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Synthesis and 5HT Modulating Activity of Stereoisomers of 3-Phenoxymethyl-4-phenylpiperidines

Mogens Engelstoft and John Bondo Hansen

Novo Nordisk A/S, Medicinal Chemistry, Health Care Discovery, Novo Nordisk Park, DK-2760 Maaloev, Denmark

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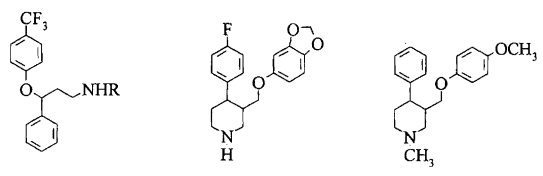
A series of pairs of enantiomers of substituted 3-phenoxymethyl-4-phenylpiperidines has been prepared from arecoline or α-methylstyrene by a combination of stereospecific reactions and optical resolutions. The ability of the compounds to modulate serotonin (5HT) neurotransmission *in vitro* was determined. Several derivatives, among which is the antidepressant paroxetine, are very potent inhibitors of 5HT reuptake. These compounds exhibit a pronounced steric requirement for inhibition of 5HT reuptake and binding to $5HT_{2A}$ and $5HT_{2C}$ receptors.

4-Phenylpiperidine is an important structural element in a number of biologically active compounds, possibly due to the similarity to the arylalkylamine pharmacophore common to neurotransmitters like serotonin (5HT), dopamine (DA), noradrenaline (NA), and to antagonists of the opiate receptor. Such compounds can be exemplified by the antipsychotic 5HT-, DA- and NA antagonist, haloperidol, the analgesic opiate antagonist, pethidine (meperidine), and the antidepressant 5HT uptake inhibitor, paroxetine.

Whereas simple 4-phenylpiperidines seldom discriminate between different receptors, the introduction of a 3-substituent, as in paroxetine, gives rise to highly selective compounds. However, the additional 3-substituent also induces chirality with concomitant synthetic implications.

Serotonin reuptake inhibitors like paroxetine and fluoxetine (Scheme 1) are effective antidepressants giving fewer side effects than the classical tricyclic drugs.[1–3] Whereas paroxetine is marketed as the pure enantiomer, (3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine, fluoxetine is a racemic mixture. Although there are no major differences in potency of (*R*)- and (*S*)-fluoxetine with respect to inhibition of 5HT uptake,[4] it has recently been described[5] that the enantiomers of fluoxetine and its metabolite, norfluoxetine, bind with different potency to 5HT receptors. Furthermore, (*S*)-norfluoxetine is more than 20 times more potent than the *R*-enantiomer as an inhibitor of 5HT uptake.[6,7]



Fluoxetine: R=CH_3 Paroxetine Femoxetine
Norfluoxetine: R=H

Scheme 1.

Several close analogs of paroxetine are potent 5HT uptake inhibitors showing interesting *in vivo* activity.[8] Among these phenylpiperidines, femoxetine, (3*R*,4*S*)-1-methyl-3-(4-methoxyphenoxymethyl)-4-phenylpiperidine has been shown to be an antidepressant in man.[1–3,9]

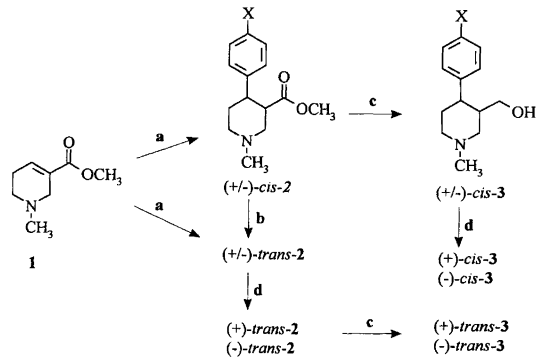
Furthermore, 3-substituted-4-phenylpiperidines have been identified as potent blockers of neuronal calcium channels, thereby reducing neuronal cell death upon ischemia,[10] and as DA-uptake inhibitors.[11]

The synthesis of a series of 3-phenoxymethyl-4-phenylpiperidines which includes several pairs of enantiomers is presented. The inhibition of 5HT uptake and affinity for 5HT receptors was measured for these compounds and a SAR is discussed.

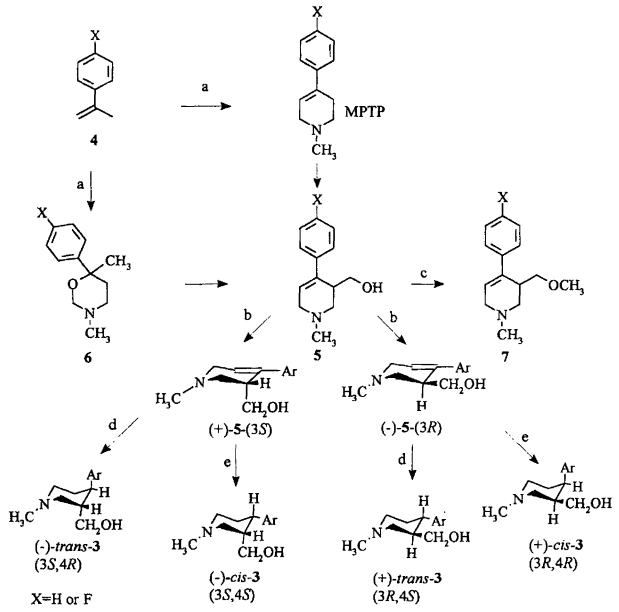
Results

Chemistry. The 3-hydroxymethyl-4-phenylpiperidines (**3**), which are pivotal intermediates in the synthesis of this series of phenylpiperidines, were prepared starting from either arecoline (**1**) (Scheme 2) or α-methylstyrene (**4**) (Scheme 3). In the reactions described below, no differences in chemical reactivity were observed between unsubstituted and *p*-fluoro-substituted phenylpiperidines.

Treatment of arecoline (**1**) with phenylmagnesium bromide in ether according to Plati[12] gave the two racemic esters (+/−)-*cis*-**2** and (+/−)-*trans*-**2**. ^1H NMR spectroscopy showed that the β-form of Plati corresponds to *cis*-, and α- to *trans*-**2**.[13] (+/−)-*cis*-**2** could be converted into the thermodynamically more stable *trans*-form by



Scheme 2. a, ArMgBr, Et_2O; b, KOtBu; c, $LiAlH_4$; d, separation, mandelic acid or dibenzoyltartaric acid.



Scheme 3. a, CH_2O, H_2NCH_3; b, dibenzoyltartaric acid; c, CH_3SO_2Cl, pyridine; d, $LiAlH_4$, THF; e, H_2–Pd–C.

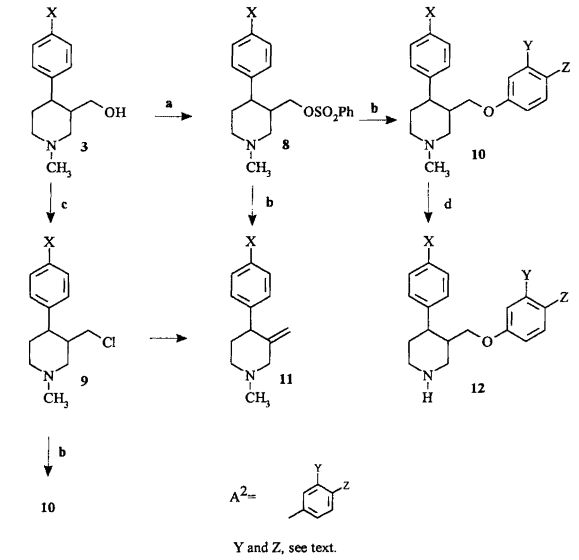
treatment with strong base. Reduction of the methyl esters with $LiAlH_4$ in ether gave the hydroxymethyl derivatives, (+/−)-*cis*-**3**, and (+/−)-*trans*-**3**, which were separated by crystallization with the antipodes of mandelic acid to the corresponding pure enantiomers. Alternatively, (+/−)-*trans*-**2** was separated using mandelic acid or dibenzoyltartaric acid, whereupon the two enantiomeric esters were reduced with $LiAlH_4$ to (+)-*trans*-**3** and (−)-*trans*-**3**.

An alternative procedure for the preparation of the carbinol **3** started from the α-methylstyrene **4** (Scheme 3), which by treatment with aqueous paraformaldehyde and methylamine gave **5**. Intermediates in this reactions are the oxazine derivative **6** and the potent neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),[14,15] which in primates and humans have been found to cause anatomical and behavioral changes analogous to those of Parkinson's disease.[16,17] Racemic **5** was easily separated into its enantiomers (+)- and (−)-**5** by crystallization of the dibenzoyltartrate.

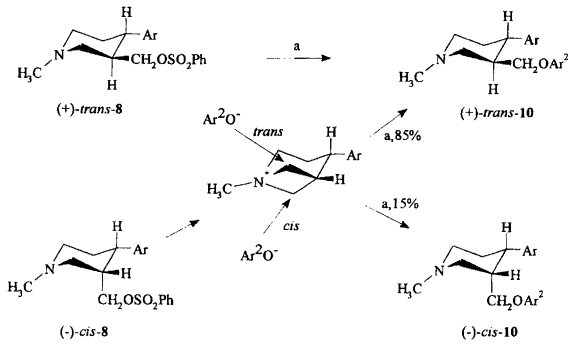
The phenyltetrahydropyridine **5** could be reduced to the piperidine derivative **3** using either catalytic hydrogenation or $LiAlH_4$ in THF. Reduction of **5** using an excess of $LiAlH_4$ gave in all cases *trans*-**3**, while using palladium catalysis, hydrogens were added to the less hindered side of the tetrahydropyridine to give primarily (85%) *cis*-**3** and only 15% *trans*-**3**. Since attempts to reduce the methyl ether **7** by $LiAlH_4$ were unsuccessful, it is likely that the carbinol group assists in the reduction, presumably through formation of aluminium alkoxide intermediate, which through an intramolecular hydrogen transfer[18] stereoselectively affords the *trans*-form.

The carbinol **3** was treated with benzenesulfonyl chloride to give **8** which upon treatment with sodium phenolate gave the phenyl ether **10** (Scheme 4). Alternatively, **3** could be transformed into **10** by the Mitsunobu procedure,[19] or via the chloromethyl derivative (**9**), which upon treatment with the sodium phenolate in DMF gave **10**. The substitution of **8** or **9** with phenolate was accompanied by elimination giving the methylene derivative **11**. While elimination was minimal starting from **8**, the use of *trans*-**9** gave 20–30% **11**, and of *cis*-**9**, >50% **11**. Demethylation of **10** was accomplished using either BrCN and $LiAlH_4$, or $ClCO_2Ph$ and basic hydrolysis to give **12**.

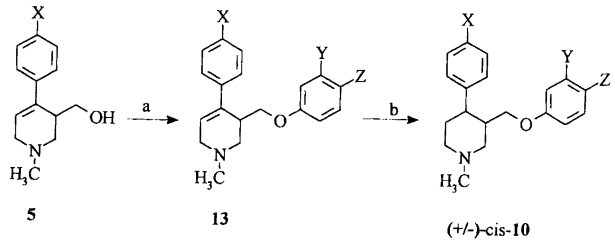
The outcome of reacting **8** with $NaOAr^2$ was dependent on the relative configuration of the starting material (Scheme 5).[20] Whereas *trans*-**8** by a normal S_N2 procedure gave exclusively *trans*-**10**, *cis*-**8** gave about 85% *trans*- and 15% *cis*-**10** as determined by HPLC. It is believed that the *cis*-isomer of **8** reacts via the intermediate 1-methyl-4-aryl-1-azoniabicyclo[3.1.1]heptane cation shown in Scheme 5.



Scheme 4. a, $PhSO_2Cl$, Et_3N; b, $NaOAr^2$; c, $SOCl_2$; d, *i*, BrCN, *ii*, $LiAlH_4$ or *i*, $ClCO_2Ar$, *ii*, NaOH, H_2O.

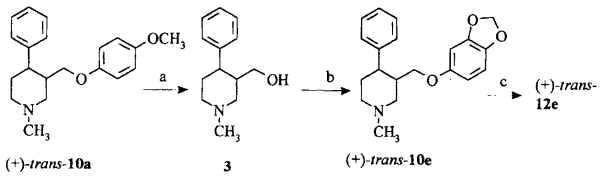


Scheme 5. a, $NaOAr^2$.



Scheme 6. a, *i*, $PhSO_2Cl$, Et_3N, *ii*, $NaOAr^2$; b, H_2–Pd–C.

By a modification of the procedure described above (+)-**5** or (+/−)-**5** was transformed into the phenyl ether (+/−)-**13** using phenylsulfonyl chloride and sodium phenolate (Scheme 6). As expected, the double bond could not be reduced with $LiAlH_4$, but catalytic hydrogenation gave (+/−)-*cis*-**10**, which was separated into its enantiomers

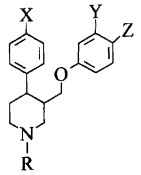


Scheme 7. a, *i*, pyridinium chloride, 160°C, 16 h, *ii*, $K_2Cr_2O_7$, H_3O^+; b, *i*, $SOCl_2$, *ii*, $NaOAr^2$; c, BrCN, $LiAlH_4$.

or demethylated and then separated to give (+)-*cis*-**12** and (−)-*cis*-**12** using tartaric acid.

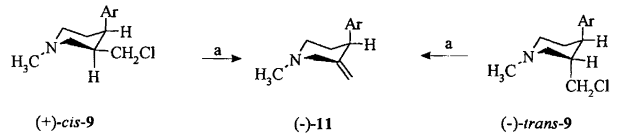
Stereochemistry. The absolute configuration of paroxetine [(−)-*trans*-**12h**] has been shown to be (3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine[21] and that of femoxetine [(+)-*trans*-**10a**] to be (3*R*,4*S*)-1-methyl-3-(4-methoxyphenoxymethyl)-4-phenylpiperidine,[22] showing that the two structures have opposite configurations. This can also be substantiated by a two-step oxidative removal of the 4-methoxyphenyl group[23] of (+)-*trans*-**10a** to give (+)-*trans*-**3** which by the procedure described above was transformed into (+)-*trans*-**10e** and subsequently (+)-*trans*-**12e** with a specific rotation equal but opposite to that of paroxetine [(−)-*trans*-**12h**] (Scheme 7). Finally, during the elimination of HCl from **9** to give **11** (Scheme 8), (−)-**11** is formed exclusively starting from either (+)-*cis*-**9** and (−)-*trans*-**9** indicating that the configuration at piperidine C-4 of these compounds is the same (4*R*). Additionally, this shows that the transformation of *trans*-**3** into *trans*-**10** takes place with retention of configuration. By establishing the

Table 1. Physical properties of 3-phenoxymethyl-4-phenylpiperidines.



Compound No.	R	X	Y	Z	Isomer	R_f/min[a]	Specific rotation[b]	M.p./°C	Formula
10a	CH_3	H	H	OCH_3	+*trans*(3*R*, 4*S*)	5.9	+89.5[c]	191–193	$C_{20}H_{25}NO_2$:HCl
10b	CH_3	H	H	OCH_3	−*trans*(3*S*, 4*R*)	7.7	−91[c]	190–192	$C_{20}H_{25}NO_2$:HCl
10c	CH_3	F	H	OCH_3	+*trans*(3*R*, 4*S*)	5.0	+73[c]	180–182	$C_{20}H_{24}FNO_2$:HCl
10d	CH_3	F	H	OCH_3	−*trans*(3*S*, 4*R*)	7.7	−75[c]	178–179	$C_{20}H_{24}FNO_2$:HCl
12a	H	H	H	OCH_3	+*trans*(3*R*, 4*S*)	5.5	+86.5[c]	141–142	$C_{19}H_{23}NO_2$:HCl:H_2O
12b	H	H	H	OCH_3	−*trans*(3*S*, 4*R*)	7.7	−84[c]	142–143	$C_{19}H_{23}NO_2$:HCl:3/4H_2O
12c	H	F	H	OCH_3	+*trans*(3*R*, 4*S*)	8.7	+80[c]	126–127	$C_{19}H_{22}FNO_2$:HCl
12d	H	F	H	OCH_3	−*trans*(3*S*, 4*R*)	12.3	−81[c]	165–168	$C_{19}H_{22}FNO_2$:CH_3CO_2H
12e	H	H	$-OCH_2O-$		+*trans*(3*R*, 4*S*)	4.6	+111[d]	182–183	$C_{19}H_{21}NO_3$:HCl
12f	H	H	$-OCH_2O-$		−*trans*(3*S*, 4*R*)	6.3	−114[c]	181–182	$C_{19}H_{21}NO_3$:HCl
12g	H	F	$-OCH_2O-$		+*trans*(3*R*, 4*S*)	8.7	+88.4[c]	121–123	$C_{19}H_{20}FNO_3$:HCl:3/4H_2O
12h	H	F	$-OCH_2O-$		−*trans*(3*S*, 4*R*)	12.5	−86[c]	124–125	$C_{19}H_{20}FNO_3$:HCl
12i	H	H	H	OCH_3	+*cis*(3*R*, 4*R*)	8.3	+113.6[e]	206–207	$C_{20}H_{25}NO_2$:HCl
12j	H	H	H	OCH_3	−*cis*(3*S*, 4*S*)	6.1	−113.6[e]	206–207	$C_{20}H_{25}NO_2$:HCl
12k	H	F	$-OCH_2O-$		+*cis*(3*R*, 4*R*)	7.5	+125[f]	223–224	$C_{19}H_{20}FNO_3$:HCl
12l	H	F	$-OCH_2O-$		−*cis*(3*S*, 4*S*)	5.9	−125[f]	224–225	$C_{19}H_{20}FNO_3$:HCl

[a] See the text for conditions. [b] $[\alpha]_D^{20}$. [c] *c*=5, 96% EtOH. [d] *c*=5, 99% EtOH. [e] *c*=5, H_2O. [f] *c*=2, CH_3OH, conc. NH_4OH (4%, v/v).



Scheme 8. a, $NaOAr^2$, DMF.

configuration of *trans*-**3** to be (3*S*,4*R*)-(−) and (3*R*,4*S*) (+) (Scheme 3) we have also determined those of **5** and **2**, since $LiAlH_4$ treatment of the purified enantiomers does not cause racemization during reduction of either of these compounds. This indicates that the configuration of (−)-*cis*-**3** is (3*S*,4*S*) and that of (+)-*cis*-**3** is (3*R*,4*R*).

Neurochemistry. In Table 1 some neurochemical activities of eight structurally different pairs of enantiomeric phenylpiperidines are described. The 4-phenylpiperidines of this series are all inhibitors of 5HT uptake. The two most potent compounds, (−)-*trans*-**12h** (paroxetine) and (−)-*trans*-**12f**, in these tests interact very stereoselectively with the uptake sites as indicated by the relatively low potency of the corresponding (+)-*trans* forms. In the series of 3,4-methylenedioxyphenoxymethylene derivatives, the 5HT uptake inhibition predominantly resides with the 3*S* forms, whereas the stereoselectivity of the 4-methoxyphenoxymethylene derivatives is less pronounced. The ability of these compounds to inhibit 5HT uptake strongly correlates with their ability to inhibit the binding of ^{3}H-paroxetine to the 5HT uptake carrier.[24]

The affinities of the phenylpiperidines to the 5HT receptors are in the micromolar range. A few compounds, however, show IC_{50}-values for the binding to the $5HT_{2A}$ receptor in the range 400–500 nM. Of all the pairs of enantiomers tested, the highest affinities for the $5HT_{2A}$ receptor can be seen within the (+)-*trans*-(3*R*,4*S*)-forms. The most potent of these compounds, (+)-*trans*-**10a** (IC_{50} = 0.43 μM), has in our hands a nearly 60-fold higher affinity for the $5HT_{2A}$ receptor than its mirror image, (−)-*trans*-**10b**. The stereoselectivity is the same or even more pronounced with respect to binding to the $5HT_{2C}$ receptor.

Conclusions. Stereoisomers of 3-phenoxymethyl-4-phenylpiperidines which have been synthesized from arecoline or α-methylstyrene stereospecifically modulate 5HT neurotransmission. Paroxetine and other analogous 3-(3,4-methylenedioxyphenoxymethyl)-4-phenylpiperidines are very potent inhibitors of 5HT reuptake. 5HT reuptake inhibition is assumed to be the pharmacological basis of the antidepressant effect of paroxetine. Compounds acting directly on 5HT receptors also modulate 5HT neurotransmission and consequently they can also have antidepressant activity. In this series of 4-phenylpiperidines several compounds with the 3*R*,4*S*-forms bind with moderate potency to $5HT_{2A}$ and $5HT_{2C}$ receptors *in vitro*. It can be speculated that some of the clinical effects of, e.g., femoxetine (**10a**), which is a relatively weak inhibitor of 5HT uptake, might be due to its effect on 5HT2 receptors.

Experimental

Compounds **3**, **5**, **10a–e** and **12a–l** were prepared according to patented procedures,[25,26] the physical properties are described in Table 2. Melting points, which are uncorrected, were taken with a Büchi melting point appa-

Table 2. In vitro biological activities of 3-phenoxymethyl-4-phenylpiperidines.

Compound no.	HT Uptake/μM[a]	$5HT_{1A}$/μM[b]	$5HT_{2A}$/μM[c]	$5HT_{2C}$/μM[d]	$5HT_3$/μM[e]
10a	0.080	13.8	0.43	0.4	—
10b	0.276	245	23.5	13	2.5
10c	0.128	59	0.46	—	>8.0
10d	0.148	257	13.5	—	>8.0
12a	0.042	30	2.66	0.6	3.4
12b	0.045	>100	85.2	55	4.14
12c	0.020	108	4.7	—	>8.0
12d	0.010	>100	50.5	—	7.3
12e	0.014	27	1.7	—	5.8
12f	0.002	2.45	63.9	—	4.5
12g	0.253	>100	5.1	2	3.4
12h	0.005	>100	47.3	22	7.1
12i	0.469	—	2.7	—	—
12j	0.414	—	5.2	—	—
12k	0.052	>100	10.5	—	—
12l	0.106	>100	2.5	—	—

[a] IC_{50} for the inhibition of uptake of $_3$H-5HT into rat brain synaptosomes.[27] [b] IC_{50} for the inhibition of binding of ^{3}H-8-HO-DPAT to rat brain synaptosomes.[28] [c] IC_{50} for the inhibition of binding of ^{3}H-ketanserin to rat brain synaptosomes.[28] [d] IC_{50} for the inhibition of binding of ^{3}H-meserguline to bovine choiod plexus.[30] [e] IC_{50} for the inhibition of binding of ^{3}H-GR65630 to rat brain synaptosomes.[29]

ratus. NMR spectra were taken on a Bruker AC 200 NMR spectrometer. The specific rotation was measured on a modified Carl Zeiss Jena 564 polarimeter or a Perkin Elmer 241 polarimeter. Optical purity was confirmed by chiral HPLC using a Chiral AGP (Chromtech) column eluting with MeOH (5%), 10 mM NaOAc (pH 4.5) (95% v/v) (**10c**, **10d**); MeOH (10%), 10 mM NaOAc (pH 5.2) (90%) (**12e**, **12f**); 2-propanol (5%), 10 mM NaOAc, (pH 5.2) (95%) (**10a**, **10b**, **12a–d**); or using an Ovomoid, ES-OUM column eluting with 2-propanol (7%), 10 mM NaOAc (pH 4.5) (93% v/v) (**12i**, **12j**); 2-propanol (4%), 10 nM NaOAc(pH 4.5) (96%) (**12k**, **12l**). The test compounds were determined to be at least 98% optical pure. R_f-values are given in Table 2.

Elemental analysis was performed by the analytical department of Novo Nordisk A/S. Receptor binding was measured using published procedures.[27–30] IC_{50} is given as an average of at least three different measurements.

*(−)-1-Methyl-3-methylene-4-phenylpiperidine hydrobromide [(−)-**11**], from (−)-*trans-**9***. 1. (−)-*trans*-3-Hydroxymethyl-1-methyl-4-phenylpiperidine (**3**).[15,25] (20 g, 0.1 mol) in 100 ml chloroform was added dropwise to 30 ml thionyl chloride in 110 ml chloroform while the temperature was kept below 10°C. The mixture was then refluxed for 6 h and concentrated *in vacuo*. Aqueous potassium carbonate [250 ml, 25% (w/v)] was added to the product which was extracted with diethyl ether. The organic phase was dried over magnesium sulfate and evaporated to give 22.9 g of an oil which was distilled *in vacuo* to give (−)-*trans*-3-chloromethyl-1-methyl-4-phenylpiperidine [(−)-*trans*-**9**] (20.7 g, 95%) (b.p. 100–104°C/0.1 mmHg).

2. To 3,4-methylenedioxyphenol (33.7 g, 0.24 mol) in 150 ml *N,N*-dimethylformamide, cooled to 0°C, was added sodium hydride (10.3 g, 55%, 0.25 mol) and subsequently (−)-*trans*-3-chloromethyl-1-methyl-4-phenylpiperidine, [(−)-*trans*-**9**] (48.4 g, 0.22 mol) dissolved in 100 ml dimethylformamide. The mixture was stirred at 120°C for 3 h and then at room temperature for 60 h, whereupon it was concentrated *in vacuo*. The product was dissolved in an excess of 1 M HCl and washed with diethyl ether whereupon it was made alkaline with 50% (w/v) aqueous NaOH and extracted with diethyl ether. The ether phase was dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was distilled *in vacuo* to give (−)-*trans*-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-phenylpiperidine [(−)-*trans*-**10**] (43.1 g, 61%) (b.p. 171–179°C/0.05 mmHg) and the free base of title compound [(−)-**11**] (11.0 g, 27%) (b.p. 70–80°C/0.1 mmHg, $[\alpha]^{20}_D = -90$ ($c = 5$, ethanol). The base was dissolved in ethanol, 48% HBr was added (to pH 4) and the solvents were evaporated off. The resulting crystals were recrystallized from abs. ethanol to give 11.5 g white crystals, m.p. 213°C. Found: C 58.22; H 7.01; N 5.07; Br 30.12. Calc. for $C_{13}H_{17}N \cdot HBr$: C 58.20; H 6.71; N 5.22; Br 29.85. NMR (200 MHz, $CDCl_3$, **11** free base): δ 1.8–2.0 (m, 1 H), 2.0–2.2 (m, 1 H), 2.2–2.3 (dt, 1 H), 2.35 (s, 3 H); 2.7 (d, $J = 12$ Hz, 1 H), 3.0 (m, 1 H), 3.2 (m, 1 H); 3.35 (d, $J = 12$ Hz, 1 H), 4.2 (s, 1 H), 4.85 (s, 1 H), 7.15–7.35 (m, 5 H).

*3-(4-Methoxyphenoxymethyl)-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (**13a**).* To 3-hydroxymethyl-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (10 g, 50 mmol) and triethylamine (11 ml) in 60 ml toluene stirred at 0°C, benzensulfonyl chloride (6.9 ml, 54 mmol) was added. The mixture was kept at 0°C for 72 h whereupon 4-methoxyphenol (9.0 g, 72 mmol) in 18 ml toluene and then a solution of sodium (3 g) in 80 ml 4-methyl-2-pentanol was added. The solution was refluxed for 4.5 h and concentrated *in vacuo*. The resulting oil was separated between toluene and water. The organic fraction was dried over potassium carbonate, evaporated and redissolved in abs. ethanol. Addition of hydrochloric acid and concentration *in vacuo* gave the desired compound, which was recrystallized from ethanol–ether to give 9.1 g white crystals (52%), m.p. 158–60°C. Found: C 69.44; H 7.20; N 3.92; Cl 10.47. Calc for $C_{20}H_{23}NO_2 \cdot HCl$: C 69.46; H 6.95; N 4.05; Cl 10.27.

*4-(4-Fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-1,2,3,6-tetrahydropyridine hydrochloride (**13b**).* This was prepared by identical methodology.

M.p. 200.8–200.9°C. Found: C 63.4; H 5.76; N 3.68; Cl 9.39. Calc. for $C_{20}H_{20}FNO_3 \cdot HCl$: C 63.6; H 5.56; N 3.71; Cl 9.40.

*Two-step oxidative synthesis of (+)-*trans*-3-hydroxymethyl-1-methyl-4-phenylpiperidine [(+)-*trans*-**3**].* Pyridine (195 g, 2.46 mol) and 200 ml concentrated hydrochloric acid were mixed and evaporated *in vacuo*, whereupon (+)-*trans*-**3**-(4-methoxyphenoxymethyl)-1-methyl-4-phenylpiperidine (80 g, 0.26 mol) and 30 ml concentrated hydrochloric acid were added. The mixture was concentrated *in vacuo* and kept at 160°C for 16 h. After cooling to room temperature ice was added, and the mixture was made alkaline with $NaHCO_3$ and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to give (+)-*trans*-3-(4-hydroxyphenoxymethyl)-1-methyl-4-phenylpiperidine as 65 g white crystals, m.p. 178–82°C, $[\alpha]^{20}_D + 75$ ($c = 2.5$, EtOH).

(+)-*trans* 3-(4-hydroxyphenoxymethyl)-1-methyl-4-phenylpiperidine (12 g, 40 mmol) in 300 ml H_2O and 10 ml conc. HCl was warmed to 80°C and added to $K_2Cr_2O_7$ (8 g, 27.2 mmol) in 110 ml H_2O. After being stirred for 30 min the aqueous mixture was washed with methylene chloride and made alkaline with 50 ml 50% (w/v) NaOH and extracted with toluene. The toluene was removed under reduced pressure and the product distilled *in vacuo* to give 4.6 g, (+)-*trans*-3-hydroxymethyl-1-methyl-4-phenylpiperidine (b.p. 125–129°C/0.3 mmHg), which was shown to be identical with the compound prepared from arecoline[12] or α-methylstyrene.[25] (Schemes 2 and 3).

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