Bioorganic & Medicinal Chemistry Letters, Vol 2, No.12, pp. 1691-1692, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

An Improved Synthesis of the Dopamine Autoreceptor Antagonist (+)-*cis*-8-Methoxy-1-methyl-2-(dipropylamino)tetralin (AJ-76)

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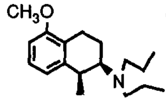
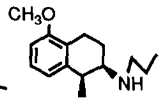
(*Received* 9 *September* 1992)

Abstract: A new and efficient synthesis of (+)-*cis*-8-methoxy-1-methyl-2-(dipropylamino)tetralin, AJ-76, and its monopropyl analog, UH-232, was achieved. Relative stereochemistry was controlled by double bond hydrogenation, followed by enantiomeric resolution with quinine to obtain optically pure material. Overall, AJ-76 is synthesized in 9 percent overall yield, including the optical resolution.

AJ-76 (**1**) and UH-232 (**2**) are of interest as selective dopamine autoreceptor antagonists, with **1** being the more selective.[1a,b] Through this receptor, they act as weak stimulants.[1c] However, since they also possess some antagonist activity at the post-synaptic dopamine receptor, they also antagonize the stimulant effects of amphetamine (which acts as an indirect dopamine agonist, causing dopamine release in nerve terminals). Biochemical and electrophysiological data support these effects. What makes these compounds unique is their preferential selectivity for the dopamine autoreceptor, which might represent a novel opportunity for therapeutic intervention in central nervous system diseases dependent upon dopaminergic activity, such as schizophrenia.



1 (+)-AJ-76



2 (+)-UH-232

The synthesis of AJ-76 and UH-232 has been reported.[1a] In this procedure, the amino group was attached to the tetralin ring *via* a reductive amination of the appropriate tetralone with (R)-alpha-methylbenzylamine. Unfortunately, the diastereomers (four possible) cannot be separated by chromatography, requiring further functionalization - chromatography - defunctionalization to obtain optically pure material for ultimate conversion into **1** and **2**. Furthermore, in our hands the diastereoselectivities claimed for this reductive amination could not be reproduced. Subsequent attempts to resolve the debenzylated 2-aminotetralin (i.e. primary amine) with various tartaric acid salts proved to be cumbersome, requiring multiple recrystallations resulting in very low recovery of the desired optically pure material.

Requiring large amounts of **1** and **2**, we developed a new synthetic procedure to obtain these compounds, resulting in the synthesis of optically pure **1** in nine percent overall yield (not optimized). Starting with commercially available 5-methoxy-1-tetralone, condensation with dimethylcarbonate[2] afforded

4, which exists in the enol tautomeric form. This material was deprotonated with sodium hydride in DME, followed by sulfonylation with trifluoromethanesulfonic (triflic) anhydride to give **5**. An attempt to use THF as the solvent instead of DME led to a large amount of THF cleavage due to the trifluoromethanesulfonic anhydride. Surprisingly, using pyridine as the base resulted in a good yield of **9**. This arose from attack by **4** at the 2-pyridine position (rather than sulfonyl transfer) after prior activation of the pyridine by triflic anhdyride. Carrying on, subsequent triflate displacement of **5** using dimethylcuprate (6 eq., -25°, 3 hr) gave a quantitative yield of **6** which was saponified to the free acid (**7**), where the *cis*-stereochemistry was introduced *via* catalytic hydrogenation (100 % yield).

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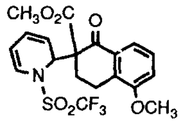
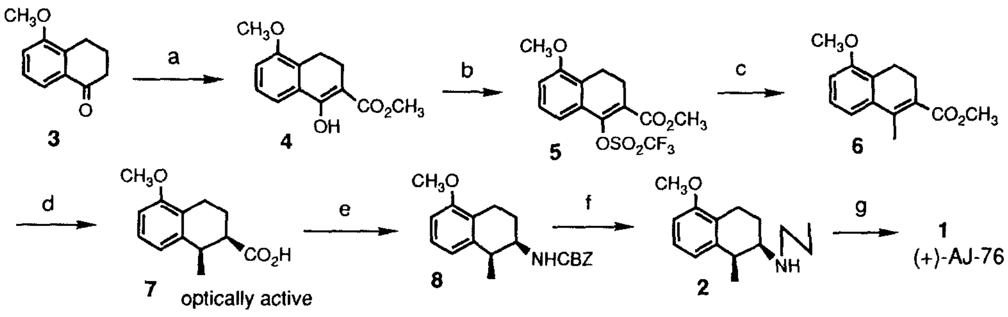


At this stage the carboxylic acid (**7**) was resolved to obtain (+)-**7** through the use of quinine, where the (+)-enantiomer was selectively crystallized.[3] The quinine resolution required four recrystallizations from 2-proponal/acetonitrile (3:4 v/v) to reach optical purity. Optically pure **7** was obtained in 24 % yield with no attempt to optimize recovery by further purifying the mother liquors. The efficiency in resolving the carboxylic acid (**7**) with quinine contrasts sharply with resolving the 2-aminotetralin (e.g **1**) with tartaric acid analogs.

At this point, (+)-**7** was condensed with diphenylphosphoryl azide to generate the acyl azide, which was thermolyzed *in situ* to undergo the Curtius rearrangement.[4] Trapping the isocyanate intermediate with benzyl alcohol provided **8** in 77 % yield. Hydrogenolysis to remove the CBZ-protecting group followed by acylation /reduction gave (+)-UH-232 (**2**) in 41 % yield.[5] Alkylation with bromopropane provided (+)-AJ-76 (**1**) in 8% overall yield (unoptimized), including the resolution step.



a. NaH, $(CH_3O)_2CO$, reflux (84%). b. NaH, DME; $(CF_3SO_2)_2O$ (91%) c. 6 eq. Me_2CuLi, -25°, THF, 30 min. (100%). d. KOH (87%); 10 % Pd/C, EtOH, H_2 (100%); quinine resolution (24%). e. $(PhO)_2P(O)N_3$, Et_3N, $PhCH_3$, reflux; $PhCH_2OH$, reflux (77%). f. 10 % Pd/C, EtOH, H_2 (100%); C_2H_5COCl, Et_3N; LAH (82%). g. C_3H_7Br, CH_3CN, Na_2CO_3, reflux (91%).

References and notes

1. a) A.M. Johansson, L.-E. Arvidsson, U. Hacksell, J.L.G. Nilsson, K. Svensson, *J. Med. Chem.*, **1987**, *30*, 602-611; b) M.F. Piercey, J.T. Lum, *Eur. J. Pharmacol.*, **1990**, *182*, 219-226; c) K. Svensson, A.M. Johansson, T. Magnusson, A. Carlsson, *Naunyn-Schmiedeb. Arch. Pharmacol.*, **1986**, *334*, 234-245.
2. D.W. Johnson, L.N. Mander, *Aust. J. Chem.*, **1974**, *27*, 1277-1286.
3. After resolution, 7 gave an optical rotation of $[\alpha]^{25}_D = +95.4°$ (c = 2.55 MeOH).
4. K. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron*, **1974**, *30*, 2151-2157.
5. All compounds gave satisfactory spectral and analytical data. M.p. for **1** (HCl salt), 273.5°. M.p. for **2** (HCl salt), 169°. The optical rotations for **1** and **2** were identical to those reported in reference 1a.