# Probes for Narcotic Receptor Mediated Phenomena. 37.[1] Synthesis and Opioid Binding Affinity of the Final Pair of Oxide-Bridged Phenylmorphans, the Ortho- and Para-b-Isomers and Their *N*-Phenethyl Analogues, and the Synthesis of the *N*-Phenethyl Analogues of the Ortho- and Para-d-Isomers

Muneaki Kurimura,[‡,||,§] Hehua Liu,[‡,||] Agnieszka Sulima,[‡,||,◆] Akihiro Hashimoto,[‡,||,⊥] Anna K. Przybyl,[‡,||,△] Etsuo Ohshima,[‡,||,○] Shinichi Kodato,[‡,||,†] Jeffrey R. Deschamps,[×] Christina M. Dersch,[¶] Richard B. Rothman,[¶] Yong Sok Lee,[∞] Arthur E. Jacobson,[‡,||] and Kenner C. Rice*[,‡,||]

*Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, 5625 Fishers Lane, Room 4N03, Bethesda, Maryland 20892-9415, Clinical Psychopharmacology Section, Chemical Biology Research Branch, National Institute on Drug Abuse, Addiction Research Center, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland 21224, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375, and Center for Molecular Modeling, Division of Computational Bioscience, CIT, National Institutes of Health, DHHS, Bethesda, Maryland 20892*

*Received July 22, 2008*

In the isomeric series of 12 racemic topologically rigid *N*-methyl analogues of oxide-bridged phenylmorphans, all but two of the racemates, the ortho- and para-b-oxide-bridged phenylmorphans **20** and **12**, have remained to be synthesized. The b-isomers were very difficult to synthesize because of the highly strained 5,6-trans-fused ring junction that had to be formed. Our successful strategy required functionalization of the position para (or ortho) to a fluorine atom on the aromatic ring using an electron-withdrawing nitro group to activate that fluorine. The racemic *N*-phenethyl analogues **24** and **16** were moderately potent $\kappa$-receptor antagonists in the [$^{35}$S]GTP$\gamma$S assay. We synthesized the *N*-phenethyl-substituted oxide-bridged phenylmorphans in the ortho- and para-d-oxide-bridged phenylmorphan series (**51** and **52**) which had not been previously evaluated using contemporary receptor binding assays to see whether they also have higher affinity for opioid receptors than their *N*-methyl relatives **46** and **47**.

## Introduction

The ability of an opioid-like ligand to interact with an opioid receptor is likely to depend on the structure and configuration of the ligand as well as its receptor. The structure of the opioid receptor complex has not been experimentally determined yet, although the crystal structure of the human $\beta_2$-adrenergic receptor, also a G-protein-coupled receptor, has been obtained using X-ray diffraction techniques at high resolution.[2−4] Until similar experiments are successful with opioid receptors, attempts to understand the ligand−opioid receptor interaction at the molecular level will continue to rely heavily on the knowledge of the structures of ligands that can or cannot interact with it. The interaction of these ligands with their receptors has been further complicated by the determination that $\mu$- and $\delta$-opioid receptors not only exist in monomeric form but can interact as homodimers or as heterodimeric complexes. In accord with that finding, $\delta$-selective ligands have been found that can influence the effects of $\mu$-opioid receptors. The oligomerization and heterodimerization of G-protein-coupled receptors enabling complex ligand−receptor interactions have been discussed.[5,6]

Because of our inability to directly visualize the ligand−opioid receptor interaction, information about the opioid receptor's binding mode has been inferred from the structure of the interacting ligand, and it would probably be most beneficial to do this with a set of isomeric and rigid ligands. It would be especially interesting if these topologically different ligands were found to selectively interact with their specific receptor as either agonists or antagonists. For these and other reasons, we have selected an isomeric series of 12 racemic (24 enantiomeric) topologically rigid *N*-methyl analogues of oxide-bridged phenylmorphans where spatial characteristics could be determined from both X-ray crystallographic analyses and quantum chemical calculations. Only 2 of the 12 racemates, which we have termed the ortho- and para-b-oxide-bridged phenylmorphans[a] (*N*-methyl substituted, Figure 1), have remained to be synthe-

* To whom correspondence should be addressed. Phone: 301-496-1856. Fax: 301-402-0589. E-mail: kr21f@nih.gov.

‡ Drug Design and Synthesis Section, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, Department of Health and Human Services.

|| This work was initiated while these authors were members of the Drug Design and Synthesis Section, Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, NIH.

§ Current address: Otsuka Pharmaceutical Co., Ltd., 463-10 Kagasuno Kawauchi-cho, Tokushima 771-0192, Japan.

◆ Current address: Imaging Probe Development Center, NHLBI, NIH.

⊥ Current address: Achillion Pharmaceuticals, Inc., New Haven, CT 06511.

△ Current address: Faculty of Chemistry, Adam Mickiewicz University, 60-780 Poznan, Poland.

○ Current address: Kyowa Hakko Kogyo Co., Ltd., Shizuoka, 411-8731 Japan.

† Current address: Bushu Pharmaceuticals Ltd., Saitama, 350-0801, Japan.

× Naval Research Laboratory.

¶ Clinical Psychopharmacology Section, National Institute on Drug Abuse.

∞ CIT.

[a] Abbreviations: ortho-b-oxide-bridged phenylmorphan, (4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol; para-b-oxide-bridged phenylmorphans, (4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol; ortho-d-oxide-bridged phenylmorphan, (3*R**,6a*S**11a*R**)-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol; para-d-oxide-bridged phenylmorphan, (3*R**,6a*S**11a*R**)-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol; (−)-*N*-phenethyl ortho-f-isomer, (1*R*,4a*R*,9a*R*)-(−)-8-hydroxy-2-(2-phenylethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-c]py-

10.1021/jm800913d 
Published on Web 11/18/2008

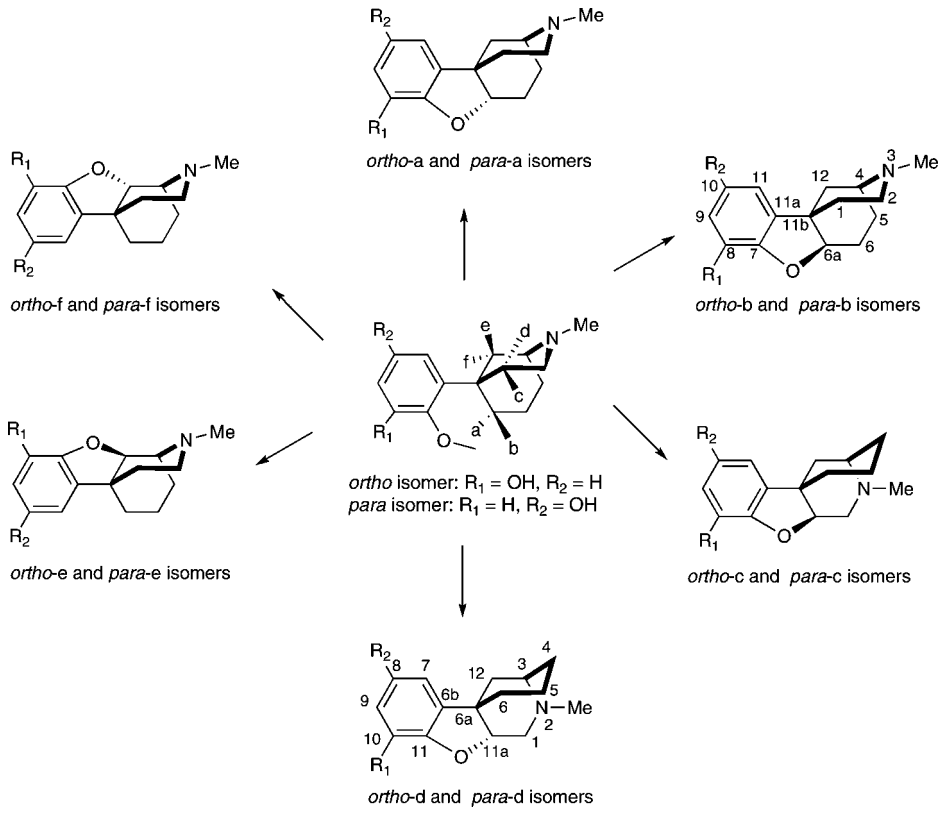



**Figure 1.** Oxide-bridged phenylmorphan structures.

sized, and that has now been accomplished. The *N*-methyl ortho- and para-hydroxyphenyl-substituted a through f isomers can be seen in Figure 1.[1,7−16] If we assume that the topology of the rigid oxide-bridged phenylmorphans influences their interaction with opioid receptors, the isomeric a−f compounds should display different affinities and, perhaps, act differently in vivo as agonists or antagonists, since they all have different topologies. Although many of the a−f compounds in Figure 1 have not been evaluated yet, some have, and the (−)-*N*-phenethyl ortho-f-isomer was found to have high affinity for $\mu$- ($K_i$ = 7 nM) and $\kappa$-receptors and was more potent than naloxone as a $\mu$-opioid antagonist in the [$^{35}$S]GTP$\gamma$S assay.[1] In contrast, the (−)-*N*-phenethyl para-e-isomer was a morphine-like antinociceptive.[1] We also found that the *N*-methyl analogues of the ortho-d-[12] and para-d-isomers (Table 2), as well as the *N*-phenethyl derivative of the ortho-e-isomer,[1] have relatively little affinity for any opioid receptor. The isomeric, topologically rigid oxide-bridged phenylmorphans then have been noted to display a wide spectrum of activity, ranging from inactive to reasonably potent $\mu$-agonist and antagonists. We now report on the synthesis of the difficult to access *N*-methyl (**20** and **12**) and *N*-phenethyl (**24** and **16**) ortho- and para-b-series of compounds and have determined the opioid binding affinity of these compounds and of the *N*-methyl (**46** and **47**) and *N*-phenethyl (**51** and **52**) analogues of ortho- and para-hydroxyphenyl-substituted d-oxide-bridged compounds,[10,12] (Figure 1) to see if conversion from the *N*-methyl substituent to an *N*-phenethyl alters the affinity of these ligands for opioid receptors.

## Chemistry

The b-isomers, like the e-isomers, were very difficult to synthesize because of the highly strained trans-fused ring junction that had to be formed.[15] In order to obtain the b-isomers, we initially applied a strategy similar to one that succeeded with other isomers, in which the oxide-bridged ring was closed by interaction between a phenolate anion and a suitable leaving group on the morphan moiety.[14] These attempts failed with the b-isomers. The successful strategy for the b-isomers (and with the e-isomers) required functionalization of the position para (or ortho) to a fluorine atom on the aromatic ring using an electron-withdrawing nitro group to activate that fluorine.

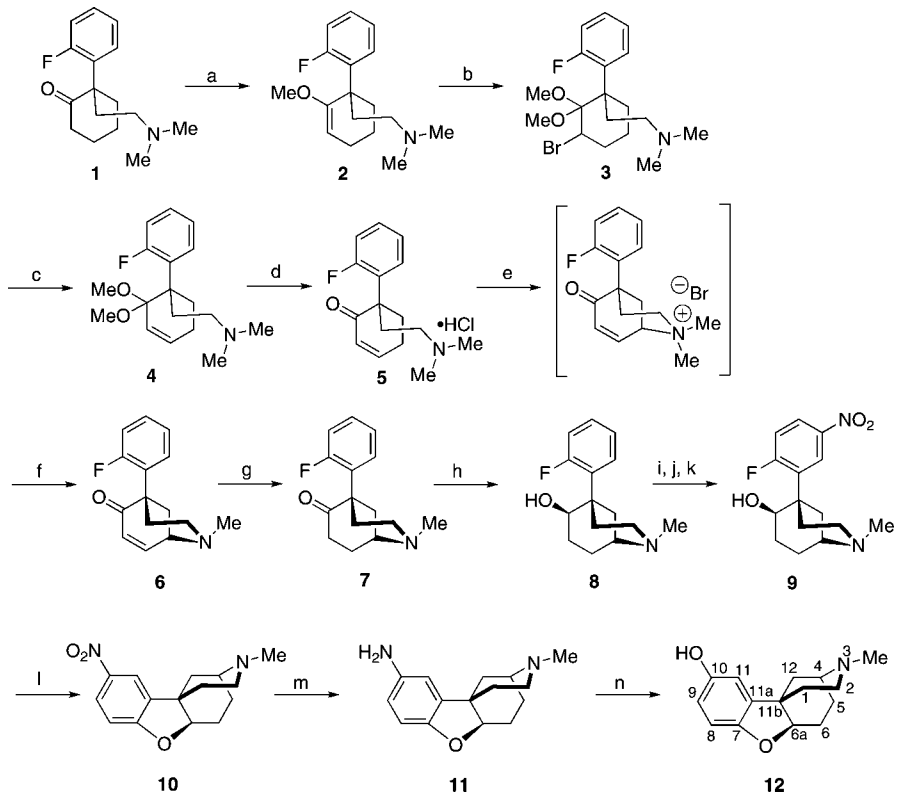
The synthesis of **12**, the para-b-isomer, was accomplished as shown in Scheme 1. The starting material, (*S**)-2-(2-(dimethylamino)ethyl)-2-(2-fluorophenyl)cyclohexanone (**1**) was obtained according to the published procedure.[15] The piperidine ring in (1*S**,5*R**)-5-(2-fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]non-7-en-6-one (**6**) was formed from (*S**)-6-(2-(dimethylamino)ethyl)-6-(2-fluorophenyl)cyclohex-2-enone hydrochloride (**5**) using *N*-bromosuccinimide, followed by heating of the intermediate dimethylammonium hydrobromide salt in diphenyl ether at 170 °C (Scheme 1). Hydrogenation of **6** to the ketone, reduction to the alcohol **8**, and nitration para to the fluorine in the aromatic ring gave a compound (**9**) that could undergo oxide ring closure to the desired azocine **10** in 85% yield.

Conversion of the nitrophenyl compound **10** to **12**, the *N*-Me para-b-isomer, through amine **11** was accomplished using standard reactions (Scheme 1). The nitrophenyl compound **10** was converted to the *N*-phenethyl analogue **16** using standard procedures (Scheme 2). The structure of **12** was established by single crystal X-ray crystallography (Figure 2).

The *N*-methyl analogue **20** was also obtained from amine **11** by conversion to the chlorophenyl compound (**17**, Scheme 3), nitration in the aromatic ring ortho to the oxide bridge, and the usual reduction to **19** and diazotization to give the desired

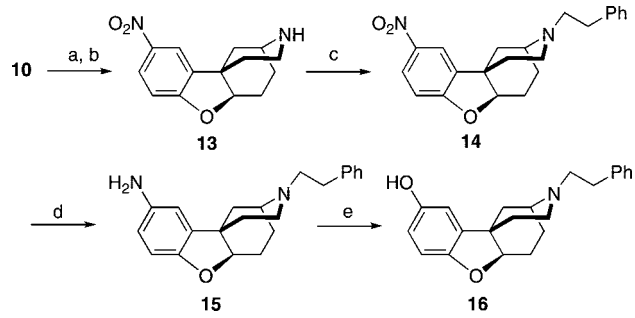
ridine; (-)-*N*-phenethyl *para*-e isomer, (1*S*,4a*S*,9a*R*)-(−)-2-phenethyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2.3-*c*]pyridin-8-ol.

**Scheme 1**[a]



[a] Reagents and conditions: (a) $HC(OMe)_3$, $H_2SO_4$, MeOH; (b) NBA, MeOH; (c) *t*-BuOK, THF; (d) (i) $HCO_2H$, $H_2O$, (ii) HCl; (e) NBS, ethylene glycol, 40 °C; (f) $Ph_2O$, 170 °C; (g) $H_2$, 10% Pd−C, EtOH (quantitative); (h) Super Hydride−THF; (i) $Ac_2O$, AcOH 90 °C; (j) fuming $HNO_3$; (k) 5 N NaOH−MeOH; (l) NaH−THF; (m) 10% Pd−C, EtOH, $H_2$; (n) $NaNO_2$, $Cu(NO_3)_2 \cdot 2.5H_2O$, $Cu_2O$, 35% $H_2SO_4$.

**Scheme 2**[a]



[a] Reagents and conditions: (a) 1-chloroethylchloroformate, $Cl(CH_2)_2Cl$, reflux; (b) MeOH, reflux; (c) $Ph(CH_2)_2Br$, NaI, $CH_3CN$, reflux; (d) 10% Pd−C, EtOH; (e) $NaNO_2$, $Cu(NO_3)_2 \cdot 2.5H_2O$, $Cu_2O$, 35% $H_2SO_4$.

ortho-b analogue **20**. The removable chlorine atom in **17** was used to block the position from unwanted nitration. Reduction of the correctly substituted **18** removed the chlorine atom and reduced the nitro moiety. This gave the amino compound **19** that was needed as the precursor for the target compound **20** with the required phenolic hydroxyl group. The structure of **20** was established by single crystal X-ray crystallography (Figure 2).

The *N*-phenethyl ortho-b-compound **24** (Scheme 4) was obtained through replacement of the *N*-methyl with *N*-phenethyl using the nitrophenyl compound **18** and subsequent removal of the chlorine and conversion of the nitro moiety to the desired ortho-b-phenol (**24**). The *N*-phenethyl ortho- and para-d-isomers **51** and **52** were prepared as shown in Schemes 5 and 6.

Scheme 5 describes the synthesis of the properly substituted bromo derivatives **40** and **41** that were used to prepare the ortho-d- and para-d-compounds shown in Scheme 6. Similar methodology was formerly used to prepare *N*-methyl para-d-isomers by Linders et al.[12]

In Scheme 6, the oxide ring in **42** was formed from **40** in 45% yield using potassium *tert*-butoxide in dry THF under argon. The N-debenzylation of **42** was accomplished directly to give **44** or after protection of the phenolic hydroxyl by forming the cyclopropymethyl ether with (bromomethyl)cyclopropane under basic conditions (potassium *tert*-butoxide) in dry DMF to give **48** in 83% yield. N-Debenzylation of **42** or **48** (Pd−C catalyzed) gave the secondary amine **44** in 98% yield or the cyclopropymethyl ether derivative of the secondary amine **49** in 83% yield. The secondary amine **44** was directly N-methylated using aqueous Pd−C, hydrogen, and 37% formaldehyde in 85% yield to give the *N*-methyl ortho-d-compound **46**, but addition of the phenethyl moiety was most successful when the phenolic hydroxyl was blocked. Thus, **49** was converted to **50** using phenethyl tosylate in DMF under basic conditions and the ether was cleaved under acidic conditions to give the desired *N*-phenethyl ortho-d-compound **51** in 69% yield. Compound **41** was used to obtain the related para-d-compounds **47** and **52** using the direct route as described in **41** to **46**. The structures of the compounds **47** and **51** were definitively ascertained by single crystal X-ray crystallography (Figure 3).

## Results and Discussion

The opioid binding affinities of the ortho- and para-b-isomers, each with an *N*-methyl (**20** and **12**, Table 1) or *N*-phenethyl substituent (**24** and **16**, Table 1), indicated that the ortho-b-isomers had higher affinity than the para-b-isomers at almost all opioid receptors, whether *N*-methyl or *N*-phenethyl substituted, and that the *N*-phenethyl ortho- and para-b-isomers **24**

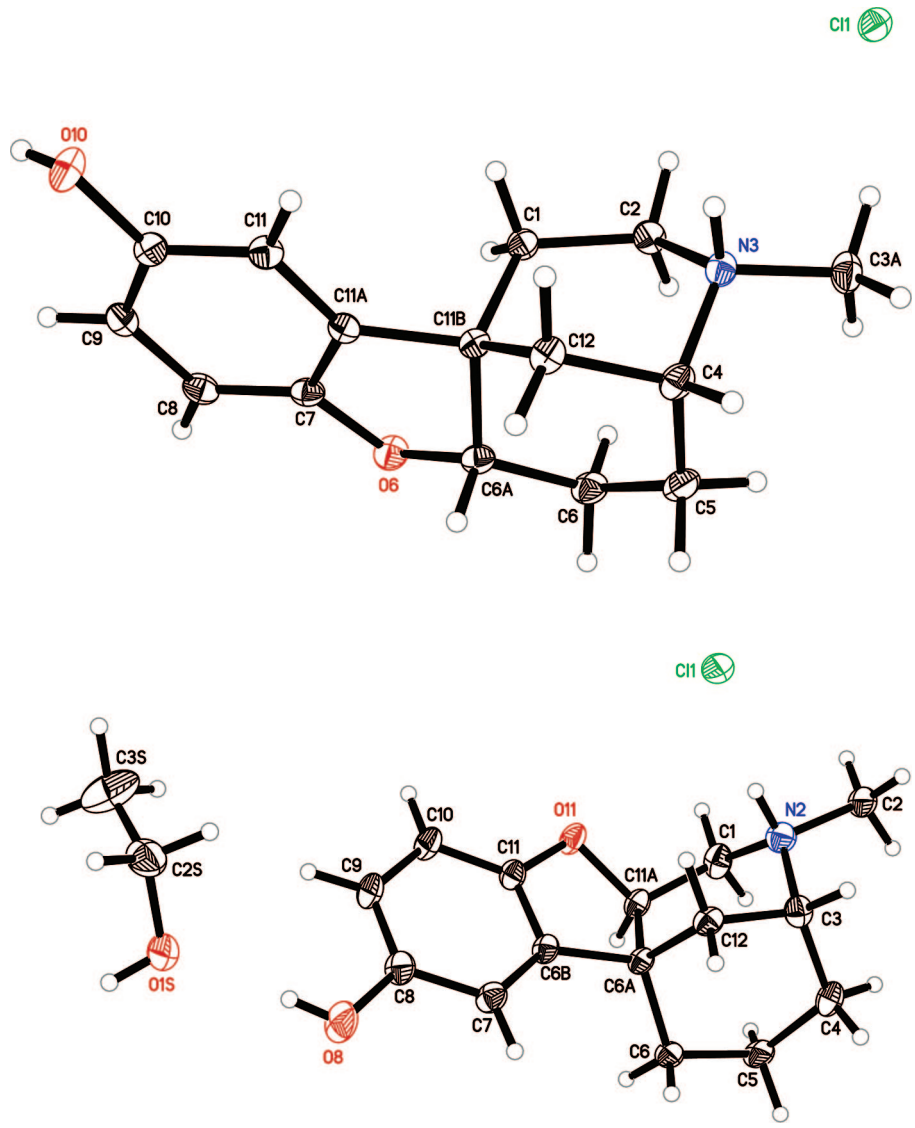
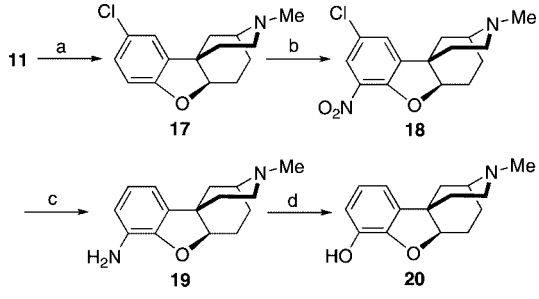


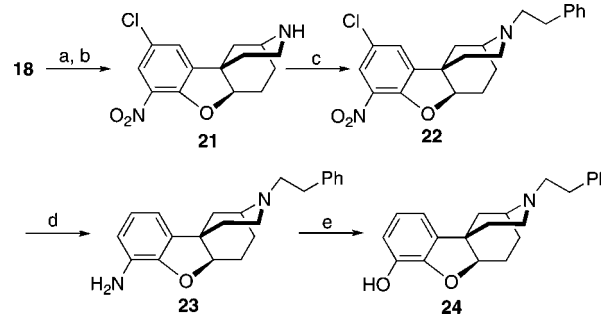

**Figure 2.** X-ray crystallographic structure of (top) **12**·HCl (*N*-methyl para-b-isomer) and (bottom) **20**·HCl (*N*-methyl ortho-b). For all four compounds displacement ellipsoids are shown at the 50% level.

**Scheme 3**[a]




[a] Reagents and conditions: (a) $NaNO_2$, 37% HCl, $CuSO_4$, NaCl, sodium bisulfite, NaOH; (b) $NaNO_2$, $CF_3CO_2H$; (c) $H_2$, 10% Pd−C, EtOH; (d) $NaNO_2$, $Cu(NO_3)_2 \cdot 2.5H_2O$, $Cu_2O$, 35% $H_2SO_4$.

**Scheme 4**[a]

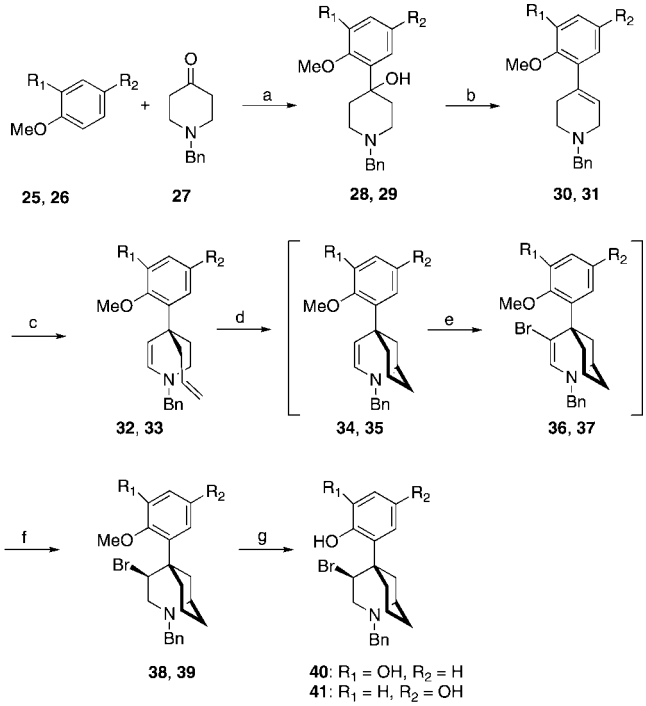



[a] Reagents and conditions: (a) 1-chloroethylchloroformate, $Cl(CH_2)_2Cl$, reflux; (b) MeOH, reflux; (c) $Ph(CH_2)_2Br$, $K_2CO_3$, NaI, $CH_3CN$, reflux; (d) 10% Pd−C, $HCO_2NH_4$, EtOH; (e) $NaNO_2$, $Cu(NO_3)_2 \cdot 2.5\ H_2O$, $Cu_2O$, 35% $H_2SO_4$.

and **16** appeared to interact best with $\kappa$-receptors ($K_i$ < 100 nM) and had less affinity at the other opioid receptors (e.g., $K_i$ = 190 nM at $\mu$-receptors for the *N*-phenethyl ortho-b-compound **24**). The *N*-phenethyl para-b-isomer **16** had little affinity ($K_i$ = 740 nM) at $\mu$-receptors, and none of the b- or d-oxide-bridged phenylmorphan analogues had much affinity for $\delta$-receptors. The *N*-phenethyl ortho- and para-d-compounds **51** and **52** had only slight affinity for $\mu$-receptors, albeit somewhat better affinity than the comparable *N*-methyl analogues (**46** and **47**, Table 2).

The ortho- and para-b compounds were screened for opioid receptor activity, and on the basis of those results, a few of the compounds (**24** and **16**) were selected for further study by

**Scheme 5**[a]




[a] Reagents: (a) *n*-BuLi, $Et_2O$; (b) *p*-toluenesulfonic acid, toluene; (c) *sec*-BuLi, THF, allyl bromide; (d) $HCO_2H$, $H_3PO_4$; (e) NBA, THF; (f) 37% HCl, $NaCNBH_3$; (g) $BBr_3$, $CH_2Cl_2$.

examining their efficacy in the [$^{35}$S]GTP$\gamma$S assay (Table 3). Both of the *N*-phenethyl b-oxide-bridged phenylmorphans **24** and **16** that had some affinity for the $\kappa$-opioid receptor acted as moderately active $\kappa$-antagonists in the functional assay. The *N*-phenethyl ortho-b-isomer **24** had weak $\mu$-antagonist activity. Since the examined compounds were racemates, it is possible that at least one of the enantiomeric *N*-phenethyl ortho-b-isomers will have appreciable affinity and efficacy for $\kappa$-receptors. The synthesis of the enantiomers of these racemates will be the subject of future work, with the hope that an enantiomer might provide compounds with greater $\kappa$-selectivity. We have focused on their $\kappa$-activity because of the contemporary interest in selective $\kappa$ antagonists as potential antidepressants[17] and their actions in reducing stress.[18]

Among the rigid oxide-bridged phenylmorphans that have been examined, we have previously found that the (-)-*N*-phenethyl ortho-f-isomer had high affinity as a $\mu$-antagonist as well as having naloxone-like efficacy as a $\kappa$-antagonist,[1] the (-)-*N*-phenethyl para-e-isomer was a weak $\mu$- and $\delta$- agonist ex vivo but had morphine-like antinociceptive activity,[1] and, now, that the racemic *N*-phenethyl ortho-b compound **24** acts as a $\kappa$-antagonist. Thus we have found several rigid oxide-bridged phenylmorphans that interact with $\mu$- or $\kappa$-opioid receptors. We have previously postulated[1,19] a possible mechanism for the action of oxide-bridged phenylmorphans on $\mu$-receptors via proton transfer from the protonated nitrogen to a proton acceptor in the $\mu$-opioid receptor complex facilitated by a water molecule.[19]

Examination of the b-oxide-bridged phenylmorphan series of rigid topological analogues indicated that the mechanism proposed to account for the very high affinity of the *N*-phenethyl substituted phenylmorphan agonist ((1*R*,5*R*,9*S*)-(−)-9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane) at the $\mu$-receptor[19] is unlikely to be applicable to the *N*-phenethyl substituted ortho-b-isomer **24** (and even less feasible for the comparable ortho-d-isomer **51**). The geometries of these compounds were optimized with density functional theory at the B3LYP/6-31G* level. The phenolic ring of the energy minimized ortho-f-compound was found to have little overlap with the phenolic ring of the high-affinity azabicyclo[3.3.1]-nonane agonist (Figure 4). The phenolic hydroxyl group and epoxide oxygen are clearly in different areas of three-dimensional space in these two molecules, and this might be related to the major difference in their pharmacological activity (agonist vs antagonist), although both have high affinity for the $\mu$-opioid receptor. If we assume that the ortho-f-compound has at least some of the topological characteristics needed to interact with $\mu$-receptors as a $\mu$-antagonist, then the ortho-b-compound should have fewer of those characteristics, since it has considerably lower $\mu$-affinity and antagonist efficacy.

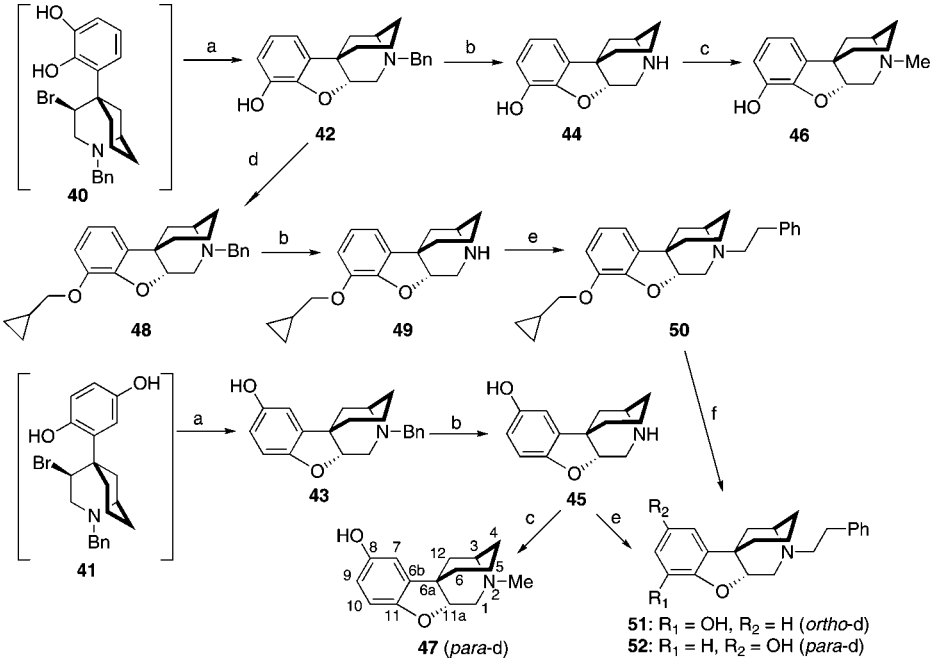
As seen in Figure 5, the phenolic ring of the ortho-b-isomer (one of the enantiomers in the racemate) is out of the plane of the ortho-f-ring, and its oxygen atoms are quite distant from those in the ortho-f-compound (the epoxide oxygen atoms are 4.0 Å apart, and the phenolic oxygen atoms are 6.7 Å apart). The ortho-b-racemate was found to have 27-fold less affinity for the $\mu$-receptor than the ortho-f-enantiomer ($K_i$ = 190 vs 7 nM). The ortho-d-compound's phenolic ring is even further from the plane of the ortho-f-compound's phenolic ring (Figure 6); it is nearly perpendicular to the phenolic ring in ortho-f-compound and has lost almost all affinity for $\mu$-receptors. With the relatively few oxide-bridged phenylmorphans available that have $\mu$-antagonist activity and the few that have $\kappa$-antagonist activity, it is not possible to hypothesize the mechanisms through which they interact with those receptors. We feel that it is likely, however, that the topological characteristics of these compounds will be found to be one of the factors that are important in their interaction with opioid receptors.

## Experimental Section

Thin layer chromatography (TLC) analyses were carried out on Analtech silica gel GHLF 0.25 mm plates using various gradients of $CHCl_3$/MeOH containing 1% $NH_4OH$ or gradients of ethyl acetate/*n*-hexanes. Visualization was accomplished under UV or by staining in an iodine chamber. Melting points were determined in open glass capillaries on Thomas-Hoover melting-point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as the internal standard. FAB and HRMS were recorded on a VG 7070E or JEOL SX 102a mass spectrometer. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220−400). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values.

**(*S**)-2-(1-(2-Fluorophenyl)-2,2-dimethoxycyclohex-3-enyl)-*N*,*N*-dimethylethanamine (2).** A solution of (*S**)-2-(2-(dimethylamino)ethyl)-2-(2-fluorophenyl)cyclohexanone[15] (**1**) (18 g, 68.35 mmol) and trimethyl orthoformate (40 mL, 340 mmol, 5 equiv in MeOH (550 mL) was stirred under an atmosphere of Ar for 12 h at room temperature in the presence of $H_2SO_4$ (7.3 mL, 137 mmol, 2 equiv). The reaction mixture was quenched with saturated $NaHCO_3$ at 0 °C and then extracted with $CHCl_3$. The organic layer was washed with $H_2O$ and brine. The solution was dried and the solvent was evaporated under reduced pressure to give a yellow oil (21 g). The crude product was purified by crystallization with oxalic acid from 2-propanol, affording 26.7 g of salt, mp 157−158 °C. After conversion to the base, compound **2** was obtained as an oil (18.42 g, 97%). $^1$H NMR ($CDCl_3$) $\delta$ 1.02−1.20 (m, 1H), 1.42−1.53 (m, 1H), 1.77 (dt, $J$ = 13.18 and 2.75 Hz, 1H), 2.00−2.31 (m, 6H), 2.23 (s, 6H), 2.50 (dt, $J$ = 11.53 and 4.67 Hz, 1H), 3.54 (s,

**Scheme 6**[a]




[a] Reagents: (a) *t*-BuOK, THF; (b) $H_2$, 10% Pd−C, HOAc/MeOH; (c) $H_2$, Escat 103 (5% Pd−C), HCHO/MeOH; (d) *t*-BuOK, DMF, (bromomethyl)cyclopropane; (e) phenethyl tosylate, DMF; (f) 37% HCl/MeOH.

3H), 4.93 (t, $J$ = 3.84 Hz, 1H), 6.94−7.20 (m, 4H). HRMS (FAB) *m*/*z* calcd for $C_{17}H_{25}ONF$, 278.1920; found, 278.1923.

**2-((1*S**)-3-Bromo-1-(2-fluorophenyl)-2,2-dimethoxycyclohexyl)-*N*,*N*-dimethylethanamine (3).** To a solution of **2** (4.86 g, 17.5 mmol) and $CH_3SO_3H$ (1.58 mL, 24.5 mmol, 1.4 equiv) in MeOH (240 mL) was added NBA (2.78 g, 20.12 mmol, 1.15 equiv) portionwise under an atmosphere of Ar at 0 °C. The mixture was stirred vigorously for 1.5 h. Then the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with $H_2O$ and brine. The solution was dried and the solvent was evaporated under reduced pressure to give a yellow oil (7.57 g). The crude product was purified by column chromatography with $CHCl_3$/MeOH/28% $NH_4OH$ (100:3:0.5), affording 6.56 g (96%) of **3** as a yellow oil that crystallized. $^1$H NMR ($CDCl_3$) $\delta$ 1.59−1.70 (m, 1H), 1.75−1.90 (m, 2H), 1.99−2.39 (m, 5H), 2.22 (s, 6H), 2.45−2.85 (m, 2H), 2.66 (s, 3H), 3.38 (s, 3H), 4.36 (t, $J$ = 3.84 Hz, 1H), 6.91−7.09 (m, 2H), 7.18−7.26 (m, 1H), 7.54−7.62 (m, 1H). HRMS (FAB) *m*/*z* calcd for $C_{18}H_{28}O_2NFBr$, 388.1287; found, 388.1290.

**(*S**)-2-(1-(2-Fluorophenyl)-2,2-dimethoxycyclohex-3-enyl)-*N*,*N*-dimethylethanamine (4).** To a solution of **3** (11.8 g, 30.4 mmol) in THF (120 mL) was added 10.2 g (91 mmol, 3 equiv) of potassium *tert*-butoxide portionwise at 0−5 °C under an atmosphere of Ar. The temperature was allowed to warm to room temperature, and the mixture was allowed to stand overnight. The resulting suspension was cooled in an ice bath, and $H_2O$ was added. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated in vacuo to give 8.5 g (91%) of **4** as a yellow oil. The crude product (**4**) was pure enough to be used in the next step without any additional purification. $^1$H NMR ($CDCl_3$) $\delta$ 1.75−1.92 (m, 2H), 2.00−2.25 (m, 4H), 2.18 (s, 6H), 2.50−2.70 (m, 2H), 3.16 (s, 3H), 3.26 (s, 3H), 5.83 (td, $J$ = 10.44, 2.20 Hz, 1H), 5.97−6.04 (m, 1H), 6.95 (ddd, $J$ = 13.80, 7.96, 1.37 Hz, 1H), 7.04 (ddd, $J$ = 7.96, 7.28, 1.37 Hz, 1H), 7.15−7.22 (m, 1H), 7.55 (ddd, $J$ = 8.24, 8.24, 1.93 Hz, 1H). HRMS (FAB) *m*/*z* calcd for $C_{18}H_{27}O_2NF$, 308.2026; found, 308.2031.

**(*S**)-6-(2-(Dimethylamino)ethyl)-6-(2-fluorophenyl)cyclohex-2-enone (5).** A mixture of formic acid (88%, 70 mL) and $H_2O$ (370 mL) was added to **4** (27.4 g, 89.1 mmol) and stirred for 1.5 h. The reaction mixture was washed with AcOEt (200 mL), and the aqueous layer was neutralized with 5 N NaOH and extracted with $CHCl_3$ (2 × 200 mL). Combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of $CHCl_3$ under reduced pressure, the residue was dissolved in MeOH (100 mL) and a 1.25 M HCl−MeOH (100 mL) solution was added. Removal of MeOH afforded a solid that was washed with ether−acetone to give **5**·HCl (16.7 g, 72%) as a white powder, mp 162−163 °C. HRMS (M + H)$^+$ calcd for $C_{16}H_{21}NOF$, 262.1607; found, 262.1607. $^1$H NMR ($CDCl_3$, free base) $\delta$ 12.40 (br s, 1H), 7.25−7.36 (m, 1H), 7.00−7.17 (m, 3H), 6.78−6.88 (m, 1H), 6.06−6.16 (m, 1H), 3.26−3.42 (m, 1H), 2.79 (d, $J$ = 4.8 Hz, 3H), 2.58−2.74 (m, 5H), 2.25−2.50 (m, 3H), 1.98−2.18 (2H, m). $^{13}$C NMR ($CDCl_3$, free base) $\delta$ 201.36, 162.95, 159.67, 150.06, 130.08, 129.97, 129.64, 129.58, 129.21, 125.30, 125.15, 124.89, 124.84, 117.11, 116.80, 54.82, 51.23, 51.20, 43.22, 42.51, 34.48, 34.42, 30.74, 30.77, 24.21. Anal. ($C_{16}H_{21}ClFNO$) C, H, N, F.

**(1*S*,5*R**)-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]non-7-en-6-one (6).** *N*-Bromosuccinimide (6.3 g, 35.3 mmol) was added to a solution of **5** (7.0 g, 23.6 mmol) in ethylene glycol (105 mL), and the mixture was stirred at 40 °C for 1 h. After further addition of NBS (0.75 g, 4.2 mmol), the reaction mixture was stirred for 2 h. A saturated $NaHCO_3$ solution (100 mL) was added to the reaction mixture followed by extraction with $CH_2Cl_2$ (2 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a crude intermediate bromide that was used without purification. Diphenyl ether (80 mL) was added to the residue, and the mixture was stirred at 170 °C for 2 h. The mixture was cooled to room temperature, dissolved in AcOEt (100 mL), and extracted with 2 M hydrochloric acid (2 × 50 mL). The combined aqueous acidic layers were neutralized with a 20% NaOH solution and extracted with $CHCl_3$ (2 × 100 mL). The organic material was dried over $MgSO_4$ and concentrated to give a brown oil that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1) to afford **6** (1.97 g, 34%) as a light-yellow powder, mp 139−140 °C. HRMS (M + H)$^+$ calcd for $C_{15}H_{17}NOF$, 246.1294; found, 246.1320. $^1$H NMR ($CDCl_3$) $\delta$ 7.22−7.35 (m, 2H), 7.11−7.19 (m, 1H), 7.00 (ddd, $J$ = 1.5, 8.1, 11.4 Hz, 1H), 6.90 (ddd, $J$ = 1.8, 6.0, 12.0 Hz, 1H), 6.52 (d, $J$ = 9.9 Hz, 1H), 3.61 (dt, $J$ = 5.7, 2.7 Hz, 1H), 2.85−2.95 (m, 1H), 2.71−2.81 (m, 1H), 2.24−2.51 (m, 5H), 2.07−2.20 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 201.09, 162.33, 159.06, 142.85, 133.56, 133.54, 131.90, 131.73, 128.98, 128.87, 127.28,

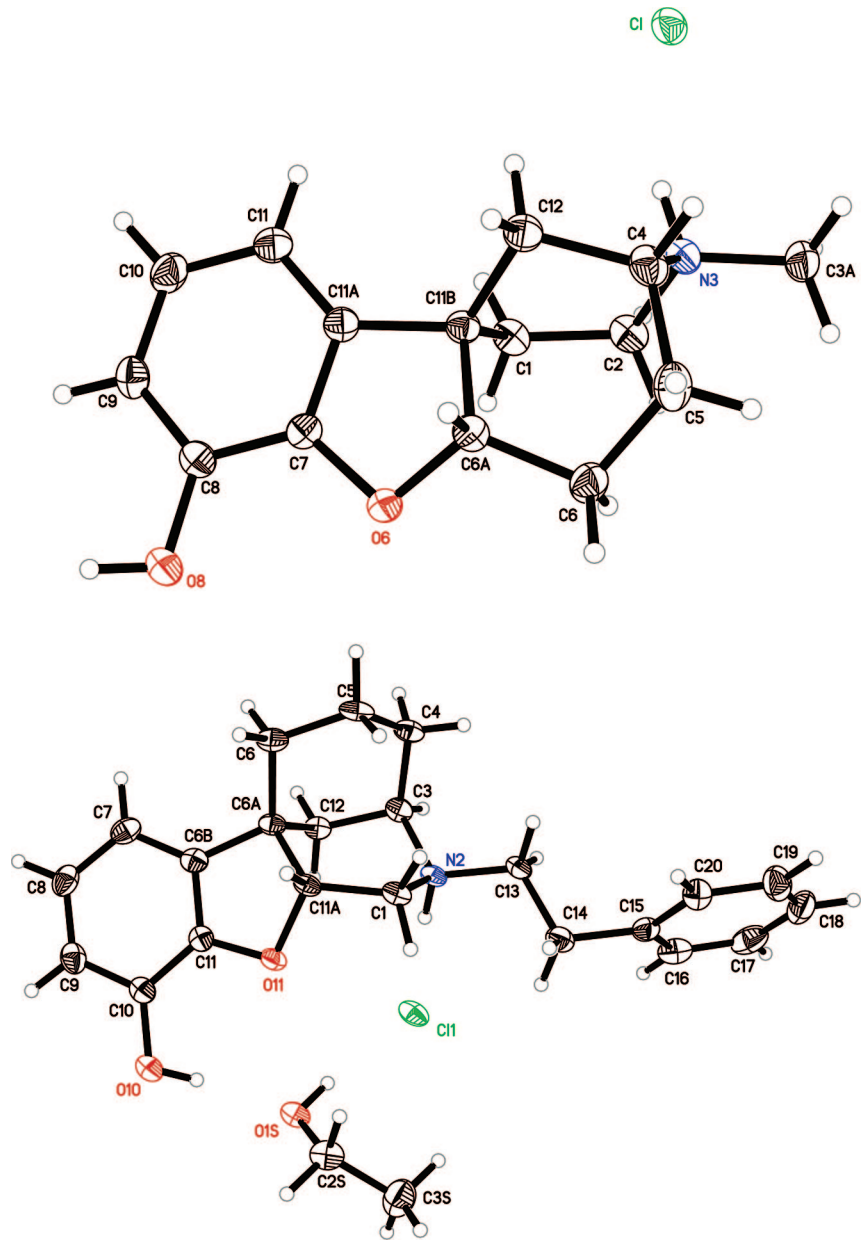
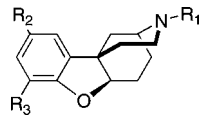



**Figure 3.** X-ray crystallographic structure of (top) **47**·HCl·EtOH (*N*-methyl para-d) and (bottom) **51**·HCl (*N*-phenethyl ortho-d). For all four compounds displacement ellipsoids are shown at the 50% level.

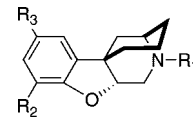
**Table 1.** [$^{125}$I]Ioxy Binding Data for Ortho- and Para-b Oxide-Bridged Phenylmorphans[a]




| | | | | $K_i \pm$ SD, nM | | |
|---|---|---|---|---|---|---|
| compd | $R_1$ | $R_2$ | $R_3$ | $\mu$ | $\delta$ | $\kappa$ |
| **12** | Me | OH | H | >10000 | >10000 | >10000 |
| **16** | phenethyl | OH | H | 740 ± 49 | 4760 ± 254 | 78 ± 3.0 |
| **20** | Me | H | OH | 3210 ± 260 | >10,000 | 910 ± 51 |
| **24** | phenethyl | H | OH | 190 ± 15 | 3710 ± 208 | 26 ± 1.6 |

[a] Assays were conducted using CHO cells, which were stably transfected and express the $\mu$-, $\delta$-, or $\kappa$-opioid receptors, respectively, as described previously.[19] For all results, $n = 3$.

**Table 2.** [$^{125}$I]Ioxy Binding Data for Ortho- and Para-d Oxide-Bridged Phenylmorphans[a]



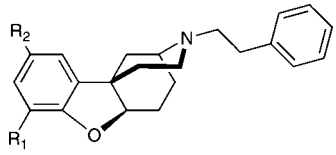

| | | | | $K_i \pm$ SD, nM | | |
|---|---|---|---|---|---|---|
| compd | $R_1$ | $R_2$ | $R_3$ | $\mu$ | $\delta$ | $\kappa$ |
| **46** | Me | OH | H | 8000 ± 406 | 3430 ± 92 | 4820 ± 198 |
| **51** | phenethyl | OH | H | 560 ± 27 | 2840 ± 56 | 200 ± 3 |
| **47** | Me | H | OH | 2930 ± 203 | 2780 ± 54 | 620 ± 21 |
| **52** | phenethyl | H | OH | 1220 ± 56 | 2530 ± 76 | 560 ± 25 |

[a] Assays were conducted using CHO cells, which were stably transfected and express the $\mu$-, $\delta$-, or $\kappa$-opioid receptors, respectively, as described previously.[19] For all results, $n = 3$.

127.21, 124.38, 124.34, 116.10, 115.80, 53.90, 47.32, 47.33, 46.27, 43.15, 40.24, 40.19, 33.05. Anal. ($C_{15}H_{16}FNO$) C, H, N, F.

**(1*R**,5*R**)-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-6-one (7).** To a solution of **6** (1.10 g, 4.5 mmol) in EtOH (20 mL) was added 10% Pd−C (0.11 g), and the mixture was stirred for 2 h under a hydrogen atmosphere. Filtration of the catalyst and removal of EtOH under reduced pressure gave compound **7** (1.11

**Table 3.** Functional Data ([$^{35}$S]GTP-$\gamma$-S)[a] for the *N*-Phenethyl Substituted Para- (**16**) and Ortho-b-Isomers (**24**)



**16**: $R_1$ = H, $R_2$ = OH
**24**: $R_1$ = OH, $R_2$ = H

| compd | $\mu$-antagonism $K_e$ (nM)[b] | $\delta$-antagonism $K_e$ ($\mu$M)[c] | $\kappa$-antagonism $K_e$ (nM)[c] |
|---|---|---|---|
| **16** | 260 ± 79 | 17 ± 4.2 | 19 ± 5.2 |
| **24** | 77 ± 13 | 8 ± 1.5 | 21 ± 3.4 |
| naloxone | 2.3 ± 0.3 | | |
| naltrindole | | 0.18 ± 0.01 | |
| norBNI | | | 0.11 ± 0.02 |

[a] [$^{35}$S]GTP-$\gamma$-S binding was conducted as previously described.[19,20] [b] For $\mu$-receptors, $K_e$ values were calculated according to the equation [test drug]/($EC_{50-2}/EC_{50-1}$ − 1), where $EC_{50-2}$ is the $EC_{50}$ value of DAMGO in the presence of a fixed concentration of the test drug and $EC_{50-1}$ is the value in the absence of the test drug. [c] For $\delta$ and $\kappa$ receptors, $K_e$ values were determined as described in the section "Data Analysis and Statistics" in Hiebel et al.[19] Each parameter value is listed with ±SD.

g, quantitative) as a white powder, mp 95−96 °C. HRMS (M + H)$^+$ calcd for $C_{15}H_{19}NOF$, 248.1451; found, 248.1450. $^1$H NMR ($CDCl_3$) $\delta$ 7.29−7.38 (m, 1H), 7.19−7.28(m, 1H), 7.10−7.18 (m, 1H), 7.00 (ddd, $J$ = 1.2, 7.8, 11.7 Hz, 1H), 3.21−3.33 (m, 1H), 2.88−3.04 (m, 1H), 2.72−2.83 (m, 1H), 2.57−2.67 (m, 1H), 2.27−2.54 (m, 3H), 2.06−2.26 (m, 2H), 1.89−2.04 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 216.88, 162.50, 159.25, 132.37, 132.19, 128.87, 128.75, 127.49, 127.42, 124.55, 124.51, 116.08, 115.77, 52.64, 48.27, 47.10, 42.57, 37.78, 37.73, 37.63, 37.57, 34.62, 18.45. Anal. ($C_{15}H_{18}FNO$) C, H, N, F.

**(1*R**,5*R**,6*S**)-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-6-ol (8).** A sample of 1 M Super Hydride in THF solution (11.6 mL, 11.6 mmol) was slowly added to a solution of **7** (0.96 g, 3.88 mmol) in THF (10 mL) at −78 °C, and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with 2 M hydrochloric acid, and the organic solvent was removed from the mixture in vacuo. The aqueous phase was neutralized with a 20% NaOH solution and extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residual material was dissolved in MeOH, and a small excess of a 1.25 M HCl−methanol solution (4.3 mL) was added. Removal of MeOH in vacuo gave a white solid that was crystallized from EtOH (15 mL) to afford **8**·HCl as a white powder. The structure of **8**·HCl was established by single crystal X-ray analysis. Then 5 N NaOH was added to the hydrochloride salt and the base **8** was extracted with $CHCl_3$ (30 mL × 2). The combined $CHCl_3$ layers were dried over $MgSO_4$. Removal of $CHCl_3$ afforded **8** (0.68 g, 70.8%) as a white powder, mp 122−123 °C. HRMS calcd for $C_{15}H_{21}NOF$ (M + H)$^+$, 250.1607; found, 250.1612. $^1$H NMR ($CDCl_3$) $\delta$ 7.32−7.41 (m, 1H), 7.18−7.25 (m, 1H), 7.08−7.15 (m, 1H), 7.02 (ddd, $J$ = 1.5, 7.8, 13.8 Hz, 1H), 4.22 (dd, $J$ = 7.2, 10.8 Hz, 1H), 2.81−3.06 (m, 3H), 2.52−2.64 (m, 1H), 2.43 (3H, s), 2.36−2.42 (m, 1H), 2.20−2.32 (m, 1H), 1.91−2.11 (m, 3H), 1.70−1.88 (m, 1H), 1.46−1.66 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 163.65, 160.36, 134.18, 129.14, 128.47, 124.25, 117.24, 116.91, 74.05, 53.40, 51.00, 43.29, 40.92, 37.88, 37.79, 31.43, 31.35, 29.00, 24.26. Anal. ($C_{15}H_{21}ClFNO$) C, H, N, F.

**(1*R**,5*R**,6*S**)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-ol (9).** A mixture of **8** (0.20 g, 0.8 mmol) and $Ac_2O$ (0.15 g, 1.5 mmol) in AcOH (0.5 mL) was stirred at 90 °C for 15 h. After removal of AcOH under reduced pressure, cool fuming $HNO_3$ (1.0 mL) was added to the residue slowly at 0 °C. The mixture was stirred for 10 min at 0 °C and for 10 min at room temperature. The reaction mixture was evaporated and dissolved in MeOH (8 mL). The 5 N NaOH (8 mL) was slowly added to the solution and the mixture was stirred for 0.5 h at 0 °C. After removal of MeOH the mixture was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of $CHCl_3$ in vacuo afforded a crude solid that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1 to $CH_2Cl_2$/MeOH/28% $NH_4OH$, 100:10:1) to give **9** (0.15 g, 62%); mp 160−161 °C. HRMS calcd for $C_{15}H_{20}FN_2O_3$ (M + H)$^+$, 295.1458; found, 295.1473. $^1$H NMR ($CDCl_3$) $\delta$ 8.35 (dd, $J$ = 3.0, 7.2 Hz, 1H), 8.08−8.18 (m, 1H), 7.16 (dd, $J$ = 9.0, 12.3 Hz, 1H), 4.12−4.26 (m, 1H), 2.80−3.06 (m, 3H), 2.53−2.68 (m, 1H), 2.44 (s, 3H), 2.18−2.34 (m, 2H), 1.94−2.14 (m, 3H), 1.46−1.92 (m, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 167.20, 163.75, 144.27, 136.38, 136.23, 125.73, 125.62, 124.26, 124.11, 118.02, 117.65, 73.42, 73.39, 53.28, 50.49, 43.14, 41.16, 41.09, 37.05, 36.96, 31.95, 28.60, 28.57, 24.29. Anal. ($C_{15}H_{19}FN_2O_3$) C, H, N, F.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-methyl-10-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (10).** NaH (92 mg, 2.3 mmol) was added to a solution of compound **9** (0.45 g, 1.5 mmol) in THF (22.5 mL) at 0 °C and stirred for 4 h at room temperature. $H_2O$ was added cautiously to the reaction mixture at 0 °C, and the THF was removed in vacuo. The mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic solution was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude solid that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 25:1 to 10: 1) to afford **10** (0.36 g, 85%) as a light-yellow powder, mp 131−132 °C. HRMS calcd for $C_{15}H_{19}N_2O_3$ (M + H)$^+$, 275.1396; found, 275.1385. $^1$H NMR ($CDCl_3$) $\delta$ 8.12 (dd, $J$ = 2.4, 8.7 Hz, 1H), 7.97 (d, $J$ = 2.4 Hz, 1H), 6.92 (d, $J$ = 9.0 Hz, 1H), 4.27 (dd, $J$ = 7.2, 11.4 Hz, 1H), 2.95−3.03 (m, 1H), 2.72−2.92 (m, 2H), 2.46−2.57 (m, 2H), 2.43 (s, 3H), 2.22−2.36 (m, 2H), 1.66−1.92 (m, 3H), 1.40−1.56 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 164.89, 142.57, 139.11, 125.60, 118.56, 110.63, 93.45, 54.43, 50.69, 43.35, 43.31, 38.14, 32.45, 27.40, 21.93. Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Amino-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (11).** To a solution of **9** (0.11 g, 0.4 mmol) in EtOH (2 mL) was added 10% Pd−C (50 mg), and the mixture was stirred for 1 h under $H_2$ atmosphere. The catalyst was removed by filtration and EtOH was removed in vacuo to give **11** (96 mg, 98%) as a white powder, mp 176−177 °C. HRMS calcd for $C_{15}H_{21}N_2O$ (M + H)$^+$, 245.1654; found, 245.1666. $^1$H NMR ($CDCl_3$) $\delta$ 6.66−6.72 (m, 1H), 6.44−6.51 (m, 2H), 4.01−4.12 (m, 1H), 3.43 (br s, 2H), 2.71−2.96 (m, 3H), 2.34−2.46 (m, 5H), 2.15−2.27 (m, 2H), 1.38−1.88 (m, 4H). $^{13}$C NMR ($CDCl_3$) $\delta$ 152.39, 140.75, 138.74, 114.44, 110.79, 110.03, 91.45, 54.78, 50.99, 43.48, 48.42, 38.51, 32.03, 27.69, 21.97. Anal. ($C_{15}H_{20}N_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (12).** A solution of $NaNO_2$ (30 mg, 0.43 mmol) in $H_2O$ (0.32 mL) was added to a solution of **11** (80 mg, 0.33 mmol) in 35% $H_2SO_4$ (0.32 mL) at 0 °C. The mixture was stirred for 5 min, and urea was added until KI-starch indicator paper did not turn purple when a drop of the mixture was placed on it. A solution of $Cu(NO_3)_2$·2.5$H_2O$ (1.18 g, 5.1 mmol) in $H_2O$ (11.2 mL) was added followed by $Cu_2O$ (47 mg, 0.33 mmol), and the mixture was vigorously stirred for 30 min at room temperature. A 28% $NH_4OH$ solution was added to the reaction mixture to adjust the pH to 11, and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic solution was dried over $MgSO_4$ and concentrated to give a crude base that was purified by preparative TLC (silica gel, $CH_2Cl_2$/MeOH, 10:1) to give **12**. It was dissolved in MeOH and converted to **12**·HCl by adding 1.25 N HCl in MeOH to the solution. MeOH was removed in vacuo to give **12**·HCl (38 mg, 41%) as a light-yellow powder. The salt was crystallized from isopropanol/$H_2O$, mp 317−318 °C (dec). The structure of **12** was established by single crystal X-ray analysis. HRMS calcd for $C_{15}H_{20}NO_2$ (M + H)$^+$, 246.1494; found, 246.14888. $^1$H NMR ($CDCl_3$, free base) $\delta$ 6.79 (d, $J$ = 2.7 Hz, 1H), 6.76 (d, $J$ = 8.1 Hz, 1H), 6.63 (dd, $J$ = 2.7, 8.4 Hz, 1H), 4.20−4.90 (m, 1H), 3.00−3.50 (m, 1H), 2.82−2.88 (m, 2H), 2.38−2.64 (m, 5H), 2.16−2.32 (m, 2H), 1.80−1.88 (m, 3H), 1.44−1.62 (m, 1H). $^{13}$C

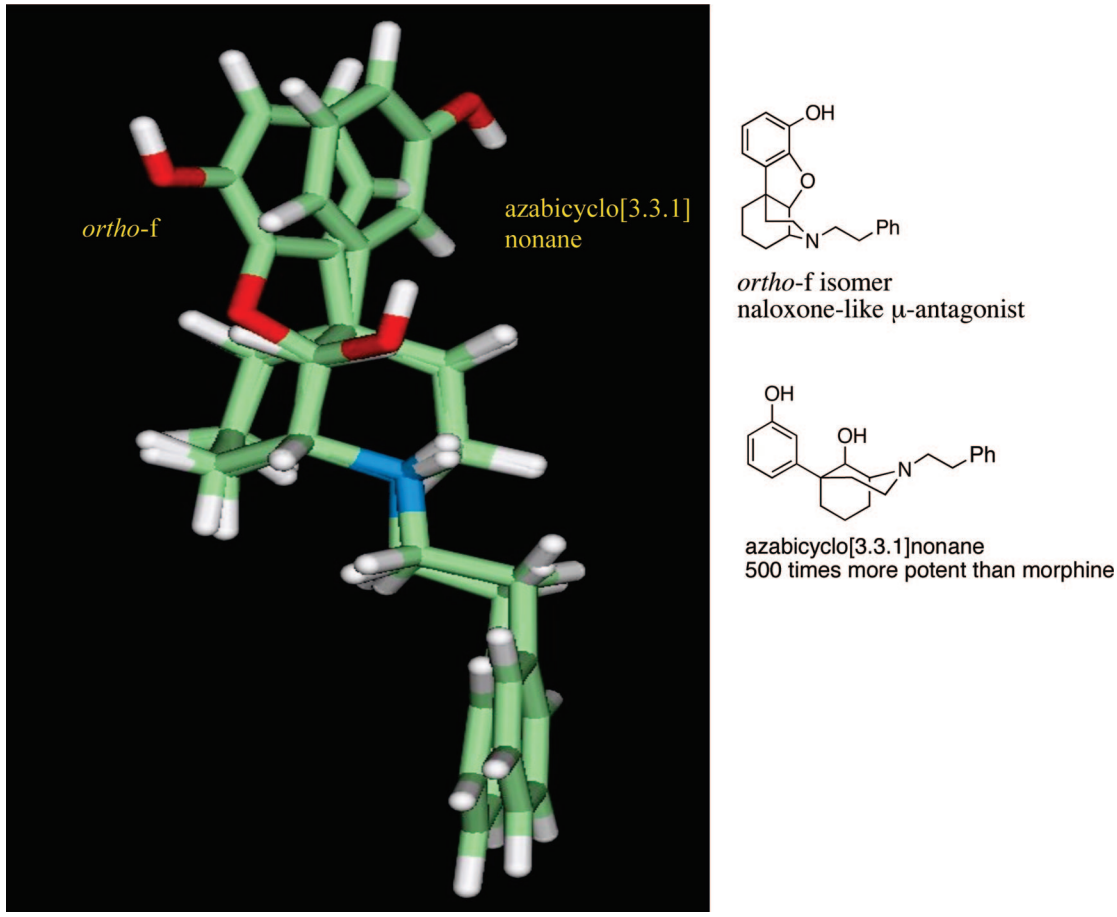



**Figure 4.** Overlay of the energy minimized (1*R*,5*R*,9*S*)-(−)-9-hydroxy-5-(3-hydroxyphenyl-2-phenethyl-2-azabicyclo[3.3.1]nonane[19] and (−)-*N*-phenethyl ortho-f-isomer.[19] Atoms are represented by colors as follows: white, hydrogen; green, carbon; blue, nitrogen; red, oxygen.

NMR ($CDCl_3$/$CD_3OD$, 5:1, free base) $\delta$ 152.07, 151.55, 137.89, 113.99, 110.62, 109.34, 91.17, 54.67, 50.63, 43.08, 42.80, 37.33, 31.34, 27.26, 21.67. Anal. ($C_{15}H_{20}ClNO_2 \cdot 0.1H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-10-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (13).** 1-Chloroethyl chlorformate (0.09 mL, 0.80 mmol) was slowly added to a solution of **10** (0.20 g, 0.73 mmol) in 1,2-dichloroethane (2 mL), and the mixture was refluxed for 15 h. After further addition of 1-chloroethyl chloroformate (52 mg, 0.36 mmol) the reaction mixture was refluxed for 3 h. 1,2-Dichloroethane was removed in vacuo, and the residue was dissolved in MeOH (2 mL). The mixture was refluxed for 2 h. MeOH was removed in vacuo to give crude **13**. It was dissolved in $CH_2Cl_2$ (20 mL) and washed with saturated aqueous $NaHCO_3$ solution, and the separated organic solution was dried over $MgSO_4$. Removal of $CH_2Cl_2$ gave a product that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1 to $CH_2Cl_2$/MeOH/28% $NH_4OH$, 100:10:1) to afford **13** (107 mg, 56%) as a yellow powder that was sufficiently pure for the next step. Starting material **10** was recovered (33 mg, 17%), mp 211−212 °C. HRMS calcd for $C_{14}H_{17}N_2O_3$ $(M + H)^+$, 261.1239; found 261.1239. $^1H$ NMR ($CDCl_3$) $\delta$ 8.15 (dd, $J$ = 2.4, 8.7 Hz, 1H), 8.01 (d, $J$ = 2.7 Hz, 1H), 6.95 (d, $J$ = 8.7 Hz, 1H), 4.27 (dd, $J$ = 5.4, 12.3 Hz, 1H), 3.40−3.66 (m, 2H), 3.04−3.20 (m, 1H), 2.30−2.64 (m, 5H), 1.60−2.10 (m, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 164.81, 142.61, 139.34, 125.67, 118.59, 110.81, 93.48, 47.61, 44.02, 41.97, 38.02, 32.94, 30.97, 27.17. Anal. ($C_{14}H_{16}N_2O_3 \cdot 1.5H_2O$) C, H. N: calcd, 6.53; found, 6.06.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-10-nitro-3-*N*-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (14).** A mixture of **13** (77 mg, 0.30 mmol), $K_2CO_3$ (82 mg, 0.59 mmol), NaI (53 mg, 0.36 mmol), and (2-bromoethyl)benzene (66 mg, 0.36 mmol) in acetonitrile (2 mL) was refluxed for 2 h. $CH_2Cl_2$ (30 mL) was added to the reaction mixture, and the organic solution was washed with $H_2O$. The separated organic solution was dried over $MgSO_4$, and $CH_2Cl_2$ was removed in vacuo. Purification by chromatography (silica gel, hexane/EtOAc, 3:1) afforded **14** (81 mg, 74%), mp 150−151 °C. HRMS calcd for $C_{22}H_{25}N_2O_3$ $(M + H)^+$, 365.1865; found, 365.1859. $^1H$ NMR ($CDCl_3$) $\delta$ 8.36 (dd, $J$ = 2.4, 9.0 Hz. 1H), 8.00 (d, $J$ = 2.4 Hz, 1H), 7.17−7.38 (m, 5H), 6.92 (d, $J$ = 8.7 Hz, 1H), 4.27 (dd, $J$ = 6.6, 12.0 Hz, 1H), 3.08−3.20 (m, 1H), 2.64−3.02 (m, 6H), 2.20−2.60 (m, 4H), 1.40−1.92 (m, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 164.90, 142.61, 140.52, 139.19, 128.88, 128.57, 126.28, 125.62, 118.63, 110.67, 93.53, 58.05, 52.90, 49.01, 43.79, 37.91, 34.80, 32.45, 27.33, 23.06. Anal. ($C_{22}H_{24}N_2O_3 \cdot 0.25H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Amino-2,3,4,5,6,6a-hexahydro-3-*N*-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (15).** To a solution of **14** (75 mg, 0.21 mmol) in EtOH was added 10% Pd−C (30 mg), and the mixture was stirred for 1 h under $H_2$. After filtration to remove the catalyst, EtOH was removed to give **15** (67 mg, 97%) as a white powder, mp 125−126 °C. HRMS calcd for $C_{22}H_{27}N_2O$ $(M + H)^+$, 335.2123; found, 335.2115. $^1H$ NMR ($CDCl_3$) $\delta$ 7.16−7.34 (m, 5H), 6.65−6.70 (m, 1H), 6.43−6.58 (m, 2H), 4.05 (dd, $J$ = 6.6, 12.0 Hz, 1H), 2.60−3.40 (m, 9H), 2.11−2.45 (m, 4H), 1.66−1.91 (m, 3H), 1.38−1.55 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 152.37, 140.76, 140.51, 138.70, 128.92, 128.60, 126.30, 114.47, 110.82, 110.07, 91.43, 58.15, 53.09, 49.40, 43.94, 38.13, 34.71, 31.88, 27.56, 22.93. Anal. ($C_{22}H_{26}N_2O \cdot 0.25H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (16).** A solution of $NaNO_2$ (16 mg, 0.24 mmol) in $H_2O$ (0.30 mL) was added to a solution of **15** (61 mg, 0.18 mmol) in 35% $H_2SO_4$ (0.30 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and urea was then added until a drop of the mixture placed on KI-starch indicator paper no longer gave a purple color. A solution of $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.66 g, 2.8 mmol) in $H_2O$ (8.40 mL) was added

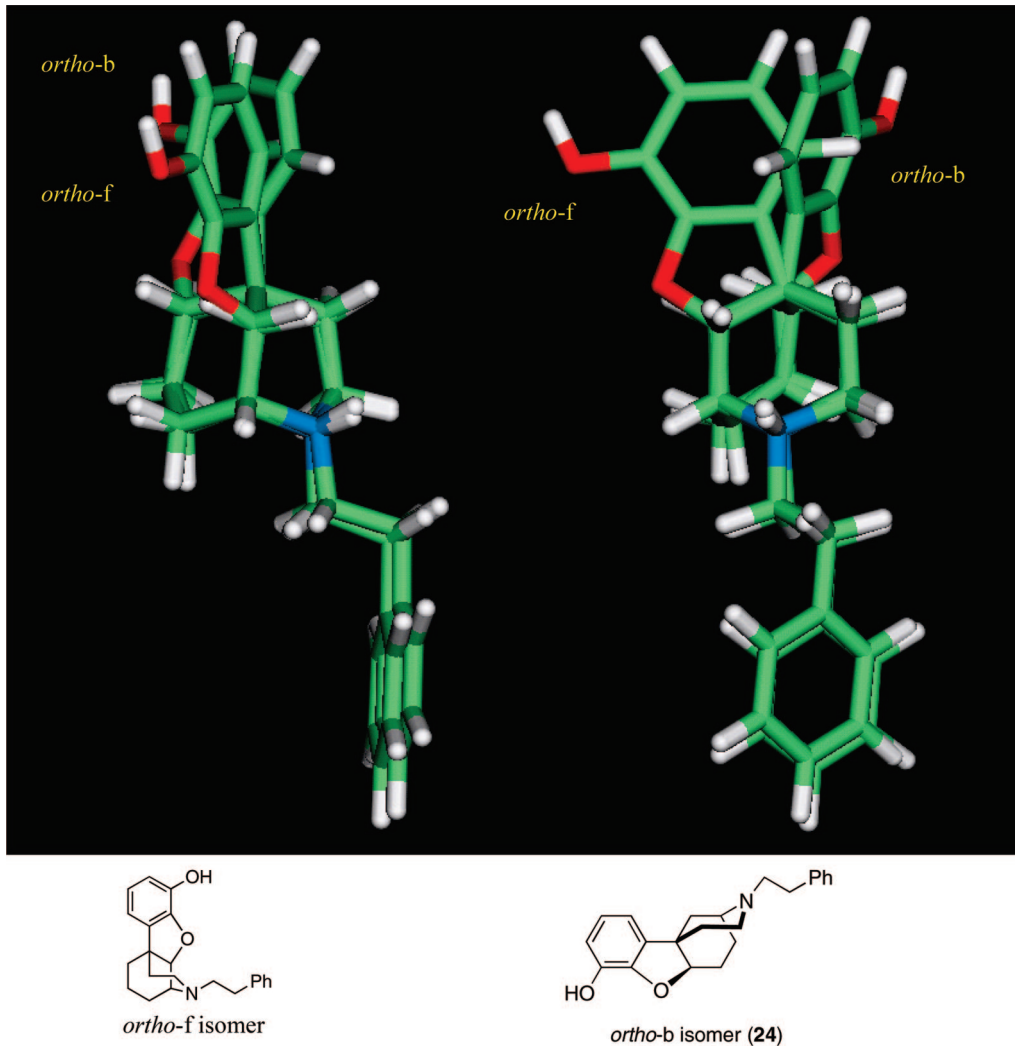



**Figure 5.** Two views of the overlay of the energy minimized ortho-f- and ortho-b-isomers.

to the mixture, followed by $Cu_2O$ (26 mg, 0.18 mmol), and the mixture was vigorously stirred for 30 min at room temperature. The pH of the reaction mixture was adjusted to 11 by addition of 28% $NH_4OH$, and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give crude **16** that was purified by preparative TLC (silica gel, $CH_2Cl_2$/MeOH, 10:1). The free base of **16** was dissolved in MeOH, and a 1.25 M hydrochloric acid solution was added. The MeOH was removed in vacuo to give **14**·HCl (24 mg, 36%) as a light-yellow powder, mp 271−272 °C (dec). HRMS calcd for $C_{22}H_{26}NO_2$ $(M + H)^+$, 336.1964; found, 336.1960. $^1$H NMR ($CDCl_3$, free base) $\delta$ 7.17−7.36 (m, 5H), 6.74 (d, $J$ = 8.4 Hz, 1H), 6.71 (d, $J$ = 2.4 Hz, 1H), 6.62 (dd, $J$ = 2.4, 8.7 Hz, 1H), 4.05−4.18 (m, 1H), 3.13−3.21 (m, 1H), 2.60−3.05 (m, 6H), 2.45−2.58 (m, 1H), 2.30−2.58 (m, 1H), 2.15−2.28 (m, 2H), 1.70−1.94 (m, 3H), 1.40−1.60 (m, 1H). $^{13}$C NMR ($CDCl_3$, free base) $\delta$ 153.02, 151.07, 150.43, 138.58, 128.97, 128.66, 126.37, 115.13, 111.14, 110.17, 91.66, 58.14, 52.76, 49.45, 44.11, 38.07, 34.28, 31.95, 27.59, 22.60. Anal. ($C_{22}H_{26}ClNO_2 \cdot 1.0H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Chloro-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (17).** Compound **11** (0.34 g, 1.40 mmol) was dissolved in concentrated hydrochloric acid (5 mL) and stirred at 0 °C in an ice bath. A solution of $NaNO_2$ (0.11 g, 1.53 mmol) in $H_2O$ (2.5 mL) was added dropwise. The mixture was stirred at 0 °C. Meanwhile a solution of $CuSO_4$ (0.26 g, 1.60 mmol) and NaCl (0.34 g, 5.80 mmol) in $H_2O$ (3.8 mL) was heated to 65 °C. To this solution was added slowly a solution of 1 M NaOH (1.4 mL) and sodium bisulfite (90 mg, 0.46 mmol) in $H_2O$ (1 mL). This mixture was stirred at 65 °C for 15 min. Urea was added to the colored diazonium solution with stirring until a drop of the mixture on KI-starch indicator paper did not show a purple color. This mixture was added to the previously prepared mixture of of $CuSO_4$ with sodium bisulfite, and the new mixture was stirred at 65 °C overnight. The reaction mixture was then basified with 28% $NH_4OH$ and extracted with $CHCl_3$ (3 × 50 mL). Combined $CHCl_3$ layers were dried over $MgSO_4$ and evaporated under reduced pressure to give a light-brown solid that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1 to 30:1) to afford **17** (0.23 g, 63%) as a light-orange powder, mp 131−132 °C. HRMS calcd for $C_{15}H_{19}ClNO$ $(M + H)^+$, 246.1155; found, 264.1158. $^1$H NMR ($CDCl_3$) $\delta$ 7.09 (dd, $J$ = 2.4, 8.7 Hz, 1H), 7.03 (d, $J$ = 2.4 Hz, 1H), 6.79 (d, $J$ = 8.1 Hz, 1H), 4.13 (dd, $J$ = 7.2, 11.4 Hz, 1H), 2.71−2.95 (m, 3H), 2.36−2.48 (m, 5H), 2.16−2.32 (m, 2H), 1.58−1.88 (m, 3H), 1.38−1.54 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 158.06, 139.69, 127.85, 126.05, 122.53, 111.70, 92.18, 54.65, 50.89, 43.72, 43.42, 38.40, 32.25, 27.56, 21.95. Anal. ($C_{15}H_{18}ClNO$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Chloro-2,3,4,5,6,6a-hexahydro-3-methyl-8-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (18).** To a solution of **17** (85 mg, 0.32 mmol) in $CF_3COOH$ (2 mL) was added $NaNO_2$ (45 mg, 0.65 mmol), and the mixture was stirred for 3 h. The reaction mixture was basified with 28% $NH_4OH$ and extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ solution was dried over $MgSO_4$ and evaporated to give a crude product that was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1) to afford **18** (77 mg, 77%) as a light-yellow powder, mp 199−200 °C. HRMS calcd for $C_{15}H_{18}ClN_2O_3$ $(M + H)^+$, 309.1006; found, 309.0962. $^1$H NMR ($CDCl_3$) $\delta$ 7.93 (d, $J$ = 2.1 Hz, 1H), 7.27 (d,

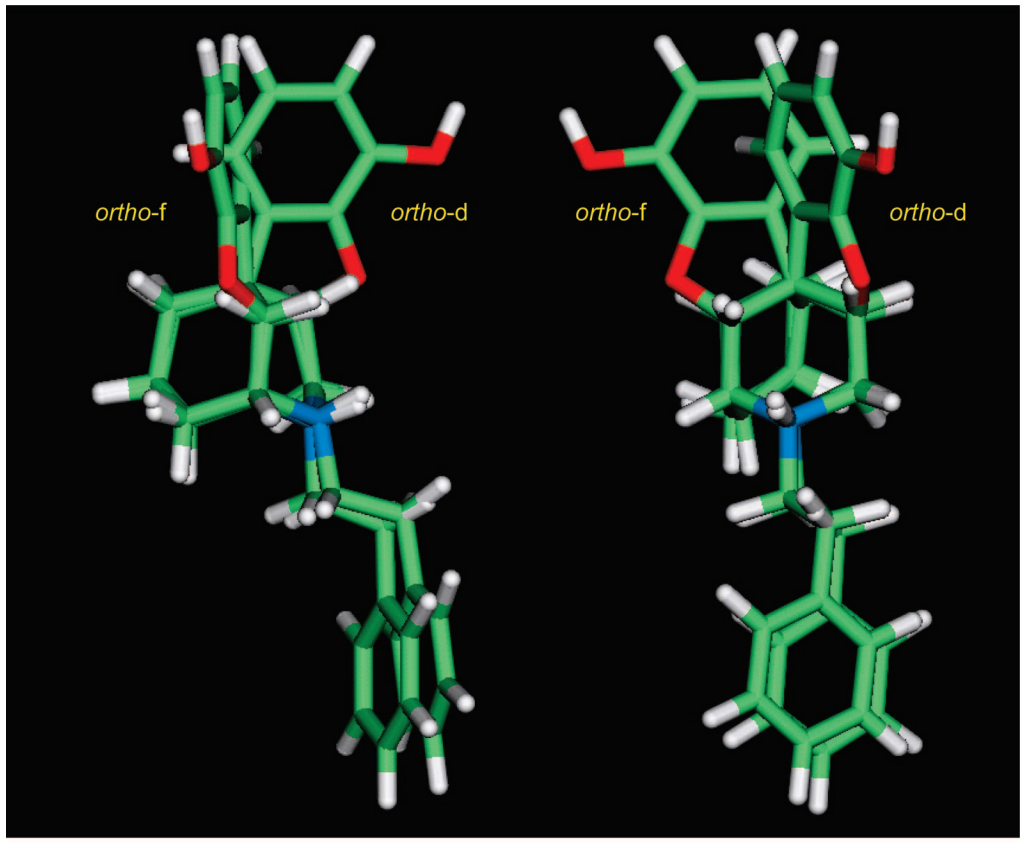



**Figure 6.** Two views of the overlay of the energy minimized ortho-f- and ortho-d-isomers.

$J$ = 2.1 Hz, 1H), 4.28−4.40 (m, 1H), 2.72−3.02 (m, 3H), 2.30−2.55 (m, 7H), 1.60−1.92 (m, 2H), 1.40−1.55 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 153.23, 144.17, 133.57, 128.35, 122.27, 123.40, 94.37, 54.37, 50.63, 43.60, 43.34, 38.25, 32.47, 27.40, 21.85. Anal. ($C_{15}H_{17}ClN_2O_3$) C, H, N.

**(4*R**,6a*S**,11b*R**)-8-Amino-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (19).** A mixture of **16** (67 mg, 0.22 mmol), ammonium formate (68 mg, 1.10 mmol), and 10% Pd−C (30 mg) in EtOH was refluxed for 2.5 h. The Pd−C was removed by filtration, and the solvent was removed in vacuo. The residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2 × 20 mL). The combined organic material was dried over $MgSO_4$, and the solvent was evaporated to give crude **19**. Purification by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1 to 20:1) afforded **19** (48 mg, 79%) as a white powder, mp 152−153 °C. HRMS calcd for $C_{15}H_{21}N_2O$ $(M + H)^+$, 245.1654; found, 245.1670. $^1$H NMR ($CDCl_3$) $\delta$ 6.71−6.78 (m, 1H), 6.54−6.60 (m, 2H), 4.12 (dd, $J$ = 6.6, 11.7 Hz, 1H), 3.59 (br s, 2H), 2.70−2.96 (m, 3H), 2.35−2.50 (m, 5H), 2.15−2.31 (m, 2H), 1.60−1.90 (m, 3H), 1.39−1.55 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 146.77, 137.82, 131.33, 122.02, 115.18, 112.19, 91.88, 54.80, 51.01, 43.70, 43.48, 38.73, 31.95, 27.73, 22.06. Anal. ($C_{15}H_{20}N_2O$) C. H, N.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (20).** A solution of $NaNO_2$ (12 mg, 0.16 mmol) in $H_2O$ (0.1 mL) was added to a solution of **19** (30 mg, 0.12 mmol) in 35% $H_2SO_4$ (0.1 mL) at 0 °C. The mixture was stirred for 1 h, and urea was then added until a drop of the mixture on KI-starch indicator paper no longer showed a purple color. A solution of $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.44 g, 1.9 mmol) in $H_2O$ (4.2 mL) was added, followed by $Cu_2O$ (18 mg, 0.12 mmol), and the mixture was vigorously stirred for 30 min at room temperature. A 28% solution of $NH_4OH$ was added to the mixture to adjust the pH to ∼11, and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a crude mixture that was purified by preparative TLC (silica gel, $CH_2Cl_2$/MeOH, 10:1) to afford **20** as a free base. It was dissolved in MeOH, and 1.25 N HCl in MeOH was added to the solution. The MeOH was removed under reduced pressure to give **20**·HCl (7.8 mg, 23%) as a light-yellow powder that crystallized from isopropanol/$H_2O$, mp 322−324 °C (dec). The structure of **20** was determined by single crystal X-ray analysis. HRMS calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$, 246.1494; found, 246.1501. $^1$H NMR ($CDCl_3$) $\delta$ 6.79 (dd, $J$ = 6.9, 8.0 Hz, 2H), 6.71 (dd, $J$ = 1.5, 8.0 Hz, 1H), 6.65 (dd, $J$ = 1, 7.2 Hz, 1H), 4.15(dd, $J$ = 7.2, 11.6 Hz, 1H), 2.96−3.08 (m, 1H), 2.78−2.94 (m, 2H), 2.15−2.59 (m, 7H), 1.70−1.90 (m, 3H), 1.41−1.61 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 146.38, 141.71, 138.64, 122.28, 115.78, 113.67, 92.16, 54.67, 50.74, 43.67, 43.12, 37.95, 31.61, 27.51, 22.07. Anal. ($C_{15}H_{20}ClNO_2 \cdot 0.5H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Chloro-2,3,4,5,6,6a-hexahydro-8-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (21).** 1-Chloroethylchloroformate (0.08 mL, 0.74 mmol) was slowly added to a solution of **18** (0.19 g, 0.62 mmol) in 1,2-dichloroethane (3 mL), and the mixture was refluxed for 2 h. After further addition of 1-chloroethylchloroformate (0.04 mL, 0.36mmol) the mixture was refluxed overnight. 1,2-Dichloroethane was removed in vacuo, and the residue was dissolved in MeOH (2 mL). The solution was

refluxed for 3 h. Solvent was removed in vacuo, and the residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The organic solution was dried over $MgSO_4$ and the $CH_2Cl_2$ removed in vacuo to give crude **21**. It was purified by chromatography (silica gel, $CH_2Cl_2$/MeOH, 50:1, to $CH_2Cl_2$/MeOH/aqueous $NH_4OH$, 100:10:1) to afford **21** (94 mg, 52%) as a yellow powder, mp 175−176 °C. Some of the starting material (**18**) was recovered (80 mg, 42%). HRMS calcd for $C_{14}H_{16}ClN_2O_3$ $(M + H)^+$, 295.0849; found, 295.0847. $^1$H NMR ($CDCl_3$) $\delta$ 7.93 (d, $J$ = 2.1 Hz, 1H), 7.29 (d, $J$ = 2.1 Hz, 1H), 4.40 (dd, $J$ = 5.7, 12.9 Hz, 1H), 3.30−3.55 (m, 2H), 2.90−3.30 (m, 1H), 2.50−2.70 (m, 1H), 2.12−2.48 (m, 3H), 1.75−2.02 (m, 4H), 1.48−1.65 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 153.13, 144.40, 133.60, 128.32, 126.25, 123.35, 94.42, 47.53, 44.30, 41.78, 37.98, 32.94, 31.20, 27.18. Anal. ($C_{14}H_{15}ClN_2O_3 \cdot 0.25H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-10-Chloro-8-nitro-3-*N*-phenylethyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (22).** A mixture of **21** (84 mg, 0.29 mmol), $K_2CO_3$ (79 mg, 0.57 mmol), NaI (64 mg, 0.36 mmol), and (2-bromoethyl)benzene (79 mg, 0.36 mmol) in $CH_3CN$ (2 mL) was refluxed for 3 h. To the reaction mixture was added $CH_2Cl_2$ (30 mL), and the mixture was washed with $H_2O$. The organic solution was dried over $MgSO_4$, and the $CH_2Cl_2$ was removed in vacuo. Purification by chromatography (silica gel, hexane/EtOAc, 3:1) gave **22** (94 mg, 83%) as a light-yellow powder, mp 165−166 °C. HRMS calcd for $C_{22}H_{24}ClN_2O_3$ $(M + H)^+$, 399.1475; found, 399.1473. $^1$H NMR ($CDCl_3$) $\delta$ 7.94 (d, $J$ = 2.4 Hz, 1H), 7.27−7.34 (m, 3H), 7.18−7.25 (m, 3H), 4.58−4.80 (m, 1H), 3.19−3.28 (m, 1H), 2.67−3.02 (m, 6H), 2.30−2.52 (m, 4H), 1.80−1.96 (m, 2H), 1.40−1.78 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 153.22, 144.23, 140.42, 133.56, 128.87, 128.59, 128.37, 126.32, 126.24, 123.36, 94.43, 57.99, 52.83, 48.93, 44.05, 38.01, 34.77, 32.44, 27.32, 22.93. Anal. ($C_{22}H_{23}ClN_2O_3$) C, H, N.

**(4*R**,6a*S**,11b*R**)-8-Amino-2,3,4,5,6,6a-hexahydro-3-*N*-phenylethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (23).** A mixture of **22** (0.13 g, 0.34 mmol), ammonium formate (0.11 g, 1.7 mmol), and 10% Pd−C (50 mg) in EtOH was refluxed for 3 h. After filtration of Pd−C, EtOH was removed in vacuo. The residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The organic solution was dried over $MgSO_4$, and $CH_2Cl_2$ was removed in vacuo to give a mixture that was purified by chromatography (silica gel, hexane/EtOAc, 3:1 to 1:1) to afford **23** (69 mg, 61%) as a white powder, mp 105−106 °C. HRMS calcd for $C_{22}H_{27}N_2O$ $(M + H)^+$, 335.2123; found, 335.211. $^1$H NMR ($CDCl_3$) $\delta$ 7.26−7.34 (m, 2H), 7.16−7.26 (m, 3H), 4.05−4.20 (m, 1H), 3.25−3.80 (br s, 2H), 3.05−3.15 (m, 1H), 2.62−3.02 (m, 5H), 2.12−2.52 (m, 4H), 1.40−2.00 (m, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$ 146.76, 140.67, 137.86, 128.92, 128.57, 126.25, 122.02, 115.19, 112.21, 91.90, 58.24, 53.08, 49.40, 44.17, 38.43, 34.85, 31.87, 27.62, 23.04. Anal. ($C_{22}H_{26}N_2O \cdot 0.33H_2O$) C, H, N.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (24).** A solution of $NaNO_2$ (16 mg, 0.24 mmol) in $H_2O$ (0.3 mL) was added to a solution of **23** (60 mg, 0.18 mmol) in 35% $H_2SO_4$ (0.3 mL) at 0 °C. The mixture was stirred for 1 h, and urea was then added until a drop of the mixture on KI-starch indicator paper did not show a purple color. A solution of $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.66 g, 2.8 mmol) in $H_2O$ (8.4 mL) was added followed by $Cu_2O$ (26 mg, 0.18 mmol), and the mixture was vigorously stirred for 30 min at room temperature. Then 28% $NH_4OH$ was added to adjust the pH of the reaction mixture to ∼11, and it was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and solvent was removed in vacuo. Purification by preparative TLC (silica gel, hexane/EtOAc, 1:1) gave **24** as a free base. It was dissolved in MeOH, and a 1.25 M hydrochloric acid solution was added to the methanol solution. The mixture was concentrated in vacuo to afford **24** (23 mg, 33%) as a white powder, mp 288−289 °C (dec). HRMS calcd for $C_{22}H_{26}NO_2$ $(M + H)^+$, 336.1964; found, 336.1965. $^1$H NMR ($CDCl_3$) $\delta$ 7.15−7.35 (m, 5H), 6.65−6.85 (m, 3H), 4.16 (d, $J$ = 6.3, 12.0 Hz, 1H), 3.15 (br s, 1H), 2.68−3.16 (m, 6H), 2.13−2.56 (m, 4H), 1.68−1.92 (m, 3H), 1.39−1.58 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 146.22, 141.27, 140.48, 138.86, 128.92, 128.61, 126.32, 122.32, 115.65, 113.93, 92.48, 58.18, 53.03, 49.30, 44.27, 38.06, 34.55, 31.78, 27.53, 22.94. Anal. ($C_{22}H_{26}ClNO_2$) C, H, N.

**1-Benzyl-4-(2,3-dimethoxyphenyl)piperidin-4-ol (28).** A solution of 1,2-dimethoxybenzene (**25**, 36.36 g, 0.25 mol) in anhydrous $Et_2O$ (225 mL) was cooled in an ice bath and stirred under Ar, while a 2.5 M solution of *n*-BuLi (80 mL, 0.20 mol) was added over a period of 30 min. The ice bath was removed, and the solution was stirred at room temperature for 19 h. The resulting white suspension was cooled to 0 °C, and a solution of 1-benzylpiperidin-4-one (**27**, 38.23 g, 0.20 mol) in $Et_2O$ (38 mL) was slowly added over 20 min to give a cloudy yellow solution that was washed with aqueous $NaHCO_3$ and filtered to remove white solid. The organic phase was washed with $H_2O$ and brine, dried over $Na_2SO_4$, and evaporated to give a crude alcohol. Column chromatography of the crude material with EtOAc/hexanes (5:1) gave **28** (40 g, 62%) as a yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 1.91 (d, $J$ = 11.4 Hz, 2H), 2.14 (td, $J$ = 12.6, 4.2 Hz, 2H), 2.59 (t, $J$ = 11.1 Hz, 2H), 2.77 (d, $J$ = 10.8 Hz, 2H), 3.59 (s, 2H), 3.87 (s, 3H), 3.97 (s, 3H), 4.25 (s, 1H), 6.86 (dd, $J$ = 7.8, 1.5 Hz, 1H), 6.92 (dd, $J$ = 7.8, 1.5 Hz, 1H), 7.02 (t, $J$ = 7.8 Hz, 1H), 7.30−7.39 (m, 5H); HRMS calcd for $C_{20}H_{26}NO_3$ $(M + H)^+$, 328.1913; found, 328.1897.

**4-(2,5-Dimethoxyphenyl)-1-benzylpiperidin-4-ol (29).** A solution of 1,4-dimethoxybenzene (104.0 g, 0.75 mol) in 1000 mL of dry $Et_2O$ was cooled in an ice bath and stirred under Ar, while a 2.5 M solution of *n*-BuLi (260 mL, 0.65 mol) was added over a period of 30 min. The ice bath was removed, and the solution was stirred for 24 h. The resulting white suspension was cooled to 0 °C, and a solution of 1-benzyl-4-piperidinone (123.0 g, 0.65 mol) in 100 mL of dry $Et_2O$ was slowly added (20 min). The light-yellow, clear solution was stirred for 45 min. To the mixture was added 200 mL of saturated aqueous $NaHCO_3$, and the mixture was stirred for 20 min and filtered. The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and $H_2O$ (2 × 50 mL). The organic phase was partly evaporated, and 4 N HCl (100 mL) was added. The organic layer was re-extracted with 200 mL of 4 N HCl. The combined aqueous layer was basified with 28% $NH_4OH$ and extracted with $Et_2O$ (3 × 100 mL). The combined organic phase was washed with $H_2O$ (50 mL) and brine, dried over $Na_2SO_4$, and evaporated to give a crude alcohol **29** (200 g).

**1-Benzyl-4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (30).** A mixture of the crude alcohol **28** (40 g, 0.122 mol) and *p*-toluenesulfonic acid monohydrate (30 g, 0.158 mol) in toluene (650 mL) was refluxed for 18 h with a Dean−Stark trap to remove water. After removal of toluene, the residual material was diluted with EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 100 mL). The combined organic phase was washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated to dryness. Column chromatography of the crude material with EtOAc/hexanes (1:5) gave **30** (26 g, 70%) as light-yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 2.54−2.58 (m, 2H), 2.68−2.72 (m, 2H), 3.16−3.19 (m, 2H), 3.66 (s, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 5.79−5.82 (m, 1H), 6.80 (dd, $J$ = 7.8, 1.8 Hz, 1H), 6.82 (dd, $J$ = 8.7, 1.8 Hz, 1H), 6.99 (t, $J$ = 8.1 Hz, 1H), 7.26−7.41 (m, 5H).

**4-(2,5-Dimethoxyphenyl)-1,2,3,6-tetrahydro-1-benzylpyridine (31).** A mixture of the crude alcohol **29** (200 g, 0.61 mol) and *p*-toluenesulfonic acid monohydrate (124 g, 0.65 mol) in toluene (1000 mL) was refluxed for 18 h with a Dean−Stark trap to remove $H_2O$. After removal of toluene, the residual material was diluted with $Et_2O$ (200 mL) and saturated $NaHCO_3$. The aqueous layer was extracted with $Et_2O$ (3 × 200 mL). The combined organic phase was washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated to dryness. Column chromatography of the crude material with EtOAc/hexanes (1:5) gave **31** (144 g, 72% over two steps) as a white solid. $^1$H NMR ($CDCl_3$) $\delta$ 2.54−2.56 (m, 2H), 2.66−2.70 (m, 2H), 3.15−3.18 (m, 2H), 3.65 (s, 2H), 3.77 (s, 6H), 5.79−5.81 (m, 1H), 6.74−6.77 (m, 3H), 7.26−7.41 (m, 5H).

**(*R**)-4-Allyl-1-benzyl-4-(2,3-dimethoxyphenyl)-1,2,3,4-**

**tetrahydropyridine (32).** *sec*-BuLi (1.4 M) in cyclohexane (62 mL, 0.086 mol) was added dropwise to a solution of **30** (26 g, 0.084 mol) in THF (500 mL) at −50 °C, and the mixture was allowed to warm slowly to −20 °C over 1 h. After the mixture was cooled to −50 °C, allyl bromide (7.44 mL, 0.086 mol) was added. The mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched by addition of $H_2O$, diluted with EtOAc, washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to give the crude enamine **32**. Column chromatography of the crude material with EtOAc/hexanes (1:8) gave **32** (20.6 g, 70%) as a yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 1.78−1.86 (m, 1H), 2.33−2.51 (m, 3H), 2.68 (d, $J$ = 12.0 Hz, 1H), 2.84 (dd, $J$ = 12.9, 5.1 Hz, 1H), 3.78 (brs, 6H), 3.90 (brs, 2H), 4.54 (d, $J$ = 7.2 Hz, 1H), 4.82−4.93 (m, 2H), 5.42−5.50 (m, 1H), 6.05 (d, $J$ = 8.4 Hz, 1H), 6.73 (d, $J$ = 7.2 Hz, 1H), 6.83−6.92 (m, 2H), 7.15−7.21 (m, 5H).

**(*R**)-4-Allyl-1-benzyl-4-(2,5-dimethoxyphenyl)-1,2,3,4-tetrahydropyridine (33).** *sec*-BuLi (1.4 M) in cyclohexane (343 mL, 0.48 mol) was added dropwise to a solution of **31** (144 g, 0.466 mol) in THF (1000 mL) at −50 °C, and the mixture was allowed to warm slowly to −20 °C over 4 h. After cooling to −50 °C, allyl bromide (41.0 mL, 0.48 mol) was added, and the mixture was allowed to warm slowly to 0 °C over 4 h and stirred overnight. The reaction was quenched by addition of $H_2O$, diluted with $CH_2Cl_2$, washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to give a crude enamine **33**. Column chromatography of the crude material with EtOAc/hexanes (1:8) gave **33** (112 g, 70%) as a white-yellow solid.

**(1*R**,5*R**)-2-Benzyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo-[3.3.1]non-3-ene (34).** Crude **32** (20.6 g, 0.059 mol) was dissolved in a mixture of 152 mL of 88% HCOOH and 152 mL of 85% $H_3PO_4$ at 0 °C. The mixture was stirred for 4 days at room temperature. Then the reaction mixture was diluted with 400 mL of $H_2O$, cooled in ice, and treated with 40% NaOH solution (to pH ∼8) and extracted with EtOAc (5 × 40 mL). The organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated to give crude enamine **34** as dark-brown oil (20 g).

**(1*R**,5*R**)-2-Benzyl-5-(2,5-dimethoxyphenyl)-2-azabicyclo-[3.3.1]non-3-ene (35).** Crude **33** (52 g, 0.149 mol) was dissolved in a mixture of 300 mL of 88% HCOOH and 300 mL of 85% $H_3PO_4$ at 0 °C. The mixture was stirred for 4 days at room temperature. Then the reaction mixture was diluted with 1000 mL of $H_2O$, cooled in ice, and treated with 40% NaOH solution (to pH ∼8) and extracted with $Et_2O$ (5 × 100 mL). The organic layer washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated to give crude enamine **35** as a dark-brown oil (35 g).

**(1*R**,5*S**)-2-Benzyl-4-bromo-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene (36).** The crude **34** (20 g, 0.058 mol) was dissolved in 200 mL of dry THF and cooled to −78 °C, and *N*-bromoacetamide (8.76 g, 0.063 mol) solution in THF (40 mL) was slowly added. After being stirred for 30 min at −78 °C, the mixture was allowed to warm slowly to room temperature and stirred at room temperature for 20 min. The solvents were evaporated, and the oily residue was partitioned between saturated aqueous $NaHCO_3$ and $CH_2Cl_2$. The organic layer was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Evaporation of solvent gave the crude **36** (21 g).

**(1*R**,5*S**)-2-Benzyl-4-bromo-5-(2,5-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene (37).** The crude **35** (35 g, 0.10 mol) was dissolved in 400 mL of dry THF and cooled to −78 °C, and *N*-bromoacetamide (14.7 g, 0.104 mol) was added in several portions. After being stirred for 30 min at −78 °C, the mixture was allowed to warm slowly to room temperature and stirred at room temperature for 20 min. The solvents were evaporated, and the oily residue was partitioned between aqueous saturated $NaHCO_3$ and $CH_2Cl_2$. The organic layer was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Evaporation of solvent gave the crude **37** (37.5 g).

**(1*R**,4S*,5S*)-2-Benzyl-4-bromo-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonane (38).** Addition of 37% HCl (17.5 mL) to a suspension of crude **36** (21 g, 0.049 mol) in MeOH (250 mL) gave a dark -brown solution to which was added $NaCNBH_3$ (3.74 g, 0.060 mol). The resulting milky mixture was stirred 30 min at room temperature and then diluted with saturated aqueous $NaHCO_3$ (100 mL). After removal of MeOH, the residue was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Evaporation of solvent gave crude oil. Column chromatography of the crude material with EtOAc/hexanes (1:10) gave **38** (5.0 g, 20% over three steps) as a white foam. $^1$H NMR ($CDCl_3$) $\delta$ 1.43−1.55 (m, 1H), 1.81−2.17 (m, 5H), 2.55−2.64 (m, 1H), 2.86 (d, $J$ = 12.9 Hz, 1H), 3.01(brs, 1H), 3.19 (dd, $J$ = 12.0, 7.5 Hz, 1H), 3.44 (t, $J$ = 12.0 Hz, 1H), 3.78 (d, $J$ = 9.6 Hz, 2H), 3.86 (s, 3H), 3.95 (s, 3H), 5.36 (dd, $J$ = 11.1, 6.9 Hz, 1H), 6.88 (dd, $J$ = 6.9, 2.4 Hz, 1H), 6.97−7.05 (m, 2H), 7.23−7.39 (m, 5H); HRMS calcd for $C_{23}H_{29}NO_2Br$ $(M + H)^+$, 430.1382, found 430.1385.

**(1*R**,4S*,5S*)-2-Benzyl-4-bromo-5-(2,5-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonane (39).** Addition of 37% HCl (30 mL) to a suspension of crude **37** (37.5 g, 0.087 mol) in MeOH (600 mL) gave a dark-brown solution to which was added $NaCNBH_3$ (7.0 g, 0.112 mol). The resulting milky mixture was stirred 30 min at room temperature and then diluted with saturated aqueous $NaHCO_3$ (100 mL). After removal of MeOH, the residue was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure afforded a crude oil (37.5 g). Column chromatography of the crude material with EtOAc/hexanes (1:10) gave **14** (9.8 g, 26% over three steps) as a white foam. $^1$H NMR ($CDCl_3$): $\delta$ 1.43−1.51 (m, 1H), 1.70−1.75 (dd, $J$ = 12.3, 1.8 Hz, 1H), 1.84−1.96 (m, 2H), 1.99−2.07 (m, 1H), 2.13−2.19 (m, 1H), 2.54−2.58 (m, 1H), 2.99−3.03 (m, 2H), 3.18 (dd, $J$ = 12.0, 7.2 Hz, 1H), 3.44 (t, $J$ = 12.0 Hz, 1H), 3.73 (d, $J$ = 13.8 Hz, 1H), 3.81 (d, $J$ = 13.2 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 5.52 (dd, $J$ = 12.0, 7.2 Hz, 1H), 6.74 (dd, $J$ = 9.0, 3.0 Hz, 1H), 6.83 (d, $J$ = 9.0 Hz, 1H), 6.94 (d, $J$ = 3.0 Hz, 1H), 7.23−7.39 (m, 5H). EI-MS $m/z$ $[M]^+$ 430.0.

**3-((1*R**,4*S**,5*S**)-2-Benzyl-4-bromo-2-azabicyclo[3.3.1]-nonan-5-yl)benzene-1,2-diol (40).** A solution of compound **38** (10.5 g, 0.024 mol) in $CH_2Cl_2$ (120 mL) was stirred at room temperature while $BBr_3$ (1.0 M) in $CH_2Cl_2$ (78 mL) was slowly added, giving an emulsion. After 1 h the reaction was terminated by cautious addition of MeOH (100 mL). Solvent was evaporated, and a crude dark-colored product obtained.

**2-((1*R**,4*S**,5*S**)-2-Benzyl-4-bromo-2-azabicyclo[3.3.1]-nonan-5-yl)benzene-1,4-diol (41).** A solution of compound **39** (9 g, 0.021 mol) in $CH_2Cl_2$ (120 mL) was stirred at room temperature while $BBr_3$ (1.0 M) in $CH_2Cl_2$ (80 mL) was slowly added, giving an emulsion. After 1 h the reaction was terminated by cautious addition of MeOH (100 mL). Solvent was evaporated, and a crude dark-colored product obtained.

**(3*R**,6a*S**,11a*R**)-2-Benzyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (42).** Potassium *tert*-butoxide (8.4 g, 0.075 mol) was added to a suspension of crude **40** (10 g, 0.024 mol) in dry THF (400 mL). The resulting gray suspension was stirred at room temperature under Ar for 30 min and then acidified with 37% HCl (10 mL), evaporated to an off-white solid, and partitioned between dilute aqueous $NaHCO_3$ and $CH_2Cl_2$. The organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Evaporation of solvent gave crude **42** as a light-yellow foam. Column chromatography of the crude product with EtOAc/hexanes (1:10) gave **42** (3.5 g, 45% over two steps) as a white foam. $^1$H NMR ($CDCl_3$): $\delta$ 1.16−1.26 (m, 1H), 1.47 (dd, $J$ = 13.2, 1.8 Hz, 1H), 1.59 (d, $J$ = 13.5 Hz, 2H), 1.71 (d, $J$ = 11.1 Hz, 1H), 1.83 (td, $J$ = 13.2, 4.8 Hz, 1H), 2.01−2.15 (m, 2H), 2.74 (dd, $J$ = 10.8, 9.6 Hz, 1H), 3.00 (brs, 1H), 3.10 (dd, $J$ = 10.8, 6.9 Hz, 1H), 3.70 (d, $J$ = 13.5 Hz, 1H), 3.78 (d, $J$ = 13.5 Hz, 1H), 4.68 (dd, $J$ = 9.0, 6.9 Hz, 1H), 6.61 (dd, $J$ = 6.6, 1.8 Hz, 1H), 6.69−6.77 (m, 2H), 7.25−7.34 (m, 5H). HRMS calcd for $C_{21}H_{24}NO_2$ $(M + H)^+$, 322.1807; found, 322.1825.

**(3*R**,6a*S**,11a*R**)-2-Benzyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (43).** To a suspension of crude **41** (8.0 g, 0.02 mol) in dry THF (400 mL) was added

potassium *tert*-butoxide (8.0 g, 0.06 mol). The resulting gray suspension was stirred at room temperature under Ar for 30 min and then acidified with 37% HCl (10 mL), evaporated to an off-white solid, and partitioned between dilute aqueous $NH_4OH$ and $CH_2Cl_2$. The organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure gave crude **43** as pale-yellow foam. Column chromatography of the crude product with EtOAc/hexanes (1:10) gave **43** (3.4 g, 50% over two steps) as a light-yellow foam. $^1$H NMR ($CDCl_3$): $\delta$ 1.16−1.23 (m, 1H), 1.40−1.44 (m, 1H), 1.56−1.62 (m, 2H), 1.73−1.83 (m, 2H), 2.01−2.14 (m, 2H), 2.71 (dd, $J$ = 10.5, 9.6 Hz, 1H), 2.98 (brs, 1H), 3.07 (dd, $J$ = 11.1, 6.9 Hz, 1H), 3.69 (d, $J$ = 13.5 Hz, 1H), 3.76 (d, $J$ = 13.5 Hz, 1H), 4.37 (brs, 1H), 4.61 (dd, $J$ = 9.0, 6.6 Hz, 1H), 6.53−6.55 (m, 3H), 7.31−7.33 (m, 5H).

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (44).** A mixture of **42** (850 mg, 2.63 mmol), 10% Pd−C (151 mg), and HOAc (15 drops) in MeOH (50 mL) was heated at 60 °C for 4 h in a hydrogen atmosphere. After cooling to room temperature, the mixture was basified with 28% $NH_4OH$ (pH ∼9), filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of the crude product with $CH_2Cl_2$/MeOH/28% $NH_4OH$ (90:10:1) gave **44** (600 mg, 98%) as light-yellow solid. $^1$H NMR ($CDCl_3$): $\delta$ 1.53 (d, $J$ = 13.2 Hz, 2H), 1.64−1.78 (m, 3H), 1.80−1.90 (m, 2H), 2.05 (d, $J$ = 13.2 Hz, 1H), 3.03 (dd, $J$ = 13.2, 9.0 Hz, 1H), 3.37 (dd, $J$ = 13.2, 6.6 Hz, 1H), 3.46 (brs, 1H), 3.93 (brs, 2H), 4.59 (dd, $J$ = 9.0, 6.6 Hz, 1H), 6.60 (dd, $J$ = 7.2, 1.5 Hz, 1H), 6.69−6.79 (m, 2H).

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (45).** A mixture of **43** (0.510 g, 1.58 mmol), 10% Pd−C (90 mg), and HOAc (12 drops) in MeOH (40 mL) was heated at 60 °C for 4 h in a hydrogen atmosphere. After cooling to room temperature, the mixture was basified with $NH_4OH$ (pH ∼9), filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of the crude product with $CH_2Cl_2$/MeOH/28% $NH_4OH$ (91:9:1) gave **45** (0.320 g, 87%) as white solid. $^1$H NMR ($CD_3OD$): $\delta$ 1.54−1.59 (m, 2H), 1.64−1.71 (m, 4H), 1.89−2.01 (m, 4H), 2.87 (dd, $J$ = 13.5, 9.0 Hz, 1H), 3.23 (dd, $J$ = 13.5, 6.6 Hz, 1H), 4.51 (dd, $J$ = 9.0, 6.6 Hz, 1H), 6.51−6.55 (m, 3H).

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (46).** A mixture of **44** (200 mg, 0.86 mmol), Escat 103 ((5% Pd/C + 50% $H_2O$), 80 mg), and 37% formaldehyde (80 $\mu$L, 1.07 mmol) in MeOH (10 mL) was stirred at room temperature for 4 h in a hydrogen atmosphere. The reaction was stopped and the mixture was filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of the crude material with $CH_2Cl_2$/MeOH/28% $NH_4OH$ (95:5:1) gave **46** (180 mg, 85%) as a white solid. Crude **46** (300 mg) was dissolved in 5 mL of MeOH, and 3 mL of methanolic HCl was added. The precipitate was dissolved by heating. Upon cooling to room temperature and scratching, **46**·HCl crystallized (260 mg, 87%) as a white salt. $^1$H NMR ($CD_3OD$, free base) $\delta$ 1.80−1.94 (m, 5H), 1.98−2.08 (m, 1H), 2.12−2.26 (m, 2H), 2.97 (s, 3H), 3.58 (brs, 1H), 3.64−3.74 (m, 1H), 3.74−3.86 (m, 1H), 4.57 (brs, 1H), 6.67−6.72 (m, 2H), 6.77−6.82 (m, 1H). HRMS calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$, 246.1494, found 246.1494. Anal. ($C_{15}H_{19}NO_2$·HCl·0.75$H_2O$) C, H, N.

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (47).** A mixture of **45** (0.314 g, 1.36 mmol), Escat 103 ((5% Pd−C + 50% $H_2O$), 126 mg), and 37% HCHO (111 $\mu$L, 1.496 mmol) in MeOH (10 mL) was stirred at room temperature for 4 h in a hydrogen atmosphere. The mixture was filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of the crude material with $CH_2Cl_2$/MeOH/28% $NH_4OH$ (95:5:1) gave **47** (0.312 g, 94%) as a light-brown foam. Crude **47** was dissolved in 5 mL of EtOH, and 3 mL of ethanolic HCl was added. The precipitate was dissolved by heating. Upon cooling to room temperature and scratching, **47**·HCl crystallized (0.203 g, 65%) as a white salt. $^1$H NMR ($CDCl_3$, free base) $\delta$ 1.22−1.31 (m, 1H), 1.42 (dd, $J$ = 13.2, 2.1 Hz, 1H), 1.59−1.64 (m, 1H), 1.69−1.92 (m, 4H), 2.01−2.06 (m, 1H), 2.44 (s, 3H), 2.77 (brs, 1H), 2.84 (dd, $J$ = 11.7, 8.1 Hz, 1H), 3.07 (dd, $J$ = 11.4, 6.3 Hz, 1H), 4.60 (t, $J$ = 7.2 Hz, 1H), 6.54−6.58 (m, 3H). Anal. ($C_{15}H_{19}NO_2$·HCl·0.75$H_2O$) C, H, N.

**(3*R**,6a*S**,11a*R**)-2-Benzyl-10-cyclopropylmethoxy-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin (48).** Potassium *tert*-butoxide (142 mg, 1.268 mmol) in dry DMF (4.0 mL) was added to a solution of **42** (340 mg, 1.058 mmol) in dry THF (5.0 mL) over a period of 10 min at 0 °C, and the mixture was stirred at 0 °C for 20 min. (Bromomethyl)cyclopropane (1.5 mL, 1.5 mmol) in dry THF was added, and the mixture was stirred at room temperature for 20 min and heated at 50 °C for 3 h. After filtration and removal of DMF, the residue was extracted with $CH_2Cl_2$. The organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. After evaporation of solvent, column chromatography of the crude product with EtOAc/hexanes (1:12) gave **48** (330 mg, 83%) of a yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 0.29−0.34 (m, 2H), 0.56−0.63 (m, 2H), 1.13−1.33 (m, 2H), 1.45 (dd, $J$ = 12.9, 1.8 Hz, 1H), 1.54−1.57 (m, 2H), 1.67−1.72 (m, 1H), 1.83 (td, $J$ = 12.9, 4.5 Hz, 1H), 2.02−2.15 (m, 2H), 2.75 (dd, $J$ = 11.1, 9.6 Hz, 1H), 2.98 (brs, 1H), 3.15 (dd, $J$ = 10.8, 6.9 Hz, 1H), 3.77 (d, $J$ = 13.5 Hz, 1H), 3.70 (d, $J$ = 13.5 Hz, 1H), 3.83 (d, $J$ = 7.2 Hz, 2H), 4.70 (dd, $J$ = 9.6, 6.9 Hz, 1H), 6.64−6.79 (m, 3H), 7.23−7.32 (m, 5H).

**3(*R**,6a*S**,11a*R**)-10-Cyclopropylmethoxyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin (49).** A mixture of **48** (230 mg, 0.612 mmol), 10% Pd−C (34 mg), and HOAc (4 drops) in MeOH (10 mL) was heated at 60 °C for 4 h in a hydrogen atmosphere. After cooling to room temperature, it was basified with 28% $NH_4OH$ (pH ∼9), filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of the crude product with $CH_2Cl_2$/MeOH/28% $NH_4OH$ (95:5:0.4) gave **49** (160 mg, 92%) as a yellow solid. $^1$H NMR ($CDCl_3$): $\delta$ 0.33−0.36 (m, 2H), 0.59−0.65 (m, 2H), 1.26−1.34 (m, 1H), 1.45−1.67 (m, 5H), 1.72−1.96 (m, 3H), 2.06−2.14 (m, 1H), 3.04 (dd, $J$ = 13.2, 9.6 Hz, 1H), 3.37 (dd, $J$ = 13.2, 6.6 Hz, 1H), 3.44 (brs, 1H), 3.86 (d, $J$ = 7.2 Hz, 2H), 4.64 (dd, $J$ = 9.6, 6.9 Hz, 1H), 6.65−6.82 (m, 3H).

**(3*R**,6a*S**,11a*R**)-10-Cyclopropylmethoxyl-1,3,4,5,6,11a-hexahydro-2-phenethyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin (50).** A mixture of **49** (160 mg, 0.56 mmol), phenethyl tosylate (310 mg, 2.0 equiv), and $K_2CO_3$ (155 mg, 3.0 equiv) in dry DMF (5.0 mL, ∼0.15 M) was heated at 60 °C for 4 h. After the cooled mixture was filtered and the solvent evaporated, the residue was diluted with EtOAc, washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated to give a crude product. Column chromatography of the crude product with EtOAc/hexanes (1:12) gave **50** (109 mg, 50%) as a yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.33−0.36 (m, 2H), 0.59−0.65 (m, 2H), 1.23−1.35 (m, 2H), 1.45−1.87 (m, 7H), 2.09−2.14 (m, 1H), 2.79−2.94 (m, 5H), 3.25 (dd, $J$ = 10.8, 6.9 Hz, 1H), 3.86 (dd, $J$ = 6.9, 0.9 Hz, 2H), 4.75 (dd, $J$ = 9.6, 6.9 Hz, 1H), 6.64−6.81 (m, 3H), 7.19−7.30 (m, 5H).

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-phenethyl-2*H*-3,6a-methanobenzofuro [2,3-*c*]azocin-10-ol (51).** Compound **50** (109 mg, 0.28 mmol) was dissolved in 37% HCl/MeOH (5 mL/5 mL, 0.03 M), and the solution was refluxed for 2 h under Ar. After cooling to room temperature, it was basified with 28% $NH_4OH$ (to pH ∼10) and extracted with EtOAc. The organic phase was washed with $H_2O$ and brine and dried over $Na_2SO_4$. Evaporation of solvent gave a crude product. Column chromatography of the crude material with EtOAc/hexanes (1:6) gave **51** (65 mg, 69%) as a yellow foam.

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-phenethyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (52).** A mixture of **45** (600 mg, 2.63 mmol), $NaHCO_3$ (660 mg, 7.8 mmol), and phenethyl tosylate (780 mg, 2.82 mmol) in DMF (12 mL) was heated at 80−90 °C for 4 h under Ar. After cooling to room temperature, it was diluted with $CH_2Cl_2$ (20 mL), washed with $H_2O$ and brine, and dried over $Na_2SO_4$. Evaporation of solvent gave a

crude product. Column chromatography of the crude material with EtOAc/hexanes (1:6) gave **52** (630 mg, 72%) as a white solid. Crude **52** was dissolved in 5 mL of EtOH, and 3 mL of ethanolic HCl was added. More EtOH (5 mL) was added, and the precipitate was dissolved by heating. Upon cooling to room temperature and scratching, **52**·HCl crystallized (570 mg, 90%) as a white salt, mp 250−251 °C. $^1$H NMR ($CDCl_3$, free base) $\delta$ 1.23−1.28 (m, 2H), 1.49 (dd, $J$ = 13.2, 1.8 Hz, 1H), 1.54−1.90 (m, 5H), 2.08−2.14 (m, 1H), 2.79−2.94 (m, 5H), 2.97 (brs, 1H), 3.19 (dd, $J$ = 10.8, 6.6 Hz, 1H), 4.72 (dd, $J$ = 9.3, 6.6 Hz, 1H), 6.61 (dd, $J$ = 6.3, 2.1 Hz, 1H), 6.71−6.78 (m, 2H), 7.19−7.31 (m, 5H). $^{13}$C NMR ($CDCl_3$, free base) $\delta$ 18.14, 30.34, 33.93, 34.85, 35.77, 44.14, 49.77, 52.84, 58.88, 87.29, 114.56, 114.99, 121.34, 125.96, 128.33, 128.71, 136.11, 140.19, 149.39, 145.52. HRMS calcd for $C_{22}H_{26}NO_2$ ($M + H)^+$, 336.1964; found, 336.1974. Anal. ($C_{22}H_{25}NO_2$·HCl·0.25$H_2O$) C, H, N. Anal. ($C_{22}H_{25}NO_2$·0.75$H_2O$) C, H, N.

**Binding and Efficacy Assays.** The methodology used has been previously discussed.[19,20]

**X-ray Crystal Structure of (4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (12), (4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (20), (3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-c]azocin-8-ol (47), and (3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-hexahydro-2-phenethyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (51).** Single-crystal X-ray diffraction data of compounds **12**, **20**, **47**, and **51** were collected using Mo Kα radiation and a Bruker APEX 2 CCD area detector. The structures was solved by direct methods and refined by full-matrix least-squares on $F^2$ values using the programs found in the SHELXTL suite (Bruker, SHELXTL, version 6.10, 2000, Bruker AXS, Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model (coordinate shifts of C applied to H atoms) with C−H distance set at 0.96 Å.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (12).** A 0.49 × 0.34 × 0.05 mm$^3$ crystal of **12** was prepared for data collection, coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (103 K) on the diffractometer. The crystal was monoclinic in space group $P2_1/c$ with unit cell dimensions $a$ = 11.7456(9) Å, $b$ = 10.3351(6) Å, $c$ = 11.5850(9) Å, and $\beta$ = 107.823(4)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 98.9% complete to 29.58° $\theta$ (approximately 0.72 Å) with an average redundancy of 3.5.

**(4*R**,6a*S**,11b*R**)-2,3,4,5,6,6a-Hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (20).** A 0.24 × 0.24 × 0.06 mm$^3$ crystal of **20** was prepared for data collection, coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (103 K) on the diffractometer. The crystal was monoclinic in space group $P2_1/c$ with unit cell dimensions $a$ = 11.8590(15) Å, $b$ = 10.2338(13) Å, $c$ = 11.9158(15) Å, and $\beta$ = 111.168(2)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 100% complete to 28.34° $\theta$ (approximately 0.75 Å) with an average redundancy of 4.0.

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (47).** A 0.62 × 0.28 × 0.19 mm$^3$ crystal of **47** was prepared for data collection, coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (103 K) on the diffractometer. The crystal was triclinic in space group $P\bar{1}$ with unit cell dimensions $a$ = 6.9290(9) Å, $b$ = 11.9176(15) Å, $c$ = 12.103(2) Å, α = 118.820(3)°, $\beta$ = 102.080(4)°, and $\gamma$ = 95.427(3)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 97.1% complete to 29.57° $\theta$ (approximately 0.72 Å) with an average redundancy of 1.97.

**(3*R**,6a*S**,11a*R**)-1,3,4,5,6,11a-Hexahydro-2-phenethyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (51).** A 0.84 × 0.54 × 0.30 mm$^3$ crystal of **51** was mounted on a glass rod and transferred to the diffractometer and data collected at room temperature (298 K). The crystal was triclinic in space group $P\bar{1}$ with unit cell dimensions $a$ = 7.3609(6) Å, $b$ = 11.5732(12) Å, $c$ = 13.7532(13) Å, α = 75.948(4)°, $\beta$ = 88.850(4)°, and $\gamma$ = 74.693(4)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 96.2% complete to 29.56° $\theta$ (approximately 0.72 Å) with an average redundancy of 1.95.

**Quantum Chemical Method and Superposition.** Geometry optimization for the ortho-b-, ortho-d-, and ortho-f-compounds (Figures 4−6) was done in the gaseous phase with the density functional theory at the level of B3LYP/6-31G*.[21] These optimized structures were overlaid onto a previously described high affinity $\mu$-ligand (1*R*,5*R*,9*S*)-(−)-9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane[19] using the rigid fit of Quanta 2008 (Accelrys). The C1−C9 atoms of the morphan moiety of (1*R*,5*R*,9*S*)-(−)-9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane[19] were used a common docking point.

**Acknowledgment.** The research of the Drug Design and Synthesis Section, CBRB, NIDA and NIAAA, was supported by the NIH Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Drug Abuse (NIDA), and the National Institute of Alcohol Abuse and Alcoholism, and NIDA supported the research of the Clinical Psychopharmacology Section. We thank Dr. John Lloyd (NIDDK) for the mass spectral data, and we thank NIDA for support of the X-ray crystallographic studies (NIDA Contract Y1-DA6002). The quantum chemical study utilized PC/LINUX clusters at the Center for Molecular Modeling of the NIH (http://cit.nih.gov) and this research was supported by the NIH Intramural Research Program through the Center for Information Technology.

**Supporting Information Available:** Elemental analysis results and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org. Atomic coordinates for compounds **12**, **20**, **47**, and **51** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 683056, 683057, 683054, and 683055, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. [fax +44(0)-1223-336033 or e-mail deposit@ccdc.cam.ac.uk.

## References

(1) Zezula, J.; Singer, L. B.; Przybyl, A. K.; Hashimoto, A.; Dersch, C. M.; Rothman, R. B.; Deschamps, J.; Lee, Y. S.; Jacobson, A. E.; Rice, K. C. Synthesis and pharmacological effects of the enantiomers of the *N*-phenethyl analogues of the ortho and para e- and f-oxide-bridged phenylmorphans. *Org. Biomol. Chem.* **2008**, *6*, 2868−2883.

(2) Cherezov, V.; Rosenbaum, D. M.; Hanson, M. A.; Rasmussen, S. G. F.; Thian, F. S.; Kobilka, T. S.; Choi, H.-J.; Kuhn, P.; Weis, W. I.; Kobilka, B. K.; Stevens, R. C. High-resolution crystal structure of an engineered human 2-adrenergic G protein coupled receptor. *Science* **2007**, *318*, 1258–1265.

(3) Rosenbaum, D. M.; Cherezov, V.; Hanson, M. A.; Rasmussen, S. G. F.; Thian, F. S.; Kobilka, T. S.; Choi, H.-J.; Yao, X.-J.; Weis, W. I.; Stevens, R. C.; Kobilka, B. K. GPCR engineering yields high-resolution structural insights into 2-adrenergic receptor function. *Science* **2007**, *318*, 1266–1273.

(4) Ranganathan, R. Signaling across the cell membrane. *Science* **2007**, *318*, 1253–1254.

(5) Park, P. S.-H.; Palczewski, K. Diversifying the repertoire of G protein-coupled receptors through oligomerization. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8793–8794.

(6) Prinster, S. C.; Hague, C.; Hall, R. A. Heterodimerization of G protein-coupled receptors: specificity and functional significance. *Pharmacol. Rev.* **2005**, *57*, 289–298.

(7) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Silverton, J. V. Probes for Narcotic Receptor Mediated Phenomena. 3. Oxide Bridged 5-Phenylmorphans. In *Problems of Drug Dependence*

*1983*; Harris, L. S., Ed.; National Institute on Drug Abuse Research Monograph 49; DHHS ((ADM) 84-1316): Washington, DC, 1984; Vol. 49, pp 109−113.

(8) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. Probes for narcotic receptor mediated phenomena. 4. Synthesis of (±)-2,3,4,5,6,6a-hexahydro-3-methyl-8-hydroxy-1*H*-4,11b-methanobenzofuro[2,3-*d*]azocine, an oxide-bridged 5-(*m*-hydroxyphenyl)morphan. *J. Org. Chem.* **1984**, *49*, 1051–1056.

(9) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. Probes for narcotic receptor mediated phenomena. 6. Synthesis of (±)-(1α,4aα,9a*β*)-1,3,4,9a-tetrahydro-2-methyl-2*H*-1,4-propanobenzofuro[2,3-*c*]pyridin-8-ol, an oxide-bridged 5-(3-hydroxyphenyl)morphan. *J. Org. Chem.* **1984**, *49*, 2508–2510.

(10) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Huang, H. C.; Silverton, J. V. Probes for narcotic receptor mediated phenomena. 9. Synthesis of (±)-(3α,6aα,11a*β*)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol, an oxide-bridged 5-(*m*-hydroxyphenyl)morphan. *J. Med. Chem.* **1986**, *29*, 748–751.

(11) Yamada, K.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor mediated phenomena; 29: synthesis of *rac*-(4*R*,6a*R*,11b*R*)-3-methyl 2,3,4,5,6,6a hexahydro-1*H* 4,11b-methanobenzofuro[3,2-*d*]azocin-10-ol, the para-a oxide-bridged phenylmorphan isomer, and a new route to *rac*-(4*R*,6a*R*,11b*R*)-3-methyl-2,3,4,5,6,6a-hexahydro-1*H*-4 11b-methanobenzofuro[3,2-*d*]azocin-8-ol, the ortho-a oxide-bridged phenylmorphan isomer. *Synthesis* **2002**, 2359–2364.

(12) Linders, J. T. M.; Mirsadeghi, S.; Flippen-Anderson, J. L.; George, C.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor mediated phenomena. Part 30. Synthesis of *rac*-(3*R*,6a*S*,11a*R*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol, an epoxy isomer of 5-phenylmorphan. *Helv. Chim. Acta* **2003**, *86*, 484–493.

(13) Kodato, S.; Linders, J. T. M.; Gu, X.-H.; Yamada, K.; Flippen-Anderson, J. L.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. Synthesis of *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2.3-*c*]pyridin-6-ol. An unusual double rearrangement leading to the ortho- and para-f oxide-bridged phenylmorphan isomers. *Org. Biomol. Chem.* **2004**, *2*, 330–336.

(14) Tadic, D.; Linders, J. T. M.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor mediated phenomena. Part 31: Synthesis of rac-(3*R*,6a*S*,11a*S*-2-methyl-1,3,4,5,6,11a-hexahydro 2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol, and azocine-8-ol, the ortho-c and the para-c oxide-bridged phenylmorphan isomers. *Tetrahedron* **2003**, *59*, 4603–4614.

(15) Hashimoto, A.; Przybyl, A. K.; Linders, J. T. M.; Kodato, S.; Tian, X. R.; Deschamps, J. R.; George, C.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor-mediated phenomena. 33. Construction of a strained trans-5,6-ring system by displacement of a nitro-activated aromatic fluorine. Synthesis of the penultimate oxide-bridged phenylmorphans. *J. Org. Chem.* **2004**, *69*, 5322–5327.

(16) Zezula, J.; Jacobson, A. E.; Rice, K. C A novel divergent synthesis of ortho-hydroxy-e and -f oxide-bridged 5-phenylmorphans. *Heterocycles* **2007**, *71*, 881–889.

(17) Mague, S. D.; Pliakas, A. M.; Todtenkopf, M. S.; Tomasiewicz, H. C.; Zhang, Y.; Stevens, W. C. J.; Jones, R. M.; Portoghese, P. S.; Carlezon, W. A. J. Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 323–330.

(18) Reindl, J. D.; Rowan, K.; Carey, A. N.; Peng, X.; Neumeyer, J. L.; McLaughlin, J. P. Antidepressant-like effects of the novel kappa opioid antagonist MCL-144B in the forced-swim test. *Pharmacology* **2008**, *81*, 229–235.

(19) Hiebel, A. C.; Lee, Y. S.; Bilsky, E. J.; Giuvelis, D.; Deschamps, J. R.; Parrish, D. A.; Aceto, M. D.; May, E. L.; Harris, E. M.; Coop, A.; Dersch, C. M.; Partilla, J. S.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor mediated phenomena. 34. Synthesis and structure−activity relationships of a potent *μ*-agonist *δ*-antagonist and an exceedingly potent antinociceptive in the enantiomeric C9-substituted 5-(3-hydroxyphenyl)-*N*-phenylethylmorphan series. *J. Med. Chem.* **2007**, *50*, 3765–3776.

(20) Cheng, K.; Kim, I. J.; Lee, M. J.; Adah, S. A.; Raymond, T. J.; Bilsky, E. J.; Aceto, M. D.; May, E. L.; Harris, L. S.; Coop, A.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Opioid ligands with mixed properties from substituted enantiomeric *N*-phenethyl-5-phenylmorphans. Synthesis of a *μ*-agonist *δ*-antagonist and *δ*-inverse agonists. *Org. Biomol. Chem.* **2007**, *5*, 1177–1190.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.

JM800913D