Total Synthesis and Structural Revision of Chaetoviridins A

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Supporting Information

ABSTRACT: The first synthesis of the proposed structures of chaetoviridins A 1−4 has been achieved in 10 steps by controlling the syn- or anti-aldol side chain. The angular lactone has been regioselectively introduced by condensation of a chiral dioxin-4-one to cazisochromene. Comparison of the NMR and circular dichroism data of the synthesized and reported natural products led to the complete reassignment and renaming of the chaetoviridins.

Azaphilones are bioactive secondary metabolites isolated from various fungi; they present an extremely large structural diversity as well as wide biological activity spectrum.1 Azaphilones are characterized by an oxabicyclic scaffold that bears an oxygenated quaternary center at the C-7 position (Figure 1). This 7-hydroxyl can be of (R) or (S) absolute configuration such as in (−) or (+) mitorubrin, respectively,2a with (7S)-isomers being the most common among the azaphilones. However, the 7-hydroxyl can be part of an angular or linear furanone ring such as in trichoflectin2b or rubropunctatin,7 respectively. The pyranoquinone cycle can also be reduced to a dihydropyranic ring such as in epicocconone.2d In addition to that, many reduced or rearranged skeletons exist, enhancing the structural diversity and biological activity spectrum of this family.

Azaphilones and more particularly chaetoviridins A are in the limelight of numerous researches in particular regarding the identification of gene cluster responsible for their biosynthesis and genome mining approaches providing new access to diversity in natural products.3 Chaetoviridins A have been reported to have wide biological activities, such as inhibitors of caspase 3 and cholesteryl ester transfer protein (CETP), and have antimalarial, antimycobacterial, antifungal, and cytotoxic activity.1 However, structural variations associated with a panel of biological activities make it difficult to draw any sort of structure−activity relationship.

Chaetoviridins A4−9 isolated from diverse Chaetomium species, have an angular lactone structure, a branched pentenyl side chain at position 3, and a chlorine atom at position 5 (Figure 2). On the lactone ring can be found a syn or anti aldol side chain such as in chaetoviridin A 1,4,5,7,9 and 4′- or 5′-epimers 2 and 3.7 (7R)- or (7S)-Epimers can also be found naturally such as in 5′-...
epi-chaetoviridin A 3′ (7S) or in 7,5′-bis-epi-chaetoviridin A 4′ (7R) as well as in dehydrated (7R)- or (7S)-chaetoviridin E.5,8

Another epimer of chaetoviridin A has been described, being the C-11 epimer 6; this compound was also named chaetoviridin E.5,8 As a consequence, two “chaetoviridin E” exist with different structures (5, 6).

The isolation and structural elucidation of chaetoviridin A 1 was achieved by Natori in 1990, who established the configuration of the aldol as syn, based on NMR studies.1 This configuration was adopted in subsequent studies, in particular for the structural determination of other epimers.5,7,9 However, without this being ever mentioned, Collado and Pupo reported the structural determination of other epimers.5,7,9

Functionalized azaphilones have already been synthesized,1 no unambiguously attribute their structure. Besides, while ester-synthesis of chaetoviridin A and its epimers in order to suspected structural misassignment(s), we undertook the total spectrum diffusion of the carboxylic acid

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The synthesis of the key intermediate cazisochromene 14 started with chlorination of methyl atratate 7 before protecting the phenol groups as methoxymethyl ethers (Scheme 1). Benzylic deprotonation of 8 followed by addition of CO2 yielded the carboxylic acid 9, which was activated as pentafluorophenol ester 10. Addition of the lithiated anion of trimethylsilyl methyl phosphonate onto 10 gave the β-ketoester 11 following Cossy’s procedure.12a It should be noted at this stage that use of other carboxylic acid derivatives (acid chlorides, Weinreb amides, acylbenzotriazoles, etc.) and methylphosphonate as the nucleophile did not yield the desired β-ketoester 11 with acceptable yields.27b−d Then treating 11 with freshly prepared chiral aldehyde 13 in the presence of potassium carbonate performed the Horner–Wadsworth–Emmons (HWE) reaction and lactonization to 12, installing the pentenyl side chain with 37% yield for the last two steps and without epimerization (Figure S1). Lactone 12 was reduced to the lactol by 1 equiv of DIBAL-H and oxidatively deaminated in the presence of IBX, TFA, and water25c,26 to yield cazisochromene 14 as a ~1:1 mixture of inseparable C7-epimers but with controlled 11S absolute configuration.

The second fragment, identified as dioxinone 21, was prepared via a diastereoselective titanium-based aldolization, installing the chiral syn aldol moiety of the natural product. N-Propionyl (S)-benzyl thiazolidin-2-thione 15 reacted under standard conditions28 with acetaldehyde to give the syn Evans aldol 16 in 80% yield. The chiral auxiliary was smoothly removed by methanolysis to give the corresponding methyl ester 17 in a moderate 55% yield. Claisen condensation of the lithium enolate of f-BuOAc with methyl ester 17 gave the β-ketoester 18 (91% yield), and protection of the secondary hydroxyl as an acetate gave the β-ketoester 19a in 88% yield. The formation of the dioxinone skeleton 20 was performed in 75% yield by adding H2SO4 to a mixture of 19a, Ac2O, and acetone.29 To avoid β-elimination of acetate 20 occurring under standard decacytalysis conditions (MeOH in the presence of K2CO3 or other bases), enzymatic hydrolysis with Candida cylindracea26 was performed, giving clean decacytalysis of the dioxinone 20, albeit with a slow reaction rate. The so-obtained free hydroxyl group was then reprotected as a TBS-ether giving (4S,SR)-dioxinone 21 with 70% yield for the last two steps (Scheme 2).

Figure 3. Retrosynthetic analysis.

Scheme 1. Synthesis of Cazisochromene 14

Scheme 2. Synthesis of Dioxinone (4S,SR)-21
of the nonchlorinated dihydropyranic azaphilone epicocconene, thus demonstrating the importance of the chlorine atom in the regio-outcome of the process.28 The silylated crude product 23 was directly treated by HF/pyridine to give the (7S,4’S,S’R)-chaetoviridin A 24 with 17% yield and its 7-epimer (7R,4’S,S’R)-chaetoviridin A 25 with 20% yield over two steps (Scheme 3).


Significantly, no trace of retro-aldolization, β-elimination, or epimerization products was observed, and so despite the basic conditions. Note that for simplification of the discussion throughout the Letter, the 11S stereochemical information will not be specifically mentioned, unless necessary, as it is common to all the chaetoviridins prepared here.

At this stage, the UV CD spectra of 24 and 25 were recorded and a negative Cotton effect (Δε354 = −24.3) allowed assigning the (7S) configuration for 24, whereas 25 showed a positive Cotton effect (Δε364 = +19.7), establishing the (7R) configuration (Figure S2).5,7

Surprisingly, by comparing the 1H and 13C NMR spectra of the synthetic (7S,4’S,S’R)-chaetoviridin A 24 with literature data of chaetoviridin A 1, important differences were observed in particular at δH 4.30 vs 3.89 ppm (H5) and 1.06 vs 1.18 ppm (4’-CH3) and at δC 9.9 vs 13.5 ppm (4’-CH3), 19.4 vs 21.4 ppm (C6’), 67.4 vs 70.9 ppm (C5’), and 165.3 vs 162.7 ppm (C8).5,57 However, it turned out that 1H and 13C NMR data of 24 were identical to those reported by Borges et al. for the 4’-epi-chaetoviridin 2, which has been described bearing an anti-aldol side chain.7 In our synthesis, the syn-stereocontrolled construction of the aldol moiety unambiguously fixes the syn relationship between H4’ and H5 above 24. Accordingly, the reported 4’-epi-chaetoviridin A 2, described with an anti aldol side chain, has to be corrected to syn such as in (7S,4’S,S’R)-chaetoviridin A 24.

To further confirm the misassignment of the aldol side chain of the chaetoviridins A, we undertook the preparation of chaetoviridin A epimers bearing anti aldol moieties. To this end, we synthesized the two enantiomers of the dioxinones 28 bearing the anti aldol side chain (Scheme 4). Their synthesis started with the anti-methylation of both enantiomers of methyl 3-hydroxybutanoate 26 to give the anti aldols 27.31 Then, each enantiomer was individually converted to the (R,R)-or (S,S)-dioxinone 28 in five steps, following the procedure developed for the conversion of 17 to the syn dioxinone 21 (Scheme 2). Each anti-dioxinone was then reacted with cazaroschomene 14 under thermal basic conditions, and the crude mixtures were desilylated with HF/pyridine to yield the chaetoviridins with anti aldol side chains. Starting from (S,S)-dioxinone 28, (7S,4’S,S’R)-chaetoviridin A 29 and (7R,4’S,S’R)-chaetoviridin A 30 were obtained with 14 and 15% yield, respectively. The other set of anti chaetoviridins A was prepared starting from (R,R)-dioxinone 28; accordingly, (7S,4’R,S’R)-chaetoviridin A 31 and (7R,4’R,S’R)-chaetoviridin A 32 were obtained with 11 and 14% yield, respectively. For the four compounds 29–32, the absolute configuration at C-7 was attributable, thanks to the circular dichroism, as for 24 and 25 (Figure S2).

Analysis of the NMR data of 31 revealed, as expected, that they perfectly matched the reported data of natural chaetoviridin A 1; therefore confirming that the natural product has structure 31. This also confirms that the anti structure of reported natural 4’-epi-chaetoviridin 2 has to be corrected to syn such as in 24.

In addition, NMR data of (7S,4’S,S’S)-chaetoviridin A 29 perfectly match the reported data for the natural product 7’-epi-chaetoviridin A 3, validating the anti structure of the natural product; however, natural compound 3 should be renamed 4’,7’-bis-epi-chaetoviridin A.

Concerning the reported 7’,S’-bis-epi-chaetoviridin A 4, our NMR data were found to be identical to (7S,4’R,S’S)-chaetoviridin A 30; this is in accord with the reported structure8 and further confirms the presence of the unusual epimeric (7R) center in this azaphilone; however natural compound 4 should be renamed 7’,S’-tris-epi-chaetoviridin A.

For the 11-epimer of chaetoviridin A,6 named chaetoviridin E 6, we propose to revise its name to 11-epi-chaetoviridin A and its structure to the anti aldol side chain and (7S,4’R,S’R,11R) absolute configuration. Consequently, only one chaetoviridin E will remain, possessing the β-eliminated side-chain such as in 5.

In conclusion, we have synthesized the natural product chaetoviridin A along with three related natural epimers in ten steps by preparing their biogenetic precursor cazaroschomene. The synthesis of this fragment involved two key steps, the lactonisation/HWE one-pot process to build the 3-vinylisoconmarine core, and an oxidative dearomatization to obtain the pyranochromene scaffold. The condensation of a functionalized chiral acylketene to cazaroschomene allowed the tricyclic skeleton of chaetoviridins A to be built regioselectively. Detailed analysis of NMR and circular dichroism data allowed us to unambiguously revise the structure of all the chaetoviridins A. Of note, easy separation of C7-epimers at the last step of the
synthesis offers a divergent access to natural and/or unnatural chaetoviridins A.

Accordingly, these results will now allow clear identification of these metabolites when studying their biosynthesis and the gene clusters of their producing fungi. Quantification of the production of these metabolites is also made possible by providing standards.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02053.

Experimental procedures, characterization data, and copies of the $^1$H and $^{13}$C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES