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TETRAHEDRON: *ASYMMETRY*

A short and efficient asymmetric synthesis of (1*S*,2*R*)-(+)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin hydrochloride (UH-232)

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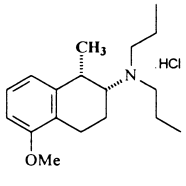
Abstract

A general practical asymmetric synthesis of (1*S*,2*R*)-(+)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin hydrochloride (UH-232) was developed in a short and efficient method in high optical purity starting from commercially available 5-methoxy-1-tetralone. Asymmetric hydroboration of 5-methoxy-1-methyl-3,4-dihydronaphthalene with monoisopinocampheylborane followed by treatment with $NaOH/H_2O_2$ afforded key intermediate tetrahydronaphthol **4**. Compound **4** was converted to the target molecule **1** using straightforward reactions.

It has been reported earlier that (1*S*,2*R*)-(+)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin hydrochloride (**1**, UH-232) is a dopamine (DA) antagonist with preferential action on presynaptic DA autoreceptors, while the corresponding (1*R*,2*S*)-(−) enantiomer, particularly the hydroxy analog, appears to be a centrally acting DA receptor agonist.[1] The selectivity of compound **1** for DA autoreceptors makes it interesting as a pharmacological tool and also potentially as a therapeutic agent.[2] The compounds fit a stereomodel of dopaminergic agonists and antagonists in which the preferred direction of the lone pair of the nitrogen atom or hydrogen of the ammonium ion determines an agonist or antagonist profile.[3] Because of the opposite profiles of the enantiomers, it is necessary to synthesize **1** with high optical purity.



1 (UH-232)

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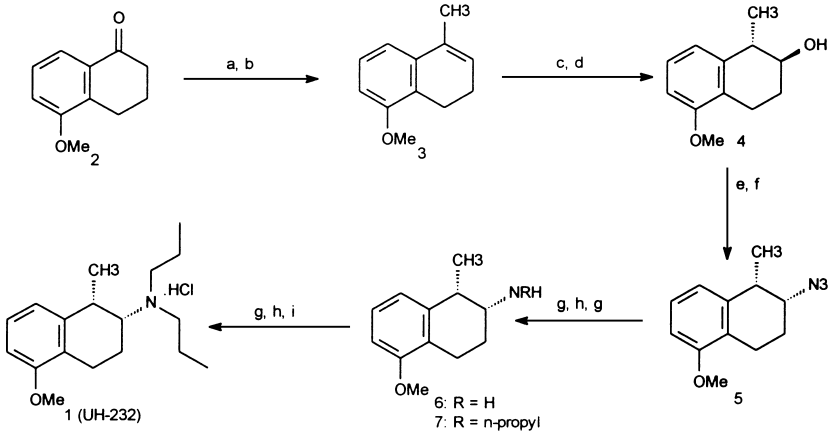
The limited synthetic methods in the literature for **1** require multiple steps and chemical resolution for separation of the enantiomers. Furthermore, the methods use commercially inaccessible and/or difficult to prepare starting materials such as 5-methoxy-2-tetralone. For example, the initial synthesis of **1** involved a mixture of diastereomers which could not be separated by fractional crystallizations and/or column chromatography.[1] After repeated fractional crystallizations of the corresponding trifluoroacetamide derivatives, it was possible to isolate the compound in 96% diastereomeric excess as determined by GC analysis.

Here, we report a short and efficient asymmetric synthesis of **1** (UH-232) in 88% enantiomeric purity as determined by chiral HPLC. More importantly the synthesis starts from a commercially available 5-methoxy-1-tetralone (**2**). Tetralone **2** was alkylated with MeMgBr in *t*-butyl methyl ether (*t*-BME) followed by treatment with *p*-TSA in toluene to afford 1-methyl-3,4-dihydronaphthalene (**3**) in 79% yield.[4] Hydroboration of **3** with monoisopinocampheylborane (generated from commercially available *R*-Alpine-Boramine™ with BF_3–Et_2O or prepared from α-pinene as per literature method[5]) in THF at −16 to −20°C followed by treatment with NaOH and 30% H_2O_2 resulted in *trans*-5-methoxy-1-methyl-1,2,3,4-tetrahydro-2-naphthol (**4**) in 71% yield after column chromatography.[6] The tosylate prepared (tosyl chloride/pyridine) in 86% yield was treated with sodium azide (Caution!) in H_2O–DMF to give *cis*-1-methyl-2-azido-5-methoxy-1,2,3,4-tetrahydronaphthaline (**5**) in 84% yield (Scheme 1).



Scheme 1. *Reagents*: (a) MeMgBr/*t*-BME; (b) *p*-TSA/toluene; (c) IPC-BH_2/THF; (d) NaOH/H_2O_2; (e) TsCl/Pyr; (f) NaN_3/H_2O–DMF; (g) LAH/THF; (h) CH_3CH_2COCl/Et_3N; (i) 1.0 M HCl/MeOH

Reduction of the azide (**5**) with LAH in THF afforded the amine **6** in 82% yield. Reductive alkylation of **6** with propionyl chloride followed by LAH in THF afforded *cis*-1-methyl-2-(*n*-propylamino)-5-methoxy tetralin (**7**) in 74% yield. Chiral HPLC/MS analysis of the amine indicated an enantiomeric ratio of 94:6. The specific rotation of **7**·HCl ([α]=(+)−48.8 (*c* 1.0, EtOH) was found to be in comparable range with related analogs.[1]

Compound **7**, upon treatment with propionyl chloride, followed by reduction of the amide with LAH in THF, afforded the desired product in 81% yield. The ratio of enantiomers was determined by chiral HPLC analysis (Chiral column ULTRON ES-OVM, Detector UV @ 220 nm, NH_4OAc buffer–CH_3CN 90:10 as mobile phase) and were found to be 94:6 (area%) with retention times of 5.72 and 4.34 min, respectively, and isomers were confirmed by MS. The free base was converted to its HCl salt (**1**, UH-232)[7] with 1.0 M HCl–MeOH.

In summary, we have developed a short and efficient asymmetric synthesis of 5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin hydrochloride (**1**, UH-232) in high optical purity starting from commercially

available and inexpensive 5-methoxy-1-tetralone. This synthesis enabled us to generate (+)-UH-232 in multigram quantities for further pharmacological studies.

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