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Probes for Narcotic Receptor-Mediated Phenomena. 33.[1] Construction of a Strained *trans*-5,6-Ring System by Displacement of a Nitro-Activated Aromatic Fluorine. Synthesis of the Penultimate Oxide-Bridged Phenylmorphans

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Received March 24, 2004

The synthesis of the *ortho*- and *para*-e isomers in the oxide-bridged 5-phenylmorphan series of rigid tetracyclic compounds was accomplished via *rac*-5-(2-fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9β-ol (**(±)-10**), an intermediate containing an aromatic nitro-activated fluorine atom. The fluorine atom was used as the leaving group for the formation of the strained tetracyclic *trans*-fused 5,6-ring system in *rac*-(1α,4aα,9aα)-1,3,4,9a-tetrahydro-2-methyl-6-nitro-2*H*-1,4a-propanobenzofuro[2,3-c]pyridine (**(±)-11**), although preference for cis ring fusion during the formation of tricyclic tetra- and hexahydrodibenzofurans has been well-documented. Single-crystal X-ray crystallographic study of the desired *para*-e isomer (**(±)-2**), as well as of two intermediates in its synthesis, provided assurance of the correct structures. The e-isomers are among the last of the 12 oxide-bridged 5-phenylmorphans to be synthesized. We envisioned the syntheses of these rigid, tetracyclic compounds in order to determine the three-dimensional pattern of a ligand that would enable interaction with opioid receptors as agonists or antagonists.

Introduction

Methods that were previously used[1−6] to prepare oxide-bridged 5-phenylmorphans were unsuccessful when used to synthesize the racemic (1*R*,4a*R*,9a*S*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol (**1**) and (1*R*,4a*R*,9a*S*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol (**2**), the e-isomers in this rigid series of phenylmorphans (Figure 1). These *o*- and *p*-e oxide-bridged phenylmorphans contain a *trans*-fused 5,6-membered ring that is sterically strained and has proved difficult to synthesize. Although we have prepared the c-isomers that also have that ring-strained *trans*-fused 5,6-structure, the procedure used for their synthesis did not succeed with the e-isomers[2] possibly because the 5,6-structure in the c-isomers involves the piperidine ring, and that ring may have more flexibility. Thus, we anticipated that the major challenges for the synthesis of the rigid *trans* tetracyclic system would lie in deciding when to close the central furan ring, and how it could be achieved, since it has been well demonstrated that there is preference for *cis* ring fusion during the formation of tricyclic tetra- and hexahydrodibenzofurans. A number of synthetic approaches involving furan ring closure between the two six-membered rings to give tricyclic structures have afforded exclusively *cis* isomers.[7−11] Further, the same trend was also followed when the tetrahydrodibenzofuran was

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Published on Web 07/02/2004

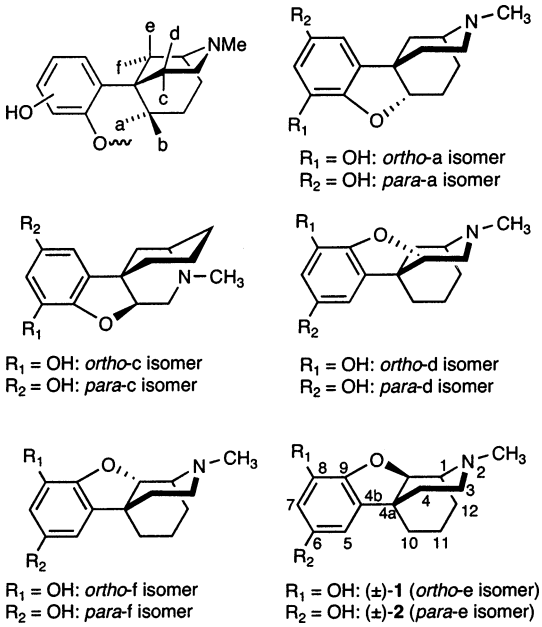

FIGURE 1. Oxide-bridged phenylmorphans.

subjected to a variety of reduction reagents.[12] The only unique route that led to the benzodihydrofuran skeleton possessing the *trans* stereochemical relationship was the photolysis of a vinyl aryl ether[13−15] in aprotic solvents (benzene, toluene, hexane, etc.), although these conditions normally furnished a mixture of products. However, exclusive formation of *trans*-dihydrofurans was observed with certain fused-ring aryloxyenones.[15,16] Further, irradiation of the same type of substrates in protic solvents produced exclusively the less strained *cis* isomer in excellent yields.[15,17,18] This heteroatom-directed photoarylation protocol was unsuccessfully attempted for the synthesis of the *cis* tetracyclic b-isomer of the oxide-bridged 5-phenylmorphan in our laboratory.[5,6] In addition to the photochemical approach, the only other reported synthetic pathway[12] to the simple *trans* tricyclic hexahydrodibenzofurans involved constructing the furan ring prior to six-membered ring formation so as to establish the desired trans geometry at the 5,6-ring junction. However, extension of this route to the synthesis of our target molecules would require incorporation of suitable functionality at C_{4a} and C_1 to build the piperidine ring, which might prove extremely challenging in terms of both stereochemical control and compatibility of functionality.

The successful path to the e-isomers was found through an intermediate containing an aromatic nitro-activated fluorine atom as a leaving group. The envisioned procedure then necessitated subsequent formation of the correct phenolic moiety.

Each of the a−f oxide-bridged phenylmorphan isomers holds the phenolic ring at a fixed, distinct angle to the piperidine ring that is determinable through single-crystal X-ray diffraction studies. We hypothesized that a three-dimensional pattern existed that was needed for ligands to efficiently interact with opioid receptors as agonists or antagonists and that this steric pattern could be discerned by the synthesis of the a−f isomers. We conceptualized that the initial synthesis of 12 racemic oxide-bridged 5-phenylmorphan isomers, the *o*- and *p*-hydroxy derivatives of a series of six compounds, a−f (Figure 1), and their subsequent pharmacological evaluation, would provide the data needed for determination of which of these isomers should be resolved. It is well-known that enantiomers can have distinctly different pharmacological properties than the racemic mixture. The 5-phenylmorphans,[19] the basis for the molecules in this series, have been found to be remarkably interesting and have been examined over the past 50 years. They have been found to be a class of opioids in which a considerable number of the members of the group display at least morphine-like potency as antinociceptive agents and have high affinity to opioid receptors. The *N*-methyl analogue, for example, is as potent as morphine as an antinociceptive,[20] and its (1*R*,5*S*)-(−)-enantiomer was about four times more potent than morphine in mice.[21] The (1*S*,5*R*)-(+)-enantiomer with the *N*-methyl moiety was found to have mixed agonist−antagonist activity. Its potency as an antagonist was similar to nalorphine.[21,22] It was later noted that steric hindrance to the free rotation of the aromatic ring, and concurrent conversion to an *N*-phenylethyl analogue, resulted in the formation of a pure, potent, opioid antagonist.[23] However, we have found that the steric hindrance appeared only to increase potency; a nonsterically hindered *N*-phenylethyl enantiomer also showed pure opioid antagonist activity.[24] Thus, the angular relationship of the aromatic ring and piperidine ring embodied in the sterically hindered compound[23] might, or might not, show the optimal three-dimensional pattern.[25] Also, the phenolic ring in that compound[23] was not fixed at a specific angle, but rather held to a limited, but still relatively large area in which the phenolic ring could freely rotate. To determine a more precise three-dimensional pattern a rigid skeleton was required, such as could be obtained in the a−f oxide-

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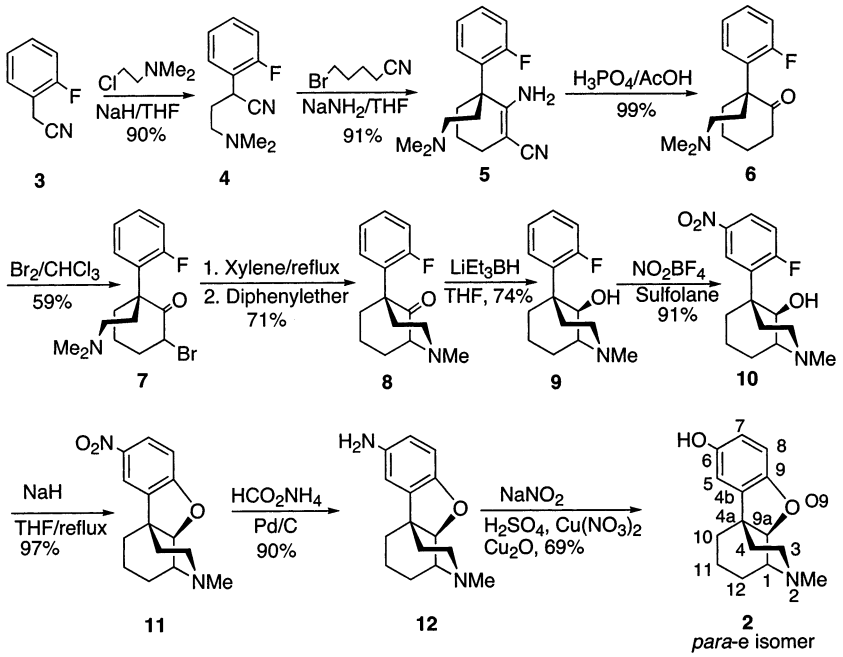
SCHEME 1



bridged 5-phenylmorphans. We have succeeded, thus far, in synthesizing the racemic *o*-a oxide-bridged phenylmorphan isomer ((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)[4,5,26] and its *p*-a analogue ((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),[4] the *o*- and *p*-c isomers ((3*R*,6a*S*,11a*S*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol and (3*R*,6a*S*,11a*S*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]-azocin-8-ol)[2], the *o*- and *p*-d compounds (3*R*,6a*S*,11a*R*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol and (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),[3,27] the *o*- and *p*-f isomers (1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol and (1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-4,4a-propanobenzofuro[2.3-*c*]pyridin-6-ol,[1,5,26] and have now obtained the penultimate isomers in this series, the racemic *o*- and *p*-e compounds (Figure 1).

Results and Discussion

The coupling of 2-fluorophenylacetonitrile (**3**) and 2-(dimethylamino)ethyl chloride gave the racemic 4-(dimethylamino)-2-(2-fluorophenyl)butyronitrile ((±)-**4**), and it was reacted with 5-bromovaleronitrile in a Thorpe−Ziegler reaction to give 2-amino-3-(2-dimethylaminoethyl)-3-(2-fluorophenyl)cyclohex-1-enecarbonitrile ((±)-**5**) as shown in Scheme 1. Acid hydrolysis of (±)-**5** gave 2-(2-dimethylaminoethyl)-2-(2-fluorophenyl)cyclohexanone ((±)-**6**). Bromination and heating in xylene, followed by heating in diphenyl ether, gave the key intermediate (±)-**8** (5-(2-fluorophenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-9-one). The hydroxy compound with the required configuration, compound (±)-**9** (Scheme 1, 5-(2-fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9β-ol) was obtained by selective reduction of (±)-**8** with Super Hydride. The structure of (±)-**9** was confirmed by X-ray crystal structure analysis of the hydrobromide salt (Supporting Information, Figure 2).

To activate the aromatic fluorine atom that would allow ring closure to the oxygenated 5,6-*trans* ring system, we introduced the *p*-nitro functional group using nitronium tetrafluoroborate. A single racemic isomer was obtained, 5-(2-fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-9β-ol ((±)-**10**). X-ray structure analysis of the hydrobromide salt of (±)-**10** confirmed its molecular structure (Supporting Information, Figure 3). Refluxing the free base of (±)-**10** with sodium hydride in tetrahydrofuran gave the desired 5,6-*trans* ring compound (±)-**11**.

Reduction to the amino compound (±)-**12** with ammonium formate and Pd/C, and conversion to the phenol, provided the *p*-e isomer (±)-**2**. The structure of (±)-**2** was unambiguously determined by X-ray crystallographic analysis (Supporting Information, Figure 4). This X-ray crystallographic study also enabled the determination of the angular relationship between the least-squares plane of the aromatic ring and the four coplanar atoms in the piperidine ring (C1, C3, C4, and C9a). The angle between the planes in the e-isomer was found to be 63.4°. The angular data will be used in future structure−activity studies that correlate the three-dimensional structure of these opioid-like oxide-bridged phenylmorphans with their binding affinities to opioid receptors and their actions as opioid agonists or antagonists.

The amino compound (±)-**12** also served to provide an entry to the *ortho*-series, through conversion to the bromo derivative (±)-**13** and nitration of (±)-**13** to (±)-**14** (Scheme 2). Reduction of the nitro moiety with concomi-

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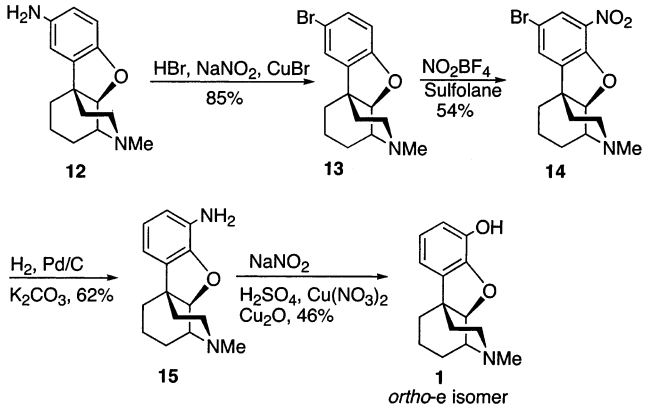
SCHEME 2



tant hydrogenolysis of the bromine substituent gave the *o*-amino analogue (±)-**15**, and that was converted via the diazonium salt to the desired *o*-e isomer, the phenolic compound (±)-**1**.

Experimental Section

***rac*-4-Dimethylamino-2-(2-fluorophenyl)butyronitrile ((±)-4).** Under argon, sodium hydride (10.2 g, 430 mmol) was added to a solution of 2-fluorophenylacetonitrile (**3**, 53.0 g, 390 mmol) in THF (350 mL) in portions and the reaction mixture was refluxed with stirring for 30 min. A solution of the free base of 2-(dimethylamino)ethyl chloride in benzene (the free base solution in benzene was obtained from the hydrochloride salt (59.3 g, 420 mmol) by treatment with KOH/H_2O and extraction with benzene; the solution was dried over Na_2SO_4) was then added, and the reaction was refluxed for an additional 2 h. The reaction mixture was cooled and concentrated to remove THF. The remaining solution was acidified to pH ∼1 with an aqueous solution of citric acid and washed with diethyl ether. The aqueous solution was neutralized with K_2CO_3 powder and extracted with $CHCl_3$ (3×). The extracts were dried over Na_2SO_4 and filtered, the solvent was removed, and the product was purified by column chromatography (silica gel, hexane/ethyl acetate, 1:1) to give an oil, (±)-**4** (73.0 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (1H, m), 7.29−7.36 (1H, m), 7.18 (1H, m), 7.09 (1H, m), 4.33 (1H, t, J = 7.4 Hz), 2.55 (1H, m), 2.34 (1H, m), 2.24 (6H, s), 2.03 (2H, dt, J = 7.4, 6.3 Hz). FAB-MS: m/z 207 $[M + H]^+$. Anal. Calcd for $C_{12}H_{15}FN_2$: C, 69.88; H, 7.33; N, 13.58. Found: C, 70.04; H, 7.40; N, 13.65.

***rac*-2-Amino-3-(2-dimethylaminoethyl)-3-(2-fluorophenyl)cyclohex-1-enecarbonitrile ((±)-5).** To a solution of the nitrile (±)-**4** (20.0 g, 97.0 mmol) in THF (150 mL) was added $NaNH_2$ (12.6 g, 323 mmol) under argon, and the reaction mixture was stirred for 30 min at a carefully maintained temperature of 50−52 °C. A solution of 5-bromovaleronitrile (17.3 g, 108 mmol) in THF (20 mL) was then added, while the temperature was maintained at 50−53 °C. The mixture was stirred for 2 h at 53 °C. The reaction mixture was cooled, and the solvent was removed. The residue was acidified to pH ∼1 with aqueous citric acid solution (0.5 M) and washed with ether. The aqueous layer was neutralized by adding K_2CO_3 powder and extracted with $CHCl_3$ (3×). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in 2-propanol (200 mL), and excess HBr was added to give the hydrobromide salt of (±)-**5**, which was collected and dried (26.5 g, 74%). A second crop was obtained by evaporation of the mother liquor and recrystallization from 2-propanol (6.4 g, 17%). Mp: 221 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−7.27 (2H, m), 7.10 (1H, m), 7.00 (1H, m), 6.20 (2H, s), 2.15−2.30 (6H, m), 2.12 (2H, m), 2.04 (6H, s), 1.46−1.72 (2H, m). FAB-MS: m/z 288 $[M + H]^+$. Anal. Calcd for $C_{17}H_{23}BrFN_3$: C, 55.44; H, 6.29; N, 11.41. Found: C, 55.46; H, 6.34; N, 11.25.

***rac*-2-(2-Dimethylaminoethyl)-2-(2-fluorophenyl)cyclohexanone ((±)-6).** The mixture of (±)-**5**·HBr (22.8 g, 62.0 mmol), H_3PO_4 (80 mL), AcOH (4 mL), and water (4 mL) was refluxed for 24 h. It was then cooled, neutralized with aqueous K_2CO_3, and extracted with $CHCl_3$ (3×). The extracts were dried over Na_2SO_4, filtered, and concentrated to give the keto compound (±)-**6** (16.2 g, 99%). Mp: 53−54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23−7.35 (2H, m), 7.18 (1H, m), 7.04 (1H, m), 2.70−2.79 (1H, m), 2.42−2.55 (1H, m), 2.31−2.38 (1H, m), 1.92−2.18 (10H, m), 1.60−1.82 (5H, m). CIMS (NH_3): m/z 264 $[M + H]^+$. Anal. Calcd for $C_{16}H_{22}FNO$: C, 72.97; H, 8.42; N, 5.32. Found: C, 73.25; H, 8.49; N, 5.39.

***rac*-6-Bromo-2-(2-dimethylaminoethyl)-2-(2-fluorophenyl)cyclohexanone ((±)-7).** Bromine (3.4 mL, 67 mmol) was added to a solution of (±)-**6** (16.0 g, 61.0 mmol) in $CHCl_3$ (30 mL), and the mixture was stirred for 1 h at room temperature. The solvent was evaporated, and a few drops of HBr were added. The resulting solid was stirred with 2-propanol (10 mL), filtered, and dried to give crystalline (±)-**7**·HBr (15.1 g, 59%). Mp: 199−200 °C. ^{1}H NMR: δ 7.19−7.36 (3H, m), 7.09 (1H, m), 4.69−4.78 (1H, m), 2.80−2.89 (1H, m), 2.46−2.56 (1H, m), 2.05−2.28 (9H, m), 1.90−2.04 (2H, m), 1.64−1.86 (3H, m). CIMS (NH_3): m/z 342 $[M + H]^+$. Anal. Calcd for $C_{16}H_{22}Br_2FNO$: C, 45.41; H, 5.24; N, 3.31. Found: C, 45.41; H, 5.00; N, 3.00.

***rac*-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one ((±)-8).** (±)-**7**·HBr (1.0 g, 2.4 mmol) was converted to its free base with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried, concentrated, and further dried under high vacuum. The free base was then dissolved in xylene (25 mL), and the mixture was refluxed with stirring for 15 h. After cooling, crystals formed and were collected by filtration. The crystals were then dissolved in diphenyl ether (5 mL), and the solution was heated at 200 °C for 5 h. It was cooled and acidified with aqueous HCl to pH ∼1, and the mixture was extracted with diethyl ether to remove the diphenyl ether. The aqueous layer was basified by adding K_2CO_3 and extracted with $CHCl_3$. The extracts were combined, dried over Na_2SO_4, and concentrated. The residue was chromatographed (silica gel, EtOAc) to afford (±)-**8** (412 mg, 71%), which was converted to its hydrobromide salt and recrystallized from absolute ethanol. Mp: 216−217 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.31 (2H, m), 7.04−7.15 (2H, m), 3.02−3.20 (1H, m), 2.72−2.82 (1H, m), 2.30−2.56 (6H, m), 2.06−2.54 (3H, m), 1.64−1.82 (2H, m). CIMS (NH_3): m/z 248 $[M + H]^+$. Anal. Calcd for $C_{15}H_{19}BrFNO$: C, 54.89; H, 5.83; N, 4.27. Found: C, 55.06; H, 5.96; N, 4.31.

***rac*-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9β-ol ((±)-9).** To a solution of (±)-**8** (free base, 125 mg, 0.50 mmol) in THF was added dropwise a 1 M solution of Super Hydride in THF (1.5 mL, 1.5 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. Water (0.75 mL) and concentrated HCl (0.25 mL) were added, and the reaction mixture was refluxed with stirring for 30 min. The solvent was removed, and the residue was basified with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4 and concentrated to give the 9β-ol (±)-**9** as the free base. Crude **9** was then converted to its HBr salt, which was recrystallized from EtOH to give pure (±)-**9**·HBr (124 mg, 74%). Mp: 237−238 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.54 (1H, m), 7.07−7.21 (2H, m), 6.94−7.02 (1H, m), 4.23 (1H, d, J = 3.8 Hz), 2.90−3.08 (2H, m), 2.70−2.79 (1H, m), 2.43 (3H, s), 2.26−2.38 (3H, m), 2.34−2.25 (1H, m), 1.44−1.92 (5H, m). CIMS (NH_3): m/z 249 $[M - H]^+$. Anal. Calcd for $C_{15}H_{21}BrFNO$: C, 54.56; H, 6.41; N, 4.24. Found: C, 54.67; H, 6.32; N, 4.18.

***rac*-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-9β-ol ((±)-10).** (±)-**9**·HBr (2.0 g, 6.1 mmol) was converted to its free base ((±)-**9**, 1.5 g) using aqueous $NaHCO_3$. To a solution of (±)-**9** in sulfolane (20 mL) was added 0.5 M nitronium tetrafluoroborate solution in sulfolane (14.5 mL, 7.30 mmol) at room temperature. The mixture was stirred for

2 h, additional nitronium tetrafluoroborate solution in sulfolane (14.5 mL, 7.30 mmol) was added, and stirring was continued for another 2 h. Aqueous $NaHCO_3$ was added, and the reaction mixture was extracted with EtOAc. The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give compound (±)-**10** as free base (1.6 g, 91%), which was then converted to its hydrobromide salt. Mp: 292−293 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (1H, dd, J = 6.9, 2.8 Hz), 8.10 (1H, m), 7.13 (1H, dd, J = 11.7, 10.4 Hz), 4.28 (1H, d, J = 3.6 Hz), 2.90−3.08 (2H, m), 2.78−2.88 (1H, m), 2.70−2.79 (1H, m), 2.47 (3H, s), 2.25−2.35 (3H, m), 2.12−2.20 (1H, m), 1.50−1.90 (5H, m). CIMS (NH_3): m/z 295 $[M + H]^+$. Anal. Calcd for $C_{15}H_{20}BrFN_2O_3$: C, 48.01; H, 5.37; N, 7.47. Found: C, 48.14; H, 5.27; N, 7.38.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-6-nitro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((±)-11).** To a solution of the free base of (±)-**10** (1.3 g, 4.5 mmol) in THF (50 mL) was added sodium hydride (0.22 g, 8.7 mmol), and the reaction mixture was refluxed with stirring for 24 h. After additional sodium hydride (0.11 g, 4.4 mmol) was added, refluxing was continued for another 24 h. The reaction was cooled, quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (3×). The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give (±)-**11** as the free base (1.2 g, 97%), which was converted to its hydrobromide salt and recrystallized from absolute ethanol. Mp: 240−242 °C dec. ^{1}H NMR: δ 8.13 (1H, dd, J = 2.5, 8.6 Hz), 7.98 (1H, d, J = 2.5 Hz), 6.95 (1H, d, J = 8.6 Hz), 4.22 (1H, d, J = 3.0 Hz), 3.49 (1H, m), 2.80−2.90 (1H, m), 2.70−2.78 (1H, m), 2.54 (3H, s), 2.35−2.45 (2H, m), 1.70−2.00 (5H, m), 1.20−1.27 (1H, m). CIMS (NH_3): m/z 275 $[M + H]^+$. Anal. Calcd for $C_{15}H_{19}BrN_2O_3$: C, 50.79; H, 5.39; N, 7.89. Found: C, 50.48; H, 5.42; N, 7.75.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-6-amino-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((±)-12).** Ammonium formate (230 mg, 3.60 mmol) and a catalytic amount of 5% Pd/C were added to a solution of (±)-**11**·HBr (200 mg, 0.70 mmol) in MeOH (10 mL), and the mixture was refluxed with stirring for 1 h. The catalyst was removed by filtration and washed with 10 mL of hot MeOH, and the combined filtrates were concentrated in vacuo. The residue was basified with aqueous $NaHCO_3$ and extracted with EtOAc (3×). The extracts were combined, dried over Na_2SO_4, and concentrated to give (±)-**12** (149 mg, 90%), which was used for the next reaction without purification.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol ((±)-2).** To a solution of (±)-**12** (145 mg, 0.60 mmol) in 35% H_2SO_4 (0.6 mL) was added a solution of $NaNO_2$ (53 mg, 0.8 mmol) in water (0.5 mL) at 0 °C. The mixture was stirred for 5 min, and urea was added until KI−starch paper did not show a purple color. A solution of $Cu(NO_3)_2$·$3H_2O$ (2.25 g, 9.30 mmol) in water (21 mL) was then added, followed by Cu_2O (79 mg, 0.6 mmol). The resulting mixture was vigorously stirred for 30 min at room temperature. The color of the reaction mixture changed from blue to greenish/black. The mixture was basified with NH_4OH and extracted with EtOAc (3×). The extracts were combined, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give (±)-**2** (100 mg, 69%) as a free base, which was converted to the hydrobromide salt and recrystallized from absolute ethanol. Mp: 288−289 °C. ^{1}H NMR: δ 6.74 (1H, d, J = 8.2 Hz), 6.55 (1H, dd, J = 8.2, 2.7 Hz), 6.61 (1H, d, J = 2.7 Hz), 5.20 (1H, s), 4.03 (1H, d, J = 2.4 Hz), 3.41 (1H, m), 2.67−2.90 (2H, m), 2.52 (3H, s), 2.20−1.40 (2H, m), 1.70−1.90 (5H, m), 1.40−1.50 (1H, m). HRMS (FAB): calcd for $(M + H)^+$ $C_{15}H_{19}NO_2$ 246.1494, found 246.1486.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-6-bromo-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((±)-13).** A solution of $NaNO_2$ (28 mg, 0.4 mmol) in water (0.5 mL) was added to a solution of (±)-**12** (100 mg, 0.40 mmol) in a mixture of concentrated hydrobromic acid (0.34 mL) and water (1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and urea was added until KI−starch paper did not show a purple color. CuBr (68 mg, 0.5 mmol), concentrated HBr (0.13 mL), and water (0.3 mL) were then added consecutively, and the reaction mixture was vigorously stirred for 1 h at room temperature. It was basified with NH_4OH and extracted with EtOAc (3×). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give (±)-**13** (107 mg, 85%), which was converted to its hydrobromide salt and recrystallized from absolute ethanol. Mp: 122−123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (1H, dd, J = 8.3, 2.0 Hz), 7.17 (1H, d, J = 2.0 Hz), 6.78 (1H, d, J = 8.3 Hz), 4.07 (1H, d, J = 3.0 Hz), 3.43 (1H, m), 2.67−2.90 (2H, m), 2.52 (3H, s), 2.20−2.40 (2H, m), 1.85−1.90 (2H, m), 1.70−1.85 (3H, m), 1.40−1.50 (1H, m). HRMS (FAB): calcd for $C_{15}H_{19}BrNO$ $(M + H)^+$ 308.0644 $[M + H]^+$, requires 308.0650.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-6-bromo-8-nitro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((±)-14).** As in the preparation of (±)-**10**, 0.5 M nitronium tetrafluoroborate solution in sulfolane (2.57 mL, 1.30 mmol) was added to a solution of (±)-**13** (330 mg, 1.10 mmol) in sulfolane (5 mL) at room temperature, and the reaction mixture was stirred for 2 h. Additional nitronium tetrafluoroborate in sulfolane (1.29 mL, 0.60 mmol) was added, and the stirring was continued for an additional 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3×). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to afford (±)-**14** (203 mg, 54%), which was converted to its hydrobromide salt. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (1H, d, J = 2.0 Hz), 7.4 (1H, d, J = 2.0 Hz), 4.30 (1H, d, J = 3.0 Hz), 3.58 (1H, m), 2.67−2.90 (2H, m), 2.52 (3H, s), 2.30−2.45 (2H, m), 1.85−1.90 (2H, m), 1.70−1.85 (3H, m), 1.40−1.50 (1H, m). HRMS (FAB): calcd for $(M + H)^+$ $C_{15}H_{18}BrN_2O_3$ 353.0501, found 353.0517.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-8-amino-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((±)-15).** A mixture of (±)-**14** (200 mg, 0.60 mmol), K_2CO_3 (157 mg, 1.10 mmol), and 10% Pd/C (50 mg) in MeOH (20 mL) was stirred under H_2 (40 psi) for 1 h at 40 °C. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a residue which was chromatographed (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give of (±)-**15** (86 mg, 62%), which was converted to its hydrobromide salt and recrystallized from absolute ethanol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (1H, dd, J = 8.5, 7.2 Hz), 6.53−6.60 (2H, m), 4.06 (1H, d, J = 2.7 Hz), 3.65 (2H, m), 3.46 (1H, m), 2.67−2.90 (2H, m), 2.53 (3H, s), 2.30−2.45 (2H, m), 1.70−1.90 (5H, m), 1.40−1.50 (1H, m). HRMS (FAB): calcd for $(M + H)^+$ $C_{15}H_{21}N_2O$ 245.1654, found 245.1654.

***rac*-(1α,4aα,9aα)-1,3,4,9a-Tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol ((±)-1, *o*-e Isomer).** This material was prepared using the procedure described for (±)-**2**. A solution of $NaNO_2$ (29 mg, 0.4 mmol) in water (0.3 mL) was added to a solution of (±)-**15** (80 mg, 0.3 mmol) in 35% H_2SO_4 (0.33 mL) at 0 °C. The mixture was stirred 5 min, and urea was then added until KI−starch indicator paper did not show a purple color. A solution of $Cu(NO_3)_2$·$3H_2O$ (1.24 g, 5.10 mmol) in H_2O (11.5 mL) was added, followed by Cu_2O (44 mg, 0.3 mmol), and the mixture was vigorously stirred for 30 min at room temperature. The color of the reaction mixture changed from blue to greenish/black. The mixture was basified with NH_4OH and extracted with EtOAc (3×). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH, 100:10:1) to give (±)-**1** (37 mg, 46%), which was converted to its hydrobromide salt and recrystallized from absolute ethanol. Mp: 287−288 °C. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 6.75−6.82 (2H, m), 6.67 (1H, dd, J = 6.0, 2.5 Hz), 4.10 (1H, d, J = 3.0 Hz), 3.65 (2H, m), 3.46 (1H, m), 2.67−2.90 (2H, m), 2.53 (3H, s), 2.30−2.45 (2H, m), 1.70−1.90 (5H, m), 1.40−1.50 (1H, m). HRMS (FAB): calcd for $(M + H)^+$ $C_{15}H_{20}NO_2$ 246.1494, found 246.1504.

Single-Crystal X-ray Diffraction Analysis of Compounds (±)-9, (±)-10, and (±)-2. Single-crystal X-ray diffraction data for compounds (±)-**10** and (±)-**2** were collected at −170 °C using Mo Kα radiation on a four-circle diffractometer (Bruker) equipped with a SMART 1000 CCD area detector (Bruker) and incident beam monochromator. For compound (±)-**9** diffraction data were collected at −75 °C using Cu Kα radiation on a three circle diffractometer (Bruker) equipped with a SMART 6000 CCD area detector (Bruker) and Göbel optics. All of the crystals remained stable during data collection. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 values using programs found in the SHELXTL system of programs.[28] Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-H atoms. H 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. Coordinates only were refined for the hydroxyl hydrogen. Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 232384, 232385, and 232386, for compounds (±)-**9**, (±)-**10**, and (±)-**2**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(O)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Compound (±)-9: $C_{15}H_{21}BrFNO$, FW = 330.24 (0.37 × 0.16 × 0.08 mm^3), monoclinic space group $P2_1/c$, a = 15.8054(2) Å, b = 7.1618(1) Å, c = 12.9254(1) Å, β = 91.108(1)°, V = 1462.82(3) $Å^3$, Z = 4, ρ_{calc} = 1.499 mg mm^{-3}, λ(Cu Kα) = 1.541 78 Å, μ = 3.866 mm^{-1}, F(000) = 680, T = 198(1) K, R1 = 0.0405 for 2322 observed ($I > 2\sigma I$) reflections and 0.0412 for the full set of 2427 reflections.

Compound (±)-10: $C_{15}H_{20}BrFN_2O_3$, FW = 375.24 (0.24 × 0.18 × 0.12 mm^3), monoclinic space group $P2_1$/c, a = 16.931-(2) , b = 7.0518(7) , c = 12.845(1) Å, β = 96.494(2)°, V = 1523.8-(3) $Å^3$, Z = 4, ρ_{calc} = 1.636 mg mm^{-3}, λ(Mo Kα) = 0.710 73 Å, μ = 2.723 mm^{-1}, F(000) = 768, T = 93(1) K, R1 = 0.0521 for 3031 observed ($I > 2\sigma I$) reflections and 0.0686 for the full set of 3737 reflections.

Compound (±)-2: $C_{15}H_{19}BrNO_2$; FW = 325.22 (0.44 × 0.21 × 0.14 mm^3), monoclinic space group $P2_1/n$, a = 6.3039(5) Å, b =24.092(2) Å, c = 9.7132(8) Å, β = 107.731(1)°, V = 1405.1-(2) $Å^3$, Z = 4, ρ_{calc} = 1.537 mg mm^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 2.923 mm^{-1}, F(000) = 778, T = 93(1) K, R1 = 0.0336 for 2671 observed ($I > 2\sigma I$) reflections and 0.0453 for the full set of 3380 reflections.

Acknowledgment. The authors (at LMC, NIDDK, DHHS) thank the National Institute on Drug Abuse, NIH, DHHS, for partial financial support of our research program, and thank Noel Whittaker and Victor Livingood (NIDDK, DHHS) for the mass spectral data. The X-ray crystallographic work was supported in part by the National Institute on Drug Abuse, NIH, DHHS, and the Office of Naval Research.

Supporting Information Available: X-ray crystal structure data for compounds (±)-**9**, (±)-**10**, and (±)-**2**, and General Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org. The crystal structure for (±)-**9**, (±)-**10**, and (±)-**2** have been deposited at the Cambridge Crystallographic Data Center (CCDC 232384, 232385, and 232386, respectively). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO040159K

(28) Bruker. *SHELXTL v 6.1*; Bruker AXS, Inc.: Madison, WI, 2000.