Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 7099-7102, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01583-3

Facile Synthesis of 6-Hydroxyindole-3-acetic Acid: On the Structure of the Aromatic Subunit of Nephilatoxin-1~6

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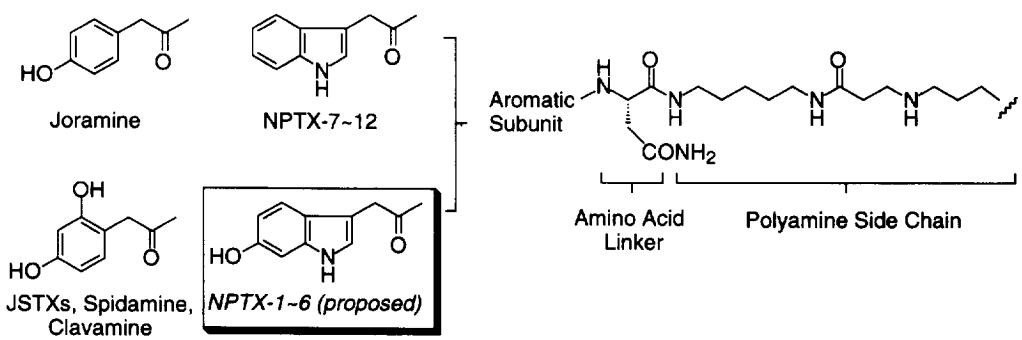
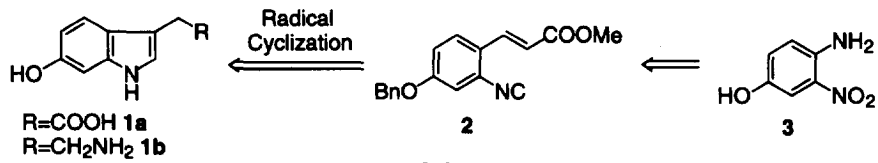
Abstract: A facile synthesis of 6-hydroxyindole-3-acetic acid **1a**, which is the proposed aromatic subunit of NPTX-1~6, is described. Radical cyclization of isonitrile **2** successfully afforded **9** in high yield. The aromatic subunit of NPTX-1~6 was confirmed as 4-hydroxyindole-3-acetic acid **12** by comparison of the ^{1}H-NMR spectra with those of authentic 4- and 6-hydroxyindole-3-acetic acids.

Polyamine toxins isolated from *Nephila clavata* (joro gumo) have attracted considerable attention with their intriguing pharmacological actions on vertebrate and invertebrate excitable transmitter receptors, and the mast cell degranulation.[1] These toxins consist of an aromatic subunit, an amino acid linker, and a polyamine side chain, which are linked in sequence as shown in Scheme 1, and are classified into four groups on the basis of the variety of aromatic subunits.[2] Among them, the structures of JSTXs, clavamine, and NPTX-7~12 have been confirmed by the total syntheses.[3] In contrast to the extensive synthetic efforts along these lines, there are no examples of synthesis of NPTX-1~6. Therefore, the structures of NPTX-1~6 have not been confirmed yet. It is considered that the lack of efficient methods for synthesis of 6-hydroxyindole-3-acetic acid (6-OHIA),[4,5] which was proposed as the aromatic subunit of NPTX-1~6, has impeded this study. In this paper, we report a facile synthesis of **1a** and 6-hydroxytryptamine **1b** *via* the Fukuyama indole synthesis[6] as the key step (Scheme 2), and structure elucidation of the aromatic subunit of NPTX-1~6.

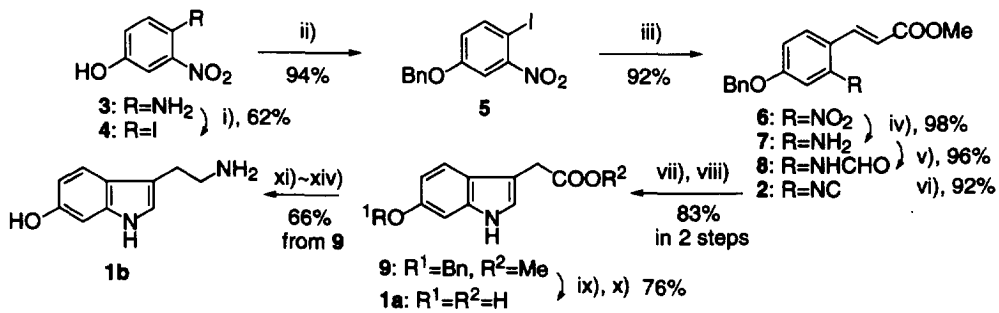


Scheme 1



Scheme 2

The key to making this route effective and practical included the preparation of 2,5-disubstituted isonitrile **2** used for the radical cyclization. We envisaged the conversion of commercially available 5-hydroxy-2-amino-1-nitroaniline **3** into **2** by selective and mild aromatic substitution reactions. Diazotization of **3** and the subsequent treatment with potassium iodide gave iodophenol **4** which was protected with a benzyl group to afford **5**. The Heck reaction of **5** with methyl acrylate proceeded smoothly to give methyl nitrocinnamate **6** in high yield. Chemoselective reduction of the nitro group was successfully achieved by treatment of **6** with zinc in acetic acid to give **7**. The isonitrile **2** was accessible by formylation of **7** and dehydration of the resulting **8** with triphosgene in the presence of triethylamine. The radical cyclization of **2** with tributyltin hydride followed by treatment with dilute hydrochloric acid provided ester **9**, which was subjected to the following sequence of reactions: i) hydrolysis and debenzylation to give 6-OHIA **1a**, ii) reduction, azidation via mesylate, and reduction to give 6-hydroxytryptamine **1b**[7].



Conditions: i) $NaNO_2$, HCl, then KI; ii) BnBr, K_2CO_3, acetone, Δ; iii) methyl acrylate, $Pd(OAc)_2$, $(Tol)_3P$ Et_3N, MeCN, Δ; iv) Zn, AcOH; v) AcOCHO, Py, CH_2Cl_2; vi) triphosgene, Et_3N, CH_2Cl_2; vii) Bu_3SnH, AIBN, MeCN, Δ, viii) dil. HCl, 0°C; ix) NaOH, H_2O-THF; x) H_2, 10%Pd-C, MeOH; xi) DIBAL, CH_2Cl_2, -78°C, xii) MsCl, Py, CH_2Cl_2, 0°C; xiii) NaN_3, DMF; xiv) H_2, 10%Pd-C, MeOH.

Scheme 3

We next compared the structure of the aromatic subunit of NPTX-1~6 with the authentic 6-OHIA **1a**. A crude mixture of polyamine toxins was extracted from seven venoms of *Nephila clavata* and subjected to hydrolysis to isolate the hydroxyindole subunit as a hydroxyindole-3-acetic acid.[2] A comparison of ^{1}H-NMR spectra of the hydroxyindoleacetic acid revealed that the chemical shift values and proton spin systems of the aromatic protons differed from those of 6-OHIA **1a**, but were in agreement with those of CNS 2103[3e] having 4-OHIA **12** as the aromatic subunit (Fig. 1). In order to confirm the aromatic subunit of NPTX-1~6, 4-OHIA **12** was prepared from 4-hydroxyindole **10** in a similar manner to the reported method[8] (Scheme 4). The ^{1}H-NMR spectrum of the aromatic subunit of NPTX-1~6 was identical with that of the authentic 4-OHIA **12**.

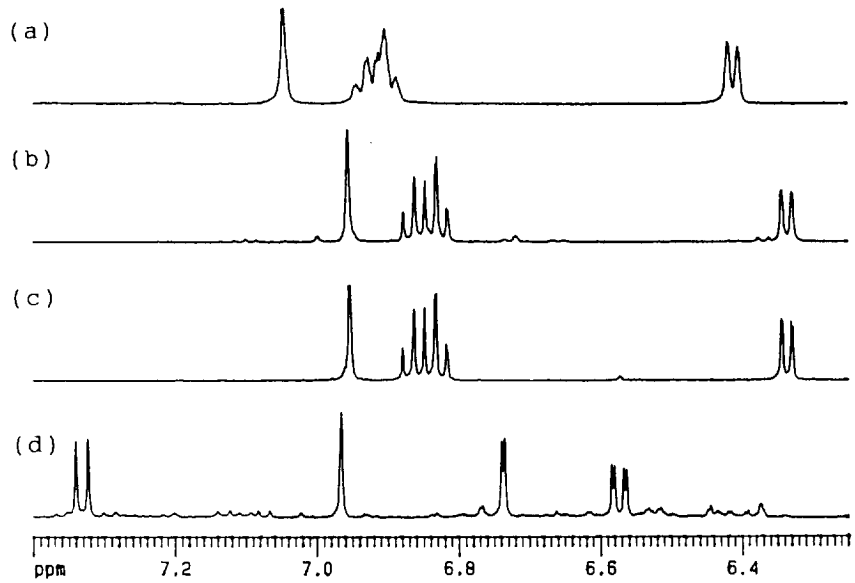
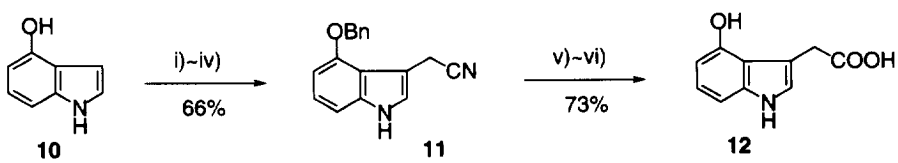


Figure 1. ^{1}H-NMR spectra [500 MHz, CD_3OD, δ in ppm] of the aromatic protons of (a) A crude mixture of NPTX-1~6, (b) hydroxyindole-3-acetic acid (from hydrolysis of NPTX-1~6), (c) 4-OHIA **12** (authentic sample), and (d) 6-OHIA **1** (authentic sample).



Conditions: i) BnBr, K_2CO_3, acetone, Δ; ii) 50% Me_2NH, 37%HCHO, AcOH, MeOH; iii) MeI; iV) NaCN, H_2O, Δ; v) KOH, H_2O, Δ; vi) 10% Pd-C, MeOH.

Scheme 4

In conclusion, a facile synthesis of 6-OHIA **1a** and 6-hydroxytryptamine **1b** was achieved. The aromatic subunit of NPTX-1~6 has been revised as shown in Fig. 2 through ^{1}H-NMR studies of the authentic 4- and 6-OHIAs. 6-Hydroxyindole derivatives **1a** and **1b** appear promising as potential synthons for pharmacologically important indole alkaloids[9] represented by reserpine, harmaline, and vindoline.

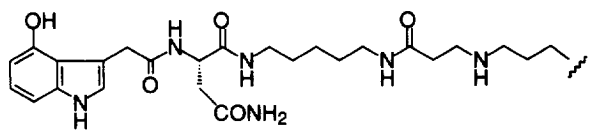


Figure 2

Acknowledgments: We are grateful to Dr. T. Toki for his helpful discussion. We thank Dr. K. Saito and Mrs. C. Matsuda for their assistance with NMR measurments.

REFERENCES AND NOTES

1. For reviews; (a) Kawai, N.; Nakajima, T. *Natural and Synthetic Toxins, Chapter 9, Neurotoxins from Spider Venoms*; Harvey, A. L. Ed. Academic Press, Inc.: London, 1993, pp 319-345. (b) Usherwood, P. N. R.; Blagbrough, I. S. *Pharmac. Ther.*, **1991**, *52*, 245-268. (c) McCormick K. D.; Meinwald, J. *J. Chem. Ecology* **1993**, *19*, 2411-2442. (d) Schafer, A.; Benz, H.; Fiedler, W.; Guggisberg, A.; Bienz, S.; Hesse, M. *The Alkaloids, Chemistry and Pharmacology, Vol 45: Polyamine Toxins from Spiders and Wasps*; Academic Press, Inc.: Boston, 1994, pp1-125.
2. JSTXs: (a) Aramaki, Y.; Yasuhara, T.; Higashijima, T.; Yoshioka, M.; Miwa, A.; Kawai, N.; Nakajima, T. *Proc. Jpn. Acad.* **1986**, *62B*, 359-362. (b) Aramaki, Y.; Yasuhara, T.; Shimazaki, K.; Kawai, N.; Nakajima, T. *Biomed. Res.* **1987**, *8*, 241-245. NPTXs: (a) Toki, T.;Yasuhara, T.; Aramaki, Y.; Kawai, N.; Nakajima, T. *Biomed. Res.* **1988**, *9*, 75-79. (b) Toki, T.; Yasuhara, T.; Aramaki, Y.; Osawa, K.; Miwa, A.; Kawai, N.; Nakajima, N. *Biomed. Res.* **1988**, *9*, 421-428. Clavamine: Yoshioka, M.; Narai, N.; Kawai, N.; Numata, M.; Nakajima, T. *Biogenic Amines* **1990**, *7*, 375-384. Joramine and Spidamine: Chiba, T.; Akizawa, T.; Matsukawa, M.; Pan-Hou, H.; Kawai, N.; Yoshioka, M. *Chem. Pharm. Bull.* **1995**, *43*, 2177-2181.
3. Recent progress on synthetic studies of polyamine toxins; (a) Blagbrough, I. S.; Moya, E. *Tetrahedron Lett.* **1995**. *36*, 9393-9396. (b) Ashton, M. R.; Moya, E.; Blagbrough, I. S. *Tetrahedron Lett.* **1995**, *36*, 9397-9400. (c) Matsushita, M.; Kanemura, T.; Hatakeyama, S.; Irie, H.; Toki, T.; Miyashita, M. *Tetrahedron* **1995**, *51*, 10687-10698. (d) Bycroft, B. W.; Chan, W. C.; Hone, N. D.; Millington, H. S.; Nash, I. A. *J. Am. Chem. Soc.* **1994**, *116*, 7415-7416. (e) McCormick, K. D.; Kobayashi, K.; Goldin, S. M.; Reddy, N. L.; Meinwald, J. *Tetrahedron* **1993**, *49*, 11155-11168. See also references cited therein.
4. There are no examples, to our knowledge, of synthesis of 6-OHIA **1**.
5. Very recently, an efficient synthesis of 6-hydroxyindole was reported. Teranishi, K.; Nakatsuka, S.; Goto, T. *Synthesis* **1994**, 1018-1020. See also references cited therein.
6. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127-3128.
7. **1b** HCl salt (pale yellow oil): ^{1}H-NMR (400 MHz, CD_3OD) 7.36 (1H, d, *J*=8.4 Hz), 7.00 (1H, s), 6.80 (1H, d, *J*=2 Hz), 6.63 (1H, dd, *J*=8.4, 2 Hz), 3.20 (2H, br t, *J*=7.2 Hz), 3.06 (2H, t, *J*=7.2 Hz).
8. Stoll, A.; Troxler, F.; Peyer, J.; Hofmann, A. *Helv. Chem. Acta* **1955**, *38*, 1452-1472.
9. (a) Brown, R. T.; *The Chemistry of Heterocyclic Compounds, Vol. 25, Indoles Part 4*; Weissberger, A.; Taylor, E. C. Eds. John Wiley and Sons, Inc.: New York, 1983. (b) Szantay, C.; Blasko, G.; Honty, K.; Dornyei, G. *The Alkaloids, Vol. 27*; Brossi, A. Ed. Academic Press, Inc.: New York, 1986.

(*Received in Japan* 10 *July* 1996; *revised* 5 *August* 1996; *accepted* 12 *August* 1996)