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Synthesis of Phantasmidine†

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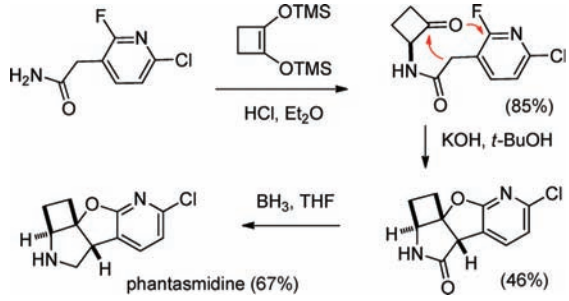
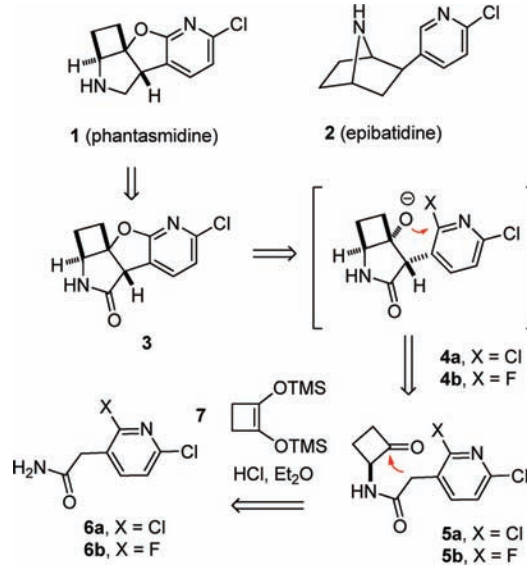
ABSTRACT



Reaction of 6-chloro-2-fluoro-3-pyridineacetamide with 1,2-bis(trimethylsilyloxy)cyclobutene in ether saturated with hydrogen chloride afforded the keto amide in 85% yield. In the key step, treatment of the keto amide with aqueous KOH in *t*-BuOH resulted in a tandem intramolecular aldol reaction−intramolecular nucleophilic aromatic substitution sequence to give the tetracylic lactam in 46% yield. Reduction of the lactam with BH_3 in THF gave phantasmidine in 67% yield.

The biological properties[1] and chemical synthesis[2] of the potent nicotinic agonist epibatidine (**2**) (see Scheme 1) have been intensively studied since it was isolated from the skin of the Ecuadorian poison frog *Epipedobates anthonyi* and characterized in 1992 by Daly and co-workers. Fitch, Daly, and co-workers recently isolated phantasmidine (**1**), a rigid tetracyclic congener of epibatidine from the same source.[3] The structure of phantasmidine was tentatively assigned from a combination of GC-MS and GC-FTIR analysis with on-column derivatization and 1D and 2D NMR spectroscopy of HPLC-purified **1** and its acetamide with a total sample of only ~20 μg. Preliminary biological studies with the limited material available indicated that phantasmidine (**1**) differs from epibatidine (**2**) by being selective for β4-containing

Scheme 1. Retrosynthesis of Phantasmidine (**1**)



† Dedicated to the late Dr. John W. Daly of NIDKK, NIH, Bethesda, Maryland for his pioneering work on biologically active natural products.

(1) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Decker, M. W.; Sullivan, J. P.; Williams, M. *Nat. Prod. Rep.* **2000**, *17*, 131–135. (b) Carroll, F. I. *Biorg. Med. Chem. Lett.* **2004**, *14*, 1889–1896. (c) Daly, J. W. *Cell. Mol. Neurobiol.* **2005**, *25*, 513–552. (d) Garraffo, H. M.; Spande, T. F.; Williams, M. *Heterocycles* **2009**, *79*, 207–218.

(2) Olivio, H. F.; Hemenway, M. S. *Org. Prep. Proc. Int.* **2002**, *34*, 1–26, and references cited therein.

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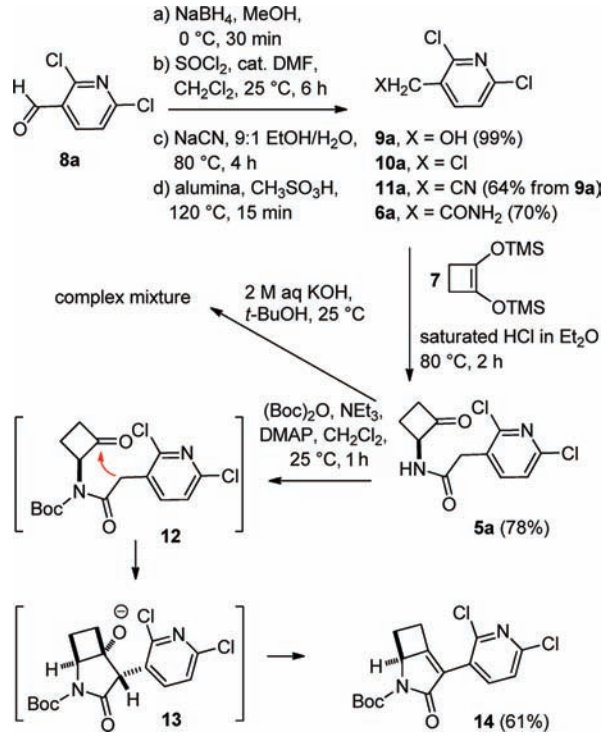
nicotinic receptors suggesting that phantasmidine might fill a niche for characterization of these receptors. However, the limited natural material available precluded detailed pharmacological analysis and definitive structure determination. We therefore undertook the synthesis of phantasmidine (**1**).

We thought that phantasmidine (**1**) should be readily available by reduction of lactam **3**. In the key step of the proposed synthesis we planned to prepare lactam **3** from keto amide **5** by a novel tandem intramolecular aldol reaction−intramolecular nucleophilic aromatic substitution sequence. Addition of the amide enolate of **5** to the cyclobutanone carbonyl group should provide alkoxide **4**, which should undergo a nucleophilic aromatic substitution reaction[4] at the activated 2-halopyridine to form the furan ring of **3**. Although two stereoisomeric aldol products can be formed, the alkoxide can displace the halide only in **4**. The aldol reaction is reversible so the two isomers should be in equilibrium with the reaction driven to completion by the cyclization of the desired stereoisomer **4** to give lactam **3**. Keto amide **5** should be readily available by the reaction of primary amide **6** with 1,2-bis(trimethylsilyloxy)cyclobutene (**7**), the readily available acyloin formed from succinate esters, in ether saturated with hydrogen chloride by the literature procedure.[5] We chose to start with the more readily available, but less reactive, dichloroamide **6a**. Schlosser has shown that nucleophilic substitution of a 2-fluoropyridine is ∼320 times faster than substitution of a 2-chloropyridine.[6] The use of fluorochloroamide **6b** therefore offered an attractive alternative if nucleophilic aromatic substitution of dichloropyridine **4a** to form the furan ring of **3** failed.

Commercially available 2,6-dichloropyridine-3-carboxaldehyde (**8a**)[7] was reduced with $NaBH_4$ in MeOH at 0 °C for 30 min to give primary alcohol **9a**[8] in 99% yield (see Scheme 2). Reaction with thionyl chloride and catalytic DMF in CH_2Cl_2 at 25 °C for 6 h gave chloride **10a**,[9] which was treated with NaCN in aqueous EtOH at reflux for 4 h to give nitrile **11a**[9] in 64% yield from alcohol **9a**. Hydrolysis[10] of nitrile **11a** with methanesulfonic acid and alumina at 120 °C for 15 min afforded the requisite dichloroamide **6a** in 70% yield. Reaction of primary amide **6a** with 1,2-bis(trimethylsilyloxy)cyclobutene (**7**) in ether saturated with hydrogen chloride in a sealed tube at 80 °C for 2 h afforded cyclobutanone amide **5a** in 78% yield.[5]

Scheme 2. Unsuccessful Route to (±)-Phantasmidine (**1**)



Unfortunately all attempts to convert keto amide **5a** to tetracyclic lactam **3** were unsuccessful. For instance, treatment of **5a** with aqueous potassium hydroxide in *t*-BuOH gave a complex mixture of products. Based on limited literature precedent,[11] we thought that acylation of the amide would not only remove the acidic NH proton, but would also facilitate enolization and the intramolecular aldol reaction because the α-protons of an imide are more acidic than those of an amide. Treatment of **5a** with $(Boc)_2O$, NEt_3, and DMAP in CH_2Cl_2 at 25 °C acylated the amide to give imide **12**, which underwent the desired aldol reaction to give alkoxide **13**. Unfortunately, nucleophilic aromatic substitution with displacement of the chloride was sufficiently slow so that only the unstable α,β-unsaturated lactam **14** resulting from dehydration of the aldol product was isolated in 61% yield. Since we were unable to form the furan ring of phantasmidine from dichloropyridine **5a**, we turned our attention to the preparation of the more reactive chlorofluoropyridine **5b**.

Metalation of 2-choro-6-fluoropyridine (**15**) adjacent to the fluoride with LDA in THF at −78 °C by the literature

(4) An intramolecular nucleophilic aromatic substitution to form a furan was achieved by heating 2,6-dichloro-3-(2-hydroxyphenyl)pyridine with potassium carbonate in acetonitrile at reflux for 5 h to give the benzofuropyridine in 70% yield. See: Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261–3269.

(5) (a) Bisel, P.; Breitling, E.; Frahm, W. *Eur. J. Org. Chem.* **1998**, 729–733. (b) Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536–1547. (c) Armoush, N.; Syal, P.; Becker, D. P. *Synth. Commun.* **2008**, *38*, 1679–1687.

(6) Schlosser, M.; Rausis, T. *Helv. Chim. Acta* **2005**, *88*, 1240–1249.

(7) Aldehyde **8a** can be easily prepared by metalation of 2,6-dichloropyridine with LDA at the 3-position and addition of DMF. See: Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793–4796.

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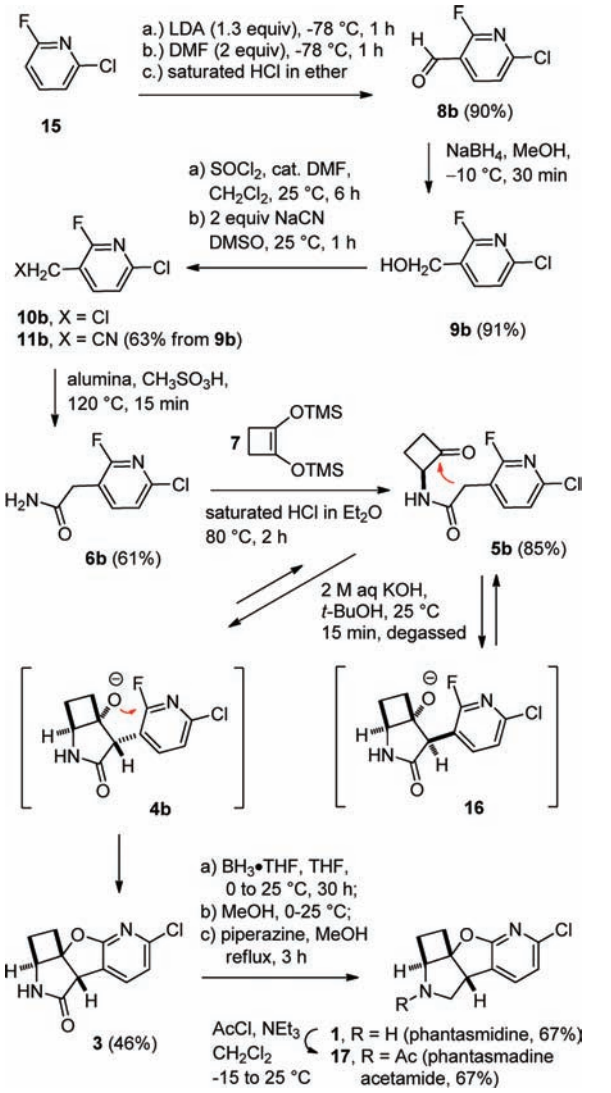
Scheme 3. Synthesis of (±)-Phantasmidine (**1**)



procedure[12] and trapping with DMF afforded the known aldehyde **8b**[12a] in 90% yield (Scheme 3). The 2-fluoropyridine is very sensitive to nucleophilic attack by the $LiNMe_2$ formed by addition of the carbanion to DMF, so the reaction was quenched by addition of saturated hydrogen chloride in ether at −78 °C.[13] Reduction of the aldehyde of **8b** with $NaBH_4$ in MeOH at −10 °C gave alcohol **9b** in 90% yield. Conversion of the alcohol to the chloride with thionyl chloride and catalytic DMF in CH_2Cl_2 proceeded uneventfully to give **10b** because the reaction conditions are acidic. Substitution of the benzylic chloride without hydrolysis of the 2-fluoropyridine was best accomplished by reaction with sodium cyanide in DMSO at 25 °C for 1 h to give nitrile **11b** in 63% yield from alcohol **9b**. Hydrolysis of the nitrile to the amide with methanesulfonic acid and alumina at 120 °C for 15 min afforded fluorochloroamide **6b** in 61% yield, which was converted to keto amide **5b** in 85% yield by reaction with **7** in ether saturated with hydrogen chloride for 2 h at 80 °C in a sealed tube. The sensitivity of the 2-fluoropyridine to nucleophilic attack was not an issue in the last two reactions that were run under acidic conditions.

Fortunately, the increased reactivity of the fluoride of keto amide **5b** was sufficient to facilitate formation of the furan ring of lactam **3**. Treatment of a degassed solution of **5b** in *t*-BuOH with degassed 2 M aqueous KOH resulted in aldol cyclization to give alkoxide **4b**, which underwent the desired nucleophilic aromatic substitution reaction to form furan **3** in 46% yield. The yields were slightly lower if the solution was not carefully degassed, suggesting that the enolate is susceptible to autoxidation. The structure of **3** was readily assigned by analysis of the NMR spectra and was confirmed by X-ray crystal structure determination. No other products were isolated. This suggests that either the aldol reaction to give **4b** is stereospecific or, more likely, the aldol reaction is reversible and the undesired stereoisomer **16** reverts to **5b** which then recyclizes to give **4b** and then **3**.

Reduction of lactam **3** with borane in THF afforded the borane complex of phantasmidine which was decomplexed[14] by treatment with piperazine to give phantasmidine (**1**) in 67% yield. Reduction of lactam **3** with alane (LAH and $AlCl_3$)[15] was less successful affording phantasmidine (**1**) in 20−30% yield. Addition of 1 equiv of TFA to a CD_3OD solution of phantasmidine afforded the monocation, whose ^1H NMR spectrum is identical to that reported for natural phantasmidine•DCl.[3] Pyrrolidine **1** was treated with AcCl and NEt_3 in CH_2Cl_2 at −15 to 25 °C to give acetamide **17** in 67% yield. The ^1H and ^{13}C NMR spectra of **17** (mixture of rotamers) are identical to those reported for the acetamide of phantasmidine.[3] The GC retention times of synthetic and natural phantasmidine are identical as are the mass spectra of synthetic and natural phantasmidine and phantasmidine acetamide. Therefore the synthesis of **1** validates the structure of phantasmidine assigned from the incomplete data obtained from the very limited amount (∼20 μg) of natural material available.[3]

This synthesis leads to racemic phantasmidine. The coupling of **6b** and **7** affords racemic keto amide **5b**. However, even if we were able to prepare **5b** in enantiomerically pure form, it would likely be racemized under the very basic conditions of the tandem intramolecular aldol reaction−intramolecular nucleophilic aromatic substitution sequence. We therefore investigated the resolution of phantasmidine and found that the two enantiomers are very readily separated by chiral HPLC on a Chiralcel OJ-H column with retention times of 27 and 40 min. This facile separation makes both enantiomers readily available for full biological investigation.

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In conclusion, we have developed a short, efficient synthesis (8 steps, 8% overall yield) of (±)-phantasmidine that confirms the structure assigned from the incomplete data obtained from the very limited amount (~20 μg) of natural material available. This synthesis makes material readily available for further biological evaluation, which is currently in progress. The key step, a novel tandem intramolecular aldol reaction−intramolecular nucleophilic aromatic substitution that converts keto amide **5b** with aqueous KOH in *t*-BuOH to tetracylic lactam **3**, should be broadly useful for making phantasmidine analogues.

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Supporting Information Available: Complete experimental procedures, copies of ^{1}H NMR, ^{13}C NMR, and CD spectral data, and CIF file and drawing of X-ray crystal structure of lactam **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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