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Divergent Synthesis of Natural Derivatives of (+)-Saxitoxin Including 11-Saxitoxinethanoic Acid

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Abstract: The bis-guanidinium toxins are a collection of natural products that display nanomolar potency against select isoforms of eukaryotic voltage-gated Na^+ ion channels. We describe a synthetic strategy that enables access to four of these poisons, including 11-saxitoxinethanoic acid, C13-acetoxy saxitoxin, decarbamoyl-saxitoxin, and saxitoxin. Highlights of this work include an unusual Mislow-Evans rearrangement and a late-stage Stille ketene acetal coupling. The IC_{50} of 11-saxitoxinethanoic acid has been measured against rat $Na_V1.4$, and found to be 17.0 nM, similar to sulfated toxins gonyautoxin II and III.

The bis-guanidinium toxins, as exemplified by saxitoxin (STX, Figure 1), are a distinct collection of natural products that target voltage-gated sodium channels (Na_Vs).[1] Structural variations among STX congeners occur primarily at two positions, C11 and C13.[2] Although most C11-modified toxins are oxidized at this site, among the 57 known natural STX derivatives, 11-saxitoxinethanoic acid (SEA) and zetekitoxin AB (ZTX) are the only two that bear C11-carbon substituents. Little is known about the potency, Na_V isoform selectivity, and toxicity of SEA;[3] the more complex agent, ZTX, is reported to display sub-nanomolar IC_{50} against three Na_V subtypes.[4] The lack of material from natural sources restricts further investigations of either molecule. Inspired by the synthetic challenges presented by SEA and ZTX as well as questions regarding the influence of C11-substitution on toxin binding to Na_Vs, we initiated efforts to prepare these unique isolates. Herein, we report a divergent strategy for asymmetric synthesis of SEA and three additional toxin natural products.

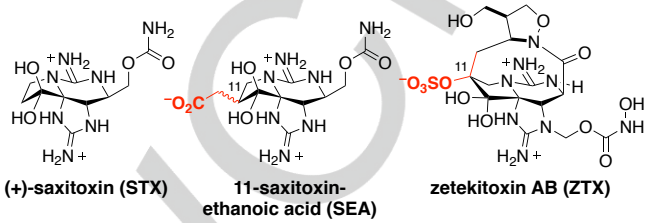
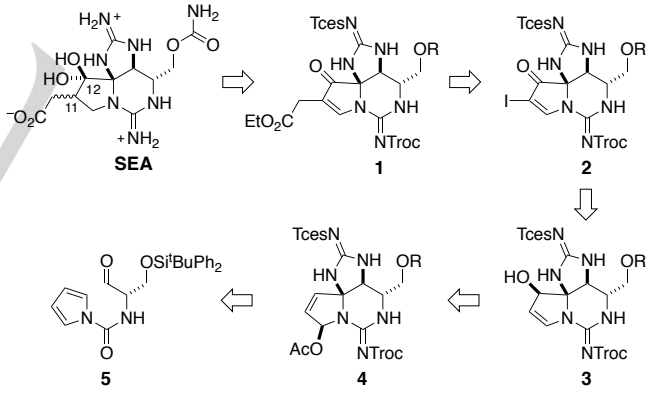


Figure 1. Selected bis-guanidinium natural products.

A number of synthetic routes to bis-guanidinium toxins have been delineated, including a recent effort by Nagasawa and coworkers to prepare SEA.[5,6,7] For our purposes, we desired a synthesis of C11-modified toxins that would allow for introduction of the C11 group on an advanced intermediate, thereby facilitating access to SEA, ZTX, and related analogues. Cross-coupling of an appropriate nucleophilic partner with α-iodoenaminone **2** was envisioned as a solution to this problem (Scheme 1). This substrate would be available through oxidation of allylic alcohol **3** followed by α-halogenation. Access to **3** could be achieved by rearrangement of *N*,*O*-acetal **4**, an intermediate obtained from pyrrole **5** by way of a Pictet-Spengler reaction.[5a,b]



Scheme 1. Retrosynthetic analysis of 11-saxitoxinethanoic acid (SEA). Tces = 2,2,2-trichloroethoxysulfonyl, Troc = 2,2,2-trichloroethoxycarbonyl, R = Si^tBuPh_2.

The assembly of *N*,*O*-acetal **4** from L-serine methyl ester is possible on multigram scales using a well-established process developed in our lab.[5a,b] The *N*,*O*-acetal is susceptible to reduction under conditions that employ a Lewis acid and trialkylsilane. Other nucleophiles exchange with **4** quite readily, including PhSH to give the corresponding *N*,*S*-acetal **6** (Scheme 2).[8,9] In order to introduce the requisite oxygenation at C12, a structural feature common to all bis-guandinium toxins, a plan involving Mislow-Evans [2,3]-rearrangement of sulfoxide **7** was conceived. The stability of this unusual acetal and limited precedent for such a sequence of steps, however, raised questions about the viability of this idea.[9] These issues notwithstanding, selective oxidation of **6** proceeded without event and afforded the desired sulfoxide **7** as a stable, 1:1 mixture of diastereomers.[10]

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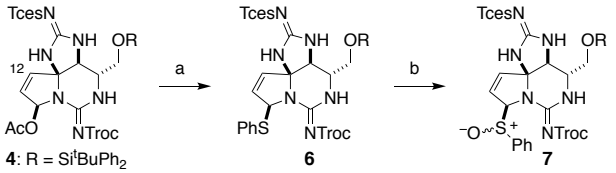
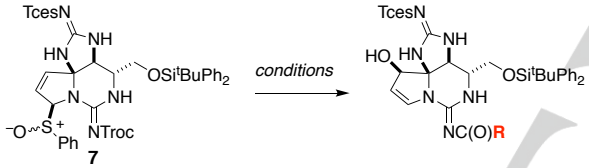


Scheme 2. Sulfoxide synthesis from *N,O*-acetal **4**. Reagents and conditions: (a) PhSH, BF_3•OEt_2, CH_2Cl_2, 84%; (b) urea•H_2O_2, HFIP, 88%. HFIP = hexafluoro-2-propanol.

Initial attempts to effect [2,3]-rearrangement of sulfoxide **7** using conventional conditions ($P(OMe)_3$, MeOH, 65 °C) surprisingly returned starting material (entry 1, Table 1). Switching to EtOH solvent and heating the reaction to 80 °C resulted in formation of the corresponding allylic alcohol product, albeit in modest yield (42%, entry 2). In addition, exchange of the Troc-protecting group to an ethyl carbamate was also noted. Use of 2,2,2-trichloroethanol as solvent rendered the exchange reaction redundant; however, the product was not easily separated from $P(OMe)_3$ (entry 3). After screening alternative reductants, sodium thiophenolate was identified as an optimal additive (entry 4). When employed in combination with trichloroethanol, the desired alcohol **3** was obtained in 89% yield. Accordingly, conversion of *N,O*-acetal **4** to this compound follows an efficient three-step sequence, giving access to a particularly versatile intermediate for preparing toxin derivatives.

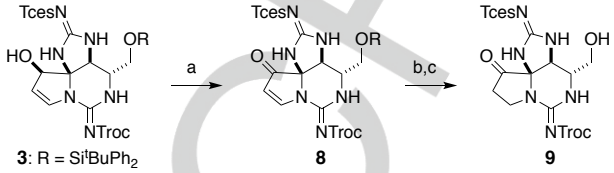
Table 1. Evaluating reaction conditions for Mislow-Evans [2,3]-rearrangement.



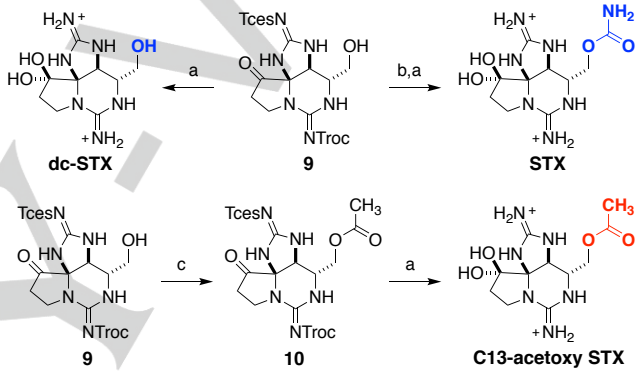
Entry	Conditions	R	%Yield
1	$P(OMe)_3$, MeOH, 65 °C	–	NR
2	$P(OMe)_3$, EtOH, 80 °C	OEt	42
3	$P(OMe)_3$, Cl_3CCH_2OH, 80 °C	OCH_2CCl_3	80
4	**NaSPh, Cl_3CCH_2OH, 80 °C**	**OCH_2CCl_3**	**89**

Oxidation of alcohol **3** with Dess-Martin periodinane afforded enaminone **8** in 95% yield (Scheme 3). With this compound, it is possible to synthesize decarbamoyl STX (dc-STX), STX, and C13-acetoxy-STX. The sequence to all three natural products involves enaminone 1,4-reduction and C13-desilylation to generate a protected form of dc-STX (**9**). Conjugate reduction of **8** was first attempted using different Cu-hydride sources, but these conditions generally resulted in Troc-deprotection without concomitant reduction of the C10,C11-alkene.[11] Of the many methods and protocols tested, hydrogenation with catalytic $[Ir(cod)(PCy_3)(py)]PF_6$ in combination with $B(O^iPr)_3$, a critical additive for promoting catalyst turnover, proved uniquely successful and furnished the saturated ketone in 75% yield.[12] Following desilylation of this material with acetic acid-buffered tetrabutylammonium fluoride to give **9**, removal of the two guanidine protecting groups under hydrogenolytic conditions (H_2, cat. $PdCl_2$) gave dc-STX (Scheme 4).

To complete a synthesis of STX from **9**, carbamoylation of the alcohol group was first attempted with trichloroacetyl isocyanate; use of this reagent, however, resulted in competitive guanidine functionalization.[7c, 13] Instead, successful installation of the carbamate group was possible using 1,1'-carbonyldiimidazole (CDI) and NH_3 (Scheme 4). Esterification of **9** also proceeded smoothly with acetyl cyanide to give the corresponding acetate ester **10**. Upon removal of the Tces- and Troc-groups from these intermediates, STX and C13-acetoxy STX were obtained. The latter is a natural congener of STX produced by the freshwater cyanobacterium *Lyngba wollei*, and to our knowledge has not been prepared previously.[14, 15]

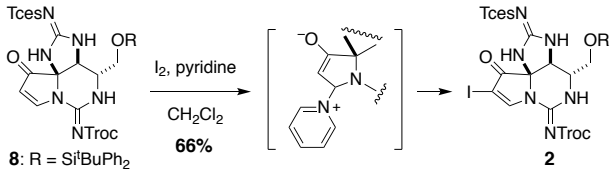


Scheme 3. Synthesis of the fully elaborated bis-guanidine toxin core. Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2, 95%; (b) 25 mol % $[Ir(cod)(PCy_3)(py)]PF_6$, $B(O^iPr)_3$, 500 psi H_2, CH_2Cl_2, 75%; (c) *n*-Bu_4NF, AcOH, THF, –78–23 °C, 86%.



Scheme 4. Access to three bis-guanidinium toxin natural products from a common precursor **9**. Reagents and conditions: (a) 1 atm H_2, $PdCl_2$, CF_3CO_2H, MeOH/H_2O, 14–46%. (b) 1,1'-carbonyldiimidazole, THF; then 0.5 M NH_3 in THF, 69%; (c) $CH_3C(O)CN$, DMAP, CH_2Cl_2, 64%.

Turning our focus towards the synthesis of C11-substituted bis-guanidinium toxins, SEA and ZTX, we investigated methods for C11-functionalization of enaminone **8**. Our inability to identify suitable conditions for conjugate hydride addition precluded a tandem 1,4-reduction/enolate alkylation sequence. Thus, we became interested in Baylis-Hillman-type processes to introduce an alkyl group at C11. Although we were unsuccessful in developing such a protocol, it was possible to transform **8** into the α-iodinated product using I_2 and pyridine (Scheme 5).[16] We speculate based on literature precedent that this reaction occurs through reversible formation of a pyridinium adduct.[17] Under these conditions, the iodinated product was isolated in 66% yield.



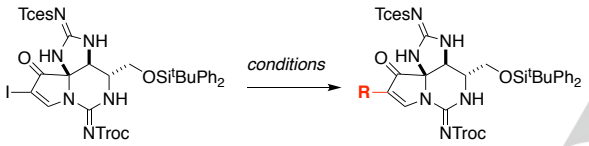
Scheme 5. Selective α-iodination of enaminone **8**.

To complete a synthesis of SEA, cross-coupling reactions of **2** with a primary ester enolate or suitable equivalent were examined. Exposure of this substrate to reagents such as the zinc enolate of ethyl acetate and Pd(0) sources, however, resulted in unproductive consumption of starting material (entry 1, Table 2).[18,19,20,21,22] Iodoenaminone **2** is particularly unstable

to base (including fluoride ion), and thus we were compelled to explore neutral, Stille-based methods to effect the desired coupling reaction.[23] Unfortunately, the $^{n}Bu_3Sn$-enolate of ethyl acetate proved unreactive as a cross-coupling partner (entry 2). Other organostannanes such as tributyl(vinyl)tin fared only slightly better, affording a trace amount of the desired product (entry 3). In light of these results, we were surprised to find that treatment of iodoenaminone **2** with *cis*-tributyl(2-ethoxyvinyl)tin, a commercially available acetaldehyde synthon, and 10 mol% $Pd(PPh_3)_4$ resulted in a productive reaction (entry 4).[24, 25] Starting material was fully consumed and the enol ether product **14** (R = *cis*-(EtO)CH=CH)) was isolated as a fluorescent yellow compound in 67% yield.[26] These results motivated subsequent investigation of ketene acetal stannane derivatives as acetate ester surrogates.

A method for preparing the novel reagent tributyl(2,2-diethoxyvinyl)tin **13** was devised starting from 1,1,-dibromo-2,2-diethoxyethane **11** (Scheme 6). Treatment of **11** with $KO^{t}Bu$ effected bromide elimination to give olefin **12**. As first demonstrated in 1937, low temperature lithium-halogen exchange of this compound is possible without concomitant loss of LiOEt.[27,28,29] Subsequent trapping of the incipient vinyl anion with $^{n}Bu_3SnCl$ afforded **13** in 75% yield.[30]

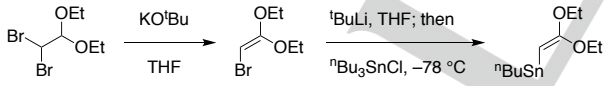
Table 2. Cross-coupling conditions evaluated with iodoenaminone **2.**



2 **14**

Entry	Nucleophile	Pd cat/ligand	Additive	Result
1	$BrZnCH_2CO_2{}^{t}Bu$	$Pd_2(dba)_3$/dppf[a]	none	decomp.
2	$^{n}Bu_3SnCH_2CO_2Et$	$PdCl_2(P(o\text{-tol})_3)_2$	CuF_2	NR
3	$^{n}Bu_3SnCH{=}CH_2$	$Pd(PPh_3)_4$	CuI	< 5%
4	$^{n}Bu_3SnCH{=}CH(OEt)$	$Pd(PPh_3)_4$[a]	CuCl,LiCl	67%
5	$^{n}Bu_3SnCH{=}C(OEt)_2$	$Pd(PPh_3)_4$[a]	CuCl,LiCl	0-40%[b]
6	**$^{n}Bu_3SnCH{=}C(OEt)_2$**	**$Pd(PPh_3)_4$[a]**	**CuTC**	**60%[b]**

[a]Reaction in THF; [b]Yield determined after ketene acetal hydrolysis with saturated aqueous NH_4Cl. CuTC = Copper(I) thiophene-2-carboxylate.

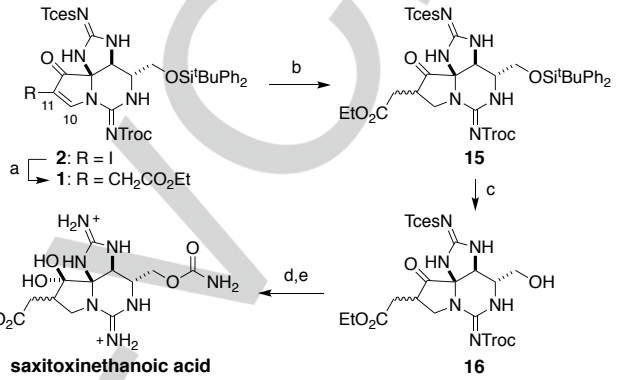


11 **51%** **12** **75%** **13**

Scheme 6. Preparation of (2,2-diethoxyvinyl)tin **13** for Pd-mediated Stille cross coupling.

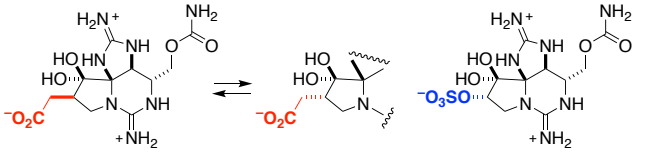
Despite the successful coupling reaction of iodoenaminone **2** with *cis*-tributyl(2-ethoxyvinyl)tin (entry 4, Table 2), the analogous reaction with **13** delivered the ketene acetal product in highly variable yields (entry 5). Forced to examine alternative Pd sources, phosphine ligands, and additives, we identified Cu(I) thiophene-2-carboxylate (CuTC)[31] as an optimal reagent. In combination with $Pd(PPh_3)_4$ and CuTC, reaction of **2** and **13** reproducibly afforded the vinylated product (entry 6 & Scheme 7). Mild acid hydrolysis of this material furnished the corresponding ethyl ester **1** in 60% isolated yield.

Synthesis of SEA from **1** was completed following the four-step sequence used to access STX (*vide supra*). Initial reduction of the C10,11-alkene in **1** was achieved with H_2 under Ir-catalysis (2.5:1 dr), conditions that do not result in cleavage of either the Troc- or Tces-groups (Scheme 7). Subsequent desilylation of **15** and installation of the requisite carbamate moiety gave a protected form of SEA. Finally, hydrogenolytic removal of both guanidine protecting groups and ethyl ester hydrolysis yielded the natural product. SEA was obtained as a ~3:1 mixture of C11 epimers, in keeping with the original isolation data and with a recent disclosure from Nagasawa and coworkers.[6] NMR and HRMS for the synthetic material agree with the reported literature values. In addition, pH-dependent D_2O exchange is observed for the C11 hydrogen atom.



Scheme 7. Completed synthesis of 11-saxitoxinethanoic acid. Reagents and conditions: (a) $^{n}Bu_3SnCH{=}C(OEt)_2$, 50 mol% $Pd(PPh_3)_4$, CuTC, NMP; then NH_4Cl. 35%; (b) 30 mol% $[Ir(cod)(PCy_3)(py)]PF_6$, $B(O\text{-}i\text{-}Pr)_3$, 500 psi H_2, CH_2Cl_2, 80%, 2.5:1 dr; (c) *n*-Bu_4NF, AcOH, THF, –78–23 °C, 80%; (d) CDI, THF then 0.5 M NH_3 in THF, 35%; (e) 1 atm H_2, $PdCl_2$, CF_3CO_2H, MeOH/H_2O; then 1.0 M aqueous HCl, 50%. NMP = *N*-methyl-2-pyrrolidone.

Successful access to SEA has enabled whole-cell electrophysiological characterization of this toxin against a recombinant voltage-gated sodium channel α-subtype. Using heterologously expressed rat $Na_V1.4$ (CHO cells), the IC_{50} for SEA was determined to be 17.0 ± 1.9 nM. Interestingly, the C11-sulfated toxin, GTX-III, shows comparable potency (14.9 ± 2.1 nM) against this same Na_V isoform, despite the fact that SEA is applied to cells as a ~3:1 mixture of C11-α/β epimers. Given the lability of the C11-H to solvent exchange, it is possible that toxin diastereomers are resolved upon binding to the channel and that the β-form is favored. Studies to address this question and to characterize the action of SEA and related C11-derivatives against additional Na_V isoforms and channel mutants are ongoing.



α-11-SEA **β-11-SEA** **(+)-gonyautoxin III**

IC_{50} = 17.0 ± 1.9 ($Na_V1.4$) IC_{50} = 14.9 ± 2.1 ($Na_V1.4$)

Figure 2. Comparative potencies of C11-substituted toxins against $Na_V1.4$.

We have successfully prepared four bis-guanidinium toxin isolates – STX, dcSTX, C13-acetoxy STX, and SEA – through a divergent sequence that capitalizes on enaminone **8**. This synthetically versatile intermediate was obtained through a sulfoxide [2,3]-rearrangement, and can be easily processed to toxins bearing no substitution at C11. The challenge of assembling 11-saxitoxinethanoic acid required invention of stannane **13** as a novel ester enolate equivalent and the development of optimal conditions for cross-coupling this

reagent with iodide **2**. All told, the versatile chemistry described in this report enables access to natural and non-natural toxin-based probes to support our studies of Na_V structure, function, and physiology.[1,15]

Acknowledgements

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Keywords: guanidinium toxins • sodium channel • sulfoxide rearrangement • Stille coupling

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[30] Yield determined by ^{1}H NMR integration against an internal standard.

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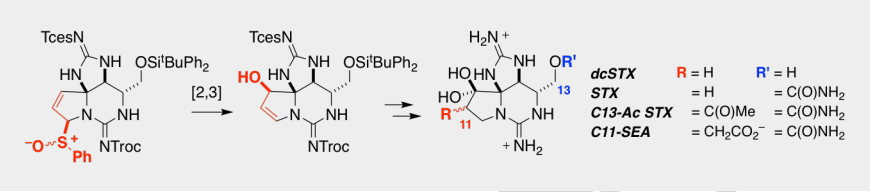

A synthetic strategy that enables access to four naturally occurring guanidinium toxins, including saxitoxin, decarbamoyl saxitoxin, C13-acetoxy saxitoxin, and C11-saxitoxinethanoic acid, is highlighted.

*James R. Walker‡, Jeffrey E. Merit‡, Rhiannon Thomas-Tran, Doris T. Y. Tang, J. Du Bois**

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Divergent Synthesis of Natural Derivatives of (+)-Saxitoxin Including 11-Saxitoxinethanoic acid