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Asymmetric Total Synthesis of Asperversin A

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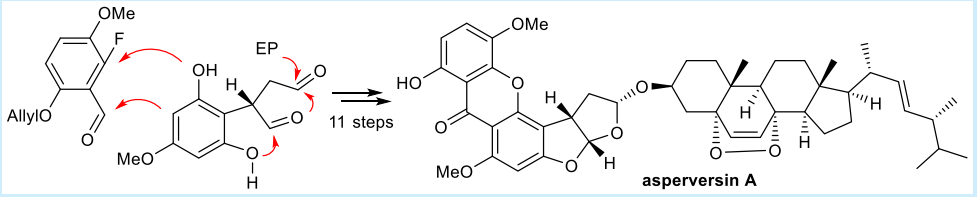

ABSTRACT: Asperversin A represents the first example of a steroid−sterigmatocystin heterodimer. We report the concise asymmetric total synthesis of this natural product in 11 steps (the longest linear sequence). The polycyclic ring system was constructed by a cascade dialdehyde cyclization and the late stage xanthene formation by a phenol-assisted reductive alkylation and a S_NAr reaction. The acetal linkage with ergosterol peroxide was furnished by a glycosylation-inspired approach.

The sterigmatocystins make up a class of emerging mycotoxins that constitute a serious risk factor for human and animal health.[1] The elucidation of their metabolic pathways and cellular mechanisms of toxicity is important to fully understand the potential risk associated with their exposure. Among various approaches, the identification of adducts of sterigmatocystin [**2** (Figure 1)] with other endogenous molecules could provide solid evidence and inspiring hints for studying the related biological processes. Two metabolic adducts of sterigmatocystin with guanine (**5**) and *N*-acetylcysteine (**6**), formed through epoxidation of the vinyl ether moiety and oxidation of the phenol ring to an *o*-quinone intermediate, respectively, have been identified, shedding light on the possible origins of the carcinogenesis and genotoxicity of this mycotoxin.[2] In this context, we were attracted by the structure of asperversin A [**1** (Figure 1)], which was isolated from algicolous fungi by the group of Ji in 2012.[3] This natural product represents the first described example of a steroid−sterigmatocystin heterodimer. Interestingly, some steroids have been reported to have protective effects against the cytotoxicity of mycotoxins.[4] Thus, the steroid−sterigmatocystin adduct has the potential to serve as a chemical probe for the study of the biological relevance of sterigmatocystins.

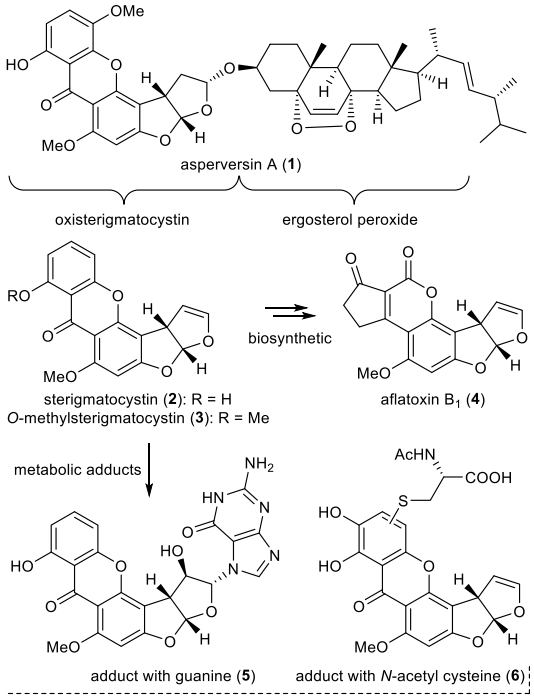

Figure 1. Asperversin A and sterigmatocystins.

The structure of asperversin A contains an oxysterigmatocystin and an ergosterol peroxide that are linked together in an acetal form. The synthesis of its oxysterigmatocystin part should be, to some extent, analogous to that of sterigmatocystins **2** and **3**, which feature a xanthone nucleus attached to a dihydrobisfuran (Figure 1). The sequence of the assembly of these two moieties has been a dilemma. The vulnerability of the dihydrobisfuran could be barely compatible with the harsh reaction conditions for xanthone formation. Alternatively, construction of the dihydrobisfuran after xanthone formation

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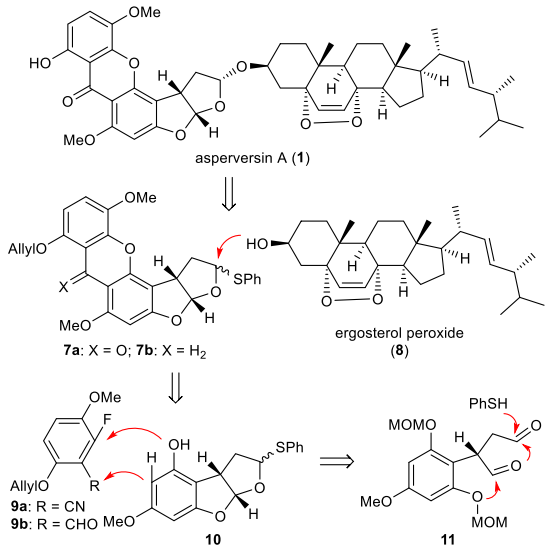
should pay attention to the electrophilicity of the xanthone carbonyl.

Toward the synthesis of *O*-methylsterigmatocystin (**3**), the late stage xanthone formation on a known tricyclic precursor[5a] was studied by Rance and Roberts in 1970, which turned out to be very tedious and gave a low yield.[6a] Envisioning the difficulties associated with the late stage xanthone formation, the group of Townsend strategically utilized an alternative "early xanthone" approach that, coupled with the development of a protocol for xanthone protection/deprotection, successfully led to the racemic total synthesis of **3** in 14 steps.[7] So far, to the best of our knowledge, no catalytic enantioselective total synthesis of sterigmatocystins has been realized. In view of the relatively limited success of the total synthesis of sterigmatocystins and the inspiring biological relevance of asperversin A, we herein report the first asymmetric total synthesis of this natural product.

The retrosynthetic analysis of asperversin A is outlined in Scheme 1. Asperversin A could be generated by late stage

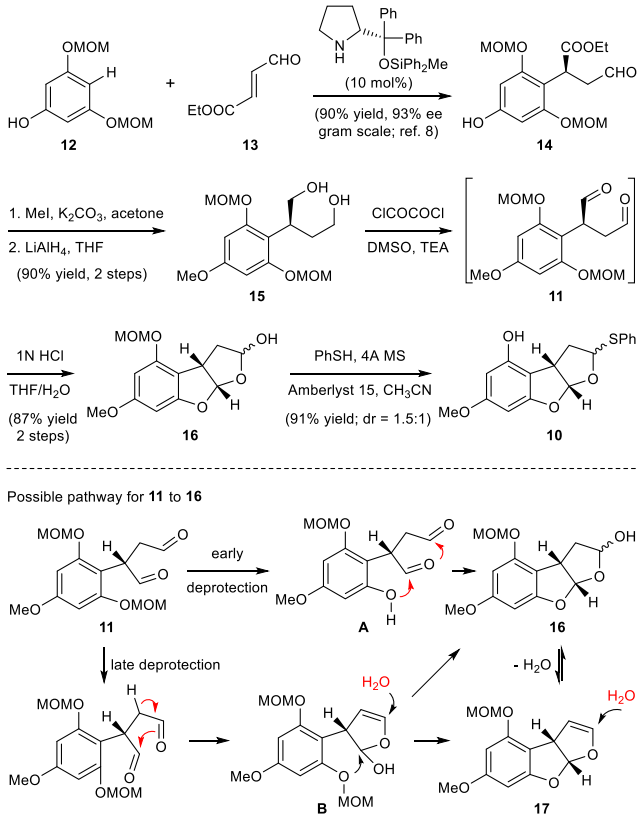
Scheme 1. Retrosynthetic Analysis of Asperversin A



acetal formation between either xanthone **7a** or xanthene **7b** and ergosterol peroxide **8**. Due to the vulnerability of both coupling partners, suitable and mild conditions for the activation of the thioacetal group are required. With regard to the synthesis of **7**, while we were mindful of the potential difficulties in the coupling of **9** and **10**, we still preferred such a "late xanthone" approach, which is more convergent and allows for facile structural modifications of the xanthone ring if necessary. The synthesis of **10** could be efficiently achieved by a cascade cyclization of 1,4-dialdehyde **11** followed by trapping with thiophenol if the strong tendency of the 1,4-dialdehyde to cyclize to furan via Paal–Knorr pathway could be inhibited. The chiral center and required functionality in **11** could be introduced by an organocatalytic direct alkylation of phloroglucinol derivatives developed by our group previously.[8]

The first goal of our synthesis was to rapidly build up the hydrobisfuran system from compound **14**, which was previously prepared by our group through an organocatalytic enantioselective Friedel–Crafts alkylation of phloroglucinol derivative **12** with enal **13** (Scheme 2).[8] The method successfully introduced chirality as well as the required functionality from simple starting materials with excellent

Scheme 2. Asymmetric Synthesis of the Hydrobisfuran System



enantioselectivity. Diol **15** could be subsequently generated by O-methylation and $LiAlH_4$ reduction. Among various oxidants used in attempts to convert **15** to dialdehyde **11**, only the Swern condition turned out to be fruitful.[9] Due to the lability of the dialdehyde, **11** was used for the next step directly without purification. We surmised that in the presence of a suitable acid, the deprotection of the MOM group and subsequent cascade cyclization would occur (**A**), generating hemiacetal **16** in a highly efficient manner. In such a pathway, the deprotection must proceed very fast, thus kinetically competing with the Paal–Knorr cyclization of 1,4-dialdehyde to furan. However, this cascade process turned out to be problematic. In the presence of a variety of acids in different organic solvents, either decomposition of the starting material or formation of complex mixtures was observed. Then we reconsidered the reaction pathway to **16** and realized that an alternative possibility involving "late deprotection" might also be operative. The Paal–Knorr-like cyclization of 1,4-dialdehyde **11** might occur first to afford intermediate **B**, which could lead to **16** directly by the hydration of the vinyl ether and then ring closure or through **17** if ring closure occurred prior to hydration.[10] The accumulation of **B** and **17** would presumably lead to a variety of side reactions. We envisioned that carrying out the transformation of **11** to **16** in aqueous media would accelerate the hydration of **B** and **17** and inhibit the dehydration of **B** to furan and **16** to **17**. To our great delight, when the reaction was carried out in THF and water in the presence of 1 N HCl, the desired product **16** was isolated in 87% yield over two steps. Subsequent trapping of the hemiacetal with thiophenol and the concomitant deprotection of the second MOM group afforded hydro-

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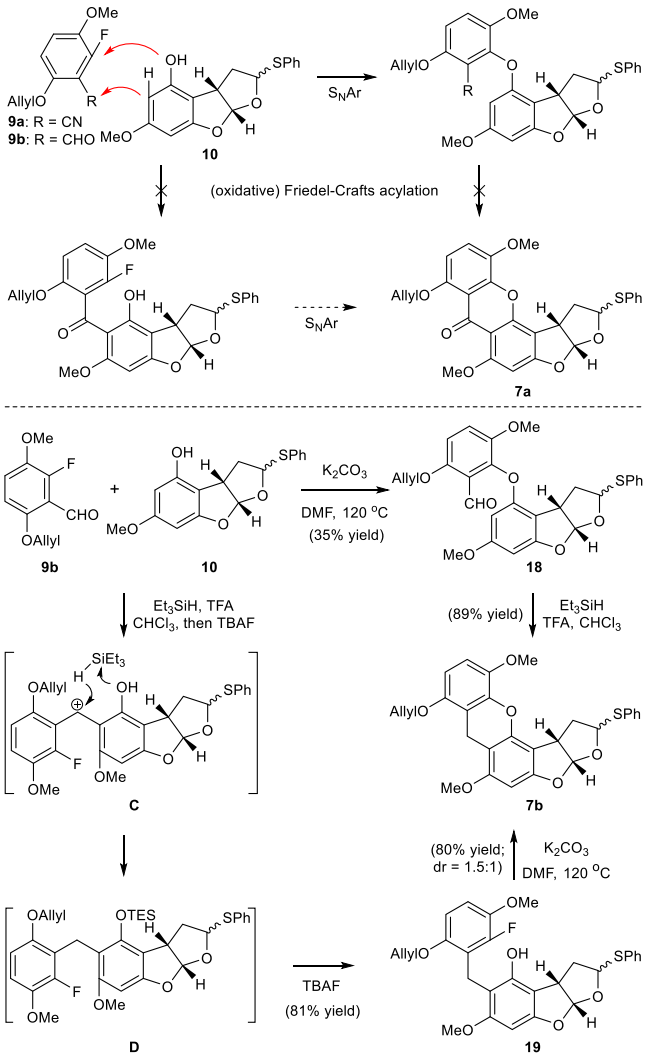
bisfuran thioacetal **10** as a mixture of two epimers (1.5:1 exo:endo).[11] The rapid asymmetric assembly of **10** in only six steps (five purifications) laid a solid foundation for our synthesis.

The next goal of our synthesis was to construct xanthone nucleus **7a** from **10** (Scheme 3). The most straightforward approach is the direct coupling of two aryl fragments via sequential carbonyl and ether linkages. We selected nitrile **9a** and aldehyde **9b** as the substrates that were designed to form the ether linkage via nucleophilic aromatic substitution (S_NAr) and the carbonyl connection by Houben–Hoesch type Friedel–Crafts acylation[12] or oxidative Friedel–Crafts acylation.[13] As expected, the introduction of the xanthone nucleus onto labile **10** turned out to be very challenging. Intermolecular Friedel–Crafts acylation or oxidative Friedel–Crafts acylation between **10** and **9** was not successful under either acidic or transitional metal-mediated conditions. In an alternative sequence, the intermolecular S_NAr reaction was possible, but the subsequent ring closure to form the carbonyl linkage could not be realized in our hands. The difficulties mainly arose from the sensitivity of the hydrobisfuran thioacetal to harsh reaction conditions.

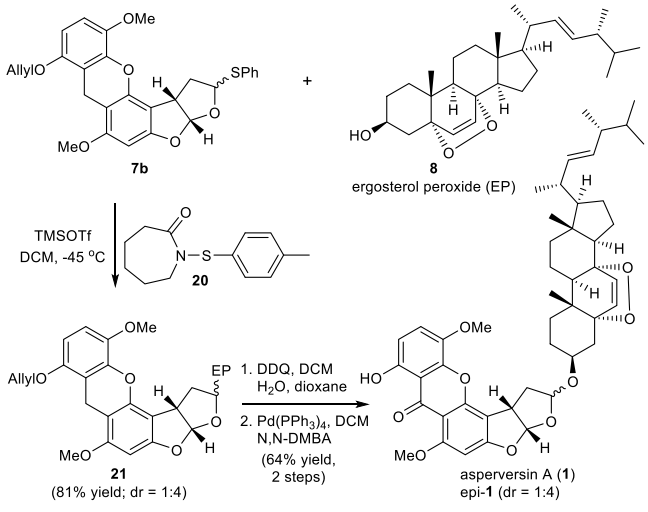
Scheme 3. Late Stage Xanthone/Xanthene Formation



Then we turned to the synthesis of xanthene **7b** via S_NAr reaction followed by reductive alkylation[14] from aldehyde **9b** (Scheme 3). The coupling of **9b** and **10** under mild basic condition afforded **18**, albeit in low yield, which could indeed be converted to **7b** upon treatment with TFA and triethyl silane. We were excited by the successful formation of xanthene **7b**, but our efforts to increase the yield of the S_NAr reaction were not fruitful due to the slow reaction rate and the decomposition of **10** even under mild basic conditions. Mechanistically, the reversal of the sequence of these two connections would be less practical, as the intermolecular reductive alkylation became slower and the subsequent S_NAr reaction would be difficult on an arene bearing two electron-donating groups. Serendipitously we found that both reactions worked unexpectedly well. The intermolecular reductive alkylation between **9b** and **10** was very fast, first affording TES ether **D** within 0.5 h. While **D** could be slowly deprotected under the reaction conditions, the prolonged presence of the product in the reaction mixture would lead to side reactions. Thus, we added TBAF to facilitate fast desilylation to afford **19** in 81% yield. The formation of **D** pointed to a phenol-assisted reductive alkylation pathway (**C**), which might account for the fast reaction rate. While the hydrosilylation of carbonyls by Et_3SiH has been well-known,[15] to the best of our knowledge, the described phenol-assisted reductive alkylation has not been reported previously and should inspire further reaction development. From **19**, the subsequent S_NAr reaction on the arene bearing two electron-donating groups proceeded very well, generating xanthene **7b** in 80% yield. The unusual intramolecular S_NAr reaction was successful likely due to the forced proximity of the phenol and arene, despite being electron rich. The oxidation of xanthene **7b** to xanthone **7a** at this stage was not practical[16] presumably due to the sensitivity of the thioacetal to oxidants; thus, we postponed this step to a later stage of our synthesis.

Finally, we turned to the total synthesis of asperversin A (Scheme 4). The remaining task was to form the acetal linkage with ergosterol peroxide (EP) **8**.[17] Due to the labile nature of both coupling partners, apparently such a coupling requires the suitable and mild conditions for the activation of the thioacetal group. Upon simple treatment of **7b** and **8** with different acids, we did not observe any formation of **21**. Inspired by the usage

Scheme 4. Total Synthesis of Asperversin A and Its Epimer



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of *N*-(arylthio)-caprolactams as promotors for the activation of thioglycosides,[18] we applied reagent **20**[18b] to the coupling of **7b** and **8**. The formation of acetal **21** was thus realized in 81% yield. Finally, oxidation of the xanthene to xanthone and deallylation afforded asperversin A and its epimer (1:4 dr). The natural product asperversin A was the minor product of the reaction, which was consistent with the fact that it was formed from the sterically more congested face. The characterization data of our synthetic sample matched those of the isolated sample very well.[3]

In conclusion, we have achieved the first asymmetric total synthesis of asperversin A. This natural product represents an unusual example of a steroid−sterigmatocystin heterodimer that would be inspiring and useful as a chemical probe for studying the biological relevance of sterigmatocystins. Key reactions of our synthesis include the use of an organocatalytic enantioselective Friedel−Crafts alkylation to introduce the chirality, the cascade dialdehyde cyclization to afford the hydrobisfuran system, the late stage xanthene formation by a phenol-assisted reductive alkylation and an unusual S_NAr reaction, and the late stage acetal formation using a glycosylation-inspired approach. The successful realization of several challenging processes on very labile structures should be inspiring for the further synthesis of related natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00366.

Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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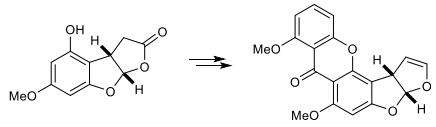

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