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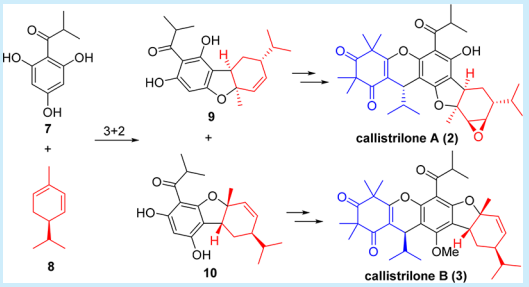
Biomimetic Syntheses of Callistrilones A−E via an Oxidative [3 + 2] Cycloaddition

Yonghong Guo, Yuhan Zhang, Mingxing Xiao, and Zhixiang Xie*

State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

Supporting Information

ABSTRACT: Concise total syntheses of callistrilones A−E have been achieved from **7** and commercially available α-phellandrene (**8**). The synthetic strategy, which was primarily inspired by the biogenetic hypothesis, was enabled by an oxidative [3 + 2] cycloaddition followed by a Michael addition and an intramolecular nucleophilic addition to construct the target molecules. Moreover, viminalin I was also synthesized, and its absolute configuration was unambiguously confirmed.



The Myrtaceae family has a wide distribution in tropical and warm-temperate regions of the world and is typically common in many of the world's biodiversity hotspots. According to a recently estimated suggestion, the Myrtaceae family includes approximately 5950 species in ca. 132 genera.[1] Many species of this widely distributed family, such as *Myrtus communis* L. (Myrtaceae),[2] have been used as folk medicine for centuries because of their significant antimicrobial, antitumor, and anti-inflammatory properties.[3] For example, myrtucommulone A (**1**), isolated from the plant (Figure 1),[4] exhibits strong antibacterial activity against Gram-positive bacteria.[5] Continuing phytochemical investigations of the leaves of *Myrtus communis* L. led to the isolation of myrtucommulones J, K, and L by Cottiglia[6] and five meroterpenoids by Wang.[7] Recently, three of these isolated meroterpenoids were synthesized by our group via a biomimetic approach.[8]

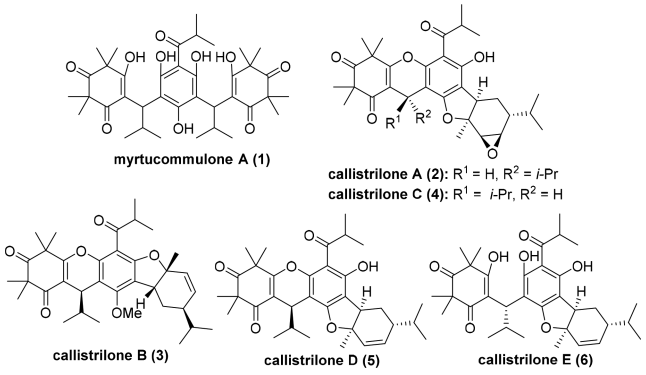


Figure 1. Structures of myrtucommulone A and callistrilones A−E.

Callistrilones A (**2**) and B (**3**), with a new triketone−phloroglucinol−monoterpene hybrid skeleton, were isolated from *Callistemon rigidus* (Myrtaceae).[9] Bioactivity research showed that **2** has moderate activity against Gram-positive bacteria, including multiresistant strains. The unprecedented pentacyclic ring system and the biosynthetic pathway feature inspired us to engage in total syntheses of these two compounds, which have just been accomplished by the adoption of a biomimetic [3 + 2] cycloaddition as the key step. Very recently, Li and co-workers isolated callistrilones C−E, which are closely related to callistrilones A and B in structure, and accomplished elegant catalytic asymmetric total syntheses of callistrilones A, C, D, and E.[10] Almost at the same time, callistrilones A, B, and D were biomimetically synthesized via catalytic Friedel−Crafts alkylation and palladium-catalyzed Wacker-type oxidative cyclization by Dethe.[11] Following our syntheses of callistrilones A and B, callistrilones C−E were also synthesized by us with the same strategy. Herein we report these new biomimetic syntheses of callistrilones A−E.

In the isolation paper,[9] Ye and co-workers postulated biosynthetic pathways for callistrilones A and B. It has been reported that acylphloroglucinol and flavesone are two major components of *Callistemon* plants.[12] In the proposed biosynthetic pathway, an oxidative [3 + 2] cycloaddition first takes place between isobutyrylphloroglucinol (**7**) and α-phellandrene (**8**), a common monoterpene in *Callistemon* plants, giving rise to intermediates **9** and **10** (Scheme 1).[13] Intermediate **9** is coupled with the precursor isobutylidenesyncarpic acid (**11**) via Michael addition to deliver callistrilone E (**6**)[10] and **12**,[14] which can be transformed to **13** and callistrilone D (**5**) via intramolecular nucleophilic addition. Callistrilone A (**2**) and callistrilone C (**4**) are accessed via epoxidation of **13** and **5**, respectively. As shown in Scheme 1, on the basis of the family tree of biogenetic pathways proposed for callistrilones A−E, compounds **12** and **13** would be natural

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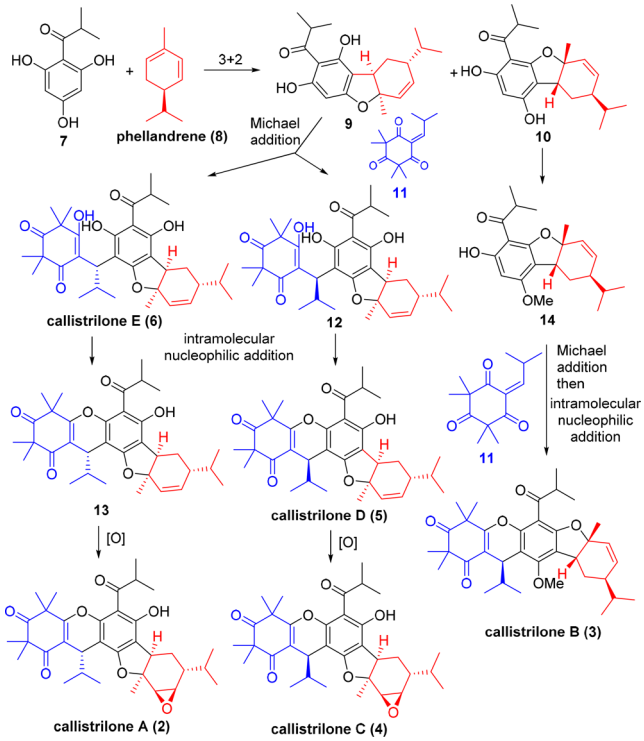
Scheme 1. Biomimetic Pathway Proposed for Callistrilones A–E

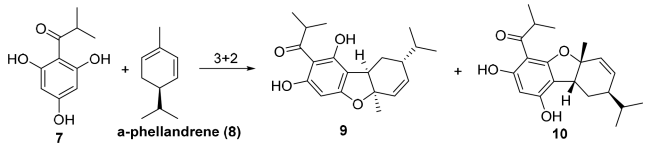


products as well, which might be discovered from plants in the future. On the other hand, methylation of **10** then leads to the formation of intermediate **14**, which was also isolated from *Callistemon rigidus*.[9] Compound **14** is further coupled with the precursor isobutylidenesyncarpic acid (**11**) via Michael and intramolecular nucleophilic additions to deliver callistrilone B (**3**).[14]

Inspired by the proposed biogenetic pathway of callistrilones A–E, the total syntheses of these natural products were initiated from an oxidative [3 + 2] cycloaddition between **7** and commercially available compound **8**. Isobutyrylphloroglucinol (**7**) was synthesized from phloroglucinol by Friedel–Crafts acylation with isobutyryl chloride in 85% yield.[8,15] With **7** in hand, we then focused on the biomimetic oxidative [3 + 2] cycloaddition, a powerful approach to construct dihydrobenzofuran skeletons from phenols and olefins.[16] Several kinds of oxidants have been applied for the synthesis of dihydrobenzofuran derivatives from phenols and olefins, such as single-electron metal oxidants,[17] high-valence iodine reagents,[18] DDQ,[19] $FeCl_3$/DDQ,[20] $FeCl_3{\cdot}(H_2O)_6$/DTBP,[21] and electrochemical oxidation.[22] This kind of oxidation has also been achieved under conditions of photoredox catalysis, such as visible light/$Ru(bpz)_3(PF_6)_2$/$(NH_4)_2S_2O_8$[23] or visible light/mesoporous graphitic carbon nitride/air.[24] Initially, we used the procedure of Lei[19b] and treated compounds **7** and **8** with DDQ in the presence of a catalytic amount of $FeCl_3$. However, it did not work. The reason might be the poor solubility of compound **7** in toluene. Then the solvent was changed from toluene to DMF. However, oxidative [3 + 2] cycloaddition between **7** and **8** still did not happen. Instead, a [4 + 2] cycloaddition[25] product from **8** and DDQ was obtained (see the Supporting Information for details). As DDQ was not a suitable oxidant for **8** to proceed with this oxidative [3 + 2] cycloaddition, we turned our attention to $FeCl_3{\cdot}(H_2O)_6$/DTBP conditions,[21] but this attempt resulted in the formation of complicated compounds.

Thus, an extensive screening of reaction conditions was needed for this oxidative [3 + 2] cycloaddition. Nair and co-workers reported a [3 + 2] cycloaddition between 2-hydroxy-1,4-naphthoquinone and conjugated dienes that uses CAN as an oxidant.[26] Following their protocol, treatment of **7** and **8** with CAN gave **9** and **10** in 9% and 14% yield, respectively (Table 1, entry 1). Encouraged by this initial finding, we

Table 1. Screening for an Oxidative [3 + 2] Cycloaddition[a]



				yield (%)[b]	
entry	oxidant	solvent	T (°C)	**9**	**10**
1	CAN	CH_3CN	0	9	14
2	AgOAc	CH_3CN	50	0	48
3	Ag_2O	CH_3CN	rt	0	50
4	Ag_2CO_3	CH_3CN	50	trace	35
5	$Mn(OAc)_3$	CH_3CN	30	0	33
6	$PhI(OAc)_2$	CH_3CN	50	trace	trace
7	CAN	DCM	0	12	19
8	CAN	THF	0	4	26
9	CAN	acetone	0	14	33
10[c]	CAN	acetone	0	14	40
11[d]	CAN	acetone	0	15	37
12[e]	CAN	acetone	0	24	35

[a]Conditions: unless indicated otherwise, the reactions were performed with **7** (0.28 mmol) and **8** (0.56 mmol, 2.0 equiv) in the solvent (5.6 mL) under Ar, and the oxidant (0.64 mmol, 2.3 equiv) was added. [b]Isolated yields. [c]Oxidant (3.5 equiv). [d]**8** (5.0 equiv) and oxidant (3.5 equiv). [e]**8** (10.0 equiv) and oxidant (6.0 equiv).

continued to test various single-electron metal oxidants. The representative results are included in Table 1 as entries 2–5. The reaction gave **10** as the major product when Ag salts and Mn salts were used as oxidants. The best yield was obtained using Ag_2O as the oxidant. The high-valence iodine reagent $PhI(OAc)_2$, on the other hand, is not suitable for this reaction (entry 6). For diverse syntheses of callistrilones, the yield of **9** also needed to be improved. We tried to convert **10** into **9**, but this effort was in vain. As using CAN as the oxidant gave both **9** and **10**, we chose this oxidant for further optimization. Various solvents such as DCM, THF, and acetone were examined to improve the yield of **9**, and the best result was obtained when acetone was used as the solvent (entries 7–9). When the amounts of CAN and **8** were increased, the yield of **9** slightly increased (entries 10–12). It should be noted that the major compound was **10** in all of these cases because the *o*-phenol is more nucleophilic as a result of hydrogen bonding between the *o*-phenol and the ketone.[27] Moreover, a high concentration of CAN and long reaction time would decrease the yield.[17a]

As compound **10** was main product of the oxidative [3 + 2] cycloaddition, we turned to the total synthesis of callistrilone B from **10** according to the biosynthetic hypothesis. As shown in Scheme 2, methylation of **10** delivered biosynthetic intermediate **14**, which was isolated from *Callistemon rigidus* and has the optical rotation value of +70.[9] In 2018, the same group[28] reported that the optical rotation value of **14**, isolated from the

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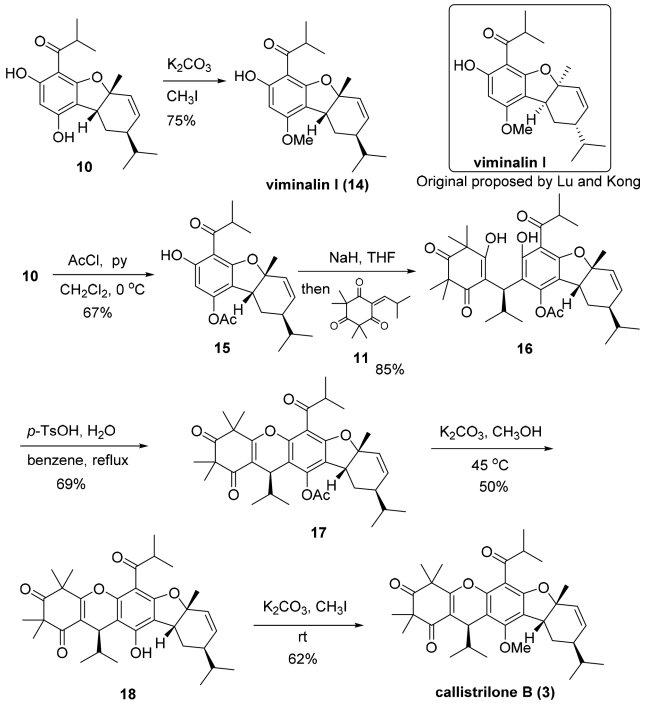
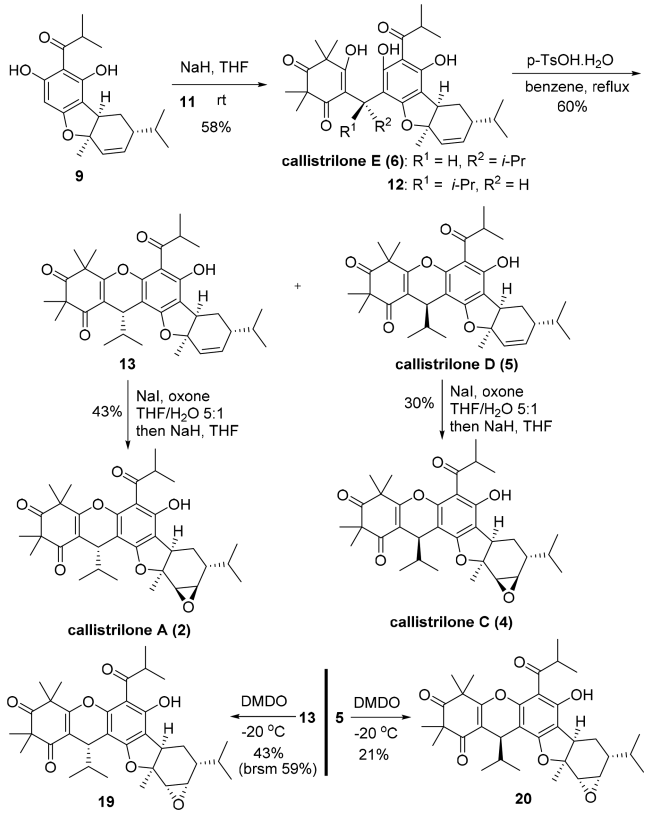
Scheme 2. Syntheses of Viminalin I and Callistrilone B



Scheme 3. Syntheses of Callistrilones A, C, D, and E



same plant, was −68.7.[29] Viminalin I, isolated from *Callistemon viminalis*, was originally proposed as the enantiomer of **14**, and the reported optical rotation value was −30.7.[13] Compound **14** synthesized in the present study has an optical rotation value of −65.3. Obviously, the absolute configuration of viminalin I is consistent with that shown for **14** in Scheme 2.

Following the preparation of viminalin I (**14**), the synthesis of callistrilone B proceeded by testing the Michael and intramolecular nucleophilic additions of **14** to **11**. Compound **11** was prepared from flavesone in one pot.[8] To our surprise, no product was observed when **14** was reacted with **11** under basic conditions such as NaH and *t*-BuOK. The results remained disappointing under Lewis acidic conditions, such as $Ni(ClO_4)\cdot 6H_2O$ and $FeCl_3$.[27] In addition, complex products were detected when **10** was used instead of **14**.

We speculated that the reason for this failure might be that the electron-donating methoxy group reduces the nucleophilicity of **11**, and thus, we changed the −OMe group to the electron-withdrawing −OAc group for further investigations.[30] To our delight, after this manipulation the Michael addition proceeded smoothly in the presence of NaH, giving compound **16** in 85% yield as a single diastereoisomer (Scheme 2). Treatment of **16** with *p*-toluenesulfonic acid (PTSA) then afforded **17**.[31] A stepwise procedure involving deacetylation and methylation successfully gave callistrilone B (**3**). The spectra and physical properties of the synthesized compound were identical to those of the reported natural product.[7]

Moving forward, the Michael addition of **9** with **11** proceeded smoothly to give a pair of regioisomers, callistrilone E and **12** (Scheme 3). Then callistrilone E and **12** were successfully converted to **13** and callistrilone D through a sequence mediated by PTSA in 39% and 21% yield, respectively. Next, the seemingly simple epoxidation of the C=C bond proved to be challenging. Direct epoxidation of compound **13** or callistrilone D with *m*-CPBA or dimethyldioxirane (DMDO) provided undesired stereoselective product **19** or **20**. It was believed that the steric hindrance was the primary cause. Therefore, we adapted a stepwise sequence[32] to overcome this obstacle. The best result[10] was obtained when iodohydroxylation of the disubstituted double bond was conducted with NaI/oxone and then a NaH-promoted diastereoselective cyclization was implemented to give the desired callistrilones A and C. The ^1H and ^{13}C NMR spectra were in agreement with the literature data.[7,10]

In summary, callistrilones A−E have been synthesized via oxidative [3 + 2] cycloaddition followed by Michael and intramolecular nucleophilic additions as key reactions. Moreover, viminalin I was also synthesized, and its absolute configuration was unambiguously confirmed. By providing efficient access to the 2,3-dihydrobenzofuran core, this biomimetic oxidative [3 + 2] cycloaddition strategy allowed us to construct an array of natural and unnatural products from acylphloroglucinol and α-phellandrene.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00238.

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

Accession Codes

CCDC 1818783 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge

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Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: xiezx@lzu.edu.cn.

ORCID

Zhixiang Xie: 0000-0001-5809-3084

Notes

The authors declare no competing financial interest.

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