## Synthesis of a Racemic Nicotine–Lobeline Hybrid

Tsiresy Ranaivondrambola,<sup>a</sup> Wilfried Hatton,<sup>a</sup> François-Xavier Felpin,<sup>a,1</sup> Michel Evain,<sup>b</sup> Monique Mathé-Allainmat,<sup>\*a</sup> Jacques Lebreton<sup>\*a</sup>

- <sup>a</sup> Université de Nantes, CNRS, Laboratoire CEISAM–UMR 6230, Faculté des Sciences et des Techniques, 2 Rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France
- Fax +33(2)51125562; E-mail: monique.mathe@univ-nantes.fr; E-mail: jacques.lebreton@univ-nantes.fr <sup>b</sup> Université de Nantes, CNRS, Institut des Matériaux Jean Rouxel UMR 6502,
- 2 Rue de la Houssinière, BP 32229, 44322 Nantes Cedex 3, France

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Dedicated to the memory of Dr. Christian Marazano

**Abstract:** The first synthesis of a racemic nicotine–lobeline hybrid is described based on a diastereoselective allylation and an RCM reaction as key steps. This synthetic route paves the way to the preparation of original potential ligands of nAChRs.

Key words: alkaloids, ring-closing metathesis, total synthesis, neuronal nicotinic acetylcholine receptors

Neuronal nicotinic acetylcholine receptors (nAChRs) play important roles in the central nervous system (CNS) and have multiple physiological functions.<sup>2</sup> This family of ligand-gated ion channels is built up from pentameric assemblies of  $\alpha$ - and  $\beta$ -protein subunits. To date, nine  $\alpha$ -subunits ( $\alpha 2$ - $\alpha 10$ ) and three  $\beta$ -subunits ( $\beta 2$ - $\beta 4$ ) have been characterized in mammals, thus affording multiple populations of hetero- and homomeric receptor subtypes.<sup>3</sup> For many years, these nAChRs have been recognized as crucial therapeutic targets for the treatment of several neurological and psychiatric disorders including Parkinson's and Alzheimer's diseases, schizophrenia, Tourette's syndrome, certain epilepsies, chronic pain, and nicotine addiction.<sup>4</sup> Various natural alkaloids, including (–)-nicotine (1), (-)-epibatidine (2), (-)-anatoxin-a (3), and (-)-lobeline (4, see Figure 1), have been identified as potent but nonselective agonists.<sup>5</sup> To improve the pharmacological properties of these natural compounds, a huge effort in fundamental research as well as in drug development, both in academia and in the pharmaceutical industry, has been conducted for many years.<sup>6</sup> Due to the diversity of nAChRs, numerous analogues of this set of alkaloids have been prepared and evaluated to find potent and subtypespecific ligands with or without substantially reduced side effects. Several analogues of these natural products appear promising and are in various stages of preclinical and clinical evaluation although others have been abandoned. In 2001, acetylcholine-binding protein (AChBP), a novel homopentameric protein with high similarity to the extracellular ligand-binding domain of the nAChR, was isolated from the freshwater snail Lymnaea stagnalis.<sup>7</sup> The crystal structure of AChBP<sup>8</sup> offered the first high-resolu-

SYNLETT 2010, No. 11, pp 1631–1634 Advanced online publication: 10.06.2010 DOI: 10.1055/s-0029-1219966; Art ID: G09210ST © Georg Thieme Verlag Stuttgart · New York tion structure of this family of receptors providing a great opportunity to better understand the structure–activity relationship of various nAChR agonists and therefore to identify the structural factors that may contribute to improving subtype selectivity.<sup>9</sup>



Figure 1 Structures of (-)-nicotine (1), (-)-epibatidine (2), (-)-anatoxin-a (3), and (-)-lobeline (4)

In addition, combining the key structural features of these alkaloids, a hybrid of (–)-anatoxin-a (**3**) and (–)-epibatidine (**2**), named UB-165 (**5**, see Figure 2), in which the acetyl group of the first is replaced by a 5-(2-chloropyridyl) moiety of the second, has been studied and used as a lead compound for drug candidates.<sup>10</sup> A few years ago, we published the total synthesis of (–)-nicotine (**1**)<sup>11</sup> and (–)-lobeline (**4**).<sup>12</sup> However, to our surprise and to the best of our knowledge, no attempt to prepare a hybrid of these two important alkaloids has since been reported in the literature. In order to find new ligands of nAChR with higher affinity and better subtype selectivity than their parent alkaloids, we wish to describe in this paper the first synthesis of nicotine–lobeline hybrid molecules **6** and **7**.

Our synthetic strategy towards the nicotine–lobeline hybrid molecules **6** and **7** is outlined in Scheme 1. In considering a synthetic route to our target hybrids, we were guided by previous investigations in our group on the diastereoselective allylation of imines such as intermediate **10**.<sup>13</sup> This latter compound, bearing an imine function and a styryl moiety, offers the opportunity to add an allyl organometallic reagent to access to diene **11** with a stereo-



Figure 2 Structures of (-)-UB-165 (5), racemic nicotine-lobeline hybrid molecules 6 and 7

control of the protected alcohol function followed by an RCM reaction to form the piperidine ring. Retrosynthetic analysis for the first intermediate **9** suggested that the Mukaiyama aldol reaction on the starting material **8** with benzaldehyde followed by diastereoselective ketone reduction and further functional-group transformation would give the desired amine intermediate **9**. It was further expected that condensation of this amine with nicotinaldehyde would lead to the formation of the corresponding imine **10**. It should be pointed out that these two latter transformations in this strategy, in both cases using an aldehyde, would be a way to implant diversity on aromatic or/and heteroaromatic rings to prepare analogues.



Scheme 1 Retrosynthetic plan for the preparation of racemic nicotine–lobeline hybrid 7

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The synthesis of the first intermediate  $(\pm)$ -9 commenced with the BF<sub>3</sub>·OEt<sub>2</sub>-mediated Mukaiyama-aldol reaction between the silylenolether  $8^{14}$  and benzaldehyde to furnish the adduct 12 which was then protected as silyl ether to give the intermediate 13 in 83% overall yield, as outlined in Scheme 2. The reduction of the racemic protected aldol 13 with lithium aluminium hydride in THF-diethyl ether at low temperature took place with a good diastereoselectivity (up to 9:1), affording the desired monoprotected syn-diol 14 as the major product in 91% yield on a 10 g scale. The observed diastereoselectivity was in agreement with a six-membered chelate model and, according to this model, the hydride was delivered by the less hindered face opposite the phenyl ring. Attempts to increase the diastereoselectivity by lowering the temperature from -100 to -120 °C resulted in no significant improvement. The reduction with zinc borohydride was found to be less efficient: in the best conditions, an 8:2 ratio was obtained. The relative configuration of the aldol adducts 14 was unambiguously ascertained by removal of the TBS protecting group and acetonide formation. Using the empirical Rychnovsky's acetonide <sup>13</sup>C NMR spectra analysis<sup>15</sup> in the major diastereomer 14, the signals of the methyl groups of the isopropylidene moiety occurred at  $\delta = 30.4$ and 20.3 ppm, which indicated that the six-membered acetonide ring was present in a chair form, in accordance with a syn-1,3-diol system. In the minor diastereomer, however, the anti-1,3-diol acetonide adopted a twist-boat conformation, having both signals of the methyl groups at  $\delta = 25.3$  ppm.

The resulting mixture of diol 14 was further converted into the corresponding azide 15 in 86% yield with an integral switch to anti stereochemistry upon treatment with diphenylphosphoryl azide in the presence of DBU.<sup>16</sup> Subjecting a mixture of the anti- and syn-azides 15 to Zn and NH<sub>4</sub>Cl in EtOH-H<sub>2</sub>O (3:1) at reflux resulted in a clean reduction to yield, after purification on silica gel, the desired pure anti-amino alcohol 9 in 66% yield (the minor isomer was isolated in 12% yield).<sup>17</sup> It should be noted that, in our initial experiment, we performed this reduction by treatment with SnCl<sub>2</sub>.<sup>11a</sup> However, with substrate 15 the workup was found to be rather tricky due to the formation of an emulsion. Applying a one-pot two-step sequence that has been successfully developed in our group,<sup>13</sup> the amine anti-9 was treated with the nicotinaldehyde in the presence of anhydrous MgSO<sub>4</sub> in diethyl ether to form in situ the corresponding imine 10. To this latter ethereal solution at -78 °C was added an excess of allyl Grignard reagent to provide an 85:15 mixture of dienes 11 and 16 in 85% yield. After chromatographic purification on silica gel, the desired diene 11 was obtained in 57% overall yield. Two arguments are worth mentioning to support the unambiguous assignment of the relative configuration of the major diastereomer 11. First, this latter transformation has also been performed with other aromatic aldehydes such as benzaldehyde leading to similar results, in terms of yield and diastereoselectivity. Moreover, after an RCM reaction with one of these dienes (vide infra), we were



**Scheme 2** *Reagents and conditions*: (a) PhCHO, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1 h (91%); (b) TBSCl, Et<sub>3</sub>N, DMAP, DMF, r.t., 8 h (92%); (c) LiAlH<sub>4</sub>, Et<sub>2</sub>O–THF (9:1), -100 °C, 4 h (91%, ratio *syn*-**14**/*anti*-**14** = 9:1); (d) DPPA, DBU, PhMe, r.t., 20 h (86%, ratio *anti*-**15**/*syn*-**15** = 9:1); (e) Zn, NH<sub>4</sub>Cl, EtOH–H<sub>2</sub>O (3:1), reflux, 2 h (for *anti*-**9** 66% and for *syn*-diastereomer 12%); (f) 3-Pyr-CHO, MgSO<sub>4</sub>, Et<sub>2</sub>O, r.t., 7 h, then allyl-MgBr, -78 °C to r.t., 4 h (85%, ratio **11/16** = 85:15); (g) TBAF, 0 °C to r.t., 7 h (82%); (h) Grubbs II, PTSA, CH<sub>2</sub>Cl<sub>2</sub>-*t*-BuOH (20:1), reflux, 24 h (67%); (i) H<sub>2</sub>, Pd/C, EtOH, r.t., 48 h (83%); (j) NaH, CDI, THF, reflux, 3 h then LAH in excess, r.t., 12 h (82%); (k) CICO–COCI, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, then (±)-**6**, 15 min, Et<sub>3</sub>N, -78 °C to r.t. (95%).

able to confirm the stereochemistry based on an X-ray structure analysis (see Supporting Information). Further proof concerning the relative configuration of the major diastereomer 11 came after the RCM reaction step, as discussed below. Contrary to our previous work,<sup>13</sup> the formation of the diastereomer 11 could be rationalized by the lack of internal chelation between the alcohol function, protected in this substrate 10 as silvlether, and the nitrogen atom of the imino function. Indeed, with a free-hydroxy substrate, an internal chelation of the magnesium atom of the Grignard reagent with the corresponding alcoholate and the imino nitrogen should form a six-membered ring. This would favor an attack of the allyl reagent by the less hindered face to afford the adduct with the same relative configuration as in the minor diastereomer 16. Nevertheless, the origin of this diastereoselectivity with compound 10 still remains unclear. Thus, some complementary experiments are under way in order to elucidate the mechanism. As expected, this pyridinic substrate 11 turned out to be problematic for the RCM reaction.<sup>18</sup> Attempts to perform the RCM reaction with Grubbs second-generation catalyst on the corresponding dihydrochloride salt of the substrate 11 failed to provide the desired compound in decent yield, due mainly to its insolubility in refluxing dichloromethane. We also observed partial cleavage of the silvlether which afforded a mixture of compounds. So, at this point of our synthesis, we decided to remove the silyl protecting group by classical treatment with TBAF; the alcohol 17 was then isolated in 82% yield after purification. Fortunately, the RCM reaction on

the latter intermediate 17 as its ditosylate salt occurred with the use of Grubbs second-generation catalyst in a mixture of dichloromethane and tert-BuOH (20:1) to furnish the cyclized adduct 18 in 67% isolated yield. It is noteworthy that the use of t-BuOH as co-solvent proved to be essential for the good solubility of the ditosylate salt and therefore the success of this transformation. Moreover, an NOE experiment on the RCM reaction product 18 revealed a *cis* configuration between the two hydrogen atoms on C-2 and C-6 of the piperidine ring, allowing the unambiguous assignment of the relative configuration of the diastereomer **11**. As previously used by  $us^{11}$  in the total synthesis of (S)-N-methylanabasine, we attempted to treat intermediate 18 under hydrogen in the presence of palladium on carbon in a mixture of ethanol and formaldehyde to afford 6 directly. Under these modified Eschweiler-Clarke conditions, the double bond of 18 was hydrogenated, and the secondary amine was converted by reaction with formaldehyde to the corresponding iminium which, instead of being reduced to the N-methylated derivative, reacted in an intramolecular fashion with the free secondary alcohol function to give the undesired sixmembered cyclic N,O-acetal in good yield. Owing to these difficulties, we decided to rely on a nice piece of chemistry described by Bates and co-workers in the route to sedamine.<sup>19</sup> Hydrogenation of the double bond in **18** under classical conditions gave the compound 19 in 83% yield. The amino alcohol 19 was treated with N,N'-carbonyldiimidazole and sodium hydride to furnish the cyclic carbamate intermediate 20 which was then reacted with an

excess of lithium aluminium hydride leading to the desired N-methylated compound  $6^{20}$  in 82% overall yield after purification by silica gel chromatography. Finally, this latter intermediate 6 was converted into the target hybrid  $7^{21}$  in 95% yield upon Swern oxidation.

In conclusion, we have described the first synthesis of nicotine–lobeline hybrid molecules  $(\pm)$ -6 and  $(\pm)$ -7. Furthermore, application of this synthetic strategy to the preparation of different analogues with various substituents on both aromatic and pyridine rings is currently in progress and will be published in due course with their binding results on nAChRs.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and spectroscopic data for compounds: *anti-9, syn-9, 11, 16–19, 6, and 7.* Copies of NMR data of compounds 6 and 7, and single-crystal X-ray.

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- (20) Selected Physico-Chemical Data for Compound 6 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.39-8.46$  (m, 2 H), 7.57– 7.64 (m, 1 H), 7.15–7.22 (m, 1 H), 7.13–7.34 (m, 5 H), 5.18 (dd, 1 H, *J* = 3.0, 11.5 Hz), 2.99 (dd, 1 H, *J* = 3.0, 11.2 Hz), 2.46–2.57 (m, 1 H), 2.26 (ddd, 1 H, *J* = 3.6, 11.2, 15.1 Hz), 2.16 (s, 3 H), 2.04 (dq, 1 H, *J* = 3.2, 12.5 Hz), 1.65–1.87 (m, 3 H), 1.46–1.58 (m, 2 H), 1.35–1.49 (m, 1 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 149.0$ , 148.8, 145.1, 140.1, 134.4, 128.3 (2×), 127.0, 125.5 (2×), 124.0, 71.9, 68.4, 63.7, 41.4, 39.9, 36.2, 29.9, 24.2 ppm. HRMS (CI): *m/z* calcd for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O [M + H<sup>+</sup>]: 297.1961; found: 297. 1967.
- (21) Selected Physico-Chemical Data for Compound 7 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.58$  (br s, 1 H), 8.52 (br d, 1 H, J = 4.6 Hz), 8.02 (dm, 2 H, J = 7.4 Hz), 7.66–7.82 (m, 1 H), 7.56–7.65 (m, 1 H), 7.46–7.56 (m, 2 H), 7.22–7.31 (m, 1 H), 3.42–3.57 (m, 1 H), 3.10–3.22 (m, 1 H), 2.84–3.07 (m, 2 H), 2.01 (s, 3 H), 1.70–1.88 (m, 3 H), 1.47–1.66 (m, 3 H) pm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 199.2$ , 149.3, 148.5, 148.4, 137.2, 134.8, 133.2, 128.7 (2 C), 128.2 (2 C), 123.6, 68.2, 60.5, 44.6, 40.9, 36.1, 32.9, 24.4 ppm. HRMS (CI): *m/z* calcd for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O [M + H<sup>+</sup>]: 295.1805; found: 295.1810.

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