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Total Synthesis of (–)-Sigillin A: A Poly-Chlorinated and Poly-Oxygenated Natural Product

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Supporting Information Placeholder

ABSTRACT: The total synthesis of (–)-sigillin A, a highly chlorinated and oxygenated octahydroisocoumarin, is described herein. A hexahydroisocoumarin skeleton was constructed from (*R*)-4-(trichloromethyl)oxetan-2-one in seven steps. Its unique manganese oxidation provided an enone as the key intermediate of sigillin A. Stereoselective installation of two hydroxy groups and formation of *gem*-dichloroalkene from the corresponding ketone led to the total synthesis of (–)-sigillin A in a total of 16 steps.

Halogenated compounds are often used in the pharmaceutical and agricultural industries.¹ Approximately 40% of the drugs that are a part of the market or used in clinical trials are halogenated compounds; this is because incorporation of halogen atoms into drug candidates improves the metabolic stability, the lipophilicity, and the drug target affinity.² Recently the number of reports on halogenated natural products has been increased owing to the development of isolation and identification technologies.^{3,4} Thus, efficient syntheses of newly isolated halogenated products would be attractive for the development of various areas of chemistry such as drug discovery.

Sigillin A (**1**) and its congeners **2–9** are polychlorinated octahydroisocoumarins that have been isolated previously from the snow flea *Ceratophysella sigillata* (Collembola) in 2015 by Schulz's group (**Figure 1**).⁵ The structure and the absolute configuration of **1** was revealed by X-ray crystallographic analysis. Sigillins have characteristic structural features in these rather compact skeletons: **1** possesses five chlorine atoms and three hydroxy groups in four consecutive stereocenters decorated in a *trans*-fused octahydroisocoumarin structure. This molecule has showed high repellent activity in a bioassay against predatory ant *Myrmica rubra* and some cell toxicity. We have been fascinated by these structural features and biological activities, which has led us to investigate the total synthesis of this molecule.

Total synthesis of **1** and related natural products have not been accomplished to date. Schulz's group reported the synthesis of desoxysigillin A, which lacks hydroxy groups at the C-5 and C-6 positions (**Scheme 1**).^{5,6} They found that the installation of a *gem*-dichloroalkene moiety, one of the unique functional groups of **1**, is quite challenging and gives the desired compound **11** with only 2% yield. Thus, the major challenge in the synthesis of this natural product is the introduction of these hydroxy groups and *gem*-dichloroalkene group.

Figure 1. Structure of Sigillins 1–9.

Herein, we report the first asymmetric total synthesis of sigillin A. Our synthetic plan is depicted in **Scheme 2**. We envisioned that the synthesis of sigillin A could be accomplished by dichloromethylenation of the corresponding ketone **12**, which would be prepared using enone **13** via a boron conjugate

addition. Enone **13** would be sourced from hexahydroisocoumarin **14** by performing several oxidations. The carbon framework of sigillin **14** was expected to be constructed from the β -keto- δ -valerolactone **15** via double allylations and ring-closing metathesis. Furthermore, **15** could be synthesized by Claisen condensation of the known optically active β -lactone **16**⁷ with *tert*-butyl propionate, followed by lactonization.

Scheme 1. Synthesis of desoxysigillin A by Schulz⁶

Scheme 2. Our synthetic plan

Scheme 3. Construction of the Carbon Skeleton of Sigillin A

We initiated the synthesis of hexahydroisocoumarin **21** with the known enantiopure β -lactone **16** (Scheme 3). Claisen condensation of β -lactone **16** with *tert*-butyl propionate produced 5-hydroxy-3-oxoester **17** at a yield of 82%, which was subjected to cyclization under acidic conditions to afford the β -keto- δ -valerolactone **15** (fragment of sigillin A on the left). Next, we performed the electrophilic allylation of keto-lactone **15**. Tsuji-Trost allylation^{8a} of **15** using allyl acetate produced the desired compound **19** in 70% yield albeit with low diastereoselectivity (dr = 60:40). Even the use of chiral ligands, such as PHOX^{8b} and the Trost ligand^{8c} could not improve the diastereoselectivity. We turned our attention to the intramolecular variant of this reaction, referred to in Mulzer's protocol,⁹ to improve the diastereoselectivity. The allyl carbonate **18** could be prepared from **15** using allyl chloroformate in an almost quantitative yield. As expected, allylation of **18** catalyzed by 3 mol % of Pd(dba)₃·CHCl₃ with 15 mol % of PPh₃ as a ligand proceeded even at -78 °C to obtain **19** and showed good diastereoselectivity (dr = 85:15) and high yield (90%).¹⁰ After screening several phosphine ligands, (2-furyl)₃P was found to be suitable (dr = 94:6). Furthermore, the amount of catalyst loading could be reduced to 1 mol % of the palladium source without any loss in yield and diastereoselectivity (dr = 94:6). Nucleophilic allylation of **19** (dr = 94:6) with allylzinc bromide¹¹ led to the production of alcohol **20** with a 95% yield that exhibited high diastereoselectivity (dr = 94:6). The crude was directly purified by recrystallization to produce **20** in 78% yield as a single stereoisomer, whose structure was confirmed by X-ray crystallography. Then, **20** was subject to ring-closing metathesis and silyl protection to achieve the synthesis of compound **21** on a >5 gram scale. Thus, we successfully constructed a carbon framework of sigillin A from the known (R)-4-trichloromethyl-2-oxetanone in 7 steps.

Scheme 4. Oxidative Stage toward the Synthesis of Sigillin A^a

^aORTEP view of compounds **23** and **1** with thermal ellipsoids drawn at the 80% probability level.

To increase the oxidation level toward sigillin A appropriately, several oxidation reactions were attempted. First, we examined the allylic oxidation of **21** to introduce an oxygen functionality at C-6 position. The use of SeO_2 , $\text{Pd}(\text{OAc})_2/\text{BQ}$ and CrO_3 resulted in the formation of complex mixtures. After tremendous effort of oxidations, we found that $\text{Mn}(\text{OAc})_3$ -catalyzed allylic oxidation^{12a} of **21** proceeded with unexpected regioselectivity to afford enone **22** in high yield (Scheme 4). We assumed that this regioselectivity arose from the bulkiness of silyl group. Initially, the hydrogen atom at C-6 position might be abstracted by the peroxy radical. After the generated allyl radical was delocalized, oxidation would occur at the less hindered position to produce enone **22**.^{12b} Then, enone **22** was employed in the installation of a hydroxy group at the C-9 position. *In situ* Rubottom oxidation¹³ of triethylsiloxy diene using DMDO led to successful installation of a hydroxy group with the desired configuration to afford diol **23** as a single diastereomer.¹⁴ The unpredicted diol **23** was obtained as a result of the loss of TMS protecting group of the tertiary hydroxy group. The structure of **23** was confirmed by X-ray crystallographic analysis. We speculated that TMS group might translocate to the secondary hydroxy group and then be removed under aqueous basic conditions. Protection of diol **23** with dichlorodialkylsilane led to the production of the bridged silyl protected compound **24**. For installation of a hydroxy group at the C-6 position, copper-promoted conjugate addition¹⁵ of a boron pinacol ester to enone **24** gave the desired product **25** as a single diastereomer. Boron would attack enone **24** to avoid the steric hindrance of the bulky diisopropylsilyl group. As mentioned in the previous report,^{5,6} transformation of carbonyl group into dichloroalkene proved to be problematic for us. Several methods for the formation of dichloroalkene from ketone are reported.¹⁶ The most reliable methods using Wittig-type reactions with spe-

cies such as the CCl_4 /phosphine system¹⁷ did not lead to a reaction with **25**, and the reactions were complicated in more forcing conditions such as refluxing or under microwave-assisted conditions. β -Elimination-based reactions¹⁸ have also been investigated. However, the formation of trichloromethyl carbinol using **25** with LiCCl_3 has remained unsuccessful. To our delight, the transformation was achieved using Wittig-Horner reactant¹⁹ $(\text{EtO}_2)\text{P}(\text{O})\text{CCl}_2\text{Li}$ to produce dichloroalkene **26** in 40% yield. The key to success was that the corresponding carbanion was more nucleophilic than the Wittig-type phosphonium ylide²⁰ and less reactive than carbanions such as LiCCl_3 , which prevented side reactions. Oxidative cleavage of the C–B bond followed by acetylation afforded **27** in 78% yield over 2 steps. Removal of the silyl group by HF -pyridine produced sigillin A (**1**) in a total of 16 steps from (*R*)-4-trichloromethyl-2-oxetanone.

In summary, we accomplished the first asymmetric total synthesis of (–)-sigillin A in 16 steps by using enantiomerically pure β -lactone **16**. The keys to the success of the synthesis were 1) an unexpected manganese allylic oxidation to form enone **22**; 2) stereoselective installation of two hydroxy groups via Rubottom oxidation and borylation/oxidation using enone **22**; 3) formation of *gem*-dichloroalkene **26** by the Wittig-Horner reaction. These late-stage oxidation strategies proved to be effective in the synthesis of sigillin A. The syntheses and biological evaluation of related analogues of sigillin A are currently under way.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experiment procedures, Supplemental figure, Copies of ^1H and ^{13}C NMR spectra (PDF)

Crystallographic information for **20** (CIF)
Crystallographic information for **23** (CIF)
Crystallographic information for **1** (CIF)

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Notes

The authors declare no competing financial interest.

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