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RESEARCH ARTICLE

One-pot Tandem Coupling Method for the Short Step Formal Synthesis of Riccardin C

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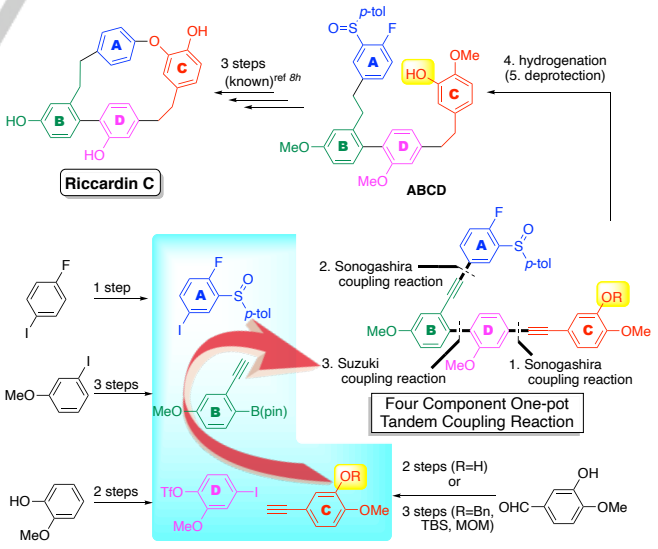
Abstract: One-pot reactions reduce reagent amounts and circumvent process treatments, such as work-up and purifications in multi-step reactions. In this study, we achieved the formal total synthesis of riccardin C through a one-pot reaction by simultaneously linking four units through two Sonogashira coupling reactions and one Suzuki coupling reaction, followed by reduction and deprotection. Thus, this one-pot method comprised five steps and did not require the purification of intermediate reaction mixtures, which saves resources, such as reagents and solvents, and expedites the work process.

Introduction

Liverworts produce many bisbibenzyls and their analogs, some of which exhibit various pharmaceutical activities.[1] Riccardin C was first isolated and structurally determined from *Reboulia hemisphaerica*, a species of liverworts, in 1982 by Asakawa *et al*.[2] Later research shows that it has been isolated from liverworts in various regions of the world; however, the amounts of riccardin C isolated from different types of liverworts have been variable.[3] In addition, it was recently isolated from the rhizomes of *Primulaceae*, which is of significant botanical interest.[4] The structure of riccardin C comprises a macrocyclic bis(bibenzyl)-type moiety with four aryl groups. It is a pluripotent natural product that exhibits various pharmacological activities.[3–7] Notably, riccardin C exhibits antibacterial activity against various Gram-positive bacteria, especially against methicillin-resistant Staphylococcus aureus (MRSA).[6] Therefore, various studies have conducted the total synthesis of riccardin C and its analogs to investigate their structure-activity relationships.[7–9] In these processes, the skeleton of riccardin C is formed step-by-step by connecting the four aryl groups; however, each of these steps requires the isolation and purification of intermediates, which is very inefficient.[8–9] Moreover, since many methods utilize multiple coupling reactions using metal catalysts such as palladium, the number of metal catalysts used increases as the number of reaction steps increases. Therefore, to synthesize such polyaryl compounds, we developed a one-pot tandem coupling method, in which substituents with different reactivities are arranged in each unit, and the desired coupling reactions are sequentially achieved using readily available metal catalysts.[10] This method is beneficial for library construction based on combinatorial chemistry approaches. In fact, more than 100 analogs of *in silico* designed non-ceramide mimetic ceramide transport protein (CERT) inhibitors have been successfully synthesized, resulting in the development of a novel, highly potent compound, HPCB-5.[11] Therefore, we show that this method can be successfully applied to the one-pot economy[12]-oriented synthesis of riccardin C, which can also be used to readily construct libraries.

Four units were designed to synthesize the overall framework of riccardin C by the one-pot coupling of two Sonogashira coupling reactions[13] and one Suzuki coupling reaction[14] (Scheme 1). After the one-pot coupling, the acetylene moiety was reduced and deprotected for the S_NAr reaction to achieve the formal synthesis. To improve its reactivity and solubility, we prepared the terminal unit C with three protecting groups in addition to the protecting group-free unit **C1**. These units can be easily synthesized in one to three steps from commercially available materials.

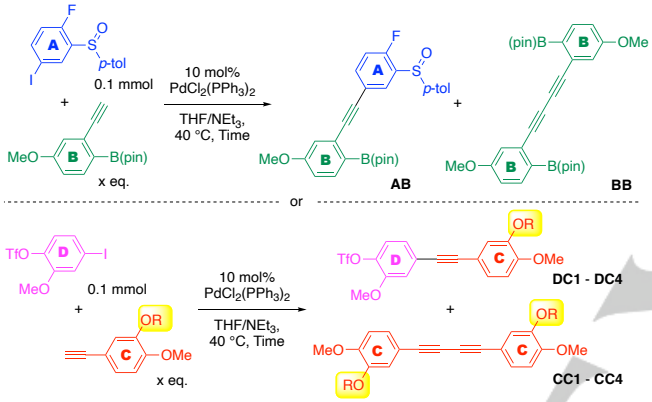


Scheme 1. Retrosynthesis of riccardin C.

Results and Discussion

Sonogashira coupling reactions between units **A+B** and **D+C** were investigated independently, and it was confirmed that the desired coupling reactions proceeded without the addition of copper salts such as copper iodide (Table 1).[15] When a highly reactive acetylene substrate was used, a homocoupling reaction called Glaser coupling occurred in the reaction mixture.[16] This reaction was also observed with the substrates used in this experiments, and some homo-coupling reactions produced by-products **BB** or **CC1**–**CC4**. Although the Sonogashira coupling reaction between units **A+B** (entries 1–3) required a relatively longer reaction time, the reaction proceeded quantitatively even when the amount of catalyst was reduced (entry 3). The Sonogashira coupling reaction forming the **DC** units (entries 4–7) required a long time to complete when unprotected **C1** was used (entry 4); however, the reaction proceeded readily when a protecting group was used (entries 5–7).

Table 1. Copper-free Sonogashira coupling reactions for **AB** or **DC** units.[a]

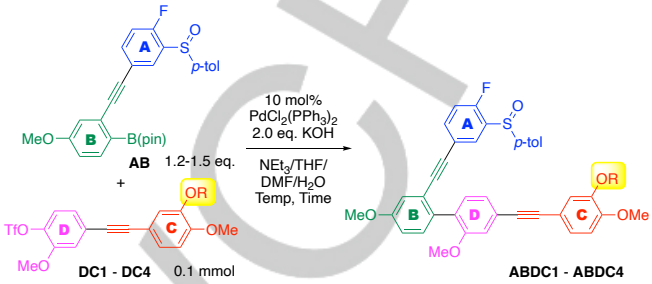


Entry	**Units/** R for **C**	**B** or **C**: x (eq.)	Time (h)	Cross-coupling yield (%)[b]	Homo-coupling yield (%)[c]
1	**A+B**	1.1	10	62 (**AB**)	5 (**BB**)
2	**A+B**	1.3	15	94 (**AB**)	9 (**BB**)
3[d]	**A+B**	1.2	26	quant (**AB**)	7 (**BB**)
4	**D+C**/H (**C1**)	1.2	14	98 (**DC1**)	12 (**CC1**)
5	**D+C**/Bn (**C2**)	1.2	3	97 (**DC2**)	12 (**CC2**)
6	**D+C**/TBS (**C3**)	1.2	3	96 (**DC3**)	12 (**CC3**)
7	**D+C**/MOM (**C4**)	1.2	2	96 (**DC4**)	9 (**CC4**)

[a] Reaction conditions: Unit **A** or **D** (0.1 mmol), unit **B** or **C** (x mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol, 10 mol%) in THF (0.6 mL), NEt_3 (0.3 mL). For details, see the Supporting Information. [b] Isolated yield. [c] The yield was determined by crude ^{1}H-NMR analysis. [d] 5 mol% $PdCl_2(PPh_3)_2$ was used.

Next, we examined the Suzuki coupling reaction using the isolated units **AB** and **DC** (Table 2). Interestingly, in this case, the reactivity of the reaction changed significantly depending on the presence or absence of the protecting group on unit **C**. When the protecting group was absent, the reaction required a higher temperature. Moreover, when **DC1** is used as a substrate, changing the ratio of DMF and water as a mixed solvent has a significant effect on the yield of the desired product **ABDC1** due to the solubility of **DC1** (entries 1–3). In contrast, when protected **C** was used, the reaction proceeded even under mild conditions at 70 °C (entries 4–6). When a TBS group was used as the protecting group, deprotection proceeded simultaneously under basic heating conditions. Consequently, the Suzuki coupling reaction required higher temperature conditions than the other two reactions. Therefore, we expect that the four-component tandem coupling reaction can be achieved by first performing the two types of Sonogashira coupling reactions, followed by the Suzuki coupling reaction, which requires a higher temperature.

Table 2. Suzuki-Miyaura coupling reaction of **AB** and **DC** units.[a]



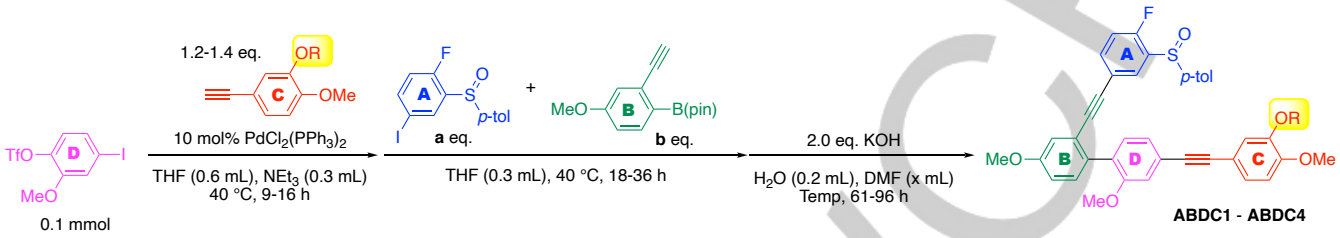
Entry	**AB** + **DC** R =	DMF/H_2O (mL)	T (°C)	Time (h)	Yield (%)[b]
1	H (**DC1**)	0.1/0.3	100	24	71 (**ABDC1**)
2	**DC1**	0.3/0.3	100	48	70 (**ABDC1**)
3	**DC1**	0.8/0.2	100	13	60 (**ABDC1**)
4	Bn (**DC2**)	0.8/0.2	70	30	70 (**ABDC2**)
5	TBS (**DC3**)	0.8/0.2	70	30	63 (**ABDC1**)
6	MOM (**DC4**)	0.8/0.2	70	30	66 (**ABDC4**)

[a] Reaction conditions: Unit **DC** (0.1 mmol), unit **AB** (0.12–0.15 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), KOH (0.2 mmol) in THF (0.6 mL), NEt_3 (0.3 mL), DMF (0.1–0.8 mL), and H_2O (0.2–0.3 mL). For details, see the Supporting Information. [b] Isolated yield.

Based on the results of the initial studies, the one-pot tandem coupling reaction with four components was studied again (Table 3). The starting materials in the first reaction step should be completely consumed to prevent unwanted cross-coupling reactions, such as those of units **A+C** and **B+D**. Therefore, we performed the coupling reaction of units **C** and **D** first. After confirming that the starting materials were completely consumed in the first Sonogashira coupling reaction, the Sonogashira coupling of units **A** and **B** was carried out. After completion of the two tandem coupling reactions, the reaction temperature was increased, and the Suzuki coupling was carried out. The total reaction time varied because the reaction mixture was analyzed using thin layer chromatography (TLC) after each step to confirm the consumption of the starting materials. From Table 2, the reaction temperature and amount of solvent (DMF) in the Suzuki coupling reaction significantly influenced the yield of the product. The Suzuki coupling reaction using isolated units **AB** and **DC** proceeded even at a reaction temperature of 100 °C; however, in the four-component one-pot tandem coupling reaction, the deborylation of unit **AB** and detriflation of unit **DC** progressed simultaneously. We assumed that the generation of these by-products was caused by the presence of hydrogen iodide, a side product of the Sonogashira reaction. Because the Suzuki coupling reaction hardly proceeds at low temperatures, we investigated the appropriate temperature required for the Suzuki coupling reaction to avoid unwanted side reactions. We determined that 70 °C was the optimal temperature (Table 3, entries 1–4). In addition, no homo-coupling reaction with unit **B**

proceeded in the case of the four-component one-pot reaction as in the case of the Sonogashira coupling reaction to unit **AB** alone. Therefore, approximately one equivalents of unit **B** to **A** was sufficient (entries 2 vs. 3). The amount of DMF added depends on the presence or absence of the protecting group in unit **C**. Less solvent is better for the unprotected **C1** unit (entry 3 vs. 5), while more is better for the benzyl-protected **C2** and MOM-protected **C4** units (entries 6–9). However, in the case of the TBS-protected **C3**, the yield was the same as that of **C1** because the deprotection also proceeded during the reaction, which was observed during the Suzuki coupling reaction.

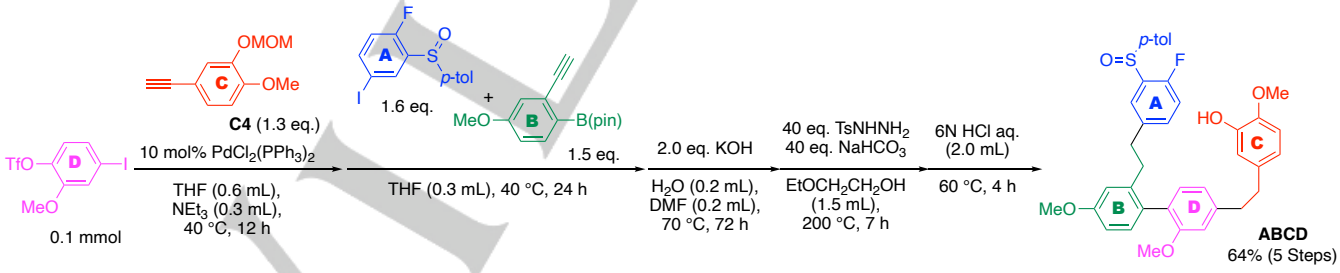
Table 3. One-pot tandem Sonogashira Suzuki-Miyaura coupling reaction of **A**, **B**, **D**, and **C** units.



Entry	(**D+C**)+(**A+B**); R	Unit **A** (**a** eq.)	Unit **B** (**b** eq.)	DMF (mL)	T (°C)	Yield (%)[a]
1	H (**C1**)	1.3	1.7	0.2	80	34 (**ABDC1**)
2	**C1**	1.3	1.8	0.2	70	64 (**ABDC1**)
3	**C1**	1.6	1.5	0.2	70	75 (**ABDC1**)
4	**C1**	1.5	1.5	0.2	60	10 (**ABDC1**)
5	**C1**	1.6	1.6	0.8	70	48 (**ABDC1**)
6	Bn (**C2**)	1.6	1.5	0.8	70	71 (**ABDC2**)
7	TBS (**C3**)	1.6	1.5	0.8	70	47 (**ABDC1**)
8	MOM (**C4**)	1.7	1.5	0.8	70	86 (**ABDC4**)
9	**C4**	1.3	1.2	0.2	70	69 (**ABDC4**)

[a] Isolated yield.

In the formal total synthesis of riccardin C, the reduction of alkynes and deprotection of unit **C** in the isolated product were examined. Initially, a hydrogen reduction reaction using a palladium catalyst was planned;[17] however, blowing hydrogen into the reaction system resulted in poor reproducibility.[18] Although the diimide reduction with tosylhydrazine required high-temperature conditions, the reaction proceeded with the amount of the diimide added, and the target product was successfully obtained in a maximum yield of 93%.[18] Because the MOM group can be easily deprotected by subsequent acid treatment, the one-pot five-step formal total synthesis of riccardin C, including the tandem coupling reaction using the **C4** unit, was carried out (Scheme 2). Using the identified optimal combination of conditions, the desired compound was obtained in 64% yield without any intermediate purification steps. Because this compound **ABCD** can be converted to riccardin C in three steps as per known methods,[8h] the formal total synthesis of riccardin C was achieved with this product.



Scheme 2. Five-step one-pot formal total synthesis of riccardin C using unit **C4**.

Conclusion

In summary, we achieved the formal total synthesis of riccardin C by a one-pot tandem coupling method. By optimizing each step, four individual units were connected by two Sonogashira coupling reactions and one Suzuki coupling reaction, followed by diimide reduction and acid deprotection. Thus, this one-pot method comprised five steps and did not require the purification of intermediate reaction mixtures, which saves resources, such as reagents and solvents, and expedites the work process. Another advantage of this method is that the analogs of each unit can be

synthesized and combined to construct a library, which may facilitate the investigation of their structure-activity relationship. Further reaction development for the construction of a comprehensive library is under consideration.

Experimental Section

General Information. All reagents were purchased from commercial sources (Tokyo Chemical Industry Co. Ltd., Tokyo, Japan, Kanto Chemical Co. Inc., Tokyo, Japan, or FUJIFILM Wako Pure Chemical Co. Ltd., Osaka, Japan), and further purified by standard methods if necessary. Solvents were purchased super dehydrated grade and stored under inert dry gas. An EYELA (TOKYO RIKAKIKAI Co. Ltd., Tokyo, Japan) ChemiStation aluminum brock heating system was used, and the reaction temperature measured outside of the vessel. All reactions were performed in an argon atmosphere unless stated otherwise. For column chromatography, silica gel (Silica gel 60N, spherical neutral, particle size 63–210 μm) from Kanto Kagaku Co., Ltd., was used. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F (FUJIFILM Wako Pure Chemical Co. Ltd., Osaka, Japan) for purification. Nuclear magnetic Resonance (NMR) spectra were recorded on a JEOL JNM-ECS 400 spectrometer (JEOL Ltd., Tokyo, Japan), operating at 400 MHz for ^{1}H-NMR, 128 MHz for ^{11}B-NMR, 100 MHz for ^{13}C-NMR, and 250 MHz for ^{19}F-NMR, in $CDCl_3$ (Merck KGaA, Darmstadt, Germany) unless otherwise noted. Tetramethylsilane (TMS) was used as the internal standard (δ = 0.0 ppm) for ^{1}H NMR and chloroform ($CHCl_3$) in minimum 99.8% $CDCl_3$ as the internal standard (δ = 77.0 ppm) for ^{13}C NMR. Melting points (mps) were determined using a SMP-300CTD apparatus (Sansyo Co. Ltd, Tokyo, Japan) and are uncorrected. High-resolution mass spectrometry (HRMS) was performed using an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer (Micromass® LCT Premier XE, Waters Corp., Manchester, UK) coupled with an ACQUITY UPLC® system (Waters Corp.) or an atmospheric pressure chemical ionization time-of-flight (APCI-TOF) mass spectrometer XEVO Q-TOF MS system (Waters Corp.).

Typical procedure for copper-free Sonogashira coupling reaction (Table 1, entry 2). A 10 mL two-necked flask equipped with stirring bar and reflux condenser was flame-dried under vacuum, and filled with Ar. To this flask, bis(triphenylphosphine)palladium(II) dichloride (10.0 mol%, 7.5 mg, 0.010 mmol), and 1-fluoro-4-iodo-2-(p-tolylsulfinyl)benzene **A** (36.0 mg, 0.10 mmol) in THF (0.6 mL), and triethylamine (0.3 mL) were added successively. This reaction mixture was stirred at 40 °C and 2-ethynyl-4-methoxyphenylboronic acid pinacol ester **B** (1.4 eq., 33.5 mg, 0.13 mmol) in THF (0.3 mL) was added. The reaction mixture was filtered through a Celite® pad with ethyl acetate (20 mL) after further stirring until the starting material disappeared by TLC analysis. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 6:1, v/v) to yield target material **AB** (43.6 mg, 94%) as a brown solid, along with Glaser coupling by-product **BB** (1.2 mg, 9%) as an amorphous solid.

2-(4-fluoro-3-(p-tolylsulfinyl)phenyl)ethynyl-4-methoxy-phenylboronic acid pinacol ester (**AB**). Mp: 50.0–52.5 °C. HRMS (ESI-MS) *m*/*z*: $[M+Na]^+$ calcd. for $C_{28}H_{28}O_4BFSNa$, 513.1683; found, 513.1696. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.16 (1H, dd, *J* = 6.4, 1.8 Hz), 7.76 (1H, d, *J* = 8.2 Hz), 7.61–7.58 (3H, m), 7.27 (2H, d, *J* = 7.8 Hz), 7.07 (1H, d, *J* = 2.3 Hz), 7.02 (1H, t, *J* = 8.9 Hz), 6.89 (1H, dd, *J* = 8.2, 2.3 Hz), 3.85 (3H, s), 2.37 (3H, s), 1.40 (12H, d, *J* = 1.8 Hz). ^{13}C-NMR ($CDCl_3$) δ (ppm): 161.3, 157.5 (d, *J* = 250.6 Hz), 142.2, 141.2, 137.4, 135.3 (d, *J* = 8.3 Hz), 133.7 (d, *J* = 16.6 Hz), 130.1, 129.1, 128.2 (d, *J* = 2.8 Hz), 125.1 (d, *J* = 1.8 Hz), 121.7 (d, *J* = 3.7 Hz), 117.0, 116.2, 116.0, 114.5, 91.7 (d, *J* = 1.8 Hz), 88.8, 83.7, 55.3, 25.0 (d, *J* = 1.8 Hz), 21.5. ^{11}B-NMR ($CDCl_3$) δ (ppm): 29.9. ^{19}F-NMR ($CDCl_3$) δ (ppm): –13.16 (1F, dt, *J* = 20.7, 10.4 Hz).

4-((3-hydroxy-4-methoxyphenyl)ethynyl)-2-methoxyphenyl trifluoromethanesulfonate (**DC1**). Mp: 122.8–123.9 °C. HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{17}H_{14}O_6F_3S$, 403.0463; found, 403.0461. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.17 (1H, d, *J* = 8.2 Hz), 7.15 (1H, d, *J* = 1.8 Hz), 7.10–7.08 (3H, m), 6.82 (1H, d, *J* = 8.2 Hz), 5.68 (1H, br s), 3.93 (3H, s), 3.91 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 151.1, 147.4, 145.3, 138.2, 124.8, 124.4, 124.1, 122.4, 118.7 (q, *J* = 320.4 Hz), 117.1, 115.9, 115.2, 110.5, 90.8, 86.3, 56.2, 55.9. ^{19}F-NMR ($CDCl_3$) δ: 26.3 ppm.

4-((3-benzyloxy-4-methoxyphenyl)ethynyl)-2-methoxyphenyl trifluoromethanesulfonate (**DC2**). Mp: 97.1–99.1 °C. HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{24}H_{20}O_6F_3S$, 493.0933; found, 493.0930. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.45 (2H, d, *J* = 7.3 Hz), 7.39 (2H, t, *J* = 7.4 Hz), 7.33–7.31 (1H, m), 7.18–7.14 (3H, m), 7.09 (2H, dt, *J* = 11.0, 3.9 Hz), 6.87 (1H, d, *J* = 8.4 Hz), 5.16 (2H, s), 3.92 (3H, s), 3.91 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 151.1, 150.5, 147.8, 138.2, 136.6, 128.6, 128.0, 127.3, 125.6, 124.7, 124.1, 122.4, 118.7 (q, *J* = 321.0 Hz), 116.6, 115.8, 114.4, 111.5, 90.9, 86.4, 70.9, 56.2, 55.9. ^{19}F-NMR ($CDCl_3$) δ: 26.3 ppm.

4-((3-tert-butyldimethylsilyloxy-4-methoxyphenyl)ethynyl)-2-methoxyphenyl trifluoromethanesulfonate (**DC3**). Mp: not determined (colorless oil). HRMS (APCI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{23}H_{27}O_6F_3SSi$, 517.1328; found, 517.1332. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.18–7.16 (2H, m), 7.14–7.11 (2H, m), 7.02 (1H, d, *J* = 1.8 Hz), 6.82 (1H, d, *J* = 8.2 Hz), 3.94 (3H, s), 3.84 (3H, s), 1.01 (9H, s), 0.17 (6H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.5, 151.1, 144.8, 138.2, 126.0, 124.9, 124.1, 124.0, 122.4, 115.9, 114.5, 111.7, 90.9, 86.2, 56.3, 55.4, 25.7, 18.4, –4.7. ^{19}F-NMR ($CDCl_3$) δ: 26.3 ppm.

2-methoxy-4-((4-methoxy-3-methoxymethoxyphenyl)ethynyl)phenyl trifluoromethanesulfonate (**DC4**). Mp: not determined (colorless oil). HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{19}H_{18}O_7F_3S$, 447.0725; found, 447.0724. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (1H, d, *J* = 1.8 Hz), 7.19 (3H, td, *J* = 9.2, 1.7 Hz), 7.12 (1H, dd, *J* = 8.2, 1.8 Hz), 6.88 (1H, d, *J* = 8.7 Hz), 5.27 (2H, s), 3.94 (3H, s), 3.91 (3H, s), 3.54 (3H, s). ^{13}C-NMR ($CDCl_3$) (ppm)δ: 151.1, 150.4, 146.2, 130.2, 126.5, 124.8, 124.1, 122.4, 119.1, 118.7 (q, *J* = 320.7 Hz), 115.9, 114.7, 111.4, 95.4, 90.8, 86.5, 56.3, 56.2, 55.9. ^{19}F-NMR ($CDCl_3$) δ: 26.3 ppm.

Typical procedure for Suzuki coupling reaction of unit AB with DC (Table 2, entry 1). A 10 mL two-necked flask equipped with stirring bar and reflux condenser was flame-dried under vacuum, and filled with Ar. To this flask, bis(triphenylphosphine)palladium(II) dichloride (10.0 mol%, 7.4 mg, 0.010 mmol), unit **DC1** (40.2 mg, 0.10 mmol), THF (0.6 mL), triethylamine (0.3 mL), and 0.67 N aqueous KOH (2.0 eq., 0.3 mL, 0.2 mmol) were added successively. This reaction mixture was stirred at 100 °C and a 0.467 M THF solution of unit **AB** (1.40 eq., 0.3 mL, 0.14 mmol) and DMF (0.1 mL)were added. After further stirring until the starting material disappeared by TLC analysis (24 h), the reaction mixture was quenched by adding water (10 mL), filtered through a Celite® pad, and washed with ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic solution was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 3:1, v/v), affording the target compound **ABDC1** (44.0 mg, 71%) as a colorless solid.

5-((2'-((4-fluoro-3-(p-tolylsulfinyl)phenyl)ethynyl)-2,4'-dimethoxy-[1,1'-biphenyl]-4-yl)ethynyl)-2-methoxyphenol (**ABDC1**). Mp: 205.0–207.5 °C. HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{38}H_{30}O_5FS$, 617.1798; found, 617.1813. HRMS (ESI-MS) m/z: $[M+Na]^+$ calcd. for $C_{38}H_{29}O_5FSNa$, 639.1617; found, 639.1619. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.90 (1H, dd, *J* = 6.4, 2.3 Hz), 7.59 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 7.6 Hz), 7.27 (2H, d, *J* = 7.6 Hz), 7.22–7.19 (2H, m), 7.15–7.12 (3H, m), 7.10 (1H, dd, *J* = 8.2, 1.8 Hz), 6.97 (1H, dd, *J* = 8.2, 2.7 Hz), 6.93 (1H, t, J = 8.9 Hz), 6.82 (1H, d, *J* = 8.2 Hz), 5.66 (1H, s), 3.92 (3H, s), 3.88 (3H, s), 3.81 (3H, s), 2.33 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 157.5 (d, *J* = 184.2 Hz), 147.0, 145.3, 142.2, 141.1, 135.4 (d, *J* = 8.2 Hz), 135.4, 133.2, 131.6, 131.4, 130.1, 129.4, 128.0, 127.9, 124.9, 124.9, 124.3, 123.7, 123.5, 123.1, 121.1, 117.5, 116.4, 116.2, 116.0, 116.0, 115.4, 113.7, 110.4, 90.3, 89.4, 89.4, 88.2,

55.9, 55.7, 55.4, 21.4. ^{19}F-NMR ($CDCl_3$) δ: –42.87 ppm (1H, dt, *J* = 20.7, 10.4 Hz).

4-((3-(benzyloxy)-4-methoxyphenyl)ethynyl)-2'-((4-fluoro-3-(p-tolylsulfinyl)phenyl)ethynyl)-2,4'-dimethoxy-1,1'-biphenyl (**ABDC2**). Mp: not determined (colorless oil). HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{45}H_{36}O_5FS$, 707.2268; found, 707.2230. HRMS (ESI-MS) *m*/*z*: $[M+Na]^+$ calcd. for $C_{45}H_{35}O_5FSNa$, 729.2087; found, 729.2097. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.89 (1H, d, *J* = 6.0 Hz), 7.60 (2H, d, *J* = 7.8 Hz), 7.45 (2H, d, *J* = 8.2 Hz), 7.39–7.37 (4H, m), 7.33–7.31 (3H, m), 7.25 (2H, d, *J* = 5.0 Hz), 7.20–7.19 (3H, m), 7.14–7.13 (3H, m), 6.97 (1H, dd, *J* = 8.5, 2.5 Hz), 6.93 (1H, t, *J* = 8.9 Hz), 6.87 (1H, d, *J* = 8.2 Hz), 5.14 (2H, s), 3.91 (3H, s), 3.88 (3H, s), 3.81 (3H, s), 2.32 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 158.5, 156.6, 150.1, 147.8, 142.2, 141.1, 136.7, 135.4, 135.3, 133.8, 133.2, 131.6, 131.4, 130.1, 129.4, 128.6, 128.3, 128.0, 127.4, 125.5, 124.9, 123.7, 123.5, 123.1, 121.1, 121.1, 116.6, 116.4, 116.2, 116.0, 115.4, 115.3, 113.6, 111.5, 90.3, 89.5, 89.4, 88.2, 70.9, 56.0, 55.7, 55.4, 21.4. ^{19}F-NMR ($CDCl_3$) δ: –13.15 ppm (1F, dt, *J* = 19.6, 9.8 Hz).

2-((4-fluoro-3-(p-tolylsulfinyl)phenyl)ethynyl)-2',4-dimethoxy-4'-((4-methoxy-3-(methoxymethoxy)phenyl)ethynyl)-1,1'-biphenyl (**ABDC4**). Mp: not determined (colorless oil). HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{40}H_{34}O_6FS$, 661.2060; found, 661.2065. HRMS (ESI-MS) *m*/*z*: $[M+Na]^+$ calcd. for $C_{40}H_{33}O_6FSNa$, 683.1880; found, 683.1888. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.90 (1H, dd, *J* = 6.4, 2.3 Hz), 7.59 (2H, d, *J* = 8.2 Hz), 7.38 (1H, d, *J* = 1.8 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.24–7.18 (3H, m), 7.15 (2H, d, *J* = 2.3 Hz), 6.98 (1H, dd, *J* = 8.7, 2.7 Hz), 6.94 (1H, t, *J* = 8.9 Hz), 6.87 (1H, d, *J* = 8.2 Hz), 5.26 (2H, s), 3.91 (3H, s), 3.88 (3H, s), 3.81 (3H, s), 3.53 (3H, s), 2.33 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 158.7, 158.4, 156.6, 156.1, 150.1, 146.1, 142.1, 141.0, 135.4, 135.3, 133.8, 133.6, 133.1, 131.6, 131.4, 130.1, 129.4, 127.9, 127.9, 126.3, 124.8, 123.7, 123.1, 121.1, 121.1, 119.1, 116.3, 116.2, 116.0, 115.5, 115.3, 113.6, 111.4, 95.4, 90.3, 89.4, 89.3, 88.3, 60.4, 56.2, 55.9, 55.6, 55.4, 21.4, 14.1. ^{19}F-NMR ($CDCl_3$) δ (ppm): –13.16 (1H, dt, *J* = 20.7, 10.4 Hz).

5 Steps one-pot formal total synthesis of riccardin C using unit C4 (Scheme 2). A 10 mL two-necked flask equipped with stirring bar and reflux condenser was flame-dried under vacuum, and filled with Ar. To this flask, bis(triphenylphosphine)palladium(II) dichloride (10.0 mol%, 7.5 mg, 0.010 mmol), a unit **C4** (1.4 eq., 26.5 mg, 0.14 mmol) in THF (0.3 mL), and triethylamine (0.3 mL) were added successively. This reaction mixture was stirred 40 °C and unit **D** (1.0 eq., 39.0 mg, 0.10 mmol) in THF (0.3 mL) was added. After further stirring for 12 h, unit **A** (1.6 eq., 59.3 mg, 0.16 mmol) and a unit **B** (1.5 eq., 41.5 mg, 0.15 mmol) in THF (0.3 mL) were successively added to the reaction mixture. After further stirring for 27 h, 0.2 mL 1 N aqueous KOH (2.0 eq., 0.20 mmol) and DMF (0.2 mL) were added, and the reaction temperature was raised to 70 °C. After further stirring for 72 h, almost all solvent was removed under reduced pressure. To this reaction residue, *p*-toluenesulfonylhydrazide (39.3 eq., 747.0 mg, 4.01 mmol), $NaHCO_3$ (42.4 eq., 363.0 mg, 4.32 mmol), and ethoxyethanol (1.5 mL) were added and the reaction mixture stirred for 7 h at 200 °C. After cooling to 60 °C, 6 N HCl (2.0 mL) was added and stirred continued for 4 h. Then, the reaction mixture was filtered through a Celite® pad and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1, v/v), to yield cyclic precursor **ABCD** (40.9 mg, 64%) as a colorless oil.

HRMS (ESI-MS) *m*/*z*: $[M+H]^+$ calcd. for $C_{38}H_{38}O_5FS$, 625.2424; found, 625.2408. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.81 (1H, d, *J* = 8.2 Hz), 7.59–7.51 (4H, m), 7.31 (1H, d, *J* = 8.2 Hz), 7.27–7.21 (2H, m), 7.11–7.02 (1H, m), 6.85–6.73 (7H, m), 5.71 (1H, s), 3.86 (3H, s), 3.78 (3H, s), 3.71 (3H, s), 2.94–2.90 (6H, m), 2.77–2.68 (4H, m), 2.43–2.32 (2H, m), 2.36 (3H, s). ^{13}C-NMR ($CDCl_3$) δ (ppm): 158.7, 145.4, 145.3, 144.8, 142.6, 142.5, 141.9, 140.9, 136.0, 135.1, 132.5, 132.4. 130.8, 130.0, 129.7, 128.3, 127.5, 126.4, 125.0, 124.4, 119.7, 119.7, 114.8, 114.6, 114.3, 111.3, 111.0, 110.6, 110.4, 56.0, 55.4, 55.1, 38.1, 37.2, 35.1, 31.1, 21.4. ^{19}F-NMR ($CDCl_3$) δ: –18.76 ppm (1F, d, *J* = 32.7 Hz).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study (preparation method of each unit, experimental procedures, characterization data of the corresponding products, and copies of ^{1}H, ^{13}C NMR spectra of products) are available in the supplementary material of this article.

Keywords: Cross-coupling • riccardin C • Green chemistry • One-pot synthesis • Tandem reaction

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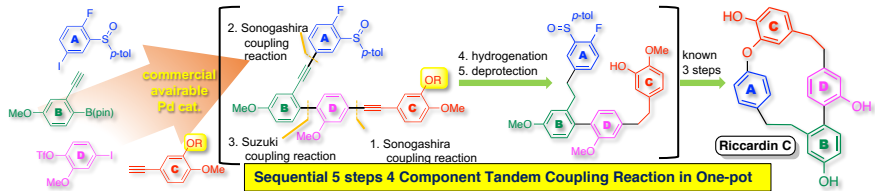
[18] Suzuki *et al.* were unsuccessful in reducing compounds with similar structures and considered the sulfinyl group to be catalytically poisonous. Therefore, they performed the diimide reduction reaction. See ref. 8h.

Entry for the Table of Contents



We achieved the formal total synthesis of riccardin C by a sequential five steps four component one-pot tandem coupling method. By optimizing each step, four individual units were connected by two Sonogashira coupling reactions and one Suzuki coupling reaction, followed by diimide reduction and acid deprotection.