Chlorinated Natural Products

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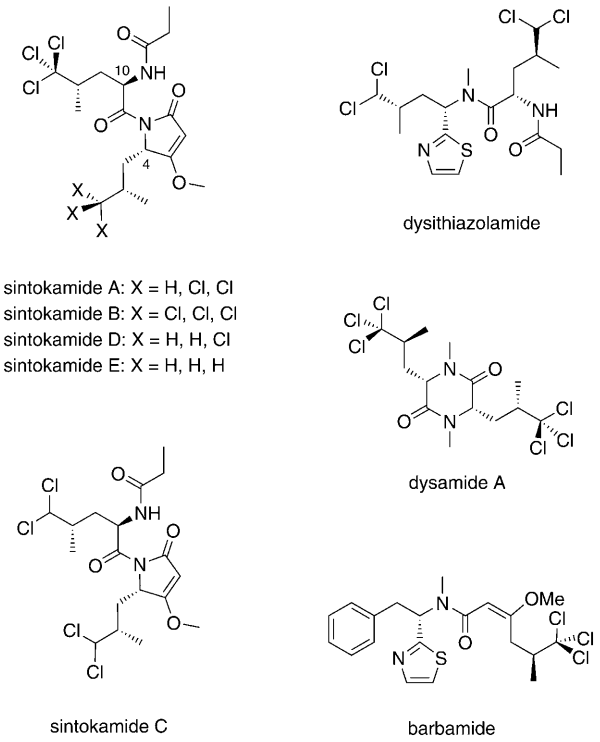
Concise Total Synthesis of Sintokamides A, B, and E by a Unified, Protecting-Group-Free Strategy**

*Zhenhua Gu and Armen Zakarian**

Considered rare and exotic only about 50 years ago, more than 4000 halogenated natural products have been isolated and characterized to date.[1] These compounds exhibit a wide range of biological activity, including antitumor,[2] anti-HIV,[3] and analgesic activity.[4] Chlorinated marine natural products containing dichloromethyl or trichloromethyl groups, such as barbamide,[5] dysithiazolamide,[6] and dysamide,[7] constitute an important subclass of compounds. In 2006, the Gerwick and Walsh groups uncovered a novel class of halogenating enzymes that catalyzed halogenation at unactivated aliphatic carbon atoms of amino acid residues linked to a peptide carrier protein.[8] However, chemical methods for stereoselective di- or trichloromethylation are still limited.[9] Recently, our research group described a practical and efficient method for the haloalkylation of titanium enolates with high diastereoselectivity.[10]

The cyanobacterial metabolites sintokamides A–E were isolated by Sadar et al. from the marine sponge *Dysidea* sp. collected near Palau Sintok, Indonesia, during the search for natural product derived drugs for the treatment of hormone-refractory prostate cancer (Scheme 1).[11] The relative and absolute configuration of sintokamide A was established by X-ray diffraction analysis. The sintokamides are the first natural products reported to selectively block transactivation of the N terminus of the androgen receptor in prostate cancer cells. Furthermore, it was found that sintokamide A is as effective as bicalutamide in blocking androgen-induced proliferation in androgen-sensitive LNCaP prostate cancer cells.[11]

The molecular structure of the sintokamides contains readily recognizable (2*S*,4*S*)- or (2*R*,4*S*)-5-chloroleucine subunits (with various degrees of chlorination) united by a tetramic acid fragment: the *O*-methyltetramate is structurally related to L-leucine. Sintokamide C is the only member of the group that does not contain a 5,5,5-trichloroleucine fragment. Its synthesis was recently completed by Ye and co-workers, who relied on a unique strategy that is not readily applicable to the synthesis of trichloromethyl-substituted sintokamides.[12] Among our goals was the development of a concise, general synthesis of sintokamides with the capacity to deliver substantial quantities of the marine natural products for subsequent biological studies. Herein, we describe the total synthesis of sintokamides A, B, and E by a unified strategy that requires no use of protecting groups.



Scheme 1. A diverse group of halogenated natural products derived from chlorinated leucine.

The recently developed stereoselective ruthenium-catalyzed radical haloalkylation of titanium enolates occupied a central position in our planned synthesis (Scheme 2).[10] This methodology provides a convenient, experimentally simple approach to the stereoselective introduction of the dichloro- and trichloromethyl groups found in sintokamides and related natural products. Construction of the central tetramic acid subunit at the final stage of the synthesis was designed to avoid the known N-acylation procedures for pyrrolones, which require multiple protecting-group manipulations.[13] One of the key challenges anticipated in the construction of the tetramic acid core was to maintain the integrity of the stereogenic centers at C4 and C10.[14] Accordingly, sintokamide A (**1**), which we selected as an initial target because of its intriguing bioactivity, could be formed directly from carboxylic acid **4** in the final step of the synthesis, thus

[*] Dr. Z. Gu, Prof. Dr. A. Zakarian
Department of Chemistry and Biochemistry
University of California at Santa Barbara
Santa Barbara, California 93106 (USA)
Fax: (+1) 805-893-4120
E-mail: zakarian@chem.ucsb.edu

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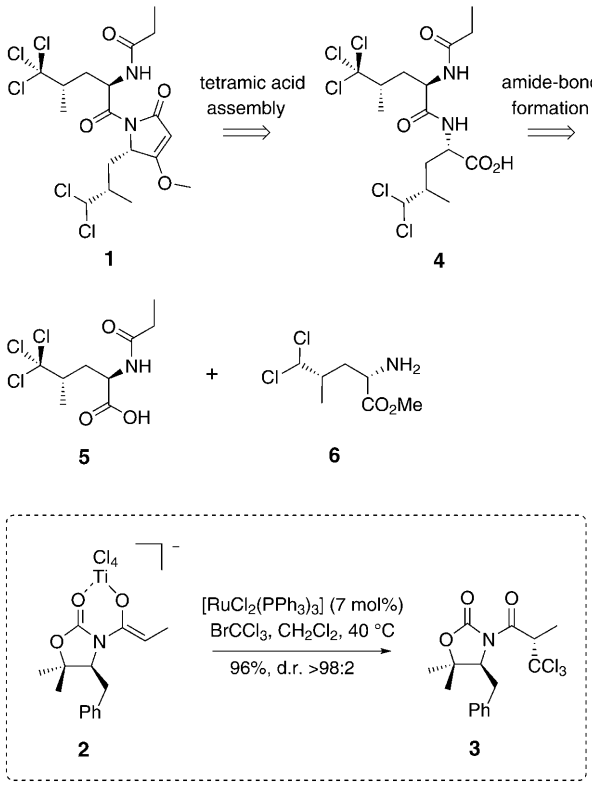
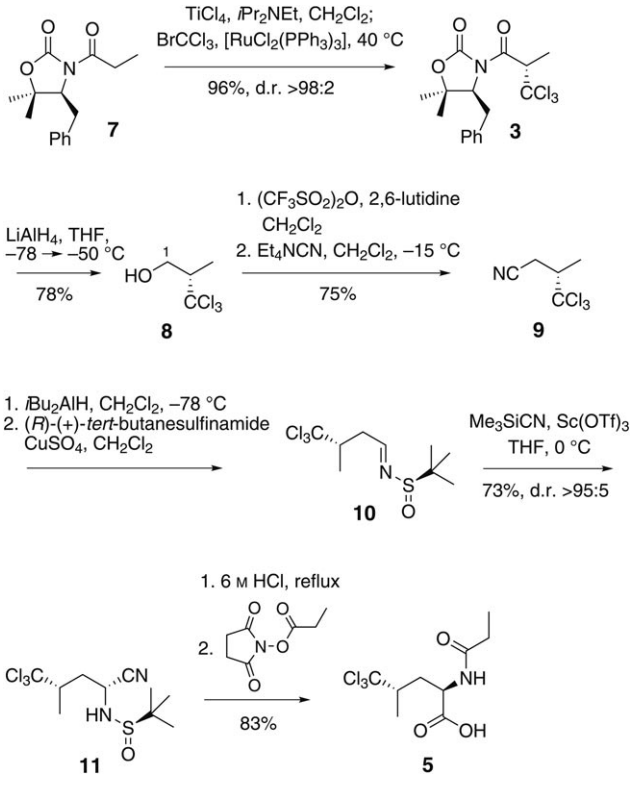


Scheme 2. Outline of the synthetic plan.



Scheme 3. Synthesis of (2*R*,4*S*)-*N*-propionyl-5,5,5-trichloroleucine (**5**). Tf = trifluoromethanesulfonyl.

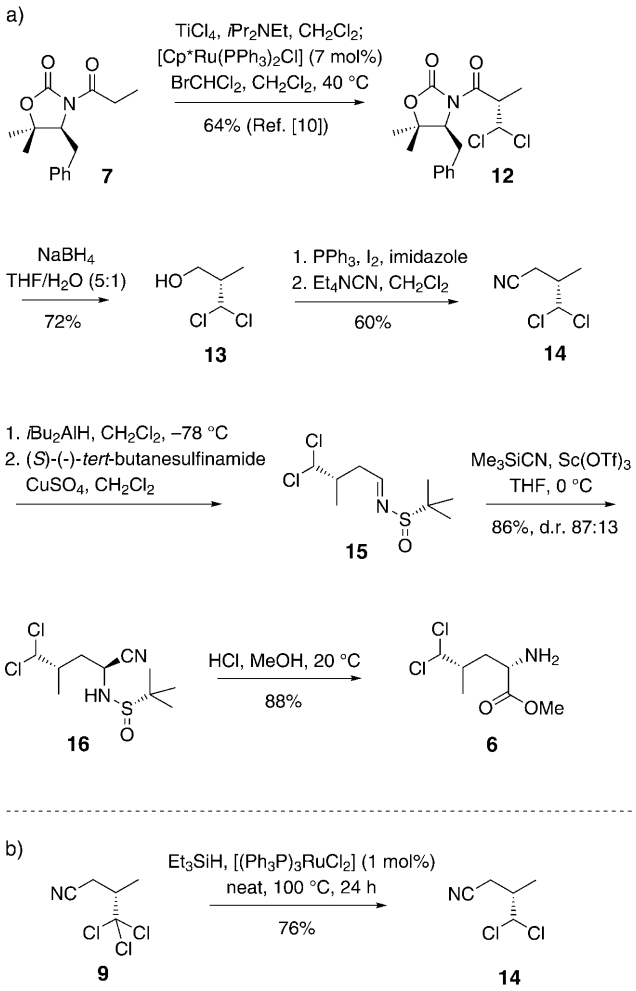
eliminating the need for protecting groups in the assembly of the pyrrolone ring. Intermediate **4** could be accessed directly by standard amide-bond formation from chlorinated precursors **5** and **6**. Convenient preparation of the stereochemically divergent chlorinated amino acids **5** and **6** was enabled by a modular approach based on two key transformations: 1) asymmetric chloroalkylation and 2) an asymmetric Strecker reaction.

The synthesis of (2*R*,4*S*)-*N*-propionyl-5,5,5-trichloroleucine (**5**) commenced with the direct, ruthenium-catalyzed trichloromethylation of oxazolidinone **7** via its titanium enolate **2** generated in situ (Scheme 3). The reaction proceeded in 96% yield with essentially complete stereoselectivity on a multigram scale. To access **8**, we initially subjected the oxazolidinone to reductive cleavage with $NaBH_4$ in aqueous THF. Significant monodechlorination was observed under these conditions at various temperatures, regardless of whether the solvent used was degassed or oxygenated. The extent of the side reaction was minimized with $LiAlH_4$ as the reducing agent (78% yield of **8**, <3% yield of **13**).[15] We found that derivatives of alcohol **8** were remarkably deactivated for nucleophilic substitution at the 1-position; therefore, formation of the stable trifluoromethanesulfonate was necessary for an efficient substitution with cyanide to give nitrile **9**. After a two-step transformation of **9** into sulfinimine **10**,[16] a diastereoselective scandium-catalyzed Strecker reaction furnished nitrile **11** in 73% yield (d.r. > 95%).[17] Hydrolysis of **11** in 6 M aqueous HCl, followed by direct N-propionylation, completed the preparation of **5**.

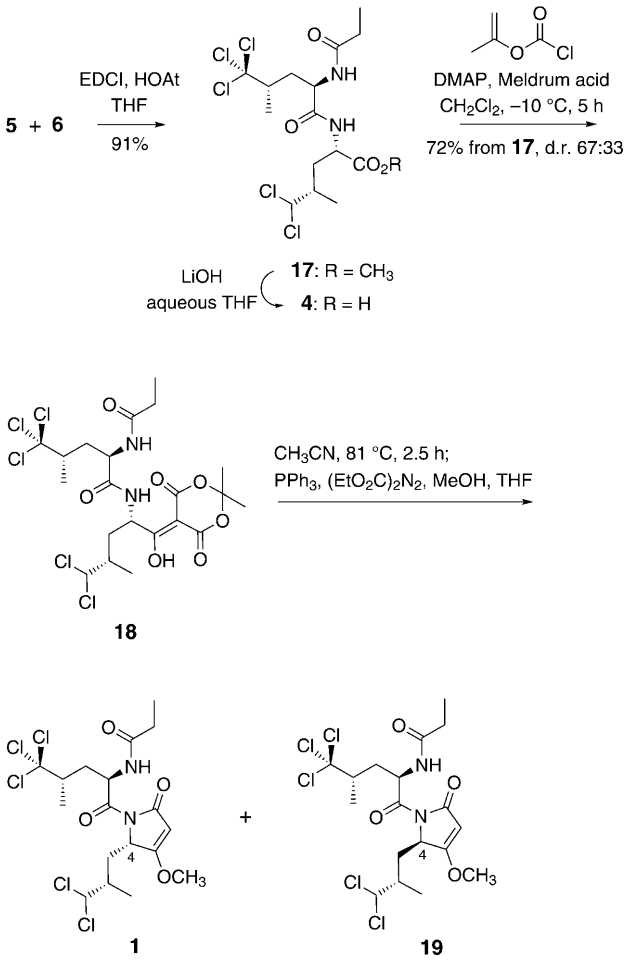
Stereoselective dichloromethylation of **7** was required for the synthesis of (2*S*,4*S*)-5,5-dichloroleucine methyl ester (**6**; Scheme 4a). A more active ruthenium catalyst was needed for this transformation than that used for the trichloromethylation of **7**. With $[Cp^*Ru(PPh_3)_2Cl]$, **12** was formed in 64% yield with complete stereoselectivity. Reduction with sodium borohydride, followed by iododehydroxylation and substitution with cyanide, provided nitrile **14** uneventfully. Thus, we observed a notable difference in reactivity between **8** and **13**. By analogy with the synthesis of **5**, reduction, sulfinimine formation, a scandium-catalyzed Strecker reaction, and acidic methanolysis completed the synthesis of **6**.

An alternative synthesis of **6** involved the highly efficient monodechlorination of **9** with triethylsilane in the presence of the catalyst $[(Ph_3P)_3RuCl_2]$ (1 mol%; Scheme 4b).[18] Although the transformation was very clean and efficient (96% conversion), separation of the volatile product from Et_3SiCl formed during the course of the reaction proved to be somewhat challenging and resulted in a diminished yield of 76%. Overall, we preferred this route, as it enabled a more unified synthesis of key fragments **5** and **6**.

Our main concern in the next step of the synthesis of sintokamide A, the peptide coupling between **5** and **6**, was the stereochemical integrity of the α-amido group in **5**. These type of stereogenic centers are known to be particularly sensitive to epimerization during peptide coupling. Several methods have been developed to suppress epimerization with this type of substrate. Thus, although all attempts for the preparation of activated derivatives of acid **5**, including its pentafluorophenyl[19] or *N*-hydroxysuccinimide esters, were unproductive,[20] the requisite amide formation proceeded smoothly with EDCI and HOAt to deliver peptide **17** in



Scheme 4. Synthesis of amino methyl ester **6**. Cp* = pentamethylcyclopentadienyl.



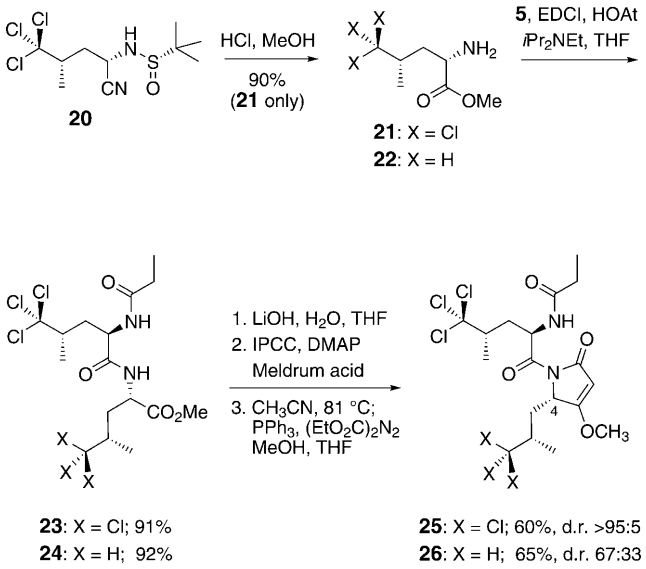
Scheme 5. Completion of the synthesis of sintokamide A (**1**). DMAP = 4-dimethylaminopyridine, EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, HOAt = 1-hydroxy-7-azabenzotriazole, Meldrum acid = 2,2-dimethyl-1,3-dioxane-4,6-dione.

excellent yield as a single diastereomer (Scheme 5). The presence of HOAt was essential for the suppression of epimerization at C10, as expected.[10,21]

Methyl ester hydrolysis with lithium hydroxide in aqueous THF at 0 °C provided **4** in high yield without epimization at the α position. Among various procedures for the crucial assembly of the tetramic acid fragment, the reaction sequence described by Jouin and Castro proved to be optimal for sintokamides and required only a minor modification.[22,23] Thus, the treatment of a mixture of carboxylic acid **4**, the Meldrum acid, and DMAP in dichloromethane with isopropenyl chloroformate at −10 °C was followed by thermolysis of intermediate **18** and O-methylation in the presence of methanol, triphenylphosphane, and diethyl azodicarboxylate in THF.[24] Synthetic sintokamide A (**1**) was isolated in 48% yield along with the readily separable C4 epimer **19** (24% yield). The physical data for the synthetic material (^{1}H and ^{13}C NMR spectra, optical rotation, high-resolution mass spectrum) were identical to those reported for natural sintokamide A, although we found that the chemical shifts in the ^{1}H NMR spectrum were significantly concentration-dependent.

As a demonstration of the generality of the developed approach for the synthesis of other members of the sintokamide family of chlorinated peptides, and in anticipation of subsequent biological studies, we also completed the synthesis of sintokamides B and E (Scheme 6). Accordingly, methanolysis of aminonitrile **20**, prepared by a reaction sequence analogous to that used for the synthesis of **11**,[10] afforded (2*S*,4*S*)-5,5,5-trichloroleucine methyl ester (**21**). Condensation of carboxylic acid **5** with amine **21** (EDCI, HOAt, THF) provided peptide **23** in 91% yield. The synthesis of hexachlorinated sintokamide B (**25**) was completed in three additional steps required for the installation of the tetramic acid. Remarkably, very little (< 5%) isomerization at the 4-position was observed in this case, as evident from TLC and ^{1}H NMR spectroscopic analysis of the crude product mixture.

Sintokamide E (**26**) was accessed in a similar manner from commercially available L-leucine methyl ester hydrochloride. As in the synthesis of sintokamide A, substantial isomerization at C4 occurred during the formation of the tetramic acid. The structure of the C4 epimer was confirmed by an independent synthesis starting from D-leucine methyl ester hydrochloride (see the Supporting Information). The physical



Scheme 6. Completion of the synthesis of sintokamides B (**25**) and E (**26**).

data for synthetic sintokamides B and E matched those reported for the natural samples.

In summary, a highly stereoselective, ruthenium-catalyzed radical di- and trichloromethylation of titanium enolates enabled the total synthesis of sintokamides A, B, and E by a concise, unified strategy involving no protecting-group manipulations, as are usually required in the synthesis of peptides.[25,26] The chlorinated marine natural products were synthesized in 14 steps (longest linear sequence from commercially available (*S*)-(−)-4-benzyl-5,5-dimethyl-2-oxazolidinone) and 14% overall yield in the case of sintokamides A and E, and in 19% overall yield in the case of sintokamide B. Biological studies to explore the interaction of sintokamides (synthesized by this approach) with the N-terminal domain of the androgen receptor in hormone-refractory cancer cells are now in progress.

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