 1.39−1.45 (m, 1H), 1.03−1.12 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 59.7 (CH_2), 55.5 (CH), 43.6 (CH_2), 42.9 (CH), 37.4 (CH), 34.1 (CH_2) 24.1 (CH_2), 24.0 (CH_2), 139.7 (C), 139.1 (C), 137.3 (C), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.3 (CH), 126.7 (CH), 125.7 (CH), 125.6 (CH), 11.6 (CH_3). The free base was converted to the hydrochloride salt. Anal. ($C_{24}H_{26}ClN\cdot H_2O$) C, H, N.

(1*R*,5*R*,9*R*)-2-Benzyl-9-ethyl-6,7-benzomorphan (2b). Using a procedure similar to that described for (1*S*,5*S*,9*S*)-**2b**, 229 mg (0.78 mol) of (1*R*,2*S*)-**10b** provided 40 mg (18%) of (1*R*,5*R*,9*R*)-**2b**. The free base was converted to the hydrochloride salt: $[\alpha]^{22}_D$ −53° (*c* 0.085, EtOH); mp 147 °C dec. Anal. ($C_{21}H_{26}ClN$) C, H, N.

(1*S*,5*S*,9*S*)-2-Benzyl-9-isopropyl-6,7-benzomorphan (2c). Using a procedure analogous to that described for (1*S*,5*S*,9*S*)-**2b**, cyclization of 380 mg (1.24 mol) of (1*S*,2*R*)-**10c** gave 190 mg (50%) of (1*S*,5S,9*S*)-**2b**: ^{1}H NMR ($CDCl_3$) δ 7.04−7.41 (m, 9H), 3.78 (AB, J = 13.6 Hz, 2H), 3.66, 3.28 (bs, 1H), 3.15 (bs, 1H), 3.08 (d, J = 18.6 Hz, 1H), 2.65 (dd, J = 6.1, 18.6 Hz, 1H), 2.40−2.47 (m, 1H), 1.96−2.20 (m, 2H), 1.47−1.70 (m, 2H), 1.11−1.35 (m, 1H), 0.88 (dd, J = 1.5, 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 59.8 (CH_2), 53.8 (CH), 48.2 (CH), 43.2 (CH_2), 36.0 (CH), 34.2 (CH_2), 26.9 (CH), 24.1 (CH_2), 20.7 (CH_3), 139.7 (C), 139.1 (C), 137.6 (C), 128.9 (CH), 128.6 (CH), 128.1 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 125.6 (CH). The free base was converted to the hydrochloride salt: $[\alpha]^{24}_D$ +79 (*c* 0.135, EtOH); mp 123 °C dec. Anal. ($C_{22}H_{28}ClN\cdot 0.5H_2O$) C, H, N.

(1*R*,5*R*,9*R*)-2-Benzyl-9-ethyl-6,7-benzomorphan (2c). Using a procedure analogous to that described for (1*S*,5*S*,9*S*)-**2c**, 439 mg (1.44 mmol) of (1*R*,2*S*)-**10c** provided 219 mg (48%) of (1*R*,5R,9*R*)-**2c**. The free base was converted to the hydrochloride salt: $[\alpha]^{22}_D$ −79 (*c* 0.12, EtOH); mp 124 °C dec. Anal. ($C_{22}H_{28}ClN\cdot 0.5H_2O$) C, H, N.

Membrane Preparation. Crude P_2 membrane fraction was prepared from frozen guinea pig brains (Pel-Freeze, Rogers, AK) minus cerebellum. Brains were allowed to thaw slowly on ice before homogenization. Crude P_2 membrane fraction was also prepared from the livers of male Sprague−Dawley rats (150−200 g; Taconic Farms). Animals were killed by decapitation and the livers removed and minced before homogenization. Alternatively, livers were immediately frozen on dry ice and stored at −80 °C before use. Tissue homogenization was carried out at 4 °C in 10 mL/g tissue weight of 10 mM Tris-HCl/0.32 M sucrose, pH 7.4, using 10 motor-driven strokes in a Potter-Elvehjem Teflon−glass homogenizer. The crude homogenate was centrifuged for 10 min at 1000*g* and the pellet discarded. The resultant supernatant was centrifuged at 31000*g* for 15 min. The pellet was resuspended in 3 mL/g 10 mM Tris-HCl, pH 7.4, by vortexing, and the suspension was allowed to incubate at 25 °C for 15 min. Following centrifugation at 31000*g* for 15 min, the pellet was resuspended to 1.53 mL/g in 10 mM Tris-HCl, pH 7.4, and aliquots were stored at −80 °C until use. Protein concentration of the suspension was determined by the method of Lowry[41] and was 20−25 mg of protein/mL.

σ_1 Binding Assay. Guinea pig brain membranes (325−500 μg of protein) were incubated with 3 nM [^{3}H]-(+)-pentazocine (51.7 Ci/mmol) in 0.5 mL of 50 mM Tris-HCl, pH 8.0, for 120 min at 25 °C. Nonspecific binding was determined in the presence of 10 μM haloperidol. Test compounds were added in concentrations ranging from 0.005 to 1000 nM or from 0.05 to 10000 nM. Assays were terminated by the addition of 5 mL of ice-cold 10 mM Tris-HCl, pH 8.0, followed by rapid filtration through glass-fiber filters using a Brandel cell harvester (Gaithersburg, MD). Filters were then washed twice with 5 mL of ice-cold buffer. Prior to use, filters were soaked in 0.5% poly(ethylenimine) for at least 30 min at 25 °C.

σ_2 Binding Assay. Rat liver membranes (160−200 μg of protein) were incubated with 3 nM [^{3}H]DTG (39.4 Ci/mmol) in the presence of 1 μM unlabeled dextrallorphan. Incubations were carried out in 0.5 mL of 50 mM Tris-HCl, pH 8.0 for 120 min at 25 °C. Nonspecific binding was determined in the presence of 10 μM haloperidol. Test compounds were added in concentrations ranging from 0.005 to 1000 nM or from 0.05 to 10000 nM. Assays were terminated by the addition of 5 mL of ice-cold 10 mM Tris-HCl, pH 8.0, followed by rapid filtration through glass-fiber filters using a Brandel cell harvester (Gaithersburg, MD). Filters were then washed twice with 5 mL of ice-cold buffer. Prior to use, filters were soaked in 0.5% poly(ethylenimine) for at least 30 min at 25 °C.

All scintillation counting was carried out in Cytoscint (National Diagnostics, Manville, NJ) after an overnight extraction of counts.

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