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Bioinspired Total Synthesis of (±)-Chaetophenol C Enabled by a Pd-Catalyzed Cascade Cyclization

Yun Li,*[†,‡] Qingyu Zhang,[†] Hongyu Wang,[†] Bin Cheng,[†] and Hongbin Zhai*[,⊥]

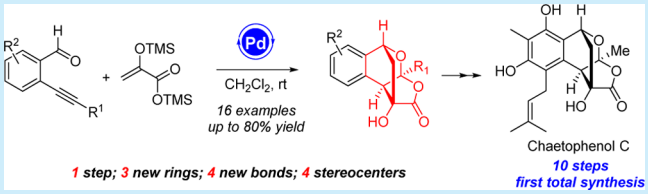
[†]State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China

[‡]State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[⊥]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China

Supporting Information

ABSTRACT: A novel Pd(II)-catalyzed cascade reaction has been developed that consists of a highly regio- and stereoselective oxa [4 + 2] cycloaddition reaction of *o*-alkynylbenzaldehydes and an intramolecular carboxylic group quenching of the in situ generated oxonium ion. This new reaction provides a one-step construction of the tetracyclic core structure of chaetophenol C from two simple starting materials. The developed chemistry was successfully applied to the first total synthesis of chaetophenol C and dozens of its analogues.



Chaetophenol C (**1**; Scheme 1) was isolated in 2013 from epigenetic manipulated *Chaetomium indicum* by Oshima and co-workers.[1] The structure of **1** is particularly striking in that it contains a rigid polycyclic core with a pentasubstituted γ-lactone to bridge the [2.2.2] ring system. To the best of our knowledge, no synthetic study on such a molecule has ever been reported to date. This, together with the inability to acquire sufficient quantities of chaetophenol C for further biomedical studies, makes it warranted to develop a facile access to the polycyclic core structure of such an interesting molecule. In this paper, we report a novel cascade reaction along with the first total synthesis of chaetophenol C in 10 steps.

o-Alkynylbenzaldehydes (I, Scheme 1 A) are known to readily undergo transition-metal-catalyzed cycloisomerization to generate benzopyrilium species[2] (II, Scheme 1 A), which may serve as a heterodiene[2c,m,k,3] in [4 + 2] or a 1,3-dipole equivalent[4] in [3 + 2] cycloaddition reactions. Therefore, we speculated that chaetophenol C might be accessible according to the retrosynthetic analysis in Scheme 1 B: The [2.2.2] ring system was expected to be accessed by a stereoselective [4 + 2] cycloaddition reaction of the isochromenylium species **2** (Scheme 1 B) with an enol ether, while the lactone motif could be installed by a subsequent trapping of the in situ generated oxonium intermediate with a carboxylate properly located within the same molecule. This prospective high efficiency of the so far unexplored route to chaetophenol C promoted us to believe that it would be a worthy synthetic endeavor. However, challenges did exist: (1) the competition between [4 + 2] and [3 + 2] cycloaddition reactions and (2) the stereoselectivity of the desired [4 + 2] pathway (endo vs exo). A [4 + 2] cycloaddition with the desired stereoselectivity apparently is a prerequisite for the formation of the lactone functionality because the subsequent trapping reaction would be possible only when the carboxylate group and the oxonium ion were accessible to one another in the intermediate **2** (Scheme 1B).

Oshima[1a] has postulated that chaetophenol C is biogenetically generated by the condensation of chaetophenol A (**3**, Scheme 1B) with pyruvic acid in the living system while the stereochemical fidelity over this condensation is governed by enzyme(s). Enlightened by this biosynthetic hypothesis, we began our explorations of the desired cascade cyclization with *o*-alkynylbenzaldehyde **4a** and pyruvic acid. However, initial results were disappointing; no desired product could be detected under a variety of conditions tested.[5] This observation led us to examine other dienophiles instead of pyruvic acid, and eventually trimethylsilyl 2-[(trimethylsilyl)oxy] acrylate **5** was found to be effective in the presence of a catalytic amount of AgOTf (Table 1, entry 1). The reaction gave the desired polycyclic product **6a**[6] as a single diastereoisomer, with the chemical structure and relative configuration being secured by X-ray crystallographic analysis.[7] A brief screening of catalysts reveals that $Pd(OAc)_2$ gave the highest yield (entry 2) of product. $AuCl_3$, $Zn(OTf)_2$, and $PtCl_2$−CO were relatively less effective (entry 4−7). Increasing the catalyst loading of $Pd(OAc)_2$ to 10 mol % did not show further improvement of the isolated yield (entry 8). Other solvents such as toluene and THF (entries 9 and 10) gave inferior results compared with dichloromethane.

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Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Reactivities of Benzopyrilium Ion and the Synthetic Strategy for Chaetophenol C

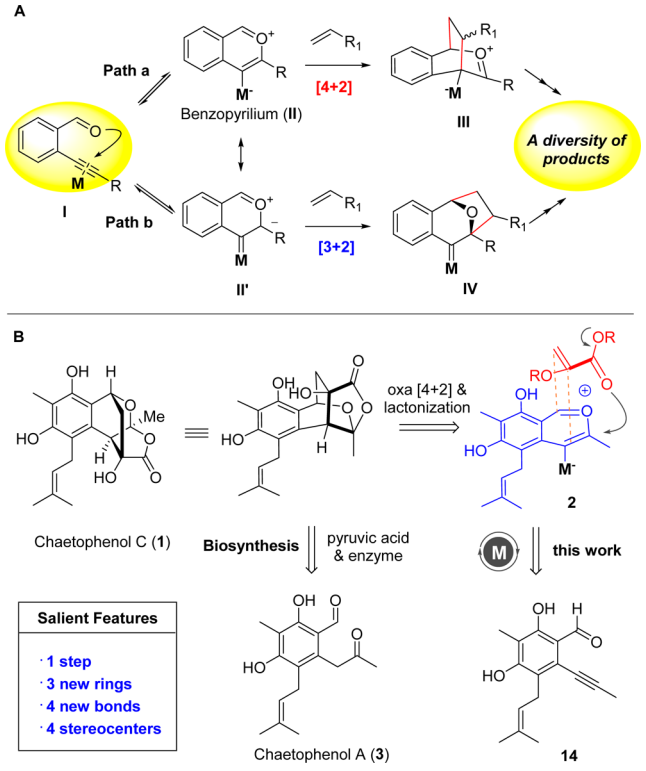
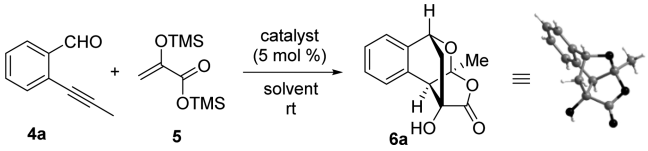


Table 1. Catalyst Screening and Condition Optimization of the Cascade Cyclization[a]

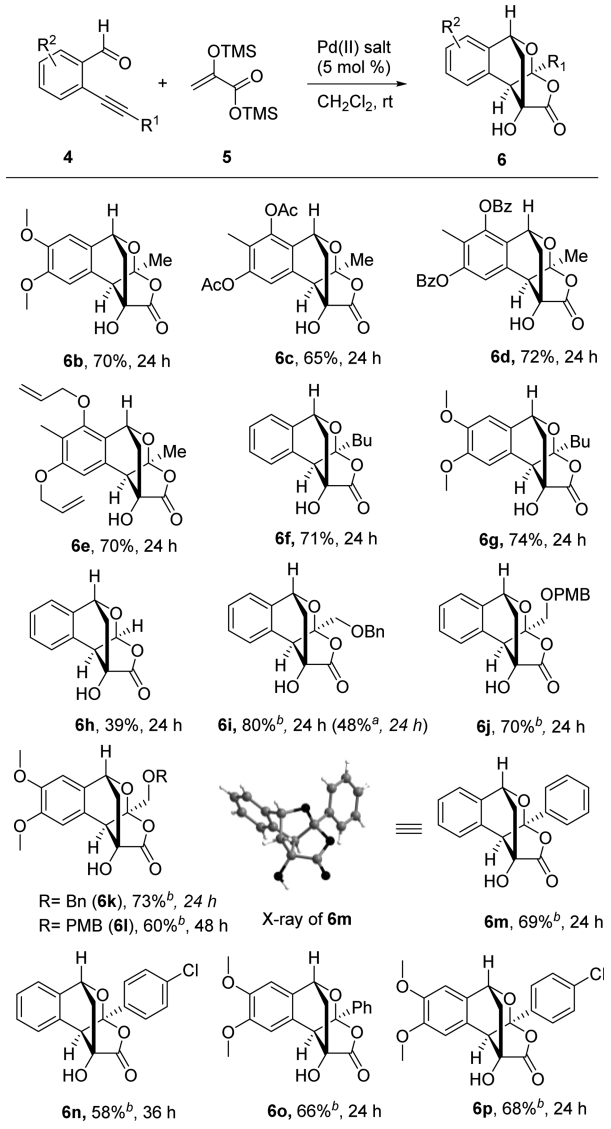


entry	catalyst	solvent	time (h)	yield[b] (%)
1	AgOTf	CH_2Cl_2	24	58
2	$Pd(OAc)_2$	CH_2Cl_2	24	75
3	$Cu(OTf)_2$	CH_2Cl_2	24	59
4	$AuCl_3$	CH_2Cl_2	48	6
5	$Zn(OTf)_2$	CH_2Cl_2	48	5
6[c]	$PtCl_2$/CO	CH_2Cl_2	24	14
7[d]	$PtCl_2$/CO	1,4-dioxane	24	complex
8[e]	$Pd(OAc)_2$	CH_2Cl_2	24	56
9	$Pd(OAc)_2$	toluene	24	51
10	$Pd(OAc)_2$	THF	24	8

[a]The reactions were performed by adding the catalyst (5 mol %) to a solution of **4a** (1 equiv) and **5** (12 equiv) in solvent (c = 0.05 M) at ambient temperature and stirring the mixture for 10−40 h until TLC showed full consumption of **4a**. [b]Isolated yield based on **4a**. [c]10 mol % of $PtCl_2$ was used under 1 atm of CO. [d]The reaction was performed at 80 °C under 1 atm of CO, with 10 mol % of $PtCl_2$ as the catalyst. [e]10 mol % of $Pd(OAc)_2$ was used.

With optimized conditions in hand, we next examined the scope of the cascade reaction, which amazingly allowed for the formation of four new bonds, three rings and four stereocenters (including two quaternary ones) in a one-flask manner with a range of *o*-alkynylbenzaldehydes. As illustrated in Scheme 2, this reaction proceeded very well at ambient temperature for all substrates (**4b**−**p**) examined, leading to the expected products (**6b**−**p**) in good to excellent yields.

Scheme 2. Analogues of Chaetophenol C[a]



[a]The reactions were performed by adding $Pd(OAc)_2$ (5 mol %) to a solution of **4** (1 equiv) and **5** (12 equiv) in CH_2Cl_2 (c = 0.05 M) at ambient temperature and stirring for 10−40 h until TLC showed full consumption of **4**. [b]With $Pd(TFA)_2$ (5 mol %) as the catalyst.

The substituents on the phenyl ring showed only a negligible influence on the cyclization compared with the groups attached to the alkyne motif. Butyl substituted substrates (**4f**, **4g**) gave as good yields as **4a**. However, when the substituent R_1 contained an ethereal subunit (**4i**−**l**) or was an aryl group (**4m**−**p**), the reactivity of the substrates was significantly reduced; the starting *o*-alkynylbenzaldehydes could not be fully consumed, presumably because of additional coordination to the palladium and/or the increased steric crowding. Interestingly, it was found that when $Pd(TFA)_2$, a more cationic palladium(II) salt, was used as the catalyst instead of $Pd(OAc)_2$, substrates **4i**−**p** all afforded the corresponding products **6i**−**p** in satisfactory yields. The structure of **6m** was further confirmed by X-ray crystallographic analysis.[7] However, it is worth mentioning that substrate **4a**, which reacted well when using $Pd(OAc)_2$ as

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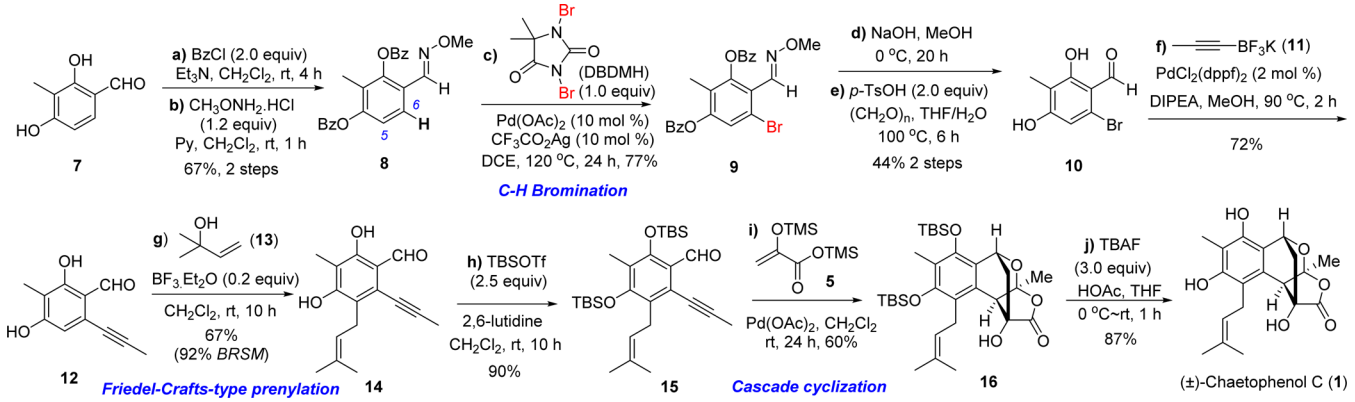
Scheme 3. Total Synthesis of Chaetopenol C



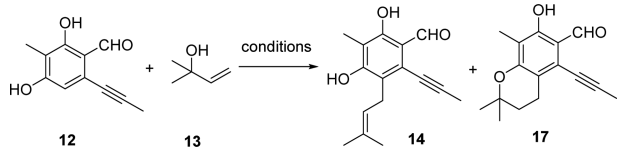
the catalyst, only gave 46% yield under the $Pd(TFA)_2$ conditions, along with significant amounts of unidentified side products. A substrate with a terminal alkyne (**4h**) gave a much lower yield of the polycyclic product even under the milder $Pd(OAc)_2$ conditions, presumably because the highly reactive **4h** was prone to other undesired transformations in the presence of the palladium catalyst.

To demonstrate the utility of this newly developed methodology, the total synthesis of chaetophenol C was then attempted. As outlined in Scheme 3, the synthesis commenced with the commercially available phenol **7**. Benzoyl protection and oxime formation of **7** were carried out to produce the *O*-methyloxime **8** in 67% combined yield over two steps. Subsequent bromination at the C-6 of compound **8** was initially achieved through a five-step sequence (i.e., nitration at the C-5, hydrogenation, bromination, nitrosylation, and reduction) according to a previously reported protocol.[3d,8] Strategically, the *ortho*-directed C−H functionalization apparently offers quick access to desired C-6 bromination.[9] To this end, Fabis' condition[10] was first tested, which was indeed feasible. However, the reaction only gave 52% yield of **9** together with a mass of unreacted **8** as an inseparable mixture. Then, after extensive examinations, we eventually found that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) was much superior to NBS as in Fabis' original protocol, which delivered the desired product **9** in 77% yield. To the best of our knowledge, this is the first report on the utilization of DBDMH as the brominating reagent in C−H bromination.

After removing the benzoyl and oxime group in **9**, the propynyl group was then installed onto aldehyde **10** through a modified Suzuki coupling.[11] It is noteworthy that Sonogashra reaction was inapplicable here because of the high volatility of propyne. Considering the hindrance at C5 position of compound **12**, an intramolecular reaction was believed to be more feasible for the following functionalization at C5. Thus, phenol **12** was initially converted to its allylic ether **4e** and various Claisen rearrangement conditions were attempted for the C5 allylation. However, the desired transformation did not proceed under dozens of classical conditions. These negative results forced us to seek other alternatives.

Enlightened by Manners' report,[12] which employed 2-methylbut-3-en-2-ol (**13**) as the prenylation reagent for a biogenetic-type synthesis of *o*-isopentenylphenols, an array of catalysts were evaluated in this prenylation reaction (see Table 2, entries 1−7) including formic acid,[12] Amberlyst 15,[13] Cu−Al−KIT-5,[14] phosphormolybdic acid (PMA), and $BF_3{\cdot}Et_2O$.[15]

Table 2. Screening of Conditions for the Direct Prenylation Reaction[a]



entry	catalyst	solvent	yield[b] (%)
1	formic acid	H_2O	complex
2	Amberlyst 15	CH_2Cl_2	NR
3[c]	Cu−Al−KIT-5	$(CH_2Cl)_2$	NR
4	PMA[d]	CH_2Cl_2	**14** (35); **17** (0)
5	$BF_3{\cdot}Et_2O$	CH_2Cl_2	**14** (48); **17** (10)
6	$BF_3{\cdot}Et_2O$	CCl_4	**14** (20)
7	$BF_3{\cdot}Et_2O$	1,4-dioxane	NR
8[e]	$BF_3{\cdot}Et_2O$	CH_2Cl_2	**14** (67)

[a]The reactions were performed by adding the catalyst (0.1 equiv) to a solution of **12** (0.1 mmol) and **13** (0.25 mmol) in 0.5 mL of solvent at 0 °C and stirring the mixture for 10−40 h at ambient temperature. [b]Isolated yield based on **12**. [c]Performed at 80 °C. [d]PMA = phosphormolybdic acid. [e]0.2 equiv of $BF_3{\cdot}Et_2O$ was used with a concentration [**12**] = 0.1 M.

Among them, $BF_3{\cdot}Et_2O$ gave the best results under a much-diluted concentration (entry 8).

With compound **14** in hand, the two hydroxyl groups were then converted to corresponding bis-TBS ether **15** in decent yield. The resulting alkynylbenzaldehyde **15** was subjected to the optimal conditions for the cascade cyclization. To our gratification, the reaction proceeded smoothly and delivered the desired polycyclic compound **16** in 60% yield. It is noteworthy that the cascade cyclization reaction did not work when diphenol **14** was directly used as the substrate. We suspect that the intramolecular hydrogen bonding might be responsible for the failure of the desired cyclization. Subsequent removal of the TBS protection of **16** with TBAF buffered with acetic acid[16] gave chaetophenol C in 87% yield, with all spectroscopic data identical to those reported by Oshima.[1a]

In summary, we have developed a palladium-catalyzed cascade cycloaddition/cyclization reaction of *o*-alkynylbenzaldehydes giving products containing the [2.2.2] bicyclic lactone core structural unit found in chaetophenol C. The efficacy of this process was showcased by the ease with which novel, highly composite scaffolds could be assembled from steadily available materials in one chemical step. The practicality of the transformation was also demonstrated in the first total synthesis

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of chaetophenol C, which was accomplished in 10 steps from a commercially available starting material.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02124.

Synthetic procedures; ^{1}H and ^{13}C NMR spectra for all organic products (PDF)
X-ray data for compound **6a** (ZIP)
X-ray data for compound **6m** (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: liyun@lzu.edu.cn
*E-mail: zhaihb@pkusz.edu.cn

ORCID

Yun Li: 0000-0003-2236-9880
Bin Cheng: 0000-0002-8276-6653
Hongbin Zhai: 0000-0003-2198-1357

Notes

The authors declare no competing financial interest.

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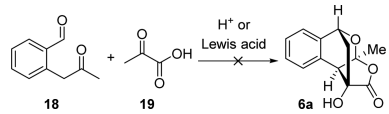
(5) Most Bronsted acids gave a complex mixture, while the Lewis acids such as $Pd(OAc)_2$, $CoCl_2$, and $Cu(OTf)_2$ gave small amounts of hydrolyzed methyl ketone (**18**) as the product. In addition, we also tested the reaction of methyl ketone **18** and pyruvic acid according to the Oshima biosynthetic proposal for chaetophenol C. However, complex mixtures were observed ether under the presence of protic acids (TFA, TsOH) or Lewis acids such as $Pd(OAc)_2$ and $Cu(OTf)_2$.



(6) A H^+ source for the protonolysis of the bridgehead Pd−C bond might comes from the moisture contained in trimethylsilyl 2-[(trimethylsilyl)oxy] acrylate, which was used as it crude form in the cyclization.

(7) CCDC 1546892 and CCDC 1552890 contain the supplementary crystallographic data for compound **6a** and **6m**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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