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Total Synthesis of Chaetoglobin A via Catalytic, Atroposelective Oxidative Phenol Coupling

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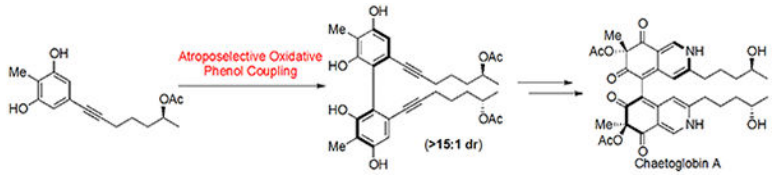
Abstract

The first total synthesis of chaetoglobin A (**1**), which features a chiral axis between two identical highly oxygenated bicyclic cores, was successfully completed in 12 steps from 2,6-dimethoxytoluene. Vanadium-catalyzed oxidative phenol coupling, as a key step, enabled generation of the axial chirality.

Abstract



Chaetoglobin A is one of the azaphilone dimers, which contains two identical oxygenated bicyclic cores incorporating tertiary alcohol stereocenters that are connected through a chiral axis (Figure 1). It is isolated from the endophytic fungus *chaetomium globosum*, which lives in the stem of *Imperata cylindrical*. In 2008, Tan et al. reported its inhibitory ability on the propagation of human breast cancer and colon cancer cell lines.[1] Previous studies on the biosynthesis of azaphilone alkaloids indicate that its core backbone is of polyketide origin.[2] However, the nature of the dimerization and generation of attendant axial chiral stereochemistry has not been delineated. Specifically, it is unclear whether the stereochemistry of the chiral axis forms first and directs formation of the tertiary alcohol

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Author Contributions

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Supporting Information

Experimental procedures, compound characterization, crystallographic data, NMR spectra. The Supporting Information is available free of charge on the ACS Publications website.

centers (via **3**), if the tertiary alcohol centers form first and then direct formation of the chiral axis (via **4**), or if these stereoelements are formed independently.

Due to their intriguing structures and biological activities, numerous attempts to synthesize the azaphilone alkaloids have been reported since the early 1970s.[3] Approaches to introducing the bicyclic core proceed from either a keto-formyl precursor or alkynyl-formyl precursor that generate benzopyrylium salts or pyronoquinones as key intermediates. Often, acid-catalyzed cycloisomerization, followed by oxidation, was used to construct the 2*H*-isoquinoline-2,6-dione backbone. However, no synthetic efforts have been reported toward azaphilone dimers to date. Recently, we reported an efficient method to construct a chiral biaryl axis by means of vanadium-catalyzed enantioselective oxidative phenol coupling.[4] The oxidative coupling permits the formation of chiral axes effectively. Here, we describe the total synthesis of chaetoglobin A utilizing this stereooselective oxidative phenol coupling to generate an axial chiral bisphenol dimer **7** as a key intermediate.

In our retrosynthetic analysis, the final isoquinoline moiety could be prepared by amination of **5** (Scheme 1). Lewis acid-catalyzed dearomatization followed by oxidation would allow for construction of the corresponding bicyclic core from formylated dimer **6**. We hypothesize that the axial chirality of **6** could direct formation of the tertiary alcohol centers of **5**. In doing so, we could determine the feasibility one of the possible biosynthetic pathways (i.e. via **3**)(Figure 1). Vilsmeier-Haack formylation could install the necessary formyl groups on tetraphenol **7**. We envisioned the atroposelective oxidative phenol coupling of **8** to afford pure atropoisomer **7**. We anticipated that the acetoxy stereocenters of **8** would have little effect on stereochemical course of the phenol coupling with the chiral catalyst exerting control. Internal alkynyl monomer **8** would be prepared from the Sonogashira cross-coupling of bisphenol **9** and alkyne **10**.

Synthetic efforts commenced with preparation of phenol **9** and alkyne **10** as shown in Scheme 2. Iridium-catalyzed borylation[5] of commercially available **11**, followed by halogenation allowed for the formation of bromide **13**. Due to need for a more reactive electrophile for Sonogashira cross-coupling, halogen exchange was undertaken to generate iodophenol **9** after demethylation. Surprisingly, stepwise iodination via halogen exchange[6] from bromide **13** proved to be more efficient than direct iodination[7] from boronic ester **12**. Following a literature report[8] to prepare enantiomerically pure hydroxyalkyne **17**, a nucleophilic ring opening with commercially available propylene oxide **14** and butyne **15** gave internal alkyne **16**. Sequential alkyne isomerization was effected with a Li/KO*t*-Bu in 1,3-diaminopropane. Acetate protection of the free hydroxyl group provided the desired alkyne **10** in 74% yield over three steps.

Optimization of Sonogashira coupling between iodide **9** and alkyne **10** led to the formation of oxidative phenol coupling precursor **8** in 98% yield (Scheme 3). Using our recently reported atroposelective oxidative coupling of phenols,[4] vanadium catalyst **18** was applied to this transformation. Notably, complete catalyst control over the diastereoselectivity was observed with the opposite enantiomer of the catalyst providing the diastereomeric product with comparable dr. The additives, LiCl and HOAc, which are theorized to activate the vanadium catalyst result in significant improvements (Table 1). Treatment of **8** with LiCl as

an additive gave high diastereoselectivity (Table 1, entry 2). Increased catalyst loading showed neither a significant improvement in yield, nor selectivity (Table 1, entry 3). Among alternative solvents, chlorobenzene seemed a promising candidate in terms of improving yield (Table 1, entry 2 vs 4 and entry 5 vs 6). Improved yield and comparable selectivity of dimer were realized with HOAc as the additive and chlorobenzene as solvent (Table 1, entry 6). Finally, further improved yield and diastereoselectivity was achieved under more concentrated reaction conditions (Table 1, entry 7). Use of chiral vanadyl catalyst **18** under the optimized conditions formed dimer **7** in 67% yield establishing the axial chiral element with >15:1 dr. The absolute stereochemistry of product **7** was confirmed by X-ray crystallographic analysis of the *para*-bromobenzoyl substituted derivative **19**.[9]

With the coupled atropoisomer in hand, our attention turned to the key oxidative dearomatization reaction, developed by Porco and coworkers, to generate the bicyclic core featuring a tertiary alcohol stereocenter.[11] Initially, we tested this transformation using monomeric formylated phenol **20**, which was easily prepared from monomer **8** in 85% yield (Scheme 4). Based on the literature, $Au(OAc)_3$ was the optimal Lewis acid for this transformation. These conditions efficiently provided the desired oxygenated core **21** upon IBX oxidation as assessed by a monomer **22** after acetylation (72% yield over three steps).

With dimer 7, several methods to formylate adjacent to the alkyne chain were surveyed.[10] Ultimately, the Vilsmeier-Haack formylation with preformed (chloromethylene)dimethyliminium chloride at −35 °C provided bisformylated product **6** in 86% yield (Scheme 5) without acyl deprotection, which occurred in many of the other conditions screened due to acid byproducts formed during generation of the active acylating species.

With dimer **6**, however, $Au(OAc)_3$-catalyzed dearomatization did not generate desired product **5**, but caused decomposition. After screening several Lewis acids, we found that AgOTf[12] gave a similar result in the model system from Scheme 4 (63% overall yield from **20**). To our delight, cycloisomerization of **6** performed simlarly with AgOTf, and subsequent oxidation with a hypervalent iodine reagent, IBX, allowed access to bicyclic dimer **5** (Scheme 5). We had theorized that the chiral axis would influence the stereochemistry during formation of this tertiary alcohol center with the bulk of the 2*H*-isoquinoline-2,6-dione backbone blocking one stereoface. However, the reaction gave a 1:1:1 mixture of the three possible isomers (7*S*,7'*S*; 7*S*,7'*R*; 7*R*,7'*R*), indicating that the axial stereochemistry does not create a strong facial bias. Fortunately, sufficient amounts of each isomer could be obtained to proceed with the synthesis. The following section describes the results obtained with the faster eluting symmetric diastereomer, which could not be definitively assigned as 7*S*,7'*S* or 7*R*,7'*R* at this stage.

At this juncture, selective acylation of the tertiary alcohol centers was needed, which could be achieved either by deacylation of the secondary alcohols followed by selective acylation of the tertiary alcohols or by global acetylation followed by selection deacylation of the less hindered secondary alcohols. The former possibility takes advantage of the greater reactivity of the alcohols adjacent to the ketone.[13] Upon removal of the acetyl groups from **5**, the resultant product was found to be prone to decomposition. As such, the latter alternative

became a focus. Acetylation of **5** afforded product **23** in 22% over three steps from **6**, which represent six sets of chemical transformations due to the dimeric nature of the material (Scheme 4). Unexpectedly, selective deprotection of the secondary acetoxy group in the presence of the sterically congested tertiary acetoxy group was challenging. Attempted hydrolysis of **23** with acidic or basic conditions led decomposition that was faster than deprotection. We explored a wide range of hydrolysis conditions,[14] including enzymatic methods,[15] and finally established that 10 equiv of $Ti(O\textit{i}\text{-}Pr)_4$ in CH_2Cl_2 at elevated temperature afforded free hydroxylated **24** in 52% yield (Scheme 4). Exposure of oxygenated bicycle **24** to excess NH_4OAc furnished synthetic chaetoglobin A (**1**) in nearly quantitative yield.

The spectroscopic data from synthetic **1** was in accord with those reported in the literature for chaetoglobin **A**.[1] In particular, the ^{13}C NMR gave 17 differentiable carbons supporting the symmetric structure. The chemical shifts of those signals closely matched those from the natural product securing evidence that the correct diastereomeric relationship between the tertiary alcohols and the stereoaxis had been generated. Importantly, circular dichroism data obtained from the synthetic material proved identical to that from the natural product (Figure 2), which indicates that both the same absolute and relative stereochemistries are established.

In conclusion, we have accomplished the first total synthesis of chaetoglobin A in 4.3% overall yield, with 12 steps in the longest linear sequence. A vanadium-catalyzed atroposelective oxidative phenol coupling serves as a key step in the formation of stereoaxis of chiral azaphilone dimer **1**. The stereochemical results from oxidative cyclization after formation of the stereoaxis raise interesting questions about the operating biosynthetic pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(16). CCDC 1822188 ((*P*)-**19**), and 1822189 (**19**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre

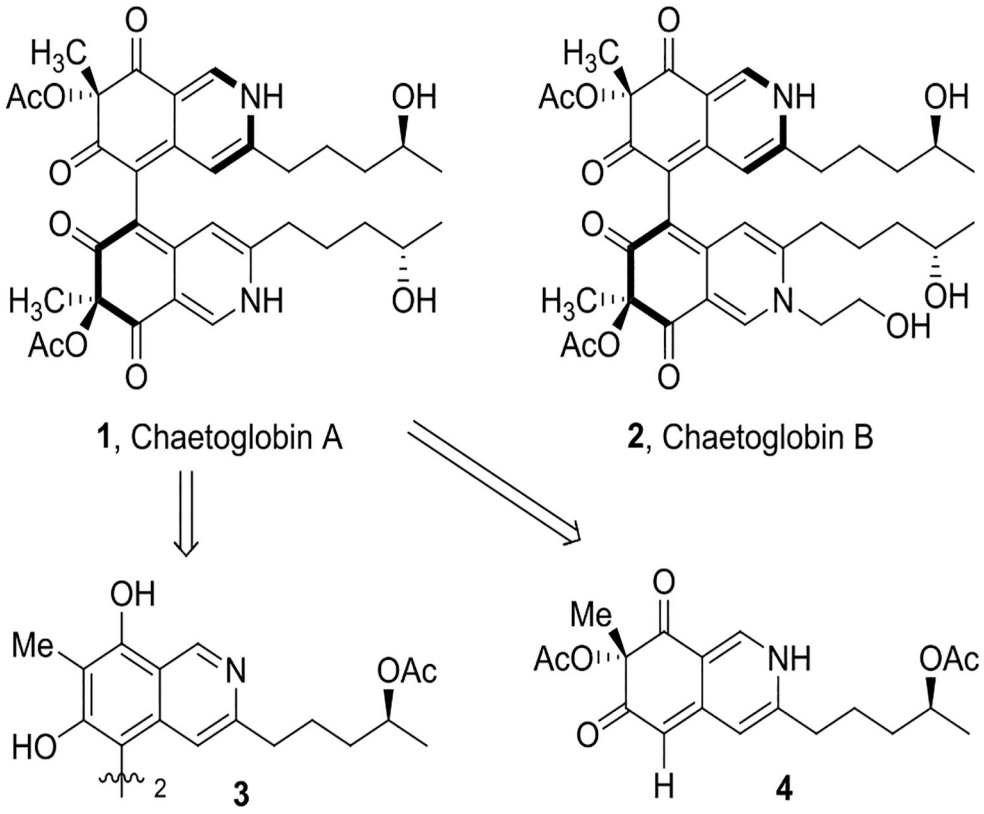


Figure 1.
Structure of chaetoglobin A (**1**) and B (**2**)

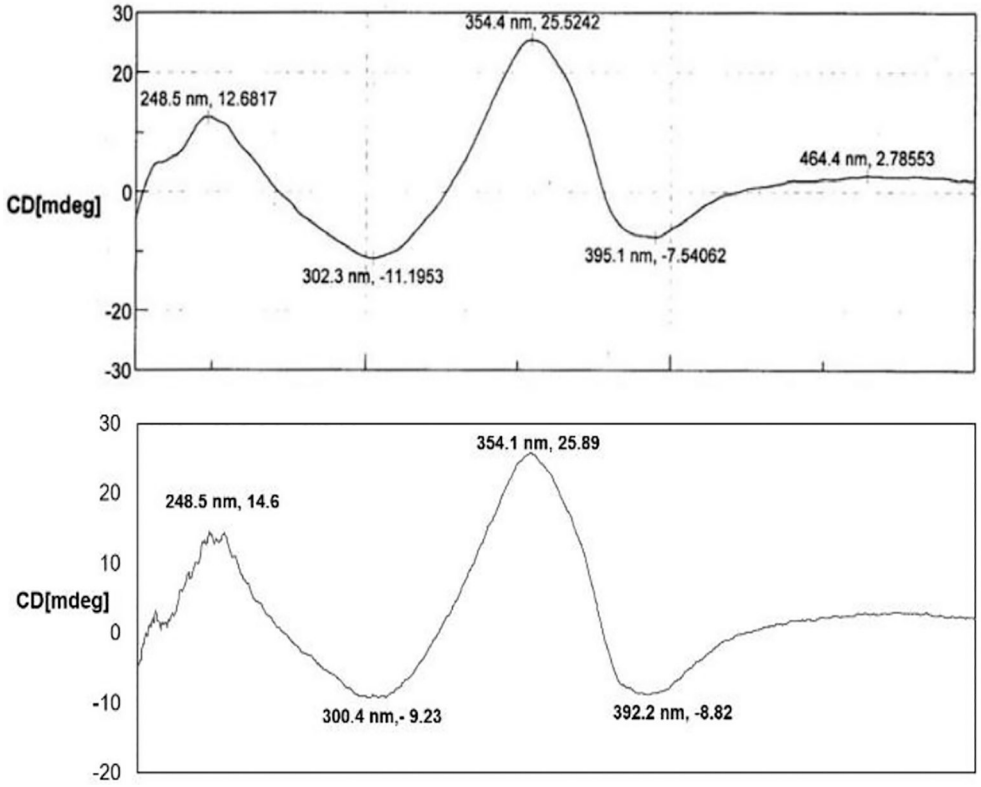
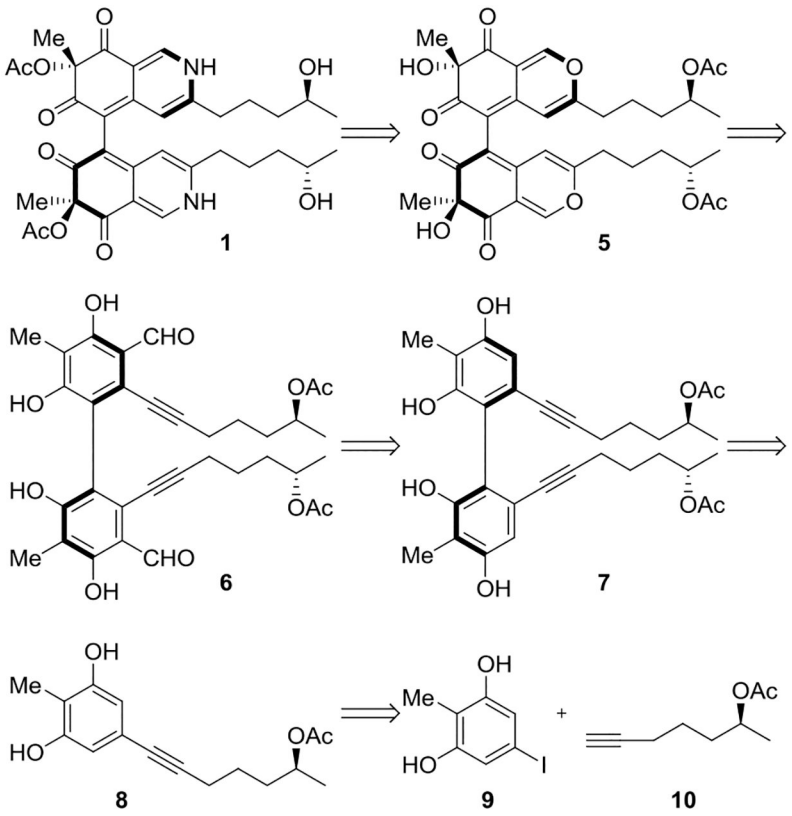
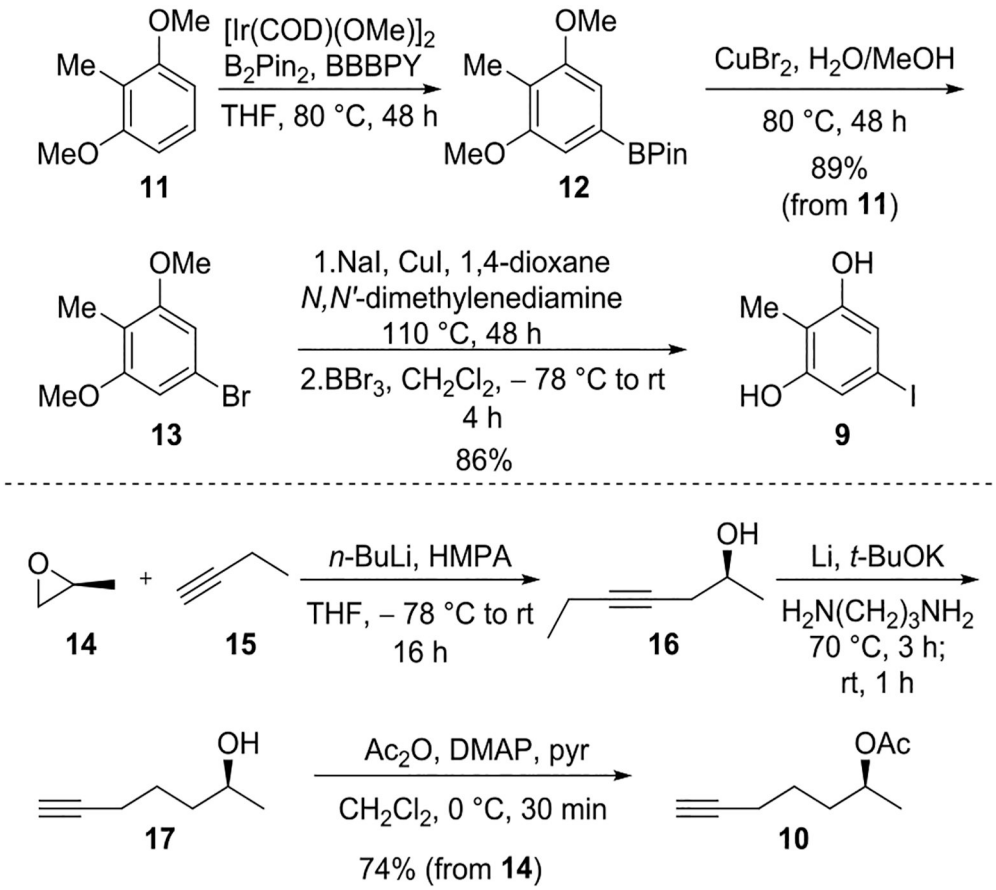


Figure 2.

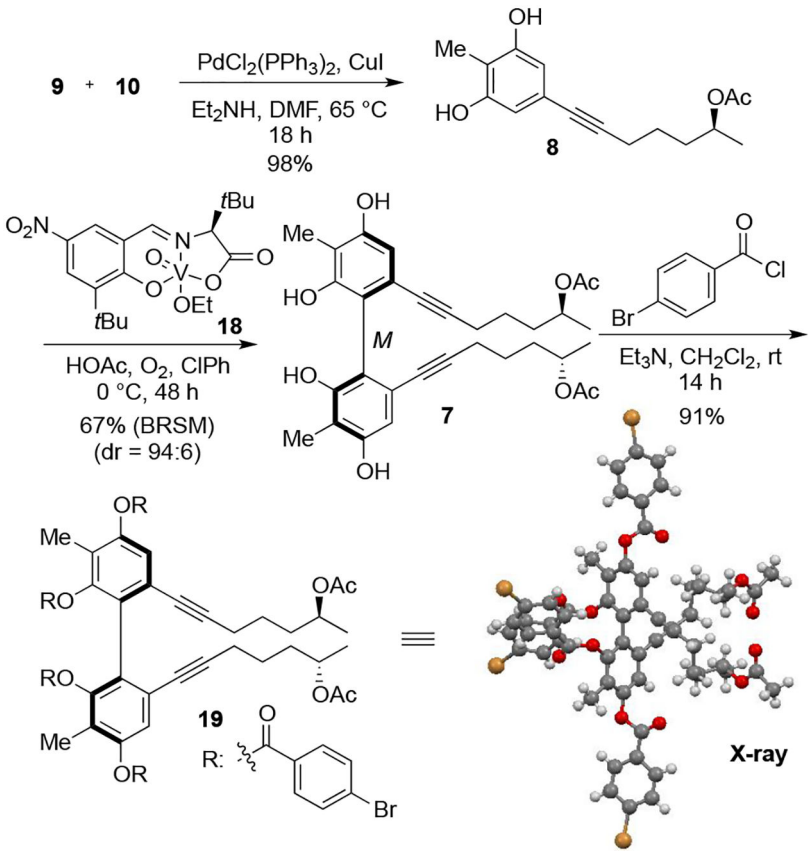
Comparing circular dichroism of chaetoglobin A (**1**) (a) CD spectrum of natural product isolate. Adapted from reference 1 with permission of The Royal Society of Chemistry; (b) synthetic **1** CD spectrum.



Scheme 1.
Retrosynthetic Analysis of Chaetoglobin A (1)

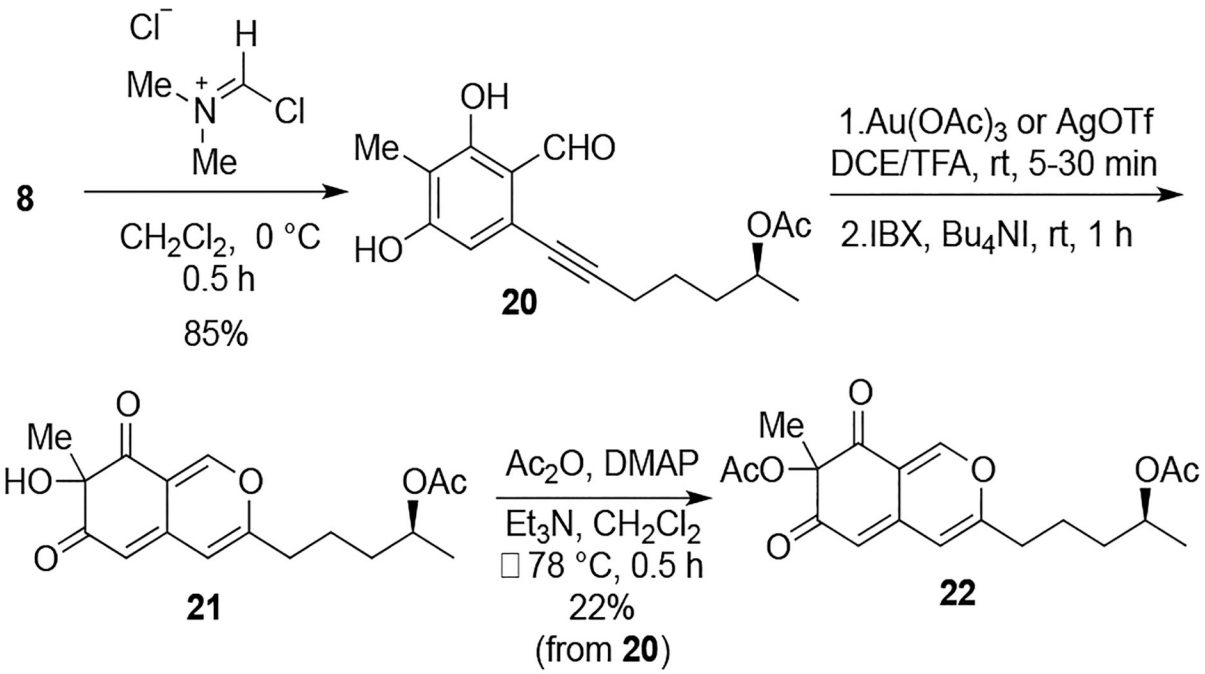


Scheme 2.
Syntheses of Sonogashira Coupling Fragments 9 and 10

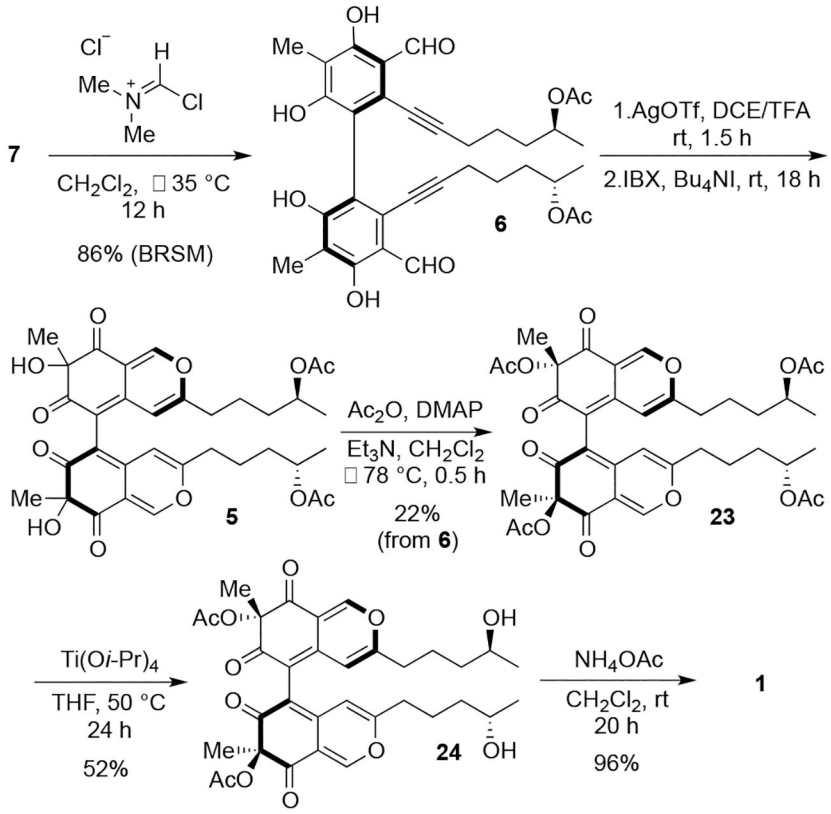


Scheme 3.

Atroposelective Oxidative Phenol Coupling and Determination of Absolute Axial Stereochemistry



Scheme 4.
Oxidative Dearomatization with Monomer 22



Scheme 5.
Completion of Synthesis of Chaetoglobin A (1)

Table 1.

Diastereoselective Oxidative Coupling of 8

entry	V-cat 18	additive[a]	solvent[b]	yield (%)[c]	dr
1	20 mol %	–	chlorobenzene[d]	34 (44)	79:21
2	20 mol %	LiCl	toluene	52 (59)	92:8
3	40 mol %	LiCl	toluene	49 (52)	93:7
4	20 mol %	LiCl	chlorobenzene	54 (60)	90:10
5	20 mol %	HOAc	toluene	49 (55)	87:13
6	20 mol %	HOAc	chlorobenzene	49 (64)	90:10
7	20 mol %	HOAc	chlorobenzene[d]	58 (67)	94:6

[a] 20 mol %

[b] 0.3 M

[c] Isolated yield based on recovery of substrate in parentheses

[d] 0.5 M