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Stereocontrolled synthesis of (−)-5,11-dideoxytetrodotoxin

Masanori Asai, Toshio Nishikawa, Norio Ohyabu, Noboru Yamamoto and Minoru Isobe*

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

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Abstract—Asymmetric synthesis of (−)-5,11-dideoxytetrodotoxin, an analog of puffer fish toxin, was accomplished from a common key intermediate through a novel hydroxylation at the C-8 position with neighboring group participation of trichloroacetamide, a highly stereoselective addition of acetylide as an equivalent of carboxylic acid, and a new guanidine synthesis from trichloroacetamide as key steps. This study presents the first asymmetric synthesis among tetrodotoxin and its analogs.

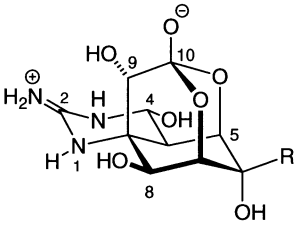
1. Introduction

Tetrodotoxin (**1**), originally isolated from puffer fish, is a well-known marine natural product, because of the unique chemical structure and the potent biological activities.[1] The complex structure was determined to comprise of polyhydroxylated cyclohexane ring with unprecedented zwitter ion between hemilactal and guanidine by three groups including Hirata-Goto, Tsuda and Woodward in 1964.[2] In the same year, action mechanism of tetrodotoxin was reported to be a specific inhibition for voltage dependent Na-channels.[3] Since this finding, tetrodotoxin has been widely used as an important biochemical tool in neurophysiological studies.[4] Tetrodotoxin and its analogs have been isolated from puffers, newts, frogs and other animals.[5] Naturally occurring tetrodotoxin analogs[6] shown in Fig. 1 are regarded as the biosynthetic precursors of tetrodotoxin or its metabolites. A number of interesting problems are associated with tetrodotoxin, e.g. the details of bound structure of tetrodotoxin to the protein,[7] the biosynthesis,[8] mechanisms of the accumulation,[9] detoxification, the actual biological functions,[10] etc. In order to elucidate these biologically interesting problems on a molecular level, a variety of tetrodotoxin derivatives have been desired as probe molecules.[11] However, it is difficult to prepare such tetrodotoxin derivatives from natural tetrodotoxin because of the complex structure and unique chemical properties. In spite of many efforts,[12] only one total synthesis of the racemic tetrodotoxin was accomplished by Kishi, Goto and co-workers in 1972.[13] The highly functionalized structure of this small molecule coupled with the potent biological activity still make them attractive target for total synthesis. In this context, we recently achieved a highly stereocontrolled synthesis of 5,11-dideoxytetrodotoxin (**2**) in an enantiomerically pure form.[14]

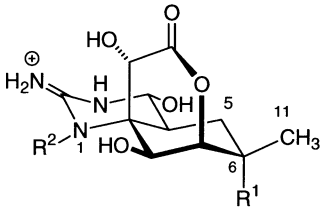
2. Results and discussion

2.1. Synthetic plan

The synthetic plan for 5,11-dideoxytetrodotoxin (**2**) is



tetrodotoxin (**1**) R = CH_2OH
11-deoxytetrodotoxin (**3**) R = CH_3



5,11-dideoxytetrodotoxin (**2**) R^1 = OH R^2 = H
5,6,11-trideoxytetrodotoxin (**4**) R^1 = H R^2 = H
1-hydroxy 5,11-dideoxytetrodotoxin (**5**) R^1 = OH R^2 = OH

Figure 1. Structures of tetrodotoxin and its analogs.

Keywords: tetrodotoxin; guanidine; asymmetric synthesis; marine metabolites.
* Corresponding author. Tel.: +81-52-789-4109; fax: +81-52-789-4111; e-mail: isobem@agr.nagoya-u.ac.jp

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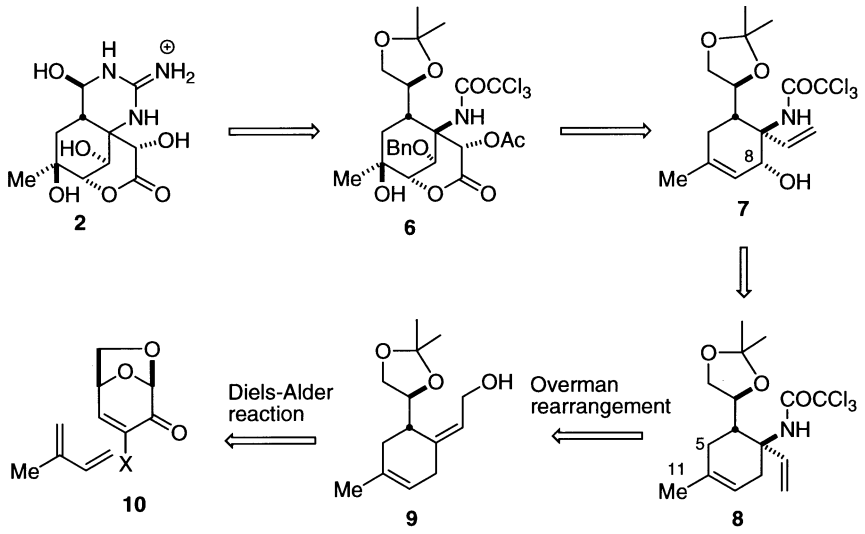
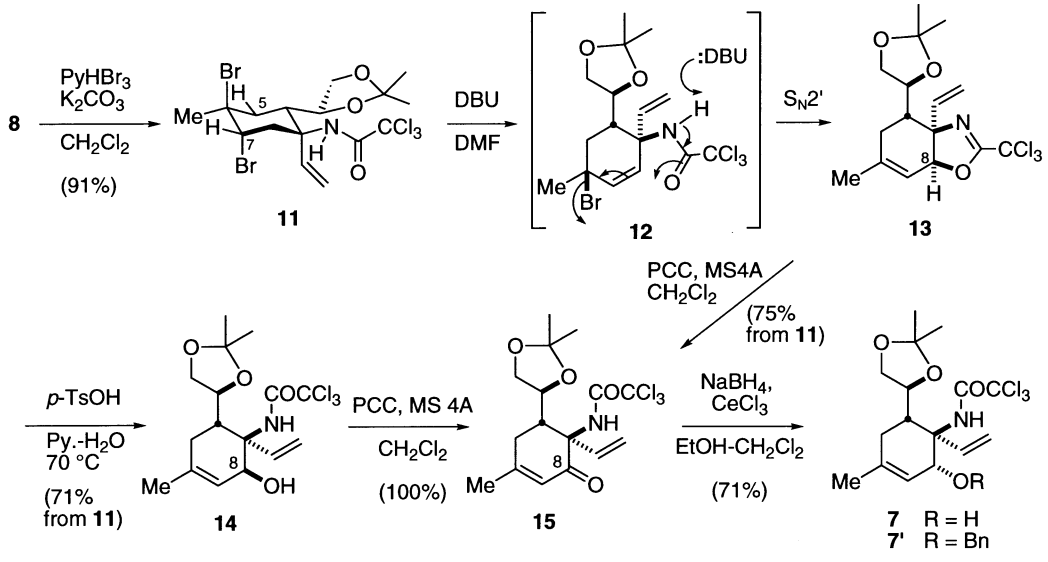


Scheme 1. Synthetic plan.

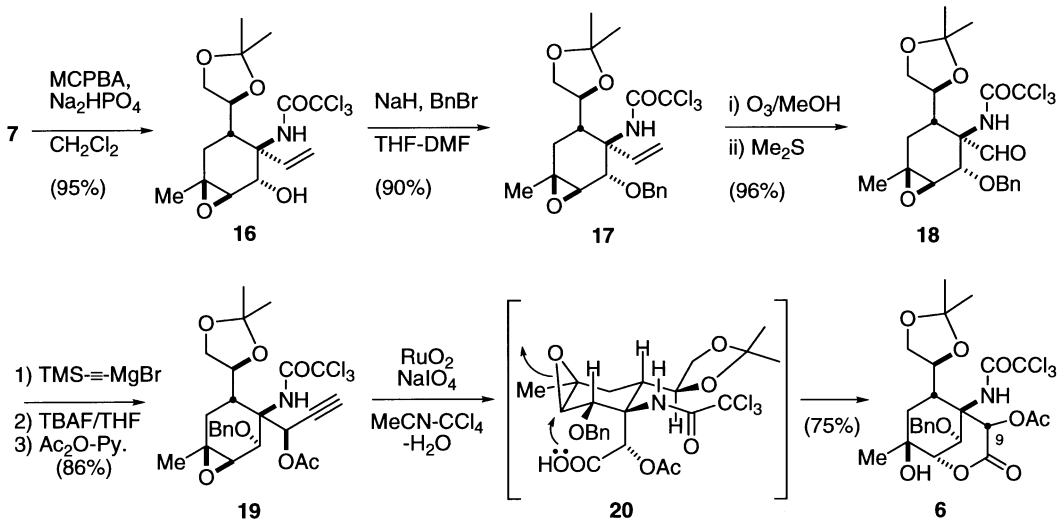
shown in Scheme 1. Considering the instability and low solubility of the guanidine-containing intermediates, we planned that introduction of guanidine moiety of **2** should be carried out at the latest stages of the synthesis. The cyclic guanidine moiety could be constructed from the corresponding aldehyde and guanidine, in which the aldehyde would be derived from a protected 1,2-glycol as an acetonide, while the guanidine would be prepared from protected amino group such as trichloroacetamide. Consequently, we envisioned a lactone **6** would be a possible precursor for **2**. Then, this lactone **6** was retrosynthesized into a readily preparable intermediate **8** through a diene-alcohol **7** having a hydroxy group at the C-8 position. The transformation from **7** to **6** included construction of the lactone from the vinyl group, and the latter transformation from **8** to **7** involved a critical hydroxylation at the C-8 position. The compound **8** is regarded as a common key intermediate[15] for a variety of tetrodotoxin analogs as shown in Fig. 1, and has already been synthesized from levoglucosenone **10** (X=H)[16] as a chiral starting material via 9 steps sequence including the stereoselective Diels–Alder reaction of bromolevoglucosenone **10** (X=Br) with isoprene and highly stereoselective introduction of the amino group by the Overman rearrangement of the *exo*-allylic alcohol **9** as key steps.[15] Throughout the synthesis of lactone **6** from the key intermediate **8**, stereochemical control was relied on the conformation of cyclohexane ring fixed by the equatorially oriented bulky trichloroacetamide as described later. Based on this synthetic plan, we have developed a stereocontrolled synthesis of polyhydroxylated cyclohexane,[17] a lactone synthesis from the vinyl group[18] and a novel guanidine synthesis from trichloroacetamide,[19] which culminated in a successful asymmetric synthesis of 5,11-dideoxytetrodotoxin (**2**)[14] that has not been isolated to date. In this paper, we describe the full details of our investigation.

2.2. Stereoselective synthesis of lactone intermediates

Stereoselective introduction of α-hydroxy group at the C-8



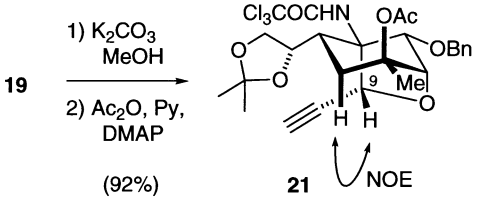
Scheme 2. Hydroxylation of C-8 position.



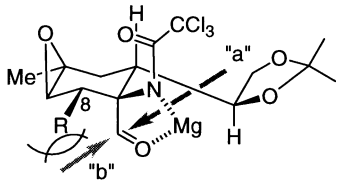
Scheme 3. Synthesis of lactone **6**.

position was indispensable, because the hydroxy group is common among all the naturally occurring tetrodotoxin and its analogs. Our initial studies revealed that direct allylic oxidation of **8** with SeO_2 or CrO_3 based reagents[20] did not give the desired product oxidized at the C-8 position, but gave an aldehyde at the C-11 position and a ketone or β-alcohol at the C-5 position. After many exploratory experiments, a novel hydroxylation of the C-8 position was fortunately found as described below (Scheme 2). Bromination of **8** with pyridinium bromide perbromide gave a dibromide **11**, which was treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in DMF at room temperature to give an oxazoline **13** in one operation. This reaction involves a regioselective dehydrobromination of the dibromide **11** and subsequent S_N2' reaction[21] of the resulting allylic bromide **12** with the neighboring trichloroacetamide group in a stereospecific manner. Although the stereochemistry of the dibromide **11** has not been established,[22] the trans-diaxal dibromide is consistent with the above reaction mechanisms. The oxazoline **13** was hydrolyzed under mild acidic conditions (*p*-TsOH in aqueous pyridine)[23] to give a hydroxy trichloroacetamide **14** without providing a free amine. The stereochemistry of a newly generated asymmetric center at the C-8 position was established from analysis of NOESY spectra of **13**; correlation peaks were observed between H-8 and vinylic protons. The dibromide **11** contains three abstractable protons (H-5, H-8 and H-11) that are situated in diaxal relationship with the bromo atoms. However, only the proton of the C-8 position was abstracted to give the intermediate **12** under the conditions. This fact suggested that dehydrobromination proceeded via an intramolecular proton abstraction from the C-8 position in assistance with the neighboring trichloroacetamide. Since the configuration of the hydroxy group of **13** was opposite to that of naturally occurring tetrodotoxins, it was inverted by oxidation with pyridinium chlorochromate (PCC) and reduction with $NaBH_4$–$CeCl_3$[24] to afford the desired 8*R* alcohol **7** in a highly stereoselective manner (18:1–20:1). This high stereoselectivity is attributed to the steric hindrance of the axially oriented vinyl group. It was noted that a mixed solvent of EtOH and CH_2Cl_2[25] for the reduction step, was indispensable for the good yield and the high stereoselectivity; when methanol was employed as a solvent in this reduction according to Luche's report,[24] a considerable amount of starting material **15** was recovered even if a large excess of the reducing reagent was added. Unexpectedly, the α,β-unsaturated ketone **15** was also obtained by treatment of **13** with PCC in CH_2Cl_2 in good yield.

Next issue was to functionalize the vinyl group of **7** to carboxylic acid in the lactone **6**. In order to differentiate the two alkenes in **7**, the trisubstituted olefin was epoxidized with *m*-chloroperbenzoic acid (MCPBA) to give a β-epoxide **16** as an only stereoisomer (Scheme 3). The stereochemistry of the epoxide was owing to a severe steric hindrance rather than an orientation of the neighboring hydroxy group known as Henbest rule.[26] The hydroxy group was then protected as benzylether to afford **17** in a high yield. Although stereochemical outcome of the epoxidation of benzylether **7′** was the same as that of **7**, the former route was adapted because of the total efficiency and easily operations. The vinyl group of **17** was strongly shielded by the bulky trichloroacetamide group and therefore was extremely inert toward a variety of reaction such as hydroboration, epoxidation, etc. This olefin was, however, cleaved by ozonolysis to afford an aldehyde **18**, which was transformed into a hydroxycarboxylic acid by the addition of a carboxylic acid equivalent. Vinylmagnesium bromide employed in our previous report[18] and smaller nucleophile MeLi did not react with the aldehyde **18**. In sharp contrast, less hindered nucleophile such as acetylide and cyanide anion underwent addition to the aldehyde. Lithium acetylide reacted with **18** in high yield, but no



Scheme 4.



18 R = OBn path "a"
22 R = H path "b"

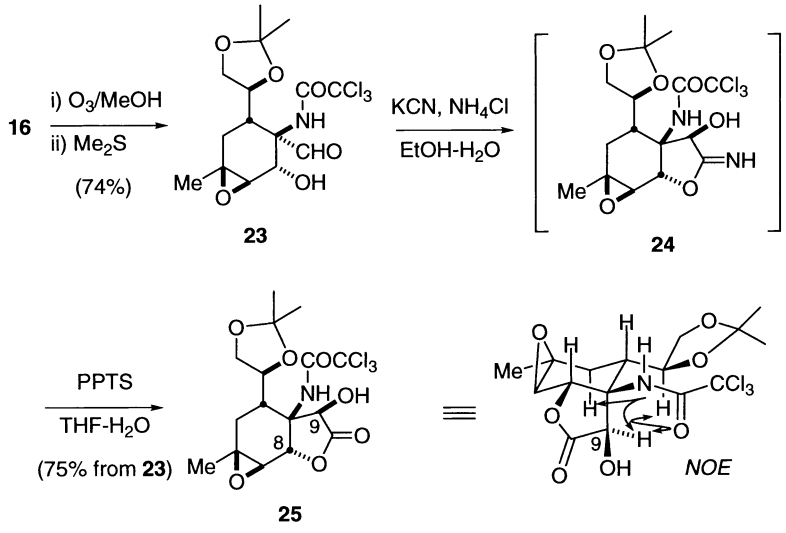
Figure 2.

stereoselectivity (ca. 1:1), while magnesium acetylide added the aldehyde **18** to give a propargylic alcohol as a single stereoisomer. The resulting product was unstable under even weak acidic conditions, it was immediately transformed into **19** in two steps including successive desilation with tetra-*n*-butylammonium fluoride (TBAF) in THF and acetylation in excellent overall yield. The newly generated stereogenic center of the C-9 position was established as shown in Scheme 4. Deprotection of the acetyl group with K_2CO_3 in MeOH afforded a five-membered ether compound, which was acetylated to give **21** to make NMR analysis easier. NOESY spectra of **21** indicated that the configuration of the C-9 position was the same as that of natural tetrodotoxin. The stereochemical outcome of the Grignard acetylide addition might be rationally explained through an intermediary of a five-membered chelate containing magnesium cation as depicted in Fig. 2 (for intermediate **18**), in which the nucleophile approached from less hindered back side of the chelate face through path 'a' (opposite to the bulky benzyloxy group at C-8). This proposed mechanism might be supported by the result of the reaction of a deoxy substrate **22** with vinyl Grignard reagent.[18] That is, vinylmagnesium bromide added **22** to give a 5:1 mixture in favor of the undesired diastereomer, presumably via the attack from the front side through path 'b'. Finally, the acetylenic moiety of **19** was cleaved with ruthenium tetraoxide[27] to carboxylic acid **20**, which spontaneously opened the epoxide to furnish the six-membered lactone **6** in good overall yield. The resulting lactone **6** contained all the requisite functionalities with correct stereochemistries except the guanidine moiety for 5,11-dideoxytetrodotoxin.

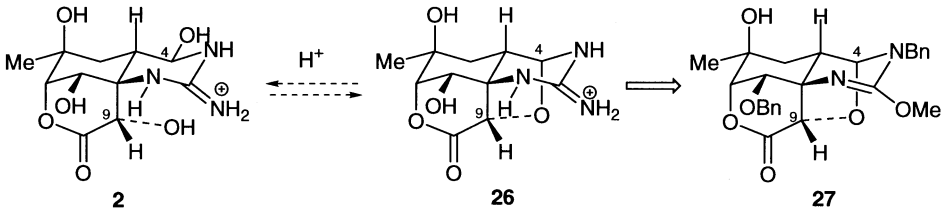
It should be noted that another less hindered nucleophile, cyanide could add to an aldehyde **23** prepared from ozonolysis of the epoxyalcohol **16** (Scheme 5), while benzyl-protected aldehyde **18** could not be served as a substrate for this reaction. The reaction of **23** with potassium cyanide proceeded in the presence of NH_4Cl in EtOH to give an unstable product, which was treated with pyridinium *p*-toluenesulfonate (PPTS) without purification to afford a lactone **25** as a single product in 75% yield. The IR spectrum of the unstable intermediate indicated the absence of nitrile group, and the behavior on thin-layer chromatography (TLC) suggested that the initial adduct was iminoether **24** as shown in Scheme 5. Although NOESY spectra of **25** revealed that the hydroxy group of the C-9 position had the undesired configuration, this route might be potentially useful for the future synthesis of ^{13}C-labeled tetrodotoxin derivative from a commercially available [^{13}C]KCN.

2.3. Introduction of guanidine and completion of the synthesis

With the lactone intermediate **6**, we turned to focus on the crucial construction of the cyclic guanidine moiety. This transformation seemed to be easy, because only two transformation including installation of guanidine group and oxidative cleavage of the acetonide would give the cyclic guanidine moiety. As it turned out later, however, this transformation was the most difficult to realize throughout our synthesis of 5,11-dideoxytetrodotoxin. Attempted deprotections of the trichloroacetamide group of **6** were unsuccessful, because the hydroxy group at the C-9 position was easily epimerized even under mild basic conditions such as K_2CO_3 in MeOH. Reductive deprotection method[28] was also unsuccessful. Consequently, we could not use the conventional guanidine synthesis from non-protected amine derived from **6** with a variety of guanylation reagents.



Scheme 5.

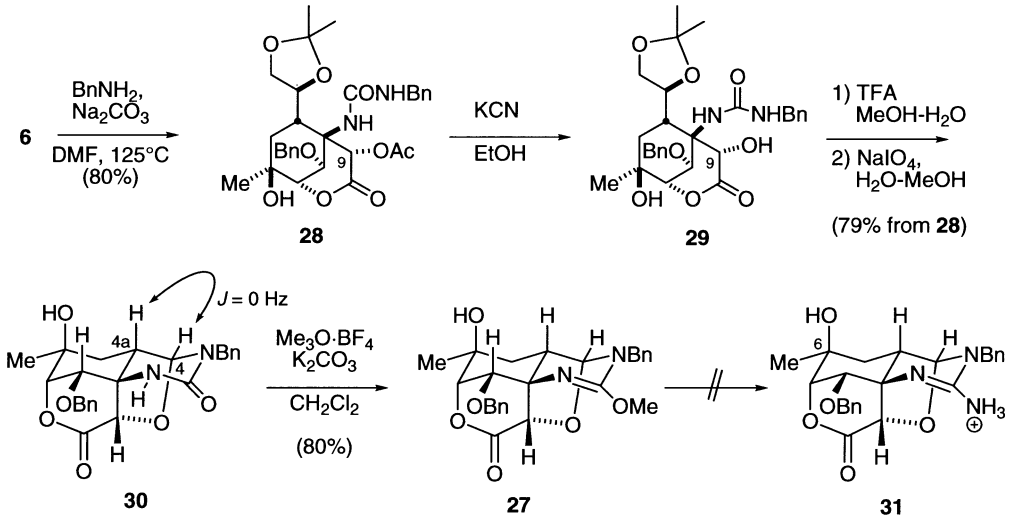


Scheme 6.

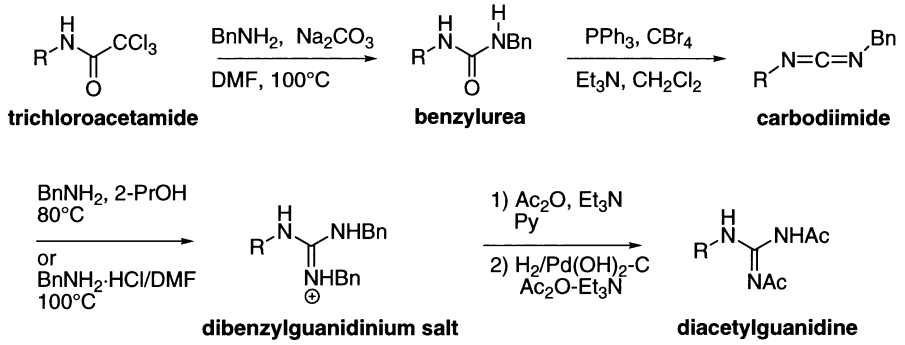
At this juncture, we explored a several alternative routes as described followings.

In the first approach, we focused on an interconvertible nature of tetrodotoxin and its 4,9-anhydrotetrodotoxin.[2] Although there was no report about the equilibration between 5,11-dideoxytetrodotoxin **2** and the corresponding anhydrotetrodotoxin **26** under acidic conditions, we anticipated that 4,9-anhydro-5,11-dideoxytetrodotoxin **26** was a synthetic equivalent of 5,11-dideoxytetrodotoxin **2** as shown in Scheme 6. Consequently, the corresponding isourea **27** was envisaged as a precursor for **26**. A little precedents converting isourea to guanidine in complex natural product synthesis[29] promoted us to examine this approach. The isourea **27** was synthesized from the lactone **6** as shown in Scheme 7. Trichloroacetamide **6** was heated at 125°C with benzylamine in the presence of Na_2CO_3 in DMF[30] to give a benzylurea **28**, which was deacetylated with potassium cyanide in EtOH[31] to afford **29** without epimerization. Hydrolysis of the acetonide of **29** was followed by oxidative cleavage with $NaIO_4$ to give an aldehyde, which spontaneously cyclized to tetracyclic urea **30** under the conditions. This tetracyclic structure of **30** was supported by observing no coupling between H-4a and H-4 in ^1H NMR spectra. This data was identical to that of 4,9-anhydro-11-deoxytetrodotoxin.[6c] The cyclic urea of **30** was converted to an isourea **27** with $Me_3O{\cdot}BF_4$.[29a] However, since all attempts to transform the isourea **27** to guanidine **31** were unsuccessful, this approach was abandoned.

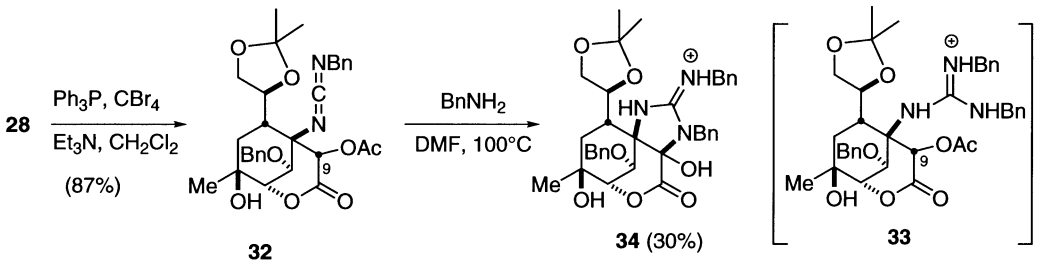
To overcome the difficulty of guanidine installation, we had developed a new guanidine synthesis from trichloroacetamide group not through an unprotected amino intermediate as outlined in Scheme 8.[19] That is, trichloroacetamide was transformed to benzylurea under the above mentioned conditions. The urea was dehydrated with Ph_3P and



Scheme 7.



Scheme 8. Guanidine synthesis from trichloroacetamide.

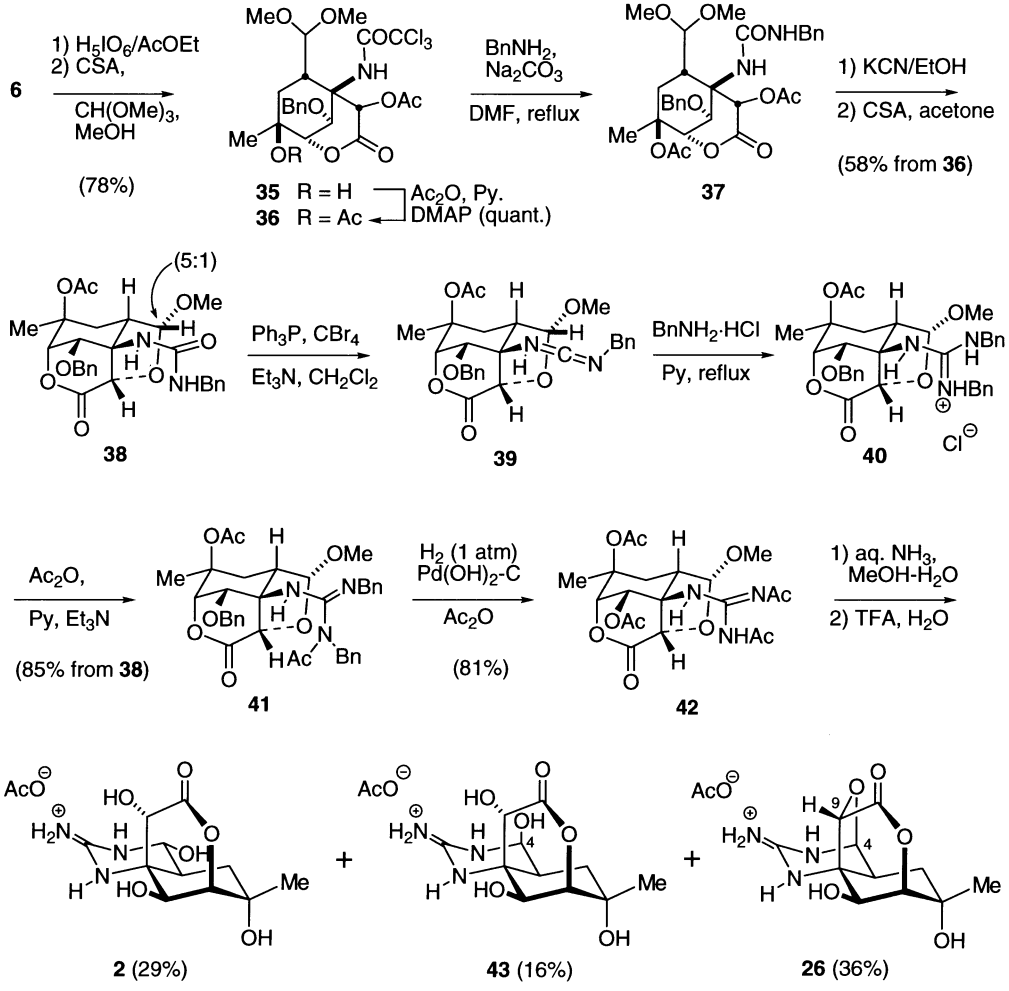


Scheme 9.

CBr_4[32] to give a carbodiimide, which reacted with benzylamine under several conditions to afford dibenzylguanidinium salt. The benzyl groups of dibenzylguanidinium salt was difficult to deprotect under hydrogenolytic conditions, while the benzyl groups of acetylbenzylguanidine could easily be removed under the same conditions to furnish diacetyl guanidine. Thus, 5 step-sequence from trichloroacetamide to diacetylguanidine was established. In the next approach to introduce the guanidine group, we would directly apply this methodology to the urea **28**, readily prepared from the lactone intermediate **6**.

The urea **28** was dehydrated with Ph_3P and CBr_4[32] to a stable benzyl carbodiimide **32**, which could be purified by silica gel chromatography (Scheme 9). IR spectra (ν_{max} 2135 cm^{-1}) of **32** suggested the formation of carbodiimide. However, the addition of benzylamine or its hydrochloride proved difficult to give **33** under a variety of conditions, probably because of the severe steric hindrance around the carbodiimide group. The benzylurea **28** was obtained as a major product along with one minor product, whose structure was tentatively assigned as guanidine-containing product **34** based on the spectroscopic data. This fact suggested the necessity of suitable protection for hydroxy group at the C-9 position.[33]

In the third and successful approach, we considered that an intramolecular mixed ketal **38** was an ideal choice for the



Scheme 10. Synthesis of 5,11-dideoxytetrodotoxin.

Table 1. Comparison of ^{1}H- and ^{13}C NMR spectra between synthetic 5,11-dideoxytetrodotoxin (**2**) and natural 1-hydroxy-5,11-dideoxytetrodotoxin (**5**)[6b] in 4% CD_3COOD/D_2O

	5,11-dideoxytetrodotoxin (**2**)[a]		1-hydroxy-5,11-dideoxytetrodotoxin (**5**)	
No.	^{1}H (δ) (mult., J (Hz))	^{13}C (δ)	^{1}H (δ) (mult., J (Hz))	^{13}C (δ)
2		156.1		158.9
4	5.18 (d, 9.5)	77.5	5.14 (d, 9.4)	77.5
4a	2.26 (ddd, 13.2, 9.5, 3.9)	42.8	2.77 (ddd, 13.2, 9.3, 3.9)	38.8
5α	2.06 (ddd, 15.8, 3.9, 1.5)	33.5	2.14 (ddd, 15.6, 3.7, 1.4)	34.3
5β	1.31 (dd, 15.8, 13.2)		1.38 (dd, 15.7, 13.3)	
6		74.2		69.8
7	4.36 (dd, 2.2, 1.5)	87.6	4.46 (dd, 3.9, 1.4)	81.2
8	4.43 (d, 2.2)	71.5	4.58 (d, 3.9)	67.5
8a		61.5		74.1
9	4.64 (s)	72.4	4.80 (s)	69.9
10		176.8		176.6
11	1.38 (s)	27.7	1.35 (s)	27.9

[a] The spectra were recorded on Brucker ARX-600 spectrometer, 600 MHz for ^{1}H and 150 MHz for ^{13}C. The signal due to CHD_2COOD at 2.06 ppm was used as reference for ^{1}H NMR, and that due to $^{13}CD_3COOD$ at 22.4 ppm was used for ^{13}C NMR.

protection of the C-9 position, because the mixed ketal was expected to be stable enough during the above guanidine synthesis. The synthesis of **37** is summarized in Scheme 10. Direct oxidative cleavage of the acetonide[34] in **6** was followed by protection of the resulting aldehyde to afford a dimethylacetal **35**. In order to increase the solubility of the intermediate, *tert*-alcohol of **35** was acetylated (Ac_2O/pyridine, 4-dimethylaminopyridine (DMAP)) and then the trichloroacetamide group was transformed into the acetal-urea **37** under the above-mentioned conditions. Selective deacetylation (KCN/EtOH)[31] and subsequent partial hydrolysis of the dimethylacetal with camphorsulfonic acid (CSA) in acetone gave the urea **38** (as a 5:1 diastereomeric mixture of the acetal carbon). The major isomer **38** was easily separated by silica gel column chromatography and dehydrated with Ph_3P and CBr_4[32] to afford a carbodiimide **39**. As we encountered the difficulties in the second approach, the addition of benzylamine was also difficult under the conditions used before. Further extensive examination led us to find that in this specific case pyridine reflux was only the condition to obtain the dibenzylguanidine **40**, which was acetylated to an acetylbenzylguanidine **41** in a high yield. In the event, **41** was hydrogenolyzed in acetic anhydride under 1 atm of hydrogen to give a diacetylguanidine **42** in a good yield.[35] Under the reaction conditions, the benzylether in **41** was also converted to an acetyl group. At this stage, all the protective groups were unified to acetyl groups except for the acetal.

To complete the synthesis of 5,11-dideoxytetrodotoxin (**2**), deprotection of two kinds of protecting group was necessary. All the acetyl groups of **42** were removed with ammonium hydroxide and then the acetal was hydrolyzed with aqueous trifluoroacetic acid (TFA). The crude product was separated by HPLC with a cation-exchange resin (Hitachi gel 3013c),[6] to afford 5,11-dideoxytetrodotoxin (**2**), 4-*epi*-5,11-dideoxytetrodotoxin (**43**), and 4,9-anhydro-5,11-dideoxytetrodotoxin (**26**) in 29, 16, and 36% yield, respectively. These structures were confirmed by full characterization using COSY, HMBC, HSQC and FAB-MS spectra. Table 1 shows the comparison of ^{1}H and ^{13}C NMR spectra between synthetic 5,11-dideoxytetrodotoxin (**2**) and naturally occurring 1-hydroxy-5,11-dideoxytetrodotoxin (**5**).[6b] The compound **26** is the first example of 4,9-anhydrotetrodotoxin among a series of 5-deoxytetrodotoxin analogs.

3. Conclusions

In summary, we have successfully achieved a highly stereocontrolled synthesis of (−)-5,11-dideoxytetrodotoxin and its isomers. This is a first asymmetric synthesis of tetrodotoxin analogs and provides a practical route accessible to labeled compounds for biochemical studies. Further studies toward naturally occurring tetrodotoxin (**1**) and other analogs are currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Brucker ARX-600 (600 MHz), ARX-400 (400 MHz) and Varian Gemini-2000 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (δ=0.00 ppm) as an internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broadened, m=multiplet), coupling constant (*s*), and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Brucker ARX-600 (150 MHz), ARX-400 (100 MHz) and Varian Gemini-2000 (75 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane using the solvent resonance as an internal standard ($CDCl_3$: δ=77.0 ppm). Hetero 2D NMR (HSQC and HMBC) were measured on Brucker ARX-600. Low resolution EI mass spectra were recorded on a JEOL JMS-D 100 spectrometer. Low resolution FAB mass spectra were recorded on a JEOL DX-705L and JEOL Mstation spectrometers in the positive mode, in which 3-nitrobenzyl alcohol

or glycerol were used as a matrix. High resolution mass spectra (HRMS) were recorded on a JEOL DX-705L and JEOL Mstation spectrometers, and reported in *m/z*. Elemental analyses were performed by Analytical Laboratory at School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by TLC on 0.25 mm silica gel coated glass plates $60F_{254}$ (Merck, #1.05715). Merck silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for open-column chromatography. Preparative TLC separations were carried out on 0.5 mm silica gel plates $60F_{254}$ (Merck, #1.05774) or prepared silica gel 60 PF_{254} (Merck, #1.07747), layer thickness 2.0 mm. Unless otherwise noted, non-aqueous reaction were conducted in oven-dried (200°C) or flame-dried glassware under inert atmosphere of dry nitrogen with balloon. Dry THF was distilled from potassium metal with benzophenone. Anhydrous ethyl ether was purchased from Kanto Chemical Co., Inc. in a bottle as Ethyl Ether Anhydrous. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. Pyridine and triethylamine were dried over anhydrous KOH. All other commercially available reagents were used as received.

4.1.1. Dibromide 11. To an ice-cold solution of the trichloroacetamide **8** (10.21 g, 26.7 mmol) and K_2CO_3 (7.4 g, 53.5 mmol) in dry CH_2Cl_2 (300 mL) was added pyridinium bromide perbromide (17.1 g, 53.5 mmol) portionwise over 10 min. After stirring at 0°C for 1 h, the mixture was poured into an ice-cold sat. NH_4Cl solution (500 mL). The mixture was extracted with AcOEt (400 mL ×1, 200 mL ×2) and the combined organic layer was washed with aq. $CuSO_4$ solution (1 L ×1), brine (1 L ×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 300 g, ether/hexane=1:5→1:3) to give dibromide **11** (13.11 g, 91%) as a colorless amorphous solid. $[\alpha]_D^{27}=+36°$ (*c* 0.84, $CHCl_3$). IR (KBr) ν_{max} 3305, 2988, 1721, 1523, 1382, 1251, 1159, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s, C*H*$_3$ of acetonide), 1.45 (3H, s, C*H*$_3$ of acetonide), 1.49 (1H, ddd, *J*=15, 3, 2.5 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 1.87 (1H, dd, *J*=15, 12.5 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 2.07 (3H, s, C*H*$_3$–C), 2.56 (1H, ddd, *J*=12.5, 10, 3 Hz, –C*H*–), 3.00 (1H, dd, *J*=16, 4.5 Hz, Br–CH–C*H*$_A$H$_B$), 3.60 (1H, dd, *J*=16, 2.5 Hz, Br–CH–CH$_A$*H*$_B$), 3.59–3.65 (1H, m, O–C*H*$_A$H$_B$–CH–O), 4.06–4.13 (2H, m, O–CH$_A$*H*$_B$–C*H*–O), 4.79 (1H, dt, *J*=4.5, 2.5 Hz, Br–C*H*), 5.33 (1H, d, *J*=17 Hz, CH=C*H*$_A$H$_B$), 5.36 (1H, d, *J*= 11 Hz, CH=CH$_A$*H*$_B$), 6.74 (1H, dd, *J*=17, 11 Hz, C*H*=CH$_2$), 8.79 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.5, 35.5, 35.6, 39.6, 46.0, 55.3, 61.0, 68.1, 69.0, 76.0, 93.6, 110.2, 115.7, 134.3, 160.6. MS (FAB) *m/z* 540 (M+H), 542 (M+H), 544 (M+H), 546 (M+H). Anal. calcd for $C_{16}H_{22}Br_2Cl_3O_3N$: C, 35.42; H, 4.09; N, 2.58. Found C, 35.27; H, 4.17; N, 2.53.

4.1.2. Oxazoline 13. To a solution of the dibromide **11** (15.17 g, 28.0 mmol) in DMF (450 mL) was added DBU (9.2 mL, 61.5 mmol). After stirring at rt for 6 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution. The mixture was extracted with AcOEt (×3) and the combined organic layer was washed with water (×2), brine (×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give crude oxazoline **13** (12.41 g) as a yellow oil, which was used for the next reaction without purification. IR (KBr) ν_{max} 2986, 1654, 1381, 1250, 1213, 1054, 919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s, C*H*$_3$ of acetonide), 1.42 (3H, s, C*H*$_3$ of acetonide), 1.87 (3H, br s, C*H*$_3$–C=CH), 1.93 (1H, m, CH=CMe–C*H*$_{ax}$H$_{eq}$), 2.10–2.20 (2H, m, CH=CMe–CH$_{ax}$*H*$_{eq}$ and –C*H*–), 3.72 (1H, dd, *J*=9, 7 Hz, O–C*H*$_A$H$_B$–CH–O), 3.94 (1H, dd, *J*=9, 7 Hz, O–CH$_A$*H*$_B$–CH–O), 4.55 (1H, td, *J*=7, 3 Hz, O–CH$_2$–C*H*–O), 4.77 (1H, dt, *J*=4, 1 Hz, MeC=CH–C*H*), 5.24 (1H, dd, *J*=17.5, 1 Hz, CH=C*H*$_A$H$_B$), 5.27 (1H, dd, *J*=11, 1 Hz, CH=CH$_A$*H*$_B$), 5.74 (1H, m, MeC=C*H*), 5.95 (1H, dd, *J*=17.5, 11 Hz, C*H*=CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 24.6, 26.2, 43.9, 65.4, 73.2, 73.9, 86.4, 107.5, 115.4, 116.9, 135.9, 144.0, 161.8. MS (EI) *m/z* 364 (M–Me), 366 (M–Me), 368 (M–Me). HRMS (EI) for $C_{15}H_{17}O_3NCl_3$ (M–Me), calcd 364.0274, found 364.0275.

4.1.3. Allylic alcohol 14. The crude oxazoline **13** (12.41 g) was dissolved in pyridine (280 mL) and H_2O (70 mL). To this solution was added *p*-TsOH·H_2O (5.33 g, 28.0 mmol) at rt. After stirring at 70°C for 1.5 h, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The mixture was extracted with AcOEt (×3), and the combined organic layer was washed with aq. $CuSO_4$ solution (×2) and brine (×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 500 g, ether/hexane=1:1→2:1) to give allylic alcohol **14** (7.92 g, 71%, 2 steps from **11**). Mp 111–112°C (as colorless prisms from ether–hexane). $[\alpha]_D^{27}=+104°$ (*c* 0.86, $CHCl_3$). IR (KBr) ν_{max} 3503, 3316, 2983, 1726, 1542, 1162, 1062, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, s, C*H*$_3$ of acetonide), 1.42 (3H, s, C*H*$_3$ of acetonide), 1.63 (1H, m, CH=CMe–CH$_{ax}$*H*$_{eq}$), 1.74 (3H, br s, C*H*$_3$–C=CH), 1.77 (1H, dd, *J*=18, 5.5 Hz, CH=CMe–C*H*$_{ax}$H$_{eq}$), 2.27 (1H, d, *J*=6 Hz, O*H*), 2.38 (1H, ddd, *J*=12, 9, 5.5 Hz, –C*H*–), 3.65 (1H, dd, *J*=9, 8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.04 (1H, td, *J*=9, 5.5 Hz, O–CH$_2$–C*H*–O), 4.11 (1H, dd, *J*=8, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 4.95 (1H, br t, *J*=6 Hz, HO–C*H*), 5.36 (1H, dd, *J*=11, 1 Hz, CH=C*H*$_A$H$_B$), 5.39 (1H, dd, *J*=17.5, 1 Hz, CH=CH$_A$*H*$_B$), 5.66 (1H, m, MeC=C*H*), 5.68 (1H, dd, *J*=17.5, 11 Hz, C*H*=CH$_2$), 9.24 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 26.4, 26.5, 30.4, 38.5, 65.1, 66.1, 68.9, 75.9, 93.5, 110.2, 117.6, 121.3, 132.5, 136.4, 161.3. MS (FAB) *m/z* 398 (M+H), 400 (M+H), 402 (M+H). Anal. calcd for $C_{16}H_{22}O_4NCl_3$: C, 48.20; H, 5.56; N, 3.51. Found C, 48.20; H, 5.81; N, 3.48.

4.1.4. Enone 15 from 14. To a suspension of the allylic alcohol **14** (7.92 g, 19.9 mmol) and MS 4A (ca. 8 g) in dry CH_2Cl_2 (250 mL) was added PCC (12.90 g, 59.8 mmol). After stirring at rt for 11 h, the reaction mixture was diluted with Et_2O, and Super-Cel was added. After vigorous stirring at rt for additional 10 min, the mixture was filtered through a pad of Super-Cel, and the precipitate was washed with Et_2O. The combined filtrate was evaporated. Purification of the residue by column chromatography (silica gel 400 g, ether/hexane=2:1→3:1) gave enone **15** (7.86 g, 100%) as a colorless amorphous solid. $[\alpha]_D^{27}=+30.9°$ (*c* 1.20, $CHCl_3$). IR (KBr) ν_{max} 3429, 2989, 1713, 1677, 1501, 1222, 1063 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s, C*H*$_3$ of acetonide), 1.36 (3H, s, C*H*$_3$ of acetonide), 1.98 (3H, br s, C*H*$_3$–C=CH), 2.12 (1H, dd, *J*=18.5,

6 Hz, CH=CMe–$CH_{ax}H_{eq}$), 2.23 (1H, m, CH=CMe–$CH_{ax}H_{eq}$), 3.04 (1H, ddd, *J*=12, 9, 6 Hz, –C*H*–), 3.62 (1H, m, O–CH_AH_B–CH–O), 4.08–4.20 (2H, m, O–CH_AH_B–C*H*–O), 5.38 (1H, d, *J*=18 Hz, CH=CH_AH_B), 5.48 (1H, d, *J*=11 Hz, CH=CH_AH_B), 6.05 (1H, dd, *J*=18, 11 Hz, C*H*=CH_2), 6.05 (1H, m, MeC=C*H*), 7.38 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.8, 26.4, 30.8, 42.5, 65.9, 68.2, 75.3, 92.7, 109.6, 119.7, 125.6, 130.3, 158.9, 160.3, 191.3. MS (FAB) *m/z* 396 (M+H), 398 (M+H), 400 (M+H). Anal. calcd for $C_{16}H_{20}O_4NCl_3$: C, 48.44; H, 5.08; N, 3.53. Found C, 48.43; H, 5.12; N, 3.48.

4.1.5. Enone 15 from 11. To a solution of the dibromide **11** (1.336 g, 2.46 mmol) in DMF (50 mL) was added DBU (0.81 mL, 5.42 mmol). After stirring at rt for 4 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution. The mixture was extracted with AcOEt (×3) and the combined organic layer was washed with water (×2) and brine (×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and MS 4A (ca. 1 g) and PCC (1.6 g, 7.38 mmol) were added. After stirring for 6 h, the reaction mixture was diluted with Et_2O, and Super-Cel was added. After vigorous stirring at rt for additional 10 min, the mixture was filtered through a pad of Super-Cel, and the precipitate was washed with Et_2O. The combined filtrate was evaporated. The residue was dissolved in Et_2O. The solution was passed through a column packed with anhydrous Na_2SO_4 and silica gel (to remove residual chromium), and evaporated. The residue was purified by column chromatography (silica gel 45 g, ether/hexane=1:1→2:1→3:1) to give enone **15** (727 mg, 75%, in 2 steps).

4.1.6. Allylic alcohol 7. To a solution of the enone **15** (8.01 g, 20.3 mmol) dissolved in EtOH (175 mL) and CH_2Cl_2 (175 mL) was added $CeCl_3{\cdot}7H_2O$ (15.11 g, 40.6 mmol). The solution was stirred for 30 min at rt and then cooled to −78°C. To this solution was added a suspension of $NaBH_4$ (1.53 g, 40.6 mmol) in EtOH (35 mL) dropwise over 20 min. After stirring at 0°C for 2 h, the reaction mixture was allowed to warm up to rt. After stirring at rt for additional 30 min, the reaction was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (×3), 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, ether/hexane=1:3→1:2→1:1→5:1) to give allylic alcohol **7** (5.71 g, 71%), its epimer **14** (0.36 g, 4%), and unreacted enone **15** (0.90 g, 11%). **7**. Mp 115–116°C (as colorless prisms from ether–hexane). $[\alpha]_D^{27}$=+30.1° (*c* 1.43, $CHCl_3$). IR (KBr) ν_{max} 3371, 3284, 2992, 1704, 1548, 1059, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3 of acetonide), 1.42 (3H, s, CH_3 of acetonide), 1.65 (1H, dd, *J*=17, 5.5 Hz, CH=CMe–$CH_{ax}H_{eq}$), 1.70–1.80 (1H, m, CH=CMe–$CH_{ax}H_{eq}$), 1.73 (3H, br s, CH_3–C=CH), 2.10 (1H, ddd, *J*=11.5, 9, 5.5 Hz, –C*H*–), 3.64 (1H, m, O–CH_2–C*H*–O), 4.06–4.13 (2H, m, O–CH_2–CH–O), 4.47 (1H, m, HO–C*H*), 5.34 (1H, dd, *J*=17.5, 1 Hz, CH=CH_AH_B), 5.39 (1H, m, MeC=C*H*), 5.45 (1H, br d, *J*=11 Hz, CH=CH_AH_B), 5.83 (1H, dd, *J*=17.5, 11 Hz, C*H*=CH_2), 5.92 (1H, d, *J*=1.5 Hz, O*H*), 9.61 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 26.4, 26.5, 29.9, 43.9, 67.5, 68.8, 73.6, 75.7, 93.6, 110.4, 117.7, 124.0, 130.8, 132.1, 163.2. MS (FAB) *m/z* 398 (M+H), 400 (M+H), 402 (M+H). Anal. calcd for $C_{16}H_{22}O_4NCl_3$: C, 48.20; H, 5.56; N, 3.51. Found C, 48.14; H, 5.62; N, 3.49.

4.1.7. Epoxy alcohol 16. To a solution of the allylic alcohol **7** (5.71 g, 14.4 mmol) in CH_2Cl_2 (200 mL) were added Na_2HPO_4 (6.13 g, 43.1 mmol) and MCPBA (70% purity, 5.32 g, 21.6 mmol). After stirring at rt for 24 h, the reaction mixture was diluted with CH_2Cl_2, and quenched with sat. Na_2SO_3 solution. The mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 300 g, ether/hexane=1:1→2:1) to give epoxy alcohol **16** (5.67 g, 95%). Mp 144–145.5°C (as colorless prisms from ether–hexane). $[\alpha]_D^{27}$=+5.5° (*c* 1.11, $CHCl_3$). IR (KBr) ν_{max} 3395, 3276, 3081, 2983, 2870, 1703, 1562, 1219, 1162, 1066 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, CH_3), 1.38 (6H, s, CH_3 ×2), 1.52 (1H, dd, *J*=15, 12 Hz, Me–C–C$H_{ax}H_{eq}$), 1.60 (1H, m, Me–C–$CH_{ax}H_{eq}$), 1.98 (1H, ddd, *J*=12, 9, 5 Hz, –C*H*–), 3.10 (1H, s, epoxidic), 3.59 (1H, dd, *J*=9, 8 Hz, O–CH_AH_B–CH–O), 4.01 (1H, td, *J*=9, 5.5 Hz, O–CH_2–C*H*–O), 4.07 (1H, d, *J*=1.5 Hz, HO–C*H*), 4.09 (1H, dd, *J*=8, 5.5 Hz, O–CH_AH_B–CH–O), 5.29 (1H, dd, *J*=17.5, 1 Hz, CH=CH_AH_B), 5.48 (1H, br d, *J*=11 Hz, CH=CH_AH_B), 5.78 (1H, dd, *J*=17.5, 11 Hz, C*H*=CH_2), 5.87 (1H, d, *J*=1.5 Hz, O*H*), 9.65 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 26.3, 26.4, 29.2, 38.9, 57.3, 61.8, 66.6, 68.8, 73.1, 75.4, 93.3, 110.5, 118.1, 130.2, 163.5. MS (FAB) *m/z* 414 (M+H), 416 (M+H), 418 (M+H). Anal. calcd for $C_{16}H_{22}O_5NCl_3$: C, 46.34; H, 5.35; N, 3.34. Found C, 46.23; H, 5.51; N, 3.37.

4.1.8. Benzylether 17. NaH (60% purity, 3.11 g, 77.8 mmol) was washed with anhydrous hexane (10 mL×3), and dry THF (150 mL) and DMF (50 mL) were added. To this suspension was added a THF (10+8 mL) solution of the epoxy alcohol **16** (7.14 g, 17.3 mmol) via cannular tubing. After stirring at rt for 30 min, BnBr (4.11 mL, 34.6 mmol) was added dropwise. After stirring at rt for additional 22 h, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The mixture was extracted with AcOEt (×3). The combined organic layer was washed with water (×2) and brine (×1), and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel 400 g, ether/hexane=1:1→2:1) afforded benzylether **17** (7.75 g, 90%). Mp 100–101°C (as white tiny needles from ether–hexane). $[\alpha]_D^{26}$=−22.3° (*c* 1.10, $CHCl_3$). IR (KBr) ν_{max} 3432, 2989, 2857, 1717, 1515, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, CH_3 of acetonide), 1.32 (3H, s, CH_3 of acetonide), 1.34 (3H, s, CH_3), 1.42 (1H, dd, *J*=15, 13 Hz, Me–C–C$H_{ax}H_{eq}$), 1.75 (1H, dd, *J*=15, 5 Hz, Me–C–$CH_{ax}H_{eq}$), 2.75 (1H, ddd, *J*=13, 9.5, 5 Hz, –C*H*–), 3.05 (1H, br s, epoxidic), 3.53 (1H, m, O–CH_2–C*H*–O), 3.90–3.99 (2H, m, O–CH_2–CH–O), 4.53 (1H, s, BnO–C*H*), 4.70 (2H, s, O–CH_2–Ph), 5.38 (1H, d, *J*=18 Hz, CH=CH_AH_B), 5.54 (1H, d, *J*=11 Hz, CH=CH_AH_B), 5.99 (1H, dd, *J*=18, 11 Hz, C*H*=CH_2), 7.14 (1H, br s, N*H*), 7.26–7.38 (5H, m, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 26.2, 26.3, 29.9, 36.6, 57.7, 61.3, 63.6, 68.2, 73.6, 75.1, 76.4, 93.7, 109.5, 117.6, 127.8, 127.9, 128.4, 134.1, 137.7,

159.8. MS (FAB) *m/z* 504 (M+H), 506 (M+H), 508 (M+H). Anal. calcd for $C_{23}H_{28}O_5NCl_3$: C, 54.72; H, 5.59; N, 2.77. Found C, 54.65; H, 5.63; N, 2.77.

4.1.9. Aldehyde 18. The benzylether **17** (7.81 g, 15.5 mmol) was dissolved in methanol (250 mL), and the solution was cooled to −78°C. Ozone gas was passed into this solution until the color of the solution became purple, and the mixture was stirred at −78°C for 1 h 10 min. After purging with nitrogen, dimethylsulfide (5.70 mL, 77.6 mmol) was added, and the mixture was allowed to warm up to rt. The mixture was poured into an ice-cold sat. $NaHCO_3$ solution, and the resulting solution was immediately extracted with CH_2Cl_2 (×3). 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 300 g, ether/hexane=1:1→2:1) to give aldehyde **18** (7.55 g, 96%). Mp 103–105°C (as white needles from ether–hexane). $[\alpha]_D^{27}=-29°$ (*c* 0.78, $CHCl_3$). IR (KBr) ν_{max} 3387, 2988, 1713, 1508, 1379, 1073, 859 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s, C*H*$_3$ of acetonide), 1.30 (3H, s, C*H*$_3$ of acetonide), 1.44 (3H, s, C*H*$_3$), 1.82 (1H, dd, *J*=16, 13.5 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 2.07 (1H, dd, *J*=16, 5.5 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 3.04 (1H, ddd, *J*=13.5, 8, 5.5 Hz, –C*H*–), 3.22 (1H, s, epoxidic), 3.48 (1H, t, *J*=8 Hz, O–C*H*$_A$H$_B$–CH–O) 3.76 (1H, td, *J*=8, 6 Hz, O–CH$_2$–C*H*–O), 3.92 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.65 (2H, s, C*H*$_2$–Ph), 4.77 (1H, s, BnO–C*H*), 7.23–7.36 (5H, m, aromatic), 8.05 (1H, br s, N*H*), 9.75 (1H, s, –C*H*O). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 25.8, 26.0, 30.0, 35.5, 58.1, 60.4, 67.6, 68.3, 74.5, 74.6, 75.7, 92.8, 109.9, 127.9, 128.2, 128.5, 136.8, 160.4, 196.5. MS (FAB) *m/z* 506 (M+H), 508 (M+H), 510 (M+H). Anal. calcd for $C_{22}H_{26}O_6NCl_3$: C, 52.14; H, 5.17; N, 2.76. Found C, 52.15; H, 5.27; N, 2.77.

4.1.10. Propargyl alcohol 19. To an ice-cold solution of trimethylsilylacetylene (25.4 mL, 0.179 mol) in dry THF (230 mL) was added EtMgBr (ca. 3 M in ether, 49.8 mL, 0.150 mol) dropwise over 15 min. The reaction mixture was allowed to warm up to rt and stirred for 20 min. After cooling to 0°C, the aldehyde **18** (7.55 g, 15.0 mmol) in THF (10+6 mL) was added dropwise over 20 min via cannular tubing. The mixture was stirred at rt for additional 2 h, and poured into an ice-cold sat. NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (×3), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude propargyl alcohol (9.16 g). The crude product was dissolved in THF (280 mL) and *n*-Bu_4NF (1 M in THF, 15 mL, 15 mmol) was added. After stirring for 2.5 h at rt, the reaction mixture was diluted with AcOEt. The resulting solution was washed with sat. NH_4Cl solution (×1) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine (100 mL) and Ac_2O (100 mL) and stirred for 5.5 h. The reaction mixture was diluted with toluene (100 mL), and concentrated in vacuo. The residue was purified by column chromatography (silica gel 300 g, ether/hexane=1:1→2:1) to give acetate **19** (7.37 g, 86%, 3 steps from **18**). Mp 100–102°C (as colorless needles from ether–hexane). $[\alpha]_D^{27}=-16.7°$ (*c* 1.08, $CHCl_3$). IR (KBr) ν_{max} 3263, 2986, 2127, 1752, 1728, 1534, 1374, 1251, 1221, 1074 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s, C*H*$_3$ of acetonide), 1.34 (3H, s, C*H*$_3$ of acetonide), 1.35 (3H, s, C*H*$_3$), 1.75 (1H, dd, *J*=15, 5 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 2.07 (3H, s, O*Ac*), 2.22 (1H, dd, *J*=15, 13 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 2.66 (1H, ddd, *J*=13, 9, 5 Hz, –C*H*–), 2.67 (1H, d, *J*=2.5 Hz, C≡C*H*), 3.06 (1H, s, epoxidic), 3.48 (1H, dd, *J*=9, 8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.12 (1H, dd, *J*=8, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 4.56 (1H, td, *J*=9, 5.5 Hz, O–CH$_2$–C*H*–O), 4.66 (1H, s, BnO–C*H*), 4.73 (2H, br s, O–C*H*$_2$–Ph), 6.38 (1H, d, *J*=2.5 Hz, C*H*–OAc), 7.26–7.40 (5H, m, aromatic), 7.68 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.6, 26.4, 26.5, 30.4, 38.0, 58.6, 61.7, 64.3, 64.9, 70.0, 73.6, 76.4, 78.8, 93.6, 109.8, 127.8, 128.4, 137.6, 159.9, 169.8. MS (FAB) *m/z* 574 (M+H), 576 (M+H), 578 (M+H). Anal. calcd for $C_{26}H_{30}O_7NCl_3$: C, 54.32; H, 5.26; N, 2.44. Found C, 54.32; H, 5.32; N, 2.29.

4.1.11. Cyclic ether 21. To a solution of the epoxide **19** (7.6 mg, 0.013 mmol) in MeOH (0.38 mL) was added K_2CO_3 (19 mg, 5% w/v of solvent). After vigorous stirring at rt for 15 min, the mixture was quenched with sat. NH_4Cl solution, and the resulting solution was extracted with CH_2Cl_2 (×3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine (0.4 mL) and acetic anhydride (0.4 mL), and DMAP (trace) was added. After stirring at rt for 30 min, the reaction mixture was diluted with toluene, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel ether/hexane=3:1) to give the acetate **21** (11 mg, 92%, 2 steps from **19**) as a white solid. $[\alpha]_D^{26}=+22°$ (*c* 0.61, $CHCl_3$). IR (KBr) ν_{max} 3372, 3249, 2866, 2109, 1726, 1710, 1519, 1373, 1264, 1066 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, s, C*H*$_3$ of acetonide), 1.33 (1H, dd, *J*=15, 13 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.35 (3H, s, C*H*$_3$ of acetonide), 1.50 (3H, s, C*H*$_3$), 1.89 (1H, ddd, *J*=15, 5.5, 1 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 1.96 (3H, s, O*Ac*), 2.84 (1H, d, *J*=2 Hz, C≡C*H*), 3.01 (1H, ddd, *J*=13, 7.5, 5.5 Hz, –C*H*–), 3.57 (1H, t, *J*=8 Hz, O–C*H*$_A$H$_B$–CH–O), 3.94 (1H, ddd, *J*=8, 7.5, 6 Hz, O–CH$_2$–C*H*–O), 3.99 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.51 (1H, s, BnO–CH–C*H*), 4.53 (1H, d, *J*=12 Hz, C*H*$_A$H$_B$–Ph), 4.64 (1H, d, *J*=12 Hz, CH$_A$*H*$_B$–Ph), 4.87 (1H, s, BnO–C*H*), 4.97 (1H, d, *J*=2 Hz, C*H*–C≡CH), 7.22–7.36 (5H, m, aromatic), 7.43 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.1, 26.0, 26.3, 33.6, 39.0, 66.6, 67.9, 70.5, 71.4, 75.9, 78.4, 78.9, 79.0, 82.3, 83.0, 92.7, 109.7, 127.5, 127.6, 128.1, 137.5, 161.1, 170.1. MS (EI) *m/z* 558 (M–Me), 560 (M–Me), 562 (M–Me). HRMS (EI) for $C_{25}H_{27}O_7NCl_3$ (M–Me), calcd 558.0853, found 558.0848.

4.1.12. Hydroxy lactone 6. To a solution of the acetate **19** (4.65 g, 8.12 mmol) in CCl_4 (40 mL), CH_3CN (40 mL) and H_2O (60 mL) were added $NaIO_4$ (6.94 g, 32.5 mmol) and $RuO_2(H_2O)_x$ (27 mg, 0.20 mmol) successively. After vigorous stirring at rt for 4.5 h, the solution was diluted with CH_2Cl_2 (10 mL), and two drops of 2-propanol and K_2CO_3 (4.49 g, 32.5 mmol) were added to the mixture. After stirring for additional 10 min, the reaction mixture was poured into sat. NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (×4). 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, ether/hexane=5:1→ether only)

to give hydroxy lactone **6** (3.60 g, 75%). Mp 173–174°C (as colorless prisms from ether–hexane). $[\alpha]_D^{27}=-20°$ (*c* 0.53, $CHCl_3$). IR (KBr) ν_{max} 3439, 3398, 2986, 1783, 1762, 1699, 1534, 1373, 1178, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, s, C*H*$_3$ of acetonide), 1.35 (3H, s, C*H*$_3$ of acetonide), 1.37 (3H, s, C*H*$_3$), 1.38 (1H, m, Me–C–CH$_{ax}$*H*$_{eq}$), 1.44 (1H, dd, *J*=15.5, 13 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 2.26 (3H, s, O*Ac*), 3.21 (1H, ddd, *J*=13, 10, 5 Hz, –C*H*–), 3.48 (1H, dd, *J*=9, 8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.09 (1H, dd, *J*=8, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 4.24 (1H, t, *J*=2 Hz, BnO–CH–C*H*), 4.37 (1H, ddd, *J*=10, 9, 5.5 Hz, O–CH$_2$–C*H*–O), 4.65 (1H, d, *J*=11.5 Hz, C*H*$_A$H$_B$–Ph), 4.76 (1H, d, *J*=11.5 Hz, CH$_A$*H*$_B$–Ph), 5.40 (1H, d, *J*=2 Hz, BnO–C*H*), 6.03 (1H, s, C*H*–OAc), 7.26–7.36 (5H, m, aromatic), 7.66 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 26.2, 26.5, 26.8, 34.0, 38.8, 63.6, 69.9, 70.3, 71.1, 72.0, 73.1, 76.8, 82.4, 92.8, 109.8, 128.0, 128.1, 128.5, 137.2, 160.7, 166.1, 171.4. MS (FAB) *m*/*z*594 (M+H), 596 (M+H), 598 (M+H). Anal. calcd for $C_{25}H_{30}O_9NCl_3$: C, 50.48; H, 5.08; N, 2.35. Found C, 50.47; H, 5.08; N, 2.30.

4.1.13. Aldehyde 23. The epoxy alcohol **16** (92 mg, 0.22 mmol) was dissolved in methanol (6 mL), and the solution was cooled to −78°C. Ozone gas was passed into this solution until the color of the solution became purple, and the mixture was stirred at −78°C for 8 min. After purging with nitrogen, dimethylsulfide (0.16 mL, 2.2 mmol) was added, and the mixture was allowed to warm up to rt. The mixture was poured into an ice-cooled sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (×3). 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 6 g, ether/hexane=2:1) to give aldehyde **23** (69 mg, 74%) as a white solid. $[\alpha]_D^{26}=-22.9°$ (*c* 1.98, $CHCl_3$). IR (KBr) ν_{max} 3376, 3277, 2988, 1738, 1709, 1547, 1384, 1250, 1161, 1065 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, s, C*H*$_3$ ×2), 1.47 (3H, s, C*H*$_3$), 1.78–1.89 (2H, m, Me–C–C*H*$_2$), 2.22 (1H, td, *J*= 10, 7.5 Hz, –C*H*–), 3.32 (1H, s, epoxidic), 3.55 (1H, dd, *J*= 9.5, 8.5 Hz, O–C*H*$_A$H$_B$–CH–O) 3.85 (1H, ddd, *J*=10, 9.5, 5.5 Hz, O–CH$_2$–C*H*–O), 4.11 (1H, dd, *J*=8.5, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 4.29 (1H, d, *J*=2.5 Hz, C*H*–OH), 5.73 (1H, d, *J*=2.5 Hz, CH–O*H*), 9.49 (1H, br s, N*H*), 9.74 (1H, s, C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 26.2, 26.3, 29.3, 38.4, 57.9, 61.5, 68.9, 70.1, 71.9, 75.6, 92.6, 111.0, 164.8, 196.0. HRMS (FAB) for $C_{15}H_{22}O_6N$ (M+H), calcd 416.0434, found 416.0498.

4.1.14. Lactone 25. To a solution of the aldehyde **23** (23 mg, 0.055 mmol) in EtOH (0.7 mL) and H_2O (0.35 mL) were successively added NH_4Cl (5 mg, 0.094 mmol) and KCN (7 mg, 0.11 mmol). After stirring at 0°C for 2 h, the solution was diluted with CH_2Cl_2 (5 mL), and sat. $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2 (×3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue (26 mg) was dissolved in THF (0.5 mL) and H_2O (0.5 mL), and PPTS (14 mg, 0.058 mmol) was added. After stirring at rt for 2 h, the mixture was quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (×3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, ether only) to give lactone **25** (18 mg, 75%, 2 steps from **23**). IR (KBr) ν_{max} 3430, 2930, 1791, 1717, 1507, 1165, 1121, 1064, 1017 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s, C*H*$_3$ of acetonide), 1.36 (3H, s, C*H*$_3$ of acetonide), 1.41 (3H, s, C*H*$_3$), 1.77 (1H, dd, *J*=15.5, 12.5 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.92 (1H, dd, *J*=15.5, 4.5 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 2.57 (1H, ddd, *J*=12.5, 9, 4.5 Hz, –C*H*–), 3.16 (1H, d, *J*=1 Hz, epoxidic), 3.56 (1H, dd, *J*=9, 8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.11 (1H, dd, *J*=8, 5.5 Hz, O–CH$_A$*H*$_B$–CH–O), 4.20 (1H, td, *J*=9, 5.5 Hz, O–CH$_2$–C*H*–O), 4.47 (1H, s, C*H*–OH), 5.14 (1H, d, *J*=1 Hz, CO–O–C*H*), 8.35 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 26.2, 26.5, 28.2, 35.6, 56.5, 57.6, 60.8, 66.2, 68.6, 75.7, 92.3, 110.3, 162.6, 174.2. HRMS (FAB) for $C_{16}H_{21}O_7NCl_3$ (M+H), calcd 444.0384, found 444.0361.

4.1.15. Benzylurea 28. The hydroxy lactone **6** (153 mg, 0.258 mmol) was dissolved in DMF (12 mL). To this solution were successively added Na_2CO_3 (136 mg, 1.29 mmol) and $BnNH_2$ (0.034 mL, 0.309 mmol). The reaction mixture was vigorously stirred at 125°C for 30 min. After cooling to rt, the mixture was diluted with AcOEt, and the resulting solution was poured into an ice-cold sat. NH_4Cl solution. The mixture was extracted with AcOEt (×3), 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 8 g, AcOEt/hexane=2:1→3:1) to give benzylurea **28** (120 mg, 80%) as a colorless amorphous solid. $[\alpha]_D^{27}=-54.6°$ (*c* 1.99, $CHCl_3$). IR (KBr) ν_{max} 3406, 2933, 1760, 1664, 1554, 1373, 1264, 1219 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30–1.44 (2H, m, Me–C–C*H*$_2$), 1.31 (3H, s, C*H*$_3$), 1.32 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 2.19 (3H, s, O*Ac*), 3.28 (1H, ddd, *J*=12.5, 8, 6.5 Hz, –C*H*–), 3.60 (1H, t, *J*=8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.05 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.15 (1H, dd, *J*=15, 5 Hz, NH–C*H*$_A$H$_B$–Ph), 4.27 (1H, d, *J*=2 Hz, BnO–CH–C*H*), 4.37 (1H, td, *J*=8, 6 Hz, O–CH$_2$–C*H*–O), 4.42, (1H, dd, *J*=15, 6 Hz, NH–CH$_A$*H*$_B$–Ph), 4.67 (1H, d, *J*= 11.5 Hz, O–C*H*$_A$H$_B$–Ph), 4.72 (1H, m, N*H*–CH$_2$–Ph), 4.72 (1H, d, *J*=11.5 Hz, O–CH$_A$*H*$_B$–Ph), 4.87 (1H, br s, C–N*H*–CO–), 5.46 (1H, d, *J*=2 Hz, BnO–C*H*), 5.89 (1H, s, C*H*–OAc), 7.22–7.32 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 25.9, 26.2, 26.8, 33.8, 39.3, 61.9, 65.8, 69.7, 70.7, 71.0, 73.1, 73.6, 76.9, 83.4, 109.1, 127.5, 127.7, 128.4, 128.7, 138.1, 138.8, 157.1, 167.1, 171.0. MS (EI) *m*/*z* 582 (M^+), 567 (M–Me). HRMS (EI) for $C_{31}H_{38}O_9N_2$ (M^+), calcd 582.2577, found 582.2562.

4.1.16. Alcohol 29. To a solution of the benzylurea **28** (138 mg, 0.237 mmol) in EtOH (5 mL) was added KCN (8 mg, 0.12 mmol). After stirring at rt for 2 h, sat. $NaHCO_3$ solution was added. The mixture was extracted with AcOEt (×3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude alcohol **29** (134 mg) was used for the next reaction without purification. ^1H NMR (300 MHz, CD_3OD) δ 1.31 (3H, s, C*H*$_3$), 1.33 (3H, s, C*H*$_3$), 1.38 (3H, s, C*H*$_3$), 1.56 (1H, ddd, *J*=15, 4, 1 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 1.67 (1H, dd, *J*=15, 13 Hz, Me–C–C*H*$_{ax}$-H$_{eq}$), 2.44 (1H, ddd, *J*=13, 6, 4 Hz, –C*H*–), 3.73 (1H, t, *J*=8 Hz, O–C*H*$_A$H$_B$–CH–O), 4.03 (1H, dd, *J*=8, 6 Hz, O–CH$_A$*H*$_B$–CH–O), 4.23 (1H, dt, *J*=8, 6 Hz, O–CH$_2$–C*H*–O), 4.48 (1H, dd, *J*=2, 1 Hz, BnO–CH–C*H*), 4.59

(1H, br s, BnO–C*H*), 4.66 (1H, d, *J*=11.5 Hz, O–CH_AH_B–Ph), 4.73 (1H, d, *J*=11.5 Hz, O–CH$_A$$H_B$–Ph), 4.80–4.94 (2H, m, N–CH_2–Ph), 5.25 (1H, s, HO–C*H*), 7.24–7.34 (10H, m, aromatic).

4.1.17. Cyclic benzylurea 30. To a solution of the crude alcohol **29** (134 mg) in MeOH (3.6 mL) and H_2O (1.2 mL) was added TFA (0.24 mL, 5% v/v of solvent) at rt. After stirring at 60°C for 30 min, the mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (3.6 mL) and H_2O (1.2 mL), and $NaIO_4$ (76 mg, 0.36 mmol) was added. After stirring at rt for 3.5 h, the reaction mixture was diluted with sat. $NaHCO_3$ solution and extracted with AcOEt (×3). 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, CH_2Cl_2/acetone=10:1→5:1) to give cyclic benzylurea **30** (87 mg, 79%, 3 steps from **29**) as a white amorphous solid. $[\alpha]_D^{26}=-30.2°$ (*c* 1.63, $CHCl_3$). IR (KBr) ν_{max} 3386, 2927, 1744, 1660, 1455, 1093, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (1H, dd, *J*=16, 11.5 Hz, Me–C–CH_{ax}H$_{eq}$), 1.40 (3H, s, CH_3), 1.81 (1H, ddd, *J*=16, 7, 1 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.69 (1H, dd, *J*=11.5, 7 Hz, –C*H*–), 4.11 (1H, d, *J*=15 Hz, CH_AH$_B$–Ph), 4.43 (1H, dd, *J*=2.5, 1 Hz, BnO–CH–C*H*), 4.50 (1H, d, *J*=2.5 Hz, BnO–C*H*), 4.51 (1H, d, *J*=11.5 Hz, CH_CH$_D$–Ph), 4.77 (1H, d, *J*=11.5 Hz, CH$_C$$H_D$–Ph), 4.78 (1H, s, BnN–C*H*, or O–C*H*–CO), 4.79 (1H, s, BnN–C*H*, or O–C*H*–CO), 5.01 (1H, d, *J*=15 Hz, CH$_A$$H_B$–Ph), 5.53 (1H, br s, N*H*), 7.21–7.43 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 31.4, 42.5, 49.3, 60.6, 71.0, 71.4, 72.5, 78.8, 82.5, 90.0, 127.6, 127.8, 128.0, 128.6, 128.7, 128.8, 136.5, 137.4, 155.7, 168.0. HRMS (FAB) for $C_{25}H_{27}O_6N_2$ (M+H), calcd 451.1821, found 451.1869.

4.1.18. Methylisourea 27. To a suspension of the cyclic benzylurea **30** (58 mg, 0.125 mmol) and anhydrous K_2CO_3 (172 mg, 1.25 mmol) in dry CH_2Cl_2 (3 mL) was added $Me_3O{\cdot}BF_4$ (184 mg, 1.25 mmol). After stirring at rt for 3.5 h, the reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (×5). 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 3.5 g, AcOEt/hexane=1:1→2:1) to give methylisourea **27** (48 mg, 80%) as a white amorphous. $[\alpha]_D^{27}=-25°$ (*c* 0.44, $CHCl_3$). IR (KBr) ν_{max} 3446, 2930, 1733, 1629, 1455, 1206, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, s, CH_3), 1.40 (1H, dd, *J*=15, 11 Hz, Me–C–CH_{ax}H$_{eq}$), 1.76 (1H, ddd, *J*=15, 6.5, 1 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.54 (1H, dd, *J*=11, 6.5 Hz, –C*H*–), 3.78 (3H, s, OCH_3), 4.15 (1H, d, *J*=15 Hz, CH_AH$_B$–Ph), 4.32 (1H, dd, *J*=2.5, 1 Hz, BnO–CH–C*H*), 4.40 (1H, d, *J*=2.5 Hz, BnO–C*H*), 4.64 (1H, s, BnN–C*H*, or O–C*H*–CO), 4.70 (1H, d, *J*=15 Hz, CH$_A$$H_B$–Ph), 4.79 (1H, s, BnN–C*H*, or O–C*H*–CO), 4.93 (1H, d, *J*=12 Hz, CH_CH$_D$–Ph), 5.10 (1H, d, *J*=12 Hz, CH$_C$$H_D$–Ph), 7.21–7.47 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 32.2, 41.9, 50.2, 53.9, 62.5, 72.7, 72.8, 73.0, 82.9, 84.5, 90.8, 127.4, 127.6, 127.7, 128.3, 128.6, 137.9, 138.6, 155.9, 169.0. Anal. calcd for $C_{26}H_{28}O_6N_2$: C, 67.23; H, 6.08; N, 6.03. Found C, 67.22; H, 6.16; N, 6.00.

4.1.19. Carbodiimide 32. To a solution of the benzylurea **28** (57 mg, 0.0978 mmol) and PPh_3 (385 mg, 1.47 mmol) in dry CH_2Cl_2 (2.5 mL) was added Et_3N (0.27 mL, 1.96 mmol). After stirring for 30 min at rt, a solution of CBr_4 (486 mg, 1.47 mmol) in dry CH_2Cl_2 (0.2 mL) was added dropwise, and the stirring was continued for additional 7 h at rt. The reaction mixture was concentrated, and the residue was purified by column chromatography (silica gel 4 g, ether/hexane=3:1→ether only) to give carbodiimide **32** (48 mg, 87%) as a colorless oil. $[\alpha]_D^{26}=-37.4°$ (*c* 1.53, $CHCl_3$). IR (KBr) ν_{max} 3448, 2932, 2135, 1765, 1213, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.42 (1H, dd, *J*=15.5, 14 Hz, Me–C–CH_{ax}H$_{eq}$), 1.70 (1H, ddd, *J*=15.5, 4.5, 1.5 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.14 (3H, s, O*Ac*), 2.33 (1H, ddd, *J*=14, 4.5, 2.5 Hz, –C*H*–), 3.84 (1H, dd, *J*=9, 5.5 Hz, O–CH_AH$_B$–CH–O), 3.98 (1H, dd, *J*=9, 7 Hz, O–CH$_A$$H_B$–CH–O), 4.18 (1H, d, *J*=2 Hz, BnO–C*H*), 4.21 (1H, dd, *J*=2, 1.5 Hz, BnO–CH–C*H*), 4.26 (1H, d, *J*=15 Hz, CH_AH$_B$Ph), 4.30 (1H, d, *J*=15 Hz, CH$_A$$H_B$Ph), 4.64 (1H, ddd, *J*=7, 5.5, 2.5 Hz, O–CH$_2$–C*H*–O), 4.66 (2H, s, CH_2–Ph), 6.05 (1H, s, C*H*–OAc), 7.21–7.34 (10H, m, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 24.0, 26.5, 27.3, 30.7, 43.8, 49.7, 63.7, 65.5, 69.9, 71.5, 73.0, 74.5, 78.3, 81.9, 107.7, 127.2, 127.5, 127.8, 128.0, 128.5, 128.6, 137.0, 137.6, 137.7, 167.3, 168.9. MS (EI) *m*/*z* 564 (M^+), 549 (M–Me), 521 (M–Ac). HRMS (EI) for $C_{31}H_{36}O_8N_2$ (M^+), calcd 564.2471, found 564.2484.

4.1.20. Cyclic guanidine 34. A solution of the benzylcarbodiimide **32** (11.5 mg, 0.020 mmol) and $BnNH_2$ (11 μL, 0.10 mmol) in DMF (0.75 mL) was heated at 100°C for 18.5 h. The reaction mixture was concentrated in vacuo and the residue was purified by repeated preparative TLC (silica gel) with two different solvents (CH_2Cl_2/acetone/MeOH=8:1:1 and CH_2Cl_2/MeOH=9:1 ×2) to give cyclic guanidine **34** (3.6 mg, 30%). IR (KBr) ν_{max} 3365, 2928, 1750, 1661, 1455, 1384, 1109, 1069 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.92 (1H, ddd, *J*=14, 3, 1.5 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.63 (1H, t, *J*=14 Hz, Me–C–CH_{ax}H$_{eq}$), 3.28 (1H, dd, *J*=14, 3 Hz, –C*H*–), 4.03 (1H, d, *J*=16.5 Hz, CH_AH$_B$–Ph), 4.22 (1H, dd, *J*=9, 7.5 Hz, O–CH_AH$_B$–CH–O), 4.30 (1H, t, *J*=7.5 Hz, O–CH$_A$$H_B$–CH–O), 4.52 (1H, d, *J*=14 Hz, CH_CH$_D$–Ph), 4.68 (1H, d, *J*=14 Hz, CH$_C$$H_D$–Ph), 4.70 (1H, dd, *J*=9, 7.5 Hz, O–CH$_2$–C*H*–O), 4.75 (1H, d, *J*=10.5 Hz, CH_EH$_F$–Ph), 4.76 (1H, m, BnO–CH–C*H*), 4.80 (1H, d, *J*=10.5 Hz, CH$_E$$H_F$–Ph), 4.88 (1H, d, *J*=2.5 Hz, BnO–C*H*), 5.50 (1H, d, *J*=16.5 Hz, CH$_A$$H_B$–Ph), 6.87–7.40 (15H, m, aromatic), 7.99 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.0, 26.8, 29.7, 37.2, 39.0, 46.1, 47.9, 69.0, 71.0, 72.8, 76.3, 78.1, 82.0, 87.9, 110.0, 126.8, 127.4, 128.0, 128.1, 128.3, 128.4, 128.8, 128.9, 129.3, 134.0, 135.0, 137.2, 157.7, 166.3. MS (FAB) *m*/*z* 628 (M+H). HRMS (FAB) for $C_{36}H_{42}O_7N_3$ (M+H), calcd 628.3023, found 628.2958.

4.1.21. Dimethylacetal 35. To a solution of the hydroxy lactone **6** (1.023 g, 1.73 mmol) in AcOEt (35 mL) was added H_5IO_6 (511 mg, 2.24 mmol). After stirring at rt for 24 h, the mixture was quenched with sat. $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue (891 mg) was dissolved in

MeOH (18 mL), and $CH(OMe)_3$ (9 mL) and *DL*-CSA (200 mg, 0.855 mmol) were added. After stirring at rt for 10 h, the mixture was quenched with sat. $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic layer was washed with brine (×1) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel 50 g, ether/hexane=5:1) to give dimethylacetal **35** (772 mg, 78%, 2 steps from **6**) as a colorless amorphous solid. $[\alpha]_D^{27}=-45°$ (*c* 0.92, $CHCl_3$). IR (KBr) ν_{max} 3477, 3358, 2935, 1745, 1718, 1535, 1375, 1217, 1167, 1081 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, s, C*H*$_3$), 1.46 (1H, dd, *J*=16, 13 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.89 (1H, ddd, *J*=16, 4.5, 2 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 2.28 (3H, s, O*Ac*), 3.24 (3H, s, OC*H*$_3$), 3.26 (3H, s, OC*H*$_3$), 3.47 (1H, ddd, *J*=13, 8.5, 4.5 Hz, –C*H*–), 4.24 (1H, t, *J*=2 Hz, BnO–CH–C*H*), 4.63 (1H, d, *J*=8.5 Hz, C*H*(OMe)$_2$), 4.64 (1H, d, *J*=11.5 Hz, C*H*$_A$H$_B$–Ph), 4.73 (1H, d, *J*=11.5 Hz, CH$_A$*H*$_B$–Ph), 5.35 (1H, d, *J*=2 Hz, BnO–C*H*), 5.93 (1H, s, C*H*–OAc), 7.26–7.35 (5H, m, aromatic), 7.65 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 26.8, 33.5, 36.2, 50.2, 54.1, 63.0, 70.1, 70.9, 72.5, 73.1, 82.4, 92.6, 104.0, 128.0, 128.1, 128.5, 137.2, 160.7, 166.0, 171.4. MS (FAB) *m/z* 536 (M–OMe), 538 (M–OMe), 540 (M–OMe). Anal. calcd for $C_{23}H_{28}O_9NCl_3$: C, 48.56; H, 4.96; N, 2.46. Found C, 48.56; H, 4.82; N, 2.55.

4.1.22. Diacetate 36. To a solution of the dimethylacetal **35** (489 mg, 0.839 mmol) in pyridine (7 mL) and acetic anhydride (7 mL) was added DMAP (5 mg). After stirring at rt for 24 h, the reaction mixture was diluted with toluene (20 mL), and concentrated in vacuo. The residue was purified by column chromatography (silica gel 25 g, ether/hexane=3:1→5:1) to give diacetate **36** (528 mg, 100%). Mp 109–110°C (as colorless needles from ether–hexane). $[\alpha]_D^{27}=-24°$ (*c* 0.89, $CHCl_3$). IR (KBr) ν_{max} 3402, 2939, 1779, 1750, 1727, 1527, 1373, 1222, 1173, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (1H, dd, *J*=16, 13 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.61 (3H, s, C*H*$_3$), 2.01 (3H, s, O*Ac*), 2.29 (3H, s, O*Ac*), 2.48 (1H, ddd, *J*=16, 4.5, 2 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 3.21 (3H, s, OC*H*$_3$), 3.25 (3H, s, OC*H*$_3$), 3.38 (1H, ddd, *J*=13, 8, 4.5 Hz, –C*H*–), 4.63 (1H, d, *J*=11.5 Hz, C*H*$_A$H$_B$–Ph), 4.64 (1H, d, *J*=8 Hz, C*H*(OMe)$_2$), 4.68 (1H, d, *J*=11.5 Hz, CH$_A$*H*$_B$–Ph), 5.03 (1H, t, *J*=2 Hz, BnO–CH–C*H*), 5.06 (1H, d, *J*=2 Hz, BnO–C*H*), 5.95 (1H, s, C*H*–OAc), 7.29–7.38 (5H, m, aromatic), 7.69 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 21.6, 21.9, 31.0, 35.5, 49.7, 54.0, 62.6, 69.9, 71.1, 73.0, 79.0, 80.3, 92.6, 103.5, 128.3, 128.4, 128.6, 136.5, 160.9, 165.7, 169.8, 171.4. MS (FAB) *m/z* 578 (M–OMe), 580 (M–OMe), 582 (M–OMe). Anal. calcd for $C_{25}H_{30}O_{10}NCl_3$: C, 49.15; H, 4.95; N, 2.29. Found C, 49.24; H, 4.97; N, 2.31.

4.1.23. Benzylurea 37. To a solution of the diacetate **36** (1.25 g, 2.04 mmol) in DMF (40 mL) were successively added Na_2CO_3 (1.08 g, 10.2 mmol) and $BnNH_2$ (0.29 mL, 2.65 mmol). The solution was vigorously stirred at 140°C for 15 min. After cooling to rt, the mixture was diluted with AcOEt, and the resulting solution was poured into an ice-cold sat. NH_4Cl solution. The mixture was extracted with AcOEt (×3). The combined organic layer was washed with water (×2) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product **37** (1.35 g) was used for the next reaction without purification. A portion of this material was purified by column chromatography (ether/hexane=5:1→ether only). IR (KBr) ν_{max} 3416, 2939, 1743, 1684, 1545, 1373, 1244, 1166 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (1H, dd, *J*=16.5, 14 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.58 (3H, s, C*H*$_3$), 2.05 (3H, s, O*Ac*), 2.20 (3H, s, O*Ac*), 2.38 (1H, ddd, *J*=16.5, 4.5, 2 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 3.21 (3H, s, OC*H*$_3$), 3.25 (3H, s, OC*H*$_3$), 3.38 (1H, ddd, *J*=14, 7, 4.5 Hz, –C*H*–), 4.25 (1H, dd, *J*=15, 6 Hz, NH–C*H*$_A$H$_B$–Ph), 4.38 (1H, dd, *J*=15, 6 Hz, NH–CH$_A$*H*$_B$–Ph), 4.61 (1H, d, *J*=7 Hz, C*H*(OMe)$_2$), 4.66 (2H, s, O–C*H*$_2$–Ph), 4.76 (1H, br t, *J*=6 Hz, N*H*–CH$_2$–Ph), 4.82 (1H, br s, C–N*H*–CO), 5.04 (1H, t, *J*=2 Hz, BnO–CH–C*H*), 5.16 (1H, d, *J*=2 Hz, BnO–C*H*), 5.87 (1H, s, C*H*–OAc), 7.24–7.34 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.6, 22.0, 30.9, 37.5, 44.0, 51.8, 53.2, 60.6, 70.3, 72.5, 72.8, 79.9, 80.7, 103.7, 127.3, 127.9, 128.1, 128.4, 128.6, 137.4, 139.1, 157.0, 166.8, 170.0, 171.0. MS (FAB) *m/z* 599 (M+H), 567 (M–OMe).

4.1.24. Methylacetal 38. To a solution of the crude benzylurea **37** (1.35 g) in EtOH (40 mL) was added KCN (13 mg, 0.204 mmol). After stirring at rt for 1 h, the mixture was diluted with sat. $NaHCO_3$ solution, and extracted with AcOEt (×3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in acetone (40 mL) and *DL*-CSA (47 mg, 0.204 mmol) was added. After stirring at rt for 2 h, the reaction mixture was quenched with sat. $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (×3). 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 80 g, ether/hexane=1:1→3:1→5:1) to give methylacetal **38** (618 mg, 58%, 3 steps from **36**) and its C-4 epimer (133 mg, 12%, 3 steps from **36**). **38**. Mp 184–185°C (as white tiny needles from ether–hexane). $[\alpha]_D^{26}=-108°$ (*c* 0.41, $CHCl_3$). IR (KBr) ν_{max} 3394, 2908, 1754, 1736, 1646, 1552, 1237 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, s, C*H*$_3$), 1.64 (1H, dd, *J*=16.5, 11.5 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 2.06 (3H, s, O*Ac*), 2.18 (1H, ddd, *J*=16.5, 8, 1 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 3.42 (1H, ddd, *J*=11.5, 8, 4 Hz, –C*H*–), 3.44 (3H, s, OC*H*$_3$), 4.11 (1H, s, MeO–CH–O–C*H*), 4.27 (1H, dd, *J*=15, 6 Hz, NH–C*H*$_A$H$_B$–Ph), 4.32 (1H, dd, *J*=15, 6 Hz, NH–CH$_A$*H*$_B$–Ph), 4.42 (1H, d, *J*=11.5 Hz, O–C*H*$_A$H$_B$–Ph), 4.60 (1H, d, *J*=11.5 Hz, O–CH$_A$*H*$_B$–Ph), 4.80 (1H, d, *J*=2 Hz, BnO–C*H*), 4.84 (1H, br s, C–N*H*–CO), 5.02 (1H, br t, *J*=6 Hz, N*H*–CH$_2$–Ph), 5.19 (1H, dd, *J*=2, 1 Hz, BnO–CH–C*H*), 5.26 (1H, d, *J*=4 Hz, C*H*–OMe), 7.19–7.34 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.5, 27.6, 41.5, 43.9, 57.8, 62.9, 69.4, 71.7, 77.9, 78.2, 80.5, 109.0, 127.3, 128.1, 128.2, 128.4, 128.7, 136.9, 139.0, 156.9, 169.9, 170.6. MS (FAB) *m/z* 525 (M+H). Anal. calcd for $C_{28}H_{32}O_8N_2$: C, 64.11; H, 6.15; N, 5.34. Found C, 64.12; H, 6.19; N, 5.34.

The epimer at C-4 of 38. Mp 185–186°C (as white tiny needles from ether–hexane). $[\alpha]_D^{28}=+4.4°$ (*c* 0.69, $CHCl_3$). IR (KBr) ν_{max} 3420, 3347, 2922, 1745, 1734, 1693, 1554, 1256, 1200, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (1H, dd, *J*=15.5, 11 Hz, Me–C–C*H*$_{ax}$H$_{eq}$), 1.58 (3H, s, C*H*$_3$), 2.09 (3H, s, O*Ac*), 2.53 (1H, ddd, *J*=15.5, 8, 1 Hz, Me–C–CH$_{ax}$*H*$_{eq}$), 3.20 (1H, dd, *J*=11, 8 Hz, –C*H*–), 3.32 (3H, s, OC*H*$_3$), 4.30 (1H, dd, *J*=15, 6 Hz,

NH–CH_AH$_B$–Ph), 4.38 (1H, dd, J=15, 6 Hz, NH–CH$_A$$H_B$–Ph), 4.44 (1H, s, MeO–CH–O–CH), 4.59 (1H, d, J=11 Hz, O–CH_AH$_B$–Ph), 4.67 (1H, d, J=11 Hz, O–CH$_A$$H_B$–Ph) 4.76 (1H, br s, C–N$H$–CO), 4.78 (1H, s, C$H$–OMe), 4.84 (1H, br t, J=6 Hz, NH–CH$_2$–Ph), 5.02 (1H, dd, J=2.5, 1 Hz, BnO–CH–CH), 5.12 (1H, d, J=2.5 Hz, BnO–CH), 7.24–7.34 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 22.2, 31.6, 44.0, 44.8, 56.3, 62.7, 70.1, 72.4, 78.9, 80.6, 81.1, 112.1, 127.2, 127.4, 127.9, 128.4, 128.7, 137.4, 139.2, 157.3, 168.7, 170.5. MS (FAB) m/z 525 (M+H). Anal. Calcd for $C_{28}H_{32}O_8N_2$: C, 64.11; H, 6.15; N, 5.34. Found C, 64.12; H, 6.17; N, 5.34.

4.1.25. Benzylcarbodiimide 39. To an ice-cold solution of CBr_4 (1.30 g, 3.92 mmol) in dry CH_2Cl_2 (10 mL) was added PPh_3 (1.03 g, 3.92 mmol) in one portion. After being stirred at 0°C for 5 min, a solution of the methylacetal **38** (205 mg, 0.390 mmol) and Et_3N (1.09 mL, 7.85 mmol) in dry CH_2Cl_2 (2 mL) was added. The mixture was stirred at rt for additional 4 h and then diluted with AcOEt (20 mL). The mixture was filtered through a pad of Super-Cel and the precipitate was washed with AcOEt. The combined filtrate was washed with sat. NH_4Cl solution (×1), sat. $NaHCO_3$ solution (×1) and brine (×1), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g, ether/hexane=1:1→3:1→5:1) to give benzylcarbodiimide **39** (228 mg) as a colorless oil. IR (KBr) ν_{max} 2931, 2132, 1756, 1457, 1217, 1173, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, s, CH_3), 1.60 (1H, dd, J=16, 11 Hz, Me–C–CH_{ax}H$_{eq}$), 1.95 (3H, s, OAc), 2.10 (1H, ddd, J=16, 7, 1 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.25 (1H, dddd, J=11, 7, 3.5, 0.5 Hz, –CH–), 3.46 (3H, s, OCH_3), 3.90 (1H, d, J=2 Hz, BnO–CH), 4.26 (2H, s, CH_2–Ph), 4.32 (1H, d, J=0.5 Hz, MeO–CH–O–CH), 4.49 (1H, d, J=11.5 Hz, CH_AH$_B$–Ph), 4.72 (1H, d, J=11.5 Hz, CH$_A$$H_B$–Ph), 5.10 (1H, d, J=3.5 Hz, CH–OMe), 5.23 (1H, dd, J=2, 1 Hz, BnO–CH–CH), 7.18–7.37 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.4, 27.5, 44.3, 50.0, 57.9, 66.0, 71.2, 72.4, 76.2, 78.7, 81.2, 108.4, 127.5, 127.8, 128.2, 128.5, 128.8, 136.5, 137.6, 139.0, 168.7, 170.0. MS (EI) m/z 506 (M$^+$). HRMS (EI) for $C_{28}H_{30}O_7N_2$ (M$^+$), calcd 506.2053, found 506.2067.

4.1.26. Benzylguanidine hydrochloride 40. A solution of the benzylcarbodiimide **39** (228 mg) and $BnNH_2$·HCl (323 mg, 2.25 mmol) in pyridine (9 mL) was heated at a reflux temperature for 5.5 h. The reaction mixture was diluted with toluene, and concentrated in vacuo. The residue was dissolved with AcOEt and H_2O, and sat. $NaHCO_3$ solution was added. The resulting mixture was extracted with AcOEt (×3). The combined organic layer was washed with sat. NH_4Cl solution (×1) and brine (×1), and then dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude benzylguanidine **40** (276 mg) was used for the next reaction without purification. IR (KBr) ν_{max} 2935, 1740, 1629, 1456, 1384, 1176, 1060 cm^{-1}. MS (EI) m/z 613 (M$^+$), 554 (M–OAc). HRMS (EI) for $C_{35}H_{39}O_7N_3$ (M$^+$), calcd 613.2788, found 613.2772.

4.1.27. Acetyl dibenzylguanidine 41. A solution of the crude dibenzylguanidine **40** (276 mg) in pyridine (5 mL), acetic anhydride (2.5 mL) and Et_3N (0.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with toluene, and concentrated in vacuo. The residue was purified by column chromatography (silica gel 15 g, ether/hexane=3:1→5:1) to give acetyl dibenzylguanidine **41** (218 mg, 85%, 3 steps from **38**) as a light yellow amorphous solid. IR (KBr) ν_{max} 3352, 2936, 1741, 1675, 1645, 1354, 1249, 1216, 1087, 1066 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (3H ×1/2, s, CH_3), 1.57 (3H ×1/2, s, CH_3), 1.58(3H ×1/2, s, *Ac*), 1.61 (3H ×1/2, s *Ac*), 1.66 (1H ×1/2, dd, J=16.5, 11 Hz, Me–C–CH_{ax}H$_{eq}$), 1.73 (1H ×1/2, dd, J=16.5, 11 Hz, Me–C–CH_{ax}-H$_{eq}$), 1.96 (3H ×1/2, s, *Ac*), 2.00 (3H ×1/2, s, *Ac*), 2.17 (1H ×1/2, br dd, J=16.5, 8 Hz, Me–C–CH$_{ax}$$H_{eq}$), 2.23 (1H ×1/2, br dd, J=16.5, 8 Hz, Me–C–CH$_{ax}$$H_{eq}$), 3.31 (1H ×1/2, ddd, J=11, 8, 3.5 Hz, CH), 3.36 (3H ×1/2, s, OCH_3), 3.45 (3H ×1/2, s, OCH_3), 3.48 (1H ×1/2, ddd, J=11, 8, 3.5 Hz, CH), 3.85 (1H ×1/2, d, J=14 Hz, CH_AH$_B$–Ph), 3.90 (1H ×1/2, s, MeO–CH–O–CH), 3.97–4.10 (1H, m, CH_CH$_D$–Ph), 4.01 (1H ×1/2, br d, J=2.5 Hz, BnO–CH–CH), 4.03 (1H ×1/2, d, J=14 Hz, CH_AH$_B$–Ph), 4.21–4.35 (1H, m, CH$_C$$H_D$–Ph), 4.30 (1H ×1/2, d, J=11 Hz, CH_EH$_F$–Ph), 4.31 (1H ×1/2, d, J=2.5 Hz, BnO–CH), 4.43 (1H ×1/2, d, J=4 Hz, MeO–CH), 4.46 (1H ×1/2, d, J=11 Hz, CH_EH$_F$–Ph), 4.71 (1H ×1/2, d, J=11 Hz, CH$_E$$H_F$–Ph), 4.75 (1H ×1/2, d, J=11 Hz, CH$_E$$H_F$–Ph), 5.05 (1H ×1/2, d, J=14 Hz, CH$_A$$H_B$–Ph), 5.22 (1H ×1/2, d, J=4 Hz, MeO–CH), 5.22 (1H ×1/2, d, J=14 Hz, CH$_A$$H_B$–Ph), 5.34 (1H ×1/2, s, MeO–CH–O–CH), 5.37 (1H ×1/2, br d, J=2.5 Hz, BnO–CH–CH), 5.39 (1H ×1/2, d, J=2.5 Hz, BnO–CH), 7.06–7.36 (15H, m, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.25, 21.32, 21.38, 21.43, 22.73, 22.75, 27.59, 27.77, 40.17, 40.52, 48.78, 49.47, 52.43, 52.45, 57.45, 57.83, 63.92, 64.00, 67.48, 68.43, 70.54, 70.78, 76.59, 76.81, 78.02, 78.37, 80.78, 80.84, 107.88, 108.66, 126.78, 126.86, 126.91, 127.79, 128.10, 128.16, 128.30, 128.37, 128.49, 128.52, 128.55, 128.63, 128.77, 128.91, 129.09, 136.47, 136.64, 136.79, 140.13, 140.23, 145.26, 146.20, 168.33, 168.58, 169.08, 170.47. MS (EI) m/z 655 (M$^+$), 612 (M–Ac). HRMS (EI) for $C_{37}H_{41}O_8N_3$ (M$^+$), calcd 655.2893, found 655.2879.

4.1.28. Diacetylguanidine 42. To a solution of the acetyl dibenzylguanidine **41** (266 mg, 0.406 mmol) in acetic anhydride (10 mL) was added 20% palladium hydroxide on carbon (Pearlman's catalyst, ca. 30 mg), and the reaction flask was replaced with hydrogen. The mixture was vigorously stirred under atmospheric pressure of hydrogen at rt for 3 days. The reaction mixture was filtered through a pad of Super-Cel, and the precipitate was washed with AcOEt. The combined filtrate was diluted with toluene, and concentrated in vacuo. The TLC analysis of the residue indicated the reaction was not completed. The residue was again dissolved in acetic anhydride (10 mL), and 20% palladium hydroxide on carbon (Pearlman's catalyst, ca. 30 mg) was added. The reaction flask was replaced with hydrogen. The mixture was vigorously stirred under atmospheric pressure of hydrogen at rt for 5 days. The reaction mixture was filtered through a pad of Super-Cel, and the precipitate was washed with AcOEt. The combined filtrate was diluted with toluene, and concentrated in vacuo. Purification by column chromatography (silica gel 15 g, acetone/CH_2Cl_2=1:20→1:10→1:5) gave diacetylguanidine **42** (154 mg, 81%) as a white amorphous solid. $[\alpha]_D^{27}$=−128° (c 0.66, $CHCl_3$). IR (KBr) ν_{max} 1756, 1618, 1371, 1214, 1043 cm^{-1}. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.68 (3H, s, CH_3), 1.75 (1H, dd, J=16.5, 10.5 Hz, Me–C–C$H_{ax}H_{eq}$), 2.08 (3H, s, *Ac*), 2.13 (3H, s, *Ac*), 2.15 (3H, s, *Ac*), 2.20 (3H, s, *Ac*), 2.48 (1H, ddd, J=16.5, 7.5, 1 Hz, Me–C–C$H_{ax}H_{eq}$), 3.50 (3H, s, OCH_3), 3.78 (1H, dddd, J=10.5, 7.5, 4, 0.5 Hz, –C*H*–), 4.34 (1H, d, J=0.5 Hz, MeO–CH–O–C*H*), 5.03 (1H, dd, J=2, 1 Hz, AcO–CH–C*H*), 5.27 (1H, d, J=4 Hz, MeO–C*H*), 6.50 (1H, d, J=2 Hz, AcO–C*H*–CH), 9.31 (1H, br s, N*H*), 13.04 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 22.2, 22.4, 24.9, 27.3, 28.9, 41.0, 57.8, 63.5, 64.6, 77.7, 79.1, 80.9, 108.1, 154.1, 167.3, 169.3, 169.7, 173.2, 185.6. MS (FAB) *m/z* 470 (M+H), 438 (M–OMe), 410 (M–OAc). Anal. calcd for $C_{20}H_{27}O_{10}N_3$: C, 51.17; H, 5.80; N, 8.95. Found C, 51.00; H, 5.61; N, 8.72.

4.1.29. 5,11-Dideoxytetrodotoxin (2), 4-*epi*-5,11-dideoxytetrodotoxin (43) and 4,9-anhydro-5,11-dideoxytetrodotoxin (26). To a solution of the diacetylguanidine **42** (20 mg, 0.0043 mmol) in H_2O (0.8 mL) and MeOH (0.4 mL) was added NH_4OH (28%, 0.4 mL). After stirring at rt for 20 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (2 mL) and TFA (1 mL). After stirring at rt for 34 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by HPLC on a Hitachi-gel #3013-c column (H^+ form, 0.4×15 cm, 0.05N AcOH) to give 5,11-dideoxytetrodotoxin **2** (4.3 mg, 29%), 4-*epi*-5,11-dideoxytetrodotoxin **43** (2.4 mg, 16%) and 4,9-anhydro-5,11-dideoxytetrodotoxin **26** (5.0 mg 36%) as a white solid, respectively. **2**. $[\alpha]_D^{27}=-8.8°$ (*c* 0.22, aq. 0.05N HOAc). IR (KBr) ν_{max} 3347, 1734, 1670, 1616, 1559, 1419, 1121 cm^{-1}. ^{1}H and ^{13}C NMR data were shown in Table 1. MS (FAB) *m/z* 288 (M+H), 270 (M–OH). HRMS (FAB) for $C_{11}H_{18}O_6N_3$ (M+H), calcd 288.1195, found 288.1195. **43**. $[\alpha]_D^{26}=-46°$ (*c* 0.12, aq. 0.05N HOAc). IR (KBr) ν_{max} 3449, 1734, 1669, 1618, 1560, 1420, 1121 cm^{-1}. ^{1}H NMR (600 MHz, 4% CD_3COOD/D_2O) δ 1.39 (3H, s, CH_3), 1.47 (1H, dd, J=15.9, 13.8 Hz, Me–C–C$H_{ax}H_{eq}$), 1.81 (1H, ddd, J=15.9, 4.0, 1.5 Hz, Me–C–C$H_{ax}H_{eq}$), 2.70 (1H, dt, J=13.8, 4.0 Hz, C*H*), 4.37 (1H, dd, J=2.1, 1.5 Hz, COO–C*H*), 4.48 (1H, d, J=2.1 Hz, COO–CH–C*H*–OH), 4.71 (1H, s, OCO–C*H*–OH), 4.95 (1H, d, J=4.0 Hz, NH–C*H*–OH). ^{13}C NMR (150 MHz, 4% CD_3COOD/D_2O) δ 27.6, 33.5, 39.3, 60.4, 70.9, 72.2, 74.1, 74.7, 87.5, 156.0, 176.4. MS (FAB) *m/z* 288 (M+H), 270 (M–OH). HRMS (FAB) for $C_{11}H_{18}O_6N_3$ (M+H), calcd 288.1195, found 288.1203. **26**. $[\alpha]_D^{26}=-22°$ (*c* 0.25, aq. 0.05N HOAc). IR (KBr) ν_{max} 3357, 1735, 1675, 1560, 1411 cm^{-1}. ^{1}H NMR (600 MHz, 4% CD_3COOD/D_2O) δ 1.24 (1H, dd, J=16.2, 11.6 Hz, Me–C–C$H_{ax}H_{eq}$), 1.36 (3H, s, CH_3), 2.11 (1H, ddd, J=16.1, 7.1, 1.0, Hz, Me–C–C$H_{ax}H_{eq}$), 2.80 (1H, dd, J=11.6, 7.1 Hz, C*H*), 4.52 (1H, dd, J=2.7, 1.0 Hz, COO–C*H*), 4.86 (1H, d, J=2.7 Hz, COO–CH–C*H*–OH), 5.04 (1H, s, OCO–C*H*–O), 5.27 (1H, s, NH–C*H*–O). ^{13}C NMR (150 MHz, 4% CD_3COOD/D_2O) δ 28.0, 32.5, 42.7, 63.0, 65.5, 74.3, 84.3, 86.8, 87.1, 156.8, 172.4. MS (FAB) *m/z* 270 (M+H). HRMS (FAB) for $C_{11}H_{16}O_5N_3$ (M+H), calcd 270.1090, found 270.1092.

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References

1. Review: (a) Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel. Kao, C. Y., Lovinson, S., Eds. *Ann. N.Y., Acad. Sci. New York*, **1986**, *479*, 1–355 (b) Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*, Pergamon, 1999; pp 480–489.
2. (a) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059–2088. (b) Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, R.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull.* **1964**, *12*, 1357–1374. (c) Woodward, R. B. *Pure. Appl. Chem.* **1964**, *9*, 49–74.
3. Narahashi, T.; Moore, J. W.; Scott, W. R. *J. Gen. Physiol.* **1964**, *47*, 965–974.
4. (a) Narahashi, T. *Physiol. Rev.* **1974**, *54*, 813–889. (b) Hucho, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 39–50.
5. Fuhrman, F. A. Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel. Kao, C. Y., Lovinson, S., Eds. *Ann. N.Y. Acad. Sci. New York* **1986**, *479*, 1–14.
6. (a) 5,6,11-Trideoxytetrodotoxin (**4**): Yotsu-Yamashita, M.; Yamagishi, Y.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *51*, 9329–9332. (b) 1-Hydroxy-5,11-dideoxytetrodotoxin (**5**): Kotaki, Y.; Shimizu, Y. *J. Am. Chem. Soc.* **1993**, *115*, 827–830. (c) 11-Deoxytetrodotoxin (**3**) and 6-*epi*-17-tetrodotoxin: Yasumoto, T.; Yotsu, M.; Murata, M.; Naoki, M. *J. Am. Chem. Soc.* **1988**, *110*, 2344–2345.
7. (a) Nakayama, H.; Hatanaka, Y.; Takai, M.; Yoshida, E.; Kanaoka, Y. *Ann. N.Y. Acad. Sci.* **1993**, *707*, 349. (b) Lipkind, G. M.; Fozzard, H. A. *Biophys. J.* **1994**, *66*, 1–13.
8. (a) Shimizu, Y.; Kobayashi, M. *Chem. Pharm. Bull.* **1983**, *31*, 3625–3631. (b) Shimizu, Y. *Ann. N.Y. Acad. Sci. New York* **1986**, *479*, 24–31.
9. (a) Matsui, T.; Yamamori, K.; Furukawa, K.; Kono, M. *Toxicon* **2000**, *38*, 463–468. (b) Yasumoto, T. *Chemistry Today (Gendai Kagaku)* **1994**, *282*, 47–52 (in Japanese).
10. Matsumura, K. *Nature* **1995**, *378*, 563–564.
11. For examples of some labeled tetrodotoxin derivatives, see: (a) Balerna, M.; Lombet, A.; Chicheportiche, R.; Romey, G.; Lazdunski, M. *Biochim. Biophys. Acta* **1981**, *644*, 219–225. (b) Bontemps, J.; Cantineau, R.; Grandfils, C.; Leprince, P.; Dandrifosse, G.; Schoffeniels, E. *Anal. Biochem.* **1984**, *139*, 149–157. (c) Wu, B. Q.; Yang, L.; Kao, C. Y.; Levinson, S. R.; Yotsu-Yamashita, M.; Yasumoto, T. *Toxicon* **1996**, *34*, 407–416.
12. For leading references from other laboratories, see: (a) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960–5968. (b) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 1609–1618. (c) Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *J. Chem. Lett.* **1991**, 1559–1562. (d) Nachman, R. J.; Hönel, M.; Williams,

T. M.; Halaska, R. C.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 4802–4806. (e). Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B. *J. Org. Chem.* **1983**, *48*, 3621–3626 see also 3627–3631. (f). Upreslacis, J., Ph.D. Thesis, Harvard University, 1975.

13. (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217–9219. (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219–9221.
14. Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3081–3084.
15. Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Fukuda, Y.; Isobe, M. *Tetrahedron* **2001**, *57*, 3875–3883.
16. Isobe, M.; Yamamoto, N.; Nishikawa, T. In *Levoglucosenone and Levoglucosans, Chemistry and Applications*, Witczak, Z. J., Ed.; ATL, 1994; pp 99–118.
17. (a) Isobe, M.; Nishikawa, T.; Pikul, S.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 6485–6488. (b) Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron* **1998**, *54*, 6639–6650.
18. Yamamoto, N.; Nishikawa, T.; Isobe, M. *Syn. lett.* **1995**, 505–506.
19. (a) Yamamoto, N.; Isobe, M. *Chem. Lett.* **1994**, 2299–2302. (b) Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **1999**, *55*, 4325–4340.
20. For review, see: (a) Bulman Page, P. C.; McCarthy, T. J. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 7, pp 83–117. (b) Woggon, W.-D. *Stereoselective Synthesis E 21 (Houben-Weyl.)*, Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 8, pp 4947–4956.
21. For the review of S_N2' reactions, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1930.
22. The stereochemistry of **11** has strongly been supported by a long-range coupling (J=2.5 Hz) observed between 7-H_{eq} and 5-H_{eq}. The diaxial orientation of these two bromides seems to be compensated due to their dipole–dipole interaction.
23. (a) Gent, P. A.; Gigg, R.; May, S.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2748–2750. (b) Pauls, H. W.; Fraser-Reid, B. *Carbohydr. Res.* **1986**, *150*, 111–119.
24. Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848–5849.
25. Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368–4378.
26. (a) Henbest, H. B.; Wilson, R. A. *J. Chem. Soc.* **1959**, 1958–1965. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
27. Carisen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
28. Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437–2449.
29. (a) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818–2819. (b) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549–557. (c) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657–2658.
30. Petrov, J.; Atanassova, I.; Balabanova, A.; Mollov, N. *Izv. Khim.* **1990**, *23*, 53–57.
31. Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790–791.
32. Appel, R.; Kleinstück, R.; Ziehn, K. D. *Chem. Ber.* **1971**, *104*, 1335–1336.
33. The lability of the acetoxy group at the C-9 position was reported in Kishi's total synthesis of tetrodotoxin. See: (a) Ref. 13(b). (b)Tanino, H.; Inoue, S.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1974**, *15*, 335–338.
34. (a) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179. (b) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586–3588.
35. The mixed solvent of Ac_2O and Et_3N used in the model experiments gave unreproducible results.