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Total Synthesis of (−)-5,6,11-Trideoxytetrodotoxin and Its 4-Epimer

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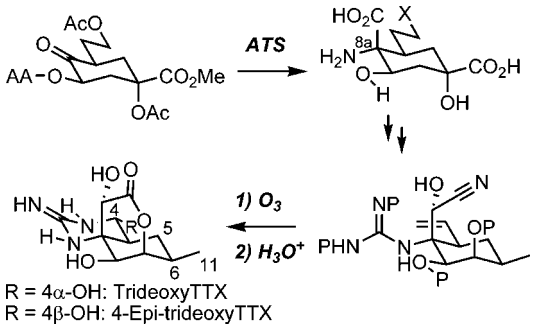
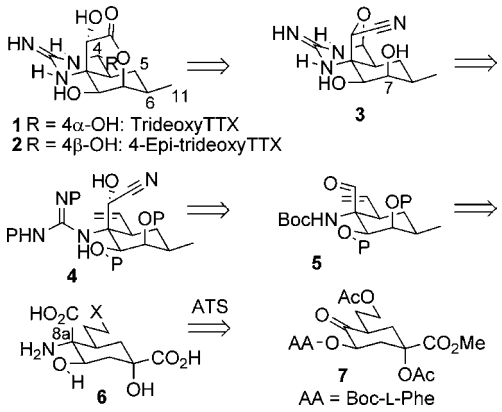
ABSTRACT



The first total synthesis of 5,6,11-trideoxytetrodotoxin (1) and its 4-epimer were achieved. The synthesis is characterized by the stereoselective construction of the quaternary amino carbon center at C8a by an asymmetric transferring Strecker synthesis and the highly efficient conversion of cyanohydrin 4 to 1 via intramolecular cyclization reactions.

5,6,11-Trideoxytetrodotoxin (trideoxyTTX) (**1**) and its 4-epimer **2** were isolated from the ovaries of the puffer fish, *Fugu poecilonotus*, by Yamashita and Yasumoto (Scheme 1).[1] These are natural congeners of tetrodotoxin (TTX), known as a principal toxin of puffer fish poisoning.[2] TTX exhibits specific blocking activities of the voltage-dependent Na^+ channels. Structure−activity relationship studies with natural TTX congeners indicated that the sodium channel blocking activity of **1** was much less potent than that of TTX.[2] Recently, Yamashita and co-workers analyzed TTX and its congeners in eggs of the puffer fish by a novel ESI-LC/MS method. It is interesting to note that large amounts

Scheme 1. Synthetic Plan



(1) (a) Yotsu-Yamashita, M.; Yamagishi, Y.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9329−9332. (b) Nakagawa, T.; Jang, J.; Yotsu-Yamashita, M. *Anal. Biochem.* **2006**, *352*, 142−144.

(2) (a) Kao, C. Y.; Lovinson, S., Eds. In Tetrodotoxin, Saxitoxin and the Molecular Biology of the Sodium Channels. *Ann. N.Y. Acad. Sci.* **1986**, *479*, 52−67. (b) Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*; Pergamon: Oxford, UK, 1999; Vol. 8, p 480. (c) Yotsu-Yamashita, M.; Sugimoto, A.; Takai, A.; Yasumoto, T. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1688−1696. (d) Cestele, S.; Catterall, W. A. *Biochimie* **2000**, *82*, 883−892. (e) Wood, J. N. *Curr. Opin. Pharmacol.* **2001**, *1*, 17−21. (f) Yotsu-Yamashita, M. *J. Toxicol. Toxin Rev.* **2001**, *20*, 51−66.

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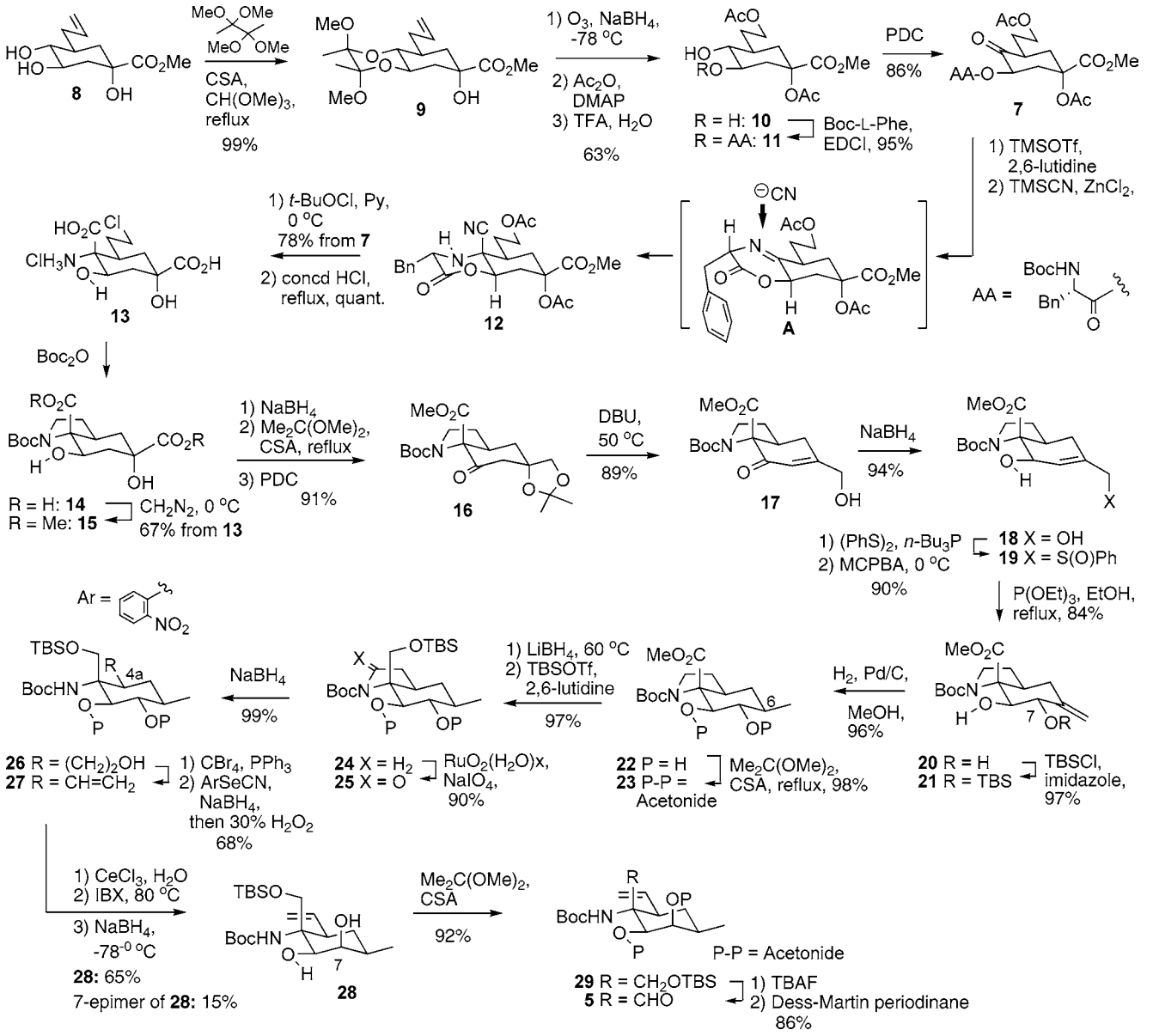
Scheme 2. Synthesis of the Key Intermediates **15** and **5**



of trideoxyTTX **1** were accumulated in the eggs and its concentration was greater than that of TTX.[1b] These results indicated a possibility that **1** and **2** could be an important biosynthetic precursor of TTX or an antidotal metabolite of TTX.[3]

TTX and its congeners are a class of highly functionalized natural products possessing a variety of functional groups that are densely juxtaposed on the cyclohexane skeleton. Substantial efforts have been devoted to the total synthesis of TTX and its congeners[4,5] due to their structural and pharmacological interests. On the other hand, the total synthesis of the naturally occurring 5-deoxy congeners has not been reported.[6]

Herein, we report the first total synthesis of (−)-5,6,11-trideoxyTTX (**1**) and its 4-epimer **2**. Our total synthesis features a simple approach to **1** and **2** via the intramolecular cyclization of a nitrile **3** placed on a conformationally rigid

(3) The biosynthesis and metabolic pathways of TTX are unknown and remain a challenging subject in this field as mentioned in ref 4h.

(4) Total synthesis of (−)-5,11-dideoxyTTX as an unnatural TTX analogue was reported by Isobe and Nishikawa in 2001. See ref 4c.

(5) Total sythensis of TTX and its congeners, see: (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217−9219. (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219−9221. (c) Asai, M.; Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **2001**, *57*, 4543−4558. (d) Nishikawa, T.; Asai, M.; Isobe, M. *J. Am. Chem. Soc.* **2002**, *124*, 7847−7852. (e) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Org. Lett.* **2002**, *4*, 2679−2682. (f) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798−8805. (g) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510−11511. (h) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782−4785. (i) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Chem. Eur. J.* **2004**, *10*, 452−462. (j) Sato, K.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496−7504. For a recent review see: (k) Koert, U. *Angew. Chem., Int. Ed.* **2004**, *43*, 5572−5576.

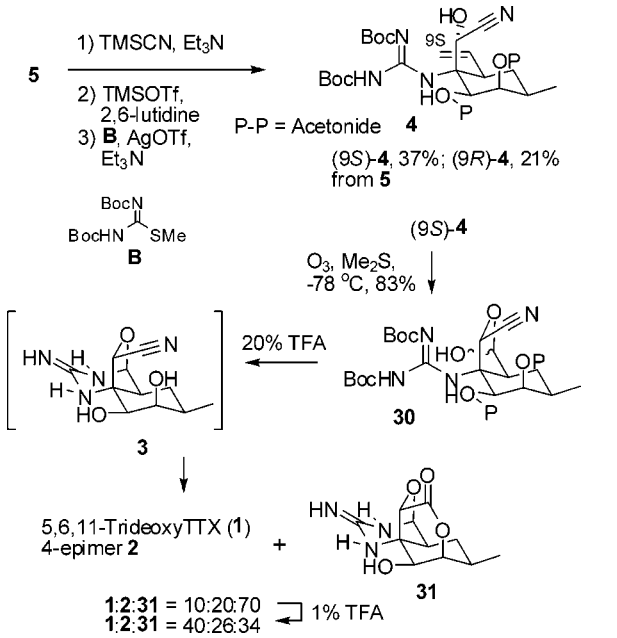
cyclohexane platform. The cyclic aminal **3** would be derived from **4** by oxidative cleavage of the olefin followed by removal of the protecting groups. Inspection of molecular models suggested that the cyanide moiety and C7 hydroxy group of **3** are in close proximity, facilitating the desired lactonization. The cyanohydrin **4** would be obtained from **6** via the aldehyde **5**. We postulated that an asymmetric transferring Strecker synthesis (ATS) of α-acyloxyketone **7** would effect the stereocontrolled construction of the C8a quaternary amino carbon center of **6**.[7] L-Phe was chosen as the chirality transferring group, which would induce a perfect diastereofacial selectivity upon cyanide addition to C8a (vide supra).[7b]

We began the synthesis with the triol **8**,[8] derived from (−)-quinic acid, which was converted into the ATS precursor **7** by the following sequence of transformations: (1) initial protection of **8** and subsequent conversion to diol **10**, (2) regioselective installation of Boc-L-Phe to **10**, and (3) oxidation (Scheme 2). Removal of the Boc group with TMSOTf and 2,6-lutidine[9] followed by treatment with TMSCN in the presence of $ZnCl_2$ gave the amino nitrile **12** as a single diastereomer. The stereochemical outcome was rationalized by the preferential approach of the cyanide ion from the upper face of the ketimine intermediate **A** having a stacking conformation as was discovered in a simple cyclohexane system.[7b] Removal of the chirality transferring group from **12** was performed by the initial oxidation to α-imino nitrile and subsequent hydrolysis. Under these conditions, replacement of the primary acetate by a chlorine atom occurred concomitantly. Protection of the resulting amino acid **13** with a Boc group followed by esterification produced the *N*-Boc pyrrolidine **15**. This structure was unambiguously confirmed by X-ray analysis.[10]

With the protected amino acid **15** in hand, efforts focused on the synthesis of the aldehyde **5**. The conversion was accomplished by a series of sequential transformations: (i) introduction of a C7 hydroxy group by the Mislow−Evans rearrangement,[11] (ii) stereoselective construction of the C6 stereogenic center, (iii) pyrrolidine ring opening to install a vinyl group at C4a, and (iv) introduction of the axial hydroxy group at C7. Along this line, **15** was transformed into the ketone **16** via selective reduction of the α-hydroxy ester moiety. Treatment of **16** with DBU provided the α,β-unsaturated ketone **17**, which was stereoselectively reduced to **18**. Mislow−Evans rearrangement of the sulfoxide **19** (a 1:1 mixture of diastereomers), synthesized from **18**, gave the olefin **20** bearing an equatorial hydroxy group at C7.[12] Hydrogenation of the TBS ether **21** in the presence of Pd/C proceeded in a stereoselective manner to afford **22** (20:1).[13] The resulting *trans*-1,2-diol was converted to the TBS ether **24** via the acetonide **23** in 3 steps. The pyrrolidine ring was successfully opened by initial RuO_4 oxidation of **24** and subsequent reduction of the resulting lactam **25** to give the alcohol **26**, which, following a selenylation/ deselenylation sequence, yielded **27** possessing the requisite vinyl group. Inversion of the C7 hydroxy group was performed by the successive oxidation and reduction of **27** to afford **28** (7β:7α = 4.5:1). The major isomer was converted to the aldehyde **5** in 3 steps via protection of the diol moiety with an acetonide.

The aldehyde **5** was transformed to the cyanohydrin **4** by treatment of **5** with TMSCN in the presence of Et_3N followed by installation of a Boc protected guanidine moiety (Scheme 3). With the key precursor (9*S*)-**4** in hand,[14] this was

Scheme 3. Total Synthesis of TrideoxyTTXs (**1**) and Its 4-Epimer **2** from **5**



subjected to ozonolysis and the resulting aldehyde cyclized spontaneously to produce the acetal **30**. To our delight, it was found that the treatment of **30** with 20% aqueous TFA afforded a mixture of trideoxyTTX **1**, 4-epimer **2**, and anhydro-derivative **31** [10:20:70]. These results indicated that

(6) Synthetic studies of TTX and its congeners, see: (a) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B.; Ferguson, G.; Parvez, M. *J. Org. Chem.* **1983**, *48*, 3627−3631. (b) Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.* **1991**, 1559−1562. (c) Fraser-Reid, B.; Burgey, C. S.; Vollerthun, R. *Pure Appl. Chem.* **1998**, *70*, 285−288. (d) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960−5968. (e) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323−1325. (f) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619−622. (g) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768−7771.

(7) (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127−5143. (b) Shinada, T.; Kawakami, T.; Sakai, H.; Matsuda, H.; Umezawa, T.; Kawasaki, M.; Namba, K.; Ohfune, Y. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 768−774.

(8) Toscano, M. D.; Frederickson, M.; Evans, D. P.; Coggins, J. R.; Abell, C.; Gonzalez-Bello, C. *Org. Biomol. Chem.* **2003**, *1*, 2075−2083.

(9) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.

(10) CCDC 610332 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac. uk/data _request/cif.

(11) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155.

(12) The stereochemical outcome is attributed to the steric effect of the methoxycarbonyl group at C8a.

(13) The hydrogenation of **20** gave a 10:1 mixture of **22** and its α-isomer.

(14) As a preliminary experiment, we found that the product ratio of (9*S*)-**4** and (9*R*)-**4** was improved to be 85:15 by using NaCN in the presence of $MgCl_2$ in MeOH. The synthesis of ^{13}C-labeled **1** and **2** under this condition is in progress. The full details will be reported in due course.

the following sequential transformations were effective under the reaction conditions: (i) removal of the Boc group, (ii) an acetal exchanging reaction to form the conformationally rigid **3**, (iii) removal of the acetonide, (iv) formation of imidate, (v) hydrolysis of the resulting imidate, and (vi) hydrolysis of the aminal.[15] Yields of the desired natural products **1** and **2** were improved by an equilibrium experiment with 1% aqueous TFA [**1**:**2**:**31** = 40:26:34]. The mixture was purified by ion-exchange column chromatography. Analytical data of the synthetic **1** and **2** were identical with those of the authentic samples.

In conclusion, we have achieved the first total synthesis of 5,6,11-trideoxyTTX (**1**) and its 4-epimer **2**. The synthesis was highlighted by the efficient final approach to furnish the total synthesis with use of the cyanohydrin **4**. This strategy opens the way to supply the ^{13}C-labeled trideoxyTTX as a biological probe for elucidation of the biosynthetic pathway of TTX.

(15) Treatment with 80% aq TFA gave **31** as a sole product.

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Supporting Information Available: Experimental details and NMR, IR, and MS data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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