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Synthesis of Two Conformationally Constrained Analogues of the Minor Tobacco Alkaloid Anabasine

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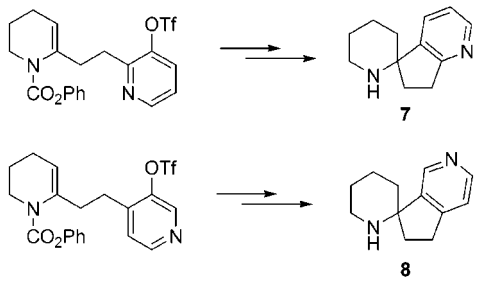
ABSTRACT



The anabasine analogues spiro[4-azaindan-1,2′-piperidine] (7) and spiro[6-azaindan-1,2′-piperidine] (8) have been prepared. A series of palladium-catalyzed reactions, where an intramolecular cyclization constituted a key reaction, were utilized for the preparation of the two target compounds.

Selective nicotine receptor ligands have potential as therapeutic agents for CNS diseases and other disorders.[1] The (*S*)-(−)-enantiomer of nicotine **1** (Figure 1) displays higher affinity than the (*R*)-(+)-enantiomer at nicotine receptors. However, there are observations in functional assays that (*S*)-(−)-nicotine is not always more potent, suggesting that the enantiomers of nicotine may interact differently with different types of nicotine receptors.[2] Molecular modeling studies suggest that the pyridine and pyrrolidine rings of nicotine are skewed and nearly perpendicular[3] in low-energy conformations, but the exact bioactive conformation(s) is not known. The synthesis and evaluation of conformationally restricted analogues[4] of nicotine should help to determine

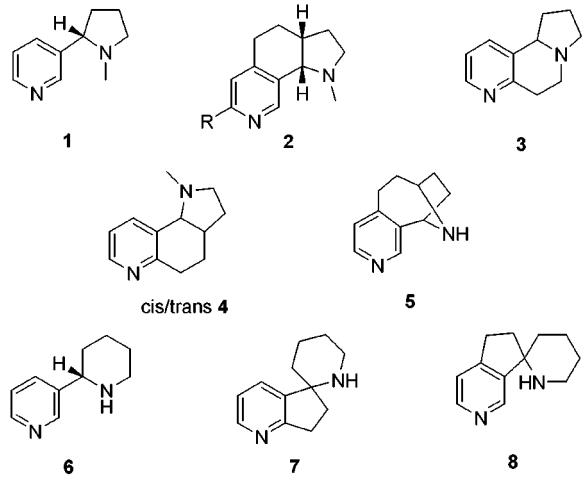


Figure 1.

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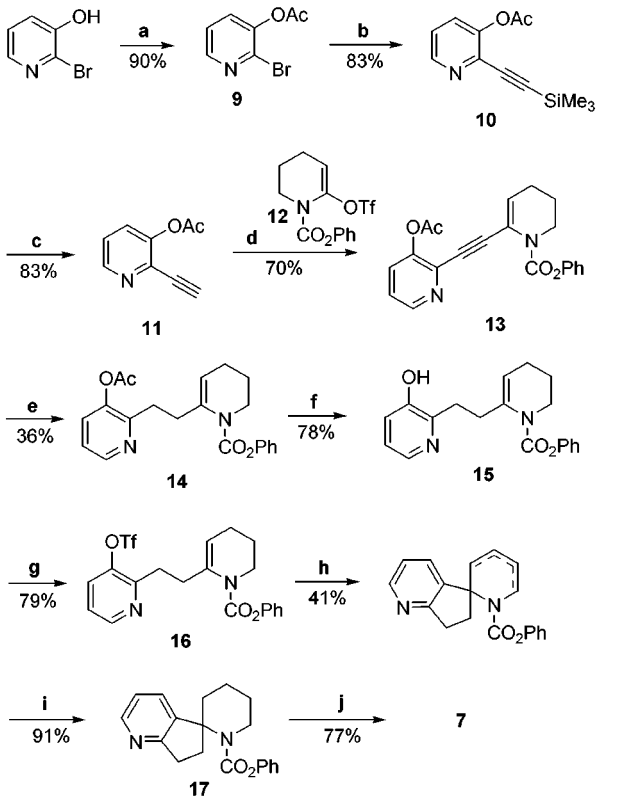
the conformation(s) that induce ion channel opening. A limited number of restricted analogues have been synthesized[5] and among these the fused (+) and (−) isomers of **2** bind with low affinities,[5c,g] compounds **3**[5a] and **4**[5b] exhibited no appreciable activity, while the bridged nicotinoid **5**[5d] was very potent in binding and functional assays.[5e] A recent study that describes the effect of the minor tobacco alkaloids, (*S*)-(−)-anabasine **6** and its *N*-methyl analogue on dopamine release from superfused rat stratial slices, suggests that these compounds produce comparative and in some cases more pronounced effects than (*S*)-(−)-nicotine (**1**) and (*S*)-(−)-nornicotine.[6]

We herein present the syntheses of two rigid anabasine analogues, the spiro compounds **7** and **8**, where we have used an intramolecular Heck arylation[7] onto an enamide, as a key step.

The synthesis of **7** commenced with acylation of commercially available 2-bromo-3-hydroxypyridine to give **9** (Scheme 1). Compound **9** was reacted with trimethylsilylacetylene under palladium catalysis in the presence of a catalytic amount CuI.[8] The coupled product **10**, isolated in 83% yield was thereafter desilylated by tetrabutylammonium fluoride in THF−water to give **11**. Subsequent palladium-catalyzed coupling with the triflate **12**,[9] where CuI was used as cocatalyst, delivered the enyne **13** in 70% yield. A selective hydrogenation of the triple bond was conducted with Pd/C-quinoline to give **14** in modest yield (36%).[10] Ester hydrolysis to give **15**, followed by a reaction with triflic anhydride afforded the triflate **16**, the precursor for the palladium-catalyzed intramolecular reactions.

In the initial cyclization experiments, we employed palladium acetate with tri-2-furylphosphine[11] as the catalytic system and triethylamine as the base using acetonitrile as solvent. Only traces of spiro compounds were formed under these conditions. Neither an increase of reaction temperature nor the addition of lithium chloride[12] improved the outcome. We previously employed (*S*)-(−)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-4,5-dihydrooxazole,[13] as a chiral nitrogen−phosphorus bidentate ligand[14] with diisopropylethylamine as base in related intramolecular coupling reactions where we obtained very high enantiomeric excesses.[15] No conversion of **16** proceeded under these reaction conditions, neither with THF nor with toluene as solvents, and substitution of diisopropylethylamine for triethylamine and use of DPPF[16] as ligand led to no significant improvement. However, the intramolecular cyclization could be accomplished in reasonable yield with BINAP,[17] a ligand that has been successfully utilized for control of double-bond migration

Scheme 1[a]



[a] (a) Ac_2O, Δ; (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, $HCCSiMe_3$, THF, RT; (c) TBAF, THF/H_2O, 0 °C; (d) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, RT; (e) H_2, Pd/C, quinoline, EtOAc, RT; (f) $NaHCO_3$, MeOH/H_2O, RT; (g) $(Tf)_2O$, Et_3N, CH_2Cl_2, −78 °C; (h) $Pd(OAc)_2$, (*R*)-BINAP, Et_3N, CH_3CN; (i) H_2, Pd/C; (j) KOH, $H_2NNH_2 \cdot H_2O$, H_2O/ethylene glycol.

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(7) For the preparation of anabasine by an intermolecular Heck reaction see: Nilsson, K.; Hallberg A. *J. Org. Chem.* **1990**, *55*, 2464−2470.

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(10) The reaction was stopped when **14** was formed in highest amount relative to the yields of the partially and fully reduced products. **14** was obtained after chromatography and recrystallization.

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(16) DPPF = 1,1′-bis(diphenylphosphino)ferrocene

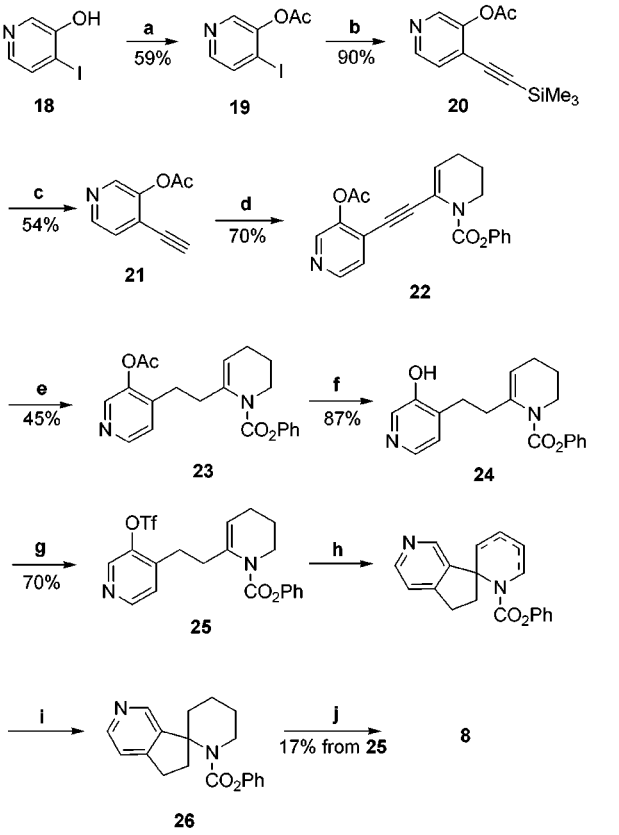
(17) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350.

in related cyclizations.[18] A mixture of the three double-bond isomers was afforded.[19] Reduction of this mixture and subsequent determination of the enantiomeric excess[20] revealed that a moderate enantioselectivity had been obtained in THF (THF, 41% ee; acetonitrile, 10% ee; DMAA, 9% ee; DMF, 2% ee). No product attributed to the undesired endo cyclization was traced under these conditions but the reductive elimination of the triflate group constituted a major side reaction, which frequently became the predominant reaction. In a preparative experiment we employed acetonitrile since the highest yield was achieved in this solvent. A 41% yield of the mixture of spiro compounds was isolated. Hydrogenation on Pd/C gave **17**, which was hydrolyzed, employing KOH and hydrazine in water/ethylene glycol, furnishing **7** in 77% yield.

The synthesis of **8** was executed essentially according to the strategy used for the synthesis of **7**. The iodopyridine derivative **18** was prepared from 3-hydroxypyridine by transformation to its diethylaminocarbamate,[21] followed by directed lithiation, subsequent iodination, and hydrolysis of the carbamate function.[22] The reaction sequence as depicted in Scheme 2 was thereafter followed. For the preparation of triflate **25**, *N*-(5-chloro-2-pyridyl)triflimide[23] was found to be superior as compared to triflic anhydride in promoting the reaction. The palladium-catalyzed intramolecular cyclization of **25** was sluggish under the same conditions as those used for the cyclization of **16** and a longer reaction time was required for complete conversion of **25**. Reduction of the triflate group was the predominant reaction. Hydrogenation of the double-bond isomers and hydrolysis of the carbamate delivered the rigid anabasine analogue **8**.

In conclusion we have described the synthesis of two conformationally restricted anabasine analogues where we have employed a series of palladium-catalyzed reactions to achieve our goal. These potential nicotine receptor ligands comprise a piperidine that is nearly perpendicular to the plane of the pyridine ring. The biological testing will be reported elsewhere.

Scheme 2[a]



[a] (a) Ac_2O, 70 °C; (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, $HCCSiMe_3$, THF, RT; (c) TBAF, THF/H_2O, 0 °C; (d) **12**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, RT; (e) H_2, Pd/C, quinoline, EtOAc, RT; (f) $NaHCO_3$, MeOH/H_2O, RT; (g) *N*-(5-chloro-2-pyridyl)triflimide, Et_3N, CH_2Cl_2; (h) $Pd(OAc)_2$, (*R*)-BINAP, Et_3N, CH_3CN; (i) H_2, Pd/C; (j) KOH, $H_2NNH_2 \cdot H_2O$, H_2O/ethylene glycol.

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Supporting Information Available: Experimental procedures and full characterization data for compounds **7**−**26**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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(19) Reaction in the presence of ammonium formate lead to a sluggish reaction and a complex reaction mixture.

(20) Analytical separations of the enantiomers were achieved by gas chromatography, on a chiral capillary column (10 m × 0.32 mm) coated with 20% octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin in OV 1701, with H_2 as carrier gas and a flame ionization detector. The column was prepared and developed by Professor W. A. König, Institut für Organische Chemie, Universität Hamburg, D-201 46 Hamburg, Germany.

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