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Novel and Stereocontrolled Synthesis of (±)-Tetrodotoxin from *myo*-Inositol

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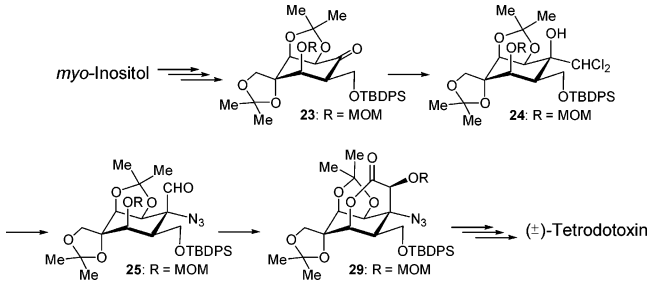

The novel and stereocontrolled synthesis of (±)-tetrodotoxin from *myo*-inositol is described. The key steps involve the stepwise oxidation of hydroxyl groups to the carbonyl function, followed by the addition of specific nucleophiles, including the successive spiro α-chloroepoxide formation and its ring-opening with the azide anion, to give the desired branched chain structures (**5**→**6**, **17**→**18**→**19**→**20** and **23**→**24**→**25**) with the desired regio- and stereoselectivities in high yields. The stepwise conversion of the α-azido aldehyde **25** to the δ-lactone **29**, followed by reduction of the azide, introduction of a guanidine moiety, aldehyde formation, and deprotection, produced the (±)-tetrodotoxin.

Introduction

Tetrodotoxin (TTX, **1**), one of the best-known marine toxins, was originally isolated from the puffer fish.[1] At the 30th International Natural Product Chemistry Conference in 1964, the structural determination of TTX was described by the Tsuda,[2] Hirata,[3] Woodward,[4] and Mosher[5] groups (they originally used the name "tarichatoxin") (Figure 1). It is known that TTX selectively combines with elements in the sodium channel, thus inhibiting its function in the cell membrane.[6] Therefore, TTX is utilized as a tool for the analysis of various vital phenomena, which occur via the sodium channel.[7] TTX has been found and isolated from not only the puffer fish, but also from the newt, frog, octopus, crab, shellfish, and other animals. It is also clear that the animals themselves do not produce TTX, which is produced by bacteria such as *Alteromonas sp.*, *Vibrio sp.*, *Shewanella sp*., etc.[8] From the structure of TTX and its analogues,[9] the biosynthetic pathway was proposed by Yasumoto.[10] TTX and its analogues are expected to provide very important information for pharmacological studies, such as the elucidation of structure−activity relationships and biological roles.[11] Therefore, it is very important to synthesize

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(1) Tahara, Y. *Biochem. Z.* **1911**, *30*, 255−275.
(2) Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, K.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull*. **1964**, *12*, 1357−1374.
(3) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059−2088.
(4) (a) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49−74. (b) Woodward, R. B.; Gougoutas, J. Z. *J. Am. Chem. Soc*. **1964**, *86*, 5030.
(5) Mosher, H. S.; Fuhrman, F. A.; Buchwald, H. D.; Fischer, H. G. *Science* **1964**, *144*, 1100−1110.
(6) Narahashi, T.; Moore, J. W.; Scott, W. R. *J. Gen. Physiol.* **1964**, *47*, 965−974.
(7) (a) Narahashi, T. *Physiol. Rev*. **1974**, *54*, 813−889. (b) Hucho, F. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 39−50. (c) Balerna, M.; Lombet, A.; Chicheportiche, R.; Romey, G.; Lazdunski, M. *Biochim. Biophys. Acta* **1981**, *644*, 219−225. (d) Bontemps, J.; Cantineau, R.; Grandfils, C.; Lprince, P.; Dandrifosse, G.; Schoffeniels, E. *Anal. Biochem*. **1984**, *139*, 149−157. (e) Wu, B. Q.; Yang, L.; Kao, C. Y.; Levinson, S. R.; Yotsu-Yamashita, M.; Yasumoto, T. *Toxicon* **1996**, *34*, 407−416.
(8) (a) Yasumoto, T.; Yasumura, D.; Yotsu, M.; Michishita, T.; Endo, A.: Kotaki, Y. *Agric. Biol. Chem.* **1986**, *50*, 793−795. (b) Noguchi, T.; Jeon, J.-K.; Arakawa, O.; Sugita, H.; Deguchi, Y.; Shida, Y.; Hashimoto, K. *J. Biochem*. **1986**, *99*, 311−314.

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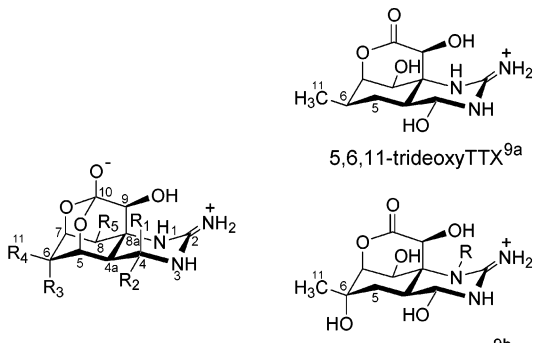


	R_1	R_2	R_3	R_4	R_5
TTX[4,5]	H	OH	OH	CH_2OH	OH
4-*epi*TTX[9c]	OH	H	OH	CH_2OH	OH
6-*epi*TTX[9d]	H	OH	CH_2OH	OH	OH
11-deoxyTTX[9d]	H	OH	OH	CH_3	OH
8,11-dideoxyTTX[9e,f]	H	OH	OH	CH_3	H
11-oxoTTX[9g]	H	OH	OH	CHO	OH
11-norTTX-6(*R*)-ol[9h]	H	OH	H	OH	OH
11-norTTX-6(*S*)-ol[9i]	H	OH	OH	H	OH

FIGURE 1. Tetrodotoxin and its analogues.

larger amounts of TTX and its analogues, than are now available. However, it is difficult to prepare modified TTX derivatives from naturally occurring compounds due to its unique structural and chemical properties.[12] The total synthesis of TTX and their analogues remains a fascinating and extremely difficult challenge to synthetic chemists. Despite the attempts of many research groups to synthesize TTX,[13] a more efficient or optically active TTX synthesis has not been reported during the 30 years following Kishi and co-workers first total synthesis of (±)-TTX.[14] However, quite recently, the Isobe and Du Bois research groups have both succeeded in the synthesis of (−)-TTX.[15]

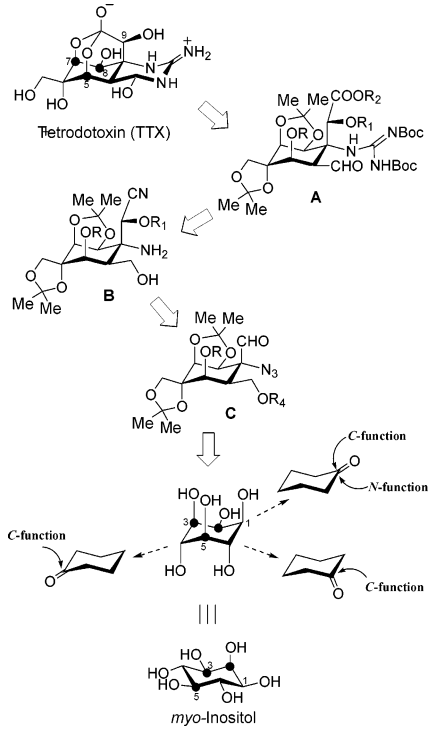


FIGURE 2. Retrosynthetic analysis of tetrodotoxin.[19]

We have long been engaged in the study of the total syntheses of naturally occurring branched chain cyclitol compounds, such as cyclophellitol,[16] mytillitol, laminitol,[17] and (−)-TTX,[18] from D-glucose. On the basis of these results, we conceived a new synthetic strategy toward (±)-TTX from *myo*-inositol. Herein, we describe our accomplished synthetic route of (±)-tetrodotoxin.

Results and Discussion

Retrosynthetic Analysis of TTX.[19] Our synthetic plan for TTX is shown as the retrosynthetic analysis in Figure 2. We envision TTX to be chemically equivalent to compound **A**. The cyclic guanidine aminal may be constructed by the neighboring group participation of the

(9) For examples of TTX analogues, 5,6,11-trideoxyTTX: (a) Yotsu-Yamashita, M.; Yamagishi, Y.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9329−9332. 1-hydroxy-5,11-dideoxyTTX: (b) Kotaki, Y.; Shimizu, Y. *J. Am. Chem. Soc.* **1993**, *115*, 827−830. 4-*epi*TTX: (c) Yasumoto, T.; Michishita, T. *Agric. Biol. Chem.* **1985**, *49*, 3077−3088. 6-*epi*TTX, 11-deoxyTTX: (d) Yasumoto, T.; Yotsu, M.; Murata, M.; Naoki, H. *J. Am. Chem. Soc.* **1988**, *110*, 2344−2345. 8,11-dideoxyTTX: (e) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Chem.-Eur. J.* **2004**, *10*, 452−462. (f) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Org. Lett.* **2002**, *4*, 2679−2682. 11-oxoTTX: (g) Khora, S. S.; Yasumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4393−4394. 11-norTTX-6(R)-ol: (h) Endo, A.; Khora, S. S.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1988**, *29*, 4127−4128. 11-norTTX-6(S)-ol: (i) Yotsu, M.; Hayashi, Y.; Khora, S. S.; Sato, S.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 370−371. 5,11-dideoxyTTX: (j) Asai, M.; Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **2001**, *57*, 4543−4558. Several TTX analogues (review): (k) Yotsu-Yamashita, M. *J. Toxicol. Toxin Rev.* **2001**, *20*, 50−66.

(10) (a) Yasumoto, T.; *Kagaku to Seibutsu* (*in Japanese*) **1989**, *27*, 401−406; *Chem. Abstr.* **1989**, *111*, 72582z. (b) Yotsu-Yamashita, M.; Yamagishi, Y.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9329−9332. (c) Shimizu, Y.; Kobayashi, M. *Chem. Pharm. Bull.* **1983**, *31*, 3625−3631. (d) Shimizu, Y. *Ann. N.Y. Acad. Sci.* **1986**, *479*, 24−31.

(11) (a) Kodama, M.; Ogata, T.; Sato, S. *Mar. Biol.* **1985**, *87*, 199−202. (b) Matsumura, K. *Nature* **1995**, *378*, 563−564. (c) Saito, T.; Noguchi, T.; Harada, T.; Murata, O.; Hashimoto, K. *Nippon Suisan Gakkaishi* (*in Japanese*) **1985**, *51*, 1175−1180; *Chem. Abstr.*, **1985**, *103*, 120354k.

(12) (a) Kao, C. Y.; Lovinson, S. *Ann. N.Y. Acad. Sci.* **1986**, *479*, 52−67. (b) Kobayashi, J.; Ishibashi, M. *Comprehensive Natural Products Chemistry*; Paragamon: Oxford, 1999; pp 415−649.

(13) (a) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960−5968. (b) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 1609−1618. (c) Nachman, R. J.; Honel, M.; Williams, T. M.; Halaska, R. C.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 4802−4806. (d) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B. *J. Org. Chem.* **1983**, *48*, 3621−3626. (e) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B. *J. Org. Chem.* **1983**, *48*, 3627−3631. (f) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323−1325.

(14) (a) Kishi, Y.; Aratani, M.; Fukuyama, M.; 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.

(15) (a) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798−8805. (b) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782−4785. (c) Hinmam, A.; Du Bois, J. *J. Am. Chem. Soc*. **2003**, *125*, 11510−11511.

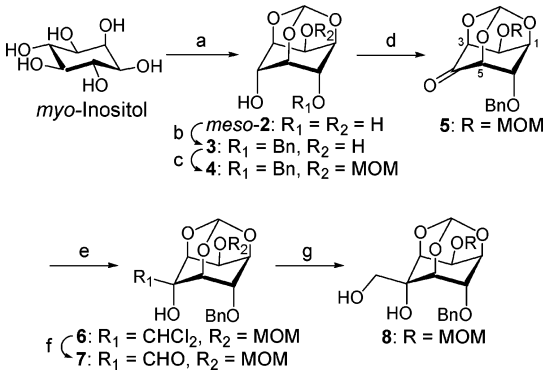
(16) Sato, K.; Bokura, M.; Moriyama, H.; Igarashi, T. *Chem. Lett.* **1994**, 37−40.

(17) Sato, K.; Bokura, M.; Taniguchi, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1633−1640.

(18) (a) Akai, S. Nakamura, Y.; Kajihara, Y.; Yoshimura, J.; Sato, K. *Anal. Sci.* **1999**, *15*, 503−504. (b) Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.* **1991**, 1559−1562.

(19) All intermediates were racemic unless otherwise noted.

SCHEME 1[a] [19]



[a] Reagents and conditions: (a) $CH(OEt)_3$, TsOH/DMF (70%); (b) NaH, BnBr/DMF (81%); (c) MOM−Cl, *i*-Pr_2NEt/CH_2Cl_2 (74%); (d) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2 (quant.); (e) LDA, CH_2Cl_2 (76%); (f) *n*-Bu_4NOH/Me_2SO; (g) $NaBH_4$/MeOH (two steps, 81%).

guanidine moiety and the aldehyde function. The ortho ester structure may be constructed by the neighboring group participation of the carboxyl and axially oriented hydroxyl groups. The aldehyde function of **A** can be introduced by oxidation of the hydroxymethyl group of **B**. The introduction of the di-*N*-Boc-guanidine moiety is planned for the last stage of the synthesis due to the instability of the intermediates, as anticipated from previous studies.[14,15] The cyanohydrin group of **B** may be prepared by the reaction of the α-azido aldehyde function of **C** with a CN anion. Compound **C** can be synthesized from the corresponding carbonyl compound using dichloromethyllithium by employing new methods[20] for the stereocontrolled construction of functionalized branched chains. The asymmetric carbon atoms, *C*-5, *C*-7, and *C*-8, of TTX can be transformed into the *C*-5, *C*-3, and *C*-2 carbon atoms of *myo*-inositol, respectively. Following this outline, *myo*-inositol was modified using the following standard protection and deprotection steps.

Construction of the Branched Chains at *C*-4 and *C*-6 of *myo*-Inositol, and Selective Protection of the Hydroxyl Groups.[19] The starting compound **3** was synthesized via the orthoformate **2** from *myo*-inositol.[21] The equatorial hydroxyl group of the mono-*O*-benzylated **3** was selectively protected by a methoxymethyl (MOM) group to give **4** in 74% yield. Compound **4** was then oxidized under Swern conditions to quantitatively give the carbonyl compound **5**. The reaction of **5** with lithium diisopropylaminde (LDA) and dichloromethane[20a,b] gave the corresponding dichloroethanol derivative **6** as a single stereoisomer in 76% yield. **6** was converted into an unstable α-hydroxy aldehyde derivative **7**,[20a,b] which was immediately reduced with $NaBH_4$ without further purification to give the hydroxymethyl derivative **8** in good yield (Scheme 1). The stereochemistry of the quaternary carbon atom in **6** and **8** was confirmed by the NOE measurements shown in Figure 3. The stereochemistry

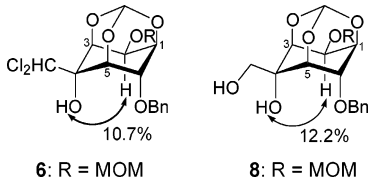


FIGURE 3. NOE correlations of **6** and **8**.

of these conversions for constructing the branched chain function was reported by Sato et al.[20]

The complete benzylation of **8** to **9**, followed by treatment with 0.1 M HCl−MeOH, gave the corresponding tetrol derivative **10** in 97% yield. The treatment of **10** with *tert*-butyldimethylsilyl chloride (TBDMS−Cl) and imidazole gave both the desired and the undesired mono-*O*-silylated compounds, **11** and **12**, in 62% and 18% yields, respectively. The structures of **11** and **12** were confirmed by derivation into the corresponding acetates, **11a** and **12a**. **12** was recycled to **11** by de- and reprotections via **10**. The reaction of the *cis*-diol of **11** with 2,2-dimethoxypropane and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) then gave the corresponding acetonide **13** in 93% yield. The conformation of **13** was confirmed by NMR analysis ($J_{1,2}$ = 3.1 Hz, $J_{2,3}$ = 7.3 Hz, $J_{1,6}$ = 8.9 Hz, $J_{6,5}$ = 3.1 Hz) of the corresponding acetyl derivative **13a**. Compound **13** was then treated with dimethoxymethane and P_2O_5 to give the fully protected cyclitol derivative **14** in 75% yield. The removal of the benzyl group of **14** under catalytic reducing conditions gave **15** in 88% yield, which was then transformed into the acetonide **16** in 99% yield. The resulting alcohol **16** was oxidized to give the carbonyl compound **17** in 95% yield (Scheme 2).

The stereoselective introduction of the hydroxymethyl branched chain at the *C*-6 position of *myo*-inositol is important for this study. Considering the stereochemistry, the introduction of the hydroxymethyl branched chain was first envisioned to result from Wittig methylation[22] of the carbonyl compound **17** followed by hydroboration-oxidation, but the alkene **19** could not be obtained. This was likely due to steric hindrance of the protecting groups (MOM and/or TBDMS). Petersons' olefination[23] of **17** was then examined to give **19** via the trimethylsilylmethyl compound **18** in 50% yield (two steps). The methylene compound **19** was transformed into the hydroxymethyl compound **20** in 74% yield (two steps) by hydroboration-oxidation and de-silylation with the tetra-*n*-butylammonium fluoride (TBAF). The conformation of **20** and its configuration at the hydroxymethyl branching carbon were confirmed by NMR analysis of its acetylated compound **20a** ($J_{5,6}$ = 5.8 Hz, $J_{6,1}$ = 5.2 Hz) and **21** ($J_{5,6}$ = 3.3 Hz, $J_{6,1}$ = 3.3 Hz, and NOE experiments, Scheme 3). The primary hydroxyl group of **20** was selectively protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give the corresponding monohydroxyl compound **22** in 87% yield. **22** was then oxidized with Dess−Martin periodinane[24] to give **23** in 99% yield, a key precursor for constructing TTX.

(20) (a) Sato, K.; Suzuki, K.; Ueda, M.; Kajihara, Y.; Hori, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 225−230. (b) Sato, K.; Yamamoto, Y.; Hori, H. *Tetrahedron Lett.* **1996**, *37*, 2799−2800. (c) Sato, K.; Sekiguchi, T.; Hozumi, T.; Yamazaki, T.; Akai, S. *Tetrahedron Lett.* **2002**, *43*, 3087−3090.

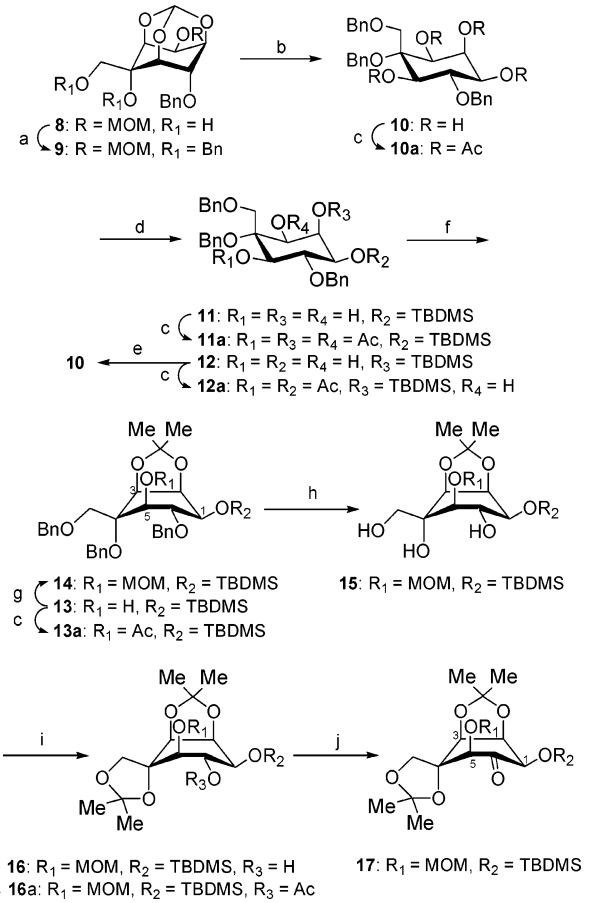
(21) (a) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402−4404. (b) Billington, D. C.; Baker, R. *J. Chem. Soc., Chem. Commun*. **1987**, 1011−1013. (c) Baudin, G.; Glazer, B. I.; Swaminathan, K. S.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 1367−1378.

(22) Inch, T. D.; Lewis, G. J. *Carbohydr. Res.* **1972**, *22*, 91−101.

(23) Chan, T. H.; Chang, E.; Vinokur, E. M. *Tetrahedron Lett*. **1970**, *14*, 1137−1140.

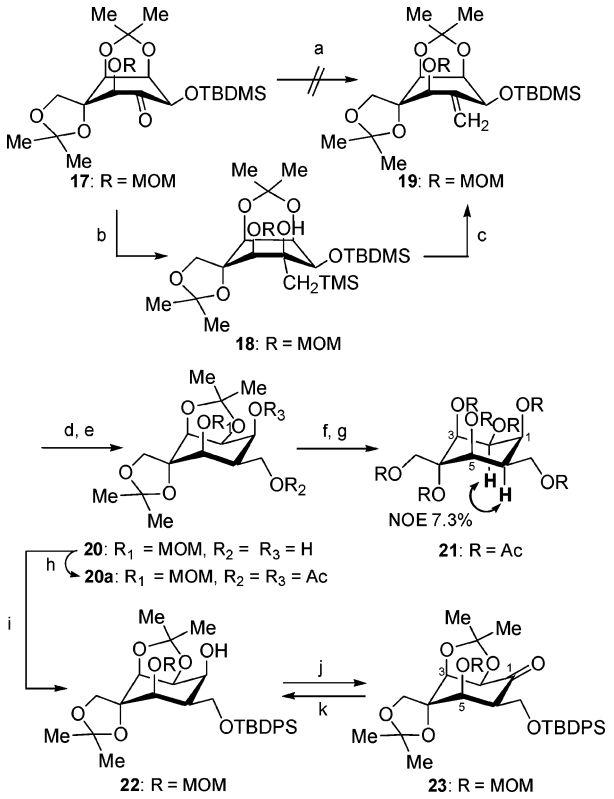
(24) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

SCHEME 2[a] [19]



[a] Reagents and conditions: (a) NaH, BnBr/DMF (89%); (b) 0.1 M HCl−MeOH (97%); (c) Ac_2O, Py. (quant.); (d) TBDMS−Cl, imidazole/DMF (**11**, 62%; **12**, 18%); (e) 70% AcOH (quant.); (f) $Me_2C(OMe)_2$, PPTS/CH_2Cl_2 (93%); (g) $CH_2(OMe)_2$, P_2O_5/CH_2Cl_2 (75%); (h) 10% Pd(OH)$_2$−C, H_2/EtOH (88%); (i) $Me_2C(OMe)_2$, PPTS/CH_2Cl_2 (99%); (j) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2 (95%).

SCHEME 3[a] [19]

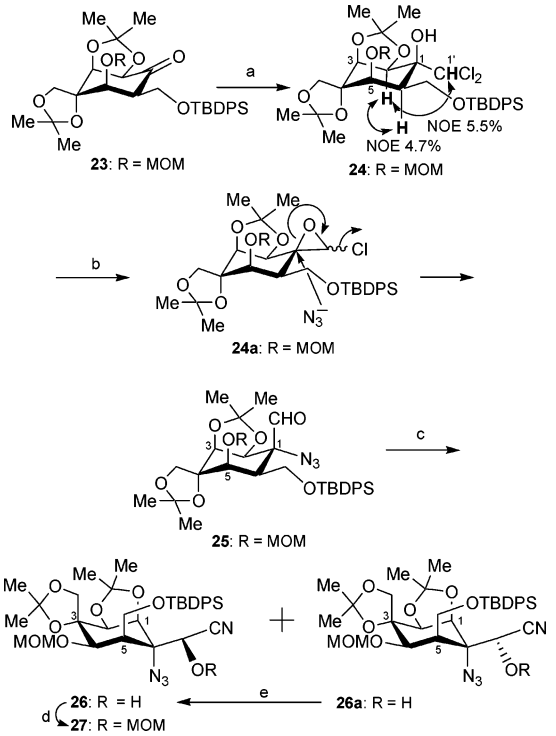


[a] Reagents and conditions: (a) $Ph_3P{=}CH_3Br$, BuLi/THF; (b) $TMSCH_2MgCl/Et_2O$ (63%); (c) NaH/THF (79%); (d) BH_3−THF, NaOH aq, then H_2O_2 aq; (e) TBAF/CH_2Cl_2 (two steps, 74%); (f) 70% AcOH aq; (g) Ac_2O, TsOH (two steps, quant.); (h) Ac_2O, Py. (quant.); (i) TBDPS−Cl, imidazole/CH_2Cl_2 (87%); (j) Dess−Martin periodinane/CH_2Cl_2 (99%); (k) $NaBH_4$/EtOH (95%).

Introduction of Amino Function and Ortho Ester Moieties of C and B.[19] To construct the α-azido aldehyde branched chain of **C**, **23** was treated with LDA and dichloromethane at −78 °C. The expected dichloroethanol derivative **24** was obtained in 79% yield.[20a,b] The stereochemistry at *C*-6 of **24** was determined by NOE experiments (Scheme 4) together with the results from the stereoselective reduction of **23** to **22**. Hence, the ketone **23** was reduced with $NaBH_4$ to give only the corresponding axial alcohol **22**. The stereoselectivity of the nucleophilic reactions by **23** might be controlled by the 1,3-diaxial relationship of the *C*-3 and *C*-5 substituents. The resulting dichloroethanol derivative **24** was then treated with NaN_3 in 15-crown-5 ether and Me_2SO to give the corresponding α-azido aldehyde **25** in 63% yield.[20a,c] It is noteworthy that the reaction proceeded both stereoselectively and regioselectively. The stereochemistry at *C*-6 of **25** was further verified by X-ray crystal structure analysis of the cyanohydrin derivative **26**, which was synthesized by the reaction of **25** with a CN anion as follows. The reaction of the α-azido aldehyde **25** and TMS−CN/Et_3N in MeOH gave the corresponding epimeric cyanohydrin derivatives **26**[18a] and **26a** in 45% and 29% yields, respectively. Careful monitoring of the cyanohydrin reaction by TLC (6:1 hexanes−EtOAc) suggested that **25** was completely converted into the kinetically controlled product **26a** within 3 min, after which it gradually converted into the equilibrium mixture (6:4) of **26** and **26a**. The more polar product **26** was then treated with P_2O_5 and dimethoxymethane to give the corresponding protected methoxymethyl (MOM) derivative **27** in 93% yield. In contrast, the less polar isomer **26a** could not be protected under these conditions. The undesired isomer **26a** could be transformed into the desired isomer **26** by treatment with TMS−CN/Et_3N in MeOH in 44% yield (Scheme 4). The configurations at *C*-6 and *C*-6′ (*C*-8a and *C*-9 with TTX numbering) of **26** were determined by an X-ray crystal structure analysis.[18a] The ORTEP diagram of **26** shows that the conformation of the six-membered ring is the $^3C_6$ form and the configuration at *C*-6′ (*C*-9 with TTX numbering) is the same as that of natural TTX (Figure 4).

Introduction of Ortho Ester and Guanidine Groups to 27.[19] The cyanohydrin derivative **27** was treated with diisobutylaluminum hydride (DIBAL−H) to give the corresponding aldehyde derivative **28** in 87% yield. The selective deprotection of the MOM group at *O*-4 (*O*-5 with TTX numbering) of **28** and subsequent treatment with Jones' reagent gave the δ-lactone derivative **29** as a single product in 90% yield. The structure of **29** was confirmed by NMR analysis (W-shaped long-range coupling: $J_{5,6'}$ ($J_{4a,9}$ with TTX numbering) = 1.4 Hz,

SCHEME 4[a 19]



[a] Reagents and conditions: (a) LDA, CH_2Cl_2/THF (79%); (b) NaN_3, 15-crown-5/Me_2SO (63%); (c) TMS−CN, Et_3N/MeOH (**26**, 45%; **26a**, 29%); (d) $CH_2(OMe)_2$, P_2O_5/CH_2Cl_2 (93%); (e) TMS−CN, Et_3N/MeOH (**26**, 44%; **26a**, 25%).

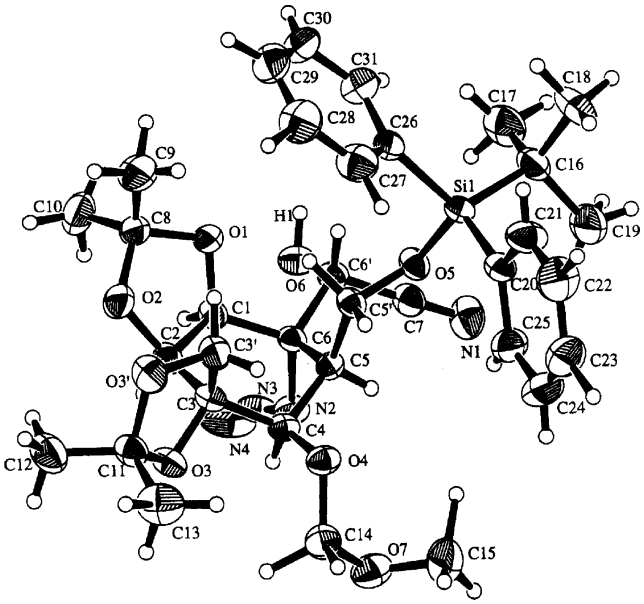


FIGURE 4. ORTEP diagram of **26** with the atomic numbering scheme.

NOESY, and HMBC experiments), as shown in Figure 5. To introduce the guanidine moiety, the azido group of **29** was first reduced with 10% Pd−C and H_2 to quantitatively give the amino derivative **30**. The TBDPS group of **30** was then deprotected using TBAF in 90% yield. Thus, the obtained amino derivative **31** was then treated with bis(*t*-butoxycarbonyl)thiourea, mercury(II) chloride, and triethylamine[25] to give the guanidine derivative **32**

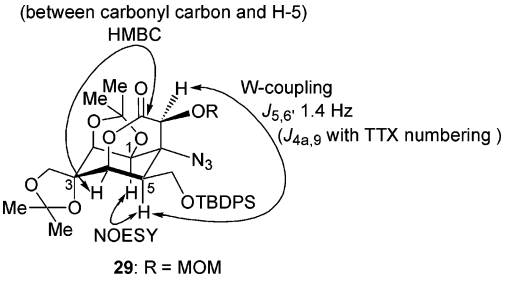
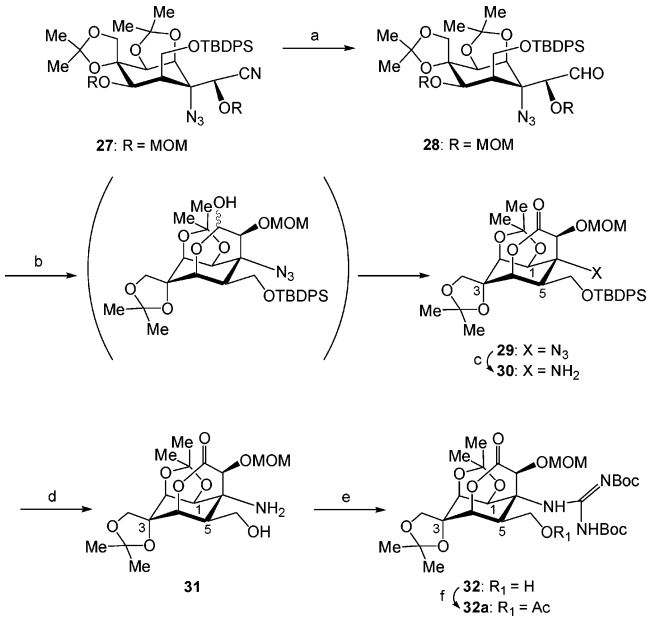


FIGURE 5. NOE correlations of **29**.

SCHEME 5[a 19]

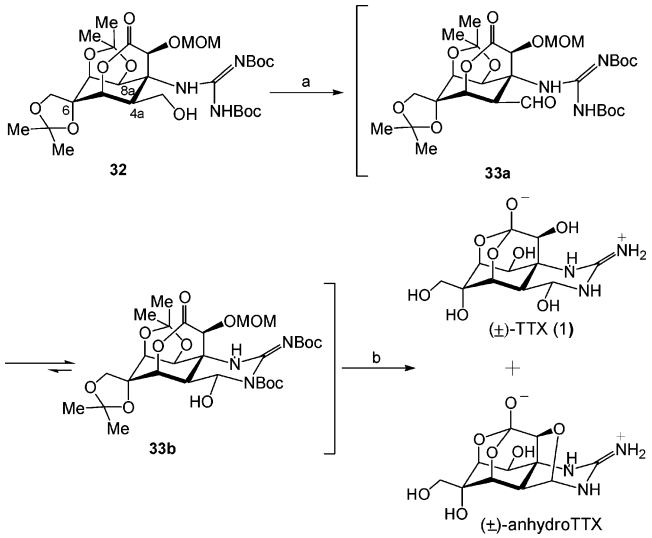


[a] Reagents and conditions: (a) DIBAL−H/CH_2Cl_2 (87%); (b) CrO_3 in aq H_2SO_4/CH_2Cl_2−acetone (90%); (c) 10% Pd−C, H_2/EtOH (quant.); (d) TBAF/THF (90%); (e) $(BocNH)_2C{=}S$, $HgCl_2$, Et_3N/DMF (72%); (f) Ac_2O, Py. (quant.).

in 72% yield. The structure of **32** was confirmed by conversion to the corresponding acetates **32a** (Scheme 5). Finally, the oxidation of **32** with pyridinium chlorochromate (PCC) and subsequent treatment of the product with 4 M HCl−dioxane/MeOH,[15a,b] then a 30% aq TFA solution and 4% aq acetic acid solution, provided a mixture of TTX, 4,9-anhydro-4-*epi*TTX (anhydroTTX), and other polar decomposition compounds. The mixture was purified by HPLC on a Hitachi-gel #3013-c column (H^+ form, 0.05 N aqueous AcOH)[15a] to give (±)-TTX (including a slight lactone form by ^{1}H NMR), and (±)-anhydroTTX in 30% and 10% yields (from **32**), respectively (Scheme 6). Isomerization of the anhydroTTX to TTX in 4% aq acetic acid solution is very slow below rt. The spectral data for the synthetic TTX completely agreed with that of the natural TTX[26] (^{1}H and MS)[9d,15a,b] (Table 1). In the above oxidation reaction, the signals in the ^{1}H NMR spectrum of the oxidation product were broadened, which made the confirmation of the signals of the original aldehyde impossible. This result suggested that the resistant aldehyde **33a** was interconvertible with

(25) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7195−7196.
(26) A sample of natural (−)-tetrodotoxin was obtained from Sankyo Co. Ltd. (Tokyo, Japan).

SCHEME 6[a] [19]



[a] Reagents and conditions: (a) PCC/CH_2Cl_2; (b) (i) 4 M HCl−dioxane; (ii) 30% aq TFA; (iii) 4% aq AcOH (**1**, 30%; anhydro, 5%, from **32**).

TABLE 1. Comparative ^{1}H NMR Data[a]

position	synthetic TTX	natural TTX[9e]
4	5.50 (d, J = 8.9 Hz)	5.50 (d, J = 9.4 Hz)
4a	2.35 (d, J = 9.6 Hz)	2.35 (d, J = 9.5 Hz)
5	4.26 (br s)	4.25 (br s)
7	4.09 (t, J = 2.1 Hz)	4.08 (t, J = 1.8 Hz)
8	4.30 (d, J = 2.1 Hz)	4.30 (d, J = 1.5 Hz)
9	3.96 (s)	3.96 (s)
11	4.01 (d, J = 12.4 Hz)	4.02 (d, J = 12.6 Hz)
	4.06 (d, J = 12.4 Hz)	4.04 (d, J = 12.6 Hz)

[a] 600 MHz, in 3% CD_3COOD/D_2O, referenced to C*H*D_2COOD (2.06 ppm).

the aminal compound **33b**. A similar phenomenon has been reported for 1,2-*O*-isopropylidene-3-*C*-acetaminomethyl-α-D-*xylo*-pentodialdofranose.[27] Treatment of the other oxidation products (Dess−Martin,[24] Swern, or 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO)[28] oxidation products) under acidic conditions (condition (b) in Scheme 6) did not provide (±)-TTX nor (±)-anhydroTTX at all. It seems that some side reactions have occurred during the oxidation of the primary hydroxyl group of **32**. These oxidation products showed different R_f values as compared to that of **33a**(**33b**) on TLC. The determination of its structure is not easy, because of its broadened ^{1}H NMR spectra.

In conclusion, we have accomplished the total synthesis of (±)-TTX from *myo*-inositol in a highly stereocontrolled fashion and in excellent yields. Some of the key steps were the 1,3,5-orthoformylation of *myo*-inositol with conformational inversion to differentiate the remaining three free OH groups. These groups were stepwise oxidized to the carbonyl function, followed by the specific nucleophilic addition, including the successive spiro α-chloroepoxide formation and its ring-opening with an azide anion, to give the desired branched chain structure. This synthetic method would then be applicable to synthesize not only TTX and its analogues, but also highly complex natural products having branched chain structures. We have just now achieved the total synthesis of the optically active (−)-TTX from D-glucose via two different routes employing the Ferrier reaction[29] and the Henry reaction[30] as key transformations.

Experimental Section[19]

6-*O*-Benzyl-2-*O*-methoxymethyl-4-*C*-dichloromethyl-*myo*-inositol 1,3,5-Orthoformate (6). To a stirred solution of diisopropylamine (12.0 mL, 85 mmol) in THF (400 mL) was added *n*-butyllithium (1.63 M solution in hexane, 52.0 mL, 85 mmol) at −78 °C under argon, which was stirred for 30 min, and then dry CH_2Cl_2 (18.0 mg, 281 mmol) was added dropwise during 5 min and stirred further for 5 min. To the above reaction mixture was added **5** (9.1 g, 28.1 mmol) in THF (30 mL) dropwise during 10 min, and kept until the disappearance of **5** on TLC with 1:1 hexanes−EtOAc. After 10 min, to the reaction mixture was added aq NH_4Cl solution (150 mL) was added, and THF was evaporated to half volume, to give a residue. The residue was extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 3:1 hexanes−EtOAc to give **6** (8.71 g, 76% yield); syrup. IR (KBr neat): ν 3424 cm^{-1} (OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41−7.32 (m, 5H, Ph*H*), 6.52 (d, 1H, $J_{4',OH}$ 1.2 Hz, H-4′), 5.50 (d, 1H, $J_{CH,2}$ 1.5 Hz, CH), 4.85, 4.80 (2 × d, 2H, $J_{A,B}$ 7.0 Hz, CH_2OCH_3), 4.72, 4.70 (2 × d, 2H, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.53 (d, 1H, OH), 4.47 (ddd, 1H, $J_{3,2}$ 4.0, $J_{3,1}$ 1.8, $J_{3,5}$ 1.8 Hz, H-3), 4.45 (dd, 1H, $J_{6,1}$ 4.0, $J_{6,5}$ 4.0 Hz, H-6), 4.40 (ddd, 1H, $J_{5,1}$ 1.8 Hz, H-5), 4.30 (dddd, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.15 (ddd, 1H, H-2), 3.45 (s, 3H, CH_2OCH_3). Differential NOE correlations: OH−H-2 (10.7%). Anal. Calcd for $C_{17}H_{20}Cl_2O_7$: C, 50.14; H, 4.95. Found: C, 50.20; H, 5.07.

6-*O*-Benzyl-2-*O*-methoxymethyl-4-*C*-hydroxymethyl-*myo*-inositol 1,3,5-Orthoformate (8). To a stirred solution of dichloroethanol derivative **6** (425 mg, 1.04 mmol) in Me_2SO (4 mL) was added tetra-*n*-butylammonium hydroxide (40 wt % solution in water, 3.4 mL, 5.19 mmol), which was stirred at rt for 5 min. After the disappearance of **6** on TLC with 1:1 hexanes−EtOAc, the reaction mixture was poured into aq NH_4-Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give crude **7**. Following, crude **7** was dissolved in MeOH (100 mL), stirred at 0 °C, and then a suspension of sodium borohydride (47 mg, 1.24 mmol) in water (40 mL) was added, and stirred for 10 min. After the disappearance of **7** on TLC with 1:3 hexanes−EtOAc, acetone (3 mL) was added, and stirred for 10 min. The reaction mixture was then evaporated to half volume, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 1:3 hexanes−EtOAc to give **8** (301 mg, 0.849 mmol, two steps, 81% yield).

7; syrup. IR (KBr neat): ν 1634 cm^{-1} (C=O).

8; syrup. IR (KBr neat): ν 3478 cm^{-1} (OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.32 (m, 5H, Ph*H*), 5.49 (d, 1H, $J_{CH,2}$ 1.2 Hz, C*H*), 4.84, 4.80 (2 × d, 2H, $J_{A,B}$ 7.0 Hz, CH_2OCH_3), 4.72, 4.69 (2 × d, 2H, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.50 (d, 1H, $J_{OH,4'a}$ 1.5 Hz, 4-OH), 4.47 (dd, 1H, $J_{1,6}$ 4.0, $J_{5,6}$ 4.0 Hz, H-6), 4.31 (dddd, 1H, $J_{1,3}$ 1.8, $J_{1,2}$ 4.0, $J_{1,5}$ 1.8 Hz, H-1), 4.21 (ddd, 1H, $J_{5,3}$ 1.8 Hz, H-5), 4.13 (ddd, 1H, $J_{2,3}$ 4.0 Hz, H-2), 4.08 (ddd, 1H, $J_{4'a,4'b}$ 11.3, $J_{4'a,OH}$ 8.6 Hz, H-4′a), 4.06 (ddd, 1H, H-1), 3.76

(27) Yoshimura, J.; Kobayashi, K.; Sato, K.; Funabashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1806−1812.
(28) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **1975**, *40*, 2764−2769.
(29) For reviews of the Ferrier reaction, see: Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831.
(30) For reviews of the Henry reaction, see: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945.
(31) Funabashi, M.; Wakai, H.; Sato, K.; Yoshimura, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, *1*, 14−19.

(dd, 1H, $J_{4'b,OH}$ 4.9 Hz, H-4′b), 3.45 (s, 3H, CH_2OCH_3), 2.14 (dd, 1H, 4′-OH). Differential NOE correlations: OH−H-2 (12.2%). Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.80; H, 6.29.

1-*O*-*tert*-Butyldimethylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4-*C*-hydroxymethyl-*myo*-inositol (16). To a solution of triol derivative **15** (1.195 g, 2.92 mmol) in CH_2Cl_2 (40 mL) were added acetone dimethylketal (3.6 mL, 29.4 mmol) and pyridinium/*p*-toluenesulfonate (100 mg, 0.398 mmol), which was stirred until the disappearance of starting compound **15** on TLC with 1:2 hexanes−EtOAc. After 5 min, the reaction mixture was quenched with Et_3N and evaporated to give a residue. The remaining residue was purified on a column of silica gel with 4:1 hexanes−EtOAc to afford **16** (1.299 g, 99% yield); syrup. IR (KBr): ν 3508 cm^{-1} (OH). ^1H NMR (200 MHz, $CDCl_3$): δ 4.95, 4.68 (2 × d, 2H, $J_{A,B}$ 6.8 Hz, CH_2OCH_3), 4.37 (dd, 1H, $J_{2,1}$ 2.9, $J_{2,3}$ 7.6 Hz, H-2), 4.24 (dd, 1H, $J_{3,5}$ 1.0 Hz, H-3), 4.21 (s, 2H, H-4′), 4.00 (dd, 1H, $J_{1,6}$ 9.3 Hz, H-1), 3.93 (ddd, 1H, $J_{6,5}$ 4.2, $J_{6,OH}$ 1.2 Hz, H-6), 3.72 (br dd, 1H, H-5), 3.44 (s, 3H, CH_2OCH_3), 2.73 (d, 1H, 6-OH), 1.49, 1.41, 1.39, 1.31 (4 × s, 12H, 2 × $C(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.14, 0.14 (2 × s, 6H, $Si(CH_3)_2$). Anal. Calcd for $C_{21}H_{40}O_8Si$: C, 56.22; H, 8.99. Found: C, 56.10; H, 9.00.

The structures of **16** were confirmed by derivatization to its acetyl derivative **16a**.

6-*O*-Acetyl-1-*O*-*tert*-butyldimethylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4-*C*-hydroxymethyl-*myo*-inositol (16a). Di-*O*-isopropilydene derivative **16** (90 mg, 201 μmol) was dissolved in 1:1 Ac_2O−pyridine (2 mL) and stirred at rt until the disappearance of **16** on TLC with 4:1 hexanes−EtOAc. After 8 h, MeOH (1 mL) was added to the reaction mixture, then evaporated and coevaporated with toluene to give **16a**; syrup. IR (KBr neat): ν 1744 cm^{-1} (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ 5.29 (dd, 1H, $J_{6,1}$ 8.9, $J_{6,5}$ 3.1 Hz, H-6), 4.83, 4.58 (2 × d, 2H, $J_{A,B}$ 6.7 Hz, CH_2OCH_3), 4.41 (dd, 1H, $J_{2,1}$ 3.1, $J_{2,3}$ 7.6 Hz, H-2), 4.21 (dd, 1H, $J_{3,5}$ 1.2 Hz, H-3), 4.21, 4.16 (2 × d, 2H, $J_{a,b}$ 9.5 Hz, H-4′), 4.15 (dd, 1H, H-1), 3.69 (dd, 1H, H-5), 3.35 (s, 3H, CH_2OCH_3), 2.07 (s, 3H, $COCH_3$), 1.51, 1.41, 1.39, 1.31 (4 × s, 12H, 2 × $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.11, 0.08 (2 × s, 6H, $Si(CH_3)_2$). Anal. Calcd for $C_{23}H_{42}O_9Si$: C, 56.30; H, 8.63. Found: C, 56.63; H, 8.39.

1-*O*-*tert*-Butyldimethylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4-*C*-hydroxymethyl-6-oxo-*myo*-inositol (17). To stirred solution of $(COCl)_2$ (85 μL, 996 μmol) in CH_2Cl_2 (10 mL) was added Me_2SO (118 μL, 1.66 μmol) at −78 °C under argon. After 30 min, a solution of alcohol **16** (150 mg, 334 μmol) in CH_2Cl_2 (1 mL) was added dropwise to the reaction mixture at −78 °C under argon and stirred. After 30 min, Et_3N (422 μL, 3.04 μmol) was added dropwise to the above mixture and stirred for 5 min. After the disappearance of **16** on TLC with 4:1 hexanes−EtOAc, the reaction mixture was poured into aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was diluted with EtOAc and washed with brine, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 4:1 hexanes−EtOAc to give **17** (142 mg, 95% yield); syrup. IR (KBr neat) 1748 cm^{-1} (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 5.08, 4.70 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2OCH_3), 4.86 (d, 1H, $J_{1,2}$ 4.3 Hz, H-1), 4.68 (dd, 1H, $J_{2,3}$ 6.9 Hz, H-2), 4.36 (d, 1H, H-3), 4.32, 4.22 (2 × d, 2H, $J_{a,b}$ 9.6 Hz, H-4′), 3.97 (s, 1H, H-5), 3.45 (s, 3H, CH_2OCH_3), 1.47, 1.42, 1.38, 1.32 (4 × s, 12H, 2 × $C(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.17, 0.07 (2 × s, 6H, $Si(CH_3)_2$). Anal. Calcd for $C_{21}H_{38}O_8Si$: C, 56.48; H, 8.58. Found: C, 56.37; H, 8.47.

(1,2,3,5/4(OH))-1-*O*-*tert*-Butyldimethylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4-*C*-hydroxymethyl-6-*C*-methylenecyclohexane-1,2,3,4,5-pentol (19). To a solution of **18** (2.520 g, 4.71 mmol) in THF (50 mL) was added sodium hydride (60% dispersion in mineral oil, 0.565 g, 14.1 mmol) under argon, which was stirred at reflux condition for 3 h. After disappearance of **18** on TLC with 5:1 hexanes−EtOAc, the reaction mixture was poured into aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The remaining residue was diluted with EtOAc and washed with brine, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 6:1 hexanes−EtOAc to give **19** (1.660 g, 79% yield); syrup. ^1H NMR (270 MHz, $CDCl_3$): δ 5.43, 5.31 (2 × m, 2H, H-6′ exo CH_2), 4.80, 4.75 (2 × d, 2H, $J_{A,B}$ 6.9 Hz, CH_2OCH_3), 4.53 (m, 1H, H-1), 4.42 (dd, 1H, $J_{2,3}$ 6.9, $J_{2,1}$ 4.3 Hz, H-2), 4.21 (d, 1H, H-3), 4.15 (s, 2H, H-4′), 4.15 (m, 1H, H-5), 3.43 (s, 3H, CH_2OCH_3), 1.48, 1.43, 1.41, 1.33 (4 × s, 12H, 2 × $C(CH_3)_2$), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.14, 0.12 (2 × s, 6H, $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{40}O_7Si$: C, 59.43; H, 9.07. Found: C, 59.31; H, 8.97.

(1,2,3,5,6/4(OH))-6′-*O*-*tert*-Butyldiphenylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4,6-di-*C*-hydroxymethylcyclohexane-1,2,3,4,5-pentol (22). To a solution of diol **20** (730 mg, 2.10 mmol) in CH_2Cl_2 (25 mL) were added *tert*-butyldiphenylsilyl chloride (647 mg, 2.52 mmol) and imidazole (571 mg, 8.39 mmol), and the mixture was stirred for 10 min at rt. After the disappearance of starting compound **20** on TLC with EtOAc, the reaction mixture was poured into aq $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried over anhyd $MgSO_4$, and evaporated to give **22** (1.074 g, 87% yield), which was purified on a column of silica gel with 4:1 hexanes−EtOAc; amorphous solid. IR (KBr): ν 3508 cm^{-1} (OH). ^1H NMR (270 MHz, $CDCl_3$): δ 7.69−7.35 (m, 10H, 2 × Ph*H*), 4.71, 4.60 (2 × d, 2H, $J_{A,B}$ 6.9 Hz, CH_2OCH_3), 4.35, 4.29 (2 × d, 2H, $J_{a,b}$ 9.6 Hz, H-4′), 4.14 (d, 1H, $J_{3,2}$ 5.3 Hz, H-3), 4.10 (dd, 1H, $J_{2,1}$ 5.3 Hz, H-2), 4.05 (br s, 1H, H-5), 4.02 (dd, 1H, $J_{6'a,6}$ 9.2, $J_{6'a,6'b}$ 10.2 Hz, H-6′a), 3.87 (dd, 1H, $J_{6'b,6}$ 6.3 Hz, H-6′b), 3.77 (m, 1H, H-1), 3.31 (s, 3H, CH_2OCH_3), 3.29 (d, 1H, $J_{OH,1}$ 9.9 Hz, OH), 2.09 (m, 1H, H-6), 1.56, 1.44, 1.42, 1.40 (4 × s, 12H, 2 × $C(CH_3)_2$), 1.05 (s, 9H, $Si(CH_3)_3$). NOE correlations: H-2−H-6; H-4′−H-3, H-5. Anal. Calcd for $C_{32}H_{46}O_8Si$: C, 65.50; H, 7.90. Found: C, 65.17; H, 7.98.

(2,3,5,6/4(OH))-6′-*O*-*tert*-Butyldiphenylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-O-methoxymethyl-4,6-di-*C*-hydroxymethyl-2,3,4,5-tetrahydroxycyclohexanone (23). To a solution of silyl ether derivative **22** (0.876 g, 1.49 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (1.268 g, 2.99 mmol), and the mixture was stirred at rt for 15 min. After the disappearance of starting compound **22** on TLC with 4:1 hexanes−EtOAc, the reaction mixture was poured into aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **23** (865 mg, 99% yield), which was purified on a column of silica gel with 4:1 hexanes−EtOAc; amorphous solid. IR (KBr): ν 1728 cm^{-1} (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ 7.66−7.35 (m, 10H, 2 × Ph*H*), 4.61, 4.54 (2 × d, 2H, $J_{A,B}$ 6.7 Hz, CH_2OCH_3), 4.44 (dd, 1H, $J_{3,5}$ 2.1, $J_{3,2}$ 6.1 Hz, H-3), 4.43, 4.35 (2 × d, 2H, $J_{a,b}$ 9.8 Hz, H-4′), 4.39 (d, 1H, H-2), 4.36 (dd, 1H, $J_{5,6}$ 2.1 Hz, H-5), 4.02 (dd, 1H, $J_{6'a,6}$ 4.9, $J_{6'a,6'b}$ 11.0 Hz, H-6′a), 3.93 (dd, 1H, $J_{6'b,6}$ 10.1 Hz, H-6′b), 3.30 (s, 3H, CH_2OCH_3), 3.28 (ddd, 1H, H-6), 1.51, 1.49, 1.36, 1.33 (4 × s, 12H, 2 × $C(CH_3)_2$), 1.05 (s, 9H, $SiC(CH_3)_3$). Anal. Calcd for $C_{32}H_{44}O_8Si$: C, 65.73; H, 7.58. Found: C, 65.64; H, 7.58.

The structure of **23** was further confirmed by reduction into **22**.

To a solution of carbonyl derivative **22** (38 mg, 65 μmol) in MeOH (1 mL) was added a solution of sodium borohydride (12 mg, 32 μmol) in 1:1 H_2O−MeOH (400 μL), which was stirred for 10 min. After the disappearance of **23** on TLC with 4:1 hexanes−EtOAc, the reaction mixture was poured into aq NH_4Cl solution, washed with brine, dried over anhyd $MgSO_4$, and evaporated to give **22** (36 mg, 95% yield), which was purified on a column of silica gel with 4:1 hexanes−EtOAc.

(1(OH),2,3,5,6/4(OH))-6′-*O*-*tert*-Butyldiphenylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-1-*C*-dichloromethyl-4,6-di-*C*-hydroxymethylcyclohexane-1,2,3,4,5-pent ol (24). To stirred solution of diisopropylamine (599 μL, 4.26 mmol) in THF (40 mL) was added *n*-butyllithium (1.54

M solution in hexane, 2.77 mL, 4.27 mmol) at −78 °C under argon. Stirring was continued for 30 min, and then dry dichloromethane (910 μL, 14.2 mmol) was added dropwise during 5 min, and the mixture was stirred for 5 min. To the above reaction mixture, ketone **23** (389 mg, 665 μmol) in THF (3 mL) was added dropwise with stirring for 10 min, and kept until the disappearance of **23** on TLC with 4:1 hexanes−EtOAc. After 10 min, to the reaction mixture was added satd aq NH_4Cl solution (10 mL), and evaporated THF to the half volume, to give a residue. The residue was extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **24** (355 mg, 79% yield), which was purified on a column of silica gel with 8:1 hexanes−EtOAc; amorphous solid. IR (KBr): ν 3460 cm^{-1} (OH). ^1H NMR (500 MHz, $CDCl_3$): δ 7.68−7.35 (m, 10H, 2 × Ph*H*), 5.70 (s, 1H, H-1′), 4.82, 4.68 (2 × d, 2H, $J_{A,B}$ 6.7 Hz, CH_2OCH$_3$), 4.48 (d, 1H, $J_{2,3}$ 6.1 Hz, H-2), 4.47 (s, 1H, OH), 4.36, 4.32 (2 × d, 2H, $J_{a,b}$ 9.5 Hz, H-4′), 4.33 (dd, 1H, $J_{5,6}$ 2.1, $J_{5,3}$ 1.2 Hz, H-5), 4.26 (dd, 1H, H-3), 4.16 (dd, 1H, $J_{6'a,6}$ 5.5, $J_{6'a,6'b}$ 10.4 Hz, H-6′a), 3.95 (dd, 1H, $J_{6'b,6}$ 10.4 Hz, H-6′b), 3.35 (s, 3H, CH$_2$OCH_3), 2.64 (ddd, 1H, H-6), 1.52, 1.46, 1.42, 1.39 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.06 (s, 9H, SiC(CH_3)$_3$). Differential NOE correlations: H-2−CHCl$_2$ (5.5%), H-6 (4.7%). Anal. Calcd for $C_{33}H_{46}Cl_2O_8Si$: C, 59.18; H, 6.92. Found: C, 58.99; H, 6.86.

(2,3,5,6/1(N$_3$),4(OH))-1-Azido-6′-*O*-*tert*-butyldiphenylsilyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-4,6-di-*C*-hydroxymethyl-2,3,4,5-tetrahydroxycyclohexane-1-carbaldehyde (25). To a solution of dichloroethanol derivative **24** (355 mg, 530 μmol) in Me_2SO (7 mL) were added sodium azide (207 mg, 3.18 mmol) and 15-crown-5 (315 μL, 1.59 mmol), and the mixture was stirred at 90 °C for 14 h. After the disappearance of **24** on TLC with 6:1 hexanes−EtOAc, the reaction mixture was poured into aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **25** (217 mg, 63% yield), which was purified on a column of silica gel with 6:1 hexanes−EtOAc; amorphous solid. IR (KBr): ν 2110 cm^{-1} (N$_3$), 1719 cm^{-1} (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ 9.70 (s, 1H, CHO), 7.66−7.34 (m, 10H, 2 × Ph*H*), 4.72, 4.58 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2OCH$_3$), 4.50 (d, 1H, $J_{2,3}$ 6.3 Hz, H-2), 4.44, 4.36 (2 × d, 2H, $J_{a,b}$ 9.6 Hz, H-4′), 4.39 (br d, 1H, H-3), 4.17 (br d, 1H, H-5), 3.89 (dd, 1H, $J_{6'a,6}$ 4.3, $J_{6'a,6'b}$ 10.6 Hz, H-6′a), 3.36 (dd, 1H, $J_{6'b,6}$ 10.9 Hz, H-6′b), 3.33 (s, 3H, CH$_2$OCH_3), 2.31 (ddd, 1H, $J_{6,5}$ 2.0 Hz, H-6), 1.48, 1.45, 1.42, 1.38 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.03 (s, 9H, SiC(CH_3)$_3$). NOE correlations: H-4′−H-3, H-5; H-2−H-6. Anal. Calcd for $C_{33}H_{45}N_3O_8Si$: C, 61.95; H, 7.09; N, 6.57. Found: C, 61.79; H, 7.37; N, 6.20.

Racemate of (1,2,4,5/3(OH),6(N$_3$))-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-1,2;3,3′-di-*O*-isopropylidene-4-*O*-methoxymethyl-6-*C*-(*S*)-(6′-cyano-6′-hydroxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol and Its Enantiomer (26) and Racemate of (1,2,4,5/3(OH),6(N$_3$))-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-1,2;3,3′-di-*O*-isopropylidene-4-*O*-methoxymethyl-6-*C*-(*R*)-(6′-cyano-6′-hydroxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol and Its Enantiomer (26a). To a solution of aldehyde **25** (151 mg, 236 μmol) in MeOH (70 mL) were added triethylamine (320 μL, 2.3 mmol) and trimethylsilyl cyanide (610 μL, 4.6 mmol), and the mixture was stirred at 50 °C for 5 h. After the disappearance of **25** on TLC with 4:1 hexanes−EtOAc, acetic acid (500 μL) was added, and then the mixture was poured into brine, extracted with EtOAc, washed with brine, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 4:1 hexanes−EtOAc to give **26** (R_f 0.3, 72 mg, 45% yield) and **26a** (R_f 0.4, 44 mg, 29% yield), respectively.

26, R_f 0.3 (4:1 hexanes−EtOAc); mp 170−172 °C (hexanes−EtOAc). IR (KBr): ν 3358 cm^{-1} (OH), 2110 cm^{-1} (N$_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 7.61−7.24 (m, 10H, 2 × Ph*H*), 5.10 (d, 1H, $J_{6',OH}$ 6.9 Hz, H-6′), 4.59, 4.49 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2-OCH$_3$), 4.39 (dd, 1H, $J_{1,2}$ 6.9, $J_{1,5}$ 0.7 Hz, H-1), 4.28 (d, 1H, H-2), 4.02 (d, 1H, $J_{4,5}$ 3.3 Hz, H-4), 3.79 (dd, 1H, $J_{5'a,5}$ 1.7, $J_{5'a,5'b}$ 10.2 Hz, H-5′a), 3.81, 3.74 (2 × d, 2H, $J_{a,b}$ 8.6 Hz, H-3′), 3.73 (dd, 1H, $J_{5'b,5}$ 10.2 Hz, H-5′b), 3.57 (d, 1H, OH), 3.27 (s, 3H, CH$_2$OCH_3), 2.53 (dddd, 1H, H-5), 1.34, 1.33, 1.30, 1.23 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.02 (s, 9H, SiC(CH_3)$_3$). Anal. Calcd for $C_{34}H_{46}N_4O_8Si$: C, 61.24; H, 6.95; N, 8.40. Found: C, 61.44; H, 6.70; N, 8.22.

26a, R_f 0.4 (4:1 hexanes−EtOAc); mp 168−170 °C (hexanes−EtOAc). IR (KBr): ν 3346 cm^{-1} (OH), 2110 cm^{-1} (N$_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 7.64−7.29 (m, 10H, 2 × PhH), 5.21 (d, 1H, $J_{6',OH}$ 5.6 Hz, H-6′), 4.71, 4.53 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2OCH$_3$), 4.21 (d, 1H, OH), 4.18 (d, 1H, $J_{2,1}$ 6.6 Hz, H-2), 4.02 (d, 1H, $J_{4,5}$ 4.6 Hz, H-4), 3.98 (dd, 1H, $J_{1,5}$ 1.7 Hz, H-1), 3.83 (dd, 1H, $J_{5'a,5}$ 2.3, $J_{5'a,5'b}$ 10.1 Hz, H-5′a), 3.58 (dd, 1H, $J_{5'b,5}$ 10.3 Hz, H-5′b), 3.48, 3.42 (2 × d, 2H, $J_{a,b}$ 7.9 Hz, H-3′), 3.33 (s, 3H, CH$_2$OCH_3), 2.71 (dddd, 1H, H-5), 1.30, 1.28, 1.26, 1.16 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.02 (s, 9H, SiC(CH_3)$_3$). Anal. Calcd for $C_{34}H_{46}N_4O_8Si$: C, 61.24; H, 6.95; N, 8.40. Found: C, 61.43; H, 6.86; N, 8.14.

Racemate of (1,2,4,5/3(OH),6(N$_3$))-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-1,2:3,3′-di-*O*-isopropylidene-4-*O*-methoxymethyl-6-*C*-(*S*)-(6′-cyano-6′-methoxymethoxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol and Its Enantiomer (27). To a solution of cyanohydrin **26** (118 mg, 177 μmol) in CH_2Cl_2 (6 mL) were added dimethoxymethane (790 μL, 8.9 mmol) and molecular sieves 4A (50 mg), and P_2O_5 (20 mg, 140 μmol), and the mixture was stirred at rt. After the disappearance of **26** on TLC with 4:1 hexanes−EtOAc, the reaction mixture was quenched with triethylamine, and then molecular sieves were filtered off, poured into aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 4:1 hexanes−EtOAc to give **27** (118 mg, 93% yield); syrup. IR (KBr): ν 2110 cm^{-1} (N$_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 7.69−7.33 (m, 10H, 2 × Ph*H*), 5.45 (s, 1H, H-6′), 4.94, 4.82 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2OCH$_3$), 4.71, 4.59 (2 × d, 2H, $J_{A,B}$ 6.6 Hz, CH_2OCH$_3$), 4.49 (dd, 1H, $J_{1,2}$ 6.6, $J_{1,5}$ 1.7 Hz, H-1), 4.35 (d, 1H, H-2), 4.22 (d, 1H, $J_{4,5}$ 4.3 Hz, H-4), 3.71 (dd, 1H, $J_{5'a,5}$ 3.0, $J_{5'a,5'b}$ 10.2 Hz, H-5′a), 3.57 (dd, 1H, $J_{5'b,5}$ 10.2 Hz, H-5′b), 3.60, 3.52 (2 × d, 2H, $J_{a,b}$ 7.9 Hz, H-3′), 3.52, 3.36 (2 × s, 6H, 2 × CH$_2$OCH_3), 2.55 (dddd, 1H, H-5), 1.38, 1.33, 1.32, 1.24 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.10 (s, 9H, SiC(CH_3)$_3$). Anal. Calcd for $C_{36}H_{50}N_4O_9Si$: C, 60.82; H, 7.09; N, 7.88. Found: C, 60.96; H, 7.30; N, 7.58.

Racemate of (1,2,4,5/3(OH),6(N$_3$))-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-1,2:3,3′-di-*O*-isopropylidene-6-*C*-(*S*)-(6′-formyl-6′-methoxymethoxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol-6″,4-lactone and Its Enantiomer (29). To a solution of DL-**28** (73 mg, 102 μmol) in 1:1 acetone−CH_2Cl_2 (7 mL) was added Jones reagent (2.67 M aq H_2SO_4 solution, 90 μL, 240 μmol) at 0 °C, which was stirred for 30 min. After the disappearance of **28** on TLC with 3:1 hexanes−EtOAc, the reaction mixture was quenched with isopropyl alcohol (100 μL) and poured into aq $NaHCO_3$ solution. The mixture was then extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The residue was purified on a column of silica gel with 3:1 hexanes−EtOAc to give **29** (61 mg, 90% yield); syrup. IR (KBr): ν 2108 cm^{-1} (N$_3$), 1755 cm^{-1} (CO). ^1H NMR (600 MHz, $CDCl_3$): δ 7.78−7.38 (m, 10H, Ph*H*), 4.81, 4.51 (2 × d, 2H, $J_{A,B}$ 6.5 Hz, CH_2OCH$_3$), 4.76 (s, 1H, H-4), 4.55 (d, 1H, $J_{2,1}$ 6.2 Hz, H-2), 4.43, 4.27 (2 × d, 2H, $J_{a,b}$ 10.0 Hz, H-3′), 4.38 (d, 1H, $J_{6',5}$ 1.4 Hz, H-6′), 4.32 (dd, 1H, $J_{1,5}$ 1.4 Hz, H-1), 4.01 (dd, 1H, $J_{5'a,5}$ 10.7 Hz, H-5′a), 3.93 (dd, 1H, $J_{5'a,5'b}$ 11.0, $J_{5'b,5}$ 3.3 Hz, H-5′b), 3.26 (s, 3H, OCH_3), 2.41 (dddd, 1H, H-5), 1.52, 1.46, 1.45, 1.37 (4 × s, 12H, 2 × C(CH_3)$_2$), 1.05 (s, 9H, SiC(CH_3)$_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.0, 135.5, 135.5, 133.2, 133.1, 129.8, 129.8, 127.8, 127.7, 111.7, 110.5, 96.6, 79.4, 79.0, 78.6, 78.0, 70.6, 69.1, 64.1, 59.3, 56.5, 38.6, 27.1, 26.8, 26.1, 24.7, 24.5, 19.2. Anal. Calcd for $C_{34}H_{45}N_3O_9Si$: C, 61.15; H, 6.79; N, 6.29. Found: C, 61.40; H, 7.17; N, 6.34.

Racemate of (1,2,4,5/3(OH),6(NH))-6-*N*-[*N*,*N*′-bis-(*tert*-buthoxycarbonyl)-guanidino]-1,2:3,3′-di-*O*-isopropylidene-6-*C*-(*S*)-(6′-methoxymethoxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol-6″,4-lactone and Its Enantiomer (32). To a solution of amine **31** (20 mg, 49.6 μmol) in dry *N*,*N*′-dimethylformamide (2 mL) were added *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea[23] (205 mg, 0.7 mmol) and triethylamine (97 μL, 0.7 mmol), and then at 0 °C mercury(II) chloride (27 mg, 0.1 mmol) was added, and stirred at 5−10 °C. After 10 min, the reaction mixture was cooled to 0 °C again, mercury(II) chloride (27 mg, 0.1 mmol) was added, warmed to 5−10 °C again, and stirred for 10 min. This procedure was repeated five times with the use of mercury(II) chloride (27 mg × 5, 0.1 mmol × 5), and stirred for 20 min. After the disappearance of **30** on TLC with 1:1 hexanes−EtOAc, the reaction mixture was filtered through a pad of Celite, washed with chloroform, and evaporated to give a residue. The residue was purified on a column of silica gel with 3:2 hexanes−EtOAc to give guanidine derivative **32** (23 mg, 72% yield); syrup. IR (KBr neat): ν 3527 cm^{-1} (OH), 3257 cm^{-1} (NH), 1747, 1726, 1645, 1633, 1626 cm^{-1} (C=O and C=N). ^{1}H NMR (600 MHz): 11.29 (s, 1H, NH), 8.49 (s, 1H, NH), 5.18 (s, 1H, H-6′), 5.13 (d, 1H, $J_{1,2}$ 6.9 Hz, H-1), 4.89, 4.84 (2 × d, 2H, $J_{A,B}$ 6.4 Hz, CH_2-OCH$_3$), 4.73 (dd, 1H, $J_{5'a,5'b}$ 5.5, $J_{5'a,5}$ 11.9 Hz, H-5′a), 4.36 (dd, 1H, $J_{2,4}$ 1.0 Hz, H-2), 4.36 (dd, 1H, $J_{5'b,5}$ 5.5 Hz, H-5′b), 4.32, 4.22 (2 × d, 2H, $J_{A,B}$ 9.6 Hz, H-3′), 3.83 (ddd, 1H, $J_{4,5}$ 6.2, $J_{4,OH}$ 11.7 Hz, H-4), 3.41 (s, 3H, CH$_2$OCH_3), 3.08 (ddd, 1H, H-5), 2.71 (d, 1H, OH), 1.48, 1.47 (2 × s, 18H, COC(CH_3)$_3$), 1.48, 1.47, 1.39, 1.32 (4 × s, 12H, 2 × C(CH_3)$_2$). ESI-TOF-MS calcd for $C_{29}H_{48}N_3O_{13}$ *m*/*z* [M + H]$^+$: 646.3182. Found: 646.3187.

Racemate of (1,2,4,5/3(OH),6(NH))-5′-*O*-acetyl-6-*N*-[*N*,*N*′-bis-(*tert*-buthoxycarbonyl)-guanidino]-1,2:3,3′-di-*O*-isopropylidene-6-*C*-(*S*)-(6′-methoxymethoxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol-6″,4-lactone and Its Enantiomer (32a). Guanidine derivative **32** (5 mg, 7.7 μmol) was dissolved in 1:1 Ac$_2$O−pyridine (1 mL), and stirred at rt until the disappearance of **32** was indicated by TLC with 2:1 hexanes−EtOAc. After 24 h, MeOH (1 mL) was added to the reaction mixture, then evaporated and coevaporated with toluene to give **32a** (5.3 mg, quantitatively); mp 151−152 °C (hexanes−ethanol). IR (KBr neat): ν 3444 cm^{-1} (NH), 1745, 1737, 1728, 1643, 1620 cm^{-1} (C=O and C=N). ^{1}H NMR (600 MHz) δ 11.32, 8.78 (1H, s, NH), 5.77 (d, 1H, H-2, $J_{2,1}$ 6.4 Hz), 5.09, 4.77 (2 × d, 2H, $J_{A,B}$ 6.4 Hz), 4.52 (s, 1H, H-4), 4.51 (d, 1H, H-6′, $J_{6',1}$ 1.4 Hz), 4.45, 4.16 (2 × d, 2H, $J_{a,b}$ 9.8 Hz, H-3′), 4.37 (dd, 1H, H-1), 4.28 (dd, 1H, $J_{1'a,1'b}$ 11.7, $J_{1'a,1}$ 4.1 Hz, H-1′a), 4.25 (dd, 1H, $J_{1'b,1}$ 9.3 Hz, H1′b), 4.15 (dd, 1H, H-1), 3.50 (s, 3H, CH$_2$OCH_3), 2.02 (s, 3H, COCH_3), 1.47, 1.46 (2 × s, 18H, COC(CH_3)$_3$), 1.54, 1.45, 1.42, 1.36 (4 × s, 12H, 2 × C(CH_3)$_2$). ESI-TOF-MS calcd for $C_{31}H_{50}N_3O_{14}$ *m*/*z* [M + H]$^+$: 688.3287. Found: 688.3250.

(±)-Tetrodotoxin. To a solution of *N*,*N*′-bis(*tert*-butoxycarbonyl)guanidine **32** (2.7 mg, 4.77 μmol) in dry dichloromethane (0.3 mL) was added pyridinium chlorochromate (PCC) (8 mg, 37 μmol), and the mixture was stirred at rt for 30 min. After the disappearance of **32** by TLC analysis with 1:1 hexanes−EtOAc, the reaction mixture was filtered through a pad of Celite, washed with chloroform, and evaporated to give a residue. The remaining residue was purified on a column of silica gel with EtOAc to give oxidation mixture **33** (**33a** and **33b**, quantitatively). Following, the mixture **33** was dissolved in MeOH (0.3 mL) and HCl (4 M solution of 1,4-dioxane, 0.1 mL), and stirred at rt for 24 h. The mixture was concentrated under reduced pressure to give a residue. The remaining residue was dissolved in 30% aq TFA, and stirred for 12 h. The mixture was concentrated under reduced pressure to give a residue. Finally, the mixture was dissolved in 4% aq AcOH, and stirred at rt for 14 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by HPLC on a Hitachi-gel #3013-c column (H$^+$ form, 4.6 × 150 mm, 0.05 N aq AcOH, peaks were monitored by RID)[15a] to give (±)-TTX (including a slight lactone form by ^{1}H NMR), and (±)-anhydroTTX in 30% (450 μg) and 10% yield (150 μg) (from DL-**32**), respectively.

(±)-Tetrodotoxin. ^{1}H NMR (600 MHz, in 3% CD$_3$COOD/D$_2$O, referenced to C*H*D$_2$COOD (2.06 ppm)): δ 5.50 (d, 1H, *J* 8.9 Hz, H-4), 4.30 (d, 1H, *J* 2.1 Hz, H-8), 4.25 (br s, 1H, H-5), 4.09 (t, 1H, *J* 2.1 Hz, H-7), 4.06, 4.01 (2 × d, 2H, *J* 12.4 Hz, H-11), 3.96 (s, 1H, H-9), 2.35 (d, 1H, *J* 9.6 Hz, H-4a). ESI-TOF-MS calcd for $C_{11}H_{18}N_3O_8$ *m*/*z* [M + H]$^+$: 320.1094. Found: 320.1085.

(±)-4,9-Anhydro-4-*epi*-tetrodotoxine. ^{1}H NMR (600 MHz, in 3% CD$_3$COOD/D$_2$O, referenced to C*H*D$_2$COOD (2.06 ppm)): δ 5.53 (s, 1H, H-4), 4.63 (d, 1H, *J* 2.1 Hz, H-8), 4.58 (s, 1H, H-9), 4.36 (dd, 1H, *J* 2.2, *J* 2.6 Hz, H-5), 4.17 (t, 1H, *J* 2.1, *J* 2.6 Hz, H-7), 4.00, 3.92 (2 × d, 2H, *J* 12.2 Hz, H-11), 2.94 (d, 1H, *J* 2.6 Hz, H-4a). ESI-TOF-MS calcd for $C_{11}H_{16}N_3O_7$ *m*/*z* [M + H]$^+$: 302.0983. Found: 302.1022.

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Supporting Information Available: Experimental details and analytical and spectral characterization data for **4**, **5**, **9**−**15**, **18**, **20**, **20a**, **21**, **24a**, **28**, **30**, and **31**; copies of ^{1}H NMR of **27**−**31**, **32a**, synthetic (±)-tetrodotoxin, and synthetic (±)-4,9-anhydro-4-*epi*-tetrodotoxine; ESI-TOF-MS spectrometric data for **32** and **32a**, and synthetic (±)-tetrodotoxin and (±)-4,9-anhydro-4-*epi*-tetrodotoxine; X-ray crystal structures of **26** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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