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Full Paper

Synthesis and X-Ray Crystal Structure of Cynandione B Analogues

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The synthesis of analogues of cynandione B, a phenolic acetophenone from *Cynanchum taiwanianum*, is described. The one-step conversion of benzochromenones to the heptacyclic spiroacetal core of cynandione B using methylmagnesium bromide is investigated and structural requirements for this novel transformation established. X-ray crystal structure analysis has established the relative configuration in these unusual heterocycles.

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Introduction

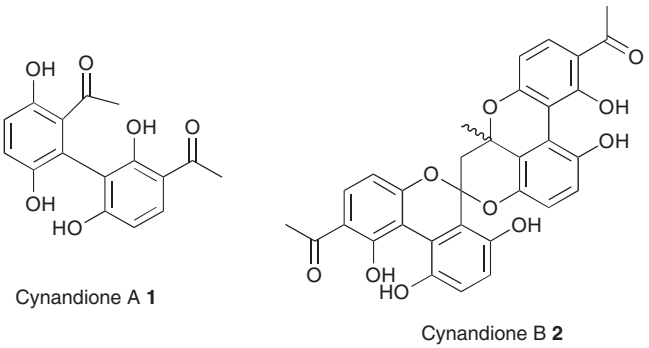
Phenolic compounds are well recognized for their antioxidant activity, which results principally from their ability to act as radical scavengers. A classic example is that of α-tocopherol, the most potent biologically active chain-breaking antioxidant in the mixture of tocopherols that make up vitamin E.[1] Cynandiones A **1** and B **2** (Fig. 1) are novel phenolic acetophenones isolated from the rhizome of *Cynanchum taiwanianum*.[2] Cynandione A **1** has been shown to be an antioxidant,[3] facilitating the breakdown of hydrogen peroxide resulting in reduced neurotoxicity to cultured rat cortical neurons, and also protects hepatocytes injured by CCl_4 due to its radical scavenging properties.[4] Cynandione B **2** shows significant in vitro cytotoxic activity against both human urinary bladder carcinoma T-24 cell lines (ED_{50} 2.5 μg mL^{-1}) and PLC/PRF/5 human liver hepatoma cell lines (ED_{50} 2.7 μg mL^{-1}),[5] and also displays antiinflammatory activity.[6] Although the complex spiroacetal containing compound cynandione B **2** is likely to be an artefact of the isolation process,[7] the enhanced cytotoxic activity of cynandione B **2** relative to that of its monomeric counterpart cynandione A **1**, along with the novelty of the spiroacetal system that it contains, makes it an interesting target for synthesis.

Recently we reported the one-step transformation of the isochromanone (*S*)-mellein **3** to the pentacyclic spiroacetal system **4** (Scheme 1),[8] a core fragment of cynandione B **2**. We felt that this novel transformation should be applicable to the synthesis of additional analogues more closely related to cynandione B **2** and, herein, report our recent efforts in this area.

Results and Discussion

Before embarking on the synthesis of cynandione B **2**, we thought it necessary to investigate the generality of the key dimerization/spiroacetal-forming reaction. It can be envisaged that formation of the core heptacyclic ring system **5** (Scheme 2) found in cynandione B **2** may be achieved by exposure of the dibenzopyranone **6** to methylmagnesium bromide under the previously established conditions.[8] Clearly, for formation of the spiroacetal core to take place a hydroxyl group is required *ortho* to the lactone carbonyl in **6**, as this ultimately forms part of the spiroacetal system. However, joining of the two non-symmetrical halves in compound **5**, via formation of the C-C bond indicated in Scheme 2, is likely to occur before spiroacetal formation and is thus not seemingly dependent upon the presence of a phenolic group. With this in mind we initially explored the dimerization process with an unsubstituted biaryl lactone.

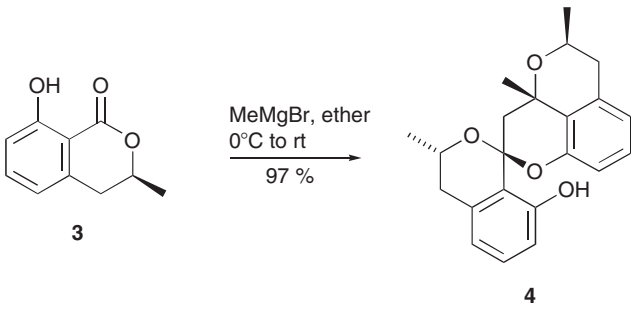
Benzochromenone **8** was prepared in two steps from 2-iodobenzoic acid **7** by esterification with phenol and biaryl coupling (Scheme 3).[9] When dibenzopyranone **8** was treated with methylmagnesium bromide at room temperature, under our previously developed conditions,[8] the only product isolated



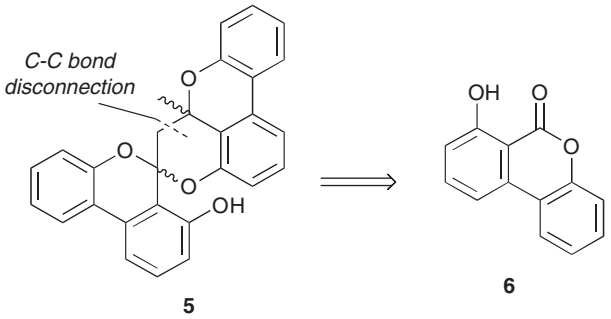
Cynandione A **1**

Cynandione B **2**

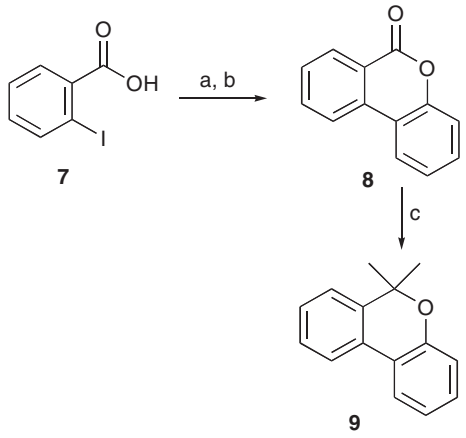
Fig. 1. Phenolic constituents from *Cynanchum taiwanianum*.



Scheme 1. Diastereoselective one-step conversion of (*S*)-mellein **3** to spiroacetal **4**.[8]



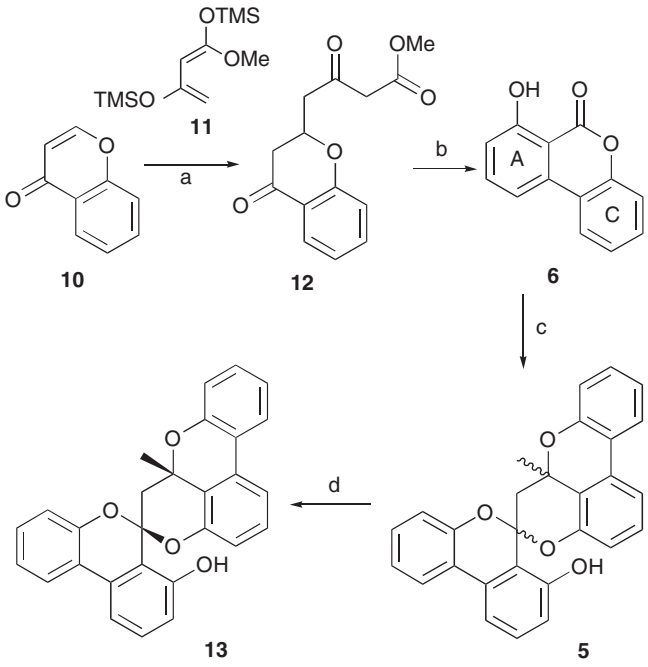
Scheme 2. Proposed retrosynthesis of the heptacyclic core **5** of cynandione B **2**.



Scheme 3. Reagents and conditions: (a) PhOH, DCC, DMAP, CH_2Cl_2, rt, 1.5 h; (b) PPh_3, $Pd(OAc)_2$, K_2CO_3, DMA, 150°C, 1.5 h (40 %, 2 steps); (c) MeMgBr (4 equiv.), THF, 0°C to rt, 3 h (41 %).

(41 % yield) was the benzochromene **9**. A similar result has been observed previously under more forcing conditions,[10] and indicates that the phenolic group is not only required as a structural component of the ultimately required spiroacetal ring system, but plays a more critical role in the initial dimerization step. A possible role for the phenolic substituent is discussed in further detail below.

We then turned to the biaryl system **6** that includes a hydroxyl group *ortho* to the lactone (Scheme 4), which was readily prepared from chromenone **10** following the procedure of Appel and co-workers.[11] Thus, reaction of chromenone **10** with diene



Scheme 4. Reagents and conditions: (a) 1) Me_3SiOTf, rt, 1 h; 2) CH_2Cl_2, 2,6-lutidine, 0°C to rt, 16 h; (b) NEt_3, EtOH, 40°C, 72 h (52 %, 2 steps); (c) MeMgBr (4 equiv.), THF, 0°C to rt, 3 h; (d) $CHCl_3$, 2 M HCl, rt, 16 h (97 %, 2 steps).

11 gave the Michael-addition product **12**, which underwent base-catalyzed rearrangement and aromatization to the biaryl **6**. Biaryl **6** was obtained in 52 % yield over the 2 steps with the spectroscopic data of the product in full accord with those reported.[11]

With the required phenolic substrate **6** in hand, we were able to attempt its possible conversion to a spiroacetal system. Thus, addition of methylmagnesium bromide (4 equiv.) to the biaryl **6** in THF led to formation of a near equal mixture of diastereoisomers **5**. The ^{1}H NMR spectrum of this mixture showed the expected complexity in the aromatic region (28 aromatic proton signals expected from the diastereoisomeric mixture **5**); however, at high field, signals indicative of this heterocyclic system[8] were evident. In particular, methyl singlets were seen at δ 1.48 and 1.70, whilst two sets of diastereotopic methylene protons appeared between δ 2.73 and 3.14. Unable to separate this mixture of diastereoisomers, the crude product mixture was exposed to acid resulting in simplification of the ^{1}H NMR spectrum to a single set of signals that included 14 aromatic signals, signals arising from a pair of geminally coupled ($J = 14.4$ Hz) methylene protons (δ 2.73 and 2.87), and a methyl singlet at δ 1.70. These data, along with the ^{13}C NMR spectrum that contained 28 individual signals including an acetal signal at δ 103.3, are consistent with structure **13**.

The relative stereochemistry depicted for racemic spiroacetal **13** (Scheme 4), in which the methyl group is oriented away from the phenolic group, would be expected by analogy with spiroacetal **4**.[8] The structure **13**, including relative stereochemistry, was confirmed by single crystal X-ray analysis (Fig. 2). The spiroacetal **13** crystallized with two independent molecules in the asymmetric unit, the two rigid molecules adopting essentially identical conformations. The hemiacetal carbon of spiroacetal **13** is characterized by the presence of one anomeric effect (n_O-σ^*_{CO}), where O3 is the donor atom and the C13-O2

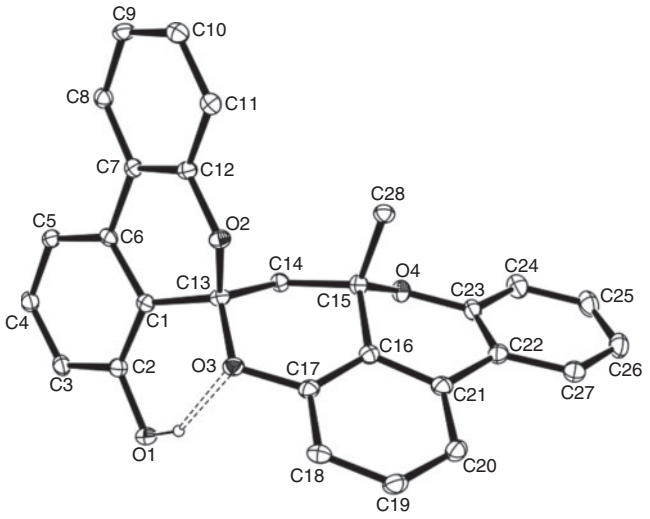
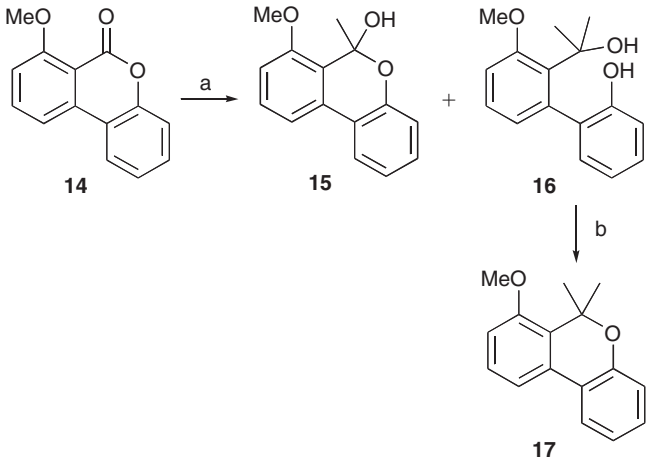


Fig. 2. X-ray crystal structure of one of the independent molecules of spiroacetal **13**; ellipsoids are at the 20 % probability level.



Scheme 5. Reagents and conditions: (a) MeMgBr (4 equiv.), THF, 0°C to rt, 3 h (**15** 37 %, **16** 30 %); (b) $BF_3.Et_2O$, benzene, rt, 5 min (86 %).

bond is the acceptor, as highlighted by the dihedral angles: C17-O3-C13-O2–86.2°; C12-O2-C13-O3–162.2°. However, there is little difference in the two C-O bond distances at the anomeric centre; thus, the O3-C13 bond distances, which are 1.428(3) and 1.425(3) Å, respectively, for molecules 1 and 2, are barely shorter than the C13-O2 bond distances 1.434(3) and 1.432(3), respectively, for molecules 1 and 2. The lack of significant structural effects associated with the anomeric effect may be due to the intrinsically weak donor ability of the phenoxy oxygen (O3), but also the presence of the intramolecular hydrogen bond (O1-H · · · O3) would further weaken this effect.

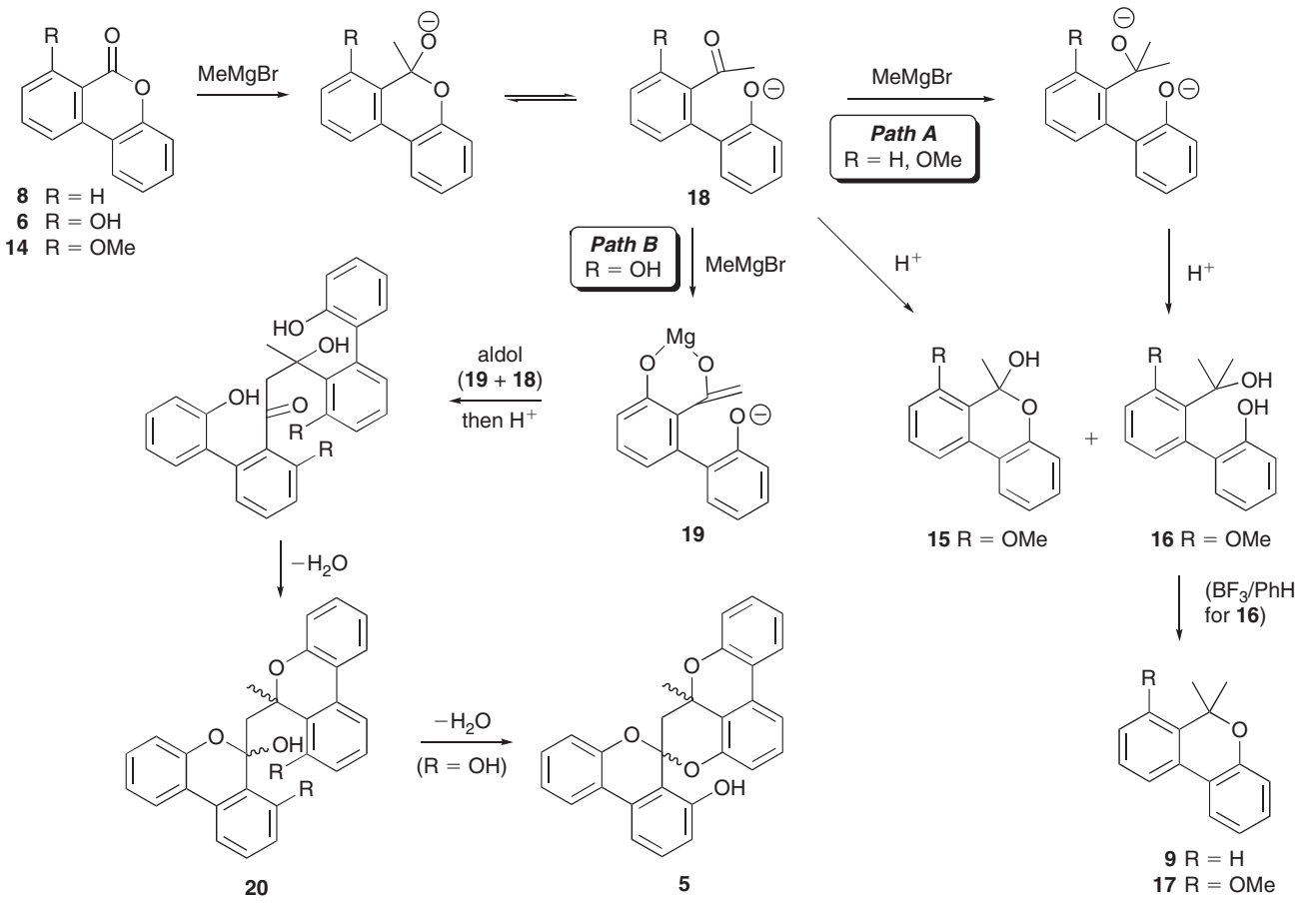
The contrasting results obtained upon treatment of the dibenzopyranones **8** and **6** with methylmagnesium bromide indicate the necessary presence of a phenolic group in these systems, not just to allow spiroacetal formation but also to assist C-C bond formation between the monomeric units. The requirement of a phenolic, and not just an oxygen substituent, at C-7 was further highlighted when the methyl ether **14** (Scheme 5), prepared from phenol **6**,[11] was exposed to methylmagnesium bromide. Under the same conditions described previously, two products could be isolated, the lactol **15** resulting from the addition of a single methyl group to **14**, and the diol **16**. The structure of the diol **16** was established from the ^{1}H NMR spectrum, which included two broad one-proton signals (δ 4.59 and 4.82) and two methyl signals (δ 1.30 and 1.46) and the IR spectrum, which included a strong absorption at 3191 cm^{-1}. No product resulting from coupling of two monomeric units was either isolated or evident in the ^{1}H NMR spectrum of the crude reaction mixture. Treatment of diol **16** with boron trifluoride in benzene[12] led to dehydration and formation of the dimethylpyran **17**. The assigned structure **17** was supported by spectroscopic analysis including the ^{1}H NMR spectrum that now showed only a single upfield methyl resonance (δ 1.72) integrating as six protons.

With regard to the mechanism of these processes, the aforementioned observations indicate that an *ortho*-phenolic group is a minimal requirement for not only spiroacetal formation but also dimerization to take place. The results, summarized in Scheme 6, show that substrates such as **8** and **14**, which lack a phenolic group, will proceed via acetophenone **18** (R = H, OMe) along path A giving only the products of addition, whereas the phenolic substrate **6** proceeds exclusively via path B to give dimeric products. This outcome may be explained by stabilization of enolate **19** via chelation, thus promoting a subsequent aldol reaction. A similar process to that described by path B has been suggested as the likely mechanism by which the conversion of cynandione A **1** to cynandione B **2** occurs during the isolation process.[7]

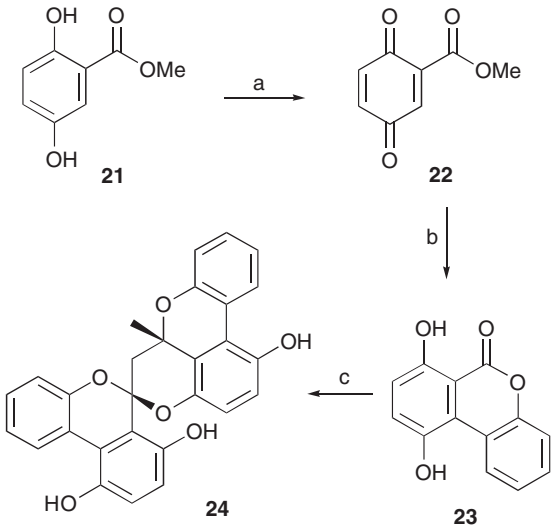
It is interesting to note that even in the absence of the phenolic group, acetophenone intermediates such as **18** (R = H, OMe) could still proceed via path B as far as the dimer **20** (R = H, OMe); however, no trace of such a compound or related intermediate was observed. This emphasizes the necessity for efficient enolate formation to occur, via the magnesium complex **19**, to enable aldol coupling (path B) to compete with further Grignard addition (path A).

Having demonstrated the formation of spiroacetal **13** from dibenzopyranone **6** we sought to extend this process further to analogues more closely related to cynandione B **2**. The approach used to form biaryl **6** (Scheme 4) has been used to prepare dibenzopyranones with a variety of substituents in the C-ring by the use of differently substituted chromenones. However, formation of a *para*-dihydroxylated A-ring would not be feasible using this approach. Thus, we adopted the strategy developed by Müller and co-workers for forming benzochromenones that takes advantage of the highly electrophilic nature of 2-carboxybenzoquinones.[13] In this approach 2-carboxybenzoquinones were combined with substituted phenols to give benzochromenones that incorporate hydroxy groups in the A-ring with the required *para*-substitution. To this end, the hydroquinone **21** (Scheme 7) was oxidized with silver(II) oxide to give the corresponding benzoquinone **22**, which was immediately reacted with phenol in the presence of trifluoroacetic acid to give the product **23** in 49 % yield, the spectroscopic data for **23** being in full accord with the assigned structure.

Treatment of **23** with methylmagnesium bromide under our standard conditions led to incomplete consumption of the starting phenol **23**, possibly as a result of the decreased solubility of **23** and its initially formed dianion in the reaction medium. Longer reaction times led to ~50 % consumption of **23** and formation of a 2 : 1 mixture of diastereoisomeric products. Subsequent exposure of the mixture to acid effected near complete conversion to a single diastereoisomer, the



Scheme 6. Pathways leading to formation of compounds **5**, **9**, **15**, and **16**.



Scheme 7. Reagents and conditions: (a) Ag_2O, Et_2O, $MgSO_4$, rt, 1.5 h; (b) PhOH, TFA, CH_2Cl_2, rt, 4 h (49 %, 2 steps); (c) 1) MeMgBr (6 equiv.), THF, 0°C to rt, 24 h; 2) $CHCl_3$, 2 M HCl, rt, 16 h (**24** 24 %, recovered **23** 48 %, 2 steps).

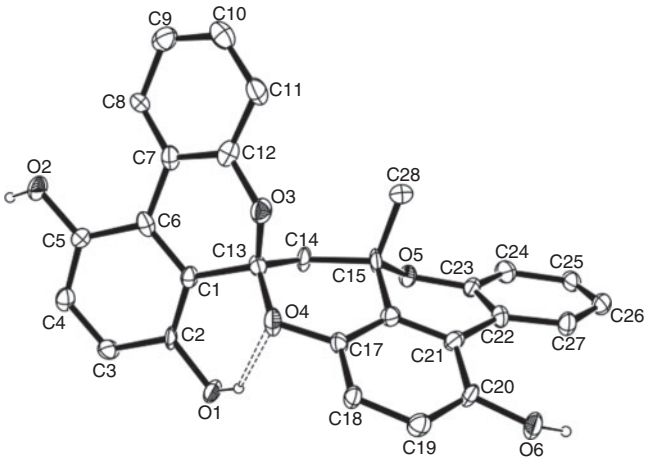


Fig. 3. X-ray crystal structure of one of the independent molecules of spiroacetal **24**; ellipsoids are at the 20 % probability level.

spectroscopic data of which were consistent with structure **24**. As with the complex spiroacetal described earlier, the product showed a pair of diastereotopic methylene signals (δ 2.74 and 3.69, *J* 14.0 Hz) and a methyl singlet (δ 1.78) in the ^{1}H NMR spectrum, whilst the ^{13}C NMR spectrum included an acetal signal at δ 101.4.

Again, the relative stereochemistry in **24** was confirmed by X-ray analysis which showed the expected orientation of the methyl substituent away from the phenolic group (Fig. 3). Compound **24** crystallized as thin needles from dichloromethane. The structure contained two molecules in the

asymmetric unit and one disordered molecule of dichloromethane. The two molecules of **24** were essentially identical. The configuration of **24** at the anomeric centre is the same as that observed for **13** and the structure is also stabilized by an intramolecular hydrogen bond (O1-H · · · O4). The low quality of the data obtained for **24** makes any discussion of bond distances inappropriate.

Conclusion

We have demonstrated that the one-step dimerization of benzochromenones to complex spiroacetal systems, constituting the core of cynandione B **2**, is possible using methylmagnesium bromide. The sequence of events leading to formation of these novel systems and the crucial role of the phenolic substituent have been identified. Future work will involve the preparation of additional analogues more closely related to cynandione B **2**, which may be assessed for antioxidant/antiinflammatory and cytotoxic activities.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded using a Varian-500 spectrometer operating at 500 MHz and 125 MHz, respectively. NMR spectra were obtained in either $CDCl_3$, [D6]acetone, or [D6]DMSO, as indicated. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Gas chromatography-mass spectrometry (GCMS) spectra were recorded on an Agilent 7890A GC system using a HP-5MS column (30 m, i.d. 0.25 mm, film thickness 0.25 μm) and 5975C MS system (EI, 70 eV). GC heat program: $100_5 \rightarrow 250_5$, heating rate 5°C min^{-1}. The retention time (R_t) and selected fragment ions as their mass/charge ratio (*m/z*) are reported. All moisture sensitive reactions were performed under a dry nitrogen or argon atmosphere in oven-dried or flame-dried glassware. Anhydrous tetrahydrofuran (THF) was pre-dried over activated alumina under argon. Thin-layer chromatography was performed on pre-coated silica plates (Merck $60GF_{254}$) and compounds were visualized at 254 and 365 nm or stained with either phosphomolybdic acid or potassium permanganate solutions. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh) using the indicated solvent system.

X-Ray Crystallography

Intensity data were collected with an Oxford Diffraction SuperNova CCD diffractometer using Cu-Kα radiation (graphite crystal monochromator $\lambda = 1.54184$ Å); the temperature during data collection was maintained at 130.0(1) K using an Oxford Cryosystems cooling device.

The structures were solved by direct methods and difference Fourier synthesis.[14] Thermal ellipsoid plots were generated using the program *ORTEP-3*[15] integrated within the *WINGX*[16] suite of programs.

Crystal data for 13. $C_{28}H_{20}O_4$, $M = 420.44$, $T = 130.0(1)$ K, $\lambda = 1.5418$ Å, monoclinic, space group $P\ 2_1/c$, $a = 5.2023(3)$, $b = 28.093(2)$, $c = 27.097(2)$ Å, $\beta = 91.156(6)^o$, $V = 3959.3(5)$ Å^3, $Z = 8$, $D_c = 1.411$ mg M^{-3} μ(Cu-Kα) 0.757 mm^{-1}, F(000) = 1760, crystal size 0.35 × 0.02 × 0.02 mm. 27143 reflections measured, 7136 independent reflections ($R_{int} = 0.1045$), the final R was 0.0416 [$I > 2\sigma(I)$], and *w* R(F^2) was 0.0820 (all data).

Crystal data for 24. $(C_{28}H_{20}O_6)_2$ (CH_2Cl_2), $M = 989.81$, $T = 130.0(1)$ K, $\lambda = 1.5418$ Å, monoclinic, space group $P2_1/c$, $a = 12.727(2)$, $b = 26.418(5)$, $c = 13.5955(19)$ Å, $\beta = 97.70(2)^o$, $V = 4530.0(14)$ Å^3, $Z = 4$, $D_c = 1.451$ mg M^{-3} μ(Cu-Kα) 1.879 mm^{-1}, F(000) = 2056, crystal size 0.28 × 0.08 × 0.02 mm. 14816 reflections measured, 6734 independent reflections ($R_{int} = 0.1735$), the final R was 0.0873 [$I > 2\sigma(I)$], and *w* R(F^2) was 0.1622 (all data).

Synthesis

6,6-Dimethyl-6H-benzo[c]chromene **9**

To lactone **8** (50 mg, 0.27 mmol) in THF (2.5 mL) at 0°C under nitrogen was added MeMgBr (3 M in Et_2O, 0.35 mL, 1.05 mmol) dropwise. The reaction was allowed to stir at 0°C for 45 min, then at room temperature for 2.5 h. 2 M HCl was then added and the product extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated under vacuum then purified via flash chromatography ($CHCl_3$: petrol 3 : 1) to yield the benzopyran **9** as a colourless oil (22 mg, 41 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (6H, s), 6.95 (1H, dd, *J* 8.1, 1.0 Hz), 7.02 (1H, ddd, *J* 7.5, 7.5, 1.1 Hz), 7.21–7.26 (2H, m), 7.30 (1H, ddd, *J* 7.4, 7.4, 1.5 Hz), 7.35 (1H, ddd, *J* 7.5, 7.5, 1.5 Hz), 7.72–7.74 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 77.5, 118.0, 121.5, 122.2, 122.5, 122.8, 123.2, 127.7, 127.9, 128.6, 129.4, 139.5, 152.7. ν_{max}(neat)/cm^{-1} 2979, 1484, 1437, 1251, 1151, 1105. GCMS (R_t 20.40 min) *m/z* 210 ([M]$^+$, 13 %), 195 (100).

The ^{1}H NMR data is in agreement with reported data.[10]

Spiro-dimer **13**

To lactone **6** (50 mg, 0.24 mmol) in THF (2.5 mL) at 0°C under nitrogen was added MeMgBr (3 M in Et_2O, 0.32 mL, 0.96 mmol) dropwise. The reaction was allowed to stir at 0°C for 45 min, then at room temperature for 2.5 h. 2 M HCl was then added and the product extracted with EtOAc (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) then concentrated under vacuum. The crude product in a mixture of $CHCl_3$ (4 mL) and 2 M HCl (0.5 mL) was then stirred vigorously at room temperature overnight. The mixture was diluted with water and the product extracted with $CHCl_3$ (3 × 5 mL), dried ($MgSO_4$), concentrated under vacuum then purified via flash chromatography (gradient elution, $CHCl_3$: petrol 1 : 1 to 4 : 1) to yield the spiroacetal **13** as a colourless solid (48 mg, 97 %). A small sample was recrystallized from CH_2Cl_2 : hexane to obtain crystals suitable for X-ray analysis, mp 184–187°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (3H, s), 2.73 (1H, d, *J* 14.4 Hz), 2.87 (1H, d, *J* 14.4 Hz), 6.87 (1H, dd, *J* 8.1, 1.2 Hz), 6.92 (1H, dd, *J* 8.1, 1.2 Hz), 6.95 (1H, dd, *J* 7.6, 1.5 Hz), 7.05–7.10 (3H, m), 7.12 (1H, ddd, *J* 7.6, 7.6, 1.2 Hz), 7.23–7.29 (2H, m), 7.37–7.43 (3H, m), 7.47 (1H, dd, *J* 7.8, 1.0 Hz), 7.79 (1H, dd, *J* 7.8, 1.7 Hz), 7.82 (1H, dd, *J* 7.9, 1.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6 (CH_3), 40.6 (CH_2), 70.8 (C), 103.3 (C), 114.5 (CH), 115.7 (CH), 117.4 (CH), 117.7 (CH), 117.8 (CH), 117.9 (C), 118.5 (CH), 119.2 (C), 120.8 (C), 122.0 (CH), 122.68 (C), 122.70 (CH), 123.5 (CH), 123.7 (CH), 129.7 (CH), 130.01 (C), 130.04 (CH), 130.1 (CH), 130.6 (C), 131.0 (CH), 148.0 (C), 149.6 (C), 151.9 (C), 153.2 (C). ν_{max}(neat)/cm^{-1} 3451, 3063, 1591, 1460, 1434, 1246, 1228, 1106, 1069. LRMS (ESI) *m/z* 421 ([M+H]$^+$, 8 %), 211 (100). HRMS (ESI) found 421.1435, $C_{28}H_{21}O_4$ [M+H]$^+$ requires 421.1434.

7-Methoxy-6-methyl-6H-benzo[c]chromen-6-ol ***15*** *and 2′-(2-hydroxypropan-2-yl)-3′-methoxybiphenyl-2-ol* ***16***

To lactone **14** (50 mg, 0.22 mmol) in THF (2.5 mL) at 0°C under nitrogen was added MeMgBr (3M in Et_2O, 0.30 mL, 0.90 mmol) dropwise. The reaction was allowed to stir at 0°C for 30 min, then at room temperature for 2 h. 2 M HCl was then added and the product extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated under vacuum then purified via flash chromatography ($CHCl_3$: THF 95 : 5) to yield the lactol **15** as a colourless oil (20 mg, 37 %) and the diol **16** as a colourless solid (17 mg, 30 %), mp 152–155°C.

Benzochromenol **15** data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (3H, s), 3.94 (3H, s), 4.56 (1H, s), 6.92 (1H, dd, *J* 8.0, 1.0 Hz), 7.04 (2H, m), 7.26 (1H, m), 7.39 (1H, dd, *J* 8.1, 8.1 Hz), 7.44 (1H, dd, *J* 8.1, 1.1 Hz), 7.72 (1H, dd, *J* 8.5, 1.3 Hz). ν_{max}(neat)/cm^{-1} 3428, 2936, 1596, 1464, 1428, 1256, 1069, 1054, 1019. GCMS (R_t 27.69 min) *m/z* 224 ([M-H_2O]$^+$, 64 %), 209 (100), 165 (49), 152 (27).

Diol **16** data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (3H, s), 1.46 (3H, s), 3.98 (3H, s), 4.59 (1H, br s), 4.82 (1H, br s), 6.76 (1H, m), 6.92 (2H, m), 7.03 (2H, m), 7.25 (1H, m), 7.28 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.9 (CH_3), 31.2 (CH_3), 55.8 (CH_3), 74.5 (C), 112.1 (CH), 115.4 (CH), 120.0 (CH), 125.8 (CH), 127.6 (CH), 129.0 (CH), 129.6 (CH), 130.7 (C), 134.6 (C), 136.3 (C), 152.4 (C), 158.1 (C). ν_{max}(neat)/cm^{-1} 3191, 2943, 1444, 1359, 1248, 1155, 1089, 1018. GCMS (R_t 26.39 min) *m/z* 240 ([M-H_2O]$^+$, 12 %), 225 (100), 210 (20). HRMS (ESI) found 281.1148, $C_{16}H_{18}NaO_3$ [M+Na]$^+$ requires 281.1148.

7-Methoxy-6,6-dimethyl-6H-benzo[c]chromene ***17***

To diol **16** (15 mg, 0.06 mmol) in benzene (0.5 mL) at room temperature was added BF_3.Et_2O (10 μL, 0.08 mmol). The reaction was allowed to stir at room temperature for 5 min then diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated under vacuum then purified via flash chromatography (EtOAc : petrol 1 : 1) to yield the benzopyran **17** as a colourless oil (12 mg, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (6H, s), 3.85 (3H, s), 6.86 (1H, dd, *J* 8.2, 1.0 Hz), 6.91 (1H, dd, *J* 8.1, 1.2 Hz), 6.98 (1H, m), 7.20 (1H, m), 7.29 (1H, m), 7.37 (1H, dd, *J* 7.9, 1.1 Hz), 7.64 (1H, dd, *J* 7.9, 1.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.5 (CH_3), 55.4 (CH_3), 78.3 (C), 110.9 (CH), 114.9 (CH), 117.8 (CH), 121.2 (CH), 121.9 (C), 123.4 (CH), 128.1 (C), 128.3 (CH), 129.3 (CH), 130.5 (C), 152.7 (C), 155.7 (C). ν_{max}(neat)/cm^{-1} 2932, 1594, 1464, 1427, 1267, 1253, 1085, 1022. GCMS (R_t 25.12 min) *m/z* 240 ([M]$^+$, 15 %), 225 (100), 210 (24). HRMS (ESI) found 241.1223, $C_{16}H_{17}O_2$ [M+H]$^+$ requires 241.1223.

7,10-Dihydroxy-6H-benzo[c]chromen-6-one ***23***

To hydroquinone **21** (0.25 g, 1.49 mmol) in diethyl ether (5 mL) was added $MgSO_4$ (0.52 g, 4.32 mmol) and silver(I) oxide (0.85 g, 3.67 mmol). The reaction was stirred for 2 h in the dark and then filtered, washed with chloroform (10 mL) and concentrated under vacuum to give crude quinone **22** as an orange oil. The quinone **22** in CH_2Cl_2 (2 mL) was added dropwise to a solution of phenol (140 mg, 1.49 mmol) and trifluoroacetic acid (0.1 mL) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 4 h. After removal of solvent under vacuum the residual solid was recrystallized from acetone to give **23** (165 mg, 49 %) as pale yellow crystals, mp 255–257°C. ^{1}H NMR (500 MHz, [D6]DMSO) δ 7.01 (1H, d, *J* 8.9 Hz), 7.39 (3H, m), 7.51 (1H, m), 9.11 (1H, d, *J* 8.2 Hz), 11.08 (1H, br s). ^{13}C NMR (125 MHz, [D6]DMSO) δ 105.7 (C), 116.8 (CH), 117.2 (CH), 118.5 (C), 119.0 (C), 125.1 (CH), 126.4 (CH), 128.3 (CH), 129.6 (CH), 147.6 (C), 149.4 (C), 154.8 (C), 165.4 (C). ν_{max}(neat)/cm^{-1} 3359, 3199, 1656, 1590, 1436, 1185. LRMS (ESI) *m/z* 229 ([M+H]$^+$, 100 %), 227 (90). HRMS (ESI) found 229.0495, $C_{13}H_9O_4$ [M+H]$^+$ requires 229.0495.

Spiro-dimer ***24***

To lactone **23** (50 mg, 0.22 mmol) in THF (10 mL) at 0°C under nitrogen was added MeMgBr (3 M in Et_2O, 0.45 mL, 1.35 mmol) dropwise. The reaction was allowed to stir at 0°C for 15 min, then at room temperature for 24 h. 2 M HCl was then added and the product extracted with $CHCl_3$ (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) then concentrated under vacuum. The crude product in a mixture of $CHCl_3$ (4 mL) and 2 M HCl (0.5 mL) was then stirred vigorously at room temperature overnight. The mixture was diluted with water and the product extracted with $CHCl_3$ (3 × 5 mL), dried ($MgSO_4$), concentrated under vacuum then purified via flash chromatography ($CHCl_3$: EtOAc 95 : 5) to yield the starting lactone **23** (24 mg, 48 %) and spiroacetal **24** as a colourless solid (12 mg, 24 %). A small sample was recrystallized from CH_2Cl_2 : hexane to obtain crystals suitable for X-ray crystal analysis, mp 200–205°C (dec.). ^{1}H NMR (500 MHz, [D6]acetone) δ 1.78 (3H, s), 2.74 (1H, d, *J* 14.0 Hz), 3.69 (1H, d, *J* 14.0 Hz), 6.65 (1H, d, *J* 8.8 Hz), 6.83 (1H, d, *J* 8.8 Hz), 6.88 (1H, d, *J* 8.8 Hz), 6.92 (1H, dd, *J* 8.1, 1.1 Hz), 6.93 (1H, dd, *J* 8.0, 1.1 Hz), 6.98 (1H, d, *J* 8.8 Hz), 7.04 (1H, m), 7.07 (1H, m), 7.20–7.24 (2H, m), 8.08 (1H, br s), 8.60 (1H, dd, *J* 8.0, 1.6 Hz), 8.67 (1H, br s), 8.68 (1H, br s), 8.78 (1H, dd, *J* 8.2, 1.6 Hz). ^{13}C NMR (125 MHz, [D6]acetone) δ 25.2, 41.4, 72.7, 101.4, 115.6, 117.4, 117.8, 118.0, 118.2, 118.3, 118.5, 119.0, 121.6, 122.0, 122.2, 122.6, 123.7, 129.2, 129.4, 129.5, 143.4, 147.9, 148.6, 149.5, 150.6, 152.9; (2 signals obscured). ν_{max}(neat)/cm^{-1} 3375, 2921, 1471, 1429, 1228. LRMS (ESI) *m/z* 453 ([M+H]$^+$, 5 %), 227 (100). HRMS (ESI) found 453.1334, $C_{28}H_{21}O_6$ [M+H]$^+$ requires 453.1333.

Supplementary Material

^{1}H and ^{13}C NMR spectra for compounds **9**, **13**, **16**, **17**, **23** and **24** are available from the Journal's website. Crystallographic information files for **13** and **24** have been deposited with the Cambridge Crystallographic Data Centre and assigned the deposit codes 851887 and 851888, respectively. These can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

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