HETEROCYCLES, Vol. 71, No. 4, 2007, pp. 881 - 889. © The Japan Institute of Heterocyclic Chemistry
Received, 12th January, 2007, Accepted, 8th February, 2007, Published online, 9th February, 2007. COM-07-11000

A NOVEL DIVERGENT SYNTHESIS OF *ORTHO*-HYDROXY-E AND -F OXIDE-BRIDGED 5-PHENYLMORPHANS

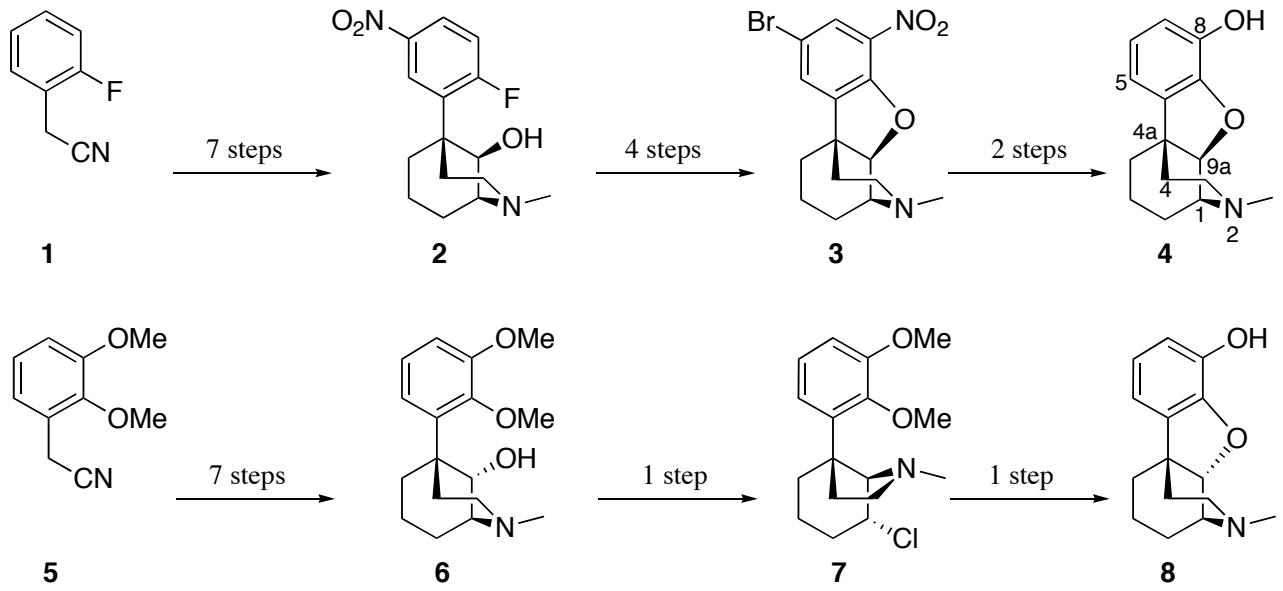
Josef Zezula, Arthur E. Jacobson, and Kenner C. Rice*

Drug Design and Synthesis Section, Chemical Biology Research Branch, Building 8, Room B1-23, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, 20892-0815, USA. E-mail: kr21f@nih.gov

Abstract – 5-(2-Bromo-3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one was prepared in six steps from a known phenylacetonitrile. Stereoselective reduction of the ketone furnished the corresponding β- or α-alcohols and their deprotonation, intramolecular cyclization, and demethylation gave *ortho*-hydroxy-e and -f oxide-bridged 5-phenylmorphans, respectively. This new synthetic route has the desired oxygenation pattern in place, eliminating the problematic diazonium reactions used in former syntheses.

INTRODUCTION

The *ortho*-hydroxy-e and -f oxide-bridged 5-phenylmorphans *rac*-(1*R*,4a*R*,9a*S*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-c]pyridin-8-ol (**4**) and *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol (**8**), were previously prepared[1-3] (Scheme 1) as probes for the determination of the spatial and molecular requirements of ligands necessary for selective interaction with specific opioid receptors. One of them (**8**), proved to have high affinity for the μ-opioid receptor and larger quantities were needed for further pharmacological evaluation. During our recent efforts towards preparation of *N*-phenethyl analogues of **4**, the known route[3] to this oxide-bridged phenylmorphan was modified, specifically the chloride rather than the corresponding bromide **3** was prepared. This significantly improved the yield in the nitration step. The aromatic nucleophilic substitution approach[3] was then expanded to the synthesis of the *ortho*-f oxide-bridged compound **8**. The diazonium reactions used to confer the desired oxygenation pattern in **4** and **8** proved particularly problematic, affording in addition to the desired products numerous impurities from diazonium coupling and other reactions.

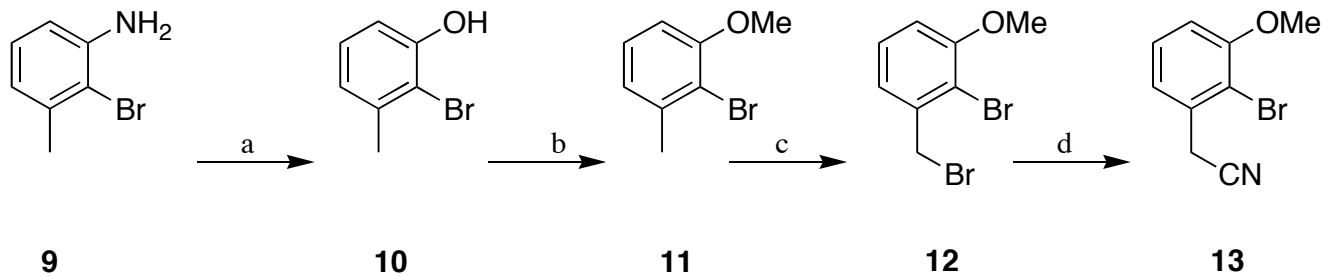


Scheme 1. Known route to *ortho*-e (**4**) and *ortho*-f (**8**) oxide-bridged phenylmorphans.

In addition, the product distribution obtained in these reactions varied widely as a function of temperature and concentration. The methodology described herein eliminates the diazonium reactions by starting with the desired oxygenation pattern in place.

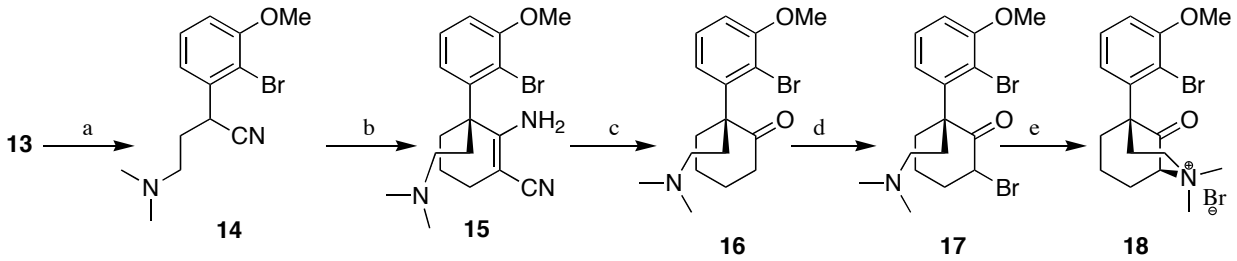
RESULTS AND DISCUSSION

We envisioned that the elements of both the syntheses shown in Scheme 1 and our recent expansion of the former could be molded into both a new and a divergent approach to both *ortho*-e and –f oxide-bridged compounds starting from the known bromomethoxy derivative **13**, prepared according to literature procedures[4] from commercially available 2-bromo-3-methylaniline **9** as outlined in Scheme 2.



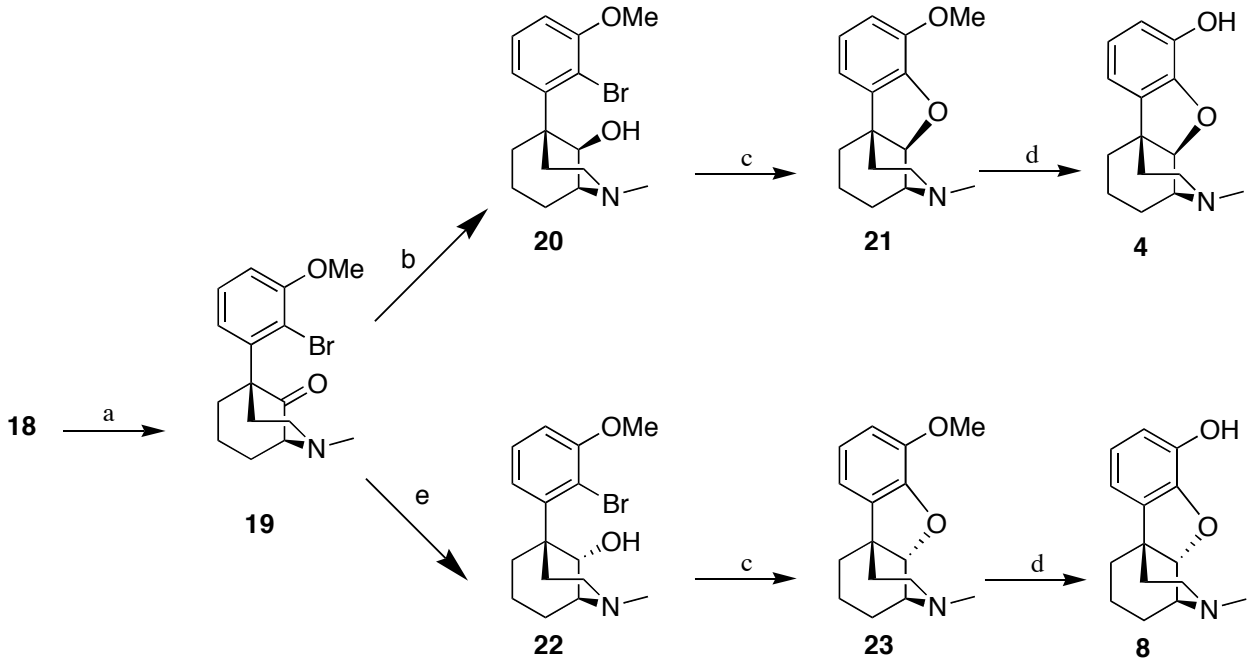
Scheme 2. *Reagents and conditions:* (a) $H_2SO_4/NaNO_2/0$ °C then Δ (88%), (b) NaH/MeI (84%), (c) NBS/$(PhCO)_2O/CCl_4/\Delta$, (d) NaCN/DMSO (31%, over 2 steps).

Deprotonation and alkylation with *N,N*-dimethylaminoethyl chloride provided nitrile **14**, which was submitted to Thorpe-Ziegler cyclization to give amine **15**. Hydrolysis to ketone **16** and it's bromination, followed by the quarternization of crude **17** yielded salt **18** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) NaH/THF/$Me_2NCH_2CH_2Cl$ (64%), (b) NaH/5-bromo valeronitrile/THF (27%), (c) $CF_3COOH/H_2O/\Delta$ (73%), (d) $Br_2/CHCl_3$, (e) *i*-PrOH/Δ (39%, over 2 steps).

Dry distillation of **18** provided amine **19** in good yield. Two different reduction protocols[1] were then applied: a) reduction with lithium triethylborohydride at –78 ºC to give β-alcohol **20,** b) conversion to a hydrochloride salt in methanol and reduction with $NaBH_4$ to give the α-alcohol **22** (Scheme 4). Cyclization of alcohols **20** and **22** were then attempted using Buchwald's conditions[5] ($Pd(OAc)_2$/BINAP/*t*-BuONa/toluene), but the reaction appeared to progress very slowly. Better results were achieved using the reported procedure[6] (NaH/CuCl/toluene/cat. EtOAc) for intramolecular cyclization of an aryl chloride and primary alkoxide. The reaction conditions using a stoichiometric amount of CuCl, without much optimization, gave good yields of cyclized materials, with some recovery of the starting materials. Compounds **21** and **23** were deprotected with BBr_3 in chloroform[7] to yield the



Scheme 4. *Reagents and conditions*: (a) 250 ºC/0.3 mm Hg (94%), (b) $LiEt_3BH$/THF/-78 ºC (88%), (c) NaH/PhMe then CuCl/EtOAc (cat.)/Δ (60 - 74%), (d) $BBr_3/CHCl_3$ then NH_4OH (60 - 75%), (e) HCl/MeOH then $NaBH_4$ (74%).

desired phenols **4** and **8**. The NMR and TLC data of **4** and **8** were identical to those prepared by previous routes.[1,3]

In conclusion, *ortho*-e and –f oxide-bridged compounds **4** and **8** were prepared in 9 steps starting from known nitrile **13**, which is comparable to the previously reported approach to *ortho*-f oxide-bridged compounds that also used 9 steps from the similar nitrile **5**. However, it is significantly shorter than the approach to the *ortho*-e oxide-bridged compound (13 steps). Moreover the new approach offers easier access to both the e and f oxide-bridged compounds from ketone **19** (3 steps). This approach could eventually prove useful for the synthesis of larger quantities of these compounds, avoiding the multiple operations that were necessary to adjust the proper substitution pattern of the benzene ring in the previously reported approach.[3] It is interesting to note that this synthesis could also provide access to compounds with the hydroxy group in a different position on the aromatic ring.

EXPERIMENTAL

General Procedures: Dry solvents were purchased from Sigma-Aldrich Fine Chemicals, Milwaukee, WI, USA, and used without further purification. Melting points were determined on a Thomas Hoover apparatus or on an automatic Büchi B-545 apparatus and are uncorrected. NMR spectra were obtained on a Varian Gemini 300 spectrometer in $CDCl_3$, unless otherwise stated, with 0.1% v/v tetramethylsilane ($\delta = 0$) as an internal standard (chemical shifts (δ) are given in parts per million (ppm), coupling constants *J* values are given in Hertz (Hz) and are reported to the nearest 0.1 Hz). Mass spectral analyses (HRMS) were obtained on a Waters/Micromass LCT ESI-TOF mass spectrometer at NIDDK, NIH. Dry distillation was carried out in a Büchi distillation oven (Kugelrohr). Thin layer chromatography (TLC) was performed on 250 mm Analtech GHLF silica gel plates using $CHCl_3$:CH_3OH:conc. NH_4OH (CMA, 90:9:1) as the solvent system and iodine vapors for detection.

***rac*-2-(2-Bromo-3-methoxyphenyl)-4-(dimethylamino)butanenitrile (14)**: A solution of (2-bromo-3-methoxyphenyl)acetonitrile[4] (4.34 g, 19.18 mmol) in dry THF (50 mL) was added dropwise over ca. 30 min. into a refluxing suspension of 60% NaH (0.88 g, 22.06 mmol, 1.15 eq.) in dry THF (30 mL) under an argon atmosphere. The resulting dark red solution was refluxed for an additional 2 h. A solution of *N,N*-dimethylaminoethyl chloride (free base) in toluene (80 mL) was prepared from 4.14 g (28.77 mmol, 1.5 eq.) of hydrochloride salt and aq. KOH. The solution of *N,N*-dimethylaminoethyl chloride was dried over magnesium sulfate, filtered and added to the refluxing nitrile solution, and the mixture was heated to reflux for an additional 2 h. The reaction mixture was cooled to rt and quenched with ice chips, treated with 18% hydrochloric acid (25 mL of conc. HCl and 25 mL of H_2O). Neutral impurities were extracted into Et_2O (4 x 30 mL), the basicity of the aqueous phase was adjusted to pH 14 by addition of 60 mL of a 30% KOH solution and sufficient solid KOH. The product was extracted as

the free-base with $CHCl_3$ (4 x 50 mL), the organic solution was dried over Na_2SO_4, filtered and evaporated. Crude product was distilled under reduced pressure to give **14** (3.63 g, 64%), bp 185-186 °C/13 mm Hg. ^{1}H-NMR: 7.33 (t, 1H, 8.1 Hz), 7.21 (dd, 1 H, 7.8, 1.5 Hz), 6.87 (dd, 1 H, 8.1, 1.5 Hz), 4.56 (dd, 1 H, 9.6, 5.1 Hz), 3.91 (s, 3H), 2.62 (m, 1 H), 2.39 (m, 1 H), 2.27 (s, 6 H), 2.11 (m, 1H), 1.90 (m, 1 H); ^{13}C-NMR: 156.5, 137.4, 128.9, 121.0, 120.5, 112.8, 111.5, 56.7 (2 C's), 45.7, 35.4, 32.5. HRMS $[M+H]^+$ calc. for $C_{13}H_{18}N_2OBr$: 297.0602, found 297.0604.

***rac*-2-Amino-3-(2-bromo-3-methoxyphenyl)-3-(2-(dimethylamino)ethyl)cyclohex-1-enecarbonitrile (15)**: A solution of **14** (3.60 g, 12.11 mmol) in dry THF (50 mL) was added dropwise over ca. 30 min into a refluxing suspension of 60% NaH (1.45 g, 36.34 mmol, 3.00 eq.) in dry THF (30 mL) with a catalytic amount of *t*-BuOH, under an argon atmosphere. After the resulting dark red solution was refluxed for an additional 3 h, a solution of 5-bromovaleronitrile (1.63 mL, 13.93 mmol, 1.15 eq.) in dry THF (20 mL) was added over 5 min. The mixture was refluxed for 2 days, cooled to rt, quenched with ice chips, treated with 18% hydrochloric acid (20 mL of conc. HCl and 20 mL of H_2O). Neutral impurities were extracted into Et_2O (3 x 30 mL), and the basicity of the aqueous phase was adjusted to pH 9 by addition of conc. NH_4OH (40 mL). The amine free-base **15** was extracted with $CHCl_3$ (5 x 50 mL), dried over Na_2SO_4, filtered and evaporated. The desired product was purified by column chromatography (silica, 3:1 $CHCl_3$:CMA) to give **15** (1.25 g, 27%). The HCl salt was prepared and recrystallized from *i*-PrOH-H_2O. Mp (HCl salt) 246.7–246.8 °C; ^{1}H-NMR: 7.24 (t, 1H, 8.4 Hz), 7.03 (dd, 1 H, 8.1, 1.5 Hz), 6.84 (dd, 1 H, 8.1, 1.5 Hz), 3.90 (s, 3H), 2.89 (m, 1 H), 2.59 (m, 1 H), 2.41 – 2.02 (m, 4 H), 2.07 (s, 6 H), 2.07 (m, 1 H), 1.52 (m, 2 H), 1.14 (m, 1 H); ^{13}C-NMR: 162.0, 156.5, 142.4, 127.9, 125.8, 122.3, 112.7, 110.7, 73.8, 56.7, 56.4, 50.9, 45.7, 45.3, 35.6, 34.2, 25.0, 18.8. HRMS $[M+H]^+$ calc. for $C_{18}H_{25}N_3OBr$: 378.1181, found 378.1164.

***rac*-2-(2-Bromo-3-methoxyphenyl)-2-(2-(dimethylamino)ethyl)cyclohexanone (16)**: Compound **15** (1.17 g, 3.09 mmol) was dissolved in aq. TFA (45 mL of TFA and 5 mL H_2O) and the solution was refluxed for 67 h. After cooling to rt the reaction mixture was slowly poured into a mixture of conc. NH_4OH (100 mL) and ice. The crude product was extracted into $CHCl_3$ (7 x 50 mL) and the organic solution was dried over Na_2SO_4, filtered and evaporated. Purification by chromatography (silica, 2:1 $CHCl_3$:CMA) yielded the desired ketone **16** (0.795 g, 73 %). ^{1}H-NMR: 7.33 (t, 1H, 7.8 Hz), 7.05 (d, 1 H, 8.4 Hz), 6.86 (d, 1 H, 8.4 Hz), 3.90 (s, 3H), 2.88 (bd, 1 H, 12.0 Hz), 2.52 (m, 1 H), 2.40 – 2.22 (m, 2 H), 2.18 (m, 2 H), 2.15 (s, 6 H), 2.01 (m, 2H), 1.86 – 1.61 (m, 4 H); ^{13}C-NMR: 214.8, 156.9, 142.3, 127.8, 122.3, 114.6, 110.6, 60.0, 56.6, 54.9, 45.6, 41.0, 40.3, 32.8, 30.5, 21.9. HRMS $[M+H]^+$ calc. for $C_{17}H_{25}NO_2Br$: 354.1069, found 354.1074.

6-Bromo-2-(2-bromo-3-methoxyphenyl)-2-(2-(dimethylamino)ethyl)cyclohexanone (17): Ketone **16** (0.756 g, 2.13 mmol) was dissolved in Et_2O (70 mL) and cooled in an ice bath and a solution of 48% HBr

(425 μL, 1.1 eq.) in Et_2O (10 mL) was added dropwise. The hydrobromide salt of **17** precipitated as an oil, the solvent was removed under reduced pressure and the crude salt was redissolved in $CHCl_3$ (50 mL). After cooling to ca. 0 ºC a solution of bromine (120 μL, 2.35 mmol, 1.1 eq.) in $CHCl_3$ (10 mL) was added dropwise and the reaction mixture was allowed to slowly warm up to rt over 4 h. A saturated solution of K_2CO_3 was added (50 mL) and mixture was vigorously shaken for 5 min. The aqueous layer was re-extracted with $CHCl_3$ (4 x 50 mL). The combined organic solution was dried over Na_2SO_4, filtered and evaporated to give **17** (0.874 g, 95%), which was used without further purification. ^{1}H-NMR: 7.34 (t, 1H, 7.8 Hz), 7.01 (d, 1 H, 7.8 Hz), 6.88 (dd, 1 H, 1.2 Hz, 8.1 Hz), 4.67 (dd, 1H, 5.7, 12.3 Hz), 3.90 (s, 3H), 2.97 (m, 1 H), 2.50 –2.28 (m, 2 H), 2.30 – 1.60 (m, 7 H), 2.12 (s, 6 H); ^{13}C-NMR: 205.9, 156.9, 141.1, 128.2, 122.0, 114.5, 110.9, 61.0, 56.6, 55.0, 54.8, 45.6, 42.1, 39.7, 33.9, 22.5. HRMS $[M+H]^+$ calc. for $C_{17}H_{24}NO_2Br_2$: 432.0174, found 432.0171.

5-(2-Bromo-3-methoxyphenyl)-2,2-dimethyl-9-oxo-2-azonia-bicyclo[3.3.1]nonane bromide (18): The free-base of bromoketone **17** (0.830 g, 2 mmol) was dissolved in 2-propanol (100 mL) and heated to reflux under an argon atmosphere for 6 days. After cooling to rt the reaction mixture was concentrated *in vacuo*, and the residue was crystallized from 2-propanol-water to give quaternary salt **18** (0.329 g, 39%). Mp 253.5–255.9 ºC; ^{1}H-NMR ($CDCl_3$/CD_3OD): 7.35 (m, 1H), 6.96 (t, 2 H, 7.2 Hz), 4.53 (ddd, 1H, 5.7, 13.8, 14.1 Hz), 4,21 (dd, 1H, 6.3, 14.1 Hz), 4.00 (bs, 1H), 3.92 (s, 3H), 3.60 and 3.58 (s, 6H), 3.10 - 2.98 (m, 1 H), 2.93–2.88 (m, 1 H), 2.74 (m, 2H), 2.60 – 2.40 (m, 3H), 2.05 (m, 1 H). *Anal*. Calcd for $C_{17}H_{23}NO_2Br_2$•0.75 H_2O: C, 45.71; H 5.53; N 3.14%. Found C, 45.62; H 5.27; N 3.00.

5-(2-Bromo-3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one (19): Quaternary salt **18** (0.222 g, 0.51 mmol) was dry distilled in a Kugelrohr apparatus (ca. 220 ºC/ 0.050 mm Hg) to give amine **19** as an oil, solidifying on standing (0.163 g, 94%). ^{1}H-NMR: 7.26 (t, 1H, 8.4 Hz), 6.95 (dd, 1 H, 8.1, 1.2 Hz), 6.87 (dd, 1 H, 8.1, 1.2 Hz), 3.90 (s, 3H), 3.27 – 3.05 (m, 2 H), 2.60 (m, 1 H), 2.51 (s, 6 H), 2.40 – 2.20 (m, 3 H), 1.80 (m, 2 H); ^{13}C-NMR: 212.4, 156.7, 144.9, 127.8, 120.5, 114.7, 111.0, 70.0, 56.6, 53.9, 50.7, 44.0, 43.3, 37.8, 33.4, 20.0; HRMS $[M+H]^+$ calc. for $C_{16}H_{21}BrNO_2$: 338.0756, found 338.0744. *Anal*. Calcd for $C_{16}H_{20}NO_2Br$•0.5 H_2O: C 55.34% H 6.10% N 4.03%. Found: C, 55.05; H, 5.97; N 3.81%.

***rac*-5-(2-Bromo-3-methoxy-phenyl)-2-methyl-2-aza-bicyclo[3.3.1]nonan-9-ol (20)**: A solution of ketone **19** (0.040 g, 0.118 mmol) in dry THF (4 mL) was cooled to –75 ºC under an argon atmosphere and a solution of lithium triethylborohydride was added (148 μL, 0.148 mmol, 1.25 eq., 1M solution in THF). After 3 h, an additional amount of Superhydride (89 μL, 0.75 eq.) was added to complete the reaction. Upon completion (TLC) the reaction mixture was quenched with ice chips and 2*N* HCl (5 mL) and stirred 30 min at rt. The THF was removed under reduced pressure and the residue was made alkaline by addition of conc. NH_4OH (10 mL) followed by extraction with $CHCl_3$ (6 x 10 mL). Combined extracts were dried over Na_2SO_4, filtered and evaporated. Purification of the residue by preparative TLC (2:1

$CHCl_3$:CMA) yielded **20** (0.035 g, 88%) as a pink solid. ^{1}H-NMR: 7.33 (dd, 1H, 1.5, 8.1 Hz), 7.26 (t, 1 H, 8.1 Hz), 6.80 (dd, 1 H, 1.5, 8.1 Hz), 4.35 (d, 1H, 3.3 Hz), 3.87 (s, 3H), 3.17 (m, 1H), 2.98 (m, 2 H), 2.84 (m, 1H), 2.70 (dd, 1H, 7.2, 12.0 Hz), 2.42 (s, 3H), 2.30 – 2.08 (m, 2H), 1.80 (m, 1H), 1.70 – 1.50 (m, 3 H); ^{13}C-NMR: 156.7, 147.8, 127.9, 121.8, 113.2, 110.2, 71.2, 60.4, 56.7, 49.7, 43.8, 42.5, 34.0, 27.7, 23.5, 22.2. HRMS $[M+H]^+$ calc. for $C_{16}H_{23}NO_2Br$: 340.0912, found 340.0920.

***rac*-(1*S*,4a*S*,9a*R*)-8-Methoxy-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*] pyridine (21)**: Sodium hydride (4 mg, 0.088 mmol, 1.50 eq., 60% wt. oil) was added to a solution of **20** (20 mg, 0.059 mmol) in dry toluene (5 mL) and the suspension was heated to ca. 50 ºC under argon for 1 h, after which a catalytic amount of EtOAc (3 μL) and copper (I) chloride (6 mg, 0.059 mmol, 1.0 eq.) were added and the reaction vessel sealed and heated in an oil bath to 130 ºC for 3 days. After cooling to rt the reaction mixture was diluted with toluene (10 mL) and filtered through a celite plug. Evaporation of solvent and purification by preparative TLC provided the oxide-bridged compound **21** (9.2 mg, 60%) as a yellow solid. ^{1}H-NMR: 6.85 (dd, 1H, 7.2, 8.1 Hz), 6.76 (dd, 1H, 1.5, 8.4 Hz), 6.73 (dd, 1.2, 7.2 Hz), 4.09 (d, 1H, 2.7 Hz), 3.86 (s, 3 H), 3.47 (m, 1 H), 2.86 – 2.68 (m, 2 H), 2.51 (s, 3 H), 2.30 (m, 2 H), 2.00 – 1.74 (m, 5 H), 1.50 – 1.37 (m, 1H); ^{13}C-NMR: 147.3, 145.8, 141.8, 121.8, 113.9, 111.7, 90.5, 56.3, 56.1, 49.5, 43.9, 40.5, 34.3, 33.9, 24.3, 22.2. HRMS $[M+H]^+$ calc. for $C_{16}H_{22}NO_2$: 260.1651, found 260.1656.

***rac*-5-(2-Bromo-3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-ol (22):** Conc. hydrochloric acid (24 μL, 0.289 mmol, 1.15 eq.) was added to a stirred solution of ketone **19** (0.085 g, 0.251 mmol) in MeOH (10 mL) and the acidic mixture was stirred at room temperature for 10 min, cooled in an ice bath, and sodium borohydride was added (0.029 g, 0.754 mmol, 3.0 eq.). TLC indicated the completion of reaction after 1 h, MeOH was evaporated and the residue suspended in H_2O (10 mL) and extracted with $CHCl_3$ (6 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Crude product was purified by preparative TLC (1:1.5 $CHCl_3$:CMA) to give **22** (0.063 g, 74%) as a white solid. ^{1}H-NMR: 7.26 (m, 2H), 6.82 (m, 1H), 4.79 (d, 1H, 3.6 Hz), 3.89 (s, 3 H), 3.00 – 2.10 (m, 4H), 2.49 (s, 3 H), 2.20 – 1.68 (m, 8 H); ^{13}C-NMR: 156.8, 147.1, 128.1, 121.5, 113.1, 110.4, 70.9, 60.1, 56.7, 50.4, 43.4, 43.2, 33.2, 27.6, 21.5, 18.7. HRMS $[M+H]^+$ calc. for $C_{16}H_{23}BrNO_2$: 340.0912, found 340.0903. *Anal*. Calcd for $C_{16}H_{22}NO_2Br$: C, 56.48; H, 6.52; N, 4.12%. Found: C, 56.69; H, 6.65; N, 4.00%.

***rac*-(1*S*,4a*S*,9a*S*)-8-Methoxy-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*] pyridine (23)**: Sodium hydride (4 mg, 0.092 mmol, 1.25 eq., 60% wt oil) was added to a solution of **22** (25 mg, 0.073 mmol) in dry toluene (4 mL) and suspension was heated to ca. 50 ºC under argon for 15 min, after which a catalytic amount of EtOAc (1 μL) and copper (I) chloride (7 mg, 0.077 mmol, 1.0 eq.) were added and the reaction vessel sealed and heated in an oil bath to 130 ºC for 3 days. TLC analysis showed the presence of starting material, so extra amounts of sodium hydride (2.5 mg, 0.75 eq.) and copper (I) chloride (7.0 mg, 1.0 eq.) were added and the reaction mixture was heated for an additional day.

After cooling to rt the reaction mixture was diluted with toluene (10 mL) and filtered through a celite plug. Evaporation of the filtrate yielded orange oil. Purification by preparative TLC provided the oxide-bridged compound **23** (14.0 mg, 74%) as a pink oil. Unreacted starting material (6.0 mg, 24%) was also recovered. ^{1}H-NMR: 6.86 (dd, 1H, 7.2, 8.4 Hz), 6.78 (dd, 1H, 1.2, 8.1 Hz), 6.73 (dd, 1H, 1.2, 7.2 Hz), 4.19 (d, 1H, 3.3 Hz), 3.90 (s, 3 H), 3.41 (m, 1 H), 3.07 (ddd, 1 H, 6.3, 12.3, 11.9 Hz), 2.88 (dd, 1 H, 6.3, 12.9 Hz), 2.54 (s, 3 H), 2.30 – 2.08 (m, 2 H), 1.90 – 1.40 (m, 6 H); ^{13}C-NMR: 147.3, 145.5, 141.6, 121.9, 113.9, 111.3, 89.4, 56.1, 55.4, 50.9, 42.5, 41.3, 33.9, 32.8, 21.0, 20.6. HRMS $[M+H]^+$ calc. for $C_{16}H_{22}NO_2$: 260.1651, found 260.1661.

***rac*-(1*S*,4a*S*,9a*R*)-2-Methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine-8-ol (4)**: Compound **4** was prepared in 60% yield using the same procedure as for compound **8**. This sample was identical to that previously prepared by Hashimoto, *et al*.,[3] by TLC and ^{1}H-NMR. HRMS $[M+H]^+$ calc. for $C_{15}H_{20}NO_2$: 246.1494, found 246.1499.

***rac*-(1*S*,4a*S*,9a*S*)-2-Methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine-8-ol (8)**: A 1M solution of boron tribromide in CH_2Cl_2 (300 μL, 0.301 mmol, 6.0 eq.) was added dropwise to a solution of **23** (13 mg, 0.050 mmol) in $CHCl_3$ (3 mL), and the reaction mixture was stirred under an argon atmosphere at rt for 2 h. After carefully quenching the reaction with ice chips, conc. NH_4OH was added (10 mL) and the reaction mixture was stirred for an additional 30 min. Extraction with $CHCl_3$ (6 x 10 mL), drying over Na_2SO_4 and evaporation of solvent gave crude **8**. Purification by preparative TLC (silica, 1:1 $CHCl_3$:CMA) furnished the desired phenol (9 mg, 75%). Compound **8** was shown to be identical to a previously prepared sample by TLC and ^{1}H-NMR. HRMS $[M+H]^+$ calc. for $C_{15}H_{20}NO_2$: 246.1494, found 246.1498.

ACKNOWLEDGEMENTS

This work was initiated while the authors were members of the Drug Design and Synthesis Section, Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, NIH. The research was supported by the NIH Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute on Drug Abuse. We also thank Dr. John Lloyd (NIDDK, NIH) for the mass spectral data.

REFERENCES

1. S. Kodato, J. T. M. Linders, X.-H. Gu, K. Yamada, J. L. Flippen-Anderson, J. R. Deschamps, A. E. Jacobson, and K. C. Rice, *Org. Biomol. Chem.*, 2004, **2**, 330.
2. J. T. M. Linders, J. L. Flippen-Anderson, C. F. George, and K. C. Rice, *Tetrahedron Lett.*, 1999, **40**, 3905.

3. A. Hashimoto, A. K. Przybyl, J. T. M. Linders, S. Kodato, X. R. Tian, J. R. Deschamps, C. George, J. L. Flippen-Anderson, A. E. Jacobson, and K. C. Rice, *J. Org. Chem.*, 2004, **69**, 5322.
4. S. Saito, O. Tamura, Y. Kobayashi, F. Matsuda, T. Katoh, and S. Terashima, *Tetrahedron*, 1994, **50**, 6193; T. Inoi, P. Gericke, and W. J. Horton, *J. Org. Chem.*, 1962, **27**, 4597.
5. M. Palucki, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 10333.
6. J. Zhu, B. A. Price, S. X. Zhao, and P. M. Skonezny, *Tetrahedron Lett.*, 2000, **41**, 4011.
7. K. C. Rice, *J. Med. Chem.*, 1977, **20**, 164.