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Biomimetic Total Syntheses of Callistrilones A, B, and D

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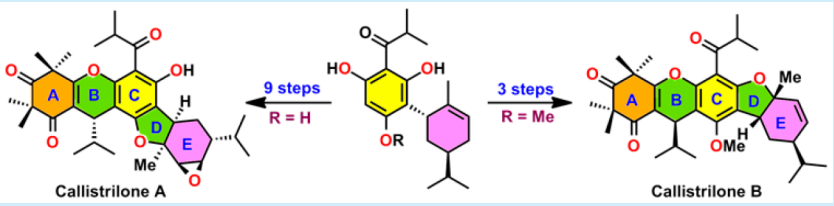
Supporting Information



ABSTRACT: A biomimetic total syntheses of antibacterial natural products (±)-callistrilones A, B, and D, the first triketone−phloroglucinol−monoterpene hybrids with an unprecedented [1]benzofuro[2,3-*a*]xanthene and [1]benzofuro[3,2-*b*]xanthene pentacyclic ring system along with the postulated biosynthetic intermediate, isolated from the leaves of *Callistemon rigidus*, were achieved. The total synthesis features highly regio- and diastereoselective catalytic Friedel−Crafts alkylation, palladium-catalyzed Wacker-type oxidative cyclization, Michael addition, and late-stage diastereoselective epoxide formation from the extremely hindered β face as key steps.

Phloroglucinols containing natural products have been a great source of inspiration for synthetic organic chemists over a long period of time. Because of their complex structural features and diverse biological effects, natural products of this class have become attractive targets for organic chemists.[1] Recently, Shaheen and co-workers[2] isolated a phloroglucinol adduct containing unprecedented carbon skeletons with two kinds of building blocks from *Myrtus communis*, a new inhibitor of reactive oxygen species (ROS). In 2016, Ye and co-workers isolated the first triketone−phloroglucinol−monoterpene hybrids callistrilones A (**1**) and B (**2**) along with the postulated biosynthetic intermediate **3** (Figure 1) from the plant *Callistemon rigidus*,[3] popularly known as bottlebrush because of its cylindrical brushlike flowers resembling a traditional bottle brush. The bottlebrush plant is used as a diuretic and for relieving problems of the urinary tract. Australian natives use bottlebrush flowers as a natural energy drink. Callistrilones A and B represent a new carbon skeleton with unprecedented [1]benzofuro[2,3-*a*]xanthene and [1]benzofuro[3,2-*b*]-xanthene pentacyclic ring systems composed of three kinds of building blocks combined via two different coupling partners to form dihydrofuran (ring D) and pyran (ring B) rings. The structures of **1**−**3** were elucidated by spectral analysis, X-ray diffraction, and electronic circular dichroism (ECD) calculations. The crude methanol extract of the fresh leaves of *C. rigidus* also indicated the presence of **1**−**3** (analyzed by HPLC−HRESIMS), confirming the natural occurrence of these compounds. While our manuscript was being prepared, Cheng et al. reported the isolation of callistrilones C (**4**), D (**5**), and E (**6**) and the catalytic asymmetric total syntheses of callistrilones A (**1**), C (**4**), D (**5**), and E (**6**).[4] Herein, we report biomimetic total syntheses of callistrilones A (**1**), B (**2**), and D (**5**) and the postulated biosynthetic intermediate **3**.

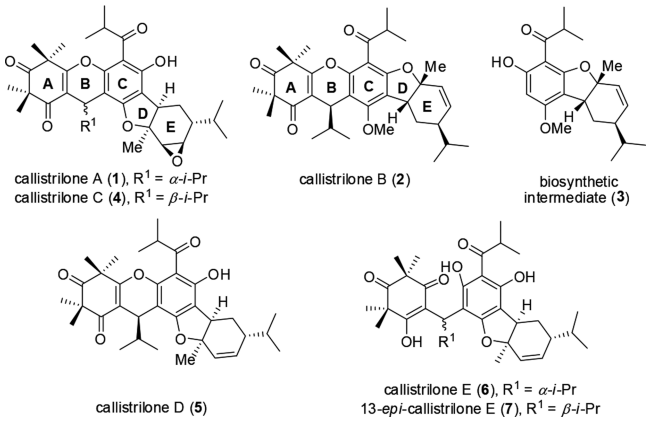


Figure 1. Structures of callistrilones A (**1**) and B (**2**) and the biosynthetic intermediate **3**.

Ye and co-workers postulated that callistrilones A (**1**) and B (**2**) might be biosynthetically derived from intermediate **8** and **3**, respectively (Scheme 1).[3] The intermediates **3** and **8** were assumed to be obtained by the radical addition of isobutyrylphloroglucinol (**9**) across phellandrene (**10**) and further intramolecular cyclization between phenolic 2-OH and the carbocation of **11**. Based on the biosynthetic pathway, we proposed retrosynthetic analysis for callistrilones A (**1**), B (**2**), and D (**5**) and the biosynthetic intermediate **3** as depicted in Scheme 2. It was envisioned that callistrilone A (**1**) could be obtained from 13-*epi*-callistrilone D (**12**) by stereoselective epoxidation of the isolated double bond. 13-*epi*-Callistrilone D

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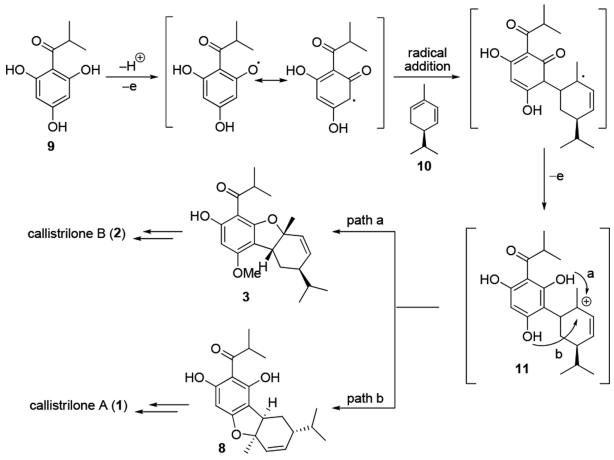
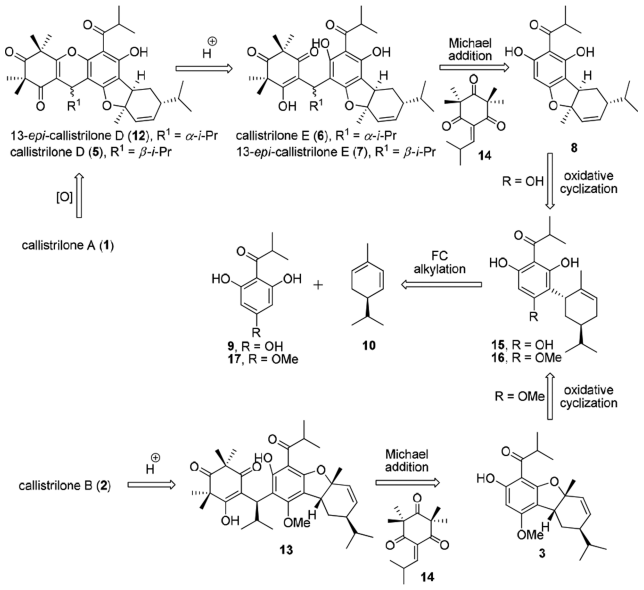
Scheme 1. Biosynthetic Pathway for 1−3 Proposed by Ye and Co-workers



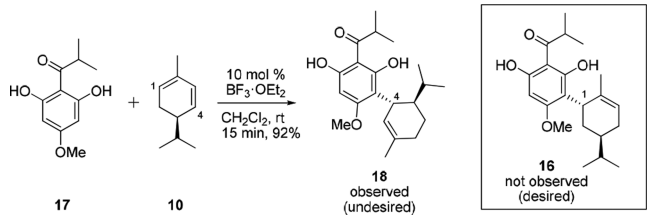
Scheme 2. Retrosynthetic Analysis for Callistrilones A (1), B (2), and D (5) and the Biosynthetic Intermediate 3



(**12**) and callistrilones D (**5**) and B (**2**) could be accessed from compounds **6**, **7**, and **13**, respectively, by acid-mediated intramolecular cyclization, while compounds **6**, **7**, and **13** could be prepared by base-mediated Michael addition of tricyclic intermediate **8** and **3** across isobutylidenesyncarpic acid (**14**). It should be possible to synthesize compounds **8** and **3** from **15** and **16** by Wacker-type oxidative cyclization. As postulated by Ye and co-workers, it was thought that alkenes **15** and **16** could be accessed via Friedel−Crafts alkylation of phloroglucinol derivatives **9** and **17** with phellandrene (**10**).

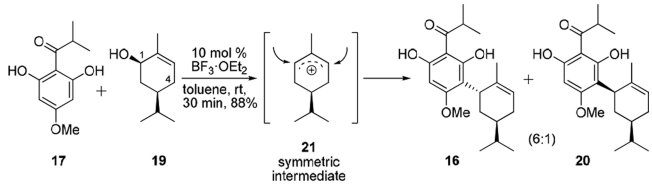
Our explorations to test this overall hypothesis began with the reaction of phloroglucinol derivative **17** and phellandrene **10** in the presence of 10 mol % of $BF_3{\cdot}OEt_2$ in toluene or CH_2Cl_2 did not generate the expected C-1 coupling product **16**; instead, formation of C-4 coupling product **18** was observed (Scheme 3). It was thought that, instead of using phellandrene (**10**), dihydrocarveol (**19**) could generate carbocation at C-1 under acidic conditions and would lead to the formation of the desired product **16**. To our delight, phloroglucinol derivative **17** and dihydrocarveol (**19**) (see the

Scheme 3. Attempted Coupling of Phloroglucinol Derivative 17 and Phellandrene (10)



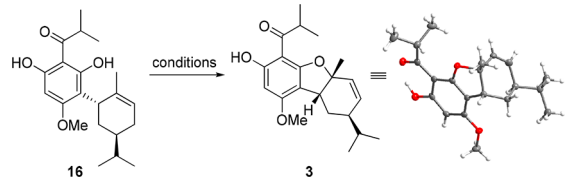
SI for preparation) on treatment with 10 mol % of $BF_3{\cdot}OEt_2$ led to the formation of a diastereomeric mixture of **16** and **20** in a 6:1 ratio with 88% yield. As expected, compounds **16** and **20** showed zero optical rotation, since dihydrocarveol (**19**) on treatment with Lewis acid generates the symmetrical allylic carbocation **21**; and the attack of electron-rich arene on symmetrical intermediate **21** is possible from both sides (Scheme 4).

Scheme 4. Friedel−Crafts Reaction between Phloroglucinol Derivative 14 and Dihydrocarveol (16)



The next task was regioselective Wacker-type oxidative cyclization, for which various palladium catalysts and oxidants were screened (Table 1). Among the catalysts screened, 10 mol

Table 1. Optimization Table for Palladium Catalyzed Wacker-Type Oxidative Cyclization



entry	catalyst	oxidant	solvent	temp (°C)	yield[a] (%)
1	$PdCl_2$	O_2	toluene	reflux	17
2	$PdCl_2$	O_2	toluene	rt	7
3	$Pd(TFA)_2$	O_2	toluene	reflux	21
4	$PdBr_2$	AgOAc	toluene	reflux	19
5	$Pd(OAc)_2$	O_2	toluene	reflux	28
6	$Pd(OAc)_2$	AgOAc	toluene	rt	17
7	$Pd(OAc)_2$	MnO	toluene	reflux	52
8	$Pd(OAc)_2$	MnO	CH_3CN	rt	86

[a]Isolated yields.

% $Pd(OAc)_2$ and 3 equiv MnO in acetonitrile at room temperature gave the best yield of 86% for tricyclic compound **3**. The spectral data (^1H, ^{13}C, IR, HRMS) were in complete agreement with those of natural **3**. The stereochemistry of **3** was unambiguously established by single-crystal X-ray analysis. Although there are literature reports on oxidative cyclizations using palladium catalyst,[5] this is one rare example where the transformation is carried out at ambient temperature.

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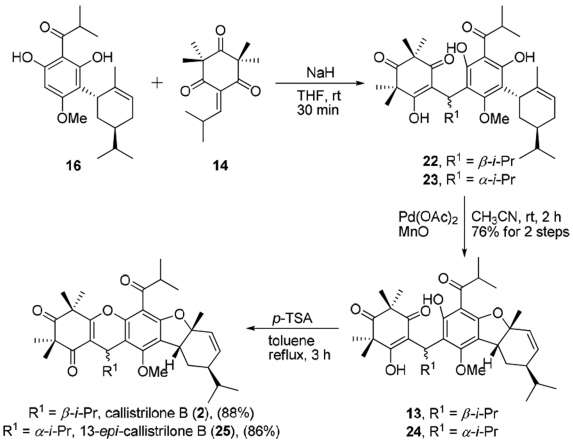
Next, we focused our attention on the total synthesis of callistrilone B (**2**). Alas, tricyclic compound **3**, when subjected to Michael addition with isobutylidenesyncarpic acid (**14**) (see the SI for preparation) using NaH[6] in THF or DMF, resulted in the decomposition of the starting material **3**, with no trace amount of product formation. Due to strong intramolecular hydrogen bonding, deprotonation of phenolic OH (chelated with carbonyl oxygen) of compound **3** proved to be problematic. Hence it was thought that compound **16**, which contains two phenolic OH groups, might react with isobutylidenesyncarpic acid (**14**). As expected, compound **16** when treated with NaH[6] followed by addition of isobutylidenesyncarpic acid (**14**), led to the formation of inseparable 1:1 diastereomeric mixture of Michael adducts **22** and **23**, which on further treatment with $Pd(OAc)_2$ and MnO in acetonitrile resulted in the formation of oxidative cyclized products **13** and **24** in 76% yield over two steps (Scheme 5). Independent

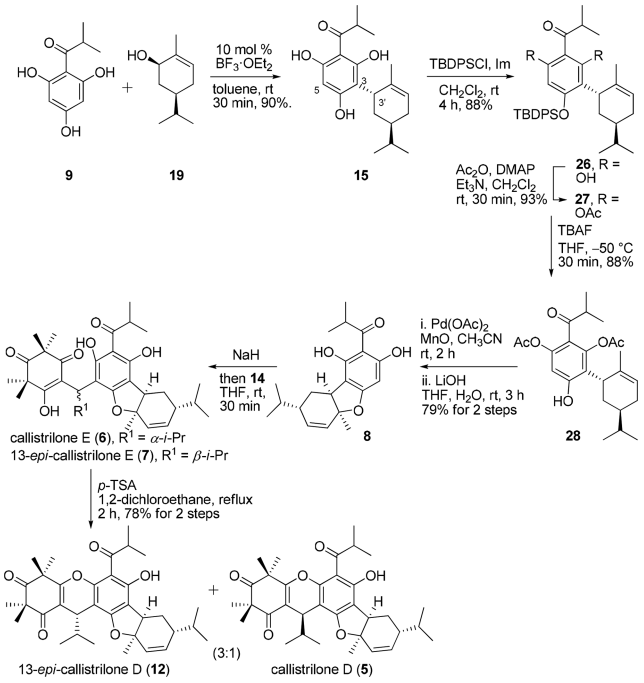
Scheme 5. Completion of Total Synthesis of (±)-Callistrilone B (2)



treatment of compounds **13** and **24** with *p*-TSA in toluene under reflux conditions resulted in the formation of callistrilone B (**2**) and 13-*epi*-callistrilone B (**25**)[7] in 88% and 86% yields, respectively. The spectral data of synthetic callistrilone B (**2**) (^{1}H, ^{13}C, IR and HRMS) were in complete agreement with those of natural **2**.[3] The structure of 13-*epi*-callistrilone B (**25**) was further confirmed by single-crystal X-ray analysis.

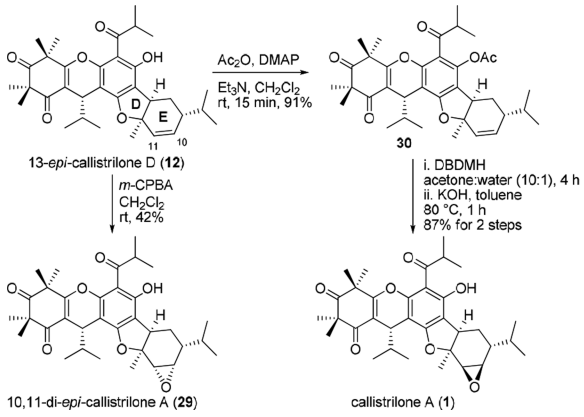
After the completion of the synthesis of **3** and callistrilone B (**2**), our next target was callistrilone A (**1**) and D (**5**). Isobutyryl phloroglucinol (**9**) and dihydrocarveol (**19**) on treatment with 10 mol % of $BF_3{\cdot}OEt_2$ led to the formation of a diastereomeric mixture of rotameric compounds **15** and **15a** (only major isomer is shown in Scheme 6) in a 6:1 ratio with 90% yield (see the SI for a detailed discussion). Next, protection of phenolic OH was considered to avoid the formation of undesired products during oxidative cyclization. Taking advantage of hydrogen bonding, the phenolic OH of compound **15** was regioselectively protected as a TBDPS ether, followed by acetylation of remaining phenolic OH groups, and finally, deprotection of the TBDPS group furnished the desired diacetate compound **28** (Scheme 6). Compound **28** on Wacker-type oxidative cyclization using $Pd(OAc)_2$ and MnO followed by the hydrolysis of the acetate groups using LiOH led to the formation of advanced tricyclic intermediate **8** in 79% yield for two steps. Tricyclic compound **8**, when subjected to Michael addition with isobutylidenesyncarpic acid (**14**) in

Scheme 6. Synthesis of Pentacyclic 13-*epi*-Callistrilone D (12) and Callistrilone D (5)



THF, furnished an inseparable diastereomeric mixture of callistrilone E (**6**) and 13-*epi*-callistrilone E (**7**), which on further treatment with *p*-TSA in 1,2-dichloromethane under reflux conditions afforded compounds 13-*epi*-callistrilone D (**12**) and callistrilone D (**5**) in a 3:1 ratio with 78% yield for two steps. The stereochemistry of compounds **12** and **5** was unambiguously established by single-crystal X-ray analysis. Compound **12** on epoxidation using *m*-CPBA resulted in the formation of 10,11-di-*epi*-callistrilone A (**29**) in 42% yield, where epoxidation took place from undesired α face (Scheme 7). Epoxidation using various other reagents such as DMDO,

Scheme 7. Completion of Total Synthesis of Callistrilone A (1)



$VO(acac)_2$,[8] $MnSO_4$,[9] or NO_2[10] resulted in either decomposition of starting material or formation of α epoxide with low yield. From the X-ray crystal structure of compound **12**, it was evident that the angle between fused rings D and E is ~90°, making the β face extremely hindered and hence epoxidation under the above conditions proceeded from the least hindered

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α face. Finally, after trying various reagents and conditions to get β epoxide, we relied on the formation of halohydrin, a case where C10−C11 double bond in **12** would form α bromonium ion (from the least hindered face) which, upon diaxial opening with water, would result in the halohydrin formation. Then, finally nucleophilic attack of the hydroxy group on halide under basic conditions would result in the formation of the desired β epoxide. Unfortunately, compound **12**, when subjected to halohydrin formation using NBS or 1,3-dibromo-5,5- dimethylhydantoin,[11] resulted in decomposition of starting material. It was thought that the aromatic ring in compound **12** is highly electron rich and hence prone to oxidation under above conditions. Hence, it was decided to protect phenolic OH group of compound **12** as its acetate. Thus, compound **12** on treatment with Ac_2O and Et_3N in the presence of catalytic amount of DMAP afforded acetate **30** in 91% yield. Compound **30** on treatment with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[11] smoothly generated halohydrin product, which on exposure to KOH resulted in the formation of the desired β epoxide and concurrent hydrolysis of acetate group to give callistrilone A (**1**) in 87% yield over two steps. The spectral data of synthetic callistrilone A (**1**) (^1H,^{13}C, IR and HRMS) were in complete agreement with those of natural **1**.[3]

In summary, a biomimetic total syntheses of callistrilones (±)-A, B, and D and the postulated biosynthetic intermediate were achieved in 10, 4, 7, and 2 steps, respectively, with 21, 22, 26, and 65% overall yield using a highly regio- and diastereoselective Friedel−Crafts alkylation, palladium-catalyzed Wacker-type oxidative cyclization, and stereoselective epoxide formation from extremely hindered β face as a key reactions. This method is fairly general to the synthesis of other natural products of this class as well as their analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03815.

Details of the experimental procedure and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1560549 and 1560553−1560555 contain 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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