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Stereoselective and Efficient Total Synthesis of Optically Active Tetrodotoxin from D-Glucose

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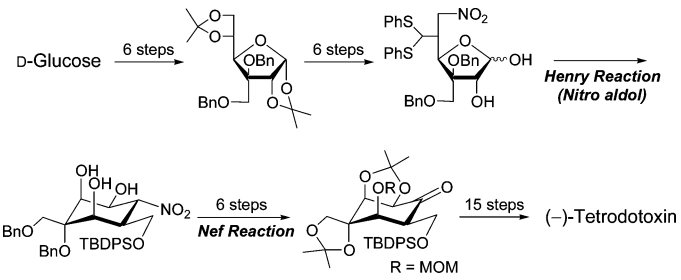

A stereoselective and efficient total synthesis of optically active tetrodotoxin (TTX) is described. A polyfunctionalized key cyclitol compound containing branched-chains for the synthesis of TTX was prepared from D-glucose employing the Henry reaction (Nitro aldol reaction) as the key transformation. Stereoselective construction of the α-azido-aldehyde branched-chain was achieved via the key spiro α-chloroepoxide intermediate.

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 reported by four research groups: Tsuda et al.,[2] Hirata et al.,[3] Woodward et al.,[4] and Mosher et al.[5] (the original name was "taricatoxin") (Figure 1). TTX is known to selectively interact with elements of the sodium channel, thus inhibiting its activity in the cell membrane.[6] Therefore, TTX is utilized as a tool to analyze various vital events that occur via the sodium channel.[7] TTX has been found and isolated not only from the puffer fish, but also from newts, frogs, octopi, crabs, shellfish, and numerous other animals. Furthermore, it is clear that the animals themselves do not produce TTX, but rather, it is produced by bacteria such as *Alteromonas sp.*, *Vibrio sp.*, and *Shewanella*, etc.[8] Yasumoto proposed the biosynthetic pathway of TTX based on the structure of TTX and its analogues.[9,10] TTX and its analogues are expected to provide much important information toward progress in areas such as pharmaceutical studies, elucidation of structure−activity relationships, and biological roles.[11] Therefore, a facile and large-scale synthesis of TTX and its

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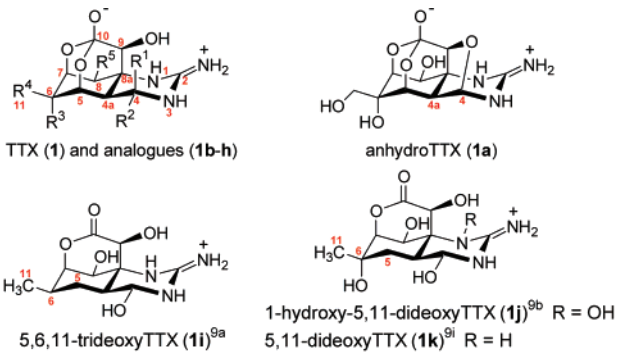
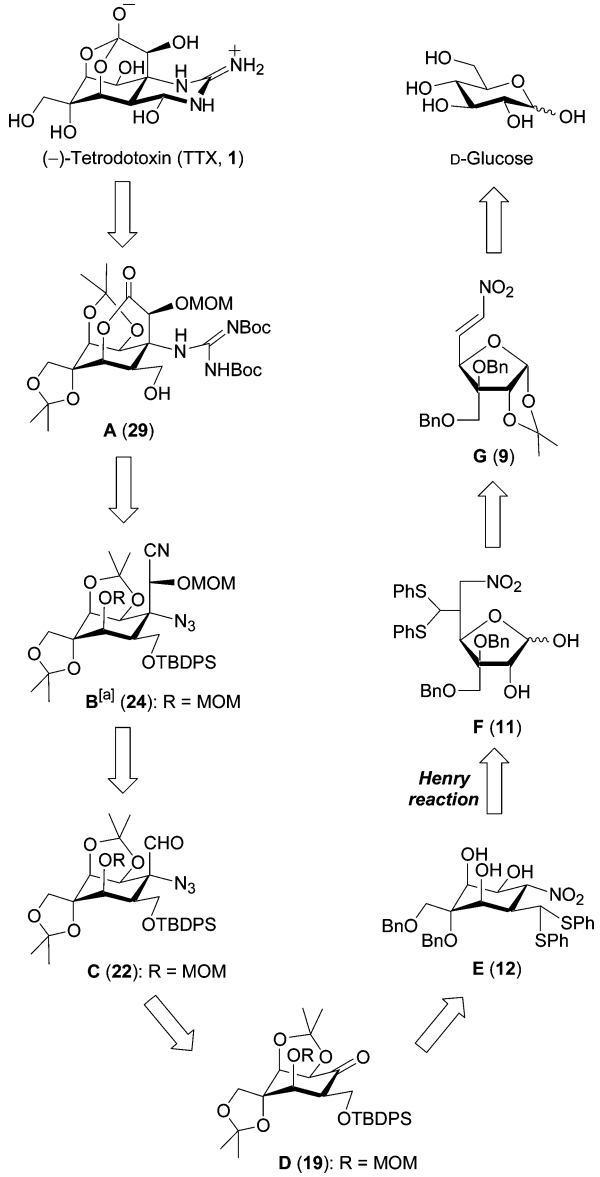


	R^1	R^2	R^3	R^4	R^5
TTX (**1**)[4,5]	H	OH	OH	CH_2OH	OH
4-*epi*TTX (**1b**)[9c]	OH	H	OH	CH_2OH	OH
6-*epi*TTX (**1c**)[9d]	H	OH	CH_2OH	OH	OH
11-deoxyTTX (**1d**)[9d]	H	OH	OH	CH_3	OH
8,11-dideoxyTTX (**1e**)[9e]	H	OH	OH	CH_3	H
11-oxoTTX (**1f**)[9f]	H	OH	OH	CHO	OH
11-norTTX-6(*R*)-ol (**1g**)[9g]	H	OH	H	OH	OH
11-norTTX-6(*S*)-ol (**1h**)[9h]	H	OH	OH	H	OH

FIGURE 1. Tetrodotoxin (**1**) and its analogues (**1a**−**k**).

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

SCHEME 1. Retrosynthetic Analysis of (−)-TTX from D-Glucose



[a] The actual conformation of **B** is different: see compound **24**.

We have been engaged in the total syntheses of naturally occurring branched-chain cyclitol compounds such as cyclophellitol,[16] mytillitol, laminitol,[17] and (−)-TTX[18] starting from

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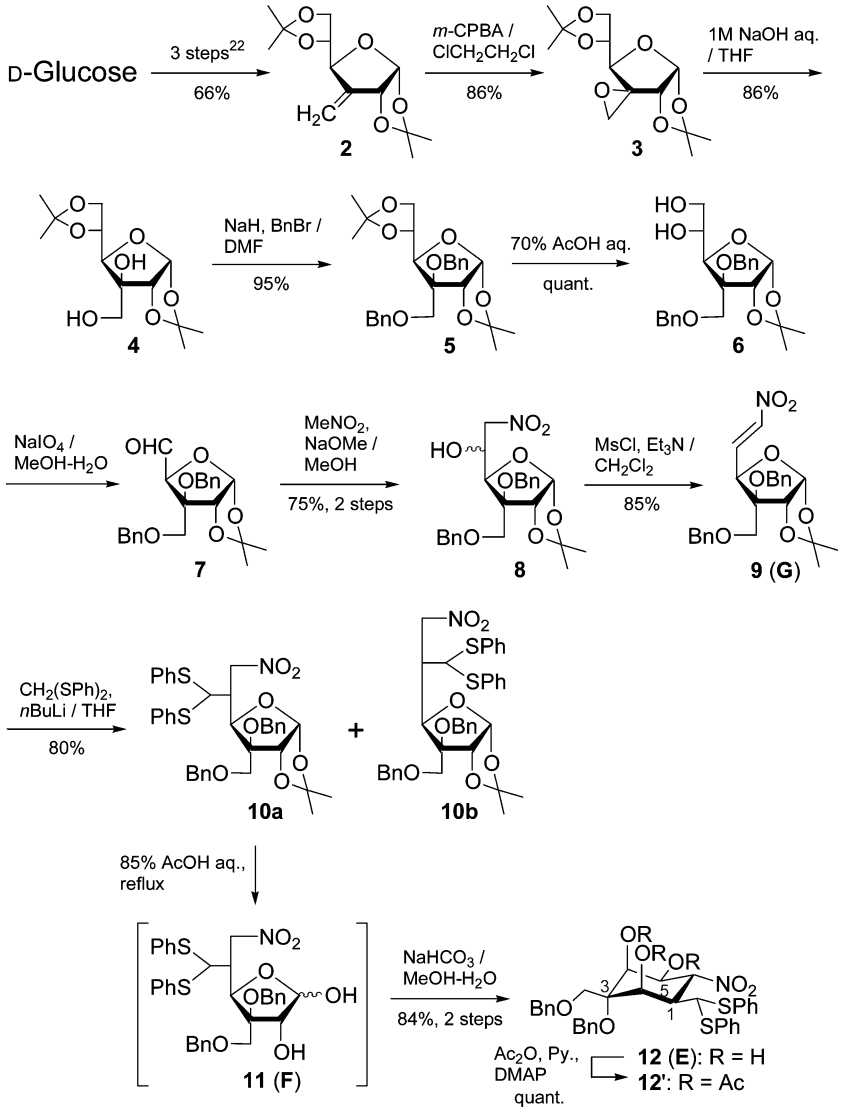
SCHEME 2. Synthesis of the Nitro Cyclitol 12 (E) Employing the Henry Reaction



D-glucose. On the basis of these investigations, we have recently accomplished a novel and stereoselective synthesis of (±)-TTX from *myo*-inositol.[19] Herein, we describe the total synthesis of optically active TTX from D-glucose employing the Henry reaction (Nitro aldol reaction)[20] as the key transformation.

Scheme 1 shows the retrosynthetic plan for the synthesis of (−)-TTX from D-glucose, which focuses on the preparation of the key intermediate, ketone **D**. This intermediate has previously been successfully converted to TTX in our laboratory.[19] In a previous work, we synthesized (±)-TTX via compounds **A**, **B**, **C**, and **D**. Therefore, synthesis of optically active compound **D** from D-glucose was a promising route to the synthesis of (−)-TTX. Compound **D** can be synthesized from compound **E** by employing the Henry reaction, as previously described.[18c] The key intermediate, **E**, was synthesized using standard reactions from D-glucose, as described below.

Results and Discussion

3-*C*-Hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hexofuranose (**4**)[21] was prepared by stereoselective *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose (**2**)[22] derived from D-glucose, followed by hydrolysis with 1 M aq NaOH. The two hydroxyl groups of **4** were protected with a

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(21) Yoshimura, J.; Kobayashi, K.; Sato, K.; Funabashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1806−1812.

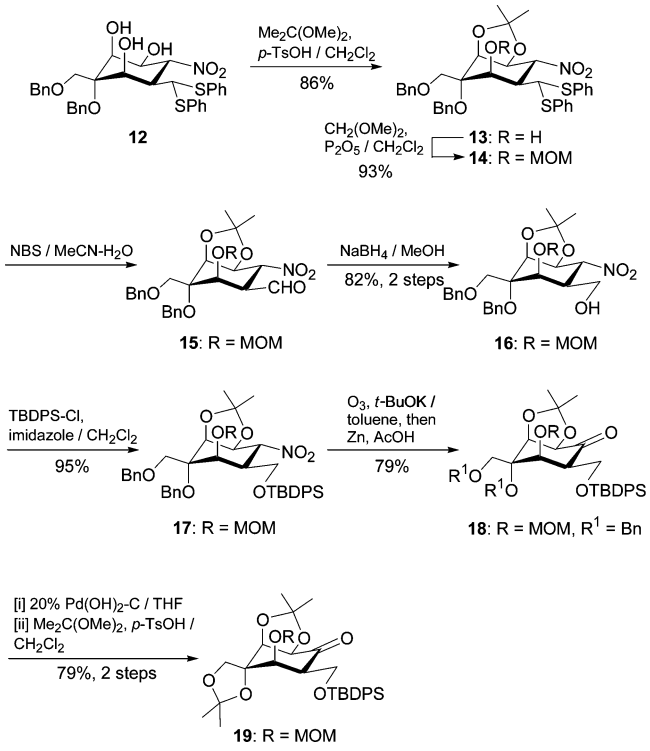
benzyl (Bn) group to give 3,3′-di-*O*-benzyl derivative **5** in 80% yield. Compound **5** was then selectively hydrolyzed using 70% aq acetic acid at room temperature to give the 5,6-diol **6** in quantitative yield. Oxidative degradation of **6** with sodium metaperiodate in aqueous methanol gave the corresponding aldehyde **7**, which was then treated with nitromethane in methanol in the presence of sodium methoxide to give nitro alcohol **8** (diastereomer ratio = ca. 10:1) in 75% yield (2 steps). The diastereomeric mixture of nitro alcohol **8** was treated with methanesulfonyl chloride in the presence of triethylamine to give the corresponding single nitro-olefin **9** (**G** in Scheme 1) in 85% yield. Reaction of **9** with lithium diisopropylamide (LDA) and bis(phenylthio)methane gave the branched bis(phenyl)dithioacetal derivative **10a** and **10b**. The ratio of **10a**:**10b** (ca. 10:1) was determined by ^{1}H NMR (comparison of the intensities of H-5) of the crude mixture. The addition of dithioacetal anion proceeded with higher stereoselectivity (ca. 10:1) than that of our previous report[18c] using 1,3-dithiane (ca. 5:4). The higher stereoselectivity might be induced by the bulkiness of the reagent, bis(phenylthio)methane. The desired compound **10a** was isolated by fractional crystallization in 80% yield. The configuration at *C*-5 of **10a** was determined by derivation into the corresponding cyclitol compound **12′**, as described below.

The 1,2-*O*-isopropylidene group of **10a** was hydrolyzed upon treatment with 85% aq acetic acid under reflux. The resultant nitro-sugar **11** (**F** in Scheme 1) was treated with 1.5 mol equiv of sodium hydrogencarbonate in aqueous methanol to give a crystalline *muco*-inositol derivative (**12**)[23] (**E** in Scheme 1) in 84% yield (2 steps). Acetylation of **12** under standard conditions gave tri-*O*-acetate **12′** quantitatively. The coupling constant for **12′** ($J_{1,2}$ = 2.5 Hz, $J_{4,5}$ = 3.5 Hz, $J_{1,6}$ = $J_{5,6}$ = 11.0 Hz) suggested the shown configuration for *C*-5 (*C*-8 in TTX numbering). In the above reaction (Henry reaction), the formation of four stereoisomers including **12** is possible, but the undesired three stereoisomers were not isolated at all. This stereoselectivity might be rationalized by the thermodynamic stability of **12**.

Reaction of the *vicinal*-diol of **12** with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) gave the corresponding acetonide **13** in 86% yield. Acetonide **13** was then treated with dimethoxymethane and diphosphorous pentoxide to give the fully protected cyclitol **14** in 93% yield. Treatment of **14** with *N*-bromosuccinimide (NBS) in aqueous acetonitrile gave the unstable aldehyde **15**, which was immediately reduced with sodium borohydride to give the hydroxymethyl derivative **16** in 82% yield (2 steps). Silylation of **16** with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole gave the fully protected nitro cyclitol **17** in 95% yield (Scheme 3).

The transformations of the nitro derivative into the carbonyl derivative were subsequently examined. Initially, compound **17** was treated with potassium *tert*-butoxide (*t*-BuOK) and *m*-CPBA in benzene[24a] to give a polar decomposed compound(s) and a very slight amount of the desired product **18** (ca. 5% yield). It seems that some side reactions (mainly retro-aldol reaction and

SCHEME 3. Synthesis of Key Intermediate 19 (D)



subsequently decomposition under basic conditions) had been proceeding in the oxidation of the nitronate intermediate. Therefore, McMurry's transformation[24b] from the nitronate to the carbonyl was applied as follows. Compound **17** was treated with *t*-BuOK, and the resulting nitronate was subjected to ozonolysis (O_3) in toluene at −78 °C to give the required ketone **18** in moderate yield (79%). The transformation of **18** into compound **19** (**D** in Scheme 1) was achieved by catalytic reduction, and subsequent acetonide protection of the resulting diol in 79% yield (2 steps) (Scheme 3).

The further conversion of ketone **19** into (−)-TTX was carried out to established our route for (±)-TTX synthesis including successive spiro α-chloroepoxide formation and its ring-opening with azide anion[25] as a crucial key step.

To obtain compound **22**, ketone **19** was treated with lithium diisopropylamide (LDA) and dichloromethane at −78 °C to give the expected dichloroethanol derivative **20** as a single isomer in 79% yield. The dichloroethanol derivative **20** was treated with NaN_3 and 15-crown-5 ether in DMSO (Me_2SO) at 75 °C to give the α-azido-aldehyde **22** (**C** in Scheme 1) via spiro α-chloroepoxide derivative **21** in 64% yield, with complete stereo- and regioselectivities. The structure of **22** including the stereochemistry at *C*-6 (*C*-8a in TTX numbering) was determined by X-ray structure analysis. The reaction of α-azido-aldehyde **22** and TMS−CN/Et_3N in MeOH gave the corresponding cyanohydrin **23** and its epimer **23a** in 56% and 17% yields, respectively. The stereochemistry at *C*-6′ (*C*-9 in TTX numbering) of **23** was the same as that observed in the total

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(23) The IUPAC name of compound **11** is 1-L-(1,2,3′,4,5/3,6)-3-hydroxymethyl-3,3′-di-*O*-benzyl-6-nitro-2,3,4,5-tetrahydroxy cyclohexanecarbaldehyde diphenyldithioacetal.

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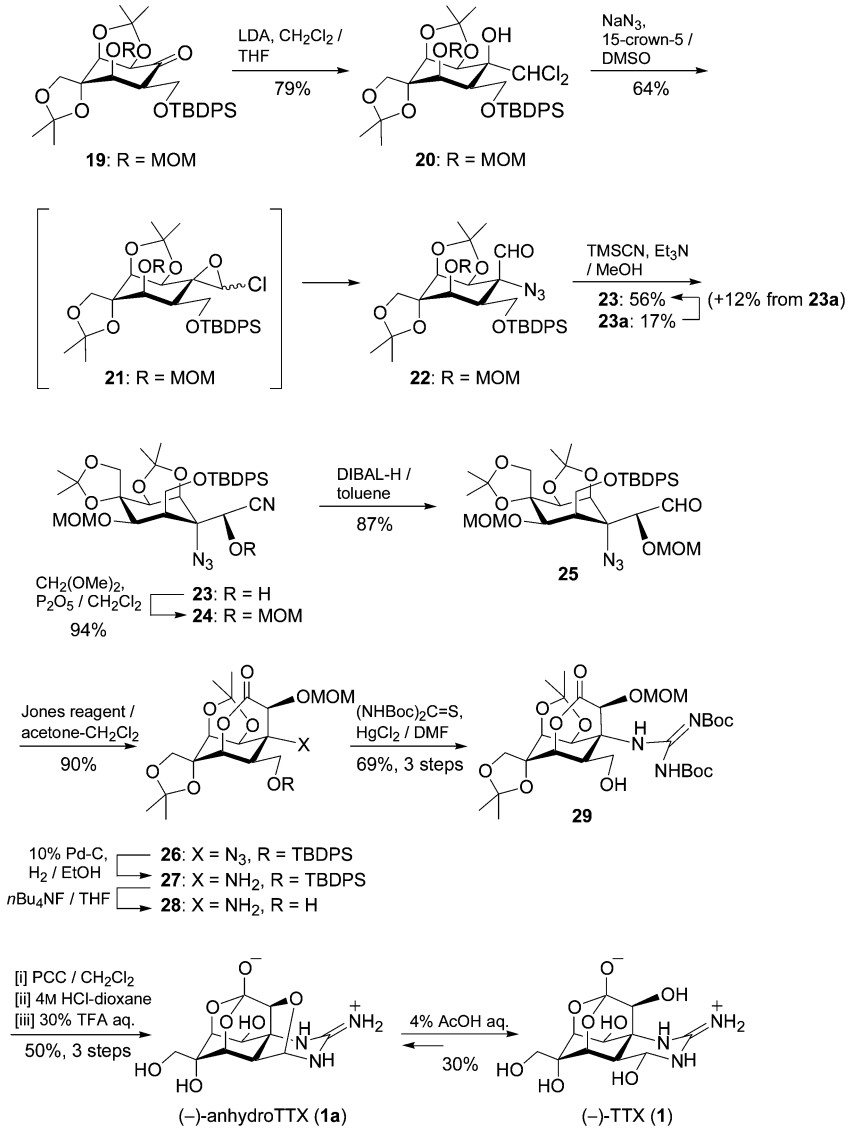
SCHEME 4. The Further Conversion of Ketone 19 (D) into (−)-TTX (1)



synthesis of (±)-TTX.[19] The undesired isomer **23a** could be isomerized into the desired isomer **23** under the same reaction conditions. After two cycles of this operation, the total yield of **23** was 68%. To introduce amino and orthoester moieties, the hydroxyl group of **23** was protected with the methoxymethyl (MOM) group, and subsequently treated with diisobutylaluminium hydride (DIBAL-H) to give the corresponding aldehyde **25** in 82% yield. Selective deprotection of the MOM group at *O*-4 (*O*-5 in TTX numbering) of **25** and subsequent treatment with Jones' reagent gave the *δ*-lactone **26** in 90% yield as a single product. The monitoring of the reactions of aldehyde **24** by TLC (hexane/ethyl acetate 4:1) suggested that the deprotection of the MOM group was first undertaken to form the hemiacetal intermediate **25′**, then it was immediately oxidized into *δ*-lactone **26**. To introduce the guanidine moiety, the azido group of **26** was first reduced with 10% Pd−C and H_2 to give the amine **27** in quantitative yield. Subsequent deprotection of the TBDPS group using tetra-*n*-butylammononium fluoride (TBAF) gave alcohol **28**. Guanidinylation[26] of **28** provided the precursor **29** (**A** in Scheme 1), which was converted to 4,9-anhydro-4-*epi*-TTX (anhydroTTX, **1a**) by oxidation with pyridinium chlorochromate (PCC) and subsequent treatment with 4M HCl−dioxane/MeOH,[15a,b] and followed by 30% aq CF_3COOH solution in 50% yield. Isomerization of **1a** by treatment with 4% aq acetic acid solution at 60 °C for 2 days yielded a 1:4 mixture of **1a** and **1**. The mixture was purified by HPLC[15a] to give **1** in 56% yield (Scheme 4). The spectral data (^1H, MS) for synthetic **1** were in good agreement with those of the natural TTX[9d,15a,b,27] (Scheme 4 and Table 1). Moreover, the specific rotation of the synthetic **1a** and **1** was $[\alpha]_D^{28}$ +1.2 (*c* 0.18, 3% AcOH aq) and $[\alpha]_D^{28}$ −3.75 (*c* 0.13, 3% AcOH aq), respectively. Both rotation values were in good agreement with that reported by Isobe's group.[15a−c,e] Full experimental details for conversion of **19** into (−)-TTX are available in the Supporting Information.

In conclusion, we have accomplished the total synthesis of optically active (−)-TTX from D-glucose employing the Henry reaction as a key framework with a highly stereoselective

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(27) A sample of natural (−)-tetrodotoxin was obtained from Sankyo Co. Ltd. (Tokyo, Japan).

TABLE 1. Comparative ^{1}H NMR Data of Tetrodotoxin

position	synthetic TTX[a]	natural TTX[b]	synthetic anhydroTTX
4	5.50 (d, J = 8.9 Hz)	5.50 (d, J = 9.4 Hz)	5.53 (s)
4a	2.35 (d, J = 9.6 Hz)	2.35 (d, J = 9.5 Hz)	2.94 (d, J = 2.6 Hz)
5	4.25 (br s)	4.25 (br s)	4.36 (dd, J = 2.2, 2.6 Hz)
7	4.09 (t, J = 2.1 Hz)	4.08 (t, J = 1.8 Hz)	4.17 (t, J = 2.2, 2.6 Hz)
8	4.30 (d, J = 2.1 Hz)	4.30 (d, J = 1.5 Hz)	4.63 (d, J = 2.2 Hz)
9	3.96 (s)	3.96 (s)	4.58 (s)
11	4.01 (d, J = 12.4 Hz)	4.02 (d, J = 12.6 Hz)	4.00 (d, J = 12.2 Hz)
	4.06 (d, J = 12.4 Hz)	4.04 (d, J = 12.6 Hz)	3.96 (d, J = 12.2 Hz)

[a] 600 MHz, in 3% CD_3COOD/D_2O, referenced to C*H*D_2COOD (2.06 ppm). [b] Reference 9d.

manner in 34 steps from D-glucose (0.38% overall yield). This synthetic methodology will be applicable to the synthesis of not only TTX and its analogues, but also highly complex natural cyclitols bearing branched-chain structures.

Experimental Section

3,3′-Di-*O*-benzyl-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5). To a solution of 3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hexofuranose (**4**)[21] (7.9 g, 27.2 mmol) in dry DMF (60 mL) was added sodium hydride (60% dispersion in mineral oil, 4.4 g, 108.8 mmol), and the solution was stirred at rt. After 30 min, benzyl bromide (9.8 mL, 81.6 mmol) was added dropwise to the reaction mixture, with continued stirring at rt for 1 h. After the disappearance of **4** on TLC with 1:1 hexane−EtOAc, 1 M MeONa−MeOH (15 mL) was added, stirring was continued for 1 h, then the solution was evaporated to give a residue. The remaining residue was poured into aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **5** (12.1 g, 95% yield), which was purified on a column of silica gel with 30:1−8:1 toluene−acetone; colorless syrup; $[\alpha]_D^{25}$ +17.6 (*c* 1.22, $CHCl_3$); ^{1}H NMR (600 MHz) δ 7.32−7.19 (10H, m, Ph*H*), 5.79 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.77, 4.72 (2H, 2 × d, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.64 (1H, d, H-2), 4.55, 4.51 (2H, 2 × d, $J_{A,B}$ = 12.0 Hz, CH_2Ph), 4.38 (1H, ddd, $J_{5,4}$ = 6.5 Hz, $J_{5,6}$ = 6.5 Hz, $J_{5,6'}$ = 6.5 Hz, H-5), 3.99 (1H, d, H-4), 3.96 (1H, dd, $J_{6,6'}$ = 8.6 Hz, H-6), 3.94 (1H, dd, H-6′), 3.93, 3.80 (2H, 2 × d, $J_{a,b}$ = 11.0 Hz, H-3′), 1.46, 1.34, 1.28, 1.27 (12H, 4 × s, 2 × C(CH_3)$_2$). Anal. Calcd for $C_{27}H_{34}O_7$ (470.54): C, 68.92; H, 7.28. Found: C, 68.70; H, 7.37.

3,3′-Di-*O*-benzyl-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-glucofuranose (6). Di-*O*-benzyl derivative **5** (9.0 g, 19.2 mmol) was dissolved in 70% aq acetic acid solution, and the solution was stirred for 12 h. After the disappearance of **5** on TLC with 2:1 hexane−EtOAc, the reaction mixture was evaporated to give **6** (8.23 g, quantitatively): mp 63.0−64.5 °C (colorless prisms, ether-hexane); $[\alpha]_D^{25}$ +29.1 (*c* 1.10, $CHCl_3$); IR (KBr, disk) ν 3500 cm^{-1} (OH); ^{1}H NMR (600 MHz) δ 7.36−7.25 (10H, m, Ph*H*), 5.83 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 4.67, 4.53 (2H, 2 × d, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 4.66, 4.56 (2H, 2 × d, $J_{A,B}$ = 11.4 Hz, CH_2Ph), 4.58 (1H, d, H-2), 4.42 (1H, br d, $J_{OH,5}$ = 1.3 Hz, 5-OH), 4.12 (1H, d, $J_{4,5}$ = 8.8 Hz, H-4), 4.10, 3.81 (2H, 2 × d, $J_{a,b}$ = 11.3 Hz, H-3′), 4.05 (1H, dddd, $J_{5,6}$ = 3.4 Hz, $J_{5,6'}$ = 4.8 Hz, H-5), 3.83 (1H, dd, $J_{6,6'}$ = 1.5 Hz, H-6), 3.73 (1H, dd, H-6′), 2.35 (1H, br s, 6-OH), 1.50, 1.29 (2 × s, 6H, C(CH_3)$_2$). Anal. Calcd for $C_{24}H_{30}O_7$ (430.48): C, 66.96; H, 7.02. Found: C, 66.63; H, 7.00.

3,3′-Di-*O*-benzyl-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentoaldofranose (7). To a solution of diol **6** (8.0 g, 18.6 mmol) in 3:1 MeOH−H_2O was added a solution of $NaIO_4$ (4.75 g, 22.3 mmol) in water (45 mL), and the mixture was stirred at 0 °C for 30 min, then at rt for 30 min. After the disappearance of **6** on TLC with 8:1 toluene−acetone, the reaction mixture was poured into brine, extracted with $CHCl_3$, washed with brine and water, and evaporated to give **7** (7.4 g): colorless syrup; IR (KBr, neat) ν 1750 cm^{-1} (C=O); ^{1}H NMR (500 MHz) δ 9.74 (1H, d, $J_{CHO,4}$ = 1.2 Hz, CHO), 7.36−7.21 (10H, m, Ph*H*), 6.06 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.67 (1H, d, H-2), 4.65, 4.63 (2H, 2 × d, $J_{A,B}$ = 11.6 Hz, CH_2Ph), 4.62, 4.56 (2H, 2 × d, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.47 (1H, d, H-4), 4.04, 3.95 (2H, 2 × d, $J_{a,b}$ = 11.0 Hz, H-3′), 1.57, 1.34 (6H, 2 × s, C(CH_3)$_2$). ESI-TOF-MS calcd for $C_{23}H_{27}O_6$ *m*/*z* $[M + H]^+$ 399.1808, found 399.1808.

3,3′-Di-*O*-benzyl-6-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (8*R*) and 3,3′-Di-*O*-benzyl-6-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-*β*-L-idofuranose (8*S*). To a solution of aldehyde **7** (6.3 g, 18.7 mmol) in MeOH (15 mL) was added a mixture of CH_3NO_2 (8 mL, 148 mmol) and NaOMe (1.0 M solution in methanol, 15 mL) with continued stirring at rt. After 30 min, the reaction mixture was neutralized with acetic acid, poured into brine, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **8** (diastereomer ratio = ca. 10:1−5:1) (6.4 g, 75% yield from 6); IR (KBr, neat) ν 3350 (OH), 1556 cm^{-1} (NO_2); ^{1}H NMR (600 MHz) δ 7.37−7.25 (10H, m, Ph*H*), 5.95 (*miner*) and 5.82 (*major*) (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.72 (1H, m, H-5), 4.67 (2H, m, H-6,6′), 4.69, 4.51 (2H, 2 × d, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.61, 4.52 (2H, 2 × d, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 4.57 (1H, d, H-2), 4.52 (1H, d, $J_{5,OH}$ = 11.0 Hz, OH), 4.11 (1H, d, $J_{4,5}$ = 8.2 Hz, H-4), 4.10, 3.75 and 4.08, 3.74 (2H, 2 × d, $J_{a,b}$ = 11.3 Hz, H-3′), 1.50 (*major*), 1.29 (*major*) and 1.48 (*miner*), 1.30 (*miner*) (6H, 2 × s, C(CH_3)$_2$); ^{1}H NMR (600 MHz in C_6D_6) (*major*) δ 7.23−7.08 (10H, m, Ph*H*), 5.64 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.84 (1H, dddd, H-5), 4.46 (1H, dd, $J_{6,5}$ = 3.2 Hz, $J_{6,6'}$ = 12.4 Hz, H-6), 4.44 (1H, d, $J_{5,OH}$ = 3.0 Hz, OH), 4.40, 4.14 (2H, 2 × d, $J_{A,B}$ = 11.4 Hz, CH_2Ph), 4.16, 4.00 (2H, 2 × d, $J_{A,B}$ = 11.8 Hz, CH_2Ph), 4.34 (1H, dd, $J_{6',5}$ = 7.6 Hz, H-6′), 4.23 (1H, d, H-2), 4.22 (1H, d, $J_{4,5}$ = 8.9 Hz, H-4), 3.76, 3.64 (2H, 2 × d, $J_{a,b}$ = 11.4 Hz, H-3′), 1.40, 1.10 (6H, 2 × s, C(CH_3)$_2$). Anal. Calcd for $C_{24}H_{29}NO_8$ (459.49): C, 62.73; H, 6.36; N, 3.05. Found: C, 62.74; H, 6.41; N, 2.99.

3,3′-Di-*O*-benzyl-5,6-dideoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (9, G). To a stirred solution of nitro alcohol **8** (1.48 g, 3.22 mmol) in CH_2Cl_2 (15 mL) was added methanesulfonyl chloride (0.75 mL, 9.66 mmol) at 0 °C, then triethylamine (1.80 mL, 12.9 mmol) was added dropwise. After the disappearance of starting compound on TLC with 2:1 hexane−EtOAc, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aq $NaHCO_3$ solution, brine, and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The remaining residue was purified on a column of silica gel with 5:1 to 3:1 hexane−EtOAc to give **9** (G) (1.21 g, 85% yield): mp 90.0−91.0 °C (colorless prisms, ether-hexane); $[\alpha]_D^{28}$ +10.1 (*c* 1.04, $CHCl_3$); IR (KBr, disk) ν 1670 (C=C), 1540 cm^{-1} (NO_2); ^{1}H NMR (600 MHz) δ 7.54 (1H, dd, $J_{4,6}$ = 3.6 Hz, $J_{5,6}$ = 13.2 Hz, H-6), 7.38−7.20 (11H, m, Ph*H*, H-5), 5.94 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.89 (1H, dd, $J_{4,5}$ = 2.1 Hz, H-4), 4.62, 4.57 (2H, 2 × d, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.60, 4.54 (2H, 2 × d, $J_{A,B}$ = 12.2 Hz, CH_2Ph), 4.53 (1H, d, H-2), 4.02, 3.84 (2H, 2 × d, $J_{a,b}$ = 11.2 Hz, H-3′), 1.49, 1.31 (6H, 2 × s, C(CH_3)$_2$); ^{13}C NMR (150 MHz) δ 140.5, 138.0, 137.7, 137.2, 128.5, 128.4, 128.0, 127.7, 127.6, 126.6, 113.0, 105.1, 87.3, 82.2, 80.9, 73.7, 67.4, 66.3, 27.1, 26.4. Anal.

Calcd for $C_{24}H_{27}O_7N$ (441.47): C, 65.29; H, 6.16; N, 3.17. Found: C, 64.92; H, 6.16; N, 3.11.

5-*C*-Bis(phenylthio)methyl-3,3′-di-*O*-benzyl-5,6-dideoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (10a). To a stirred solution of bis(phenyl)thiomethane (616 mg, 2.65 mmol) in THF (6 mL) was added butyllithium (1.6 M solution in hexane, 2.3 mL, 3.68 mmol) at −78 °C under argon. After 15 min, a solution of nitro-olefin **9** (730 mg, 1.66 mmol) in THF (3 mL) was added to the above mixture, then the solution was stirred for 30 min. After the disappearance of **9** on TLC with 3:1 hexane−EtOAc, acetic acid (5 mL) and subsequently methanol (50 mL) were added then evaporated to give a residue. The residue was diluted with $CHCl_3$, washed with aq $NaHCO_3$ solution, brine, and water, dried over anhyd $MgSO_4$, and evaporated to give a residue. The remaining residue was purified on a column of silica gel with 6:1 to 3:1 hexane−EtOAc to give **10a** (900 mg, 80% yield): mp 120−121 °C (colorless prisms, ether−hexane); $[\alpha]_D^{25}$ −64.7 (*c* 0.98, $CHCl_3$); IR (KBr, disk) ν 1560 cm^{-1} (NO_2); ^1H NMR (600 MHz) δ 7.48−7.14 (20H, m, Ph*H*), 5.83 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 5.06 (1H, dd, $J_{5,6}$ = 3.4 Hz, $J_{6,6'}$ = 14.7 Hz, H-6), 4.90 (1H, dd, $J_{5,6'}$ = 9.0 Hz, H-6′), 4.77 (1H, d, $J_{4,5}$ = 1.5 Hz, H-4), 4.69 (1H, d, $J_{5,5'}$ = 3.6 Hz, H-5′), 4.61, 4.54 (2H, 2 × d, $J_{A,B}$ = 11.5 Hz, C*H*$_2$Ph), 4.59 (1H, d, H-2), 4.37, 4.29 (2H, 2 × d, $J_{A,B}$ = 12.4 Hz, C*H*$_2$Ph), 3.92, 3.50 (2H, 2 × d, $J_{a,b}$ = 10.8 Hz, H-3′), 3.64 (1H, dddd, H-5), 1.60, 1.34 (6H, 2 × s, C(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz) δ 137.8, 137.2, 134.1, 133.5, 132.4, 130.2, 128.8, 128.7, 128.7, 128.1 × 2, 127.7, 127.4, 127.3, 127.2, 127.0 × 2, 112.5, 104.5, 87.0, 80.6, 79.9, 74.3, 73.1, 68.3, 66.2, 60.1, 40.5, 27.0, 26.4. Anal. Calcd for $C_{37}H_{39}O_7NS_2$ (673.84): C, 65.95; H, 5.83; N, 2.08. Found: C, 65.79; H, 5.85; N, 2.11.

1L-(1,2,3′,4,5/3,6)-3,3′-Di-*O*-benzyl-3-*C*-hydroxymethyl-6-nitro-2,3,4,5,6-tetrahydroxycyclohexancarbaldehyde Bis(phenyldithio)acetal (12, E). A mixture of **10a** (820 mg, 1.19 mmol) in aq 85% acetic acid solution (30 mL) was stirred under reflux conditions for 6 h. After the disappearance of starting compound **10a** on TLC with 2:1 hexane−EtOAc, the reaction mixture was evaporated to give crude **11**. **11** was diluted with MeOH (15 mL), and then $NaHCO_3$ (200 mg) and water (5 mL) were added and the solution was stirred at rt. After 8 h, the above reaction mixture was neutralized with ion-exchange resin (Amberlite IR-120B (H^+ form)), filtered off, and evaporated to give **12** (650 mg, 84% yield from **10a**), which was purified on a column of silica gel with 8:1 toluene−acetone: mp 113.0−114.5 °C (colorless prisms, ether−hexane); $[\alpha]_D^{28}$ −74.7 (*c* 1.25, EtOH); IR (KBr, neat) ν 3417 (OH), 1560 cm^{-1} (NO_2); ^1H NMR (600 MHz) δ 7.59−6.96 (20H, m, Ph*H*), 5.39 (1H, dd, $J_{6,1}$ = 11.7 Hz, $J_{6,5}$ = 10.3 Hz, H-6), 5.13 (1H, ddd, $J_{2,1}$ = 2.4 Hz, $J_{2,4}$ = 1.4 Hz, $J_{2,OH}$ = 7.9 Hz, H-2), 4.63, 4.61 (2H, 2 × d, $J_{A,B}$ = 12.0 Hz, C*H*$_2$Ph), 4.45, 4.26 (2H, 2 × d, $J_{A,B}$ = 11.0 Hz, C*H*$_2$Ph), 4.40 (1H, dd, $J_{5,4}$ = 3.4 Hz, $J_{5,OH}$ = 10.0 Hz, H-5), 4.35 (1H, d, $J_{1,1'}$ = 4.1 Hz, H-1′), 4.17 (1H, ddd, $J_{4,OH}$ = 7.4 Hz, H-4), 4.08, 4.04 (2H, 2 × d, $J_{a,b}$ = 11.5 Hz, H-3′), 3.45 (1H, d, 4-OH), 3.22 (1H, d, 2-OH), 3.13 (1H, ddd, H-1), 2.83 (1H, d, 5-OH). Anal. Calcd for $C_{34}H_{35}O_7NS_2$ (633.78): C, 64.44; H, 5.57; N, 2.21. Found: C, 64.81; H, 5.87; N, 2.18.

1L-(1,2,3′,4,5/3,6)-2,4,5,-Tri-*O*-acetyl-3,3′-di-*O*-benzyl-3-*C*-hydroxymethyl-6-nitro-2,3,4,5,-tetrahydroxycyclohexancarbaldehyde Bis(phenylthio)acetal (12′). To a solution of **12** (100 mg, 0.15 mmol) in Py (2 mL) were added acetic anhydrous (1 mL) and a catalytic amount of DMAP then the solution was stirred at rt. After 24 h, the reaction mixture was evaporated to give a residue. The remaining residue was purified on a column of silica gel with 2:1 hexane−EtOAc to quantitatively give **12′** (115 mg): mp 63.0−66.0 °C (colorless prisms, ether−hexane); $[\alpha]_D^{28}$ −49.8 (*c* 1.46, EtOH); IR (KBr neat) ν 1758 (C═O), 1560 cm^{-1} (NO_2); ^1H NMR (200 MHz) δ 7.60−6.89 (20H, m, Ph*H*), 6.18 (1H, d, $J_{2,1}$ = 1.5 Hz, H-2), 5.94 (1H, d, $J_{4,5}$ = 1.7 Hz, H-4), 5.62 (2H, m, $J_{5,6}$ = $J_{6,1}$ = 11.0 Hz, H-5, H-6), 4.71, 4.59 (2 H, 2 × d, $J_{A,B}$ = 11.0 Hz, C*H*$_2$Ph), 4.51, 4.30 (2H, 2 × d, $J_{A,B}$ = 11.7 Hz, C*H*$_2$Ph), 4.13 (1H, d, $J_{1',1}$ = 4.6 Hz, H-1′), 3.67, 3.42 (1H, 2 × d, $J_{a,b}$ = 9.8 Hz, H-3′), 3.34 (1H, ddd, H-1), 2.15, 1.97, 1.95 (9H, 3 × s, 3 × OCOC*H*$_3$). Anal. Calcd for $C_{40}H_{41}O_7NS_2$ (759.89): C, 63.22; H, 5.44; N, 1.84. Found: C, 63.62; H, 5.32; N, 1.93.

1L-(1,2,4,5/3(OH),6)-3,3′-Di-*O*-benzyl-1-*C*-bis(phenylthio)-methyl-3-*C*-hydroxymethyl-4,5-*O*-isopropylidene-6-nitro-2,3,4,5-cyclohexanetetrol (13). To a solution of nitro cyclitol derivative **12** (36 mg, 60.2 μmol) in dry dichloromethane (1 mL) were added 2,2-dimethoxypropane (75 μL, 602 μmol) and *p*-toluenesulfonic acid monohydrate (1 mg, 6.02 μmol) with continued stirring for 1 h. After the disappearance of **12** on TLC with 2:1 hexane−EtOAc, the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **13** (35 mg, 86% yield), which was purified on a column of silica gel with 3:1 hexane−EtOAc: colorless oil; $[\alpha]_D^{26}$ −99.2 (*c* 0.83, $CHCl_3$); IR (KBr, neat) ν 3507 (OH), 1552 cm^{-1} (NO_2); ^1H NMR (600 MHz) δ 7.58−6.93 (20H, m, Ph*H*), 5.42 (1H, dd, $J_{6,1}$ = 12.2 Hz, $J_{6,5}$ = 8.3 Hz, H-6), 5.14 (1H, br ddd, $J_{2,1}$ = 2.0 Hz, $J_{2,4}$ = 1.3 Hz, $J_{2,OH}$ = 8.9 Hz, H-2), 4.69, 4.61 (2H, 2 × d, $J_{A,B}$ = 12.0 Hz, C*H*$_2$Ph), 4.63 (1H, dd, $J_{5,4}$ = 4.9 Hz, H-5), 4.58, 4.31 (2H, 2 × d, $J_{A,B}$ = 10.7 Hz, C*H*$_2$Ph), 4.35 (1H, d, $J_{1',1}$ = 3.9 Hz, H-1′), 4.41 (1H, dd, H-4), 4.10, 3.99 (2H, 2 × d, $J_{a,b}$ = 11.3 Hz, H-3′), 3.09 (1H, ddd, H-1), 2.75 (1H, d, H-1), 1.66, 1.36 (6H, 2 × s, C(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz) δ 137.7, 137.5, 135.0, 133.5, 130.4, 129.2, 129.1, 128.5, 128.3, 127.9, 127.8, 127.5, 127.4, 127.3, 111.0, 88.4, 77.4, 76.9, 76.6, 73.8, 68.3, 68.0, 65.3, 59.4, 41.61, 28.34, 25.80. Anal. Calcd for $C_{37}H_{39}O_7NS_2$ (673.84): C, 65.95; H, 5.83; N, 2.08. Found: C, 65.98; H, 6.00; N, 2.20.

1L-(1,2,4,5/3(OH),6)-3,3′-Di-*O*-benzyl-1-*C*-bis(phenylthio)-methyl-3-*C*-hydroxymethyl-4,5-*O*-isopropylidene-2-*O*-methoxymethyl-6-nitro-2,3,4,5-cyclohexanetetrol (14). To a solution of isopropylidene derivative **13** (5.72 g, 8.49 mmol) in dry dichloromethane (175 mL) were added dimethoxymethane (7.51 mL, 84.9 mmol) and P_2O_5 (300 mg) with continued stirring for 2 h at rt. After the disappearance of **13** on TLC with 3:1 hexane−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 **14** (5.70 g, 93% yield), which was purified on a column of silica gel with 4:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{26}$ −100.3 (*c* 0.98, $CHCl_3$); IR (KBr, neat) ν 1551 cm^{-1} (NO_2); ^1H NMR (600 MHz) δ 7.55−6.93 (20H, m, Ph*H*), 5.46 (1H, dd, $J_{6,1}$ = 11.9 Hz, $J_{6,5}$ = 8.7 Hz, H-6), 5.01, 4.93 (2H, 2 × d, $J_{A,B}$ = 6.3 Hz, C*H*$_2$OCH$_3$), 4.94 (1H, br d, $J_{2,1}$ = 1.7 Hz, H-2), 4.75, 4.54 (2H, 2 × d, $J_{A,B}$ = 11.9 Hz, C*H*$_2$Ph), 4.61, 4.39 (2H, 2 × d, $J_{A,B}$ = 10.7 Hz, C*H*$_2$Ph), 4.55 (1H, dd, $J_{2,1}$ = 5.3 Hz, H-5), 4.34 (1H, br d, $J_{1',1}$ = 4.4 Hz, H-1′), 4.33 (1H, br d, H-4), 4.15, 3.93 (2H, 2 × d, $J_{a,b}$ = 11.0 Hz, H-3′), 3.41 (3H, s, OC*H*$_3$), 3.13 (1H, ddd, H-1), 1.62, 1.25 (6H, 2 × s, C(C*H*$_3$)$_2$). Anal. Calcd for $C_{37}H_{39}O_7NS_2$ (673.84): C, 65.25; H, 6.04; N, 1.95. Found: C, 65.20; H, 5.98; N, 1.99.

1L-(1,2,4,5/3(OH),6)-3,3′-Di-*O*-benzyl-3-*C*-hydroxymethyl-4,5-*O*-isopropylidene-2-*O*-methoxymethyl-6-nitro-2,3,4,5-tetrahydroxycyclohexanecarbaldehyde (15). To a solution of methoxymethyl ether derivative **14** (1.70 g, 2.37 mmol) in 70% CH_3CN aqueous solution (50 mL) was added *N*-bromosuccineimide (2.53 g, 14.2 mmol) with continued stirring for 10 min at rt. After the disappearance of **14** on TLC with 2:1 hexane−EtOAc, the reaction mixture was poured into aq sodium thiosulfate solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **15** (1.105 g, 85% yield), which was purified on a column of silica gel with 4:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{25}$ −43.7 (*c* 0.64, $CHCl_3$); IR (KBr, disc) ν 1726 (C═O), 1554 cm^{-1} (NO_2); ^1H NMR (600 MHz) δ 9.57 (1H, s, C*H*O), 7.39−7.25 (10H, m, Ph*H*), 5.00 (1H, dd, $J_{6,1}$ = 11.9 Hz, $J_{6,5}$ = 8.8 Hz, H-6), 4.78, 4.50 (2H, 2 × d, $J_{A,B}$ = 6.9 Hz, C*H*$_2$OCH$_3$), 4.70 (2H, s, C*H*$_2$Ph), 4.69 (1H, dd, $J_{2,1}$ = 2.1 Hz, $J_{2,4}$ = 1.5 Hz, H-2), 4.64, 4.53 (2H, 2 × d, $J_{A,B}$ = 11.7 Hz, C*H*$_2$Ph), 4.44 (1H, dd, $J_{5,4}$ = 5.2

Hz, H-5), 4.26 (1H, dd, H-4), 4.03, 3.88 (2H, 2 × d, $J_{a,b}$ = 11.2 Hz, H-3′), 3.62 (1H, dd, H-1), 3.20 (3H, s, OCH_3), 1.58, 1.33 (6H, 2 × s, C(CH_3)$_2$). Anal. Calcd for $C_{27}H_{33}O_9N$ (515.55): C, 62.90; H, 6.45; N, 2.72. Found: C, 62.67; H, 6.40; N, 2.53.

1D-(1,2,4,5/3(OH),6)-3,3′-Di-*O*-benzyl-3,5-di-*C*-hydroxymethyl-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-6-nitro-1,2,3,4-cyclohexanetetrol (16). To a solution of aldehyde **15** (1.105 mg, 2.14 mmol) in methanol (50 mL) was added $NaBH_4$ (269 mg, 7.10 mmol) with continued stirring at rt for 1 h. After the disappearance of **15** on TLC with 2:1 hexane−EtOAc, the reaction mixture was poured into aq $NaHCO_3$ solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **16** (1.076 g, 97% yield), which was purified on a column of silica gel with 4:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{28}$ +3.29 (*c* 1.03, $CHCl_3$); IR (KBr, neat) ν 3444 (OH), 1552 cm^{-1} (NO_2); ^{1}H NMR (600 MHz) δ 7.39−7.26 (10H, m, Ph*H*), 4.83, 4.66 (2H, 2 × d, $J_{A,B}$ = 6.3 Hz, CH_2OCH$_3$), 4.71 (1H, dd, $J_{6,5}$ = 11.2 Hz, $J_{6,1}$ = 10.0 Hz, H-6), 4.72, 4.62 (2H, 2 × d, $J_{A,B}$ = 11.2 Hz, CH_2Ph), 4.66 (1H, dd, $J_{1,2}$ = 4.9 Hz, H-1), 4.62, 4.54 (2H, 2 × d, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 4.37 (1H, dd, $J_{4,5}$ = 2.3 Hz, $J_{4,2}$ 0.9 Hz, H-4), 4.27 (1H, dd, H-2), 4.02, 3.85 (2H, 2 × d, $J_{a,b}$ = 10.9 Hz, H-3′), 3.67 (1H, ddd, $J_{5,5'a}$ = 9.7 Hz, $J_{5'a,5'b}$ = 11.7 Hz, H-5′a), 3.43 (3H, s, OCH_3), 3.52 (1H, ddd, $J_{5,5'b}$ = 4.9 Hz, H-5′b), 3.02 (1H, dd, $J_{OH,5'a}$ = 6.6 Hz, $J_{5,5'b}$ = 7.4 Hz, OH), 2.70 (1H, dddd, H-5), 1.52, 1.32 (6H, 2 × s, C(CH_3)$_2$). Anal. Calcd for $C_{27}H_{35}O_9N$ (517.57): C, 62.66; H, 6.82; N, 2.71. Found: C, 62.37; H, 7.06; N, 2.63.

1D-(1,2,4,5/3(OH),6)-3,3′-Di-*O*-benzyl-5′-*O*-*tert*-butyldiphenylsilyl-3,5-di-*C*-hydroxymethyl-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-6-nitro-1,2,3,4-cyclohexanetetrol (17). To a solution of hydroxymethyl derivative **16** (906 mg, 1.80 mmol) in dichloromethane (30 mL) were added *tert*-butyldiphenylsilyl chloride (554 μL, 2.16 mmol) and imidazole (220 mg, 3.24 mmol) with continued stirring for 2 h at rt. After the disappearance of **16** on TLC with 2:1 hexane−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 **17** (1.26 g, 95% yield), which was purified on a column of silica gel with 5:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{25}$ −41.7 (*c* 0.1, $CHCl_3$); IR (KBr, neat) ν 1556 cm^{-1} (NO_2); ^{1}H NMR (600 MHz) δ 7.59−7.24 (20H, m, Ph*H*), 4.77, 4.60 (2H, 2 × d, $J_{A,B}$ =11.0 Hz, CH_2Ph), 4.77−4.60 (4H, m, CH_2OCH$_3$, H-1, H-6), 4.66, 4.56 (2H, 2 × d, $J_{A,B}$ = 12.0 Hz, CH_2Ph), 4.50 (1H, br d, $J_{4,5}$ = 1.7 Hz, H-4), 4.37 (1H, dd, $J_{2,1}$ = 3.8 Hz, H-2), 4.07, 3.93 (2H, 2 × d, $J_{a,b}$ = 10.8 Hz, H-3′), 3.74 (1H, dd, $J_{5'a,5}$ = 10.0 Hz, $J_{5'a,5'b}$ = 10.3 Hz, H-5′a), 3.49 (1H, dd, $J_{5'b,5}$ = 5.2 Hz, H-5′b), 3.27 (3H, s, OCH_3), 2.76 (1H, dddd, $J_{5,6}$ = 11.5 Hz, H-1), 1.48, 1.33 (6H, 2 × s, C(CH_3)$_2$), 1.01 (9H, s, C(CH_3)$_3$). Anal. Calcd for $C_{43}H_{53}NO_9Si$ (755.97): C, 68.32; H, 7.07; N, 1.85. Found. C, 68.39; H, 6.78; N, 2.15.

2D-(2,3,5,6/4(OH))-4,4′-Di-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-4,6-di-*C*-hydroxymethyl-2,3-*O*-isopropylidene-5-*O*-methoxymethyl-2,3,4,5-tetrahydroxycyclohexanone (18). To a solution of silylether derivative **17** (1.10 g, 1.46 mmol) in dry toluene (30 mL) was added potassium *tert*-butoxide (327 mg, 2.92 mmol) with continued stirring at rt. After 30 min, O_3 gas was babbled into the reaction mixture for 10 min at −78 °C. After the disappearance of **17** on TLC with hexane−EtOAc (3:1 v/v), acetic acid (550 μL) and zinc powder (550 mg) were added to the above mixture, which was then warmed to rt. The above reaction mixture was poured into aq $NaHCO_3$ solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give carbonyl compound **18** (817 mg, 79% yield), which was purified on a column of silica gel with 5:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{25}$ +1.38 (*c* 0.32, $CHCl_3$); IR (KBr, neat) ν 1732 cm^{-1} (C═O); ^{1}H NMR (500 MHz) δ 7.65−7.24 (20H, m, Ph*H*), 4.88, 4.73 (2H, 2 × d, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.71 (1H, dd, $J_{5,6}$ = 2.4 Hz, $J_{5,3}$ = 10.7 Hz, H-5), 4.69, 4.58 (2H, 2 × d, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.63, 4.59 (2H, 2 × d, $J_{A,B}$ = 6.4 Hz, CH_2OCH$_3$), 4.61 (1H, dd, $J_{3,2}$ = 6.2 Hz, H-3), 4.42 (1H, d, H-2), 4.14, 4.01 (2H, 2 × d, $J_{A,B}$ = 10.9 Hz, H-4′), 4.02 (1H, dd, $J_{6'a,6}$ = 5.0 Hz, $J_{6'a,6'b}$ = 10.6 Hz, H-6′a), 3.95 (1H, dd, $J_{6b',6}$ = 10.0 Hz, H-6′b), 3.34 (1H, ddd, H-6), 3.22 (3H, s, OCH_3), 1.37, 1.36 (6H, 2 × s, C(CH_3)$_2$), 1.04 (9H, s, C(CH_3)$_3$). Anal. Calcd for $C_{43}H_{52}O_8Si$ (724.95): C, 71.24; H, 7.23. Found. C, 71.25; H, 7.13.

2D-(2,3,5,6/4(OH))-6′-*O*-*tert*-butyldiphenylsilyl-4,6-di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-2,3,4,5-tetrahydroxycyclohexane (19). A solution of carbonyl derivative **17** (1.04 g, 1.47 mmol) (120 mg, 0.21 mmol) in THF (41 mL) was hydrogenated in the presence of a catalytic amount of 20% Pd(OH)$_2$−C (ca. 500 mg) under hydrogen at 50 °C for 2 h. After the disappearance of starting compound **18** on TLC with 2:1 hexane−EtOAc, catalyst was filtered off, and the solution was evaporated to give a colorless syrup. Subsequently this syrup was dissolved in dichloromethane (5 mL), and next, 2,2-dimethoxypropane (75 μL, 0.602 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg, 6.02 μmol) were added with stirring for 1 h at rt. After the disappearance of starting compound on TLC with 2:1 hexane−EtOAc, the reaction mixture was diluted with $CHCl_3$, washed with aq $NaHCO_3$ solution, and brine wand water, dried over anhyd $MgSO_4$, and evaporated to give corresponding acetonide **19** (620 mg, 79% yield), which was purified on a column of silica gel with 3:1 hexane−EtOAc: colorless syrup; $[\alpha]_D^{26}$ +17.0 (*c* 0.83, $CHCl_3$); IR (KBr, neat) ν 1732 cm^{-1} (C═O); ^{1}H NMR (600 MHz) δ 7.65−7.34 (10H, m, Ph*H*), 4.62, 4.54 (2H, 2 × d, $J_{A,B}$ = 6.7 Hz, CH_2OCH$_3$), 4.44 (1H, dd, $J_{3,2}$ = 6.0 Hz, $J_{3,5}$ = 1.9 Hz, H-3), 4.43, 4.35 (2H, 2 × d, $J_{a,b}$ = 9.6 Hz, H-4′), 4.40 (1H, d, H-2), 4.37 (1H, dd, $J_{5,6}$ = 2.1 Hz, H-5), 4.01 (1H, dd, $J_{6'a,6}$ = 4.8 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′a), 3.93 (1H, dd, $J_{6b',6}$ = 10.3 Hz, H-6′b), 3.30 (3H, s, OCH_3), 3.28 (1H, ddd, H-6), 1.51, 1.50, 1.36, 1.34 (12H, 4 × s, C(CH_3)$_2$), 1.04 (9H, s, C(CH_3)$_3$). Anal. Calcd for $C_{32}H_{44}O_8Si$ (584.77): C, 65.73; H, 7.58. Found. C, 65.79; H, 7.33.

1D-(1,2,3,5,6/4(OH))-6′-*O*-*tert*-butyldiphenylsilyl-1′-*C*-dichloromethyl-4,6-di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-1,2,3,4,5-cyclohexanepentol (20). $[\alpha]_D^{26}$ −24.8 (*c* 0.91, $CHCl_3$).

1D-(1,2,3,5,6/4(OH))-1′-Azido-6′-*O*-*tert*-butyldiphenylsilyl-4,6-di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-2,3,4,5-tetrahydroxycyclohexanecarbaldehyde (22). $[\alpha]_D^{26}$ −62.7 (*c* 1.07, $CHCl_3$).

1D-(1,2,3,4,5/3(OH),6)-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-6′-*C*-[2(*S*)-hydroxycyanomethyl]-3,5-di-*C*-hydroxymethyl-1,2:3,3′-di-*O*-isopropylidene-4-*O*-methoxymethyl-1,2,3,4-cyclohexanetetrol (23). $[\alpha]_D^{26}$ −0.60 (*c* 1.01, $CHCl_3$).

1D-(1,2,3,4,5/3(OH),6)-6-Azido-5′-*O*-*tert*-butyldiphenylsilyl-6′-*C*-[2(*R*)-hydroxycyanomethyl]-3,5-di-*C*-hydroxymethyl-1,2:3,3′-di-*O*-isopropylidene-4-*O*-methoxymethyl-1,2,3,4-cyclohexanetetrol (23a). $[\alpha]_D^{26}$ +29.4 (*c* 1.01, $CHCl_3$).

1D-(1,2,3,4,5/3(OH),6)-6-azido-5′-*O*-*tert*-butyldiphenylsilyl-6′-*C*-[2(*S*)-hydroxycyanomethyl]-3,5-di-*C*-hydroxymethyl-1,2:3,3′-di-*O*-isopropylidene-4,6′-di-*O*-methoxymethyl-1,2,3,4-cyclohexanetetrol (24). $[\alpha]_D^{26}$ −3.61 (*c* 0.95, $CHCl_3$).

1D-(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′-formyl-6′-methoxymethoxymethyl)-3,5-di-*C*-hydroxymethylcyclohexane-1,2,3,4-tetrol (25). $[\alpha]_D^{26}$ +49.3 (*c* 1.21, $CHCl_3$).

1D-(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 (26). $[\alpha]_D^{26}$ −57.9 (*c* 0.33, $CHCl_3$).

1D-(1,2,4,5/3(OH),6(N$_3$))-6-Amino-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 (27). $[\alpha]_D^{26}$ −53.5 (*c* 0.73, $CHCl_3$).

1D-(1,2,4,5/3(OH),6(NH$_2$))-6-Amino-1,2:3,3′-di-*O*-isopropylidene-6-*C*-(*S*)-6′-methoxymethoxymethyl-3,5-di-*C*-hydroxy-

methylcyclohexane-1,2,3,4-tetrol 6″,4-Lactone (28). $[\alpha]_D^{26}$ +25.0 (*c* 0.3, $CHCl_3$).

1D-(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 (29). $[\alpha]_D^{25}$ +1.54 (*c* 0.86, $CDCl_3$).

(−)-4,9-Anhydro-*epi*-TTX (1a). $[\alpha]_D^{28}$ +1.2 (*c* 0.18, 3% AcOH).

(−)-Tetrodotoxin (1). $[\alpha]_D^{28}$ −3.75 (*c* 0.13, 3% AcOH);

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Supporting Information Available: Experimental details and analytical and spectral characterization data, sa well as copies of ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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