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A Corey-Seebach Macrocyclisation Strategy for the Synthesis of Riccardin C and an Unnatural Macrocyclic Bisbibenzyl Analogue

Faisal A. Almalki[a] and David C. Harrowven*[a]

Abstract: A total synthesis of riccardin C has been accomplished using a Corey-Seebach reaction to effect macrocyclisation. The versatility of the strategy has also been demonstrated with a mimetic synthesis of an unnatural bisbibenzyl analogue.

Keywords: natural products • total synthesis • macrocyclisation • synthesis (org.) • Corey-Seebach

Introduction

Macrocyclic bisbibenzyl natural products have largely been found in liverworts and other bryophytes,[1,2] with riccardin C **10** alone in being identified in a higher plant species.[3,4] In Nature, all are derived from lunularin **4** (Figure 1).[5] First, an oxidative dimerisation leads to perrottetin E **3** or isoperrottetin A **6**. Then, related oxidative biaryl or biaryl ether formation occurs leading to the macrocyclic cores **1**, **2**, **7** and **8** of the different familial groups.[1,2,5] Siblings are then derived by benzylic or arene oxidation, phenolic methylation, oxidative dimerisation or further oxidative cyclisation (*e.g.* **10** → cavicularin **9** and asterelin A **11**,[6,7] Figure 2).

The largest familial group is based on macrocyclic core **2** and has riccardin C **10** at its helm (Figures 1 and 2).[3,4] A popular synthetic target for many years,[8–14] riccardin C recently gained prominence when a screen seeking new leads against cardiovascular disease found that it acted as an agonist for the cholesterol-regulating liver X receptor LXRα and an antagonist for LXRβ.[11] Indeed, it has been tested in many pharmacological screens,[1,2] to reveal antifungal,[15] antibacterial,[16] and cytotoxic activity against various cancer cell lines.[17] A limited number of structure-activity relationships have also been conducted, largely based on isolated natural products and simple analogues derived therefrom.[11,18]

Herein, we show how convergent synthesis can unlock pathways to analogues with and without precedent in Nature, as demonstrated by syntheses of riccardin C and the unnatural analogue **5**. Although the ring system in **5** has a similar constitution to those found in Nature, the biaryl bond linking arenes B and D is not consistent with macrocyclic bisbibenzyl biosynthesis as in natural products these rings are necessarily bound within the macrocycle via *ortho*- and *para*-linkages.[1,2,5] Through the simple expedient of activating either the *ortho*- or the *meta*-carbon in arene D, we were able to gain access to both a natural and an unnatural product series respectively (Schemes 1 and 2).

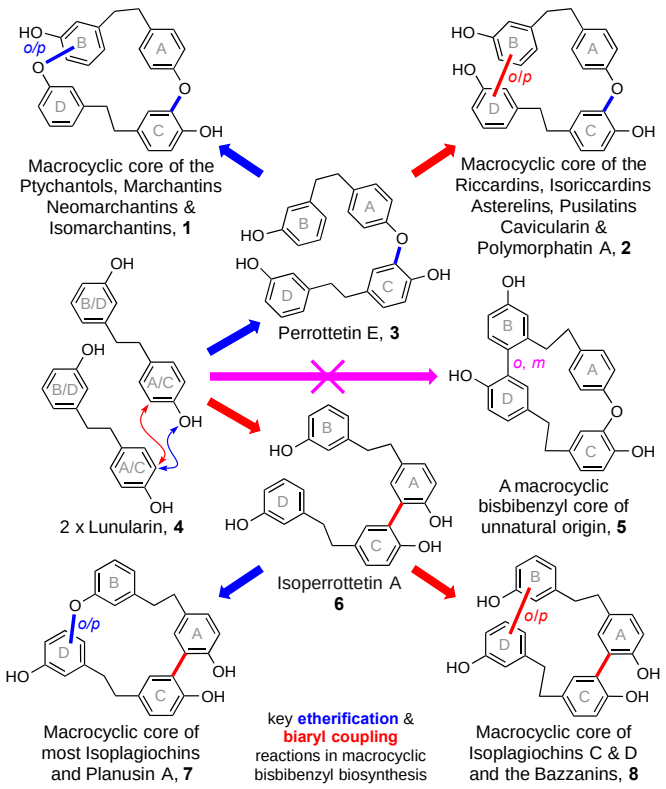

Figure 1. Structural relationships in macrocyclic bisbibenzyl natural products and the unnatural analogue herein targeted by synthesis.

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Mindful of the fact that syntheses of riccardin C **10** proceeding via macrocycle **12** also constitute formal total syntheses of cavicularin **9**[10,12,13,19,20] and asterelin A **11** (Figure 2),[21] we decided to deploy an orthogonal protecting group strategy for the phenol in arene D to those in arenes B and C. In previous syntheses several strategies have been developed to tackle the challenge of forming its 18-membered ring (Figure 1).[8–14,20] These include macrocyclisation protocols using Wurtz,[8] Wittig[9-11] and McMurry[11,12] reactions to effect closure via either of the ethano bridges; Pd(0) cross-coupling[13] and S_NAr[14] reactions for closure via the biaryl or biaryl ether linkages and two approaches to cavicularin based on the *de novo* construction of a arene A.[20] Herein we report a new strategy wherein a Corey-Seebach reaction[22-24] is used to achieve the critical macrocyclisation step.[25] Importantly, while this reaction has been widely use in macrocycle synthesis,[22-24] its use in the context of macrocyclisation is extremely rare.[25]

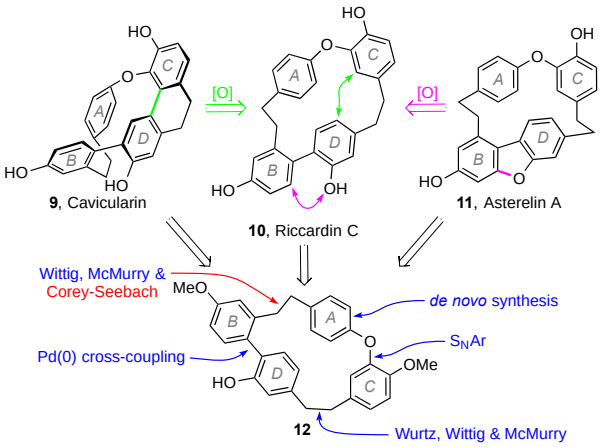


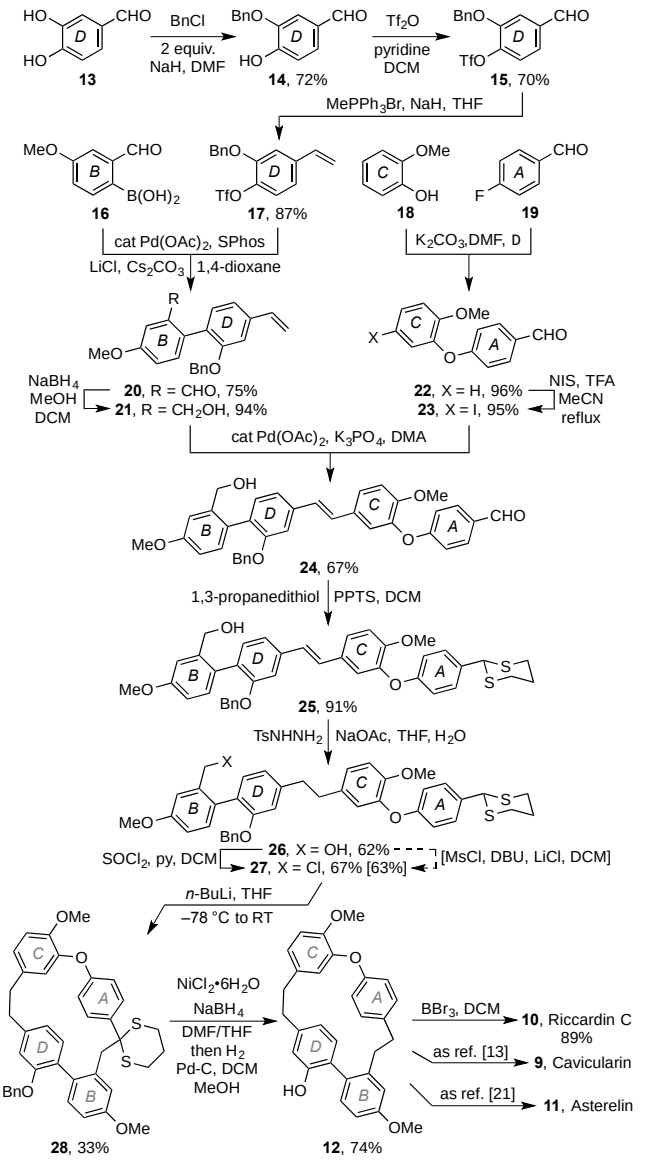
Figure 2. Macrocyclisation strategies used to prepare riccardin C (blue), the approach detailed herein (red) and formal syntheses by intersection with **12**.

Results and Discussion

Development of a Convergent Synthesis.

Drawing on previous experience,[10,12] we identified arenes **16**-**19** as the key building blocks required for our synthesis, as all but arene **17** were products of commerce (Scheme 1). Moreover, the synthesis of **17** from catechol **13** was readily achieved by sequential benzylation, triflation and Wittig methylenation using standard protocols. In the first step we found that 2 equivalents of NaH were needed to achieve optimal regioselectivity while in the third step its use prevented triflate hydrolysis, as observed when employing KOtBu.

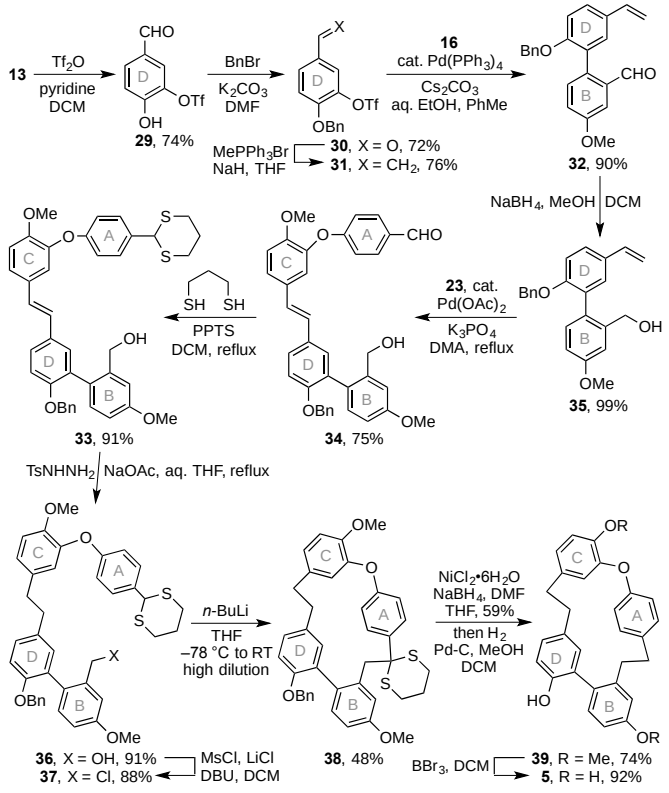
The stage was now set to assemble the macrocyclisation precursor **27**. First, union of arenes D and B, **16** and **17**, was accomplished by means of a Suzuki–Miyaura coupling[26] then the resulting biaryl aldehyde **20** was reduced to benzyl alcohol **21**. Contemporaneously, arenes C and A, **18** and **19**, were advanced to biaryl ether **23** using the known S_NAr and iodination sequence.[12] At this juncture various permutations were examined to advance the synthesis. The most convenient involved coupling of alcohol **21** and aldehyde **23** prior to installation of the dithiane unit (Scheme 1). In this way the Heck reaction leading to tetraarene **25** could be realised in a good yield consistently using catalytic $Pd(OAc)_2$ under ligand-free conditions.[27] Indeed, the yield given was almost twice that attained when the order of these steps was reversed. Alkene reduction to **26** was next facilitated by diimide,[10,12] then the alcohol was transformed into chloride **27** through the action of MsCl or $SOCl_2$ (Scheme 2). Though the former proved capricious when using 2,6-lutidine as base, a good yield was attained using DBU with LiCl.[28]



Scheme 1. Total synthesis of riccardin C and formal total syntheses of cavicularin and asterelin A.

The stage was now set to examine the macrocyclisation step.[25] Pleasingly, deprotonation of dithiane **27** with BuLi at –78 °C, followed by warming to ambient temperature, gave the requisite macrocycle **28** in 33% yield. Reductive removal of the dithiane[29] and benzyl ether functions then gave riccardin C dimethyl ether **12** from which riccardin C **10** was readily prepared by deprotection with boron tribromide. As routes to cavicularin **9**[19] and asterelin A **11**[22] have been described from **12**, the approach also constitutes formal total syntheses of those natural products.

Having demonstrated the applicability of the convergent 'plug and play' strategy in natural product target synthesis, we next sought to show how it could be adapted to give access to an unnatural macrocyclic bisbibenzyl motif such as **5**. To that end, we re-ran the entire synthesis using the regioisomeric styrene **31** in place of the arene D component **17** (Scheme 2). Pleasingly, we were able to mirror every step in the synthesis and achieved an improved outcome for the Corey-Seebach marcocyclisation, **37** → **38**, which was realised in 48% yield.



Scheme 2. A re-run of the synthesis with regioisomeric styrene **32** to prepare the unnatural macrocyclic bisbibenzyl analogue **5**.

Conclusion

In summary, a total synthesis of riccardin C **10** has been developed in which macrocyclisation was achieved by means of a Corey-Seebach reaction (Scheme 1). Importantly, while that reaction is synonymous with the assembly of macrocyclic products,[23,24] its use in the context of macrocyclic ring closure is extremely rare.[25] We have also shown how the convergent nature of our synthesis allows it to be used as a template to build related macrocyclic bisbibenzyls, as exemplified by our mimetic synthesis of the unnatural analogue **5** (Scheme 2).

Experimental Section

*2-(Benzyloxy)-4-formylphenyl trifluoromethanesulfonate (**15**):* To a cooled (0 °C) solution of phenol **14**[30] (110 mg, 0.48 mmol) and pyridine (0.046 mL, 0.57 mmol) in DCM (2 mL) was added Tf_2O (0.088 mL, 0.52 mmol). After 5 h at RT the reaction mixture was concentrated *in vacuo* and purified by column chromatography (20% Et_2O/petrol) to afford the *title compound* **15** as a colourless oil (120 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.51–7.47 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.46–7.35 (m, 3H), 5.26 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2 (CH), 151.3 (C), 142.8 (C), 136.7 (C), 134.8 (C), 128.7 (2 × CH), 128.5 (CH), 127.4 (2 × CH), 124.1 (CH), 123.2 (CH), 118.6 (q, *J* = 320.6 Hz, CF_3), 113.1 (CH), 71.4 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.83 ppm; IR (film): ν 2838, 1701, 1602, 1497, 1423, 1381, 1205, 1136, 1100, 1007, 871, 736 cm^{-1}; MS (EI$^+$) *m/z* (%): 360 (M^+, 2%), 108 (5%), 108 (30%), 91 (100%); HRMS (EI): *m/z* calcd for $C_{15}H_{11}O_5F_3S$ $[M]^+$ 360.02738; found: 360.02703.

*2-(Benzyloxy)-4-vinylphenyl trifluoromethanesulfonate (**17**):* To a cooled (0 °C) solution of aldehyde **15** (8.25 g, 22.89 mmol) in THF (230 mL) were added sequentially 60% sodium hydride in mineral oil (2.75 g, 68.69 mmol) and methyltriphenylphosphonium bromide (12.26 g, 34.33 mmol). After 18 h at RT the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (10% Et_2O/petrol) to afford the *title compound* **17** as a colourless oil (7.20 g, 87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (br d, *J* = 8.7 Hz, 2H), 7.46–7.34 (m, 3H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.68 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.74 (d, *J* = 17.5 Hz, 1H), 5.35 (d, *J* = 10.9 Hz, 1H), 5.21 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (C), 138.9 (C), 138.3 (C), 135.6 (C), 135.4 (CH), 128.6 (2 × CH), 128.2 (CH), 127.3 (2 × CH), 122.4 (CH), 119.1 (CH), 115.9 (CH_2), 118.7 (q, *J* = 320.6 Hz, CF_3), 111.9 (CH), 71.0 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.95 ppm; IR (film): ν 3035, 1596, 1502, 1418, 1275, 1247, 1203, 1179, 1137, 1101, 1010, 869 cm^{-1}; MS (EI$^+$) *m/z* (%): 358 (M^+, 12%), 91 (100%); HRMS (EI): *m/z* calcd for $C_{16}H_{13}O_4F_3S$ $[M]^+$ 358.04812; found: 358.04732.

*2'-(Benzyloxy)-4-methoxy-4'-vinyl-[1,1'-biphenyl]-2-carbaldehyde (**20**):* To a solution of triflate **17** (100 mg, 0.27 mmol) and boronic acid **16** (98.9 mg, 0.55 mmol) in 1,4-dioxane (2 mL) was added Cs_2CO_3 (340 mg, 1.06 mmol), LiCl (110 mg, 2.67 mmol) and SPhos (43 mg, 0.1 mmol). The resulting mixture was degassed under argon for 15 min then $Pd(OAc)_2$ (2.4 mg, 0.01 mmol) was added. After heating at reflux for 3 h, the reaction was cooled to RT and water (5 mL) added. The aqueous phase was extracted with EtOAc (3 × 10 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (10% Et_2O/petrol) to afford the title compound **20** as a white solid (74 mg, 75%); MP 76–77 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.34–7.31 (m, 2H), 7.30–7.28 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.23–7.19 (m, 3H), 7.15 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.79 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.9 Hz, 1H), 5.07 (s, 2H), 3.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4 (CH), 159.2 (C), 156.1 (C), 139.2 (C), 136.5 (C), 136.4 (CH), 135.0 (C), 134.6 (C), 132.5 (CH), 131.9 (CH), 128.5 (2 × CH), 127.8 (CH), 126.9 (2 × CH), 126.9 (C), 121.1 (CH), 119.4 (CH), 114.7 (CH_2), 110.4 (CH), 109.5 (CH), 70.6 (CH_2), 55.6 (CH_3) ppm; IR (solid): ν 2932, 2851, 1687, 1603, 1486, 1458, 1416, 1393, 1316, 1271, 1241, 1162, 1136, 1038 cm^{-1}; MS (EI$^+$) *m/z* (%): 344 (M^+, 3%), 237 (35%), 91 (100%); HRMS (EI): *m/z* calcd for $C_{23}H_{20}O_3$ $[M]^+$ 344.14070; found: 344.14146.

*(2'-(Benzyloxy)-4-methoxy-4'-vinyl-[1,1'-biphenyl]-2-yl)methanol (**21**):* To a suspension of aldehyde **20** (1.69 g, 4.91 mmol) in methanol (25 mL) and DCM (25 mL) at 0 °C was added $NaBH_4$ (370 mg, 9.82 mmol). The reaction mixture warmed to RT and after 4 h, water (20 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 50 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (40% Et_2O/petrol) to afford the *title compound* **21** as a colourless oil (1.60 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 3H), 7.25–7.14 (m, 7H), 6.96 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.78 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.81 (d, *J* = 17.5 Hz, 1H), 5.34 (d, *J* = 10.9 Hz, 1H), 5.05 (s, 2H), 4.47 (br, 2H), 3.91 (s, 3H), 2.24 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C), 155.9 (C), 140.8 (C), 138.3, (C) 136.5 (CH), 136.4 (C), 131.7 (CH), 131.3 (CH), 130.3 (C), 129.4 (C), 128.5 (2 × CH), 127.9 (CH), 127.1 (2 × CH), 119.8 (CH), 114.2 (CH_2), 113.4 (CH), 113.2 (CH), 111.5 (CH), 71.2 (CH_2), 63.6 (CH_2), 55.3 (CH_3) ppm; IR (film): ν 3420 br, 3008, 2937, 1604, 1485, 1271, 1232, 999, 908, 749 cm^{-1}; MS (EI$^+$) *m/z* (%): 346 (M^+, 5%), 239 (70%), 91 (100%); HRMS (EI): *m/z* calcd for $C_{23}H_{22}O_3$ $[M]^+$ 346.15635; found: 346.15576.

*4-(5-Iodo-2-methoxyphenoxy)benzaldehyde (**23**):*[10] To a solution of benzaldehyde **22**[10,31] (100 mg, 0.44 mmol) in MeCN (3 mL) were added trifluoroacetic acid (0.009 mL, 0.13 mmol) and *N*-iodosuccinimide (110 mg, 0.48 mmol). The reaction was heated at reflux for 13 h then cooled to RT and ice water (2 mL) was added. The product was extracted with Et_2O (3 × 5 mL), then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (10-20% Et_2O/petrol) to afford the *title compound* **23** as an orange gum that crystallised on standing (0.14 g, 90%); MP 48–49 °C (Et_2O/petrol) [Lit. 48 °C (CH_2Cl_2)[10]]; all spectroscopic and physical data matched that previously reported.

*(E)-4-(5-(2-(2-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (**24**):* A solution of styrene **21** (1.51 g, 4.36 mmol), iodide **23** (1.40 g, 3.96 mmol) and potassium phosphate (1.18 g, 5.54 mmol) in DMA (5 mL) was degassed by sonication for 20 min under argon then $Pd(OAc)_2$ (44 mg, 0.19 mmol) was added. The reaction mixture was heated at 110 °C for 18 h then cooled to RT, concentrated *in vacuo* and purified by column chromatography (50% Et_2O/petrol) to afford the *title compound* **24** as a white solid (1.53 g, 67 %) MP 66–67 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.31–7.27 (m, 3H), 7.23–7.16 (m, 5H), 7.14 (d, *J* = 2.7 Hz, 1H), 7.09–7.01 (m, 5H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.05 (s, 2H), 4.46 (br s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 2.16 (t, *J* = 6.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7 (CH), 163.4 (C), 159.3 (C), 156.1 (C), 151.3 (C), 143.1 (C), 140.8 (C), 138.0 (C), 136.4 (C), 131.9 (3 × CH), 131.3 (CH), 131.1 (C), 131.0 (C), 130.1 (C), 129.4 (C), 128.5 (2 × CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 127.1 (2 × CH), 125.0 (CH), 120.0 (CH), 119.9 (CH), 116.2 (2 × CH), 113.4 (CH), 113.3 (CH), 113.1 (CH), 111.6 (CH), 71.3 (CH_2), 63.7 (CH_3), 56.0 (CH_2), 55.3 (CH_3) ppm; IR (neat): ν 3447 br, 2925, 2852, 1690, 1598, 1573, 1503, 1460, 1423, 1271, 1227, 1155, 1123, 1024; MS (ESI$^+$) *m/z* (%): 595 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{37}H_{32}NaO_6$ $[M+Na]^+$ 595.2091; found: 595.2077.

*(E)-(4'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (**25**):* A solution of arene **24** (1.31 g, 2.28 mmol), propan-1,3-dithiol (0.69 mL, 6.84 mmol) and PPTS (130 mg, 0.54 mmol) in DCM (35 mL) were heated at reflux for 18 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (60% Et_2O/petrol) afforded the *title compound* **25** as a white solid (1.39 g, 91%); MP 72–73 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 2H), 7.34–7.25 (m, 4H), 7.23 (d, *J* = 2.1 Hz, 1H), 7.20–7.13 (m, 6H), 7.11 (d, *J* = 2.6 Hz, 1H), 7.06–6.97 (m, 3H), 6.97–6.93 (m, 2H), 6.91 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.18 (s, 1H), 5.03 (br s, 2H), 4.43 (br s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.12–3.03 (m, 2H), 2.92 (app. td, *J* = 14.0, 3.8 Hz, 2H), 2.19 (m, 1H), 2.09 (t, *J* = 6.1 Hz, 1H), 1.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C), 158.0 (C), 156.0 (C), 151.4 (C), 144.6 (C), 140.8 (C), 138.2 (C), 136.5 (C), 133.1 (C), 131.8 (CH), 131.3 (CH), 130.8 (C), 129.9 (C), 129.5 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.0 (CH), 127.9 (CH), 127.2 (2 × CH), 127.1 (CH), 123.8 (CH), 119.9 (CH), 119.2 (CH), 116.9 (2 × CH), 113.4 (CH), 113.3 (CH), 112.9 (CH), 111.6 (CH), 71.3 (CH_2), 63.8 (CH_2), 56.1 (CH_3), 55.3 (CH_3), 50.8 (CH), 32.2 (2 × CH_2), 25.0 (CH_2) ppm; IR (solid): ν 3437 br, 2933, 1602, 1503, 1441, 1422, 1272 , 1227, 1167, 1025; MS (ESI+) *m/z* (%): 685

([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{38}NaO_5S_2$ [M+Na]$^+$ 685.2053; found: 685.2061.

(4'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxyphenethyl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol ***(26)****:* A solution of stilbene **25** (100 mg, 0.15 mmol), tosylhydrazone (290 mg, 1.57 mmol) and NaOAc (130 g, 1.57 mmol) in 1:1 v/v THF and water (2 mL each) was heated at reflux for 18 h then cooled to RT. Water (5 mL) and HCl (2M, 2 mL) were added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (30% EtOAc/petrol) to afford the *title compound* **26** as a white solid (62 mg, 62%); MP 78–79 °C (EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.6 Hz, 2H), 7.30–7.26 (m, 3H), 7.18–7.06 (m, 5H), 6.99–6.81 (m, 8H), 5.15 (s, 1H), 4.95 (br s, 2H), 4.40 (br s, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.07 (br t, *J* = 13.1 Hz, 2H), 2.97–2.84 (m, 6H), 2.21 (br s, 1H), 2.15 (m, 1H), 1.95 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C), 158.2 (C), 155.7 (C), 149.9 (C), 144.0 (C), 142.4 (C), 140.8 (C), 136.6 (C), 134.7 (C), 132.8 (C), 131.4 (CH), 131.4 (CH), 129.7 (C), 129.0 (2 × CH), 128.5 (2 × CH), 128.3 (C), 127.8 (CH), 127.2 (2 × CH), 125.0 (CH), 121.9 (CH), 121.8 (CH), 116.7 (2 × CH), 114.3 (CH), 113.4 (CH), 113.3 (CH), 112.9 (CH), 71.3 (CH_2), 63.8 (CH_2), 56.1 (CH_3), 55.3 (CH_3), 50.8 (CH), 37.9 (CH_2), 36.8 (CH_2), 32.2 (2 × CH_2), 25.1 (CH_2) ppm; IR (solid): ν 3437 br, 2933, 1602, 1503, 1422, 1272, 1227, 1167, 1126, 1025; MS (ESI$^+$) *m/z* (%): 687 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{40}O_5S_2$ [M+Na]$^+$ 687.2209; found: 687.2201.

2-(4-(5-(2-(2-(Benzyloxy)-2'-(chloromethyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)-2-methoxyphenoxy)phenyl)-1,3-dithiane ***(27)****:* To a solution of benzyl alcohol **26** (75 mg, 0.11 mmol) and pyridine (0.013 mL, 0.16 mmol) in DCM (5 mL) at 0 °C was added thionyl chloride (0.012 mL, 0.16 mmol). The temperature was raised to RT and after 18 h, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (30% Et_2O/petrol) to afford the *title compound* **27** as a white solid (51 mg, 67%).
Alternatively, to a solution of benzyl alcohol **26** (0.25 g, 0.37 mmol) in DCM (18 mL) was added DBU (0.17 g, 1.12 mmol), LiCl (157 mg, 0.37 mmol) and MsCl (0.12 g, 1.12 mmol). After 18 h the reaction mixture was concentrated in *vacuo* and purified by column chromatography (30% Et_2O/petrol) to afford the *title compound* **27** as a colourless oil (0.16 g, 63%); MP 59–60 °C (EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.7 Hz, 2H), 7.31–7.24 (m, 3H), 7.19–7.13 (m, 4H), 7.11 (d, *J* = 2.7 Hz, 1H), 6.96–6.82 (m, 7H), 6.79 (d, *J* = 0.8 Hz, 1H), 5.15 (s, 1H), 4.98 (s, 2H), 4.44 (br, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.12–3.01 (m, 2H), 2.95–2.83 (m, 6H), 2.18 (m, 1H), 1.91 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C), 158.2 (C), 155.6 (C), 149.9 (C), 144.1 (C), 142.6 (C), 137.2 (C), 137.1 (C), 134.7 (C), 132.8 (C), 131.9 (CH), 131.5 (CH), 130.5 (C), 129.0 (2 × CH), 128.4 (2 × CH), 127.5 (CH), 127.1 (C), 126.7 (2 × CH), 125.0 (CH), 121.9 (CH), 121.2 (CH), 116.7 (2 × CH), 114.4 (CH), 113.9 (CH), 113.5 (CH), 112.8 (CH), 70.3 (CH_2), 56.1 (CH_3), 55.3 (CH_3), 50.8 (CH), 44.8 (CH_2), 37.9 (CH_2), 36.8 (CH_2), 32.2 (2 × CH_2), 25.1 (CH_2) ppm; IR (solid): ν 2932, 1605, 1577, 1501, 1270, 1223, 1166, 908, 729; MS (ESI$^+$) *m/z* (%): 707 ([M{^{37}Cl}+Na]$^+$, 40%), 705 ([M{^{35}Cl}+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{40}H_{39}ClNaO_4S_2$ [M+Na]$^+$ 705.1870; found: 705.1857.

1,2,3,17,18,29-Hexahydro-21-Benzyloxy-13,26-dimethoxy-1,5-dithia-11-oxa-7,10-etheno-12,16-metheno-19,22-ethenobenzo[w]spiro[5,19]pentacosadodecaene ***(28)****:* To a solution of dithiane **27** (120 mg, 0.18 mmol) in THF (15 mL) at –78 °C was added *n*-BuLi (2.44 M in hexanes, 0.1 mL, 0.24 mmol). The reaction mixture was slowly warmed to RT and after 18 h sat. NH_4Cl (5 mL) and water (10 mL) were added. The aqueous phase was separated and extracted with Et_2O (3 × 20 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (30% Et_2O/petrol) to afford the *title compound* **28** as a white solid (34 mg, 33%); MP 83–85 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (br s, 1H), 7.55 (br s, 1H), 7.33–7.24 (m, 4H), 7.21–7.17 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.88–6.78 (m, 5H), 6.52 (d, *J* = 1.3 Hz, 1H), 6.34 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.69 (d, *J* = 2.1 Hz, 1H), 4.87 (br, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.48 (s, 2H), 2.90–2.77 (br, 2H), 2.76–2.63 (br, 2H), 2.61–2.45 (br, 4H), 2.19–1.88 (br, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5 (C), 154.8 (C), 153.3 (C), 147.6 (C), 147.1 (C), 141.2 (C), 139.4 (C), 137.1 (C), 133.8 (C), 133.7 (C), 133.4 (C), 132.1 (CH), 131.7 (CH), 130.3 (CH), 129.5 (CH), 128.4 (C), 128.3 (2 × CH), 127.5 (CH), 126.8 (2 × CH), 122.5 (CH), 122.1 (CH), 122.1 (CH), 121.6 (CH), 118.5 (CH), 116.7 (CH), 113.5 (CH), 113.3 (CH), 112.0 (CH), 70.1 (CH_2), 58.6 (C), 56.2 (CH_3), 55.4 (CH_3), 49.8 (CH_2), 37.6 (CH_2), 36.4 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 25.1 (CH_2) ppm; IR (solid): ν 2926, 1604, 1513, 1494, 1420, 1261, 1230, 1165, 1128, 733; MS (ESI$^+$) *m/z* (%): 669 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{40}H_{38}NaO_4S_2$ [M+Na]$^+$ 669.2104; found: 669.2098.

Riccardin C dimethyl ether ***(12)****:*[19,21] To a solution of $NiCl_2.6H_2O$ (170 mg, 0.74 mmol) in DMF (1 mL) was added sequentially a solution of dithiane **28** (30 mg, 0.046 mmol) in THF (1 mL) and $NaBH_4$ (55 mg, 1.47 mmol). After 18 h, the mixture was filtered through Celite© and water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was next dissolved in EtOH (3 mL) and DCM (3 mL) and 10% Pd-C (4.8 mg) was added. The flask was evacuated and purged with argon three times then evacuated and filled with hydrogen twice. After a further 18 h, the reaction mixture was filtered through Celite©, concentrated *in vacuo* and purified by column chromatography (35% Et_2O/hexane) to afford the *title compound* **12** as a white solid (15 mg, 71%); MP 140–141 °C (Et_2O/hexane) [Lit. oil,[19]]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.92–6.76 (m, 5H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.78 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.44 (d, *J* = 0.7 Hz, 1H), 6.30 (d, *J* = 7.6 Hz, 1H), 5.44 (d, *J* = 1.5 Hz, 1H), 4.79 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.15–3.02 (m, 1H), 3.02–2.83 (m, 2H), 2.83–2.58 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C), 153.0 (C), 151.9 (C), 148.6 (C), 146.9 (C), 143.6 (C), 142.0 (C), 139.3 (C), 133.8 (C), 132.5 (CH), 131.5 (CH), 129.3 (CH), 129.3 (CH), 128.0 (C), 124.5 (C), 122.7 (CH), 122.5 (CH), 121.6 (CH), 121.4 (CH), 116.6 (CH), 116.3 (CH), 115.9 (CH), 112.6 (CH), 111.8 (CH), 56.1 (CH_3), 55.3 (CH_3), 38.2 (CH_2), 37.7 (CH_2), 37.0 (CH_2), 35.2 (CH_2) ppm; IR (solid): ν 3467 br, 2927, 2853, 1605, 1506, 1420, 1260, 1229, 1164, 1127; MS (ESI$^+$) *m/z* (%): 453 ([M+H]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{30}H_{29}O_4$ [M+H]$^+$ 453.2060; found: 453.2060.

Riccardin C ***(10)****:* To a solution of riccardin C dimethyl ether **12** (7.5 mg, 0.016 mmol) in DCM (2 mL) was added boron tribromide (1 M solution in DCM, 0.16 mL, 0.16 mmol). After 5 h, water (5 mL) was added then the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (60% Et_2O/petrol) to afford the *title compound* **10** as a white solid (4.9 mg, 71%). All spectroscopic and physical data matched that previously reported by us and others.[3,4,8–14]

5-Formyl-2-hydroxyphenyl trifluoromethanesulfonate ***(29)****:* To a cooled (0 °C) solution of phenol **13** (10.0 g, 72.4 mmol) and pyridine (7.03 mL, 86.88 mmol) in DCM (240 mL) was added Tf_2O (12.18 mL, 72.4 mmol) over 5 min. The reaction was allowed to warm to RT and after 13 h, sat. NH_4Cl (100 mL) and water (100 mL) were added. The aqueous phase was separated and extracted with DCM (3 × 100 mL), then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (50% Et_2O/cyclohexane) to afford the *title compound* **29** as a colourless oil (14.65 g, 74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.03 (s, 1H), 8.04 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.3 (CH), 144.2 (C), 141.2 (C), 136.9 (C), 130.7 (CH), 124.5 (CH), 123.7 (CH), 118.5 (q, *J* = 320.6 Hz, CF_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.83 ppm; IR (film): ν 3528, 2979, 1605, 1417, 1205, 1134, 1096, 907, 864 cm^{-1}; MS (EI$^+$) *m/z* (%): 270 (M$^+$, 4%), 149 (87%), 69 (100%).

2-(Benzyloxy)-5-formylphenyl trifluoromethanesulfonate ***(30)****:* To a solution of **29** (22.5 g, 83.28 mmol) in MeCN (200 mL) were added potassium carbonate (17.26 g, 124.92 mmol) and benzyl bromide (11.89 mL, 99.94 mmol). After 13 h, water (100 mL) and Et_2O (50 mL) were added. The aqueous phase was separated and extracted with Et_2O (2 × 50 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (20-25% Et_2O/petrol) to afford the *title compound* **30** as an orange oil (17.1 g, 72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 7.85 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.49–7.35 (m, 5H), 7.22 (d, *J* = 8.5 Hz, 1H), 5.29 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0 (CH), 155.4 (C), 139.3 (C), 134.5 (C), 131.8 (CH), 130.1 (C), 128.8 (2 × CH), 128.6 (C), 127.3 (2 × CH), 123.0 (CH), 114.2 (CH), 118.6 (q, *J* = 320.6 Hz,CF_3), 71.6 (CH_2) ppm; IR (film): ν 1697, 1607, 1508, 1423, 1318, 1278, 1247, 1209, 1137, 1090, 905, 725 cm^{-1}; MS (ESI$^+$) *m/z* (%): 361 (MH$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{15}H_{11}F_3NaO_5S$ [M+Na]$^+$ 383.0171; found: 383.0180.

2-(Benzyloxy)-5-ethenylphenyl trifluoromethanesulfonate ***(31)****:* To a cooled (0 °C) solution of aldehyde **30** (5.00 g, 13.88 mmol) in THF (125 mL) were added sequentially sodium hydride (1.66 g, 41.63 mmol) and methyltriphenylphosph-onium bromide (7.43 g, 20.82 mmol). The reaction mixture was warmed to RT and after 30 min was concentrated *in vacuo* and purified by column chromatography (5–10% Et_2O/petrol) to afford the *title compound* **31** as a yellow oil (3.81 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.35–7.30 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.65 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 10.9 Hz, 1H), 5.20 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C), 139.0 (C), 135.6 (C), 134.6 (CH), 131.5 (C), 128.6 (2 × CH), 128.2 (CH), 127.2 (2 × CH), 126.9 (CH), 119.8 (CH), 114.4 (CH), 114.0 (CH_2), 118.7 (q, *J* = 320.6 Hz, CF_3), 71.0 (CH_2) ppm; IR (film): ν 2953, 1615, 1509, 1419, 1270, 1247, 1201, 1137, 1092, 942, 734 cm^{-1}; MS (EI$^+$) *m/z* (%): 358 (M$^+$, 10%), 91 (100%); HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{13}F_3NaO_4S$ [M+Na]$^+$ 381.0379; found: 381.0389.

2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-carbaldehyde ***(32)****:* To a solution of triflate **31** (2.49 g, 6.95 mmol) and boronic acid **16** (1.5 g, 8.38 mmol) in a mixed solvent system of PhMe/EtOH/water (150/75/75 mL) was added Cs_2CO_3 (4.53 g, 13.9 mmol). The resulting mixture was degassed with argon for 20 min then $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol) was added and the solution was heated at reflux for 14 h. On cooling to RT, water (100 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (10-15% Et_2O/cyclohexane) to afford the *title compound* **32** as a yellow oil (2.11 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.31–7.21 (m, 5H), 7.18 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.16–7.10 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.62 (dd, *J* = 17.6, 0.6 Hz, 1H), 5.16 (dd, *J* = 10.9, 0.6 Hz, 1H), 5.00 (br, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4 (CH), 159.2 (C), 155.6 (C), 136.5 (C), 135.7 (CH), 134.9 (C), 134.7 (C), 132.5 (CH), 130.9 (C), 129.6 (CH), 128.4 (2 × CH), 127.8 (CH), 127.4 (CH), 127.4 (C), 126.9 (2 × CH), 121.2 (CH), 112.8 (CH), 112.7 (CH_2), 109.4 (CH), 70.5 (CH_2), 55.6 (CH_3) ppm; IR (film): ν 2927, 2854, 1698, 1603, 1489, 1455, 1419, 1393, 1315, 1269, 1225, 1161, 1148, 1043, 1016 cm^{-1}; MS (ESI$^+$) *m/z* (%): 344 ([M +Na]$^+$, 100%).

(2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-yl)methanol ***(35)****:* To a suspension of aldehyde **32** (11.85 g, 34.4 mmol) in methanol (140 mL) and DCM (140 mL) at 0 °C was added $NaBH_4$ (2.60 g, 68.8 mmol). The reaction mixture warmed to RT and after 2 h, water (100 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 250 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (30–40% Et_2O/petrol) to afford the *title compound* **35** as a colourless oil (11.90 g, 34.4 mmol, 99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.34–7.27 (m, 4H), 7.22–7.18 (m, 3H), 7.16 (d, *J* = 2.7 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.7 Hz,

1H), 6.71 (dd, *J* = 17.6, 10.9, Hz, 1H), 5.68 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 11.0 Hz, 1H), 5.03 (br, 2H), 4.56–4.36 (br, 2H), 3.90 (s, 3H), 2.24 (br. s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C), 155.5 (C), 140.7 (C), 136.4 (C), 135.9 (CH), 131.2 (CH), 131.2 (C), 130.6 (C), 129.4 (C), 129.3 (CH), 128.5 (2 × CH), 127.9 (CH), 127.0 (2 × CH), 126.6 (CH), 113.7 (CH), 113.3 (CH), 113.2 (CH), 112.4 (CH_2), 71.1 (CH_2), 63.6 (CH_2), 55.3 (CH_3) ppm; IR (film): ν 3450 br, 2939, 1604, 1489, 1266, 1228, 1012, 904, 724 cm^{-1}; MS (ESI$^+$) *m/z* (%): 369 ([M+Na}$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{23}H_{22}NaO_3$ [M+Na]$^+$ 369.1461; found: 369.1469.

*(E)-4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (**34**):* A solution of styrene **35** (4.78 g, 13.4 mmol), iodide **23** (5.14 g, 14.8 mmol) and potassium phosphate (4.01 g, 18.8 mmol) in DMA (55 mL) was degassed by sonication for 20 min under argon then $Pd(OAc)_2$ (150 mg, 0.67 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT and partitioned between water (100 mL) was and EtOAc (50 mL). The aqueous phase was separated and extracted with EtOAc (2 × 50 mL) then the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (65% Et_2O/petrol) to afford the *title compound* **34** as a white solid (5.84 g, 75 %); MP 70–71 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.33–7.26 (m, 5H), 7.20–7.16 (m, 3H), 7.12 (d, *J* = 2.7 Hz, 1H), 7.04–6.98 (m, 4H), 6.94–6.90 (m, 3H), 5.02 (br, 2H), 4.35-4.51 (br, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 2.15 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8 (CH), 163.4 (C), 159.4 (C), 155.4 (C), 151.0 (C), 143.1 (C), 140.7 (C), 136.4 (C), 131.9 (2 × CH), 131.4 (C), 131.3 (CH), 130.9 (C), 130.9 (C), 130.7 (C), 129.4 (C), 129.4 (CH), 128.5 (2 × CH), 127.9 (CH), 127.1 (2 × CH), 127.0 (C), 126.9 (CH), 126.0 (CH), 124.7 (CH), 119.7 (CH), 116.2 (2 × CH), 113.9 (CH), 113.4 (CH), 113.3 (CH), 113.1(CH), 71.2 (CH_2), 63.7 (CH_2), 56.0 (CH_3), 55.3 (CH_3) ppm; IR (solid): ν 3438 br, 2933, 2836, 1689, 1596, 1581, 1501, 1454, 1269, 1225, 1153, 725; MS (ESI$^+$) *m/z* (%): 595 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{37}H_{32}NaO_6$ [M+Na]$^+$ 595.2091; found: 595.2082.

*(E)-(5'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (**33**):* A solution of arene **34** (4.53 g, 7.93 mol), propan-1,3-dithiol (2.58 g, 23.8 mmol) and PPTS (490 mg, 1.90 mmol) in DCM (88 mL) was heated at reflux for 18 h then cooled to RT. Water (30 mL) and saturated aqueous $NaHCO_3$ (100 mL) were then added and the aqueous phase was extracted with Et_2O (60 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (70% Et_2O/petrol) to afford the *title compound* **33** as a white foamy solid (4.79 g, 91%); MP 85–87 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 3H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.30–7.25 (m, 3H), 7.24 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.19–7.15 (m, 4H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.99 (t, *J* = 8.1 Hz, 2H), 6.94–6.87 (m, 5H), 5.16 (s, 1H), 5.01 (br, 2H), 4.55–4.35 (br, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.11–3.01 (m, 2H), 2.91 (dt, *J* = 14.0, 3.7 Hz, 2H), 2.21–2.11 (m, 2H), 1.97–1.86 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C), 158.0 (C), 155.3 (C), 151.0 (C), 144.5 (C), 140.7 (C), 136.4 (C), 133.0 (C), 131.3 (CH), 131.1 (C), 130.9 (C), 130.8 (C), 129.5 (C), 129.3 (CH), 129.0 (2 × CH), 128.5 (2 × CH), 127.1 (CH), 126.9 (2 × CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 123.5 (CH), 118.9 (CH), 116.9 (2 × CH), 113.9 (CH), 113.4 (CH), 113.2 (CH), 112.9 (CH), 71.2 (CH_2), 63.7 (CH_2), 56.0 (CH_3), 55.3 (CH_3), 50.7 (CH), 32.1 (2 × CH_2), 25.0 (CH_2) ppm; IR (solid): ν 3445 br, 2933, 2897, 1605, 1501, 1454, 1441, 1422, 1268, 1222, 1166, 1124, 1023, 907, 727; MS (ESI+) *m/z* (%): 685 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{38}NaO_5S_2$ [M+Na]$^+$ 685.2053; found: 685.2058.

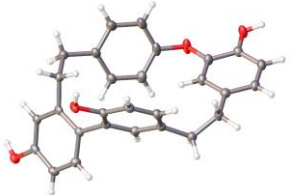
*(5'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxyphenethyl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (**36**):* A solution of stilbene **33** (1.50 g, 2.26 mmol), tosylhydrazone (4.21 g, 22.62 mmol) and NaOAc (1.86 g, 22.62 mmol) in 1:1 v/v THF and water (30 mL each) was heated at reflux for 18 h then cooled to RT. Saturated K_2CO_3 (50 mL) and water (10 mL) were added and the reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (50% Et_2O/petrol) to afford the *title compound* **36** as a white solid (1.37 g, 91%); MP 90–92 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.7 Hz, 2H), 7.31–7.27 (m, 3H), 7.20–7.15 (m, 2H), 7.13–7.10 (m, 2H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.93–6.89 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.81 (br s, 1H), 5.14 (s, 1H), 4.98 (br, 2H), 4.48–4.29 (br, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.14–2.98 (m, 2H), 2.90 (dt, *J* = 14.1, 3.7 Hz, 2H), 2.86 (br s, 4H), 2.31 (t, *J* = 6.2 Hz, 1H), 2.17 (m, 1H), 1.92 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C), 158.1 (C), 154.0 (C), 149.7 (C), 143.9 (C), 140.7 (C), 136.7 (C), 134.6 (C), 134.5 (C), 132.7 (C), 131.8 (CH), 131.2 (CH), 130.4 (C), 129.7 (C), 128.9 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.8 (CH), 127.1 (2 × CH), 125.0 (CH), 121.8 (CH), 116.6 (2 × CH), 113.9 (CH), 113.3 (CH), 113.1 (CH), 112.7 (CH), 71.3 (CH_2), 63.6 (CH_2) 56.0 (CH_3), 55.3 (CH_3), 50.7 (CH), 36.9 (CH_2), 36.9 (CH_2), 32.1 (2 × CH_2), 24.8 (CH_2) ppm; IR (solid): ν 3447 br, 2933, 1605, 1501, 1269, 1223, 1164, 1123, 1024, 906; MS (ESI$^+$) *m/z* (%): 687 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{40}O_5S_2$ [M+Na]$^+$ 687.2209; found: 687.2203.

*2-(4-(5-(2-(6-(Benzyloxy)-2'-(chloromethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)phenyl)-1,3-dithiane (**37**):* To a solution of benzyl alcohol **36** (0.76 g, 1.14 mmol) in DCM (55 mL) was added DBU (0.52 g, 3.42 mmol), LiCl (0.053g, 1.25 mmol) and MsCl (0.39 g, 3.42 mmol). After 18 h the reaction mixture was concentrated in *vacuo* and purified by column chromatography (30% Et_2O/petrol) to afford the *title compound* **37** as a colourless oil (0.69 g, 88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.7 Hz, 2H), 7.31–7.23 (m, 3H), 7.20–7.17 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 2.6 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.93–6.87 (m, 4H), 6.85–6.80 (m, 3H), 5.11 (s, 1H), 5.00 (s, 2H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.09–2.98 (m, 2H), 2.89 (dt, *J* = 14.1, 3.8 Hz, 2H), 2.84 (s, 4H), 2.16 (m, 1H), 1.90 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C), 158.2 (C), 154.0 (C), 149.7 (C), 143.9 (C), 137.3 (C), 137.1 (C), 134.8 (C), 134.0 (C), 132.7 (C), 131.9 (CH), 131.7 (CH), 130.6 (C), 129.2 (C), 128.9 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.5 (CH), 126.7 (2 × CH), 125.1 (CH), 121.9 (CH), 116.7 (2 × CH), 114.4 (CH), 113.9 (CH), 113.1 (CH), 112.8 (CH), 70.5 (CH_2), 56.1 (CH_3), 55.4 (CH_3), 50.8 (CH), 44.8 (CH_2), 37.0 (CH_2), 36.9 (CH_2), 32.1 (2 × CH_2), 25.0 (CH_2) ppm; IR (film): ν 2930, 1605, 1503, 1456, 1369, 1270, 1225, 1165, 905; MS (ESI$^+$) *m/z* (%): 707 ([M{^{37}Cl}+Na]$^+$, 40%), 705 ([M{^{35}Cl}+Na]$^+$, 100%).

*2,3,4,17,18,30-Hexahydro-22-Benzyloxy-13,27-dimethoxy-1,5-dithia-11-oxa-7,10-etheno-12,16-metheno-19,23-methenobenzo[x]spiro[5,20]hexacosatridecaene (**38**):* To a solution of dithiane **37** (200 mg, 0.29 mmol) in THF (30 mL) at –78 °C was added *n*-BuLi (2.44 M in hexanes, 0.13 mL, 0.32 mmol) over 3 min. The reaction mixture was warmed to RT and after 18 h. sat. NH_4Cl (10 mL) and water (5 mL) were added. The aqueous phase was separated at extracted with Et_2O (3 × 20 mL), then the combined organic phases were dried over $MgSO_4$, concentrated in *vacuo* and purified by column chromatography (40-50 % Et_2O/petrol) to afford the *title compound* **38** as a white solid (92 mg, 48%); MP 118–120 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (br s, 1H), 7.42 (d, *J* = 2.7 Hz, 1H), 7.37–7.23 (m, 7H), 7.06 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.89–6.78 (m, 4H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 3.91 (s, 6H), 3.62 (d, *J* = 14.2 Hz, 1H), 3.52 (d, *J* = 14.0 Hz, 1H), 3.19–2.95 (m, 3H), 2.72–2.55 (m, 4H), 2.47 (m, 1H), 1.98–1.87 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6 (C), 154.6 (C), 153.1 (C), 148.8 (C), 147.2 (C), 137.2 (C), 136.3 (C), 135.6 (C), 134.8 (C), 134.6 (C), 133.4 (CH), 131.9 (C), 131.7 (CH), 130.8 (C), 128.4 (2 × CH), 127.6 (CH), 127.2 (CH), 127.2 (2 × CH), 127.1 (2 × CH), 122.0 (CH), 117.5 (CH), 116.1 (CH), 113.8 (2 × CH), 113.0 (CH), 112.1 (2 × CH), 71.1 (CH_2), 59.7 (C), 56.3 (CH_3), 55.3 (CH_3), 49.5 (CH_2), 34.0 (CH_2), 31.8 (CH_2), 28.2 (CH_2), 27.5 (CH_2), 25.2 (CH_2) ppm; IR (solid): ν 2925, 2852, 1605, 1513, 1496, 1463, 1270, 1230, 1166, 1128; MS (ESI$^+$) *m/z* (%): 669 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{40}H_{38}NaO_4S_2$ [M+Na]$^+$ 669.2104; found: 669.2103.

*1,2,13,14-Tetrahydro-9,23-dimethoxy-18-hydroxy-3,6-etheno-8,12-metheno-15,19-metheno-7-oxabenzo[t]cycloeicosadecaene (**39**):* To a solution of $NiCl_2.6H_2O$ (310 mg, 1.28 mmol) in DMF (1 mL) was added sequentially a solution of dithiane **38** (0.052 g, 0.08 mmol) in THF (2 mL) and $NaBH_4$ (96 mg, 2.56 mmol). After 18 h the mixture filtered through Celite©, concentrated *in vacuo* and partitioned between water (10 mL) and Et_2O (15 mL). The aqueous phase was separated and extracted with Et_2O (2 × 15 mL), then the combined organic phases were dried over $MgSO_4$, concentrated in *vacuo* and purified by column chromatography (30 % Et_2O/petrol) to give a white solid (25 mg). That material was dissolved in EtOH (3 mL) and DCM (3 mL) and 10% Pd-C (10 mg) added. The flask was evacuated and purged with argon three times then evacuated and purged with hydrogen twice. After 6 h the reaction mixture was filtered through Celite©, concentrated *in vacuo* and purified by column chromatography (50-70% Et_2O/hexane) to afford the *title compound* **39** as a white solid (15.8 mg, 74%); MP 85–87 °C (Et_2O/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 2.6 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.88 (dd, *J* = 8.6, 2.7 Hz, 2H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.80 (d *J* = 8.1 Hz, 1H), 6.77–6.70 (m, 3H), 6.62 (d, *J* = 1.8 Hz, 1H), 6.33 (br s, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.62 (s, 1H), 3.92 (s, 6H), 3.18 (br dd, *J* = 13.5, 3.9 Hz, 1H), 3.07–2.85 (m, 5H), 2.49–2.73 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C), 153.7 (C), 150.1 (C), 149.8 (C), 147.0 (C), 141.0 (C), 137.6 (C), 136.3 (C), 134.8 (C), 133.1 (2 × CH), 130.4 (CH), 129.9 (CH), 129.3 (CH), 129.2 (C), 128.5 (CH), 126.8 (C), 121.5 (CH), 121.0 (CH), 115.4 (CH), 114.9 (CH), 114.8 (CH), 113.0 (CH), 111.6 (CH), 56.2 (CH_3), 55.3 (CH_3), 37.8 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.4 (CH_2) ppm; IR (solid): ν 3447 br, 2956, 2924, 2854, 1505, 1463, 1269, 1230, 1128; MS (ESI$^+$) *m/z* (%): 475 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{30}H_{28}NaO_4$ [M+Na]$^+$ 475.1880; found: 475.1879.

*1,2,13,14-Tetrahydro-9,18,23-trihydroxy-3,6-etheno-8,12-metheno-15,19-metheno-7-oxabenzo[t]cycloeicosadecaene (**5**):* To a stirred solution of the macrocyclic bisbibenzyl **39** (150 mg, 0.33 mmol) in DCM (33 mL) was added boron tribromide (1 M solution in DCM, 3.31 mL, 3.31 mmol). After 5 h, water (10 mL) was added then the aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (40% Et_2O/petrol) to afford the *title compound* **5** as a white solid (130 mg, 92%); MP 154–155 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, CD_3OD): δ = 6.93 (d, *J* = 2.6 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 1.2 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.66–6.62 (m, 2H), 6.61–6.56 (m, 3H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.32 (br s, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 3.04 (br dd, *J* = 12.9, 4.8 Hz, 1H), 2.96–2.65 (m, 6H), 2.43 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 157.9 (C), 155.6 (C), 152.8 (C), 149.6 (C), 145.5 (C), 143.4 (C), 139.8 (C), 136.6 (C), 135.0 (C), 133.4 (CH), 132.8 (CH), 132.4 (C), 130.7 (CH), 129.7 (C), 128.5 (CH), 122.7 (br, 2 × CH), 121.6 (br, 2 × CH), 116.9 (CH), 116.8 (CH), 116.8 (CH), 116.3 (CH), 114.4 (CH), 38.8 (CH_2), 37.1 (CH_2), 36.0 (CH_2), 34.5 (CH_2) ppm; IR (solid): ν 3363 br, 2954, 2923, 2853, 1505, 1445, 1222, 1163; MS (ESI$^-$) *m/z* (%): 447 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{28}H_{25}O_4$ [M+H]$^+$ 425.1747; found: 425.1743; X-ray: see insert.



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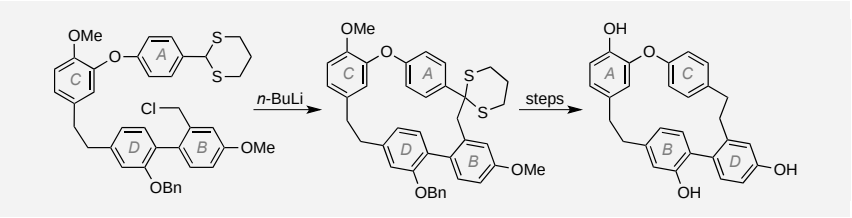
A Corey-Seebach Macrocyclisation Strategy for the Synthesis of Riccardin C and an Unnatural Macrocyclic Bisbibenzyl Analogue.



A total synthesis of riccardin C has been achieved featuring the use of a Corey-Seebach reaction to effect macrocyclisation. Through intersection with a late stage intermediate, formal syntheses of cavicularin and asterelin A have also been realised. More importantly, the approach has been used mimetically to prepare a new unnatural macrocyclic bisbibenzyl core.