Stereocontrolled Synthesis of 8,11-Dideoxytetrodotoxin, An Unnatural Analogue of Puffer Fish Toxin

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Abstract: 8,11-Dideoxytetrodotoxin, an unnatural tetrodotoxin analogue, was synthesized in a highly stereoselective manner from a common intermediate from our synthetic studies on tetrodotoxin. The key features in the synthesis were as follows: neighboring group participation of a trichloroacetamide to allow regioselective and stereoselective hydroxylation, protection of a δ-hydroxylactone as an ortho ester, and guanidine installation through the use of Boc-protected isothiourea. Global deprotection of the fully protected intermediate under acidic conditions gave 8,11-dideoxytetrodotoxin, which exhibited very weak biological activities.

Keywords: asymmetric synthesis · ion channels · natural products · tetrodotoxin · total synthesis

Introduction

Tetrodotoxin (**1**, TTX), the principle neurotoxin from the puffer fish, is one of the most famous and important marine natural products[1] because of its novel structure[2] and potent biological activity which may lead to death. Because the action mechanism has been revealed to be a specific blockage of voltage-dependent sodium channels responsible for nerve and muscle excitability, the toxin has been widely employed as an important biochemical tool in neurophysiology.[3] In fact, tetrodotoxin has been indispensable in the identification/purification of sodium channel proteins.[4] However, despite extensive efforts such as photoaffinity labeling and site-directed mutagenesis, details of the bound structure have not yet been elucidated[5] because the tertiary structure of the sodium channel protein has not been elucidated on an atomic level.[6] Modification of tetrodotoxin is extremely limited because of its complex structure and unusual chemical properties. Thus, the structure–activity relationship of tetrodotoxin has primarily been studied by using naturally occurring analogues of tetrodotoxin[7] and a few synthetic derivatives from the natural product.[8–10] These studies have revealed that the guanidinium group with a hemiaminal, an ortho ester, and hydroxy groups at C-4 and C-9 are crucial, while the hydroxy group at C-11 can be modified without a significant loss of biological activity. However, the role of the hydroxy group at the C-8 position in sodium channel inhibition has remained to be solved, since 8-deoxy analogues of tetrodotoxin have not been available from natural sources or chemical methods.[11]

In the course of our synthetic studies on tetrodotoxin, we have completed the asymmetric syntheses of 5,11-dideoxytetrodotoxin (**4**)[12] and 11-deoxytetrodotoxin (**2**),[13] which has opened the way to creating new tetrodotoxin analogues for biological studies (Figure 1).[14,15] To clarify the biological role of the hydroxy group at the C-8 position, we therefore synthesized 8,11-dideoxytetrodotoxin (**3**). Herein, we disclose the full details of our synthetic studies of 8,11-dideoxytetrodotoxin (**3**), which is quite difficult to prepare from naturally occurring tetrodotoxins.[16]

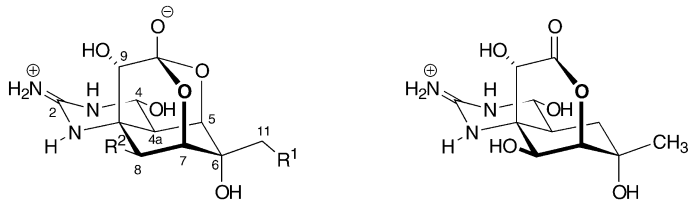

Figure 1. Structures of tetrodotoxin and its analogues.

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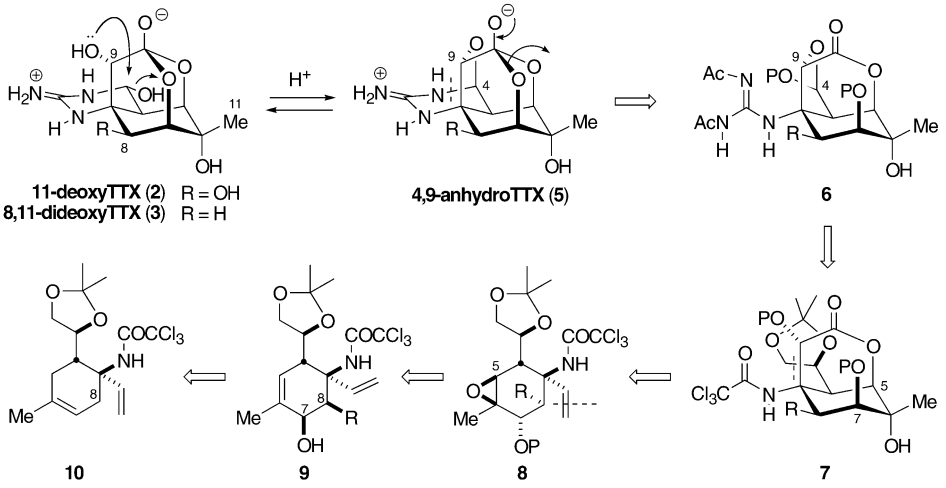
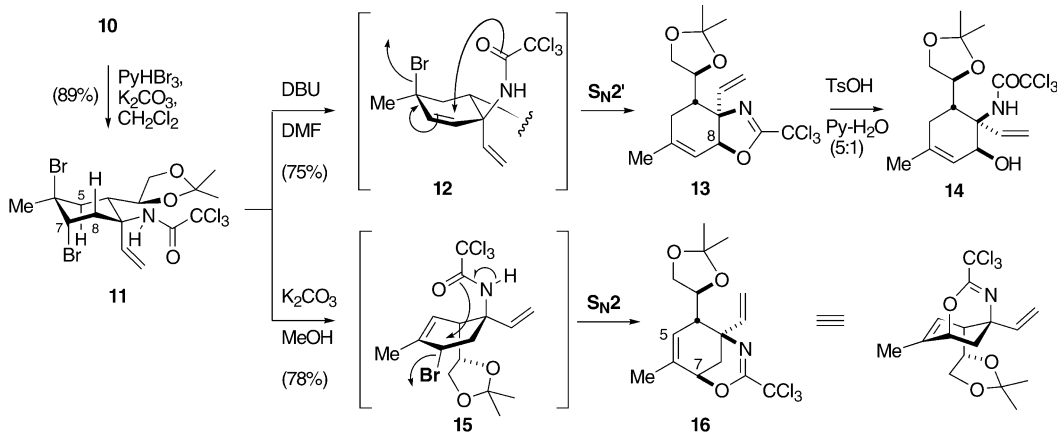
Results and Discussion

Synthetic plan: Planning was based on the successful synthesis of 11-deoxytetrodotoxin (**2**).[17] As for tetrodotoxin (**1**) and the other related analogues, 8,11-dideoxytetrodotoxin (**3**) should be in equilibrium with its 4,9-anhydro derivative **5** in acidic media (Scheme 1). Because the cyclic guanidine unit with a hemiaminal could be prepared from guanidine and aldehyde, **6** was considered to be a suitable precursor in which an intramolecular acetal was designed for protection of the labile hydroxy group at the C-9 position. The guanidine group could be prepared from trichloroacetamide according to a method developed in our laboratory,[18] while the intramolecular acetal would be synthesized from the corresponding 1,2-glycol protected as its acetonide. This retrosynthetic analysis led us to lactone **7** as a key intermediate. The lactone structure at the C-5 and not the C-7 position was anticipated to prevent β-elimination of the C-5 hydroxy group during preparation of the corresponding aldehyde by cleavage of the 1,2-diol.[19] The lactone intermediate **7** could be synthesized from a vinyl derivative **8** through cleavage of the vinyl group followed by installation of a carboxylic acid equivalent. The vinyl derivative **8** could be synthesized from the common intermediate **10**[20] via an allylic alcohol intermediate **9**.



Scheme 1. Retrosynthetic analysis.

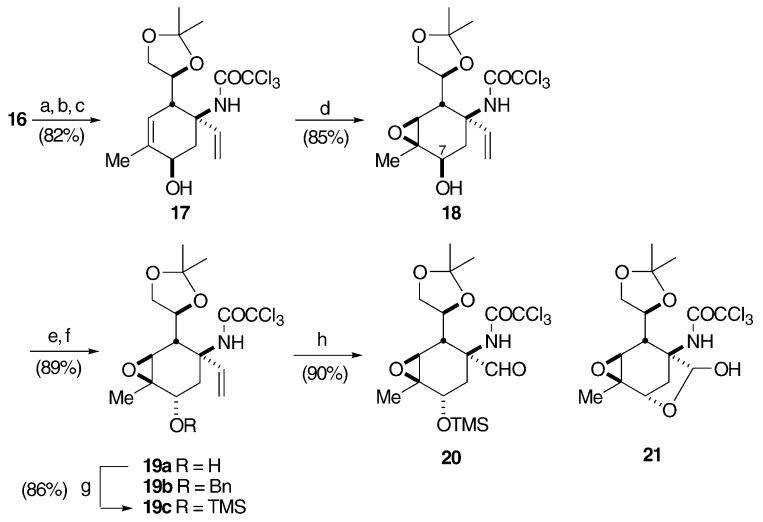
Hydroxylation and functionalization of the cyclohexane ring: In our previous syntheses of tetrodotoxin analogues, hydroxylation at the C-8 position of the common intermediate **10** was accomplished by neighboring group participation of trichloroacetamide[12] (Scheme 2). The trisubstituted alkene of **10** was brominated to give diaxial dibromide **11**, which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to give oxazoline **13**. Hydrolysis under mild acidic conditions afforded allylic alcohol **14**, a pivotal intermediate for the syntheses of 5,11-dideoxytetrodotoxin and 11-deoxytetrodotoxin. In contrast, treatment of the dibromide **11** with K_2CO_3 in methanol exclusively afforded the cyclic iminoether **16** instead of **13**. The marked difference of these two reactions might be explained by the regioselective dehydrobromination of **11**[21] whose selectivity was controlled by the reaction conditions. When DMF was employed as an aprotic solvent, the acidic NH proton should be abstracted by the base. The resulting anion would then intramolecularly abstract the hindered but proximate axial proton at the C-8 position leading to the unstable allylic bromide **12**,[22] which would further react with trichloroacetamide in an S_N2' manner to give the oxazoline **13**. In contrast, when the protic solvent methanol was used, the less hindered axial proton (at C-5) would be abstracted intermolecularly to generate another allylic bromide **15**,[22] which would undergo an S_N2 reaction with trichloroacetamide to afford **16**. Here, we have established a complete switch from the formation of oxazoline **13** to the formation of bicyclic iminoether **16** from



Scheme 2. Regioselective and stereoselective hydroxylation with neighboring group participation by trichloroacetamide.

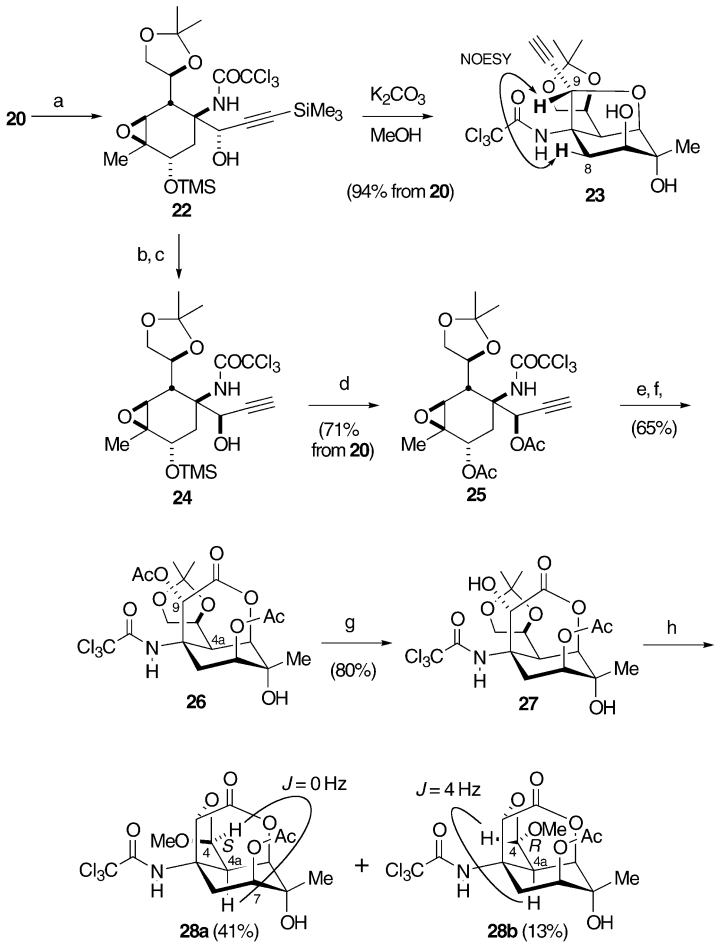
the same intermediate **11** by a simple change of the basic conditions.

The compound **16** is synthetically equivalent to **9** in Scheme 1. In contrast to the hydrolysis of oxazoline **13**, however, one-step conversion of **16** to **17** proved difficult. Upon treatment of **16** with the conditions (*p*TsOH, Py/H_2O, at 70°C) employed for the partial hydrolysis of **13**, the starting material **16** was recovered. Forcing conditions gave a mixture of amino alcohol and recovered **16**. Eventually the desired product **17** was prepared from **16** in three steps: 1) acid hydrolysis of the iminoether to give an amino alcohol, 2) trichloroacetylation of both amino and hydroxy functions, and 3) methanolysis of the trichloroacetate (Scheme 3). Epoxidation of allylic alcohol **17** with *m*-chloroperbenzoic acid (MCPBA) gave β-epoxide **18** in 85% yield along with a trace amount of the corresponding bis-epoxide. The configuration of the hydroxy group at the C-7 position was inverted in two steps by oxidation with pyridinium chlorochromate (PCC) and subsequent reduction with $NaBH_4$ to give α-alcohol **19a** in 89% overall yield from **18**.[23,24] We initially protected the hydroxy group at the C-7 position as benzyl ether **19b** because the protecting group was expected to be compatible with further transformations until the final stage of deprotection. For example, in the synthesis of 5,11-dideoxytetrodotoxin,[12] a benzyl ether was employed as the protecting group for the hydroxy group at the C-8 position, and was successfully deprotected under hydrogenolytic conditions. According to the synthesis, a fully protected 8,11-didexytetrodotoxin **31b** (see Scheme 5) was synthesized from **19b**. However, deprotection of the benzyl ether in the later stages proved problematic. Hence, a trimethylsilyl (TMS) ether was chosen as the temporary protecting group as was employed in the synthesis of 11-deoxytetrodotoxin.[13] The vinyl group of **19c** was ozonized upon treatment with Et_3N[25] to give an unstable aldehyde **20**, while conventional work-up with dimethyl sulfide caused a partial desilylation of TMS, leading to hemiacetal **21**.



Scheme 3. a) AcOH, THF, H_2O, room temperature; b) CCl_3COCCl, Py; c) K_2CO_3, MeOH; d) MCPBA, Na_2HPO_4, CH_2Cl_2, room temperature; e) PCC, 4-Å MS, CH_2Cl_2; f) $NaBH_4$, MeOH; g) TMSCl, Et_3N, THF; h) O_3, CH_2Cl_2, −78°C; Et_3N.

Synthesis of lactone intermediate: The epoxy aldehyde **20** was transformed into lactone **26** by an analogous route to that used in the synthesis of **2** (Scheme 4). The aldehyde **20** reacted with lithium trimethylsilylacetylide to give **22** as a single diastereomer; use of magnesium acetylide in THF in place of lithium trimethylsilylacetylide gave decreased diastereoselectivity (ca. 4:1). The configuration of the newly generated asymmetric center was established to be the undesired *S* from NOESY correlation between H-9 and H-8 of cyclic ether **23**, which was prepared from **22** with K_2CO_3 in methanol. The configuration was therefore inverted by oxi-



Scheme 4. a) TMS-C≡C-Li, THF, −78°C; b) PDC, 3-Å MS, CH_2Cl_2; c) $NaBH_4$, $CeCl_3(H_2O)_7$, MeOH, 0°C; d) Ac_2O, DMAP, Py; H_2O; e) $RuCl_3 \cdot n H_2O$, $NaIO_4$, CCl_4, H_2O, CH_3CN; f) PPTS, CH_2Cl_2; g) K_2CO_3, MeOH, 0°C; h) $HIO_4 \cdot 2H_2O$, AcOMe, room temperature; MeOH, reflux.

dation with PDC followed by Luche reduction[26] to give the unstable propargyl alcohol **24**. The stereoselectivity of these two nucleophilic addition reactions was very high and can be uniformly explained by invoking similarly chelated intermediates **a** and **b** (Figure 2), in which the acetonide plays an important role. Nucleophiles such as acetylide or hydride attack these intermediates from the less hindered front side as a result of the steric hindrance from the acetonide.

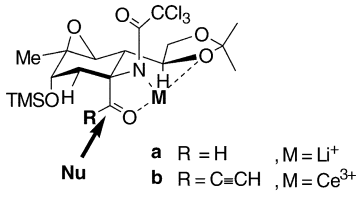
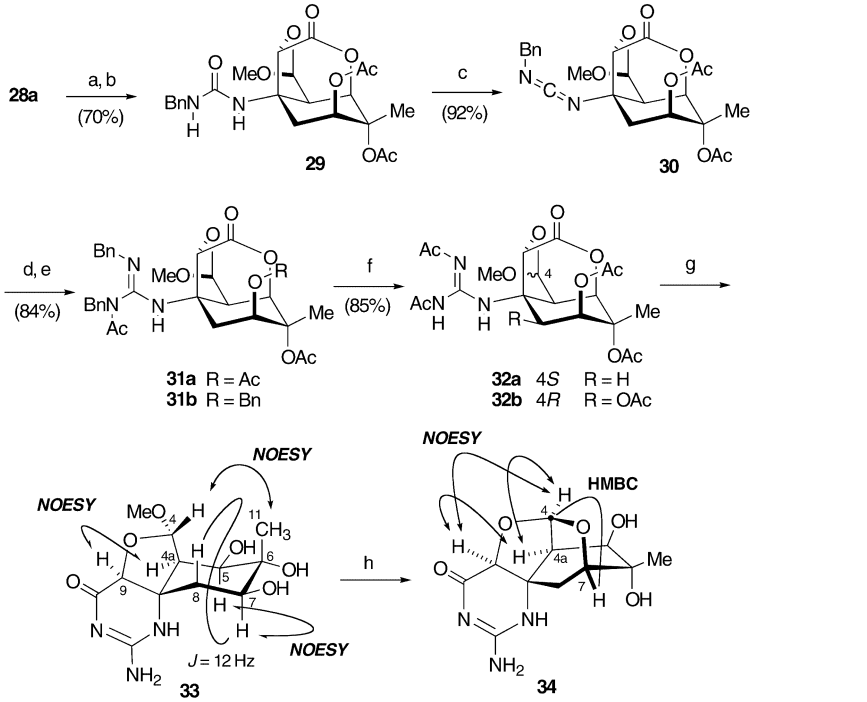


Figure 2. Proposed rationalization for the stereoselectivity of nucleophilic additions to chelated intermediates **a** and **b**.

Fortunately, in the Luche reduction step, the alkyne TMS group was immediately removed upon dissolving the ynone in methanol dried over 3-Å molecular sieves. The resulting product **24** was subjected to acetylation; a small amount of water drove the in situ deprotection of the TMS ether, and the subsequent acetylation gave diacetate **25** in one pot as a stable product in good overall yield.[27] The acetylenic moiety of **25** was cleaved with RuO_4 under Sharpless conditions[28] to give the corresponding carboxylic acid. Because spontaneous lactonization through epoxide opening was very slow under the conditions employed, acid treatment was necessary to afford the lactone **26** in good yield.[29] At this stage, the *S* configuration of the C-9 position was confirmed by observing NOESY correlation between H-9 and H-8 as well as W-shaped long-range coupling ($J = 1$ Hz) between H-9 and H-4a of **26**. Prior to installing the guanidine functionality, the hydroxy group at the C-9 position was protected as an intramolecular mixed acetal with the aldehyde at the C-4 position. Selective deacetylation of the C-9 acetate of **26** was carried out by treatment with K_2CO_3 in methanol at 0 °C, since deacetylation under the conditions (KCN in ethanol) used in the synthesis of 11-deoxytetrodotoxin was very sluggish.[30] Oxidative cleavage of the acetonide[31] was followed by acetalization in methanol at reflux to provide a 4:1 separable mixture of **28a** and **28b**. The C-4 configurations of **28a** and **28b** were established to be *S* and *R*, respectively, by examination of the coupling constants between H-4 and H-4a.[32]

Guanidinylation and deprotection: The guanidine functionality was installed in the major isomer **28a** according to procedure used for the successful synthesis of 11-deoxytetrodotoxin.[13,18] Thus, the tertiary alcohol of **28a** was acetylated, and the trichloroacetamide group was transformed to benzylurea **29** by heating with benzylamine in the presence of Na_2CO_3 in DMF at reflux (Scheme 5). Dehydration with Ph_3P and CBr_4 gave carbodiimide **30**, which treated with benzylamine in pyridine at reflux. The resulting dibenzylguanidinium salt was acetylated to afford the corresponding acetate **31a**. Hydrogenolytic deprotection of benzyl groups in Ac_2O gave **32a** in good yield. We had believed that a two-step deprotection of **32a** would afford 8,11-dideoxytetrodotoxin (**3**) and its anhydro derivative **5**, since deprotection of the similar compound **32b** under the same conditions proceeded without problems to furnish 11-deoxytetrodotoxin (**2**).[13]

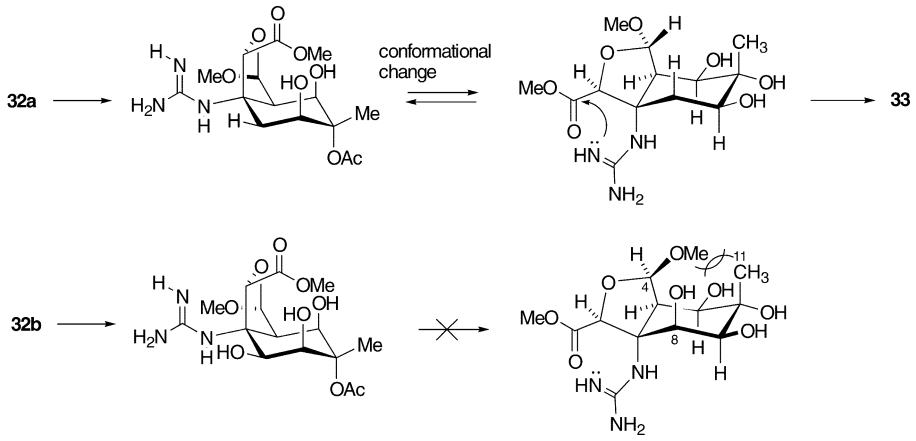


Scheme 5. a) Ac_2O, DMAP, Py; b) $BnNH_2$, Na_2CO_3, DMF, reflux; c) Ph_3P, CBr_4, Et_3N, CH_2Cl_2; d) $BnNH_2$·HCl, Py, reflux; e) Ac_2O, Et_3N, Py; f) H_2, $Pd(OH)_2$-C, Ac_2O; g) NH_3 (aq.), MeOH, room temperature; h) TFA, H_2O, room temperature.

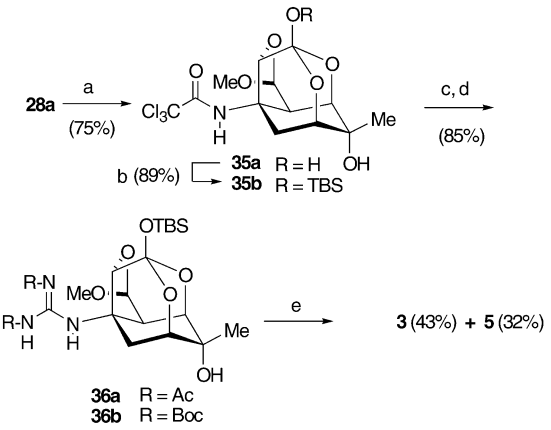
However, attempted deacetylation of **32a** with aqueous ammonia in methanol followed by hydrolysis of the acetal with aqueous trifluoroacetic acid (TFA) gave neither **3** nor **5**. Unexpectedly, the product from the methanolysis was revealed to be dihydropyrimidine **33**, based on extensive NMR analyses (HH-COSY, NOESY), FAB-MS, and UV spectra.[33] The NOESY correlations observed between H-5 and H-7, H-4 and H-11 (methyl), and H-4a and H-9 indicat-

ed the inverted conformation adopted in **33**, which was also supported by the large coupling constant ($J=12$ Hz) between H-7 and H-8. The subsequent treatment of **33** with aqueous TFA gave an unstable product **34**, whose structure was determined by extensive NMR experiments (e.g., NOESY and HMBC) and HRMS.

The formation of the unexpected product **33** might be explained as shown in Scheme 6; methanolysis of the lactone **32a** allowed inversion of the cyclohexane conformation, which enabled the free guanidine group to attack the lactone. This result implies that the hydroxy group at the C-8 position of naturally occurring tetrodotoxins may stabilize the conformation. Another possible explanation is that the *R* configuration of the C-4 position (acetal) of **32b** inhibited the conformational change to the inverted conformation, as in **33**, because of a severe 1,3-diaxal interaction between the methoxy group at the C-4 position and the 11-methyl group.[34]



Scheme 6. Proposed rationalization for the formation of dihydropyrimidine **33** from **32a** and the lack of formation of the corresponding dihydropyrimidine from **32b**.



Scheme 7. Synthesis of 8,11-dideoxytetrodotoxin. a) K_2CO_3, MeOH, rt; b) TBSOTf, Py, CH_3CN; c) DIBAL-H, CH_2Cl_2, -78 °C; d) BocN=C(SMe)NHBoc, $HgCl_2$, Et_3N, DMF; e) TFA, MeOH, H_2O.

Guanidinylation of ortho ester intermediate and completion of the synthesis: To overcome the aforementioned problem, we could protect the lactone as an ortho ester,[35] which should block the lactone carbonyl from nucleophilic attack of the guanidine (Scheme 7). Thus, the acetate at the C-7 position of **28a** was hydrolyzed with K_2CO_3 in methanol at room temperature to afford the ortho ester **35a**, which was protected as *tert*-butyldimethylsilyl (TBS) ether **35b**.[36] The presence of the ortho ester moiety instead of the lactone for **35a** and **35b** was confirmed by observing characteristic signals ($\delta=109.7$, 109.0 ppm) in the ^{13}C NMR spectra. The trichloroacetamide was reductively removed with (diisobutyl aluminum hydride) DIBAL-H[37] to give the corresponding amine, which was directly guanidinylated with diacetyl-*S*-methylisothiourea[38] in the presence of $HgCl_2$[39] to afford diacetylguanidine **36a** in 58% yield from **35b**. However, deprotection of **36a** was unsuccessful. On the other hand, Boc-protected guanidine **36b** prepared from **35b** with bis-Boc-*S*-methylisothiourea[40] was treated with aqueous TFA to provide 8,11-dideoxytetrodotoxin (**3**) and 4,9-anhydro-8,11-dideoxytetrodotoxin (**5**) in 43% and 32% yields, respectively. Owing to the interconvertible nature of tetrodotoxin and its analogues, 4,9-anhydro-8,11-dideoxytetrodotoxin (**5**) was equilibrated in 1% [D]TFA/D_2O to reach a mixture of 8,11-dideoxytetrodotoxin (**3**), its 4,9-anhydroderivative (**5**), and its 4-epimer in a 7:1:0.8 ratio (from ^1H NMR spectroscopy). The structures of these products were confirmed by full assignment of ^1H and ^{13}C NMR spectra by two-dimensional NMR experiments including HMBC. The synthetic 8,11-dideoxytetrodotoxin (**3**) exhibited significantly weaker sodium channel inhibition activities relative to those of 11-deoxytetrodotoxin (**2**), indicating the importance of the 8-hydroxy group in binding between tetrodotoxins and sodium channel proteins.[41]

Conclusion

We have accomplished the synthesis of 8,11-dideoxytetrodotoxin (**3**) in a highly stereoselective manner. This study should open up a new efficient route for synthesizing tetrodotoxin analogues through the use of an ortho ester protecting group and guanidine installation. Total synthesis of tetrodotoxin **1** along these lines is currently under investigation.[42]

Experimental Section

General: Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra (IR) were record-

ed on a JASCO FT/IR-8300 spectrophotometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AMX-600 (600 MHz), JEOL A-600 (600 MHz), Bruker ARX-400 (400 MHz), or Varian Gemini-2000 (300 MHz) spectrometer. NMR samples were dissolved in $CDCl_3$, CD_3OD, or D_2O, and chemical shifts are reported in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) in $CDCl_3$ or in ppm relative to the residual undeuterated solvent (CD_3OH as $\delta = 4.78$, DHO as $\delta = 4.82$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broadened, m = multiplet), coupling constant, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AMX-600 (150 MHz), JEOL A-600 (150 MHz), Bruker ARX-400 (100 MHz), or Varian Gemini-2000 (75 MHz) spectrometer. NMR samples were dissolved in $CDCl_3$ or CD_3OD, and chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ as $\delta = 77.0$ ppm, CD_3OD as $\delta = 49.0$ ppm). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 spectrometer and are reported in *m/z*. Elemental analyses were performed by the Analytical Laboratory at the Graduate School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography (TLC) on 0.25-mm silica gel $60\,F_{254}$ (Merck 1.05715)-coated glass plates. Cica reagent silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for open-column chromatography. Preparative thin-layer chromatographic separations were carried out on 0.5-mm silica gel $60\,F_{254}$ (Merck 1.05774) plates. Unless otherwise noted, nonaqueous reactions were carried out in oven-dried (120 °C) or flame-dried glassware under nitrogen atmosphere. Dry THF was distilled from potassium metal with benzophenone. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. Et_3N, pyridine, and 2,6-lutidine were dried over anhydrous KOH. All other commercially available reagents were used as received.

Cyclic iminoether 16: K_2CO_3 (15.0 g) was added to a solution of dibromide **11** (12.3 g, 22.6 mmol) in MeOH (300 mL). After stirring at room temperature for 15 h, the reaction mixture was poured into an ice-cold saturated solution of NH_4Cl (250 mL). The resulting mixture was extracted with CH_2Cl_2 (1 × 600 mL and 2 × 300 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 450 g, CH_2Cl_2 eluant) to afford cyclic iminoether **16** (6.74 g, 78 %) as a white solid. M.p. 147.5–148.5 °C (as white tiny needles from ether/hexane); $[\alpha]_D^{26} = +164$ ($c = 1.14$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 2987$, 1668, 1236, 1075, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (3H, s; C*H*$_3$ of acetonide), 1.36 (3H, s; C*H*$_3$ of acetonide), 1.86 (1H, dd, $J = 13.5$, 3 Hz; C*H*$_A$H$_B$), 1.90 (3H, t, $J = 1.5$ Hz; CH=C–C*H*$_3$), 1.93 (1H, dd, $J = 13.5$, 3 Hz; CH$_A$*H*$_B$), 2.80 (1H, m; –C*H*–), 3.52 (1H, dd, $J = 9$, 7.5 Hz; O–CH–C*H*$_A$H$_B$–O), 3.87 (1H, dd, $J = 7.5$, 5.5 Hz; O–CH–CH$_A$*H*$_B$–O), 4.11 (1H, dt, $J = 9$, 5.5 Hz; O–C*H*–CH$_2$–O), 4.74 (1H, t, $J = 3$ Hz; O–C*H*–C–CH$_3$), 5.21 (1H, dd, $J = 10.5$, 1 Hz; CH=C*H*$_A$H$_B$), 5.30 (1H, dd, $J = 17$, 1 Hz; CH=CH$_A$*H*$_B$), 5.68 (1H, m; C*H*=CCH$_3$), 6.22 ppm (1H, dd, $J = 17$, 10.5 Hz; C*H*=CH$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 21.2$, 25.8, 26.3, 28.5, 47.9, 55.8, 66.1, 73.4, 74.9, 92.7, 108.2, 114.0, 124.8, 133.3, 141.0, 151.9 ppm; elemental analysis calcd (%) for $C_{16}H_{20}Cl_3NO_3$: C 50.48, H 5.30, N 3.68; found: C 50.47, H 5.35, N 3.75.

Allylic alcohol 17: A solution of cyclic iminoether **16** (6.74 g, 17.7 mmol) in THF (150 mL), H_2O (75 mL), and AcOH (75 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with toluene and concentrated in vacuo (×6). The resulting crude aminoalcohol (8.28 g) was dissolved in pyridine (300 mL), and the solution was cooled to between −5 and 0 °C. CCl_3COCl (5.93 mL, 53.1 mmol) was added dropwise to this solution, and the ice bath was then removed. After stirring for 10 min, the reaction mixture was cooled to 0 °C and MeOH (2.15 mL, 53.1 mmol) was added dropwise; the ice bath was then removed. After stirring for 5 min, the reaction mixture was diluted with toluene and concentrated in vacuo (×3). The crude product (20.7 g) was dissolved in MeOH (300 mL), and K_2CO_3 (15 g) was added. The mixture was stirred at room temperature for 1 h, then filtered through a pad of Super-Cel. The precipitate was washed with MeOH. The combined filtrate was concentrated. The residue was dissolved in AcOEt (100 mL), saturated aqueous NH_4Cl solution (100 mL), and H_2O (50 mL), and the resulting solution was partitioned. The aqueous layer was extracted with AcOEt (3 × 100 mL). The combined organic layer was washed with brine (1 × 300 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 240 g; diethyl ether/hexane, 1:2→3:1) to afford allylic alcohol **17** (5.78 g, 82 % over 3 steps from **16**) as a yellow amorphous solid. $[\alpha]_D^{26} = +90.8$ ($c = 1.08$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3482$, 3353, 2982, 1728, 1527, 1063, 854 cm−1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (3H, s; C*H*$_3$ of acetonide), 1.43 (3H, s; C*H*$_3$ of acetonide), 1.82 (3H, m; CH=C–C*H*$_3$), 1.84 (1H, dd, $J = 13$, 9.5 Hz; C*H*$_{ax}$H$_{eq}$), 2.72 (1H, dq, $J = 10$, 2.5 Hz; –C*H*–), 3.44 (1H, dd, $J = 13$, 6 Hz; CH$_{ax}$*H*$_{eq}$), 3.69 (1H, t, $J = 8$ Hz; O–CH–C*H*$_A$H$_B$–O), 4.01 (1H, ddd, $J = 10$, 8, 6 Hz; O–C*H*–CH$_2$–O), 4.20 (1H, dd, $J = 8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.27 (1H, m; C*H*–OH), 4.90 (1H, m; C*H*=CMe), 5.32 (1H, d, $J = 11$ Hz; CH=C*H*$_A$H$_B$), 5.34 (1H, d, $J = 17.5$ Hz; CH=CH$_A$*H*$_B$), 5.88 (1H, dd, $J = 17.5$, 11 Hz; C*H*=CH$_2$), 8.57 ppm (1H, br s; N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.2$, 25.7, 26.6, 39.8, 48.3, 62.0, 68.0, 68.8, 76.1, 93.7, 109.9, 116.5, 119.4, 133.1, 139.5, 160.6 ppm; elemental analysis calcd (%) for $C_{16}H_{22}Cl_3NO_4$: C 48.20, H 5.56, N 3.51; found: C 48.34, H 5.74, N 3.62.

***β*-Epoxide 18**: Na_2HPO_4 (5.95 g, 41.9 mmol) and MCPBA (80 % purity, 4.80 g, 22.2 mmol) were added to a solution of allylic alcohol **17** (5.55 g, 13.9 mmol) in CH_2Cl_2 (160 mL). After stirring at room temperature for 7 h, the reaction mixture was poured into ice-cold saturated aqueous Na_2SO_3 (200 mL). The resulting solution was partitioned, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 200 g, diethyl ether/hexane, 2:1→3:1) to afford *β*-epoxide **18** (4.87 g, 85 %). M.p. 158–159 °C (as prism from diethyl ether/hexane); $[\alpha]_D^{26} = +34.4$ ($c = 1.01$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3562$, 3309, 1716, 1529, 1075, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (3H, s; C*H*$_3$ of acetonide), 1.45 (3H, s; C*H*$_3$ of acetonide), 1.47 (3H, s; C*H*$_3$), 1.50 (1H, dd, $J = 13$, 11 Hz; C*H*$_{ax}$H$_{eq}$), 1.51 (1H, d, $J = 10$ Hz; O*H*), 2.19 (1H, d, $J = 11$ Hz; –C*H*–), 2.53 (1H, s; epoxidic), 3.36 (1H, dd, $J = 13$, 6 Hz; CH$_{ax}$*H*$_{eq}$), 3.87 (1H, t, $J = 8$ Hz; O–CH–C*H*$_A$H$_B$–O), 4.07 (1H, ddd, $J = 11$, 10, 6 Hz; C*H*–OH), 4.18 (1H, ddd, $J = 11$, 8, 6 Hz; O–C*H*–CH$_2$–O), 4.33 (1H, dd, $J = 8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 5.34 (1H, d, $J = 17$ Hz; CH=C*H*$_A$H$_B$), 5.41 (1H, d, $J = 11$ Hz; CH=CH$_A$*H*$_B$), 5.70 (1H, dd, $J = 17$, 11 Hz; C*H*=CH$_2$), 8.38 ppm (1H, br s; N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.0$, 25.5, 26.6, 36.0, 48.9, 59.6, 60.6, 61.5, 68.2, 68.9, 74.9, 93.6, 110.4, 117.9, 132.1, 160.5 ppm; elemental analysis calcd (%) for $C_{16}H_{22}Cl_3NO_5$: C 46.34, H 5.35, N 3.38; found: C 46.35, H 5.40, N 3.42.

***α*-Alcohol 19a**: PCC (4.78 g, 22.2 mmol) was added to a suspension of *β*-epoxide **18** (4.58 g, 11.0 mmol) and 4-Å molecular sieves (7.54 g) in dry CH_2Cl_2 (150 mL). After stirring at room temperature for 3 h, the reaction mixture was diluted with Et_2O (750 mL), vigorously stirred for 10 min, and filtered through a pad of Super-Cel. The precipitate was washed with Et_2O, and the combined filtrate was passed through a column packed with anhydrous Na_2SO_4 and silica gel and then concentrated. The residue was dissolved in Et_2O, and the solution was again passed through a column packed with anhydrous Na_2SO_4 and silica gel and then concentrated. The crude ketone (4.36 g) was dissolved in MeOH (150 mL), and the solution was cooled to 5 °C. $NaBH_4$ (402 mg, 10.6 mmol) was then added portionwise. After stirring at 5 °C for 25 min, the reaction was quenched with AcOH (5 mL) and concentrated under reduced pressure. The residue was suspended with saturated aqueous NaCl (40 mL) and H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 150 g; diethyl ether/hexane, 1:3→1:1) to afford *α*-alcohol **19a** (4.08 g, 89 % over 2 steps from **18**). M.p. 132–134 °C (as tiny needles from diethyl ether/hexane); $[\alpha]_D^{26} = +2.3$ ($c = 0.94$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3494$, 3291, 1713, 1521, 1059, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (3H, s; C*H*$_3$), 1.45 (6H, s; C*H*$_3$ × 2), 1.98 (1H, dd, $J = 15$, 5.5 Hz; C*H*$_A$H$_B$), 2.16 (1H, d, $J = 4.5$ Hz; O*H*), 2.16 (1H, d, $J = 10.5$ Hz; –C*H*–), 2.52 (1H, s, epoxidic), 3.11 (1H, dd, $J = 15$, 2.5 Hz; CH$_A$*H*$_B$), 3.86 (1H, t, $J = 8$ Hz; O–CH–C*H*$_A$H$_B$–O), 4.23 (1H, ddd, $J = 10.5$, 8, 6 Hz; O–C*H*–CH$_2$–O), 4.26 (1H, m, C*H*–OH), 4.32 (1H, dd, $J = 8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 5.23 (1H, d, $J = 17$ Hz; CH=C*H*$_A$H$_B$), 5.32 (1H, d, $J = 10.5$ Hz; CH=CH$_A$*H*$_B$), 6.26 (1H, dd, $J = 17$, 10.5 Hz; C*H*=CH$_2$), 8.43 ppm (1H, br s, N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 18.9$, 25.5, 26.6, 36.5, 49.3, 59.0, 59.1, 59.6, 66.9, 68.5, 75.1, 93.6, 110.2, 115.3, 134.7, 160.7 ppm; elemental analysis calcd (%) for $C_{16}H_{22}Cl_3NO_5$: C 46.34, H 5.35, N 3.38; found: C 46.34, H 5.43, N 3.41.

Trimethylsilylether 19c: TMSCl (2.0 mL, 16.1 mmol) was added dropwise to an ice-cold solution of α-alcohol **19a** (3.34 g, 8.05 mmol) and Et_3N (9.0 mL, 64.4 mmol) in THF (100 mL) and the reaction was then allowed to warm to room temperature. After stirring for 11 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (100 mL) and then extracted with AcOEt (3×100 mL). The combined organic layer was washed with H_2O (2×200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 60 g, AcOEt/hexane, 1:10→1:5) to afford trimethylsilylether **19c** (3.37 g, 86 %) as a colorless oil. $[\alpha]_D^{25}=-5.4$ ($c=0.73$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}=3331$, 1730, 1522, 1253, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.17$ (9H, s; TMS), 1.34 (3H, s; C*H*$_3$ of acetonide), 1.35 (3H, s; C*H*$_3$), 1.44 (3H, s; C*H*$_3$ of acetonide), 1.86 (1H, dd, $J=14.5$, 4.5 Hz; CH_AH$_B$), 2.14 (1H, d, $J=10.5$ Hz; –C*H*–), 2.46 (1H, s, epoxidic), 3.07 (1H, dd, $J=14.5$, 2.5 Hz; CH$_A$*H*$_B$), 3.85 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.17 (1H, m, C*H*–OTMS), 4.21 (1H, ddd, $J=10.5$, 8, 6 Hz; O–C*H*–CH$_2$–O), 4.29 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 5.17 (1H, d, $J=17$ Hz; CH=CH_AH$_B$), 5.23 (1H, d, $J=11$ Hz; CH=CH$_A$*H*$_B$), 6.27 (1H, dd, $J=17$, 11 Hz; C*H*=CH$_2$), 8.33 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=-0.1$, 19.3, 25.5, 26.6, 35.8, 49.2, 59.1, 59.4, 59.7, 67.7, 68.6, 75.1, 93.8, 110.2, 114.3, 135.1, 160.5 ppm; elemental analysis calcd (%) for $C_{19}H_{30}Cl_3NO_5Si$: C 46.87, H 6.21, N 2.88; found: C 46.87, H 6.27, N 2.82.

Aldehyde 20: A solution of trimethylsilylether **19c** (875 mg, 1.80 mmol) dissolved in CH_2Cl_2 (30 mL) at −78 °C. Ozone was passed through the solution for 15 min followed by nitrogen for 15 min. The reaction mixture was treated with Et_3N (2.5 mL, 18.0 mmol) at −78 °C, and stirred at −78 °C for 20 min. The mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (30 mL) and partitioned. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL); the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (Merck silica gel 60 N, spherical neutral, particle size 0.063–0.210 mm, 30 g; AcOEt/hexane, 1:15→1:7) to afford aldehyde **20** (793 mg, 90 %) as a colorless oil. IR (KBr): $\tilde{\nu}_{max}=$ 3372, 1713, 1506, 1254, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.15$ (9H, s; TMS), 1.32 (3H, s; C*H*$_3$), 1.36 (3H, s; C*H*$_3$), 1.40 (3H, s; C*H*$_3$), 1.82 (1H, dd, $J=14$, 3 Hz; CH_AH$_B$), 2.89 (1H, s; epoxidic), 2.95 (1H, dd, $J=14$, 3.5 Hz; CH$_A$*H*$_B$), 3.22 (1H, d, $J=7$ Hz; –C*H*–), 3.72 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.16 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.21 (1H, brt, $J=3$ Hz; C*H*–OTMS), 4.27 (1H, ddd, $J=8$, 7, 6 Hz; O–C*H*–CH$_2$–O), 8.22 (1H, brs; N*H*), 9.86 ppm (1H, s; –C*H*O); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=0.2$, 19.1, 25.3, 25.8, 36.9, 41.3, 60.0, 60.7, 63.0, 68.2, 68.4, 75.2, 92.8, 110.2, 160.6, 197.3 ppm.

Propargyl alcohol 22: *n*BuLi (1.56 M in hexane, 2.90 mL, 4.56 mmol) was added dropwise to a solution of trimethylsilylacetylene (770 μL, 5.47 mmol) in dry THF (15 mL) at −78 °C. The solution was allowed to warm to 0 °C and stirred over 10 min. After cooling to −78 °C, aldehyde **20** (446 mg, 0.912 mmol) in dry THF (3 mL) was added dropwise by cannula. After stirring at −78 °C for 20 min, the mixture was stirred at −50 °C for 20 min. The mixture was then poured into ice-cold hydrochloric acid (0.12 M, 38 mL), and extracted with AcOEt (3×30 mL). The combined organic layer was washed with H_2O (2×60 mL) and brine (1×60 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was used for the next reaction without purification. ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.14$ (9H, s; TMS), 0.27 (9H, s; TMS), 1.30 (3H, s; C*H*$_3$), 1.42 (3H, s; C*H*$_3$ of acetonide), 1.45 (3H, s; C*H*$_3$ of acetonide), 1.88 (1H, dd, $J=15$, 4 Hz; CH_AH$_B$), 2.16 (1H, d, $J=10$ Hz; –C*H*–), 2.65 (1H, s; epoxidic), 3.03 (1H, dd, $J=15$, 2.5 Hz; CH$_A$*H*$_B$), 3.92 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.21 (1H, m, C*H*–OTMS), 4.40 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.95 (1H, d, $J=5$ Hz; HO–C*H*–C≡CTMS), 5.01 (1H, ddd, $J=10$, 8, 6 Hz; O–C*H*–CH$_2$–O), 5.40 (1H, d, $J=5$ Hz; O*H*), 8.60 ppm (1H, brs; N*H*).

Propargyl alcohol 24: The crude propargyl alcohol **22** (535 mg) was dissolved in dry CH_2Cl_2 (15 mL), and then 3-Å molecular sieves (454 mg) and PDC (414 mg, 1.10 mmol) were successively added. The mixture was stirred vigorously at room temperature for 3.5 h and then diluted with Et_2O. After vigorous stirring for 15 min, the resulting mixture was filtered through a pad of Super-Cel, and the precipitate was washed with Et_2O. The combined filtrate was concentrated to give the crude ynone. The product was used for the next reaction without purification. ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.15$ (9H, s; TMS), 0.24 (9H, s; TMS), 1.34 (6H, s; C*H*$_3$×2), 1.41 (3H, s; C*H*$_3$), 2.33 (1H, dd, $J=14$, 6 Hz; CH_AH$_B$), 2.38 (1H, dd, $J=14$, 6 Hz; CH$_A$*H*$_B$), 2.62 (1H, dd, $J=7.5$, 1.5 Hz; –C*H*–), 3.02 (1H, brs; epoxidic), 3.73 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.04 (1H, t, $J=6$ Hz; C*H*–OTMS), 4.17 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.32 (1H, ddd, $J=8$, 7.5, 6 Hz; O–C*H*–CH$_2$–O), 8.15 ppm (1H, brs; N*H*).

A solution of crude ynone (487 mg) dissolved in MeOH (15 mL, dried over 3-Å molecular sieves) was stirred at room temperature for 25 min and then $CeCl_3\cdot 7H_2O$ (412 mg, 1.11 mmol) was added. The solution was cooled to 0 °C, and $NaBH_4$ (44 mg, 1.16 mmol) was added. Stirring was continued at 0 °C for 20 min, and then the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and concentrated. ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.19$ (9H, s; TMS), 1.31 (3H, s; C*H*$_3$), 1.42 (3H, s; C*H*$_3$ of acetonide), 1.45 (3H, s; C*H*$_3$ of acetonide), 2.39 (1H, ddd, $J=15.5$, 4.5, 1.5 Hz; CH_AH$_B$), 2.47 (1H, d, $J=11$ Hz; –C*H*–), 2.52 (1H, d, $J=1$ Hz; epoxidic), 2.49 (1H, d, $J=2$ Hz; C≡C*H*), 3.28 (1H, dd, $J=15.5$, 2 Hz; CH$_A$*H*$_B$), 3.81 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.26 (1H, m; C*H*–OTMS), 4.38 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.58 (1H, ddd, $J=11$, 8, 6 Hz; O–C*H*–CH$_2$–O), 4.64 (1H, ddd, $J=12$, 2, 1.5 Hz; C*H*-C≡CH), 5.84 (1H, d, $J=12$ Hz; O*H*), 7.82 ppm (1H, brs; N*H*).

Diacetate 25: Acetic anhydride (10 mL) and a catalytic amount of DMAP were added to a solution of the crude propargyl alcohol **24** (422 mg) in pyridine (10 mL). After stirring at room temperature for 1 h, H_2O (20 μL) was added. After stirring at room temperature for an additional 32 h, the reaction mixture was diluted with toluene and concentrated in vacuo (×3). The residue was purified by column chromatography (silica gel 15 g; AcOEt/hexane, 1:5→1:3 and then silica gel 10 g; AcOEt/hexane, 1:7→1:5) to afford diacetate **25** (342 mg, 71 % over 4 steps from **20**) as a yellow amorphous solid. $[\alpha]_D^{23}=-22.8$ ($c=0.89$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}=3304$, 1750, 1272, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.31$ (3H, s; C*H*$_3$), 1.42 (3H, s; C*H*$_3$), 1.46 (3H, s; C*H*$_3$), 2.09, (3H, s; Ac), 2.14 (3H, s; Ac), 2.22 (1H, dd, $J=10.5$, 2 Hz; –C*H*–), 2.35 (1H, dd, $J=15.5$, 5 Hz; CH_AH$_B$), 2.63 (1H, d, $J=2$ Hz; C≡C*H*), 2.71 (1H, d, $J=2$ Hz; epoxidic), 2.78 (1H, dd, $J=15.5$, 5.5 Hz; CH$_A$*H*$_B$), 3.84 (1H, t, $J=8$ Hz; O–CH–CH_AH$_B$–O), 4.38 (1H, dd, $J=8$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.75 (1H, ddd, $J=10.5$, 8, 6 Hz; O–C*H*–CH$_2$–O), 5.23 (1H, brt, $J=5.5$ Hz; CH$_2$–C*H*–OAc), 5.96 (1H, d, $J=2$ Hz; HC≡C–C*H*–OAc), 8.24 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=17.6$, 20.7, 20.8, 25.8, 26.6, 32.8, 48.8, 58.3, 59.5, 60.7, 64.3, 68.1, 69.0, 74.9, 77.2, 78.9, 93.0, 110.4, 161.0, 168.4, 169.8 ppm; elemental analysis calcd (%) for $C_{21}H_{26}Cl_3NO_8$: C 47.88, H 4.97, N 2.66; found: C 47.75, H 4.87, N 2.49.

Cyclic ether 23: *n*BuLi (1.56 M in hexane, 175 μL, 0.28 mmol) was added dropwise to a solution of trimethylsilylacetylene (50 μL, 0.33 mmol) in dry THF (1.0 mL) at −78 °C. The solution was allowed to warm to 0 °C and was stirred for 10 min, and then cooled to −78 °C again. Aldehyde **20** (27 mg, 0.055 mmol) in dry THF (0.5 mL) was added dropwise by cannula to the resultant acetylide solution. After stirring at −78 °C for 20 min, the mixture was allowed to warm to −50 °C. After stirring for 20 min at this temperature, the reaction mixture was poured into ice-cold water (2 mL). The mixture was extracted with AcOEt (3×5 mL). The combined organic layer was washed with H_2O (2×15 mL) and brine (1×15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resultant crude propargyl alcohol **22** (41 mg) was dissolved in MeOH (1.5 mL), and K_2CO_3 (24 mg) was added. After stirring at room temperature for 45 min, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), and then H_2O (1 mL) was added. The mixture was extracted with CH_2Cl_2 (3×5 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 2 g; AcOEt/hexane, 3:1) to afford diol **23** (23 mg, 94 % over 2 steps from **20**) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.36$ (3H, s; C*H*$_3$), 1.45 (3H, s; C*H*$_3$ of acetonide), 1.47 (3H, s; C*H*$_3$ of acetonide), 2.01, (1H, brs; O*H*), 2.12 (1H, dd, $J=14$, 5 Hz; CH_AH$_B$), 2.63 (1H, d, $J=2$ Hz; C≡C*H*), 2.70 (1H, d, $J=10.5$ Hz; –C*H*–), 2.98 (1H, brd, $J=14$ Hz; CH$_A$*H*$_B$), 3.62 (1H, t, $J=7.5$ Hz; O–CH–CH_AH$_B$–O), 3.64 (1H, s; C*H*–O–CH–C≡CH), 3.75 (1H, brs; CH$_2$–C*H*–OH), 4.22 (1H, dd, $J=7.5$, 6 Hz; O–CH–CH$_A$*H*$_B$–O), 4.99 (1H, ddd, $J=10.5$, 7.5, 6 Hz; O–C*H*–CH$_2$–O), 5.66 (1H, d, $J=2$ Hz; O–C*H*–C≡CH), 9.22 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=23.8$, 25.5, 26.9, 39.3, 49.6, 63.9,

69.1, 72.0, 72.5, 73.9, 74.6, 77.3, 80.4, 84.7, 92.7, 110,2. 162.1 ppm; HRMS (FAB): *m/z* calcd for $C_{17}H_{23}Cl_3NO_6$ [M^++H]: 442.0591; found: 442.0588.

Lactone 26: $RuCl_3(H_2O)_n$ (45 mg, 0.24 mmol) in H_2O (4.5 mL) was added to a solution of $NaIO_4$ (444 mg, 2.08 mmol) in CH_3CN (3 mL) and CCl_4 (3 mL). After stirring at room temperature for 5 min, a solution of diacetate **25** (308 mg, 0.585 mmol) in CH_3CN (2 mL) and CCl_4 (2 mL) was added to the reaction mixture, and then H_2O (3 mL) was added. After stirring at room temperature for 45 min, the reaction mixture was treated with K_2CO_3 (322 mg, 2.33 mmol) and *i*PrOH (3 mL), and then diluted with CH_2Cl_2. After vigorous stirring for 15 min, saturated aqueous NH_4Cl (10 mL) and hydrochloric acid (0.12 M, 2 mL) were added. The organic layer was partitioned and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (8 mL), and pyridinium *p*-toluenesulfonate (PPTS, 16 mg, 0.064 mmol) was added. After stirring at room temperature for 9 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and then partitioned. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g; AcOEt/hexane, 1:3→1:1) to afford lactone **26** (207 mg, 65 % in 2 steps from **25**). M.p. 242–243 °C (as prism from diethyl ether/hexane); $[\alpha]_D^{23} = -62.4$ ($c = 1.01$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3488$, 3308, 1758, 1221, 854 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (6H, s; CH_3×2), 1.48 (3H, s; CH_3), 2.10 (3H, s; Ac), 2.11 (3H, s; Ac), 2.36 (1H, dd, $J = 15$, 4 Hz; CH_AH_B), 2.74 (1H, brd, $J = 10$ Hz; –C*H*–), 3.33 (1H, dd, $J = 15$, 2.5 Hz; CH_AH_B), 3.68 (1H, t, $J = 8$ Hz; O–CH–CH_AH_B–O), 3.95 (1H, t, $J = 1$ Hz; C*H*–OCO), 4.32 (1H, dd, $J = 8$, 5.5 Hz; O–CH–CH_AH_B–O), 4.65 (1H, ddd, $J = 10$, 8, 5.5 Hz; O–C*H*–CH_2–O), 5.11 (1H, m; CH_2–C*H*–OAc), 6.20 (1H, d, $J = 1$ Hz; CO–C*H*–OAc), 8.93 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.6$, 20.8, 23.2, 25.9, 26.6, 34.7, 40.0, 56.7, 68.4, 69.1, 69.8, 72.0, 74.3, 81.7, 92.7, 110.8, 161.1, 165.7, 167.4, 169.1 ppm; elemental analysis calcd (%) for $C_{20}H_{26}Cl_3NO_{10}$: C 43.93, H 4.79, N 2.56; found: C 43.94, H 4.69, N 2.54.

Diol 27: K_2CO_3 (24 mg, 0.17 mmol) was added to an ice-cold solution of lactone **26** (184 mg, 0.337 mmol) in MeOH (10 mL). After stirring at 0 °C for 40 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and then H_2O (5 mL) was added. The resulting solution was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g; AcOEt/hexane, 1:1) to afford diol **27** (136 mg, 80 %) as an amorphous solid. $[\alpha]_D^{25} = -14.3$ ($c = 0.82$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3446$, 3311, 1732, 1223, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (3H, s; CH_3), 1.39 (3H, s; CH_3), 1.45 (3H, s; CH_3), 2.04 (3H, s; Ac), 2.30 (1H, s; O*H*), 2.42 (1H, dd, $J = 15$, 4 Hz; CH_AH_B), 2.73 (1H, brd, $J = 10$ Hz; –C*H*–), 3.02 (1H, dd, $J = 15$, 2 Hz; CH_AH_B), 3.26 (1H, d, $J = 4$ Hz; O*H*), 3.65 (1H, t, $J = 8$ Hz; O–CH–CH_AH_B–O), 3.95 (1H, brs; C*H*–OCO), 4.26 (1H, dd, $J = 8$, 5.5 Hz; O–CH–CH_AH_B–O), 4.73 (1H, ddd, $J = 10$, 8, 5.5 Hz; O–C*H*–CH_2–O), 4.86 (1H, dd, $J = 4$, 1 Hz; C*H*–OH), 5.06 (1H, m; CH_2–C*H*–OAc), 8.96 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 20.8, 23.3, 25.8, 26.7, 34.9, 39.9, 57.2, 68.8, 70.0, 72.4, 74.2, 81.8, 92.8, 110.6, 162.2, 169.1, 170.5 ppm; HRMS (FAB): *m/z* calcd for $C_{18}H_{25}Cl_3NO_9$ [M+H]$^+$: 504.0595; found: 504.0563.

Acetal 28a and 28b: $HIO_4 \cdot 2H_2O$ (42 mg, 0.18 mmol) was added to a solution of diol **27** (46 mg, 0.091 mmol) in AcOMe (3 mL). After stirring at room temperature for 3 h, MeOH (1.5 mL) was added. The reaction mixture was heated at reflux for 10 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous Na_2SO_3 (2 drops) were added. The mixture was extracted with AcOEt (5 mL×3), and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/acetone, 10:1, ×2) to afford acetal **28a** (16 mg, 41 %) as a white amorphous solid and acetal **28b** (5.3 mg, 13 %) as a colorless oil.

Acetal 28a: $[\alpha]_D^{24} = +22.1$ ($c = 0.82$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3469$, 3364, 1752, 1238, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (3H, s; CH_3), 2.07 (3H, s; Ac), 2.45 (1H, brs; O*H*), 2.59 (1H, dd, $J = 16$, 5 Hz; CH_AH_B), 2.85 (1H, dd, $J = 16$, 4 Hz; CH_AH_B), 3.14 (1H, dd, $J = 2.5$, 1.5 Hz; –C*H*–), 3.48 (3H, s; OMe), 4.34 (1H, dd, $J = 2.5$, 1 Hz; CH–OCO), 4.87 (1H, d, $J = 1.5$ Hz; C*H*–COO), 4.97 (1H, ddd, $J = 5$, 4, 1 Hz; CH_2–C*H*–OAc), 5.23 (1H, s; C*H*–OMe), 7.97 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.8$, 22.8, 29.0, 44.7, 55.9, 58.8, 71.0, 72.3, 80.4, 80.7, 92.4, 105.8, 161.3, 165.5, 170.4 ppm; HRMS (FAB): *m/z* calcd for $C_{15}H_{19}Cl_3NO_8$ [M+H]$^+$: 446.0176; found: 446.0147.

Acetal 28b: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (3H, s; CH_3), 2.06 (1H, dd, $J = 15.5$, 6.5 Hz; CH_AH_B), 2.09 (3H, s; Ac), 2.76 (1H, dd, $J =$ 15.5, 6 Hz; CH_AH_B), 3.03 (1H, brs; O*H*), 3.55 (3H, s; OMe), 3.67 (1H, brdt, $J = 4$, 2 Hz; –C*H*–), 4.43 (1H, d, $J = 1.5$ Hz; C*H*–COO), 4.61 (1H, d, $J = 2$ Hz; C*H*–OCO), 5.18 (1H, brt, $J = 6$ Hz; CH_2–C*H*–OAc), 5.31 (1H, d, $J = 4$ Hz; C*H*–OMe) 6.78 ppm (1H, brs; N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.9$, 22.1, 29.5, 40.1, 57.6, 61.5, 71.6, 75.0, 79.0, 79.9, 92.0, 104.9, 161.4, 165.6, 171.4 ppm; HRMS (FAB): *m/z* calcd for $C_{15}H_{19}Cl_3NO_8$ [M^++H]: 446.0176; found: 446.0186.

Benzylurea 29: The acetal **28a** (66 mg, 0.15 mmol) was dissolved in pyridine (2 mL) and acetic anhydride (2 mL) and a catalytic amount of DMAP were added. After stirring at room temperature for 13 h, the mixture was diluted with toluene and concentrated in vacuo (×3). The residue was purified by column chromatography (silica gel 5 g; AcOEt/hexane, 1:1) to afford diacetate (48 mg, 80 %) as an amorphous solid. A solution of diacetate (48 mg, 0.098 mmol), Na_2CO_3 (53 mg, 0.50 mmol), and $BnNH_2$ (20 μL, 0.20 mmol) in DMF (5 mL) was stirred for 15 min at reflux. After cooling to room temperature, saturated aqueous NH_4Cl (7 mL) was added. The mixture was extracted with AcOEt (3×5 mL), and the combined organic layer was washed with H_2O (2×20 mL) and brine (1×20 mL), the solution was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 3 g; AcOEt/hexane, 3:1) to afford benzylurea **29** (41 mg, 88 %) as a yellow amorphous solid. $[\alpha]_D^{26} = +34$ ($c = 0.93$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3366$, 1748, 1653, 1230, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.61$ (3H, s; Me), 2.03 (3H, s; OAc), 2.09 (3H, s; OAc), 2.64 (1H, dd, $J = 16$, 5.5 Hz; CH_AH_B), 2.68 (1H, m; –C*H*–), 2.89 (1H, dd, $J = 16$, 2.5 Hz; CH_AH_B), 3.40 (3H, s; OMe), 4.25 (1H, dd, $J = 15$, 5.5 Hz; N–CH_AH_B–Ph), 4.40 (1H, dd, $J = 15$, 5.5 Hz; N–CH_AH_B–Ph), 4,66 (1H, brt, $J = 5.5$ Hz; N*H*–Bn), 4.86 (1H, d, $J = 2$ Hz; C*H*–COO), 5.10 (1H, s; C*H*–OMe), 5.18 (1H, dd, $J = 2.5$, 1 Hz; CH–OCO), 5.23 (1H, m; CH_2C*H*OAc), 5.43 (1H, brs; N*H*), 7.25–7.37 ppm (5H, m; aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 17.8$, 20.8, 22.0, 30.8, 44.4, 44.7, 56.5, 57.0, 68.9, 77.5, 79.8, 81.8, 106.6, 127.3, 127.4, 128.7, 138.7, 156.9, 166.2, 169.4, 169.6 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{28}N_2O_9$ [M^++H]: 477.1873; found: 477.1873.

Carbodiimide 30: Ph_3P (214 mg, 0.819 mmol) was added to a solution of CBr_4 (271 mg, 0.819 mmol) in CH_2Cl_2 (2 mL). A solution of Et_3N (0.23 mL, 1.6 mmol) and benzylurea **29** (39 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) were then added to the reaction mixture. After stirring for 35 min at room temperature, the mixture was diluted with AcOEt and then stirred vigorously. The resulting precipitate (Ph_3P=O) was removed by filtration through a pad of Super-Cel. The filtrate was concentrated and purified by column chromatography (Merck silica gel 60 N, spherical neutral, particle size 0.063–0.210 mm, 2 g; AcOEt/hexane, 1:1) to afford carbodiimide **30** (35 mg, 92 %) as a yellow oil. IR (KBr): $\tilde{\nu}_{max} = 2134$, 1742, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.60$ (3H, s; Me), 2.02 (3H, s; OAc), 2.03 (3H, s; OAc), 1.97 (1H, dd, $J = 16$, 1 Hz; CH_AH_B), 2.31 (1H, dd, $J = 16$, 5.5 Hz; CH_AH_B), 2.56 (1H, dd, $J = 2$, 1.5 Hz; –C*H*–), 3.49 (3H, s; OMe), 4.24 (1H, d, $J = 1.5$ Hz; C*H*–COO), 4.42 (1H, d, $J =$ 14 Hz; N–CH_AH_B–Ph), 4.46 (1H, d, $J = 14$ Hz; N–CH_AH_B–Ph), 5.11 (1H, m; CH_2C*H*OAc), 5.12 (1H, s; C*H*–OMe), 5.18 (1H, dd, $J = 2$, 1 Hz; C*H*–OCO), 7.27–7.39 ppm (5H, m; aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 17.9$, 20.7, 21.9, 33.2, 46.8, 50.0, 56.9, 60.1, 68.9, 78.0, 79.3, 83.3, 106.9, 127.5, 127.7, 128.7, 138.0, 138.6, 166.1, 169.3 ppm (2 peaks).

Dibenzylacetylguanidine 31a: $BnNH_2 \cdot HCl$ (53 mg, 0.37 mmol) was added to a solution of carbodiimide **30** (35 mg, 0.076 mmol) in pyridine (2 mL). After stirring for 2 h at reflux, the mixture was diluted with toluene and concentrated in vacuo. The residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL) and Et_3N (0.2 mL) were added. After stirring for 12 h at room temperature, the mixture was diluted with toluene and concentrated in vacuo. The residue was purified by column chromatography (silica gel 3 g; AcOEt/hexane, 3:1) to afford dibenzylacetylguanidine **31a** (39 mg, 84 % over 2 steps) as a yellow oil. $[\alpha]_D^{26} = +28$ ($c = 0.76$ in $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3383$, 1744, 1653, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.60$ (3H×$^1/_2$, s; Me), 1.62 (3H×$^1/_2$, s; Me), 1.95 (3H×$^1/_2$, s; Ac), 1.98 (3H×$^1/_2$, s; Ac), 2.03 (3H×$^1/_2$, s; Ac), 2.04 (3H×

$^1/_2$, s; Ac), 2.05 (3H×$^1/_2$, s; Ac), 2.06 (3H×$^1/_2$, s; Ac), 2.30 (1H×$^1/_2$, dd, J=16, 5.5 Hz; CH_AH$_B$), 2.45 (1H×$^1/_2$, t, J=1.5 Hz; –CH–), 2.70 (1H×$^1/_2$, dd, J=16, 5.5 Hz; CH_AH$_B$), 2.90 (1H×$^1/_2$, t, J=1.5 Hz; –CH–), 2.91 (1H×$^1/_2$, dd, J=16, 3 Hz; CH$_A$$H_B$), 3.00 (1H×$^1/_2$, dd, J=16, 3 Hz; CH$_A$$H_B$), 3.38 (3H×$^1/_2$, s; OMe), 3.41 (3H×$^1/_2$, s; OMe), 3.74 (1H×$^1/_2$, d, J=15.5 Hz; CH_AH$_B$–Ph), 4.01 (1H, d, J=15.5 Hz; CH$_A$$H_B$–Ph), 4.09 (1H, d, J=15 Hz; CH_AH$_B$–Ph), 4.21 (1H×$^1/_2$, d, J=15 Hz; CH$_A$$H_B$–Ph), 4.33 (1H×$^1/_2$, d, J=14 Hz; CH_AH$_B$–Ph), 4.34 (1H×$^1/_2$, d, J=14 Hz; CH_AH$_B$–Ph), 4.83 (1H×$^1/_2$, brs; NH), 4.92 (1H×$^1/_2$, d, J=1.5 Hz; CH–OCO), 4.94 (1H×$^1/_2$, d, J=14 Hz; CH$_A$$H_B$–Ph), 4.98 (1H×$^1/_2$, d, J=14 Hz; CH$_A$$H_B$–Ph), 5.06 (1H×$^1/_2$, brs; N$H$), 5.08 (1H×$^1/_2$, s; C$H$–OMe), 5.10 (1H×$^1/_2$, m; C$H$–COO), 5.13 (1H×$^1/_2$, d, J=1.5 Hz; CH–COO), 5.15 (1H×$^1/_2$, s; CH–OMe), 5.09–5.21 (3H×$^1/_2$, m; CH–OAc×2, CH–OCO), 6.94–7.38 ppm (m; 10H, aromatic); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=17.8, 20.8, 21.1, 21.2, 21.8, 22.0, 29.3, 29.6, 44.7, 44.8, 44.9, 48.6, 48.8, 52.2, 52.3, 56.5, 56.7, 57.2, 57.7, 69.2, 69.5, 77.7, 79.8, 80.0, 80.2, 106.4, 106.7, 106.8, 126.5, 126.8, 126.6, 126.9, 127.4, 127.8, 128.1 128.2, 128.3, 128.6, 128.7, 128.8, 129.2, 129.2, 136.3, 136.8, 140.0, 140.2, 144.4, 166.3, 168.8, 169.0, 169.3, 169.4, 169.6 ppm; HRMS (FAB): m/z calcd for C$_{32}$H$_{37}$N$_3$O$_9$ [M+H]$^+$: 608.2608; found: 608.2582.

Diacetylguanidine 32a: 20% Pd(OH)$_2$ on carbon (Pearlman's catalyst, 35 mg) was added to a solution of dibenzylacetylguanidine **31a** (35 mg, 0.075 mmol) in acetic anhydride (3 mL), and the reaction flask was filled with hydrogen. After stirring under atmospheric pressure of hydrogen for 24 h at room temperature, the reaction mixture was filtered through a pad of Super-Cel and washed with AcOEt. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel 3 g; AcOEt/hexane, 2:1) to afford diacetylguanidine **32a** (23 mg, 85%) as an amorphous solid. $[\alpha]_D^{25}$=+68 (c=0.81 in CHCl$_3$); IR (KBr): $\tilde{\nu}_{max}$= 3233, 2935, 1773, 1746, 1617, 1210 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ= 1.64 (3H, s; Me), 2.07 (3H, s; Ac), 2.09 (3H, s; Ac), 2.10 (3H, s; Ac), 2.18 (3H, s; Ac), 2.54 (1H, dd, J=16, 5 Hz; CH_AH$_B$), 2.89 (1H, dd, J= 2.5, 1.5 Hz; –CH–), 3.17 (1H, dd, J=16, 4.5 Hz; CH$_A$$H_B$), 3.42 (3H, s; OMe), 5.15 (1H, d, J=1.5 Hz; CH–COO), 5.18 (1H, s; CH–OMe), 5.18 (1H, m; CH–OCO), 5.28 (1H, m; CH–OAc), 9.68 (1H, brs; NH), 13.60 ppm (1H, brs; NH); ^{13}C NMR (CDCl$_3$, 150 MHz): δ=17.7, 20.8, 22.1, 24.9, 28.8, 30.1, 45.1, 55.7, 58.1, 69.5, 77.6, 80.0, 80.8, 105.7, 153.7, 166.1, 169.3, 169.4, 172.0, 185.5 ppm; HRMS (FAB): m/z calcd for C$_{20}$H$_{27}$N$_3$O$_{10}$ [M+H]$^+$: 470.1775; found: 470,1801.

Dihydropyrimidine 33: Aqueous NH$_3$ (20%, 0.3 mL) was added to a solution of diacetylguanidine **32a** (5 mg) in MeOH (0.3 mL) and H$_2$O (0.6 mL). After stirring for 24 h at room temperature, the reaction mixture was concentrated in vacuo to give crude dihydropyrimidine **33** (6 mg). $\lambda_{max}^{H_2O}$=237, 210 nm (ε=7.28×10^3, 1.06×10^4); ^{1}H NMR (300 MHz, D$_2$O): δ=1.21 (3H, s; Me), 1.62–1.79 (2H, m; CH_2), 2.69 (1H, dd, J= 7.5, 4.5 Hz; –CH–), 3.50 (3H, s; OMe), 3.68 (1H, brd, J=12 Hz; CH–CH$_2$), 4.05 (1H, d, J=7.5 Hz; CH–CH–CMe), 4.60 (1H, brs; CH–CO–N), 5.38 ppm (1H, d, J=4.5 Hz; CH–OMe); HRMS (FAB): m/z calcd for C$_{12}$H$_{19}$N$_3$O$_6$ [M+H]$^+$: 302.1352, found: 302.1327.

Compound 34: TFA (0.3 mL) was added to a solution of the crude dihydropyrimidine **33** (6 mg) in H$_2$O (0.6 mL). After stirring for 15 h at room temperature, the reaction mixture was concentrated in vacuo to give crude **34** (10 mg). ^{1}H NMR (300 MHz, D$_2$O): δ=1.33 (3H, s; Me), 2.18 (1H, dd, J=15, 4 Hz; CH_AH$_B$), 2.44 (1H, d, J=15 Hz; CH$_A$$H_B$) 2.91 (1H, t, J=3.5 Hz; CH–CH–OH), 3.80 (1H, brd, J=4 Hz; CH$_2$–CH–O), 4.20 (1H, d, J=3 Hz; CH–OH), 4.71 (1H, s; CH–CO–N), 5.66 ppm (1H, d, J=4 Hz; O–CH–O); HRMS (FAB): m/z calcd for C$_{11}$H$_{16}$N$_3$O$_5$ [M^++H]: 270.1090; found: 270.1104.

Ortho ester 35a: K$_2$CO$_3$ (15 mg, 0.11 mmol) was added to a solution of acetal **28a** (33 mg, 0.074 mmol) in MeOH (2 mL). After stirring at room temperature for 1 h, the reaction was quenched with saturated aqueous NH$_4$Cl (2 mL), and the resulting mixture was extracted with CHCl$_3$ (5 mL×3). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 2 g; AcOEt/hexane, 4:1) to afford ortho ester **35a** (23 mg, 75%) as an amorphous solid. $[\alpha]_D^{27}$=+13.8 (c=0.29 in MeOH); IR (KBr): $\tilde{\nu}_{max}$=3367, 2925, 1713, 1525, 822 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD): δ=1.48 (3H, s; Me), 2.64 (1H, d, J= 12 Hz; CH_AH$_B$), 2.66 (1H, d, J=12 Hz; CH$_A$$H_B$), 2.96 (1H, dd, J=3.5, 1 Hz; –CH–), 3.34 (3H, s; OMe), 3.76 (1H, m; CH$_2$–CH–O), 3.78 (1H, dd, J=3.5, 1.5 Hz; CH–CH–C–Me), 4.33 (1H, d, J=1 Hz; CH–C–NH), 5.07 ppm (1H, s; CH–OMe); ^{13}C NMR (CD$_3$OD, 150 MHz): δ=24.8, 28.2, 46.9, 55.7, 60.1, 65.2, 77.7, 77.9, 82.0, 94.1, 108.4, 109.7, 162.3 ppm; HRMS (FAB): m/z calcd for C$_{13}$H$_{17}$Cl$_3$NO$_7$ [M+H]$^+$: 404.0071; found: 404.0071.

Ortho ether 35b: Ortho ester **35a** (23 mg, 0.057 mmol) and pyridine (30 μL, 0.30 mmol) were dissolved in CH$_3$CN (1 mL), and the solution was cooled to −40°C. TBSOTf (40 μL, 0.17 mmol) was added to the solution, and then the cooling bath was removed. After stirring for 1 h, the reaction mixture was poured into ice-cold H$_2$O (5 mL), and the resulting solution was extracted with AcOEt (7 mL×3). The combined organic layer was washed with saturated aqueous NH$_4$Cl (20 mL) and brine (20 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 2 g; AcOEt/hexane, 1:1) to afford ortho ether **35b** (27 mg, 93%). M.p. 182–183.5°C (as tiny needles from diethyl ether/hexane); $[\alpha]_D^{23}$=−3.0 (c=0.31 in CHCl$_3$); IR (KBr): $\tilde{\nu}_{max}$=3480, 1719, 1250, 842 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.18 (6H, s; Si(CH_3)$_2$), 0.91 (9H, s; Si–tBu), 1.62 (3H, s; CH_3), 2.63 (1H, dd, J=13.5, 2 Hz; CH_AH$_B$), 2.80 (1H, dd, J=3.5, 1.5 Hz; –CH–), 3.06 (1H, dd, J=13.5, 4 Hz; CH$_A$$H_B$), 3.43 (3H, s; OMe), 3.83 (1H, dd, J=3.5, 2 Hz; –CH–CH–O–C–OSi), 3.88 (1H, dt, J=4, 2 Hz; –CH$_2$–CH–O–C–OSi), 4.33 (1H, d, J=1.5 H, CH–C–OSi), 5.09 (1H, s; CH–OMe), 7.81 ppm (1H, brs; NH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=−3.2, −3.1, 17.8, 25.4, 25.7, 26.6, 46.1, 55.4, 58.9, 65.2, 76.0, 76.2, 82.3, 93.0, 106.5, 109.0, 160.9 ppm; HRMS (FAB): m/z calcd for C$_{19}$H$_{31}$Cl$_3$NO$_7$Si [M^++H]: 518.0935; found: 518.0911.

***N*,*N*′-Bis(*tert*-butoxycarbonyl)guanidine 36b**: Ortho ether **35b** (13 mg, 0.026 mmol) was dissolved in CH$_2$Cl$_2$ (1 mL) and the solution was cooled to −78°C. DIBAL-H (0.93 M in hexane, 0.14 mL, 0.13 mmol) was then added to this solution. After stirring at −78°C for 1 h, the mixture was quenched with AcOEt (0.5 mL), and then allowed to warm to room temperature. Saturated aqueous NH$_4$Cl (5 drops) and Et$_2$O (10 mL) were added, and the mixture was vigorously stirred for 3 h. Anhydrous Na$_2$SO$_4$ was added, and the mixture was further stirred for 1 h. The resulting mixture was filtered through a pad of Super-Cel, and the precipitate was washed with Et$_2$O. The combined filtrate was concentrated. The residue was dissolved in DMF (1 mL), and Et$_3$N (11 μL, 0.077 mmol) and *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (13 mg, 0.045 mmol) were added. The solution cooled to 0°C and HgCl$_2$ (13 mg, 0.048 mmol) was added. After stirring at room temperature for 90 min, AcOEt (5 mL) was added. After stirring for 1 h, the resulting mixture was filtered through a pad of Super-Cel with AcOEt, and the combined filtrate was washed with H$_2$O (20 mL) and brine (20 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (diethyl ether/hexane, 1:1) to afford *N*,*N*′-bis(*tert*-butoxycarbonyl)guanidine **36b** (14 mg, 85% in 2 steps from **35b**) as a white amorphous solid. $[\alpha]_D^{23}$=+31 (c=0.22 in CHCl$_3$); IR (KBr): $\tilde{\nu}_{max}$=3269, 1729, 1644, 1617, 1351, 1132 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.19 (6H, s; Si(CH_3)$_2$), 0.91 (9H, s; Si–tBu), 1.44 (9H, s; Boc), 1.48 (9H, s; Boc), 1.55 (3H, s; CH_3), 2.30 (1H, dd, J=14, 3.5 Hz; CH_AH$_B$), 3.34 (3H, s; OMe), 3.37 (1H, dd, J=14, 2 Hz; CH$_A$$H_B$), 3.41 (1H, dd, J=3.5, 1.5 Hz; –CH–), 3.83 (1H, dd, J=3.5, 2 Hz; CH–CH–O–C–OSi), 3.86 (1H, m; CH$_2$–CH–O–C–OSi), 4.11 (1H, d, J=1.5 Hz; CH–C–OSi), 5.05 (1H, s; CH–OMe), 8.67 (1H, brs; NH), 11.26 ppm (1H, brs; NH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=−3.3, −3.1, 17.9, 23.6, 25.8, 28.0, 28.2, 29.1, 44.3, 55.2, 56.8, 65.5, 76.3, 76.5, 78.8, 83.0, 83.6, 107.0, 109.1, 152.7, 155.0, 162.5 ppm; HRMS (FAB): m/z calcd for C$_{28}$H$_{50}$N$_3$O$_{10}$Si [M^++H]: 616.3265; found: 616.3237.

8,11-Dideoxytetrodotoxin (3) and 4,9-anhydro-8,11-dideoxytetrodotoxin (5): *N*,*N*′-Bis(*tert*-butoxycarbonyl)guanidine **36b** (13 mg, 0.021 mmol) was dissolved in MeOH (0.5 mL), H$_2$O (0.5 mL), and TFA (0.5 mL). The solution was stirred at room temperature for 15 h, and then concentrated under reduced pressure. The residue was purified by HPLC on a Hitachi-gel 3013-c column (H$^+$ form, 0.4×15 cm, 0.025 M AcOH) to afford 8,11-dideoxytetrodotoxin (**3**) (2.6 mg, 43%) and 4,9-anhydro-8,11-dideoxytetrodotoxin (**5**) (1.8 mg, 32%) as a white solid.

8,11-Dideoxytetrodotoxin (3): $[\alpha]_D^{26}$=+1.5 (c=0.065 in 0.05 M AcOH); ^{1}H NMR (600 MHz, 4% CD$_3$COOD/D$_2$O) (hemilactal form): δ=1.62 (3H, s; Me-11), 2.17 (1H, dd, J=13, 4 Hz; H-8α), 2.34 (1H, d, J=13 Hz; H-8β), 2.45 (1H, d, J=9.5 Hz; H-4a), 3.61 (1H, s; H-9), 4.03 (1H, brs; H-7), 4.10 (1H, brs; H-5), 5.46 (1H, d, J=9.5 Hz; H-4); (lactone form): δ=1.48 (3H, s; Me-11), 2.37 (1H, dd, J=14, 4 Hz; H-8α), 2.42 (1H, dd,

J=9.5, 2.5 Hz; H-4a), 2.50 (1H, brd, J=14 Hz; H-8β), 3.90 (1H, brs; H-5), 4.27 (1H, s; H-9), 4.42 (1H, brs; H-7), 5.49 ppm (1H, d, J=9.5 Hz; H-4); ^{13}C NMR (4% CD_3COOD/D_2O, 150 MHz) (hemilactal form): δ= 25.6, 36.7, 41.5, 55.6, 68.1, 75.3, 76.2, 78.1, 79.2, 110.9, 156.4; (lactone form) δ=24.7, 34.7, 46.9, 56.1, 72.5, 73.5, 75.2, 78.4, 82.6, 155.8, 176.6 ppm; HRMS (FAB): m/z calcd for $C_{11}H_{18}N_3O_6$ $[M+H]^+$: 288.1196; found: 288.1198.

4,9-Anhydro-8,11-dideoxytetrodotoxin (5): $[\alpha]_D^{26}=+14$ (c=0.090 in 0.05 M AcOH); ^{1}H NMR (600 MHz, 4% CD_3COOD/D_2O): δ=1.56 (3H, s; Me-11), 2.27 (1H, dd, J=13, 4 Hz; H-8α), 2.58 (1H, d, J=13, 1.5 Hz; H-8β), 2.87 (1H, d, J=3 Hz; H-4a), 4.09 (1H, dt, J=4, 2 Hz; H-7), 4.15 (1H, dd, J=3, 2 Hz; H-5), 4.33 (1H, s; H-9), 5.42 ppm (1H, s; H-4); ^{13}C NMR (4% CD_3COOD/D_2O, 150 MHz): δ=25.9, 29.5, 42.7, 58.7, 67.7, 77.0, 78.7, 85.2, 89.3, 110.5, 157.4 ppm; HRMS (FAB): m/z calcd for $C_{11}H_{16}N_3O_5$ $[M^+ +H]$: 270.1090; found: 270.1068.

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