Published in final edited form as:

Org Lett. 2011 February 4; 13(3): 526–529. doi:10.1021/ol102929m.

Synthesis of Phantasmidine†

Quan Zhou and Barry B. Snider*

Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

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 tetracyclic lactam in 46% yield. Reduction of the lactam with BH₃ in THF gave phantasmidine in 67% yield.

The biological properties¹ and chemical synthesis² 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 coworkers. Fitch, Daly, and coworkers 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 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

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

snider@brandeis.edu.

Supporting Information Available: Complete experimental procedures, copies of ¹H NMR, ¹³C 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>.

reaction⁴ 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, dichloro amide **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 fluoro chloro amide **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 NaBH₄ in MeOH at 0 °C for 30 minutes to give primary alcohol **9a** in 99% yield (see Scheme 2). Reaction with thionyl chloride and catalytic DMF in CH₂Cl₂ at 25 °C for 6 hours gave chloride **10a**⁹ which was treated with NaCN in aqueous EtOH at reflux for 4 hours to give nitrile **11a**⁹ in 64% yield from alcohol **9a**. Hydrolysis¹⁰ of nitrile **11a** with methanesulfonic acid and alumina at 120 °C for 15 minutes afforded the requisite dichloro amide **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

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, NEt₃, and DMAP in CH₂Cl₂ 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-chloro-6-fluoropyridine (**15**) adjacent to the fluoride with LDA in THF at -78 °C by the literature procedure¹² and trapping with DMF afforded the known aldehyde **8b**^{12a} in 90% yield (see Scheme 3). The 2-fluoropyridine is very sensitive to nucleophilic attack by the LiNMe₂ 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 NaBH₄ 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 CH₂Cl₂ 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 hour 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 minutes afforded fluoro chloro amide **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 recycles to give **4b** and then **3**.

Reduction of lactam **3** with borane in THF afforded the borane complex of phantasmidine which was decomplexed¹⁴ by treatment with piperazine to give phantasmidine (**1**) in 67% yield. Reduction of lactam **3** with alane (LAH and AlCl₃)¹⁵ was less successful affording phantasmidine (**1**) in 20–30% yield. Addition of 1 equivalent of TFA to a CD₃OD solution of phantasmidine afforded the monocation, whose ¹H NMR spectrum is identical to that reported for natural phantasmidine•DCI.³ Pyrrolidine **1** was treated with AcCl and NEt₃ in CH₂Cl₂ at –15 to 25 °C to give acetamide **17** in 67% yield. The ¹H and ¹³C 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 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 minutes. This facile separation makes both enantiomers readily available for full biological investigation.

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 tetracyclic lactam **3**, should be broadly useful for making phantasmidine analogues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank the National Science Foundation for partial support of this work through grant CHE-0521047 for the purchase of a new X-ray diffractometer. We thank Mr. Brian A. Provencher, Brandeis University, for assistance with the resolution of phantasmidine. We thank Doctors H. Martin Garraffo and Thomas F. Spande, National Institute of Diabetes, Digestive and Kidney Diseases, for comparing the GC retention times of synthetic and natural phantasmidine.

References

1. (a) Daly JW, Garraffo HM, Spande TF, Decker MW, Sullivan JP, Williams M. *Nat Prod Rep.* 2000; 17:131–135. [PubMed: 10821107] (b) Carroll FI. *Bioorg Med Chem Lett.* 2004; 14:1889–1896. (c) Daly JW. *Cell Mol Neurobiol.* 2005; 25:513–552. [PubMed: 16075378] (d) Garraffo HM, Spande TF, Williams M. *Heterocycles.* 2009; 79:207–218.
2. Olivio HF, Hemenway MS. *Org Prep Proc Int.* 2002; 34:1–26. and references cited therein.
3. Fitch RW, Spande TF, Garraffo HM, Yeh HJC, Daly JW. *J Nat Prod.* 2010; 73:331–337. [PubMed: 20337496]
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 hours to give the benzofuopyridine 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 MS, Ramtohl YK, James MNG, Vederas JC. *J Org Chem.* 2002; 67:1536–1547. [PubMed: 11871884] (c) Armoush N, Syal P, Becker DP. *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.
8. (a) Newkome GR, Lee HW. *J Org Chem.* 1982; 47:2800–2802. (b) Leonard K, Marugan JJ, Raboisson P, Calvo R, Gushue JM, Koblish HK, Lattanze J, Zhao S, Cummings MD, Player MR, Maroney AC, Lu T. *Bioorg Med Chem Lett.* 2006; 16:3463–3468. [PubMed: 16647257]
9. (a) Horn U, Mutterer F, Weis CD. *Helv Chim Acta.* 1976; 59:190–211. (b) Lieb, F.; Hagemann, H.; Widdig, A.; Ruther, M.; Fischer, R.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U.; Graff, A.; Dahmen, P.; Dollinger, M.; Gallenkamp, B. *Ger Pat. DE 19651841.* 1997. *Chem Abstr.* 1997; 128:22816. (c) Bailly, J.; Hertel, C.; Hunziker, D.; Lerner, C.; Obst Sander, U.; Peters, J-U.; Pflieger, P.; Schulz-Gasch, T. *PCT Int Appl WO 2009040288.* 2009. p. A1Chem Abstr. 2009; 150:374301. (d) Cordingley, MR.; Turnbull, MD.; Carter, NB.; Crowley, PJ. *PCT Int Appl WO 2009090402.* 2009. p. A2Chem Abstr. 2009; 151:165630.
10. Sharghi H, Sarvari MH. *Synth Commun.* 2003; 33:207–212.
11. (a) Jacobi PA, DeSimone RW, Ghosh I, Guo, Leung SH, Pippin D. *J Org Chem.* 2000; 65:8478–8489. [PubMed: 11112567] (b) Miyazaki H, Ogiku T, Sai H, Moritani Y, Ohtani A, Ohmizu H. *Chem Pharm Bull.* 2009; 57:979–985. [PubMed: 19721260]
12. (a) Altman, M.; Christopher, M.; Grimm, JB.; Haidle, A.; Konrad, K.; Lim, J.; Maccoss, RN.; Machacek, M.; Osimboni, E.; Otte, RD.; Siu, T.; Spencer, K.; Taoka, B.; Tempest, P.; Wilson, K.; Woo, HC.; Young, J.; Zabierek, A. *PCT Int Appl. WO 2008156726.* 2008. *Chem Abstr.* 2008; 150:77500. (b) Beutner GL, Kuethe JT, Kim MM, Yasuda N. *J Org Chem.* 2009; 74:789–794. [PubMed: 19067568]
13. Schlosser M, Rausis T. *Eur J Org Chem.* 2004:1018–1024.
14. (a) Brown HC, Choi YM, Narasimhan S. *J Org Chem.* 1982; 47:3153–3163. (b) Couturier M, Tucker JL, Andresen BM, Dube P, Negri JL. *Org Lett.* 2001; 3:465–467. [PubMed: 11428040]
15. Yoon NM, Brown HC. *J Am Chem Soc.* 1968; 90:2927–2938.

Scheme 1.
Retrosynthesis of Phantasmidine (1)

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

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