Total Synthesis and Structural Assignment of (−)-Fusaequisin A

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Abstract: (−)-Fusaequisin A is an irregularly assembled polyketide isolated from the ascomycete *Fusarium equiseti*. Fusaequisin A shares a carbon backbone with curvicollide C from the ascomycete *Podospora curvicolla* but its absolute configuration remained hitherto unsettled. Herein, we document the total synthesis of (−)-fusaequisin A and its 4-*O*-desmethyl derivative following a central-to-lateral building block strategy. Catalytic asymmetric Claisen rearrangement, Julia-Kocienski olefination and olefin cross-metathesis served as key C/C-connecting transformations. The constitution and absolute configuration of (−)-fusaequisin A was deduced and the original structural assignment was adjusted.

Total synthesis contributes to structural elucidation of natural products by enabling adjustment or settlement of the original structural assignment.[1,2] The isolation of the fungal metabolites curvicollide A–C (**1a**–**c**) from an ascomycete of the genus *Podospora* (order *Sordariales*) was reported by Gloer et al. in 2004 (Figure 1).[3] Structural elucidation was initially limited to the overall constitution and the relative configuration of the defining central γ-lactone segment of the polyketide. We completed the structural assignment of (−)-curvicollide C (**1c**) by total synthesis of a small collection of diastereomers of (+)-curvicollide C (**2**).[4] During our quest for structural assignment of curvicollide C by total synthesis, Shiono et al. revealed the isolation of (−)-fusaequisin A (**3**) from an ascomycete of the genus *Fusarium (*order *Hypocreales)* in 2013.[5,6] The structural assignment of fusaequisin A originally included the overall constitution and the relative configuration of the γ-lactol methyl ether segment.

We were occupied by the proposal that (−)-curvicollide C from *P. curvicolla* (*Sordariales*) and (−)-fusaequisin A from *F. equiseti* (*Hypocreales*) feature identical carbon scaffolds because the producing organisms are members of different taxonomical orders and were collected from different habitats in different regions of the world. Postulating identical absolute configurations for (−)-curvicollide C and (−)-fusaequisin A seemed tempting but ambitious at that time and required verification by total synthesis of (−)-fusaequisin A (**4**). The free induction decays (FIDs) of the ^{1}H and ^{13}C NMR experiments with natural fusaequisin A were made available to us and were used for structural assignment.[7]

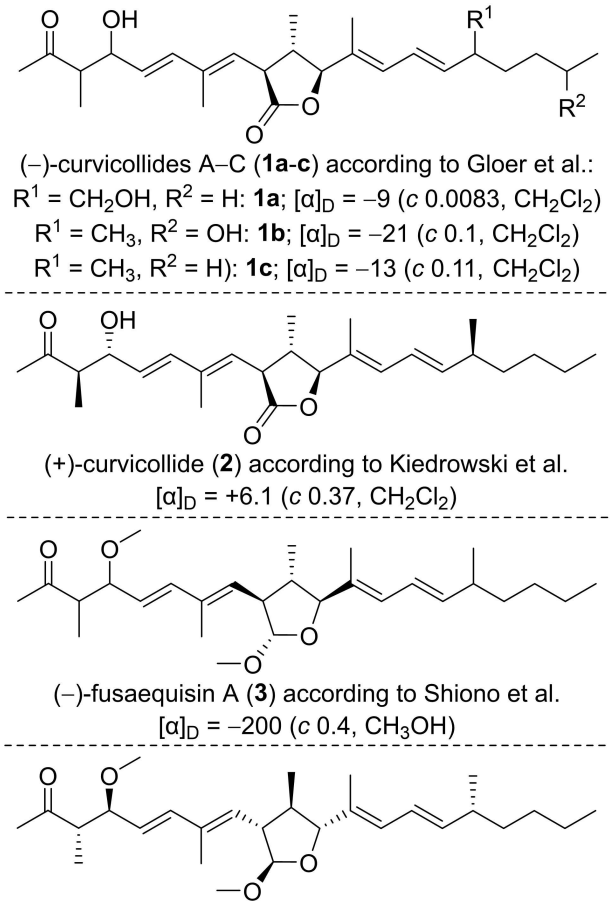

Figure 1. Curvicollide-fusaequisin-type polyketides.

Our synthetic planning was guided by a modular central-to-lateral synthetic design (Scheme 1). We sought to develop a unified approach wherein we could, in principle, access known, yet unknown, and derivatized members of the curvicollide-fusaequisin family of polyketides. Retrosynthetic simplification

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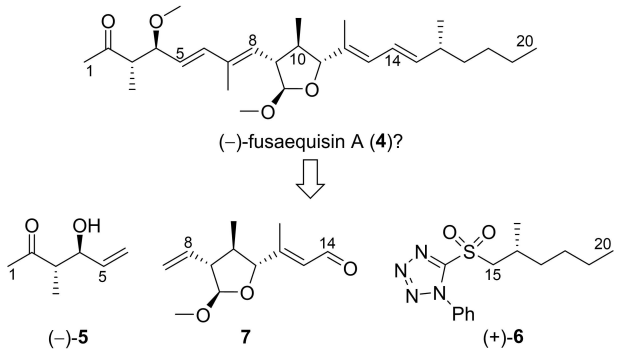
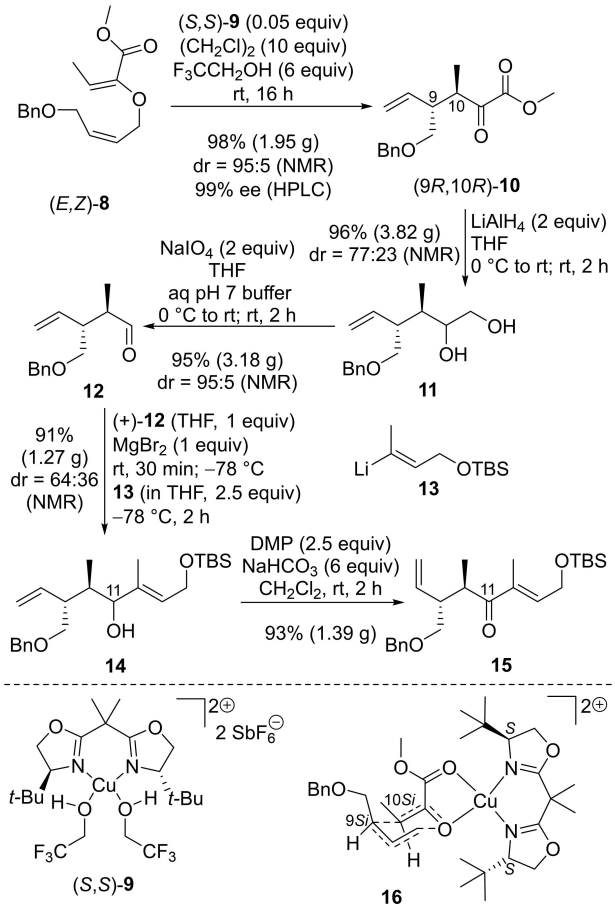


Scheme 1. Modular synthetic layout.

of the proposed structure of (−)-fusaequisin A yielded three chiral building blocks. The western C1–C5 aldol (−)-**5** and the eastern C15–C20 (+)-**6** sulfone were previously synthesized in our laboratory.[8] The C8–C14 α,β-enal **7** was designed to introduce the defining γ-lactol ether segment. To allow for consecutive chain elongation in the eastern and the western direction, the termini of the central building block **7** were designed to be directly addressable. Accordingly, Julia-Kocienski olefination between α,β-enal **7** and sulfone (+)-**6** was planned with confidence. Projecting olefin cross-metathesis (CM) to serve for the late-stage construction of the C5–C8 diene moiety, however, was feared to be complicated or even derailed by reactivity and selectivity issues.

Our efforts toward **4** commenced with the enantioselective synthesis of the all-*trans* configured α,β-enal **7** starting with the catalytic asymmetric Claisen rearrangement of the Gosteli-type allyl vinyl ether (*E*,*Z*)-**8** developed in our laboratory (Scheme 2).[9] Subjecting (*E*,*Z*)-**8** to the 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]-derived copper(II) catalyst complex (S,S)-**9** at room temperature delivered the α-keto ester (9*R*,10*R*)-**10** as a single configurational isomer in 98% yield (1.95 g isolated mass). The chair-like transition state structure **16** accounts for the formation of (9*R*,10*R*)-**10**; peak-affinity transition-state stabilization drives the turnover under catalytic conditions at ambient temperature.[10] Subsequent reduction with lithium aluminum hydride followed by oxidative glycol (**11**) cleavage tailored the α-keto ester **10** to the aldehyde **12** (91%). Pairing the $MgBr_2$-complexed aldehyde **12** with the in situ prepared vinyl lithium reagent **13** by nucleophilic addition delivered the allylic alcohol **14** as 2:1 mixture of diastereomers (91%). In order to converge the C11 diastereomers, **14** was oxidized to the α,β-enone **15** using the Dess-Martin periodinane[11] (DMP) in 93% yield

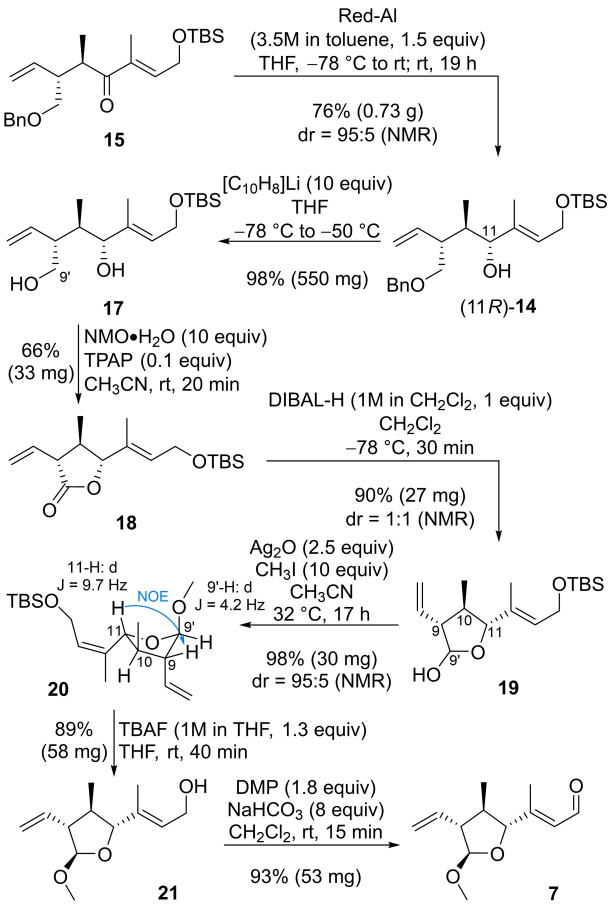
With the α,β-enone **15** in hand, efforts to complete the asymmetric synthesis of the central building block **7** were launched (Scheme 3).[12] Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) reduction of **15** delivered the (11*R*)-configured allylic alcohol **13** as a single diastereomer (76%); the initial assignment of the absolute configuration of the non-aldol stereotriad is in accordance with the Cram-Felkin-Anh model,[13] and was later corroborated by NOE experiments (see below). Reductive removal of the



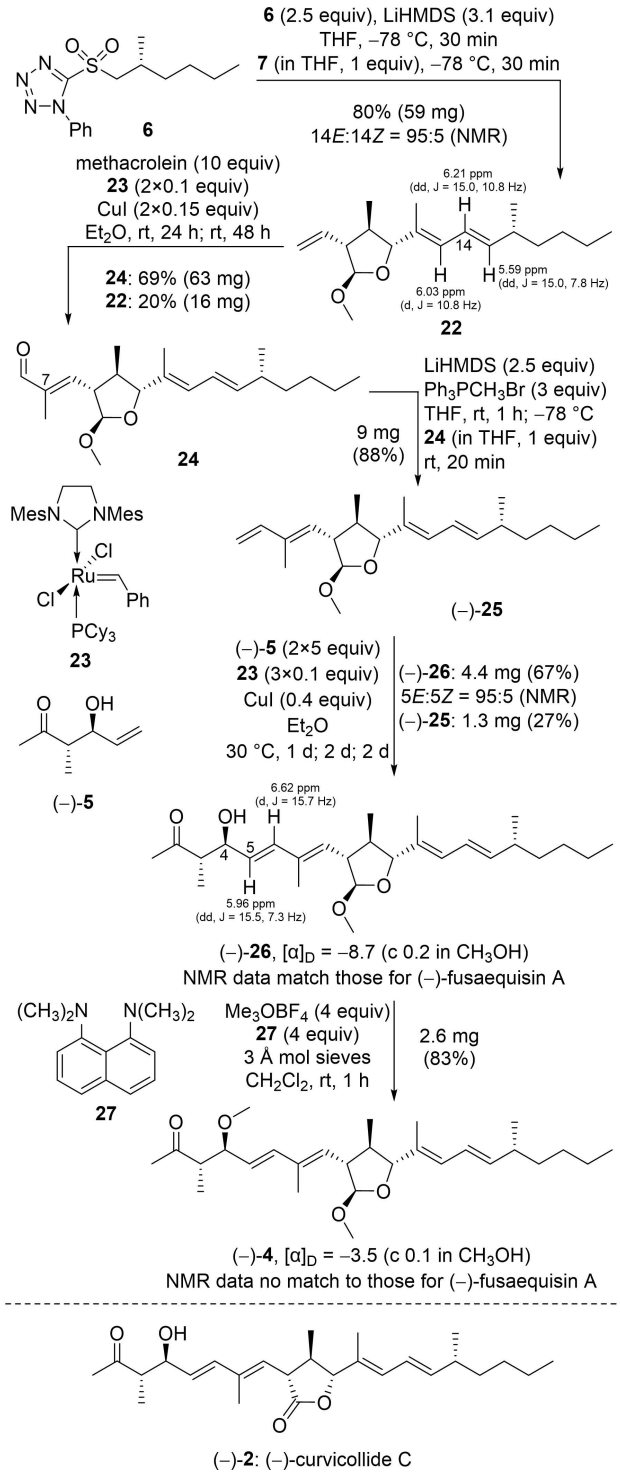
Scheme 2. Catalytic enantioselective synthesis of α,β-enone **15**.

benzyl protecting group delivered the diol **17**. Subsequent efforts to directly promote γ-lactolisation by regioselective oxidation at C9′ of **17** met with failure. Alternatively, Griffith-Ley oxidation[14] of **17** afforded γ-lactone **18** in moderate yield (66%). Reduced reaction times triggered formation of inseparable mixtures consisting of **18** and the corresponding γ-lactole **19**. Thus, we opted for a reliable redox sequence to access the cyclic hemiacetale **19**; in this event, diisobutylaluminum hydride (DIBAL-H) reduction of **18** provided **19** as an equimolar mixture of anomers (90%). Subsequent diastereoselective γ-lactol methyl ether formation was accomplished with methyl iodide in the presence of silver oxide at slightly elevated temperature (98%);[15] careful temperature control is required because mixtures of diastereomers were obtained at temperatures exceeding 35 °C. The results of a NOE experiment and coupling constants are in accordance with an all-*trans* configuration of the γ-lactone methyl ether **20**. Removal of the allylic TBS ether and allylic oxidation proceeded uneventfully to deliver the central building block **7** in 83% yield from **20**.

With the α,β-enal **7** secured, efforts shifted next to the attachment of the eastern segment by Julia-Kocienski olefination (Scheme 4).[16] Lithiation of the chiral sulfone (+)-**6** was accomplished using an excess of lithium



Scheme 3. Synthesis of the central building block **7**.



Scheme 4. Attaching the laterals to the center.

hexamethyldisilazide (LiHMDS) in THF; subsequent addition of the THF solution of the lithiated sulfone to a solution of the α,β-enal **7** at −78 °C delivered the 12*E*,14*E*-configured triene **22**; rigorous temperature control is required to ensure the synthetically useful 14*E*/14*Z*-diastereoselectivity. To forge ahead, the triene **22** was subjected to CM with methacrolein to install the trisubstituted *E*-configured C7/C8 double bond. Initially feared as a potential obstacle due to steric hindrance and the presence of the 12,14-diene moiety, the CM progressed slowly but steady under the conditions of Lipshutz[17] to deliver the α,β-enal **24** in useful yield (69%), and some starting material (20%). To set the stage for a second CM, **24** was subjected to Wittig methylenation to afford the tetraene **25** (88%).[18] Progressing on single digit milligram scale was considered sufficient for structural assignment. From key intermediate **25**, 4-*O*-desmethyl fusaequisin A (−)-**27** was then completed by CM with the aldol (−)-**5**. Surprisingly, however, comparison of the NMR data of synthetic (−)-**26** with those taken from the original FIDs for the natural product named (−)-fusaequisin A matched perfectly, however, with one notable exception (Figure 2 and Supporting Information).[19]

Conspicuously, a singlet at 3.62 ppm of the ^{1}H NMR spectrum at 400 MHz pyridine-D_5 of the natural product (Figure 2, top) finds no counterpart in the ^{1}H NMR spectrum of our synthetic 4-*O*-desmethyl fusaequisin A (−)-**26** (Figure 2, middle). However, when adding 1 equiv. of methanol to the NMR sample of synthetic (−)-**26**, we observed an additional singlet at 3.62 ppm of an otherwise unchanged NMR spectrum of (−)-**26**, indicating a possible contamina-

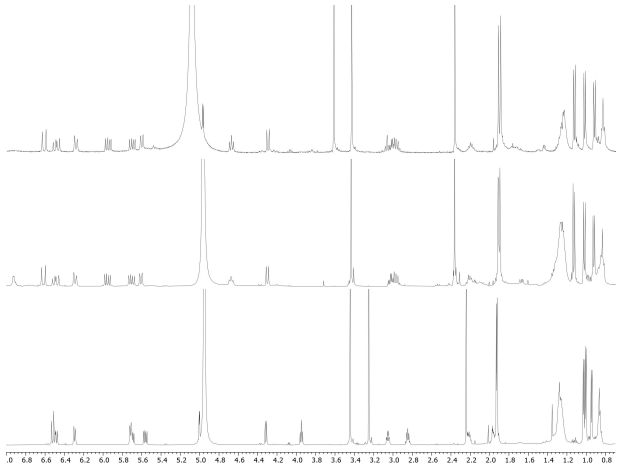


Figure 2. ^{1}H NMR spectra at 400 MHz in pyridine-d_5 (referenced to most downfield shifted signal of pyridine at $\delta = 8.74$ ppm); top: natural product **3** (FID provided by Y. Shiono); middle: synthetic (−)-**26**; bottom: synthetic (−)-**4**.

tion of the NMR sample of the natural product with methanol.[20]

Perplexed by the unexpected congruence of the NMR spectra of (−)-**26** and the natural product, we concluded the total synthesis of (−)-**4** by 4-*O*-methylation of (−)-**26**. As expected, the NMR spectra of synthetic (−)-**4** and those available for the natural product named (−)-fusaequisin A deviate globally (Figure 2 and Supporting Information). Accordingly, reassignment of the reported constitution of fusaequisin A is inevitable. We found a convincing match between the NMR data of (−)-4-*O*-desmethyl fusaequisin A (**26**) and the NMR data of the natural product, as processed from Shiono's FIDs (Figure 2). Hence, we suggest assigning the constitution and relative configuration of **26** to the natural product named fusaequisin A. The absolute configuration of (−)-fusaequisin A (**26**) was assigned by the polarimetrically determined sense of optical rotation.[21]

Reassigned fusaequisin A (**26**) from *Fusarium equiseti* embodies the γ-lactol methyl ether of curvicollide C (**2**) from *Podospora curvicolla* (Scheme 4). Accordingly, fusaequisin A (**26**) should be renamed to fusaequisin C. We suggest the γ-lactol methyl ethers of curvicollide A ("fusaequisin A") and B ("fusaequisin B") as natural products that await future isolation from *Fusarium* sp., *Podospora* sp., or any ascomycete equipped with the required biosynthetic machinery.

In conclusion, we have accomplished the first enantioselective synthesis of (−)-4-*O*-desmethyl fusaequisin A (**26**) and of (−)-fusaequisin A (**4**). A convergent central-to-lateral synthetic design was implemented. Our catalytic asymmetric Claisen rearrangement was utilized for building block synthesis. Olefin cross-metathesis enabled rapid assembling of the C5–C8 2-methyl-1,3-diene segment. Physical data evaluation provides sufficient evidence to justify an adjustment of the originally assigned constitution of the natural product named fusaequisin A (**4**). On grounds of NMR data similarity and polarimetry, we appoint (−)-4-*O*-desmethyl fusaequisin A (**26**) as the natural product originally isolated from *Fusarium equiseti* by Shiono et al.[5]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · natural products · polyketides · structural elucidation · total synthesis

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[17] K. Voigtritter, S. Ghorai, B. H. Lipshutz, *J. Org. Chem.* **2011**, *76*, 4697–4702 Note that **23** and CuI were added in a portion-wise manner.
[18] The enantiomeric tetraene (+)-**25** was previously accessed in our lab on a different route from the achiral (*Z*,*Z*)-configured Gosteli-type allyl vinyl ether **8**, see Reference 4. By developing a synthetic sequence to (−)-**25** starting with achiral (*E*,*Z*)-**8**, we were able to reduce the step count and to access the "natural" absolute configuration of curvicollide-fusaequisin-type polyketides.
[19] For instance, we consider the chemical shifts of the proton at the carbon atom 4 and the chemical shift of the carbon atom 4 itself as of diagnostic value: ^{1}H NMR (400 MHz, C_5D_5N) $\delta = 4.68$ ppm (−)-**26**; 3.95 ppm (−)-**4**; 4.68 ppm (Shiono's FID of natural product). ^{13}C NMR

(176 MHz, C_5D_5N) $\delta = 75.9$ ppm (−)-**26**; 85.9 ppm (−)-**4**; 75.8 ppm (Shiono's FID of natural product, 100 MHz). See Supporting Information for comprehensive NMR data comparison.

[20] According to Ref. [5], natural (−)-fusaequisin A was purified by silica gel flash chromatography using a mixture of $CHCl_3$ and CH_3OH. We observed a slow conversion of 4-*O*-desmethyl fusaequisin A (**26**) in methanol to fusaequisin A (**4**) in the presence of molecular sieves.

[21] However, a large deviation exists between our measured angle of optical rotation for **26** ($[\alpha]_D^{20}$ −8.7 (c 0.2 in CH_3OH) and the reported value (reference 5: $[\alpha]_D^{20}$ −200 (c 0.4, CH_3OH)) for the natural product. Considering the angles of optical rotation for curvicollide-fusaequisin-type compounds (Figure 1), the latter value appears immense.

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