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Total synthesis of riccardin C and (\pm) -cavicularin via Pd-catalyzed Ar–Ar cross couplings



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ABSTRACT

Riccardin C, a specific LXR α agonist, is a representative macrocyclic bisbibenzyl-type natural product. As part of our synthetic studies on macrocyclic bisbibenzyls, the synthesis of riccardin C and its analog cavicularin was examined. The total synthesis of riccardin C was accomplished via a Pd-catalyzed intramolecular Suzuki–Miyaura coupling as the key macrocyclization step. This synthetic strategy was also extended in the synthesis of (±)-cavicularin, which was then attained by constructing the dihydrophenanthrene moiety using a Pd-catalyzed Ar–Ar coupling reaction.

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1. Introduction

Macrocyclic bisbibenzyls are natural products that occur mainly in liverworts and feature two bibenzyl structures double-linked by ether bonds and/or biphenyl bonds. It is known that macrocyclic bisbibenzyl compounds exhibit a variety of biological activities.¹ Riccardin C (1), originally isolated from *Reboulia hemisphaerica*, is a representative bisbibenzyl compound with notable biological activity² (Fig. 1). Compound **1** was found to bind directly to the liver X receptor α (LXR α), a member of the nuclear receptor super family, leading to the activation of LXR α /RXR-dependent reporter gene transcription.³ Interestingly, riccardin C acts as an antagonist, not an agonist, of LXR β . Moreover, it has no ability to activate other nuclear receptors, such as PPAR γ , RAR α , RAR β , RAR γ , FXR, and RXR α , and increases LXR-target gene expression in macrophages. On the basis of these results, **1** has been expected to be a lead compound for the treatment of cardiovascular-related diseases, such as arteriosclerosis, because LXRs are thought to regulate cholesterol metabolites.

Investigation of the structure–activity relationships of **1** is a current important assignment, and riccardin C analogs and derivatives are also expected to be LXR α agonist candidates.^{3,4} In



Fig. 1. Structures of riccardin C (1) and cavicularin (2).

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particular, highly strained cavicularin (**2**), which is assumed to be biosynthetically formed via an intramolecular oxidative coupling between the 3' and 10' positions of riccardin C, has attracted



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attention as not only a biologically active compound,^{1a} but also a synthetic target. Cavicularin was isolated from the liverwort *Cavicularia densa* by Toyota and Asakawa in 1996⁵ and is one of the most interesting natural products from a synthetic perspective (Fig. 1). The rigid cyclophane structure of **2** causes benzene ring A to bend into a boat-like form with a dihedral angle of 212°; therefore, **2** is an optically active compound with planar chirality ($[\alpha]_D^{21}$ +168, *c* 0.25, MeOH).

Thus, the intriguing structures and biological activity of the macrocyclic bisbibenzyls have made them attractive synthetic targets.⁶ The synthesis of riccardin C has been reported by five groups to date. Nógrádi et al. achieved the first total synthesis of **1** in 1988.⁷ They used Wurtz coupling to construct the 18-membered macrocyclic ring. Eicher et al.⁸ and Harrowven et al.⁹ separately applied Wittig olefination reactions to the macrocyclization to accomplish the total synthesis of **1**. Recently, Suzuki et al.¹⁰ and Kagechika et al.¹¹ each reported syntheses of **1** that employed an S_NAr reaction for the key macrocyclization step. On the other hand, cavicularin has been synthesized by just three groups. In 2005, Harrowven et al. reported the first total synthesis of (\pm) -cavicularin by applying a radical transannulation for the formation of the dihydrophenanthrene moiety,⁹ and subsequently reported improvements to the protocol in 2011.¹² Dam and Baran applied an intramolecular [4+2] cyclization of ring A for the synthesis of **2**.^{13,14} Recently, Zhao and Beaudry reported a similar synthesis of 2 using a highly regioselective Diels–Alder reaction.¹⁵ We also have continued synthetic studies of macrocyclic bisbibenzyl compounds using an independent strategy involving Pd-catalyzed macrocyclization and previously reported the syntheses of plagiochin A and D,¹⁶ isoplagiochin D,¹⁷ and asterelin A.¹⁸ Herein, we describe the synthesis of riccardin C^4 and (\pm) -cavicularin by applying two types of Pdcatalyzed reactions, one to form the 18-membered macrocyclic rings, and the other to construct the highly strained dihydrophenanthrene moiety of 2.

The common synthetic strategy for riccardin C and cavicularin is shown in Scheme 1. Starting units 3, 4, and 5 would be condensed by Horner-Wadsworth-Emmons (HWE) reactions. After borylation of the bromide on ring B, the macrocycles of 1 and 2 could be formed via intramolecular Suzuki-Miyaura coupling. For the synthesis of cavicularin, regioselective iodination on the C-10' position would then be required, which would be made possible by protecting the phenolic hydroxyl group at C-13['] as a MOM ether. After iodination, transannulation between C-3' and C-10' via Pdcatalyzed Ar-Ar coupling would construct the dihydrophenanthrene embedded within the cavicularin skeleton. Although Pdcatalyzed Ar–Ar coupling has already proved to be an effective method for the formation of a biphenyl bond,¹⁹ the synthetic strategy based on Pd-chemistry described here is not only challenging, but also attractive for constructing the highly strained and hindered cavicularin skeleton.

2. Results and discussion

The synthesis of **1** commenced with commercially available 4bromobenzaldehyde (**9**), which corresponds to ring A (Scheme 2). In the presence of CuO and K₂CO₃, the Ullmann coupling of **9** with methyl 3-hydroxy-4-methoxybenzoate (**10**) afforded biphenyl ether **3** in 76% yield. Next, the HWE reaction with phosphonate **4** proceeded smoothly to give **11**. Successive LiAlH₄ reduction of **11** and bromination of the resulting alcohol **12** with SOBr₂ followed by Arbuzov reaction of bromide **13** gave phosphonate **14** in 96% yield over three steps. Subsequently, the HWE reaction of **14** with aldehyde **15** afforded **16**, which contains all four of the arene rings of **1** and **2**, in 87% yield. Reduction of the two alkenes and removal of the MOM groups were achieved by treatment with Et₃SiH in TFA to give **17** in 74% yield.²⁰ The liberated hydroxy group of **17** was then



Scheme 1. Synthetic strategy for riccardin C (1) and cavicularin (2).

converted to a triflate with Tf_2NPh and Cs_2CO_3 . Subsequently, chemoselective borylation²¹ of the bromide over the triflate of **18** was carried out with Pd(PPh_3)₄, bis(pinacolato)diboron, and K₃PO₄ in dioxane, giving rise to **19** in 95% yield.

With boron ester **19** successfully obtained, Suzuki–Miyaura coupling was attempted to achieve the 18-membered macrocyclization (Table 1). Firstly, 10 mol % Pd(PPh₃)₄/K₃PO₄/DMF, which was effective for the synthesis of isoplagiochin D, was employed for this cyclization. However, the desired product **20** was obtained in only 9% yield (entry 1). Using 5 mol % Pd₂(dba)₃/SPhos/aqNa₂CO₃/DMF, the yield was improved to 16% (entry 2). Then, it was found that this macrocyclization is highly dependent on the base. Aqueous Na₂CO₃ enhanced the reactivity to give the desired product in 48% yield, along with 25% of the undesired cyclic dimer **21** (entry 3). Other solvents such as toluene, THF, and DMSO were less effective for this cyclization (entries 4–6).

Finally, treatment of **20** with BBr₃ in DCM completed the synthesis of riccardin C. The spectroscopic data for synthetic **1** were consistent with those for natural riccardin C (Scheme 3).

Next, our attention was focused on the synthesis of cavicularin (Scheme 4). The synthesis began with the common intermediate **14**. The HWE reaction with aldehyde **22**, which contained a protected phenolic 3-OH group as the MOM ether, afforded **23** in 94% yield. After diimide reduction²² of the two alkenes and removal of the benzyl group to give **24**, the liberated hydroxyl group was converted to a triflate with Tf₂O and DMAP. Selective borylation of **25** was carried out using the same conditions as described above, giving rise to **26** in 81% yield. Subsequently, Suzuki–Miyaura



Scheme 2. Preparation of boronic ester 19.

coupling was attempted. Unfortunately, the 5 mol % Pd₂(dba)₃/ SPhos/aqNa₂CO₃/DMF (0.005 M) system that was employed in the synthesis of riccardin C mainly brought about protonation of the boronic ester moiety. This protonation may have been due to the presence of H₂O in the reaction mixture; therefore, anhydrous Na₂CO₃ was used along with freshly distilled DMF under otherwise identical conditions. To our delight, the reaction yield was improved to 53%. Finally, by optimizing the reaction concentration and the reaction time to 0.001 M and 15 h, respectively, a further increase in the yield of **27** up to 72% was achieved.

The next step was the Pd-catalyzed Ar–Ar coupling reaction to construct the crucial dihydrophenanthrene structure (Scheme 5).

Firstly, the MOM protecting group of **27** was removed under acidic conditions to give rise to phenol **28**, which was then regioselectively iodinated at C-10' with Nal, NaClO, and NaOH in MeOH to give **29** in good yield.²³ In order to increase the reactivity of the subsequent Pd-catalyzed Ar–Ar coupling reaction and prevent the undesired coordination of the Pd complex with the phenolic OH group, **29** was acetylated, giving **30** in 97% yield.

We were now in a position to investigate the crucial Pdcatalyzed Ar-Ar coupling for construction of the dihydrophenanthrene moiety. The reaction was first carried out under standard conditions of 20 mol % Pd(OAc)₂ and 2 equiv of Ag₂CO₃ in DMF at 120 °C, which gave deiodinated **32** as the sole product (Table 2, entry 1). In order to obtain the desired product 31, a range of ligands were screened. The use of 40 mol % (o-tol)₃P or t-Bu₃P as the ligand afforded only **32** (entries 2 and 3). However, 40 mol % *n*-Bu₃P²⁴ was found to provide product **31** in 39% yield, along with **32** in 36% yield (entry 4). The more compact ligand Et₃P provided no desired product, which may be due to its inability to reduce Pd(II) to Pd(0) efficiently (entry 6). On the other hand, reducing the ligand load from 40 mol % to 20 mol % increased the yield of **31** up to 50% (entry 5). It was also noted that microwave irradiation or the addition of a pivalate salt (CsOPiv) was not effective for improving the yield of **31**. Interestingly, some reactions using chiral ligands such as (*S*,*S*)chiraphos ((15,2S)-(-)-bis(diphenylphosphino)butane), (S)-BINAP, or (*R*,*R*)-Me-BPE ((+)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano) ethane), gave 31 with low ee. However, a satisfactory ee has not been obtained to date (entries 8-10).

Due to the electron rich character of ring C possessing one alkoxy and one aryloxy groups, there are three plausible reaction mechanisms for this Pd-catalyzed transannulation (Scheme 6).²⁶ The first is a true C–H activation mechanism that proceeds via a four- (X=I) or six- (X=OAc) membered transition state. The second is an electrophilic substitution mechanism. Both of these mechanisms would conclude via reductive elimination. The third possible mechanism is a Heck reaction-type carbopalladation. Generally, this route would be improbable because anti-elimination of H–Pd–X is required.^{19a} However, in this case, elimination of the Pd–X moiety would be facilitated by the electron donation from the alkoxy group. Although it is not clear, which particular mechanism is in effect, small ligands such as *n*-Bu₃P and bidentate ligands are suitable for forming the above transition states and intermediates inside of the macrocyclic ring.

Finally, hydrolysis of the acetyl group in (\pm) -**32** followed by treatment with BBr₃ gave rise to (\pm) -cavicularin in 71% yield over two steps (Scheme 7). The spectroscopic data for **2** were consistent with those of natural cavicularin.

3. Conclusion

The total synthesis of riccardin C (1) and (\pm) -cavicularin (2) was successfully accomplished in 11 steps and 17 steps, respectively. Intramolecular Suzuki–Miyaura coupling reactions were utilized for the formation of the 18-membered macrocycles of 1 and 2, and a Pd-catalyzed Ar–Ar coupling reaction was employed for the construction of the highly strained dihydrophenanthrene moiety of 2. The design and optimization of asymmetric catalysts for the Pd-catalyzed transannulation are currently underway in order to realize the synthesis of (+)-cavicularin.

4. Experimental section

4.1. General methods

Commercially available reagents, general solvents, and dry solvents were used as received. Column chromatography was performed using silica gel (63–210, 45–75, and 40–50 μ m), ¹H NMR

Table 1

Intramolecular Suzuki-Miyaura coupling of 19





^b 5 mol %.

^c 2 M aqueous Na₂CO₃ solution was used.



Scheme 3. Completion of the synthesis of riccardin C (1).

spectra were recorded at 300, 400, and 500 MHz and chemical shifts are referenced to TMS (δ =0). ¹³C NMR spectra were recorded at 75, 100, and 125 MHz and chemical shifts are referenced to CDCl₃ (δ =77.03). Coupling constants (*J*) are quoted in hertz (Hz). HRMS were recorded on Magnetic Sector (Double Focusing) mass spectrometer equipped with EI, CI, and FAB source. FTIR spectra were recorded with ATR.

4.2. Methyl 3-(4-formylphenoxy)-4-methoxybenzoate (3)

4-Bromobenzaldehyde (9) (4.05 g, 32.6 mmol), K₂CO₃ (1.06 g, 7.67 mmol), and copper(II) oxide powder (608 mg, 7.63 mmol) were added to a solution of methyl 3-hydroxy-4-methoxybenzoate (10) (995 mg, 5.46 mmol) in pyridine (10.0 mL). After stirring at reflux for 16 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by column chromatography eluted with toluene, to give 3(1.18 g, 76%) as a pale vellow prism. ¹H NMR (300 MHz, CDCl₃) δ 3.86 (3H, s), 3.89 (3H, s), 6.99 (2H, d, J=8.6 Hz), 7.06 (1H, d, J=8.6 Hz), 7.78 (1H, d, J=2.0 Hz), 7.83 (2H, d, J=8.6 Hz), 7.97 (1H, dd, J=2.0, 8.6 Hz), 9.92 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 52.1, 56.1, 112.1, 116.3, 123.4, 123.8, 128.5, 131.2, 131.9, 142.6, 155.5, 163.0, 166.0, 190.7; IR (ATR) 1716, 1692, 1600, 1579, 1504, 1437, 1280, 1226, 115, 1130, 1094, 1022, 833, 770 cm⁻¹; EIMS *m*/*z* (relative intensity) 286 [M]⁺ (100), 255 (94); HR-EIMS *m*/*z*: [M]⁺ calcd for C₁₆H₁₄O₅ 286.0841; found 286.0850; mp 94.5-96.2 °C.



Scheme 4. Construction of the macrocycle of 2 and preparation of 27.



4.3. Dimethyl 2-bromo-5-methoxybenzylphosphonate (4)

A mixture of 1-bromo-2-(bromomethyl)-4-methoxybenzene (10.0 g, 35.7 mmol) and trimethyl phosphite (13.0 mL, 107 mmol) was stirred at reflux for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography eluted with EtOAc, to give **4** (10.8 g, 98%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 3.38 (2H, d, *J*=22.0 Hz), 3.69 (3H, s), 3.74 (3H, s), 3.79 (3H, s), 6.69 (1H, dd, J=2.8, 8.8 Hz), 7.00 (1H, d, J=2.8 Hz), 7.44 (1H, d, *I*=8.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 31.8, 33.7, 52.9, 55.4, 114.7, 115.1, 116.7, 132.2, 133.3, 158.7; IR (ATR) 3470, 2953, 2849, 1596, 1572, 1474, 1415, 1315, 1283, 1239, 1183, 1164, 1149, 1109, 1014, 942, 860, 803, 749, 732, 690, 665 cm⁻¹; CIMS *m*/*z* (relative intensity) 311 [M+H]⁺ (91), 309 [M+H]⁺ (90), 229 (100); HR-CIMS m/z: $[M+H]^+$ calcd for C₁₀H₁₅O₄BrP 308.9891; found 308.9908.

Table 2

Examination of the intramolecular Pd-catalyzed Ar-Ar coupling for the synthesis of 2



Scheme 6. Plausible mechanisms for the Pd-catalyzed transannulation.

4.4. (E)-Methyl 3-(4-(2-bromo-5-methoxystyryl)phenoxy)-4methoxybenzoate (11)

To a solution of 4 (8.89 g, 28.6 mmol) in THF (26.0 mL) was added a suspension of 60% NaH (1.53 g, 38.2 mmol) in THF

	30 – 2	Table 20 mol% Pd(OAc) ₂ Ag_2CO_3 , DMF 120 °C	MeO OAc 31	MeO-CACO	MeO H H	
Entry	Ligand		Mol % of L	31	32	ee ²⁵
1	_		20	0	74	_
2	(o-tol) ₃ P		40	0	81	_
3	t-Bu ₃ P		40	0	78	_
4	n-Bu ₃ P		40	39	36	_
5	n-Bu₃P		20	50	31	
6	Et ₃ P		40	0	0	_
7	Dppe		20	41	43	_
8	(S,S)-Chiraph	105	20	23	0	11
9	(S)-BINAP		20	18	0	7
10	(R,R)-Me-BPE	E	20	12	0	6



Scheme 7. Completion of the synthesis of cavicularin (2).

(5.00 mL) at 0 °C. After stirring at the same temperature for 1 h, a solution of 3 (5.43 g, 19.0 mmol) in THF (5.00 mL) was added to the mixture. After stirring at rt overnight, the reaction was quenched with satd NH₄Cl at 0 °C and extracted with EtOAc. The combined extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (10:1) to give **11** (8.74 g, 98%) as a colorless prism. ¹H NMR (300 MHz, CDCl₃) δ 3.84 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 6.66 (1H, dd, J=2.7, 8.8 Hz), 6.93 (2H, d, J=8.8 Hz), 6.96 (1H, d, J=16.2 Hz), 7.00 (1H, d, J=8.5 Hz), 7.14 (1H, d, J=2.7 Hz), 7.30 (1H, d, J=16.2 Hz), 7.42 (1H, d, J=8.8 Hz), 7.48 (2H, d, J=8.8 Hz), 7.68 (1H, d, *J*=2.1 Hz), 7.86 (1H, dd, *J*=2.1, 8.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 51.9, 55.4, 56.0, 111.5, 111.8, 114.7, 114.8, 117.3, 122.1, 123.0, 126.3, 127.2, 128.1, 130.6, 131.7, 133.4, 137.7, 144.3, 155.2, 157.4, 158.9, 166.1; IR (ATR) 2950, 2839, 1712, 1603, 1583, 1566, 1503, 1462, 1436, 1419, 1321, 1273, 1225, 1165, 1128, 1112, 1094, 1057, 1016, 992, 962, 909, 847, 815, 7634, 729, 694 cm⁻¹; CIMS *m*/*z* (relative intensity) 469 $[M+H]^+(100)$, 468 $[M]^+$ (60); HR-CIMS m/z: $[M+H]^+$ calcd for C₂₄H₂₂O₅Br 469.0651; found 469.0637; mp 93.5–94.5 °C.

4.5. (*E*)-3-(4-(2-Bromo-5-methoxystyryl)phenoxy)-4-methoxyphenylmethanol (12)

To a solution of **11** (1.36 g, 2.91 mmol) in THF (30.0 mL) was added lithium aluminum hydride (209 mg, 2.91 mmol). After stirring at 0 °C for 30 min, the reaction mixture was guenched with aqueous potassium sodium tartrate tetrahydrate and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (2:3) to give alcohol **12** (1.25 g, 98%) as a colorless prism. ¹H NMR (300 MHz, CDCl₃) δ 3.77 (3H, s), 3.78 (3H, s), 4.54 (2H, s), 6.63 (1H, dd, *J*=3.0, 8.8 Hz), 6.88 (2H, d, *J*=8.6 Hz), 6.91 (1H, d, *J*=16.1 Hz), 6.93 (1H, d, *J*=8.6 Hz), 6.96 (1H, d, *J*=1.9 Hz), 7.09 (1H, dd, *J*=1.9, 8.6 Hz), 7.10 (1H, d, J=3.0 Hz), 7.24 (1H, d, J=16.1 Hz), 7.39 (1H, d, J=8.8 Hz), 7.42 (2H, d, J=8.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 55.6, 56.1, 64.7, 111.6, 112.8, 114.8, 117.4, 120.0, 123.7, 126.2, 128.2, 130.4, 130.8, 131.5, 133.5, 134.0, 137.9, 144.8, 150.9, 157.9, 159.0; IR (ATR) 3377, 2934, 1505, 1463, 1440, 1425, 1271, 1227, 1167, 1124, 1015, 961, 844, 808, 729, 633, 625, 608 cm⁻¹; CIMS *m*/*z* (relative intensity) 441 [M+H]⁺ (40), 440 $[M]^+$ (70), 361 (100); HR-CIMS m/z: $[M+H]^+$ calcd for C₂₃H₂₂O₄Br 441.0701; found 441.0721; mp 82.8-83.2 °C.

4.6. (*E*)-Dimethyl 3-(4-(2-bromo-5-methoxystyryl)phenoxy)-4-methoxybenzylphosphonate (14)

To a solution of alcohol **12** (4.31 g 9.85 mmol) in toluene (100 mL) was added thionyl bromide (1.00 mL, 12.8 mmol) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with H_2O and brine, and dried over Na_2SO_4 and concentrated in vacuo. To a solution of the residue in benzene was added trimethyl phosphite (5.85 mL, 49.5 mmol). After stirring

at 100 °C for 24 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (15:85) to give **14** (5.12 g, 98%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 3.07 (2H, d, *J*=21.3 Hz), 3.65 (3H, s), 3.69 (3H, s), 3.82 (6H, s), 6.68 (1H, dd, *J*=2.9, 8.8 Hz), 6.93 (2H, d, *J*=8.7 Hz), 6.95 (1H, d, *J*=2.5 Hz), 6.96 (1H, d, *J*=8.3 Hz), 6.97 (1H, d, *J*=16.4 Hz), 7.09 (1H, dd, *J*=2.5, 8.3 Hz), 7.16 (1H, d, *J*=8.7 Hz); 7.30 (1H, d, *J*=16.4 Hz), 7.44 (1H, d, *J*=8.8 Hz), 7.45 (2H, d, *J*=8.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 31.2, 32.6, 52.9, 55.5, 56.0, 111.6, 113.0, 114.8, 116.8, 117.3, 122.5, 122.6, 126.2, 128.1, 130.3, 130.8, 131.5, 133.5, 137.9, 144.5, 150.5, 157.9, 159.0; IR (ATR) 2952, 2838, 1584, 1503, 1463, 1442, 1425, 1222, 1167, 1128, 1053, 1025, 961, 891, 852, 802, 772, 689, 664 cm⁻¹; EIMS *m/z* (relative intensity) 533 [M]⁺ (100), 343 (50); HR-EIMS *m/z*: [M]⁺ calcd for C₂₅H₂₇O₆BrP 533.0687; found 533.0713.

4.7. 1-Bromo-4-methoxy-2-(4-(2-methoxy-5-(3-methoxy-4-(methoxymethoxy)styryl)phenoxy)styryl)benzene (16)

To a solution of 14 (595 mg, 3.03 mmol) in THF (5.00 mL) was added 60% NaH (513 mg, 12.8 mmol). After stirring at 0 °C for 10 min, **15** (1.30 g, 2.51 mmol) was added to the solution. After stirring at 0 °C for 3 h, the reaction mixture was guenched with water and extracted with ether. The combined extracts were washed with H₂O and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (7:3) to give 16 (2.10 g, 87%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.44 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 3.85 (3H, s), 5.16 (2H, s), 6.63 (1H, dd, *J*=2.9, 8.8 Hz), 6.81 (2H, s), 6.91 (2H, d, *J*=8.7 Hz), 6.92 (1H, d, *J*=16.2 Hz), 6.93 (3H, m), 7.04 (1H, d, J=8.2 Hz), 7.11 (1H, d, J=2.9 Hz), 7.13 (1H, d, J=1.9 Hz), 7.20 (1H, dd, J=1.9, 8.2 Hz), 7.25 (1H, d, J=16.2 Hz), 7.38 (1H, d, J=8.8 Hz), 7.44 (1H, d, J=8.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 55.5, 55.9, 56.1, 56.2, 95.5, 108.6, 109.2, 111.6, 112.9, 114.8, 116.3, 116.5, 117.3, 118.7, 119.5, 123.4, 126.2, 127.2, 128.2, 130.8, 131.1, 131.5, 132.0, 133.6, 138.0, 144.8, 146.2, 149.8, 150.9, 158.0, 159.0; IR (ATR) 2932, 1504 cm⁻¹; EIMS m/z (relative intensity): 604 [M]⁺ (100), 602 [M]⁺ (96); HR-EIMS m/z: [M]⁺ calcd for C₃₃H₃₁BrO₆ 602.1304; found 602.1299.

4.8. 4-(**3-**(**4-**(**2-**Bromo-**5-**methoxyphenethyl)phenoxy)-**4-**methoxyphenethyl)-**2-**methoxyphenol (17)

To a solution of 16 (1.20 g, 2.05 mmol) in TFA (36.0 mL) was added Et₃SiH (18.2 mL, 114 mmol). After stirring at 60 °C for 2.5 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (7:3) to give 17 (853 mg, 74%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 2.78 (4H, s), 2.86 (2H, m), 2.97 (2H, m), 3.74 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 5.48 (1H, s), 6.59 (1H, dd, J=1.9, 6.0 Hz), 6.60 (1H, m), 6.65 (1H, dd, *J*=2.9, 8.8 Hz), 6.70 (1H, d, *J*=2.9 Hz), 6.73 (1H, d, *J*=1.4 Hz), 6.80 (1H, d, J=8.1 Hz), 6.83 (2H, d, J=8.8 Hz), 6.89 (1H, d, J=1.5 Hz), 7.13 (2H, d, J=8.8 Hz), 7.42 (1H, d, J=8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 35.4, 37.3, 37.6, 38.7, 55.4, 55.8, 56.1, 111.1, 112.7, 113.4, 114.2, 114.9, 116.2, 117.3, 120.8, 121.1, 124.2, 129.5, 133.3, 133.4, 134.8, 135.5, 141.9, 143.7, 145.1, 146.2, 149.4, 156.1, 158.9; IR (ATR) 3522, 2933, 1503 cm⁻¹; EIMS *m*/*z* (relative intensity): 562 [M]⁺ (54), 363 (100), 137 (96); HR-EIMS *m*/*z*: [M]⁺ calcd for C₃₁H₃₁O₅Br 562.1355; found 562.1362.

4.9. 4-(3-(4-(2-Bromo-5-methoxyphenethyl)phenoxy)-4methoxyphenethyl)-2-methoxyphenyl trifluoromethanesulfonate (18)

To a solution of **17** (639 mg, 1.14 mmol) in MeCN/DMF=9:1 (30 mL) was added Tf_2NPh (614 mg, 1.72 mmol) and $CsCO_3$ (565 mg, 1.72 mmol). After stirring at rt for 8 h, the reaction mixture was

quenched with satd NaHCO₃ and extracted with ether. The combined extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (4:1) to give **18** (754 mg, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.84 (6H, m), 2.97 (2H, m), 3.74 (3H, s), 3.83 (3H, s), 3.83 (3H, s), 6.63 (1H, dd, *J*=3.1, 8.8 Hz), 6.70 (1H, d, *J*=3.1 Hz), 6.71 (1H, d, *J*=8.8 Hz), 6.72 (1H, m), 6.73 (1H, d, *J*=2.0 Hz), 6.84 (2H, d, *J*=8.6 Hz), 6.86 (1H, dd, *J*=2.2, 8.6 Hz), 6.89 (1H, br s), 7.08 (1H, d, *J*=8.0 Hz), 7.13 (2H, d, *J*=8.6 Hz), 7.42 (1H, d, *J*=8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 35.4, 36.6, 37.8, 38.7, 55.4, 56.1, 56.1, 112.7, 113.3, 114.8, 116.1, 117.1, 117.3, 120.3, 120.6, 120.7, 122.1, 124.2, 129.5, 133.3, 133.9, 135.6, 137.0, 141.8, 143.2, 145.3, 149.6, 151.0, 156.0, 158.9; IR (ATR) 2935, 1504 cm⁻¹; EIMS *m/z* (relative intensity): 694 [M]⁺ (47), 696 (54), 495 (100), 425 (33); HR-EIMS *m/z*: [M]⁺ calcd for C₃₂H₃₀BrF₃O₇S 694.0848; found 694.0877.

4.10. 2-Methoxy-4-(4-methoxy-3-(4-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)phenoxy)phenethyl)phenyl trifluoromethanesulfonate (19)

To a solution of 18 (71.3 mg, 100 µmol) in dioxane (1.00 mL) was added tetrakis(triphenylphosphine)palladium(0) (11.8 mg, 10.0 µmol), bis(pinacolato)diboron (61.8 mg, 240 µmol), and K₃PO₄ (66.2 mg, 310 μ mol). After stirring at 100 °C for 4 h, the reaction mixture was filtered through Celite®535RVS and concentrated in vacuo. The residue was purified by preparative TLC eluted with hexane/DCM (3:7) to give **19** (72.0 mg, 95%) as a pale yellow oil. 1 H NMR (400 MHz, CDCl₃) δ 1.35 (12H, s, Me), 2.78–2.87 (6H, m), 3.13 (2H, m), 3.80 (3H, s), 3.84 (6H, s), 6.72 (1H, dd, *J*=2.3, 11.2 Hz), 6.70–6.76 (3H, m), 6.77 (1H, d, J=2.1 Hz), 6.85 (2H, d, J=8.7 Hz), 6.85 (1H, dd, *J*=2.1, 8.4 Hz), 7.08 (1H, d, *J*=8.0 Hz), 7.20 (2H, d, I=8.7 Hz), 7.79 (1H, d, I=8.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.9, 36.7, 37.8, 38.9, 39.0, 55.0, 56.1, 56.1, 83.2, 110.6, 112.7, 113.3, 115.2, 117.2, 120.6, 120.7, 122.1, 124.1, 129.5, 133.9, 137.0, 137.0, 138.4, 143.2, 145.4, 149.7, 151.0, 151.4, 155.7, 161.8; IR (ATR) 2976, 1602, 1348 cm⁻¹; CIMS *m*/*z* (relative intensity): 643 (100), 743 [M+1]⁺ (42), 742 $[M]^+$ (68); HR-CIMS m/z: $[M]^+$ calcd for $C_{38}H_{42}O_9F_3SB$ 742.2595; found 742.2566.

4.11. Trimethylriccardin C (20)

To a solution of 19 (32.8 mg, 44.0 μ mol) in DMF (8.8 mL) was added 2 M Na₂CO₃ (67.0 µL, 134 µmol), tris(dibenzylideneacetone) dipalladium(0) (4.0 mg, 4.3 µmol), and SPhos (3.6 mg, 8.7 µmol). After stirring at 100 °C for 12 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by recycle HPLC eluted with CHCl₃ to give **20** (10.0 mg, 48%) as a colorless solid and 21 (5.1 mg, 25%) as a colorless amorphous. Compound **20**: ¹H NMR (400 MHz, CDCl₃) δ 2.63 (3H, br s), 2.82 (2H, br s), 2.86 (2H, br s), 3.08 (1H, br s), 3.64 (3H, s), 3.88 (3H, s), 3.94 (3H, s), 5.36 (1H, d, *J*=1.9 Hz), 6.24 (1H, dd, *J*=1.5, 7.6 Hz), 6.44 (1H, d, *I*=1.5 Hz), 6.73–6.83 (6H, m), 6.83 (1H, d, *I*=7.6 Hz), 6.89 (1H, d, J=8.3 Hz), 6.96 (1H, d, J=2.8 Hz), 7.06 (1H, d, J=8.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 35.6, 36.6, 37.5, 38.6, 55.2, 55.4, 56.1, 110.9, 111.0, 112.6, 114.4, 116.9, 120.3, 120.9, 124.4, 127.8, 129.2, 130.7, 131.3, 131.5, 134.8, 136.4, 142.0, 142.3, 145.0, 149.7, 156.0, 156.7, 158.9; IR (ATR) 2932, 2833, 1505, 1463, 1230, 1128, 729 cm⁻¹; EIMS *m/z* (relative intensity): 466 [M]⁺ (100), 239 (75); HR-EIMS *m*/*z*: [M]⁺ calcd for C₃₁H₃₀O₄ 466.2144; found 466.2163. Compound **21**: ¹H NMR (400 MHz, CDCl₃) δ 2.62–2.95 (16H, m), 3.78 (6H, s), 3.79 (6H, s), 3.85 (6H, s), 6.70 (2H, br s), 6.71-6.83 (16H, m), 6.87 (2H, d, J=2.0 Hz), 6.89 (2H, d, J=2.5 Hz), 7.00 (2H, d, J=7.5 Hz), 7.10 (2H, d, I=8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 36.5, 36.6, 37.5, 38.6, 55.2, 55.4, 56.1, 110.9, 111.0, 112.6, 114.4, 116.9, 120.3, 120.9, 124.4, 127.8, 129.2, 130.7, 131.3, 131.5, 134.8, 136.4, 142.0, 142.3, 145.0, 149.7, 156.0, 156.7, 158.9; IR (ATR) 3006, 2925, 2853, 1604, 1575, 1503, 1463, 1418, 1268, 1214, 811, 750 cm⁻¹; FABMS m/z: 933 [M+1]⁺; HR-FABMS m/z: [M+1]⁺ calcd for C₆₂H₆₁O₈ 933.4366; found 933.4347.

4.12. Riccardin C (1)

To a cooled solution of 20 (19.3 mg, 63.0 µmol) in DCM (5.00 mL) was added BBr₃ (1 M DCM solution, 550 uL, 550 umol). After stirring at 0 °C for 24 h, the reaction mixture was guenched with H₂O and extracted with DCM. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (3:2) to give **1** (25.9 mg, 97%) as a colorless prism. 1 H NMR (400 MHz, CDCl₃) δ 2.68 (5H, m), 2.93 (2H, m), 3.04 (1H, m), 4.75 (1H, s), 4.88 (1H, s), 5.35 (1H, d, J=2.0 Hz), 5.58 (1H, s), 6.23 (1H, dd, *J*=1.8, 7.7 Hz), 6.39 (1H, d, *J*=1.5 Hz), 6.74 (1H, dd, *J*=2.0, 8.1 Hz), 6.77-6.87 (6H, m), 6.92 (1H, d, J=8.0 Hz), 6.98 (1H, d, J=2.5 Hz), 7.05 (1H, d, J=8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 34.9, 37.1, 37.8, 38.1, 114.3, 114.9, 116.0, 116.0, 117.5, 121.7, 122.2, 122.5, 122.5, 124.3, 128.2, 129.5, 129.5, 131.4, 132.9, 133.1, 139.8, 142.0, 143.3, 143.8, 146.3, 151.8, 152.5, 155.9; IR (ATR) 3422, 2925, 1506 cm⁻¹; CIMS m/z (relative intensity): 425 [M+1]⁺ (82), 424 [M]⁺ (100); HR-CIMS *m*/*z*: [M]⁺ calcd for C₂₈H₂₄O₄ 424.1675; found 424.1679; mp 189.3-190.6 °C.

4.13. 4-(Benzyloxy)-3-hydroxybenzaldehyde

To a solution of 3,4-dihydroxybenzaldehyde (2.03 g, 14.7 mmol) in acetone (150 mL) was added K₂CO₃ (3.05 g, 22.1 mmol) and benzyl bromide (1.74 mL, 14.7 mmol). After stirring at reflux for 4 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by column chromatography eluted with toluene/EtOAc (13:1) to give 4-(benzy-loxy)-3-hydroxybenzaldehyde (2.12 g, 63%) as a colorless prism. ¹H NMR (300 MHz, CDCl₃) δ 5.21 (2H, s), 5.77 (1H, s), 7.05 (1H, d, *J*=8.2 Hz), 7.37–7.43 (7H, m), 9.86 (1H, s); ¹³C NMR (75 MHz) δ 71.2, 111.5 114.4, 124.4, 127.9, 128.8, 128.9, 130.8, 135.2, 146.3, 150.9, 191.0; IR (ATR) 3201, 1671, 1604, 1577, 1511, 1454, 1389, 1343, 1283, 1165, 1151, 1015, 962, 874, 811, 786, 738, 698, 678 cm⁻¹; EIMS *m/z* (relative intensity) 228 [M]⁺ (40), 91 (100); HR-EIMS *m/z*: [M]⁺ calcd for C₁₄H₁₂O₃ 228.0786; found 228.0789; mp 120.0–122.0 °C.

4.14. 4-(Benzyloxy)-3-(methoxymethoxy)benzaldehyde (22)

To a solution of 4-(benzyloxy)-3-hydroxybenzaldehyde (2.60 g, 11.4 mmol) in DCM (114 mL) was added MOMCl (1.73 mL, 22.8 mmol) and DIPEA (3.98 mL, 22.8 mmol). After stirring at 0 °C for 12 h, the reaction mixture was quenched with water and extracted with DCM. The combined extracts were washed with H₂O and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (3:1) to give **22** (2.44 g, 84%) as a yellow oil. ¹H NMR (300 MHz) δ 3.50 (3H, s), 5.21 (2H, s), 5.26 (2H, s), 7.00 (1H, d, *J*=8.4 Hz), 7.36–7.47 (6H, m), 7.66 (1H, d, *J*=1.9 Hz), 9.80 (1H, s); ¹³C NMR (75 MHz) δ 56.3, 70.7, 95.3, 113.0, 116.0, 126.6, 127.1, 128.1, 128.6, 130.1, 135.9, 147.1, 154.2, 190.6; IR (ATR) 2826, 1685, 1582, 1505, 1454, 1434, 1389, 1258, 1151, 1126, 1075, 990, 918, 808, 779, 730, 695, 628 cm⁻¹; EIMS *m/z* (relative intensity) 272 [M]⁺ (78), 227 (35), 181 (40), 91 (100); HR-EIMS *m/z*: [M]⁺ calcd for C₁₆H₁₆O₄ 272.1049; found 272.1041.

4.15. 1-(Benzyloxy)-4-((*E*)-3-(4-((*E*)-2-bromo-5-methoxystyryl)phenoxy)-4-methoxystyryl)-2-(methoxymethoxy)benzene (23)

To a solution of **14** (5.44 g, 8.95 mmol) in THF (90.0 mL) was added 60% NaH (716 mg, 17.9 mmol). After stirring at 0 $^{\circ}$ C for 1 h, **22** (2.92 g, 10.7 mmol) was added to the solution. After stirring at 0 $^{\circ}$ C

for 24 h, the reaction mixture was quenched with satd NH₄Cl and extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (4:1) to give **23** (5.70 g, 94%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.54 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 5.16 (2H, s), 5.26 (2H, s), 6.67 (1H, dd, *J*=3.0, 8.8 Hz), 6.84–6.81 (3H, m), 6.97–7.03 (5H, m), 7.17–7.52 (13H, m); ¹³C NMR (100 MHz, CDCl₃) δ 55.5, 56.1, 56.3, 71.0, 95.7, 111.6, 112.8, 114.5, 114.8, 117.3, 118.7, 121.1, 123.4, 126.1, 127.1, 126.2, 127.2, 127.9, 128.2, 128.6, 130.8, 131.1, 131.2, 131.4, 133.5, 137.0, 138.0, 144.8, 147.2, 148.7, 150.9, 158.0, 159.0; IR (ATR) 1588, 1503, 1461, 1267, 1226, 1166, 1125, 1075, 1000, 959, 847, 808, 735, 697, 660 cm⁻¹; EIMS *m/z* (relative intensity): 678 [M]⁺ (20), 91 (100), 41 (70); HR-EIMS *m/z*: [M]⁺ calcd for C₃₉H₃₅BrO₆ 678.1585; found 678.1601.

4.16. 1-(Benzyloxy)-4-(3-(4-(2-bromo-5-methoxyphenethyl) phenoxy)-4-methoxyphenethyl)-2-(methoxymethoxy)ben-zene (23a)

To a solution of **23** (5.13 g, 7.55 mmol) in EtOCH₂CH₂OH (75.0 mL) was added *p*-toluenesulfonyl hydrazide (14.0 g, 75.5 mmol) and NaHCO₃ (6.34 g, 75.5 mmol). After stirring at 135 $^{\circ}$ C for 3 h, the reaction mixture was filtered through Celite[®]535RVS and the solution was washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by HPLC eluted with hexane/EtOAc (9:1) to give **23a** (5.00 g, 97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.77 (4H, s), 2.85–2.97 (4H, m), 3.50 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 5.11 (2H, s), 5.18 (2H, s), 6.68 (1H, dd, J=3.5, 8.8 Hz), 6.67 (1H, d, J=2.0 Hz), 6.69 (1H, d, J=3.2 Hz), 6.75 (1H, d, J=1.3 Hz), 6.79-6.91 (6H, m), 7.13 (2H, dd, J=2.0, 8.5 Hz), 7.29-7.43 (6H, m); ¹³C NMR (100 MHz, CDCl₃) δ 35.4, 37.0, 37.3, 38.7, 55.4, 56.1, 56.2, 71.1, 95.7, 112.6, 113.3, 114.5, 114.8, 116.1, 117.3, 117.8, 120.8, 122.3, 124.2, 127.2, 127.8, 128.5, 129.5, 133.2, 134.7, 135.0, 135.4, 137.3, 141.9, 145.0, 146.8, 147.3, 149.4, 156.1, 158.8; IR (ATR) 2928, 1589, 1504, 1469, 1423, 1265, 1222, 1154, 1125, 1076, 1006, 922, 805, 736, 697 cm⁻¹; EIMS *m*/*z* (relative intensity): 682 [M]⁺ (10), 91 (100), 45 (30); HR-EIMS m/z: [M]⁺ calcd for C₃₉H₃₉BrO₆ 682.1930; found 682.1903.

4.17. 4-(3-(4-(2-Bromo-5-methoxyphenethyl)phenoxy)-4methoxyphenethyl)-2-(methoxymethoxy)phenol (24)

To a solution of 23a (45.3 mg, 66.3 µmol) in CHCl₃/MeOH=9:1 (2.50 mL) was added Pd(OH)₂/C (4.0 mg). After stirring vigorously under hydrogen atmosphere at rt for 10 min, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by column chromatography eluted with DCM to give the phenol 24 (36.6 mg, 93%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 2.76 (4H, s), 2.85–2.97 (4H, m), 3.49 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 5.13 (2H, s), 5.78 (1H, s), 6.63 (1H, dd, *J*=3.2, 8.8 Hz), 6.68 (1H, dd, *J*=2.0, 8.0 Hz), 6.70 (1H, d, *J*=5.6 Hz), 6.72 (1H, d, J=1.6 Hz), 6.83 (4H, m), 6.89 (2H, m), 7.13 (2H, d, J=8.4 Hz), 7.42 (1H, d, *J*=8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 35.4, 37.2, 37.4, 38.7, 55.4, 56.1, 56.4, 96.0, 112.7, 113.3, 115.0, 115.8, 116.1, 117.3, 120.8, 123.0, 124.2, 129.5, 133.3, 133.6, 134.7, 135.4, 141.9, 144.2, 144.4, 145.0, 149.4, 156.1, 158.8; IR (ATR) 3447, 2931, 1604, 1505, 1471, 1270, 1226, 1153, 1125, 1078, 1054, 998, 924, 813 cm⁻¹; EIMS *m*/*z* (relative intensity): 592 [M]⁺ (69), 560 (74), 435 (96) 361 (96), 211 (100); HR-EIMS *m*/*z*: $[M]^+$ calcd for C₃₂H₃₃BrO₆ 592.1461; found 592.1469.

4.18. 4-(3-(4-(2-Bromo-5-methoxyphenethyl)phenoxy)-4methoxyphenethyl)-2-(methoxymethoxy)phenyl trifluoromethanesulfonate (25)

To a solution of phenol 24 (35.9 mg, 60.6 μ mol) in DCM (1.00 mL) was added trifluoromethanesulfonic anhydride (12.0 μ L, 121 μ mol)

and DMAP (9.0 mg, 121 μ mol). After stirring at -78 °C for 1 h, the reaction mixture was guenched with satd NaHCO₃ and extracted with DCM. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with DCM/hexane (1:1) to give **25** (42.2 mg, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) § 2.80–2.95 (6H, m), 2.95–2.97 (2H, m), 3.49 (3H, s), 3.74 (3H, s), 3.83 (3H, s), 5.18 (2H, s), 6.68 (1H, dd, *J*=3.2, 8.8 Hz), 6.70 (1H, d, *J*=2.8 Hz), 6.73 (1H, d, *J*=1.6 Hz), 6.77 (1H, dd, *J*=2.4, 8.4 Hz), 6.84–6.91 (3H, m), 7.00 (1H, d, *J*=1.6 Hz), 7.09 (1H, d, *J*=8.4 Hz), 7.15 (2H, d, *J*=8.8 Hz), 7.42 (1H, d, *J*=8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 35.4, 36.4, 37.7, 38.7, 55.4, 56.1, 56.5, 95.0, 112.7, 113.4, 114.8, 116.1, 116.6, 117.4, 120.6, 122.0, 122.1, 124.2, 129.5, 133.3, 133.9, 135.6, 137.3, 141.8, 143.3, 145.2, 148.8, 149.6, 156.0, 158.9; IR (ATR) 2924, 2851, 1604, 1504, 1470, 1420, 1270, 1245, 1211, 1141, 1104, 1078, 992, 924, 880, 814, 773, 702 cm⁻¹; EIMS *m*/*z* (relative intensity): 724 [M]⁺ (20), 525 (40), 45 (100); HR-EIMS m/z: [M]⁺ calcd for C₃₃H₃₂BrF₃O₈S 724.0956; found 724.0989.

4.19. 4-(4-Methoxy-3-(4-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)phenoxy)phenethyl)-2-(methoxymethoxy)phenyl trifluoromethanesulfonate (26)

To a solution of 25 (12.0 mg, 166 µmol) in dioxane (1.00 mL) was added tetrakis(triphenylphosphine)palladium(0) (2.0 mg, 1.66 µmol), bis(pinacolato)diboron (8.4 mg, 332 µmol), and K₃PO₄ (10.5 mg, 500 µmol). After stirring at 100 °C for 12 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by preparative TLC eluted with hexane/EtOAc (4:1) to give **26** (10.4 mg, 81%) as a colorless oil. ¹H NMR (400 MHz, $CDCl_3$) δ 1.35 (12H, s), 2.79-3.15 (8H, m), 3.49 (3H, s), 3.80 (3H, s), 3.83 (3H, s), 5.18 (2H, s), 6.71 (1H, d, J=2.4 Hz), 6.74 (1H, dd, J=2.4, 8.4 Hz), 6.76 (1H, d, J=2.0 Hz), 6.77 (1H, dd, J=2.0, 8.4 Hz), 6.85 (1H, dd, J=2.0, 8.4 Hz), 6.86 (2H, d, J=8.4 Hz), 6.90 (1H, d, J=8.4 Hz), 7.01 (1H, d, J=2.0 Hz), 7.09 (1H, d, J=8.4 Hz), 7.21 (2H, d, J=8.4 Hz), 7.79 (1H, d, J=8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.9, 36.6, 37.6, 38.8, 38.9, 55.0, 56.1, 56.4, 83.2, 95.0, 110.6, 112.7, 115.2, 116.6, 117.1, 120.6, 121.9, 122.0, 124.1, 129.5, 133.9, 136.9, 137.3, 138.3, 143.3, 145.4, 148.8, 149.6, 151.4, 155.8, 161.8; IR (ATR) 2930, 1601, 1505, 1421, 1380, 1348, 1271, 1212, 1143, 1077, 1034, 994, 861, 612 cm⁻¹; EIMS *m*/*z* (relative intensity): 772 [M]⁺ (20), 615 (30), 525 (40), 359 (60), 45 (100); HR-EIMS *m*/*z*: [M]⁺ calcd for C₃₉H₄₄F₃O₁₀SB 772.2700; found 772.2712.

4.20. Dimethylmethoxymethylriccardin C (27)

To a solution of 26 (79.2 mg, 103 µmol) in DMF (100 mL) was added Na₂CO₃ (32.6 mg, 308 µmol), tris(dibenzylideneacetone) dipalladium(0) (9.4 mg, 10.3 µmol), and SPhos (8.3 mg, 20.7 µmol). After stirring at 100 °C for 15 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by HPLC eluted with hexane/EtOAc (9:1) to give 27 (36.5 mg, 72%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 2.52–2.62 (3H, m), 2.82–2.88 (3H, m), 2.95–2.99 (1H, m), 3.09-3.14 (1H, m), 3.33 (3H, s), 3.90 (3H, s), 3.94 (3H, s), 4.93 (1H, d, *J*=6.0 Hz), 5.00 (1H, d, *J*=6.0 Hz), 5.38 (1H, d, *J*=1.9 Hz), 6.25 (1H, dd, J=1.5, 7.5 Hz), 6.66 (1H, br), 6.72 (1H, d, J=1.5 Hz), 6.72 (1H, br), 6.77 (1H, br), 6.78 (1H, dd, *J*=1.9, 8.0 Hz), 6.82 (1H, br s), 6.83 (1H, d, J=7.5 Hz), 6.88 (1H, d, J=8.0 Hz), 6.91 (1H, br), 6.96 (1H, d, J=2.7 Hz), 7.04 (1H, d, J=8.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 35.7, 37.2, 37.9, 38.2, 55.2, 56.1, 56.2, 95.1, 111.4, 111.7, 115.2, 115.4, 116.6, 121.5, 122.3, 122.5, 123.5, 128.8, 129.0, 129.6, 131.1, 132.3, 132.5, 133.7, 139.6, 141.3, 143.2, 146.8, 148.5, 152.7, 153.8, 159.1; IR (ATR) 2931, 2840, 1605, 1505, 1442, 1420, 1395, 1261, 1230, 1152, 1128, 1077, 1012, 907, 851, 808, 730 cm⁻¹; EIMS *m*/*z* 497 [M+H]⁺ (51), 496 [M]⁺ (100), 451 (66), 225 (51); HR-EIMS *m*/*z*: [M]⁺ calcd for C₃₂H₃₂O₅ 496.2250; found 496.2250.

4.21. Dimethylriccardin C (28)

To a solution of 27 (39.0 mg, 81.6 µmol) in MeOH/EtOAc=2:1 (1.00 mL) was added Dowex[®]. After stirring at 70 °C for 3 h, the reaction mixture was filtered through Celite®535RVS and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/DCM (1:1) to give **28** (32.4 mg, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.60–2.81 (5H, m), 2.82-3.01 (2H, m), 3.03-3.16 (1H, m), 3.90 (3H, s), 3.94 (3H, s), 4.79 (1H, s), 5.42 (1H, d, *J*=2.1 Hz), 6.28 (1H, dd, *J*=1.6, 7.7 Hz), 6.43 (1H, d, J=1.6 Hz), 6.80 (6H, m), 6.88 (2H, dd, J=2.6, 8.4 Hz), 7.03 (1H, d, *I*=2.7 Hz), 7.10 (1H, d, *I*=8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 35.1, 37.0, 37.7, 38.2, 55.4, 56.0, 111.7, 112.6, 115.9, 116.3, 116.6, 121.4, 121.6, 122.5, 122.7, 124.5, 128.0, 129.0, 129.3, 131.5, 132.6, 133.8, 139.3, 142.0, 143.6, 146.8, 148.6, 151.9, 152.9, 160.0; IR (ATR) 3462, 2929, 2854, 1605, 1504, 1442, 1420, 1346, 1259, 1228, 1165, 1127, 1032, 983, 898, 851, 807, 734, 701 cm⁻¹; EIMS *m/z* 452 [M]⁺ (100), 255 (70); HR-EIMS m/z: [M]⁺ calcd for C₃₀H₂₈O₄ 452.1988; found m/z452.1990.

4.22. 10'-Iodo-dimethylriccardin C (29)

To a solution of $\boldsymbol{28}$ (13.4 mg, 29.6 $\mu mol)$ and NaI (4.50 mg, 30.0 µmol) and NaOH (4.6 mg, 32.9 µmol) in MeOH (1.00 mL) was added NaOCl (6.2 µL, 88.8 µmol). After stirring at rt for 3 h, the reaction mixture was quenched with aq Na₂S₂O₃ and 2 N HCl and extracted with DCM. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with toluene to give **29** (12.9 mg, 75%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 2.67-2.82 (4H, m), 2.90-3.03 (4H, m), 3.90 (3H, s), 3.95 (3H, s), 4.87 (1H, s), 5.36 (1H, d, J=2.1 Hz), 6.37 (1H, s), 6.79-6.91 (7H, m), 7.03 (1H, d, J=2.5 Hz), 7.09 (1H, d, J=9.0 Hz), 7.40 (1H, s); $^{13}{\rm C}$ NMR (125 MHz, CDCl_3) δ 35.0, 36.1, 38.2, 41.7, 55.4, 56.1, 89.3, 111.9, 112.7, 116.1, 116.7, 117.9, 121.7, 122.6, 122.9, 126.3, 127.3, 129.0, 129.3, 132.1, 133.1, 139.2, 141.6, 143.7, 143.9, 147.0, 149.0, 152.3, 153.0, 160.2; IR (ATR) 3458, 2947, 1605, 1506, 1420, 1383, 1261, 1230, 1127, 1046, 851, 734 cm⁻¹; EIMS *m*/*z* 578 [M]⁺ (100), 452 (28); HR-EIMS m/z: [M]⁺ calcd for C₃₀H₂₇O₄I 578.0954; found 578.0958.

4.23. 10'-Iodo-dimethylacetylriccardin C (30)

To a solution of 29 (7.0 mg, 12.1 µmol) and DMAP (1.5 mg, 12.2 µmol) in THF (1.00 mL) was added Ac₂O (2 µL, 21.2 µmol). After stirring at rt for 2 h, the reaction mixture was quenched with satd NaHCO3 and extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (4:1) to give 30 (7.3 mg, 97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.03 (3H, s), 2.64 (1H, dd, *I*=10.6, 10.6 Hz), 2.76–3.00 (7H, m), 3.88 (3H, s), 3.95 (3H, s), 5.27 (1H, d, J=2.0 Hz), 6.56 (1H, s), 6.76-6.82 (4H, m), 6.87 (1H, dd, J=2.8, 8.4 Hz), 6.89–6.93 (2H, m), 6.95 (1H, d, J=2.8 Hz), 6.97 (1H, d, J=8.8 Hz), 7.58 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 20.8, 35.3, 36.5, 38.2, 41.5, 55.3, 56.1, 97.6, 111.7, 112.0, 115.7, 121.8, 122.5, 122.7, 124.2, 127.8, 129.4, 129.5, 132.0, 132.8, 133.8, 139.5, 142.6, 143.0, 143.9, 147.0, 147.7, 149.1, 152.7, 159.8, 169.1; IR (ATR) 2933, 1762, 1606, 1506, 1470, 1365, 1260, 1231, 1200, 1150, 1128, 1046, 1010, 909, 852, 730 cm⁻¹; EIMS *m*/*z* 620 [M]⁺ (100), 578 (44); HR-EIMS *m*/*z*: [M]⁺ calcd for C32H29O5I 620.1060; found 620.1067.

4.24. Dimethylacetylcavicularin (31)

To a solution of **30** (4.0 mg, 6.45 μ mol) in DMF (1.00 mL) was added Ag₂CO₃ (1.8 mg, 7.09 μ mol), Pd(OAc)₂ (0.3 mg, 1.34 μ mol),

and *n*-Bu₃P (0.3 µL, 14.5 µmol). After stirring at 120 °C for 6 h, the reaction mixture was filtered through Celite[®]535RVS and concentrated in vacuo. The residue was purified by preparative TLC eluted with hexane/Et₂O (3:1) to give **31** (1.6 mg, 50%) as a colorless oil and **32** (1.0 mg, 31%) as a colorless oil. Compound **31**: ¹H NMR (500 MHz, CDCl₃) δ 2.30 (1H, ddd, *J*=3.0, 14.0, 14.0 Hz), 2.52 (1H, ddd, J=3.0, 12.0, 12.0 Hz), 2.64–2.78 (4H, m), 2.90 (2H, m), 3.87 (3H, s), 3.94 (3H, s), 6.01 (1H, dd, J=2.5, 8.5 Hz), 6.08 (1H, dd, J=2.0, 8.5 Hz), 6.40 (1H, dd, J=2.0, 8.5 Hz), 6.66 (1H, s), 6.73 (1H, dd, J=2.5, 8.5 Hz), 6.75 (1H, dd, J=2.5, 8.5 Hz), 6.79 (1H, d, J=8.5 Hz), 6.84 (1H, d, J=2.5 Hz), 6.85 (1H, s), 6.94 (1H, d, J=8.0 Hz), 7.04 (1H, d, *I*=8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 20.7, 29.7, 30.1, 30.3, 37.6, 38.1, 55.2, 56.7, 111.2, 111.5, 114.2, 115.4, 117.9, 119.8, 122.3, 123.8, 127.3, 129.4, 130.1, 130.3, 130.5, 130.7, 132.1, 133.1, 134.3, 139.3, 141.1, 145.6, 151.6, 154.4, 158.8, 168.8; IR (ATR) 2921, 2852, 1749, 1606, 1505, 1437, 1418, 1258, 1244, 1197, 1097, 1042, 805, 667, 637, 606 cm⁻¹; EIMS *m*/*z* 492 [M]⁺ (43), 450 (100), 359 (33); HR-EIMS m/z: [M]⁺ calcd for C₃₂H₂₈O₅ 492.1937; found 492.1931. Compound **32**: ¹H NMR (500 MHz, CDCl₃) δ 2.01 (3H, s), 2.56–2.74 (3H, m), 2.79-2.89 (3H, m), 2.96-3.08 (2H, m), 3.88 (3H, s), 3.95 (3H, s), 5.33 (1H, d, J=2.0 Hz), 6.51 (1H, dd, J=2.0, 7.5 Hz), 6.62 (1H, dd, J=2.0 Hz), 6.67 (1H, br d, J=8.0 Hz), 6.74 (1H, br d, J=8.0 Hz), 6.78 (1H, dd, J=2.0, 8.5 Hz), 6.79–6.82 (1H, m), 6.81 (1H, dd, J=2.0, 8.5 Hz), 6.89 (1H, d, J=8.5 Hz), 6.92 (1H, br s), 6.90-6.95 (1H, m), 6.94 (1H, d, *J*=7.5 Hz), 6.95 (1H, d, *J*=2.0 Hz), 6.99 (1H, d, *J*=8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 20.8, 35.3, 37.2, 37.6, 38.2, 55.3, 56.1, 111.5, 115.5, 115.8, 116.5, 121.5, 122.3, 122.5, 122.8, 127.5, 129.2, 129.5, 129.7, 131.5, 132.2, 132.4, 133.4, 139.5, 141.4, 142.5, 146.9, 147.4, 148.5, 152.8, 159.4, 169.3; IR (ATR) 2927, 2855, 1761, 1606, 1505, 1420, 1368, 1261, 1231, 1203, 1128, 1014, 920, 810, 731, 639 cm^{-1} ; EIMS *m*/*z* 494 [M]⁺ (92), 452 (100), 225 (60); HR-EIMS *m*/*z*: [M]⁺

4.25. Determination of ee by HPLC

calcd for C₃₂H₃₀O₅ 494.2093; found 494.2106.

Column=Kromasil 3-CelluCoat 150 mm×4.6 mm, hexane/ iPrOH=10:1, flow rate=1 mL/min.

4.26. Cavicularin (2)

To a solution of **31** (1.2 mg, 2.43 µmol) in MeOH (1.00 mL) was added K_2CO_3 (1.0 mg, 7.31 µmol). After stirring at rt for 5 h, the reaction mixture was guenched with 2 N HCl and extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (4:1) to give dimethylcavicularin (1.1 mg) as colorless oil. Subsequently, to a cooled solution of dimethylcavicularin (1.8 mg, 39.9 µmol) in DCM (1.00 mL) was added BBr₃ (1 M DCM solution, 10.2 µL, 10.2 µmol). After stirring at rt for 24 h, the reaction mixture was guenched with H₂O and extracted with DCM. The combined extracts were washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/EtOAc (7:3) to give 2 (1.2 mg, 71% over two steps) as an amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 2.28 (1H, ddd, J=3.5, 12.5, 14.0 Hz), 2.55 (1H, ddd, J=3.5, 12.5, 14.0 Hz), 2.63–2.78 (4H, m), 2.92–2.98 (2H, m), 4.75 (1H, s), 4.85 (1H, s), 6.10 (1H, dd, *J*=2.5, 8.5 Hz), 6.12 (1H, s), 6.15 (1H, dd, *J*=2.5, 8.5 Hz), 6.40 (1H, s), 6.47 (1H, dd, J=2.5, 8.5 Hz), 6.68 (1H, s), 6.72 (1H, dd, J=2.5, 8.5 Hz), 6.76 (1H, dd, J=2.5, 8.5 Hz), 6.83 (1H, d, J=8.5 Hz), 6.88 (1H, d, J=2.5 Hz), 6.94 (1H, d, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 30.2, 30.5, 37.4, 38.1, 113.0, 113.3, 114.7, 115.1, 116.9, 117.8, 123.0, 123.3, 124.0, 124.0, 127.8, 128.9, 130.0, 131.1, 131.7, 131.7, 135.0, 138.5, 140.5, 141.6, 147.9, 150.2, 153.8, 155.5; IR (ATR) 3394, 2923, 2853, 1605, 1505, 1438, 1238, 1185, 995,

815, 720, 636, 618, 607 cm⁻¹; EIMS m/z 420 [M]⁺ (100), 331 (35); HR-EIMS *m*/*z*: [M]⁺ calcd for C₂₈H₂₂O₄ 422.1518; found 422.1521.

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Supplementary data

¹H and ¹³C NMR spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.064.

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