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Total Synthesis of Sintokamide C

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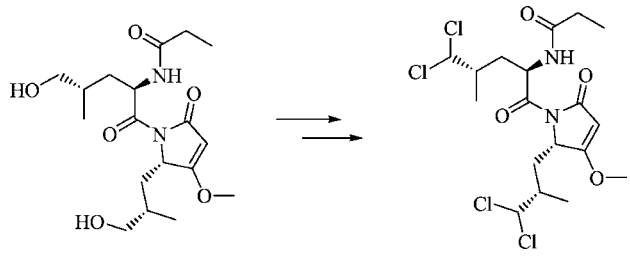
ABSTRACT



A convergent stereoselective synthesis of sintokamide C was accomplished in 14 steps with an overall yield of 3.8% starting from Garner's aldehyde, unambiguously confirming its structure.

Almost five thousand natural products that contain one or more carbon−halogen bonds have been isolated. The structures vary from simple phenolic and aliphatic compounds to complex polyketides and oligopeptides.[1,2] These natural products exhibit a variety of biological activities, including analgesic,[2] antitumor,[3] anti-HIV,[4] insecticidal,[5] antimicrobial,[6] and antibiotic properties.[7] Most of these halogenated natural products are secondary metabolites produced by marine organisms, which have been found among various species of algae, fungi, sediment-derived bacteria, sponges, mollusks, coelenterates, and several marine worms. Some of these compounds have been proven useful in studies directed toward the elucidation of their biochemical pathways. Several groups of halogenating enzymes have been discovered and investigated on the biochemical and genetic levels.[8] Enzymatic halogenation through oxidative mecha-

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nisms is the most common route to these metabolites, though direct halogenation via halide anion incorporation is also known to proceed through both enzymatic and nonenzymatic pathways.[1a,9]

Marine cyanobacterium *Lyngbya majuscula*[10] and sponge genus *Dysidea* produced chlorinated peptides.[11] We have been interested for some time in marine peptides and view their syntheses as a key route to structural modification and subsequent activity control.[12] Early on, we have reported the total synthesis of dichlorinated cyclodepsipeptide lyngbyabellin A.[12h] Here we report on our efforts in the total synthesis of tetrachlorinated peptide sintokamide C.

Sintokamides were isolated from specimens of the marine sponge *Dysidea* sp. collected in Indonesia.[13] Their structures were elucidated by a combination of spectroscopic and single-crystal X-ray diffraction analyses. The sintokamides are the first small molecules known to selectively block transactivation of the *N*-terminus of the androgen receptor in prostate cancer cells.[13] The biological potential as well as the remarkably novel tetrachloride structure of sintokamide C makes it an interesting synthetic target.

Structurally, sintokamide C contains an unusual *N*-acylpyrrolinone moiety that is connected by an amide linkage. The tetrachlorinated-peptide-based natural products are rarely encountered and they have only been reported in the context of dysamide B[14] and dysithiazolamide.[15]

Retrosynthetic analysis (Figure 1) suggested that sintokamide C (**1**) might arise from bis-aldehyde **2**. As the *gem*-

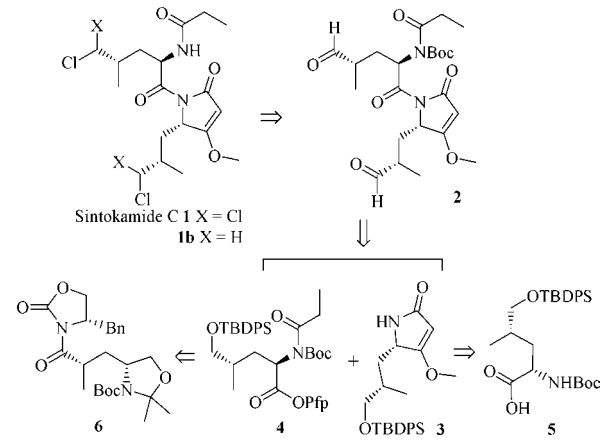
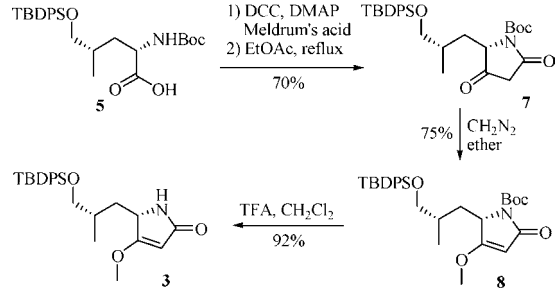


Figure 1. Retrosynthetic analysis.

chloride is highly labile and undergoes base-promoted dehydrohalogenation, the *gem*-chloride moieties in **1** would be formed at the final stage in the synthesis. Further disconnection of **2** at the *N*-acyl-pyrrolinone linkage provides two intermediates (**3** and **4**) of similar structural complexity. Both **3** and **4** could be synthesized rapidly from commercially available compounds.

The fragment **3** (Scheme 1) was constructed in three steps from the known intermediate **5**.[15b] Condensation of acid **5**

Scheme 1



with Meldrum's acid in the presence of DCC and DMAP, followed by thermolysis of the intermediate produced tetramic acid **7** in good yield.[16] Conversion of tetramic acid **7** into its *O*-methylated derivative (**8**) was accomplished by

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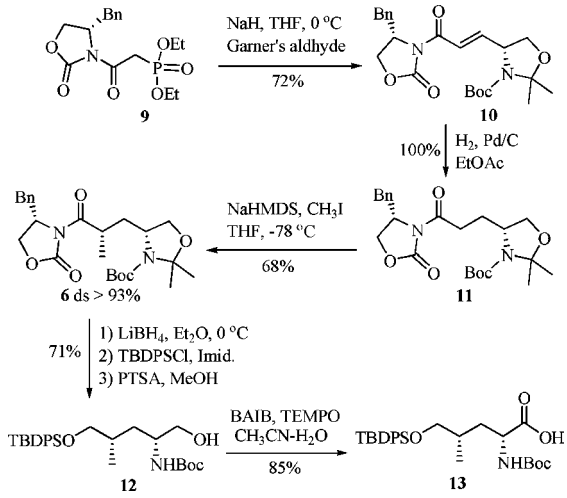
treatment with diazomethane. Removal of the *N*-Boc protecting group in **8** with TFA produced tetramic acid **3** in 92% yield.

The synthesis of the amino acid derivative **13** (Scheme 2) commenced with Horner−Wadsworth−Emmons olefination

Scheme 2



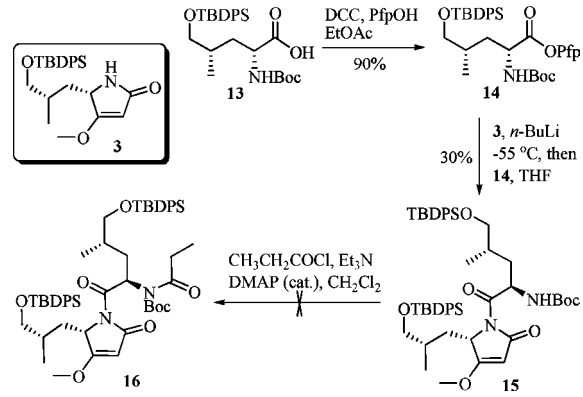
of Garner's aldehyde with phosphonate **9** to provide the corresponding (*E*)-α,*β*-unsaturated oxazolidinone **10**, in 72% yield.[17] Enoate **10** was hydrogenated to give **11**, which was then converted into its sodium enolate and methylated to give **6** in 68% yield with >93% diastereoselectivity.[18]

Reductive cleavage of the auxiliary followed by protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether gave the acetonide, which was cleaved under acidic conditions to afford **12** in 71% yield (over three steps). Oxidation of the resulting primary alcohol with TEMPO-BAIB[19] afforded the corresponding acid **13**, which set the stage for fragment assembly.

Our initial approach for assembling the core structure of sintokamide C envisioned capture of the anion derived from deprotonation of the secondary amide of tetramic acid **3** by an active ester derived from acid **13** (Scheme 3). Thus, activation of the carboxylic functionality of **13** as its pentafluorophenol ester (**14**),[20] followed by condensation with the lithium amide of **3** afforded **15** in 30% yield. To our disappointment and surprise, all attempts to achieve the *N*-propionylation of *tert*-butyl carbamate **15** with propionyl chloride were unsuccessful.

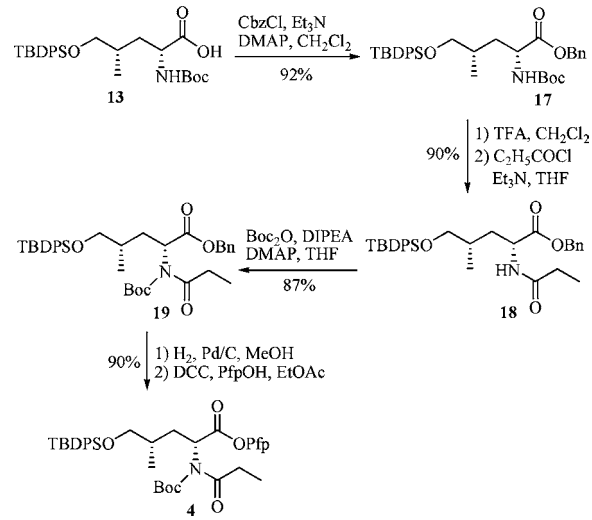
In an effort to facilitate the installation of the propionyl side chain, a revised route was developed (Scheme 4)

Scheme 3



wherein the *N*-propionylation was performed before reprotection of the amide nitrogen with Boc_2O in the presence of DMAP. Thus, benzyl ester **17** was prepared from acid **13** with benzyl chloroformate and DMAP.[21] After removal of the Boc protecting group in **17**, the resulting amine was treated with propionyl chloride in the presence of triethylamine to afford amide **18** in 90% yield. Reprotection of the amide nitrogen in **18** as its Boc derivative next produced **19** in 87% yield. Hydrogenolytic cleavage of the benzyl ester produced the corresponding carboxylic acid, which was then converted into its pentafluorophenol ester **4** under the condition described for the synthesis of **14**.

Scheme 4



Further review of the literatures indicated the optimized conditions for *N*-acylation of 4-alkylated pyrroline-2-ones has been developed by Tønder and co-workers.[22] With the synthesis

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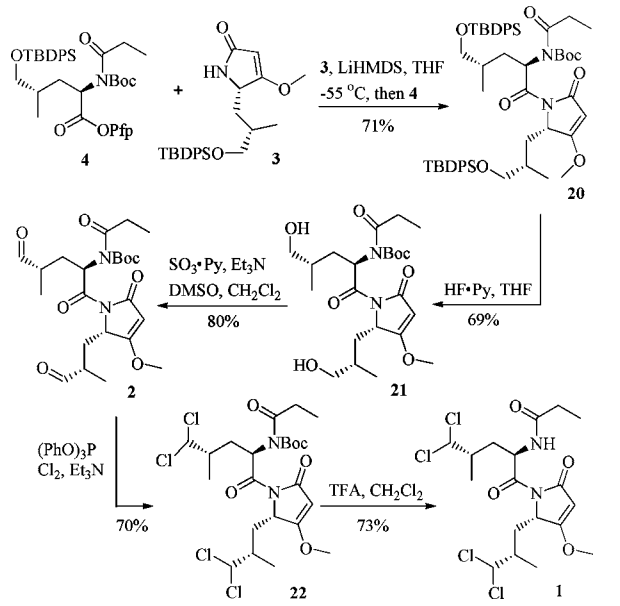
of the key subunits **3** and **4** completed, the assembling of these subunits leading to **20** was investigated (Scheme 5). Thus, treatment of **3** in THF with lithum hexamethyldisilazide at −55 °C for 20 min provided the lithium anion, which was reacted

Scheme 5



with pentafluorophenol ester **4** at −55 to −45 °C for 3 h to afford **20** in 71% yield after chromatography over silica gel. HF/pyridine cleavage of two primary TBDPS ethers afforded alcohol **21**, which was subsequently oxidized by using the Parikh−Doering protocol[23] to afford the corresponding bis-aldehyde **2** in 80% yield. The stage was now set for the generation of the two critical dichloromethyls. Although the use of various chlorination agents for the conversion of aldehydes to the corresponding dichloromethyls is known, only the Rodríguez's modification[24] of the Takeda conditions[25] has been successfully applied to the total synthesis of dysamide B[14b] and (−)-dysithiazolamide.[15b] Much to our disappointment, reaction of bis-aldehyde **2** under the modified Takeda conditions yielded multiple degradation products. Recently, Prati and co-workers[26] developed a mild protocol for the synthesis of *gem*-dihalides using triphenyl phosphate-halogen-based reagents. Gratifyingly, chlorination of bis-aldehyde **2** according to Prati's procedure proceeded without any complications to afford tetrachlorides **22** in 70% yield.

Finally, the Boc group of **22** was removed uneventfully with trifluoroacetic acid in dichloromethane to deliver **1** in 73% yield after chromatography over silica gel. The spectral data for synthetic **1** (^{1}H, ^{13}C NMR and HMRS) were identical with those published for the natural product,[13] and the optical rotation of our product, $[\alpha]^{20}_D$ +63.3 (*c* 0.1, CH_2Cl_2), corresponded well with the literature value,[13] $[\alpha]^{25}_D$ +58.7 (*c* 0.26, CH_2Cl_2), leading us to conclude that synthetic **1** was of the same absolute stereochemistry as natural sintokamide C. In addition, we also synthesized the dichlorides analogue (**1b**).[27]

The synthetic sample of sintokamide C was observed to exert its biological activity by inhibiting cell proliferation on the androgen receptor-expressing LNCaP cell line with IC_{50} at 35 μM (Figure 2). However, **1** did not suppress the

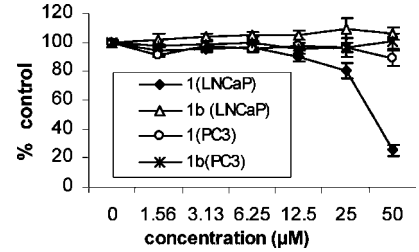


Figure 2. Effect of sintokamide C and **1b** on prostate cancer cell proliferation. LNCaP and PC3 were cultured for 48 h in the presence of various concentrations of sintokamide C and **1b**. Proliferation was measured by MTS assay as described in the Supporting Information.

proliferation of the androgen-independent PC3 cell line (Figure 2). The proliferation of LNCaP and PC3 was completely unaffected by analogue **1b**.[27] Our findings indicated that sintokamide C inhibited the proliferation of prostate cancer cells through blocking androgen receptor activity.

In summary, we have developed a convergent synthesis of sintokamide C. Key steps en route to this natural product include the application of Tønder protocol for *N*-acylation of 4-alkylated pyrroline-2-ones and the chlorination of bis-aldehyde by the use of Prati's procedure to produce *gem*-dihalides.

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Supporting Information Available: Full details for experimental procedures for compounds **1**, **1b**, **3**, **4**, **6**−**8**, **10**−**15**, and **17**−**22**, and ^{1}H and ^{13}C NMR spectra for compounds **1**, **1b**, **2**−**4**, **6**−**8**, **10**−**12**, **15**, and **17**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) For the synthesis of dichlorides analogue **1b**, please see the Supporting Information.