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Tetrahedron 62 (2006) 2240–2246
Tetrahedron

Synthesis of conformationally restricted nicotine analogues by intramolecular [3+2] cycloaddition

Xiaobao Yang,[a,†] Shengjun Luo,[a,‡] Fang Fang,[a] Peng Liu,[a] Yong Lu,[b] Mingyuan He[b] and Hongbin Zhai*

[a]*Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Shanghai Key Laboratory of Green Chemistry and Chemical Processes (GCCP), Department of Chemistry, East China Normal University, Shanghai 200062, China*

Received 28 October 2005; revised 5 December 2005; accepted 6 December 2005

Available online 9 January 2006

Abstract—We describe the synthesis of a series of conformationally constrained nicotine analogues **2**–**5** from appropriate pyridine-containing enals, featuring an intramolecular azomethine ylide–alkene [3+2] cycloaddition. The objective of the current project is to develop new selective nAChRs-targeting ligands. Of the nicotine analogues that we have studied, the conformation-restricting ring B unit can be either a five-membered carbocycle, or a six-membered carbocycle or heterocycle. The present work constitutes a general method for rapid assembly of other related tricyclic nicotine analogues.

1. Introduction

(−)-Nicotine (**1**, Fig. 1) is a well-known alkaloid present in tobacco at 0.2–5% levels and can target and activate nicotinic acetylcholine receptors (nAChRs), a family of ligand-gated ion channels widely distributed in the human brain.[1] These receptors participate in various biological processes related to numerous nervous system disorders.[2] Over the past decades, nicotine analogues have aroused tremendous attention in the areas of both organic synthesis and medicinal chemistry, because of the therapeutic potential of (−)-nicotine for the central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, and Tourette's diseases.[2] Among the nicotine analogues, those with constrained conformation have emerged as the most attractive candidates for new selective nAChRs-targeting ligands.[2a,3,4] This phenomenon might partially be accounted for by the discovery of epibatidine, an alkaloid with a rigid structure, which displays strong activity despite of its toxicity.[5] Furthermore, molecular modeling approaches have illustrated that the two rings of nicotine structure are skewed and approximately perpendicular to one another in order to secure low energy conformations.[3,6]

Aiming at the cures for nervous system disorders, we have been engaged in designing, synthesizing, and evaluating new selective nAChRs-targeting ligands for years. In this paper, we wish to disclose our findings in constructing conformationally restricted, tricyclic, nicotine analogues **2**,[4a,b] **3**,[4j] **4**,[4g,7] and **5** (Fig. 1). The conformational rigidity was achieved as a result of a one- (in **2**) or two-atom (in **3**–**5**) bridge erected between C-4 and C-5′ of nicotine (**1**). Our synthesis features an intramolecular azomethine ylide–alkene [3+2] cycloaddition[4a,b,8] in effectively assembling the tricyclic framework of these ligands.

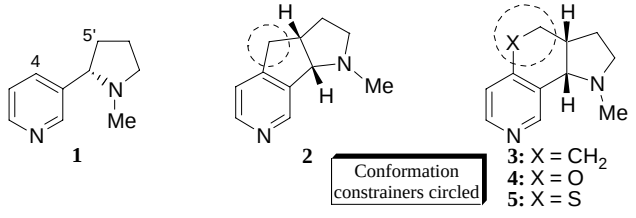

Figure 1.

Keywords: Conformationally restricted; Intramolecular [3+2] cycloaddition; Nicotine analogues; Synthesis.
* Corresponding author. Tel.: +86 21 54925163; fax: +86 21 64166128; e-mail: zhaih@mail.sioc.ac.cn
† Current address: Graduate School, East China University of Science and Technology, 130 Meilong Road, Shanghai, China 200237.
‡ Current address: Unilever Research China, 3/F, Xinmao Building, 99 Tianzhou Road, Shanghai, China 200233.

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doi:10.1016/j.tet.2005.12.032

2. Results and discussion

The general strategy to synthesize the nicotine analogues in question is outlined in Figure 2. The ligands represented by structure **6** were envisioned to be obtainable from appropriate pyridine-containing enal **8** via azomethine ylide **7**. Intramolecular [3+2] cycloaddition constitutes a perfect choice in achieving the desired transformation.

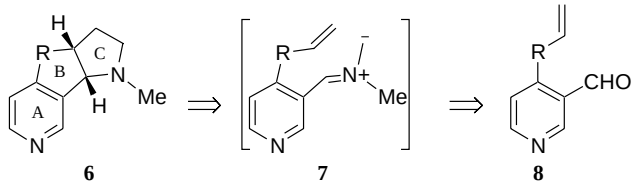
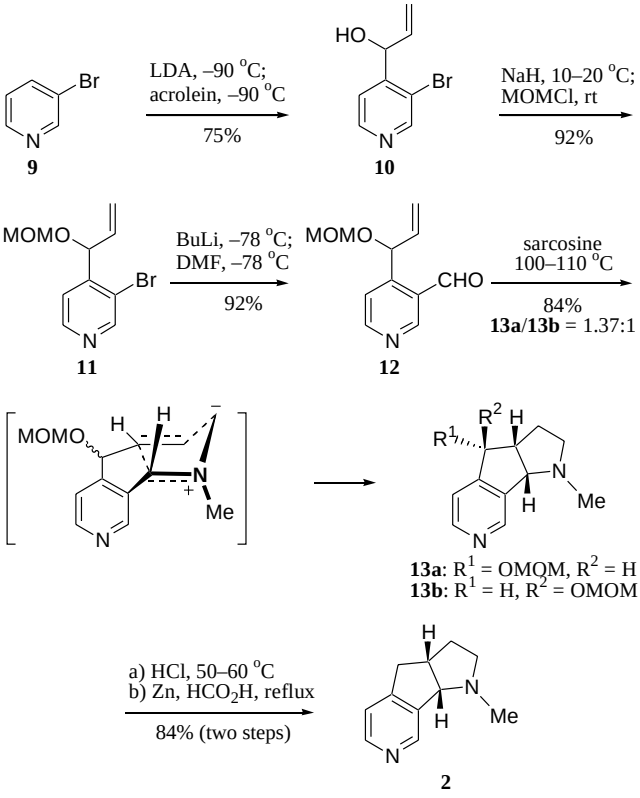


Figure 2.

2.1. Synthesis of nicotine analogue with five-membered carbocyclic ring B

As outlined in Scheme 1, the synthesis of nicotine analogue **2** commenced from 3-bromopyridine (**9**). *Ortho* lithiation with LDA at −90 °C followed by treatment with acrolein at the same temperature furnished alcohol **10** in good yield (75%). Deprotonation at lower temperature than −78 °C resulted in higher yield of the product by diminishing pyridyne formation. Alcohol **10** was protected as ether **11** by exposure to MOMCl in the presence of NaH. Use of a slight excess of base, compared to MOMCl, was found to be effective in preventing the formation of the rearranged enol ether byproducts. Formylation of **11** (BuLi, −78 °C; DMF, −78 °C) led conveniently to aldehyde **12** in 92% yield, setting the stage for intramolecular azomethine ylide–alkene [3+2] cycloaddition. After extensive experimentation, we found that treatment of **12** with sarcosine in DMF at 100–110 °C for 6 h effected the desired cycloaddition to give two isomers **13a/13b** in a combined yield of 84% and in a diastereomeric ratio of 1.37:1 (deduced from ^{1}H NMR integrals). The structures of **13a** and **13b** were assigned based on the coupling constants for the hydrogen atoms at C-4 (J=8.1, 4.5 Hz, respectively). Deprotection of **13a/13b** mixture (4 M HCl, 50–60 °C) followed by zinc-mediated reductive dehydroxylation (Zn powder, formic acid, reflux) afforded **2** in 84% overall yield for the two steps.[4b]

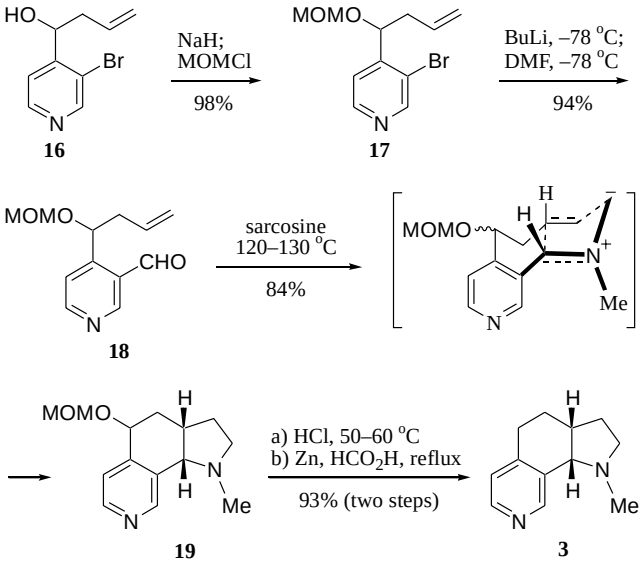


Scheme 1.

A second-generation synthesis of **2** was accomplished in only two steps. In this case, the precursor for the intramolecular azomethine ylide–alkene [3+2] cycloaddition, that is, 4-allyl-3-pyridinecarboxaldehyde (**15**), was formed efficaciously in a single step from 3-pyridinecarboxaldehyde (**14**) via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.[4a]

2.2. Synthesis of nicotine analogue with six-membered carbocyclic ring B

As shown in Scheme 2, the synthesis of **3** started with a known alcohol, **16**, which was prepared by a Barbier reaction of 3-bromo-4-pyridinecarboxaldehyde with allyl bromide and zinc powder.[9] Protection of **16** as MOM ether (NaH, rt; MOMCl, rt, 98%) followed by formylation at C-3 (BuLi, −78 °C; DMF, −78 °C, 94%) afforded enal **18** in high yield. Exposure of **18** to sarcosine in DMF at 120–130 °C for 8 h effected the desired intramolecular azomethine ylide–alkene [3+2] cycloaddition to produce a pair of diastereomers **19** (dr=2.57:1) in a combined yield of 84%. By following the protocol developed for **13a/13b** (Scheme 1), the cycloaddition products **19** underwent deprotection (6 M HCl, 50–60 °C) and the subsequent zinc-mediated reductive dehydroxylation (Zn powder,

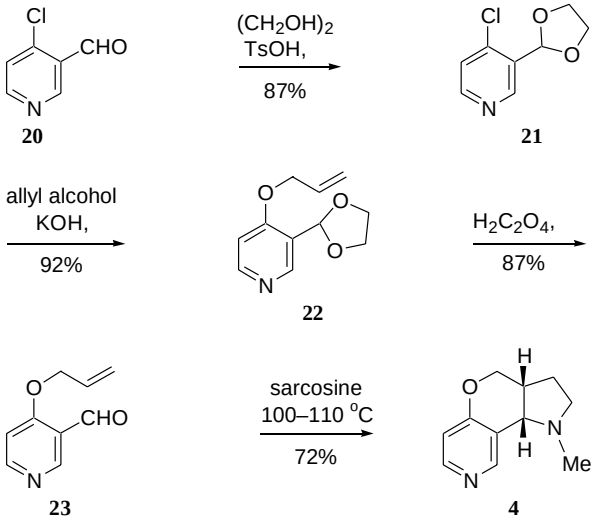


Scheme 2.

formic acid, reflux) to lead to **3**[4j] in 93% overall yield for the two steps.

2.3. Synthesis of nicotine analogue with six-membered oxygen-containing heterocyclic ring B

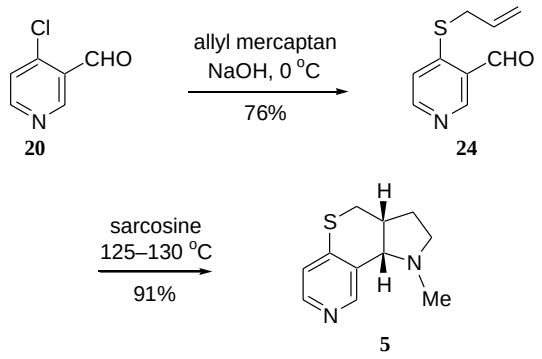
The preparation of the cycloaddition precursor, enal **23**, was not as trivial as expected. Direct treatment of 4-chloro-3-pyridinecarboxaldehyde[10] (**20**) with allyl alcohol and KOH in refluxing THF gave rise to 4-chloro-3-(hydroxymethyl)-pyridine. However, after being protected as the acetal **21** (ethylene glycol, $TsOH\cdot H_2O$, benzene, reflux, 87%), the etherification at the C-4 of the pyridine ring (allyl alcohol, KOH, THF, reflux) proceeded cleanly to furnish allyl ether **22** in 92% (Scheme 3). Heating **22** with oxalic acid dihydrate in refluxing acetone–water (1/1) effected acetal deprotection to provide in 87% yield enal **23**, which underwent intramolecular azomethine ylide–alkene [3+2] cycloaddition to form the oxygen-containing tricycle **4** in moderate yield (72%) when heated with sarcosine in DMF at 100–110 °C.



Scheme 3.

2.4. Synthesis of nicotine analogue with six-membered sulfur-containing heterocyclic ring B

Reaction 4-chloro-3-pyridinecarboxaldehyde[10] (**20**) with allyl mercaptan (generated in situ from thiourea and allyl bromide in basic medium) and NaOH in ethanol at rt resulted in the formation of thioether **24** (76%) (Scheme 4), which was contrary to what we observed with the etherification of **20** with allyl alcohol. Obviously the reaction condition for thioetherification was much milder because of the stronger nucleophilicity of allyl mercaptan compared to that of allyl alcohol. Finally, upon treatment with sarcosine in hot DMF (125–130 °C), enal **24** was converted to the sulfur-containing tricycle **5** in 91% yield through intramolecular azomethine ylide–alkene [3+2] cycloaddition. According to our literature search, compound **5** represents a new nicotine analogue with restricted conformation.



Scheme 4.

3. Conclusion

In summary, we have accomplished the synthesis of a series of conformationally constrained nicotine analogues **2–5** from appropriate pyridine-containing enals, featuring an intramolecular azomethine ylide–alkene [3+2] cycloaddition. The objective of the current project is to develop new selective nAChRs-targeting ligands. Of the nicotine analogues that we have studied, the conformation-restricting ring B unit can be either a five-membered carbocycle, or a six-membered carbocycle or heterocycle. The pharmacological investigations of these compounds are under way. The present work constitutes a general method for rapid assembly of other related tricyclic nicotine analogues.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. Column chromatography was performed on silica gel. CH_2Cl_2, DMF and diisopropylamine were stored over calcium hydride and freshly distilled prior to use. THF and benzene were distilled over sodium benzophenone ketyl prior to use. Ethanol was distilled over magnesium prior to use.

4.1.1. 3-Bromo-4-(1-hydroxy-2-propenyl)pyridine (10). BuLi (1.6 M, 8.00 mL, 12.8 mmol) was added to a solution of diisopropylamine (2.00 mL, 14.3 mmol) in THF (26 mL) at −78 °C over 10 min. After 30 min, the resultant LDA solution was cooled to −90 °C, and a solution of 3-bromopyridine (0.90 mL, 9.3 mmol) in THF (3 mL) was added dropwise at this temperature over 3 min. The mixture was stirred for 25 min, and then a solution of acrolein (1.10 mL, 16.5 mmol) in THF (5 mL) was added dropwise over 40 min. The mixture was warmed up to −78 °C and stirred for 2 h, quenched with saturated aqueous $NaHCO_3$ solution (2 mL) at −78 °C, warmed up to rt, and evaporated. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/hexanes, 1:10–1:5) to give **10** (1.50 g, 75%) as colorless

crystals: mp 61–62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07–4.21 (br s, 1H), 5.22 (d, J=0.9 Hz, 1H), 5.25–5.50 (m, 2H), 5.88–5.99 (m, 1H), 7.52 (d, J=4.8 Hz, 1H), 8.40 (d, J=4.8 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.3, 116.9, 120.4, 122.5, 137.0, 148.3, 151.1, 151.4. MS (EI): 215, 213 (M^+). Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; N, 6.54. Found: C, 45.02; H, 3.57; N, 6.40.

4.1.2. 3-Bromo-4-(1-(methoxymethoxy)-2-propenyl)-pyridine (11). To a 100-mL three-necked flask equipped with two dropping funnels and a nitrogen gas inlet tube, were added 60% mineral oil dispersion of NaH (620 mg, 15.5 mmol) and anhydrous THF (50 mL). While the temperature of the suspension was maintained between 10–20 °C, a solution of **10** (2.20 g, 10.3 mmol) in THF (10 mL) was added dropwise over 10 min. Then a solution of MOMCl (1.02 mL, 13.4 mmol) in THF (15 mL) was added immediately over 10 min at 10–20 °C. The resultant mixture was stirred at rt for 3 h. Saturated aqueous $NaHCO_3$ (20 mL) was added carefully to the solution, and the mixture was concentrated to remove THF. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (Et_2O/petroleum ether, 10:1) to give **11** (2.44 g, 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (s, 3H), 4.55 (d, J=6.7 Hz, 1H), 4.70 (d, J=6.7 Hz, 1H), 5.20–5.37 (m, 3H), 5.70–5.78 (m, 1H), 7.40 (d, J=5.0 Hz, 1H), 8.45 (d, J=5.0 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.6, 75.8, 94.2, 118.1, 120.7, 122.6, 134.8, 148.4, 148.7, 151.8. MS (EI): 259, 257 (M^+). Anal. Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.72; H, 4.80; N, 5.60.

4.1.3. 4-(1-(Methoxymethoxy)-2-propenyl)-3-pyridinecarboxaldehyde (12). BuLi (1.6 M, 2.00 mL, 3.20 mmol) was added dropwise to a solution of **11** (686 mg, 2.66 mmol) in THF (25 mL) at −78 °C over 10 min. After 1 h, a solution of DMF (0.30 mL, 3.9 mmol) in THF (3 mL) was added at −78 °C over 10 min. The mixture was stirred at this temperature for 1 h, quenched with saturated aqueous $NaHCO_3$ solution at −78 °C, warmed up to rt, and evaporated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10–1:5) to afford **12** as a pale yellow oil (506 mg, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.34 (s, 3H), 4.63 (d, J=6.6 Hz, 1H), 4.79 (d, J=6.6 Hz, 1H), 5.22–5.42 (m, 2H), 5.86–5.98 (m, 2H), 7.64 (d, J=5.2 Hz, 1H), 8.80 (d, J=5.2 Hz, 1H), 9.01 (s, 1H), 10.31 (s, 1H). MS (EI): 207 (M^+).

4.1.4. (3a*R*,4*R,8b*S*)-4-(Methoxymethoxy)-1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyridine (13a) and (3a*S*,4*R**,8b*R*)-4-(methoxymethoxy)-1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyridine (13b).** A mixture of aldehyde **12** (1.21 g, 5.84 mmol) and sarcosine (546 mg, 6.13 mmol) in DMF (30 mL) was heated under N_2 at 100–110 °C for 6 h, cooled to rt, and evaporated. The residue was diluted with brine (10 mL) and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOH/CH_2Cl_2, 1:10) to give **13a/13b** mixture (1.15 g, 84%, **13a/13b**=1.37:1, as judged by ^{1}H NMR integrals of **13a/13b** mixture) as a pale yellow oil, which was suitable for use in the next step. Compound **13a**: R_f=0.23; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86–1.89 (m, 1H), 1.98–2.00 (m, 1H), 2.58–2.62 (m, 1H), 2.63 (s, 3H), 2.86–2.92 (m, 1H), 3.28–3.33 (m, 1H), 3.50 (s, 3H), 3.98 (d, J=7.8 Hz, 1H), 4.82–4.83 (m, 2H), 5.04 (d, J=8.1 Hz, 1H), 7.29–7.33 (m, 1H), 8.52–8.55 (m, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 41.8, 46.0, 55.8, 57.2, 71.6, 77.9, 96.4, 120.3, 138.1, 147.0, 148.8, 151.4. MS (EI): 235 (M^++H). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.87; N, 11.89. Compound **13b**: R_f=0.20; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88–1.96 (m, 1H), 2.23–2.27 (m, 1H), 2.50 (s, 3H), 2.52–2.58 (m, 1H), 3.03–3.11 (m, 2H), 3.46 (s, 3H), 3.87 (d, J=7.8 Hz, 1H), 4.81–4.87 (m, 2H), 5.07 (d, J=4.5 Hz, 1H), 7.33 (d, J=4.8 Hz, 1H), 8.57 (d, J=4.8 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 41.7, 45.8, 55.7, 57.1, 71.4, 77.8, 96.3, 120.2, 138.0, 146.8, 148.6, 151.3. MS (EI): 234 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.41; H, 7.80; N, 12.01.

4.1.5. *cis*-1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]-pyridine (2). MOM ethers **13a/13b** (270 mg, 1.15 mmol) was heated in 4 M HCl (4 mL) at 50–60 °C for 6 h, cooled to rt, neutralized with 50% NaOH, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was mixed with zinc powder (560 mg, 8.57 mmol) and formic acid (12.5 mL), refluxed for 25 h, and cooled to rt. The solid was filtered off and washed thoroughly with $CHCl_3$–IPA (3/1). The filtrate was concentrated under reduced pressure, the residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (petroleum ether/CH_2Cl_2/MeOH, 10:10:1) to give 169 mg (84%) of **2** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.74 (m, 1H), 2.15–2.25 (m, 1H), 2.44–2.55 (m, 1H), 2.55 (s, 3H), 2.77–2.86 (m, 1H), 2.99–3.21 (m, 3H), 3.80 (d, J=7.6 Hz, 1H), 7.13 (d, J=5.2 Hz, 1H), 8.42 (d, J=5.2 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.2, 39.2, 40.5, 41.9, 57.6, 73.4, 120.3, 139.2, 145.8, 148.3, 153.0. MS (EI): 174 (M^+). Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.69; H, 7.84; N, 16.38.

4.1.6. 3-Bromo-4-(1-(methoxymethoxy)-3-butenyl)pyridine (17). To a suspension of NaH (60% in mineral oil, 620 mg, 15.5 mmol) in dry THF (100 mL) under a nitrogen atmosphere, was added a solution of **16** (2.30 g, 10.1 mmol) in dry THF (20 mL). After the mixture was stirred at rt for 20 min, a solution of MOMCl (1.0 mL, 13 mmol) in dry THF (15 mL) was slowly added. The mixture was stirred at rt for 2 h, diluted with saturated aqueous $NaHCO_3$ solution, evaporated, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10) to give **17** (2.69 g, 98%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43–2.54 (m, 2H), 3.35 (s, 3H), 4.52 (d, J=6.6 Hz, 1H), 4.63 (d, J=6.9 Hz, 1H), 5.01 (dd, J=7.8, 4.4 Hz, 1H), 5.07 (t, J=1.1 Hz, 1H), 5.11 (d, J=4.8 Hz, 1H), 5.75–5.90 (m, 1H), 7.42 (d, J=4.8 Hz, 1H), 8.51 (d, J=5.1 Hz, 1H), 8.66

(s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 39.9, 55.6, 75.5, 94.9, 117.9, 120.5, 122.3, 133.1, 148.2, 149.8, 151.6. MS (EI) 272 (M^+, 25), 230 (36). Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.41; H, 5.17; N, 5.19.

4.1.7. 4-(1-(Methoxymethoxy)-3-butenyl)-3-pyridinecarboxaldehyde (18). A solution of *n*-BuLi (2.2 M, 4.4 mL, 9.7 mmol) in hexane was added dropwise to a solution of **17** (2.22 g, 8.16 mmol) in dry THF (80 mL) at −78 °C under a nitrogen atmosphere. After the mixture was stirred at −78 °C for 20 min, a solution of DMF (0.95 mL, 12 mmol) in dry THF (10 mL) was introduced. The mixture was stirred at −78 °C for 30 min, allowed to warm to rt, stirred at rt for 30 min, diluted with saturated aqueous $NaHCO_3$ solution, evaporated, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10) to give **18** (1.70 g, 94%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22–2.34 (m, 2H), 3.13 (s, 3H), 4.35 (dd, J=6.9, 1.5 Hz, 1H), 4.47 (dd, J=6.6, 1.2 Hz, 1H), 4.84–4.86 (m, 1H), 4.90 (t, J=1.2 Hz, 1H), 5.41 (dd, J=7.5, 4.8 Hz, 1H), 5.64–5.70 (m, 1H), 7.46 (d, J=5.1 Hz, 1H), 8.60 (dd, J=5.0, 1.4 Hz, 1H), 8.81 (s, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 41.2, 55.4, 72.9, 95.0, 117.7, 121.2, 127.8, 133.3, 153.0, 153.6, 154.3, 191.4. MS (EI) 180 (M−41, 22), 45 (100).

4.1.8. 2,3,3a,4,5,9b-Hexahydro-5-(methoxymethoxy)-1-methyl-1*H*-pyrrolo[3,2,-*h*]isoquinoline (19). A solution of **18** (534 mg, 2.41 mmol) and sarcosine (236 mg, 2.65 mmol) in DMF (15 mL) was heated at 125–130 °C under N_2 for 8 h, cooled to rt, and evaporated. The residue was diluted with brine and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (CH_3OH/EtOAc, 1:20) to give a pair of diastereomers **19** (505 mg, 84%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) diastereomers, 2.57:1, δ 1.53–1.66 (m, 1H), 1.70–1.82 (m, 0.28H), 1.88 (td, J=11.9, 11.7 Hz, 0.72H), 2.05–2.22 (m, 2H), 2.26 (s, 0.84H), 2.41 (dt, J=9.0, 9.0 Hz, 1H), 2.45 (s, 2.16), 2.49–2.56 (m, 0.72H), 2.67–2.70 (m, 0.28H), 3.04 (t, J=7.8 Hz, 0.28H), 3.06 (d, J=6.6 Hz, 1H), 3.24 (td, J=8.1, 3.0 Hz, 0.72H), 3.47 (s, 0.84H), 3.49 (s, 2.16H), 4.60 (dd, J=11.0, 5.3 Hz, 0.72H), 4.79 (d, J=6.0 Hz, 0.28H), 4.82 (t, J=6.5 Hz, 0.28H), 4.83 (d, J=6.3 Hz, 0.72H), 4.91 (d, J=6.0 Hz, 0.28H), 4.94 (d, J=6.0 Hz, 0.72H), 7.46 (d, J=4.8 Hz, 0.72H), 7.49 (d, J=5.1 Hz, 0.28H), 8.37 (s, 0.28H), 8.49 (s, 0.72H), 8.50 (d, J=5.1 Hz, 0.72H), 8.54 (d, J=5.1 Hz, 0.28H). MS (EI) 249 (M+1, 7), 248 (M^+, 0.6), 203 (91), 43 (100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.77; H, 7.81; N, 11.21.

The major product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.67 (m, 1H), 1.82–1.94 (m, 1H), 2.08–2.20 (m, 2H), 2.40–2.59 (m, 2H), 2.46 (s, 3H), 3.11 (d, J=5.4 Hz, 1H), 3.25 (td, J=9.0, 3.0 Hz, 1H), 3.48 (s, 3H), 4.61 (dd, J=11.0, 5.3 Hz, 1H), 4.81 (dd, J=6.9, 1.2 Hz, 1H), 4.94 (dd, J=6.8, 1.4 Hz, 1H), 7.47 (d, J=5.1 Hz, 1H), 8.47–8.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 29.4, 33.3, 36.4, 40.7, 55.3, 55.5, 62.9, 73.4, 95.3, 120.2, 130.4, 147.4, 148.1, 150.5.

The minor product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.65 (m, 1H), 1.73–1.86 (m, 1H), 2.10 (ddd, J=12.8, 4.1, 2.7 Hz, 1H), 2.17–2.29 (m, 2H), 2.29 (s, 3H), 2.72 (t, J=7.4 Hz, 1H), 3.11 (td, J=8.1, 8.0 Hz, 2H), 3.47 (s, 3H), 4.81 (t, J=3.9 Hz, 1H), 4.83 (dd, J=6.8, 1.7 Hz, 1H), 4.91 (dd, J=6.9, 1.8 Hz, 1H), 7.51 (d, J=4.8 Hz, 1H), 8.38 (s, 1H), 8.55 (d, J=5.1 Hz, 1H).

4.1.9. 2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[3,2,-*h*]-soquinoline (3). A mixture of the two isomers of **19** (399 mg, 1.61 mmol) and 6 M HCl (20 mL) was heated at 50–60 °C under N_2 for 8 h, cooled to rt, neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, and filtered. Evaporation of the volatiles gave the crude products of diastereomeric 2,3,3a,4,5,9b-hexahydro-5-hydroxy-1-methyl-1*H*-pyrrolo[3,2,-*h*]isoquinoline, which could be used directly for the next reaction.

A mixture of the above-mentioned crude alcohols and zinc power (816 mg, 12.5 mmol) in anhydrous formic acid (40 mL) was heated at reflux for 15 h under N_2, cooled to rt, and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (CH_3OH/EtOAc, 1:20) to give **3** (281 mg, 93% for two steps from **19**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.62 (m, 1H), 1.69–1.84 (m, 2H), 2.09–2.16 (m, 1H), 2.24–2.39 (m, 1H), 2.34 (s, 3H), 2.51–2.62 (m, 2H), 2.78–2.88 (m, 1H), 3.08–3.11 (m, 2H), 7.09 (dd, J=4.7, 2.0 Hz, 1H), 8.34 (d, J=2.7 Hz, 1H), 8.40 (dd, J=5.0, 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.1, 28.9, 29.7, 36.0, 40.3, 55.6, 64.4, 123.4, 132.1, 148.0, 149.4, 150.2. MS (EI) 188 (M^+, 68), 187 (100). Anal. Calcd for $C_{12}H_{16}N_2\cdot 2HCl\cdot 1/3H_2O$ (the HCl salt of **3**): C, 53.94; H, 7.04; N, 10.48. Found: C, 54.04; H, 7.22; N, 10.44.

4.1.10. 4-Chloro-3-(1,3-dioxolan-2-yl)pyridine (21). A mixture of **20** (270 mg, 1.91 mmol), ethylene glycol (0.55 mL, 9.9 mmol) and the *p*-toluenesulfonic acid monohydrate (328 mg, 1.72 mmol) in benzene (30 mL) was boiled for 3 h, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:5) to give **21** (307 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00–4.13 (m, 2H), 4.14–4.25 (m, 2H), 6.17 (s, 1H), 7.33 (d, J=5.4 Hz, 1H), 8.50 (d, J=5.1 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 65.6, 99.9, 124.6, 131.1, 143.5, 149.3, 151.0. MS (EI) 184 (M−1). Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.81; H, 4.24; N, 7.43.

4.1.11. 4-(Allyloxy)-3-(1,3-dioxolan-2-yl)pyridine (22). A mixture of **21** (88 mg, 0.47 mmol), allyl alcohol (0.50 mL, 7.4 mmol) and KOH (819 mg, 14.6 mmol) in THF (20 mL) was heated at reflux for 6 h, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **22** (90 mg,

92%) as a colorless solid: mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.99–4.10 (m, 2H), 4.10–4.21 (m, 2H), 4.66 (d, J=5.4 Hz, 2H), 5.33 (dd, J=10.5, 1.2 Hz, 1H), 5.43 (dd, J=17.7, 1.2 Hz, 1H), 5.99–6.03 (m, 1H), 6.20 (s, 1H), 6.79 (d, J=5.7 Hz, 1H), 8.47 (d, J=6.0 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 65.4, 68.8, 98.8, 107.2, 118.4, 122.1, 131.8, 148.8, 152.0, 162.8. MS (EI) 206 (M−1). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.31; N, 6.69.

4.1.12. 4-(Allyloxy)nicotinaldehyde (23). A mixture of **22** (180 mg, 0.869 mmol) and oxalic acid dihydrate (547 mg, 4.34 mmol) in acetone and water (1:1, 40 mL) was heated at reflux overnight, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **23** (123 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.70 (d, J=5.0 Hz, 2H), 5.36 (dd, J=10.5, 1.2 Hz, 1H), 5.44 (dd, J=17.1, 1.2 Hz, 1H), 5.96–6.09 (m, 1H), 6.88 (d, J=6.0 Hz, 1H), 8.57 (dd, J=6.0, 1.5 Hz, 1H), 8.85 (s, 1H), 10.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 69.2, 108.1, 119.1, 120.5, 130.9, 150.7, 155.8, 165.7, 188.6; MS (EI) 162 (M−1). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.86; H, 5.56; N, 8.40.

4.1.13. 2,3,3a,4,5,9b-Hexahydro-1-methyl-5-oxa-1*H*-pyrrolo[3,2,-*h*]isoquinoline (4). A solution of **23** (156 mg, 0.956 mmol) and sarcosine (94.0 mg, 1.06 mmol) in DMF (15 mL) was heated at 100–110 °C under N_2 for 8 h, cooled to rt, and evaporated. The residue was diluted with brine and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **4** (131 mg, 72%) as a pale oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41–1.46 (m, 1H), 2.08–2.13 (m, 1H), 2.30–2.46 (m, 2H), 2.44 (s, 3H), 2.94 (d, J=5.1 Hz, 1H), 3.13 (td, J=9.0, 2.1 Hz, 1H), 3.92 (dd, J=11.4, 10.8 Hz, 1H), 4.12 (dd, J=10.8, 5.4 Hz, 1H), 6.80 (d, J=5.4 Hz, 1H), 8.30 (d, J=5.4 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 24.5, 34.0, 39.4, 54.5, 60.1, 67.6, 112.3, 117.6, 149.8, 152.7, 161.6. MS (EI) 189 (M−1). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.30; H, 7.42; N, 14.82.

4.1.14. 4-(Allylthio)nicotinaldehyde (24). A solution of allyl bromide (0.24 mL, 2.8 mmol) and thiourea (210 mg, 2.76 mmol) in absolute ethanol (20 mL) was refluxed for 1 h. After NaOH (220 mg, 5.50 mmol) was added, the reaction mixture was refluxed for another 1 h and cooled to 0 °C. After compound **20** (260 mg, 1.84 mmol) was introduced to the system, the mixture was stirred at 0 °C for 1 h, diluted with cold water, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:5) to give **24** (251 mg, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (dd, J=5.4, 1.2 Hz, 2H), 5.29 (dd, J=9.9, 1.2 Hz, 1H), 5.42 (dd, J=17.1, 1.2 Hz, 1H), 5.88–5.95 (m, 1H), 7.29 (d, J=5.4 Hz, 1H), 8.53 (dd, J=5.7, 1.2 Hz, 1H), 8.85 (s, 1H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 33.9, 119.5, 119.8, 128.0, 131.0, 152.2, 153.0, 155.0, 190.3. MS (EI) 179 (M^+). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.41; H, 5.28; N, 7.88.

4.1.15. 2,3,3a,4,5,9b-Hexahydro-1-methyl-5-thia-1*H*-pyrrolo[3,2,-*h*]isoquinoline (5). A solution of **24** (136 mg, 0.759 mmol) and sarcosine (74 mg, 0.83 mmol) in DMF (15 mL) was heated at 125–130 °C under N_2 for 8 h, cooled to rt, evaporated, diluted with brine, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **5** (143 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90–1.94 (m, 1H), 2.14–2.17 (m, 1H), 2.31 (s, 3H), 2.31–2.36 (m, 1H), 2.74 (d, J=9.9 Hz, 2H), 2.92–2.99 (m, 1H), 3.12–3.19 (m, 2H), 7.18 (d, J=5.1 Hz, 1H), 8.25 (s, 1H), 8.26 (d, J=5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 28.8, 32.0, 37.7, 40.1, 54.5, 63.9, 122.9, 129.0, 147.3, 147.5, 151.7. MS (EI) 206 (M^+). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.74; H, 7.17; N, 13.97.

Acknowledgements

We thank NSFC (No. 20372073), STCSM ('Post-Venus' Program, No. 05QMH1416), GCCP of ECNU, and Ministry of Human Resources of PRC for financial support.

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