Review

Chemical construction and structural permutation of neurotoxic natural product, antillatoxin: importance of the three-dimensional structure of the bulky side chain

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Abstract: Antillatoxin 1 is a unique natural product that displays potent neurotoxic and neuritogenic activities through activation of voltage-gated sodium channels. The peptidic macrocycle of 1 was attached to a side chain with an exceptionally high degree of methylation. In this review, we discuss the total synthesis and biological evaluation of 1 and its analogues. First we describe an efficient synthetic route to 1. This strategy enabled the unified preparation of nine side chain analogues. Structure-activity relationship studies of these analogues revealed that subtle side chain modification leads to dramatic changes in activity, and detailed structural analyses indicated the importance of the overall size and three-dimensional shape of the side chain. Based on these data, we designed and synthesized a photoresponsive analogue, proving that the activity of 1 was modulated via a photochemical reaction. The knowledge accumulated through these studies will be useful for the rational design of new tailor-made molecules to control the function and behavior of ion channels.

Keywords: total synthesis, natural products, amino acids, ion channels, biological activity, structure-activity relationships

Introduction

Natural products continue to provide valuable tools for chemical biology and lead compounds for drug discovery.1) They are secondary metabolites that can be subdivided according to their chemical structure as peptides, polysaccharides, isoprenoids, alkaloids, etc. Not only have these substances been optimized for a specific function during evolution, they also represent a promising basis for the development of compounds with novel bioactivities.3)–5) One path to this goal is the artificial modification of natural product structures through organic synthesis. Our research group focuses on efficient, practical and flexible syntheses of biologically important natural molecules with architecturally complex structures. At the core of this research program is the development of new strategies for assembling complex natural products in a concise fashion. Since the start of this effort in 2007, we have achieved the synthesis of six complex natural products and two analogues of different molecular classes (Fig. 1). Polytheonamide B6) and yaku’amide A7) (cytotoxic peptides), antillatoxin (neurotoxic peptide),8) 19-hydroxysarmentogenin (cardiac steroid),9) resolvins E2,10) and E3,11) and maresin12) (anti-inflammatory lipid mediators), and 9-demethyl-10,15-dideoxyrynanodol,13) and resiniferatoxin skeleton14) (terpenoid structures) were chemically synthesized by employing newly developed methodologies and strategies. Established routes for the total syntheses were then applied to the synthesis of structurally varied

Abbreviations: BOC: t-butoxycarbonyl; t-Bu: tert-butyl; dppe: 1,1’-bis(diphenylphosphino)ferrocene, mCPBA: m-chloroperbenzoic acid; HOAt: 1-hydroxy-7-azabenzotriazole; NB: 2-nitrobenzyl; NOE: nuclear Overhauser effect; SAR: structure-activity relationship; VGSC: voltage-gated sodium channels.

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analogue for structure-activity relationship (SAR) studies, allowing the structural elements important for the potent biological activities of the parent natural products to be deciphered.\textsuperscript{15,16}

To showcase our research efforts, this review focuses on the total synthesis and biological evaluation of antillatoxin 1 and analogues.\textsuperscript{8} The general synthetic routes to 1 provided the first chemical basis for systematically correlating its unusual side chain structure with biological functions. Specifically, SAR studies of the synthetic analogues were performed to elucidate the three-dimensional shape of the side chain that is essential to its toxicity.\textsuperscript{17,18} The obtained topochemical information was applied to the rational design and synthesis of an artificial analogue with a photoresponsive function that the original natural product does not possess.\textsuperscript{19}

**Total synthesis of antillatoxin**\textsuperscript{8}

Voltage-gated sodium channels (VGSC) are transmembrane proteins that initiate action potentials in nerve, muscle and other electrically excitable cells, thereby playing a central role in neurotransmission.\textsuperscript{20} Since various neuronal cell functions are dependent on the regulation of Na\textsuperscript{+} through VGSCs, VGSC modulators are useful research tools for neuroscience, as well as therapeutic agents for neurological disorders.\textsuperscript{21,22} The six distinct specific binding sites on VGSCs for small molecules are classified with respect to their binding characteristics.\textsuperscript{23,24}
Antillatoxin (1, Fig. 1), a cyclic lipopeptide, was isolated from the marine cyanobacterium *Lyngbya majuscula* as a potent ichthyotoxic compound.\(^{25}\) Exposure to *L. majuscula* blooms are associated with adverse human health effects, including respiratory irritation, eye inflammation, and severe contact dermatitis. Goldfish toxicity measurements with 1 showed it to be among the most ichthyotoxic metabolites isolated to date from a marine plant (LD\(_{50}\) 0.05 µg/mL), exceeded in potency only by brevetoxins. Detailed biological studies of this peptide revealed that 1 is an activator of VGSC,\(^{26-28}\) although its binding site on VGSC is unknown. Compound 1 exhibits potent cytotoxicity toward Neuro 2a mouse neuroblastoma cells (EC\(_{50}\) = 45 nM), which express VGSCs on their membranes. Furthermore, enhancement of neurite outgrowth in cerebrocortical neurons by 1 was reported at a concentration of 30–100 nM after 24 h incubation.\(^{29}\) These VGSC-activating and neuritogenic activities both emphasize the potential use of 1 as a new biological probe.\(^{30}\)

![Fig. 2. Total synthesis of antillatoxin.](image)

The macrocycle of 1 is composed of a ω-hydroxycarboxylic acid, glycine, N-methyl-L-valine and L-alanine (Fig. 1).\(^{31-35}\) One of the most characteristic structural features of 1 is a 9-t-butyl-6,8-dimethyl-6,8-diene unit attached to C5 of the cyclic peptide backbone. We speculated that the unique three-dimensional shape of the lipophilic side chain may play an important role in allosteric activation of the channels through hydrophobic interactions. To uncover the structural function of the side chain in the neurotoxicity of 1, we devised a unified strategy for synthesizing 1 and its analogues with distinct side chains (Fig. 2). Therefore, the diene was envisioned to be elongated from the common intermediate 9 through C7–C8 bond formation by a Suzuki-Miyaura coupling reaction.\(^{36}\) This synthetic scheme allowed us to access a variety of side chain modified analogues by varying the final reaction.

The synthesis of 1 started from an anti-selective asymmetric aldol reaction\(^{37}\) between silyl enol ether 2 and aldehyde 3 to set the two stereocenters at C4 and C5 of 4 (Fig. 2). The nine-step functional group manipulations from 4 led to the right half 5 of the common intermediate 9. Coupling of the left half 6 with 5 resulted in the formation of ester 7. Then, chemoselective mCPBA oxidation of sulfinyl 7 generated the corresponding sulfoxide, which underwent a Pummerer reaction,\(^{38}\) leading to thioester 8. The use of the C1-acetal structure as a thioester surrogate was particularly important for the success of the synthesis, because premature formation of an sp\(^2\) carbon at C1 allowed the C3/C12 exo-olefin to isomerize into a C2/C3 conjugated olefin under the conditions used.
After removal of the Boc group of 8 under acidic conditions, the thioester was effectively activated by AgNO₃ in the presence of HOAt and i-Pr₂NEt to give the common intermediate 9 through high-yield macrolactam formation (Fig. 2). Finally, the requisite boronic ester 10 was coupled with vinyl iodide 9 under Suzuki-Miyaura reaction conditions using a reagent combination of PdCl₂(dppf), Ph₃As and Cs₂CO₃ giving rise to antillatoxin 1.

Hence, an efficient synthetic route to the antillatoxin structures was successfully developed. Use of a phenylsulfonyl methylthiomethyl group as a thioester surrogate and the introduction of carbon chains by the cross coupling reaction at the last stage are two key features of this synthesis. The route enabled a gram scale preparation of 9, which was used for generation of a variety of structural analogues of antillatoxin.

Importance of the bulky side chain of antillatoxin

The tert-butyl (t-Bu) group has been incorporated in numerous synthetic organic compounds because of its steric bulkiness, hydrophobic property and unique reactivity. In contrast, relatively few natural products bearing the t-Bu substructure have been structurally determined, yet representative examples of these natural products, such as ginkgolide A, apratoxin A and polytheonamide B, were demonstrated to exhibit potent and selective biological activities.

To investigate the effect of the terminal C9-t-Bu group on the toxicity of 1, the C9-substituent was replaced with five other groups of varying sizes, and antillatoxin 1 and analogues 12a–e were subjected to a cytotoxicity assay (Table 1). Specifically, vinyl iodide 9, which was used as the intermediate for the total synthesis of 1, was coupled with boronic esters 11a–e under the aforementioned Suzuki-Miyaura conditions, delivering adducts 12a–e.

The cytotoxicities of 1 and the obtained 12a–e were evaluated using Neuro 2a cells. Although the parent natural product 1 exhibited the most potent cytotoxicity, four compounds 12b–e with different van der Waals volumes of the C9-substituents (69–210 Å³) all showed submicromolar level activities (EC₅₀ = 62–990 nM) in the assay. Surprisingly, introduction of the significantly larger adamantyl (12d) and trisopropylsilyl groups (12e) did not lead to loss of activity, while elimination of the three methyl groups from 1 diminished the potency 440-fold (12a). Therefore, these focused SAR studies on the five C9-substituted antillatoxin analogues 12a–e demonstrated that the bulkiness of the C9-terminal group of the side chain strongly correlates to potent cytotoxicity, and the activity of 1 is influenced more by terminal-truncation (12a) and less by terminal-enlargement (12d,e). Importance of the large side chain was also confirmed by negligible toxicity of the common intermediate 9 (EC₅₀ > 100,000 nM).

Importance of the orientation of the terminal t-Bu group

We speculated that not only the bulkiness of the t-Bu group, but also the overall three-dimensional shape of the t-Bu substituted side chain, may possess a specific function in the activity. To address this issue, we specifically designed four side chain analogues 14, 15, 18a and 18b, in which the conformation of the 6,8-diene moiety was modified without changing the molecular size or the chemical properties of 1 (Fig. 3). Synthesis and biological evaluation of 14, 15, 18a and 18b uncovered the

| compd. | R        | yield (%) | cytotoxicity (EC₅₀/nM) | volume of R (Å³) |
|--------|----------|-----------|------------------------|-----------------|
| 12a    | CH₃      | 75        | 29,000                 | 33              |
| 12b    |          | 86        | 320                    | 69              |
| 1      |          | 78        | 45                     | 87              |
| 12c    |          | 80        | 160                    | 110             |
| 12d    |          | 80        | 62                     | 160             |
| 12e    |          | 78        | 990                    | 210             |

aAgainst Neuro 2a mouse neuroblastoma cells. bVolume of terminal group R was estimated as van der Waals volume of H-R by using Spartan ‘08 software (Wavefunction Inc.: Irvine, CA) at the HF level with internally stored 6-31G** basis set.
crucial orientation of the terminal t-Bu group for the potent activity of 1.

Derivatization from the common intermediate 9 again allowed us to access a variety of side chain modified analogues by only varying the final reaction (Fig. 3). Upon use of 13, the C8-demethyl analogue 14 was generated using a reagent combination of PdCl2(dppf), Ph3As and Cs2CO3. In sharp contrast to the potent toxicity of the parent natural product 1 (EC50 45 nM) toward Neuro 2a (Table 2), the C8-demethyl analogue 14 was found to be approximately 250 times less toxic than 1 (EC50 11,000 nM), even though the dienes of 1 and 14 have similar steric bulkiness. This result clearly shows that the methyl substituent at C8 (CH3-15) plays a decisive role in the potent neurotoxicity of antillatoxin.

To gain insight into the relationship between the assay data and the conformational behavior of the molecules, detailed NMR analyses of 1 and 14 were carried out. The 1H NMR chemical shifts for the core of 14 were in excellent agreement with those of 1. Thus, the structure of the macro lactam core of 14 was virtually identical to that of 1, and deletion of the CH3-15 group had no influence on the specific conformation of the macrocycle. In contrast, the conformations of the side chains of 1 and 14 were different based on the 1H NMR chemical shifts, as well as the 3JHH and NOE data (Fig. 4). The C8-demethyl antillatoxin 14 shows a NOE only between C9-H and C7-H, and the value of 3JHH between C7-H and C8-H was measured as 10.3 Hz. Both of these findings indicated that the conjugated diene moiety of 14 adopts a planar s-trans conformation around the C7–C8 bond as a single stable isomer, and thus that the C6–C7–C8–C9 torsion angle (φ) should be approximately 180°. In contrast, the diene of antillatoxin 1 apparently deviates from the planar conjugated conformation, since C9-H of 1 is in spatial proximity not only to C7-H in a 1,3-relationship, but also to C14-H in a 1,5-relationship, based on the NOEs.

To clarify the conformational preference of the dienes of 1 and 14, ab initio calculations were carried out using model structures at the RHF/6-31G** level (Fig. 5a). The C6–C7–C8–C9 torsion angle (φ) was varied from 0° to 360° and energy-minimized using MMFF40 prior to the MO calculations, while the coordinates of the macrolactam core were fixed as the energy-minimized conformation of 1 which satisfied the NMR data. The diene moiety of C8-demethyl 14 was found to exhibit a single most-stable s-trans
conformation ($\phi = 180^\circ$), which agreed with the results of the NOE experiment. The three dimensional structure of the stable $s$-trans conformation of 14 is shown in Table 2. On the other hand, the $s$-trans conformation is significantly destabilized in 1. This would be explained by a greater destabilization energy from the steric interactions between the CH$_3$-14 and CH$_3$-15 in a 1,3-relationship compared to the stabilizing conjugation energy gained from the planar conformation.41) Accordingly, the diene of 1 has two stable twisted conformations, 1a ($\phi = 60^\circ$) and 1b (300°), in which C9-H is proximal to both C7-H and C14-H, as shown in the NOE data (Fig. 4 and Table 2). Importantly, the three-dimensional orientation of the bulkiest $t$-butyl group in these two conformations of 1 is significantly different from that of 14. Based on the NMR and simulation data for 1 and 14, we hypothesized that the twisted shape of the $t$-Bu-substituted diene of 1 was critical in the activation of the sodium channel, resulting in neurotoxicity.

This hypothesis was further corroborated by the synthesis and biological evaluation of analogue 15 (Fig. 3). Analogue 15 has tetrahedral sp$^3$ carbons at C8 and C9 in place of the planar sp$^2$ carbons of 14, and thus is expected to provide more rotational freedom around the C8–C9 bond. Chemoselective hydrogenation of the C8–C9 double bond of triene 14 was accomplished using Pd(OH)$_2$/C under a hydrogen atmosphere in benzene, giving rise to 8-demethyl-8,9-dihydro-antillatoxin 15. Interestingly, 15 showed NOEs from C9-H to both C7-H and C14-H, suggest-

Table 2. Side chain structures, stable conformers and cytotoxicity data of antillatoxin and analogues

| stable conformer(s) | $\phi$ ($E_{360}$) | EC$_{50}$/nM |
|---------------------|-------------------|-------------|
| 1a                  | 60°   | 45          |
| 1b                  | 300°  |             |
| 14                  | 180°  | 11,000      |
| 15a                 | 120°  | 1,200       |
| 15b                 | 250°  |             |
| 18a                 | 140°  | 350         |
| 18b                 | 230°  | 5,700       |

Fig. 5. *Ab initio* conformation energy profiles of the $\phi$ [C6–C7–C8–C9] dihedral angles of a) 1, 14, and 15, and b) 18a and 18b.
ing a twisted conformation of the side chain (Fig. 4). Non-planar gauche conformations, 15a (φ = 120°) and 15b (φ = 250°), were found to be the two most favored conformations based on ab initio calculations (Fig. 5a). It is notable that 1,3-allylic strain with the C14-methyl group is avoided in these conformations, and the shapes of 15a and 15b are similar to those of 1a and 1b, respectively (Table 2). Importantly, compound 15, possessing a saturated twisted side chain, indeed exhibited approximately 10 times stronger neurotoxicity than the planar demethyl compound 14 (EC50 = 1,200 nM, Table 2). Therefore, we were able to regain the biological activity of 15 only by introducing two hydrogens at C8 and C9 of 14.

Cytotoxicity evaluation of 1 and 15 indicated that the two twisted conformations 1a/1b and 15a/15b play a significant role in potent neurotoxicity. Next, we determined the bioactive orientation of the t-Bu group in regard to the side chain. To do so, the two C8-epimeric isomers of C8,15-dehydro antillatoxin (18a and 18b) were designed (Fig. 3) as their C8 stereocenters would restrict conformational flexibility. As shown in the calculated energy profiles of 18a and 18b (Fig. 5b), their most prefered dihedral angles (φ) are 140° and 230°, respectively, at which the 1,3-allylic strain with the C14-methyl group is minimized. Thus, C8-epimers 18a and 18b would serve as mimics of conformers 1a/15a and 1b/15b, respectively (Table 2).

The Suzuki-Miyaura coupling reaction between the common intermediate 9 and boronic ester 16 gave rise to 17, a regiosomer of original natural product 1 (Fig. 3). When 17 was treated with 2,4,6-trisopropylbenzenesulfonoylhydrazide42,43 and Et3N, in situ generated diimide chemoselectively reduced the C8,C15-disubstituted olefin in the presence of other two olefins to produce a mixture of 18a and 18b. The obtained mixture was purified using reversed phase HPLC to afford 18a (48%) and 18b (24%). The C8 stereochemistries of these compounds were determined through chemical derivatization.

The difference in cytotoxic potency between 18a and its C8-epimer 18b was evaluated using Neuro 2a cells (Table 2). As a result, 18a (350 nM) was found to be 15 times more potent than 18b (5,700 nM), indicating that the t-Bu orientation of 18a is more appropriate than that of 18b for high toxicity. Since 18a is a mimic of conformer 1a, these data suggested that 1a (φ = 60°) has a more desirable stable conformation than 1b (φ = 300°) for exerting bioactivity.

Thus, we achieved the syntheses of 8-demethyl 14, 8-demethyl-8,9-dihydro 15 and 8,9-dihydroantillatoxins 18a and 18b. Structural and biological studies of these compounds revealed that the specific orientation of the bulky t-Bu-group is extremely important for the potent activity of 1. The strategy of conformation design employed here may have applications for defining the bioactive shape of various natural products and pharmaceuticals. In addition, the present structure-activity relationship study provides valuable information for developing useful VGSC activators and potent neuritegenic agents.

Rational design of a photoresponsive analogue of antillatoxin

Switching a specific biological process on/off by an external stimulus such as light provides a powerful means to investigate dynamic phenomena in a time-resolved fashion.44-49 We envisioned that the creation of light-sensitive antillatoxin analogues would be useful for the spatiotemporal control of antillatoxin-induced biological events. A prerequisite to the design of such molecules is to define an appropriate site within 1 where photoresponsive functional groups can be readily attached.

The SAR data in Tables 1 and 2 revealed that a small shape alteration in the C5-side chain modulates the bioactivity of antillatoxin derivatives. In particular, the large differences in cytotoxicity between 12a and 1 in Table 1 suggested that the cytotoxic activity of the antillatoxin structure would be artificially switched off by light-promoted truncation of its C5-side chain terminus.

Figure 6 shows the molecular design and synthesis of photoresponsive antillatoxin 20, where a 2-nitrobenzyl (NB) group was installed as the photo-cleavable substitution group.50,51 The diene side chain of 1 was simplified to the styrene side chain of 20 to the requisite boronic ester fragments for the styrene structure could be easily synthesized. Importantly, the bioactive twisted conformation around the C7–C8 bond of 1 would be reproduced in 20 by steric interaction between the C14-methyl group and two carbons of the phenyl ring (highlighted in gray circles).

The aryl boronic acid with the sterically cumbersome bis-NB acetal structure 19 was attached to the C7 of the common intermediate 9 using PdCl2(dppf), Ph3As, and Cs2CO3, leading to the adduct 20 (Fig. 6). Compound 20 was exposed to UV light to test if the NB groups could be efficiently
The photodeactivation of 20 affected activity even when Neuro 2a cells were present (Fig. 7). One set of samples comprising Neuro 2a and 20 was treated with the UV fluorescent light for 30 min prior to the incubation, and the other set was kept in the dark before the incubation. A significant loss of activity (EC50 = 50,000 nM) was observed for the UV pre-irradiated wells in comparison to the control (EC50 = 700 nM). Thus, the activity of the antillatoxin analogues was successfully reduced in situ by a factor of 1/70 via the photoinduced change of the side chain of 20.

In summary, based on knowledge from SAR studies, we designed and synthesized analogue 20 containing photocleavable NB groups at the terminus of the styrene side chain. Cytotoxicity assays of 20 with and without photo-stimulus proved that the biological activity of antillatoxin is modulated by altering the size of the terminal group. Therefore, the photoresponsive analogue 20 represents a structural basis for development of new tools in neuroscience to investigate and control the biological actions of antillatoxin in a time-resolved fashion.

**Conclusion**

The total synthesis of antillatoxin 1, a neurotoxic natural product, was achieved though introduction of a carbon chain to the common intermediate 9 using the Suzuki-Miyaura coupling reaction as the final transformation. Five C9-substituted analogues (12a–e) and four C8-modified analogues (14, 15, 18a, 18b) were efficiently prepared by chaining the coupling partner of 9 at the last stage. SAR studies of the ten synthetic molecules demonstrated that the three-dimensional shape of the t-Bu attached side chain significantly affects the potent neurotoxicity of 1: the bulkiness of the C9-substituent and the specific dihedral angle of the C7–C8 bond strongly correlated to potent cytotoxicity, and truncation of the terminus induced activity loss. Furthermore, the photoresponsive antillatoxin derivative 20 was designed and synthesized as a new prototype molecule for the spatiotemporal control of antillatoxin-induced biological events. Bis-NB acetal derivative 20 exhibited high toxicity and was effectively deactivated by photochemical conversion into 21.

The SAR studies of antillatoxin and the artificial analogues taken together have not only deepened our understanding of the precise structural requirements for the biological functions of antillatoxin, but also have led to the discovery of a new molecule with a
photoresponsive function. These achievements demonstrate the benefits of total synthesis endeavors and the importance of efficient construction of complex molecules, and offer a unique opportunity for further exploration in chemical biology studies and drug discovery efforts. Further studies on complex natural products will lead to the rational generation of novel natural product based molecules for functional control of ion channels, and the discovery of new therapeutic agents for a variety of ion channel-related disorders.

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Profile

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