Synthetic and biological studies on the *spiro*-mamakone system†

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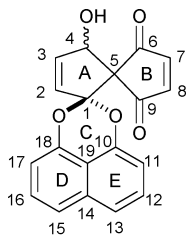
An exploration of the chemistry of the *spiro*-mamakone system, exemplified by the cytotoxic, fungal metabolite *spiro*-mamakone A, is presented. The first reported synthesis of the *spiro*-mamakone carbon skeleton was achieved, as well as the synthesis of a variety of closely related analogues of the natural product. Biological testing of the synthetic analogues generated a structure–activity profile for the natural product, establishing the importance of the enedione moiety to biological activity.

Introduction

As part of on-going studies on biologically active fungal metabolites from New Zealand sources, our group recently disclosed the structure of *spiro*-mamakone A, **1**, isolated from a non-sporulating, endophytic fungus of the New Zealand native tree *Knightia excelsa* (rewarewa).[1] This compound, and related natural products,[2] represent new members of the spirobisnaphthalene family of natural products.[3] The spirobisnaphthalenes are a relatively new and diverse class of compounds in which two naphthalene-derived C_{10} units are bridged by a *spiro*-acetal linkage with, in some cases, further bridging bonds: an additional oxygen bridge for the preussomerins and a C–C bond in the case of the spiroxins.[4,5] This class displays a variety of biological activities, with many possessing antimicrobial, herbicidal and antitumour properties.



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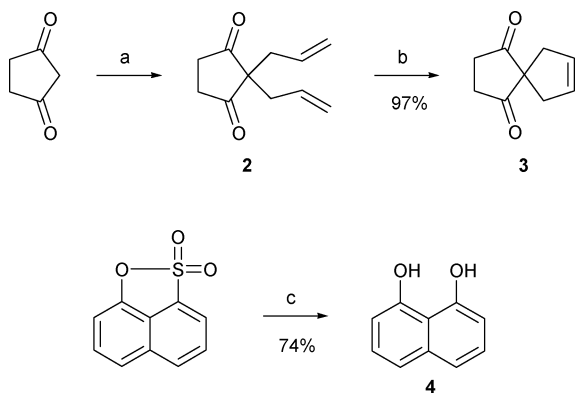
spiro-Mamakone A displays potent cytotoxicity (IC_{50} of 0.33 μM against the murine leukaemia cell line P388) and antimicrobial activity. It is particularly interesting from a structural perspective, containing an unprecedented *spiro*-nonadiene motif which features a high degree of oxidation and unsaturation. This entity has been shown by our group to be derived biosynthetically from one of the naphthalene units *via* oxidative rearrangement of an epoxide followed by decarboxylation and ring-closure.[6] Interestingly, *spiro*-mamakone A was isolated as a racemate, which is accounted for by the proposed biosynthetic pathway. The relationship between the chemical structure of this unusual motif and the biological activity of **1** is of interest, and an exploration of the chemistry of the *spiro*-mamakone system was undertaken. The preparation of a series of *spiro*-mamakone analogues is presented here, along with their observed biological activities.

Results and discussion

Synthetic studies

The carbon skeleton of the *spiro*-mamakone system was assembled *via* modification of the synthetic strategy reported by Taylor and co-workers in their synthesis of palmarumycin CP_1, CP_2 and other spirobisnaphthalenes.[7,8] Thus, the *spiro*-acetal linkage between 1,8-dihydroxynaphthalene and an appropriate ketone was to be generated. The known *spiro*[4.4]nonadione, **3**,[9] was chosen as the precursor as it has the appropriate C_9 skeleton and contains orthogonal functionality in each ring. The synthesis of **3** was undertaken, with minor changes to the original literature protocol (Scheme 1). Thus, diallylation of cyclopentanone was accomplished *via* the recent procedure reported by Kayaki *et al.*[10] and ring-closing metathesis was carried out using Grubbs' 2nd, rather than 1st, generation catalyst. It was found that the yield of the *spiro*-annulated adduct **3** could be improved if crude **2** was subjected directly to ring-closing metathesis, such that near quantitative yields could be obtained over two steps.



Scheme 1 Preparation of starting materials: (a) allyl alcohol, $Pd_2(dba)_3$, $P(OC_6H_5)_3$; (b) Grubbs' 2nd generation catalyst; (c) KOH, Δ.

1,8-Dihydroxynaphthalene, **4**, was synthesised following the protocol employed by Taylor and co-workers, and first described by Erdmann (Scheme 1).[11] Next, coupling of **3** and **4** to form a *spiro*-acetal linkage was investigated. A variety of acids and

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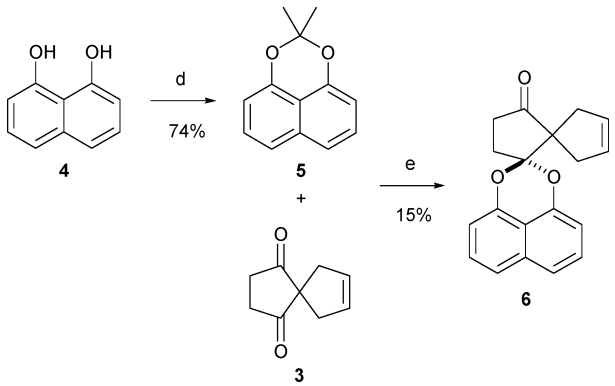
dehydration conditions were surveyed but without success. The oxidative autopolymerisation of 1,8-dihydroxynaphthalene to give a black tar competed with acetal formation under these conditions, despite efforts to preclude oxygen.

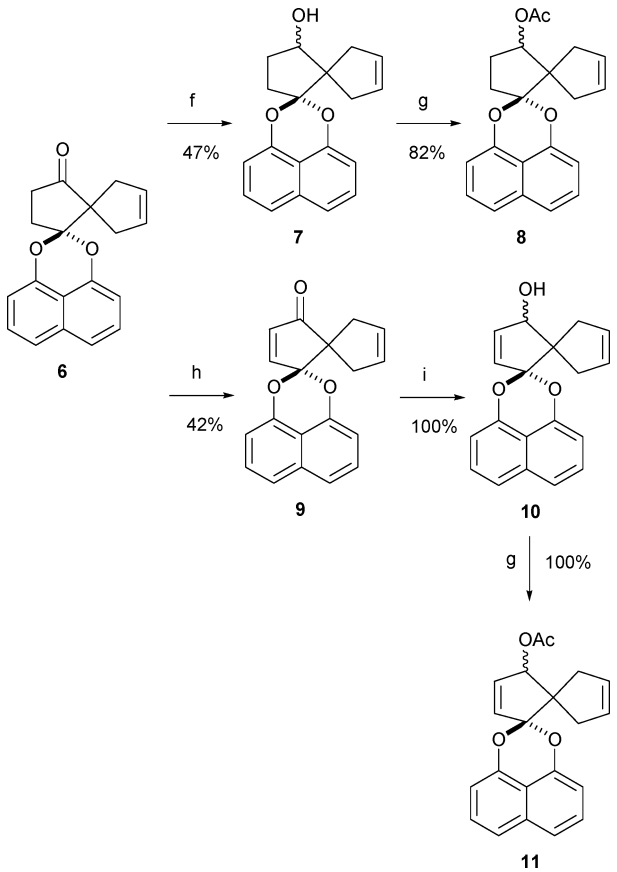
An acetal exchange method was successfully employed to form the crucial *spiro*-acetal linkage (Scheme 2). 1,8-Dihydroxynaphthalene was converted to the acetonide, **5**, and an acetal exchange with **3** yielded **6** in the presence of triflic acid under gentle heating, albeit in a modest 15% yield (60%, based on recovered starting material).



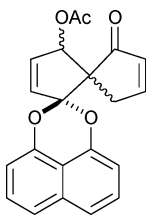
Scheme 2 Preparation of *spiro*-mamakone skeleton: (d) dimethoxypropane, pTSA; (e) triflic acid.

With the *spiro*-mamakone carbon skeleton in hand, attention was turned to exploring the oxidation level of the northern hemisphere (Scheme 3). Manipulation of ring A was first examined. Ketone **6** was reduced to racemic alcohol **7**. Whilst treatment of **6** with DDQ (in refluxing benzene or dioxane) returned only starting material, reaction with IBX, with *N*-methoxypyridine-*N*-oxide hydrate as an additive, at elevated temperatures afforded enone **9** in moderate yield (42%).[12] Enone **9** was selectively reduced to the allylic alcohol **10** under Luche reduction conditions.[13] Alcohols **7** and **10** were converted to acetates, **8** and **11** respectively, to facilitate further chemical modifications.

Having prepared analogues with varying degrees of oxidation in ring A, including allylic alcohol **10** which is directly analogous to the natural product, manipulation of ring B was next examined. Analogues featuring an enone in place of the enedione of the parent natural product, such as **12**, would be useful for comparison in a structure–activity profile. A single allylic oxidation was therefore investigated with analogues **6**, **8**, **9** and **11**. The rhodium-catalysed, allylic oxidant system developed by Catino *et al.* successfully oxidized these substrates to yield enones.[14] However, ^{1}H and 2D NMR spectroscopy suggested that the enones formed were not analogous to enone **12**, and were instead enones formed with olefin migration (Scheme 4). Specifically, it was observed that the COSY coupling between the down-field enone protons (for example 7.55 ppm in enone **13**) and the methylene protons (2.94 and 2.50 ppm) which would be anticipated, was absent. To unambiguously distinguish between the regioisomeric enone possibilities, **18** and its enantiomer were reduced under Luche reduction conditions (Scheme 5). This yielded one major isomer, whose ^{1}H and COSY NMR data corresponded to **19**, confirming that allylic oxidation had occurred with olefin migration. Several alternative allylic oxidant systems were also examined ($Pd(OH)_2$–^{t}BuOOH,[15] CrO_3–DMP,[16] PDC–^{t}BuOOH[17] and $Bi(NO_3)_3\cdot 5H_2O$–^{t}BuOOH[18]), but these also yielded enones with olefin migration and furthermore, were slower in achieving the oxidation than the rhodium-catalysed oxidation. Allylic oxidation of olefins **8** and **11** yielded separable mixtures of enones **14** and **15** (ratio of 1 : 1.3, as judged by ^{1}H NMR of the crude mixture), and **17** and **18** (ratio of 1 : 2.4) respectively.

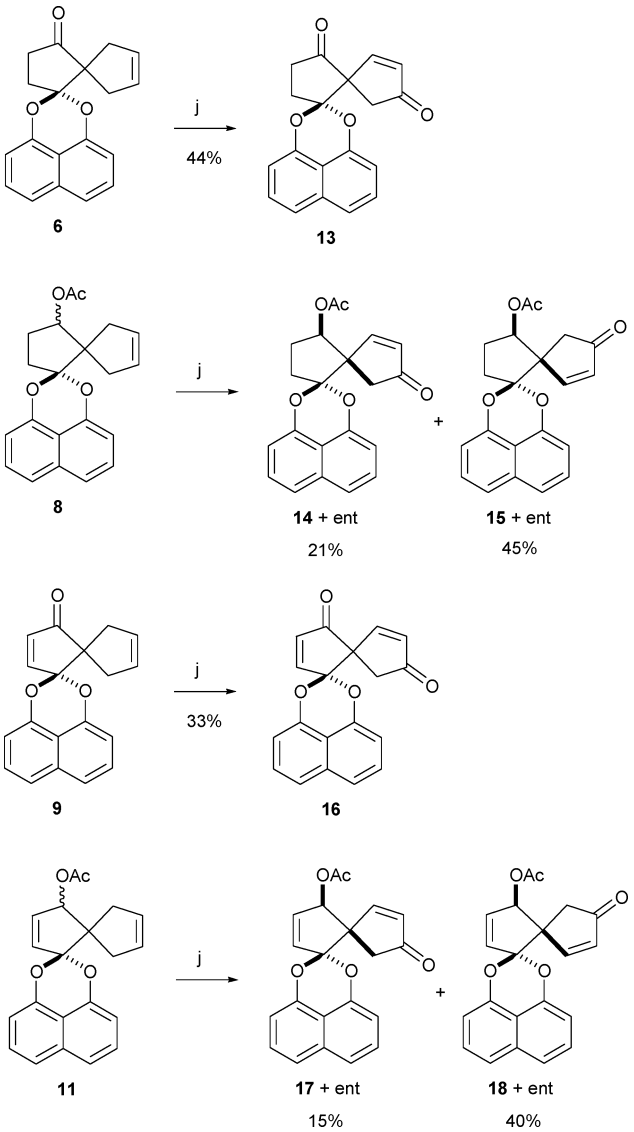


Scheme 3 Manipulation of the degree of oxidation of ring A: (f) $NaBH_4$; (g) Ac_2O, pyridine; (h) IBX, MPO; (i) $NaBH_4$, $CeCl_3$, MeOH.

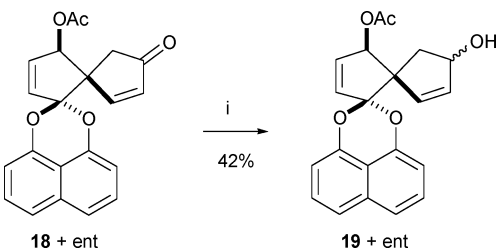


The generation of allylic alcohol **19** led to the consideration of a cyclopentadiene analogue of *spiro*-mamakone A, *via* dehydration (Scheme 6), as a target. Luche reduction of the mixture of diastereoisomers **17** and **18** gave a complex mixture of diastereoisomeric allylic alcohols, **20**. Dehydration of this mixture using Burgess' reagent yielded the cyclopentadiene analogue, **21**.[19,20] The unprotected analogue of **20**, **22**, was also obtained, *via* the selective 1,2 enone reduction of both enones of **16** (Scheme 7), and its fully protected analogue, **23** was generated *via* acetylation of **22**.

Finally, the introduction of halogens on ring B was briefly examined, *via* allylic bromination of the olefin using enone **9** as a

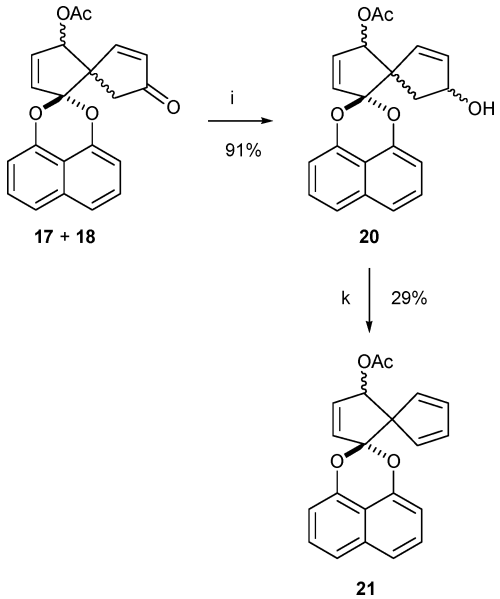


Scheme 4 Allylic oxidation of ring B of synthetic *spiro*-mamakone analogues: (j) $Rh_2(cap)_4$, ^tBuOOH, $NaHCO_3$.

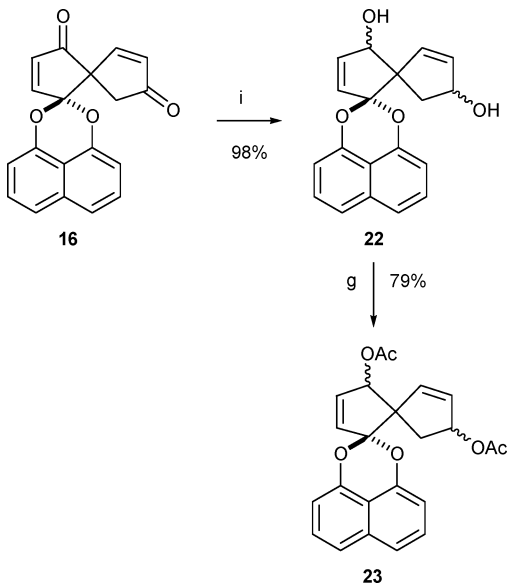


Scheme 5 Confirmation of enone regiochemistry.

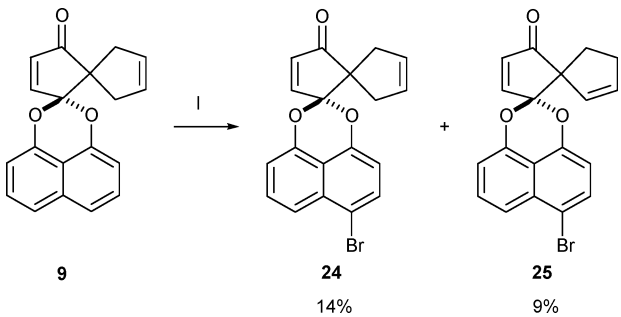
model system. However, the activated naphthalene moiety proved more reactive towards the bromine generated *in situ*, yielding analogue **24** (Scheme 8). Interestingly, the product of an olefin migration, analogue **25**, was also obtained from the reaction mixture.



Scheme 6 Preparation of a cyclopentadiene analogue: (k) Burgess' reagent.



Scheme 7 Synthesis of further analogues.



Scheme 8 Reactivity under bromination conditions: (l) NBS, AIBN.

With a variety of compounds based on the *spiro*-mamakone skeleton prepared, their biological activities were next explored.

Biological testing

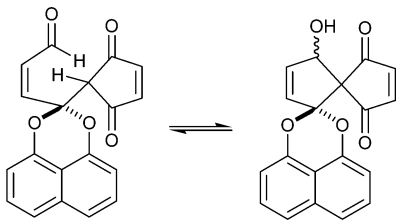
The potent cytotoxicity displayed by *spiro*-mamakone A (IC_{50} of 0.33 μM in the murine leukaemia cell line P388 assay) prompted the testing of all synthetic analogues described above for equivalent biological activity, in order to develop a structure–activity profile for the *spiro*-mamakone system. The results are presented in Table 1. The most striking conclusion which can be drawn from these results is that *spiro*-mamakone A represents a highly refined entity with respect to its biological activity. The synthetic analogues tested all share the carbon skeleton of *spiro*-mamakone A, but vary widely in the degree and positions of oxidation on the northern hemisphere. Most analogues displayed at least 100-fold lower biological activity than the natural product, including some which feature very similar substitution. The lack of, or weak activity of analogues **10** and **22**, which differ from the natural product only in the substitution of the right-hand ring, highlights the importance of the enedione moiety to biological activity. Interestingly, two synthetic analogues, enones **9** and **16**, display cytotoxicity of the same order of magnitude as the natural product. Brominated enones **24** and **25** also display significant biological activity. Since enones are known biological pharmacophores, and are not present in the natural product, it is possible that the biological activity of these analogues is due to a different biological mechanism. However, the low activities of enones **13** to **15**, **17** and **18** indicate that an enone moiety is not sufficient to induce potent cytotoxicity in this class of compounds. It is interesting to note that the biologically active analogues have an enone located in ring A, but when the enone is located in ring B they are inactive. This suggests that the biologically active form of *spiro*-mamakone A may possibly require an enone or equivalent in ring A. Biosynthetic studies[6] established that the most likely final step in the biosynthesis of *spiro*-mamakone A was the aldol type formation of the C4-C5 bond to form ring A from the likes of the α,β-unsaturated aldehyde **26** (Scheme 9) and that this step was possibly freely reversible (as the enedione motif is a stable leaving group). We therefore speculate that an enone in ring A may mimic this ring-opened isomer of *spiro*-mamakone A, and may also explain the low activities of allylic alcohols **10** and **22**, which do not contain an enedione, and therefore cannot isomerise to an α,β-unsaturated aldehyde.

Conclusion

The carbon skeleton of *spiro*-mamakone A has been successfully assembled and manipulated, yielding a series of synthetic analogues of the natural product. These analogues feature a wide variety of oxidation patterns in the northern hemisphere. Biological testing of the synthetic analogues allowed a structure–activity relationship profile to be developed, and thereby allow speculation on the active form of the natural product and its chemical reactivity at its biological target. The significant biological activities of several synthetic analogues prepared suggests that the natural product may prove to be a useful platform for lead optimisation.

Table 1 Summary of biological activity against murine leukaemia cell-line P388 displayed by *spiro*-mamakone A and synthetic analogues

	IC_{50}/μM
1	0.33
6	>42
7	>42
8	>37
9	0.9
10	43
11	>37
13	36
14	>36
15	30
16	0.7
17	>36
18	30
20	>36
21	>38
22	>41
23	25
24	10
25	9



26 **1**

Scheme 9 Biosynthetic precursor of *spiro*-mamakone A.

Experimental

General experimental

Anhydrous $CHCl_3$ and DCM were distilled under nitrogen over calcium hydride, while anhydrous benzene was distilled under nitrogen over sodium. Reagents obtained from commercial suppliers were used without further purification. Column chromatography was performed using silica gel (230–400 mesh, 60 Å pore size) and commercial grade solvents. IR measurements were taken on a Shimadzu FTIR-8201PC spectrophotometer or a Perkin Elmer Spectrum One FTIR spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 or 75 MHz) spectra were recorded on Varian NMR instruments in $CDCl_3$ (referenced using tetramethylsilane). Samples were analysed on a Micromass LCT mass spectrometer equipped with an electrospray ionisation (ESI) probe or on a high resolution VG-70SE mass spectrometer equipped with electron ionisation or chemical ionisation (using ammonia gas) probes. Where noted, flash chromatography was carried out on silica which was first deacidified by addition of triethylamine (~1–2%) to a suspension of silica in the initial eluent. Analytical high pressure liquid chromatography (HPLC) was carried out on a Dionex HPLC instrument. For the P388 cytotoxicity assays, two-fold dilution series for each synthetic analogue were incubated for 72 h with fast-growing murine leukaemia cells (ATCC CCL 46 P388D1). The concentration of the sample required to inhibit cell growth to 50% of the growth of a cell control (IC_{50}) was determined

by interpolation from the absorbances obtained upon staining with MTT tetrazolium. The positive control was mitomycin C (0.06 μg mL^{-1}), which inhibited cell growth by 43–75%.

***spiro*[4.4]Nona-7-ene-1,4-dione, 3.** Crude 2,2-diallylcyclopentane-1,3-dione (**2**, ~1.8 g, ~10 mmol)[10] was dissolved in anhydrous DCM (30 mL), Grubbs' 2nd generation catalyst was added (350 mg, 0.41 mmol, 4 mol%) and the reaction was stirred under an inert atmosphere for 18 h. Removal of solvents *in vacuo* and silica chromatography using a gradient of 20 to 30% diethyl ether in petroleum ether gave **3** as an off-white crystalline solid (1.48 g, 9.88 mmol, 97% over two steps). R_f 0.18 (silica, 4 : 1 petroleum ether–EtOAc, PMA); mp 91–93 °C (diethyl ether, lit. 89–90 °C);[9] IR (diffuse reflectance) ν_{max}/cm^{-1} 1751, 1713, 1443, 1273, 1227, 1111; δ_H (500 MHz, $CDCl_3$, Me_4Si) 5.62 (2H, br s), 2.83 (4H, s), 2.67 (4H, br s);[9] δ_C (75 MHz, $CDCl_3$) 214.4, 127.4, 61.3, 41.1, 34.9; HRCIMS m/z = 150.0684 $[M]^{+\bullet}$ 2.0 ppm (150.0681 calcd for $C_9H_{10}O_2$).

1,8-Dihydroxynaphthalene acetonide, 5. 1,8-Dihydroxynaphthalene (**4**, 640 mg, 4.0 mmol)[8,11] was dissolved in dimethoxypropane (10 mL) and pTSA (10 mg, 0.06 mmol) added. The reaction was refluxed for 16 h, then cooled to room temperature. Diethyl ether (10 mL) was added and the mixture was washed with $NaHCO_{3(aq)}$ (1 M, 2 × 10 mL). The organic phase was dried over $MgSO_4$ and filtered. The crude residue was passed through a short silica column eluting with petroleum ether and the solvent removed *in vacuo* to give a yellow solid. The residue was then passed through a C_{18} reverse phase pad with a solution of 60% MeCN in H_2O. Removal of MeCN *in vacuo* yielded an aqueous suspension which was extracted exhaustively using diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield **5** as a white crystalline solid (590 mg, 2.95 mmol, 74%). Mp 61–64 °C (petroleum ether); R_f 0.75 (silica, 4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1608, 1411, 1385, 1375, 1281, 1265; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.44–7.36 (4H, m, 3/4/5/6-H), 6.86 (2H, dd, 6.8 Hz, 1.4 Hz, 2/8-H), 1.66 (6H, s, $C(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 148.0 (C-1/8), 134.2 (C-4a), 127.3 (C-3/6), 120.0 (C-4/5), 113.5 (C-8a), 108.7 (C-2/7), 101.7 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$); HREIMS m/z = 200.0835 $[M]^{+\bullet}$ 1.0 ppm (200.0837 calcd for $C_{13}H_{12}O_2$).

***spiro*[4.4]Nona-7-ene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal, 6.** 1,8-Dihydroxynaphthalene acetonide (**5**, 900 mg, 4.50 mmol, 1.7 eq) and *spiro*[4.4]nona-7-ene-1,4-dione (**3**, 400 mg, 2.66 mmol) were dissolved in anhydrous $CHCl_3$ (6 mL) and triflic acid (40 μL, 0.45 mmol, 0.17 eq) was added. The reaction mixture became a dark brown colour upon addition of the acid and was stirred at 45 °C for 48 h. The reaction mixture was then diluted with diethyl ether (2 mL) and washed with $NaHCO_{3(aq)}$ (1 M, 2 × 1 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude residue was purified on Florisil® using a gradient of 0 to 20% diethyl ether in petroleum ether. This gave **6** as an off-white solid (120 mg, 0.41 mmol, 15%). Starting material, **3**, was also recovered (180 mg, 1.20 mmol, 45%). Mp 150–151 °C (diethyl ether); R_f 0.46 (silica, 4 : 1 petroleum ether–EtOAc, UV/PMA); IR (diffuse reflectance) ν_{max}/cm^{-1} 1744, 1611, 1414, 1275, 1248; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.49 (2H, dd, 8.4 Hz, 0.7 Hz, 13/15-H), 7.41 (2H, dd, 8.4 Hz, 7.5 Hz, 12/16-H), 6.91 (2H, dd, 7.5 Hz, 0.7 Hz, 11/17-H), 5.70 (2H, br m, 7/8-H), 3.05 (2H, br d, 14.0 Hz, 6/9-H), 2.61 (2H, br d, 14.0 Hz, 6/9-H), 2.53 (2H, dd, 8.2 Hz, 7.7 Hz, 2-H or 3-H), 2.17 (2H, dd, 8.2 Hz, 7.7 Hz, 2-H or 3-H); δ_C (75 MHz, $CDCl_3$) 214.3 (C, C-4), 147.5 (C, C-10/18), 134.2 (C, C-14), 128.1 (CH, C-7/8), 127.3 (CH, C-12/16), 120.6 (CH, C-13/15), 113.9 (C, C-19), 109.3 (CH, C-11/17), 108.1 (C, C-1), 62.0 (C, C-5), 36.4 (CH_2, C-6/9), 33.7 (CH_2, C-2 or C-3), 28.1 (CH_2, C-2 or C-3); HRESIMS m/z = 293.1187 $[M + H]^+$ 3.1 ppm (293.1178 calcd for $C_{19}H_{17}O_3$).

4-Hydroxy-*spiro*[4.4]nona-7-ene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 7. *spiro*[4.4]Nona-7-ene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal (**6**, 10 mg, 0.034 mmol) was dissolved in MeOH (1 mL) and $NaBH_4$ (7.5 mg, 0.20 mmol, 5.9 eq) was added. The reaction was stirred at room temperature for 16 h, then $NaHCO_{3(aq)}$ (1 M, 2 mL) was added and the reaction extracted with EtOAc (3 × 2 mL). After drying over $MgSO_4$, filtration and removal of solvent *in vacuo*, the crude product was purified on deacidified silica using a gradient of 0 to 10% diethyl ether in petroleum ether, to give **7** as a colourless oil (4.8 mg, 0.016 mmol, 47%). R_f 0.26 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 3406, 2926, 1609, 1411, 1381, 1275; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.47 (1H, dd, 8.3 Hz, 0.9 Hz, 13-H or 15-H), 7.46 (1H, dd, 8.3 Hz, 0.9 Hz, 13-H or 15-H), 7.40 (1H, dd, 8.3 Hz, 7.4 Hz, 12-H or 16-H), 7.395 (1H, dd, 8.3 Hz, 7.4 Hz, 12-H or 16-H), 6.89 (1H, dd, 7.4 Hz, 0.9 Hz, 11-H or 17-H), 6.88 (1H, dd, 7.4 Hz, 0.9 Hz, 11-H or 17-H), 5.77 (1H, m, 7-H or 8-H), 5.69 (1H, m, 7-H or 8-H), 4.08 (1H, m, 4-H), 3.05 (1H, m, 6-H or 9-H), 2.86 (1H, m, 6-H or 9-H), 2.76 (1H, m, 6-H or 9-H), 2.48 (1H, d, 9.3 Hz, O*H*), 2.31 (1H, m, 3-H), 2.15 (1H, m, 6-H or 9-H), 2.06 (1H, m, 2-H), 1.80 (2H, m, 2/3-H); δ_C (75 MHz, $CDCl_3$) 148.4 (C, C-10 or C-18), 147.6 (C, C-10 or C-18), 134.4 (C, C-14), 129.9 (CH, C-7 or C-8), 127.8 (CH, C-7 or C-8), 127.3 (CH, C-12 or C-16), 127.2 (CH, C-12 or C-16), 120.6 (CH, C-13 or C-15), 120.4 (CH, C-13 or C-15), 114.0 (C, C-19), 112.0 (C, C-1), 109.3 (CH, C-11 or C-17), 109.2 (CH, C-11 or C-17), 77.8 (CH, C-4), 58.9 (C, C-5), 39.2 (CH_2, C-6 or C-9), 32.7 (CH_2, C-6 or C-9), 30.7 (CH_2, C-2), 29.7 (CH_2, C-3); HRESIMS m/z 295.1339 $[M + H]^+$ 1.7 ppm (295.1334 calcd for $C_{19}H_{19}O_3$).

***O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-7-ene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 8.** 4-Hydroxy-*spiro*[4.4]nona-7-ene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal (**7**, 20 mg, 0.068 mmol) was dissolved in pyridine (500 μL) and acetic anhydride was added (200 μL, 2.1 mmol, 31 eq). The reaction was stirred at room temperature for 16 h. Deionised H_2O (3 mL) was added and the mixture extracted with diethyl ether (4 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. No further purification was required. The product (**8**, 19 mg, 0.056 mmol, 82%) was obtained as a colourless oil. IR (thin film) ν_{max}/cm^{-1} 1738, 1609, 1412, 1381, 1243; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.45–7.36 (4H, m, 12/13/15/16-H), 6.90 (1H, d, 7.5 Hz, 11-H or 17-H), 6.88 (1H, d, 7.5 Hz, 11-H or 17-H), 5.71–5.65 (2H, m, 7/8-H), 5.41 (1H, dd, 8.2 Hz, 6.7 Hz, 4-H), 3.05 (1H, m, 6-H or 9-H), 2.85 (1H, m, 6-H or 9-H), 2.68 (1H, m, 6-H or 9-H), 2.42 (1H, m, 6-H or 9-H), 2.28 (1H, m, 3-H), 2.09 (3H, s, 21-H), 1.93 (2H, m, 2-H), 1.72 (1H, m, 3-H); δ_C (75 MHz, $CDCl_3$) 171.3 (C, C-20), 148.5 (C, C-10 or C-18), 148.4 (C, C-10 or C-18), 134.5 (C, C-14), 129.01 (CH, C-7 or C-8), 128.97 (CH, C-7 or C-8), 127.6 (CH, C-12 or C-16), 127.5 (CH, C-12 or C-16), 120.6 (CH, C-13 or C-15), 120.5 (CH, C-13 or C-15), 114.4 (C,

C-19), 110.0 (C, C-1), 109.7 (CH, C-11 or C-18), 109.4 (CH, C-11 or C-18), 79.3 (CH, C-4), 57.8 (C, C-5), 38.2 (CH_2, C-6 or C-9), 34.4 (CH_2, C-6 or C-9), 30.9 (CH_2, C-2), 26.3 (CH_2, C-3), 21.5 (CH_3, C-21); HREIMS m/z = 336.1366 $[M]^{+\bullet}$ 1.2 ppm (336.1362 calcd for $C_{21}H_{20}O_4$).

***spiro*[4.4]Nona-2,7-diene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal, 9.** *spiro*[4.4]Nona-7-ene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal, (**6**, 95 mg, 0.33 mmol), IBX (380 mg, 1.36 mmol, 4.1 eq) and *N*-methoxypyridine-*N*-oxide hydrate (170 mg, 1.36 mmol, 4.1 eq) were dissolved in DMSO (1.4 mL) at 70 °C (over 15 min) to form a clear reddish solution. The reaction was then stirred at 70 °C for 20 h during which time a white precipitate formed. $NaHCO_{3(aq)}$ was slowly added (1 M, approximately 2 mL) and the resulting mixture was extracted with diethyl ether (4 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude product was purified by chromatography on deacidified silica using a gradient of 0 to 2% diethyl ether in petroleum ether. The product, **9**, was obtained as a white solid (40 mg, 0.14 mmol, 42%) and remaining starting material, **6**, eluted after. Mp 142–144 °C (diethyl ether); R_f 0.56 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (diffuse reflectance) ν_{max}/cm^{-1} 1725, 1611, 1411, 1278, 1262, 1250; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.51 (2H, dd, 8.4 Hz, 0.7 Hz, 13/15-H), 7.43 (2H, dd, 8.4 Hz, 7.5 Hz, 12/16-H), 7.38 (1H, d, 6.1 Hz, 2-H or 3-H), 6.93 (2H, dd, 7.5 Hz, 0.7 Hz, 11/17-H), 6.39 (1H, d, 6.1 Hz, 2-H or 3-H), 5.65 (2H, br s, 7/8-H), 3.22 (2H, br d, 16.0 Hz, 6/9-H), 2.64 (2H, br d, 16.0 Hz, 6/9-H); δ_C (75 MHz, $CDCl_3$) 206.6 (C, C-4), 153.3 (CH, C-2), 147.6 (C, C-10/18), 135.2 (CH, C-3), 134.2 (C, C-14), 128.0 (CH, C-7/8), 127.5 (CH, C-12/C16), 120.9 (CH, C-13/C15), 113.7 (C, C-19), 109.3 (CH, C-11/17), 105.8 (C, C-1), 61.2 (C, C-5), 38.0 (CH_2, C-6/9); HRESIMS m/z = 291.1030 $[M + H]^+$ 3.1 ppm (291.1021 calcd for $C_{19}H_{15}O_3$).

4-Hydroxy-*spiro*[4.4]nona-2,7-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 10. *spiro*[4.4]Nona-2,7-diene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal (**9**, 10 mg, 0.034 mmol) and $CeCl_3$ (anhydrous, 9 mg, 0.036 mmol, 1.1 eq) were dissolved in MeOH (500 μL) and cooled to 0 °C. $NaBH_4$ (1.3 mg, 0.034 mmol, 1 eq) was added and the reaction stirred at 0 °C for 1 h. $NaHCO_{3(aq)}$ (1 M, 1 mL) was added and the reaction extracted with diethyl ether (4 × 1 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude product was purified by chromatography on deacidified silica using a gradient of 0 to 12% diethyl ether in petroleum ether, to give **10** as a colourless oil (10 mg, 0.034 mmol, ~100%). R_f 0.31 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1607, 1413, 1382, 1277, 1100; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.47 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.45 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.40 (1H, dd, 8.3 Hz, 7.5 Hz, 12-H or 16-H), 7.38 (1H, dd, 8.3 Hz, 7.5 Hz, 12-H or 16-H), 6.91 (1H, dd, 7.5 Hz, 0.8 Hz, 11-H or 17-H), 6.83 (1H, dd, 7.5 Hz, 0.8 Hz, 11-H or 17-H), 6.35 (1H, dd, 6.0 Hz, 2.7 Hz, 3-H), 6.02 (1H, d, 6.0 Hz, 2-H), 5.76 (1H, m, 7-H or 8-H), 5.69 (1H, m, 7-H or 8-H), 4.39 (1H, d, 2.7 Hz, 4-H), 3.19 (1H, ddd, 16.9 Hz, 2.6 Hz, 2.4 Hz, 6-H or 9-H), 2.85 (2H, m, 6/9-H), 2.09 (1H, 16.9 Hz, 1.9 Hz, 1.6 Hz, 6-H or 9-H); δ_C (75 MHz, $CDCl_3$) 148.6 (C, C-10 or C-18), 148.3 (C, C-10 or C-18), 140.3 (CH, C-3), 134.3 (C, C-14), 132.9 (CH, C-2), 129.5 (CH, C-7 or C-8), 128.2 (CH, C-7 or C-8), 127.3 (CH, C-12/16), 120.5 (CH, C-13 or C-15), 120.4 (CH, C-13 or C-15), 114.1 (C, C-19), 111.0 (C, C-1), 109.2 (CH, C-11 or C-17), 108.8 (CH, C-11 or C-17), 81.1 (CH, C-4), 59.9 (C, C-5), 40.3 (CH_2, C-6/9); HRESIMS m/z = 293.1186 $[M + H]^+$ 2.7 ppm (293.1178 calcd for $C_{19}H_{17}O_3$).

***O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-2,7-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 11.** 4-Hydroxy-*spiro*[4.4]nona-2,7-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal (**10**, 5 mg, 0.017 mmol) was dissolved in pyridine (500 μL) and acetic anhydride was added (200 μL, 2 mmol, 120 eq). The reaction was stirred at room temperature for 20 h, then diethyl ether was added (2 mL) and the mixture extracted with $NaHCO_{3(aq)}$ (1 M, 3 × 2 mL). After drying over $MgSO_4$, filtration and removal of solvent *in vacuo*, the crude product was purified on deacidified silica using a gradient of 0 to 12% diethyl ether in petroleum ether, to give **1** as a colourless oil (5.5 mg, ~0.017 mmol, ~100%). R_f 0.69 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1738, 1607, 1412, 1381, 1279, 1219; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.46 (1H, dd, 8.4 Hz, 0.9 Hz, 13-H or 15-H), 7.45 (1H, dd, 8.4 Hz, 0.9 Hz, 13-H or 15-H), 7.40 (1H, dd, 8.4 Hz, 7.5 Hz, 12-H or 16-H), 7.39 (1H, dd, 8.4 Hz, 7.5 Hz, 12-H or 16-H), 6.91 (1H, dd, 7.5 Hz, 0.9 Hz, 11-H or 17-H), 6.86 (1H, dd, 7.5 Hz, 0.9 Hz, 11-H or 17-H), 6.17 (1H, dd, 6.0 Hz, 2.2 Hz, 3-H), 6.05 (1H, dd, 6.0 Hz, 1.2 Hz, 2-H), 5.74 (1H, dd, 2.2 Hz, 1.2 Hz, 4-H), 5.68 (2H, m, 7/8-H), 3.18 (1H, m, 6-H or 9-H), 2.97 (1H, m, 6-H or 9-H), 2.60 (1H, m, 6-H or 9-H), 2.45 (1H, m, 6-H or 9-H), 2.11 (3H, s, 21-H); δ_C (75 MHz, $CDCl_3$) 170.8 (C, C-20), 148.8 (C, C-10 or C-18), 148.5 (C, C-10 or C-18), 136.8 (CH, C-3), 134.3 (C, C-14), 133.2 (CH, C-2), 128.7 (CH, C-7 or C-8), 128.4 (CH, C-7 or C-8), 127.32 (CH, C-12 or C-16), 127.28 (CH, C-12 or C-18), 120.4 (CH, C-13 or C-15), 120.3 (CH, C-13 or C-15), 114.1 (C, C-19), 109.9 (C, C-1), 108.9 (CH, C-11/17), 82.1 (CH, C-4), 60.5 (C, C-5), 38.9 (CH_2, C-6 or C-9), 34.3 (CH_2, C-6 or C-9), 21.1 (CH_3, C-21); HRESIMS m/z = 335.1293 $[M + H]^+$ 3.0 ppm (335.1283 calcd for $C_{21}H_{19}O_4$).

***spiro*[4.4]Nona-6-ene-1,4,8-trione-1,1-[1,8-dihydroxynaphthalene]-acetal, 13.** *spiro*[4.4]Nona-7-ene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal (**6**, 12 mg, 0.041 mmol) was dissolved in anhydrous DCM (1 mL) and dirhodium(II)tetrakis(caprolactam) (0.3 mg, 0.45 μmol, 1 mol%) and $NaHCO_3$ (1.5 mg, 0.018 mmol, 0.4 eq) were added. ^{t}Butyl hydroperoxide (anhydrous, 5 M in decanes, 40 μL, 0.20 mmol, 5 eq) was added and an immediate colour change from light purple to deep pink was observed. The reaction was stirred at room temperature for 16 h, then filtered through a deacidified silica pad using DCM. The crude product was purified on deacidified silica using a gradient of 0 to 24% diethyl ether in petroleum ether to give **13** as a colourless oil (5.5 mg, 0.018 mmol, 44%) and recovered starting material (**6**, 3 mg, 0.010 mmol, 24%). R_f 0.23 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1750, 1718, 1609, 1270; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.55 (1H, d, 5.7 Hz, 6-H), 7.523 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.518 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.44 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 7.43 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 6.93 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.92 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.36 (1H, d, 5.7 Hz, 7-H), 2.94 (1H, d, 18.3 Hz, 9-H), 2.69 (2H, m, 2-H or 3-H), 2.50 (1H, d, 18.3 Hz, 9-H), 2.46 (1H, ddd, 14.0 Hz, 9.4 Hz, 6.0 Hz, 2-H or 3-H), 2.33 (1H, ddd, 14.0 Hz, 9.4 Hz, 7.4 Hz, 2-H or 3-H); δ_C (75 MHz, $CDCl_3$) 210.4 (C, C-4), 205.9 (C, C-8), 157.6 (CH, C-6), 146.8 (C, C-10 or C-18), 146.6 (C, C-10 or C-18), 136.6 (CH, C-7), 134.2 (C, C-14), 127.5 (CH, C-12 or C-16), 127.4 (CH,

C-12 or C-16), 121.2 (CH, C-13/15), 113.5 (C, C-19), 109.6 (CH, C-11 or C-17), 109.4 (CH, C-11 or C-17), 107.1 (C, C-1), 66.8 (C, C-5), 38.3 (CH_2, C-9), 35.1 (CH_2, C-2 or C-3), 29.1 (CH_2, C-2 or C-3); HRESIMS $m/z = 307.0979$ $[M + H]^+$ 2.9 ppm (307.0970 calcd for $C_{19}H_{15}O_4$).

***O*-Acetyl-4-hydroxy-*spiro*-nona-6-ene-1,8-dione-1,1-[1,8-dihydroxynaphthalene]-acetal, 14 ([4*R*,5*S*] and [4*S*,5*R*]), and 15 ([4*R*,5*R*] and [4*S*,5*S*]).** *O*-Acetyl-4-hydroxy-*spiro*-nona-7-ene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal (**8**, 19 mg, 0.056 mmol) was dissolved in DCM (1 mL) and dirhodium(II)tetrakis(caprolactam) (0.4 mg, 0.56 μmol, 1 mol%) and $NaHCO_3$ (2.3 mg, 0.028 mmol, 0.5 eq) were added. ^{t}Butyl hydroperoxide (anhydrous, 5 M in decanes, 0.5 mL, 2.5 mmol, 45 eq) was added and an immediate colour change from light purple to deep pink was observed. The reaction was stirred at room temperature for 16 h then filtered through a deacidified silica pad using DCM. The crude product was further purified on deacidified silica using a gradient of 0 to 20% diethyl ether in petroleum ether to give the isomeric products **14** (4.1 mg, 0.012 mmol, 21%) and **15** (8.7 mg, 0.025 mmol, 45%) as colourless oils.

14. R_f 0.14 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1738, 1721, 1609, 1412, 1379, 1276, 1236, 1054; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.65 (1H, d, 5.9 Hz, H9), 7.48 (2H, d, 8.1 Hz, H13 and H15), 7.41 (1H, t, 7.4 Hz, H12 or H16), 7.39 (1H, t, 7.4 Hz, H12 or H16), 6.91 (1H, d, 7.5 Hz, H11 or H17), 6.87 (1H, d, 7.5 Hz, H11 or H17), 6.31 (1H, d, 5.8 Hz, H8), 5.46 (1H, dd, 8.1 Hz, 6.3 Hz, H4), 3.06 (1H, d, 18.9 Hz, H6), 2.45 (1H, m, H3), 2.43 (1H, d, 18.8 Hz, H6), 2.21 (1H, m, H2), 2.10 (1H, m, H2), 2.09 (3H, s, H21), 1.95 (1H, m, H3); δ_C (75 MHz, $CDCl_3$) 207.5 (C, C6), 170.7 (C, C20), 160.6 (CH, C9), 147.8 (C, C10 or C18), 147.5 (C, C10 or C18), 136.2 (C, C14), 134.5 (C, C8), 127.7 (CH, C12 or C16), 127.6 (CH, C12 or C16), 121.2 (CH, C13 or C15), 121.1 (CH, C13 or C15), 114.0 (C, C19), 109.9 (CH, C11 or C17), 109.6 (CH, C11 or C17), 108.9 (C, C1), 78.8 (CH, C4), 61.7 (C, C5), 40.7 (CH_2, C9), 31.9 (CH_2, C2), 27.3 (CH_2, C3), 21.2 (CH_3, C21); HRESIMS $m/z = 351.1242$ $[M + H]^+$ 2.8 ppm (351.1232 calcd for $C_{21}H_{19}O_5$).

15. R_f 0.19 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1741, 1721, 1610, 1411, 1380, 1276, 1236, 1053; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.67 (1H, d, 5.8 Hz, H6), 7.49–7.36 (4H, m, H12, H13, H15 and H16), 6.97 (1H, d, 7.4 Hz, H11 or H17), 6.86 (1H, d, 7.4 Hz, H11 or H17), 6.18 (1H, d, 5.8 Hz, H7), 5.72 (1H, t, 8.5 Hz, H4), 2.86 (1H, d, 18.1 Hz, H9), 2.66 (1H, d, 18.1 Hz, H9), 2.43 (1H, m, H3), 2.16 (1H, m, H2), 2.05 (1H, m, H2), 2.04 (3H, s, H21), 1.82 (1H, m, H3); δ_C (75 MHz, $CDCl_3$) 207.4 (C, C8), 170.7 (C, C20), 162.6 (CH, C6), 147.6 (C, C10 or C18), 147.4 (C, C10 or C18), 136.5 (C, C14), 134.5 (CH, C7), 127.7 (CH, C12 or C16), 127.6 (CH, C12 or C16), 121.2 (CH, C13 or C15), 121.1 (CH, C13 or C15), 114.0 (C, C19), 109.8 (CH, C11 or C17), 109.6 (CH, C11 or C17), 108.9 (C, C1), 74.9 (CH, C4), 61.7 (C, C5), 36.8 (CH_2, C9), 32.1 (CH_2, C2), 26.8 (CH_2, C3), 21.2 (CH_3, C21); HRESIMS $m/z = 351.1235$ $[M + H]^+$ 0.9 ppm (351.1232 calcd for $C_{21}H_{19}O_5$).

***spiro*[4.4]Nona-2,6-diene-1,4,8-trione-1,1-[1,8-dihydroxynaphthalene]-acetal, 16.** *spiro*[4.4]Nona-2,7-diene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal (**9**, 10 mg, 0.034 mmol) was dissolved in anhydrous DCM (1 mL) and dirhodium(II)tetrakis(caprolactam) (0.2 mg, 0.3 μmol, 1 mol%) and $NaHCO_3$ (1.4 mg, 0.017 mmol, 0.5 eq) were added. ^{t}Butyl hydroperoxide (anhydrous, 5 M in decanes, 35 μL, 0.17 mmol, 5 eq) was added and an immediate colour change from light purple to deep pink was observed. The reaction was stirred at room temperature for 20 h, then filtered through a deacidified silica pad using DCM. The crude product was further purified on deacidified silica using a gradient of 0 to 16% diethyl ether in petroleum ether, to give **16** as a colourless oil (3.4 mg, 0.011 mmol, 33%). R_f 0.20 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1732, 1725, 1609, 1581, 1411, 1378, 1270; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.59 (1H, d, 6.0 Hz, 2-H), 7.56 (1H, d, 5.6 Hz, 6-H), 7.55 (2H, m, 13/15-H), 7.454 (1H, dd, 8.4 Hz, 7.6 Hz, 12-H or 16-H), 7.448 (1H, dd, 8.4 Hz, 7.6 Hz, 12-H or 16-H), 6.97 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.95 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.52 (1H, d, 6.0 Hz, 3-H), 6.33 (1 H, d, 5.6 Hz, 7-H), 3.09 (1H, d, 18.7 Hz, 9-H), 2.62 (1H, d, 18.7 Hz, 9-H); δ_C (75 MHz, $CDCl_3$) 206.5 (C, C-8), 201.5 (C, C-4), 159.1 (CH, C-6), 154.3 (CH, C-2), 146.6 (C, C-10/18), 135.4 (CH, C-7), 135.1 (CH, C-3), 134.2 (C, C-14), 127.6 (CH, C-12 or C-16), 127.5 (CH, C-12 or C-16), 121.52 (CH, C-13 or C-15), 121.49 (CH, C-13 or C-15), 109.6 (CH, C-11/17), 105.3 (C, C-1), 65.0 (C, C-5), 39.0 (CH_2, C-9), C-19 not observed; HRESIMS $m/z = 305.0821$ $[M + H]^+$ 2.3 ppm (305.0814 calcd for $C_{19}H_{13}O_4$).

***O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-2,6-diene-1,8-dione-1,1-[1,8-dihydroxynaphthalene]-acetal, 17 ([4*R*,5*R*] and [4*S*,5*S*]) and 18 ([4*R*,5*S*] and [4*S*,5*R*]).** *O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-2,7-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal (**11**, 5 mg, 0.015 mmol) was dissolved in anhydrous DCM (1 mL) and dirhodium(II)tetrakis(caprolactam) (0.1 mg, 0.15 μmol, 1 mol%) and $NaHCO_3$ (0.7 mg, 0.008 mmol, 0.5 eq) were added. ^{t}Butyl hydroperoxide (anhydrous, 5 M in decanes, 20 μL, 0.08 mmol, 5 eq) was added and an immediate colour change from light purple to deep pink was observed. The reaction was stirred at room temperature for 16 h, then filtered through a deacidified silica pad using DCM. The crude product was purified on deacidified silica using a gradient of 8 to 16% diethyl ether in petroleum ether, to give **17** (0.8 mg, 0.0023 mmol, 15%) and **18** (2.1 mg, 0.0060 mmol, 40%) as colourless oils.

17. R_f 0.16 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1740, 1722, 1608, 1412, 1221; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.58 (1H, d, 5.8 Hz, 6-H), 7.50 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.48 (1H, dd, 8.3 Hz, 0.8 Hz, 13-H or 15-H), 7.41 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 7.40 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 6.89 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.87 (1H, dd, 7.6 Hz, 0.8 Hz, 11-H or 17-H), 6.28 (1H, d, 5.8 Hz, 7-H), 6.24 (1H, dd, 6.1 Hz, 1.6 Hz, 2-H or 3-H), 6.13 (1H, dd, 6.1 Hz, 1.6 Hz, 2-H or 3-H), 5.95 (1H, t, 1.6 Hz, 4-H), 3.2 (1H, d, 19.0 Hz, 9-H), 2.74 (1H, d, 19.0 Hz, 9-H), 2.07 (3H, s, 21-H); δ_C (125 MHz, observed by 2D NMR, $CDCl_3$) 207.8 (C, C-8), 170.4 (C, C-20), 161.8 (CH, C-6), 147.8 (C, C-10/18), 136.6 (CH, C-2 or C-3), 135.1 (CH, C-7), 134.5 (C, C-14), 132.3 (CH, C-2 or C-3), 127.6 (CH, C-12/16), 121.0 (CH, C-13/15), 113.9 (C, C-19), 109.5 (CH, C-11/17), 109.3 (C, C-1), 81.6 (CH, C-4), 63.4 (C, C-5), 40.3 (CH_2, C-9), 21.0 (CH_3, C-21); HRESIMS $m/z = 349.1082$ $[M + H]^+$ 1.7 ppm (349.1076 calcd for $C_{21}H_{17}O_5$).

18. R_f 0.18 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1742, 1723, 1607, 1412, 1225; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.80 (1H, d, 5.7 Hz, 6-H), 7.49 (1H, dd, 8.4 Hz, 0.9 Hz, 13-H or 15-H), 7.48 (1H, dd, 8.4 Hz, 0.9 Hz, 13-H or 15-H) 7.41 (2H, dd, 8.4 Hz, 7.5 Hz, 12/16-H), 6.93 (1H, dd, 7.5 Hz, 0.9 Hz, 11-H or 17-H), 6.89 (1H, dd, 7.5 Hz, 0.9 Hz, 11-H or 17-H), 6.24 (1H, dd, 6.1 Hz, 1.8 Hz, 3-H), 6.21 (1H, d, 5.7 Hz, 7-H), 6.11 (1H, dd, 6.1 Hz, 1.8 Hz, 2-H), 6.05 (1H, t, 1.8 Hz, 4-H), 3.06 (1H, d, 18.8 Hz, 9-H), 2.63 (1H, d, 18.8 Hz, 9-H), 2.11 (3H, s, 21-H); δ_C (125 MHz, observed by 2D NMR, $CDCl_3$) 207.6 (C, C-6), 170.5 (C, C-20), 162.2 (CH, C-6), 148.3 (C, C-10 or C-18), 147.6 (C, C-10 or C-18), 137.1 (CH, C-3), 136.0 (CH, C-7), 134.4 (C, C-14), 132.5 (CH, C-2), 127.5 (CH, C-12/16), 121.1 (CH, C-13/15), 113.8 (C, C-19), 109.5 (C/CH, C-11/17/1), 78.0 (CH, C-4), 63.5 (C, C-5), 37.3 (CH_2, C-9), 20.9 (CH_3, C-21); HRESIMS m/z = 349.1081 $[M + H]^+$ 1.4 ppm (349.1076 calcd for $C_{21}H_{17}O_5$).

***O*$_4$-Acetyl-4,8-dihydroxy-*spiro*[4.4]nona-2,6-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 19.** *O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-2,6-diene-1,8-dione-1,1-[1,8-dihydroxynaphthalene]acetal (**18**, 2 mg, 0.006 mmol) was dissolved in MeOH (1 mL) with $CeCl_3$ (anhydrous, 3 mg, 0.012 mmol, 2 eq). The mixture was cooled in an ice-bath and $NaBH_4$ (0.3 mg, 0.008 mmol, 1.3 eq) was added. The mixture was stirred at 0 °C for 1 h, then $NaHCO_{3(aq)}$ (1 M, 2 mL) was added. The mixture was extracted with diethyl ether (4 × 2 mL) and the combined organic phases dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The residue was purified on deacidified silica using a gradient of 10 to 24% diethyl ether in petroleum ether to obtain **19** as a colourless oil (0.9 mg, 0.003 mmol, 42%). R_f 0.21 (2 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 3400–3200, 1738, 1606, 1413, 1381, 1226; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.50 (1H, d, 8.3 Hz, 13-H or 15-H), 7.47 (1H, d, 8.3 Hz, 13-H or 15-H), 7.41 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 7.40 (1H, dd, 8.3 Hz, 7.6 Hz, 12-H or 16-H), 6.96 (1H, d, 7.6 Hz, 11-H or 17-H), 6.87 (1H, d, 7.6 Hz, 11-H or 17-H), 6.20 (1H, dd, 6.1 Hz, 1.8 Hz, 2-H or 3-H), 6.12 (1H, d, 5.7 Hz, 6-H), 6.08 (1H, dd, 5.7 Hz, 2.3 Hz, 7-H), 6.05 (1H, dd, 6.1 Hz, 1.8 Hz, 2-H or 3-H), 5.92 (1H, t, 1.8 Hz, 4-H), 4.81 (1H, ddd, 7.1 Hz, 2.6 Hz, 2.3 Hz, 8-H), 2.50 (1H, dd, 14.7 Hz, 7.1 Hz, 9-H), 2.25 (1H, dd, 14.6 Hz, 2.6 Hz, 9-H), 2.14 (3H, s, 21-H); δ_C (75 MHz, $CDCl_3$) 170.4 (C-20), 148.3 (C, C-10 or C-18), 147.8 (C, C-10 or C-18), 137.7 (CH, C-6 or C-7), 137.4 (CH, C-2 or C-3), 134.3 (CH, C-6 or C-7), 134.1 (C, C-14), 131.9 (CH, C-2 or C-3), 127.5 (CH, C-12 or C-16), 127.2 (CH, C-12 or C-16), 121.0 (CH, C-13 or C-15), 120.6 (CH, C-13 or C-15), 114.0 (C, C-19), 109.20 (CH, C-11 or C-17), 109.17 (CH, C-11 or C-17), 109.0 (C, C-1), 78.9 (C, C-4), 75.9 (C, C-8), 67.0 (C, C-5), 35.5 (CH_2, C-9), 21.1 (CH_3, C-21); HRESIMS m/z = 333.1120 $[M - OH]^+$ 2.1 ppm (333.1127 calcd for $C_{21}H_{17}O_4$).

***O*$_4$-Acetyl-4,8-dihydroxy-*spiro*[4.4]nona-2,6-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 20 (stereoisomeric mixture).** A mixture of *O*-acetyl-4-hydroxy-*spiro*[4.4]nona-2,6-diene-1,8-dione-1,1-[1,8-dihydroxynaphthalene]-acetal stereoisomers (**17** and **18**, 12 mg, 0.034 mmol) were dissolved in MeOH (1 mL) with $CeCl_3$ (anhydrous, 10 mg, 0.041 mmol, 1.2 eq). The mixture was cooled in an ice-bath and $NaBH_4$ (1.3 mg, 0.034 mmol, 1 eq) was added. The mixture was stirred at 0 °C for 1 h, then $NaHCO_{3(aq)}$ (1 M, 3 mL) was added. The mixture was extracted with diethyl ether (4 × 3 mL) and the combined organic phases dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The residue was purified on deacidified silica using a gradient of 10 to 24% diethyl ether in petroleum ether. **20** was obtained as a mixture of stereoisomers as a colourless oil (11 mg, 0.031 mmol, 91%). IR (thin film) ν_{max}/cm^{-1} 3400–3100, 2916, 1729, 1719, 1607, 1412, 1379; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.51–7.36 (4H, m, 12/13/15/16-H), 6.98–6.82 (2H, m, 11/17-H), 6.22–5.75 (5H, m, 2/3/4/6/7-H), 4.84–4.79 (1H, m, 8-H), 3.52–1.77 (2H, m, 9-H), 2.14 (~2H, s, 21-H), 2.10 (~1H, s, 21-H); HRESIMS m/z = 333.1124 $[M - OH]^+$ 0.9 ppm (333.1127 calcd for $C_{21}H_{17}O_4$).

***O*-Acetyl-4-hydroxy-*spiro*[4.4]nona-2,6,8-triene-1,1-[1,8-dihydroxynaphthalene]-acetal, 21.** Allyl alcohol **20** (mixture of isomers, 11 mg, 0.031 mmol) was dissolved in anhydrous benzene (2 mL) and Burgess' reagent (15 mg, 0.063 mmol, 2 eq) was added.[21] The reaction was stirred at 50 °C for 16 h, then cooled to room temperature. Diethyl ether (3 mL) was added and the mixture was extracted with $NaHCO_{3(aq)}$ (1 M, 2 × 3 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude residue was purified by chromatography on deacidified silica using a gradient of 0 to 6% diethyl ether in petroleum ether, which gave **21** as a colourless oil (3 mg, 0.01 mmol, 29%). R_f 0.41 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1739, 1607, 1412, 1380, 1274, 1233, 1222, 1025; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.42 (1H, d, 8.4 Hz, 13-H or 15-H), 7.41 (1H, d, 8.4 Hz, 13-H or 15-H), 7.37–7.33 (2H, m, 12/16-H), 6.85 (1H, dd, 7.6 Hz, 0.9 Hz, 11-H or 17-H), 6.80 (1H, dd, 7.6 Hz, 0.9 Hz, 11-H or 17-H), 6.38 (1H, dd, 5.9 Hz, 2.2 Hz, 3-H), 6.31 (1H, ddd, 5.3 Hz, 2.2 Hz, 1.5 Hz, 6-H, 7-H, 8-H or 9-H), 6.29–6.26 (2H, m, 2-H and 6-H, 7-H, 8-H or 9-H), 6.18–6.14 (2H, m, 6-H, 7-H, 8-H or 9-H), 6.00 (1H, dd, 2.2 Hz, 1.1 Hz, 4-H), 2.03 (3H, s, 21-H); δ_C (75 MHz, $CDCl_3$) 170.3 (C, C-20), 148.3 (C, C-10 or C-18), 148.1 (C, C-10 or C-18), 136.4 (CH, C-3), 135.9 (CH, C-6, C-7, C-8 or C-9), 134.4 (CH, C-2, C-6, C-7, C-8 or C-9), 134.3 (CH, C-2, C-6, C-7, C-8 or C-9), 132.6 (CH, C-6, C-7, C-8 or C-9), 132.2 (CH, C-6, C-7, C-8 or C-9), 127.1 (CH, C-12 and C-16), 120.4 (CH, C-13 or C-15), 120.3 (CH, C-13 or C-15), 113.9 (C, C-19), 111.6 (C, C-1), 108.8 (CH, C-11 or C-17), 108.7 (CH, C-11 or C-17), 78.3 (CH, C-4), 72.8 (C, C-5), 21.0 (CH_3, C-21); HRESIMS m/z = 333.1117 $[M + H]^+$ 3.0 ppm (333.1127 calcd for $C_{21}H_{17}O_4$).

4,8-Dihydroxy-*spiro*[4.4]nona-2,6-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 22 (mixture of diastereoisomers). *spiro*-[4.4]Nona-2,7-diene-1,4,6-trione-1,1-[1,8-dihydroxynaphthalene]-acetal (**16**, 3.2 mg, 0.010 mmol) and $CeCl_3$ (anhydrous, 5.4 mg, 0.022 mmol, 2.1 eq) were dissolved in MeOH (500 μL) and cooled to 0 °C. $NaBH_4$ (0.8 mg, 0.022 mmol, 2.1 eq) was added and the reaction stirred at 0 °C for 1 h. $NaHCO_{3(aq)}$ (1 M, 1 mL) was added and the reaction extracted with diethyl ether (4 × 1 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude product, obtained as a colourless oil (**22**, mixture of isomers, 3.2 mg, 0.010 mmol, 98%), was used directly in the next step. IR (thin film) ν_{max}/cm^{-1} 3400–3200, 1607, 1412, 1381, 1275; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.55–7.34 (4H, 12/13/15/16-H), 7.0–6.82 (2H, 11/17-H), 6.38–5.94 (4H, 2/3/7/6-H), 4.98–4.62 (2H, 4/8-H), 2.91–2.63 (1H, 9-H), 2.32–1.96 (1H, 9-H); HRESIMS m/z = 331.0961 $[M + Na]^+$ 4.5 ppm (331.0946 calcd for $C_{19}H_{16}O_4Na$).

***O*,*O*-Diacetyl-4,8-dihydroxy-*spiro*[4.4]nona-2,6-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal, 23.** 4,8-Dihydroxy-*spiro*-[4.4]nona-2,6-diene-1-one-1,1-[1,8-dihydroxynaphthalene]-acetal (**22**, 3.2 mg, 0.010 mmol) was dissolved in pyridine (500 μL) and acetic anhydride was added (200 μL). The reaction was stirred at room temperature for 16 h, then diethyl ether was added (2 mL) and the mixture extracted with $NaHCO_{3(aq)}$ (1 M, 3 × 2 mL). After drying the organic phase over $MgSO_4$, filtration and removal of solvent *in vacuo*, the crude product was purified on deacidified silica using a gradient of 0 to 12% diethyl ether in petroleum ether, to give **23** as a colourless oil (mixture of isomers, 3.1 mg, 79%). R_f 0.35 (4 : 1 petroleum ether–EtOAc, UV/PMA); IR (thin film) ν_{max}/cm^{-1} 1735, 1607, 1412, 1372, 1238; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.49–7.35 (4H, 12/13/15/16-H), 6.95–6.82 (2H, 11/17-H), 6.22–5.72 (6H, 2/3/4/6/7/8-H), 3.15–2.41 (2H, 9-H), 2.17–2.04 (6H, 21/23-H); HRESIMS $m/z = 415.1167$ $[M + Na]^+$ 2.2 ppm (415.1158 calcd for $C_{23}H_{20}O_6Na$).

***spiro*-Nona-2,7-diene-1,4-dione-1,1-[1,8-dihydroxy-4-bromonaphthalene]-acetal, 24, and *spiro*-nona-2,6-diene-1,4-dione-1,1-[1,8-dihydroxy-4-bromo-naphthalene]-acetal, 25.** *spiro*-Nona-2,7-diene-1,4-dione-1,1-[1,8-dihydroxynaphthalene]-acetal (**9**, 5 mg, 17 μmol) was dissolved in CCl_4 (500 μL), NBS (3.3 mg, 0.019 mmol, 1.1 eq) and AIBN (trace) were added and the reaction was stirred at room temperature for 20 h. Additional NBS (1.1 eq) was then added and the reaction stirred for a further 24 hours. After removal of the solvent *in vacuo*, the crude mixture was partially purified on deacidified silica using a gradient of 0 to 6% diethyl ether in petroleum ether, giving a crude mixture of products. **25** (R_t 16.96 min, 0.6 mg, 1.6 μmol, 9%) was purified by separation on an analytical C_{18} HPLC column using 70% MeCN in H_2O (isocratic), then **24** (R_t 17.29 min, 0.9 mg, 2.4 μmol, 14%) was separated from an impurity on an analytical C_{18} HPLC column using 80% MeOH in H_2O (isocratic).

Mixture—R_f 0.54–0.63 (4 : 1 petroleum ether–EtOAc, UV/PMA).

24. IR (thin film) ν_{max}/cm^{-1} 1732, 1609, 1413, 1365, 1268; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.81 (1H, dd, 8.6 Hz, 0.7 Hz, H15), 7.70 (1H, d, 8.1 Hz, H12), 7.56 (1H, dd, 8.5 Hz, 7.7 Hz, H16), 7.35 (1H, d, 6.1 Hz, H2), 7.01 (1H, dd, 7.7 Hz, 0.7 Hz, H17), 6.83 (1H, d, 8.1 Hz, H11), 6.41 (1H, d, 6.1 Hz, H3), 5.65 (2H, br s, H7/H8), 3.18 (2H, m, H6/H9), 2.63 (2H, m, H6′/H9′); δ_C (125 MHz, observed by 2D NMR, $CDCl_3$) 206.5 (C, C4), 152.9 (CH, C2), 147.6 (C, C18), 147.3 (C, C10), 135.9 (CH, C3), 132.8 (C, C14), 131.1 (CH, C12), 129.1 (CH, C16), 128.2 (CH, C7/C8), 121.0 (CH, C15), 114.3 (C, C19), 114.0 (C, C13), 110.8 (CH, C17), 110.5 (CH, C11), 106.4 (C, C1), 61.4 (C, C5), 38.3 (CH_2, C6/C9); HRESIMS $m/z = 369.0131$ $[M + H]^+$ 1.4 ppm (369.0126 calcd for $C_{19}H_{14}{}^{79}BrO_3$).

25. IR (thin film) ν_{max}/cm^{-1} 1729, 1609, 1413, 1365, 1269; δ_H (500 MHz, $CDCl_3$, Me_4Si) 7.80 (1H, dd, 8.6 Hz, 0.7 Hz, H15), 7.69 (1H, d, 8.1 Hz, H12), 7.56 (1H, dd, 8.6 Hz, 7.6 Hz, H16), 7.45 (1H, d, 6.1 Hz, H2), 7.01 (1H, dd, 7.6 Hz, 0.7 Hz, H17), 6.80 (1H, d, 8.1 Hz, H11), 6.47 (1H, d, 6.1 Hz, H3), 6.01 (1H, m, H7 or H8), 5.60 (1H, m, H7 or H8), 2.51 (2H, m, H6/9), 2.17 (2H, m, H6′/9′); δ_C (125 MHz, observed by 2D NMR, $CDCl_3$) 206.5 (C, C4), 153.7 (CH, C2), 147.8 (C, C18), 147.4 (C, C10), 137.0 (CH, C7 or C8), 136.2 (CH, C3), 133.0 (C, C14), 131.2 (CH, C12), 129.0 (CH, C16), 128.7 (CH, C7 or C8), 120.9 (CH, C15), 114.5 (C, C19), 110.6 (CH, C17), 110.5 (CH, C11), 69.9 (C, C5), 32.5 (CH_2, C6 or C9), 29.4 (CH_2, C6 or C9), C1/C13 not observed; HRESIMS $m/z = 369.0115$ $[M + H]^+$ 3.0 ppm (369.0126 calcd for $C_{19}H_{14}{}^{79}BrO_3$).

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