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AUTHOR(S):

Yamaoka, Yousuke; Nakayama, Takamori; Kawai, Shota; Takasu, Kiyosei

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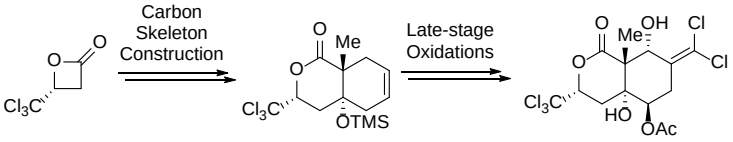
Total Synthesis of (–)-Sigillin A: A Poly-Chlorinated and Poly-Oxygenated Natural Product

Yousuke Yamaoka,* Takamori Nakayama, Shota Kawai, and Kiyosei Takasu*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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.

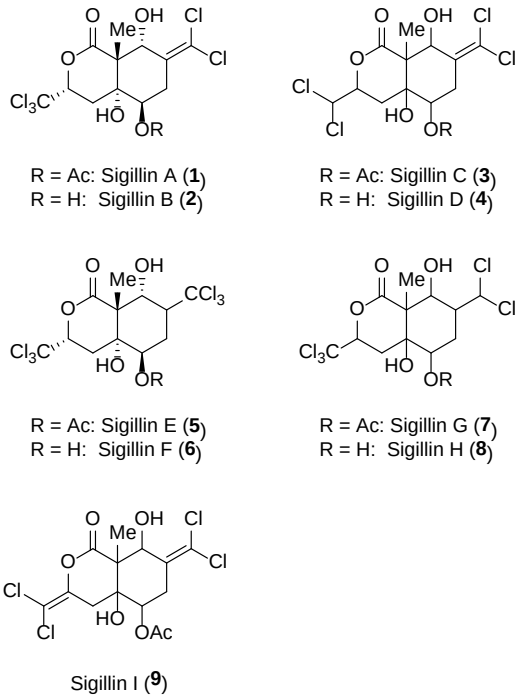
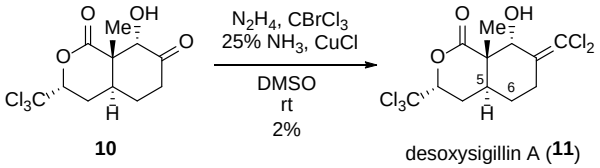


Figure 1. Structure of Sigillins **1–9**.

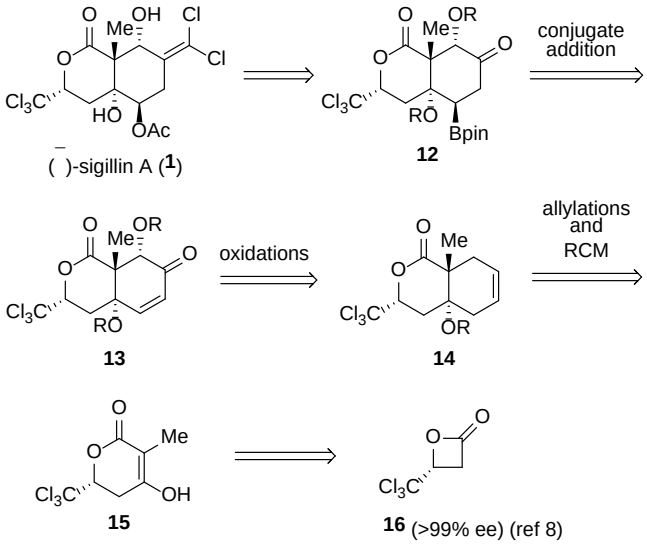
Herein, we report the first asymmetric total synthesis of sigillin A. Our synthetic plan is depicted in **Scheme 2**. We envisioned that the synthesis of sigillin A could be accomplished by dichloromethylenation of the corresponding ketone **12**, which would be prepared using enone **13** via a boron 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 Schulz[6]

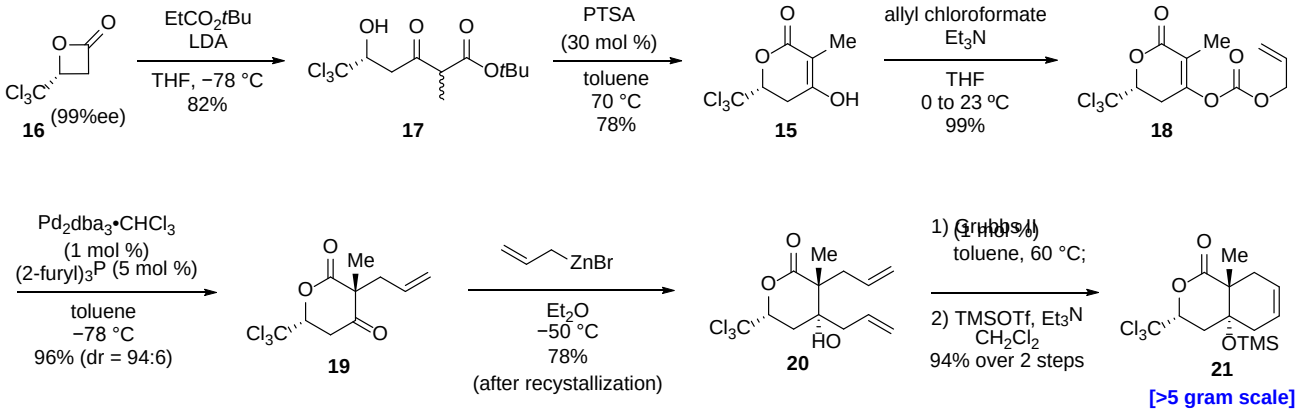


Scheme 2. Our synthetic plan

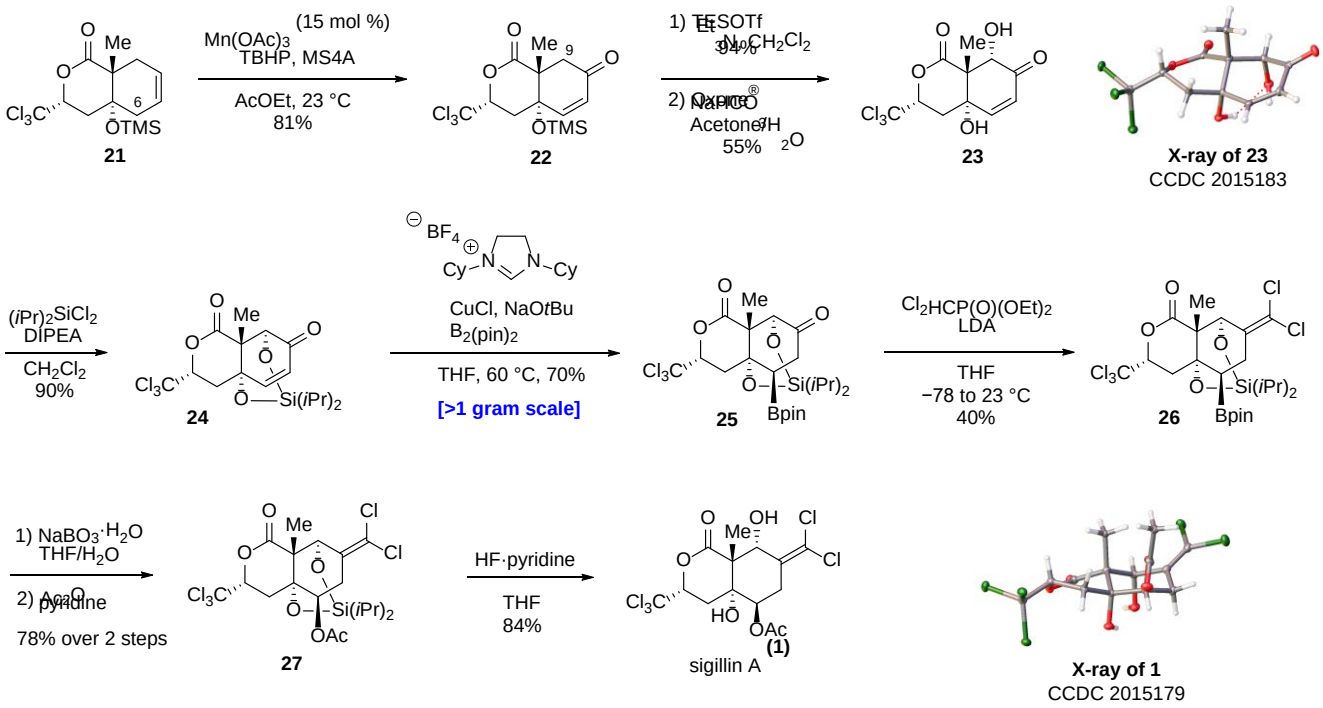


We initiated the synthesis of hexahydroisocoumarin **21** with the known enantiopure β-lactone **16 (Scheme 3)**. Claisen condensation of β-lactone **16** with *tert*-butyl propionate produced 5-hydroxy-3-oxoester **17** at a yield of 82%, which was subjected to cyclization under acidic conditions to 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 $Pd_2dba_3{\cdot}CHCl_3$ with 15 mol % of PPh_3 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, $(2\text{-furyl})_3P$ 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 bromide[11] 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 3. Construction of the Carbon Skeleton of Sigillin A



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



[a]ORTEP 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, $Pd(OAc)_2$/BQ and CrO_3 resulted in the formation of complex mixtures. After tremendous effort of oxidations, we found that $Mn(OAc)_3$-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 oxidation[13] 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 addition[15] 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 species such as the CCl_4/phosphine system[17] 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 reactions[18] 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 reactant[19] $(EtO_2)P(O)CCl_2Li$ to produce dichloroalkene **26** in 40% yield. The key to success was that the corresponding carbanion was more nucleophilic than the Wittig-type phosphonium ylide[20] 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)

AUTHOR INFORMATION

Corresponding Author

* yyamaoka@pharm.kyoto-u.ac.jp
* kay-t@pharm.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

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