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A Synthetic Strategy for Saxitoxin Skeleton by a Cascade Bromocyclization: Total Synthesis of (+)-Decarbamoyl-α-saxitoxinol

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Supporting Information

ABSTRACT: A new synthetic strategy for the formation of the ABC tricyclic framework of saxitoxin was developed. The BC ring moiety, including a *spiro*-aminal structure, was first constructed stereoselectively by a newly designed cascade bromocyclization of a readily available internal alkyne bearing guanidine and urea. The A ring was then synthesized by a guanylation of a cyclic urea, easily prepared via the oxidative cleavage of the diol of the cascade product, followed by addition of cyanide. This strategy enables the concise stereocontrolled total synthesis of (+)-decarbamoyl-α-saxitoxinol, which is a naturally occurring saxitoxin analogue.

Saxitoxin (STX, **1**; Figure 1), a paralytic shellfish poison (PSP),[1] is one of the best-known marine toxins along with

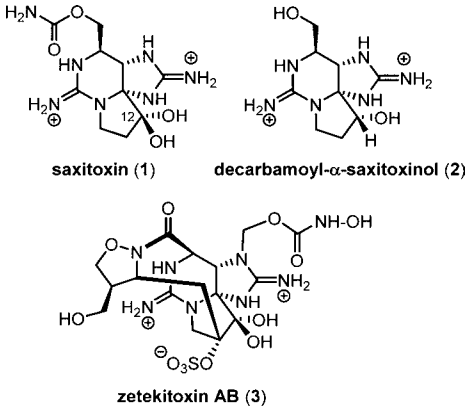
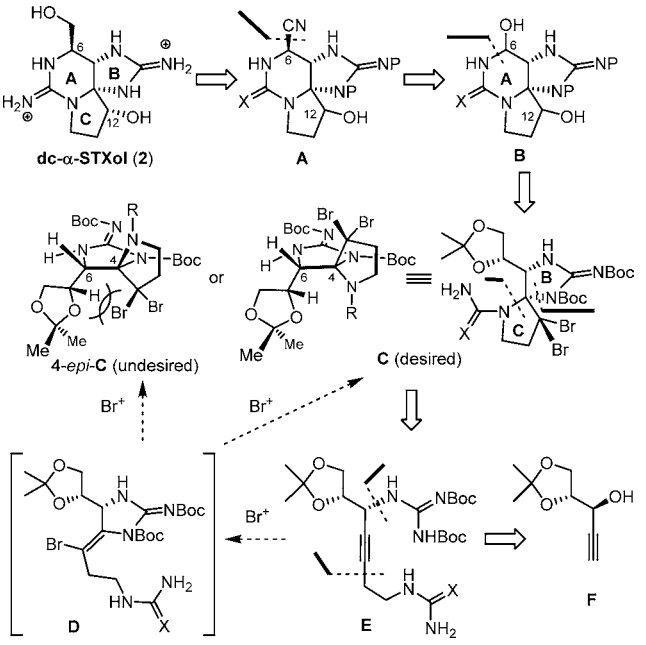


Figure 1. Chemical structures of saxitoxin and its analogues.

tetrodotoxin (TTX), i.e., the puffer fish toxin. Since these two guanidine-containing natural products exhibit potent and highly selective inhibitory activity toward voltage-gated sodium channels (VGSC), both have found widespread use as indispensable biochemical tools in physiological experiments associated with ion channels.[2] Recently, STX has been featured as a scaffold in the development of subtype-selective inhibitors of VGSCs, which are expected to be useful in the analysis of the functions of individual subtypes of VGSCs.[3] In order to prepare diverse STX analogues, including naturally occurring neoSTX, GTX, and zetekitoxin AB (**3**), efficient synthetic routes for a range of STX analogues have been developed.[4−8] We have also developed a synthetic strategy for the generation of the STX skeleton via a Br^+-triggered cascade cyclization of guanidino acetylene, which may find applications in the exploration of subtype-selective blockers of VGSCs.[9] Herein, we describe an efficient alternative strategy toward the STX skeleton, in which a different cascade bromocyclization reaction is a key step.

The newly designed synthetic strategy for the STX skeleton is shown in Scheme 1 and exemplified by the synthesis of the naturally occurring STX analogue decarbamoyl-α-saxitoxinol (dc-α-STXol, **2**).[10] We envisioned that **2** could be prepared from intermediate **A** (X = NH_2: guanidine, or X = O: urea) by transforming the nitrile into a primary alcohol and by

Scheme 1. Synthetic Plan for the Formation of the STX Skeleton



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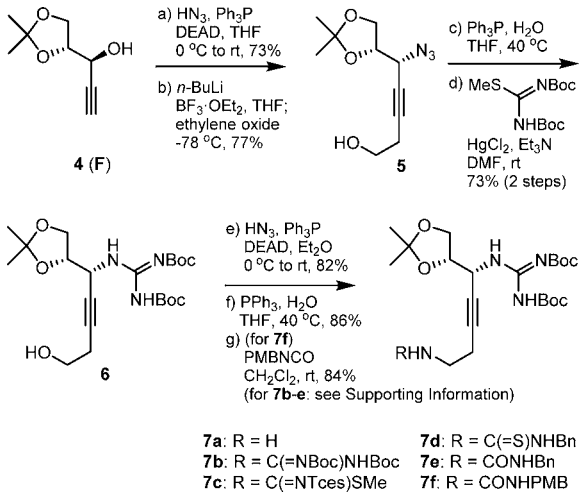
guanylation of urea. Since the nitrile is synthetically equivalent to a variety of functional groups, intermediate **A** might be used as a common intermediate for the synthesis of diverse STX analogues that differ at the C-6 position. The nitrile moiety could be introduced stereoselectively by addition of cyanide to the *N,O*-acetal of **B** from the convex face of the AB ring. Compound **B** could be easily prepared from **C** including a *spiro*-aminal structure, whose structure has not been utilized before because *spiro*-aminals are difficult to prepare in general;[11] the *N,O*-acetal should be prepared by cleavage of the 1,2-glycol moiety of **C**, while the hydroxy group at the C-12 position could be prepared from *gem*-dibromomethylene via a previously developed radical-mediated oxygenation.[12]

We envisaged that the *spiro*-aminal structure of **C** could be constructed in a single step by a Br^+-triggered cascade cyclization from alkyne **E**, which bears guanidine at the propargyl position, and guanidine (X = NH_2) or its equivalent (e.g., X = O) at the end of the side chain. The cascade reaction would proceed via intermediate **D** generated by the first bromocyclization of **E**. We anticipated that the second cyclization of **D** proceeds through a late transition state, furnishing the desired diastereomer **C**, because the undesired diastereomer 4-*epi*-**C** exhibits severe steric repulsion between the incoming nitrogen nucleophile and the acetonide-containing side chain. As the nucleophilicity and steric hindrance of nitrogen nucleophiles are strongly influenced by the protective groups or substituents, a screening of the substituents of the amino function and of the reaction conditions would be necessary. Precursor **E** could be prepared from the known propargyl alcohol **F**[13] in several steps. With this analysis in mind, we initially investigated the cascade cyclization of precursor **E**.

Precursors **E** (**7b**–**f**) were synthesized from known chiral acetylene **4** (**F** in Scheme 1), which was readily prepared from D-arabitol in three steps (Scheme 2).[13] The introduction of an

Scheme 2. Synthesis of 7b–f for the Cascade Cyclization



azide group at the propargyl position of **4** was achieved using Mitsunobu conditions (N_3H/Ph_3P, DEAD). Subsequently, the terminal acetylene was hydroxyethylated by the addition of lithium acetylide to ethylene oxide in the presence of BF_3·OEt_2[14] to afford **5** in 77% yield. The reduction of the azide moiety of **5** under Staudinger conditions (Ph_3P, THF–H_2O) was followed by guanylation with di-Boc-*S*-methylisothiourea in the presence of $HgCl_2$ and Et_3N to afford **6** in 73% yield over two steps. The primary alcohol in **6** was transformed into an amine in two steps by the aforementioned reaction sequence. The resulting amine **7a** was used for the preparation of precursors bearing guanidine and its equivalents, e.g., isothiourea, thiourea, and ureas **7b**–**f**.[15] With these precursors in hand, we investigated the Br^+-induced cascade cyclization reaction for the construction of *spiro*-aminal **C**.

Table 1 shows the results of typical experiments for the development of the cascade bromocyclization using **7b**–**f**. We initially attempted the cascade cyclization of **7b**, bearing diBoc-guanidine at the terminus of the side chain, using the previously optimized conditions for the synthesis of *spiro*-*N,O*-acetals.[9,16]

When **7b** was treated with 1.3 equiv of pyridinium tribromide ($PyHBr_3$) in the presence of K_2CO_3 in CH_2Cl_2/H_2O, monocyclic guanidine **9b**[17] was obtained in 66% yield (entry 1). However, **9b** was not consumed, even with an excess of $PyHBr_3$ (entry 2).[18] The reaction of *S*-methyl-isothiourea **7c** with 1.3 equiv of $PyHBr_3$ also afforded the corresponding monocyclized product **9c** in good yield (entry 3). However, the use of an excess of the reagent (3 equiv) led to the decomposition of **9c** and furnished a complex mixture of products (entry 4), which is probably due to the oxidation of the methyl sulfide moiety in **9c**. In the reaction of thiourea **7d** with $PyHBr_3$, the desired product **8a** and monocyclized product **9d** were not detected (entry 5), suggesting facile oxidation of the thiourea under these conditions. Conversely, when benzyl urea **7e** was treated with an excess of $PyHBr_3$, **8e** (23%) was observed for the first time together with **9e** (14%) (entry 6). As expected, the desired *R* configuration for the *spiro* center of **8e** was confirmed by single-crystal X-ray diffraction analysis.[19] This result encouraged us to explore the conditions for the use of **7e** in more detail. We found that $NaHCO_3$ and EtOH were the best base and solvent, respectively, affording *spiro*-aminal **8e** in 47% yield (entry 7). These conditions were also applicable to a gram-scale reaction of PMB urea **7f** to afford *spiro*-product **8f** in a similar yield (entry 8). Accordingly, we established a stereocontrolled synthesis of the BC ring of STX, including an unprecedented *spiro*-aminal structure, through a Br^+-initiated cascade cyclization reaction by the judicious choice of substituent R.

Encouraged by the successful construction of the BC ring structure, we focused on the synthesis of the A ring from **8f** possessing a readily deprotectable PMB group (Scheme 3). As our preliminary experiments showed that the *gem*-CBr_2 group was unstable under several conditions, we initially investigated its transformation into a more stable hydroxy function. However, the attempted formal hydrolysis of *gem*-CBr_2 under previously reported radical-mediated conditions (Ac_2O, Et_3N, and air in CH_2Cl_2/H_2O)[12] was unsuccessful, producing a mixture of unidentified products. After numerous experiments, we discovered that monoBoc-protected guanidine **10**, prepared by treatment of **8f** with periodic acid (1 equiv), undergoes a radical-mediated oxygenation under modified conditions (Ac_2O, Et_3N, and air in CH_3CN/H_2O) to provide a mixture of the corresponding ketone and enol acetate, both of which possess an acetate moiety on the guanidine fragment.[20] Reduction of the mixture with $NaBH_4$ yielded acetate **11** as the single product[21] in good overall yield. The protected diol in **11** was cleaved with periodic acid (2 equiv) to form cyclic urea **12** with an *N,O*-acetal as a single diastereomer. A nitrile was introduced using acetone cyanohydrin under Mitsunobu-type conditions (TMAD and Me_3P),[22] furnishing single diastereo-

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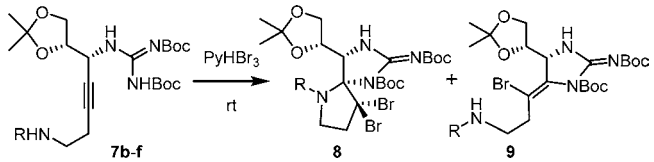
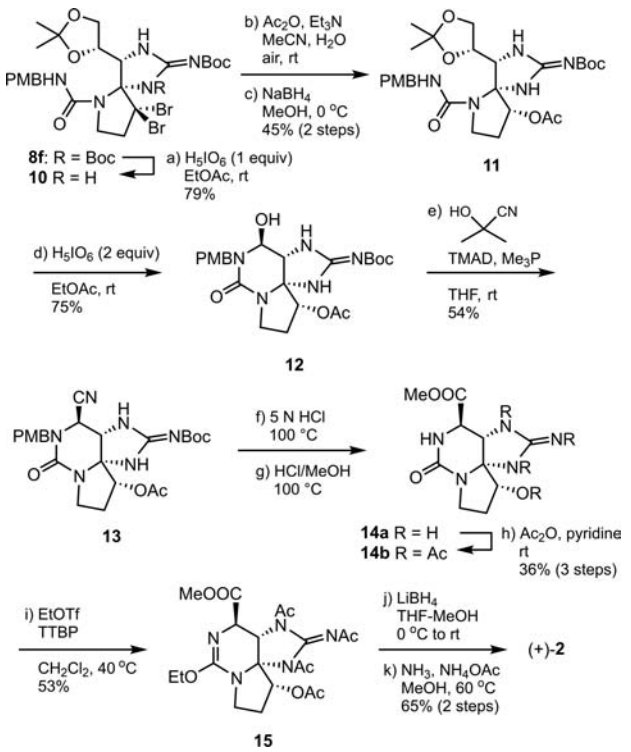
Table 1. Br$^+$-Triggered Cascade Cyclization of 7b–f



7b-f 8 9

entry	substrate R	conditions PyHBr$_3$ (equiv)	base	solvent(s)	yield (%) 8b–f	9b–f
1	**7b**: C(=NBoc)NHBoc	1.3	K_2CO_3	CH_2Cl_2–H_2O	**8b** 0	**9b** 66
2	**7b**	3.0	K_2CO_3	CH_2Cl_2–H_2O	**8b** 0	**9b** 62
3	**7c**: C(=NTces)SMe	1.3	K_2CO_3	CH_2Cl_2–H_2O	**8c** 0	**9c** 69
4	**7c**	3.0	K_2CO_3	CH_2Cl_2–H_2O	complex mixture	
5	**7d**: C(=S)NHBn	1.3	K_2CO_3	CH_2Cl_2–H_2O	complex mixture	
6	**7e**: CONHBn	3.0	K_2CO_3	CH_2Cl_2–H_2O	**8e** 23	**9e** 14
7	**7e**	5.0	$NaHCO_3$	EtOH	**8e** 47	**9e** trace
8	**7f**: CONHPMB	5.0	$NaHCO_3$	EtOH	**8f** 46	**9f** trace

Scheme 3. Synthesis of the A Ring and Total Synthesis of dc-α-STXol (2)



meric product **13**,[23] which contains all the carbons necessary for the synthesis of the STX skeleton. When the nitrile moiety in **13** was hydrolyzed by heating with hydrochloric acid, concomitant elimination of all protective groups was observed. The resulting carboxylic acid was methylated with hydrogen chloride in MeOH and **14a** was acetylated to provide tetraacetate **14b** in moderate overall yield from **13**. Finally, *O*-ethylisourea **15**, obtained in 53% yield from the reaction of **14b** with EtOTf,[4c] was treated with $LiBH_4$.[24] An ammonolysis of the resulting *O*-ethylisourea furnished (+)-dc-α-STXol (**2**) in 65% overall yield from **15**. All spectroscopic data obtained were consistent with previously reported data.[10]

In summary, we have developed a short synthetic route for the formation of the STX skeleton, which relied on a newly designed cascade bromocyclization reaction of the internal alkyne. This one-pot process provides an easily accessible route to a *spiro*-aminal structure containing a five-membered guanidine and pyrrolidine corresponding to the BC ring, which has not been prepared before. This new route is thus based on a strategy that is substantially different from previously reported synthetic approaches. Moreover, this study provides access to several STX analogues that differ with respect to the substituents at the C-6 position. This feature may be a key element for the development of subtype-selective inhibitors of VGSCs. In this study, we also have expanded the range of utility of the Br$^+$-triggered cascade cyclization of alkyne with two heteroatom nucleophiles in the synthesis of heterocyclic compounds containing not only *N*,*O*-acetal[25] and *O*,*O*-acetal[26] but also the aminal structure. The synthesis of other STX analogues via this new route and further applications of this cascade cyclization reaction are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03262.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The structures of **9b** to **9e** were assigned on the basis of a 2D NMR spectroscopic analysis.

(18) We reasoned that the Boc groups of the acyclic guanidine should shield the *N*-Boc enamine moiety of **9b** from Br^+, thus promoting the formation of **9b**. Long-time exposure to an excess of the reagents resulted in the decomposition of **9b**.

(19) CCDC-1496945 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) Conventional conditions using $AgNO_3$ in aqueous CH_3CN did not afford the desired ketone, but an aminoimidazole as the major product.

(21) The configuration of C-12 could not be assigned; an α was tentatively assigned by comparison with the NMR spectra of **2**.

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(23) The stereochemistry at the C-6 position was determined on the basis of the coupling constant (J = 0 Hz) between H6 and H5 in the ^{1}H NMR spectra, which is identical to that of the natural product (J = 0 Hz).

(24) Under these conditions, the methyl ester was reduced to the corresponding hydroxymethyl group and the acetyl groups were removed.

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