ORGANIC LETTERS

2010
Vol. 12, No. 9
2150−2153

Total Synthesis of (+)-Decarbamoylsaxitoxin and (+)-Gonyautoxin 3

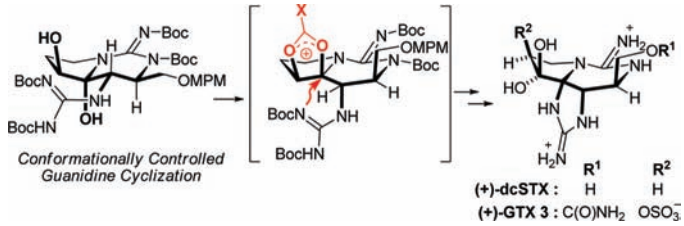
Osamu Iwamoto and Kazuo Nagasawa*

Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology (TUAT), 2-24-16 Nakamachi, Koganei, Tokyo 184-8588, Japan

knaga@cc.tuat.ac.jp

Received March 21, 2010

ABSTRACT



Facile construction of the complex saxitoxin (STX) skeleton is carried out by using a novel, conformationally controlled, guanidine cyclization process that relies on the use of neighboring group participation. The utility of this methodology is verified by its employment in syntheses of both natural and unnatural STX derivatives.

Saxitoxin (STX, **1**) and its analogues (Figure 1), the causative agents of paralytic shellfish poisoning (PSP), are potent neurotoxins produced by dinoflagellates.[1] PSP is attributed to the potent affinities of STXs against voltage gated sodium channels (NaChs), where binding strongly blocks the influx of sodium ions and inhibits neuronal cell depolarization processes. Owing to their characteristic pharmacological profiles, STXs have been used as biological tools to investigate the properties of NaChs.

STXs have a unique tricyclic bis-guanidine structure containing a quaternary C4 *N*,*N*-aminal carbon. The two guanidium ions in STXs serve as the sodium cation mimics. X-ray crystallographic analysis of STXs clearly show that

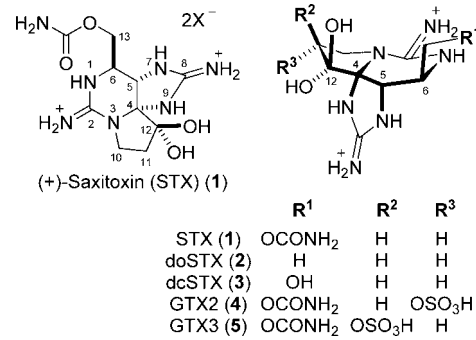


Figure 1. (+)-Saxitoxin (**1**) and its analogues (**2**−**5**).

both the C5 and C6 substituents are oriented in an anti-diaxial arrangement.[2] As a result of unique, highly polar, and heteroatom-rich structural features, STXs have attracted the interest of synthetic groups that have accomplished four total syntheses of members of this alkaloid family. Kishi and coworkers were the first to describe total syntheses of (±)-STX (**1**) and (−)-decarbamoylsaxitoxin (dcSTX) (*ent*-**3**) in

(1) Review for STX and its analogues: (a) Llewellyn, L. E. *Nat. Prod. Rep.* **2006**, *23*, 200–222, and references therein. For recent isolation of new STXs: (b) Lim, P.-T.; Sato, S.; Thuoc, C. V.; Tu, P. T.; Huyen, N. T. M.; Takata, Y.; Yoshida, M.; Kobiyama, A.; Koike, K.; Ogata, T. *Harmful Algae* **2007**, *6*, 321–331.

(2) (c) Dell'Aversano, C.; Walter, J. A.; Burton, I. W.; Stirling, D. J.; Fattorusso, E.; Quilliam, M. A. *J. Nat. Prod.* **2008**, *71*, 1518–1523. (a) Bordner, J.; Thiessen, W. E.; Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 6008–6012. (b) Schantz, E. J.; Ghazarossian, V. E.; Schnoes, H. K.; Strong, F. M.; Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 1238–1239.

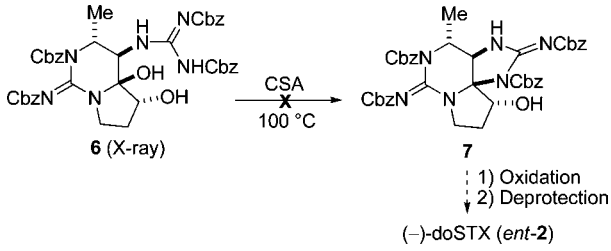
10.1021/ol1006696
Published on Web 03/31/2010

1977 and 1992, respectively.[3] Jacobi and co-workers also developed a strategy for the synthesis of (±)-STX (**1**) that is based on an azomethine imine cycloaddition process.[4] More recently, Du Bois and co-workers devised routes for the preparation of (+)-STX (**1**) and (+)-gonyautoxin 3 (GTX 3) (**5**) that employ a Rh-catalyzed amination strategy.[5]

We recently completed total syntheses of (−)- and (+)-decarbamoyloxysaxitoxin (doSTX) (*ent*-**2** and **2**) and a formal synthesis of (+)-STX (**1**) that utilize a 1,3-dipolar cycloaddition process and a unique IBX oxidation reaction.[6] Below, we describe the results of our continuing studies in this area, which have resulted in total syntheses of (+)-dcSTX (**3**) and (+)-GTX 3 (**5**) that rely on divergent approaches involving a *protected* saxitoxinol intermediate and a newly developed guanidine ring constructing methodology.

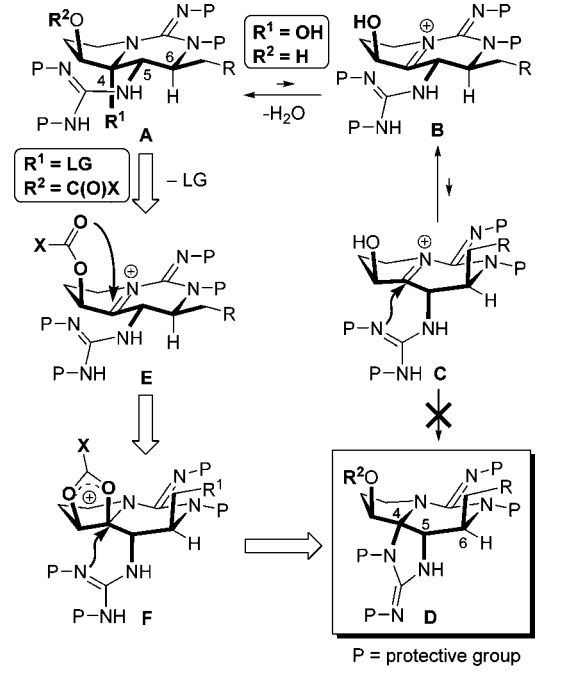
In routes for syntheses of highly polar and water-soluble natural product targets like those found in guanidine-containing alkaloid families, deprotection step(s) are usually carried out at final stages in order to avoid solubility and purification problems.[7] In our early work on the synthesis of (−)-doSTX (*ent*-**2**), attempts to construct the STX skeleton in the protected form **7** by acid treatment of the bis-guanidine precursor **6** met with failure (Scheme 1). In contrast,

Scheme 1. Early Attempts To Prepare Protected Saxitoxinol **7**



cyclization involving the guanidine and aminal moieties in **6** could be carried out under strongly acidic conditions after removal of the Cbz guanidine protecting groups. By using this approach, we were able to prepare (−)-doSTX (**2**).[6a] The development of a mild method to promote the key cyclization remains as a significant challenge in employing the strategy we have devised for the preparation of a variety of STX derivatives. In considering possible reasons why cyclization of **6** is problematic, we assumed that two key processes must take place in order for this reaction to occur efficiently. First, the iminium cation **B** must be generated from the precursor **A** (Scheme 2). Second, a conformational

Scheme 2. Hypothesis of Guanidine Cyclization Reaction



change must take place to transform **B** to **C**, in which the guanidinium moiety is correctly oriented for stereoelectronically governed axial addition to the iminum cation. We believed that in the case of **6**, the electron withdrawing Cbz group on the endocyclic guanidine moiety suppresses iminium ion formation even under acidic conditions. In addition, the conformational change required to create the bis-pseudoaxial C5 conformer **C** would be difficult owing to the presence of bulky substituents in **B**. If this reasoning is correct, activation of the leaving group at C4 in **A** and stabilization of conformer **C** would facilitate the cyclization process. In order to circumvent both problems, we planned to install a leaving group at C4 in order to accelerate iminium ion generation (**A** to **E**, Scheme 2) and an acyloxy neighboring group at C12 that would generate a bridged acyloxonium ion intermediate **F**, in which the C5 and C6 substituents are oriented in an anti-di-axial manner. On the basis of this analysis, we anticipated that cyclization of **F** would proceed to generate the protected saxitoxinol **D**.

These proposals were explored by using the bis-guanidines **9a**−**d**, derived from alcohol **8** that was synthesized in multigram quantities (Scheme 3).[6b] Cyclization reactions of

(3) (a) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818–2819. (b) Kishi, Y. *Heterocycles* **1980**, *14*, 1477–1495. (c) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001–7006. Kishi reported synthetic studies on GTX 2 and 3; see: (d) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833–3835.

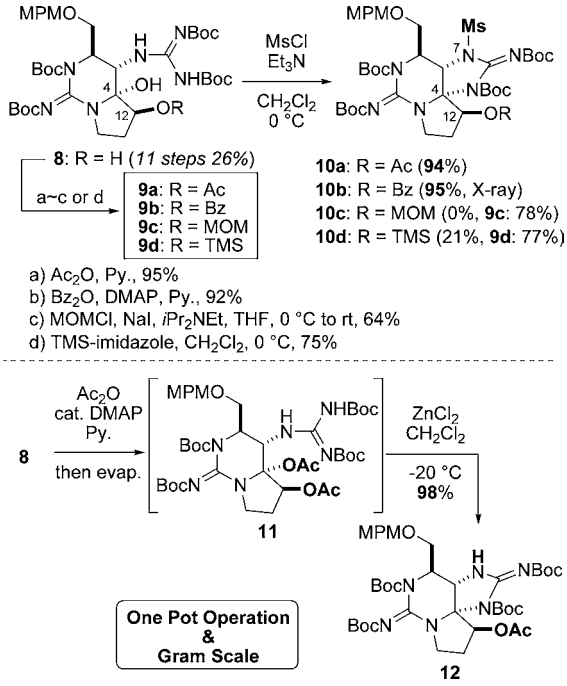
(4) (a) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594–5598. (b) Martinelli, M. J.; Brownstein, A. D.; Jacobi, P. A.; Polanc, S. *Croat. Chem. Acta* **1986**, *59*, 267–295. (c) Jacobi, P. A. *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, pp 191−219.

(5) (a) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926–3927. (b) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964–9975. (c) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630–12631. Recently Du Bois reported derivatization of STX: (d) Andresen, B. M.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 12524–12525.

(6) (a) Iwamoto, O.; Koshino, H.; Hashizume, D.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8625–8628. (b) Iwamoto, O.; Shinohara, R.; Nagasawa, K. *Chem. Asian J.* **2009**, *4*, 277–285.

(7) Recent review for guanidine alkaloids: (a) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919–954. Selected articles: (b) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511. (c) Urabe, D.; Nishikawa, T.; Isobe, M. *Chem Asian J.* **2006**, *1*−*2*, 125–135. (d) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284–1286. (e) Imaoka, T.; Iwamoto, O.; Noguchi, K.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3799–3801.

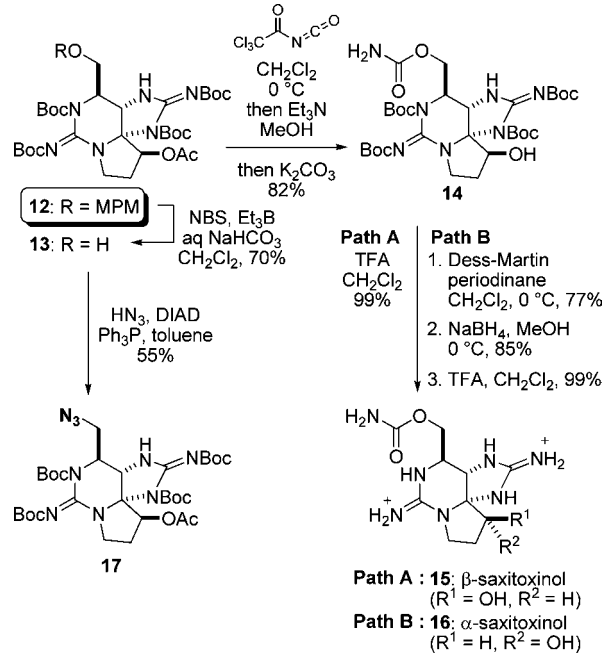
Scheme 3. Synthesis of Protected Saxitoxinols (**10** and **12**)



9a−**d** were promoted by methanesulfonyl chloride induced formation of the corresponding amido methanesulfonates. In the cases of **9a** and **9b**, cyclization reaction takes place smoothly under these conditions to afford the respective *protected* saxitoxinols **10a** (94%) and **10b** (95%) as N7 methanesulfonamide derivatives.[8] In contrast, treatment of **9c** and **9d**, containing MOM and TMS C12 hydroxyl protecting groups, with methanesulfonyl chloride did not effect this cyclization. Encouraged by these results, more selective conditions to promote the cyclization reaction but avoid formation of methansulfonamide products were explored. We observed that reaction of bis-guanidine **8** with acetic anhydride in the presence of catalytic DMAP led to generation of the C4,12-diacetate **11**, which when treated with zinc(II) chloride in dichloromethane at −20 °C yielded the tricyclic acetate **12** (98% from **8**), a *protected* saxitoxinol.[9] Notably, this two-step cyclization reaction could be performed in one pot on a practical scale.

In order to demonstrate the synthetic utility of the cyclization strategy we have developed, the *protected* saxitoxinol **12** was converted into the α- and *β*-saxitoxinols **15** and **16**.[10] The MPM ether protecting group on the C6 side chain alcohol in **12** was removed by reacting with NBS and Et_3B as the radical initiator,[11] and the resulting alcohol **13** was converted into the carbamate **14** by treatment with trichloroacetyl isocyanate, followed by stepwise methanolysis to remove the trichloroacetyl and acetyl groups. Finally, *β*-saxitoxinol (**15**) was produced by removal of the four Boc groups from **14** with trifluoroacetic acid in near quantitative yield (Path A, Scheme 4). The α-isomer **16** was also

Scheme 4. Synthesis of α- and *β*-Saxitoxinols (**15** and **16**) and Azide Derivative (**17**)



produced from **14** via a three-step route (65%, Path B) involving alcohol oxidation followed by stereoselective reduction of resulting ketone with $NaBH_4$ and treatment with trifluoroacetic acid. The C13 azide **17**, an unnatural nitrogen-substituted STX derivative, was also easily prepared by reaction of the alcohol **13** under Mitsunobu conditions.

The chemistry described above clearly demonstrates that C12- and C13-functionalized derivatives of saxitoxinol can be readily prepared from the *protected* saxitoxinol **12**. The advantageous features of this approach are further exemplified by routes we have developed for syntheses of the naturally occurring STX derivatives (+)-dcSTX (**3**) and (+)-GTX 3 (**5**) (Scheme 5). The sequences were initiated by removal of the acetyl group in **12** by methanolysis and oxidation of the resulting alcohol with the Dess−Martin reagent to generate the ketone **18** (92%, 2 steps). Simultaneous removal of the Boc and MPM ether protecting groups by treatment of **18** with HCl generated (+)-dcSTX (**3**) in quantitative yield. (+)-GTX 3 (**5**) is also prepared from **18**

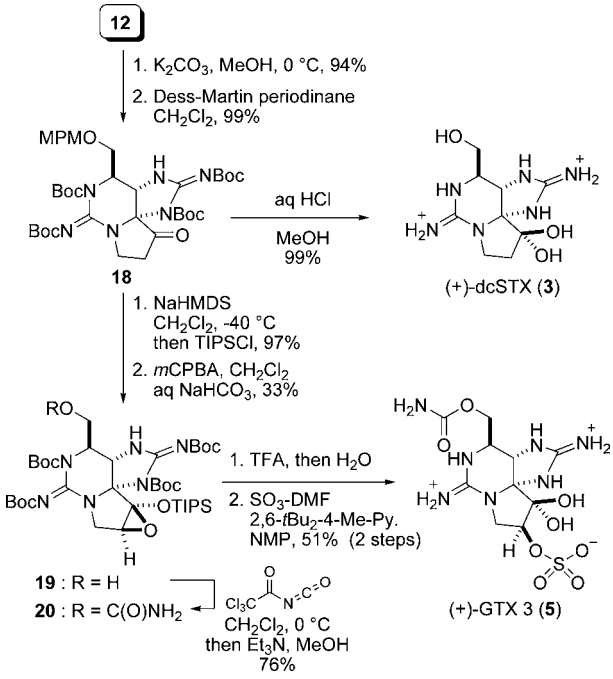
(8) The di-axial conformation of **13b** at C5,6 was confirmed with X-ray analysis, and its dihedral angle was estimated. See Supporting Information.

(9) To investigate details of this cyclization reaction, control experiments, i.e., treatment of **9a** with $ZnCl_2$ or reaction of **9c** with Ac_2O and DMAP followed by treatment with $ZnCl_2$, were conducted. In these cases, no corresponding cyclized products were obtained. Thus, both C4- and C12-OAc groups were revealed to be mandatory for this cyclization by activation and neighboring effect, respectively.

(10) Koehn, F. E.; Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Bioorg. Chem.* **1981**, *10*, 412–428.

(11) Standard conditions (DDQ, CAN or Pd/C-H_2, etc.) did not give **13**, and Boc groups in **12** were deprotected. To the best of our knowledge, NBS-Et_3B or other radical initiators mediated deprotection of the MPM group has not been reported, although only the NBS condition can be seen in literature.[12] Meanwhile, treatment of **12** with NBS, $NaHCO_3$ solution in wet CH_2Cl_2 gave desired **13** with no reproducibility.

Scheme 5. Synthesis of (+)-dcSTX (**3**) and (+)-GTX 3 (**5**)



through reaction with NaHMDS and TIPSCl, followed by oxidation with *m*CPBA to produce the siloxy epoxide **19**.[13] Following transformation of the hydroxyl group in **19** to the corresponding carbamate in **20** (24% from **18**), the Boc and TIPS ether groups were removed by using TFA to give 11 β-hydroxysaxitoxin. Finally, the synthesis of (+)-GTX 3 (**5**) was accomplished by sulfation of the C11 alcohol in **20** by utilizing the method developed by Du Bois.[5c] Both synthetic (+)-dcSTX (**3**) and (+)-GTX 3 (**5**) were identical to natural products.[14]

(12) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand.* **1984**, *B38*, 419–422.

(13) In this condition, MPM ether was oxidatively cleaved and overoxidized byproduct was generated in 27% yield. See Supporting Information.

The studies described above have led to the total synthesis of (+)-dcSTX (**3**) and (+)-GTX 3 (**5**) from the *protected* saxitoxinol **12**, which was prepared by employing a protocol that is based on a newly devised conformationally controlled guanidine cyclization process. These syntheses of (+)-dcSTX (**3**) and (+)-GTX 3 (**5**) were performed in 15 steps with 24% and 19 steps with 2.9% overall yield from chiral nitrone, respectively.[15] Since the substitution or transformation at C11−13 and N7 was successfully performed from the single intermediate **12**, this methodology should serve as the foundation for a general strategy for the syntheses of diverse natural and unnatural STX derivatives. Further studies on the synthesis of STX type NaCh modulators are in progress.

Acknowledgment. Financial support of this work was provided in part by a Grant-in-Aid for Scientific Research (B) from JSPS (No. 20310130). O.I. is grateful for financial support from the education program "Human Resource Development Program for Scientific Powerhouse" provided through the TUAT and the JSPS Predoctoral Fellowships for Young Scientists. We are grateful to Prof. Kei-ichi Noguchi (TUAT) for measurement of X-ray crystallographic data of key compounds.

Supporting Information Available: Experimental details and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1006696

(14) For preparation of (+)-dcSTX (**3**) by hydrolysis of natural STX (**1**), see: (a) Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1976**, *68*, 776–780. For first identification of (+)-dcSTX (**3**) as a natural product, see: (b) Harada, T.; Oshima, Y.; Yasumoto, T. *Agric. Biol. Chem.* **1983**, *47*, 191–193. For isolation of (+)-GTX 3 (**5**), see: (c) Shimizu, Y.; Buckley, L. J.; Alam, M.; Oshima, Y.; Fallon, W. E. *J. Am. Chem. Soc.* **1976**, *98*, 5414–5416. (d) Boyer, G. L.; Schantz, E. J.; Schoes, H. K. *J. Chem. Soc., Chem. Commun.* **1978**, 889–890. (e) Onodera, H.; Satake, M.; Oshima, Y.; Yasumoto, T.; Carmichael, W. W. *Nat. Toxins* **1997**, *5*, 146–151. Also see Supporting Information.

(15) (a) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 2853–2856. (b) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 7808–7821. Details of the preparation of intermediate **8** from chiral nitrone were summarized; see Supporting Information.