The medicinal chemistry of aryl triflates
Barf, Tjeerd Andries

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Synthesis and Preliminary Pharmacological Evaluation of 8-OSO$_2$CF$_3$-2-aminotetralin Derivatives

Abstract

A series of (enantiopure) 8-triflate-substituted 2-(n-propylamino)tetralins has been synthesized and evaluated for in vitro binding to 5-HT$_{1A}$, 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors and in vivo biochemical and behavioural assays. Consequently, (R)-8-[(trifluoromethyl)sulfonyl]oxo]-2-(n-propylamino)tetralin ((R)-3; Ki = 1.3 nM) was found to be a potent and selective 5-HT$_{1A}$ receptor agonist inducing a full-blown 5-HT behavioural syndrome and a decrease of 3.9 °C in body temperature, while (S)-3 appeared to be a partial 5-HT$_{1A}$ receptor agonist. The oral bioavailability of (R)-3 was low (7.6%), probably as the result of a relatively high clearance. In an attempt to improve the oral bioavailability the C1-methylated analogues cis-1-methyl-8-[(trifluoromethyl)sulfonyl]oxo]-2-(n-propylamino)tetralin (cis-9), and its enantiomers were prepared. The activity was found to reside in the cis-(1S,2R)-9 enantiomer which displayed fairly high binding to 5-HT$_{1A}$ receptors (Ki = 7.1 nM) but moderate potency in postsynaptic 5-HT$_{1A}$ receptor agonist assays after subcutaneous or oral administration. The optical antipode cis-(1R,2S)-9 seemed to be a selective 5-HT$_{1A}$ receptor ligand with low intrinsic efficacy. The cis-1-methyl-N-monomethyl derivative (cis-10) displayed an enhanced affinity for 5-HT$_{1D\alpha}$ (Ki = 3.4 nM) and 5-HT$_{1D\beta}$ receptors (Ki = 10 nM), whereas trans-10 was inactive for the receptor subtypes tested.

2.1 Introduction

8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 1) is a potent, selective and centrally active 5-HT$_{1A}$ receptor agonist.$^{1,2,3}$ The clinical potential is low, due to extensive first-pass elimination via O-glucuronidation and N-depropylation, as was shown in the rat.$^{4}$ The electron-withdrawing aryl trifluoromethanesulfonate (triflate) group is known as a chemically$^{5}$ and biologically$^{6}$ stable entity. Accordingly, 8-
[(trifluoromethyl)sulfonyl]oxy)-2-(di-n-propylamino)tetralin (8-OSO$_2$CF$_3$-DPAT, 2) was found to retain high affinity for this receptor subtype, but displayed low potency in vivo.$^7$ Interestingly, the absolute oral bioavailability proved to be higher than that of 8-OH-DPAT (11.2% vs 2.4%; Table 1). In addition to this observation, compound 2 was found to be more potent after oral (po) than subcutaneous (sc) administration, in the in vivo biochemistry assays, suggesting the formation of (an) active metabolite(s). The monopropyl analogue (8-OSO$_2$CF$_3$-PAT, 3) was reported to be the major metabolite (in rat hepatocytes) and was subsequently found to be more potent in vivo than 8-OSO$_2$CF$_3$-DPAT.$^8$ In order to explore further the structure-affinity relationships (SAFIR) and pharmacology of this series of 2-aminotetralins, we prepared the enantiomers of 3.

<table>
<thead>
<tr>
<th>Table 2.1. Absolute Oral Bioavailabilities of 2-Aminotetralins</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>R$_1$</th>
<th>R$_2$</th>
<th>R$_3$</th>
<th>5-HT$_{1A}$, oral avail, Ki (nM)</th>
<th>%</th>
<th>ref.</th>
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</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>8-OH</td>
<td>H</td>
<td>n-Pr</td>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>8-OTf</td>
<td>H</td>
<td>n-Pr</td>
<td>0.8</td>
<td>11.2</td>
</tr>
<tr>
<td>3</td>
<td>8-OTf</td>
<td>H</td>
<td>H</td>
<td>3.8</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>8-OH</td>
<td>Me</td>
<td>n-Pr</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>5$^b$</td>
<td>5-OMe</td>
<td>Me</td>
<td>n-Pr</td>
<td>-</td>
<td>3.7</td>
</tr>
<tr>
<td>6$^c$</td>
<td>5-OMe</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>1.6</td>
</tr>
<tr>
<td>7</td>
<td>5-OTf</td>
<td>Me</td>
<td>n-Pr</td>
<td>-</td>
<td>9.4</td>
</tr>
<tr>
<td>8</td>
<td>5-OTf</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>62.2</td>
</tr>
</tbody>
</table>

(a) 8-OH-DPAT; (b) UH232; (c) AJ76.

The triflate concept can also be implemented for the cis- and trans-C1-methylated 2-aminotetralins, which were shown to exhibit interesting SAFIR for the 5-HT$_{1A}$ receptor (see Chapter 1). The C1-methylated 2-aminotetralin cis-(1S,2R)-4 retains the selectivity and potency of the parent compound 8-OH-DPAT.$^{11}$ This observation, and extrapolation of the substitution patterns of dopamine autoreceptor antagonists UH232 (5) and AJ76 (6) and their respective triflated analogues 7 and 8 led us to
predict 2-aminotetralin cis-8-OSO₂CF₃-MPAT⁺ (cis-9) to have superior oral bioavailability, without the loss of affinity or in vivo activity compared to the non-methylated congener 3. The relevant 5-HT₁A receptor binding data and absolute oral bioavailabilities of the known 2-aminotetralins are listed in Table 2.1.

The molecular structure of the selective 5-HT₁D receptor agonist sumatriptan (11)¹² and the improvement in affinity for the 5-HT₁D receptor by substituting the phenolic group of 1 with a triflate group (see Chapter 4), prompted us to replace the N-monopropyl substituent of compounds cis- and trans-9 (cis- and trans-8-SO₂CF₃-MMAT)⁺ by an N-methyl substituent, enabling us to investigate the influence on the 5-HT₁A and 5-HT₁D receptor affinity and selectivity.

2.2 Chemistry

Preparation and Resolution of (±)-8-OSO₂CF₃-PAT (3). The syntheses of the pure enantiomers of (R)-3 and (S)-3 are outlined in Scheme 2.1. 8-Methoxy-2-tetralone (12) was prepared according to literature procedures from commercially available 1,7-dihydroxynaphthalene by O-methylation followed by a Birch reduction.¹³ Racemic 13 was prepared by a reductive amination reaction using either n-propylamine with sodium cyanoborohydride (Borch reduction) or Dean-Stark conditions through the formation of an enamine and subsequent catalytic hydrogenation. The chiral cyclic phosphoric acid, 2-chlocyphos (14), was reported to be an efficient resolving agent for the resolution of amines.¹⁴ Thus, by using (R)-14 the separation of (R)-13 (15%) was effected by two recrystallizations from 2-propanol, after which enriched (S)-13 was recovered from the mother liquor and optically purified by recrystallization with (S)-14 in the same yield. The enantiomeric excesses (e.e.) were >98% as determined by HPLC analysis using a chiral column (Chiracel OD, Daicel). In addition, the optical rotations matched those reported in the literature.¹⁵ The enantiomers of the phenol derivative 15, which were obtained by refluxing (R)- and (S)-13 in 48% aqueous HBr, were triflated

* MPAT = 1-methyl-(n-propylamino)tetralin.
* MMAT = 1-methyl-(methylamino)tetralin.
using the mild triflating agent N-phenyltrifluoromethanesulfonimide.\textsuperscript{16} Phase-transfer conditions were employed in order to prevent substitution of the secondary amine. Our efforts to obtain suitable crystals of the salt of (S)-3 and (S)-14 for single X-ray crystallography succeeded, but due to the poorly resolved atomic positions of the triflate functionality the fluorine atoms could not be found. Either conformational flexibility of the triflate group in the crystal packing or the fact that the triflate group is fixed in various positions may contribute to this observation. This may be the reason why X-ray data of aromatic triflate containing molecules have not been reported previously.

Another approach, in which 14 may be applied for the resolution of 2-aminotetralins, is outlined in Scheme 2.3. Chiral phosphorinane derivatives were shown to be successful as derivatizing agents of amino acids, alcohols and amines and in the enantiomeric excess determination of these nucleophiles by means of \textsuperscript{1}H and \textsuperscript{3}P NMR.\textsuperscript{17} We envisaged derivatization of a small amount of racemic 2-aminotetralin with the phosphorinane analogue of 2-chlocyphos, which subsequently might be separated by
means of column chromatography. In addition, these chiral phosphorinane derivatives may serve as protective groups since the phosphamidates can easily be deprotonated and N-alkylated giving (enantiopure) N-monosubstituted 2-aminotetralins after deprotection.\(^{18}\) According to a method described by Hulst et al. for the deschloro derivative of 14, compound 17 is readily obtained by reduction of compound 14 to the diol 16 using LiAlH\(_4\) in THF, followed by treatment with PCl\(_3\). An Arbuzov rearrangement\(^{19}\) using ethanol yields (R)-2H-2-oxo-(R)-(2-chlorophenyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane ((2R,4R)-17; Scheme 2.2).

![Scheme 2.2. Reagents and conditions: (a) LiAlH\(_4\), THF, \(\Delta\); (b) PCl\(_3\), benzene, 0°C-RT; (c) ethanol.](image)

The coupling of 8-methoxy-2-aminotetralin (18) and (2R,4R)-17 is effected by using the Atherton-Openshaw-Todd coupling (Scheme 2.3).\(^{20}\) The reaction proceeds with inversion of configuration at the phosphorus atom via putative formation of a trichloromethylphosphonate derivative, which is substituted by the aminotetralin. The \(^{31}\)P NMR of the diastereomeric mixture of 19 showed a small chemical shift of 0.096 ppm resulting in an overlapping signal with a ratio of 67:37 which suggests that the formation of one of the diastereomers is favored. Unfortunately, our efforts to separate the isolated diastereomeric mixture using TLC (on SiO\(_2\); eluting with various combinations of solvents) did not succeed.

![Scheme 2.3. Reagents and conditions: (a) CCl\(_4\), Et\(_3\)N, ethanol, 0°C; (b) TLC on SiO\(_2\).](image)

Preparation and Resolution of cis-(±)-8-OSO\(_3\)CF\(_3\)-MPAT (cis-9). The synthesis of cis-8-[[[(trifluoromethyl)sulfonyl]oxy-1-methyl-2-(n-propylamino)tetralin (cis-9) is outlined in Scheme 2.4. The Stork enamine reaction was employed to
introduce the methyl group on the C1-position of the 2-tetralone skeleton according to the method of Arvidsson et al.\textsuperscript{11} with the exception of the purification procedure (column chromatography instead of distillation), affording cis-21 in a 55\% yield after recrystallization as the HCl salt. The reductive amination proceeded with a cis/trans ratio of 90:10 as determined by GC-MS. The demethylation and triflation reactions were accomplished as described for the preparation of the enantiomers of 3. The resolution of cis-9 was effected at the stage of cis-21 according to the method of Arvidsson and co-workers using di-p-toluoyl-tartaric acid.\textsuperscript{11a} The optical antipodes cis-(1S,2R)-9 and cis-(1R,2S)-9 were prepared as described above. The enantiomeric purity was determined on the hydroxy derivatives by HPLC using a chiral column (Chiralpak AD, Daicel), eluting with n-hexane/ethanol/diethylamine (98/2/0.1 v/v/v). The e.e. of cis-(1S,2R)-22 was 99\% whereas cis-(1R,2S)-22 was shown to have an e.e. of 98.6\%.* Interestingly, the enantiomers of the triflate derivatives exhibited reversed optical rotations.

Scheme 2.4. (a) pyrrolidine,p-TsOH, benzene,\(\Delta\); (b) Mel, dioxane,\(\Delta\); (c) H\(_2\)O, acetic acid,\(\Delta\); (d) n-PrNH\(_2\), p-TsOH, toluene,\(\Delta\); (e) 10\% Pd/C, H\(_2\), EtOH; (f) column chromatography on SiO\(_2\) eluting with CH\(_2\)Cl\(_2\)/MeOH (20:1); (g) 48\% HBr,\(\Delta\); (h) PhN(Tf)\(_2\), triton-B, 10\% NaOH, CH\(_2\)Cl\(_2\).

Preparation and cis- and trans-(±)-8-OSO\(_2\)CF\(_3\)-MMAT (cis- and trans-10). Analogous to the chemistry as utilized for the synthesis of cis- and trans-9, methylamine can be condensed with the 2-tetralone giving compounds cis- and trans-10 after O-demethylation and triflation (Scheme 2.5). We chose benzylamine for the

* A previous batch of cis-(1R,2S)-22 displayed an e.e. of 82\%.
Synthesis and Pharmacological Evaluation of 8-OS\(\text{CF}_3\)-2-aminotetralin Derivatives

reductive amination in order to have the primary amine within reach via debenzylation.\textsuperscript{21} The cis/trans ratio obtained after the first step was 50:50 as was determined by GC-MS analysis. After separation using column chromatography, the cis- and trans-isomers of 23 underwent successive N-methylation, N-debenzylation and O-demethylation. The triflation was carried out employing triton-B (benzyltrimethyl ammonium hydroxide) as the phase-transfer catalyst since tetrabutyl ammonium hydrogen sulfate gave an unexpected by-product containing a butyl group. However, the exact structure of this compound has not been elucidated.

Scheme 2.5. (a) benzylamine, p-TsOH, benzene, Δ; (b) PtO\(_2\), H\(_2\), MeOH; (c) column chromatography on SiO\(_2\) eluting with CH\(_2\)Cl\(_2\)/MeOH (20:1); (d) 37\% formaldehyde, NaCNBH\(_3\), pH 5, CH\(_3\)CN; (e) 10\% Pd/C, H\(_2\), EtOH; (f) 48\% HBr, Δ; (g) PhN(Tf)\(_2\), triton-B, 10\% NaOH, CH\(_2\)Cl\(_2\).

N-methylation of cis- and trans-23 resulted in the conformationally restricted cis- and trans-24. The presence of the C1-methyl causes steric hindrance which prevents proper rotation of the dialkylamino group around the C2-N bond. Surprisingly, the \(^1H\) NMR and \(^13C\) NMR spectra of each of the cis- and trans-isomers of 24 showed two populations. The ratio of these populations, determined by the integration of a number of individual signals, appeared to be solvent-depended for both cis- and trans-24. In CD\(_3\)OD the population ratio was approximately 59:41 for cis-24 and 42:58 for trans-24, but displayed a different ratio in DMSO-d\(_6\) (cis-24; 49:51 and trans-24;
37:63). We performed heating experiments in DMSO-d6 to investigate whether the populations represented different conformations that could isomerize at higher temperatures or that the two populations would stay locked in a certain conformation. Normally, the C1-methyl group gives one doublet in case of secondary amines. At 25 °C the C1-methyl group of cis-24 showed two doublets at 1.27 ppm and a coupling constant of $J = 13.91$ Hz separated by 0.047 ppm. At 100 °C, the two doublets coincided ($J = 5.85$ Hz) at 1.15 ppm and upon cooling to 25 °C the signal pattern resembled that of the first $^1$H NMR spectrum, displaying the same shift and coupling constant (Figure 2.1). Importantly, the conformational populations adopted the same ratio as before the heating experiment, implying that these two populations most probably have an equilibrium at room temperature. Similar observations were found with trans-24, however, the two doublet signals were shown to have a non-complete coalescence at 100 °C in DMSO-d6 (not shown).

![Figure 2.1. $^1$H NMR signals of the C1-methyl of cis24 at 25, 100 and 25°C, respectively (DMSO-d6)](image)

**Figure 2.1.** $^1$H NMR signals of the C1-methyl of cis24 at 25, 100 and 25°C, respectively (DMSO-d6)

Cis- and Trans-assignment. Compounds cis- and trans-21 were prepared according to literature procedures and for the O-demethylated 2-(di-n-propylamino)tetralins the stereochemistry has been resolved by means of X-ray crystallography and NMR spectroscopy. The spectroscopic data could be used in order to assign the correct stereochemistry to cis- and trans-23, which are new compounds. The pattern of $^1$H NMR signals, corresponding to specific protons of cis and trans compounds, is consistent throughout the C1-methylated 2-aminotetralin series. In line with the observations of Arvidsson et al., the $H_{1\beta}$ signals of the cis compounds usually exhibit a higher chemical shift than that of the $H_{1\alpha}$ signals of their trans isomers (Table 2.2). In addition, the coupling constants $J_{1\beta-2\beta}$ of the cis compounds ($J \sim 5$ Hz) are larger than the coupling constants $J_{1\alpha-2\beta}$ of the trans compounds ($J \sim 1$
Hz). When CDCl$_3$ was employed as the solvent, the coupling constant $J_{1\alpha,2\beta}$ was generally measureable as exemplified by trans-10, being 1.09 Hz. Additional evidence was generated by the independent preparation of cis-21 from cis-23 via n-propylation and N-debenzylation, providing identical GC-chromatograms for the two compounds (Scheme 2.6).

Scheme 2.6. (a) propionaldehyde, NaCNBH$_3$, pH 5, CH$_3$CN; (b) 10% Pd/C, H$_2$, EtOH.

<table>
<thead>
<tr>
<th>Table 2.2. $^1$H NMR Spectral Data of Compounds 21 and 23.</th>
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<tbody>
<tr>
<td><strong>chemical shift, $\delta$ (ppm)</strong></td>
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<tr>
<td>compound</td>
</tr>
<tr>
<td>cis-21</td>
</tr>
<tr>
<td>trans-21</td>
</tr>
<tr>
<td>cis-23</td>
</tr>
<tr>
<td>trans-23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>coupling constant, $J$ (Hz)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>compound</td>
</tr>
<tr>
<td>cis-21</td>
</tr>
<tr>
<td>trans-21</td>
</tr>
<tr>
<td>cis-23</td>
</tr>
<tr>
<td>trans-23</td>
</tr>
</tbody>
</table>

(a) Obscured. (b) Too small to determine.

2.3 Pharmacology

Receptor Binding. Compounds (R)- and (S)-3 were evaluated for their in vitro binding affinity at 5-HT$_{1A}$ receptors using $[^3]$H8-OH-DPAT, at 5-HT$_{1D_{\alpha}}$ and 5-HT$_{1D_{\beta}}$ using $[^3]$H5-HT, at dopamine D$_2$ receptors using either the antagonist $[^3]$Hspiperone or the agonist $[^3]$HU86170, and at dopamine D$_3$ receptors using $[^3]$Hspiperone (Table 2.3). The 1-methyl substituted 2-aminotetralins 9 and 10 were tested for their abilities to
compete with the radioligand $[^3H]8$-OH-DPAT (5-HT$_{1A}$) and $[^3H]5$-CT (5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$). All above receptors, except the dopamine D$_2$ receptor (rat), are human clones.

In Vivo Biochemistry of (R) and (S)-8-OSO$_2$CF$_3$-PAT ((R)- and (S)-3). The in vivo biochemical test utilizes the well-established phenomenon of receptor-mediated inhibition of the presynaptic neuron. The synthesis rate of 5-HT is inhibited by 5-HT$_{1A}$ receptor agonists. 5-Hydroxytryptophan (5-HTP) accumulation, following decarboxylase inhibition by (3-hydroxybenzyl)hydrazine (NSD 1015), was used as an indicator of the 5-HT turnover in three different brain areas (Table 2.4). For this study we used both nonpretreated and reserpine-pretreated rats (5 mg/kg sc, 18 h). This model is designed to detect directly acting agonists (with various degrees of intrinsic activity) at central 5-HT receptors through both biochemical and behavioural effects (Tables 2.4 and 2.5, respectively).

### Table 2.3. Affinities at cloned 5-HT$_{1A}$, 5-HT$_{1D\alpha}$, 5-HT$_{1D\beta}$, and D$_2$ Receptors In Vitro

<table>
<thead>
<tr>
<th>Compound</th>
<th>5-HT$_{1A}$</th>
<th>5-HT$_{1D\alpha}$</th>
<th>5-HT$_{1D\beta}$</th>
<th>D$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 ± 0.02</td>
<td>164 ± 30</td>
<td>638 ± 75</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>0.8 ± 0.1</td>
<td>12 ± 4</td>
<td>127 ± 26</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>3</td>
<td>2.8 ± 0.4</td>
<td>15 ± 1</td>
<td>169 ± 17</td>
<td>108 ± 12</td>
</tr>
<tr>
<td>(R)-3</td>
<td>1.3 ± 0.3</td>
<td>6.7 ± 0.5</td>
<td>138 ± 22</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>(S)-3</td>
<td>13 ± 0.7</td>
<td>157 ± 15</td>
<td>1255 ± 344</td>
<td>225 ± 14</td>
</tr>
<tr>
<td>cis-9</td>
<td>6.1$^b$</td>
<td>15.7$^b$</td>
<td>125$^b$</td>
<td>NT</td>
</tr>
<tr>
<td>cis-(1S,2R)-9</td>
<td>7.1$^b$</td>
<td>12$^b$</td>
<td>60$^b$</td>
<td>NT</td>
</tr>
<tr>
<td>cis-(1R,2S)-9$^c$</td>
<td>7.9$^b$</td>
<td>&gt;1000$^b$</td>
<td>200$^b$</td>
<td>NT</td>
</tr>
<tr>
<td>cis-10</td>
<td>5.7$^b$</td>
<td>3.4$^b$</td>
<td>10$^b$</td>
<td>NT</td>
</tr>
<tr>
<td>trans-10</td>
<td>&gt;1000$^b$</td>
<td>&gt;1000$^b$</td>
<td>&gt;1000$^b$</td>
<td>NT</td>
</tr>
</tbody>
</table>

(a) Ki values for displacement of 5-HT$_{1A}$ receptor agonist $[^3H]8$-OH-DPAT, 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptor agonist $[^3H]5$-CT, and dopamine D$_2$ receptor agonist $[^3H]$U86170. Data from dopamine D$_2$ and D$_3$ antagonists binding were higher than 300 nM and are not shown. Data from cloned mammalian receptors expressed in CHO-K1 cells (for experimentals see Section 4.5; receptor binding - method A), Compound-3 and the enantiomers of 3 were tested at the Upjohn Company, whereas compound cis-9 were tested at Centre de Recherche Pierre Fabre. (b) Value obtained from a single experiment (for the experimentals see Section 5.5). (c) e.e. 82%.

### Table 2.4. Effects on Rat Brain 5-HT Synthesis Rates (5-HTP Accumulation) In vivo in Reserpine-Pretreated and Nonpretreated Rats.

<table>
<thead>
<tr>
<th>5-HTP accumulation</th>
</tr>
</thead>
</table>

36
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<table>
<thead>
<tr>
<th>Compound</th>
<th>reserpine-pretreated rats, ( ED_{50} ) (( \mu )mol/kg)</th>
<th>nonpretreated rats, % of ctrl( \uparrow )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-1 sc</td>
<td>limb 0.036 striatum 0.047 hemi 0.05</td>
<td>limb 50 ± 3***( ^c ) striatum 48 ± 4***( ^c )</td>
</tr>
<tr>
<td>2 sc</td>
<td>8.3 26.9 13.8</td>
<td>NT\textsuperscript{d} NT</td>
</tr>
<tr>
<td>2 po\textsuperscript{e}</td>
<td>1.2 1.5 1.2</td>
<td>NT NT</td>
</tr>
<tr>
<td>3 sc\textsuperscript{e}</td>
<td>1.2 0.8 1.1</td>
<td>NT NT</td>
</tr>
<tr>
<td>(R)-3 sc</td>
<td>0.50 0.62 0.93</td>
<td>39 ± 4***( ^f ) 44 ± 3***( ^f )</td>
</tr>
<tr>
<td>(R)-3 po</td>
<td>NT NT NT</td>
<td>63 ± 6***( ^f ) 62 ± 4***( ^f )</td>
</tr>
<tr>
<td>(S)-3 sc</td>
<td>24.0 24.0 28.2</td>
<td>52 ± 3***( ^g ) 53 ± 3***( ^g )</td>
</tr>
</tbody>
</table>

(a) The animals were treated with the test drug 60 min and NSD1015 30 min before decapitation. Reserpinized animals received reserpine 18 h before drug treatment. Shown are the values producing a half-maximal decrease in the accumulation of 5-HTP in the limbic, striatal and hemispheral brain areas. (b) The values are the percent of control, means ± SEM (n = 16 and n = 4 in control and tested groups, respectively). (c) Dose 0.25 \( \mu \)mol/kg. (d) NT means Not Tested. (e) Taken from ref 8. (f) Dose 25 \( \mu \)mol/kg. (g) Dose 50 \( \mu \)mol/kg. ***\( P \leq 0.005 \).  

Locomotor Activity and Gross Behavioural Observations. Postsynaptic agonistic effects of the test compounds were assessed in normal rats and by reversal of reserpine-induced hypokinesia. Postsynaptically acting dopamine agonists induce locomotor activity while 5-HT\textsubscript{1A} receptor agonists induce the 5-HT behavioural syndrome (flat body posture, forepaw treading (piano playing), abducted hind limbs and straub tail; Table 2.5).\textsuperscript{23} Compound cis-9 and its enantiomers were additionally screened for their ability to induce the lower lip retraction.\textsuperscript{24} Oral administration was performed by gavage to animals that had been fasted for 18 h.
Table 2.5. Effects on 5-HT Behavioural Syndrome in Normal and Reserpinized Rats.

<table>
<thead>
<tr>
<th>Compound</th>
<th>normal (dose)</th>
<th>normal (dose)</th>
<th>reserpine (dose)</th>
<th>reserpine (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sc</td>
<td>po</td>
<td>sc</td>
<td>po</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0/25</td>
<td>-</td>
<td>0/12</td>
<td>-</td>
</tr>
<tr>
<td>(R)-1</td>
<td>4/4 (0.25)</td>
<td>NT</td>
<td>4/4 (0.25)</td>
<td>NT</td>
</tr>
<tr>
<td>(R)-3</td>
<td>4/4 (25)</td>
<td>3/4 (25)</td>
<td>4/4 (1.6)</td>
<td>NT</td>
</tr>
<tr>
<td>(S)-3</td>
<td>0/4 (50)</td>
<td>NT</td>
<td>4/4 (50)</td>
<td>NT</td>
</tr>
<tr>
<td>cis-9</td>
<td>0/4 (25)</td>
<td>0/4 (25)</td>
<td>0/4 (25)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>cis-(1R,2S)-9</td>
<td>0/4 (25)</td>
<td>0/4 (25)</td>
<td>0/4 (25)</td>
<td>0/4 (25)</td>
</tr>
</tbody>
</table>

(a) Shown is the number of rats displaying the 5-HT syndrome (flat body posture, reciprocal forepaw treading “pianoplaying”, straub tail. (b) Dose in µmol/kg. (c) NT means Not Tested. (d) Rats only displayed flat body posture and lower lip retraction.

Table 2.6. Locomotor Activity in Reserpinized-Pretreated and Nonpretreated Rats.

<table>
<thead>
<tr>
<th>Compound</th>
<th>normal (dose)</th>
<th>normal (dose)</th>
<th>reserpine (dose)</th>
<th>reserpine (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sc</td>
<td>po</td>
<td>sc</td>
<td>po</td>
</tr>
<tr>
<td>Vehicle</td>
<td>226±33</td>
<td>-</td>
<td>18±9</td>
<td>-</td>
</tr>
<tr>
<td>(R)-1</td>
<td>330±70</td>
<td>NT</td>
<td>235±82**</td>
<td>NT</td>
</tr>
<tr>
<td>cis-9</td>
<td>229±67</td>
<td>132±42</td>
<td>95±46</td>
<td>58±26</td>
</tr>
<tr>
<td>cis-(1S,2R)-9</td>
<td>288±46</td>
<td>175±64</td>
<td>52±6</td>
<td>87±22</td>
</tr>
<tr>
<td>cis-(1R,2S)-9</td>
<td>285±58</td>
<td>247±43</td>
<td>6±5</td>
<td>10±6</td>
</tr>
</tbody>
</table>

(a) The animals were treated with the test drug 30 min before the 30-min motility test. Reserpinized animals received reserpine 18 h before drug treatment. (b) Dose µmol/kg. (c) NT means Not Tested. **P≤0.01.

**Oral Bioavailability and In Vitro Metabolism of (R)-8-JOSO₂CF₃-PAT ((R)-3).** The absolute oral bioavailability of (R)-3 was determined by measuring the plasma concentrations after both oral and intravenous administration. Blood samples were collected at various time intervals up to 12 h after drug administration. The doses were 25 µmol/kg (po, n = 5) and 5 µmol/kg (iv, n = 3). The test compound was administered orally by gavage to animals that had been fasted for 18 h. The metabolism of (R)-3 was studied following incubation with suspensions of rat isolated hepatocytes. The metabolic profiles were examined by thermospray (TSP) LC/MS with or without β-
glucuronidase/sulfatase treatment of incubates. Structural information on metabolites was obtained by the MS/MS daughter ions analysis (Table 2.7).

### Table 2.7. Pharmacokinetic Data for Compounds 1, 2 and (R)-3 in the Rat.

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC ratio po/iv, %</th>
<th>half-life, min</th>
<th>clearance, mL/min kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.4 ± 0.9c</td>
<td>72</td>
<td>NT</td>
</tr>
<tr>
<td>2</td>
<td>11.2 ± 5.2d</td>
<td>90</td>
<td>57</td>
</tr>
<tr>
<td>(R)-3</td>
<td>7.6 ± 1.1e</td>
<td>110</td>
<td>75</td>
</tr>
</tbody>
</table>

(a) Blood samples were taken via arterial catheters. The absolute oral bioavailability was estimated by comparing the areas under the curves (AUC) in graphs in which the drug concentrations were plotted against time (n = 4 for both administration routes). (b) The half-lives were estimated graphically from the elimination phase of the blood-concentration curves after oral administration. (c) Dose 20 (po) and 1 (iv) µmol/kg. Number taken from ref.4. (d) Dose 40 (po) and 5 (iv) µmol/kg. Number taken from ref.8. (e) Dose 25 (po) and 5 (iv) µmol/kg.

Hypothermia. Postsynaptic activation of 5-HT<sub>1A</sub> receptors elicits hypothermia in the rat.<sup>25</sup> Compound (R)-3 and cis-(1S,2R)-9 were administered in a dose of 25 µmol/kg to normal rats. The animals that received the test compound orally were fasted for 18 h. Table 2.8 gives the effect after 30 min, as well as the maximal effect of each of the test compounds. In order to compare the relative effects, the area under the curve (AUC) for each compound was estimated in the range from the control body temperature until the maximal hypothermic effect (Figure 2.2).

### Table 2.8. Effects on Body Temperature in Rats

<table>
<thead>
<tr>
<th>compound</th>
<th>ΔT (°C)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>max. ΔT (°C)</th>
<th>ΔT (°C)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>max. ΔT (°C)</th>
<th>AUC&lt;sup&gt;b&lt;/sup&gt; po/sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-3</td>
<td>−2.0±0.3**</td>
<td>−3.9±0.3**</td>
<td>−2.0±0.2**</td>
<td>−2.4±0.4**</td>
<td>32 %</td>
</tr>
<tr>
<td>cis-(1S,2R)-9</td>
<td>−1.7±0.3**</td>
<td>−2.3±0.3**</td>
<td>−1.7±0.3**</td>
<td>−1.7±0.3**</td>
<td>47%</td>
</tr>
</tbody>
</table>

(a) Change in body temperature ± SEM) measured 30 min after administration of the test compound (n = 4). Dose of 25 µmol/kg. (b) Estimated from the curves obtained after polynomial regression. (c) n = 3.** P<0.01

2.4 Results and Discussion

Structure-Affinity Relationships. Obviously, the affinity of racemic 3 resides in the R-enantiomer, which exhibited a Ki of 1.3 nM for 5-HT<sub>1A</sub> sites. The same is true for the 5-HT<sub>1Da</sub> and 5-HT<sub>1Db</sub> receptor subtype as well as the dopamine D<sub>2</sub> agonist
binding. The S-enantiomer of 3 was found to be 10-fold less potent in 5-HT$_{1A}$ receptor binding, improving the two-fold stereoselectivity observed for the enantiomers of 8-OH-DPAT. As predicted, compound cis-9 is shown to have a comparatively similar binding profile with 3 exhibiting a two fold lower affinity for 5-HT$_{1A}$ receptors (Table 2.3). Surprisingly, the enantiomers of cis-9, unlike (R)- and (S)-3, displayed no stereoselectivity at all for the 5-HT$_{1A}$ receptor subtype, whereas the 5-HT$_{ID}$ receptor subtypes clearly discriminate between the two antipodes. When it comes to a comparison of the affinities of (S)-3 and cis-(1R,2S)-9 for the receptor subtypes considered, it is obvious that the introduction of a methyl group on the C1-position has a dramatic influence. The absence of affinity of cis-(1R,2S)-9 for 5-HT$_{ID\alpha}$ sites (Ki $>$1000 nM) and the low affinity for the 5-HT$_{ID\beta}$ site (Ki = 200 nM) results in a fairly selective 5-HT$_{1A}$ receptor ligand (Ki = 7.9 nM). The replacement of the N-n-propyl substituent of cis-9 by a N-methyl group expectedly improved the binding by approximately 5- and 13-fold for the 5-HT$_{ID\alpha}$ and 5-HT$_{ID\beta}$ sites, respectively. This leads to the assumption that the propyl group is too large in order to be properly accommodated by both 5-HT$_{ID}$ receptor subtypes and moreover, that the 5-HT$_{ID\beta}$ receptor is more sensitive to bulk at N-substituents than is the 5-HT$_{ID\alpha}$ receptor (see also Chapter 4). No major change was observed in the affinity for the 5-HT$_{1A}$ receptor, resulting in a rather non-selective compound. The trans-isomer of 10 is essentially inactive at the receptor subtypes tested.

**Structure-Activity Relationships.** On the basis of the data presented in Tables 2.3-2.8, it may be concluded that the enantiomers of compound 3 are 5-HT$_{1A}$ receptor agonists, similar in profile to 8-OH-DPAT. The (R)-enantiomer of 3 displays a potent and selective interaction with 5-HT$_{1A}$ receptors and is approximately 10 times less potent than 1 (reserpinized animals Table 2.4). Interestingly, in nonpretreated rats, a high dose (25 µmol/kg, sc) of (R)-3 induced a full-blown 5-HT$_{1A}$ behavioural syndrome along with a maximal decrease in 5-HTP accumulation, indicative of a 5-HT$_{1A}$ receptor agonist with full intrinsic activity (Tables 2.4 and 2.5). In contrast, the (S)-enantiomer was found to be a weak agonist ($>$ 40 times less potent in vivo compared to (R)-3) and did not induce the 5-HT behavioural syndrome in nonpretreated rats (Tables 2.4 and 2.5). The fairly high affinity in vitro (Ki of 13 nM; Table 2.3), along with the low potency and intrinsic activity at 5-HT$_{1A}$ receptors, may reflect possible antagonistic properties of (S)-3. Consequently, this compound was tested for the ability to antagonize the behavioural action induced by (R)-3. Interestingly, the forepaw treading of (R)-3 (1 µmol/kg, sc) in nonpretreated rats was nearly completely blocked by (S)-3 (50 µmol/kg, P < 0.05), while the flat body posture was not affected at all. No
antagonism of the biochemical effects was observed, suggesting that (S)-3 is a partial 5-HT	extsubscript{1A} receptor agonist.

The pharmacological profile of (R)-3 sharply contrasts with the absence of activity reported for compound 2. This is intriguing, since both compounds exhibited similar in vitro affinities for the 5-HT	extsubscript{1A} receptor (Table 2.3). Also Liu et al. reported the inability of both enantiomers of 2 to produce the 5-HT syndrome, hypothermia, or changes in the 5-HT turnover after sc administration. The lack of central effects were attributed to putative formation of inactive metabolites, or to the inability to penetrate the brain. The predicted logD values for compounds 1 and 3 were 1.8 and 2.0, respectively. However, the logD value for compound 2 was calculated to be 3.8, suggesting that the latter compound may be too lipophilic, allowing greater penetration of fat tissue in the rat. The first hypothesis, the formation of inactive metabolites, was opposed by Sonesson et al., who demonstrated that the major metabolite of 2 is the monopropyl analogue 3, and that 3 was more potent in vivo than 2. Indeed, 2 was more active after oral (po) than after subcutaneous (sc) administration, which supports the notion of first-pass metabolism to a pharmacologically more active compound. N-Dealkylation of 2, to yield 3, was shown to be the major metabolic pathway, as well as further metabolism to the primary amine. Oxidation was another important pathway, although the relative responses of the various metabolites were unknown, making quantification speculative. The biochemical and behavioural data from Table 2.3 and 2.4 reveal that (R)-3 elicits a maximal effect when the compound is administered sc, but not po, to normal rats. When (R)-3 was incubated with rat isolated hepatocytes, the major metabolite was the primary amine resulting from N-dealkylation. Minor oxidized metabolites were also observed. It is therefore likely that (R)-3 is metabolized by hepatic N-dealkylation when administered orally. The corresponding primary amine has not yet been synthesized and its effects remain to be tested. The oral bioavailability of (R)-3 is lower than that of 2 (7.6 vs 11.2%; Table 2.7), which may reflect the slightly higher clearance value obtained for (R)-3. In a semi-quantitative assay, the metabolism of (R)-3 in vitro was comparatively slower than that of 2, providing indirect evidence that (R)-3 would undergo less extensive first-pass metabolism in vivo. However, the oral bioavailability is slightly lower, indicating that other factors, such as absorption or inhibition of metabolism by a metabolite, play an important role in determining the bioavailability of these compounds.

Although very similar in binding profile, much of the efficacy of cis-9 for 5-HT	extsubscript{1A} receptors is lost, as compared to 3. In line with previously reported results, the behavioural pharmacology (Table 2.5) clearly indicates that cis-(1S,2R)-9 is the most active enantiomer. However, unlike (R)-3, cis-(1S,2R)-9 was not able to induce a full-
blown 5-HT syndrome in normal rats at the 25-µmol/kg dose (sc), indicating its weaker 5-HT$_{1A}$ receptor agonist activity. A parameter which has been proposed as an index of 5-HT$_{1A}$ receptor-mediated activity is the hypothermic response to systemic administration of 5-HT$_{1A}$ receptor agonists.$^{25}$ The maximal hypothermic response to cis-(1S,2R)-9 was 2.3 °C, and comparatively lower than the lowering of the body temperature induced by (R)-3 (3.9 °C). Interestingly, the maximal decrease of core temperature in rats induced by 8-OH-DPAT was reported to be approximately 2.2 °C (2 µmol/kg, sc) after 30 min.$^{25}$

Figure 2.2. The effects of (R)-3 and cis-(1S,2R)-9 on the body temperature in rats after sc and po administration.

Figure 2.2 shows the curves that were obtained when following the hypothermic response in time. We graphically estimated the area under the curve (AUC) of the individual compounds and administration routes, enabling us to compare the relative availabilities in brain. The AUC following po administration of (R)-3 was 32% of that obtained via the sc administration route, which is much greater than the oral bioavailability of 7.6%. Interestingly, the oral availability of cis-(1R,2S)-9 improved to approximately 47%, as compared to (R)-3, although the relative maximal response of cis-(1R,2S)-9 after sc administration was only 43%. Supportive information is provided by the behavioural profiles, since cis-(1R,2S)-9 elicited a partial 5-HT syndrome when administered via the sc or po route to reserpinized rats. In normal animals, the po administration route was less efficacious in evoking the 5-HT syndrome as compared to
sc administration. It is expected that cis-9 is able to penetrate the brain in sufficient amounts, as is indicated by its calculated logD value of 2.4. Taken together this suggests that cis-(1S,2R)-9 is a 5-HT$_{1A}$ receptor agonist with moderate potency but with increased oral availability relative to (R)-3. Despite the fairly high Ki value of 7.9 nM for 5-HT$_{1A}$ sites, cis-(1R,2S)-9 was devoid of any postsynaptic 5-HT$_{1A}$-receptor agonist activity. Either, the intrinsic efficacy is low or this compound behaves as a 5-HT$_{1A}$ receptor antagonist. If this is the case, this would contribute to the inability of racemic cis-9 to induce the 5-HT behavioural syndrome. Any possible antagonistic effects of cis-(1R,2S)-9 need to be investigated by means of behavioural and neurobiochemical experiments.

In summary, (R)-3 behaved as a full 5-HT$_{1A}$ receptor agonist when administered subcutaneously, but not orally, to normal rats. As indicated by in vitro hepatocyte experiments, N-depropylation seems to be the major metabolism pathway after po administration, resulting in the corresponding primary amine. This observation and the higher clearance value, as compared to 2, presumably account for the relatively low oral availability of 7.6%. In an attempt to improve the oral bioavailability cis-9, and its enantiomers were prepared and subjected to preliminary behavioural pharmacology studies. The activity resides in the cis-(1S,2R)-9 enantiomer which displayed fairly high binding to 5-HT$_{1A}$ receptors but moderate potency in postsynaptic 5-HT$_{1A}$ receptor agonist assays. In addition, the optical antipode cis-(1R,2S)-9 may turn out to be a 5-HT$_{1A}$ receptor ligand with low intrinsic activity. Both enantiomers of cis-9 deserve further investigation on the basis of the presented results. Moreover, the C-1 methyl substituent may interfere with the site which is responsible for the extensive first-pass metabolism of compounds 2 and (R)-3. This may result in drastically improved pharmacokinetic properties for (+)- and (−)-cis-9, compared to the non-C1 substituted 2-aminotetralins.

2.5 Experimental Section

General. $^1$H and $^{13}$C NMR spectra were recorded at 200 and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. CDCl$_3$ was employed as the solvent unless otherwise stated. Chemical shifts are given in $\delta$ units (ppm) and relative to TMS or deuterated solvent. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m, (multiplet), br (broad), dd (double doublet) and ddd (double double doublet). The heating experiments with cis- and trans-24 were recorded
with a 300 MHz Varian VXR-300 spectrometer. IR spectra were obtained on a ATI-Mattson spectrometer. Elemental analyses were performed in the Microanalytical department of the University of Groningen or at Parke-Davis (Ann Arbor, MI). The chemical ionization (CI) mass spectra were obtained on a Finnegan 3300 system. GC-MS (EI) mass spectra were recorded on a Unicam 610/ Automass 150 GC/MS system. Melting points were determined on a Electrothermal digital melting point apparatus and are uncorrected. Specific optical rotations were measured in methanol (c 1.0 if not stated otherwise) at 23 °C on a Perkin Elmer 241 polarimeter.

Materials. 1,7-dihydroxynaphtalene was purchased from Tokyo Kasei Kogyo Co, Ltd (Japan). 8-Methoxy-2-tetralone was prepared according to literature procedures. (R)- and (S)-2-chlocyphos were obtained from Syncom B.V. (The Netherlands). All further chemicals used were commercially available (Aldrich) and were used without further purification.

(±)-8-Methoxy-2-(n-propylamino)tetrinal (13). 8-Methoxy-2-tetralone (16.6 g, 94.0 mmol), n-propylamine (15.0 mL, 183.0 mmol) and a spatula of p-TsOH were refluxed under N2-atmosphere in toluene (400 mL) under Dean-Stark conditions. After 5 h the volatiles were evaporated in vacuo leaving a brown oil, which was immediately dissolved in dry THF (400 mL). The resulting solution was acidified with ether/HCl until pH 5 after which methanol (30 mL) and NaCNBH3 (8.45 g, 134.0 mmol) were added. The reaction mixture was magnetically stirred for 18 h, evaporated to dryness and taken up in saturated aqueous Na2CO3 (500 mL). The aqueous layer was extracted with ether (3 × 150 mL) which was dried over Na2SO4 and evaporated in vacuo affording 22.3 g of a brown oil which converted to the HCl salt and recrystallized from MeOH/ether (off-white material, 75%).

Resolution of (±)-8-Methoxy-2-(n-propylamino)tetrinal. A mixture of racemic amine (11.1 g, 50.7 mmol) and (R)-(+)2-chlocyphos (14.0 g, 50.7 mmol) in abs. ethanol (200 mL) was refluxed until all material was dissolved after which the solvent was removed in vacuo giving an off-white solid. The salt (24.1 g, 48.7 mmol) was recrystallized from 2-propanol yielding 5.16 g (10.42 mmol, 21%) of white crystals with [α]D +53.1°. A second recrystallization gave 3.74 g (7.56 mmol, 16%) salt with [α]D +60.1°. This salt (3.65 g, 7.37 mmol) was converted to the free base by stirring in 10% KOH (50 mL), extraction with ether and drying over Na2SO4. Evaporation of the solvent in vacuo yielded (R)-(+)13 (1.58 g, 15%) as a colorless oil with [α]D +76.4° (lit15 [α]22D +78.3° (c 1.05)). The residual salt (11.2 g, 22.7 mmol) was converted to the free base described as above using 10% KOH (100 mL). Repeating the above procedure with the enriched (−)-enantiomer of 13 (4.57 g, 21.7 mmol) with (S)-(−)-2-chlocyphos
(5.99 g, 21.7 mmol) gave (S)-(−)-13 (1.65 g, 15%) as a colorless oil with [α]D −77.6° (lit\textsuperscript{15} [α]\textsubscript{D}^22 −77.0° (c 1.03)).

(R)-(−)-8-Hydroxy-2-(n-propylamino)tetralin HBr ((R)-(−)-15). (R)-13.HCl (1.74 g, 6.82 mmol) was refluxed in 48% aqueous HBr (50 mL, freshly distilled) for 2 h under N\textsubscript{2}-atmosphere. The reaction mixture was allowed to cool to room temperature and evaporated to dryness giving 1.88 g (97%) of a pale-brown solid, of which 445 mg was recrystallized from ethanol/ether for purification (374 mg, 78%): mp 283-286 °C; IR (KBr) 3275 cm\textsuperscript{−1}; \textsuperscript{1}H NMR (CD\textsubscript{3}OD) \(\delta\) 1.07 (t, \(J = 7.69\), 3H), 1.70-1.91 (m, 3H), 2.33 (m, 1H), 2.60 (dd, \(J_1 = 10.25\), \(J_2 = 16.23\), 1H), 2.91 (m, 2H), 3.08 (m, 2H), 3.26-3.37 (m, 1H), 3.43-3.58 (m, 1H), 6.61 (d, \(J = 7.7\), 1H) 6.62 (d, \(J = 8.12\), 1H) 6.97 (dd, \(J_1 = 7.69\), \(J_2 = 8.12\), 1H); \textsuperscript{13}C NMR (CD\textsubscript{3}OD) \(\delta\) 11.1, 20.7, 26.6, 27.2, 28.3, 47.5, 55.8, 112.6, 120.0, 120.3, 127.8, 136.9, 156.0; MS (CI with NH\textsubscript{3}) m/e 206 (M\textsuperscript{+1}); Anal Calcd (Obsd) for C\textsubscript{13}H\textsubscript{19}NO.HBr: C: 54.55 (54.46), H: 7.04 (7.03), N: 4.89 (4.98); [α]D +63.5°.

(S)-(−)-8-Hydroxy-2-(n-propylamino)tetralin HBr ((S)-(−)-15). Demethylation of (S)-13.HCl (1.92 g, 7.53 mmol) was performed according to procedure as described for (R)-15 as above giving (S)-15 in a quantitative yield. Part of the salt (1.06 g) was recrystallized from ethanol/ether yielding 0.80 g (76%) of off-white crystals: mp 273-277 °C; IR (KBr) 3275 cm\textsuperscript{−1}; \textsuperscript{1}H NMR (CD\textsubscript{3}OD) \(\delta\) 1.07 (t, \(J = 7.69\), 3H), 1.70-1.91 (m, 3H), 2.33 (m, 1H), 2.60 (dd, \(J_1 = 10.25\), \(J_2 = 16.23\), 1H), 2.91 (m, 2H), 3.08 (m, 2H), 3.26-3.37 (m, 1H), 3.43-3.58 (m, 1H), 6.61 (d, \(J = 7.7\), 1H) 6.62 (d, \(J = 8.12\), 1H) 6.97 (dd, \(J_1 = 7.69\), \(J_2 = 8.12\), 1H); \textsuperscript{13}C NMR (CD\textsubscript{3}OD) \(\delta\) 11.1, 20.7, 26.6, 27.2, 28.3, 47.5, 55.8, 112.6, 120.0, 120.3, 127.8, 136.9, 156.0; MS (CI with NH\textsubscript{3}) m/e 206 (M\textsuperscript{+1}); Anal Calcd (Obsd) for C\textsubscript{13}H\textsubscript{19}NO.HBr: C: 54.55 (54.46), H: 7.04 (7.03), N: 4.89 (4.98); [α]D −64.5°.

(R)-(−)-8-[[[Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin HCl ((R)-(−)-3). A mixture of (R)-15 (200 mg, 0.70 mmol), N-phenyltrifluoromethanesulfonimide (376 mg, 1.05 mmol) and tetrabutyl ammoniumhydrogensulfate (24 mg, 10 mol%) in dichloromethane (8 mL) and 10% NaOH (3 mL) was stirred at room temperature for 24 h. The reaction mixture was quenched with 5% HCl solution (v/v) until pH 1, diluted with H\textsubscript{2}O (25mL) and washed with ether (50 mL). The ether layer was extracted with H\textsubscript{2}O and 5% HCl solution (20 mL). The combined aqueous layers were basified with solid Na\textsubscript{2}CO\textsubscript{3} until pH 9, extracted with ether (3 × 30 mL) after which the organic phase was washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4}. Evaporation in vacuo yielded a colorless oil which was converted to the HCl salt and recrystallized from methanol/ether (177 mg, 68%): mp 238-240 °C; IR (KBr) 1217, 1421 cm\textsuperscript{−1} (O-SO\textsubscript{2}); \textsuperscript{1}H NMR \(\delta\) 0.96 (t, \(J = 7.5\), 3H), 1.35 (br s, NH), 1.55 (m, 2H), 1.63 (m, 1H), 2.05 (m, 1H), 2.53 (dd, \(J_1 = 8.55\), \(J_2 = 16.24\), 1H), 2.69 (t, \(J = 7.5\),
Chapter 2

2H), 2.83-3.04 (m, 3H), 3.12 (dd, J₁ = 4.71, J₂ = 16.24, 1H), 7.05-7.18 (m, 3H); ¹³C NMR δ 11.8, 23.4, 27.8, 28.6, 30.7, 49.0, 52.5, 118.3, 118.6 (q, J = 321, CF₃), 126.7, 128.6, 128.7, 139.9, 148.4; MS (CI with NH₃) m/e 338 (M⁺+1); Anal Calcd (Obsd) for C₁₄H₁₈NO₃SF₃.HCl: C: 44.98 (45.18), H: 5.12 (5.12), N: 3.75 (3.86); [α]D +61.5° (HCl).

(S)-(−)-8-[(Trifluoromethyl)sulfonyl]oxy-2-(n-propylamino)tetralin HCl ((S)-(−)-3). Triflation of (S)-15 (880 mg, 3.08 mmol) was performed according to the procedure given for the synthesis of (R)-3 above giving an oil after extractive workup. Conversion to the HCl salt and subsequent recrystallization from methanol/ether gave 760 mg (66%) of a white crystals: mp 235-238 °C; IR (KBr) 1217, 1419 cm⁻¹ (O-SO₂); ¹H NMR δ 0.95 (t, J = 7.7, 3H), 1.32 (br s, NH), 1.54 (m, 2H), 1.64 (m, 1H), 2.06 (m, 1H), 2.53 (dd, J₁ = 8.55, J₂ = 16.24, 1H), 2.69 (t, J = 7.69, 2H), 2.82-3.02 (m, 3H), 3.12 (dd, J₁ = 4.7, J₂ = 16.24, 1H), 7.04-7.20 (m, 3H); ¹³C NMR δ 11.7, 23.4, 27.7, 28.6, 30.7, 49.0, 52.5, 118.3, 118.6 (q, J = 321, CF₃), 126.7, 128.6, 128.7, 139.9, 148.4; MS (CI with NH₃) m/e 338 (M⁺+1); Anal Calcd (Obsd) for C₁₄H₁₈NO₃SF₃.HCl: C: 44.98 (44.94), H: 5.12 (5.14), N: 3.75 (3.74); [α]D −61.5° (HCl).

(R)-1-((2-chlorophenyl)-2,2-dimethyl-1,3-propanediol (( R)-16). To a refluxed solution of LiAlH₄ (4.0 g, 105.3 mmol) in dry THF (100 mL), (R)-2-chlocyphos (8.2 g, 29.7 mmol) was slowly added as a solid leading to a violent reaction. The mixture was subsequently refluxed for 5 h followed by overnight stirring at room temperature. The excess LiAlH₄ was destroyed by the slow additon of aqueous 1N aqueous KOH (4.0 mL) (caution: this yields the very poisonous PH₃ gas). The resulting mixture was stirred with Celite (8.8 g) for 30 min and filtered. The ether layer was dried over Na₂SO₄ and concentrated in vacuo, yielding 3.93 g (62%) of a white crystals: mp 235-238 °C; IR (KBr) 3337 cm⁻¹ (OH); ¹H NMR δ 0.86 (s, 3H), 0.91 (s, 3H), 3.53 (m, 2H), 3.84 (br s, 2H), 5.25 (s, 1H), 7.18-7.33 (m, 4H); 7.57 (d, J = 7.69, 1H); ¹³C NMR δ 18.7, 22.4, 40.0, 72.2, 76.7, 126.5, 128.5, 129.2, 129.5, 133.3, 139.2; MS (EIPI) 196 (M⁺−H₂O).

(R)-2H-2-oxo-4-( R)-2-chlorophenyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane (( 2R,4R)-17). A magnetically stirred solution of diol 16 (3.8 g, 14.6 mmol) in benzene (30 mL) was cooled to 0 °C under N₂-atmosphere. Over a 15-min period, PCl₃ (3.0 g, 17.4 mmol) was added carefully, while the solution was degassed regularly. After this addition, the solution was stirred at room temperature for 1 h. Subsequently, ethanol (2.5 mL) was added slowly to the mixture following stirring for another hour at room temperature. Evaporation of the solvent yielded a colorless oil, which was crystallized from ether to afford pure 17 (0.39 g, 10%) as a white solid. The mother liquor was evaporated to dryness and stored in the freezer (−18 °C) until further use. IR (KBr) 1036, 1252, 1268, 1585, 2931 cm⁻¹; ¹H NMR δ 0.85 (s, 3H), 1.16 (s, 3H), 4.00 ((dd, J₁ = 26.06, J₂ = 11.54, 1H), 4.30 (dd, J₁ = 11.54, J₂ = 3.42, 1H), 5.77 (d, J =
3.42, 1H), 7.06 (d, J = 671.74, 1H), 7.24-7.39 (m, 4H); 7.54-7.59 (m, 1H); \(^{13}\text{C} \text{NMR} \delta 18.0, 20.7, 37.4, 72.3 (d, J = 671.74, 1H), 81.6 (d, J = 3.20), 126.8, 129.4, 130.0, 130.1, 132.9, 133.1; \(^{31}\text{P} \text{NMR} \delta 3.61; \text{MS (EIPI)} 261 (M^+)\).

(\pm)-N-(8-methoxy-tetralin-2-yl)-O,O'-[1-(R)-2-chlorophenyl]-2,2-(dimethyl)prop-1,3-yl]-(S)-phosponamide ((\pm)-19). A suspension of 18 (120 g, 0.68 mmol) in Et\(_3\text{N}\) (0.2 mL) and ethanol (0.2 mL) was cooled to 0 °C and treated dropwise with a solution of phosphorinane derivative (2R,4R)-17 (204 mg, 0.78 mmol) in CCl\(_4\) (135 µL) via a syringe. The resulting reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by acidification with 10% aqueous HCl (2 mL), diluted with H\(_2\text{O}\) (10 mL) and extracted with CH\(_2\text{Cl}_2\) (3 × 10 mL). The combined organic layers dried over Na\(_2\text{SO}_4\) and removed in vacuo yielding 410 mg (>100%) of a sticky colorless oil. Attempts to separate the enantiomers of 19 via TLC, trying a variety of eluent combinations did not succeed: \(^1\text{H} \text{NMR} \delta 0.83 (s, 3H), 1.07 (s, 3H), 1.71-1.83 (m, 1H), 2.11-2.16 (m, 1H), 2.54 (dd, J\(_1\) = 17.21, J\(_2\) = 8.05, 1H) 2.92 (m, 2H), 3.20 (ddd, J\(_1\) = 32.22, J\(_2\) = 17.21, J\(_3\) = 5.13, 1H), 3.39 (t, 1H) 3.79 (s, 3H) 3.83 (dd, J\(_1\) = 24.17, J\(_2\) = 11.35, 1H), 4.15-4.31 (m, 1H) 4.55 (d, J = 11.35, 1H), 6.03 (d, J = 1.47, 1H), 6.64-6.73 (m, 2H), 7.10 (t, 1H) 7.26-7.59 (m, 4H); \(^{31}\text{P} \text{NMR} \delta 5.84 (d, Δδ 0.096; ratio 67:36); \text{MS (EIPI)} 435 (M^+)\).

8-Methoxy-1-methyl-2-tetralone (20). A mixture of 12 (7.1 g, 40.2 mmol), pyrrolidine (6.7 mL, 80.5 mmol) and a spatula of p-TsOH were refluxed in benzene (150 mL) under Dean-Stark conditions. After 18 h the volatiles were removed in vacuo giving a brown oil. The enamine was dissolved in dioxane (35 mL) and stirred at 40 °C together with iodomethane (12.0 mL, 187.8 mmol) for 3 h. The temperature was raised to 75 °C for 24 h after which an additional portion of iodomethane (4.0 mL, 62.5 mmol) was added and the heating continued for another 24 h. H\(_2\text{O}\) (15 mL) and acetic acid (0.7 mL) were added and the reaction mixture was refluxed for 7 h. Evaporation in vacuo afforded a brown residue which was taken up in CHCl\(_3\) (100 mL), washed with 10% aqueous HCl (100 mL). The aqueous phase was extracted with CHCl\(_3\) (2 × 100 mL), and the combined organic layers were dried over MgSO\(_4\) and reduced to dryness. The obtained oil was purified on a silica column eluting with CH\(_2\text{Cl}_2\), collecting 30 mL fractions. Pure fractions were pooled and evaporated in vacuo giving 7.2 g (94%) of a yellow oil: IR (KBr) 1716 cm\(^{-1}\) (C=O); \(^1\text{H} \text{NMR} \delta 1.37 (d, J = 7.69, 3H), 2.37-2.54 (m, 1H), 2.69-2.82 (m, 1H), 2.88-3.01 (m, 1H), 3.09-3.25 (m, 1H), 3.84 (s, 3H), 51.3, 55.3, 108.6, 120.2, 127.3, 127.6, 136.8, 156.8.

cis- and trans-(\pm)-8-Methoxy-1-methyl-(n-propylamino)tetralin (cis- and trans-21). A solution of 20 (3.2 g, 16.8 mmol), n-propylamine (3.0 mL, 36.5 mmol) and
a spatula of p-TsOH in dry benzene (60 mL) was refluxed for 24 h in a Dean-Stark apparatus. At this time, an additional amount of n-propylamine (1.5 mL) was added and the heating continued for 48 h. Removal of the solvent in vacuo gave a brown oil which was immediately dissolved in MeOH (100 mL), transferred to a Parr-apparatus and hydrogenated under H2-atmosphere (4 atm) using 10% Pd/C. After 1 h the reaction was complete (GC/ TLC). The mixture was filtered over Celite, rinsed with MeOH and evaporated to dryness yielding a brown oil. GC-MS analysis revealed a cis/trans ratio of 90:10. The oil was chromatographed on a short silica column (6 × 6 cm), eluting with CH2Cl2/MeOH (20:1). Pure fractions were pooled and evaporated in vacuo, after which the combined intermediate fractions were subjected to another column affording 2.15 g (55%) in total of pure of cis-21 and 0.17 g (4%) of trans-21. A portion of the free bases were treated with ethereal HCl and recrystallized from EtOH/ether. cis-21HCl: mp 244-246 °C (lit 243-245 °C11a); IR (KBr) 1258, 1584 cm−1; 1H NMR (CD3OD) δ 1.06 (t, J = 7.69, 3H), 1.18 (d, J = 6.84, 3H), 1.71-1.89 (m, 2H), 1.97-2.16 (m, 2H), 2.92-3.16 (m, 4H), 3.37-3.49 (m, 1H), 3.56-3.66 (dq, J1 = 6.41, J2 = 5.13, 1H), 3.82 (s, 3H), 6.71 (d, J = 7.69, 1H), 6.78 (d, J = 8.12, 1H), 7.13 (dd, J1 = 8.12, J2 = 7.69, 1H); 13C NMR (CD3OD) δ 11.0, 14.0, 20.5, 20.8, 28.7, 29.4, 48.1, 55.5, 59.3, 108.6, 120.3, 121.7, 128.3, 135.7, 157.8; MS (EIPI) 233 (M+). trans-21HCl: mp 166-167 °C (lit 175-176 °C11a); IR (KBr) 1248, 1580 cm−1; 1H NMR (CD3OD) δ 1.02 (t, J = 7.27, 3H), 1.30 (d, J = 7.26, 3H), 1.63-1.83 (m, 2H), 2.03-2.31 (m, 2H), 2.80-2.93 (m, 2H), 2.96-3.14 (m, 2H), 3.42 (br q, J = 6.83, 1H), 3.85 (m, 1H), 3.85 (s, 3H), 6.80 (t, J = 8.98, 2H), 7.17 (t, J = 8.12, 1H); 13C NMR (CD3OD) δ 11.0, 20.2, 20.3, 21.0, 23.8, 31.0, 48.2, 55.5, 59.6, 109.0, 122.2, 125.9, 128.3, 136.0, 158.6; MS (EIPI) 233 (M+).

cis-(±)-8-Hydroxy-1-methyl-2-(n-propylamino)tetralin HBr (cis-22). Demethylation of cis-21. HCl (200 mg, 0.74 mmol) was performed according to procedure as described for (R)-15 as above giving cis-22 as a pinkish solid in a quantitative yield. The salt was recrystallized from EtOH/ether yielding 197 mg (89%) off-white crystals: mp 251-253 °C; IR (KBr) 3242 cm−1 (OH); 1H NMR (CD3OD) δ 1.07 (t, J = 7.69, 3H), 1.22 (d, J = 6.84, 3H), 1.76-1.88 (m, 2H), 1.98-2.11 (m, 2H), 2.89-2.96 (m, 2H), 3.07-3.16 (m, 2H), 3.30-3.49 (m, 1H), 3.54-3.66 (dq, J1 = 6.41, J2 = 5.13, 1H), 6.60 (t, J = 8.98, 2H) 6.96 (t, J = 8.98, 1H); 13C NMR (CD3OD) δ 11.1, 13.9, 20.5, 21.1, 28.8, 29.6, 48.1, 59.5, 113.0, 120.5, 126.7, 128.0, 135.8, 155.5; MS (CI with NH3) 220 (M+); Anal Calcd (Obsd) for C14H21NO.HBr: C: 56.01 (55.74), H: 7.39 (7.32), N: 4.67 (4.50).

cis-(±)-8-[[(Trifluoromethyl)sulfonyl]oxy]-1-methyl-2-(n-propylamino)tetralin HCl (cis-9). Triflation of cis-22 (215 mg, 0.72 mmol) was performed according to the procedure given for the synthesis of (R)-3 using Triton-B
(50 µL, 10 mol%) as the phase-transfer catalyst giving a colorless oil after extractive workup. Column chromatography on silica eluting with CH₂Cl₂/MeOH (10:1) afforded pure cis-9 (200 mg, 79%). Conversion to the HCl salt and subsequent recrystallization from acetone gave 171 mg (61%) of a white solid: mp 194-195 °C; IR (KBr) 1211, 1414 cm⁻¹ (O-SO₂); ¹H NMR δ 0.95 (t, J = 7.32, 3H), 1.11 (d, J = 7.09, 3H), 1.29 (br s, NH), 1.45-1.69 (m, 2H), 1.73-1.83 (m, 2H), 2.65-2.71 (m, 2H), 2.86-2.96 (m, 3H), 3.28-3.40 (dq, J₁ = 7.08, J₂ = 4.88, 1H), 7.06-7.21 (m, 3H); ¹³C NMR δ 11.5, 13.4, 23.2, 23.5, 28.7, 30.4, 48.5, 55.6, 118.1, 118.4 (q, J = 320.5, CF₃), 126.8, 128.8, 134.7, 138.9, 148.0; MS (CI with NH₃) 352 (M⁺). 

Resolution of cis-(±)-8-Methoxy-1-methyl-2-(n-propylamino)tetralin. The resolution of cis-21 was performed according to the method of Arvidsson et al.,¹¹a affording 63 mg (25%) of (+)-21. HCl and 67 mg (26%) of (−)-21. HCl. (1S,2R)-(+)21: [α]D +29.6° (MeOH, c 1.08; lit. [α]D +30.4° (MeOH, c 1.02). (1R,2S)-(−)-21: [α]D −29.0° (MeOH); lit. [α]D −31.1° (MeOH, c 1.02). 

 cis-(1S,2R)-(+)8-Hydroxy-1-methyl-2-(n-propylamino)tetralin HBr (cis-(1S,2R)-(+)22). The title compound was prepared as described for the synthesis of (R)-15 as above giving cis-(+)22. The crude product was stirred in acetone and collected on a glass sintered funnel as a pinkish solid (51 mg, 85%): mp 255 °C (decomp); [α]D +27.9° (MeOH, c 0.95); E.e. 99%. 

 cis-(1R,2S)-(−)8-Hydroxy-1-methyl-2-(n-propylamino)tetralin HBr (cis-(1R,2S)-(−)22). The title compound was prepared as described for the synthesis of cis-(1S,2R)-22 as above giving cis-(−)22 as a pinkish solid (60 mg, 80%): mp 254 °C (decomp); MS (CI with NH₃) 220 (M⁺); Anal Calcd (Obsd) for C₁₄H₂₁NO.HBr: C: 56.01 (55.71), H: 7.39 (7.41), N: 4.67 (4.57); [α]D −28.0° (MeOH, c 1.07). 

 cis-(1S,2R)-(−)8-[[((Trifluoromethyl)sulfonyl]oxy]-1-methyl-2-(n-propylamino)tetralin HCl (cis-(1S,2R)-(−)9). The title compound was prepared as described for the synthesis of (R)-3 using triton-B as the phase-transfer catalyst, affording cis-(1S,2R)-9 as a colorless oil (57 mg, 85%) after column chromatography. Conversion to the HCl salt and recrystallization from acetonitrile gave 41 mg (61%) colorless needles: mp 240-245 °C; Anal Calcd (Obsd) for C₁₅H₂₀NO₃SF₃.HCl: C: 46.45 (46.34), H: 5.46 (5.32), N: 3.61 (3.62); [α]D −3.7° (MeOH). 

 cis-(1R,2S)-(+)8-[[((Trifluoromethyl)sulfonyl]oxy]-1-methyl-2-(n-propylamino)tetralin HCl (cis-(1R,2S)-(+)9). The title compound was prepared as described for the synthesis of (R)-3 using triton-B as the phase-transfer catalyst, affording cis-(1R,2S)-9 as a colorless oil (55 mg, 78%) after column chromatography. Conversion to the HCl salt and recrystallization from i-propyl acetate gave 43 mg
(55%) of a white yelly, which was difficult to filter: mp 240-245 °C; $[\alpha]_D +3.5^\circ$ (MeOH, c 1.15).

cis- and trans-(±)-8-Methoxy-1-methyl-2-(benzylamino)tetralin HCl (cis- and trans-23). These compounds were made essentially according to literature procedures. A solution of 8-methoxy-1-methyl-2-tetralone (4.85 g, 25.5 mmol), benzylamine (4 mL) and p-TsOH. H$_2$O (0.09 g) in benzene (70 mL) was refluxed for 72 hours under continuous removal of H$_2$O using a Dean-Stark apparatus. The benzene and the excess benzylamine were removed in vacuo and the residue was dissolved in MeOH (150 mL). After transferring the solution to a Parr hydrogenation flask, PtO$_2$ (80 mg) was added as a catalyst and the mixture was hydrogenated for 2.5 hours under a H$_2$-pressure of 3 atmosphere. After filtration over Celite and evaporation in vacuo, the brown residual oil (cis/ trans ratio 50:50 according to GC-MS) was subjected to column chromatography (SiO$_2$) eluting with CH$_2$Cl$_2$/ MeOH (20:1) affording pure trans- (eluted 1$^{st}$) and cis-23 (eluted 2$^{nd}$). Both compounds were converted in the HCl salt and recrystallized from EtOH/ ether: cis-23 (0.91 g, 11%, white crystals): mp 239-240 °C; IR (KBr) 1253, 1582 cm$^{-1}$; $^1$H NMR $\delta$ 1.17 (d, $J = 6.96$, 3H), 1.79-1.87 (m, 2H), 2.87-2.99 (m, 3H), 3.46 (dq, $J_1 = 6.69$, $J_2 = 5.49$, 1H), 3.86 (s, 3H), 3.91 (dd, $J_1 = 44.31$, $J_2 = 12.81$, 2H), 6.71 (t, $J = 7.69$, 2H), 7.11 (t, $J = 7.69$, 1H), 7.26-7.42 (m, 5H); $^{13}$C NMR $\delta$ 13.5, 24.1, 29.3, 29.9, 51.0, 55.2, 55.9, 107.2, 121.2, 126.3, 126.9, 128.2, 128.4, 130.7, 136.7, 140.7, 157.3; MS (EI) M$^+$ 281; Anal Calcd (Obsd) for C$_{19}$H$_{23}$NO.HCl: C: 71.80 (71.55), H: 7.61 (7.50), N: 4.41 (4.37). trans-23 (0.81 g, 10%; white crystals): mp 223-224 °C; IR (KBr) 1254, 1583 cm$^{-1}$; $^1$H NMR $\delta$ 1.23 (d, $J = 6.96$, 3H), 1.90-2.01 (m, 2H), 2.69-2.76 (ddd, $J_1 = 16.84$, $J_2 = 5.49$, $J_3 = 2.56$, 1H), 2.90-3.00 (m, 2H), 3.22 (br q, $J = 6.96$, 1H), 3.84 (s, 3H), 3.98 (dd, $J_1 = 21.97$, $J_2 = 13.55$, 2H), 6.70 (d, $J = 8.06$, 1H), 6.75 (d, $J = 7.32$, 1H), 7.11 (t, $J = 8.06$, 1H), 7.26-7.37 (m, 5H); $^{13}$C NMR $\delta$ 20.9, 21.7, 24.2, 32.8, 32.9, 51.1, 55.2, 56.4, 107.4, 121.3, 126.0, 126.8, 128.2, 128.3, 138.8, 136.8, 140.8, 158.0; MS (EI) M$^+$ 281; Anal Calcd (Obsd) for C$_{19}$H$_{23}$NO.HCl: C: 71.80 (71.57), H: 7.61 (7.53), N: 4.41 (4.33).

cis-8-Methoxy-1-methyl-2-( N-methyl-benzylamino)tetralin HCl (cis-24). Compound cis-23 (1.01 g, 3.18 mmol) was dissolved in acetonitrile (15 mL), then an aqueous solution of formaldehyde (2.5 mL, 37 %) was added. Subsequently, NaCNBH$_3$ (608 mg, 9.68 mmol) and glacial acetic acid (340 µL, pH 5) were added. The resulting mixture was stirred under N$_2$-atmosphere for 1 h, after which time another amount of acetic acid (340 µL) was added. Stirring continued for 1 hour. The reaction mixture was taken up in 10% NaOH (30 mL) and extracted with ether (3 × 20 mL). The organic layers were dried over MgSO$_4$, filtered and the solvent was removed in vacuo giving
0.92 g (98 %) of a colorless oil. The HCl salt was recrystallized from EtOH/ether giving 0.67 g (64%) of a white powder: mp 207-208 °C; IR (KBr) 1252, 1584 cm⁻¹; ¹H NMR (CD₃OD) δ 1.30/1.37 (d; J = 6.59/6.59, 3H), 2.12-2.64 (m, 2H), 2.88/2.90 (s, 3H), 2.94-3.11 (m, 2H), 3.41-3.63 (m, 1H), 3.73-3.95 (m, 1H), 3.83/3.85 (two s, 3H), 4.54/4.58 (AB, J₁ = 108.17/74.47, J₂ = 13.19/13.19, 2H), 6.71-6.82 (m, 2H), 7.11-7.20 (m, 1H), 7.49-7.63 (m, 5H); Anal Calcd (Obsd) for C₂₀H₂₅NO.HCl. 0.4H₂O: C: 70.84 (70.42), H: 7.97 (7.88), N: 4.13 (4.35).

trans-8-Methoxy-1-methyl-2-(N-methyl-benzylamino)tetralin HCl (trans-24). The title compound was prepared according to the procedure as described for compound cis-24, starting from trans-23 (1.01 g, 3.18 mmol). After extractive work-up and removal of the solvent a colorless oil was obtained (0.89 g, 95%). Conversion to the HCl salt and recrystallization from EtOH/ether gave 0.70 g (66%) of a white powder: mp 192-193 °C; IR (KBr) 1254, 1584 cm⁻¹; ¹H NMR (CD₃OD) δ 1.21/1.30 (d, J = 6.83/7.08, 3H), 1.84-2.07 (m, 1H), 2.33-2.52 (m, 1H), 2.71 (s, 3H), 2.64-2.90 (m, 2H), 3.57-3.80 (m, 2H), 3.84/3.87 (s, 3H), 4.25/4.41 (AB, J₁ = 30.03/26.37, J₂ = 12.94/13.19, 2H), 6.67-6.89 (m, 2H), 7.11-7.22 (m, 1H), 7.47-7.63 (m, 5H); Anal Calcd (Obsd) for C₂₀H₂₅NO.HCl. 0.1H₂O: C: 71.99 (71.69), H: 7.91 (7.85), N: 4.20 (4.22).

cis-8-Methoxy-1-methyl-2-(methylamino)tetralin HCl (cis-25). Cis-24 (0.60 g, 1.80 mmol) was dissolved in abs EtOH (50 mL), then 10% Pd/C (0.4 g) was added and the solution was hydrogenated under a H₂-pressure of 3 atmosphere in a Parr apparatus for 1.5 h at ambient temperature. The catalyst was filtered off (celite) and the solvent was evaporated in vacuo yielding 0.35 g of a white solid. Crystallization from EtOH/ether gave 0.33 g (76 %) of white crystals: mp 222-223 °C; IR (KBr) 1256, 1583 cm⁻¹; ¹H NMR δ 1.17 (d, J = 6.84, 3H), 1.87-2.20 (m, 2H), 2.80 (s, 3H), 2.91-2.99 (m, 2H), 3.30-3.40 (m, 1H), 3.60 (dq, J₁ = 6.59, J₂ = 5.37, 1H), 3.83 (s, 3H), 6.71 (d, J = 7.81, 1H), 6.74 (d, J = 8.06, 1H), 7.13 (t, J₁ = 8.06, J₂ = 7.81, 1H); ¹³C NMR (CD₃OD) δ 12.5, 19.1, 27.3, 28.1, 29.5, 54.2, 59.1, 107.4, 120.5, 126.9, 127.0, 134.5, 156.6; MS (EI) M⁺; Anal Calcd (Obsd) for C₁₃H₁₉NO.HCl. 0.1H₂O: C: 71.99 (71.69), H: 7.91 (7.85), N: 4.20 (4.22).

trans-8-Methoxy-1-methyl-2-(methylamino)tetralin HCl (trans-25). The title compound was prepared as was described for the synthesis of cis-25, starting from trans-24 (0.60 g, 1.80 mmol). This procedure gave 0.39 g of a white solid which was crystallized from EtOH/ether yielding 0.30 g (69 %) of white crystals. mp 252-253 °C; IR (KBr) 1247, 1580 cm⁻¹; ¹H NMR δ 1.29 (d, J = 6.84, 3H), 2.06-2.35 (m, 2H), 2.72 (s, 3H), 2.79-2.94 (m, 2H), 3.40 (q, 1H, obscured), 3.84 (s, 3H), 6.77 (d, J = 8.06, 1H), 6.82 (d, 1H), 7.17 (t, J₁ = 8.06, J₂ = 7.81, 1H); ¹³C NMR (CD₃OD) δ 18.3, 19.3, 22.1, 29.5, 30.0, 54.3, 59.3, 107.8, 121.1, 124.5, 127.1, 134.5, 157.5; MS (EI) M⁺; Anal Calcd (Obsd) for C₁₃H₁₉NO.HCl.: C: 64.59 (64.29), H: 8.36 (8.40), N: 5.75 (5.76).
cis-8-Hydroxy-1-methyl-2-(methylamino)tetralin HBr (cis-26).

Demethylation of cis-25 (200 mg, 0.83 mmol) was performed according to procedure as described for (R)-15 as above giving the title compound as a brown solid, which was dissolved in hot MeOH and treated with activated charcoal. After filtration using Celite, the salt was recrystallized from MeOH/ether yielding 179 mg (79%) off-white crystals: mp 248-250 °C; IR (KBr) 3323 cm⁻¹ (OH); ¹H NMR (CD₃OD) δ 1.11 (d, J = 6.96, 3H), 1.84-2.04 (m, 2H), 2.72 (s, 3H), 2.78-2.86 (m, 2H), 3.16-3.30 (m, 1H), 3.46-3.51 (m, 1H), 6.46-6.53 (m, 2H), 6.87 (t, J = 7.69, 1H); ¹³C NMR (CD₃OD) δ 10.9, 18.0, 26.1, 26.9, 28.6, 57.9, 110.5, 117.8, 123.9, 125.4, 133.1, 152.9; MS (EI) M⁺; Anal Calcd (Obsd) for C₁₂H₁₇NO.HBr.0.2H₂O: C: 52.26 (52.25), H: 6.73 (6.77), N: 5.08 (5.05).

trans-8-Hydroxy-1-methyl-2-(methylamino)tetralin HBr (trans-26).

Demethylation of trans-25. HCl (237 mg, 0.98 mmol) was performed according to procedure as described for (R)-15 as above giving trans-26 as a brownish solid, which was dissolved in hot MeOH and treated with activated charcoal. After filtration using Celite, the salt was recrystallized from MeOH/ether yielding 155 mg (58%) off-white crystals: mp 218-219 °C; IR (KBr) 3299 cm⁻¹ (OH); ¹H NMR (CD₃OD) δ 1.24 (d, J = 6.96, 3H), 1.98-2.10 (m, 1H), 2.11-2.21 (m, 1H), 2.64 (s, 3H), 2.66-2.83 (m, 2H), 3.27-3.38 (m, 2H), 6.56 (d, J = 7.69, 2H), 6.91 (t, J = 7.69, 1H); ¹³C NMR (CD₃OD) δ 17.2, 17.7, 20.8, 28.3, 28.8, 58.1, 110.7, 118.3, 121.5, 125.4, 132.9, 153.8; MS (EI) M⁺; Anal Calcd (Obsd) for C₁₂H₁₇NO.HBr: C: 52.95 (53.21), H: 6.67 (6.79), N: 5.15 (5.18).

cis-8-[(Trifluoromethyl)sulfonyl]oxy]-1-methyl-2-(methylamino)tetralin HCl (cis-10).

Triflation of cis-26 (104 mg, 0.38 mmol) was performed according to procedure as described for (R)-3, using triton-B (20 µL, 10 mol%) as the phase-transfer catalyst. After extractive work-up the title compound was obtained in 107 mg (87%): mp 226-227 °C; IR (KBr) 1206, 1418 cm⁻¹ (O-SO₂); ¹H NMR δ 1.12 (d, J = 6.83, 3H), 1.69-2.03 (m, 2H), 2.52 (s, 3H), 2.7 (br s, NH), 2.83-3.03 (m, 3H), 3.42 (dq, J₁ = 6.83, J₂ = 4.73, 1H), 6.96-7.21 (m, 3H); ¹³C NMR δ 13.5, 22.6, 28.5, 30.0, 33.0, 57.6, 118.3, 118.4 (q, J = 320, CF₃), 126.9, 128.8, 134.2, 138.6, 147.8; MS (EI) M⁺ 323; Anal Calcd (Obsd) for C₁₃H₁₈NO₃SF₃.HCl: C: 43.40 (43.27), H: 4.76 (4.61), N: 3.89 (3.87).

trans-8-[(Trifluoromethyl)sulfonyl]oxy]-1-methyl-2-(methylamino)tetralin HCl (trans-10).

Triflation of trans-26 (124 mg, 0.46 mmol) was performed according to procedure as described for cis-10, giving the title compound in 100 mg (67%) yield: mp 212-213 °C; IR (KBr) 1208, 1397 cm⁻¹ (O-SO₂); ¹H NMR δ 1.25 (d, J = 7.32, 3H), 1.93-2.04 (m, 2H), 2.16 (br s, NH), 2.48 (s, 3H), 2.69-2.78 (ddd, J₁ = 17.58, J₂ = 5.86, J₃ = 2.56, 1H), 2.87-3.00 (m, 2H), 3.17 (dq, J₁ = 7.33, J₂ = 1.09, 1H), 7.06-7.26 (m, 3H); ¹³C NMR δ 20.8, 20.9, 23.8, 32.4, 33.6, 58.7, 118.5 (q, J = 320, CF₃), 118.6, 126.8, 129.3, 132.7, 138.8, 148.8; MS (EI) M⁺ 323.
Pharmacology. The behavioural pharmacology, biochemistry experiments and pharmacokinetic experiments for compound 1, 2, 3, (R)-3 and (S)-3 were performed according to ref 26. Animals. Male Wistar rats weighing 200-250 g were used for the gross behaviour and the motility experiments. The rats were housed eight per cage with free access to food and water. The experiments were performed between 10:00 and 16:00 h. Lights were on from 7:30−18:30 h.

Materials. All substances to be tested were dissolved in a physiological saline/solutol (90/10 v/v) solution with moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid, made up to volume with 5.5% glucose (w/v) and neutralized before use.

Receptor Binding. Compound 1, 2, 3, (R)-3 and (S)-3 were tested at Upjohn (Kalamazoo, MI). For experimental details see Chapter 4, section 4.5, Method A; Compound cis-9, cis-(1S,2R)-9, cis-(1R,2S)-9, cis-10 and trans-10 were screened at Centre Recherche Pierre Fabre, Castres, France (Chapter 5, section 5.5).

Gross Behavioural Observations. The 5-HT behavioural syndrome (flat body posture, reciprocal forepaw treading, straub tail, hindlimb abduction) and the lower lip retraction (LLR) were scored between zero and 30 min after drug-treatment, prior to the motility test. The test compounds were given subcutaneously in the neck-region or orally via gavage. The animals that were treated orally were fasted for 18 h before the experiments. Reserpinized animals received reserpine (5mg/kg, sc) 18 h prior drug-treatment.

Locomotor Activity. 30 min after drug-treatment (described as above) the rats were placed in the test cages (1 rat/cage) on the motility meters (Automex II locomotor boxes, Columbus Instruments, Columbus, Ohio). Motor activity was recorded for 30 min.

Hypothermia. The core temperature was determined by insertion of a digital temperature probe (CMA 150 Temperature Controller, Microdialysis AB, Stockholm, Sweden) into the rectum for 30 sec (n = 4). In all studies, the basal values were determined immediately after removal of animals from their home-cage. The time course experiment was stopped beyond the maximal effect. The ΔT (°C) that were obtained at each time-point in every rat were fitted via polynomial regression after which the AUC was estimated from the beginning of the experiment until the maximal effect.

Statistics. Differences between the saline- and drug-treated group in the locomotor activity test were analyzed with one-way ANOVA followed by a Bonferroni t-test. The differences between the control temperatures and the treated-group
temperatures were analyzed by one-way ANOVA with repeated measures followed by Tukey’s protected t-test.

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2.6 References