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A Concise Total Synthesis of Deoxyschizandrin and Exploration of Its Antiproliferative Effects and those of Structurally Related Derivatives

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Abstract: The natural product deoxyschizandrin has been shown to have a wide range of biological activities. In recent years the therapeutic potential of this compound against cancers has attracted significant interest. Herein we describe a concise de novo total synthesis of deoxyschizandrin based around a double organocuprate oxidation strategy. In addition, we present the results of biological studies exploring the ability of deoxyschizandrin and synthetic precursors lacking the medium ring biaryl unit to inhibit the proliferation of a human cancer cell line. These studies led to the identification of a structurally novel agent with in vitro anticancer activity.

Keywords: antitumor agents · C–C coupling · copper · medium-ring compounds · natural products

Introduction

The natural product deoxyschizandrin belongs to the dibenzocyclooctadiene class of lignans, characterised by a common carbon skeleton which consists of a biaryl unit linked by an aliphatic chain which forms an eight-membered ring system (Figure 1).[1] Deoxyschizandrin was first isolated in 1962 from the seed oil of *Schisandra chinensis*,[2] herbal preparations of which are used in traditional Chinese medicine.[3] Deoxyschizandrin has been shown to have a wide range of biological activities including antiviral[4,5] and anti-inflammatory effects.[6] In recent years the therapeutic potential of dibenzocyclooctadiene lignans against cancers has attracted significant interest;[7] several of these compounds are known to have anticancer properties[7–9] and it has been reported that pure samples of deoxyschizandrin are able to suppress the proliferation of certain human cancer cell lines.[7,10,11] However, the mechanism(s) underlying the antiproliferative effects of deoxyschizandrin (and dibenzocyclooctadiene lignans in general) have typically only been studied to a limited extent (or are not know with any great degree of certainty) and thus remain a topic of some debate.[12] Therefore there is a need for additional research into both the scope and mechanism of deoxyschizandrin's anticancer properties so that its chemotherapeutic usefulness of this natural product can be investigated and exploited further.

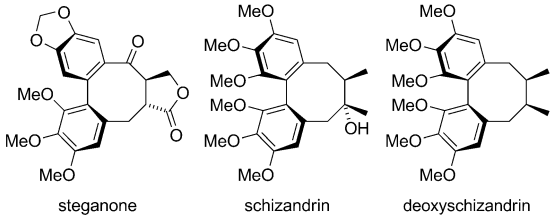

Figure 1. Examples of compounds of the dibenzocyclooctadiene class of lignans. There are two main families in this class of lignans: the steganes (e.g., steganone), which contain a butyrolactone unit, and the schizandrins (e.g., schizandrin and deoxyschizandrin) bearing two methyl substituents.[1]

Towards this end we became interested in developing a concise and efficient de novo total synthesis of deoxyschizandrin. Not only would this provide access to analytically pure samples of the natural product itself for biological testing, but it would also allow the biological activities of structurally simpler precursors generated en route to be explored and possible structure–activity relationships to be delineated; such information may provide new insight into the molecular basis of the anticancer properties of deoxyschizandrin which could ultimately facilitate the rational development of novel cancer chemotherapeutic agents. Herein we report a concise de novo total synthesis of deoxyschizandrin based around a double organocuprate oxidation strategy. In addition, we present the results of biological studies exploring the ability of deoxyschizandrin and synthetic precursors lacking the medium ring biaryl unit to inhibit the proliferation of a human cancer cell line. These studies led to the

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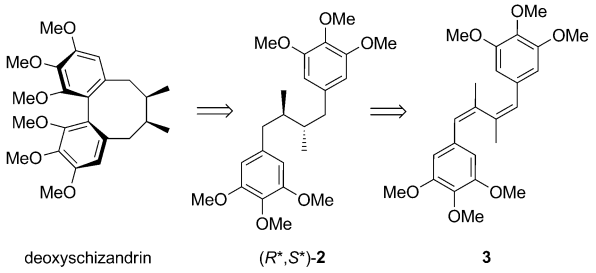
identification of a structurally novel agent with in vitro anticancer activity.

Results and Discussion

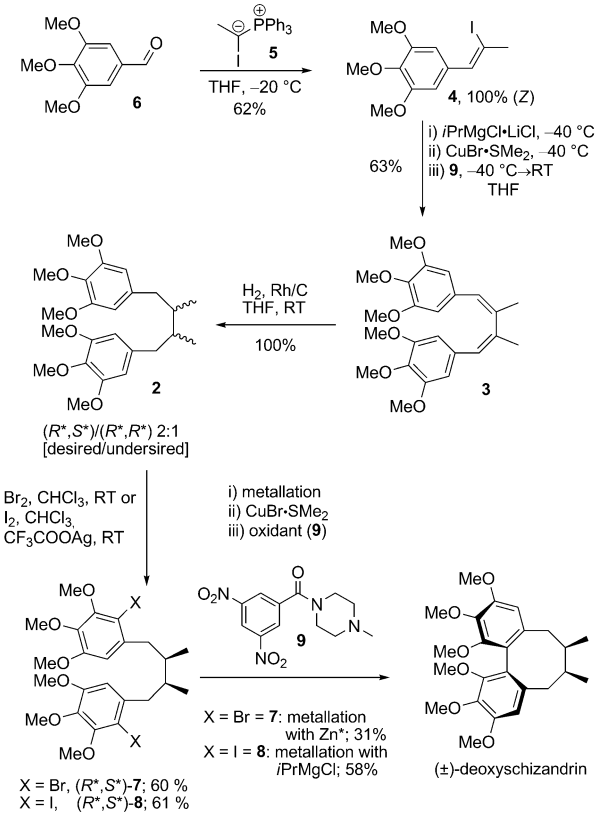
The wide range of biological activities exhibited by deoxyschizandrin, together with its interesting structural features has stimulated substantial interest from the synthetic community.[1] In this context creation of the medium ring biaryl linkage of the lignan core structure and stereoselective assembly of the methyl-substituted butane motif represent key challenges. Previous routes towards deoxyschizandrin via intramolecular biaryl bond formation have relied on various metal TFA complexes or DDQ to perform the oxidative coupling.[13–22] However it was envisaged that biaryl bond formation (with concomitant medium-ring construction) could be achieved using our previously developed methodology for aryl cuprate oxidation (Scheme 1).[23–27] In addition,



Scheme 1. Retrosynthesis of deoxyschizandrin.

we thought that the aryl substituted butane portion of the molecule could be accessed using our recently reported alkenyl cuprate homo-coupling methodology, which would provide an ideal test of the usefulness of this chemistry in complex molecule synthesis.[28] Retrosynthetically, disconnection of the biaryl bond leads to the substituted butane substrate (*R**,*S**)-**2**, from which the required aryl cuprate for bond formation could be obtained via an intermediary aryl halide (not shown). This substrate would in turn be produced from the symmetrical 1,3-diene **3** by a hydrogenation reaction and subsequent halogenation (Scheme 1). While it was recognised that this reduction would undoubtedly produce a mixture of isomers with regards to the methyl group stereochemistry, it was hoped that with an appropriate choice of hydrogenation catalyst some selectivity for the desired (*R**,*S**)-isomer could be found.

Construction of the desired symmetrical 1,3-diene **3** required alkenyl halide **4** to be synthesised. This was achieved by the use of a Stork–Wittig reaction utilising iodo ylide **5**[29] and aldehyde **6**, giving **4** in a good yield with exclusively the desired *Z* stereochemistry as determined by NOE correlations in ^{1}H NMR (Scheme 2). Attempts at homo-coupling of this substrate from the lithio-cuprate via metalation with *t*BuLi were unproductive and gave a complex reaction mixture.[27] Use of milder metalation conditions proved more



Scheme 2. Total synthesis of deoxyschizandrin.

successful, with a low temperature, functional group tolerant I/Mg exchange[30] on **4** producing an alkenyl Grignard reagent which could be transmetalated to the magnesio-cuprate and oxidised to furnish **3** in good yield (Scheme 2).This successful result with a highly sterically hindered substrate demonstrates the utility of alkenyl cuprate oxidation under difficult conditions, and again only one geometrical isomer was produced.

A range of hydrogenation catalysts were then trailed in an attempt to discover if any selectivity for the desired (*R**,*S**)-isomer of **2** could be achieved on reduction of 1,3-diene **3**. No reduction occurred with both Wilkinson and Crabtree catalysts and the reduction did not go to completion with PtO_2. Complete consumption of starting material was observed using Pd/C; however, the selectivity was slightly in favour of the undesired(*R**,*R**)-isomer giving a 1:1.4 (*R**,*S**)/(*R**,*R**)-isomer ratio. The use of Rh/C proved optimal, furnishing a mixture of (*R**,*S**)/(*R**,*R**)-isomers in a ratio of 2:1 (Scheme 2) which could not be separated by column chromatography on SiO_2.[31] However, this proved inconsequential; after bromination or iodination of this mixture the desired halogenated products isomers (*R**,*S**)-**7** and (*R**,*S**)-**8** were isolated as single diastereoisomers after recrystallization. With these intermediates in hand the key organocuprate oxidative intramolecular biaryl bond-forming reaction was attempted. Optimal results were achieved using iodo derivative (*R**,*S**)-**8**; treatment with isopropyl-

magnesium chloride, followed by transmetalation with $CuBr{\cdot}SMe_2$ and subsequent intramolecular cuprate oxidation by oxidant **9**[26] furnished the natural product (±)-deoxyschizandrin. Notably, the reaction proceeded with a good yield (considering the fact that a tetra-*ortho*-substituted biaryl and a medium ring are generated simultaneously); high dilution reaction conditions were not required and no dimer side products were observed. This result again demonstrates the utility of organocuprate oxidation under synthetically challenging conditions.

The potential of deoxyschizandrin and a range of synthetic precursors lacking the medium ring biaryl unit (**2**, **3**, **7** and **8**, Figure 2) to inhibit the proliferation of human osteosarcoma cells (U2OS line) was next examined by high-content analysis (HCA) using a Cellomics array scan. HCA is an automated microscope-based approach that enables several parameters to be assessed simultaneously at the single cell level. Cells were incubated with compounds at a range of concentrations (top concentration of 100 μM) for 24 h, then stained with a DNA dye (Hoechst) to measure cell number to assess growth inhibition and with an antibody against phosphohistone H3 (anti-PH3) to detect cells arrested in mitosis (Figure 3).

Deoxyschizandrin (and compounds **2**, **7** and **8**) was found to have relatively little effect upon cell proliferation in the HCA assay. However compound **3**, which lacks the medium ring biaryl architecture of deoxyschizadrin, caused pronounced cell death at higher concentrations and a small but significant increase in mitotic cells (Figures 3 and 4). This data suggested that **3** is capable of attenuating the proliferation of human osteosarcoma cells (U2OS line) at least in part through the inhibition of cell cycle progression by acting as a mitotic inhibitor (though cytotoxic effects also appear to be important).The fact that unsaturated analogues of **3** (**2**, **7** and **8**) were found not to have any significant effects by this assay suggests that the presence of a 1,3-diene moiety (or at least alkene(s)) in structures of this general sort is crucial for attenuating of U2OS cell proliferation by the inhibition of cell cycle progression. All compounds were subsequently screened in a 72 hour sulforhodamine B col-

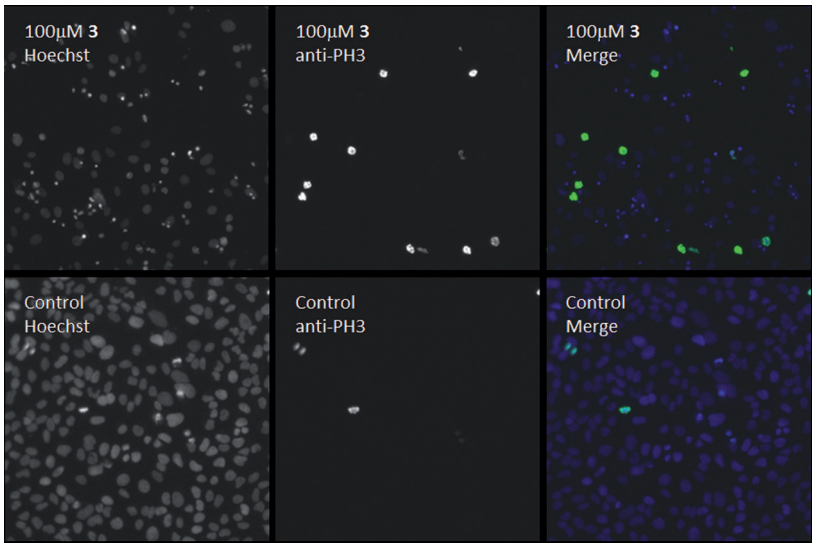


Figure 3. Images obtained from HCA which show the effect of compound **3** upon the proliferation of human osteosarcoma cells (U2OS line). Cells were incubated in the presence or absence of compound **3** (100 μM) for 24 h before being fixed and stained with a DNA dye (Hoechst) to measure cell number to assess growth inhibition (visualised in lower left and upper left panels) and with an antibody against phosphohistone H3 (anti-PH3) to detect cells arrested in mitosis (independently visualised in lower central and upper central panels). The right panels show a combined view of cells stained with both Hoechst and anti-PH3.

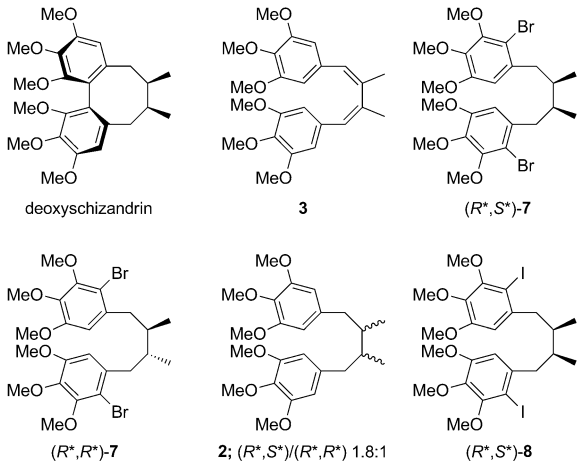


Figure 2. Compounds examined for their ability to inhibit the proliferation of human osteosarcoma cells; **3** was tested as a mixture of diastereoisomers (ratio as shown).

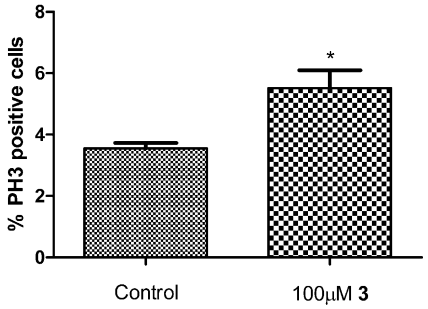


Figure 4. Effect of compound **3** (at a concentration of 100 μM) upon the number of cells arrested in mitosis. "% PH3 positive cells" refers to the proportion of cells stained with an antibody against phosphohistone H3. $P = 0.03$.

ourimetric assay for cytotoxic effects against the U2OS osteosarcoma cells. Compound **3** was once again found to be the most cytotoxic, with an IC_{50} of 43 μM. Deoxyschizandrin and **2** were found to exhibit some marginal cytotoxic effects in this longer duration assay (IC_{50} values of 127 and 166 μM, respectively).

Conclusion

In summary, we have described a concise total synthesis of deoxyschizandrin based around two key steps which both utilised organocuprate oxidation methods developed within our group. The first was the assembly a sterically congested aryl-substituted 1,3-diene with a high level of geometric purity (which was subsequently progressed to the methyl-substituted butane motif present in the final product) by the stereoselective homocoupling of an alkenyl-organocuprate. The second key step was biaryl bond formation with concomitant medium ring construction by the oxidation of an intramolecular aryl-organocuprate. These results provide a clear illustration of the usefulness of these copper-mediated coupling methodologies in complex molecule synthesis, and we envisage application of these chemistries in future target-, as well as diversity-oriented, synthesis campaigns.[32] In an attempt to further elucidate both the scope and mechanism of deoxyschizandrin's anticancer properties this natural product was assayed for its ability to inhibit the proliferation of human osteosarcoma cells (U2OS line). The compound was found to have a marginal effect, only observed under long-duration conditions, which can be primarily attributed to cytotoxicity; there was no evidence that deoxyschzandrin had any ability to induce mitotic arrest. Further studies examining the scope and mechanism of the anti-proliferative effects of this natural product against other cancer cell lines are on-going. In addition to investigating the anticancer effects of deoxyschizandrin a series of synthetic precursors lacking the medium ring architecture were also examined. This led to the discovery of **3**, a novel, non-natural derivative which inhibited the proliferation of human osteosarcoma cells, at least in part by the induction of mitotic arrest, and which also had very potent cytotoxic effects. Compound **3** may be representative of a novel structural class of compounds with anticancer properties and anti-mitotic activity; further investigation into the chemotherapeutic potential of these types molecules against other human cancers is under way and results will be reported in the near future.

Experimental Section

General methods and additional experimental details are given in the Supporting Information.

(*Z*)-5-(2-iodoprop-1-enyl)-1,2,3-trimethoxybenzene (4): *n*-Butyllithium (1.6 M in hexanes, 6.25 mL, 10.0 mmol) was added dropwise to a suspension of ethyltriphenylphosphonium bromide (3.71 g, 10.0 mmol) in anhydrous THF (50 mL) and the mixture stirred until all the solid dissolved. The resultant solution was transferred via cannula onto a pre-cooled solution of iodine (2.25 g, 8.85 mmol) in anhydrous THF (75 mL) at −78 °C and stirred for 5 min. The reaction mixture was warmed to −20 °C, sodium hexamethyldisilazane (1 M in THF, 8.5 mL, 8.5 mmol) added dropwise and the solution allowed to stir for 5 min. A solution of 3,4,5-trimethoxybenzaldehyde (**6**) (1.64 g) in anhydrous THF (25 mL) was then added and the solution stirred for a further 10 min. The reaction was poured onto saturated aqueous NH_4Cl solution (150 mL) and the organic layer separated. The aqueous layer was extracted with Et_2O (150 mL) and the combined organic extracts washed with brine (300 mL), dried ($MgSO_4$) and the solvents removed in vacuo. The residue was purified by flash column chromatography (petroleum ether (40–60)/Et_2O 1:1) to yield the title compound as a pale brown oil (1.72 g, 62 %). R_f (PE(40–60)/Et_2O 2:1) = 0.28; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (s, 2H, ArH), 6.44 (s, 1H, ArCH=C), 3.73 (s, 6H, OCH_3), 3.72 (s, 3H, OCH_3), 2.57 ppm (d, 3H, J = 1.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.2 (C), 135.9 (C), 132.7 (CH), 131.8 (C), 104.1 (CH), 97.4 (C), 69.3 (CH_3), 54.5 (CH_3), 34.1 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2938, 1581 (C=C), 1505 (C=C), 1453, 1415, 1334, 1237, 1140, 1074, 1005 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{16}O_3I$ $[M+H]^+$: 335.0144; found 335.0151; stereochemistry assigned (*Z*) on the basis of NOE correlation between signals at 6.44 and 2.57.

5,5′-((1*Z*,3*Z*)-2,3-Dimethylbuta-1,3-diene-1,4-diyl)bis(1,2,3-trimethoxybenzene) (3): Isopropylmagnesium chloride (1.96 M in THF, 1.96 mL, 3.85 mmol) was added dropwise to a suspension of lithium chloride (163 mg, 3.85 mmol) and **4** (1.17 g, 3.50 mmol) in anhydrous THF (2 mL) at −40 °C and stirred for 3 h. The resultant solution was transferred via cannula onto a pre-cooled suspension of $CuBr{\cdot}SMe_2$ (362 mg, 1.75 mmol) in anhydrous THF (2 mL) at −40 °C and stirred for 20 min. A solution of oxidant **9** (1.03 g, 3.50 mmol) in anhydrous THF (4 mL) was then added and the solution stirred at −40 °C for 30 min and at room temperature for 1 h. The reaction mixture was filtered through a plug of silica eluting with PE(40–60)/EtOAc (1:1) and the solvent removed in vacuo. The residue was purified by flash column chromatography (PE(40–60)/EtOAc 2:1) to yield the title compound as a pale yellow crystalline solid (460 mg, 63 %); R_f (PE(40–60)/EtOAc 5:1) = 0.07; m.p. 92–93 °C (PE(40–60)/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (s, 4H, ArH), 6.26 (d, 2H, J = 1.3 Hz, ArC*H*=C), 3.81 (s, 6H, OCH_3), 3.73 (s, 12H, OCH_3), 1.93 ppm (d, 6H, J = 1.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (C), 139.5 (C), 136.7 (C), 132.9 (C), 125.8 (CH), 104.5 (CH), 60.8 (CH_3), 55.8 (CH_3), 23.7 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2937, 2836, 1578 (C=C), 1504 (C=C), 1413, 1330, 1234, 1130, 1003, 728 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{31}O_6$ $[M+H]^+$: 415.2121 found 415.2141.

5,5′-(2*R,3*S**-Dimethylbutane-1,4-diyl)bis(1,2,3-trimethoxybenzene) and 5,5′-(2*R**,3*R**-dimethylbutane-1,4-diyl)bis(1,2,3-trimethoxybenzene) [(*R**,*S**)-2 and (*R**,*R**)-2]**: Diene **3** (120 mg, 0.29 mmol) was dissolved in anhydrous THF (10 mL) and the resulting solution degassed. Rhodium on activated charcoal (5 % as rhodium) was then added and the reaction mixture further degassed. The reaction mixture was then purged with hydrogen (×5) and left to stir overnight under a hydrogen atmosphere. The crude reaction mixture was filtered through Celite and the solvent removed in vacuo to yield **2** as a white solid (121 mg, 100 %) which was a 2:1 mixture of (*R**,*S**) and (*R**,*R**)-isomers as determined by comparison of integrals of characteristic signals in ^{1}H NMR. R_f (PE(40–60)/EtOAc 2:1) = 0.22; spectroscopic data for undesired (*R**,*R**)-isomer: ^{1}H NMR(400 MHz, $CDCl_3$): δ = 6.28 (s, 4H, ArH), 3.75 (s, 6H, OCH_3), 3.74 (s, 12H, OCH_3), 2.67 (dd, 2H, J = 13.4, 5.1 Hz, ArC*H*H), 2.24 (dd, 2H, J = 13.4, 9.3 Hz, ArCH*H*), 1.74–1.70 (m, 2H, C*H*CH_3), 0.80 ppm (d, 6H, J = 5.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (C), 137.4 (C), 136.0 (C), 105.8 (CH), 60.7 (CH_3), 55.9 (CH_3), 39.5 (CH_2), 38.8 (CH), 16.1 ppm (CH_3); spectroscopic data for desired (*R**,*S**)-isomer: ^{1}H NMR(400 MHz, $CDCl_3$): δ = 6.34 (s, 4H, ArH), 3.75 (s, 6H, OCH_3), 3.74 (s, 12H, OCH_3), 2.74 (dd, 2H, J = 13.4, 5.0 Hz, ArC*H*H), 2.30 (dd, 2H, J = 13.4, 9.3 Hz, ArCH*H*), 1.82–1.77 (m, 2H, C*H*CH_3), 0.80 ppm (d, 6H, J = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0 (C), 137.6 (C), 136.1 (C), 105.9 (CH), 60.9 (CH_3), 56.0 (CH_3), 39.6 (CH_2), 39.0 (CH), 16.2 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2938, 1579 (C=C), 1506 (C=C), 1462, 1416, 1332, 1239, 1123, 1008 cm^{-1}; HRMS (ESI): *m*/*z*:

calcd for $C_{24}H_{35}O_6$ $[M+H]^+$: 419.2434 found 419.2420. These data are consistent with that previously reported.[17]

5,5′-((2*R,3*S**)-2,3-Dimethylbutane-1,4-diyl)bis(4-bromo-1,2,3-trimethoxybenzene) [(*R**,*S**)-7]**: A 0.8 M solution of bromine in $CHCl_3$ (34 μL) was added dropwise to a solution of diarylbutane **2** (2:1 mixture of (*R**,*S**) and (*R**,*R**) isomers, 114 mg, 0.27 mmol) in $CHCl_3$ (6 mL) at room temperature until the yellow colour persisted. The resultant solution was stirred for 30 min and the solvent then removed in vacuo. The residue was purified by flash column chromatography (PE(40–60)/EtOAc 2:1) and the resultant oil was recrystallized (hexanes) to give (*R**,*S**)-**7** as a crystalline solid (91 mg, 60%). R_f (PE(40–60)/EtOAc 2:1) = 0.26; m.p. 136–139 °C (PE(40–60)/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (s, 2H, ArH), 3.88 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 3.85 (s, 6H, OCH_3), 2.99 (dd, 2H, J = 13.3, 3.9 Hz, (Ar)C*H*H), 2.52 (dd, 2H, J = 13.3, 10.0 Hz, (Ar)CH*H*), 1.98–1.93 (m, 2H, $CHCH_3$), 0.89 ppm (d, 6H, J = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2 (C), 150.8 (C), 141.3 (C), 136.7 (C), 111.2 (C), 110.0 (CH), 61.1 (CH_3), 60.9 (CH_3), 56.1 (CH_3), 39.7 (CH_2), 38.4 (CH), 15.8 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2939, 1567, 1479, 1394, 1337, 1108, 1011 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{32}{}^{79}Br_2O_6$ $[M+H]^+$: 575.0644; found 575.0660.

5,5′-((2*R,3*S**)-2,3-Dimethylbutane-1,4-diyl)bis(4-iodo-1,2,3-trimethoxybenzene) [(*R**,*S**)-8]**: Iodine (166 mg, 0.65 mmol) was added in portions to a slurry of diarylbutane **2** (2:1 mixture of (*R**,*S**) and (*R**,*R**) isomers(114 mg, 0.27 mmol) and silver trifluoroacetate (143 mg, 0.65 mmol) in $CHCl_3$ (15 mL) and the resultant solution stirred at room temperature for 3.5 h. The reaction mixture was then filtered through Celite and the solution washed with saturated aqueous $Na_2S_2O_3$ solution (20 mL × 2). The solvent was removed in vacuo. The residue was purified by flash column chromatography (PE(40–60)/EtOAc 3:1) and the resultant colourless oil was recrystallized (hexanes) to give (*R**,*S**)-**8** as a crystalline solid (112 mg, 62%). R_f = (PE(40–60)/EtOAc 2:1) = 0.11; m.p. 147–149 °C (PE(40–60)/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 2H, ArH), 3.87 (s, 6H, OCH_3), 3.85 (s, 6H, OCH_3), 3.83 (s, 6H, OCH_3), 3.03 (dd, 2H, J = 13.4, 3.8 Hz,(Ar)C*H*H), 2.58 (dd, 2H, J = 13.4, 10.2 Hz, (Ar)CH*H*), 2.02–1.96 (m, 2H, C*H*CH_3), 0.90 ppm (d, 6H, J = 6.7 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.2 (C), 153.0 (C), 140.3 (C),140.0 (C), 109.9 (CH),89.1 (C), 61.0 (CH_3), 60.7 (CH_3), 56.2 (CH_3), 44.1 (CH_2), 38.5 (CH_2), 15.7 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2937, 1558, 1477, 1386, 1327, 1103, 1011 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{33}I_2O_6$ $[M+H]^+$: 671.0367; found 671.0362.

(±)-Deoxyschizandrin: Isopropylmagnesium chloride (1.95 M in THF, 0.25 mL, 0.48 mmol) was added dropwise to a suspension of lithium chloride (36 mg, 0.48 mmol) and (*R**,*S**)-**8** (134 mg, 0.2 mmol) in anhydrous THF (5 mL) at −40 °C and stirred for 3 h. The resultant solution was transferred via cannula onto a pre-cooled suspension of $CuBr{\cdot}SMe_2$ (98.9 mg, 0.48 mmol) in anhydrous THF (1 mL) at −40 °C and stirred for 20 min. A solution of oxidant **9** (141 mg, 0.48 mmol) in anhydrous THF (4 mL) was then added and the solution stirred at −40 °C for 30 min and at room temperature for 1 h. The reaction mixture was filtered through a plug of silica eluting with PE(40–60)/EtOAc (1:1) and the solvent removed in vacuo. The residue was purified by flash column chromatography (PE(40–60)/EtOAc 3:1) to yield the title compound as a white solid (49 mg, 58%). R_f (PE(40–60)/EtOAc 4:1) = 0.35; m.p. 92–93 °C (PE(40–60)/EtOAc) (lit.:[33] 111–113 °C, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (s, 1H, ArH), 6.52 (s, 1H, ArH), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.86 (s, 6H, OCH_3), 3.59 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 2.57 (dd, 1H, J = 13.6, 7.3 Hz, (Ar)C*H*HCH), 2.49 (dd, 1H, J = 13.6, 1.9 Hz, (Ar)CH*H*CH), 2.27 (dd, 1H, J = 13.2, 9.2 Hz, (Ar)C*H*HCH), 2.04 (d, 1H, J = 13.0 Hz, (Ar)CH*H*CH), 1.93–1.87 (m, 1H, (Ar)CH_2C*H*), 1.82–1.77 (m, 1H, (Ar)CH_2C*H*), 0.99 (d, 3H, J = 7.2 Hz, CHC*H*$_3$), 0.73 ppm (d, 3H, J = 7.1 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (C), 151.6 (C), 151.5 (C), 151.4 (C), 140.1 (C), 139.7 (C), 139.1 (C11), 133.9 (C), 123.4 (C), 122.3 (C), 110.5 (CH), 107.2 (CH), 61.0 (CH_3), 60.9 (CH_3), 60.6 (CH_3), 60.5 (CH_3), 55.92 (CH_3), 55.89 (CH_3), 40.8 (CH), 39.1 (CH_2), 35.6 (CH_2), 33.8 (CH), 21.8 (CH_3), 12.7 ppm (CH_3); IR ($CDCl_3$): ν_{max} = 2931, 1595, 1489, 1456, 1400, 1126, 1100 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{33}O_6$ $[M+H]^+$: 417.2277 found 417.2256; these data were consistent with that previously reported.[17,33]

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[12] For example, Lin et al. reported (Ref. [10a]) that deoxyschizandrin is capable of inhibiting the proliferation of HL-60 human leukaemia cells through the induction of apoptosis. However, the authors state that it remains unclear as to whether this is the only mode of action by which deoxyschizandrin exerts this antiproliferative effect. The mechanism underlying the antiproliferative activity of deoxyschizandrin against human colorectal cancer cells observed by Gnabre et al. (Ref. [10b]) is unknown. Min et al. (Ref. [7]) do not comment upon the antiproliferative mechanism of deoxyschisandrin (referred to as schisandrin) though the lignan schisantherin C was found to induce cell cycle arrest against the same cancer cell lines. Šmejkal et al. (Ref. [10c]) have reported that deoxyschizandrin has apoptotic activity in a plant cell line but highlight the importance of carrying out further investigations in human cancer cells. Slaninová et al. (Ref. [11a]) have reported that deoxyschizandrin can inhibit growth in the doxorubicin resistant COR-L23/R human lung cancer cell line as well as its parental drug-sensitive (COR-L23) cell line. No significant changes in the cell cycle profile were observed. However, when combined with sub-toxic doses of doxorubicin, deoxyschizandrin induced cell cycle arrest in the G2M phase, which is typical for toxic doses of doxorubicin, suggesting that deoxyschizandrin increased the accumulation of doxorubicin inside the cells.

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