Synthesis and pharmacological effects of the enantiomers of the *N*-phenethyl analogues of the *ortho* and *para* e- and f-oxide-bridged phenylmorphans†‡

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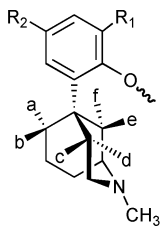
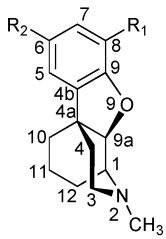
The *N*-phenethyl analogues of (1*R**,4a*R**,9a*S**)-2-phenethyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-6-ol and 8-ol and (1*R**,4a*R**,9a*R**)-2-phenethyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2.3-*c*]pyridin-6-ol and 8-ol, the *ortho*- (**43**) and *para*-hydroxy e- (**20**), and f-oxide-bridged 5-phenylmorphans (**53** and **26**) were prepared in racemic and enantiomerically pure forms from a common precursor, the quaternary salt **12**. Optical resolutions were accomplished by salt formation with suitable enantiomerically pure chiral acids or by preparative HPLC on a chiral support. The *N*-phenethyl (−)- *para*-e enantiomer (1*S*,4a*S*,9a*R*-(−)-**20**) was found to be a μ-opioid agonist with morphine-like antinociceptive activity in a mouse assay. In contrast, the *N*-phenethyl (−)-*ortho*-f enantiomer (1*R*,4a*R*,9a*R*-(−)-**53**) had good affinity for the μ-opioid receptor (K_i = 7 nM) and was found to be a μ-antagonist both in the [^{35}S]GTP-γ-S assay and *in vivo.* The molecular structures of these rigid enantiomers were energy minimized with density functional theory at the level B3LYP/6-31G* level, and then overlaid on a known potent μ-agonist. This superposition study suggests that the agonist activity of the oxide-bridged 5-phenylmorphans can be attributed to formation of a seven membered ring that is hypothesized to facilitate a proton transfer from the protonated nitrogen to a proton acceptor in the μ-opioid receptor.

Introduction

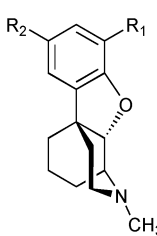
(1*R**,4a*R**,9a*S**)-2-Methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol (**1**, Chart 1) and 6-ol (**2**, Chart 1) and (1*R**,4a*R**,9a*R**)-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol (**3**, Chart 1) and 6-ol (**4**, Chart 1), the *ortho*- and *para*-e and the *ortho*- and *para*-f oxide-bridged phenylmorphans,[2–6] were previously synthesized as part of our program to prepare and pharmacologically evaluate the *ortho*- and *para*-hydroxy a through f racemic oxide-bridged phenylmorphan structural class of isomers (12 racemates, Chart 1), as well as the enantiomers of those that have reasonable affinity for opioid receptors. The *ortho* e- (1*R**,4a*R**,9a*S**) and the *ortho* f- (1*R**,4a*R**,9a*R**), or the *para* e- and *para* f-oxide-bridged



a - f Oxide-bridged phenylmorphans
ortho isomer: R_1 = OH, R_2 = H
para isomer: R_1 = H, R_2 = OH



1: R_1 = OH (ortho-e isomer)
2: R_2 = OH: (para-e isomer)



3: R_1 = OH (ortho-f isomer)
4: R_2 = OH: (para-f isomer)

Chart 1

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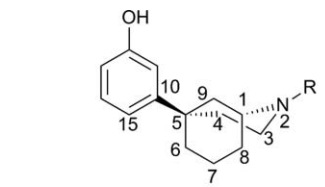
phenylmorphans are epimers and differ structurally only in their configuration at C9a.

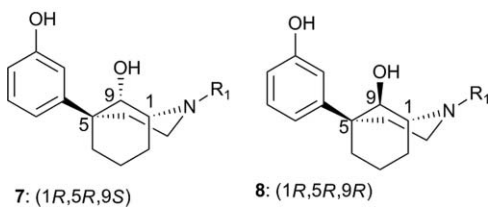
The syntheses of all of the racemic compounds have been accomplished and, except for the b-isomer, all of the syntheses have been reported.[2–11] In 1983, we noted that the *N*-methyl *ortho*-f isomer had some affinity (IC_{50} = *ca.* 100 nM) for opioid receptor preparations (from whole brain homogenate),[5] and it had intriguing, but slight, antagonist activity in the tail flick antagonism *vs.* morphine assay in mice.[5] One of the reasons that we explored the synthesis of this new class of opioids, the oxide-bridged phenylmorphans, was to determine the spatial characteristics of ligands that might be capable of interacting with opioid receptors. If some of these rigid compounds could be found that interacted with opioid receptors as agonists and others as antagonists, while acting through the same opioid receptor, we might obtain information about the three-dimensional structure of a ligand that is required for interaction with a specific opioid receptor to give the determined pharmacological activity.

Oxide-bridged phenylmorphans are based on the 5-phenylmorphan structure. The *N*-methyl-5-(3-hydroxyphenyl)morphan (**5**, Chart 2) was prepared by May and Murphy[12] as a simplified analogue of morphine and had morphine-like antinociceptive activity in mouse assays.[12] The (1*R*,5*S*)-(−)-enantiomer[13] of *N*-methyl-5-(3-hydroxyphenyl)morphan was reported to be morphine-like in analgesic activity and to have nalorphine-like antagonist activity, while the (1*S*,5*R*)-(+)-enantiomer was about three to five fold more potent than morphine in mice and did not appear to have antagonist activity in morphine-dependent monkeys.[14–16] The racemic *N*-phenethyl derivative of 5-(3-hydroxyphenyl)morphan[14] (**6**, Chart 2) had about half of the antinociceptive activity of the racemic *N*-methyl analogue and the *N*-phenethyl enantiomers[17,18] were found to be opioid antagonists in the [^{35}S]GTP-γ-S assay. The *meta*-hydroxy group is known to play a critical role in the potency of this class of analgesics.[19] The aromatic phenolic ring is not positioned similarly with respect to the piperidine ring in the morphinans and the phenylmorphans, but despite the spatial differences in that moiety between these classes of analgesics, *N*-methyl compounds from both classes usually have antinociceptive activity and some are known to be partial agonists. Much greater pharmacological differences between classes of opioids are seen with *N*-phenethyl derivatives. These are generally potent antinociceptive agents in the rigid morphinan, epoxymorphinan, and benzomorphan classes of opioids and can have either opioid agonist[1] or antagonist activity[18,20] in the 5-phenylmorphans. The *N*-phenethyl substituted 5-(3-hydroxyphenyl)morphans with a C9*S*-hydroxy ((1*R*,5*R*,9*S*)-(−)-**7**, Chart 2, (1*R*,5*R*,9*S*)-(−)-9-hydroxy-5-(3-hydroxyphenyl)-2-phenylethyl-2-azabicyclo[3.3.1]nonane) or a methylene substituent at C9 have been found to have very high (sub-nanomolar) affinity at μ- and good affinity at δ-receptors. They had potent antinociceptive activity *in vivo*. The (−)-**7** was found to be about 500 to 1000 fold more potent than morphine *in vivo*.[1] Its C9 *R*-epimer (1*R*,5*R*,9*R*)-(+)-**8** (Chart 2, (1*R*,5*R*,9*R*)-(+)-9-hydroxy-5-(3-hydroxyphenyl)-2-phenylethyl-2-azabicyclo[3.3.1]nonane) had much less affinity for opioid receptors (K_i = 59 nM at the μ receptor). *N*-Phenethyl substituted 5-(3-hydroxyphenyl)morphans usually,[17,18,20] but not always,[14] show greater receptor affinity, efficacy, or potency *in vivo* than the comparable *N*-methyl analogue.

In order to try to increase affinity in the f-series[5] of oxide-bridged phenylmorphans, where the *N*-methyl *ortho*-hydroxy racemate had poor affinity (IC_{50} *ca.* 100 nM),[10] and prepare more potent opioid agonists or antagonists we decided to synthesize their *N*-phenethyl analogues and also to examine the effect of the *N*-phenethyl substituent in the *ortho* and *para* e-series. In both the racemic *ortho* and *para* e oxide-bridged phenylmorphan series, the *N*-methyl derivatives had little or no affinity for any opioid receptor (K_i > 1 μM, Table 1). Hashimoto *et al.*,[3] obtained the racemic *ortho*- and *para*-e (1*R**,4a*R**,9a*S**)-oxide-bridged phenylmorphans *via* intramolecular aromatic nucleophilic substitution of fluorine by alkoxide, and we used that procedure, through the common intermediate **12** (Scheme 1), to obtain both the *ortho*- and *para*-e and *ortho*- and *para*-f oxide-bridged *N*-substituted 5-phenylmorphan racemates, and prepared their chiral relatives. In this report we discuss the syntheses, opioid receptor affinities of the racemic and enantiopure *N*-phenethyl derivatives of the *ortho*- and *para*-e and the *ortho*- and *para*-f oxide-bridged phenylmorphans, and the efficacies (of the more interesting compounds) determined by the [^{35}S]GTP-γ-S assay as well as through *in vivo* antinociceptive assays, and rationalize the pharmacological activities by quantum chemical studies.



N-Substituted 5-(3-hydroxyphenyl)morphan
5: R = Me;
6: R = CH_2CH_2Ph



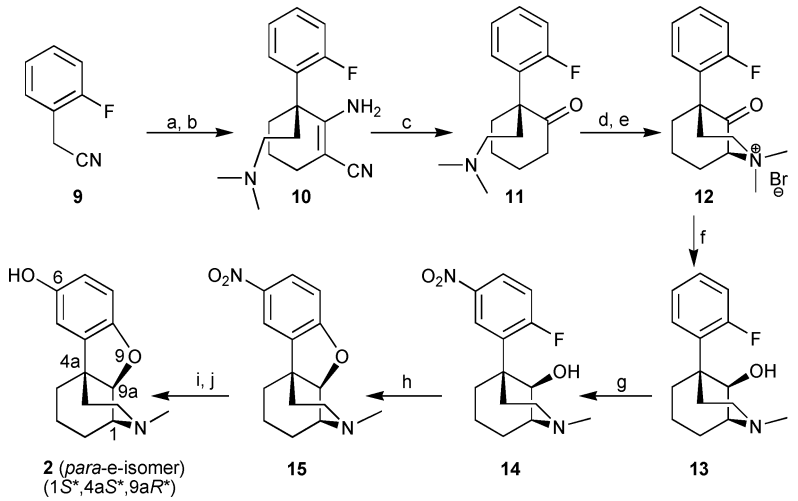
7: (1*R*,5*R*,9*S*) **8**: (1*R*,5*R*,9*R*)

Chart 2

Table 1 Binding affinity of the hydrobromide salts of the racemic *N*-methyl substituted *ortho*-e (**1**) and *para*-e (**2**) oxide-bridged phenylmorphans[a]

	*K*i (nM)		
Compound	μ (cells)	δ (cells)	κ (cells)
1 (1*R**,4a*R**,9a*S** *ortho*-e)	5800 ± 300	>5500	>6500
2 (1*R**,4a*R**,9a*S** *para*-e)	1250 ± 70	>5500	1270 ± 50

[a] Binding assays were performed using [^{3}H]DAMGO and rat brain membranes for μ-receptors, [^{3}H]DADLE and rat brain membranes for δ-receptors and [^{3}H]U69,593 and guinea pig brains membranes for κ-opioid receptors. *K*i values are derived from the pooled data of two experiments. Assays were carried out as previously noted.[19]

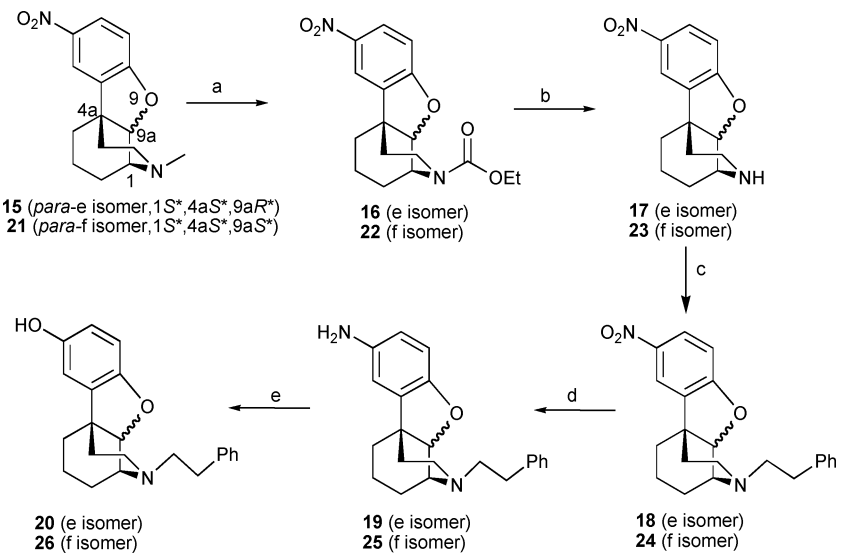


Scheme 1 Synthesis of *N*-methyl *para*-e oxide-bridged phenylmorphan **2**.[3] *Reagents and conditions*: a) NaH, THF, $Me_2NCH_2CH_2Cl$ (87%), b) NaH, 5-bromovaleronitrile, THF (69%, HCl salt), c) CF_3CO_2H, H_2O, heat (95%, HBr salt); d) Br_2, $CHCl_3$; e) *i*-PrOH, heat (69%, over 2 steps); f) $LiEt_3BH$, THF (74%, HBr salt); g) NO_2BF_4, sulfolane or 70% HNO_3 (91%); h) NaH, THF, reflux 3 days (80%), i) H_2, Pd–C, MeOH (∼quant.); j) $NaNO_2$, H_2SO_4, $Cu(NO_3)_2$, Cu_2O (25–89%).

Chemistry

Starting materials

We recently reported a novel approach to the racemic *ortho*- and *para*-e oxide-bridged phenylmorphan isomers through intramolecular aromatic nucleophilic substitution of fluorine by alkoxide.[3] Commercially available 2-fluorophenyl acetonitrile (**9**, Scheme 1) was converted into quaternary salt **12** in five steps,[3] establishing the desired carbon skeleton *via* Thorpe–Ziegler cyclization. The quaternary salt **12** was stereoselectively reduced and demethylated in a one-pot procedure and the aromatic ring was activated for the key ring-forming step by nitration.[3] We have now found that 70% nitric acid also can be used instead of nitronium tetrafluroborate to give comparable yields of the nitro compound **14**. Deprotonation and subsequent attack of alkoxide on the fluorinated aromatic ring resulted in the formation of the desired oxide-bridged derivative **15**.[3] The cyclization reaction also works well at ambient temperature in dimethylformamide. The nitro group was reduced and the resulting aniline derivative was converted into a free phenol *via* hydrolysis of the corresponding diazonium salt assisted by copper salts, furnishing the *para*-e *N*-methyl oxide-bridged phenylmorphan **2**.[3] Quaternary salt **12** was prepared in larger quantities and used as a convenient starting material for the synthesis of the *N*-phenethyl derivatives in the *para*-e oxide-bridged series (Scheme 1), as was (1*R**,4a*R**,9a*S**)-2-methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (**15**) for the *para*-f oxide-bridged series (Scheme 2).



Scheme 2 Synthesis of *N*-phenethyl *para*-e and *para*-f oxide-bridged phenylmorphans **20** and **26**. *Reagents and conditions*: a) $ClCO_2Et$, $ClCH_2CH_2Cl$, K_2CO_3 (87–89%), b) 33% HBr, AcOH, 50 °C (79–81%), c) $PhCH_2CH_2Br$, KI, CH_3CN, heat (78–80%), d) H_2, Pd–C (92–100%), e) $NaNO_2$, H_2SO_4 then H_2SO_4, heat (82–89%).

Synthesis of *N*-phenethyl derivatives of *para*-e and *para*-f oxide-bridged phenylmorphans

The 2-methyl-6-nitro derivative **15** (Scheme 2) was converted into the carbamate **16**. Both the methyl and ethyl derivatives were prepared, and the yields from the latter compound were superior. Initial alkaline hydrolysis attempts gave complex mixtures, however the hydrolysis under acidic conditions[21] proceeded smoothly to give the *N*-nor amine **17**. Direct alkylation of **17** in refluxing acetonitrile[22] gave good yields of the phenethyl derivative **18**, which was reduced to the corresponding aniline derivative **19**. Optimization of the diazotization–hydrolysis sequence, modifying conditions of Schnider and Grüssner,[23] indicated that slow addition of relatively diluted cold diazonium salt solution into boiling *ca.* 50% sulfuric acid (v/v) and brief refluxing reproducibly gave the desired phenolic product **20**, the *N*-phenethyl *para*-e oxide-bridged phenylmorphan, in good yield. Similarly, **21** was converted to **26**, the *N*-phenethyl *para*-f oxide-bridged phenylmorphan (Scheme 2).

The tertiary amine **15** was resolved *via* formation and recrystallization of diastereomeric salts with enantiomers of 3-bromo-8-camphorsulfonic acid. Enantiomeric purity was assessed by ^{1}H-NMR spectroscopy using *S*-(+)-1-phenyl-2,2,2-trifluoroethanol as a shift reagent. The presence of the other enantiomer was undetectable indicating >98% enantiomeric purity.[24] Absolute stereochemistry was determined by a single-crystal X-ray crystallographic analysis of the salt of (+)-**15** with [(1*S*)-(*endo,anti*)]-(−)-3-bromocamphor-8-sulfonic acid, and it was found to be 1*R*,4a*R*,9a*S* (Fig. 1). The synthetic sequence shown in Scheme 2 was repeated using enantiopure intermediates to give both the (+)- and (−)-enantiomers of compounds **16** and **22**. The sign of optical rotation did not change during any step of the synthetic sequence from **15** to **20** (Schemes 1 and 2), nor did it change during

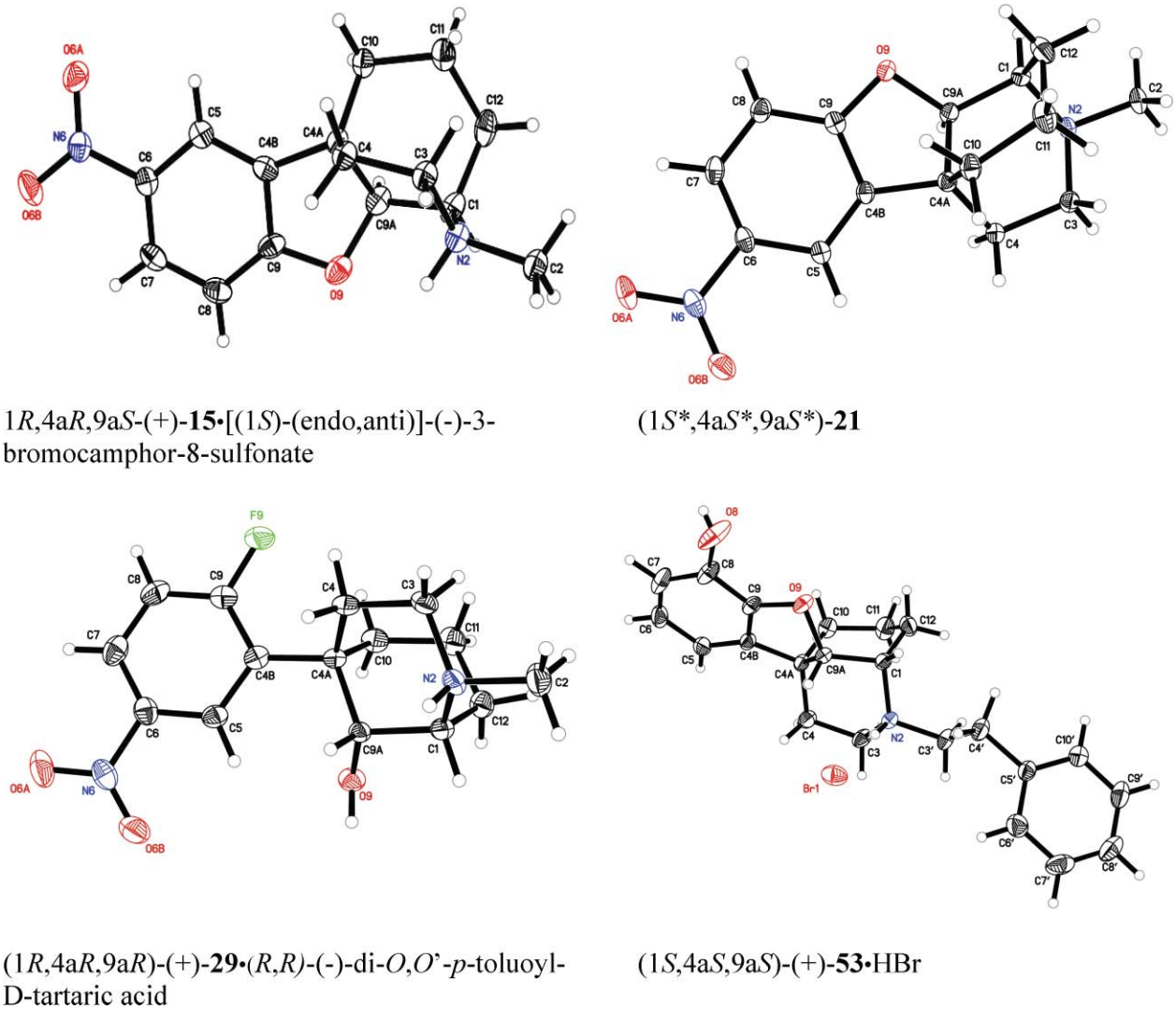
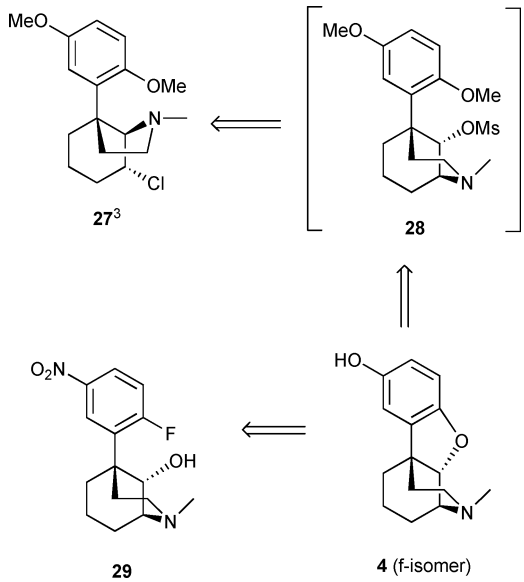


Fig. 1 X-Ray crystallographic structures of (1*R*,4a*R*,9a*S*)-2-methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine·[(1*S*)-(*endo*, *anti*)]-(−)-3-bromocamphor-8-sulfonate ((+)-**15**), (1*S**,4a*S**,9a*S**)-**21**, (1*R*,4a*R*,9a*R*)-5-(2-fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol ((+)-**29**), and (1*S*,4a*S*,9a*S*)-8-hydroxy-2-(2-phenethyl)-1,3,4,9a- tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine·HBr ((+)-**53**). For all four compounds displacement ellipsoids are shown at the 50% level.

the synthesis of the 1*R*,4a*R*,9a*S*-(+)-enantiomer of **43** from the 1*R*,4a*R*,9a*S*-(+)-enantiomer of **15** (Scheme 5).

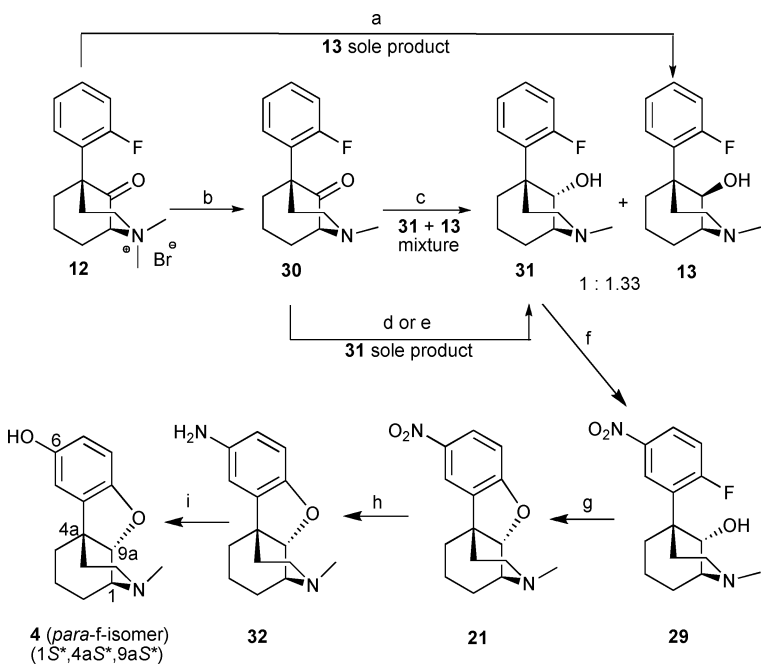
New approach to *para*-f-oxide-bridged phenylmorphans

Our previously reported synthesis of this oxide-bridged phenylmorphan relied on cyclization of a free phenol derived from compound **27**[4] (Scheme 3). This approach was complicated by ring rearrangements, *i.e.*, when the preparation of mesylate **28** from the corresponding equatorially-oriented (in the piperidine ring) alcohol and methanesulfonyl chloride was attempted the rearranged chloride **27** was obtained. However, upon generation of the free phenol from the *ortho*-methoxy moiety, compound **27** did cyclize to give the *para*-f-oxide-bridged compound **4**.[4] Preparation of an equatorially-oriented alkoxide from **29** should enable cyclization in the desired manner, as demonstrated earlier with the analogous axially-oriented alkoxide,[3] since only the configuration of the nucleophile was reversed (Scheme 3). In the former approach to the e-bridged phenylmorphans the quaternary salt **12** (Scheme 1) was stereoselectively reduced to the β-alcohol **13** and dequaternized in a one-pot process by reduction with Superhydride.[3] We theorized that compound **12** could serve as a convenient common precursor for the syntheses of both the e- and f-oxide bridged compounds by modifying the reduction protocol to selectively obtain the equatorially-oriented alcohol. Dry distillation[25] of compound **12** (Scheme 4) provided the corresponding tertiary amine **30** previously prepared by thermolysis of **12** in refluxing diphenyl ether and chromatographic purification.[3] Fortunately, there was a precedent for the desired reduction of the ketone analogous to **30**, differing only in substitution of the aromatic ring with methoxy groups.[4] Thus, gratifyingly the hydrogenation of **30** over PtO_2 gave the desired equatorially-oriented alcohol **31**, no trace of the other diastereomer was detected by NMR.



Scheme 3 New approach to *para*-f-oxide-bridged phenylmorphan **4**.

Reduction with sodium borohydride also furnished the equatorially-oriented alcohol **31**. However, it was necessary to convert the amine to its hydrochloride to achieve stereoselective reduction.[4] Reduction of the free base (Scheme 4) gave an almost equimolar mixture of equatorially-oriented and axially-oriented alcohols (**31** and **13**, respectively). Carefully monitored nitration of **31** in 70% nitric acid gave a good yield of derivative **29** (Scheme 4). Unlike its axially-oriented analogue **13**,[3] the equatorially-oriented alcohol **31** is less stable under those conditions and extensive decomposition was observed at higher temperatures and prolonged reaction times. Cyclization of the



Scheme 4 Synthesis of the *N*-methyl derivative of the *para*-f oxide-bridged phenylmorphan **4**. *Reagents and conditions*: a) $LiEt_3BH$, THF, −78 °C (74%), b) 250 °C, 0.3 mmHg (84%), c) $NaBH_4$, MeOH (70%, ratio **31** : **13** = 1 : 1.33), d) H_2, PtO_2, EtOH (94%), e) HCl, Et_2O then $NaBH_4$, MeOH (97%), f) 70% HNO_3 (77%), g) NaH, THF, reflux 3 days (80%), h) H_2, Pd–C (90%), i) $NaNO_2$, H_2SO_4 then H_2SO_4 and heat (75%).

corresponding alkoxide in refluxing tetrahydrofuran provided the desired oxide-bridged phenylmorphan **21**. The *para* hydroxy f-oxide-bridged phenylmorphan **4** was prepared in two additional steps *via* the amine **32** and its spectral data matched those published previously.[4]

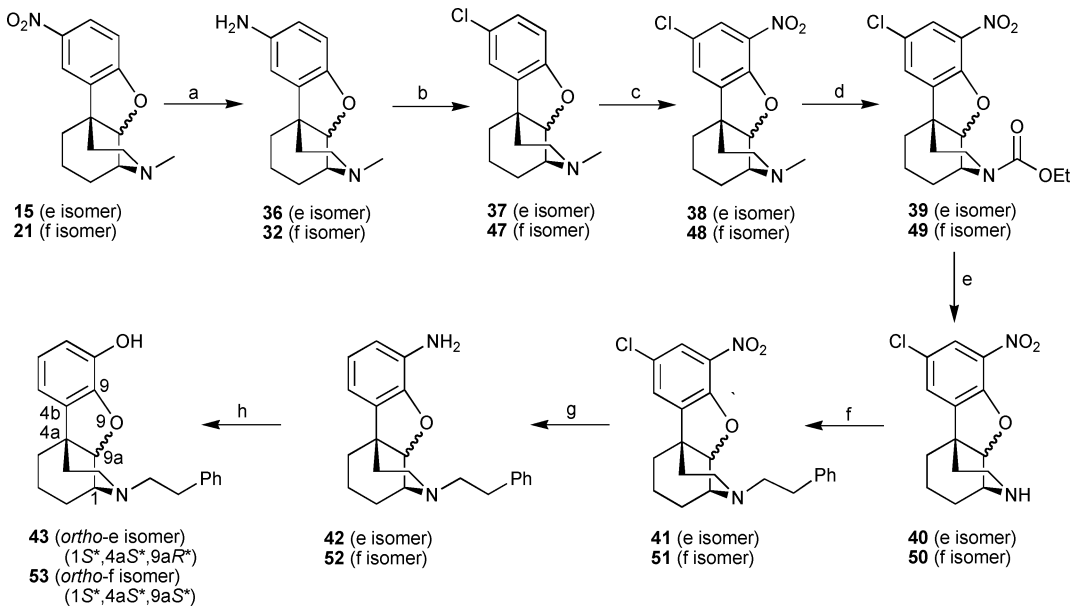
The cyclization of **29** in dimethylformamide at ambient temperature (Scheme 4) produced a complex mixture of by-products. The cyclization of the equatorially-oriented alkoxide **29**, unlike the axially-oriented alcohol **13**, was concentration sensitive. At higher concentrations the yield of compound **21** was significantly decreased by the formation of two by-products, possibly axially-oriented dimers (based on ^{1}H-NMR and HRMS) that could have formed *via* intermolecular reaction, since equatorially-oriented alkoxide **29** is much more sterically accessible for the intermolecular nucleophilic reaction than corresponding axially-oriented alkoxide **13**, which is hindered by the *syn* vicinal tertiary amine. The relative stereochemistry of **21** (1*S**,4a*S**,9a*S**) was confirmed by single-crystal X-ray analysis (Fig. 1). Repetition of the demethylation–alkylation sequence followed by transformation of the nitro group into the free phenol *via* the diazonium salt, as shown in Scheme 2, provided the *N*-phenethyl derivative (**26**).

In order to obtain enantiopure materials several chiral acids–solvent combinations were screened, but all attempts to resolve oxide-bridged compound **21** were not fruitful. However, alcohol **29** was, after some experimentation, successfully resolved through salt formation with di-*O*,*O*′-*p*-toluoyl-D- or L-tartaric acids in methanol–acetone mixture. The NMR chiral shift reagent used for compound **15** was not effective with compound **29**, therefore its enantiomeric purity was assessed by HPLC using a Daicel Chiralcel OD column. The absolute stereochemistry was determined by an X-ray crystallographic study of the salt of (+)-**29** to be 1*R*,4a*R*,9a*R* (Fig. 1). The synthetic sequence from **29** to the final product **26** was also carried out using enantiopure materials. The sign of optical rotation changes during cyclization of **29** to **21**, then stays the same through every step of the synthetic sequence leading to **26** (Scheme 2).

Synthesis of *N*-phenethyl derivatives of *ortho*-e and *ortho*-f-oxide-bridged phenylmorphans

The previously published approach[3] to the corresponding *ortho*-hydroxy *N*-methyl derivatives utilizing the bromo derivative **33** was modified because we found that the use of NO_2BF_4–sulfolane for nitration[3] gave three products (**34**, **15**, and **35**, Chart 3). In this approach we initially planned to use the intermediate **34** (Chart 3) to obtain the desired e-isomer, and to use a comparable intermediate for the f-isomer. If compound **34** could be obtained in good yield, the synthesis of the f-isomer would be considerably improved. However, nitration of **33** gave only moderate yields of the desired compound **34** using NO_2BF_4.[3] When 70% HNO_3 was used, the isomeric compound **35** along with compound **15** were the sole products in *ca.* 6 : 4 ratio (^{1}H-NMR). This could be explained by ipso nitration[26] and the resulting migration or loss of bromide giving rise to by-products **35** and **15**. The nitration was studied more intensely on bromide **44** where nitration with 70% HNO_3 at 60 °C gave a mixture of two compounds **21** and **46**. Lowering the reaction temperature to room temperature or to 0 °C did not change the outcome of the reaction. Nitration of **44** with NO_2BF_4 (2.0 equiv.) in sulfolane at room temperature gave a mixture of starting material **44** and, based on ^{1}H-NMR, two compounds **21** and **46** in a ratio of 3 : 2.9 : 1, respectively. When more forceful conditions were employed (*i.e.* $NaNO_2$–TFA[27]) the product of ipso attack, **21**, was obtained as the sole product (Chart 3).

We therefore decided to replace the bromo-substituent in **33** and **44** with a more stable halide to prevent ipso nitration and its resultant by-products. The f- and e-oxide-bridged chloro analogues **37** and **47** (Scheme 5) were prepared from the corresponding aniline derivatives **36** and **32**, and they proved to be



Scheme 5 Synthesis of the *N*-phenethyl derivative of the *ortho*-e and *ortho*-f oxide-bridged phenylmorphans **43** and **53**. *Reagents and conditions*: a) H_2, Pd–C, MeOH (85–92%), b) $NaNO_2$, HCl, $CuSO_4$, $Na_2S_2O_5$, NaOH (66–79%), c) $NaNO_2$, CF_3CO_2H (74–84%), d) $ClCO_2Et$, $ClCH_2CH_2Cl$, K_2CO_3 (88%), e) 33% HBr, AcOH, 50 °C (85–91%), f) $PhCH_2CH_2Br$, KI, CH_3CN, heat (78–85%), g) H_2, Pd–C, EtOH, $CH_3CO_2Na{\cdot}3H_2O$, 45–50 °C (86–94%), h) $NaNO_2$, H_2SO_4 then $Cu(NO_3)_2$, Cu_2O (35–61%).

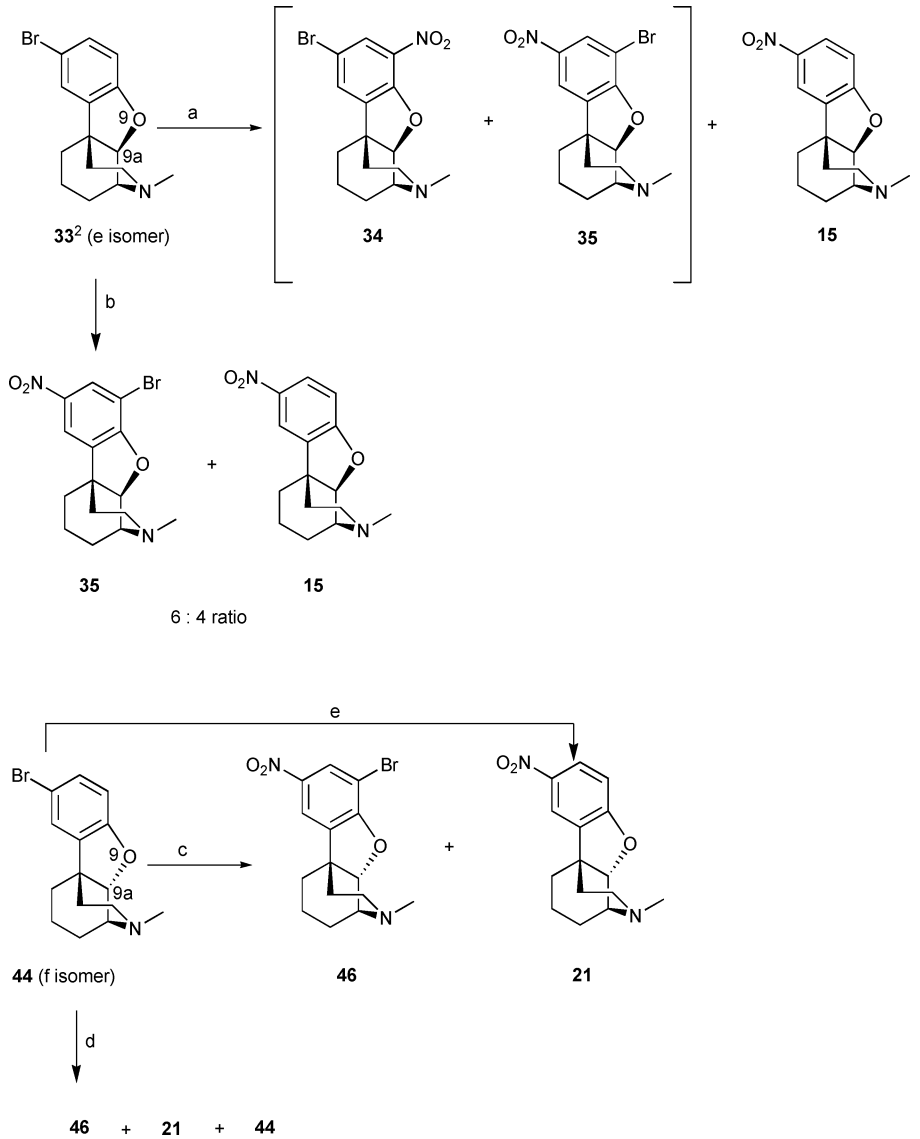


Chart 3 *Reagents and conditions*: a) NO_2BF_4, sulfolane (54% of **34**), b) 70% HNO_3, reflux; c) 70% HNO_3, 0 °C, 20 °C, or 60 °C (44% of **35**), d) NO_2BF_4 (2.0 equiv.), sulfolane, 20 °C; e) $NaNO_2$, TFA.

stable under these reaction conditions. The optimal reagent system for the nitration was found to be $NaNO_2$–TFA,[27] providing high yields of the desired 6-chloro-8-nitro-substituted derivatives **38** and **48**. The ipso nitration-derived by-products were not observed. With **48**, two re-crystallizations were necessary to remove a minor impurity (*ca.* 6% by HPLC), which could not be separated by chromatography. The *N*-methyl derivatives were converted to the corresponding ethyl carbamates **39** and **49**, and these were hydrolyzed in 33% hydrobromic acid to give the *N*-nor amines **40** and **50**.

Direct alkylation of **40** and **50** gave the desired *N*-phenethyl derivatives **41** and **51**. Each of these was reduced over Pd–C in ethanol at *ca.* 50–60 °C (dechlorination is very slow at room temperature) in the presence of sodium acetate trihydrate, to provide the corresponding dehalogenated aniline derivatives **42** and **52**. Attempted use of the conditions for the conversion to the *ortho*-phenols that had been optimized with the corresponding *para*-derivatives, failed to yield the desired products (possibly due to the decomposition of the diazonium salt in hot sulfuric acid). Instead, a milder method[28] was adapted utilizing copper salts to decompose the diazonium salt at or below room temperature. This method gave products **43** and **53**, albeit in modest yields, and their isolation required repeated chromatographic purification. The racemates were resolved by HPLC on a Daicel Chiralcel OD semi-preparative column to give the enantiomers of **43** and **53** in sufficient amounts for initial pharmacological testing. The absolute stereochemistry of the desired *N*-phenethyl derivative of the f-isomer ((+)-**53**) was determined by X-ray diffraction analysis of its HBr salt to be 1*S*,4a*S*,9a*S* (Fig. 1). The attempts to grow suitable crystals of (+)- or (−)-**43**·HBr were not successful, therefore the sequence from resolved (+)-**15** to (+)-**43** was repeated, the sign of optical rotations stays the same throughout the sequence. Proton NMR and chiral HPLC analysis confirmed the identity and purity of this material, which co-eluted with the previously obtained sample of

(+)-**43**. The absolute stereochemistry of (+)-**43** was, then, assigned to be 1*R*,4a*R*,9a*S* from the synthetic methodology used and the X-ray diffraction analyses on 1*R*,4a*R*,9a*S*-(+)-**15**.

Results and discussion

The affinity of the racemic *N*-methyl compounds are listed in Table 1, and the racemic and enantiomeric *N*-phenethyl compounds in Table 2. The functional activity of the compounds that were found to have significant affinity at μ-, δ- and/or κ-receptors is shown in Table 3. The racemic *N*-phenethyl analogues showed considerably enhanced receptor affinity compared with the racemic *ortho*- and *para*-e *N*-methyl compounds (**43** and **20**) that had slight or no affinity for opioid receptors. Two of the *N*-phenethyl enantiomers were especially interesting. The (−)-*para*-e and the (−)-*ortho*-f *N*-phenethyl compounds (1*S*,4a*S*,9a*R*-(−)-**20** and 1*R*,4a*R*,9a*R*-(−)-(−)-**53**) had fair (K_i = 23 nM) and good (K_i = 7 nM) affinity for the μ-opioid receptor, respectively. The (−)-*para* e enantiomer (−)-**20** had weak agonist activity in the [^{35}S]GTP-γ-S assay, and the (−)-*ortho* f enantiomer (−)-**53**) had fairly potent μ-antagonist activity in that assay (K_e = 1.4), four times more potent than naloxone (K_e = 6.4). The (−)-*ortho* f isomer ((−)-**53**) was also naloxone-like as an antagonist at the κ-receptor. Presumably, the *N*-phenethyl (−)-*para* e compound (−)-**20**) had good intrinsic efficacy, because it was found to be more potent than expected *in vivo*. It was morphine-like as an antinociceptive in the mouse tail-flick assay (Table 4). Corroboration of the antagonist activity of the *N*-phenethyl (−)-*ortho* f enantiomer (−)-**53** was obtained from the tail-flick *vs.* morphine antagonist assay in mice (Table 4), although it was found to be less potent *in vivo* than would have been expected from the functional assay.

In order to gain insight into the structural features of the rigid *N*-phenethyl substituted *ortho*- and *para*-e and *ortho*- and *para*-f enantiomers that might be responsible for μ-receptor affinity and activity, their spatial relationships were investigated with the aim of providing a rationale for their observed agonist activity. For this purpose, the molecular structures of the compounds in Table 5 were energy minimized with density functional theory at the B3LYP/6-31G* level, and then overlaid onto the phenylmorphan compound (1*R*,5*R*,9*S*)-(−)-**7** using the heavy atoms in the

Table 2 [^{125}I]IOXY binding data for the oxalate salts of the racemic *N*-phenethyl substituted *ortho*- and *para*-e- and *ortho*- and *para*-f oxide-bridged phenylmorphans and their enantiomers[a]

		*K*i (nM)		
Cmpd no.	Compound	μ (cells)	δ (cells)	κ (cells)
43	1*R**,4a*R**,9a*S**-*ortho*-e	2610 ± 160	2530 ± 100	353 ± 11
(−)-**43**	1*S*,4a*S*,9a*R*-(−)-*ortho*-e	2490 ± 140	2540 ± 74	156 ± 5
(+)-**43**	1*R*,4a*R*,9a*S*-(+)-*ortho*-e	3190 ± 160	2980 ± 90	2360 ± 68
20	1*R**,4a*R**,9a*S**-*para*-e	133 ± 11	377 ± 28	123 ± 4
(−)-**20**	1*S*,4a*S*,9a*R*-(−)-*para*-e	23 ± 1	156 ± 75	57 ± 1
(+)-**20**	1*R*,4a*R*,9a*S*-(+)-*para*-e	5130 ± 320	8000 ± 390	638 ± 41
53	1*R**,4a*R**,9a*R**-*ortho*-f	17 ± 0.96	1110 ± 41	32 ± 1
(−)-**53**	1*R*,4a*R*,9a*R*-(−)-*ortho*-f	7 ± 1	907 ± 32	25 ± 2
(+)-**53**	1*S*,4a*S*,9a*S*-(+)-*ortho*-f	201 ± 11	1190 ± 38	116 ± 3
26	1*R**,4a*R**,9a*R**-*para*-f	146 ± 8	920 ± 136	257 ± 9
(−)-**26**	1*R*,4a*R*,9a*R*-(−)-*para*-f	98 ± 13	1180 ± 60	758 ± 35
(+)-**26**	1*S*,4a*S*,9a*S*-(+)-*para*-f	195 ± 24	1150 ± 76	130 ± 9

[a] [^{125}I]IOXY binding used membranes prepared from CHO cells that stably express the human μ, δ or κ opioid receptors. Binding affinity is expressed as nM concentrations. All results are ± SD (n = 3). Assays were run as previously noted.[1]

Table 3 Functional data ([^{35}S]GTP-γ-S) [a]of *N*-phenethyl substituted oxide-bridged phenylmorphans

		μ agonism		δ agonism		κ agonism	
		E_{max}	ED_{50}/nM	E_{max}	ED_{50}/nM	E_{max}	ED_{50}/nM
20	*rac-para*-e	85 ± 4	770 ± 135	60 ± 4	1730 ± 400	—	NS[b]
(−)-**20**	(−)-*para*-e	75 ± 2	530 ± 41	65 ± 4	1040 ± 250	—	NS[b]
(−)-**26**	(−)-*para*-f	43 ± 3	630 ± 147	—	NS[a]	—	NS[b]
DAMGO		100	32 ± 2				
		μ antagonism Ke (nM)		δ antagonism Ke (nM)		κ antagonism Ke (nM)	
53	*rac-ortho*-f	4.5		NS		15.1	
(−)-**53**	(−)-*ortho*-f	1.4				8.9	
26	*rac-para*-f	300		NS[a]		275	
(+)-**26**	(+)-*para*-f	310		NS[a]		120	
(−)-**26**	(−)-*para*-f	244		NS[a]		NS[a]	
Naloxone		6.4				10	

[a] [^{35}S]GTP-γ-S binding was performed using CHO cells that stably express the human μ, δ or κ opioid receptors. All results are ± SD (n = 3). E_{max} values are expressed as a percent of the maximal stimulation, where 100% is defined as the stimulation produced by 1 μM DAMGO (for μ receptors), 500 nM SNC80 (δ receptors) and 500 nM (−)-U50,488 (for κ receptors). Assays were run as previously noted.[1] [b] NS = No significant activity.

Table 4 *In vivo* activity[a] of the oxalate salts of the *N*-phenethyl substituted (−)-*para*-e ((−)-**20**) and (−)-*ortho*-f ((−)-**53**) oxide-bridged phenylmorphan enantiomers

Compound	HP	PPQ	TF	TF *vs* M
(−)-**20**	6.4 (2.9–14.1)	1.4 (0.79–2.35)	1.8 (1.2–2.9)[b]	Inactive (30 mg kg^{-1})
(−)-**53**	Inactive	Inactive (30 mg kg^{-1})	Inactive 16% at 30 mg kg^{-1}	0.4 (0.24–0.54)
Morphine·SO_4	0.9 (0.39–1.9)	0.4 (0.2–0.8)	1.9 (0.89–4.14)	Inactive (30 mg kg^{-1})
Naloxone·HCl	Inactive (10 mg kg^{-1})		Inactive (30 mg kg^{-1})	0.04 (0.02–0.09)

[a] ED_{50}, mg kg^{-1}, sc (95% confidence limits); HP = hot plate assay, PPQ = phenylquinone assay, TF = tail flick assay, in mice, TF *vs* M = tail flick *vs.* morphine (μ-antagonist assay) in mice, SDS = single dose suppression in monkeys. Vehicle 5% hydroxypropyl-β-cyclodextrin in H_2O for injection. Assays were run at Virginia Commonwealth University (Drs M. Aceto and L. Harris) as previously noted.[1] [b] Mild Straub tail at 30 mg kg^{-1} in HP and 10 mg kg^{-1} in TF.

Table 5 Overlay and dihedral angles of energy-minimized structures

Compound	K_i/nM[a]	*Ex vivo*/*in vivo*	RMSD (Å)[b]	Dihedral angle (°)[c]
(1*R*,5*R*,9*S*)-(−)-**7**[1]	0.19	agonist	—	—
(1*R*,5*R*,9*R*)-(+)-**8**[1]	54	nd[d]	0.03	—
(−)-**43** ((−)-*ortho*-e)	2488	nd[d]	0.06	26.1
(−)-**53** ((−)-*ortho*-f)	7	antagonist	0.10	−25.7
(−)-**20** ((−)-*para*-e)	23	agonist	0.06	25.7
(−)-**26** ((−)-*para*-f)	98	agonist	0.11	−25.5

[a] [^{125}I]IOXY binding using CHO cells stably transfected with human μ-DNA and express the human μ receptor. [b] Root mean square deviation from morphan backbone in (1*R*,5*R*,9*S*)-(−)-**7**. [c] C9a–C4a-C4b–C9 in the oxide-bridged compounds. [d] Not determined.

morphan moiety (*i.e.*, C1–C9) as a common docking point. As noted, in the various Figures and Schemes, the C9a bonded to the O9 atom in the *ortho*- and *para*-e oxide-bridged phenylmorphan (1*R**,4a*R**,9a*S**) has the 9a*S**relative configuration, and the C9a bonded to the O9 atom in the *ortho*- and *para*-f oxide-bridged phenylmorphan (1*R**,4a*R**,9a*R**) has the epimeric 9a*R** relative configuration. The (−)-**7**, with a C9*S* configuration, as shown in Chart 2, is a very potent μ-agonist. It has a freely rotating phenolic moiety, and in our previous study[1] we hypothesized that a water molecule/chain H-bonded to the hydroxyl moiety at C9*S* of the compound (−)-**7** facilitates proton transfer from the tertiary amine to an acceptor amino acid at the active site of the receptor as depicted in Fig. 2. We noted that the ease of protonation of the acceptor might be responsible for its activity as a potent agonist. In the present work, we have attempted to further extend the hypothesis of the proton transfer to *ortho*- and *para*-e and *ortho*- and *para*-f oxide-bridged phenylmorphan isomers. These rigid isomers have a fixed 3-dimensional angular position of the phenolic ring. The e and f oxide-bridged phenylmorphans were calculated to differ by 52° in the spatial position of their phenolic ring (C9a–C4a–C4b–C9).

The rigid-fitting of the *ortho*-e ((−)-**43**), *ortho*-f ((−)-**53**), *para*-e ((−)-**20**) and *para*-f ((−)-**26**) compounds on (−)-**7** gave ≤ 0.11 Å root mean square deviation (Table 5) indicating a good overlap of the morphan backbone of these isomers to that of (−)-**7**. Nonetheless, about only half of the phenolic ring of the e- and f-isomers spatially overlaps with the phenolic ring of (−)-**7** since the five-membered oxide ring is forced to have a considerably smaller bond angle of C9a–C4a–C4b (*e.g.*, 97.1° for the *ortho*-f, (−)-**53**) than the bond angle of C9–C5–C10 (111.3°) for (−)-**7**, and that results in the pulling of the phenolic ring of the oxide-bridged isomers away from the spatial area occupied by the phenolic ring

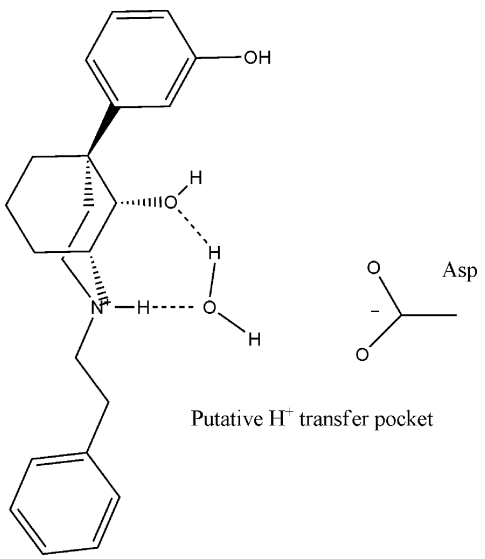


Fig. 2 Schematic representation of the formation of a seven-membered ring *via* a water molecule that was hypothesized to facilitate proton transfer from the protonated nitrogen in compound **7**[1] to an amino acid in the active site. Dotted lines indicate hydrogen bonding.

of (−)-**7** toward the C9a atom as shown in Fig. 3. Fig. 3 also illustrates that the *ortho*- and *para*-e isomers (−)-**43** and (−)-**20** differ mainly from the corresponding *ortho*- and *para*-f ((−)-**53** and (−)-**26**) isomers in the spatial position of the bridged phenolic ring as shown; for example, the calculated dihedral angle of C9a–C4a–C4b–C9 of the *ortho*-e ((−)-**43**) and the *ortho*-f ((−)-**53**) are 26.1° and −25.7°, respectively (Table 5). In addition, the bridged oxygen atoms of the *ortho*-e and *ortho*-f isomers overlap well in space with the 9*S*-OH oxygen of (−)-**7** and epimeric 9*R*-OH

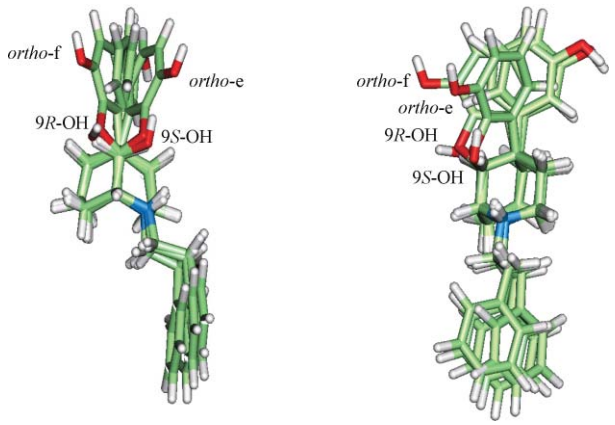


Fig. 3 Two views of the oxide-bridged phenylmorphan *ortho*-e (1*S*,4a*S*,9a*S*-(−)-**43**) and *ortho*–f (1*R*,4a*R*,9a*R*-(−)-**53**) enantiomers overlapped with (1*R*,5*R*,9*S*)-(−)-**7** (9*S*-OH) and (1*R*,5*R*,9*R*)-(+)-**8** (9*R*-OH). Atoms are represented by colors as follows: white, hydrogen; green, carbon; blue, nitrogen; red, oxygen.

oxygen of (+)-**8**, respectively; these oxygen atoms are positioned to form a seven membered ring with the phenolic hydroxyl either *via* a water molecule as illustrated in Fig. 4 for the *ortho*-f or *via* the hydroxyl group of a polar residue such as Tyr in the binding pocket. This seven membered ring might alter the orientation of the protonated nitrogen of the *ortho*-f ((−)-**53**) with respect to that of (−)-**7**, making the proton transfer unfavorable. This may be one of the reasons why the *ortho*-f ((−)-**53**) compound does not show much agonist activity. Similarly, the *ortho*-e enantiomer could form a seven-membered ring using the two oxygen atoms, and this seven-membered ring would appear in the vicinity of the

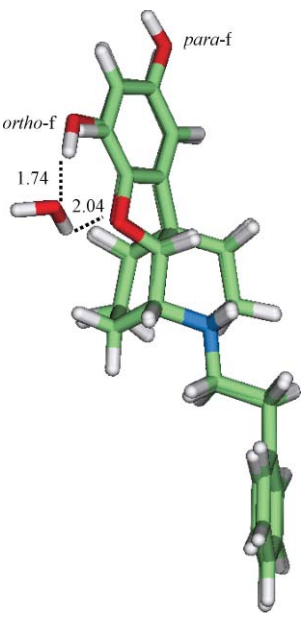


Fig. 4 Overlap of *ortho*-f (1*R*,4a*R*,9a*R*-(−)-**53**) and *para*-f (1*R*,4a*R*,9a*R*-(−)-**26**) oxide-bridged phenylmorphan isomers. The phenolic hydroxyl of the *ortho*-f can form a seven-membered ring with the bridged oxygen atom *via* a water molecule while that of the *para*-f is not positioned to form such a seven-membered ring. Dotted lines represent hydrogen bonding.

putative proton transfer pocket, and thus likely to disrupt the proton transfer process that was hypothesized to confer agonist activity to (−)-**7**.[1] In contrast, the phenolic hydroxyl of both the *para*-e and *para*-f compounds ((−)-**20** and (−)-**26**) is not positioned to form a seven-membered ring with the bridged oxygen atom (Fig. 4). However, the oxygen atom in the five-membered ring of the *para*-e isomer is only 0.35 Å away from the 9*S*-OH oxygen of (−)-**7** suggesting that this particular oxygen might play a similar role to the 9*S*-OH oxygen by forming a seven-membered ring with the protonated nitrogen *via* a water molecule, and this may be a rationale for the morphine-like agonist potency of the *para*-e isomer (−)-**20**. Unlike the *para*-e isomer, the bridged oxygen of the *para*-f isomer (−)-**26** is neither positioned to hydrogen-bond with the tertiary nitrogen *via* a water molecule (Fig. 4) nor to form a seven membered ring like *ortho*-f isomer that might alter the orientation of the protonated nitrogen, and this could be related to the much more modest agonist activity of the *para*-f isomer seen in the [^{35}S]GTP-γ-S assay (Table 3).

The binding affinity of (−)-**7** (K_i = 0.19 nM) to the μ-receptor is *ca.* 300 times better than the affinity of its epimer, (+)-**8** (K_i = 59 nM).[1] While with less affinity, a similar trend is observed for the *para*-e ((−)-**20**, K_i = 23 nM) and the *para*-f ((−)-**26**, K_i = 98 nM) isomers suggesting that the formation of the seven-membered ring between the bridged oxygen and the nitrogen atom, in a spatial area comparable to that occupied by the 9*S*-OH in (−)-**7** (Fig. 3), enhances the binding energy to the μ-receptor *via* H-bonding interactions. The bridged oxygen of the *ortho*-e ((−)-**43**), however, is only 0.35 Å away from the 9*S*-OH oxygen of (−)-**7** but its binding affinity (K_i = 2488 nM) to the μ-receptor is *ca.* 13 000 times less than (−)-**7** suggesting that the presence of the *ortho*-oriented phenolic hydroxyl is detrimental to binding, possibly because of interference with the formation of the 7-membered ring between an oxygen and nitrogen atom, as noted above. Interestingly, the binding affinity of the *ortho*-f isomer ((−)-**53**, K_i = 7 nM) is about 8 times better than (+)-**8** (Fig. 1) indicating that an *ortho*-oriented phenolic hydroxyl may enhance the interaction energy *via* H-bonding interaction possibly with a polar residue at the active site. This idea is consistent with the fact that the *ortho*-f isomer (−)-**53** binds 14 times better to the μ-receptor than the *para*-f isomer-(−)-**26**.

While there are likely to be multiple mechanisms through which the types of ligands discussed in this and our previous paper (ligands with a phenylmorphan-like structure)[1] interact with the μ-receptor, we have proposed the idea of a proton transfer from the protonated nitrogen to a proton acceptor in the μ-opioid receptor *via* a water molecule(s) as one of the keys for imparting agonist activity. Also, the idea of the possible formation of a seven-membered ring with a putative water molecule may help relate the affinity and activity of the limited group of molecules in Table 5. Nonetheless, many more compounds still need to be examined before any definitive statement can be made about the plausibility of these ideas.

Conclusions

The *N*-phenethyl (−)-*para*-e enantiomer (1*S*,4a*S*,9a*R*-(−)-**20**) was found to be a μ-opioid agonist and was as potent as morphine as an antinociceptive. The *N*-phenethyl (−)-*ortho*-f enantiomer (1*R*,4a*R*,9a*R*-(−)-**53**) had good affinity for the μ-opioid receptor

(K_i = 7 nM), and was found to be a μ-opioid antagonist in the [^{35}S]GTP-γ-S assay and *in vivo*. The epimeric difference between the rigid oxide-bridged e- and f-enantiomers gave them different fixed spatial three-dimensional patterns and this resulted in major differences in their pharmacological activity. Their spatial patterns are presumably relevant to those necessary for recognition by the μ-opioid receptor as agonists or antagonists.

The superposition study suggests that i) the bridged oxygen of the *para*-e enantiomer and the 9*S*-OH of compound **7** are likely to play similar roles in forming a seven membered ring to facilitate proton transfer between the nitrogen atom and the oxygen atom of Asp that is hypothesized[1] to give rise to the μ-agonist activity and ii) while the hydroxyl of the *ortho*-f enantiomer enhances the binding affinity *via* H-bonding interactions with a polar residue at the binding site, it may affect the alignment of the protonated nitrogen, making the proton transfer process unfavorable. Even with the few molecules that have been examined thus far, insight gained from this mechanism can lead to new types of ligands and these might shed further light on the hypothesis. The synthesis of these ligands is currently in progress.

Experimental section

Dry solvents were purchased from Aldrich and used without further purification. Compounds **12** and **15** were prepared according to published procedures.[3] All melting points were determined on a Thomas Hoover 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 TMS as an internal standard (δ values in ppm, J (Hz) assignments of ^{1}H resonance coupling). HRMS were obtained on the racemates with a Waters/Micromass LCT ESI-TOF mass spectrometer at NIDDK. Dry distillation was carried out in a Buchi distillation oven (Kugelrohr). Thin layer chromatography (TLC) was performed on 250 μm Analtech GHLF silica gel plates using a CMA ($CHCl_3$: CH_3OH : concd NH_4OH (90 : 9 : 1)) solvent system. Enantiomeric purity was assessed on Shimadzu LC-6A HPLC with Shimadzu SPD-6AV UV detector (at 254 nm) using a Daicel Chiralcel OD column (4.6 mm × 50 mm coupled to 4.6 mm × 250 mm). The mobile phase was hexanes : 2-propanol : Et_2NH (90 : 10 : 0.3) at the constant flow rate of 1 mL min^{-1}. Preparative chiral separations were carried out on Daicel's Chiralcel OD column (20 × 50 mm Guard plus 20 × 250 mm) using isocratic elution with hexanes : 2-propanol : Et_2NH (80 : 20 : 0.2) at constant flow rate of 8 mL min^{-1}, detection at 254 nm. Racemates **43** and **53** were injected as solutions in 2-propanol (150 mg per 1.5 mL, three runs, 500 μL each injection). Elemental analyses were performed on the racemic compounds by Atlantic Microlabs, Inc., Norcross, Ga.

Resolution of (1*R**,4a*R**,9a*S**)-2-methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (15)

A boiling solution of [(1*S*)-(*endo*,*anti*)]-(−)-3-bromocamphor-8-sulfonic acid (5.60 g, 18 mmol, 1.05 equiv.) in acetone (60 mL) was slowly added into a refluxing stirred solution of racemic amine **15** (4.70 g, 17 mmol) in acetone (100 mL). The reaction mixture was allowed to cool to ambient temperature and stirred overnight. After cooling in an ice bath, the yellow crystals of salt of (+)-**15** that formed were filtered off and washed with cold acetone and air-dried (4.58 g, mp 269–270 °C). One recrystallization from the mixture of acetone–MeOH gave 2.48 g of yellow crystals (+)-**15** salt (mp 275–276 °C), that were free based (concd NH_4OH–$CHCl_3$) to furnish (+)-**15** base (1.06 g, $[\alpha]_D^{26}$ +116.9 (*c* 1.0, $CHCl_3$)). A second crop was also obtained (0.98 g). The mother liquors were free-based to give the enriched (−)-enantiomer of **15**, which was dissolved in boiling acetone (50 mL) and a boiling solution of [(1*R*)-(*endo*,*anti*)]-(+)-3-bromocamphor-8-sulfonic acid (2.73 g, 8.77 mmol, 1.05 equiv.) in acetone (50 mL) was added portionwise. The reaction mixture was allowed to cool to room temperature and stirred overnight. Crystals were collected after further cooling in an ice bath and washed with cold acetone to give the salt of (−)-**15** (3.89 g). One recrystallization from an acetone–MeOH mixture gave 2.15 g of yellow crystals (mp 276–277 °C). This material was free based (concd NH_4OH–$CHCl_3$) to furnish (−)-**15** base (0.984 g, $[\alpha]_D^{23}$ −116.2 (*c* 1.0, $CHCl_3$)). A second crop was also obtained (0.97 g, mp 275–277 °C). The enantiomeric purity was assessed by NMR using *S*-(+)-1-phenyl-2,2,2-trifluoroethanol as a chiral shift reagent to be >99% ee. The presence of the other enantiomer was not detected. The absolute stereochemistry of the (+)-enantiomer was determined to be 1*R*,4a*R*,9a*S* by X-ray crystallographic analysis of the salt of (+)-**15**.

Ethyl (1*R**,4a*R**,9a*S**)-(6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-2-yl)carboxylate (16)

In a flame-dried glassware apparatus cooled to room temperature under an argon atmosphere, **15** (1.00 g, 3.64 mmol) was dissolved in dry 1,2-dichloroethane (20 mL), and K_2CO_3 (1.01 g, 7.28 mmol, 2.0 equiv.) was added followed by a slow addition of ethyl chloroformate (1.74 mL, 1.98 g, 18.24 mmol, 5.0 equiv.). The reaction mixture was heated to reflux under an argon atmosphere for 1 day. Upon completion (TLC check) the reaction mixture was cooled to room temperature, diluted with H_2O (30 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting oil was redissolved in hot isopropanol (12 mL + 3 drops of H_2O), and the solution was boiled down to *ca.* 5 mL and cooled to room temperature and placed in the refrigerator overnight. The resulting off-white crystals were filtered and dried *in vacuo* (0.98 g, 81%). Mp ((±)-**16**) 143–145.0 °C (*i*-PrOH). (1*S*,4a*S*,9a*R*-(−)-**16**): $[\alpha]_D^{25}$ −186.4 (*c* 1.0, $CHCl_3$), (1*R*,4a*R*,9a*S*-(+)-**16**): $[\alpha]_D^{24}$ +187.0 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 8.14 (dd, 1H, J = 8.7, 2.4), 8.01 (d, 1H, J = 2.4), 6.95 (d, 1H, J = 8.7), 4.86, 4.75 (bs, 1H), 4.21 (m, 3H), 4.04 (m, 1H), 3.62 (m, 2H), 2.36–1.50 (m, 8H), 1.31 (m, 3H). ^{13}C-NMR: δ 164.3, 156.3, 142.8, 140.1, 125.7, 118.1, 111.2, 90.9, 90.8, 61.6, 48.8, 40.9, 39.1, 38.8, 34.0, 33.9, 33.1, 30.4, 29.8, 18.9, 14.9, 14.8. HRMS: $[M - H]^+$ calc. $C_{17}H_{21}N_2O_5$: 333.1450, found 333.1443. $C_{17}H_{20}N_2O_5$ requires: C, 61.44; H, 6.07; N, 8.43; found: C, 61.38; H, 6.22; N, 8.32%.

(1*R**,4a*R**,9a*S**)-6-Nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (17)

Carbamate **16** (1.145 g, 3.45 mmol) was dissolved in 33% HBr–AcOH (20 mL) at room temperature, the resulting bright red solution was heated in an oil bath to 50 °C for 18 h to complete the reaction. After cooling to room temperature the reaction mixture was added dropwise into stirred mixture of concd NH_4OH

(75 mL) and ice (50 mL), the yellow free base precipitated out. The precipitate was filtered off, washed with H_2O (2 × 20 mL) and air-dried to give a yellow amorphous solid. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). Combined extracts were used to dissolve the precipitate and the solution was dried over Na_2SO_4. After filtration and the removal of solvent under reduced pressure, the residue was purified by column chromatography (silica, 2 : 1 v/v $CHCl_3$: CMA) to give **17** as a yellow solid (0.733 g, 82%). Optical rotations: (1*S*,4a*S*,9a*R*)-(−)-**17**): $[\alpha]_D^{24}$ −149.3 (*c* 1.0, $CHCl_3$), (1*R*,4a*R*,9a*S*-(+)-**17**): $[\alpha]_D^{22}$ +151.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 8.14 (dd, 1H, J = 8.7, 2.7), 7.96 (d, 1H, J = 2.7), 6.96 (d, 1H, J = 8.7), 4.06 (d, 1H, J = 2.1), 3.69 (m, 1H), 3.30 (ddd, 1H, J = 13.2, 12.9, 5.1), 2.86 (dd, 1H, J = 13.5, 7.2), 2.43 (dd, 1H, J = 12.9, 5.7), 2.13 (m, 2H), 2.00–1.70 (m, 6H), 1.53–1.38 (m, 1H); ^{13}C-NMR: δ 165.0, 142.4, 141.4, 125.6, 117.8, 111.0, 89.7, 48.8, 40.9, 40.6, 34.1, 33.1, 31.2, 21.8. HRMS: $[MH]^+$ calcd $C_{14}H_{17}N_2O_3$: 261.1239, found 261.1246. $C_{14}H_{16}N_2O_3 \cdot 0.25H_2O$ requires: C, 63.50; H, 6.28; N, 10.56; found: C, 63.74; H, 6.17; N, 10.56%.

(1*R**,4a*R**,9a*S**)-6-Nitro-2-(2-phenethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (18)

N-Nor amine **17** (660 mg, 2.54 mmol) was dissolved in dry acetonitrile (25 mL), finely ground K_2CO_3 (651 mg, 5.08 mmol, 2.0 equiv.) and KI (105 mg, 0.64 mmol, 0.25 equiv.) were added followed by (2-bromoethyl)benzene (429 μL, 3.17 mmol, 1.25 equiv., 587 mg). The reaction mixture was stirred and heated to reflux under an argon atmosphere for three days. After cooling to room temperature, the reaction mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic extracts were dried over Na_2SO_4, filtered and evaporated with small amount of silica. The crude mixture was then purified by column chromatography (silica, 85 : 15 hexanes : EtOAc). The product **18** was obtained as a yellow solid (0.860 g, 93%). Optical rotations: (1*S*,4a*S*,9a*R*)-(−)-**18**: $[\alpha]_D^{24}$ −133.4 (*c* 1.0, $CHCl_3$), mp 90–92 °C (2-propanol : H_2O), (1*R*,4a*R*,9a*S*)-(+)-**18**): $[\alpha]_D^{24}$ +133.9 (*c* 1.0, $CHCl_3$) mp 88–90 °C (2-propanol : H_2O). ^{1}H-NMR: δ 8.13 (dd, 1H, J = 8.7, 2.4), 7.99 (d, 1H, J = 2.4), 7.26 (m, 5H), 6.97 (d, 1H, J = 9.0), 4.23 (d, 1H, J = 3.0), 3.67 (m, 1H), 2.88 (m, 6H), 2.41–2.28 (m, 2H), 2.10–1.70 (m, 5 H), 1.50 (m, 1H). ^{13}C-NMR: δ 164.9, 142.4, 141.0, 140.4, 128.9, 128.6, 126.3, 125.6, 118.0, 111.4, 91.6, 58.1, 54.0, 47.9, 40.6, 34.6, 34.0, 33.3, 24.9, 22.0. HRMS: $[MH]^+$ calcd $C_{22}H_{25}N_2O_3$: 365.1865, found 365.1863. $C_{22}H_{24}N_2O_3$ requires: C, 72.50; H, 6.647; N, 7.69; found: C, 72.20; H, 6.58; N, 7.68%.

(1*R**,4a*R**,9a*S**)-6-Amino-2-(2-phenethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (19)

10% Pd–C (0.100 g, 5 mol%) was added to a solution of nitro derivative **18** (700 mg, 1.92 mmol) in abs. EtOH (120 mL). The reaction mixture was shaken in a H_2 atmosphere (45 psi) for 7 h. Catalyst was filtered on Celite pad and washed with EtOH (3 × 30 mL). The filtrate was evaporated and purified by column chromatography (silica, 7 : 1 $CHCl_3$: CMA) to give product **19** as yellow solid (0.606 g, 94%). Mp ((±)-**19**) 120–123 °C (2-propanol : H_2O). Optical rotations: (1*S*,4a*S*,9a*R*)-(−)-**19**: $[\alpha]_D^{25}$ −59.7 (*c* 1.0, $CHCl_3$), (1*R*,4a*R*,9a*S*)-(+)-**19**: $[\alpha]_D^{25}$ +58.9 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 7.26 (m, 5H), 6.73 (d, 1H, J = 8.4), 6.50 (d, 1H, J = 2.4), 6.45 (dd, 1H, J = 8.1, 2.4), 4.01 (d, 1H, J = 3.0), 3.61 (m, 1H), 3.41 (bs, 2H), 2.87 (m, 6H), 2.26 (m, 2H), 2.10–1.70 (m, 5 H), 1.50 (m, 1H). ^{13}C-NMR: δ 152.0, 140.7, 140.4, 128.9, 128.5, 126.1, 114.0, 111.5, 109.6, 89.5, 58.3, 54.2, 48.2, 34.6, 34.0, 33.5, 25.1, 22.0. HRMS: $[MH]^+$ calc. $C_{22}H_{27}N_2O$: 335.2123, found 335.2146. $C_{22}H_{26}N_2O \cdot 0.25H_2O$ requires: C, 77.96; H, 7.88; N, 8.26; found: C, 77.58; H, 7.83; N, 8.07%.

(1*R**,4a*R**,9a*S**)-6-Hydroxy-2-(2-phenethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (20)

The aniline derivative **19** (250 mg, 0.747 mmol) was dissolved in cold 35% wt H_2SO_4 (12 mL) and the resulting red solution was cooled to −3 °C. A cold solution of $NaNO_2$ (57 mg, 0.823 mmol, 1.1 equiv.) in H_2O (1 mL) was added under the surface of the stirred reaction mixture at a rate that kept the temperature below 0 °C. The reaction mixture was stirred at less than 0 °C for 1 h. Cold diazonium salt solution was then added dropwise into a vigorously stirred boiling H_2SO_4 solution (prepared by mixing concd H_2SO_4 with H_2O (20 mL each), bp *ca.* 135 °C) under argon atmosphere. The resulting red solution was refluxed for another 10 min, cooled to room temperature, and the solution was added dropwise into a cold NH_4OH (50 mL of concd NH_4OH–*ca.* 75 mL of ice) with vigorous stirring keeping the temperature below 30 °C at all times. The resulting alkaline suspension was extracted with $CHCl_3$ (5 × 100 mL), and the combined organic extracts were dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was evaporated with a small amount of silica. Purification of the preadsorbed material by chromatography (silica, 4 : 1 $CHCl_3$: CMA) gave **20** as a pink foam (0.205 g, 82%). The oxalate salt of **20** was prepared. Mp ((±)-**20**·oxalate) 205–207 °C (acetone). Optical rotations: (1*S*,4a*S*,9a*R*)-(−)-**20**·oxalate: $[\alpha]_D^{24}$ −64.1 (*c* 1.0, 90% EtOH), (1*R*,4a*R*,9a*S*)-(+)-**20**·oxalate: $[\alpha]_D^{24}$ +65.3 (*c* 1.0, 90% EtOH). Optical rotations (free bases: oils): (1*S*,4a*S*,9a*R*)-(−)-**20**: $[\alpha]_D^{25}$ −51.7 (*c* 1.0, $CHCl_3$), (1*R*,4a*R*,9a*S*))-(+)-**20**: $[\alpha]_D^{25}$ +40.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 7.31–7.17 (m, 5H), 6.74 (d, 1H, J = 8.1), 6.62 (d, 1H, J = 2.7), 6.57 (dd, 1H, J = 8.1, 2.7), 4.04 (d, 1H, J = 3.0), 3.62 (m, 1H), 2.86 (m, 6H), 2.27 (m, 2H), 2.00–1.70 (m, 5 H), 1.47 (m, 1H). ^{13}C-NMR: δ 152.9, 150.3, 141.0, 140.7, 129.0, 128.6, 126.2, 113.9, 111.5, 109.5, 89.9, 58.4, 54.3, 48.2, 41.0, 34.5, 34.0, 33.5, 25.2, 22.0. HRMS: $[MH]^+$ calcd $C_{22}H_{26}NO_2$: 336.1963, found 336.1969. $C_{22}H_{25}NO_2 \cdot C_2H_2O_4$ requires: C, 67.75; H, 6.40; N, 3.29; found: C, 67.46; H, 6.30; N, 3.31%.

(1*R**,4a*R**,9a*R**)-2-Methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (21)

A solution of **29** (2.00 g, 6.8 mmol) in dry THF (50 mL) was slowly added into refluxing suspension of NaH (0.408 g, 10.2 mmol, 1.5 equiv., 60% oil suspension) in dry THF (20 mL). The reaction mixture was refluxed under an argon atmosphere for 4 h. After cooling to room temperature, the reaction mixture was slowly quenched with ice and poured into cold H_2O (100 mL). Most of the THF was removed under reduced pressure and the aqueous solution was extracted with $CHCl_3$ (5 × 50 mL). The organic extracts were dried over Na_2SO_4, filtered and evaporated and purified by column chromatography (silica, 4 : 1 $CHCl_3$: CMA) to give 1.43 g (77%) of **21**. Mp 173–174.5 °C (2-propanol : H_2O).

Optical rotations: (1*S*,4a*S*,9a*S*)-(+)-**21**: $[\alpha]_D^{24}$ +114.8 (*c* 1.0, $CHCl_3$) (from the (−)-alcohol), (1*R*,4a*R*,9a*R*)-(−)-**21**: $[\alpha]_D^{24}$ −111.9 (*c* 1.0, $CHCl_3$) (from the (+)-alcohol). ^{1}H-NMR: δ 8.14 (dd, 1H, $J = 9.0$, 2.7), 7.97 (d, 1H, $J = 2.7$), 6.95 (d, 1H, $J = 9.0$), 4.28 (d, 1H, $J =$ 3.9), 3.40 (m, 1H), 3.11 (ddd, 1H, $J = 18.0$, 12.6, 6.0), 2.92 (dd, 1H, $J = 12.6$, 6.9), 2.55 (s, 3H), 2.30 (dd, 1H, $J = 12.9$, 6.7), 2.24–2.13 (m, 2H), 1.78–1.43 (m, 5H). ^{13}C-NMR: δ 165.0, 142.4, 144.4, 125.4, 117.8, 111.0, 90.5, 54.8, 50.5, 42.4, 40.8, 33.7, 32.2, 20.7, 20.3. HRMS: $[MH]^+$ calcd $C_{15}H_{19}N_2O_3$: 275.1383, found 275.1396. $C_{15}H_{18}N_2O_3$ requires: C, 65.68; H, 6.61; N, 10.21; found: C, 65.46; H, 6.84; N, 10.03%.

Experimental data for compounds **22** through **30** can be found in the Supplemental section.‡

(1*R**,4a*R**,9a*R**)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol (29)

Alcohol **31** (13.50 g, 54.2 mmol) was dissolved in cold 70% HNO_3 (135 mL). The stirred solution was warmed to room temperature and heated at 58–60 °C for 4 h. After cooling to room temperature the reaction mixture was added dropwise into a stirred cold NH_4OH solution (300 mL of concd NH_4OH per 100 mL of ice, cooled in ice bath). The free base **29** precipitated out as a light yellow solid. The precipitate was collected and washed with cold H_2O (*ca.* 50 mL) and recrystallized from 2-propanol : H_2O (300 mL per 40 mL, boiled down to *ca.* 100 mL), to give two crops of pure **29** (total 12.29 g, 77%). **Note:** Reaction progress must be carefully monitored (mini work-up, ^{1}H-NMR is needed, since the starting material co-elutes with the product). Overly long heating results in appreciable formation of various by-products and substantially lowers yield. Mp ((±)-**29**) 175–177 °C (EtOAc). Resolved using *O*,*O*′-di-*p*-toluoyltartaric acids (acetone–MeOH 1 : 1). The absolute stereochemistry of the (+)-enantiomer was found by single crystal X-ray analysis of the diastereomeric salt of (+)-**29** to be 1*R*,4a*R*,9a*R*. Optical rotations: (1*R*,4a*R*,9a*R*))-(+)-**29**: $[\alpha]_D^{24}$ +41.8 (*c* 1.0, $CHCl_3$) (from the salt with (−)-L-acid), (1*S*,4a*S*,9a*S*)-(−)-**29**: $[\alpha]_D^{24}$ −42.0 (*c* 1.0, $CHCl_3$) (from the salt with (+)-D-acid). ^{1}H-NMR: δ 8.49 (dd, 1H, $J = 6.6$, 2.7), 8.09 (m, 1H), 7.12 (dd, 1H, $J = 12.0$, 9.0), 4.52 (d, 1H, $J = 3.9$), 3.02 (ddd, 1H, $J = 12.0$, 11.9, 5.1), 2.93 (bs, 1H), 2.75 (m, 1H), 2.49 (s, 3H), 2.21–1.73 (m, 8H). ^{13}C-NMR: δ 167.4, 164.0, 144.5, 137.0, 136.8, 125.5, 125.4, 124.0, 123.9, 117.9, 117.6, 71.1, 60.0, 50.4, 43.2, 41.0, 40.9, 35.3, 35.2, 28.3, 28.2, 21.7, 18.1. HRMS: $[MH]^+$ calcd $C_{15}H_{20}N_2O_3F$: 295.1458, found 295.1441. $C_{15}H_{19}FN_2O_3$ requires: C, 61.21; H, 6.51; N, 9.52; found: C, 0.99; H, 6.55; N, 9.53%.

Resolution protocol

A hot MeOH solution of (+)-*O*,*O*′-di-*p*-toluoyl-D-tartaric acid (16.30 g, 42 mmol, 1.05 equiv. in 150 mL) was slowly added to a hot stirred solution of racemic amine **29** (11.82 g, 40 mmol) in acetone (150 mL). The reaction mixture was allowed to cool to ambient temperature and then chilled in an ice bath. The white crystals of the salt of (−)-**29** that formed were filtered and washed with cold acetone (10 mL) and air-dried (10.86 g, mp 153–155 °C). One recrystallization from acetone : MeOH : H_2O (155 : 155 : 15 mL, boiled down to *ca.* 300 mL) gave 8.69 g of white crystals (mp 157–158 °C). This salt was converted to the free base (concd NH_4OH–$CHCl_3$) of (−)-**29** (3.14 g, mp 205–207 °C (2-propanol : H_2O), $[\alpha]_D^{24}$ −39.8 (*c* 1.0, $CHCl_3$)). The second crop of the tartrate salt and mother liquor were pooled, converted to the free base and purified by column chromatography (silica, 1 : 1 $CHCl_3$: CMA) to give an additional 0.660 g of (−)-**29** as a white solid ($[\alpha]_D^{23}$ −42.0 (*c* 1.0, $CHCl_3$)). The mother liquor was converted to the free base to give the enriched (+) enantiomer (7.07 g of brown solid), which was dissolved in hot acetone (70 mL) and a hot solution of (−)-*O*,*O*′-di-*p*-toluoyl-L-tartaric acid (8.15 g, 21 mmol, 1.05 equiv.) in MeOH (70 mL) was added portionwise. The salt crystallized rapidly, and after cooling to room temperature and then in an ice bath, the crystals were collected and washed with cold acetone to give the salt of (+)-**29** (10.67 g, mp 153–156 °C). One recrystallization from a mixture of acetone : MeOH : H_2O (150 : 150 : 30 mL, boiled down to *ca.* 200 mL) gave 9.58 g of a white crystalline salt (mp 157.5–159 °C). This salt was converted to the free base (concd NH_4OH–$CHCl_3$) to give (+)-**29** (3.46 g, mp 205–207 °C (2-propanol : H_2O), $[\alpha]_D^{24}$ +40.6 (*c* 1.0, $CHCl_3$)). The second crop of (+)-**29** salt and mother liquor from recrystallization were pooled, converted to the free base and purified by column chromatography (silica, 1 : 1 $CHCl_3$: CMA) to give 0.382 g of white solid (+)-**29** ($[\alpha]_D^{23}$ +41.8 (*c* 1.0, $CHCl_3$)). The retention times of (+)-**25** and (−)-**29** were 6.58 and 10.44 min, respectively. The presence of any other enantiomer in the final free base products was not detected under those conditions.

(1*S**,4a*S**)-5-(2-Fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol (31)

Ketone **30** (12.16 g, 49.2 mmol) was dissolved in MeOH (120 mL) and PtO_2 (335 mg, 1.48 mmol, 0.03 equiv.) was added. The reaction mixture was hydrogenated in a Parr shaker apparatus at *ca.* 45 psi for 20 h at ambient temperature. The reaction mixture was filtered through a Celite column and the catalyst was washed with additional MeOH (*ca.* 3 × 40 mL). The filtrate was evaporated to dryness and further dried *in vacuo* to give **31** (11.50 g, 94%). ^{1}H-NMR: δ 7.45 (td, 1H, $J = 8.1$, 2.1), 7.19 (m, 1H), 7.21 (m, 1H), 7.10 (bt, 1H, $J = 7.5$), 7.02 (ddd, 1H, $J = 17.1$, 7.8, 1.2), 4.54 (d, 1H, $J = 3.9$), 2.98 (m, 2H), 2.75 (m, 1H), 2.49 (s, 3H), 2.15 (m, 4H), 1.98–1.70 (m, 6H); ^{13}C-NMR: δ 163.7, 160.4, 134.8, 134.7, 128.5, 128.4, 128.1, 127.9, 124.3, 124.2, 117.0, 116.7, 71.18, 71.1, 59.7, 50.6, 43.2, 40.5, 40.4, 35.7, 35.6, 28.5, 28.4, 21.8, 18.2. HRMS: $[MH]^+$ calcd $C_{15}H_{21}NOF$: 250.1607, found 250.1627. $C_{15}H_{20}FNO$ requires: C, 72.26; H, 8.09; N, 5.62; found: C, 72.00; H, 8.06; N, 5.62%.

(1*R**,4a*R**,9a*R**)-6-Amino-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (32)

Nitro derivative **21** (2.85 g, 10.4 mmol) was dissolved in mixture of MeOH : 2-propanol (100 mL : 100 mL), and the solution was purged with a gentle argon stream. The catalyst (10% Pd–C, 0.553 g) was then added portion-wise. The reaction mixture was hydrogenated in a Parr shaker apparatus at room temperature and 50 psi of hydrogen pressure for 3 h. The catalyst was filtered on a Celite bed, which was washed with MeOH (3 × 30 mL). The combined filtrates were evaporated and the residue was recrystallized from 2-propanol : H_2O to give **32** (2.16 g, 85%) as pink crystals. Mp ((±)-**32**) 203–204 °C. ^{1}H-NMR: δ 6.71 (d, 1H, $J = 8.1$), 6.49 (d, 1H, $J = 2.7$), 6.46 (dd, 1H, $J = 8.4$, 2.7),

4.07 (d, 1H, $J = 3.3$), 3.42 (bs, 2H), 3.33 (m, 1H), 3.06 (ddd, 1H, $J = 11.7, 11.7, 6.3$), 2.87 (ddd, 1H, $J = 12.0, 6.6, 1.5$), 2.53 (s, 3H), 2.21–2.07 (m, 3H), 1.77–1.45 (m, 5H). ^{13}C-NMR: δ 152.3, 141.3, 140.5, 113.9, 111.2, 109.7, 88.7, 55.4, 50.9, 42.5, 41.1, 33.8, 32.6, 21.1, 20.7. HRMS: $[MH]^+$ calcd $C_{15}H_{21}N_2O$: 245.1654, found 245.1666. $C_{15}H_{20}N_2O$ requires: C, 73.74; H, 8.25; N, 11.47; found: C, 73.80; H, 8.31; N, 11.44%.

Experimental data for compounds **30** and **33** through **34** can be found in the Supplemental section.‡

(1*R,4a*R**,9a*S**)-8-Bromo-2-methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (35)**

Bromide **33** (1.10 g, 3.1 mmol) was dissolved in 70% HNO_3 (10 mL) and the solution was heated to reflux for 2 h. After cooling to room temperature the reaction mixture was poured on ice and the pH was adjusted to *ca.* 9 with concd NH_4OH, followed by extraction with $CHCl_3$. The combined extracts were dried over Na_2SO_4, filtered and evaporated. ^{1}H-NMR spectra of the crude mixture revealed the presence of two products, *i.e.* **35** and **15** in *ca.* 6 : 4 ratio. Compound **35** was isolated by column chromatography to give 0.55 g (44%) of solid. Recrystallization from 2-propanol gave light yellow crystals, mp 128–129 °C. ^{1}H-NMR: δ 8.31 (d, 1H, $J = 2.2$), 7.91 (d, 1H, $J = 2.2$), 4.30 (d, 1H, $J = 2.7$), 3.55 (m, 1H), 2.89–2.70 (m, 2H), 2.53 (s, 3H), 2.45–2.31 (m, 2H), 1.99–1.88 (m, 2H), 1.86–1.78 (m, 3H), 1.49–1.40 (m, 1H). HRMS (FAB): $[MH]^+$ calcd $C_{15}H_{18}BrN_2O_3$: 353.0501, found 353.0493, and 355.0480, found 355.0492. $C_{15}H_{17}BrN_2O_3$ requires: C, 51.01; H, 4.85; N, 7.75; found: C, 50.93; H, 4.94; N, 7.73%.

Experimental data for compounds **36** through **46** can be found in the Supplemental section.‡

(1*R,4a*R**,9a*R**)-6-Chloro-2-methyl-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (47)**

The aniline derivative **32** (650 mg, 2.66 mmol) was dissolved in cold concd HCl (15 mL). The resulting yellow solution was cooled to −5 °C. A cold solution of $NaNO_2$ (208 mg, 2.93 mmol, 1.10 equiv.) was then added dropwise under the surface of the stirred reaction mixture at a rate that maintained the temperature of the reaction mixture below 0 °C. The purple reaction mixture was stirred at less than 0 °C for 75 min, while a solution of copper(II) sulfate (99%) (489 mg, 3.06 mmol, 1.15 equiv.), and NaCl (649 mg, 11.10 mmol, 4.17 equiv.) in H_2O (10 mL) was heated to 70–75 °C. Addition of a solution of sodium bisulfite (167 mg, 0.88 mmol, 0.33 mmol) and NaOH (112 mg, 2.79 mmol, 1.05 equiv.) in H_2O (10 mL) to the copper(II) sulfate solution and subsequent short heating (15 min) generated copper(I) chloride. Cold diazonium salt solution was then added dropwise and the heating continued for 1 h. Upon cessation of nitrogen evolution the reaction mixture was stirred at room temperature overnight. The resulting suspension was added dropwise into a mixture of concd NH_4OH and ice (50 mL and *ca.* 20 g, respectively). The free base precipitated and was extracted with $CHCl_3$ (4 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (silica, 5 : 1 $CHCl_3$: CMA) to give the product **47** as a white solid (0.497 g, 71%), mp ((±)-**47**) 96–98 °C (2-propanol : H_2O). ^{1}H-NMR: δ 7.08 (dd, 1H, $J = 8.4, 2.4$), 7.03 (d, 1H, $J = 2.7$), 6.81 (d, 1H, $J = 8.4$), 4.14 (d, 1H, $J = 3.9$), 3.35 (m, 1H), 3.07 (ddd, 1H, $J = 12.3, 12.0, 2.7$), 2.88 (dd, 1H, $J = 12.6, 6.9$), 2.54 (s, 3H), 2.34–2.08 (m, 3H), 1.75–1.42 (m, 5H). ^{13}C-NMR: δ 158.1, 142.1, 127.5, 125.9, 112.1, 89.4, 60.1, 55.8, 50.8, 42.5, 41.4, 33.8, 32.5, 21.0, 20.6. HRMS: $[MH]^+$ calcd $C_{15}H_{19}ClNO$: 264.1155, found 264.1156. $C_{15}H_{19}ClNO$ requires: C, 68.30; H, 6.88; N, 5.31; found: C, 68.50; H, 6.94; N, 5.30%.

(1*R,4a*R**,9a*R**)-6-Chloro-2-methyl-8-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (48)**

Chloride **47** (1.43 g, 5.4 mmol) was dissolved in trifluoroacetic acid (50 mL) and $NaNO_2$ (2.63 g, 38 mmol, 7.0 equiv.) was added in two portions (NO_x evolves vigorously). The dark brown reaction mixture was then stirred at room temperature for 2 h and the progress of the reaction was monitored by HPLC of worked up aliquots. The resulting clear orange solution was slowly added dropwise into a vigorously stirred cold NH_4OH (150 mL of concd NH_4OH with *ca.* 50 g of ice). The free base precipitated as a yellow powder, and after cooling it was collected by filtration and washed with cold H_2O (2 × 10 mL). The filter cake was dried overnight in vacuum oven (25 psi, 55 °C) to give **48** as a yellow solid (1.62 g, 98%). Two recrystallizations from 2-propanol : H_2O were necessary to remove the traces of a by-product, (presumably the 7-nitro isomer). Pure compound was obtained as light yellow crystals (1.07 g, 74%). Mp ((±)-**48**) 126–128 °C (2-propanol : H_2O). ^{1}H-NMR: δ 7.92 (d, 1H, $J = 1.8$), 7.26 (d, 1H, $J = 1.8$), 4.35 (d, 1H, $J = 3.6$), 3.49 (m, 1H), 3.10 (ddd, 1H, $J = 12.3, 12.2, 6.0$), 2.90 (dd, 1H, $J = 12.6, 7.5$), 2.55 (s, 3H), 2.29–2.10 (m, 3H), 1.79–1.45 (m, 5H). ^{13}C-NMR: δ 153.4, 146.4, 133.9, 127.5, 126.1, 122.9, 91.2, 54.6, 50.3, 42.4, 41.1, 33.6, 32.2, 20.7, 20.1. HRMS: $[MH]^+$ calcd $C_{15}H_{18}ClN_2O_3$: 309.1006, found 309.0990. $C_{15}H_{17}ClN_2O_5$ requires: C, 58.35; H, 5.55; N, 9.07; found: C, 58.47; H, 5.67; N, 9.05%.

Experimental data for compounds **49** through **51** can be found in the Supplemental section.‡

(1*R,4a*R**,9a*R**)-8-Amino-2-(2-phenylethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (52)**

Compound **51** (500 mg, 1.25 mmol) and NaOAc·3H_2O (1.656 g, 0.0125 mol, 10 equiv.) were dissolved in hot EtOH (100 mL). The solution was cooled to room temperature and then placed in an ice bath and purged with a stream of argon. The catalyst (10% Pd–C, Engelhardt C3645, 0.200 g, 15 mol% of Pd) was carefully added and the reaction mixture was hydrogenated in a Parr shaker apparatus at 45–50 psi and *ca.* 45–50 °C for 3 h, then at room temperature overnight. Reaction progress was monitored by HPLC. The reaction mixture was filtered through a Celite bed, which was washed with EtOH (3 × 10 mL). The filtrate was evaporated to dryness and the residue was converted to the free base by addition of concd NH_4OH (50 mL) and extracted with $CHCl_3$ (5 × 50 mL). The combined extracts were dried over Na_2SO_4, filtered, evaporated with a small amount of silica and purified by column chromatography (silica, 5 : 1 $CHCl_3$: CMA) to give **52** as a colorless viscous oil (0.318 g, 76%). ^{1}H-NMR: δ 7.32–7.20 (m, 4H), 6.73 (t, 1H, $J = 7.5$), 6.60–6.53 (m, 2H), 4.15 (d, 1H, $J = 3.6$), 3.60 (bs, 2H), 3.52 (m, 1H), 3.15–2.80 (m, 6H), 2.25–2.00 (m, 3H), 1.80–1.45 (m, 5H). ^{13}C-NMR: δ 146.4, 140.5, 140.2, 131.7, 128.8, 128.3, 126.0, 121.6, 115.0, 111.3, 88.7, 56.8, 53.2, 49.2, 41.5, 34.7, 33.7, 32.7, 21.1, 21.0. HRMS: $[MH]^+$

calcd $C_{22}H_{27}N_2O$: 335.2123, found 335.2104. $C_{22}H_{26}N_2O$ requires: C, 79.00; H, 7.84; N, 8.28; found: C, 79.15; H, 7.91; N, 8.28%.

(1*R**,4a*R**,9a*R**)-8-Hydroxy-2-(2-phenylethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine (53)

Amine **52** (112 mg, 0.335 mmol) was dissolved in 35% wt H_2SO_4 (14 mL) and the stirred solution was cooled to 3 °C. An aqueous solution of $NaNO_2$ (0.5 M, 1.0 mL, 0.502 mmol, 1.5 equiv.) was added dropwise over 5 min. The reaction mixture was stirred at 3 °C for 4 h then urea (0.010 g, 0.5 equiv.) was added. After an additional 5 min of stirring, a solution of copper(II) nitrate (45 mL, 1.5 M, 67.0 mmol, 200 equiv.) was added and the reaction mixture was stirred for another 5 min in a cooling bath. Finally, copper(I) oxide (60 mg, 0.419 mmol, 1.25 equiv.) was added and the reaction mixture was vigorously stirred at room temperature for 1 h (as nitrogen gas evolved some foaming occurs). The pH was adjusted to 9 by addition of concd NH_4OH (40 mL) to the chilled reaction mixture. The resulting dark blue mixture was extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated with a small amount of silica. The mixture was purified by column chromatography (silica, 4 : 1 $CHCl_3$: CMA) to give **53** as a dark yellow oil (0.096 g, 86%). Further chromatographic purification gave a yellow oil (0.068 g, 61%). ^{1}H-NMR: δ 7.33–7.18 (m, 5H), 6.80–6.74 (m, 2H), 6.63 (dd, 1H, $J = 6.3, 2.4$), 4.11 (d, 1H, $J = 3.3$), 3.72 (m, 1H), 3.07 (dd, 2H, $J = 9.9, 3.3$), 2.92 (m, 4H), 2.25–2.05 (m, 3H), 1.80–1.50 (m, 4H). ^{13}C-NMR: δ 146.3, 142.2, 141.4, 140.3, 129.0, 128.6, 126.3, 122.3, 116.8, 113.0, 89.2, 56.7, 52.3, 50.0, 41.3, 33.9, 33.2, 32.9, 21.1, 20.7. HRMS: $[MH]^+$ calcd $C_{22}H_{26}NO_2$: 336.1964, found 336.1945. $C_{22}H_{25}NO_2 \cdot C_2H_2O_4$ requires: C, 67.75; H, 6.40; N, 3.29; found: C, 67.93; H, 6.53; N, 3.49%.

Separation of the enantiomers

The racemic compound was prepared in larger quantity (*ca.* 0.150 g) and the enantiomers were separated on a chiral phase (Daicel's Chiralcel OD column (20 × 50 mm Guard plus 20 × 250 mm)) using isocratic elution with a hexane : 2-propanol : Et_2NH (80 : 20 : 0.2) mixture (8 mL min^{-1}, detection at 254 nm). Racemate was injected as a solution in 2-propanol (150 mg per 1.5 mL, three runs, 500 μL each). Retention times of the enantiomers were around 19.5 and 31 min, (+) and (−) respectively. Corresponding fractions were pooled together, evaporated and analyzed on an analytical column of the same type. The oily products were converted into corresponding oxalate salts in acetone. Optical rotations: (1*S*,4a*S*,9a*S*)-(+)-**53** (base): $[\alpha]_D^{23}$ +21.9 (*c* 1.0, $CHCl_3$), oxalate: $[\alpha]_D^{23}$ +37.0 (*c* 1.0, 90% EtOH), (1*R*,4a*R*,9a*R*)-(−)-**53** (base): $[\alpha]_D^{23}$ −26.3 (*c* 1.0, $CHCl_3$), oxalate: $[\alpha]_D^{23}$ −37.4 (*c* 1.0, 90% EtOH).

X-Ray crystal structure of (1*R*,4a*R*,9a*S*)-2-methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine ((+)-15, (1*R**,4a*R**,9a*R**)-5-(2-fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol (21), (1*R*,4a*R*,9a*R*)-5-(2-fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol ((+)-29), and (1*S*,4a*S*,9a*S*)-1,3,4,9a-tetrahydro-8-hydroxy-2-(2-phenylethyl)-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine·HBr ((+)-53·HBr)

Single-crystal X-ray diffraction data on compounds (+)-**15**, (+)-**29**, **21**, and (+)-**53**·HBr (Fig. 2) were collected using MoKα radiation and a Bruker APEX 2 CCD area detector. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C–H distance set at 0.96 Å. CCDC numbers 656371, 656369, 656370, and 656372 for compounds (+)-**15**, **21**, (+)-**29**, and (+)-**53**, respectively.‡

(1*R*,4a*R*,9a*S*)-2-Methyl-6-nitro-1,3,4,9a-tetrahydro-2*H*-1,4a-propano-benzofuro[2,3-*c*]pyridine ((+)-15·[(1*S*)-(*endo*,*anti*)]-(−)-3-bromocamphor-8-sulfonate

A 0.65 × 0.35 × 0.14 mm^3 crystal of (+)-**15** was prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (93 K) on the diffractometer. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a = 7.719(3)$ Å, $b = 13.922(5)$ Å, $c = 24.899(12)$ Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 91.8% complete to 28.51° θ (approximately 0.74 Å) with an average redundancy of 4.7. The absolute configuration was determined from the X-ray data and confirmed using a co-crystallized reference molecule ([(1*S*)-(*endo*,*anti*)]-(−)-3-bromocamphor-8-sulfonate).

(1*R**,4a*R**,9a*R**)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9α-ol (21)

A 0.64 × 0.36 × 0.28 mm^3 crystal of **21** was prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (93 K) on the diffractometer. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a = 7.4315(16)$ Å, $b = 8.4430(18)$ Å, $c = 21.576(5)$ Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 97.7% complete to 28.05° θ (approximately 0.75 Å) with an average redundancy of 4.8. The relative stereochemistry (1*R*,4a*R*,9a*R*) was determined from the X-ray data.

(1*R*,4a*R*,9a*R*)-2-Methyl-6-nitro-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2,3-*c*]pyridine ((+)-29)

A 0.50 × 0.46 × 0.14 mm^3 crystal of (+)-**29** was prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (93 K) on the diffractometer. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a = 8.7028(11)$ Å, $b = 13.9149(15)$ Å, $c = 30.493(3)$ Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 97.9% complete to 28.34° θ (approximately 0.75 Å) with an average redundancy of 5.7. The absolute configuration was set using a co-crystallized reference molecule (*R*,*R*-(−)-di-*O*,*O*′-*p*-toluoyl-D-tartaric acid).

(1*S*,4a*S*,9a*S*)-8-Hydroxy-2-(2-phenylethyl)-1,3,4,9a-tetrahydro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine·HBr ((+)-53·HBr)

A 0.84 × 0.54 × 0.30 mm^3 crystal of (+)-**53**·HBr was mounted on a glass rod and transferred to the diffractometer and data collected at room temperature (298 K) on the. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a = 7.5366(2)$ Å, $b = 11.9922(4)$ Å, $c = 21.9804(11)$ Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 97.3% complete to 30.32° θ (approximately 0.72 Å) with an average redundancy of 7.0. The absolute configuration was determined from the X-ray data.

Quantum chemical methods

Geometry optimization and energetic calculations for all the compounds in Table 5 have been conducted in the gaseous phase with the density functional theory at the level of B3LYP/6-31G*.[29] Superposition of these geometry-optimized structures was carried out using the rigid-fit of Quanta 2005 (Accelrys).

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