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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

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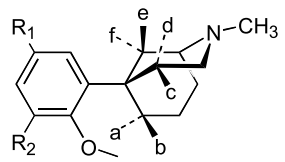
Abstract—Two of the 12 possible oxide-bridged phenylmorphans, were synthesized, *rac*-(3*R*,6a*S*,11a*S*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol (**7**) (the *ortho*-c compound), and *rac*-(3*R*,6a*S*,11a*S*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-8-ol (**8**) (the *para*-c compound). Single-crystal X-ray diffraction studies indicated that the dihedral angle between the least squares planes through the phenyl ring and the atoms C_1, C_{11a}, C_{12}, and C_3 in the piperidine ring in both **7**·$CHCl_3$ and **8**·HBr was 6.9°. The $C_{12}-C_{6a}-C_{6b}-C_{10a}$ torsion angle was found to be 139.3° for both compounds. The angular relationship between the phenolic ring and the piperidine ring in phenylmorphans that interact with specific opioid receptors as agonists or antagonists is of considerable theoretical interest.

1. Introduction

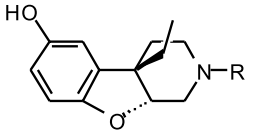
In order to determine the conformation of the 5-phenylmorphan that is required for high affinity interaction with an opioid receptor and to study the three-dimensional spatial pattern of the molecule enabling its action as an agonist or antagonist, we decided to synthesize a series of oxide-bridged 5-phenylmorphans.[1,2] Attachment of a phenolic oxygen atom to various positions on the azabicyclo ring system (Fig. 1) would enable us to examine a series of compounds where the angular relationship between the phenolic ring and the piperidine ring could be exactly determined.



ortho isomer: R_1 = H, R_2 = OH
para isomer: R_1 = OH, R_2 = H

Figure 1. *ortho*- and *para*-Substituted a through f oxide-bridged phenylmorphan isomers.

As can be seen in Figure 1, there are six possible positions (a–f) to which the phenolic oxygen atom can be attached. In the 5-phenylmorphans, compounds with and without a hydroxyl substituent oriented *meta* to the piperidine ring were compared, and the *meta*-hydroxy substituent was found to be important for potent agonist activity and lessened toxicity.[3] Thus, we decided that each of the oxide-bridged compounds should be synthesized with an *ortho*- or *para*-hydroxyl group, giving us 12 synthetic racemic targets; their optical resolution would provide a series of 24 compounds. The determination of the pharmacological effects of these compounds might give us the information that we need to allow us to determine structure–activity



1: R = CH_3, $(CH_2)_2$-C_6H_5

Keywords: oxide-bridged phenylmorphans; opioid receptor ligand; methanobenzofuro[2,3-*c*]azocines; synthesis; X-ray diffraction studies.

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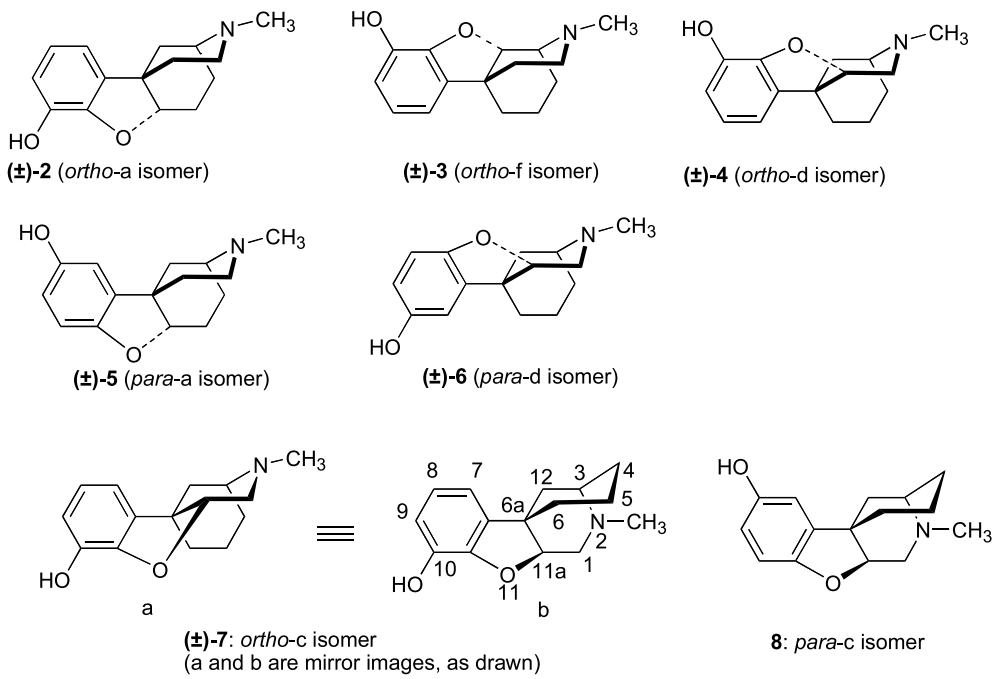


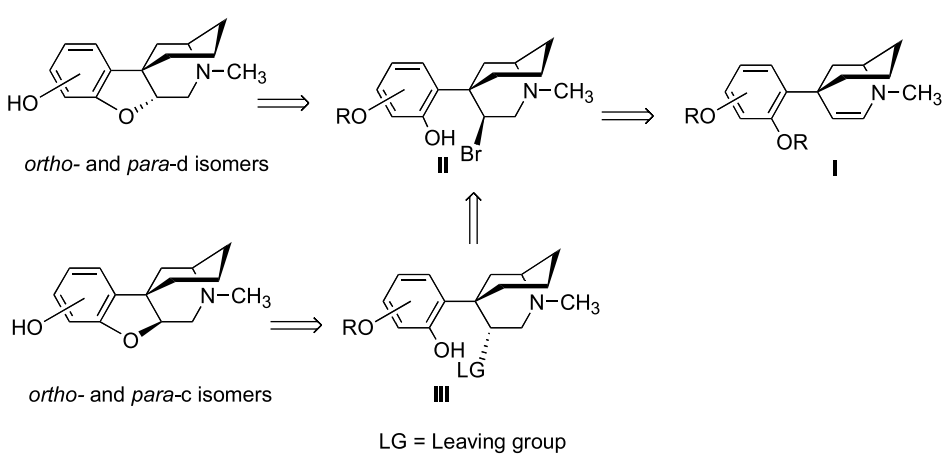
Figure 2. Synthesized oxide-bridged phenylmorphans.

relationships in this series of oxide-bridged phenylmorphans and perhaps, by extension, in structurally similar classes of opioids. It was of great interest to note, then, that some time after we began our work Hutchinson et al.[4] had found that a 5-phenylmorphan partial structure (**1**) had both good affinity for opioid receptors, and that in that series the *N*-phenylethyl analogue was a potent antinociceptive.

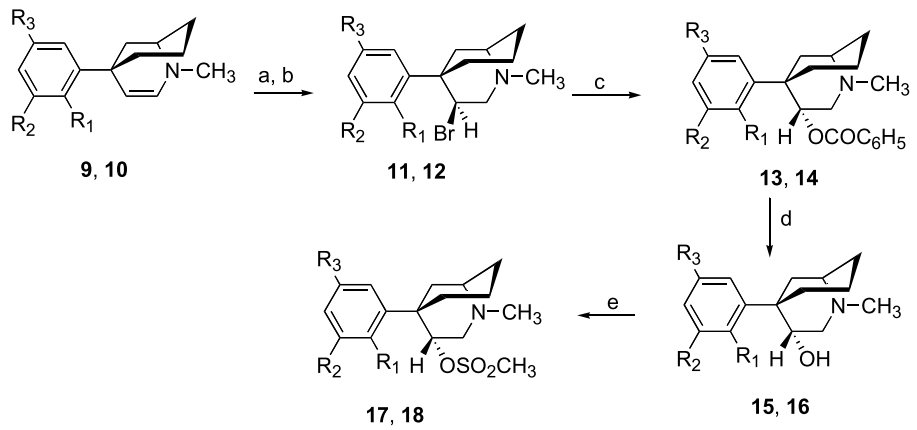
We previously reported the synthesis of the five oxide-bridged phenylmorphan isomers shown in Figure 2, *rac*-(4*R*,6a*R*,11b*R*)-3-methyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol[1,5] (**2**, the *ortho*-a oxide-bridged phenylmorphan isomer), *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol[1,6] (**3**, the *ortho*-f oxide-bridged phenylmorphan isomer), *rac*-(3*R*,6a*S*,11a*R*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol[7] (**4**, the *ortho*-d oxide-bridged phenylmorphan isomer), *rac*-(4*R*,6a*R*,11b*R*)-3-methyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]-azocine-10-ol[8] (**5**, the *para*-a oxide-bridged phenylmorphan isomer), and *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,[2] (**6**, the *para*-d oxide-bridged phenylmorphan isomer). We have also reported as an improved synthesis of the *ortho*-a oxide-bridged phenylmorphan isomer.[8] We now report the synthesis of two additional isomers, the *ortho*-c and *para*-c oxide-bridged phenylmorphans, *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 (**7**), and *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-8-ol (**8**), respectively.

2. Synthesis

Our retrosynthetic approach to the oxide-bridged phenylmorphan c-isomers is shown in Scheme 1. It is based on the successful synthesis of the *ortho*- and *para*-d isomers **4** and **6**,[2,7] which used the phenylmorphan enamine **I**, based on our

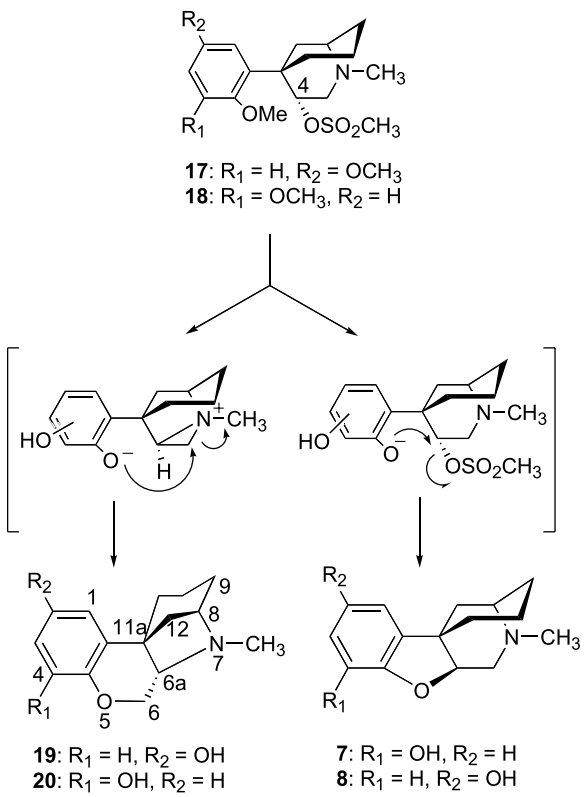


Scheme 1. Retrosynthetic approach to the oxide-bridged phenylmorphan c-isomers.



Scheme 2. *Reagents*: (a) *N*-bromoacetamide, THF; (b) HCl–MeOH, $NaCNBH_3$; (c) C_6H_5COOK, DMF; (d) LiOH, MeOH–H_2O; (e) methanesulfonyl anhydride, $CHCl_3$.

modified method of Evans et al.[9] as a strategic intermediate. Bromination and reduction of the double bond afforded **II**. The bromo substituent in **II** was displaced after deprotection of the phenolic hydroxy groups in a S_N2 reaction to give the oxide-bridged phenylmorphans **4** and **6**. In order to obtain the epimeric c-isomers, the stereochemistry of the leaving group should be inverted to give **III**. From the outset, we were aware of the possible difficult ring closure, as the c-isomers include a *trans*-fused 5,6-ring system. Furthermore, the axial disposition of the leaving group would make it susceptible to nucleophilic substitution by the amine nitrogen, forming an aziridinium ion. Nevertheless, the fact that **III** would be available in a few steps from well known **I**, assured us that we could test the viability of our approach relatively easily.



Scheme 3. *Reagents*: (a) BBr_3, $CHCl_3$, (b) KOH, MeOH/H_2O.

Bromination of enamine **9**[2] with *N*-bromoacetamide, followed by reduction of the double bond with $NaCNBH_3$, under conditions similar to those of Burke et al.[7] gave a mixture of two epimeric bromides (Scheme 2). The minor epimer was unstable, and only **11** was isolable after chromatographic purification or recrystallization of the salt. Compound **11** was obtained as the oxalate salt in 50% yield. Since the stereochemistry depicted for **11** in Scheme 2 was appropriate for ring closure under S_N2 conditions to the oxide-bridged d-isomer, we needed to invert the configuration at that carbon atom in order to obtain the c-isomer. This was accomplished through the nucleophilic displacement of the halogen atom. Treatment with potassium benzoate in DMF gave an ester **13** that was hydrolyzed to the corresponding alcohol **15**. Esterification of **15** by mesyl anhydride with Et_3N afforded an unstable mesylate **17** that was used without purification. The same procedure was used in the *ortho*-substituted series, starting with **10**.

In order to continue, we now needed to deprotect the aromatic oxygen atoms (Scheme 3). As observed with the epimeric bromide,[2] compound **17** proved difficult to didemethylate with BBr_3 in $CHCl_3$ at room temperature. The reaction mixture had to be refluxed with an excess of reagent. Upon quenching the reaction with methanol, we observed the formation of an apolar product, probably the *para* quinone, which was reconverted to the hydroquinone by treatment with an excess of $NaBH_4$. Alkaline work-up, as used for the successful formation of the *para*-d isomer **6**,[2] afforded, however, the isomeric compound **19** as the major product in 41% yield. The desired oxide-bridged phenylmorphan *para*-c isomer **8** was isolated from the reaction mixture by chromatography in 11% yield. The structure of compound **8**, as well as those of the isomeric compound **19** were unequivocally determined from single crystal X-ray analysis (Figs. 3 and 5, Tables 1 and 3) of their HBr salt. The formation of **19** in this type of reaction was previously rationalized by Burke et al.[7] As shown in Scheme 3, the

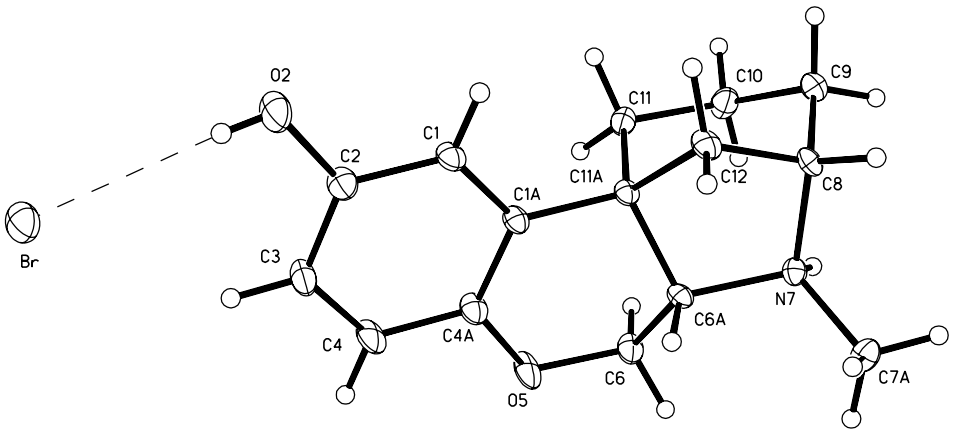


Figure 3. Results of the X-ray study on **19**·HBr drawn from the experimentally determined coordinates with displacement parameters at the 20% probability level.

proximity of the nitrogen atom to the mesylate may facilitate the internal displacement of the mesylate anion by nitrogen's lone pair electrons to give an aziridinium intermediate. That intermediate could undergo intramolecular ring opening, resulting in the observed piperidine ring contraction.

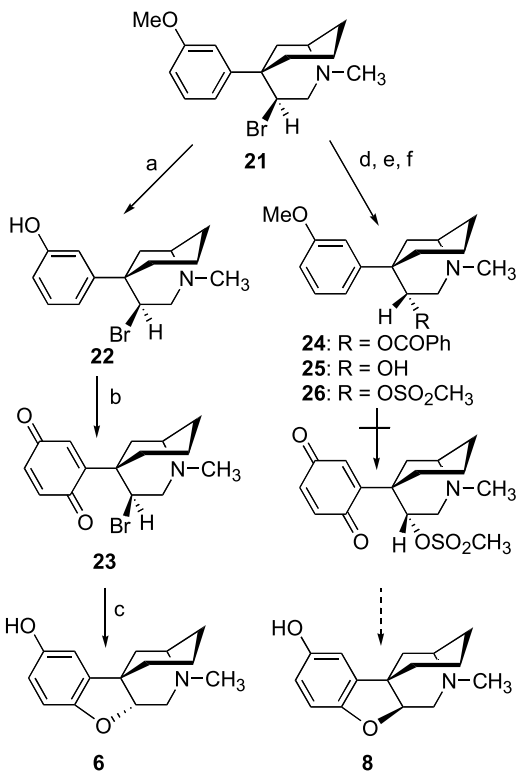
The difficulties encountered in didemethylation of **17**, possibly due to the steric hindrance between the aromatic methoxyl group and the mesylate substituent, led us to devise another approach, starting with a *meta* monosubstituted phenyl ring. We expected that this demethylation would be facile and that a Fremy's salt oxidation of the resulting phenol would give a *para* quinone that could be reduced to the diol prior to ring closure, as we have demonstrated above. However, before attempting the multistep process involved in inversion of configuration, we tried the methodology on the synthesis of the previously obtained oxide-bridged phenylmorphan d-isomer (**6**, Scheme 4). Phenol **22** was easily prepared from the corresponding methyl ether **21** (compound **21** was prepared according to an analogous route for the dimethoxy analogues **11** and **12**). Treatment of **22** with Fremy's salt gave the quinone **23**, which upon reduction with sodium borohydride and quench in aqueous potassium hydroxide gave **6**.[2]

The procedure shown in Scheme 4 gave **6** in good

Table 1. X-Ray crystal data and structure refinement of *rac*-(8α,11aα,6aα)-7-methyl-6a,8,9,10,11-pentahydro-6*H*-8,11a-methanobenzopyrano[3,4-*b*]-azepin-2-ol (**19**)

Empirical formula	$C_{15}H_{20}NO_2^+Br^-$
Formula weight	326.23
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	Triclinic
Space group	*P*1bar
Unit cell dimensions	*a*=7.5500(10) Å, α=98.150(10)°
	b=7.7710(10) Å, β=98.530(10)°
	c=12.659(2) Å, γ=95.570(10)°
Volume (Å^3)	721.77(18)
Z	2
Density (calculated) (mg/m^3)	1.501
Absorption coefficient (mm^{-1})	3.863
F(000)	336
Crystal size (mm^3)	0.39×0.20×0.20
Theta range for data collection (°)	3.58–57.56
Index ranges	$0\le h\le 8$, $-8\le k\le 8$, $-13\le l\le 13$
Reflections collected	2240
Independent reflections	1988 [*R*int=0.0221]
Completeness to θ=57.56°	100.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1988/0/179
Goodness-of-fit on F^2	1.043
Final *R* indices [$I>2\sigma(I)$]	*R*1=0.0422, *wR*2=0.1242
R indices (all data)	*R*1=0.0446, *wR*2=0.1275
Extinction coefficient	0.0061(11)
Largest diff. peak and hole (e Å^{-3})	0.729 and −0.871

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 194188. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



Scheme 4. *Reagents*: (a) BBr_3, $CHCl_3$; (b) Fremy's salt, KH_2PO_4, DMF/H_2O; (c) $NaBH_4$, MeOH; KOH, MeOH/H_2O; (d) C_6H_5COOK, DMF; (e) LiOH, MeOH/H_2O; (f) Methanesulfonyl anhydride, $CHCl_3$.

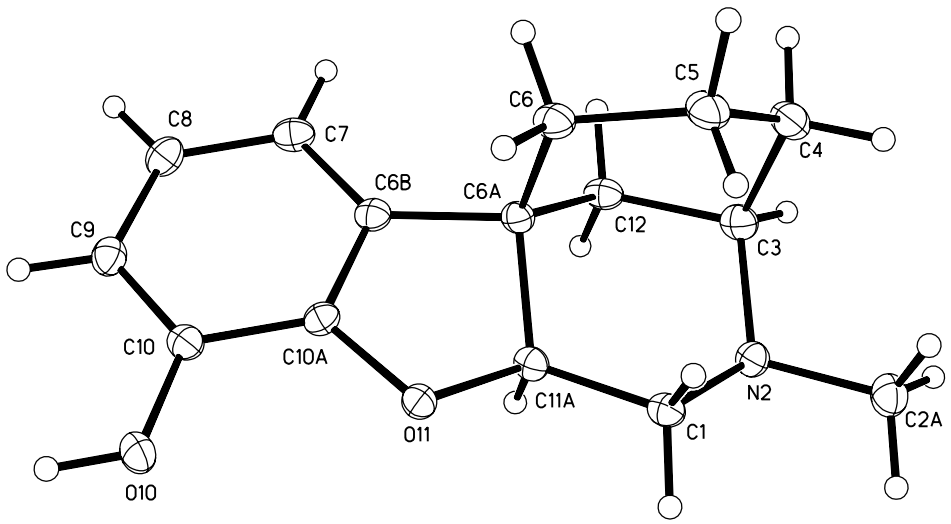


Figure 4. Results of the X-ray study on **7** drawn from the experimentally determined coordinates with displacement parameters at the 20% probability level. The disordered chloroform molecule was not included in the illustration.

overall yield. Unfortunately, its use for the synthesis of **8**, the *para*-c oxide-bridged phenylmorphan isomer, did not succeed. The intermediate compound **26** was labile, and we could not obtain a free phenol by demethylation of the ether. An alternate approach was attempted where the quinone mesylate could be obtained through the bromoquinone **23**. We found that **23** could be converted to the unstable quinone benzoate, and the purification of that compound was difficult. Although it decomposed during NMR analyses, its formation was suggested by its mass spectrum (CI-MS *m*/*z* 366 $(M+1)^+$, corresponding to $C_{22}H_{23}O_4N$). However, even immediate saponification of **24** gave a complex mixture. This strategy was abandoned.

From our experience in the synthesis of the d-isomers **4** and **6**,[2,7] we expected that bis O-demethylation would be more facile in the *ortho* series, leading to **7**, than the *para* series, leading to **8**, because of the neighboring group effect of the 3-methoxyl group and the hindered adjacent methoxyl (Scheme 3). Indeed, this reaction was successful and the didemethylation proceeded at 0–10°C. When the reaction was quenched directly with ice–NH_4OH, as previously

Table 2. X-Ray crystal data and structure refinement 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 (**7**)

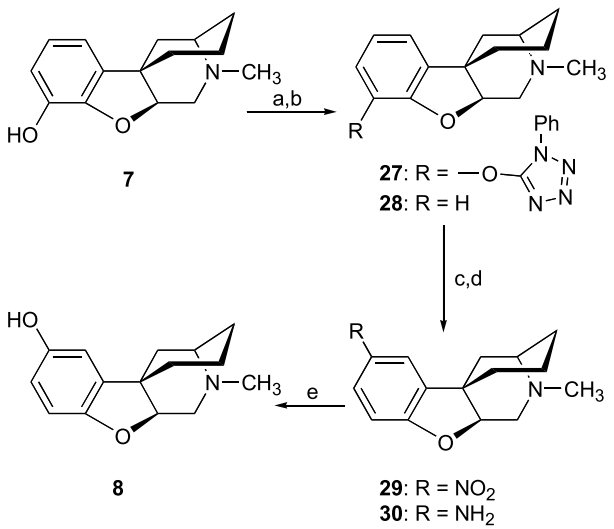
Empirical formula	$C_{15}H_{19}NO_2{\cdot}CHCl_3$
Formula weight	364.68
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a=6.968(1) Å, α=90° b=13.406(3) Å, β=91.11(2)° c=18.132(4) Å, γ=90°
Volume (Å^3)	1693.4(6)
Z	4
Density (calculated) (mg/m^3)	1.430
Absorption coefficient (mm^{-1})	0.547
F(000)	760
Crystal size (mm^3)	0.78×0.28×0.08
Theta range for data collection	1.89–22.54°
Index ranges	$-7\leq h\leq 0$, $-14\leq k\leq 0$, $-19\leq l\leq 19$
Reflections collected	2450
Independent reflections	2236 [Rint=0.0156]
Completeness to θ=22.54°	100.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2236/0/240
Goodness-of-fit on F^2	0.973
Final R indices [$I>2\sigma(I)$]	$R1$=0.0445, $wR2$=0.1157
R indices (all data)	$R1$=0.0724, $wR2$=0.1507
Extinction coefficient	0.017(3)
Largest diff. peak and hole (e Å^{-3})	0.348 and −0.287

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 194189. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 3. X-Ray crystal data and structure refinement 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-8-ol (**8**)

Empirical formula	$C_{15}H_{20}NO_2^+Br^-$
Formula weight	326.23
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	Triclinic
Space group	P1bar
Unit cell dimensions	a=7.546(1) Å, α=74.43(1)° b=10.010(1) Å, β=70.35(1)° c=10.563(1) Å, γ=85.63(1)°
Volume (Å^3)	723.7(1)
Z	2
Density (calculated) (mg/m^3)	1.497
Absorption coefficient (mm^{-1})	3.853
F(000)	336
Crystal size (mm^3)	0.62×0.60×0.42
Theta range for data collection	4.59–57.56°
Index ranges	$-7\leq h\leq 8$, $-10\leq k\leq 10$, $0\leq l\leq 11$
Reflections collected	2185
Independent reflections	1989 [Rint=0.0287]
Completeness to θ=57.56°	100.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1989/0/179
Goodness-of-fit on F^2	1.025
Final R indices [$I>2\sigma(I)$]	$R1$=0.0348, $wR2$=0.0980
R indices (all data)	$R1$=0.0352, $wR2$=0.0985
Extinction coefficient	0.0080(8)
Largest diff. peak and hole	0.728 and −0.505 e Å^{-3}

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 194187. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



Scheme 5. *Reagents*: (a) Phenylchlorotetrazole, K_2CO_3, DMF; (b) H_2, Pd/C, HOAc; (c) $NaNO_2$, TFA; (d) H_2, Pd/C, MeOH; (e) 30% H_2SO_4, $NaNO_2$, $Cu(NO_3)_2(H_2O)_3$, Cu_2O.

reported,[10] the desired product **7** was obtained in 70% yield. The molecular structure of **7** (Fig. 4) was confirmed by X-ray crystallography (Table 2). The ring-contracted by-product **20** (Scheme 3) was obtained in only 10% yield. There was a striking difference between the product ratios of the oxide-bridged phenylmorphan c-isomers and the ring contracted compound obtained from the *ortho* isomer (**7** vs **20**) and the *para* isomer (**8** vs **19**). The formation of the aziridinium ion intermediate was apparently disfavored at lower temperatures, decreasing the amount of the by-product **20** (Table 3). The *ortho*-phenolic compound **20**, *rac*-(8α,11aα,6aα)-7-methyl-6a,8,9,10,11-pentahydro-6*H*-8,11a-methanobenzopyrano[3,4-*b*]azepin-4-ol, is likely to be an isomer of the compound obtained by Burke et al.[7] by treatment of the bromo compound **12** with hot pyridine. The structure of the Burke et al. compound was indicated by X-ray crystallographic analysis[7] to be similar to **19** (and, by analogy, to **20**). As the putative aziridinium intermediates are isomeric due to the opposite configuration at C_4 of the mesylate in **17** and of the halogen atom in **12**, it is expected that the Burke et al.[7] compound and **20** are epimers at C_{6a} The mesylate group at C_4 in **17** is axially oriented in the piperidine ring. Its displacement in an intramolecular S_N2 reaction (Scheme 3) would result in an opposite orientation of the aziridinium ring in the aziridinium intermediate that, after ring opening by attack of the phenoxide anion, would result in a hydrogen atom at C_{6a} in **19** or **20** that was above the plane of the resulting pyrrolidine ring. This was observed in the single-crystal X-ray diffraction study of **19** (Fig. 3, Table 1).

Since the synthesis of **7**, unlike that of **8**, was accomplished in acceptable overall yield by the procedure shown above, we decided to convert **7** to **8** by the reaction sequence shown in Scheme 5. The deoxygenation of the phenyl ring was accomplished through formation of the tetrazolyl ether[11,12] **27**, followed by catalytic reduction to the dehydroxylated compound **28**. Nitration, using $NaNO_2$ in CF_3CO_2H,[13] afforded predominantly the mononitro compound **29**. Catalytic hydrogenation of **29** in the presence of 10% Pd/C (50 psi) in acetic acid proceeded slowly to give the amine **30**, which, under modified Sandmeyer diazotization conditions,[14] was converted to the desired *para*-c oxide-bridged phenylmorphan isomer **8**.

3. Conclusion

The oxide-bridged phenylmorphans **7** and **8** were successfully synthesized from the same strategic enamine intermediate that was used previously for the synthesis of the d-isomers **4** and **6**. The X-ray crystallographic study of the synthesized *ortho*-c and *para*-c oxide-bridged phenylmorphans (Figs. 4 and 5), *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 (**7**), and *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-8-ol (**8**), enabled the determination of the dihedral angle between the least squares planes through the phenyl ring and the atoms C_1, C_{11a}, C_{12}, and C_3 in the piperidine ring. In compound **7**, and in **8**·HBr that angle was 6.9°. The C_{12}–C_{6a}–C_{6b}–C_{10a} torsion angle was found to be 139.3° in **7**, and in **8**·HBr. The correlation between the dihedral angle and the pharmacological properties of the oxide-bridged phenylmorphan isomers will be reported in due course when their syntheses have been completed.

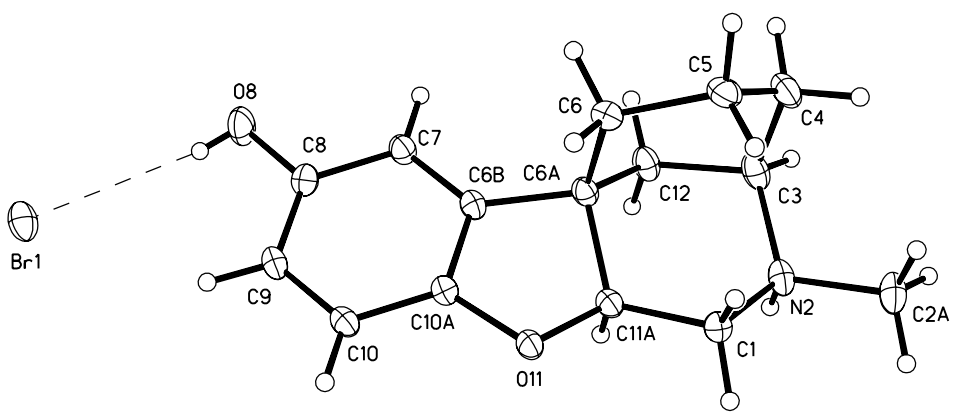


Figure 5. Results of the X-ray study on **8**·HBr drawn from the experimentally determined coordinates with displacement parameters at the 20% probability level.

4. Experimental

4.1. General

All melting points were determined on a Fisher–Johns apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini instrument using $CDCl_3$ (TMS as internal standard). IR spectra were recorded on a Beckman IR 4230 and Biorad FTS-45 spectrometer. Chemical-ionization mass spectra (CIMS) were obtained were obtained using a Finnigan 40600 mass spectrometer. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Gas chromatography was carried out on a Hewlett–Packard 5890 instrument using a flame ionization detector. Thin layer chromatography (TLC) was performed on analytical (250μ) or preparative (1000μ) Analtech silica gel Plate using $CHCl_3$/MeOH/concentrated NH_4OH (85:15:0.5) as the solvent system, unless otherwise mentioned. The $CHCl_3$ used as solvent was pentane-stabilized. Column chromatography was performed using 220–440 mesh silica gel. Elemental analyses were performed by the Section on Analytical Services and Instrumentation, NIDDK, NIH, and were within ±0.4% of the theoretical values. Single-crystal X-ray diffraction data were collected at room temperature using Cu Kα radiation (Mo Kα for **7**) on an automated Bruker P4 diffractometer equipped with a monochromator in the incident beam. All crystals remained stable during data collection. Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 values using programs found in the SHELXTLplus system of programs.[15] 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 hydroxyl hydrogens and hydrogens on N atoms (in **8** and **19**). The Cl_3 moiety of the chloroform molecule in **7** was disordered over two positions. Atomic coordinates for **7**, **8**, and **19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers (Compound **7**: CCDC 194189; Compound **8**: CCDC 194187; Compound **19**: CCDC 194188). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. *rac*-5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]non-3-ene oxalate (9·oxalate), and *rac*-5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-3-ene oxalate (10·oxalate). The previously described[2,7,9] procedure for the preparation of **9** and **10** was modified by the use of a 1:1 mixture of 85% H_3PO_4 and anhydrous formic acid at 80°C for 2 h, rather than 20°C for 66 h.[9]

4.1.2. *rac*-4-Bromo-5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane oxalate (11·oxalate), and *rac*-4-bromo-5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane oxalate (12·oxalate). Compound **11** was prepared as previously described.[2] The bromo compound (**12**), obtained as previously described[2,7] from 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-3-ene oxalate (**10**·oxalate), was crystallized as an oxalate salt from 2-propanol. Anal. calcd for $C_{17}H_{24}BrNO_2.C_2H_2O_4$: C, 51.36; H, 5.90; N, 3.15. Found: C, 51.38; H, 5.88; N, 3.13.

4.1.3. *rac*-Benzoic acid 5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (13). The oxalate salt of the bromo compound **11** was converted to the free base by partitioning between $CHCl_3$ and NH_4OH. The light yellow oily free base **11** (1.12 g, 3.41 mmol) was dissolved in DMF (130 mL) and anhydrous potassium benzoate (1.43 g, 8.97 mmol) was added while stirring. The suspension was gradually heated under nitrogen in an oil bath to 80°C (30 min), and maintained at that temperature for 2 h. It was cooled to room temperature and diluted with H_2O (200 mL). The aqueous phase was extracted with Et_2O (3×150 mL). The combined organic extracts were washed with H_2O (2×100 mL), dried over Na_2SO_4, and the solvent removed in vacuo. The product was filtered through a short column of silica gel to give the ester **13** (1.18 g, 85.8%) as a yellowish oil. IR (KBr) 1710, 1255, 1215 cm^{-1}: ^{1}H NMR δ 1.20–2.10 (m, 7H), 2.69 (s, 3H), 2.88 (m, 1H), 3.07 (m, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.55 (d, 2H), 6.68 (dd, 1H, J_{ortho}=8.5 Hz, J_{meta}=2.5 Hz), 6.79 (d, 1H, J=8.5 Hz), 6.93 (d, 1H, J=2.5 Hz), 7.33 (t, 2H, J=7.5 Hz), 7.47 (t, 1H, J=7.5 Hz, 7.76 (d, 2H, J=8 Hz); CI-MS (NH_3) m/z 396 $(M+H)^+$; HRMS (EI) calcd for $C_{24}H_{29}NO_4$: 395.2097, found: 395.2080.

4.1.4. *rac*-Benzoic acid 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (14). The oxalate salt of the bromo compound **12** was converted to the free base, a light yellow oil, as with **11**. The free base **12** (1.8 g, 5 mmol) was reacted as in the preparation of **13**, using DMF (500 mL) and potassium benzoate (2.07 g, 12.9 mmol). After cooling to room temperature, it was diluted with H_2O (500 mL). The aqueous phase was extracted with Et_2O (2×250 mL). The combined organic extracts were washed with H_2O (2×200 mL), and worked up as in **13** to give the ester **14** (0.69 g, 34.5%) as a yellow oil. IR (KBr) 1713, 1272 cm^{-1}; ^{1}H NMR: δ 1.38 (m, 1H), 1.72 (m, 4H), 2.02 (m, 3H), 2.72 (s, 3H), 3.82 (m, 1H), 3.66, (m, 1H), 3.84 (s, 3H), 4.58 (d, 2H), 6.82 (t, 1H, J=5 Hz), 6.96 (d, 2H, J=5 Hz), 7.34 (t, 2H, J=7.5 Hz), 7.48 (t, 1H, J=7.5 Hz), 7.79 (d, 2H, J=7.8 Hz); CI-MS (NH_3) m/z 396 $(M+H)^+$; HRMS (EI) calcd for $C_{24}H_{29}NO_4$: 395.2097, found: 395.2062.

4.1.5. *rac*-5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-4-ol (15). A 5% solution of LiOH in a 7:3 mixture of MeOH and H_2O (50 mL) was slowly added to a vigorously stirred solution of the ester **13** (1.18 g, 2.98 mmol) in MeOH (40 mL). The reaction mixture was stirred for 2 h at room temperature under a nitrogen atmosphere, then diluted with H_2O (20 mL), and extracted with $CHC1_3$ (2×200 mL). The organic layer was washed with H_2O (2×100 mL), dried over Na_2SO_4 and evaporated to dryness. The residue (0.8 g) was crystallized from 2-propanol to give 0.6 g (70%) of white crystals. Mp 170–171°C; IR (KBr) 3150, 1230 cm^{-1}; ^{1}H NMR ($CDC1_3$) δ 1.37 (m, 1H), 1.60–2.15 (m, 7H), 2.58 (s, 3H), 2.61 (m, 1H), 3.03 (m, 1H), 3.10 (bds, exchangeable with D_2O, alcoholic OH), 3.18 (t, 1H, J=6.5 Hz), 3.76 (s, 3H), 3.79 (s,

3H), 3.85 (m, 1H), 6.71 (dd, 1H, J_{ortho}=9 Hz, J_{meta}=3 Hz), 6.80 (m, 2H); CI-MS (NH_3) *m/z* 292 $(M+H)^+$. Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H 8.65; N 4.81. Found: C, 69.84; H 8.61; N 4.72.

4.1.6. *rac*-5-(2,3-Dimethoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-4-ol (16). A 10% solution of KOH in a 1:1 mixture of MeOH and H_2O (700 mL) was slowly added to a vigorously stirred solution of the ester **14** (8.005 g, 2.98 mmol) in MeOH (350 mL). The reaction mixture was stirred for 1 h at room temperature under a nitrogen atmosphere, then diluted with H_2O (300 mL), and extracted with $CHC1_3$ (3×300 mL). The organic layer was washed with H_2O (2×200 mL), dried over Na_2SO_4 and evaporated to dryness to give the alcohol **16** as a crude reddish solid. Crystallization from 2-propanol gave 3.55 g (60%) of white crystals. Mp 163–164°C; IR (KBr) 3144, 1467, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (m, 1H), 1.60–2.00 (m, 7H), 2.46 (m, 1H), 2.59 (s, 3H), 3.04 (m, 1H), 3.11 (t, 1H, *J*=6.5 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 3.89 (m, 1H), 6.78 (dd, 1H, J_{ortho}=8 Hz, J_{meta}=1.5 Hz), 6.82 (dd, 1H, J_{ortho}=8 Hz, J_{meta}=1.5 Hz), 6.98 (t, 1H, *J*=8 Hz); CI-MS (NH_3) *m/z* 292 $(M+H)^+$. Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H 8.65; N 4.81. Found: C, 69.82; H, 8.60; N, 4.80.

4.1.7. *rac*-Methanesulfonic acid 5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (17). Triethylamine (30 μL, 2.5 equiv.) was added to a solution of **15** (20 mg, 0.06 mmol) in $CHC1_3$ (3 mL). Methanesulfonyl anhydride (24 mg, 0.13 mmol, 2 equiv.) was added, and the colorless solution was stirred under a nitrogen atmosphere at room temperature for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$. The phases were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic material was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give the oily ester **17** (24 mg. 96% yield), which was sufficiently pure to use in the next step without further purification. ^1H NMR ($CDCl_3$) δ 1.36–1.98 (m, 7H), 2.62 (s, 3H), 2.79 (m, 1H), 2.92 (s, 3H), 3.05 (m, 1H), 3.61 (m, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.48 (m, 2H), 6.74 (dd, 1H, J_{ortho}=9 Hz, J_{meta}=3 Hz), 6.83 (m, 1H); HRMS calcd for $C_{18}H_{27}NO_5S$: *m/z* 370.1688 $(M+H)^+$, found: 370.1679; FAB-MS *m/z* 370 $(M+H)^+$.

4.1.8. *rac*-Methanesulfonic acid 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (18). Triethylamine (4.08 mL, 2.5 equiv.) was added to a solution of **16** (3.41 g, 11.75 mmol) in $CHC1_3$ (300 mL). Methanesulfonyl anhydride (4.09 g, 23.5 mmol, 2 equiv.) was added to this solution. The colorless solution turned yellow in 5 min, while stirring under a nitrogen atmosphere. Starting material disappeared (TLC) after 15 min. The reaction was quenched with a saturated solution of $NaHCO_3$ (150 mL). The phases were separated and the aqueous layer was extracted with $CHCl_3$ (2×200 mL). The combined organic material was washed with H_2O (2×200 mL), dried over Na_2SO_4 and evaporated to dryness to give **18** as a thick yellow oil (4.3 g, 99% yield), which was sufficiently pure to use in the next step without further purification. ^1H NMR ($CDCl_3$) 1.30–2,05 (m, 7H), 2.60 (m, 1H), 2.63 (s, 3H), 2.94 (s, 3H), 3.06 (m, 1H), 3.52 (m, 1H), 3.86 (s, 3H), 3.89 (s, 3H), 4.51 (m, 2H), 6.85 (d, 1H, *J*=8.5 Hz), 6.98 (t, 1H, *J*=8.5 Hz); FAB-MS *m/z* 370 $(M+H)^+$; HRMS calcd for $C_{18}H_{27}NO_5S$: 370.1688, found: 370.1675.

4.1.9. *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-8-ol (8) and *rac*-(8α,11aα,6aα)-7-methyl-6a,8,9,10,11-pentahydro-6*H*-8,11a-methanobenzopyrano[3,4-*b*]azepin-2-ol (19). Mesylate **17** (60 mg, 0.16 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and BBr_3 (0.156 mL, 0.41 g, 10 equiv.) was added by syringe under nitrogen. The mixture was refluxed for 5 h. TLC indicated the formation of the hydroquinone, together with apolar material, presumably the quinone. After cooling to 0°C, MeOH was carefully added to the reaction mixture under nitrogen, followed by 0.5 g of solid $NaBH_4$. After stirring for 1 h at room temperature, the TLC apolar spot, previously observed, disappeared. The reaction mixture was added to a vigorously stirred solution of 1 M KOH in MeOH/H_2O (1:1) at 0°C, and stirred for 1 h. Solid NH_4Cl (0.5 g) was added (pH 9), and the mixture was extracted with $CHCl_3$/MeOH (3:1). The organic layer was dried and evaporated to give a crude mixture of alcohols that were separated by preparative TLC (eluent: $CHCl_3$/MeOH/concentrated NH_4OH (90:10:0.5)) to give a mixture of **8** (4.5 mg, 0.02 mmol, 11%), and **19** (16 mg, 0.07 mmol, 41%).

The methanobenzopyrano[3,4-*b*]azepin-2-ol (**19**) was crystallized as an HBr salt from MeOH. Mp 289–290°C; IR (KBr) 3420, 1455, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–2.01 (m, 8H), 2.47 (s, 3H), 2.82 (dd, lH, *J*=6.25, 10.75 Hz), 3.19 (m, 1H), 4.33 (m, 2H), 6.48 (d, 1H, J_{meta}=3 Hz), 6.55 (dd, 1H, J_{ortho}=8.5 Hz, J_{meta}=3 Hz), 6.66 (d, 1H, J_{ortho}=8.5 Hz); CI-MS (NH_3) *m/z* 246 $(M+1)^+$. Anal. calcd for $C_{15}H_{19}NO_2$·HBr: C 55.23; H 6.18; N 4.29. Found: C 55.31; H 6.21; N 4.30.

The HBr salt (**8**·HBr) of the *para*-c isomer was crystallized from MeOH. Mp 233–234°C; IR (KBr) 3262, 1454, 1182 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.38–2.29 (m, 8H), 2.58 (s, 3H), 3.30 (broad singlet, 1H), 3.40 (m, 2H), 4.25 (dd, 1H, *J*=11.5, 5.7 Hz), 6.58 (m, 2H), 6.74 (d, 1H, *J*=8 Hz); CI-MS (NH_3) *m/z* 246 $(M+H)^+$.

4.1.10. *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 (7) and *rac*-(8α,11aα,6aα)-7-methyl-6a,8,9,10,11-pentahydro-6*H*-8,11a-methanobenzopyrano[3,4-*b*]azepin-4-ol (20). To a vigorously stirred solution of BBr_3 (12 mL, 125 mmol, 10 equiv.) in $CHCl_3$ (400 mL) cooled to −2°C, was added dropwise a solution of mesylate **18** (4.6 g, 12.5 mmol) in $CHCl_3$ (120 mL). The mixture was stirred for 1 h at 0–5°C, and quenched with a mixture of concentrated NH_4OH (400 mL) and crushed ice (300 g). TLC indicated complete consumption of the starting material 30 min after maintaining a temperature of <10°C. The mixture was then brought to room temperature, and the organic phase was separated. The aqueous layer was saturated with NaCl, extracted with $CHCl_3$/MeOH (3:1, 4×400 mL). The combined organic layers were washed with H_2O (2×500 mL), The aqueous solution was re-extracted with $CHCl_3$/MeOH (3:1, 3×300 mL). The combined organic phase was dried over Na_2SO_4 and evaporated to dryness to give 2.96 g of a crude amorphous solid. Gas chromatography showed the

presence of two products in the ratio of 85:15, compounds **7** and **20**, respectively. The crude material was dissolved in hot 2-propanol (50 mL), and a solution of fumaric acid (1.4 g) in 2-propanol (20 mL) was added to give 2.31 g (6.3 mmol, 50%) of **7**·fumarate. The mother liquor from which **7**·fumarate was obtained was evaporated to dryness and converted to a crude free base (1.17 g) by partitioning between $CHCl_3$ and concentrated NH_4OH. This free base mixture of **7** and **20** was separated by column chromatography (silica gel, eluent: $CHCl_3$/MeOH/concentrated NH_4OH, 95:5:0.25) to give 180 mg of **20** (6%) and 550 mg of **7** (total isolated yield of 70%).

The methanobenzopyrano[3,4-*b*]azepin-4-ol (**20**) was purified by column chromatography (silica gel, eluent: $CHCl_3$/MeOH, 97.5:2.5) and crystallized as a fumarate salt from MeOH, mp 184–186°C. IR (KBr) 3421, 1465, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–2.01 (m, 8H), 2.48 (s, 3H), 2.86 (dd, 1H, J=5, 11.5 Hz), 3.21 (bt, 1H), 4.37–4.49 (m, 2H), 6.53 (dd, 1H, J_{ortho}=7 Hz, J_{meta}=2 Hz), 6.74 (m, 2H); CI-MS (NH_3) m/z 245. Anal. calcd for $C_{15}H_{19}NO_2 \cdot C_4H_4O_4 \cdot 0.75H_2O$: C 60.87; H 6.39; N 3.74. Found: C 60.80; H 6.49; N 3.59.

The 6a-methanobenzofuro[2,3-*c*]azocine-10-ol (*ortho*-c isomer **7**) free base was crystallized from MeOH. Mp 195–196°C; IR (KBr) 1588, 1459, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–2.35 (m, 8H), 2.62 (s, 3H), 3.16 (bs, 1H), 3.36–3.46 (m, 2H), 4.31 (dd, 1H, J=11, 6 Hz), 6.64 (d, 1H, J=7 Hz), 6.72–6.82 (m, 2H); CI-MS (NH_3) m/z 246 $(M+H)^+$. Anal. calcd for $C_{15}H_{19}NO_2$: C 73.44; H 7.81; N 5.71. Found: C 73.52; H 7.82; N 5.74.

4.1.11. *rac*-4-Bromo-5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane oxalate (21·oxalate). 5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-3-ene[16] (3 g, 12.3 mmol), obtained by the method of Evans et al.[9] was dissolved in dry THF (150 mL), cooled to −78°C and a solution of *N*-bromoacetamide (2.04 g. 14.9 mmol) in dry THF (20 mL) was added under nitrogen. The reaction mixture was stirred for 30 min and allowed to come to room temperature. A saturated solution of $NaHCO_3$ was added and the phases separated. The aqueous layer was extracted twice with Et_2O (2×300 mL). The organic solutions were combined, washed with a saturated solution of $NaHCO_3$ (2×200 mL), H_2O (2×200 mL), and dried over Na_2SO_4. Removal of solvent gave an unstable bromo enamine base as an orange oil. It was sufficiently pure to use in the next step. This material was dissolved in MeOH (150 mL), cooled to 0°C in an ice-salt bath, and concentrated hydrochloric acid (3 mL) was added followed by the addition of $NaCNBH_3$ (1 g). The reaction mixture was stirred under nitrogen for 2 h at 0°C and then allowed to warm to room temperature. A saturated solution of $NaHCO_3$ was added and the phases separated. The aqueous layer was extracted first with hexane and than with Et_2O. The organic solutions were combined, washed with H_2O (2×200 mL) and dried over Na_2SO_4. After solvent removal, 2.98 g of a white foam (**21**) was obtained. An oxalate salt was prepared and crystallized from 2-propanol to give 2.05 g of impure beige crystals. The oxalate (1.6 g) was converted to the free base (1.3 g) by partitioning between a 10% solution of NH_4OH and Et_2O. Reconversion of this free base to its oxalate salt, and crystallization from 2-propanol gave 1.2 g of pure white crystals (**21**·oxalate). Mp 185°C; ^1H NMR ($CDCl_3$) δ 1.8–2.0 (m, 5H), 2.35 (m, 1H), 2.44 (m, 1H), 2.48 (s, 3H), 2.69 (m, 1H), 3.02 (bs, 1H), 3.24 (dd, 1H, J=12, 7 Hz), 3.43 (t, 1H, J=12 Hz), 4.59 (dd, 1H, J=11, 7 Hz), 6.78 (dd, 1H, J=8, 2.5 Hz), 7.01 (m, 2H), 7.27 (d, 1H, J=8 Hz); CI-MS (NH_3) m/z 324, 326 $(M+1)^+$. Anal. calcd for $C_{16}H_{22}BrNO.C_2H_2O_4$: C 52.18; H 5.84; N 3.38. Found: C 51.98; H 5.81; N 3.32.

4.1.12. *rac*-3-(4-Bromo-2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (22). The 2-azabicyclo[3.3.1]nonane oxalate (**21**·oxalate) (1.2 g) was converted to its free base (0.96 g, 2.96 mmol) by partitioning between dilute NH_4OH and Et_2O. The free base was dissolved in 10 mL of $CHCl_3$ and added to a cold solution of BBr_3 (1.5 mL, 5 equiv. in 25 mL of $CHC1_3$). The reaction mixture was stirred at 5–10°C for 45 min, until TLC indicated the disappearance of the starting material, added to a vigorously stirred solution of NH_4OH and ice, and the stirring was continued for 30 min. The aqueous phase was separated and extracted with $CHC1_3$/MeOH 3:1 (3×150 mL). The combined organic solution was washed with H_2O (3×150 mL), dried over Na_2SO_4 and most of the solvent removed. The residue was filtered through a pad of silica gel to give 0.94 g (99%) of **22** as a white foam after solvent removal. ^1H NMR ($CDC1_3$) δ 6 1.5–1.87 (m, 5H), 2.20 (bd, 1H), 2.40 (m, 1H), 2.44 (s, 3H), 2.61 (m, 1H), 3.06 (bs, 1H), 3.26 (dd, 1H, J=11.5, 7 Hz), 3.38 (t, 1H, J=11.5 Hz), 4.59 (dd, 1H, J=11.5, 7 Hz), 6.72 (d, 1H, J=8 Hz), 6.89 (bs, 1H), 6.93 (d, 1H, J=8 Hz), 7.22 (t, IH, J=8 Hz); CI-MS (NH_3) m/z 310, 312 $(M+H)^+$; HRMS calcd for $C_{15}H_{20}BrNO$: m/z 309.0728, found: 309.0722.

4.1.13. *rac*-2-(4-Bromo-2-methyl-2-azabicyclo[3.3.1]non-5-yl)-[1,4]benzoquinone (23). To the bromide (0.57 g, 1.7 mmol) in 48 mL of DMF was added an aqueous solution of KH_2PO_4 (480 mg in 90 mL of H_2O) and 1.58 g of Fremy's salt. After stirring 1 h, the dark violet solution became reddish-brown in color. The stirring was continued for 16 h, until starting material no longer appeared on TLC. The reaction mixture was diluted with H_2O (300 mL) and extracted with $CHC1_3$ (3×150 mL). The combined organic phase was washed with H_2O, dried (Na_2SO_4), and the solvent removed to give 0.17 g of crude residue. The aqueous material was adjusted to pH 7 with a saturated solution of $NaHCO_3$, and extracted with $CHC1_3$ to give an additional 0.11 g of **23**. The combined residues were purified by preparative TLC (eluent: $CHC1_3$/MeOH (97.5:2.5%)) to give 130 mg (22%) of the pure quinone **23**. IR (KBr) 1652 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.40–1.93 (m, 5H), 2.17–2.34 (m, 2H), 2.47 (s, 3H), 2.48 (m, 1H), 2.80 (bs, 1H), 3.20 (dd, 1H, J=12, 7 Hz), 3.37 (t, 1H, J=11.5 Hz), 5.23 (m, 1H), 6.66 (s, 1H), 6.70 (s, 2H); FAB-MS m/z 324, 326 $(M+H)^+$; HRMS calcd for $C_{15}H_{19}NO_2Br$: m/z 324.0599, found: m/z 324.0600.

4.1.14. *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[2] (6). Quinone **23** (12 mg, 0.03 mmol) was dissolved in MeOH (3 mL) and stirred under nitrogen. Excess $NaBH_4$ was added and the stirring continued for 30 min. The reaction mixture was transferred to a syringe, added

dropwise to a 10% solution of KOH in MeOH/H_2O (1:1, 10 mL) at 0°C (ice-salt bath), and stirred for 1 h at room temperature. H_2O (30 mL) was added and this mixture was slowly added to a saturated solution of NH_4C1 with stirring, adjusting the solution to pH 9. The reaction mixture was extracted with $CHCl_3$/MeOH (3:1). The combined organic phase was washed with H_2O, dried, and the solvent removed to give 7 mg of crude **6**. Preparative TLC (eluent $CHCl_3$/MeOH/NH_4OH, 9:1:0.1) gave 4 mg (44%) of pure **6** that was chromatographically and spectroscopically identical with a known sample of the *para*-d oxide-bridged phenylmorphan isomer.[2]

4.1.15. *rac*-Benzoic acid 5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (24). The 2-azabicyclo-[3.3.1]nonane oxalate (**21**·oxalate) (65 mg) was converted to the off-white solid free base **21** (50 mg, 0.154 mmol) by partitioning between $CHCl_3$ and NH_4OH. This material was dissolved in anhydrous DMF (20 mL), and potassium benzoate (60 mg, 0.375 mmol, 2.5 equiv.) was added to the solution while stirring. The light white suspension was gradually (over 30 min) heated to 80°C, under nitrogen. After 2 h at 80°C, it was cooled to room temperature and diluted with 20 mL of H_2O. The aqueous phase was extracted with Et_2O (3×30 mL). The organic phase was washed with water (2×50 mL), dried over Na_2SO_4 and nearly evaporated to dryness. The residual material was filtered through a short column of silica gel to give the pure ester **24** as a yellowish oil (60 mg, 80%). IR (KBr) 1718, 1272 cm^1; ^1H NMR ($CDCl_3$) δ 1.31–2.21 (m, 7H), 2.44 (m, 1H), 2.70 (s, 3H), 3.17 (m, 1H), 3.76 (s, 3H), 4.56 (m, 2H), 6.71 (dd, 1H, J=8, 2 Hz), 6.98 (bt, 1H), 7.02 (d, 1H, J=8 Hz), 7.22 (t, 1H, J=8 Hz), 7.33 (t, 2H, J=8 Hz), 7.49 (t, 1H, J=7.5 Hz), 7.76 (d, 2H, J=7.5 Hz); CI-MS (NH_3) m/z 366 $(M+H)^+$; HRMS calcd for $C_{23}H_{28}NO_3$: m/z 366.2069, found: m/z 366.2065.

4.1.16. *rac*-(3-Methoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-4-ol (25). The ester **24** (45 mg, 0.12 mmol) was dissolved in MeOH (2 mL) and slowly added to a solution of 3% LiOH in MeOH/H_2O (1:1, 10 mL) with vigorous stirring. The mixture was stirred for 1 h at room temperature under nitrogen, diluted with H_2O (20 mL), and extracted with $CHCl_3$ (2×50 mL). The organic phase was washed with H_2O (2×20 mL), dried over Na_2SO_4 and the solvent nearly removed. The residual material was filtered through a pad of silica gel to give 25 mg (78%) of **25** that was homogeneous on TLC. IR (KBr) 3424, 2925, 1496, 1038 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.30–1.42 (m, 2H), 1.56–1.80 (m, 4H), 1.93–2.07 (m, 2H), 2.42 (m, 1H), 2.63 (s, 3H), 2.90 (m, 1H), 3.11 (m, 1H), 3.80 (s, 3H), 3.95 (bt, 1H), 6.76 (d, 1H, J=8 Hz), 6.88 (bs, 1H), 6.93 (d, 1H, J=8 Hz), 7.24 (t, 1H, J=8 Hz); CI-MS (NH_3) m/z 262 $(M+H)^+$; HRMS calcd for $C_{16}H_{24}NO_2$: m/z 262.1807, found: 262.1778.

4.1.17. *rac*-(Methanesulfonic acid 5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-4-yl ester (26). Methanesulfonyl anhydride (12 mg, 2 equiv.) was added to a solution of **25** (10 mg, 0.03 mmol) in $CHCl_3$ (3 mL) and triethylamine (25 mL). The colorless solution was stirred under nitrogen at room temperature for 1 h, than quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$. The combined organic solutions were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give an unstable oil (8 mg). HRMS calcd for $C_{17}H_{26}NO_4S$: m/z 340.1583, found: 340.1590.

4.1.18. *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-phenyltetrazole ether (27). A mixture of the *ortho*-c oxide-bridged phenylmorphan (**7**) (1.31 g. 5.3 mmol), obtained as a white foam from conversion of **7** fumarate (2.31 g) to free base, and K_2CO_3 (1.33 g, 9.6 mmol) in DMF (200 mL) was stirred under nitrogen at room temperature. 5-Phenylchlorotetrazole (1.108 g, 6.14 mmol) was added and the stirring continued until starting material no longer appeared on TLC (32 h). The reaction mixture was diluted with H_2O (200 mL) and extracted with ether (4×25 mL). The organic phase was washed with H_2O (2×250 mL), dried over Na_2SO_4, and solvent was removed to give **27** (2.11 g, 99.5%) as a solid homogenous on TLC. IR (KBr) 1539, 1453 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.43–2.24 (m, 8H), 2.56 (s, 3H), 3.08 (bs, 1H), 3.21 (dd, 1H, J=11, 5.5 Hz), 3.38 (t, 1H, J=11 Hz), 4.35 (dd, 1H, J=11.5, 5.5 Hz), 6.96 (t, 1H, J=7.5 Hz), 7.03 (d, 1H, J=7.5 Hz), 7.21 (d, 1H, J=8 Hz), 7.5–7.63 (m, 4H), 7.86 (d, 1H, J=7.5 Hz); CI-MS (NH_3) m/z 390 $(M+H)^+$; HRMS calcd for $C_{22}H_{23}N_5O_2$: m/z 389.1852, found: 389.1851.

4.1.19. *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 (28). 10% Pd/C catalyst (2.62 g) was added to a solution of the phenyltetrazole ether (**27**) (2.11 g, 5 mmol) in glacial HOAc (250 mL). The reaction mixture was hydrogenated at room temperature at 30 psi for 24 h. The hydrogenation was continued for an additional 48 h at 50 psi until starting material could no longer be observed on TLC. The reaction mixture was filtered and the catalyst was washed with HOAc and H_2O (200 mL). Ice was added to maintain the temperature at 5°C while the combined acidic solution was carefully neutralized with of NH_4OH (15%, 400 mL). The basic aqueous solution was extracted with $CHCl_3$ (3× 250 mL) and then with $CHCl_3$/MeOH (3:1, 1×200 mL). The combined organic material was washed with H_2O (2×250 mL); and the washings were back extracted with $CHCl_3$ (200 mL). The organic extracts were dried over Na_2SO_4 and the solvent was removed to give **28** (1.94 g). Column chromatography gave pure **28** (560 mg (45%)) that was crystallized as a fumarate salt from 2-propanol/Et_2O. Mp 195–196°C; IR (KBr) 1525, 1338 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.40–2.35 (m, 8H), 2.59 (s, 3H), 3.08 (bs, 1H), 3.27 (dd, 1H, J=10, 5.5 Hz), 3.40 (dd, 1H, J=11.5, 10 Hz), 4.25 (dd, 1H, J=11.5, 5.5 Hz), 6.91 (m, 2H), 7.07–7.16 (m, 2H); CI-MS (NH_3) m/z 230 $(M+H)^+$. Anal. calcd for $C_{15}H_{19}NO{\cdot}C_4H_4O_4$: C 66.07; H 6.71; N 4.06. Found: C 65.64; H 6.64; N 4.02.

4.1.20. *rac*-(3*R*,6a*S*,11a*S*)-2-Methyl-8-nitro-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine (29). $NaNO_2$ (200 mg, 2.9 mmol, 4 equiv.) was slowly added to a solution of **28** (190 mg, 0.82 mmol) in trifluoroacetic acid (4 mL), cooled to +5°C in an ice-salt bath, and the mixture was stirred under nitrogen. After 30 min, only 50% of the starting material reacted according to TLC. An additional 45 mg of $NaNO_2$ (1 equiv.) was added and the mixture was stirred for 2 h, until the starting material was no

longer detectable on TLC. The mixture was diluted with ice water and carefully basified with NH_4OH. The aqueous solution was extracted with $CHCl_3$/MeOH (3:1, 3×200 mL). The combined organic phase was washed with H_2O (2×200 mL), dried over Na_2SO_4 and solvent removed to give 190 mg of crude **29**. Purification by column chromatography afforded 100 mg of the **29** as a white amorphous solid. Crystallization as a hydrobromide salt from 2-propanol gave **29**·HBr as light beige crystals. Mp 240–241°C; IR (KBr) 1517, 1341 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.44–2.35 (m, 8H), 2.60 (s, 3H), 3.13 (bs, 1H), 3.29 (dd, 1H, J=10, 5.5 Hz), 3.44 (t, 1H, J=10 Hz), 4.40 (dd, 1H, J=11.5, 5.5 Hz), 6.94 (d, 1H, J=9 Hz), 7.98 (d, 2H, J=2.5 Hz), 8.13 (dd, 1H, J=9, 2.5 Hz);. CI-MS (NH_3) m/z 275 $(M+H)^+$. Anal. calcd for $C_{15}H_{18}O_3N$·HBr: C 50.72; H 5.39; N 7.89. Found: C 50.77; H 5.60; N 7.75.

4.1.21. *rac*-(3*R*,6a*S*,11a*S*)-8-Amino-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine (30). The off-white crystalline free base of **29** (77 mg), obtained from the HBr salt (92 mg), was dissolved in MeOH (10 mL) containing 0.2 mL of concentrated hydrochloric acid. Pd/C catalyst (60 mg) was added and the solution was hydrogenated at room temperature for 1.5 h until the starting material was no longer detectable on TLC. The mixture was filtered and the catalyst was washed with MeOH. The filtrate was concentrated in vacuo, H_2O was added, and the aqueous solution was extracted with $CHCl_3$ (3×150 mL). The combined organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent removed. The residue was purified by column chromatography on silica gel ($CHCl_3$/5% MeOH) to afford amine **30** (45 mg, 65%). The free base crystallized from 2-propanol as light beige crystals. Mp 208°C; IR (KBr) 3415, 3318, 3194, 1479 cm^{-1}; ^1H NMR ($CDC1_3$) δ 1.44–2.35 (m, 8H), 2.60 (s, 3H), 3.12 (bs, 1H), 3.27 (dd, 1H, J=10, 5.5 Hz), 3.39 (t, 1H, J=10.5 Hz), 3.30 (broad signal, exchangeable with D_2O, 2H), 4.22 (dd, 1H, J=10, 6 Hz), 6.48 (m, 2H), 6.69 (d, 1H, J=9 Hz); EI-MS m/z 244; HRMS calcd for $C_{15}H_{20}N_2O$: m/z 244.1576, found: 244.1589. Anal. calcd for $C_{15}H_{20}N_2O.·0.3H_2O$: C 72.14; H 8.07; N 11.22. Found: C 71.95; 8.20; N 11.21.

4.1.22. *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-8-ol (8). The amine **30** (50 mg, 0.2 mmol), cooled in an ice-salt bath, was dissolved in 30% H_2SO_4 (24 mL). Ice (10 g) was added to the solution, followed by a solution of $NaNO_2$ (17 mg, 0.25 mmol, 1.2 equiv.) in H_2O (5 mL). The mixture was stirred for 2 h under nitrogen, maintaining the temperature at 0°C. This solution was added over 15 min to a cooled aqueous mixture (50 mL) of $Cu(NO_3)_2(H_2O)_3$ (1.2 g, 5 mmol) and Cu_2O (40 mg, 0.28 mmol). The stirring was continued for one h at 0°C, and the reaction mixture was poured into an aqueous solution of 10% KOH (100 mL) and ice. The pH was adjusted to 9 by the addition of a saturated solution of NH_4Cl and the aqueous solution was extracted with $CHCl_3$/MeOH (3:1) to give 20 mg of **8** which was homogeneous on TLC. Crystallization from MeOH afforded white crystalline free base (15 mg). Mp 195–196°C. The hydrobromide salt was crystallized from MeOH, mp 233–234°C. This product was chromatographically and spectroscopically identical with that prepared from **14**. Anal. calcd for $C_{15}H_{19}NO_2$·HBr.0.5H_2O: C 53.74; H 6.16; N 4.18. Found: C 53.34; H 6.09; N 4.10.

4.2. X-Ray crystal data and structure refinement of *rac*-(8α,11aα,6aα)-7-methyl-6a,8,9,10,11-pentahydro-6*H*-8,11a-methanobenzopyrano[3,4-*b*]azepin-2-ol (19)·HBr

$C_{15}H_{20}NO_2^{+1}·Br^{-1}$ (0.20×0.20×0.39 mm^3), triclinic space group $P1$bar, a=7.550(1) Å, b=7.771(1) Å, c=12.659(2) Å and α=98.15(1)°, β=98.53(1)°, and γ=95.563(1)°, V=721.8(2) $Å^3$, Z=2, ρ_{calc}=1.50 mg/mm^{-3}, μ=3.86 mm^{-1}, F(000)=336, 1988 unique data (Rint=0.022), $R1$=0.042 for 1901 observed data and 0.045 for all 1988 data.

4.3. *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 (7)·$CHCl_3$

$C_{15}H_{19}NO_2·CHCl_3$ (0.08×0.28×0.72 mm^3), monoclinic space group $P2_1/c$, a=6.968(1) Å, b=13.406(3) Å, c=18.132(4) Å and β=91.11(2)°, V=1693.4(6) $Å^3$, Z=4, ρ_{calc}=1.43 mg/mm^{-3}, μ=0.55 mm^{-1}, F(000)=760, 2236 unique data (Rint=0.02), $R1$=0.044 for 1564 observed data and 0.072 for all 2236 data.

4.4. *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-8-ol (8)·HBr

$C_{15}H_{20}NO_2^{+1}·Br^{-1}$ (0.42×0.60×0.62 mm^3), triclinic space group $P1$bar, a=7.546(1) Å, b=10.010(1) Å, c=10.563(1) Å and α=74.43(1)°, β=70.35(1)°, and γ=85.63(1)°, V=723.8(2) $Å^3$, Z=2, ρ_{calc}=1.50 mg/mm^{-3}, μ=3.85 mm^{-1}, F(000)=336, 1989 unique data (Rint=0.03), $R1$=0.035 for 1958 observed data and 0.035 for all 1989 data.

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