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Pyrrolidines bearing a quaternary α-stereogenic center. Part 1: Synthesis of analogs of ABT-418, a powerful nicotinic agonist

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Abstract

We describe herein the synthesis of various analogs of ABT-418, in which the stereogenic center is at the same time both quaternary and functional. The key step is the obtention of the aminoaldehyde **1a** by means of ring contraction of the parent heterocyclic enamine.

The positive action of nicotine on cognitive function as well as on neuroprotection is now well documented.[1] Nevertheless, the strong undesired effects of nicotine on cardiovascular and digestive systems preclude its use as a therapeutic agent. Among the different compounds recently identified as potent cholinergic agonists at neuronal nicotinic receptors,[2] ABT-418 showed great potency and selectivity, and has been evaluated as a neuroprotective agent.[2a] The structure–activity relationship studies for the design of analogs of ABT-418 involved mainly the examination of the role of the structure of both heterocycles, of the pyrrolidine substitution, and of the configuration of the stereogenic center.[3] Conformationally constrained compounds and open chain derivatives were also evaluated.[3] On the other hand, no information is currently available in the literature regarding the effect of a quaternary stereogenic center at C-(2) in the pyrrolidine ring.

As part of our studies on heterocyclic alkaloids and derivatives,[4] we decided to focus on the synthesis of compounds **1**, in which the X moiety could be a functional group (Scheme 1). Recently, we have described modifications of the Duhamel ring contraction of heterocyclic enamines[5] in order to obtain nicotine from bipyridines.[4c] In this case, the parent bipyridine was transformed into an intermediate aminoaldehyde which was decarbonylated in the final step.[4c] The present paper discloses our results in constructing an analogous aminoaldehyde (**1a**, X=CHO) in the isoxazole series, and various modifications of this compound taking advantage of the synthetic flexibility of the carbonyl group. Thus, compound **1a** was obtained as follows:

(i) construction of the biheterocyclic precursor, using a similar methodology as Elliott for the preparation of the isoxazole ring;[6]

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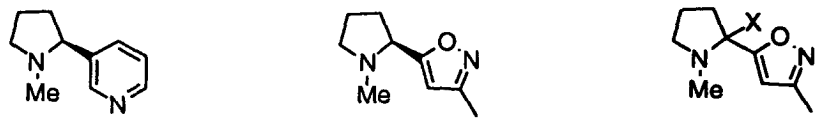
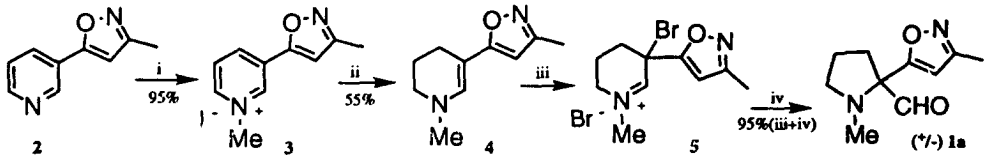


Scheme 1.

(ii) access to the required heterocyclic enamine;[7]

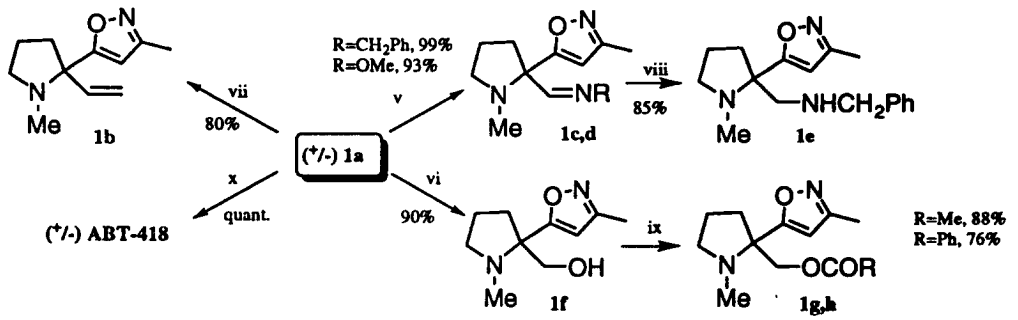
(iii) Duhamel ring contraction process leading to the aminoaldehyde (*R,S*) **1a** (Scheme 2y).[4,5] Methylation of the starting material **2** by methyl iodide occured regioselectively on the pyridine ring, giving the corresponding pyridinium iodide **3** in excellent yield. According to Wenkert,[7] hydrogenation of **3** was performed at atmospheric pressure after anion exchange by means of AgCl, since iodide anion could poison the catalyst. The moderate yield observed in the hydrogenation step was explained by the presence of the isomeric allylic amine (20% yield) which was easily removed during the purification of enamine **4** by flash chromatography (AcOEt:petroleum ether, 60:40). Finally, the ring contraction was realized under the previously reported conditions,[4c] thus efficiently giving the required aminoaldehyde **1a**, which was purified by flash chromatography (AcOEt:petroleum ether, 50:50);



Scheme 2. i: MeI (3 equiv.), MeOH, reflux; ii: AgCl, MeOH, reflux, then H_2/Pd/C (10%), Et_3N; iii: Br_2 (1.2 equiv.)/THF, −60°C; iv: H_2O, Et_3N, −60°C to rt

(iv) for the construction of various analogs **1** of ABT-418 see Scheme 3. Thus, compounds **1b–h** were readily obtained from **1a** using standard procedures and were purified by flash chromatography. Interestingly, the carbonyl group of **1a** was stable enough under most reaction conditions, thus leading to the desired quaternary products, bearing various functional groups such as imine (**1c**), oxime (**1d**), secondary amine (**1e**), hydroxymethyl (**1f**) and corresponding esters (**1g**, **1h**), and vinyl (**1b**) substituents. On the other hand, when treated with an excess of hydroxide ions under warming, decarbonylation occured as in previous examples,[4c] giving ABT-418 quantitatively. The high yields which were obtained for all compounds highlight the synthetic interest of the Duhamel ring contraction of heterocyclic enamines for the access to new pyrrolidinic compounds bearing a quaternary center in the C-(2) position. We are currently investigating extension of this method in the field of constrained aminoacids and peptidomimetics.

In conclusion, the present methodology gave a handy access to various analogs of ABT-418, in which the stereogenic center at C-(2) is at the same time quaternary and functional. Racemic ABT-418 was also obtained by deformylation of the parent aldehyde **1a**, using previously reported conditions.[4a,c] The new compounds **1a–h**, on which no biological information has been reported in the literature, are under evaluation as potential nicotinic ligands. They could be useful tools for the structure–activity relationship studies in the field of cholinergic ligands. Studies of resolution and asymmetric synthesis of the key aminoaldehyde **1a** are also under way.



Scheme 3. v: RNH_2, CH_2Cl_2, 3AMS, 0°C; vi: $NaBH_4$, DMF, –20°C; vii: $Ph_3P^+Me\ I^-$, *n*BuLi, THF, –60°C; viii: $NaBH_4$, EtOH, 0°C; ix: RCOCl, Et_3N; x: NaOH, THF, 50°C

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