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Synthesis of *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol. An unusual double rearrangement leading to the *ortho*- and *para*–f oxide-bridged phenylmorphan isomers †‡

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In an attempt to obtain the *para*-f isomer, *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol, *via* mesylation of an intermediate 9α-hydroxyphenylmorphan, we obtained, instead, a rearranged chloro compound with a 5-membered nitrogen ring, 7-chloro-3a-(2,5-dimethoxyphenyl)-1-methyl-octahydroindole. This indole underwent a second rearrangement to give us the desired *para*-f isomer. The structures of the intermediate indole and the final product were unequivocally established by X-ray crystallography. A resynthesis of the known *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, the *ortho*-f isomer, was achieved using the reaction conditions for the *para*-f isomer, as well as under Mitsunobu reaction conditions where, unusually, the oxide-bridge ring in the 5-phenylmorphan was closed to obtain the desired product. The synthesis of the *para*-f isomer adds an additional compound to those oxide-bridged phenylmorphans that were initially visualized and synthesized; the establishment of the structure and configuration of 8 of the theoretically possible 12 racemates has now been achieved. The X-ray crystallographic structure analysis of the *para*-f isomer provides essential data that will be needed to establish the configuration of a ligand necessary to interact with an opioid receptor.

Introduction

As part of our continuing study[1] of the relationship between the three-dimensional structure of ligands that interact with opioid receptors and their pharmacological effects, we have synthesized a number of oxide-bridged 5-phenylmorphans (Fig. 1). These compounds are based on the 5-phenylmorphan opioids that have been found to interact with high affinity at μ or δ opioid receptors as agonists or antagonists.[2–5] Although it has been stated that steric hindrance of the rotation of the phenolic ring in the 5-phenylmorphans can induce opioid antagonist activity,[6] as determined in the GTPγS assay, we have found that steric hindrance is not necessary to produce an opioid antagonist in this series but that the restricted rotation may increase opioid receptor affinity.[5] In order to find the optimal angle between the phenolic ring and a plane drawn through the piperidine ring that would be optimal for opioid agonist or antagonist activity, we have been engaged for some time,[7–10] in the synthesis of structurally related compounds in which that angle is fixed and determinable by X-ray crystallography.

In the oxide-bridged phenylmorphans, the oxide bridge can theoretically be established at positions a through f, as shown in Fig. 1 (**1**), fixing the dihedral angle between the phenolic and piperidine rings. Assuming that at least some of the 12 positional racemic isomers (24 enantiomers) that we will synthesize show good affinity for opioid receptors, this should provide definitive information about the necessary spatial position of the phenolic ring for interaction with an opioid receptor. Both the *ortho* and *para* phenolic compounds will be prepared because it has been found that the hydroxyl group is essential for increased affinity to the opioid receptor, and we cannot predict whether the *ortho* or *para* compound will be most effective in this new series.[11] It is likely that at least some of the oxide-bridged isomers will have pharmacological activity; a compound with a similar structure, 4a-ethyl-2-phenethyl-1,2,3,4,4a,9a-hexahydro-benzo[4,5]furo[2,3-*c*]pyridin-6-ol (**2**, Fig. 1), has been found to have nanomolar affinity for the μ-opioid receptor.[12] The syntheses of **7** of the 12 possible racemic oxide-bridged phenylmorphans have been published thus far, both *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[7,9] (**3**, the *ortho*-a oxide-bridged phenylmorphan isomer), as well as an improved synthesis of the *ortho*-a oxide-bridged phenylmorphan isomer,[13] and *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[13] (**4**, the *para*-a oxide-bridged phenylmorphan isomer), *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[1] (**5**, the *ortho*-c oxide-bridged phenyl-

† Electronic supplementary information (ESI) available: further crystallographic details. See http://www.rsc.org/suppdata/ob/b3/b312633c/

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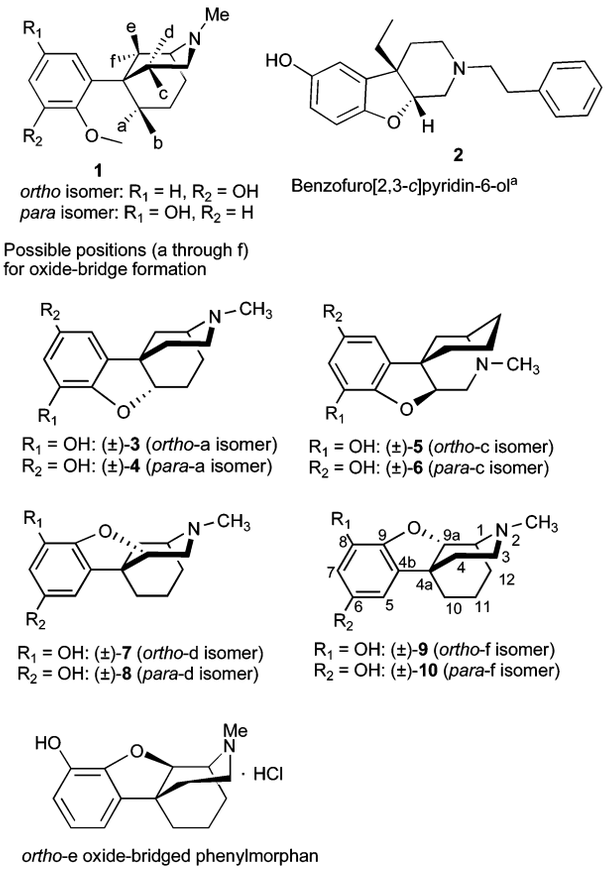


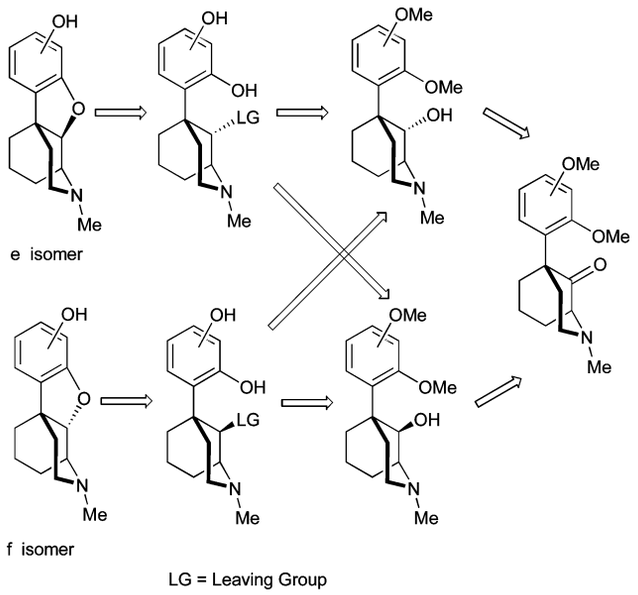
[a] Hutchinson et al.[12]

Fig. 1 Oxide-bridged phenylmorphan isomers and related compounds.

morphan), *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[1] (**6**, the *para*-c oxide-bridged phenylmorphan), *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[10] (**7**, the *ortho*-d 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,[14] (**8**, the *para*-d oxide-bridged phenylmorphan isomer), 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[7,9] (**9**, the *ortho*-f oxide-bridged phenylmorphan isomer). We now report the synthesis of the eighth isomer, *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol (**10**, Fig. 1),[7] the *para*-f oxide-bridged phenylmorphan), in which the restricted rotation of the phenyl ring enables an exact determination of the dihedral angle of the aromatic ring to the piperidine ring through an X-ray crystallographic study of this isomer. A novel synthesis of the *ortho*-f oxide-bridged phenylmorphan (**9**), in which the oxide bridge was closed under Mitsunobu reaction conditions, will also be reported.

Results and discussion

We previously reported the successful synthesis of the c- and d-oxide-bridged phenylmorphan isomers using an intramolecular nucleophilic substitution reaction of the appropriate phenol with a suitably positioned leaving group (methanesulfonyloxy or bromide) on a bicyclononane moiety.[1,14] A similar approach was attempted for the preparation of the epimeric e- and f-isomers (Fig. 1), as shown in the retrosynthetic Scheme 1. We postulated the formation of the f-oxide-bridged phenylmorphans from a compound that bore a suitable leaving group (LG) in the C9 β-position in the bicyclo framework, while the e-isomer



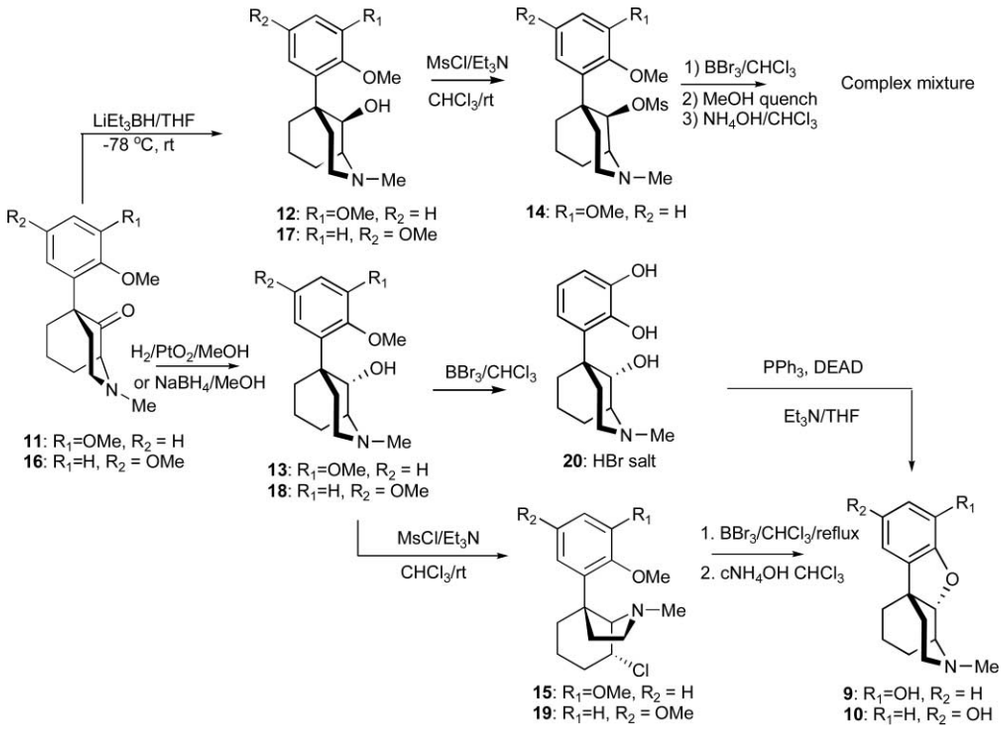
Scheme 1 Retrosynthetic approach to e and f oxide-bridged phenylmorphans.

would arise from a similar compound bearing that LG in the C9 α-position. Both alcohols could be obtained by stereoselective reduction of the 9-phenylmorphans 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one and 5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one (**11** and **16**, Scheme 2). Initially, we chose to examine the reaction pathway towards the *ortho*-f isomer since the properties of the *ortho* f-isomer compound were known.[7,9]

The ketone **11** was reduced to the C9 β-alcohol **12** with $LiEt_3BH$, and the C9 α-alcohol **13** was obtained by either PtO_2 or $NaBH_4$ reduction (Scheme 2). The stereochemistry of the alcohols was determined by ^{1}H NMR through comparison with similar compounds in the literature.[15] The C9 proton in **12**, *trans* to the nitrogen atom, was more deshielded (δ 4.51 ppm) than the C9 proton *cis* to the nitrogen atom, in **13** (δ 4.31 ppm). Awaya *et al.*[15] reported chemical shifts of δ 4.32 and 4.14 ppm for the protons *trans* and *cis* to the nitrogen atom, respectively, in their 5-phenylmorphans.

Mesylation of the β-alcohol **12** gave **14** in high yield (Scheme 2). However, upon treatment with BBr_3 and a subsequent quench in diluted ammonia, a mixture containing products from the elimination of the mesyl moiety was obtained. In contrast the mesylation reaction of the α-alcohol **13** under the same conditions resulted in a single product that was, surprisingly, not a mesylate but a rearranged chloro compound with a 5-membered nitrogen ring (**15**). The related structure of the compound in the *para*-series, 7-chloro-3a-(2,5-dimethoxyphenyl)-1-methyl-octahydroindole (**19**), was unequivocally determined by X-ray crystallography (Fig. 2). We attempted the ring closure of compound **15** in an analogous way to that formerly described as it is known that chloromethylpyrrolidines can be easily converted to 3-chloropiperidines with defined stereochemistry.[16] Gratifyingly, treatment of **15** with BBr_3, followed by ammonium hydroxide, gave us a moderate yield of the known *ortho*-f isomer, as we anticipated from the structure of the starting material (Scheme 2). The free base was essentially identical with an authentic sample by TLC, CIMS, and ^{1}H-NMR, and the HCl salt had essentially the same mp as the known *ortho*-f isomer.[9]

A similar suite of reactions led from (2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol **18** to the previously unknown *para*-f isomer **10** (Scheme 2). The stereoselective reduction of the ketone **16** gave the regioisomers **17** and **18**. Thus, $LiEt_3BH$ reduction gave the β-alcohol **17** as the major product (Scheme 2). As we found in the *ortho* series, this



Scheme 2 Synthesis of *ortho*- and *para*-f isomers.

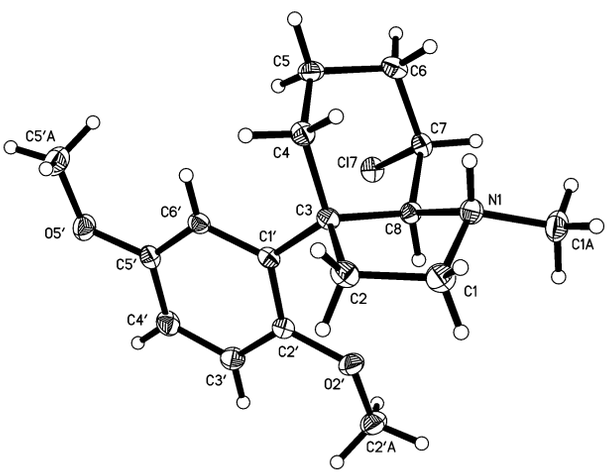


Fig. 2 X-Ray crystallographic structure of **19**·HCl.

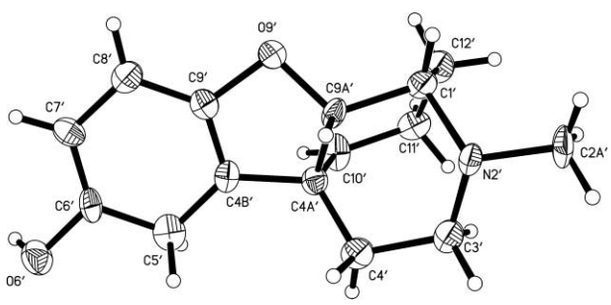
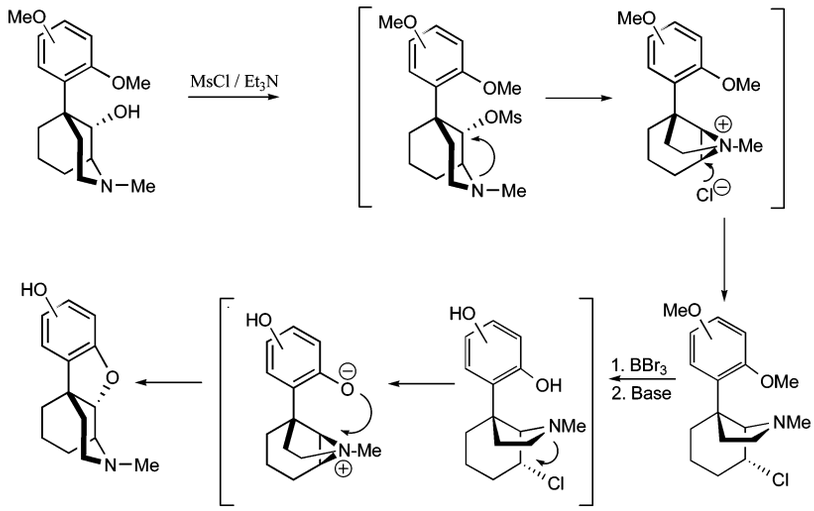


Fig. 3 X-Ray crystallographic structure of **10**·HBr.

β-alcohol **17** could be mesylated, but upon BBr_3 mediated cleavage of the methyl ethers, only a complex mixture containing the mesyl elimination products could be obtained from that compound. Hydrogenation of ketone **16** over PtO_2 or $NaBH_4$ reduction gave the α-alcohol **18** as almost the sole product. As in the *ortho* series, conversion into the chloro-compound **19**, from α-alcohol **21** was achieved by the mesylation procedure. In order to confirm the structure of **19**, we obtained X-ray diffraction data, as noted above. The result (Fig. 2) showed that this chloro-compound **19** had the 5,6-ring system (Scheme 2). Subsequent demethylation followed by base-induced ring-closure produced a compound (**10**) that was spectroscopically similar to the *ortho*-f isomer. An X-ray structure analysis confirmed that the product was indeed the desired *para*-f isomer (Fig. 3). Note that in compounds **9** and **10**, the stereochemistry is the same as in the starting alcohol. A double nucleophilic substitution reaction is invoked to explain this outcome (Scheme 3). Upon mesylation, the basic amine, which is in *trans* disposition relative to the mesylate, displaces the mesylate, and a quaternary aziridinium ion is formed that is attacked by the chloride at the least sterically hindered carbon atom with the formation of the observed 5,6-ring system. Upon deprotection of the phenolic function and treatment with base, the same sequence occurs in reverse. The amine displaces the chloride with formation of the aziridinium ion, which is ring opened intramolecularly by the phenoxide ion, yielding the epoxy-bridged phenylmorphan with the observed stereochemistry (for a comprehensive review of similar aziridium ion rearrangements, see Cossy and Pardo).[16]

We have also examined the Mitsunobu reaction as an alternative oxide-ring closure method to obtain the *ortho*-e oxide-bridged phenylmorphan (Fig. 1). The Mitsunobu reaction has emerged as a widely used methodology in preparative organic chemistry.[17,18] Although the intramolecular cyclization of an amino alcohol under the Mitsunobu reaction conditions has been used to synthesize some alkaloids, there has been no report of its use in forming the oxide-bridge in morphine-like molecules and their analogues. In order to explore that possibility, the 9α alcohol **13** was demethylated with BBr_3 affording the phenol **20** in good yield, isolated as the HBr salt. We used **20**·HBr in the Mitsunobu reaction, since attempts to isolate the phenol **20** as a free base were unsuccessful due to its instability under alkaline conditions. Upon treatment of **20**·HBr with 2.5 equivalents of PPh_3 and DEAD in anhydrous THF with or without Et_3N under argon, a cyclization product was isolated in 43% yield after purification by silica gel column chromatography. To our surprise, however, X-ray crystallographic structure analysis indicated that the product we obtained was not the expected *ortho*-e isomer, but the known *ortho*-f isomer **9** (Fig. 4). We hypothesize that the *ortho*-f isomer could have been formed



Scheme 3 Possible mechanism of rearrangements.

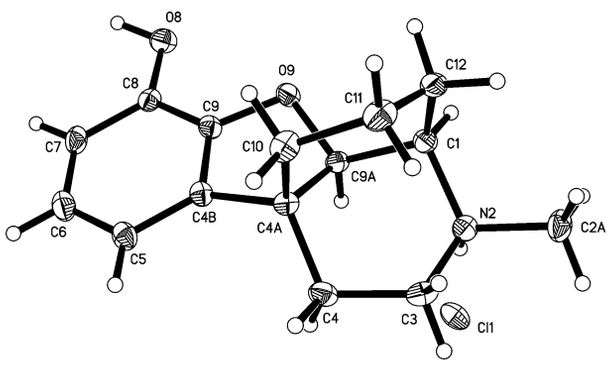


Fig. 4 X-Ray crystallographic structure of **9**·HCl.

through an intermediate aziridium ion as described above (Scheme 3). As far as we know, a 'double' nucleophilic ring closure under Mitsunobu conditions has not been previously described. Attempts to synthesize the *ortho*-e isomer from the corresponding 9β alcohol **12** under similar conditions failed, which is in accordance with the lack of success in our efforts to ring close the 9β mesylates.

Conclusions

Two methods were found that could stereospecifically close the epoxy bridge in the f-isomer series of epoxyphenylmorphans. One of the methods utilized Mitsunobu reaction conditions, resulting in a new synthesis of the *ortho*-f isomer. A new oxide-bridged phenylmorphan, the *para*-f isomer, *rac*-(1*R*,4a*R*,9a*R*)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]-pyridin-6-ol (**10**), was obtained *via* an unexpected intermediate, 7-chloro-3a-(2,5-dimethoxyphenyl)-1-methyl-octahydroindole (**19**) by a double rearrangement. The X-ray crystallographic structure analysis of the *para*-f oxide-bridged phenylmorphan **10** (and the *ortho*-isomer **9**) showed that the dihedral angle between the least-squares planes through the phenyl ring and atoms C3, C4, C9a, and C1 of the piperidine ring was 10.3° for **10** (and 9.2° for the *ortho*-isomer **9**), and the torsion angle C10–C4a–C4b–C9 was −85.5° for **10** (and −89.0° for the *ortho*-isomer **9**). These data will provide the essential input for an SAR correlation when the pharmacological data for all of these oxide-bridged phenylmorphans are in hand.

Experimental

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). Chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 40600 mass spectrometer. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Thin layer chromatography (TLC) was performed on analytical (250 μ) or preparative (1000 μ) Analtech silica gel plates using $CHCl_3$: MeOH : concentrated NH_4OH (85 : 15 : 0.5) as the solvent system, unless otherwise mentioned. 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 MoKα radiation 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 SHELXTL system of programs.[19] 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 **9** and **10**). Atomic coordinates for **9**, **10**, and **19** have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference numbers [220253–220255]. See http://www.rsc.org/suppdata/ob/b3/b312633c/ for crystallographic data in.cif or other electronic format. (Compound **9**: CCDC 220255; Compound **10**: CCDC 220253; Compound **19**: CCDC 220254.)

5-(2,3-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-9β-ol (12)

A solution of 1.0 M $LiEt_3BH$ in THF (1.3 mL, 1.3 mmol) was added dropwise under argon to 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one[13] (**11**, 188 mg, 0.65 mmol) dissolved in dry THF (5.0 mL) and cooled to −78 °C. The mixture was stirred in the cold for 10 min and then allowed to warm to room temperature for 50 min. The reaction mixture was re-cooled in a dry ice–acetone bath and quenched with acetone (1 mL). The resulting mixture was stirred at room temperature for 10 min. 3 M HCl (2 mL) was added to this, and the mixture was refluxed for 1 h. After cooling in an ice–water bath, the mixture was basified with 10% aqueous NaOH and extracted with ether (2×). The organic layers were washed with

brine and dried over anhydrous Na_2SO_4. Filtration and evaporation gave **12** (190 mg, quantitatively) as a colorless oil. The free base was converted into the HCl salt with HCl–MeOH. The crude salt was recrystallized from EtOH–ether to afford **12**·HCl (186 mg, 87%) as colorless crystals, mp 204–206 °C (dec). *m*/*z* (CIMS–NH_3): 292 (MH^+ as base peak). ^{1}H NMR of free base: δ 1.44–1.94 (4H, m), 2.10–2.33 (3H, m), 2.41–2.47 (1H, m), 2.43 (3H, s), 2.75 (1H, dd, J = 7.7, 11.6 Hz), 3.01 (2H, td, J = 5.2, 12.3 Hz), 3.85 (3H, s), 3.88 (3H, s), 4.31 (1H, d, J = 3.7 Hz), 6.81 (1H, dd, J = 1.5, 8.0 Hz), 7.01 (1H, t, J = 8.1 Hz), 7.09 (1H, dd, J = 1,5, 8.1 Hz). Found: C, 61.48; H, 8.00; N, 4.20; Cl, 10.58. Calc. for $C_{17}H_{26}ClNO_3 \cdot 0.25H_2O$: C, 61.43; H, 8.04; N, 4.21; Cl, 10.67%.

5-(2,3-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-9α-ol (13)

a) PtO_2 catalyzed reduction. A solution of ketone **11**[13] (197 mg, 0.68 mmol) in MeOH (20 mL) was hydrogenated over PtO_2 (20 mg) under H_2 gas pressure (40 psi) for 18.5 h. The mixture was filtered and the solid material was washed with MeOH. The combined filtrate and washings were evaporated to afford crude **13** (199 mg, quantitative), as a colorless foam, which was crystallized from ethyl acetate to afford colorless crystals, mp 219–222 °C. The free base was converted into the hydrochloride salt with HCl–MeOH. The crude crystals were recrystallized from a mixture of EtOH and diethyl ether to afford pure **13**·HCl (193 mg, 87%) as colorless fine needles, mp 223–224 °C (dec). *m*/*z* (CIMS–NH_3): 292 (MH^+ as base peak). ^{1}H NMR of free base: δ 1.65–2.22 (8H, m), 2.51 (3H, s), 2.77 (1H, br ddd, J = 2.3, 7.0, 11.9 Hz), 2.90 (1H, br s), 3.02 (2H, br d, J = 5.1, 11.8 Hz), 3.87 (3H, s), 3.91 (3H, s), 4.51 (1H, d, J = 4.0 Hz), 6.81 (1H, dd, J = 2.3, 7.3 Hz), 6.99 (1H, dd, J = 2.2, 8.2 Hz), 7.04 (1H, br t, J = 7.8 Hz). Found: C, 62.00; H, 8.00; N, 4.22. Calc. for $C_{17}H_{26}ClNO_3$: C, 62.28; H, 7.99; N, 4.27%.

b) $NaBH_4$ reduction. $NaBH_4$ (76 mg, 2.01 mmol) was added portionwise to an ice–water cooled solution of **11**·HCl (218 mg, 0.67 mmol) in MeOH (5.0 mL) and stirred for 30 min, followed by stirring at room temperature for another 30 min. The reaction mixture was quenched with saturated $NaHCO_3$ and the resulting mixture was stirred at room temperature for 5 min. After extraction with diethyl ether (2×), the organic layers were washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation gave crude **13** (195 mg, quantitative) as colorless crystals. In the manner described above, **13**·HCl (184 mg, 84%) was prepared as colorless fine needles, mp 223–224 °C.

Methanesulfonic acid 5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-9-yl ester (14)

Methanesulfonyl chloride (0.05 mL, 0.64 mmol) was added dropwise to an ice–water cooled solution of **12**·HCl (119 mg, 0.36 mmol) and triethylamine (0.18 mL, 1.29 mmol) in $CHCl_3$ (8.0 mL). The mixture was stirred in the cold for 5 min and at room temperature for 60 min. The reaction mixture was diluted with $CHCl_3$, washed successively with aqueous $NaHCO_3$, water, and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave a slight yellow–brown solid, which was purified by silica gel preparative TLC ($CHCl_3$: MeOH, 10 : 1) to afford **14** (125 mg, 95%) as slightly greenish–yellow crystals, mp 119 −121 °C. *m*/*z* (CIMS–NH_3): 370 (MH^+ as base peak). ^{1}H NMR: δ 1.60–2.04 (5H, m), 2.16–2.30 (2H, m), 2.4–2.6 (1H, m), 2.44 (3H, s), 2.61 (3H, s), 2.90–3.00 (1H, m), 3.05 (1H, d, J = 4.5, 12 Hz), 3.38 (1H, m), 3.84 (3H, s), 3.97 (3H, s), 5.67 (1H, br d, J = 4.0 Hz), 6.85 (1H, dd, J = 2.2, 7.7 Hz), 6.88 (1H, dd, J = 2.0, 7.6 Hz), 6.99 (1H, t, J = 7.9 Hz).

7-Chloro-3a-(2,3-dimethoxyphenyl)-1-methyl-octahydroindole (15)

To an ice–water cooled solution of **13**·HCl (103 mg, 0.31 mmol) in $CHCl_3$ (5.0 mL) was added triethylamine (0.17 mL, 1.22 mmol) followed by methanesulfonyl chloride (0.07 mL, 0.90 mmol). The mixture was stirred in the cold for 5 min and at room temperature for 2 h. The reaction mixture was diluted with AcOEt, washed successively with saturated $NaHCO_3$, water, and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave a pale brown solid (100 mg), which was purified by silica gel preparative TLC (AcOEt : hexane, 1 : 1) to afford **15** (65.5 mg, 76%) as an almost colorless crystalline solid. *m*/*z* (CIMS–NH_3): 312 (MH^+ + 2), 310 (MH^+ as base peak). ^{1}H NMR: δ 1.50–1.62 (1H, m), 1.76–1.98 (4H, m), 2.08–2.26 (3H, m), 2.40 (3H, s), 2.56 (1H, dd, J = 9.3, 18.0 Hz), 3.25 (1H, br t, J 8.5 Hz), 3.46 (1H, d, J = 5.6 Hz), 3.87 (3H, s), 3.96 (3H, s), 4.16 (1H, m), 6.86 (1H, dd, J = 2.9, 6.5 Hz), 6.96–7.03 (2H, m). The structure was confirmed by its comparison with the corresponding *para*-isomer **19**, which was established by X-ray crystallographic structure analysis.

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 (9, *ortho* f-isomer)

Under an argon atmosphere, BBr_3 (0.10 mL, 1.06 mmol) was added to a dry ice–acetone cooled suspension of **15** (32.3 mg, 0.10 mmol) in $CHCl_3$ (5.0 mL). The mixture was stirred in the cold for 5 min and at room temperature for 2 h. The solvent was removed *in vacuo* to afford a colorless foam, which was suspended in $CHCl_3$ (2.0 mL) and the mixture was cooled in an ice–water bath. Under an argon atmosphere, concentrated NH_4OH (1.5 mL) was added to this cooled suspension The resulting two-phase mixture was stirred in the cold for 1 h and at room temperature for 1 h. The reaction mixture was diluted with $CHCl_3$: MeOH (15 : 1 by volume), washed with water and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave a dark brown solid, which was purified by silica gel preparative TLC ($CHCl_3$: MeOH, 10 : 1) to afford the *ortho*-f isomer **9** (13.0 mg, 51%) as a slightly yellow–brown crystalline-solid. The free base was converted into the HCl salt with HCl–MeOH. The crude salt was recrystallized from MeOH–ether to afford **9**·HCl, mp 274–276 °C (dec) (lit.[9] mp 278–280 °C). *m*/*z* (CIMS–NH_3): 246 (MH^+ as base peak). ^{1}H NMR of free base: δ 1.48–1.82 (5H, m), 2.00–2.23 (3H, m), 2.57 (3H, s), 2.94 (1H, dd, J = 7., 12.1 Hz), 3.05 (1H, td, J = 5.4, 12.4 Hz), 3.58 (1H, m), 4.05 (1H, d, J = 3.4 Hz), 6.61 (1H, dd, J = 2.8,, 5.8Hz), 6.72–6.79 (2H, m). The NMR spectrum was essentially the same as that of the formerly described *ortho*-f isomer **9**.[9]

5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-9β-ol (17)

A solution of 1.0 M $LiEt_3BH$ in THF (11.5 mL, 11.50 mmol) was added dropwise, under argon, to a stirred solution of **16** (1100 mg, 3.80 mmol) in dry THF (20 mL) over a 25 min period at −78 °C. After the addition was complete, the mixture was stirred in the cold for 60 min and then allowed to warm to room temperature for 20 min. The reaction mixture was quenched with acetone (2.0 mL) with dry ice–acetone cooling. The resulting mixture was stirred at room temperature for 10 min, 6 M HCl (4 mL) was added to this, and the mixture was stirred for another 10 min. The solvent was removed *in vacuo* and the residue was basified with aqueous $NaHCO_3$ and extracted with AcOEt (2×). The organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave **17** (911 mg, 82%) as an almost colorless solid. The free base was converted into its HCl salt with HCl–MeOH. The crude salt was recrystallized from EtOH–ether to afford **17**·HCl, mp 134–136 °C. *m*/*z* (CIMS–NH_3): 292 (MH^+ as base peak). ^{1}H NMR of free base: δ 1.44–1.87 (4H, m), 2.10–2.45 (4H, m), 2.41 (3H, s), 2.72 (1H, dd, J = 7.4, 11.5 Hz), 2.93–3.03 (2H, td, J = 5.2, 12.3 Hz), 3.77 (3H, s), 3.79 (3H, s), 4.42 (1H, d, J = 3.7 Hz), 6.69 (1H, dd, J = 3.0, 8.8Hz), 6.81 (1H, d, J = 8.8 Hz), 7.04 (1H, J = 3.1 Hz). Found: C, 59.23; H, 8.12; N,

4.03; Cl, 10.31. Calc. for $C_{17}H_{26}ClNO_3 \cdot H_2O$: C, 59.04; H, 8.16; N, 4.05; Cl, 10.25%.

5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonan-9α-ol (18)

a) PtO_2 catalyzed reduction. : A solution of the ketone **16** (840 mg, 2.90 mmol) in MeOH (60 mL) was hydrogenated over PtO_2 (90 mg) under H_2 gas pressure (45 psi) for 16 h. The catalyst was filtered off and washed with MeOH. The combined filtrate and washings were evaporated to afford **18** (816 mg, 97%) as colorless crystals, mp 120–123 °C. The free base was converted into the HCl salt with HCl–MeOH. The crude salt was recrystallized from EtOH–ether to afford **18**·HCl as colorless needles, mp 215–216 °C (dec). *m*/*z* (CIMS–NH_3): 292 (MH^+ as base peak). ^{1}H NMR of free base δ 1.65–2.31 (8H, m), 2.51 (3H, s), 2.79 (1H, ddd, J = 3.5, 6.9, 11.6 Hz), 2 93–3.02 (2H, td, J = 5.2, 11.5 Hz), 3.76 (3H, s), 3.82 (3H, s), 4.71 (1H, d, J = 4.0 Hz), 6.73 (1H, dd, J = 2.9, 8.8 Hz), 6.84 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J = 3.0 Hz). Found: C, 62.05; H, 7.97; N, 4.20; Cl, 10.72. Calc. for $C_{17}H_{26}ClNO_3$: C, 62.28; H, 7.99; N, 4.27; Cl, 10.81%.

b) $NaBH_4$ reduction. Under an argon atmosphere, $NaBH_4$ (65 mg, 1.72 mmol) was added in one portion to a stirred suspension of **16**·HBr (200 mg, 0.54 mmol) in MeOH (5.0 mL) at −78 °C. The mixture was stirred at the same temperature for 30 min and at 0–5 °C (in an ice–water bath) for 30 min, 3 M HCl (2.0 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was basified with saturated $NaHCO_3$ and extracted with AcOEt (2×). The organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave **18** (118 mg, 75%) as a nearly colorless foam, which was crystallized from AcOEt–hexane, mp 118–121 °C.

7-Chloro-3a-(2,5-dimethoxyphenyl)-1-methyl-octahydroindole (19)

Methanesulfonyl chloride (0.44 mL, 5.66 mmol) was added dropwise to an ice–water cooled solution of **18** (816 mg, 2.80 mmol) and triethylamine (1.20 mL) in $CHCl_3$ (30 mL). The mixture was stirred in the cold for 10 min and at room temperature for 20.5 h. The reaction mixture was washed with aqueous $NaHCO_3$, water, and brine and then dried over anhydrous Na_2SO_4 and K_2CO_3. Filtration and evaporation gave a pale yellow–brown viscous oil (1 g), which was purified by silica gel column chromatography (AcOEt : hexane, 2 : 1) to afford **19** (351 mg, 41%) as a slightly yellow oil. This was converted into an HCl salt with HCl–MeOH. The crude salt was recrystallized from AcOEt to afford pure **19** as colorless small plates, mp 148–151 °C. *m*/*z* (CIMS–NH_3): 312 (MH^+ + 2), 310 (MH^+ as base peak). ^{1}H NMR of free base: δ 1.49–1.60 (1H, m), 1.75–1.95 (4H, m), 2.07–2.18 (2H, m), 2.24 (1H, ddd, J = 2.0, 8.0, 15 Hz), 2.36 (3H, s), 2.56 (1H, dd, J = 9.1, 18.2 Hz), 3.21 (1H, td, J = 2.0, 8.8 Hz), 3.52 (1H, d, J = 5.9 Hz), 3.78 (3H, s), 3.83 (3H, s), 4.09 (1H, m), 6.73 (1H, dd, J = 2.8, 8.8 Hz), 6.83 (1H, d, J = 8.9 Hz), 6.98 (1H, d, J = 2.9 Hz). Found: C, 56.24; H, 7.48; N, 3.90; Cl, 19.58. Calc. for $C_{17}H_{25}ClNO_2 \cdot H_2O$: C, 56.05; H, 7.47; N, 3.84; Cl, 19.46%. The structure was confirmed by X-ray crystallographic structure analysis.

rac-(1*R*,4a*R*,9a*R*)-2-Methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol (10, *para*-f isomer)

BBr_3 (1.10 mL, 11.64 mmol) was added dropwise to a stirred solution of **19** (192 mg, 0.55 mmol) in $CHCl_3$ (15 mL). After the addition was complete, the mixture was stirred for 1 h and then refluxed for 17 h. The solvent was removed *in vacuo* to give a brown solid, which was suspended in $CHCl_3$ (8.0 mL) and the mixture was cooled in an ice–water bath, concentrated NH_4OH (5.0 mL) was added under argon, and the resulting two phase mixture was stirred in the cold for 1 h and at room temperature for 23 h. The reaction mixture was diluted with $CHCl_3$–MeOH (15 : 1 by vol), washed with water (2×) and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation gave the *para*-f isomer **10** as a pale brown crystalline solid, mp 218–224 °C. This was dissolved in MeOH and treated with HCl–MeOH. The solvent was removed *in vacuo* to afford pale brown crystals. Recrystallization from MeOH–ether afforded the **10**·HCl (127 mg, 80%) as pale brown fine needles, mp 264–267 °C (dec). *m*/*z* (CIMS–NH_3): 246 (MH^+ as base peak). ^{1}H-NMR ($CDCl_3$-DMSO-d_6) as free base δ: 42–1.83 (5H, m), 2.07–2.25 (3H, m), 2.57 (3H, s), 2.96 (1H, dd, J = 7, 12 Hz), 3.10 (1H, td, J = 6, 12 Hz), 3.41 (1H, m), 4.13 (1H, d, J = 3.6 Hz), 6.59 (1H, dd, J = 2.8, 7.8 Hz), 6.61 (1H, s,), 6.71 (1H, d, J = 8.1 Hz), 8.01 (1H, br s). Found: C, 63.16; H, 7.20; N, 4.92; Cl, 12.47. Calc. for $C_{15}H_{20}ClNO_2 \cdot 0.2H_2O$: C, 63.13; H, 7.20; N, 4.91; Cl. 12.42%. In a similar manner, the HBr salt of **10** was obtained as colorless thin plates, mp 262–266 °C (dec). Found: C, 55.12; H, 6.36; N, 4.26. Calc. for $C_{15}H_{20}BrNO_2$: C, 55.23; H, 6.18; N, 4.29%. The structure of **10**·HBr was confirmed by X-ray crystallographic structure analysis.

3-(9α-Hydroxy-2-methyl-2-azabicyclo[3.3.1]non-5-yl)-benzene-1,2-diol (20)

BBr_3 (0.7 mL, 7.4 mmol) was added dropwise to a solution of alcohol **13** (243 mg, 0.74 mmol) in dry $CHCl_3$ at −78 °C under argon. The mixture was stirred at −78 °C for 10 min, then allowed to warm to room temperature for 2 h. The reaction mixture was re-cooled to −78 °C, and quenched carefully with MeOH. The solvent was removed and the residue dried *in vacuo*. The resulting foam was recrystallized from EtOH–EtOAc to give **20** (215 mg, 78%) as a white solid, *m*/*z* (CIMS–NH_3): 264 (MH+, 100), 246 (M-18, 20).

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 (9, *ortho*-f isomer)

Diethyl azodicarboxylate (DEAD) (775 μL, 5.14 mmol) was added dropwise to a stirred solution of **20** (679 mg, 1.97 mmol) and triphenylphosphine (509 mg, 5.14 mmol) in dry THF (35 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2 : MeOH (10 : 1) to afford **9** (209 mg, 43%) as a colorless oil. The free base was converted to the HCl salt with HCl–MeOH, and recrystallized from MeOH–isopropanol. The isomer **9**·HCl was obtained as white needles, mp 268–270 °C (dec.). X-Ray crystallographic analysis confirmed that the obtained product was the *ortho*-f isomer, rather than the expected *ortho*-e isomer.

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