

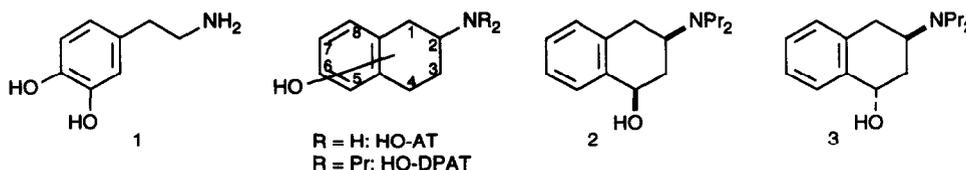
**NOVEL HO-DPAT (HYDROXY-2-DIPROPYLAMINOTETRALIN) ISOMERS:
 STEREOSELECTIVE SYNTHESIS AND RECEPTOR BINDING STUDIES**

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Abstract: The synthesis of the the novel HO-DPAT isomers **2** and **3** from the β -amino acid **4** is reported. **2** showed strong and selective affinity to the dopamine autoreceptor, labelled with [³H]-pramipexole.

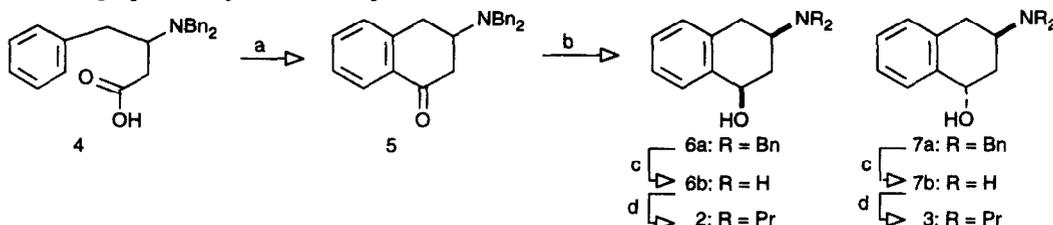
Structure-activity-relationship (SAR) studies by synthesis and receptor binding tests of regioisomers has proved to be a valuable strategy for the discovery of receptor models as well as for optimizing affinity and selectivity of the receptor ligands.¹ In the field of dopamine (**1**) research, conformationally restrained neurotransmitter analogs in different isomeric forms have been investigated with respect to the position of the catechol hydroxyl group(s).² It turned out, that one aromatic hydroxyl substituent is sufficient. The position of it, however, is very critical. Among the hydroxy substituted aminotetralins (HO-AT) and its *N,N*-dipropyl derivatives (HO-DPAT) the 5-hydroxy isomers show the most potent agonistic effects at postsynaptic D-1 and D-2 receptors. On the other hand, 7-HO-DPAT shows only moderate activity at D-1 and postsynaptic D-2 receptors but strong agonistic effects at the presynaptically localized D-2 autoreceptor. Whereas the (*S*)-enantiomers are more active in the 5-OH series the (*R*)-configured antipodes turned out to be the eutomers for 7-OH-AT and 7-HO-DPAT. For the 6-hydroxy isomers only weak activity is described. Quite different properties have been observed for (*S*)-8-OH-DPAT which is one of the most potent and selective 5-HT_{1a} antagonist and for the 1-HO-ATs revealing inhibitory effects of PNMT (phenylethanolamine N-methyltransferase).³



As an extension of those studies, we herein report the diastereoselective syntheses and the dopamine receptor binding properties of racemic *cis*- and *trans*-4-HO-DPAT (**2** and **3**).

The construction of the tetralin ring was performed starting from the readily available *N,N*-dibenzyl protected β -homophenylalanine **4**. According to our previous results, SOCl₂ initiated acid chloride formation and subsequent Friedel Crafts cyclization afforded the aminotetralone **5**.^{4,5} For the next step, a diastereoselective reduction of the keto function of **5**, existing predominantly in a half chair conformation with an equatorially positioned dibenzylamino group, was envisioned. We anticipated that a sterically demanding reducing agent should attack from the equatorial side to circumvent 1,3-diaxial interactions. On the other hand, small reagents are supposed to give a favored axial approach which is due to stereoelectronic control.⁶ In fact, these assumptions were confirmed when reduction by Li(*s*Bu)₃BH led to a 7:1 *trans*-selectivity whereas LiAlH₄

resulted in a preferred formation of the *cis*-diastereomer (**6a**:**7a** = 7:1). To avoid formation of 1-naphtol by dibenzylamine elimination as a side reaction it was advantageous to perform the reduction processes at -94°C . Complete separation of **6a** and **7a** required preparative HPLC. However, it was possible to proceed in the synthesis and to detach the minor isomers at the stage of the final products (**2,3**). Removal of the benzyl protecting groups was performed by hydrogenolysis using $\text{Pd}(\text{OH})_2/\text{C}$ as a catalyst to yield the primary amines **6b** and **7b**. Finally, **6b** and **7b** were converted to the dipropylamines **2** and **3** by treatment with an excess of propionaldehyde and NaBH_3CN .



a: ref. 4. b: for **6a**: LiAlH_4 , THF, 2h, -94°C (50%); for **7a**: $\text{Li}(\text{sBu})_3\text{BH}$, THF, 2h, -94°C (50%). c: H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, 2h, RT (74-82%). d: propionaldehyde, NaBH_3CN , MeOH, 20h, RT (37-38%).

For dopamine receptor binding studies rat striatal membranes were employed.⁷ The test compounds **2** and **3** were evaluated for their affinity to the dopamine D-1 receptor labelled with [^3H]-SCH 23390 and to the D-2 binding sites labelled with [^3H]-spiroperidol and [^3H]-pramipexole, a compound which pointed out to be an autoreceptor agonist.⁸ Both compounds failed to reveal remarkable affinity to the D-1 receptor as well as for the D-2 sites labelled by the antagonist [^3H]-spiroperidol (see Table 1). However, both isomers turned out to be potent for displacing the D-2 autoreceptor agonist [^3H]-pramipexole when *cis*-4-HO-DPAT **2** showed a 7.3-fold higher affinity ($K_i = 35.7$ nM) than *trans*-4-HO-DPAT **3**. In comparison, for (-)-PPP a K_i -value of 11.6 nM was determined. Further studies on enantiomerically pure 4-HO-DPAT isomers are in progress.

compd.	D-1 ^a	D-2 ^b	D-2 ^c
(-)-PPP	-----	7800 ± 1000	11.6 ± 0.2
2	> 50000	13950 ± 500	35.7 ± 13.2
3	> 50000	13000 ± 1300	262 ± 12

^a [^3H]-ligand: SCH 23390 (0.3 nM); k_i -values (nM) ± S.E.M.. ^b [^3H]-ligand: spiroperidol (0.5 nM); k_i -values (nM) ± S.E.M.. ^c [^3H]-ligand: pramipexole; k_i -values (nM) ± S.E.M.

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