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Synthesis of Azabicyclo[2.2.*n*]alkane Systems as Analogues of 3-[1-Methyl-2-(*S*)-pyrrolidinylmethoxy]pyridine (A-84543)

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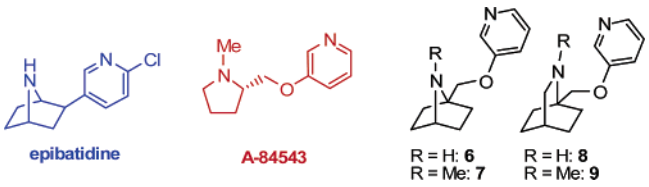
Received January 12, 2007



This work is connected with the epibatidine field and describes the synthesis of several analogues of compounds that present affinity for nicotinic acetylcholine receptors, such as 3-[1-methyl-2-(*S*)-pyrrolidinylmethoxy]pyridine (A-84543). These analogues bear a 3-pyridyl ether substituent at the bridgehead carbon of the azabicyclo[2.2.*n*]alkane system. Particularly, in the case of the 1-substituted 2-azabicyclo-[2.2.2]octane system, a new synthetic route has been developed, which involves the synthesis of a novel rigid sulfamidate that allows the straightforward introduction of nucleophiles.

The design of ligands for the nicotinic acetylcholine receptors (nAChRs) has experienced a great advance[1] due to the isolation and structural characterization of epibatidine as a potent analgesic.[2] Further studies showed that the analgesic activity resulted from interaction with nicotinic acetylcholine receptors.[3] The synthetic methodology developed for the synthesis of epibatidine, along with its toxicity, provided the means for the synthesis of a large number of epibatidine analogues, which have been evaluated for their biological activity. These analogues have provided interesting information concerning the structure−activity relationship (SAR).[4] As a result, several structural modifications aimed at improving SAR[4] have been made on the epibatidine skeleton in an effort to establish the required parameters in terms of stereochemistry, N−N distance, bioisosteric rings, level of conformational constraint, or azabicyclic changes.[5]

In this field, several 3-pyridyl ether compounds have been synthesized at Abbott Laboratories and some of them showed a subnanomolar affinity for central neuronal nicotinic acetylcholine receptors.[6] Two of these compounds, A-85380 (**1**) and A-84543 (**2**), have attractive features, and they have been the subject of diverse syntheses.[6] Moreover, a large number of analogues have been obtained, particularly with substituents at the different positions of the pyridine ring (Figure 1).[7] On the other hand, previous studies demonstrated the importance 7-azabicyclo[2.2.1]heptane system for molecular recognition of epibatidine at nAChRs.[8a] With this proposal, analogues of compounds **1** and **2** were synthesized[8b]—*exo*-**3** and *endo*-**3** stereoisomers—in which an ether linker has been incorporated in the 2-position of the 7-azabicyclo[2.2.1]heptane system; nevertheless they gave a poor response—possibly due to the large distance between nitrogen atoms (Figure 1).

In our previous work we developed the synthesis, investigated the activity, and carried out a theoretical study of ABT-418 analogues **4** and **5** using the 1-substituted 7-azabicyclo[2.2.1]-heptane as a core[9] (Figure 1). Taking into account the

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10.1021/jo0700732 CCC: $37.00
Published on Web 03/20/2007

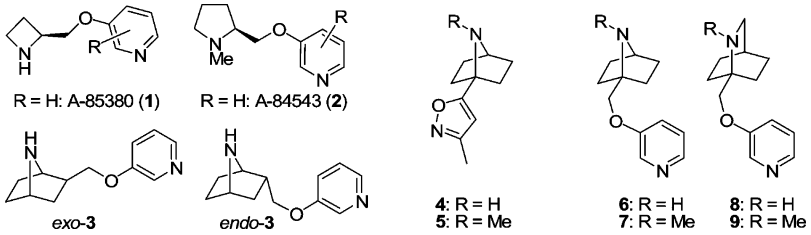

FIGURE 1. Several analogues of epibatidine and related compounds and the target compounds for this article (**6**−**9**).

aforementioned antecedents, as well as our experience in 7-azabicyclo[2.2.1]heptane systems,[10] and the little explored field of bridgehead-substituted systems,[11] we envisioned the synthesis of the 3-pyridyl ethers **6** and **7**. In order to modulate the N−N distance factor, we also considered the synthesis of the new 2-azabicyclo[2.2.2]octane systems **8** and **9** to be a reasonable goal (Figure 1).

In previous studies we developed an efficient synthesis of compound **11** starting from cyclohexanone **10**, which was obtained from methyl 2-benzamidoacrylate on a gram scale using two steps (94%).[10c] Transformation of compound **11** into alcohol **12** was achieved by reduction of the methyl ester and benzamide groups using $LiAlH_4$ in THF, followed by hydrogenolysis with Pd−C in the presence of $(Boc)_2O$ (Scheme 1).[9]

In order to obtain target **6**, and taking into account that some examples in the literature use Mitsunobu conditions as the key ether-formation step,[6a] we attempted the reaction of alcohol **12** with triphenylphosphine, diethyl azodicarboxylate, and 3-hydroxypyridine. However, in this case only starting material was recovered. Another route involves activation of the alcohol group as the methanesulfonate derivative (Scheme 1). In this way, compound **12** was transformed in moderate yield into mesylate **13** by treatment with methanesulfonyl chloride (MsCl) and triethylamine (TEA) as a base in CH_2Cl_2. The nucleophilic displacement was carried out using the potassium salt of 3-hydroxypyridine, previously formed with KOH as a base. Hydrolysis of the Boc group was carried out with aqueous 2 N HCl in THF (1:4) at rt to give compound **6** as an hydrochloride derivative. The methylated analogue was obtained by treating this compound with formic acid/formaldehyde to give a good yield of compound **7** (Scheme 1).

Once target compounds **6** and **7** had been obtained, we wanted to achieve the synthesis of the corresponding analogues with the 2-azabicyclo[2.2.2]octane skeleton. The synthesis and reactivity of these systems, called isoquinuclidines, have been thoroughly developed in studies on epibatidine analogues[12] and in other different fields.[13] To this purpose, cyclohexanone **10** was transformed into olefin **14** by Wittig methylenation using methyltriphenylphosphonium bromide and two equivalents of potassium bis(trimethylsilyl)amide (KHMDS), with addition at −78 °C and further warming at rt, to give the required alkene in 76% yield (Scheme 2).

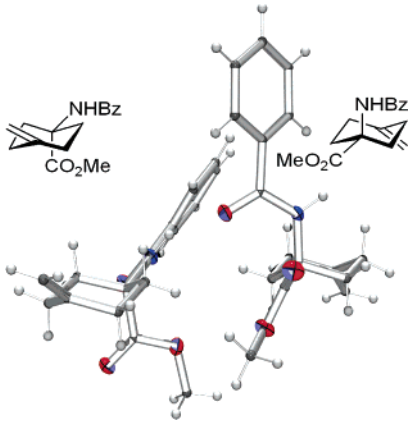

FIGURE 2. Conformers of compound **14**.

The next step was the hydroboration−oxidation sequence on the double bond to obtain the mixture of alcohols **15**. With the aim of following the same strategy as used for the 7-azabicyclic system synthesis—through activation of the alcohol group as the methanesulfonate derivative followed by intramolecular nucleophilic displacement by the benzamide group—we required the benzamide and methanesulfonate groups to be in a *syn* disposition. The crystal structure from X-ray diffraction of a monocrystal of compound **14** (Figure 2) showed the presence of the two chair conformers due to the similar energy of both isomers, a situation consistent with the poor selectivity in the hydroboration reaction. As shown in Figure 2, attack of the borane on compound **14** must take place at the opposite face to the benzamide group in order to obtain compound **17**. Several boranes were investigated, including BH_3 (several temperatures), catecholborane, catecholborane/Wilkinson catalyst, and 9-BBN.[14] The best results were obtained using BH_3 at 0 °C to give alcohol **15** in 94% yield and with a 60:40 ratio in favor of the *syn* stereoisomer. Mesylation of this mixture was carried out with MsCl and TEA, and the intramolecular nucleophilic displacement was achieved using ^{t}BuOK[10] to obtain compound **17** on a multigram scale in 31% yield from **10** in four steps or 28% yield from methyl 2-benzamidoacrylate in six steps. It is important to notice that this low yield (due to the hydroboration process) obtained for this new pipecolic acid analogue with a bicyclic structure (**17**) is so acceptable, taking into account that a similar structure bearing the *N*-benzyl group instead of *N*-benzoyl one has recently been published in 21% yield from methyl 4-hydroxybenzoate.[15]

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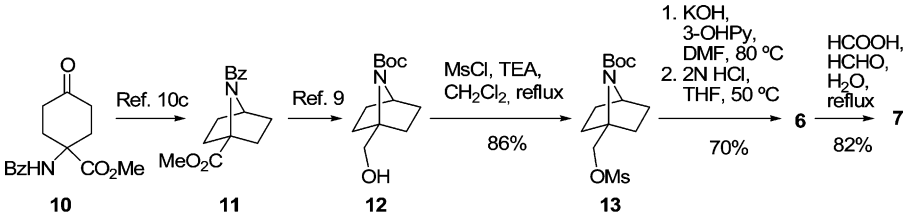
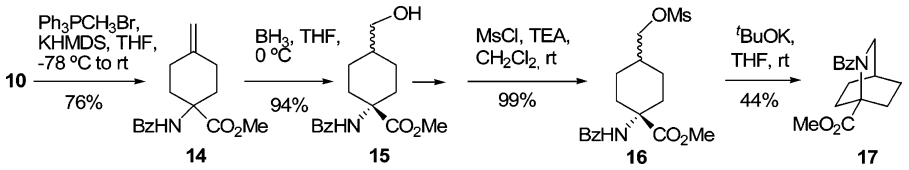
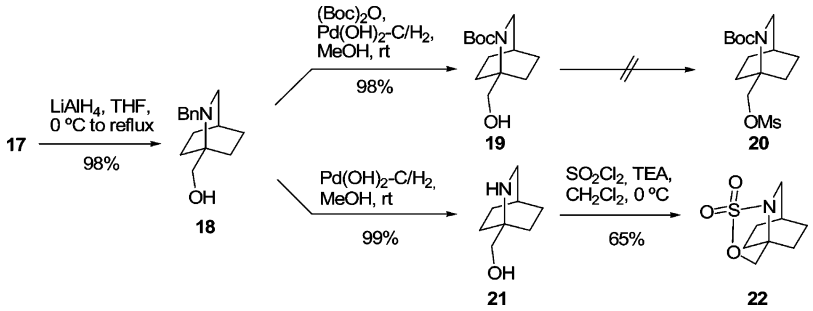
SCHEME 1. Synthetic Route for the Synthesis of the Target Compounds 6 and 7



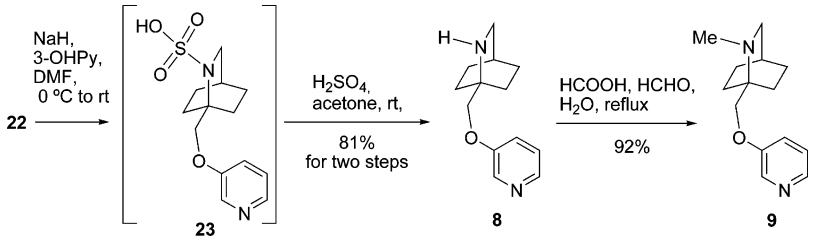
SCHEME 2. Synthesis of Compound 17



SCHEME 3. Synthesis of Sulfamidate 22



SCHEME 4. Synthesis of Target Compounds 8 and 9



In order to obtain target compound **8**, we transformed the *N*-benzamide ester **17** into the corresponding *N*-benzylated alcohol **18** by reduction with $LiAlH_4$ in THF. Hydrogenolysis of **18** with $Pd(OH)_2$−C in the presence of $(Boc)_2O$ in MeOH gave the *N*-Boc alcohol **19** in excellent yield. However, when we attempted to activate the alcohol by mesylation, poor results were obtained in forming compound **20** (Scheme 3). Mitsunobu conditions were ruled out as they had not given promising results previously and, given our experience with sulfamidates,[16] we decided to use a novel strategy based on the formation of a cyclic sulfamidate[17] derived from β-amino alcohol **21**, which allowed simultaneous protection of the nitrogen moiety and conversion of the hydroxyl into a good leaving group. In our case, the high level of strain in the tricyclic sulfamidate **22** made nucleophilic attack easy.[18] Therefore, hydrogenolysis of **18** with 10% $Pd(OH)_2$−C gave the corresponding β-amino alcohol **21** in excellent yield. Sulfamidate **22** was obtained in moderate yield by formation of the sulfamidite with thionyl chloride and subsequent oxidation in the presence of $RuCl_3 \cdot xH_2O$. In order to improve the yield, we attempted the formation of the sulfamidate using sulfuryl chloride in the presence of β-amino alcohol **21** to give **22** in 65% yield (Scheme 3). The structure of tricyclic sulfamidate **22** was unambiguously determined by X-ray diffraction analysis of the corresponding monocrystal obtained by slow evaporation in a mixture of hexane and ethyl acetate.

Compound **22** was subjected to nucleophilic displacement with the sodium salt of 3-hydroxypyridine, previously formed by treatment with NaH, to give the sulfamic acid intermediate **23**. This compound was hydrolyzed with 20% aqueous H_2SO_4 to give the target molecule **8**. The corresponding methylated analogue was obtained by treating compound **8** with formic acid/formaldehyde to give a good yield of compound **9** (Scheme 4).

In conclusion, we have developed two efficient routes for the synthesis of compounds **6** and **8** as well as their methylated

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derivatives **7** and **9**. In this context, we have developed a new route to achieve the 1-substituted 2-azabicyclo[2.2.2]octane system. The synthetic route involves the synthesis of the rigid sulfamidate **22**, and this approach could be extended in the future to the attack of other nucleophiles on this sulfamidate.

Experimental Section

1-[(Pyridin-3-yloxy)methyl]-7-azabicyclo[2.2.1]heptane (6). Potassium hydroxide (246 mg, 4.39 mmol) was added under argon to a solution of 3-hydroxypyridine (42 mg, 0.44 mmol) in dry DMF (5 mL). The solution was stirred for 30 min at rt. The mesylate compound **13** (68 mg, 0.22 mmol) was added to the mixture, and the solution was heated at 80 °C for 5 h. Water (5 mL) and ethyl acetate (10 mL) were added to the mixture, and the product was extracted. The aqueous layer was washed with ethyl acetate (2 × 10 mL), the combined organic layers were dried and filtered, and the solvent was evaporated to give the pyridine derivative. This compound was dissolved in THF (8 mL), and 2 N HCl (2 mL) was added. The mixture was stirred for 24 h at 50 °C, and the solvent was evaporated. Purification of the residue with a C18 reverse-phase sep-pak cartridge gave 31 mg (70% from **13**) of the corresponding hydrochloride of **6** as an oil. Anal. Calcd for $C_{12}H_{17}ClN_2O$: C, 59.87; H, 7.12; N, 11.64. Found: C, 59.69; H, 7.05; N, 11.75. ^{1}H NMR (300 MHz, D_2O): δ 1.80−1.92 (m, 4H), 2.03−2.10 (m, 4H), 4.20−4.24 (m, 1H), 4.47 (br s, 2H), 7.98−8.06 (m, 1H), 8.23 (d, 1H, J = 7.5 Hz), 8.45 (d, 1H, J = 5.1 Hz), 8.55 (br s, 1H). ^{13}C NMR (75 MHz, D_2O): δ 28.3, 29.4, 60.6, 68.3, 71.8, 129.2, 130.2, 133.4, 135.5, 157.6.

7-Methyl-1-[(pyridin-3-yloxy)methyl]-7-azabicyclo[2.2.1]-heptane (7). The hydrochloride of compound **6** (30 mg, 0.14 mmol) was dissolved in MeOH (5 mL), neutralized with aqueous 10% NaOH, and evaporated. To the corresponding residue were added water (0.5 mL), 99% formic acid (0.25 mL, 6.6 mmol), and aqueous 37% formaldehyde (0.25 mL, 3.2 mmol). This mixture was heated under reflux for 16 h. The reaction was concentrated and partitioned between 2 M K_2CO_3 and $CHCl_3$/^{i}PrOH (3:1). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1) (2 × 15 mL), and the combined organic extracts were dried, filtered, and concentrated. The product was purified by silica gel column chromatography, eluting first with ethyl acetate and then with MeOH/H_2O (7:3), to give a residue which was dissolved in THF (4 mL). Then, 2 N HCl (1 mL) was added, the mixture was stirred for 2 h at rt, and the solvent was evaporated. Purification of the residue with a C18 reverse-phase sep-pak cartridge gave 26 mg (82%) of compound **7** as an oily hydrochloride derivative. Anal. Calcd for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.35; H, 7.64; N, 10.94. ^{1}H NMR (300 MHz, D_2O): δ 1.58−1.74 (m, 4H), 1.88−2.08 (m, 4H), 2.51 (s, 3H), 3.79−3.85 (m, 2/3H), 3.95−3.99 (m, 1/3H), 4.32−4.46 (m, 2H), 7.78 (dd, 1H, J = 8.7, J = 5.4 Hz), 8.04−8.12 (m, 1H), 8.26 (d, 1H, J = 5.7 Hz), 8.45−8.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 29.4, 35.2, 60.1, 66.7, 72.3, 126.3, 127.1, 134.2, 138.3, 161.1.

1-[(Pyridin-3-yloxy)methyl]-2-azabicyclo[2.2.2]octane (8). Sodium hydride (60% in mineral oil, 22 mg, 0.55 mmol) was added in one portion to a cooled (0 °C), stirred solution of 3-hydroxypyridine (44 mg, 0.46 mmol) in DMF (3 mL). The cooling bath was removed, and the reaction mixture was stirred for an additional 45 min. The solution was recooled to 0 °C, and a solution of sulfamidate **22** (47 mg, 0.23 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was stirred at rt for 20 h, the solvent was evaporated, and the residue was dissolved in acetone/20% aqueous H_2SO_4 (1:1). The reaction mixture was stirred at rt for 4 h. The organic layer was evaporated, and the aqueous layer was neutralized with saturated aqueous K_2CO_3. The resulting salts were filtered off and washed with MeOH. The solvent was evaporated, and the product was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH/NH_4OH (8:2:0.1), to give 41 mg of compound **8** as a yellow oil (81%). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.34; H, 8.48; N, 12.62. ^{1}H NMR (400 MHz, D_2O): δ 1.64−1.80 (m, 6H), 1.89−1.95 (s, 1H), 2.10−2.20 (m, 2H), 3.35 (s, 2H), 4.23 (s, 2H), 7.38−7.45 (m, 1H), 7.46−7.51 (m, 1H), 8.08−8.17 (m, 1H), 8.21−8.29 (m, 1H). ^{13}C NMR (100 MHz, D_2O): δ 23.5, 25.8, 28.1, 53.0, 55.6, 72.8, 122.8, 123.5, 125.0, 136.3, 140.3.

2-Methyl-1-[(pyridin-3-yloxy)methyl]-2-azabicyclo[2.2.2]-octane (9). A mixture of amine **8** (41 mg, 0.19 mmol), water (0.5 mL), 99% formic acid (0.25 mL, 6.6 mmol), and aqueous 37% formaldehyde (0.25 mL, 3.2 mmol) was heated under reflux for 16 h. The reaction mixture was concentrated and partitioned between 5% aqueous K_2CO_3 and $CHCl_3$/^{i}PrOH (3:1). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1) (2 × 15 mL), and the combined organic extracts were dried, filtered, and concentrated. The product was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH/NH_4OH (8:2:0.1), to give 40 mg of **9** as yellow oil (92%). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.23; H, 8.75; N, 12.15. ^{1}H NMR (400 MHz, CD_3OD): δ 1.55−1.65 (m, 2H), 1.68−1.84 (m, 5H), 2.04−2.15 (m, 2H), 2.43 (s, 3H), 2.95 (s, 2H), 3.93 (s, 2H), 7.35−7.41 (m, 1H), 7.46−7.51 (m, 1H), 8.14−8.18 (m, 1H), 8.28−8.31 (m,1H). ^{13}C NMR (100 MHz, CD_3OD): δ 25.0, 25.3, 25.9, 26.0, 38.3, 59.6, 64.8, 72.3, 74.5, 123.4, 125.9, 138.6, 142.8, 156.8.

Acknowledgment. We thank the Ministerio de Educación y Ciencia and FEDER (project CTQ2006-05825/BQU and Ramón y Cajal contract for J.H.B.), the Universidad de La Rioja (project API-05/B01), and the Gobierno de La Rioja (ANGI-2004/03 and ANGI-2005/01 projects and a grant for J.C.).

Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, and crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0700732