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Expeditious synthesis of *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[3,2*h*]isoquinoline/[2,3-*f*]quinoline via azomethine ylide-alkene [3+2] cycloaddition

Zhenfa Zhang [†], Linda P. Dwoskin, Peter A. Crooks [*]

College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA

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ABSTRACT

Expeditious syntheses of *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[3,2*h*]isoquinoline/[2,3-*f*]quinoline have been developed. The syntheses started with commercially available materials and afforded excellent overall yields in straightforward steps. Intramolecular azomethine ylide-alkene [3+2] cycloaddition is the key step in the construction of these pyrroloisoquinoline and pyrroloquinoline scaffolds. This route is much more atom-economic than those reported in the literature and is appropriate for scale-up synthesis.

Structural modification of the nicotine molecule provided many novel potent and drugable nicotinic acetylcholine receptor (nAChR) ligands in CNS drug discovery.[1] In light of this strategy, conformationally restrained analogs of nicotine have attracted much attention among medicinal chemists.[2] In this regard, compounds based on two scaffolds: *cis*-1-methyl-2,3,3*a*,4,5,9*b*- hexahydro-1*H*-pyrrolo-[3,2-*h*] isoquinoline (**1**, Fig. 1) and *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[2,3-*f*]-quinoline (**3**),[3] which were designed to mimic the two isoenergetic conformers of nicotine that are believed to be present in aqueous solution,[4] demonstrated considerable potential. Compound **1** may represent a new class of analgesic because of its unique pharmacological profile,[5] and **SIB-**1663 (**2**) has been established to have distinctive nAChR subtype selectivity.[6] Additionally, haptens **4** and **5** (Fig. 1), which have the scaffold of **1** and **3**, respectively, yielded enhanced immune response as demonstrated in a new strategy for the development of nicotine vaccines.[7] Thus, an expeditious synthetic pathway to the scaffolds **1** and **3** would have important value in the CNS drug discovery area. Herein we report a new approach for the efficient construction of **1** and **3**, which will be much more viable for scale-up synthesis.

For the synthesis of compound **1**, the original route has been followed for two decades,[8] which resorts to the key intermediate 6,7-dihydro-8(5*H*)-isoquinolinone (**6**, Scheme 1). However, the approaches related to the preparation of **6** involved either harsh conditions, tedious isolation or/and rare precursors that are laborious to prepare, and additionally, all these approaches afforded relatively poor overall yields of the desired intermediate **6** and eventually product **1**. The same strategy has also been employed for the synthesis of **3** starting from the corresponding isomer **8** with similar overall yield.

An alternative route to the synthesis of compound **1** has been reported recently utilizing Diels–Alder chemistry for the construction of the central six-membered ring system.[9] Unfortunately, the key step proceeds only when multiple functional groups are

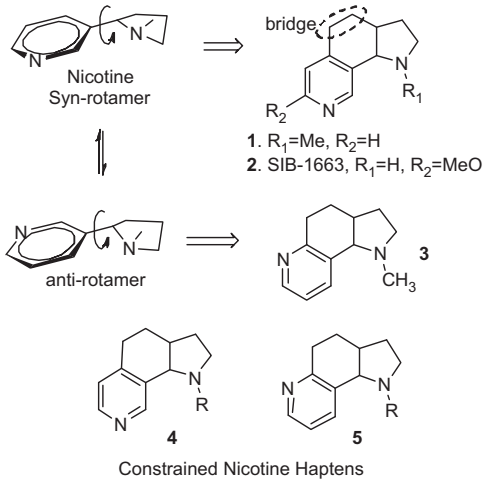

Figure 1.

* Corresponding author. Tel.: +1 859 257 1718; fax: +1 859 257 7585.
E-mail addresses: zhenfaz@email.unc.edu (Z. Zhang), pcrooks@email.uky.edu (P.A. Crooks).
† Present address: Department of Environmental Science and Engineering, School of Public Health, University of North Carolina at Chapel Hill, CB 7431, Chapel Hill, NC 27599, USA. Fax: +1 919 966 7911.

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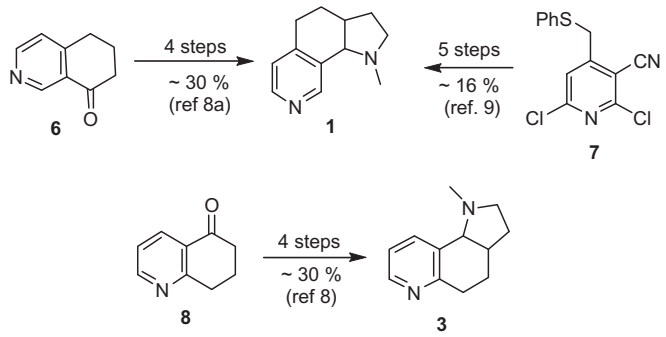
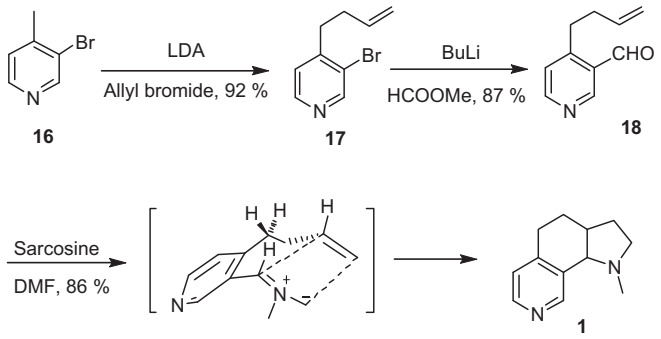


Scheme 1.



Scheme 3.

present on specific positions of the precursor molecule **7** (Scheme 1). Obviously these particular requirements, as well as the reported low yields, substantially limit the scope and utilization of this synthetic approach.

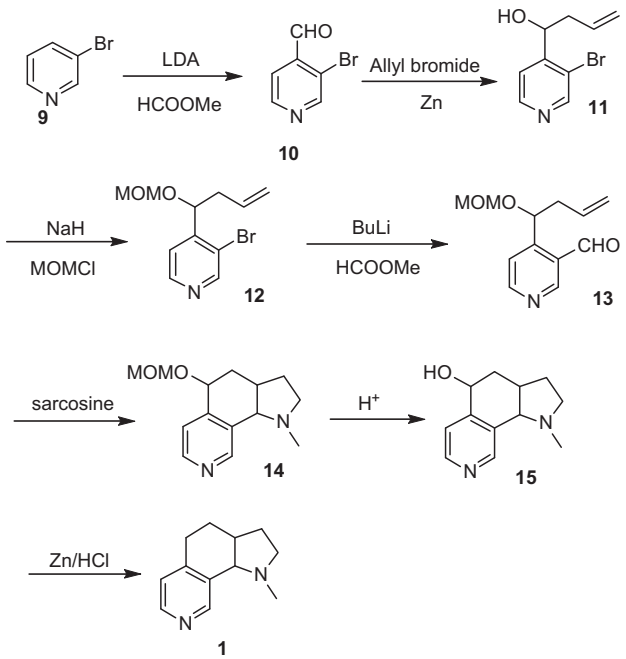
As a valuable strategy, azomethine ylide-alkene [3+2] cycloaddition constitutes an efficient method for the construction of a pyrrolidine ring. This synthetic approach has been widely employed for the synthesis of many biologically active molecules.[10] Utilizing this strategy, we have synthesized **1** in our earlier research (Scheme 2).[11] We envisaged that this approach may serve as a good starting point for the development of a new, efficient synthetic route to **1** and **3**.

Upon close analysis of the route in Scheme 2, it was realized that the stepwise introduction of the ene-containing side chain at the 4-position of 3-bromopyridine (**9**) left a hydroxyl group in the resulting molecule **11**. This hydroxyl group has to be protected (as **12**) for the next step, that is, Li-bromo exchange, to proceed smoothly.[12] Eventually, the protecting MOM group has to be removed (as **15**) and the exposed hydroxyl group reduced to furnish the final product **1**. Obviously the introduction of the hydroxyl group in **11** necessitated a few manipulations on the functional group that is not present in the final molecule, which largely depreciated the atom-economy for the whole process. Thus we developed a new synthetic route to **1** as illustrated in Scheme 3.

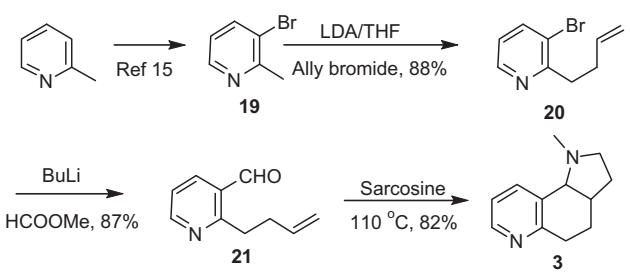
Taking advantage of the acidity of the methyl proton in commercially available 3-bromo-4-methylpyridine (**16**), we chose this as our starting material. Thus, **16** was treated with LDA and allylbromide at −78 °C to afford 3-bromo-4-(but-3-en-1-yl)pyridine (**17**) in excellent yield (92%). The resulting **17** was subjected to bromine-lithium exchange with *n*-BuLi at −78 °C followed by formylation to furnish the corresponding aldehyde **18** (87% yield). The key intermediate **18** sets the stage for intramolecular azomethine ylide-alkene [3+2] cycloaddition. Accordingly, when the mixture of **18** and sarcosine in DMF was heated at 110 °C for 4 h, the cycloadduct **1** was obtained in excellent yield (86%). The ^{1}H and ^{13}C NMR spectra of **1** were identical to those of an authentic sample prepared in this group previously following the route depicted in Scheme 2[11] or the route of Glassco et al.,[3,13a] who had established the *cis*-geometry of **1** through X-ray analysis. Only the *cis*-isomer was detected as the product of the intramolecular ylide-alkene [3+2] cycloaddition. This result is consistent with the observations of other groups.[14]

Obviously, this route for the synthesis of **1** is much more expeditious than those reported in the literature as illustrated in Schemes 1 and 2. The route starts from a commercially available material and affords an excellent overall yield of 69% in three straightforward steps. From an atom-economy point of view, this is a very efficient process for the synthesis of **1**, and affords a more appropriate process for scale-up synthesis.

Furthermore, we discovered that this route can be easily adapted for the synthesis of compound **3** (Scheme 4). Following the same process as that illustrated in Scheme 3 for the synthesis of **1**, the desired product **3** was very conveniently prepared in 3 steps from 3-bromo-2-picoline (**19**)[15]. The ^{1}H and ^{13}C NMR spectra of the resulting **3** were also identical to those of an authentic sample prepared previously following the synthetic route of Glassco et al.[3] Thus, the current route is also significantly more efficient than the reported method for the synthesis of compound **3**.[8]



Scheme 2.



Scheme 4.

In conclusion, expeditious syntheses of *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[3,2-*h*]iso-quinoline (**1**) and *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[2,3-*f*]quinoline (**3**) have been established utilizing intramolecular azomethine ylide-alkene [3+2] cycloaddition. For the synthesis of **1** and **3**, this route is considerably more efficient than the previously reported routes, and provides a viable route for large scale production of such molecules, which is important for subsequent preclinical development as therapeutic agents. Details of the synthesis and characterization data for compounds **1**, **3**, **17**, **18**, **20** and **21** are provided in the references and notes.[16–17]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.065.

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11. (a) The route in Scheme 2 depicts the reagents and conditions we used for the synthesis of **1** in the initial discovery phase without publication. This route turned out to be essentially the same as the later published route by Yang et al. (Ref. 11b) with only slight differences in reagents and conditions. Our detailed procedures are now provided in the Supplementary data along with the original characterization data for references; (b) Yang, X.; Luo, S.; Liu, F.; Fang, P.; Lu, Y.; He, M.; Zhai, H. *Tetrahedron* **2006**, *62*, 2240–2246.
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16. *Procedure for the preparation of **17** and **20***. For **17**: compound **16** (4.2 g, 24.4 mmol) was dissolved in anhydrous THF (100 mL) and LDA (2 M, 15 mL, 30 mmol) was added at −78 °C over 5 min. The mixture was stirred at −78 °C for an additional 45 min, a solution of allyl bromide (2.0 mL, 30 mmol) in THF (10 mL) was added drop-wise over 15 min. After stirring at −78 °C for another 2 h, aqueous $NaHCO_3$ was added to quench the reaction and the mixture was warmed up to RT. Most of the solvent was removed in vacuo and the resulting residue was partitioned into ethyl acetate (50 mL) and brine (50 mL). The aqueous layer was further extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, hexane:ethyl acetate, 10:1) to afford **17** (4.8 g, 92% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.62 (s, 1 H), 8.38 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 5.76–5.84 (m, 1H), 4.96–5.02 (m, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.38–2.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), 151.9, 150.0, 148.2, 136.7, 125.4, 123.3, 116.2, 35.1, 33.0. HRMS *m*/*e* 210.9993, 212.0860 (calcd for $C_9H_{10}BrN$, 210.9997; $C_9H_{10}{}^{81}BrN$, 212.0864). Following the same procedure, compound **20** was prepared form 3-bromo-2-picoline (**19**) in 88% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.47 (dd, J = 4.8, 1.5 Hz, 1H), 7.82 (dd, J = 8.4, 1.5 Hz, 1H), 7.00 (dd, J = 8.4, 4.8 Hz, 1H), 5.85–5.99 (m, 1H), 4.96–5.11 (m, 2H), 3.06 (t, J = 8.4 Hz, 2H), 2.46–2.54 (m, 2H). ^{13}C NMR (75 MHz, CDCl3), δ 159.8, 147.8, 140.4, 137.7, 122.7, 121.6, 115.4, 37.2, 32.7. HRMS *m*/*e* 210.9993 (calcd for $C_9H_{10}NBr$, 210.9997).
17. *Procedure for the preparation of **18** and **21***. For **18**: *n*-BuLi (2 M in hexane, 7 mL, 14 mmol), was added drop-wise to a solution of **17** (2.56 g. 12.1 mmol) in anhydrous THF (30 mL) under N_2 at −78 °C over 10 min. After stirring an additional 20 min at −78 °C, anhydrous methyl formate (1.5 mL, 25 mmol) was added over 10 min and the mixture stirred at −78 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and warmed up to rt. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned into ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, the residue was purified by chromatography (SiO_2, hexane/ethyl acetate, 5:1) to give **18** (1.70 g, 87%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ 10.26 (s, 1H), 8.94 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 7.22 (d, J = 4.8 Hz, 1H). 5.76–5.87 (m, 1H), 4.98–5.04 (m, 2H). 3.14 (t, J = 5.7 Hz, 2H), 2.34–2.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 191.6, 154.5, 153.6, 153.0, 136.7, 125.8, 116.3, 34.7, 32.0. HRMS *m*/*e* 161.0843 (calcd for $C_{10}H_{11}NO$, 161.0841). Following the same procedure, compound **21** was prepared from **20** in 87% yield as brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ 10.25 (s, 1H), 8.72 (dd, J = 4.5, 1.5 Hz, 1H), 8.12 (dd, J = 7.5, 1.8 Hz, 1H) 7.32 (dd, J = 7.8, 4.8 Hz, 1H), 5.81–5.94 (m, 1H), 4.96–5.07 (m, 2H), 2.98 (t, J = 7.8 Hz, 2H), 2.46–2.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 191.1, 163.51, 153.6, 138.1, 137.2, 129.5, 122.0, 116.0, 34.5, 34.4. HRMS *m*/*e* 161.0842 (calcd for $C_{10}H_{11}NO$, 161.0841).