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Total Synthesis of (−)- and (+)-Decarbamoyloxysaxitoxin and (+)-Saxitoxin

Osamu Iwamoto, Ryoko Shinohara, and Kazuo Nagasawa*[a]

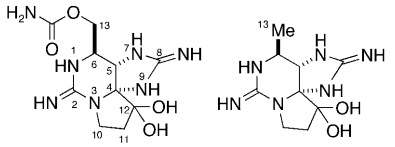
Dedicated to Professor Tadashi Nakata on the occasion of his 65th birthday

Abstract: Enantioselective total syntheses of (−)- and (+)-decarbamoyloxysaxitoxin (doSTX) and (+)-saxitoxin (STX) were achieved. The characteristic spiro-fused cyclic guanidine structure of STX was constructed by oxidation at the C4 position with IBX via an α-iminium carbonyl intermediate and acid-promoted cyclization of guanidine at the C5 position. A second-generation methodology was developed for the synthesis of STX, featuring discriminative reduction of the nitro group and N−O bond in nitroisoxazolidine. This approach provides efficient access to the key diamine intermediate for STXs.

Keywords: 1,3-dipolar cycloaddition · guanidine · oxidation · natural products · total synthesis

Introduction

The voltage-dependent sodium channel plays a critical role in depolarization and conduction in most excitable cells.[1] Saxitoxin (**1**; STX; Figure 1), isolated from poisonous shellfish,[2] is a neurotoxin that blocks ion influx through the voltage-dependent sodium channel by binding to the site-I region.[3] Many natural STX analogues have been reported, and each of them shows characteristic biological activity towards the sodium channel.[4] The key structural features of STXs lie in the bis(guanidine) functional group that constructs the compact spiro- and fused-ring system, and a ketone hydrate stabilized by the neighboring guanidine group. The complicated structure of STX and its biological importance as a pharmacological tool for ion channel studies have greatly attracted synthetic chemists. The first total synthesis of (+/−)-**1** was reported by Kishi and co-workers in 1977.[5] Jacobi and co-workers also synthesized (+/−)-**1** by the intramolecular 1,3-dipolar cycloaddition of azomethine imine to an imidazolone.[6] Recently, Du Bois and co-workers succeeded in the synthesis of (+)-STX (**1**) by using catalytic C−H amination methodology.[7] Other natural STX analogues of (−)-dcSTX and (+)-GTX3 were also synthesized by Kishi and Du Bois, respectively.[8] We are interested in the development of isoform-selective sodium channel inhibitors and therefore started a project to synthesize STX derivatives.[9] We recently reported a synthesis of the decarbamoyloxy analogue of **1**, (−)-decarbamoyloxysaxitoxin (doSTX, *ent*-**2**), a putative unnatural form, by utilizing α-iminium carbonyl formation with *o*-iodoxybenzoic acid (IBX).[10] Herein, we present full details of our synthetic studies on (−)-doSTX (**2**), and synthesis of the natural form of (+)-**2**. We also report a synthesis of (+)-STX (**1**) based upon our second-generation strategy for STXs.



	R^1	R^2	R^3	R^4
dcSTX	H	H	H	OH
neoSTX	OH	H	H	$OCONH_2$
GTX1	OH	H	OSO_3H	$OCONH_2$
GTX2	H	H	OSO_3H	$OCONH_2$
GTX3	H	OSO_3H	H	$OCONH_2$
GTX4	OH	OSO_3H	H	$OCONH_2$

Figure 1. Structures of STX (**1**) and its analogues.

[a] O. Iwamoto, R. Shinohara, Prof. Dr. K. Nagasawa
Department of Biotechnology and Life Science
Tokyo University of Agriculture and Technology
2-24-16 Naka-cho, Koganei, Tokyo 184-8588 (Japan)
Fax: (+81) 42-388-7295
E-mail: knaga@cc.tuat.ac.jp

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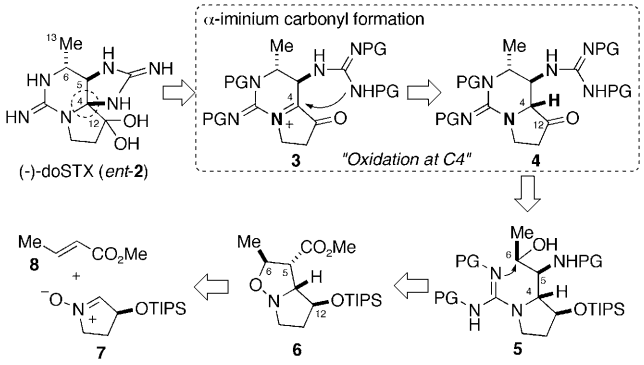
Results and Discussion

Synthesis of (−)- and (+)-doSTX (2)

Decarbamoyloxysaxitoxin (doSTX; **2**) was isolated from the Australian shellfish *Gymnodinium catenatum* in 1990.[11] The structure of doSTX (**2**) contains the common skeleton of all the natural STX analogues. Although the absolute stereochemistry of **2** has not yet been reported, it seems likely to be the same as that of STX (**1**). Our synthetic plan is illustrated in Scheme 1. The stereochemistry at C5 and C6 in **2**

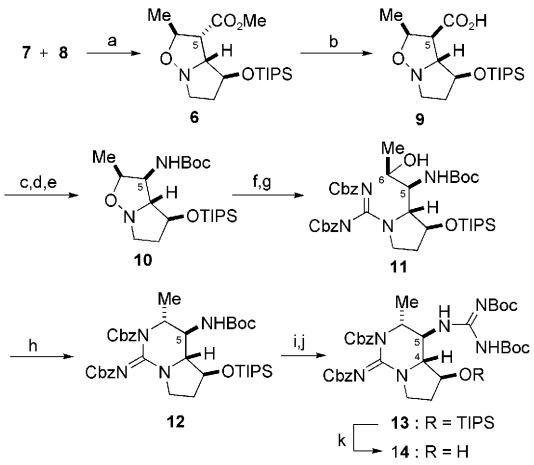


Scheme 1. Retrosynthetic analysis for (−)-doSTX (ent-**2**). PG = protecting group, TIPS = triisopropylsilyl.

are controlled by the chiral center in **7**,[12] which corresponds to the ketone hydrate at C12 in **2**, by the intermolecular 1,3-dipolar cycloaddition reaction of **7** with methyl crotonate (**8**). Construction of the characteristic bis-bicyclic guanidine structure is a challenging issue in the synthesis of STXs. We planned to cyclize the guanidine at C4 to generate the skeleton of **2** via the α-iminium cation **3**, which could be formed by the oxidation of ketone **4**.

The bis-monocyclic guanidine **14** was synthesized as follows (Scheme 2): The 1,3-dipolar cycloaddition reaction of chiral nitrone **7** with methyl crotonate (**8**) gave the isoxazolidine **6** stereoselectively in 93% yield.[13] Isomerization of the pseudoaxially oriented stereochemistry at C5 and subsequent hydrolysis of the ester group in **6** proceeded upon treatment with lithium hydroxide in aqueous THF at 0°C to give the carboxylic acid **9**. When this reaction was run at

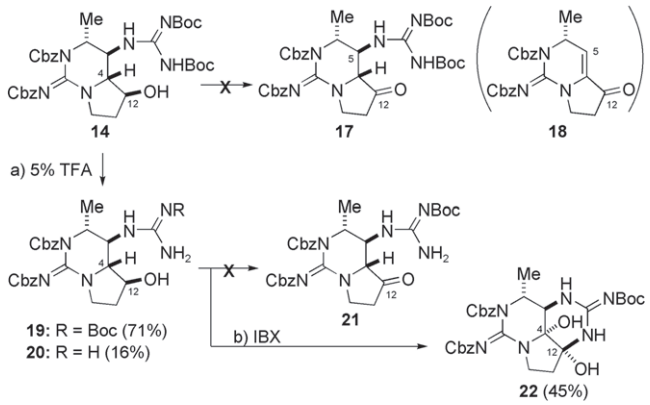
Abstract in Japanese:
ナトリウムチャネル阻害活性を有するサキシトキシン（STX）(**1**)の不斉全合成を達成した。本合成では、ニトロアルケン(**3**)と光学活性なニトロン(**2**)との1,3-双極子環化反応により得られるニトロ-イソキサゾリジン(**4**)に対し、ニトロ基とN-O結合を区別しながら還元する手法を確立した。これにより、STX類の合成中間体を効率よく得ることができるようになった。さらにIBXを用いたC4位の酸化反応を用いることで、STX(**1**)の全合成を達成した。



Scheme 2. Synthesis of bis-monocyclic guanidine alcohol **14**. Reagents and conditions: a) toluene, 80°C (93%); b) LiOH, THF/H_2O, 0°C; c) $(COCl)_2$, DMF (cat.), toluene; d) NaN_3, acetone/H_2O, 0°C; e) 1,4-dioxane, 100°C, then 10% HCl, then $(Boc)_2O$, K_2CO_3, (86% from **6**); f) H_2, $Pd(OH)_2$/C, MeOH; g) NCbz=C(SMe)NHCbz (**15**), $HgCl_2$, Et_3N, DMF; h) DEAD, Ph_3P, toluene (97% three steps); i) TFA, CH_2Cl_2; j) NBoc=C(SMe)NHBoc (**16**), $HgCl_2$, Et_3N, DMF (77% two steps); k) TBAF, THF (92%). Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, DEAD = diethyl azodicaboxylate, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid.

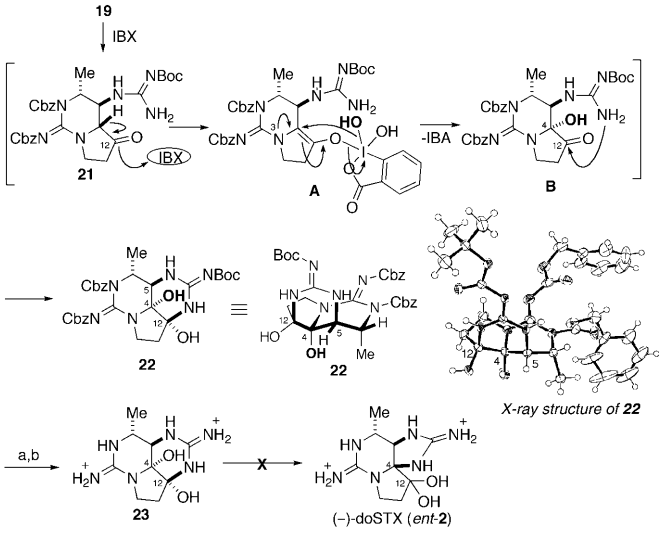
room temperature, the corresponding carboxylic acid **9** was obtained as a mixture with its C5 epimer (1:1). The carboxylic acid **9** was then converted into the *N*-Boc-protected amine **10** by Curtius rearrangement reaction: the carboxylic acid was treated with oxalyl chloride in toluene, and the resulting acid chloride was treated with sodium azide, followed by heating at 100°C in dioxane to give the corresponding amine, which was protected with Boc to give *N*-Boc-protected amine **10** in 86% yield. Direct protection of the amino group was attempted with addition of *t*BuOH to the isocyanate intermediate, but no reaction occurred. The reductive cleavage of the N−O bond of **10** was conducted with hydrogen in the presence of $Pd(OH)_2$, and a guanidine group was introduced into the resulting pyrrolidine derivative with bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea (**15**) and mercury(II) chloride to give guanidine **11**.[14] Cyclization of the guanidine group was conducted under the Mitsunobu reaction conditions with DEAD and triphenylphosphine to give cyclic guanidine **12** in 97% yield from **10**.[15] Deprotection of the Boc group of **12** with TFA, followed by reaction with bis(*tert*-butyloxycarbonyl)-2-methyl-2-thiopseudourea (**16**) in the presence of mercury(II) chloride, and deprotection of the TIPS ether with TBAF, gave the bis-monocyclic guanidine alcohol **14** in 71% yield from **12**.

After the bis-monocyclic guanidine alcohol **14** was obtained, cyclization of the guanidine at C4 through α-iminium carbonyl formation was examined by oxidation (Scheme 3). Prior to this conversion, oxidation of the alcohol at C12 was examined. We tried various oxidants, for example, chromium oxidants, 2,2,6,6-tetramethyl-l-piperidinoxyl (TEMPO), tetra-*n*-propylammonium perruthenate (TPAP), and Dess–Martin periodinane (DMP), but no reaction occurred, and



Scheme 3. Oxidation of C12 and C4. Reagents and conditions: a) 5% TFA/CH_2Cl_2 (**14**: 13%, **19**: 71%, **20**: 16%); b) IBX (4 equiv), DMSO, 70°C, (45%). IBX = *o*-iodoxybenzoic acid.

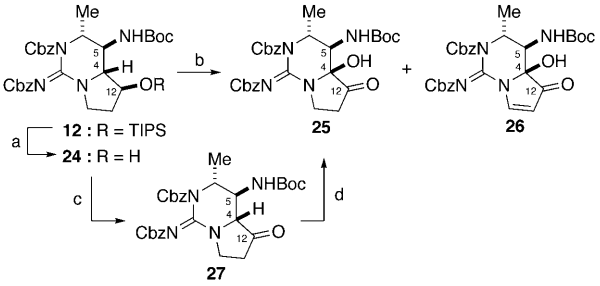
alcohol **14** was recovered quantitatively. Swern oxidation afforded enone **18** by elimination of the guanidine group at C5. We assumed that the bulky guanidine group with the two Boc protecting groups prevented the approach of the oxidants. Moreover, the character of the Boc group as an electron-withdrawing group promotes undesired β-elimination at the C5 guanidine group. Thus, deprotection of one of the Boc groups in **14** was examined. After many attempts, mono-Boc **19** was obtained in 71% yield with 5% TFA in dichloromethane, and **20** was obtained in 16% yield. Even with the mono-Boc **19**, various oxidants were ineffective for the oxidation at C12.[16] However, IBX was an exception. Treatment of the alcohol **19** with 4 equivalents of IBX in DMSO at 70°C did not give the desired ketone **21**, but an unexpected fused-type guanidine **22** was obtained in 45% yield as the sole product, the structure of which was confirmed by means of X-ray analysis (Scheme 4).[17]



Scheme 4. Proposed reaction mechanism of IBX oxidation and attempts at pinacol-type rearrangement of **23**. Reagents and conditions: a) TFA, CH_2Cl_2; b) H_2, $Pd(OH)_2$/C, MeOH; then HCl aq. (60% two steps). IBA = *o*-iodosobenzoic acid.

This unexpected formation of the bicyclic guanidine moiety in **22** was interpreted as follows (Scheme 4): After oxidation of the alcohol at C12 with IBX, the resulting ketone **21** simultaneously reacted with another molecule of IBX to form the enol intermediate **A**. Electron flow in this intermediate would take place to generate our expected α-iminium carbonyl cation, but the hydroxy group in IBX would attack intramolecularly at C4 (**A** to **B**), instead of the amino group in guanidine, to generate the fused-type bicyclic guanidine unit in **22**.[17,18] X-ray analysis of **22** revealed that the hydroxy group at C4 and the C–N bond at C12 are in an antiperiplanar orientation. Thus, conversion of **22** into *ent*-**2** was expected by a pinacol-type rearrangement reaction. Removal of the Boc and Cbz protecting groups by treatment with TFA and subsequent reduction with hydrogen in the presence of $Pd(OH)_2$ afforded fused-type guanidine **23**, the conformational structure of which was confirmed to be similar to that of **22** by ^{1}H NMR spectroscopy. Exposure of **22** to various acidic conditions (e.g., aq. H_2SO_4, aq. 7.5 N HCl, 100°C, under vacuum at 180°C,[19] or AcOH/TFA, 50°C[5a]) unfortunately resulted in no reaction.

Although the desired bicyclic guanidine formation from **19** and **23** failed, we were pleased to find that the oxidation of ketone **21** occurred to generate the α-iminium carbonyl compound and a hydroxy group could be installed selectively at C4. Therefore, we decided to apply this IBX oxidation reaction to **24**, prior to introduction of the C5 guanidine group (Scheme 5). Alcohol **24** was obtained by deprotection

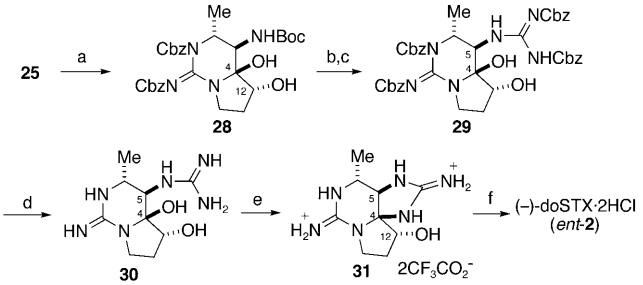


Scheme 5. Synthesis of aminal **25**. Reagents and conditions: a) TBAF, THF, 0°C (94%); b) IBX (4 equiv), DMSO, 70°C (**25**: 28%, **26**: 29%, **24**: 30%); c) $(COCl)_2$ (10 equiv), DMSO (12 equiv), Et_3N (30 equiv), CH_2Cl_2, −78°C; d) IBX (1.1 equiv), DMSO, 50°C (**25**: 64%, **26**: 0% two steps).

of the TIPS ether of **12** with TBAF at 0°C in 94% yield. IBX oxidation (4 equiv) of alcohol **24** in DMSO at 70°C gave the aminal **25** in 28% yield, together with a further oxidized product **26** (29% yield). Interestingly, ketone **27**, an intermediate for **25**, was not observed in this reaction, despite recovery of the starting material **24** in 30% yield. It seemed that the reactivity of ketone **27** with IBX is significantly higher than that of alcohol **24** or aminal **25**. Stepwise oxidation of **24** was examined to obtain the desired aminal **25** selectively. Thus, oxidation of alcohol **24** was employed with a large excess (10 equiv) of Swern reagent to give **25**.[20] The resulting ketone was treated with a limited amount of

IBX reagent (1.1 equiv) at 50 °C to give aminal **25** in 64 % yield as a sole product.

The total synthesis of (−)-doSTX (*ent*-**2**) was achieved from **25** as follows (Scheme 6): Treatment of **25** with sodium borohydride at 0 °C diastereoselectively gave the alcohol,

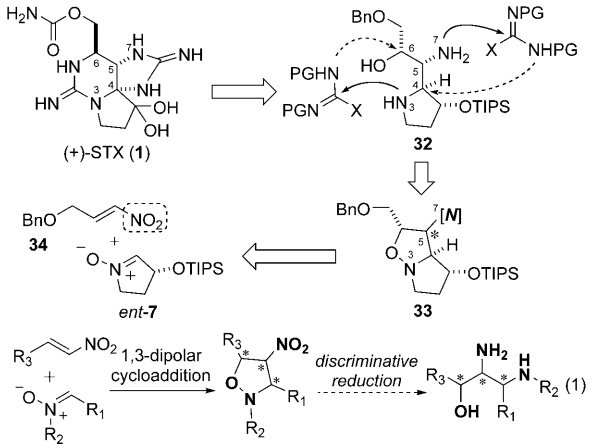


Scheme 6. Completion of the synthesis of (−)-doSTX (*ent*-**2**). Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C (72 %); b) TFA, CH_2Cl_2; c) NCbz=C(SMe)NHCbz (**16**), $HgCl_2$, Et_3N, DMF (82 % two steps); d) H_2, $Pd(OH)_2$/C, MeOH/EtOAc (2:1); e) TFA, 50 °C (60 % two steps); f) DMSO, diisopropylcarbodiimide, pyridinium trifluoroacetate (63 %).

the Boc protecting group of which was removed with TFA, and a Cbz-protected guanidine group was introduced to give **29**.[17] Removal of the four Cbz protecting groups with hydrogen in the presence of $Pd(OH)_2$ and subsequent treatment with TFA at 50 °C gave the decarbamoyloxysaxitoxinol **31** in 60 % overall yield. Finally, oxidation of the alcohol with dimethylsulfoxide and diisopropylcarbodiimide afforded (−)-doSTX (*ent*-**2**) in 63 % yield.[4b] All the spectroscopic data of the synthetic material were consistent with the reported data for the natural product. The putative natural form of (+)-doSTX (**2**) was also synthesized from (−)-nitrone (*ent*-**7**) and **8** similarly to (−)-doSTX (*ent*-**2**). The optical rotation values of (−)-doSTX (*ent*-**2**) and (+)-doSTX (**2**) were −23.3 (c = 0.2, MeOH) and +20.0 (c = 0.3, MeOH), respectively.

Synthesis of (+)-STX (1)

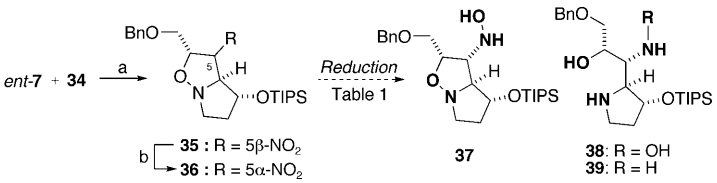
As described above, the synthesis of doSTX (**2**) was achieved by the 1,3-dipolar cycloaddition reaction of optically active nitrone **7** and **8**, and the direct oxidation at C4 of **24** with IBX via an α-iminium carbonyl intermediate. In this synthesis, the introduction of the nitrogen functional group at C5 of the 1,3-dipolar cycloaddition adduct **6** through Curtius rearrangement was tedious. Therefore, we developed a second-generation synthesis of natural (+)-STX (**1**), focusing on the direct introduction of an amino group at C5. The synthetic strategy is depicted in Scheme 7. (+)-STX (**1**) was expected to be obtained by introducing the guanidine group into the diamine **32** followed by cyclization of the resulting bis(guanidine) at C4 and C6, according to our previously developed route for STXs. In this synthesis, efficient preparation of the key diamine **32** makes the synthetic route more practical. For effective access to this key intermediate, direct and stereoselective introduction of amino groups at N3 and



Scheme 7. Synthetic plan for (+)-STX (**1**) through discriminative diamine synthesis. [N] = nitrogen-containing functional group.

N7 was planned by the use of the 1,3-dipolar cycloaddition reaction of nitrone *ent*-**7** with nitroalkene **34**.[21] There are some reports concerning this type of 1,3-dipolar cycloaddition reaction, although synthetic applications involving conversion of the resulting nitro and N−O groups in isoxazolidine into amino groups were not feasible because of the difficulty of differential reduction of these functional groups.[22] Therefore, this challenging transformation, that is, discriminative diamine synthesis [see Eq. (1) in Scheme 7], was further examined.

For the synthesis of nitroisoxazolidine **36**, 1,3-dipolar cycloaddition reaction of nitroalkene **34** with nitrone *ent*-**7** was employed (Scheme 8). The reaction proceeded under sol-



Scheme 8. Synthesis of nitroisoxazolidine **36**. Reagents and conditions: a) No solvent, 40 °C, 30 min (95 %); b) MeOH, MeONa, 0 °C (**35**:**36** = 5:95).

vent-free conditions at 40 °C within 30 minutes to give the *endo* adduct **35** in 95 % yield as a single diastereomer. The stereochemistry at C5 was epimerized with sodium methoxide in methanol at 0 °C to give **36** in a ratio of 95:5.

Next, selective reduction of the nitro group of **36** was examined (Table 1).[23] In the case of reaction with $NiCl_2$/$NaBH_4$, both the nitro group and N−O bond in isoxazolidine were reduced to give diamine **37** (Table 1, entry 1). In contrast, reaction of **36** with hydrogen in the presence of Raney Ni catalyst gave a mixture of diamine **39** and hydroxylamine **38** (Table 1, entry 2). Milder reduction conditions with Lindlar catalyst gave the desired hydroxylamine **37** together with a mixture of **38** and **39** (Table 1, entry 3). Selective reduction of the nitro group in **36** was achieved with zinc

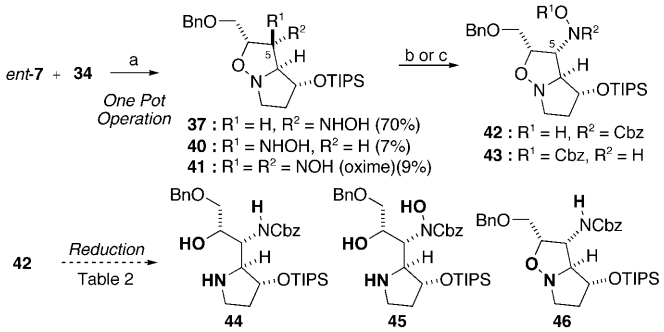
Table 1. Reduction of NO_2 group of **36**.[a]

Entry	Conditions	Product
1	$NiCl_2$, $NaBH_4$, RT	**39**
2	Raney Ni, H_2, RT	**38**, **39**
3	Lindlar cat., H_2	**37**, **38**, **39**
4	Zn powder, aq. HCl, 0 °C	**37**, **38**
5	Zn powder, AcOH, 0 °C	**37**

[a] Detected by ESI mass spectrometry.

powder in acetic acid, and hydroxylamine **37** was obtained (Table 1, entry 5).

Under these conditions, hydroxylamine **37** could be practically obtained (on a multigram scale) in 70% yield from *ent*-**7**.[24] These conversions, that is, 1) 1,3-dipolar cycloaddition reaction, 2) C5 isomerization, and 3) reduction of the NO_2 group, could be performed in one pot by successive addition of reagents without any work-up (Scheme 9). Prior to



Scheme 9. Synthesis of isoxazolidine **42**. Reagents and conditions: a) No solvent, 40 °C; then DBU, CH_2Cl_2, −60 °C; then Zn powder, AcOH, −60 °C→RT. (**37**: 70%, **40**: 7%, **41**: 9%); b) CbzCl, K_2CO_3 (3 equiv), CH_2Cl_2, 0 °C (**42**: 72%, **43**: 20%); c) CbzCl, K_2CO_3 (5 equiv), CH_2Cl_2, 0 °C; then MeOH, RT. (**42**: 87%, **43**: 0%). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

the second-step reduction, the amino group in hydroxylamine **37** was protected with a Cbz group using benzyloxycarbonyl chloride in the presence of potassium carbonate. In this reaction, mixtures of *N*-Cbz and *O*-Cbz compounds **42** and **43** were initially generated, but the mixture could be converted into *N*-Cbz **42** exclusively simply by treatment with methanol.

Next, reduction of two N−O bonds in **42** was investigated to obtain **44** (Table 2).[23] The reaction of **42** with Zn/aq. HCl gave only **45**, in which the N−O bond in isoxazolidine was cleaved (Table 2, entry 1). SmI_2 gave similar results

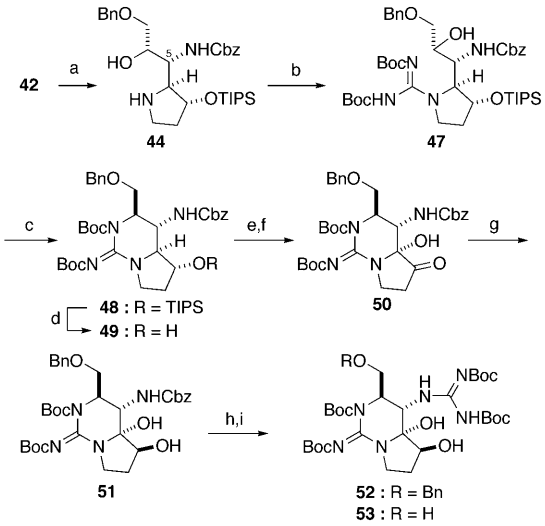
Table 2. Reduction of two N−O bonds in **42**.[a]

Entry	Reagent	Solvent	Temp.	Product
1	Zn	MeOH, aq. HCl	RT	**45**
2	SmI_2	THF	0 °C	**45**
3	$NiCl_2$, $NaBH_4$	MeOH	RT	**44**, **45**
4	$CoCl_2$, $NaBH_4$	MeOH	RT	**44**, **45**
5	$TiCl_3$, NaOAc	MeOH, aq. HCl	0 °C	**46**
6	$TiCl_3$, Zn, NaOAc	MeOH, aq. HCl	0 °C	**44**

[a] Detected by ESI mass spectrometry.

(Table 2, entry 2). In the case of $NiCl_2$/$NaBH_4$ or $CoCl_2$/$NaBH_4$, a mixture of **45** and the desired **44** was generated in very low yield (Table 2, entries 3 and 4). Interestingly, Miller's conditions, namely, $TiCl_3$ and NaOAc in MeOH/aq. HCl, were effective to reduce the N−O bond in hydroxylamine to give **46** as a sole product (Table 2, entry 5).[25] Therefore, a combination of the conditions in entries 1 and 5 of Table 2 (i.e., $TiCl_3$/NaOAc and zinc powder in MeOH/aq. HCl) was employed. We were pleased to find that this gave diamine **44** exclusively (Table 2, entry 6).

Since we had established a discriminative diamine synthesis of nitro isoxazolidine **36**, total synthesis of (+)-saxitoxin (**1**) was examined (Scheme 10). Guanidination of **44** with

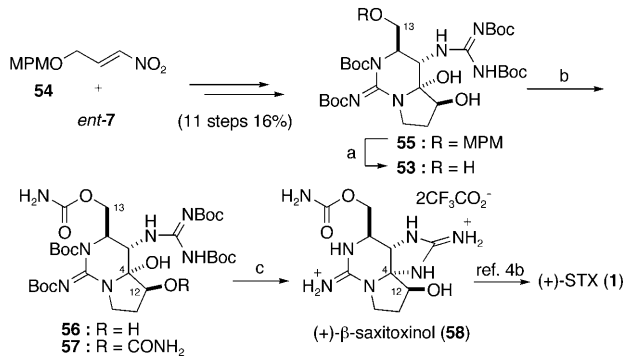


Scheme 10. Synthesis of bis(guanidine) **52**. Reagents and conditions: a) $TiCl_3$, Zn powder, NaOAc, aq. HCl, MeOH, CH_2Cl_2, 0 °C; b) NBoc=C(SMe)NHBoc (**16**), $HgCl_2$, Et_3N, DMF (60% two steps); c) $ClCH_2SO_2Cl$, iPr_2NEt, CH_2Cl_2 (98%); d) TBAF, THF, 0 °C (83%); e) $(COCl)_2$ (10 equiv), DMSO (12 equiv), Et_3N (30 equiv), CH_2Cl_2, −78 °C; f) IBX (1.1 equiv), DMSO, 50 °C (94%); e) $NaBH_4$, MeOH, 0 °C (77%); h) H_2, $Pd(OH)_2$/C, MeOH; i) NBoc=C(SMe)NHBoc (**16**), $HgCl_2$, Et_3N, DMF (92% two steps).

bis(*tert*-butyloxycarbonyl)-2-methyl-2-thiopseudourea (**16**) gave guanidine **47** in 60% yield from **42**. Subsequent cyclization by treatment with monochloromethanesulfonyl chloride and diisopropylethylamine gave cyclic guanidine **48** in 98% yield.[26] In this cyclization, Mitsunobu reaction conditions, which successfully gave the cyclized product in the synthesis of doSTX (**2**), yielded complex mixtures. Oxidation at C4 was conducted in the same way as for the doSTX synthesis. Thus, deprotection of the TIPS ether with TBAF followed by Swern oxidation of the resulting alcohol gave the corresponding ketone. Oxidation at the C4 position was performed with IBX (1.1 equiv) to give the aminal **50** in 94% yield from **49**. After reduction of the ketone in **50** with $NaBH_4$, the Cbz group was removed with hydrogen in the presence of $Pd(OH)_2$, and a Boc-protected guanidine group was introduced to the resulting amine with **16** and mercury (II) chloride to give **52** in 92% yield from **51**. Prior to the

construction of bicyclic guanidine structure, we planned to install the carbamoyl group at C13. Then, removal of the benzyl protecting group was examined. However, this deprotection was difficult under various conditions. Only reduction with hydrogen in the presence of $Pd(OH)_2$ catalyst gave alcohol **53** in 82% yield, and the reproducibility was poor.[27]

Therefore, we decided to change the benzyl group to a *p*-methoxybenzyl (MPM) group. Thus, the bicyclic guanidine bearing MPM ether **55** was synthesized from nitrone *ent*-**7** and nitroalkene **54** in a similar way to **55** in 16% yield over 11 steps (Scheme 11). The MPM group was cleanly deprotected with DDQ to give the alcohol in 90% yield. The resulting alcohol **53** was treated with trichloroacetyl isocyanate, followed by hydrolysis with potassium carbonate in MeOH to give **56** in 35% yield. In this reaction, bis(carbamoyl) **57** was also obtained in 20% yield. Finally, cyclization of guanidine and removal of the four Boc protecting groups of **57** proceeded simultaneously with boron tris(trifluoroacetate) in TFA to give an 88% yield of (+)-β-saxitoxinol (**58**),[7] which is known to be converted into (+)-saxitoxin (**1**) by oxidation at C12.[4b]



Scheme 11. Formal total synthesis of (+)-STX (**1**). Reagents and conditions: a) DDQ, CH_2Cl_2, H_2O (90%); b) $Cl_3CC(O)N=C=O$, CH_2Cl_2, then K_2CO_3, MeOH (**56**: 35%, **57**: 20%); c) $B(CF_3CO_2)_3$, TFA (88%). DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, MPM = *p*-methoxybenzyl.

Conclusions

In conclusion, total syntheses of (−)- and (+)-doSTX (**2**) and (+)-STX (**1**) have been achieved based upon oxidation at C4 with IBX. In the synthesis of (+)-STX (**1**), discriminative reduction of the nitro group and N−O bond in nitroisoxazolidine was newly developed to provide efficient access to the key diamine intermediate for STXs.

Experimental Section

General

Flash chromatography was performed on silica gel 60 (spherical, particle size 0.040–0.100 μm; Kanto). Optical rotations were measured on a JASCO DIP 1000 polarimeter using the sodium D line. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX 400 spectrometer. The spectra were referenced internally according to residual solvent signals of $CDCl_3$ (^1H NMR; $\delta = 7.26$ ppm, ^{13}C NMR; $\delta = 77.0$ ppm), D_2O (^1H NMR; $\delta = 4.79$ ppm), and CD_3CO_2D (^{13}C NMR; $\delta = 179.0$ ppm for CD_3CO_2D). Mass spectra were recorded on a JEOL JMS-T100X spectrometer in ESI-MS mode with methanol as solvent.

37, **40**, and **41**: Nitroolefin **34** (0.96 g, 4.99 mmol, 1 equiv) was added to the chiral nitrone *ent*-**7** (1.28 g, 4.99 mmol) at room temperature and stirred for 30 min at 40 °C without any solvent (1,3-dipolar cycloaddition). The mixture was then diluted with 50 mL of CH_2Cl_2 and cooled to −60 °C. DBU (803 μL, 5.70 mmol, 1.2 equiv) was added, and the solution was stirred for 1 h at that temperature (C5 isomerization). Then, AcOH (1.36 mL, 23.8 mmol) and freshly activated Zn powder (777 mg, 11.9 mmol) was added to the solution, and the resulting mixture was warmed to 0 °C over 5 h. The reaction was then quenched with saturated aq. $NaHCO_3$. and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a dark brown oil. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc; 10:1 to 4:1) to give 5α-hydroxylamine **37** (1.44 g, 70%), 5β-hydroxylamine **40** (140 mg, 7%), and oxime **41** (195 mg, 9%). **37**: $[\alpha]_D^{22} = +0.4$ ($c = 2.2$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.56$ (d, $J = 1.4$ Hz, 2H), 4.23 (dt, $J = 2.3$, 5.0 Hz, 1H), 4.15 (q, $J = 5.5$ Hz, 1H), 3.80 (m, 2H), 3.61 (m, 1H), 3.30 (m, 2H), 2.07 (dddd, $J = 5.5$, 7.3, 9.6, 12.8 Hz, 1H), 1.73 (dddd, $J = 1.8$, 3.7, 5.5, 12.8 Hz, 1H), 1.05 ppm (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.5$, 128.4, 127.9, 127.8, 77.9, 77.4, 73.7, 72.0, 68.3, 55.8, 34.4, 17.9, 12.0 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{23}H_{40}N_2O_4SiNa$ 459.2655, found 459.2695. **40**: $[\alpha]_D^{22} = +8.4$ ($c = 3.6$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (m, 5H), 4.70 (dt, $J = 3.7$, 6.9 Hz, 1H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.53 (d, $J = 11.9$ Hz, 1H), 3.96 (m, 2H), 3.69 (dd, $J = 3.7$, 7.3 Hz, 1H), 3.64 (dd, $J = 6.0$, 9.6 Hz, 1H), 3.54 (d, $J = 5.5$, 10.0 Hz, 1H), 3.26–3.38 (m, 2H), 2.12 (m, 1H), 1.78 (m, 1H), 1.06 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.7$, 128.4, 127.8, 127.7, 78.4, 77.2, 73.6, 72.5, 70.5, 70.1, 55.4, 35.0, 18.0, 12.3 ppm; HRMS (ESI, $M+H^+$) calcd for $C_{23}H_{41}N_2O_4Si$ 437.2836, found 437.2886. **41**: $[\alpha]_D^{22} = +44.5$ ($c = 2.4$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.49$ (br d, $J = 9.2$ Hz, 1H), 7.32 (m, 5H), 4.71 (d, $J = 5.0$ Hz, 1H), 4.65 (m, 2H), 4.54 (d, $J = 12.4$ Hz, 1H), 4.36 (s, 1H), 3.71 (dd, $J = 8.2$, 10.5 Hz, 1H), 3.57 (dd, $J = 3.2$, 10.5 Hz, 1H), 3.49 (dd, $J = 6.9$, 13.3 Hz, 1H), 3.39 (dt, $J = 5.0$, 13.3 Hz, 1H), 2.04 (m, 1H), 1.77 (m, 1H), 1.05 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.5$, 137.9, 128.3, 127.8, 127.6, 76.8, 75.8, 75.7, 73.3, 70.5, 56.0, 34.8, 18.0, 12.2 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{23}H_{38}N_2O_4SiNa$ 457.2499, found 457.2499.

42: CbzCl (518 μL, 3.63 mmol) was added to a solution of 5α-hydroxylamine **37** (1.44 g, 3.30 mmol) and K_2CO_3 (2.28 g, 16.5 mmol) in THF/H_2O (2:1, 30 mL) at 0 °C. The solution was stirred for 10 min at 0 °C, then methanol (30 mL) was added, and resulting mixture was warmed to room temperature. The reaction mixture was then concentrated in vacuo. The resulting material was diluted with EtOAc/H_2O and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow brown oil. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc; 8:1 to 2:1) to give *N*-benzyloxycarbonylhydroxylamine **42** (1.61 g, 87%). $[\alpha]_D^{22} = +18.0$ ($c = 3.6$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.82$ (br s, 1H), 7.22–7.35 (m, 10H), 5.19 (d, $J = 12.4$ Hz, 1H), 5.15 (d, $J = 11.9$ Hz, 1H), 4.92 (m, 1H), 4.48 (s, 2H), 4.33 (m, 1H), 4.14 (dq, $J = 3.4$, 5.5 Hz, 1H), 3.96, (t, $J = 2.8$ Hz, 1H), 3.84 (dd, $J = 11.0$, 5.5 Hz, 1H), 3.68 (dd, $J = 3.66$, 11.0 Hz, 1H), 3.40 (ddd, $J = 6.4$,9.2, 12.8 Hz, 1H), 3.16 (ddd, $J = 4.1$, 7.8,11.9 Hz, 1H), 2.02 (m,1H), 1.75 (m, 1H), 1.02 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.1$, 136.5, 135.9, 128.52, 128.47, 128.26, 128.11, 128.04, 77.4, 77.2, 76.5, 75.3, 74.1, 67.8, 67.1, 55.3, 33.9, 17.9, 17.8, 11.9 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{31}H_{46}N_2O_6SiNa$ 593.3023, found 593.3042.

47: $TiCl_3$/HCl (7.30 mL, 5.64 mmol) was added to a solution of *N*-benzyloxycarbonylhydroxylamine (1.61 g, 2.82 mmol), NaOAc (2.31 g, 28.2 mmol), and freshly activated Zn powder (1.84 g, 28.2 mmol) in CH_2Cl_2/MeOH at 0 °C under an N_2 atmosphere. The reaction mixture was stirred for 5 h, quenched with saturated aq. $NaHCO_3$, and extracted

with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give diamine **44** (1.49 g). $HgCl_2$ (766 mg, 2.82 mmol) was added to a solution of crude diamine **44** (1.49 g), bis(*tert*-butyloxycarbonyl)-2-methyl-2-thiopseudourea (**16**) (819 mg, 2.82 mmol) and Et_3N (1.18 mL, 8.46 mmol) in DMF (14 mL) at room temperature under an N_2 atmosphere. The reaction mixture was stirred for 1 h, diluted with EtOAc, and filtered through a pad of celite. The filtrates were washed with H_2O and brine twice. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give pyrrolidine as a yellow brown oil. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc; 15:1 to 5:1) to give guanidine **47** (1.35 mg, 60% steps). $[\alpha]_D^{22}=+5.6$ ($c=2.8$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=10.32$ (brs, 1H), 7.32 (m, 10H), 5.70 (brs, 1H), 5.44 (d, $J=9.6$ Hz, 1H), 5.09 (d, $J=12.4$ Hz, 1H), 5.04 (d, $J=12.4$ Hz, 1H), 4.49 (m, 1H), 4.47 (d, $J=11.9$ Hz, 1H), 4.42 (d, $J=11.9$ Hz, 1H) 4.38 (m, 1H), 3.92 (m, 2H), 3.58 (dq, $J=7.33$, 11.0 Hz, 1H), 3.50 (m, 2H), 3.36 (dd, $J=6.9$, 9.6 Hz, 1H), 2.36 (m, 1H), 1.49 (s, 9H), 1.44 (s, 9H), 0.97 ppm (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=161.3$, 157.6, 156.5, 150.2, 138.1, 136.4, 128.4, 128.3, 128.0, 127.9, 127.5, 82.3, 79.5, 73.3, 72.5, 70.8, 70.1, 66.8, 53.0, 46.8, 32.1, 28.1, 28.0, 17.8, 12.0 ppm; HRMS (ESI, M+H$^+$) calcd for $C_{42}H_{67}N_4O_9Si$ 799.4677, found 799.4637.

48: Chloromethanesulfonyl chloride (219 μL, 2.21 mmol) was added to a solution of guanidine **47** (352 mg, 0.441 mmol) and *i*Pr_2NEt (911 μL, 5.29 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C under an N_2 atmosphere. The reaction mixture was stirred for 12 h, quenched with saturated aq. $NaHCO_3$, and extracted with CH_2Cl_2 twice. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow brown oil. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc; 10:1 to 4:1) to give cyclic guanidine **48** (337 mg, 97%). $[\alpha]_D^{22}=+96.0$ ($c=2.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.32$ (m, 10H), 5.08 (m, 2H), 5.00 (d, $J=11.9$ Hz, 1H), 4.52 (d, $J=11.0$ Hz,1H), 4.42 (d, $J=2.3$ Hz, 1H), 4.35 (d, $J=10.5$ Hz, 1H), 4.25 (m, 1H), 4.00 (dt, $J=4.6$, 10.1 Hz, 1H), 3.84 (dd, $J=2.8$, 9.2 Hz,1H), 3.74 (dd, $J=4.6$, 9.2 Hz, 1H), 3.59 (dt, $J=6.7$, 11.0 Hz, 1H), 3.42 (m, 1H), 3.19 (d, $J=10.5$ Hz, 1H), 1.76 (m, 2H), 1.48 (s, 18H), 0.98 ppm (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.6$, 155.6, 151.8, 151.6, 138.1, 135.9, 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 82.6, 78.1, 74.1, 73.3, 71.6, 68.5, 67.2, 59.4, 54.4, 46.0, 32.5, 28.5, 28.1, 17.9, 12.0 ppm; HRMS (ESI, M+H$^+$) calcd for $C_{42}H_{65}N_4O_8Si$ 781.4572, found 781.4606.

49: TBAF (286 mg, 1.09 mmol) was added to a solution of cyclic guanidine **48** (569 mg, 0.729 mmol) in a solution of THF (14 mL) at 0 °C. The reaction mixture was stirred for 1 h at that temperature, quenched with saturated aq. NH_4Cl, and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc; 3:1 to 1:3) to give alcohol **49** (377 mg, 83%). $[\alpha]_D^{22}=+141.5$ ($c=2.7$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.32$ (m, 10H), 6.05 (brs, 1H), 5.11 (d, $J=12.4$ Hz, 1H), 5.07 (d, $J=12.4$ Hz, 1H), 4.48 (d, $J=10.1$ Hz, 1H), 4.34 (d, $J=10.1$ Hz, 1H), 4.21 (m, 1H), 4.11 (m, 1H), 4.01 (dt, $J=2.8$, 8.7 Hz, 1H), 3.85 (dd, $J=2.3$, 9.2 Hz, 1H), 3.74 (dd, $J=3.2$, 8.7 Hz, 1H), 3.54 (m, 1H), 3.36 (d, $J=10.1$ Hz, 1H), 3.02 (m, 1H), 1.71 (m, 2H), 1.45 (s, 9H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.1$, 156.2 ,152.0, 151.8, 137.9, 136.1, 128.5, 128.2, 128.1, 127.6, 83.4, 78.2, 73.7, 73.4, 71.9, 67.0, 65.5, 61.4, 54.8, 46.2, 31.4 ppm; HRMS (ESI, M+H$^+$) calcd for $C_{33}H_{44}N_4O_8$ 625.3237, found 625.3217.

51: $(COCl)_2$ (85 μL, 1.00 mmol) was slowly added to a solution of DMSO (85 μL, 1.2 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C under an N_2 atmosphere. The reaction mixture was stirred for 10 min, and then alcohol **49** (63 mg, 0.100 mmol) was added dropwise as a solution in CH_2Cl_2 (1.0 mL) over 15 min under an N_2 atmosphere. The reaction mixture was stirred for 1 h, then Et_3N (418 μL, 3.00 mmol) was added, and the mixture was stirred for 5 min, rapidly quenched with H_2O, and warmed to room temperature. The solution was extracted with CH_2Cl_2 three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude ketone (79 mg). IBX (31 mg, 0.110 mmol) was added to a solution of crude ketone (79 mg) in DMSO (1.0 mL), and the resulting suspension was stirred for 20 min at room temperature. Then, the reaction mixture was warmed to 50 °C and stirred for a further 1 h. The reaction was quenched with 10% aq. $Na_2S_2O_3$ and saturated aq. $NaHCO_3$, and the solution was diluted with EtOAc. The organic layer was separated and washed with saturated aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give aminal **50** (60 mg, 94%) as an inseparable mixture of its C12 hydrate. $NaBH_4$ (4 mg, 0.094 mmol) was added to a solution of aminal **50** (60 mg, 0.096 mmol) in methanol (2.0 mL) at 0 °C. After stirring for 30 min, the reaction mixture was quenched with H_2O, and the solution was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give alcohol **51** (46 mg, 77%). $[\alpha]_D^{22}=+75.9$ ($c=2.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$ (m, 10H), 5.55 (brd, $J=8.7$ Hz, 1H), 5.10 (d, $J=11.9$ Hz, 1H), 5.03 (d, $J=11.9$ Hz,1H), 4.57 (d, $J=11.9$ Hz, 1H), 4.53 (dd, $J=6.0$, 9.6 Hz, 1H), 4.47 (d, $J=11.6$ Hz, 1H), 4.18 (dt, $J=3.2$, 6.4 Hz, 1H), 4.05 (d, $J=2.75$, 1H), 3.87 (dd, $J=3.7$, 9.2 Hz, 1H), 3.82 (t, $J=9.2$ Hz, 1H), 3.66 (dd, $J=6.9$, 9.2 Hz, 1H), 3.51 (dt, $J=6.9$, 11.0 Hz, 1H), 2.14 (m, 1H), 1.87 (dd, $J=5.5$, 13.3 Hz, 1H), 1.44 (s, 9H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.0$, 157.2, 151.4, 148.8, 138.0, 035.6, 128.6, 128.4, 128.2, 128.1, 127.5, 127.4, 91.0, 83.2, 79.0, 76.9, 73.3, 71.7, 67.7, 57.0, 53.0, 46.3, 29.0, 28.2, 28.1 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{33}H_{44}N_4O_9Na$ 663.3006, found 663.3004.

52: 20% $Pd(OH)_2$/C (30 mg) was added under an N_2 atmosphere to a solution of alcohol **51** (99 g, 0.155 mmol) in methanol (5.0 mL), and the suspension was vigorously stirred under H_2 atmosphere (balloon) at room temperature. After 8 h, the reaction mixture was filtered through a pad of celite. The filtrates were concentrated in vacuo to give crude amine (84 mg). $HgCl_2$ (51 mg, 0.186 mmol) was added to a solution of amine (84 mg), Et_3N (65 μL, 0.465 mmol), and bis(*tert*-butyloxycarbonyl)-2-methyl-2-thiopseudourea (**16**) (54 mg, 0.186 mmol) in DMF (1.5 mL) at room temperature under an N_2 atmosphere. The reaction mixture was stirred for 1 h, diluted with EtOAc, and filtered through a pad of celite. The filtrates were washed with H_2O and brine twice. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow brown oil. The crude mixture was purified by chromatorex NH (Fuji Silysia) gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give bis(guanidine) **52** (106 mg, 92%). $[\alpha]_D^{22}=+50.5$ ($c=2.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.32$ (brs, 1H), 8.72 (brd, $J=8.2$ Hz, 1H), 7.25 (m, 5H), 6.87 (brs, 1H), 4.81 (dd, $J=5.5$, 8.7 Hz, 1H), 4.55 (d, $J=11.5$ Hz, 1H), 4.49 (d, $J=11.5$ Hz, 1H), 4.33 (m, 1H), 4.01 (m, 1H), 3.92 (dd, $J=4.6$, 9.2 Hz, 1H), 3.87 (m, 1H), 3.61 (m, 2H), 2.95 (brs, 1H), 2.20 (m, 1H), 1.98 (dd, $J=6.41$, 13.3 Hz, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.46 (s, 9H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=162.2$, 159.0, 156.0, 152.6, 151.1, 148.37, 138.0, 128.3, 127.4, 127.3, 91.5, 83.8, 83.2, 79.9, 79.0, 76.3, 73.1, 71.7, 56.8, 53.4, 46.4, 18.9, 28.2, 28.1, 28.0, 27.9 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{36}H_{56}N_6O_{11}Na$ 771.3905, found 771.3898.

55: $[\alpha]_D^{22}=+65.1$ ($c=1.9$, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.33$ (brs, 1H), 8.72 (brd, $J=8.7$ Hz, 1H), 7.19 (d, $J=8.7$ Hz, 2H), 6.88 (brs, 1H), 6.81 (d, $J=8.7$ Hz, 2H), 4.80 (dd, $J=5.5$, 8.7 Hz, 1H), 4.49 (d, $J=11.5$ Hz, 1H), 4.41 (d, $J=11.5$ Hz,1H), 4.32 (m, 1H), 4.01 (d, $J=3.8$ Hz, 1H), 3.89 (m, 2H), 3.78 (s, 3H), 3.61 (m, 2H), 2.15 (m, 1H), 2.00 (dd, $J=6.4$, 13.3 Hz, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.47 (s, 9H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=162.2$, 159.0, 158.9, 156.0, 152.6, 151.2, 148.3, 130.2, 128.9, 113.7, 91.4, 83.8, 83.3, 80.0, 79.1, 76.3, 72.9, 71.5, 56.9, 55.2, 53.3, 46.5, 28.9, 28.2, 28.1, 28.0, 27.9 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{37}H_{58}N_6O_{12}Na$ 801.4010, found 801.4010.

53: DDQ (86 mg, 0.381 mmol) was added to a solution of MPM ether **55** (64 mg, 0.095 mmol) in CH_2Cl_2/H_2O (2:1, 3.0 mL) at room temperature. The reaction mixture was stirred for 1 h, saturated aq. $NaHCO_3$ was added, and the resulting solution was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by Chromatorex NH (Fuji Silysia) gel column chromatography (hexane/EtOAc; 2:1 to pure EtOAc) to give alcohol **53** (47 mg, 90%). $[\alpha]_D^{22}=+52.1$ ($c=2.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.42$ (s, 1H), 8.69 (d, $J=9.16$ Hz, 1H), 6.68 (brs, 1H), 5.26 (brs, 1H), 4.60 (dd, $J=7.3$, 8.2 Hz, 1H), 4.12 (dt, $J=3.2$,

6.4 Hz, 1H), 3.98 (m, 2H), 3.82 (dd, J=8.2, 11.0 Hz, 1H), 3.47 (m, 1H), 2.2 (m, 1H), 2.00 (dd, J=6.0, 13.3 Hz, 1H), 1.50 (s, 9H), 1.49 (s, 9H), 1.47 (s, 9H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 161.7, 156.1, 152.8, 150.7, 150.3, 92.1, 84.2, 83.4, 80.3, 80.2, 77.2, 76.2, 61.3, 59.4, 51.0, 46.6, 29.1, 28.1, 28.0, 27.9 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{29}H_{50}N_6O_{11}Na$ 681.3435, found 681.3423.

56 and **57**: Trichloroacetyl isocyanate (3.0 μL, 0.025 mmol) was added to a solution of alcohol **53** (15 mg, 0.023 mmol) in CH_2Cl_2 at room temperature under an N_2 atmosphere. The reaction was stirred for 1 h, K_2CO_3 and methanol were then added at 0°C, and the solution was stirred for another 24 h at 0°C. The reaction mixture was quenched with H_2O and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc; 1:2, twice) to give monocarbamate **56** (6 mg, 35%) and bis(carbamate) **57** (3 mg, 20%). **56**: $[\alpha]_D^{22}$ = +39.4 (c=2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.37 (s, 1H), 8.74 (d, J=8.7 Hz, 1H), 6.64 (brs, 1H), 4.90 (brs, 1H), 4.62 (dd, J=6.9, 8.7 Hz, 1H), 4.38 (m, 1H), 4.26 (m, 2H), 4.00 (d, J=3.4 Hz, 1H), 3.66 (dt, J=6.0, 11.0 Hz, 1H), 2.18 (m, 1H), 1.97 (dd, J=6.0, 13.3 Hz, 1H), 15.0 (s, 9H), 1.49 (s, 9H), 1.46 (s, 9H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 158.7, 156.5, 156.0, 152.7, 152.7, 151.1, 147.8, 91.2, 84.2, 83.6, 80.3, 79.2, 76.2, 65.1, 56.2, 51.9, 46.6, 28.8, 28.2, 28.1, 28.03, 28.00 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{30}H_{51}N_7O_{12}Na$ 724.3493, found 724.3534. **57**: $[\alpha]_D^{22}$ = +16.5 (c=2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.35 (s, 1H), 9.07 (d, J=7.9 Hz, 1H), 5.1 (brs, 1H), 5.01 (d, J=3.2 Hz, 1H), 4.71 (m, 1H), 4.48 (dd, J=6.0, 6.9 Hz, 1H), 4.38 (dd, J=7.8, 11.0 Hz, 1H), 4.25 (dd, J=4.1, 11.0 Hz, 1H), 3.91 (dd, J=9.6, 10.1 Hz, 1H), 3.46 (dt, J=6.9, 11.5 Hz, 1H), 2.39 (m, 1H), 2.07 (dd, J=6.9, 13.7 Hz, 1H), 1.49 (s, 9H), 1.47 (s, 18H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.3, 158.9, 157.6, 155.6, 155.3, 152.6, 150.9, 148.0, 89.2, 83.7, 83.2, 79.9, 79.5, 79.1, 64.1, 56.2, 52.3, 44.8, 29.7, 28.1, 28.0, 27.8 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{31}H_{52}N_8O_{13}Na$ 767.3552, found 767.3569.

58: A 0.5 M solution of $B(OCOCF_3)_3$ (1.0 mL) in TFA was added to a solution of carbamate **56** (21 mg, 0.029 mmol) in TFA (0.5 mL) at room temperature. The reaction mixture was warmed to 70°C, stirred for 6 h, then cooled to room temperature, quenched with methanol, and concentrated in vacuo. The resulting residue was then dissolved with 5 mL of H_2O and desalinated with Amberlyst A 26(OH) (strongly basic resin). The resin was removed by filtration, and the filtrates were neutralized with Amberlite IRC-50 (weekly acidic resin) to trap the basic STXol. The resin was washed with H_2O (20 mL) and then 10% aq. TFA (30 mL). The aqueous TFA fraction was collected and concentrated in vacuo to give β-saxitoxinol (**58**) as the 2TFA salt (12 mg, 88%). $[\alpha]_D^{22}$ = +90.2 (c=1.2, MeOH); ^{1}H NMR (400 MHz, D_2O): δ=4.76 (d, J=1.4 Hz, 1H), 4.31 (d, J=4.1 Hz, 1H), 4.24 (dd, J=9.2, 11.5 Hz, 1H), 4.00 (dd, J=5.5, 11.5 Hz, 1H), 3.80 (ddd, J=1.4, 5.5, 9.2 Hz, 1H), 3.74 (dt, J=2.3, 10.1 Hz, 1H), 3.64 (m, 1H), 2.38 (m, 1H), 2.22 ppm (ddd, J=1.8, 8.2, 14.7 Hz, 1H); ^{13}C NMR (100 MHz, 4% CD_3CO_2D in D_2O): δ=160.7, 159.3, 157.4, 85.1, 76.1, 64.8, 59.4, 54.5, 45.4, 30.4 ppm; HRMS (ESI, M+H$^+$) calcd for $C_{10}H_{18}N_7O_3$ 284.1471, found 284.1481.

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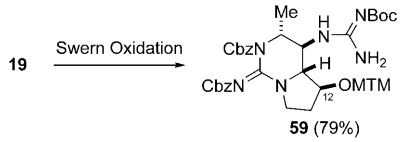
[16] Under the Swern oxidation conditions, C12 *O*-methyl thiomethyl (MTM) ether **59** was obtained in 79% yield.



59 (79%)

[17] See the Supporting Information.

[18] Nicolaou et al. reported that IBX can oxidize alcohols, ketones, and aldehydes to the corresponding α,β-unsaturated systems through enol formation of a carbonyl group and subsequent single-electron-transfer (SET) based oxidation reaction. See: a) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597;

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[20] Oxidation of alcohol **24** was difficult even though it has a less bulky group, NHBoc, at C5 than bis(guanidine) compounds **14** and **19**.

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[23] All these reactions were monitored by ESI mass spectrometry.

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