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A Stereocontrolled Synthesis of (+)-Saxitoxin

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Supporting Information

ABSTRACT: A concise stereoselective total synthesis of (+)-saxitoxin is described. A silver(I)-initiated hydroamination cascade constructs the bicyclic guanidinium ion core from a alkynyl bisguanidine. This sequence creates two C−N bonds, one C−O bond, and three rings and forms a single stereoisomer in a single synthetic transformation. This process enabled us to complete the synthesis of (+)-saxitoxin in 14 steps from *N*-Boc-L-serine methyl ester.

Unraveling the molecular basis for the toxicity of paralytic shellfish poisoning agents has proven indispensible in understanding the complex biology of voltage-gated sodium (Na_v) channels.[1] Paralytic shellfish toxins (PSTs) represent a family of at least 35 different chemical entities and are generally characterized by the presence of one or more cyclic guanidinium ion(s).[2] The flag bearer for the PSTs is undoubtedly (+)-saxitoxin (STX), whose significant toxicity has led to its use not only as an ion channel probe but also as a chemical warfare agent.[3] STX has received a great deal of attention from the synthetic community concerning the significant challenges associated with the chemical synthesis of such a polar, heteroatom-rich, and densely functionalized natural product. Advances in synthetic technology to access this natural product architecture hold promise for the further development of isoform-specific small-molecule inhibitors of Na_v channels with both improved potency and selectivity toward therapeutically relevant Na_v isoforms.[4] With these goals in mind, we engaged the synthesis of STX.

To date, STX has succumbed to synthetic campaigns by Kishi,[5] Jacobi,[6] Du Bois,[7] and Nagasawa.[8] Numerous other accounts have detailed approaches to related natural products, including a recent report by Nishikawa exploiting a halonium-induced propargylguanidine cyclization conceptually related to that detailed below.[4g,9] Our group has been interested in the metal-catalyzed hydroaminations of propargylguanidines, in particular from the vantage of controlling the selectivity in these cyclizations between the 5-exo and 6-endo manifolds.[10,11] Armed with the ability to control these processes, we became interested in STX as an intriguing skeletal system for further probing of hydroamination selectivity. As shown in Figure 1, we envisaged that the pyrrolidine ring of STX could arise from the alkylation of a pendant electrophile at C10, as in **A**. In turn, the N3−C4 or N9−C4 bonds could be formed by the oxidative cyclization of a neighboring guanidine on the ene−guanidine **B** or **C**. These intermediates were ultimately slated to arise from the competitive 5-exo versus 6-exo hydroamination of the alkynyl bisguanidine **D**. From our previous studies, we were confident that we could control the 5-exo versus 6-endo selectivity using Ag(I)

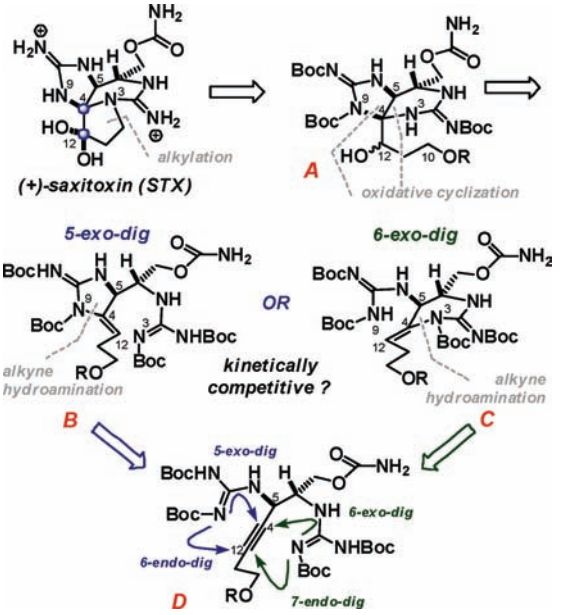

Figure 1. A strategy for (+)-saxitoxin.

to give **B**, but we were concerned that the 6-exo-dig process to give **C** would be kinetically competitive. It is likely that the 7-endo pathway would be much slower relative to the other three modes of cyclization. In the event that the 5-exo and 6-exo pathways are indeed competitive, both **B** and **C** should be viable intermediates for the oxidative cyclization to give **A**. Although this might deliver a mixture of epimers at C12, it would be inconsequential as the oxidation state of C12 would later be adjusted. Thu, both intermediates should provide the correct stereochemistry at C4 provided that the oxidative cyclization is thermodynamically controlled by the stereochemistry at C5. With this synthetic redundancy in mind, we embraced this strategy for accessing STX.

As exemplified by Du Bois in his second-generation synthesis of STX, Merino's stereoselective addition of acetylides to aldonitrones provides a straightforward and readily scalable access to the requisite propargyldiamine and thus became a natural entry point for our campaign also (Scheme 1).[7b,12] Addition of the magnesiated homopropargyl benzyl ether to L-serine aldonitrone (**1**) gave the desired *N*-hydroxydiamine **2** in good chemical yield and diastereoselectivity for the anti isomer (86%, 9:1 d.r.). Reductive cleavage of the N−O bond and acidic removal of both the silyl and carbamate protecting groups gave the diamine

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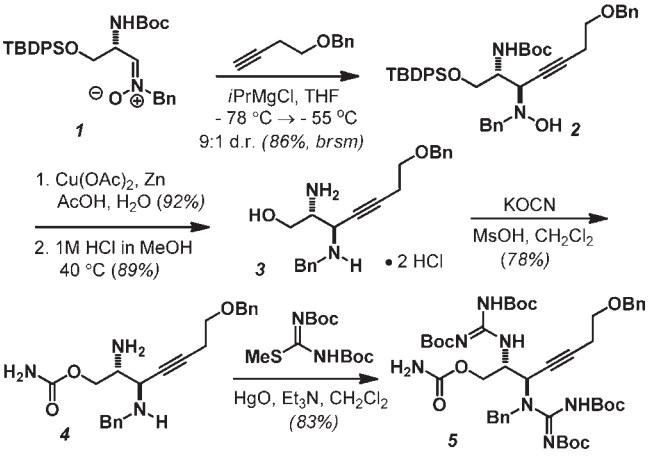
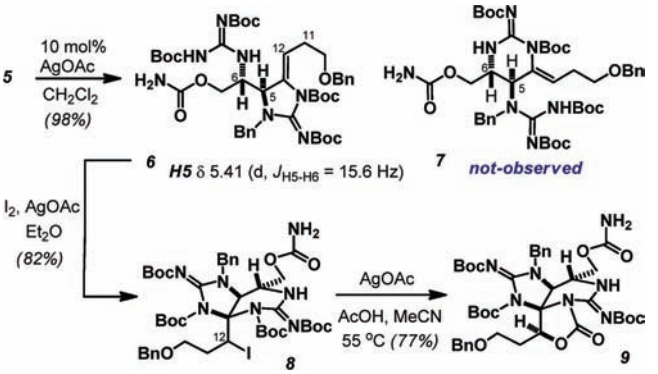
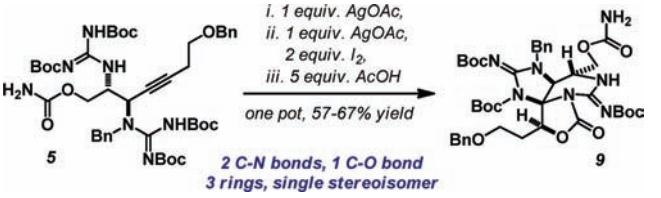
Scheme 1. Preparation of the Alkynyl bisguanidine



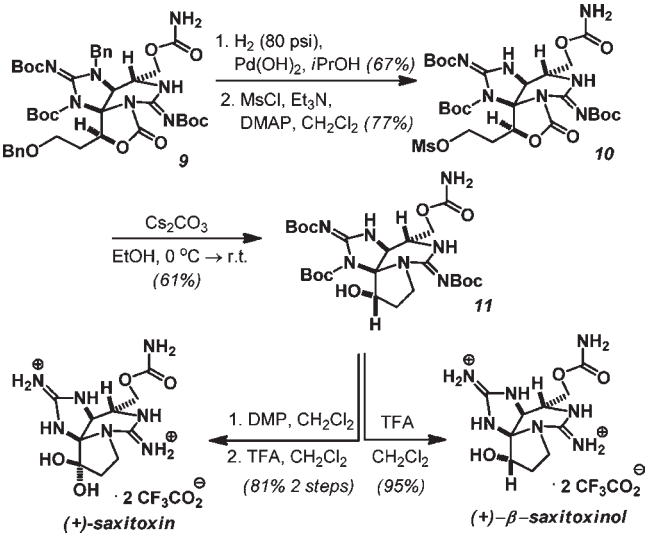
Scheme 2. Stepwise Access to the Key Tricyclic Carbamate



Scheme 3. One-Pot Synthesis of the Key Tricyclic Carbamate



Scheme 4. Completing the Synthesis of (+)-Saxitoxin



3 as its bishydrochloride salt.[13] Fearing yet another competitive cyclization pathway from an unprotected primary alcohol in our hydroamination strategy, at this point we installed the primary carbamate. This was accomplished with potassium cyanate in concentrated MsOH to give **4** as its free base after workup.[14] Mercuric oxide-assisted guanylation with di-Boc-pseudothiourea cleanly delivered alkynyl bisguanidine **5**.

Exposure of **5** to our previously reported Ag(I)-catalyzed cyclization conditions afforded a single regio- and stereoisomer of a cyclic ene−guanidine product (Scheme 2).[10b,15] On the basis of our experience with these compounds, chemical shift and multiplicity analysis persuaded us to assign the structure of this product as **6** arising from 5-exo-dig cyclization. More careful analysis, however, revealed that the protons in the 6-exo-dig product **7** would occupy identical spin systems and that this connectivity would likely be indistinguishable through routine 1D or 2D NMR techniques. Particularly troubling was the large ^3J coupling between the methine protons H5 and H6 (^3J = 15.6 Hz), which is more indicative of a trans-diaxial orientation as expected in **7**. However, a model compound lacking the guanidine capable of forming the 6-exo-product displayed analogous ^3J couplings, ^{1}H chemical shifts, and multiplicities for H5, the vinylic proton (H12), and the two allylic methylene protons (H11), suggesting that the 5-exo-dig product **6** is indeed favored.[16]

Attempts to trigger **6** oxidatively to form the bicyclic guanidine via epoxidation with DMDO or *m*CPBA proved unsuccessful. This led us to consider the possibility of using an electrophilic halogen source to trigger the formation of the C4 aminal. While this would place a halogen at C12 instead of an oxygen atom, we were hopeful that the resulting halide might be displaced by an adjacent Boc group, reminiscent of the Woodward dihydroxylation.[17] This strategic change would permit differentiation of the two guanidines needed to successfully execute the final annulation sequence. To our delight, treatment of **6** with iodine promoted the cyclization, thus providing the bicyclic aminal **8** as a single diastereomer. The stereochemistry of the secondary iodide at C12 was not confirmed but is likely that arising from iodonium ion formation on the β-face of the alkene. Treatment of this secondary alkyl iodide with Ag(I) and AcOH promoted the clean formation of oxazolidinone **9**, in which only a single Boc group had participated.[17b,18]

We recognized that the tricyclic carbamate **9** arose from alternating Ag(I)-catalyzed processes (**5** → **6** → **8** → **9**). This was conveniently streamlined to a one-pot operation providing **9** in 57−67% isolated yield (Scheme 3). This successfully forged two C−N bonds, one C−O bond, and three rings from an acyclic precursor in a single synthetic manipulation.

To ready this intermediate for the final annulation sequence, the *O*- and *N*-benzyl groups were cleaved by hydrogenolysis, and the resulting free alcohol was mesylated to give **10** (Scheme 4). We anticipated that the oxazolidinone could be preferentially

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hydrolyzed because of both steric accessibility and its increased electrophilicity. Treatment of this intermediate with Cs_2CO_3 in EtOH cleanly and selectively cleaved the cyclic carbamate without hydrolysis of the *tert*-butyl or primary carbamates.[19] The release of N1 resulted in the final five-membered-ring annulation to give **11**.

Deprotection of the remaining Boc groups in **11** with 1:1 TFA/CH_2Cl_2 cleanly gave β-saxitoxinol. Alternatively, oxidation of the secondary alcohol could be accomplished with Dess–Martin periodinane to give the corresponding ketone. This intermediate proved to be relatively unstable but could be immediately deprotected to give (+)-saxitoxin in 81% yield over the final two steps.[20]

This strategy delivered (+)-saxitoxin in 14 steps from commercially available *N*-Boc-L-serine methyl ester, which is comparable to Du Bois' second-generation synthesis.[7b] The approach is highlighted by a regio- and stereoselective one-pot Ag(I)-catalyzed cyclization cascade that generates two C–N bonds, one C–O bond, and three rings in a single synthetic manipulation. This work is poised to complement that of others in delivering new small-molecule modulators of ion channel function.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data for all new compounds, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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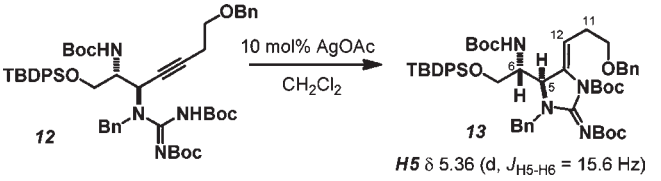
(16) Model compound **13** was prepared by the AgOAc-catalyzed cyclization of **12**. See the Supporting Information for details and comparisons of ^1H NMR spectra.



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