Alkaloid Synthesis

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Total Synthesis of (−)-Decarbamoyloxysaxitoxin**

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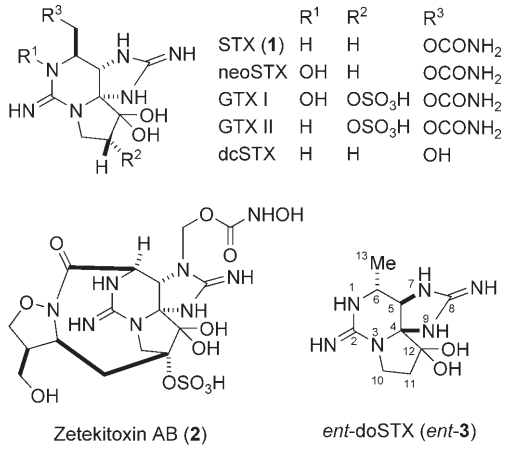
Dedicated to Professor Yoshito Kishi and Professor Tadashi Nakata

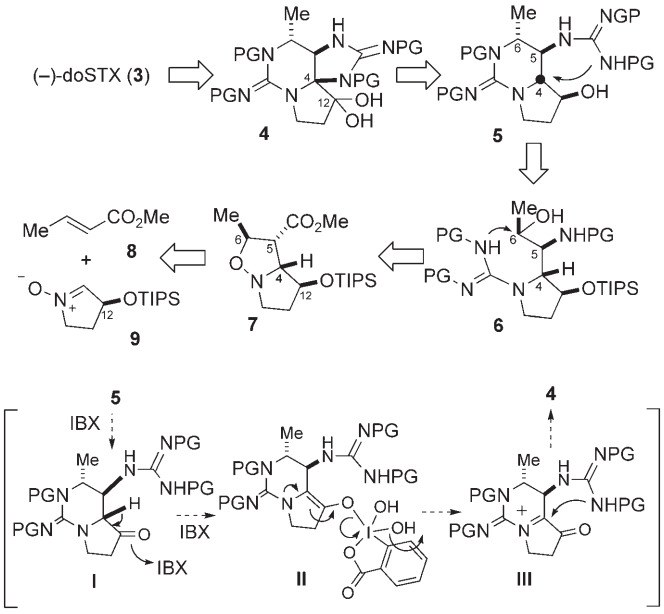
Saxitoxin (**1**, STX) is a neurotoxin that blocks voltage-gated sodium channels, which are critical for depolarization and conduction in most excitable cells.[1] It also binds to other receptor proteins, such as calcium and potassium channels,[2,3] and to saxiphilin, which is a member of the transferrin family.[4] Many natural STX analogues have been isolated (Scheme 1), with each having its own characteristic biological activity.[5] For example, the most structurally complex analogue, zetekitoxin AB (**2**), which was isolated from the Panamanian golden frog *Atelopus zeteki*, shows very high affinity for the sodium channel in rat brain, unlike STX (**1**).[6] As a consequence of their biological activities, together with their unique trialkyl tetrahydropurine (bis-bicyclic guanidine) structure, many synthetic studies have been made on STX and its analogues. Three elegant syntheses of STX (**1**) were reported by Kishi and co-workers,[7] Jacobi et al.,[8] as well as Fleming and Du Bois.[9]



Scheme 1. Structure of STX (**1**) and its analogues.

We have recently focused on the synthesis of decarbamoyloxysaxitoxin (**3**, doSTX)[10] as an entry point for the development of isoform-selective sodium-channel blockers. Decarbamoyloxysaxitoxin (**3**), which has the common STX skeleton, was isolated from the Australian shellfish *Gymnodinium catenatum* by Oshima et al. in 1990.[11] A total synthesis of racemic **3** was reported by Strichartz et al. in 1995.[12] The optical rotation of natural **3** is not yet known. Herein, we describe a total synthesis of (−)-doSTX (**3**), the putative antipode of the natural product.

The synthetic plan is illustrated in Scheme 2. In this strategy, the configurations at C5 and C6 in **3** are controlled by the stereogenic center of **9**,[10,13] which corresponds to the ketone at C12 in **3**. Direct construction of the characteristic bis-bicyclic guanidine structure **4** from monocyclic guanidine **5** is the key feature of this synthesis. For this transformation, we planned to apply the hypervalent iodine(V) reagent *o*-iodoxybenzoic acid (IBX), which is well known to be a mild oxidant for alcohols. Recently, Nicolaou et al. reported that IBX can oxidize alcohols, ketones, and aldehydes to the corresponding α,β-unsaturated systems through formation of an enol from a carbonyl group followed by an oxidation reaction based on a single electron transfer (SET).[14] In the case of the alcohol **5**, enol **II** is obtained via ketone **I** under IBX oxidation conditions.[14b] At this stage, we envisaged



Scheme 2. Synthetic plan for (−)-doSTX (**3**). PG = protecting group, TIPS = triisopropylsilyl.

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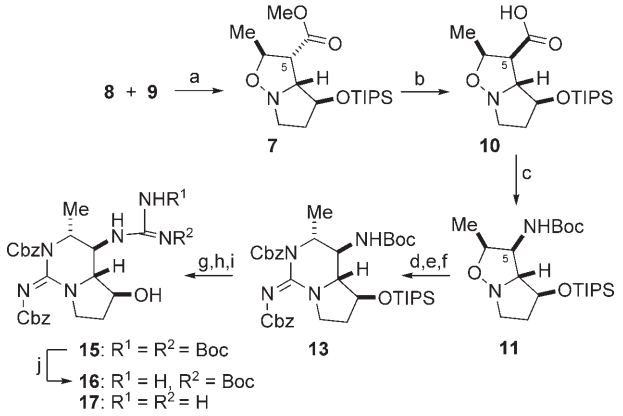
generating the iminium cation **III** from this enol **II** instead of forming the α,β-unsaturated ketone through an SET-based oxidation reaction, since this enol **II** has an enamine moiety, and might generate the bis-bicyclic guanidine **4** directly from the alcohol **5** (Scheme 2).

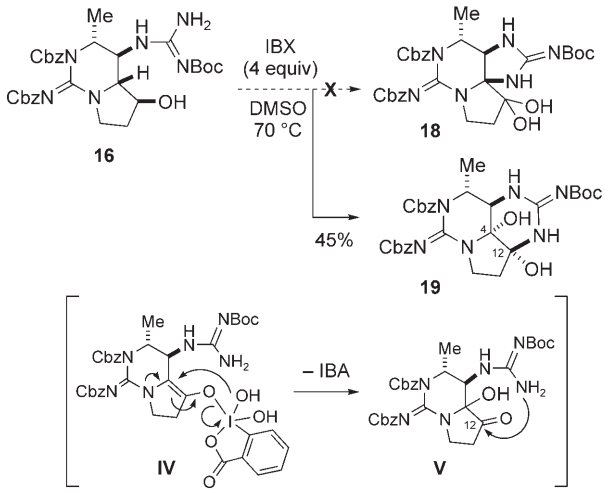
The synthesis of **16** commenced with a 1,3-dipolar cycloaddition reaction using the optically active nitrone **9** (Scheme 3).[15] The 1,3-dipolar cycloaddition reaction between methyl crotonate (**8**) and the chiral nitrone **9** gave



Scheme 3. Synthesis of bis-monocyclic guanidine **16**: a) toluene, 80 °C (93 %); b) LiOH, THF/H_2O, 0 °C; c) 1. $(COCl)_2$, DMF (cat.), toluene; 2. NaN_3, acetone/H_2O, 0 °C; 3. 1,4-dioxane, 100 °C, then 10 % HCl, then $(Boc)_2$, K_2CO_3, (86 % from **7**); d) H_2, $Pd(OH)_2$, MeOH; e) NCbz=C(SMe)NHCbz (**12**), $HgCl_2$, Et_3N, DMF; f) DEAD, PPh_3, toluene (97 %, three steps); g) TFA, CH_2Cl_2; h) NBoc=C(SMe)NHBoc (**14**), $HgCl_2$, Et_3N, DMF (77 % two steps); i) TBAF, THF (92 %); j) 5 % TFA/CH_2Cl_2, 0 °C (**15**: 13 %, **16**: 71 %, **17**: 16 %). Boc = *tert*-butyloxycarbonyl, DEAD = diethyl azodicarboxylate, Cbz = benzyloxycarbonyl, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid.

the isoxazolidine **7** in 93 % yield. Treatment of **7** with lithium hydroxide in aqueous THF at 0 °C proceeded through isomerization of the pseudoaxially oriented ester moiety at C5 to the equatorial position, followed by hydrolysis of the ester to give the carboxylic acid **10**. The carboxylic acid **10** was then converted into the *N*-Boc-protected amine **11** in 86 % yield by a Curtius rearrangement reaction. The reductive cleavage of the N–O bond of **11** was achieved with hydrogen in the presence of $Pd(OH)_2$, and a guanidine group was introduced into the resulting pyrrolidine by using bis(Cbz)-2-methyl-2-thiopseudourea (**12**) and mercury(II) chloride.[16] Under the Mitsunobu reaction conditions with DEAD and triphenylphosphine, this product afforded the cyclic guanidine **13** in 97 % yield (from **11**).[17] Removal of the Boc group of **13** with TFA, followed by reaction with bis(Boc)-2-methyl-2-thiopseudourea (**14**) in the presence of mercury(II) chloride, and cleavage of the TIPS ether with TBAF, gave alcohol **15** in 71 % yield from **13**. One of the Boc groups of **15** could be mostly removed with 5 % TFA in dichloromethane to give **16** in 71 % yield, and **17** was obtained in 16 % yield.[18]

With **16** in hand, we then examined the direct transformation of **16** into **18** with IBX (Scheme 4). Contrary to expectation, the reaction of **16** with IBX (4 equiv) in DMSO at 70 °C for 4 h failed to give **18**, and the fused-type guanidine



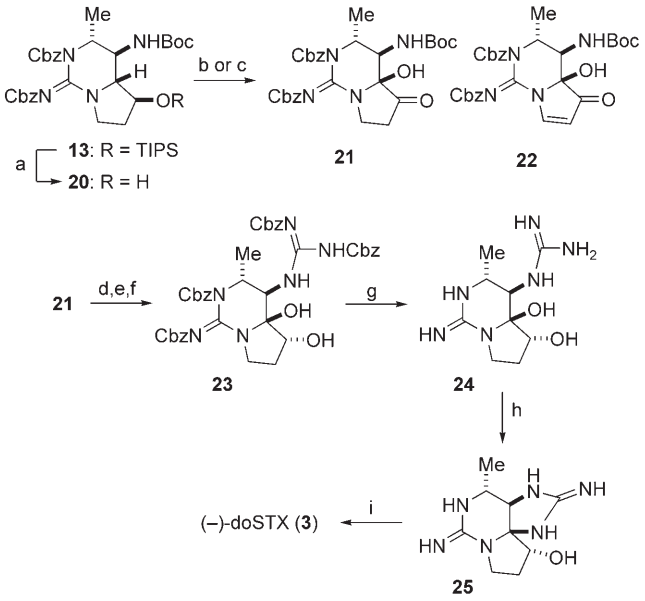
Scheme 4. IBX oxidation of **16** and the proposed reaction mechanism. IBA = iodosobenzoic acid.

19 was obtained as the sole product in 45 % yield.[19] This unexpected formation of **19** was interpreted as follows (Scheme 4): After oxidation of the alcohol at C12, the resulting ketone reacted with another molecule of IBX to form the enol intermediate **IV**. Electron transfer in this intermediate would then take place to generate the iminium cation, and the hydroxy group on IBX would attack intramolecularly at C4 (**IV** to **V**), instead of at the amino group of the guanidine, to generate **19**.[20] Although the desired compound **18** was not obtained, we were pleased to find that the hydroxy group could be installed selectively at C4, and we decided to apply this IBX oxidation reaction to the synthesis of **3**.

The IBX oxidation reaction was applied to alcohol **20**, which was obtained by removal of the TIPS ether of **13** with TBAF. When the reaction was conducted with IBX (4 equiv) in DMSO at 70 °C, the aminal **21** was obtained in 28 % yield, together with a further oxidized product, **22** (29 % yield; Scheme 5). Hence, a two-step oxidation reaction, namely, Swern oxidation of **20** followed by IBX oxidation (1.1 equiv) was examined, which gave the desired aminal **21** as a sole product in 64 % yield.

Thus, (−)-doSTX (**3**) was synthesized as follows. Treatment of **21** with sodium borohydride at 0 °C gave diastereoselectively the alcohol, whose Boc group was cleaved with TFA, and then a Cbz-protected guanidine group was installed to give **23**. The structure of **23** was confirmed unequivocally by X-ray crystallographic analysis. The synthesis of **3** from **23** was completed with the following three steps: Cleavage of the four Cbz groups with hydrogen in the presence of $Pd(OH)_2$, followed by treatment with TFA at 50 °C, gave the decarbamoyloxysaxitoxinol **25** in 60 % overall yield. Finally, oxidation of the alcohol with dimethylsulfoxide and diisopropylcarbodiimide afforded (−)-doSTX (**3**) in 63 % yield.[5b,9] All the spectroscopic data of the synthetic material were consistent with the reported data for the natural product.[22] The optical rotation value of **3** was −23.3 (c = 0.2, MeOH).

In conclusion, an enantioselective total synthesis of (−)-doSTX (**3**), the putative antipode of the natural product, has



Scheme 5. Completion of the synthesis of (−)-doSTX (**3**): a) TBAF, THF, 0 °C (94 %); b) IBX (4 equiv), DMSO, 70 °C (**21**: 28 %, **22**: 29 %); c) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; 2. IBX (1.1 equiv), DMSO, 50 °C (**21**: 64 %, **22**: 0 % two steps); d) $NaBH_4$, MeOH, 0 °C (72 %); e) TFA, CH_2Cl_2; f) NCbz=C(SMe)NHCbz (**12**), $HgCl_2$, Et_3N, DMF (82 % two steps); g) H_2, $Pd(OH)_2$, MeOH/EtOAc (2:1); h) TFA, 50 °C (60 % two steps); i) DMSO, diisopropylcarbodiimide, pyridinium trifluoroacetate (63 %).

been achieved in 17 steps from the optically active nitrone **9** in 10 % overall yield. The synthesis features a diastereoselective 1,3-dipolar cycloaddition reaction of **8** and **9**, and the direct oxidation of **20** at C4 with IBX. The optical rotation of **3** was determined. This efficient methodology provides a facile and general synthetic strategy for STX derivatives. Further work to synthesize natural STXs and various derivatives is in progress with the aim of developing isoform-selective sodium-channel inhibitors.

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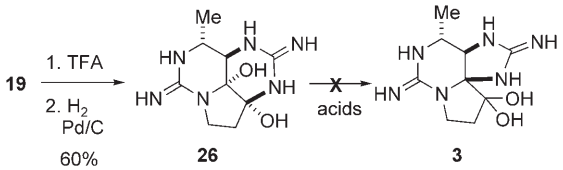
[18] Oxidation of the alcohol **15** did not take place with the various oxidants tested under various conditions. Thus, we cleaved the Boc group on guanidine.
[19] The structure of **19** was determined on the basis of X-ray analysis. Details are contained in the Supporting Information.
[20] Conversion of the fused-type bicyclic guanidine **26** into **3** was examined under various acidic dehydration conditions (aq H_2SO_4, 90 °C; 7.5 N aq HCl, 100 °C; 180 °C under vacuum conditions[21]), but no reaction occurred, and **26** was recovered quantitatively in all cases.



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[22] Spectral data for (−)-doSTX (**3**): $[\alpha]_D^{20} = -23.3$ ($c = 0.2$, MeOH); ^{1}H NMR (400 MHz, D_2O): $\delta = 4.46$ (d, $J = 1.8$ Hz, 1H), 3.76 (dt, $J = 2.3, 10.7$ Hz, 1H), 3.65 (dq, $J = 1.8, 6.9$ Hz, 1H), 3.55 (m, 1H), 2.36 (m, 1H), 1.24 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, 4% CD_3COOD in D_2O, determined by HMBC): $\delta = 159.0$, 157.5, 100,3, 84.2, 61.2, 51.9, 44.6, 34.4, 19.7 ppm; HRMS (ESI, $M+H^+$) calcd for $C_9H_{17}N_6O_2$ 241.1413; found 241.1452.

