CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201101550

Unified Syntheses of Cavicularin and Riccardin C: Addressing the Synthesis of an Arene Adopting a Boat Configuration

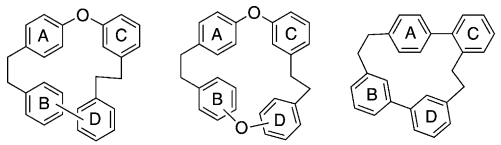
Sarah L. Kostiuk,[a] Timothy Woodcock,[a] Leo F. Dudin,[b] Peter D. Howes,[b] and David C. Harrowven*[a]

Abstract: Concise syntheses of the natural products cavicularin (ten steps) and riccardin C (seven steps) are reported. Key features of the new synthetic route are a convergent strategy to assemble acyclic precursors and a sequence of regioselective reduction and halogenation steps to facilitate Wittig macrocyclisation and transannular ring contraction reactions.

Keywords: natural products · radical reactions · strained molecules · synthetic methods · total synthesis

Introduction

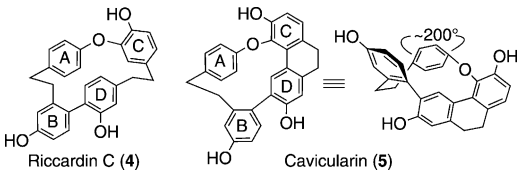
Macrocyclic bisbibenzyls are common constituents of liverworts and other bryophytes,[1] the earliest land plants.[2] To date riccardin C (**4**) is the only compound of this class to have been found in a higher flowering plant; that is, it is a constituent of *Primula macrocalyx* Bge. (Primulaceae).[3,4] Natural macrocyclic bisbibenzyls are thought to share a common origin in Nature, being derived by the dimerisation of lunularin.[1] Consequently, the vast majority conform to one of three structural motifs, **1**–**3**, which are sub-divided



into familial groups by the nature of the linkage between the arenes B and D.[1] Siblings are further discriminated through variations in the two-carbon chains linking the arenes A and B, as well as C and D, and with respect to the substituents decorating the constituent arenes.

From a biological perspective, liverworts have long been used in traditional Japanese medicine as antibacterial and antifungal agents, and as diuretics.[1] Their constituent macrocyclic bisbibenzyl natural products have been found to exhibit activity in various pharmacological screens, including antimycotic and antibacterial effects,[5–7] and cytotoxicity against P-388 mouse leukaemia and KB cell lines from nasopharyngeal carcinomas.[8] Recently, riccardin C (**4**) gained prominence as a partial liver X receptor (LXR) α agonist and LXRβ antagonist,[3,9,10] these playing a critical role in maintaining lipid homeostasis through the regulation of several genes involved in the efflux, transport and excretion of cholesterol.

From a structural perspective, cavicularin (**5**), from the Japanese liverwort *Cavicularia densa*, is unusual in having an additional linkage between arenes C and D.[11] This imparts such strain on the paracyclophane core that it induces a boat conformation in arene A.[12] Moreover, though devoid of any stereogenic carbon centres, natural cavicularin is chiral as a result of restricted conformational freedom.[12] Herein, we present a fuller account of our first generation synthesis of riccardin C (**4**) and cavicularin (**5**),[13] and a new strategy offering rapid access through a combination of convergence and telescoping.



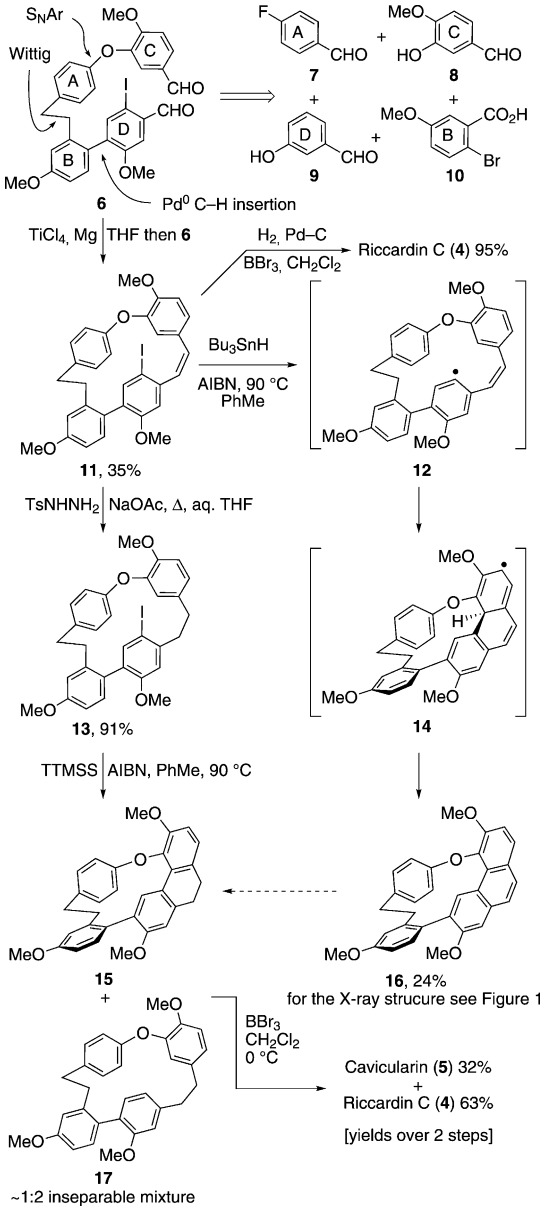
Results and Discussion

Development of a first-generation synthesis: In our first total synthesis of cavicularin, the acyclic precursor **6** was assembled in a convergent manner from the constituent starting materials **7**–**10** with a longest linear sequence of nine steps (Scheme 1). Key features included an S_NAr reaction to conjoin arenes A and C, a Pd^0-catalysed C–H insertion reaction to conjoin arenes B and D, and a Wittig reaction to unite these subunits.[13] Following a McMurry-induced mac-

[a] Dr. S. L. Kostiuk, Dr. T. Woodcock, Prof. D. C. Harrowven
Chemistry, University of Southampton, Highfield
Southampton, Hampshire, SO17 1BJ (UK)
Fax: (+44) 23-8059-6805
E-mail: dch2@soton.ac.uk

[b] Dr. L. F. Dudin, Dr. P. D. Howes
c/o GlaxoSmithKline Medicines Research Centre
Gunnels Wood Road, Stevenage, SG1 2NY (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101550.



Scheme 1. Summary of the first-generation synthesis and a previously unreported approach through stilbene **11**. Ts = tosyl, AIBN = azobisisobutyronitrile, Ac = acyl, TTMSS = tris(trimethylsilyl)silane.

rocyclisation, our plan was to effect a transannular ring contraction through the addition of an aryl radical intermediate to its proximal arene, that is, **12**→**[14]**→**16**.[14] Prior art suggested that the *cis*-alkene linking the radical donor and acceptor was crucial to promote the desired *ortho*-cyclisation pathway over *ipso*-substitution, as with saturated two-carbon tethers the ubiquitous 5-*exo*-*trig* cyclisation mode usually predominates.[15] Pleasingly, cyclisation of iodostilbene **11** to phenanthrene **16** was successful, though its efficiency was compromised by an unexpected affinity of the product for the isobutyronitrile radical (and arising from the need to use a full equivalent of AIBN as initiator).[16] X-ray analysis of **16** showed that we had achieved our goal of generating the boat-configured arene A, which displayed a 16° bend away from planarity in the solid state (Figure 1).

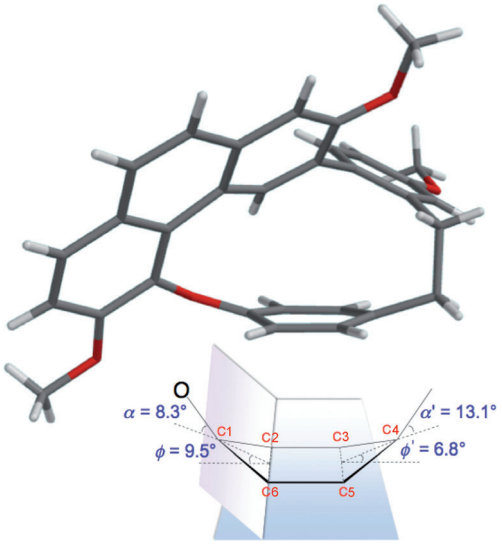


Figure 1. X-ray crystal structure for phenanthrene **16**, showing the boat-configured arene.

From this juncture, two tasks remained to complete the first total synthesis of cavicularin: the reduction of the C9–C10 phenanthrene bond and the global deprotection of the aryl methyl ethers. The former proved an intractable problem as all attempts to effect reduction of **16** to **15** either returned the starting material or gave complex product mixtures, presumed to be derived from reduction of the boat-configured arene. Consequently, we decided to explore the impact of reducing the *cis*-alkene in **11** before inducing the transannular ring contraction. Our hope was that the macrocyclic architecture of **13** would restrict conformational freedom and promote reactive conformers favouring the 6-*exo*/*endo*-*trig* cyclisation mode. Indeed, when **13** was exposed to TTMSS under standard radical-forming conditions it gave an inseparable 1:2 mixture of cavicularin trimethyl ether **15** and riccardin C trimethyl ether **17** in high yield. With the initiator now employed at substoichiometric levels we saw no evidence for addition of the isobutyronitrile radical to the product.[17] However, in removing the *cis*-alkene tether we undoubtedly slowed the rate of the transannular ring contraction significantly, allowing hydrogen-atom abstraction from the silane to become competitive. Thus, treatment of the product mixture with boron tribromide provided synthetic samples of cavicularin (**5**) and riccardin C (**4**) in 32 and 63% yield, respectively, each displaying spectral characteristics identical to those reported for the natural products.[3,4,10,11]

It is interesting to note that for riccardin C (**4**), there are many variations in the reported ^{1}H NMR data, which have been variously recorded in $CDCl_3$, [D_6]DMSO, [D_6]DMSO + $CDCl_3$ and [D_6]acetone.[3,4,10,11] In $CDCl_3$ at 25 °C the ^{1}H NMR spectrum shows significant broadening of all $ArCH_2$ signals and those of the A ring. Consequently, the

region around $\delta = 6.82$–6.72 ppm has typically been described as a 6H or 7H multiplet. Three peaks are discernable, attributed to the protons H12 ($\delta = 6.81$ ppm, dd, $J = 8.3$, 2.6 Hz), H11′ ($\delta = 6.79$ ppm, d, $J = 7.5$ Hz) and H5′ ($\delta = 6.75$ ppm, dd, $J = 8.3$, 1.9 Hz). The same phenomenon was found in [D_6]benzene and [D_8]toluene, solvents in which the signals are better resolved. This broadness can be attributed to restricted rotation within the molecule. By recording the NMR spectra at lower temperatures in [D_8]toluene, we found that the resonances for the A ring began to resolve into four distinct doublets of doublets, whereas at elevated temperatures they resolved into an AB quartet (Figure 2).

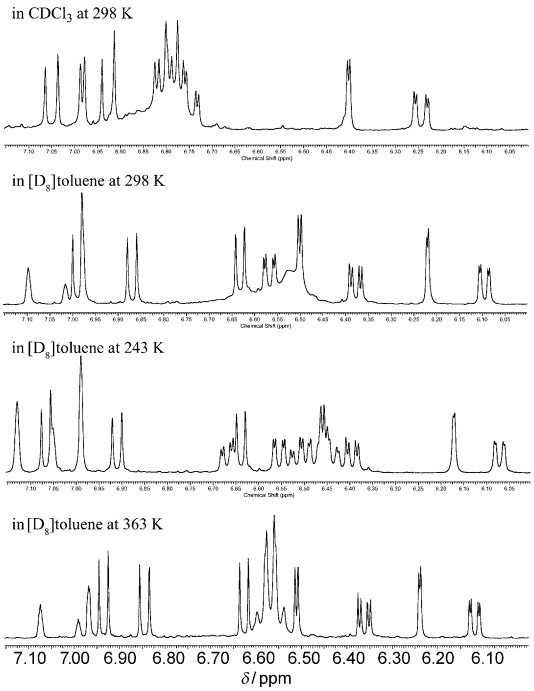
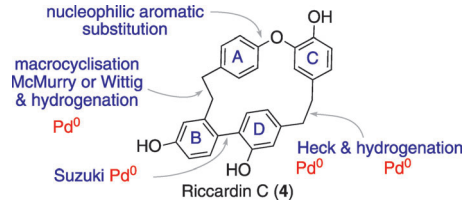


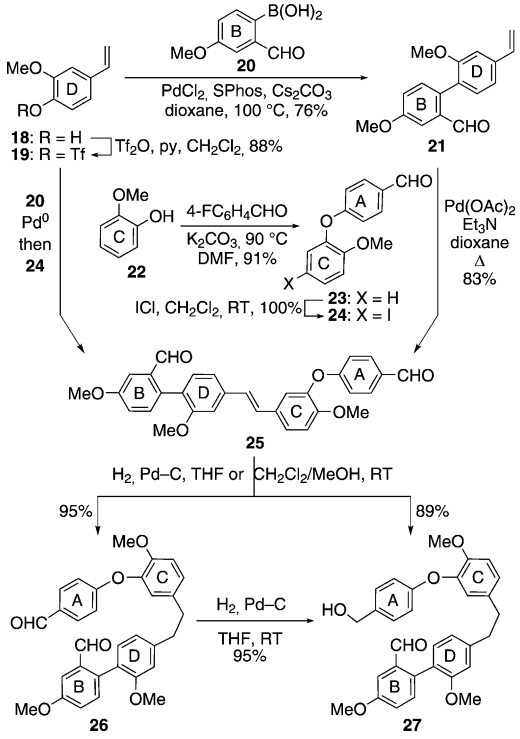
Figure 2. ^{1}H NMR data ($\delta_H = 7.15$–6.00 ppm) for riccardin C recorded in $CDCl_3$ and [D_8]toluene at 243, 298 and 363 K.

Combining the principles of convergence and telescoping: In seeking improvements to the aforementioned syntheses, we noted three low-yielding transformations (macrocyclisation **6**→**11**, ring contraction **13**→**15** and the Pd^0-catalysed C–H insertion reaction used to conjoin arenes B and D) and a high step count. To address these concerns, we formulated a new strategy based on robust coupling procedures and employment of the principles of convergence and telescoping to reduce the step count. The tactic, summarised in Scheme 2, included a switch in the site of macrocyclisation to between arenes A and B, as this allowed the constituent arenes to be assembled by using a series of palladium-catalysed coupling reactions and hydrogenation reactions. In principle, these might then be sequenced on establishing an appropriate catalyst system.

To that end, 4-fluorobenzaldehyde (arene A) and guaiacol (**22**, arene C) were coupled by nucleophilic aromatic substitution to give compound **23**, which, on iodination, gave the



Scheme 2. A new strategy for riccardin C (**4**).



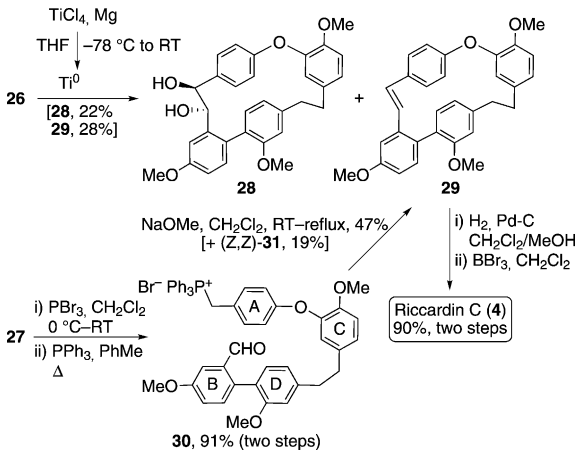
Scheme 3. Construction of the acyclic precursors **26** and **27**. SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

suitably primed biaryl ether **24** (Scheme 3). Contemporaneously, triflation of phenol **18** (arene D) to compound **19** enabled a Suzuki–Miyaura coupling with the commercially available boronic acid **20** (arene B), thereby giving our second key building block, styrene **21**.[18,19] Next, a Heck reaction facilitated union of these subunits,[20] providing tetraarene **25** in excellent overall yield and with a longest linear sequence of three steps from commercially available starting materials. Catalytic hydrogenation of **25** proceeded smoothly to give either the dialdehyde **26** in 95 or the alcohol **27** in 89% yield, depending on the reaction time employed.[21]

Although efficient telescoping of the hydrogenation steps was easily realised, attempts to sequence the Pd^0-catalysed Suzuki–Miyaura and Heck coupling reactions met with limited success (≈20% for **19**+**20**+**24**→**25**), due to an incompatibility of the catalyst systems. Cross-coupling of the electron-rich triflate **19** and boronic acid **20** proved particularly challenging, giving the corresponding product in poor yields with conventional ligand and base combinations.[19] Though

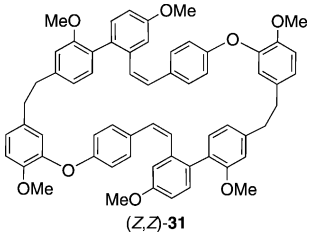
this could be overcome by the use of the SPhos ligand of Buchwald in conjunction with caesium carbonate,[22] this combination proved to be a poor mediator of the subsequent Heck reaction with iodide **24** as this favoured ligandless conditions.[23]

Total synthesis of riccardin C: With a short entry to tetraarenes **26** and **27** in hand, we were well-placed to complete a total synthesis of riccardin C. From the former it was possible to induce macrocyclisation directly by using a McMurry reaction, with this giving the strained *trans*-stilbene **29** as the main product in modest yield. Diol **28** was also recovered, albeit heavily contaminated with copolar byproducts presumed to be derived from the reduction of THF (Scheme 4).[24] Thus, the *erythro* stereochemistry ascribed to compound **28** is based on its return following re-exposure to the McMurry reagent, as the *threo* product would be expected to give (*E*)-**29**. From a synthetic perspective, either stilbene **29** or the crude product mixture could be transformed into riccardin C through exposure to H_2/Pd–C and global deprotection of the aryl methyl ethers.



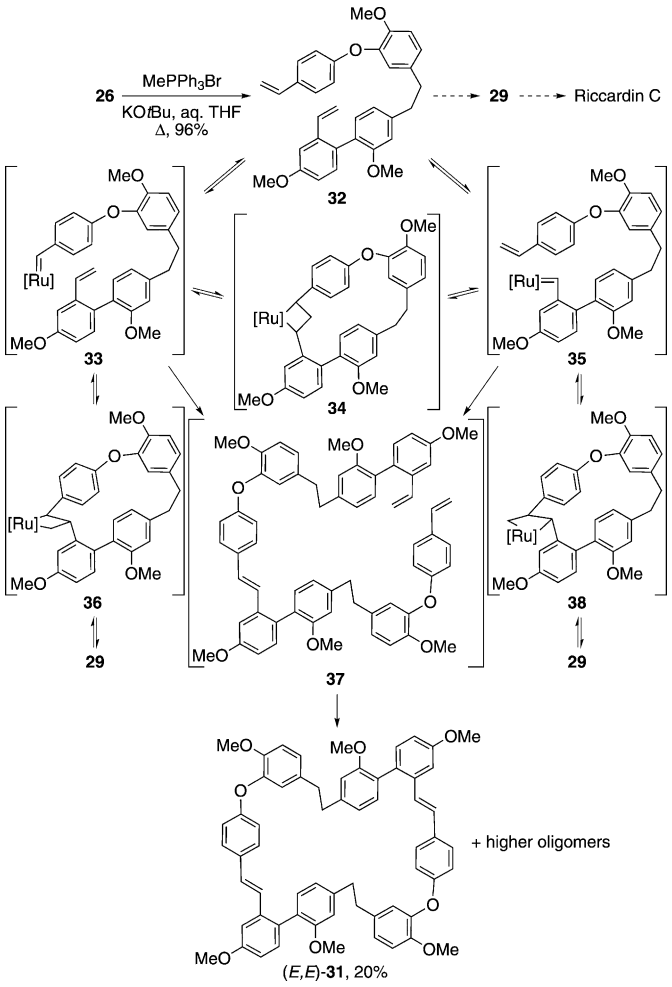
Scheme 4. New total syntheses of riccardin C.

The modest yields and capricious nature of the McMurry-induced macrocyclisation prompted an exploration of alternative routes to compound **29**. The phosphonium salt **30** was readily obtained from alcohol **27** and smoothly underwent macrocyclisation to (*E*)-**29** on treatment with sodium methoxide under pseudo-high dilution conditions (Scheme 4).[24] Interestingly, when conducted at higher concentrations the Wittig reaction gave the (*Z*,*Z*)-dimer **31** as a significant byproduct, with the alternative stereochemical preference.



The use of ring-closing metathesis for the macrocyclisation of compound **26** to **29** (via **32**) was also examined but without success. Exposure of bis-styrene **32** to the Grubbs II catalyst gave rise to a complex product mixture from which the dimer (*E*,*E*)-**31** was isolated in 32% yield (Scheme 5).[25,26] This failure can be attributed to the strain in macrocycle **29** (see below) and related intermediates, leading to reversibility and the promotion of the cross-metathesis to stilbene **37**.

Total synthesis of cavicularin: Our final task was to develop a second-generation synthesis of cavicularin with a linear step count reduced to around half that employed previously. Efficient macrocyclisation and a selective bromination procedure were therefore needed to enable transannular ring contraction. Our plan was to facilitate both through a selective double halogenation of compound **27** to benzyl bromide **39**. Though this seemed ambitious, we had observed a marked preference for the *para* halogenation of anisoles in related reactions involving linked aromatic ring systems.[27]

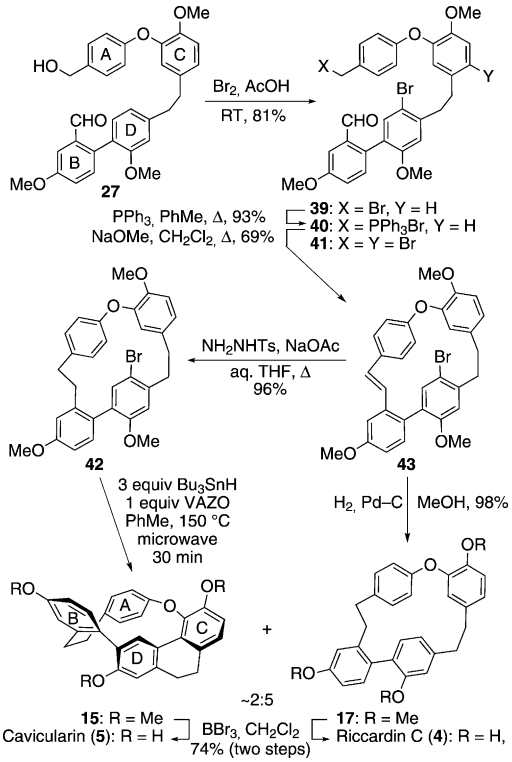


Scheme 5. Ring-closing metathesis leading to (*E*,*E*)-**31** by using the Grubbs second-generation catalyst (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium.

Of the thirteen unsubstituted aromatic carbons in tetraarene 27, only the desired site for bromination met this criterion. Thus, exposure of **27** to bromine in glacial acetic acid generated dibromide **39** in 81% yield, with the tribromide **41** being formed as a minor byproduct. The latter, which could be formed in higher yield by using bromine in excess, shows how this preference for *para* bromination can even be extend to diaryl ethers when in competition with *ortho* bromination of an anisole.

Next, treatment of dibromide **39** with triphenylphosphine gave phosphonium salt **40**, which, on exposure to NaOMe under conditions of pseudo-high dilution, afforded macrocycle **43** in 69% yield (Scheme 6). The high yield is impressive given the intrinsic strain in the product. As with *trans*-stilbene **29**, an X-ray crystal structure of compound **43** revealed a boat configuration in arene A akin to that in cavicularin itself.[10] Furthermore, its *trans*-stilbene displays a torsional angle of 167° across the double bond, which in turn has bond angles ranging from 115–129° (Figure 3).

Reduction of this alkene by catalytic hydrogenation additionally induced hydrogenolysis of the aryl bromide to give riccardin C trimethyl ether **17**. Over-reduction was eliminated by using diimide, allowing aryl bromide **42** to be formed in 96% yield. Attempts to transform this product into cavicularin trimethyl ether **15** by a Pd^0-catalysed C–H insertion reaction failed, whereas its treatment under standard radical-forming conditions (Bu_3SnH, VAZO, toluene, heating to reflux) gave poor conversion even after prolonged heating to reflux. However, by conducting the reaction at 150°C



Scheme 6. Second-generation total synthesis of cavicularin. VAZO = 1,1′-azobis(cyanocyclohexane).

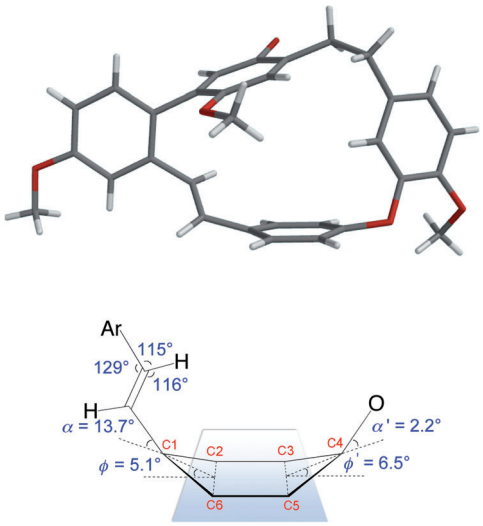


Figure 3. X-ray crystal structure of compound **43**, showing the boat-configured arene and the distorted *trans*-alkene.

under microwave irradiation, conversion was complete within 30 min to afford cavicularin trimethyl ether **15** and riccardin C trimethyl ether **17** as an inseparable 2:5 mixture.[28] Finally, removal of all six aryl methyl ethers with boron tribromide gave cavicularin (**5**) and riccardin C (**4**), in 22 and 52% yield (over two steps), respectively.

Conclusion

In summary, short and practicable total syntheses of cavicularin and riccardin C have been developed. The early stages feature a sequence of four Pd^0-catalysed coupling and hydrogenation reactions that enable the construction of the acyclic precursors **26** and **27** in four linear steps and completion of the total synthesis of riccardin C in as few as seven linear steps. For cavicularin, a short endgame involving macrocyclisation (Wittig) and a radical-induced transannular ring contraction is made possible by a humble double bromination.

Experimental Section

Reagents were obtained commercially and used without further purification unless indicated otherwise. Solvents were purified by standard procedures prior to use. Reactions were performed under an argon atmosphere in oven-dried glassware containing a Teflon-coated stirrer bar. Flash column chromatography was carried out on silica gel (60 Å, particle size 30–70 micron) with the solvent system used given in parentheses. TLC analyses were performed on commercial 60 F254 silica gel plates. Melting points were recorded on Reichert Austria apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AV-300 (300 MHz) or DPX-400 (400 MHz) spectrometer operating at 298 K. Chemical shifts are quoted in parts per million downfield of tetramethylsilane with residual solvent as the internal standard. Assignments were made on the basis of chemical shift, coupling constants, aided in some cases by COSY, HMQC, HMBC and comparison of spectra with that of related com-

pounds. Coupling constants (J) are reported in hertz and are round to the nearest 0.1 Hz. Infrared spectra were recorded neat as an oil film or solid compression using the ATR/golden gate method. Absorption maxima ($\tilde{\nu}_{max}$) are quoted in wavenumbers (cm^{-1}). ESI mass spectra were recorded using a ZMD quadrupole mass spectrometer measuring monoisotopic masses (mode: ES+ or ES−). EI mass spectra were measured on a Thermoquest Trace MS. m/z values are reported with their percentage abundance relative to the most intense signal. Values for the most abundant isotope combination are reported.

15,16-Dihydro-1,12,23-trimethoxy-6,8:17,20-dietheno-21-oxabenzo[g]naphtha[1,8-bc]cyclotetradecine (16):[13] A solution of iodide **11** (65 mg, 0.11 mmol) and tributyltin hydride (0.036 mL, 0.13 mmol) in toluene (30 mL) was heated to 90 °C, then AIBN (32 mg, 0.20 mmol) was added. After 2.5 h the reaction mixture was cooled and stirred vigorously with an aqueous solution of KF (10%, 20 mL) for 30 min. The aqueous phase was separated and extracted with diethyl ether (3×30 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by column chromatography (9:1 petroleum ether/diethyl ether then separately CH_2Cl_2). HPLC (1:4 EtOAc/hexane and recrystallisation (EtOH) afforded the title compound (12 mg, 0.026 mmol, 24%) as a white solid. M.p. (EtOH) 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.03 (s, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.3, 2.5 Hz, 1H), 6.79–6.76 (m, 1H), 6.32 (dd, J = 8.5, 2.3 Hz, 1H), 6.21 (dd, J = 8.3, 2.0 Hz, 1H), 5.73 (dd, J = 8.3, 2.5 Hz, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 3.82 (s, 3H), 2.99 (dt, J = 12.8, 3.7 Hz, 1H), 2.85 (dt, J = 12.8, 3.7 Hz, 1H), 2.63 (td, J = 12.8, 3.7 Hz, 1H), 2.01 ppm (td, J = 12.8, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (C), 155.6 (C), 154.9 (C), 152.1 (C), 142.7 (C), 139.8 (C), 134.7 (C), 133.8 (C), 132.0 (C), 131.3 (CH), 130.6 (CH), 130.2 (CH), 129.1 (C), 128.3 (CH), 128.2 (C), 127.8 (CH), 125.5 (CH), 124.9 (CH), 122.7 (C), 121.0 (C), 117.9 (CH), 115.2 (CH), 113.1 (2×CH), 111.5 (CH), 106.5 (CH), 57.5 (CH_3), 55.6 (CH_3), 38.3 (CH_2), 38.3 ppm (CH_2); UV (CH_2Cl_2): λ (ε_{max}) = 320 (15000), 274 (50700), 230 nm (42600 $mol^{-1}dm^3cm^{-1}$); IR (solid): $\tilde{\nu}$ = 2920, 1600, 1498, 1275, 1228, 1104, 1040, 930, 845 cm^{-1}; MS (ES$^+$): m/z (%): 949 [$2M$+Na]$^+$ (20), 485 [M+Na]$^+$ (100), 236 (70), 227 (70); HRMS (ES$^+$): m/z calcd for $C_{31}H_{26}NaO_4$: 485.1723; found: 485.1726; X-ray: see Figure 1.

2-Methoxy-4-vinylphenyltrifluoromethane sulfonate (19): To a solution of trifluoromethanesulfonic anhydride (2.45 g, 16.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C, a solution of 4-hydroxy-3-methoxystyrene **18** (5.07 g, 18.0 mmol) and pyridine (1.55 g, 19.6 mmol) in CH_2Cl_2 (30 mL) was added over 1 h, while keeping the reaction temperature at 0 °C. After a further 3 h, ice water (50 mL) was added and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) then dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (CH_2Cl_2) afforded the title compound (4.03 g, 88%) as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.3 Hz, 1H), 7.06 (d, J = 1.9 Hz, 1H), 7.01 (dd, J = 8.3, 1.9 Hz, 1H), 6.69 (dd, J = 17.5, 10.8 Hz, 1H), 5.77 (d, J = 17.5 Hz, 1H), 5.35 (d, J = 10.8 Hz, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6 (C), 139.1 (C), 138.3 (C), 135.7 (CH), 122.6 (CH), 119.0 (CH), 118.9 (q, J(C,F) = 320.7 Hz, CF_3), 116.1 (CH_2), 110.7 (CH), 56.3 ppm (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −74.13 ppm (CF_3); IR (neat): $\tilde{\nu}$ = 1601, 1502, 1415, 1200, 1135, 1104, 858, 819 cm^{-1}; MS (EI, 70 eV): m/z (%): 282 [M]$^+$ (23), 149 (82), 121 (34), 103 (28), 91 (67), 69 (100%); HRMS (ES$^+$): m/z calcd for $C_{10}H_9O_4F_3S$: 282.0173; found: 282.0167.

2′,4-Dimethoxy-4′-vinylbiphenyl-2-carbaldehyde (21): To a solution of triflate **19** (78 mg, 0.28 mmol) and boronic acid **20** (10 mg, 0.55 mmol) in dioxane (2 mL), LiCl (117 mg, 2.77 mmol), Cs_2CO_3 (326 mg, 1.11 mmol) and SPhos (44 mg, 0.11 mmol) were added. The reaction mixture was degassed by sonication under argon for 5 min. $PdCl_2$ (5 mg, 0.027 mmol) was added and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to RT, filtered through a glass sinter, then silica (≈1 g) was added to the filtrate and the solvent was removed in vacuo. Purification by flash column chromatography (4:1 petroleum ether/diethyl ether) afforded the title compound (55 mg, 76%) as an off-white solid.

Alternative procedure: To a solution of triflate **3** (4.00 g, 14.2 mmol) and boronic acid **4** (2.54 g, 14.2 mmol) in dioxane (80 mL) LiCl (6.016 mg, 140.8 mmol), Cs_2CO_3 (23.10 g, 70.9 mmol) and SPhos (404 mg, 1.14 mmol) were added. The reaction mixture was degassed by sonication under argon for 10 min, then $Pd(OAc)_2$ (128 mg, 0.57 mmol) was added. The reaction mixture was heated at reflux for 3 h, then cooled to RT and partitioned between water (80 mL) and CH_2Cl_2 (100 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were concentrated in vacuo and purified by flash column chromatography (2:1 petroleum ether/CH_2Cl_2) to afford the title compound (1.96 g, 52%) as a yellow crystalline solid. M.p. (heptane/ethyl acetate) 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.22 (d = 7.7 Hz, 1H), 7.19 (dd = 8.4, 2.8 Hz, 1H), 7.12 (dd, J = 7.8, 1.4 Hz, 1H), 7.00 (d, J = 1.2 Hz, 1H), 6.77 (dd, J = 17.6, 10.9 Hz, 1H), 5.82 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 10.9 Hz, 1H), 3.90 (s, 3H), 3.77 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6 (C), 159.4 (C), 156.9 (C), 139.4 (C), 136.5 (CH), 135.1 (C), 134.5 (C), 132.4 (CH), 131.9 (CH), 126.3 (C), 121.4 (CH), 119.3 (CH), 114.8 (CH_2), 109.6 (CH), 108.4 (CH), 55.7 (CH_3), 55.6 ppm (CH_3); IR (solid): $\tilde{\nu}$ = 3004, 2936, 2838, 1686, 1603, 1486, 1393, 1266, 1246, 1035 cm^{-1}; MS (ES+): m/z (%): 559 [$2M$+Na]$^+$ (9), 291 [M+Na]$^+$ (100); HRMS (ES$^+$): m/z calcd for $C_{17}H_{16}O_3Na$: 282.0173; found: 291.0994.

4-(2-Methoxyphenoxy)benzaldehyde (23):[29] To a solution of 2-methoxyphenol (**22**) (5.00 g, 40.3 mmol) and 4-fluorobenzaldehyde (5.50 g, 44.4 mmol, 4.78 mL) in DMF (25 mL) K_2CO_3 (6.12 g, 44.4 mmol) was added. The reaction mixture was heated at reflux for 24 h, then cooled to RT and poured onto ice (50 mL). The resultant emulsion was extracted with ethyl acetate (3×50 mL), then the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (chloroform) afforded the title compound (8.40 g, 91%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.24 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.10 (dd, J = 8.1, 1.5 Hz, 1H), 7.05 (dd, J = 8.3, 1.3 Hz, 1H), 7.00 (obscured m, 1H), 6.99 (d, J = 8.5 Hz, 2H), 3.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0 (C), 163.9 (C), 152.0 (C), 143.2 (C), 132.1 (2×CH), 131.2 (C), 126.7 (CH), 122.9 (CH), 121.7 (CH), 116.5 (2×CH), 113.4 (CH), 56.2 ppm (CH_3); IR (neat): $\tilde{\nu}$ = 1692, 1599, 1570, 1487, 1261, 1222, 1176, 1152, 1131 cm^{-1}; MS (EI, 70 eV): m/z (%): 228 [M^+] (100), 207 (30), 185 (20), 184 (18), 128 (42), 114 (38), 77 (55), 51 (42).

4-(5-Iodo-2-methoxyphenoxy)benzaldehyde (24): To a solution of 4-(methoxyphenoxy)benzaldehyde (**23**) (2.00 g, 9.4 mmol) in CH_2Cl_2 (20 mL) was added a solution of ICl (1.83 g, 11.3 mmol) in CH_2Cl_2 (5 mL). Light was excluded for seven days, then saturated aqueous solution of $Na_2S_2O_3$ (15 mL) was added. After 1 h the biphasic solution was separated and the aqueous phase was extracted with diethyl ether (10 mL + 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), then dried over $MgSO_4$ and concentrated in vacuo to afford the title compound (3.31 g, quantitative) as an orange gum, which crystallised on standing. M.p. (CH_2Cl_2) 48 °C sharp; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.43 (dd, J = 8.6, 2.1 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.6 Hz, 1H), 3.68 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7 (C), 163.0 (C), 152.0 (C), 143.9 (C), 135.3 (CH), 132.0 (2×CH), 131.4 (C), 131.2 (CH), 116.5 (2×CH), 115.0 (CH), 82.0 (C), 56.1 ppm (CH_3); IR (solid): $\tilde{\nu}$ = 1682, 1598, 1582, 1495, 1464, 1264, 1227, 1175, 1162, 1153, 1110, 1041, 1024, 769 cm^{-1}; MS (EI, 70 eV): m/z (%): 354 [M^+] (100), 207 (19), 184 (24), 128 (14), 79 (31), 51 (18).

2′,4-Dimethoxy-4′-[3-(4-formyl-phenoxy)-4-methoxy-phenyl-vinyl]-biphenyl-2-carbaldehyde (25): To a solution of the biaryl **21** (1.30 g, 4.49 mmol) and ether **24** (1.64 g, 4.49 mmol) in dioxane (30 mL) triethylamine (1.96 g, 19.40 mmol) was added. The reaction mixture was degassed by sonication for 10 min under argon then $Pd(OAc)_2$ (43 mg, 0.019 mmol) was added. The reaction mixture was heated at reflux for 19 h, then cooled to RT and the solvent was removed in vacuo. Purification of the residue by flash column chromatography (9:1→3:2 heptane/ethyl acetate) afforded the title compound (2.00 g, 83%) as a white solid. M.p. (petroleum ether) 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94

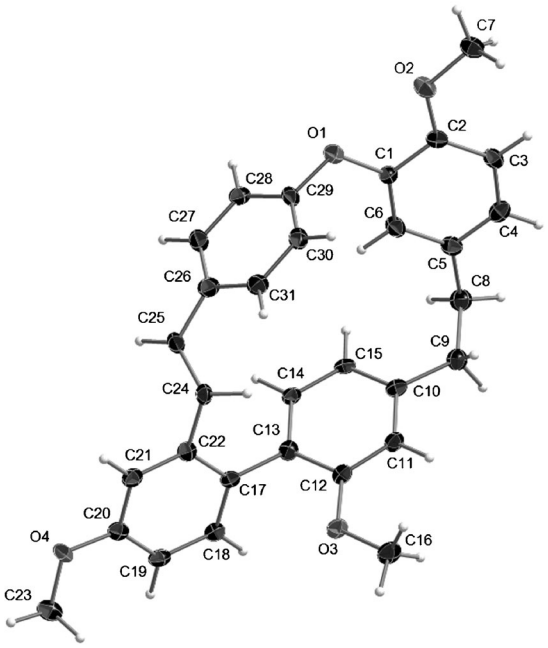
(s, 1H), 9.77 (s, 1H), 7.86 (d, $J=8.9$ Hz, 2H), 7.51 (d, $J=2.8$ Hz, 1H), 7.40 (dd, $J=8.5$, 1.9 Hz, 1H), 7.35 (d, $J=2.0$ Hz, 1H), 7.30 (d, $J=8.5$ Hz, 1H), 7.25 (d, $J=7.9$ Hz, 1H), 7.23–7.18 (m, 3H), 7.10 (d, $J=16.3$ Hz, 1H), 7.07–7.04 (m, 3H), 7.01 (d, $J=16.3$ Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=192.5$ (C), 190.9 (C), 163.6 (C), 159.4 (C), 157.1 (C), 151.7 (C), 143.4 (C), 139.1 (C), 135.1 (C), 134.4 (C), 132.6 (CH), 132.1 (2×CH), 132.1 (CH), 131.3 (C), 128.2 (CH), 127.6 (CH), 126.2 (C), 125.3 (CH), 121.4 (CH), 120.3 (CH), 119.5 (CH), 116.5 (2×CH), 113.4 (CH), 109.7 (CH), 108.5 (CH), 56.3 (CH_3), 55.8 (CH_3), 55.6 ppm (CH_3), one carbon atom was not observed; IR (solid): $\tilde{\nu}=2934$, 2839, 1689, 1600, 1501, 1271, 1227, 1155, 1032 cm^{-1}; MS (ES$^+$): *m/z* (%): 1011 [2*M*+Na]$^+$ (37), 517 [*M*+Na]$^+$ (100), 183 (99), 192 (70); HRMS (ES$^+$): *m/z* calcd for $C_{31}H_{26}NaO_6$: 517.1622; found: 517.1615.

2′,4-Dimethoxy-4′-{2-[3-(4-formylphenoxy)-4-methoxyphenyl]-ethyl}-biphenyl-2-carbaldehyde (26): To solution of the dialdehyde **25** (140 mg, 0.28 mmol) in THF (30 mL) palladium on carbon (5%, 280 mg) was added. The flask was evacuated/purged with argon three times, then evacuated/purged with hydrogen twice under vigorous stirring. After 10 min the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash column chromatography (2:3 diethyl ether/petroleum ether) afforded the title compound (133 mg, 95%) as a white solid. M.p. (EtOAc/petroleum ether) 38–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.78$ (s, 1H), 9.60 (s, 1H), 7.70 (d, $J=8.8$ Hz, 2H), 7.39 (d, $J=2.6$ Hz, 1H), 7.18–7.12 (m, 2H), 7.09 (dd, $J=8.4$, 2.8, 1H), 7.05 (d, $J=7.7$ Hz, 1H), 6.98 (dd, $J=8.4$, 2.0 Hz, 1H), 6.90–6.85 (m, 3H), 6.81 (d, $J=2.0$ Hz, 1H), 6.76 (dd, $J=7.6$, 1.3 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H), 2.87 ppm (apparent s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=192.9$ (C), 191.1 (C), 164.0 (C), 159.5 (C), 157.0 (C), 150.4 (C), 143.8 (C), 143.0 (C), 135.3 (C), 135.3 (C), 135.0 (C), 132.9 (CH), 132.3 (2 x CH), 131.9 (CH), 131.3 (C), 126.7 (CH), 124.7 (C), 123.2 (CH), 121.6 (CH), 121.5 (CH), 116.6. (CH), 116.5 (CH), 113.5 (CH), 111.4 (CH), 109.9 (CH), 56.5 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 38.5 (CH_2), 37.2 ppm (CH_2); IR (solid): $\tilde{\nu}=2938$, 1689, 1602, 1578, 1509, 1488, 1273, 1227, 1156 cm^{-1}; MS (ES$^+$): *m/z* (%): 1015 [2*M*+Na]$^+$ (97), 519 [*M*+Na]$^+$ (100).

2′,4-Dimethoxy-4′-{2-[3-(4-hydroxymethylphenoxy)-4-methoxyphenyl]-ethyl}-biphenyl-2-carbaldehyde (27): To solution of dialdehyde **25** (230 mg, 0.47 mmol) in CH_2Cl_2 (20 mL) and methanol (20 mL) palladium on carbon (10%, 460 mg) was added. The flask was evacuated/purged with argon three times, then evacuated/purged with hydrogen twice with vigorously stirring. After 20 min the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash column chromatography (2:3 diethyl ether/petroleum ether) afforded the title compound (206 mg, 89%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.66$ (s, 1H), 7.49 (d, $J=2.6$ Hz, 1H), 7.29–7.23 (m, 2H), 7.19 (dd, $J=8.4$, 2.6 Hz, 1H), 7.14 (d, $J=7.7$ Hz, 1H), 6.98–6.88 (m, 3H), 6.89 (d, $J=8.8$ Hz, 2H), 6.83 (dd, $J=7.7$, 1.5 Hz, 1H), 6.78 (d, $J=1.8$ Hz, 1H), 6.69 (d, $J=1.5$ Hz, 1H), 4.62 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 2.95–2.88 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=192.7$ (C), 159.0 (C), 157.6 (C), 156.4 (C), 149.8 (C), 144.5 (C), 143.5 (C), 134.9 (C), 134.8 (C), 134.7 (C), 134.5 (C), 132.5 (CH), 131.4 (CH), 128.5 (2×CH), 124.8 (CH), 124.1 (C), 121.5 (CH), 121.3 (CH), 121.1 (CH), 117.0 (2×CH), 112.8 (CH), 111.0 (CH), 109.3 (CH), 64.9 (CH_2), 56.1 (CH_3), 55.6 (CH_3), 55.3 (CH_3), 38.1 (CH_2), 36.8 ppm (CH_2); IR (neat): $\tilde{\nu}=3434$, 2935, 2837, 1686, 1605, 1505, 1269, 1222, 1163, 1125, 1035, 1002 cm^{-1}; MS (ES$^+$): *m/z* (%): 1019 [2*M*+Na]$^+$ (33), 521 [*M*+Na]$^+$ (100); HRMS (ES$^+$): *m/z* calcd for $C_{31}H_{30}NaO_6$: 521.1935; found: 521.1935.[21]

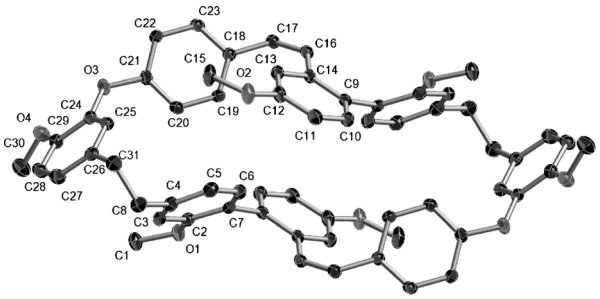
1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-etheno-8,12-metheno-12H-7-benzooxacycloeicosine (17): To an aliquot of THF (5 mL) at −78 °C containing magnesium (80 mg, 3.29 g) titanium tetrachloride (666 mg, 3.51 mmol, 0.39 mL) was added dropwise over 5 min. The reaction was allowed to warm to RT over 2 h then the resultant black solution was re-cooled to −78 °C. A solution of bisaldehyde **26** (81 mg, 0.163 mmol) in THF (10 mL) was added dropwise over 10 min then the cooling bath was removed. After 19 h at RT the reaction mixture was partitioned between water (15 mL) and chloroform (15 mL). The aqueous phase was separated and extracted with chloroform (15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in CH_2CL_2 (15 mL) and methanol (15 mL) then palladium on carbon (5%, 150 mg) was added. The flask was evacuated and purged with argon three times, then evacuated and purged with hydrogen twice. After 1 h, the reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo then purified by flash column chromatography (3:7 diethyl ether/petroleum ether) to afford the title compound (30 mg, 40%) as a viscous oil, which crystallised on trituration with petroleum ether. M.p. (petroleum ether) 153–154 °C (Lit. 155 °C (EtOH);[10c] 155–156 °C (solvent not specified);[13] Lit. 194 °C (EtOH);[10c] 199–200 °C (EtOH)[13] 205–206 °C (solvent not specified;[10d] 164 °C (solvent not specified;[10f])); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.07$ (d, $J=8.5$ Hz, 1H), 6.97 (d, $J=2.7$ Hz, 1H), 6.89 (d, $J=8.1$ Hz, 1H), 6.86–6.70 (m, 7H), 6.45 (d, $J=1.3$ Hz, 1H), 6.25 (dd, $J=7.6$, 1.6 Hz, 1H), 5.37 (d, $J=2.0$ Hz, 1H), 3.95 (s, 3H), 3.98 (s, 3H), 3.68 (s, 3H), 3.01–2.75 (m, 5H), 2.71–2.54 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.3$ (C), 156.1 (C), 152.9 (C), 148.8 (C), 147.1 (C), 143.4 (C), 141.4 (C), 139.9 (C), 134.0 (C), 132.6 (2×CH), 131.1 (C), 129.5 (CH, heavily attenuated), 129.4 (CH, heavily attenuated), 127.8 (C), 122.5 (2×CH), 121.9 (CH), 121.6 (CH), 116.8 (CH), 115.6 (CH), 112.0 (CH), 111.6 (CH), 111.3 (CH), 56.3 (CH_3), 55.4 (2×CH_3), 38.4 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 35.8 ppm (CH_2); IR (solid): $\tilde{\nu}=2926$, 1604, 1505, 1463, 1261, 1231, 1164, 1128, 1040 cm$^-$; MS (ES$^+$): *m/z* (%): 956 [2*M*+Na]$^+$ (23), 489 [*M*+Na]$^+$ (100).

(1*Z*,25*Z*)-13,14,37,38-Tetrahydro-9,17,22,33,41,46-hexamethoxy-3,7:15,18:27,30:39,42 -tetraethano-8,12:32,36-dimethano-dibenzo-[7,31-dioxa-*s*-μ]-cyclo-tetracontine ((*Z*,*Z*)-31): To a solution of NaOMe (15 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) a solution of phosphonium salt **30** (112 mg, 0.137 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 4 h. After 18 h at RT, the reaction mixture was heated at reflux for 1 h, then cooled to RT and filtered. Silica (≈4 g) was added and the solvent was removed in vacuo. Purification by flash column chromatography (7:3→2:3 petroleum ether/diethyl ether) firstly afforded *trans*-stilbene **29** (30 mg, 47%) as a white solid. M.p. ($CHCl_3$) 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.24$ (d, $J=8.5$ Hz, 1H), 7.22–7.11 (m, 2H), 7.02 (d, $J=3.0$ Hz, 1H), 6.95 (d, $J=9.0$ Hz, 1H), 6.92–6.88 (m, 2H), 6.86 (d, $J=8.0$ Hz, 1H), 6.79 (dd, $J=8.5$, 2.0 Hz, 1H), 6.63 (d, $J=7.5$ Hz, 1H), 6.58 (d, $J=16.1$ Hz, 1H), 6.52 (s, 1H), 6.04 (d, $J=16.1$ Hz, 1H), 5.77 (d, $J=2.0$ Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.66 (s, 3H), 2.97–2.75 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=158.9$ (C), 156.6 (C), 155.4



(C), 150.4 (C), 147.4 (C), 142.5 (C), 139.4 (C), 138.6 (C), 137.9 (CH), 135.8 (C), 131.9 (CH), 131.5 (C), 130.7 (C), 130.1 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 122.6 (CH), 122.6 (CH), 122.5 (CH), 119.6 (CH), 116.0 (CH), 112.5 (CH), 111.9 (CH), 110.4 (CH), 110.3 (CH), 56.2 (CH_3), 55.4 (CH_3), 55.3 (CH_3), 36.2 (CH_2), 33.7 ppm (CH_2); IR (solid): $\tilde{\nu}$ = 2933, 1602, 1510, 1500, 1260, 1227, 1161, 1126 cm^{-}; MS (ES^+): *m/z* (%): 953 $[2M+H]^+$ (34), 505 (57), 483 $[M+H]^+$ (100); HRMS (ES^+): *m/z* calcd for $C_{31}H_{29}O_4$: 465.2050; found: 465.2054.

Then the title compound (12 mg, 19%) was obtained as a crystalline solid. M.p. (CH_2Cl_2/petroleum ether) 114–116 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.06 (m, 6H), 6.94–6.61 (m, 14H), 6.49 (s, 2H), 6.21 (d, *J* = 12.1 Hz, 2H), 6.15 (d, *J* = 12.1 Hz, 2H), 3.82 (s, 6H), 3.62 (s, 6H), 3.51 (s, 6H), 2.91–2.84 ppm (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6 (2×C), 156.1 (2×C), 148.9 (2×C), 145.3 (2×C), 141.6 (2×C), 138.2 (2×C), 134.2 (2×C), 131.9 (2×CH), 131.5 (2×CH), 131.3 (2×CH), 130.7 (2×C), 130.7 (2×C), 103.4 (4×CH), 129.6 (2×CH), 128.7 (2×C), 127.3 (2×C), 123.8 (2×CH), 120.6 (2×CH), 120.1 (2×CH), 117.7 (4×CH), 113.7 (2×CH), 113.5 (2×CH), 112.7 (2×CH), 111.3 (2×CH), 56.1 (2×CH_3), 55.2 (2×CH_3), 55.1 (2×CH_3), 37.8 (2×CH_2), 36.6 ppm (2×CH_2); IR (solid): $\tilde{\nu}$ = 2933, 1602, 1504, 1463, 1422, 1270, 1227, 1167, 1125, 1038 cm^{-1}; MS (ES^+): *m/z* (%): 952 $[M+H]^+$ (13), 268 (13), 217 (100); HRMS (ES^+): *m/z* calcd for $C_{62}H_{56}NaO_8$: 951.3867; found: 951.3865.



(1*E*,25*E*)-13,14,37,38-Tetrahydro-9,17,22,33,41,46-hexamethoxy-3,7:15,18:27,30:39,42-tetraethano-8,12:32,36-dimethano-dibenzo-[7,31-dioxa-*s*-μ]-cyclo-tetracontine ((*E*,*E*)-31): A solution of bis-styrene **32** (179 mg, 0.37 mmol) and the Grubbs second generation catalyst (5 mg, 0.06 mmol) in CH_2Cl_2 was heated at reflux for 1 h and then cooled to RT. Further catalyst was added (5 mg, 0.06 mmol) and the resulting solution was heated at reflux for another 17 h. A third batch of catalyst (5 mg, 0.06 mmol) was added and after a further 2 h heating at reflux the reaction mixture was cooled to RT and concentrated in vacuo. Purification by flash column chromatography (7:3 petroleum ether/diethyl ether) afforded the title compound (38 mg, 20%) as a white crystalline solid in addition to unidentified higher oliogmers and isomers. M.p. (CH_2Cl_2/MIBK/petroleum ether; MIBK = methyl isobutyl ketone) 139–140 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.27 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 7.10–7.00 (obscured m, 2H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.03 (dd, *J* = 8.5, 2.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.92–6.80 (m, 10H), 6.77 (d, *J* = 1.5 Hz, 2H), 6.72 (d, *J* = 16.6 Hz, 2H), 3.91 (s, 6H), 3.83 (s, 6H), 3.70 (s, 6H), 2.89 pm (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (2×C), 157.5 (2×C), 156.9 (2×C), 149.7 (2×C), 144.7 (2×C), 142.4 (2×C), 137.2 (2×C), 135.0 (2×CH), 132.2 (2×C), 131.9 (2×CH), 131.9 (2×C), 130.5 (2×C), 127.9 (2×CH), 127.6 (4×CH), 127.3 (2×CH), 124.6 (2×CH), 121.2 (2×CH), 120.5 (2×CH), 117.1 (4×CH), 113.1 (2×CH), 113.1 (2×CH), 111.2 (2×CH), 109.5 (2×CH), 56.2 (2×CH_3), 55.6 (2×CH_3), 55.3 (2×CH_3), 38.8 (2×CH_2), 37.5 ppm (2×CH_2), two carbon atoms were not observed; IR (solid): $\tilde{\nu}$ = 2932, 1600, 1504, 1463, 1271, 1226, 1166, 1125, 1038, 810, 731 cm^{-1}; MS (ES^+): *m/z* (%): 951 $[M+Na]^+$ (7), 426 (46), 219 (100).

2′,4-Dimethoxy-2-vinyl-4′-{2-[3-(4-vinylphenoxy)-4-methoxyphenyl]-ethyl}biphenyl (32): To a stirred suspension of methyltriphenylphosphonium bromide (135 mg, 0.38 mmol) in THF (1 mL) at 0 °C KO*t*Bu (42 mg, 0.38 mmol) was added. After 20 min, bisaldehyde **26** (47 mg, 0.097 mmol) was added as a solution in THF (1 mL). The reaction was allowed to warm to RT and after 1.5 h the reaction mixture was partitioned between saturated aqueous NH_4Cl solution (1 mL) and CH_2Cl_2 (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×2 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (9:1 petroleum ether/ethyl acetate) afforded the title compound (34 mg, 73%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H); 6.99 (dd, *J* = 8.0, 2.0 Hz, 1H); 6.97–6.93 (m, 2H); 6.91–6.85 (m, 3H), 6.79 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.71 (s, 1H), 6.70 (dd, *J* = 17.6, 11.0 Hz, 1H), 6.49 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.65 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.64 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 5.11 (dd, *J* = 11.0, 1.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 2.91 ppm (apparent s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0 (C), 144.5 (C), 142.2 (C), 137.5 (C), 136.1 (CH), 135.8 (CH), 135.7 (C), 135.7 (C), 134.9 (C), 132.0 (C), 131.7 (CH), 131.7 (CH), 130.3 (C), 130.0 (C), 127.4 (2×CH), 127.1 (C), 124.7 (CH), 121.4 (CH), 120.4 (CH), 117.2 (C), 117.0 (2×CH), 113.8 (CH_2), 113.4 (CH), 112.9 (CH), 112.3 (CH_2), 111.2 (CH), 109.7 (CH), 56.1 (CH_3), 55.5 (CH_3), 55.3 (CH_3), 38.1 (CH_2), 36.9 ppm (CH_2); IR (neat): $\tilde{\nu}$ = 2933, 1603, 1505, 1271, 1225, 1166, 1032, 1002, 908 cm^{-1}; MS (ES^+): *m/z* (%): 515 $[M+Na]^+$ (100); HRMS (ES^+): *m/z* calcd for $C_{33}H_{32}NaO_4$: 515.2193; found: 515.2189.

3′-Bromo-4,6′-dimethoxy-2-formyl-4′-{2-[3-(4-bromomethylphenoxy)-4-methoxyphenyl]ethyl}biphenyl (39): To a solution of tetraarene **27** (95 mg, 0.19 mmol) in glacial acetic acid (2 mL) a solution of bromine (34 mg, 0.23 mmol) in glacial acetic acid (1 mL) was added. After 64 h at RT, water (2 mL) and then saturated aqueous $Na_2S_2O_3$ solution (2 mL) were added. the obtained solution was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo to give the title compound (99 mg, 81%) as a colourless oil, which was used without further purification.

4-(5-[2-{5-Bromo-2,4′-dimethoxy-2-formylbiphenyl}-ethyl]-2-methoxy phenoxy)-benzyl triphenylphosphonium bromide (40): A solution of dibromide **39** (99 mg, 0.16 mmol) and triphenylphosphine (81 mg, 0.31 mmol) in toluene (10 mL) was heated at reflux for 18 h, then cooled to 0 °C. Filtration of the reaction mixture gave the title compound (129 mg, 93%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 7.80–7.69 (m, 7H), 7.67–7.60 (m, 4H), 7.55–7.38 (m, 5H), 7.28–7.14 (m, 5H), 7.07–6.97 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85–6.75 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 5.40 (br. s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.04–2.83 ppm (m, 4H); IR (neat): $\tilde{\nu}$ = 3382, 2930, 2849, 1689, 1604, 1505, 1438, 1270, 1225, 1112 cm^{-1}; MS (ES^+) *m/z* (%): 823 $[M(^{81}Br)-Br]^+$ (100), 821 $[M(^{79}Br)-Br]^+$ (54); HRMS (ES^+): *m/z* calcd for $C_{49}H_{43}BrO_5P$: 821.2026; found: 821.2026.

(*E*)-13,14-Dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (43): To a solution of NaOMe (2 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) a solution of phosphonium salt **40** (18 mg, 0.2 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise over 20 min. After 4 h, the reaction mixture was heated at reflux for 18 h, then cooled to RT and silica (≈1 g) was added. Concentration in vacuo and purification by column chromatography (4:1 petroleum ether/diethyl ether) afforded the title compound (7.5 mg, 69%) as a white crystalline solid. M.p. (CH_2Cl_2/petroleum ether) 196–197 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (obscured m, 1H), 7.24 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.03–6.95 (m, 3H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.92–6.86 (m, 1H), 6.80 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.58 (d, *J* = 16.1 Hz, 1H), 6.43 (s, 1H), 6.10 (d, *J* = 16.1 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.56 (s, 3H), 3.15–2.94 (m, 2H), 2.87–2.70 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C), 156.1 (C), 155.5 (C), 150.5 (C), 147.6 (C), 141.1 (C), 139.7 (C), 138.6 (C), 136.4 (CH), 135.5 (C), 134.9 (CH), 131.5 (CH), 130.2 (C), 130.0 (CH), 129.9 (C), 127.7 (CH), 127.5 (CH), 123.7 (CH), 122.9 (CH), 122.1 (CH), 116.0 (CH), 114.7 (C), 112.9 (CH), 112.1 (CH), 111.4 (CH), 110.8 (CH), 56.4 (CH_3), 55.8 (CH_3), 55.5 (CH_3), 37.1 (CH_2), 33.21 ppm (CH_2); IR (solid): $\tilde{\nu}$ = 2921, 2810, 1505, 1437, 1260, 1217, 1161, 1120, 1028, 718 cm^{-1}; MS (ES^+):

m/z (%): 1107 $[2M+Na]^+$ (23), 565 $[M+Na]^+$ (86), 301 (27), 183 (71); HRMS (ES^+): *m/z* calcd for $C_{31}H_{27}BrNaO_4$: 565.0985; found: 565.0970. For the X-ray crystal structure see Figure 3.

1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (42): A solution of *trans*-stilbene **43** (163 mg, 0.30 mmol), tosylhydrazone (559 mg, 3.00 mmol) and NaOAc (246 mg, 3.00 mmol) in aqueous THF (1:1 v/v, 20 mL) was heated at reflux for 7 days and then cooled to RT. A saturated aqueous K_2CO_3 solution (10 mL) was added followed after 3 h stirring by the addition of CH_2Cl_2 (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL), then the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (4:1 petroleum ether/diethyl ether) afforded the title compound (157 mg, 96%) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.15$ (s, 1H), 7.07 (d, $J=8.5$ Hz, 1H), 6.96 (d, $J=2.7$ Hz, 1H), 6.90 (d, $J=8.2$ Hz, 1H), 6.87–6.78 (m, 5H), 6.72 (br dd, $J=8.5$, 2.1 Hz, 1H), 6.34 (s, 1H), 5.37 (d, $J=2.1$ Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.63 (s, 3H), 3.16–3.00 (m, 2H), 2.94–2.81 (m, 3H), 2.78–2.61 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.4$ (C), 157.2 (C), 155.2 (C), 154.7 (C), 153.7 (C), 152.8 (C), 149.1 (C), 143.1 (C), 139.8 (C), 139.6 (C), 136.1 (CH), 132.6 (CH), 129.5 (CH), 129.4 (CH), 122.5 (CH), 122.0 (CH), 121.6 (CH), 115.9 (CH), 115.6 (CH), 114.7 (C), 113.7 (C), 113.6 (CH), 111.9 (CH), 111.5 (CH), 56.1 (CH_3), 55.4 (CH_3), 55.2 (CH_3), 38.2 (CH_2), 37.8 (CH_2), 36.3 (CH_2), 35.4 ppm (CH_2); IR (neat): $\tilde{\nu}=2929$, 2849, 1512, 1506, 1481, 1464, 1262, 1231, 1047, 1017 cm^{-1}; MS (ES^+): *m/z* (%): 1111 $[2M+Na]^+$, 10%), 599 (39), 583 (13), 567 ([M+Na]$^+$, 30), 318 (100); HRMS (ES^+): *m/z* calcd for $C_{31}H_{29}BrNaO_4$: 567.1141; found: 567.1131.

Cavicularin (5) and Riccardin C (4)[3]: A solution of aryl bromide **42** (155 mg, 0.284 mmol) and tributyltin hydride (273 mg, 0.405 mmol) in toluene (4 mL) was degassed by sonication for 10 min, then VAZO (69 mg, 0.284 mmol) was added. The solution was heated by microwave irradiation (120 °C, 300 W) for 30 min. Silica (≈3 g) was added and the solvent was removed in vacuo. Purification by column chromatography (19:1→9:1 petroleum ether/diethyl ether, 10% K_2CO_3/silica stationary phase) afforded an inseparable 2:5 mixture of cavicularin trimethyl ether **15** and riccardin C trimethyl ether **17**. After addition of CH_2Cl_2 (5 mL) the reaction mixture was cooled to 0 °C, then BBr_3 (1.4 mL, 1.4 mmol, 1 M in CH_2Cl_2) was added over 2 min. After 18 h at RT, water (5 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL), then the combined organic phases were washed with brine (20 mL). Silica (≈2 g) was added and the solvent was removed in vacuo. Purification by column chromatography (98:2 CH_2Cl_2/methanol, 10% anhydrous K_2CO_3/silica) firstly afforded cavicularin (**5**) (26 mg, 22%) as a white solid. M.p. (diethyl ether/petroleum ether) 214–215 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.99$ (d, $J=8.0$ Hz, 1H), 6.94 (d, $J=8.0$ Hz, 1H), 6.88 (d, $J=2.5$ Hz, 1H), 6.83 (d, $J=8.3$ Hz, 1H), 6.76 (dd, $J=8.3$, 2.5 Hz, 1H), 6.72 (dd, $J=8.3$, 2.5 Hz, 1H), 6.69 (s, 1H), 6.47 (dd, $J=8.5$, 2.3 Hz, 1H), 6.41 (s, 1H), 6.16 (dd, $J=8.3$, 2.3 Hz, 1H), 6.12 (dd, $J=8.5$, 2.5 Hz, 1H), 6.11 (s, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 2.99–2.92 (m, 2H), 2.79–2.63 (m, 4H), 2.56 (apparent td, $J=13.0$, 3.7 Hz, 1H), 2.29 ppm (apparent td, $J=13.0$, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=155.6$ (C), 153.8 (C), 150.2 (C), 147.9 (C), 141.6 (C), 140.5 (C), 138.5 (C), 135.0 (C), 131.7 (C), 131.7 (CH), 131.1 (CH), 130.1 (CH), 128.9 (C), 127.8 (CH), 124.0 (C), 124.0 (C), 123.3 (C), 123.0 (CH), 117.8 (CH), 116.9 (CH), 115.1 (CH), 114.7 (CH), 113.3 (CH), 113.0 (CH), 38.1 (CH_2), 37.4 (CH_2), 30.5 (CH_2), 30.2 ppm (CH_2); IR (solid): $\tilde{\nu}=3298$, 2922, 1605, 1584, 1501, 1259, 1237, 1072, 907, 732 cm^{-1}; MS (ES^+): *m/z* (%): 867 $[2M+Na]^+$ (12), 445 $[M+Na]^+$ (100), 236 (82), 142 (90).

Secondly, riccardin C (**4**) (62 mg, 52%) was obtained as a white solid. M.p. (EtOH) 199–200 °C [Lit. 194 (EtOH),[10c] 199–200 (EtOH),[13] 205–206,[10d] 164[10f]]; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.05$ (d, $J=8.1$ Hz, 1H), 6.98 (d, J 2.9 Hz, 1H), 6.92 (d, $J=8.1$ Hz, 1H), 6.89–6.70 (m, 7H), 6.40 (d, $J=1.8$ Hz, 1H), 6.24 (dd, $J=7.7$, 1.5 Hz, 1H), 5.60 (s, 1H), 5.37 (d, $J=2.2$ Hz, 1H), 5.07 (br s, 1H), 4.79 (s, 1H), 3.11–2.59 ppm (m, 8H); ^1H NMR (400 MHz, [D_8]toluene, various temperatures): see the Supporting Information; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=156.1$ (C), 152.8 (C), 152.0 (C), 146.5 (C), 144.0 (C), 143.5 (C), 142.2 (C), 140.0 (C), 133.3 (C), 133.1 (CH), 131.6 (CH), 129.4 (2×CH, heavily attenuated), 128.5 (C), 124.5 (C), 122.4 (2×CH, heavily attenuated), 122.4 (CH), 121.9 (CH), 117.7 (CH), 116.2 (CH), 116.2 (CH), 115.1 (CH), 114.5 (CH), 38.3 (CH_2), 38.0 (CH_2), 37.3 (CH_2), 35.2 ppm (CH_2); IR (solid): $\tilde{\nu}=3408$, 2926, 1605, 1505, 1432, 1270, 1223, 1189, 907 cm^{-1}; MS (ES^+): *m/z* (%): 871 $[2M+Na]^+$ (10), 447 $[M+Na]^+$ (100).

CCDC-808507 ((*E*)-**43**), 821664 (Z,Z-**31**) and 821665 ((*E*)-**29**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We gratefully acknowledge the EPSRC, ERDF (IS:CE-Chem & Inter-Reg IVa program 4061) and GSK for funding, Dr. Gary Kelly is thanked for assistance with the sequential hydrogenation steps and Dr. Mark Light for the X-ray crystal structures.

[1] a) Y. Asakawa, *Phytochemistry* **2004**, *65*, 623–669; b) G. M. Keserü, M. Nógrádi, *Nat. Prod. Rep.* **1995**, *12*, 69–75.
[2] Y.-L. Qiu, J. D. Palmer, *Trends Plant Sci.* **1999**, *4*, 26–30.
[3] a) Y. S. Kosenkova, M. P. Polovinka, N. I. Komarova, D. V. Korchagina, N. Y. Kurochkina, V. A. Cheremushkina, N. F. Salakhutdinov, *Chem. Nat. Compd.* **2007**, *43*, 712–713; b) Y. S. Kosenkova, M. P. Polovinka, N. I. Komarova, D. V. Korchagina, S. V. Morozov, A. I. Vyalkov, N. F. Salakhutdinov, N. Y. Kurochkina, V. A. Cheremushkina, *Chem. Nat. Compd.* **2008**, *44*, 564–568.
[4] Riccardin C had previously been identified in liverworts: Y. Asakawa, R. Matsuda, *Phytochemistry* **1982**, *21*, 2143–2144.
[5] a) C. Niu, J.-B. Qu, H.-X. Lou, *Chem. Biodiversity* **2006**, *3*, 34–40; b) J. M. Scher, J. Zapp, H. Becker, N. Kather, J. Kolz, A. Speicher, M. Dreyer, K. Maksimenk, G. Bringmann, *Tetrahedron* **2004**, *60*, 9877–9881.
[6] G. Garnier, L. Bezanger-Beauquesne, G. Debraux, *Resources Médicinales de La Flore Française, Vol. 1*, Vigot Frères, Paris, **1969**, pp. 78–81.
[7] E. Kámory, G. M. Keserü, B. Papp, *Planta Med.* **1995**, *61*, 387–388.
[8] M. Tori, T. Masuya, K. Takikawa, M. Toyota, Y. Asakawa, *Ten. Yuki Kago, Tor. Koen. Yoshishu* **1986**, *28*, 9 [M. Tori, T. Masuya, K. Takikawa, M. Toyota, Y. Asakawa, *Chem. Abstr.* **1987**, *107*, 130898].
[9] N. Tamehiro, Y. Sato, T. Suzuki, T. Hashimoto, Y. Asakawa, S. Yokoyama, T. Kawanishi, Y. Ohno, K. Inoue, T. Nagao, T. Nishimaki-Mogami, *FEBS Lett.* **2005**, *579*, 5299–5304.
[10] For previous total syntheses of riccardin C see: a) Á. Gottsegen, M. Nógrádi, B. Vermes, M. Kajtár-Peredy, E. Bihátsi-Karsai, *Tetrahedron Lett.* **1988**, *29*, 5039–5040; b) Á. Gottsegen, M. Nógrádi, B. Vermes, M. Kajtár-Peredy, E. Bihátsi-Karsai, *J. Chem. Soc. Perkin Trans. 1* **1990**, 315–320; c) T. Eicher, S. Fey, W. Puhl, E. Buechel, A. Speicher, *Eur. J. Org. Chem.* **1998**, 877–888; d) K. Dodo, A. Aoyama, T. Noguchi-Yachide, M. Makishima, H. Miyachi, Y. Hashimoto, *Bioorg. Med. Chem.* **2008**, *16*, 4272–4285; e) H. Hioki, N. Shima, K. Kawaguchi, K. Harada, M. Kubo, T. Esumi, T. Hashimoto, Y. Asakawa, Y. Fukuyama, T. Nishimaki-Mogami, J.-i. Sawada, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 738–741; f) A. Speicher, M. Groh, M. Hennrich, A.-M. Huynh, *Eur. J. Org. Chem.* **2010**, 6760–6778; and reference [13].
[11] M. Toyota, T. Yoshida, Y. Kan, S. Takaoka, Y. Asakawa, *Tetrahedron Lett.* **1996**, *37*, 4745–4748.
[12] a) G. Bringmann, J. Mühlbacher, M. Reichert, M. Dreyer, J. Kolz, A. Speicher, *J. Am. Chem. Soc.* **2004**, *126*, 9283–9290; b) R. S. Coleman, M. L. Madaras in *The Chemical Synthesis of Natural Products* (Ed.: K. J. Hale), Sheffield Academic Press, Sheffield, **2000**, pp. 144–179.
[13] D. C. Harrowven, T. Woodcock, P. D. Howes, *Angew. Chem.* **2005**, *117*, 3967–3969; *Angew. Chem. Int. Ed.* **2005**, *44*, 3899–3901.

[14] a) D. C. Harrowven, I. L. Guy, L. Nanson, *Angew. Chem.* **2006**, *118*, 2300–2303; *Angew. Chem. Int. Ed.* **2006**, *45*, 2242–2245; b) D. C. Harrowven, M. I. T. Nunn, N. J. Blumire, D. R. Fenwick, *Tetrahedron Lett.* **2000**, *41*, 6681–6683.

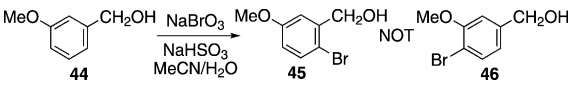
[15] a) D. C. Harrowven, M. I. T. Nunn, N. A. Newman, D. R. Fenwick, *Tetrahedron Lett.* **2001**, *42*, 961–964; b) D. C. Harrowven, B. J. Sutton, S. Coulton, *Tetrahedron Lett.* **2001**, *42*, 9061–9064; c) D. C. Harrowven, B. J. Sutton, S. Coulton, *Org. Biomol. Chem.* **2003**, *1*, 4047–4057.

[16] Y. Tobe, *Top. Curr. Chem.* **1994**, *172*, 1–40.

[17] a) D. P. Curran, A. I. Keller, *J. Am. Chem. Soc.* **2006**, *128*, 13706–13707; b) A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E. Mann, J. Parr, J. M. D. Storey, *Angew. Chem.* **2004**, *116*, 97–100; *Angew. Chem. Int. Ed.* **2004**, *43*, 95–98; c) D. C. Harrowven, B. J. Sutton, S. Coulton, *Tetrahedron* **2002**, *58*, 3387–3400.

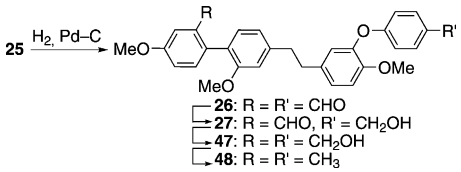
[18] a) A. Huth, I. Beetz, I. Schumann, *Tetrahedron* **1989**, *45*, 6679–6682; b) T. Oh-e, N. Miyaura, A. Suzuki, *Synlett* **1990**, 221–223; c) J.-M. Fu, V. Snieckus, *Tetrahedron Lett.* **1990**, *31*, 1665–1668; d) T. Ohe, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*, 2201–2208.

[19] In early synthetic work, we sought to use aryl bromide **46** in place of triflate **19**. Thus, 3-methoxybenzyl alcohol **44** was brominated by using the procedure described in: A. Speicher, T. Backes, S. Grosse, *Tetrahedron* **2005**, *61*, 11692–11696. The product obtained exhibited the same spectral characteristics as those reported (^{1}H, ^{13}C NMR), but subsequent derivatisation and X-ray crystallographic analysis showed that regioisomer **45** had been isolated. The discrepancy has also been noted in reference [27], in J. H. Dam, DPhil Thesis, Technical University of Denmark (Denmark), **2009** and in A. Speicher, T. Backes, K. Hesidens, J. Kolz, *Beilstein J. Org. Chem.* **2009**, *5*, No. 71. Further details are provided in the Supporting Information.



[20] a) R. F. Heck, *Org. React.* **1982**, *27*, 345–390; b) R. F. Heck, J. P. Nolley, Jr., *J. Org. Chem.* **1972**, *37*, 2320–2322; c) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

[21] Prolonging reaction times further allows reduction to diol **47** or the bistolyl derivative **48**. End points were found to be more distinct when reductions were conducted in THF.



[22] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[23] a) M. T. Reetz, G. de Vries Johannes, *Chem. Commun.* **2004**, 1559–1563; b) H. J. Li, L. Wang, *Eur. J. Org. Chem.* **2006**, 5099–5102; c) Q. Yao, E. P. Kinney, Z. Yang, *J. Org. Chem.* **2003**, *68*, 7528–7531.

[24] a) M. Kodama, Y. Shiobara, H. Sumitomo, K. Matsumura, M. Tsukamoto, C. Harada, *J. Org. Chem.* **1988**, *53*, 72–77; b) T. Eicher, S. Fey, W. Puhl, E. Buchel, A. Speicher, *Eur. J. Org. Chem.* **1998**, 877–888; c) A. Speicher, J. Kolz, R. P. Sambanje, *Synthesis* **2002**, 2503–2512.

[25] A. Gradillas, J. Pérez-Castells, *Angew. Chem.* **2006**, *118*, 6232–6247; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101.

[26] J. Tae, Y.-K. Yang, *Org. Lett.* **2003**, *5*, 741–744.

[27] S. L. Kostiuk, DPhol Thesis, University of Southampton (UK), **2009**.

[28] M. Lamberto, D. F. Corbett, J. D. Kilburn, *Tetrahedron Lett.* **2003**, *44*, 1347–1349.

[29] H. E. Ungnade, *J. Am. Chem. Soc.* **1941**, *63*, 2091–2093.

Received: May 19, 2011
Published online: August 17, 2011

