Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Total Syntheses of Pusilatins A−C, Liverwort-Derived Macrocyclic Bisbibenzyl Dimers

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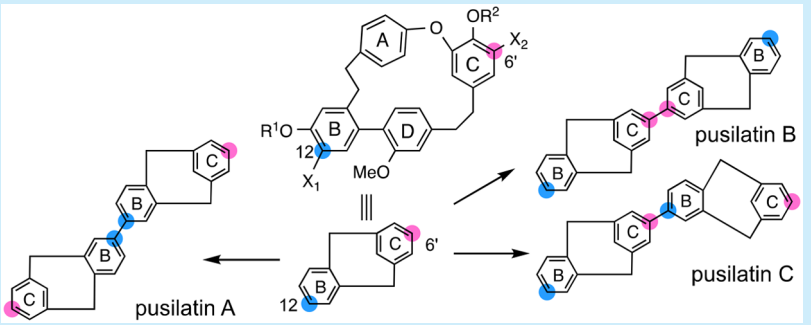
Supporting Information



ABSTRACT: The total syntheses of pusilatins A (**2**), B (**3**), and C (**5**), macrocyclic bisbibenzyl dimers isolated from Japanese liverwort are reported. The common monomeric unit (**6**) was prepared via macrocyclization of an *o*-sulfinylfluorobenzene derivative by S_NAr attack of an internal phenol, which was exploited for site-selective dimerizations en route to **2**, **3**, and **5**.

The pusilatins constitute a class of dimers of macrocyclic bisbibenzyl, which were isolated from a Japanese thallic liverwort, *Blasia pusilla L.*, by Asakawa et al.[1] Their structural diversity stems from the modes of oxidative coupling of the monomeric unit, i.e., riccardin C (**1**).[2] Pusilatins A (**2**), B (**3**), and E (**4**) are symmetrically coupled dimers, while pusilatin C (**5**) is an unsymmetrically coupled dimer (Figure 1).

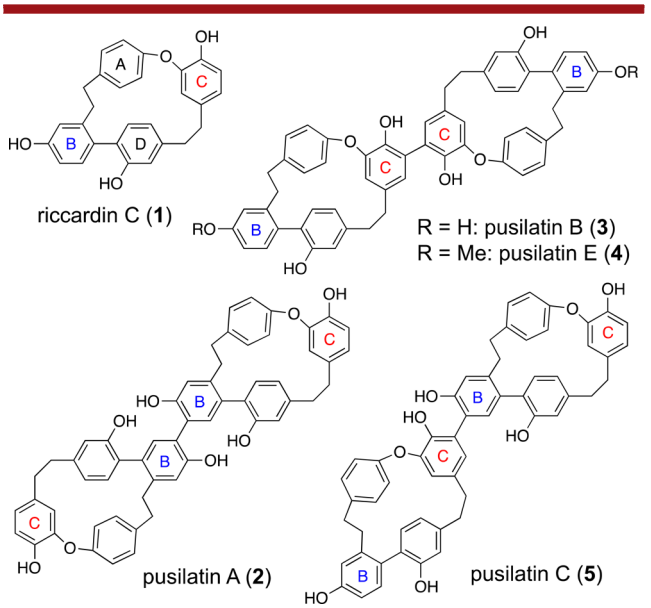


Figure 1. Structures of pusilatins and riccardin C.

These compounds are attractive synthetic targets in view of the diverse and potent biological activities[3,4] as well as the unique structures differing in the connectivity of the monomeric units. Herein, we report the total syntheses of pusilatins A, B, and C via an efficient and divergent coupling strategy.

Scheme 1 illustrates monomer **6** and the distinct connectivities (C12−C12, C6′−C6′, C6′−C12 linkages) toward **2**, **3**, and **5**. The key challenge is the regiocontrolled functionalization of the riccardin C (**1**) scaffold amenable for the mutual connection of the two monomeric units at specific positions. Importantly, symmetry consideration would allow significant simplification of the synthesis by employing a suitable common intermediate.

To this end, the design of phenol **6** should allow easy differentiation between phenols on the B- and C-rings and also allow a site-selective functionalization at the C12 (blue) or the C6′ (red) position as a handle to perform the regioselective dimerization.

We reasoned that preparation of the key intermediate **6** would be possible by exploiting the concise synthetic route of riccardin C (**1**),[2c,d] which we previously reported, with an exception that the B-ring unit is protected with a benzyl group to enable the above-stated strategy (Scheme 2). Sonogashira reaction of alkyne **7**[5] with iodide **8**[6] gave alkyne **9**, and the resulting phenol was treated with phenyl triflimide to give triflate **10**. Suzuki−Miyaura coupling of **10** with boronic acid **11**[7] gave aldehyde **12**, which was subjected to the Horner−

Received: April 30, 2018

DOI: 10.1021/acs.orglett.8b01366
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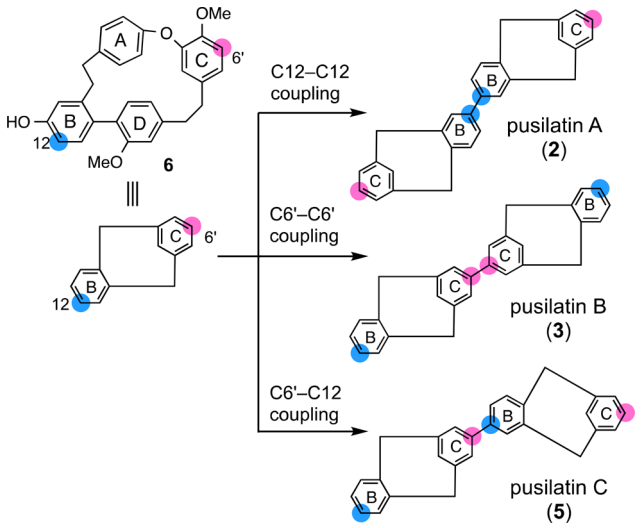
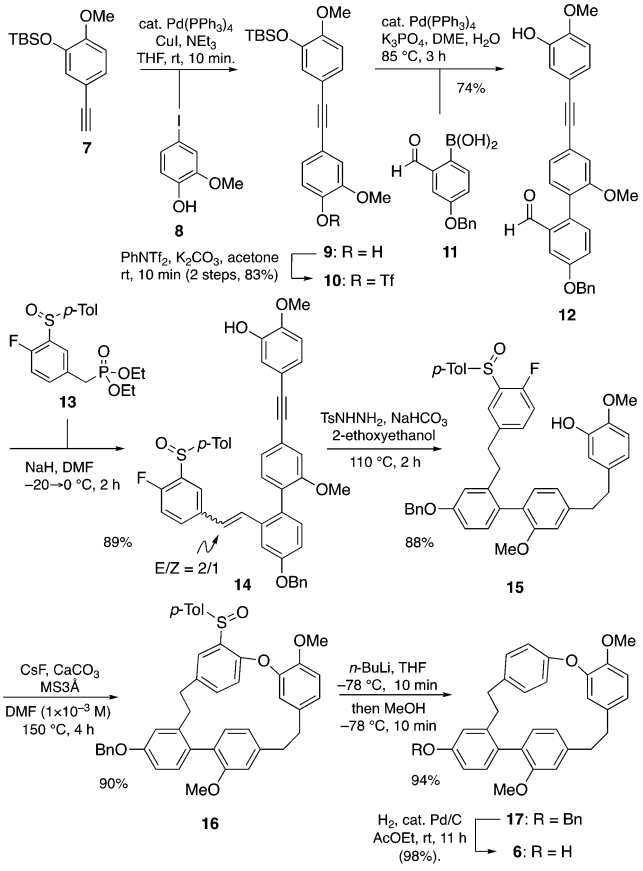
Scheme 1. Divergent Approach to Pusilatins A–C



Scheme 2. Preparation of Monomer 6[a]



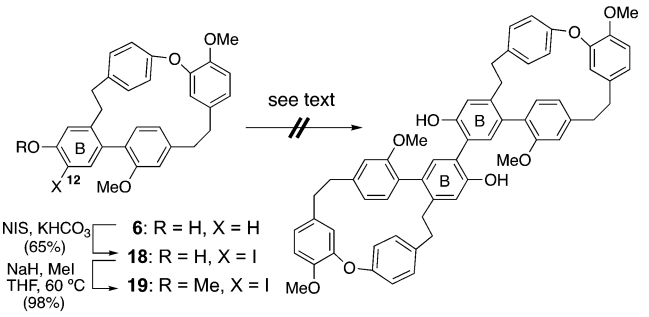
[a]DME = 1,2-dimethoxyethane, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, Tol = tolyl.

Emmons reaction with phosphonate **13**[2c,d] to give enyne **14** as a mixture of geometrical isomers (E/Z = 2/1).

Enyne **14** was reduced with diimide giving the cyclization precursor **15**. The intramolecular S_NAr reaction of **15** [CsF, $CaCO_3$, MS3 Å, DMF (1×10^{-3} M), 150 °C, 4 h][8] afforded the product **16** in excellent yield. The sulfinyl group in **16** was removed by the sulfoxide–lithium exchange[9] followed by protonolysis, and removal of the benzyl group by hydrogenolysis gave phenol **6**, ready for the key regiocontrolled dimerizations.

Our first target was pusilatin A (**2**), the symmetrical dimer with the mutual connection at the C12 positions. We initially focused on the oxidative dimerization, which is related to the biosynthetic pathway (Scheme 3).[10]

Scheme 3. Unsuccessful Approaches toward Pusilatin A



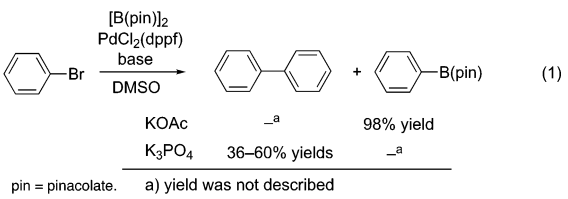
NIS = *N*-iodosuccinimide.

Despite various attempts, however, phenol **6** displayed poor reactivity in the oxidative coupling. All oxidants screened, including $Mn(OAc)_3$,[11] $CuCl_2$,[12] $CuBr_2$, MnO_2,[13] $FeCl_3 \cdot 6H_2O$,[14] DDQ, led to the recovery of the starting material.

At this juncture, we turned our attention to the Ullmann-type dimerization of iodide **18**,[15] which was prepared by regioselective iodination at the *ortho* position to the free phenol in **6**.[2h] Unfortunately, the trials failed to give the desired dimer under various conditions. Iodide **18** was recovered unchanged even under harsh conditions ($NiCl_2$, PPh_3, Zn, DMF, 150 °C). On the basis of the previous report,[15] electron-withdrawing groups *ortho* to the halogen substituent increased the reactivity of aryl halides, and thus, the free phenol in **18** was protected with a tosyl or a mesyl group. However, the projected dimerization attempts gave only deiodinated products.

At this stage, we became interested in the possibility of the *formal* symmetrical dimerization by the sequential reactions of the Miyaura borylation[16] and the in situ Suzuki–Miyaura coupling. After methylation of phenol **18** to give **19**, the Pd-catalyzed borylation was examined, which gave the corresponding arylboronate, which turned to be highly unstable and, thus, hardly tractable.

Our next idea came from the work of Miyaura (eq 1),[16] who observed direct, but unexpected, formation of biphenyl from bromobenzene[17] when a stronger base, such as K_3PO_4 or K_2CO_3, was used instead of KOAc.

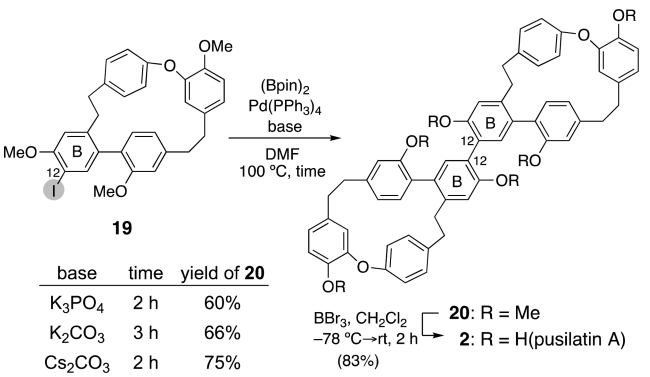


(1)

Accordingly, we examined the Pd-catalyzed borylation by using K_3PO_4 with 0.5 equiv of $(Bpin)_2$ (Scheme 4). We were pleased to find that direct dimerization of **19** proceeded to give the desired symmetrical dimer **20** in 60% yield. Use of K_2CO_3 slightly improved the yield (66%). The best result was obtained when Cs_2CO_3 was used as a base, giving **20** in 75% yield. Finally, removal of the methyl protecting groups with BBr_3

DOI: 10.1021/acs.orglett.8b01366
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Synthesis of Pusilatin A (2)



base	time	yield of **20**
K_3PO_4	2 h	60%
K_2CO_3	3 h	66%
Cs_2CO_3	2 h	75%

allowed clean production and isolation of pusilatin A (**2**). The analytical data recorded were identical in all respects with the reported data for the natural product (^{1}H and ^{13}C NMR, IR, HRMS).[1]

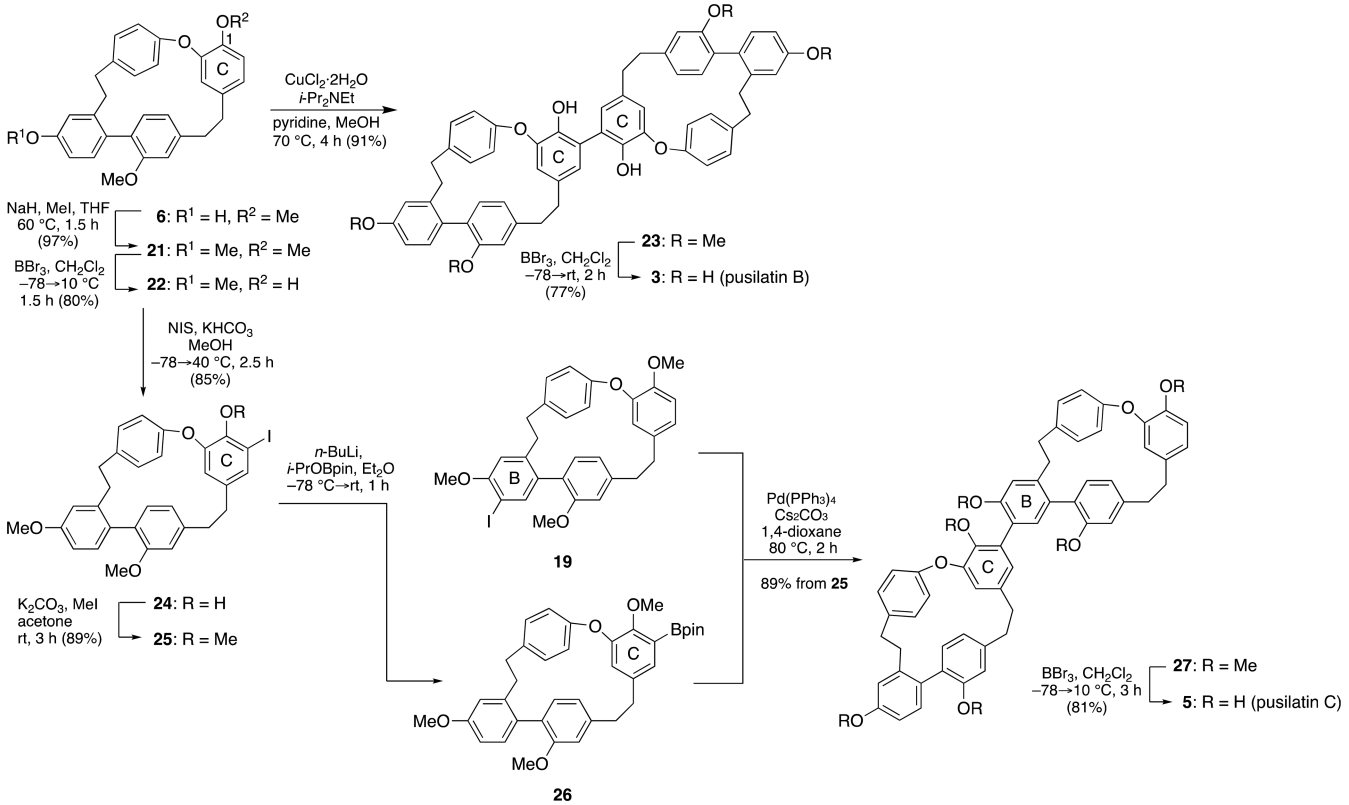
We next turned our attention to pusilatin B (**3**), one of the symmetrically coupled dimers with the connection at the C6′ positions. Previously, Asakawa reported the dimerization of the natural sample of riccardin C (**1**) by oxidative coupling to achieve the semisynthesis of pusilatin E (**4**).[11] Based on this precedent, we found that the oxidative dimerization was effective for coupling of the monomeric units at the C6′ positions. Preparation of the precursor **22** started with the key intermediate **6**, where methylation gave the methylated monomer **21**. Selective removal of the methyl group at the C1 position on the C-ring by using BBr_3 furnished the dimerization precursor **22**.

With the substrate **22** in hand, we focused on oxidative dimerization (Scheme 5). When $Mn(OAc)_3$,[11] $FeCl_3$,[14] or $TiCl_4$[18] was used as an oxidant, the desired dimer **23** was obtained in low yield. However, after treatment of **22** with $CuCl_2\cdot 2H_2O$[12] in the presence of appropriate amines (*i*-Pr_2NEt, pyridine), the oxidative dimerization proceeded smoothly (MeOH, 70 °C, 4 h) to give the desired dimer **23** in 91% yield. Finally, removal of all methyl protecting groups with BBr_3 (CH_2Cl_2, −78 °C → rt, 2 h) afforded pusilatin B (**3**), which was purified by preparative thin-layer chromatography. The synthetic material **3** showed the spectral data (^{1}H and ^{13}C NMR, IR, HRMS) in full agreement with those of the natural product.[1]

The next challenge was the synthesis of pusilatin C (**5**), a dimer connected unsymmetrically at the C6′ and the C12 positions. We envisioned that the dimerization could be achieved by the Suzuki−Miyaura coupling of the two fragments, iodide **19** and its regio-isomeric counterpart **25**. The initial attempt to convert iodide **19** to the corresponding arylboronate met with limited success because of its extreme instability. Therefore, we examined the conversion of iodide **25** to the corresponding arylboronate. Iodination at the *ortho* position of phenol **22** followed by methylation gave iodide **25**, which was employed for the coupling.

Upon treatment of **25** with *i*-PrOBpin and *n*-BuLi (Et_2O, −78 °C → rt), the desired borylation proceeded smoothly. Since the corresponding arylboronate was unstable, it was used for the coupling without purification. Thus, the generated arylboronate was employed for the next cross coupling with iodide **19** [Cs_2CO_3, $Pd(PPh_3)_4$, dioxane, 80 °C], giving the desired dimer **27** in 89% yield.

Scheme 5. Total Syntheses of Pusilatins B (3) and C (5)



DOI: 10.1021/acs.orglett.8b01366
Org. Lett. XXXX, XXX, XXX−XXX

Finally, removal of all methyl protecting groups followed by the purification on preparative thin-layer chromatography allowed clean isolation of pusilatin C (**5**). The spectral data (^{1}H and ^{13}C NMR, IR, HRMS) for the final product were in full agreement with those of the natural product.[1]

In conclusion, the total syntheses of pusilatins A (**2**), B (**3**), and C (**5**) have been achieved from a common intermediate **6**, featuring (1) one-pot sequence of the Miyaura borylation followed by the Suzuki−Miyaura coupling to synthesize **2**, (2) oxidative dimerization to synthesize **3**, and (3) unsymmetrical dimerization via Suzuki−Miyaura coupling to synthesize **5**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01366.

Full experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Toshihiro Hashimoto and Prof. Yoshinori Asakawa (Tokushima Bunri University) for providing an authentic sample of pusilatin B and NMR data for pusilatins A−C. This work was supported by JSPS KAKENHI Grant Nos. JP23000006, JP16H06351, JP16H04107, and JP18H04391.

■ DEDICATION

Dedicated to Prof. Yoshinori Asakawa on occasion of his 77th birthday.

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