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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 6010

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PAPER

Synthetic studies towards the mulberry Diels–Alder adducts: H-bond accelerated cycloadditions of chalcones†‡

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Received 15th January 2012, Accepted 7th March 2012
DOI: 10.1039/c2ob25115a

The methyl ether derivatives **2**, **4** and **6** of the mulberry Diels–Alder adducts chalcomoracin (**1**) and mulberrofuran C (**3**) and kuwanon J (**5**) respectively have been synthesized by a thermal [4 + 2]-cycloaddition reaction between a chalcone and dehydroprenyl diene. A H-bonded *ortho* OH substituent on the chalcone was found to be essential for Diels–Alder reactivity. Density functional theory calculations show that the OH group lowers the barrier for the Diels–Alder reaction by 2–3 kcal mol^{-1} compared with OMe. The acceleration by the OH group is traced to two transition-state effects: a stronger diene–chalcone interaction and better planarity of the aryl–diene unit.

Introduction

Moraceae is a family of flowering plants comprising about sixty genera and nearly 1400 species which are found in temperate, subtropical and tropical regions of the world. The mulberry tree is a typical plant of the genus *Morus*, which are widely cultivated in China, Korea and Japan. The root bark of mulberry tree has long been used in traditional Chinese medicine for anti-inflammatory, diuretic, anti-tussive, expectorant and anti-pyretic purposes.[1] The methanol extract of *Morus alba* showed antioxidant properties[2] and inhibited the proliferation of vascular smooth muscle cell[3] while the fruit extract also showed a hypolipidemic effect in rats.[4] In addition, compounds isolated from the root bark of *Morus alba* exhibit a hypoglycaemic effect in diabetic mice.[5] Chemical investigations of *Morus* species have resulted in the isolation of a wide range of natural products including the so called Diels–Alder adducts.[6] Some examples are shown in Fig. 1 and include the dehydroprenylarylbenzofuran adducts chalcomoracin (**1**)[7] and mulberrofuran C (**3**)[8] and the dehydroprenylchalcone adduct kuwanon J (**5**).[9] The trisubstituted methylcyclohexene moiety found in these molecules appears to originate from an intermolecular [4 + 2]-cycloaddition reaction between a chalcone type dienophile and dehydroprenylphenol diene.[6] Thus, adducts bearing the *cis, trans* stereochemistry on the cyclohexene ring would be derived from a Diels–Alder reaction through an *endo* transition state (Fig. 1) while the *trans, trans* stereochemistry, which is also observed in a number of these natural products, arises from the *exo* transition

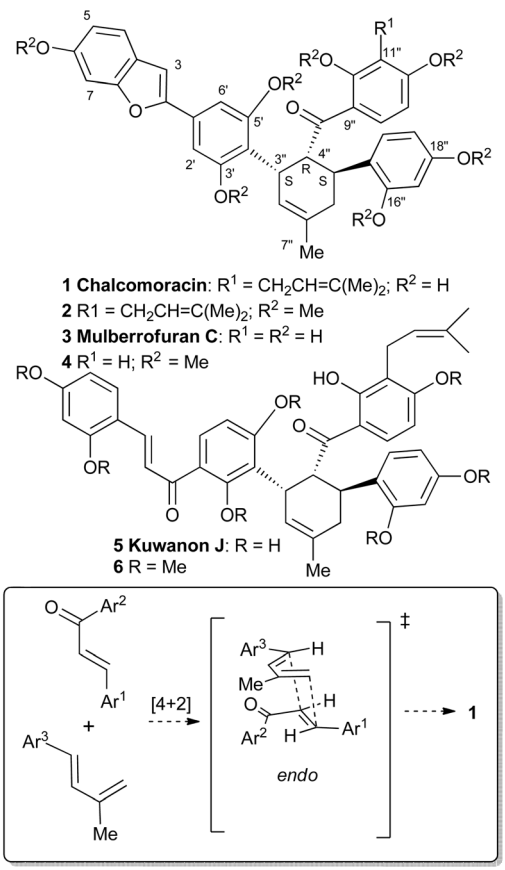

Fig. 1 Examples of mulberry Diels–Alder adducts.

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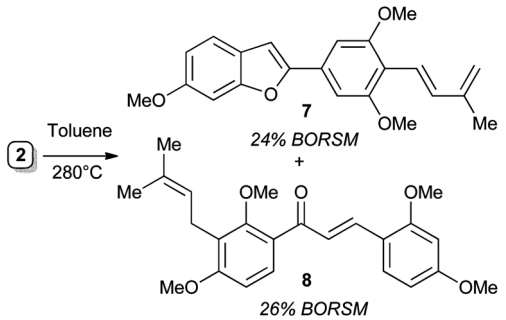
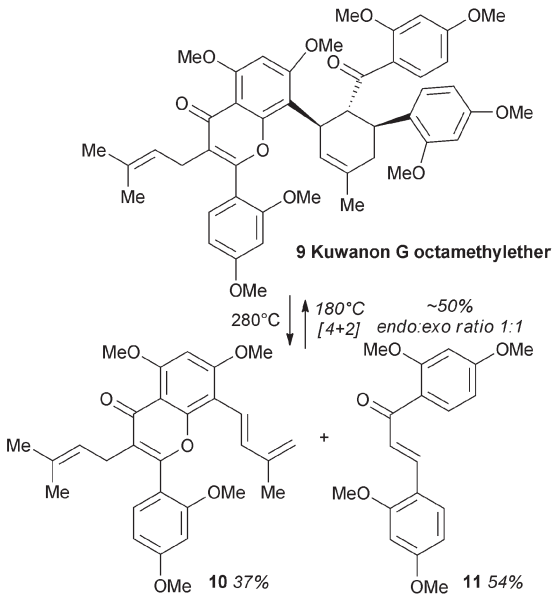
†Electronic supplementary information (ESI) available: NMR spectra of all Diels–Alder adducts and computational data. See DOI: 10.1039/c2ob25115a

‡This article is part of the Organic & Biomolecular Chemistry 10th Anniversary issue.



Scheme 1 Retro-Diels–Alder reaction of chalcomoracin heptamethylether (**2**) (ref. 16).

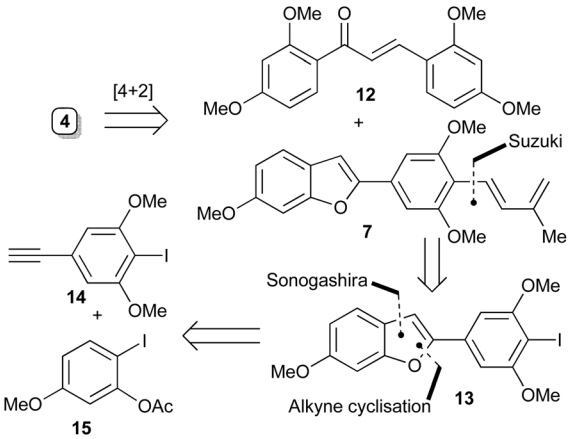


Scheme 2 Retro-Diels–Alder/Diels–Alder reaction of kuwanon G octamethylether (**10**) (ref. 17).

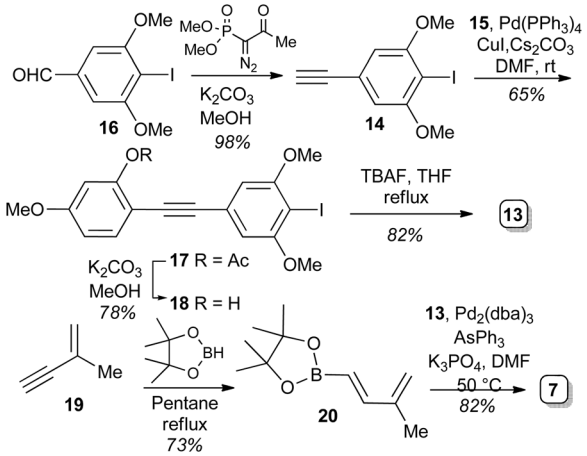
state. Interestingly, all these adducts are optically active with the absolute configuration of mulberrofuran C (**3**) determined as 3″*S*, 4″*R*, 5″*S* by a combination of CD spectroscopy and X-ray crystallography.[10,11] Furthermore, all adducts with a positive optical rotation value are *cis, trans* (*endo*)-adducts whilst the adducts with negative values are the *trans, trans* (*exo*) adducts.[10] This infers that the [4 + 2]-cycloaddition is under some type of enzymatic control[12–14] but the question of whether this process in Nature is concerted or stepwise is a subject of debate.[15,16]

Early studies showed that pyrolysis of chalcomoracin heptamethylether (**2**) resulted in retro Diels–Alder reaction to afford dehydroprenylbenzofuran **7** and chalcone **8**, with the latter compound quoted as highly unstable and therefore not fully characterised (Scheme 1).[17]

Similarly, Nomura's group reported that pyrolysis of kuwanon G octamethylether **9** gave the diene **10** and chalcone **11** which upon heating together at 180 °C in toluene in a sealed tube reformed racemic **9** along with the corresponding *endo*-isomer in 50% yield (Scheme 2).[18] Again, no experimental detail was reported for this process.



Scheme 3 Retrosynthesis of mulberrofuran C heptamethylether (**4**).

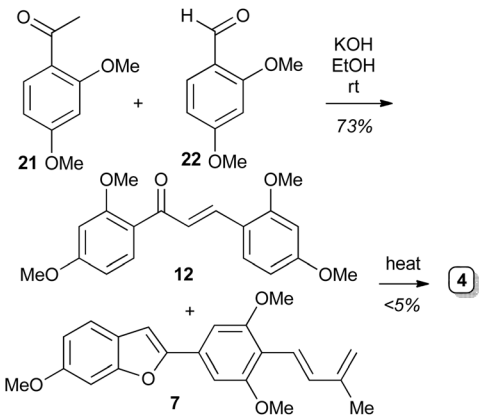


Scheme 4 Synthesis of diene **7**.

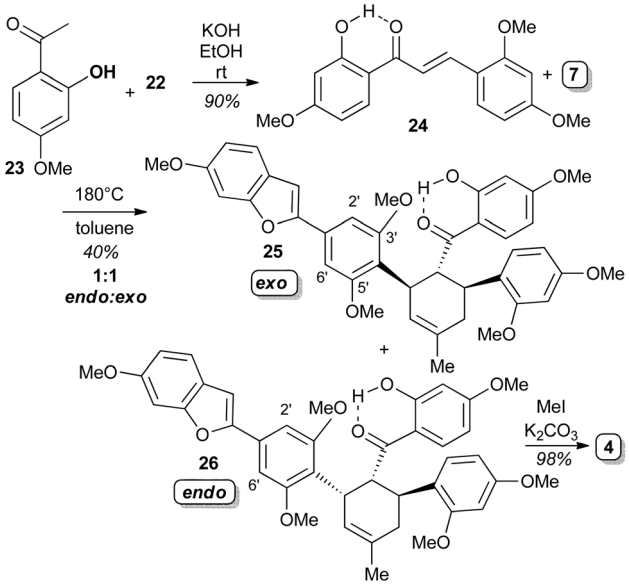
Thermal Diels–Alder reactions of chalcones with dienes such as myrcene have been reported for the synthesis of related methylcyclohexene natural products such as the nicolaioidesins, crinatusins[19] and panduratins.[20] In addition, Porco and co-workers have reported cycloadditions of chalcones catalysed by CoI_2 or silver nanoparticles which are proposed to proceed *via* a stepwise radical mechanism.[21] However, few examples of the [4 + 2]-cycloaddition of chalcones[22] and dehydroprenyl dienes to produce members of the mulberry Diels–Alder type family of natural products have been disclosed.[23,24] We were intrigued by this fact and therefore elected to investigate the synthesis of various cycloaddition partners and the subsequent Diels–Alder reaction. In this paper, we report the full details of our study,[23] including a computational investigation of the acceleration of the Diels–Alder reaction by intramolecular H-bonding.

Discussion and results

A proposed synthesis of mulberrofuran C heptamethylether (**4**) is shown in Scheme 3. This compound could originate from a [4 + 2]-cycloaddition between the simple chalcone **12** and dehydroprenylbenzofuran **7** as the diene (Scheme 4). Owing to its



Scheme 5 Attempted Diels–Alder reaction between **7** & **12**



Scheme 6 Diels–Alder reaction between **7** & phenolic chalcone **24**.

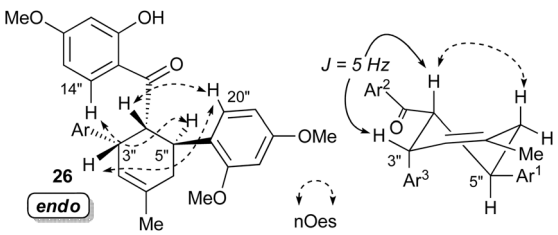


Fig. 2 Selected nOe interactions for *endo*-isomer **26**.

reported instability,[17] we first investigated the synthesis of the diene **7**. We reasoned **7** could arise from a Suzuki cross coupling[25] reaction between iodide **13** and a suitable boronate whilst the benzofuran system could be synthesized by an intramolecular cyclisation of a phenolic alkyne formed by a selective Sonogashira coupling[26] between iodoalkyne **14** and iodide **15**.

The synthesis of the diene **7** is shown in Scheme 4. Alkyne **14** arose from the known aldehyde **16**[27] *via* treatment with the Bestmann–Ohira reagent[28] in the presence of base. Sonogashira coupling with the iodide **15** was best achieved using Cs_2CO_3 as base[29] to afford the tolan **17**. Hydrolysis gave the phenol **18** which was best cyclized to the benzofuran **13** by treatment with TBAF in boiling THF.[30]

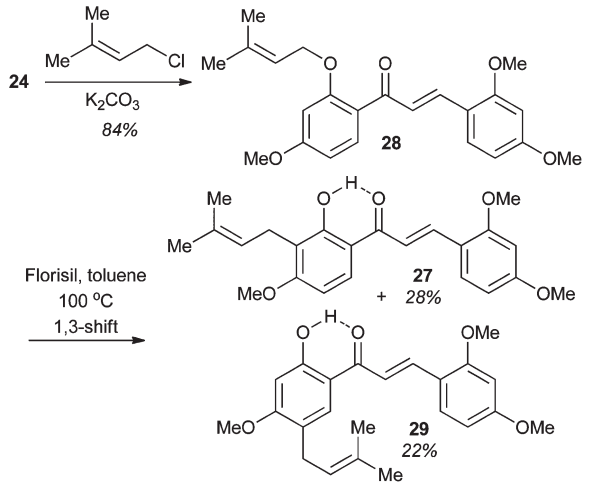
The pinacol boronate **20**[31] was synthesized from enyne **19** by hydroboration[32] with freshly prepared pinacol borane. Suzuki coupling with iodide **13** then afforded diene **7** in high yield. Whilst this compound was sensitive, it proved stable enough in our hands to be fully characterised. We next embarked on the synthesis of the chalcone dienophile as shown in Scheme 5. Claisen–Schmidt condensation[33] between acetophenone **21** and aldehyde **22** gave the chalcone **12**.[34] Unfortunately, all attempts at a thermal or Lewis acid catalysed Diels–Alder reaction between **12** and **7** gave only traces of the desired product **4** and large amounts of decomposition.

We next examined an alternative dienophile **24** which was synthesized as a precursor for the prenylated chalcones. Claisen–Schmidt condensation between phenol **23** and **22** afforded the naturally occurring chalcone **24**[35,36] which displayed a strong H-bonded phenolic resonance in its ^{1}H NMR spectrum. When a solution of **24** and **7** in toluene was heated in a sealed tube for 16 h the *exo* product **25** (mulberrofuran J hexamethylether) and *endo* isomer **26** (mulberrofuran C hexamethylether) were now formed in a 1 : 1 ratio in 40% yield (Scheme 6).

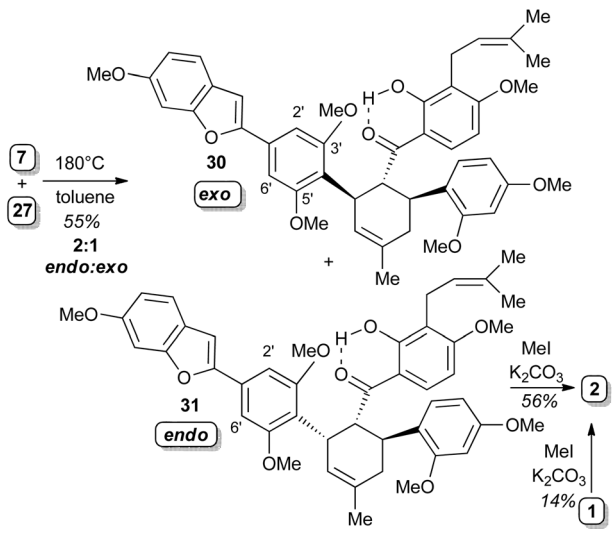
The isomers were separated by HPLC and the stereochemistry of each adduct was confirmed by ^{1}H NMR analysis (Fig. 2). The *endo*-isomer **26** showed a nOe in the NOESY spectrum between the aromatic proton H14″ and H5″ on the cyclohexene ring indicating a *cis* relationship while nOes between H20″ and H3″ and 4″ suggested these were also in *cis* arrangement. A coupling constant of 5 Hz between H3″ and 4″ indicated these were *cis* and the aryl benzofuran ring (Ar^3) is in a pseudoaxial orientation. In the *exo*-isomer **25**, the coupling between H3″ and 4″ is 10 Hz placing these protons in a *trans* arrangement. This data correlated with that for the related natural products.[7,8] Methylation of *endo*-isomer **26** gave mulberrofuran C heptamethylether (**4**) however, since NMR data was not provided in the original report of its synthesis from mulberrofuran C,[8] a direct comparison could not be made.

In addition, we noted that in the *exo*-isomer **25** the signals for H6′ and H2′ in the ^{1}H NMR spectrum appeared as two broad singlets at δ 6.89 and 7.09 ppm whilst the signals for the methoxy groups at C3′ and C5′ also appeared as broad singlets at δ 3.71 and 4.08 ppm. These signals broadened significantly on heating to 50 °C in d_6-acetone. The corresponding signals in the ^{1}H NMR spectrum of *endo* adduct appeared as two broad singlets at 6.95 ppm (2H, H2′ and 6′) and 3.59 ppm (6H, C3′ and 5′ OMe). This clearly indicates that there is restricted rotation about the C3″–C4′ bond which is more pronounced in the *exo*-isomer. This was also observed for H2′ and 6′ (6.67 and 6.83 ppm) for the natural product mulberrofuran J[37] and is possibly due to the close proximity of the aryl groups in the all *trans*-arrangement on the cyclohexene ring increasing the steric congestion.

Clearly, the presence of the H-bonded free phenol in the chalcone **24** was key to the success of the Diels–Alder reaction. In addition, heating the adduct **25** in toluene at 180 °C for 24 h resulted in little change apart form a small amount of decomposition. This indicated the Diels–Alder reaction was under kinetic



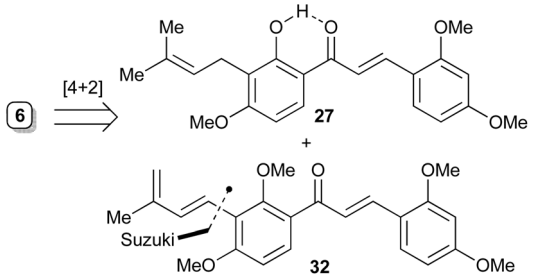
Scheme 7 Synthesis of chalcone **27**.



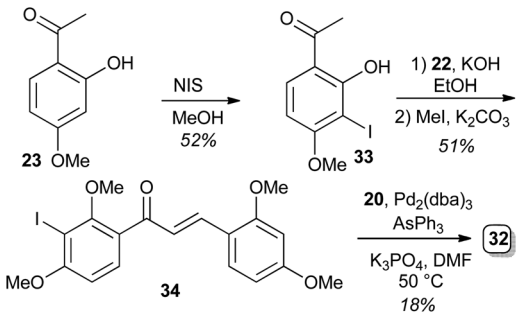
Scheme 8 Diels–Alder reaction between **7** & chalcone **27**: synthesis of chalcomoracin heptamethylether (**2**).

control. We therefore next investigated the synthesis chalcomoracin heptamethylether (**2**) which commenced with the production of the requisite prenylated chalcone **27** (Scheme 7). Prenylation of chalcone **24** with prenyl chloride gave ether **28** in good yield. A 1,3-shift[38] mediated by florisil in toluene at 100 °C yielded the desired prenylated chalcone **27** as well as the 1,5-shift product **29** in 28% and 22% yields respectively along with the phenol **24**.

The cycloaddition between diene **7** and chalcone **27** proceeded at 180 °C to afford a 55% overall yield of chalcomoracin hexamethylether **31** and mongolicin F[39] hexamethylether **30** in a ratio of 2 : 1 respectively (Scheme 8). Each of these was again separable by HPLC and compound **31** was methylated to afford chalcomoracin heptamethylether **2**.[7] Fortunately, we were able to obtain a somewhat impure authentic sample of chalcomoracin (**1**) and permethylation of this crude compound gave naturally derived chalcomoracin heptamethylether **2** in low yield. This compound was identical in all respects (apart from optical



Scheme 9 Retrosynthesis of kuwanon J heptamethylether (**6**).



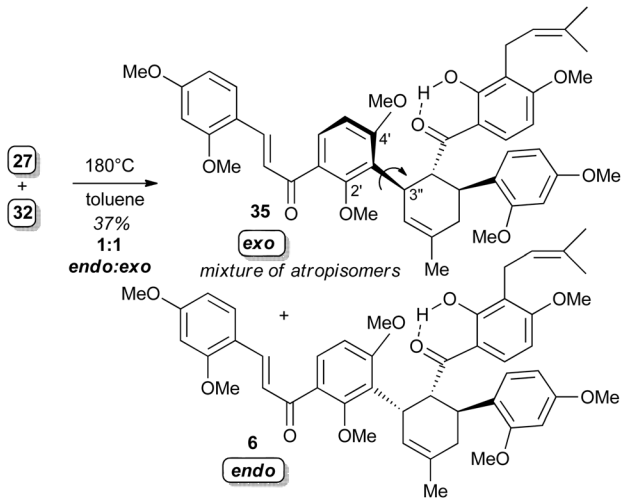
Scheme 10 Synthesis of diene **32**.

rotation) with our synthetic sample thus confirming the stereochemistry of **31**. The *endo*-isomer also had similar ^{1}H NMR characteristics to that described above for **26** and the *exo*-isomer also displayed significant hindered rotation about the C3″–C4′ bond with the signals for H2′ and 6′ appearing at 6.79 and 7.07 ppm whilst the C3′ and 5′ OMe signals appeared at 3.66 and 4.07 ppm.

To further probe the H-bond effect, we next targeted kuwanon J heptamethylether (**6**) (Scheme 9). Kuwanon J[9] (**5**) itself has been shown to arise from a single prenylated chalcone starting material which on dehydrogenation gives a diene partner.[14] Thus, compound **6** could arise from a Diels–Alder reaction between the chalcone dienophile **27** and the corresponding chalcone diene **32** followed by methylation. In this instance, one can envisage the chalcone diene **32** could also react with itself as a dienophile. However, if the H-bonded chalcone **27** reacts fast enough as a dienophile, as suggested by our earlier results, then little dimerization product should be observed and only the [4 + 2]-cycloaddition product arising from a combination of **27** and **32** should be observed. Diene **32** could be obtained by a Suzuki coupling using the same pinacol borane **20** and the appropriate iodide.

The sequence began with the synthesis of the diene **32** as shown in Scheme 10. Iodination of acetophenone **23** gave iodide **33** along with the 5-iodoisomer. Claisen–Schmidt condensation with the aldehyde **22** followed by methylation gave chalcone **34** and Suzuki coupling with boronate **20** gave diene **32** albeit in low yield. With the two cycloaddition partners in hand we next examined the Diels–Alder reaction.

The [4 + 2]-cycloaddition reaction between diene **32** and chalcone **27** afforded kuwanon J heptamethyl ether (**6**) and the *exo*-isomer, which corresponds to kuwanon I[40] heptamethylether (**35**), in a 1 : 1 ratio as the only products isolated (Scheme 11).



Scheme 11 Diels–Alder reaction between diene **32** & chalcone **27**: synthesis of kuwanon J heptamethylether (**6**).

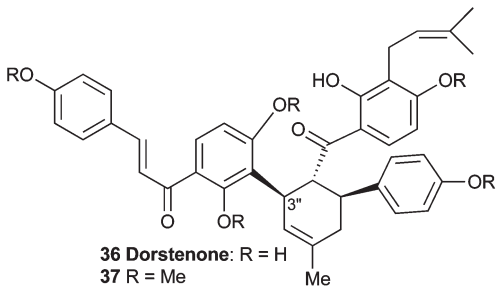
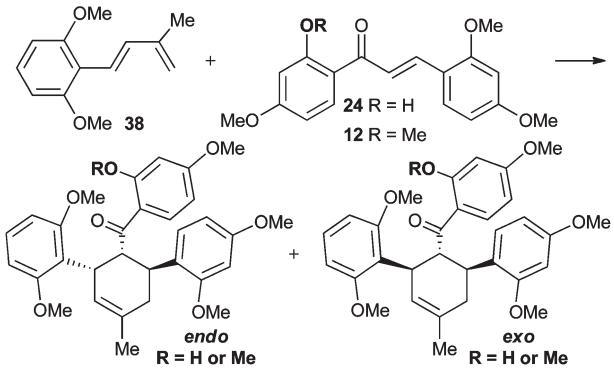


Fig. 3 Dorstenone (**36**) and dorstenone pentamethylether (**37**).

No product resulting from the Diels–Alder reaction of diene **32** with itself as the dienophile to afford kuwanon J octamethylether was detected, again indicating the importance of the H-bond. The *exo*-isomer also showed restricted rotation about the C3′–C3″ bond as shown by the arrow however in this case, most of the signals in the ^{1}H NMR spectrum were doubled (3 : 2 ratio) as a result of *atropisomerism* due to the unsymmetrical nature of the aromatic ring. When a solution of **35** in d_6-DMSO was heated to 75 °C, the signals coalesced to a single set which on cooling to 25 °C returned to the initial 3 : 2 atropisomeric mixture. In the original report of the isolation of the related natural product dorstenone (**36**)[41] (Fig. 3), a doubling of peaks was observed in the ^{1}H NMR spectrum of this compound after 4 h of dissolution of sample. Interestingly, others have observed a doubling of peaks for dorstenone pentamethylether (**37**)[24] and attributed this to an equilibrium between the *exo*- and *endo*-isomers *i.e.* by *epimerisation* at the C3″ stereocentre. This heat induced epimerisation to resolve the mixture to one *exo*-isomer (which then returns to the same *endo*/*exo* mixture on cooling to room temperature) is highly unlikely. Based on our observations it appears that the both these reported examples are also due to atropisomerism.[42]

Computational studies

To determine why the Diels–Alder reactivity of the chalcones **12** and **24** is so highly dependent on the presence of the *ortho* OH group, we performed density functional theory calculations on the Diels–Alder reactions of **12** and **24** with the model aryl diene **38**, as shown in Scheme 12.[43]



Scheme 12 Model Diels–Alder reactions between diene **38** & chalcones **12** or **24**.

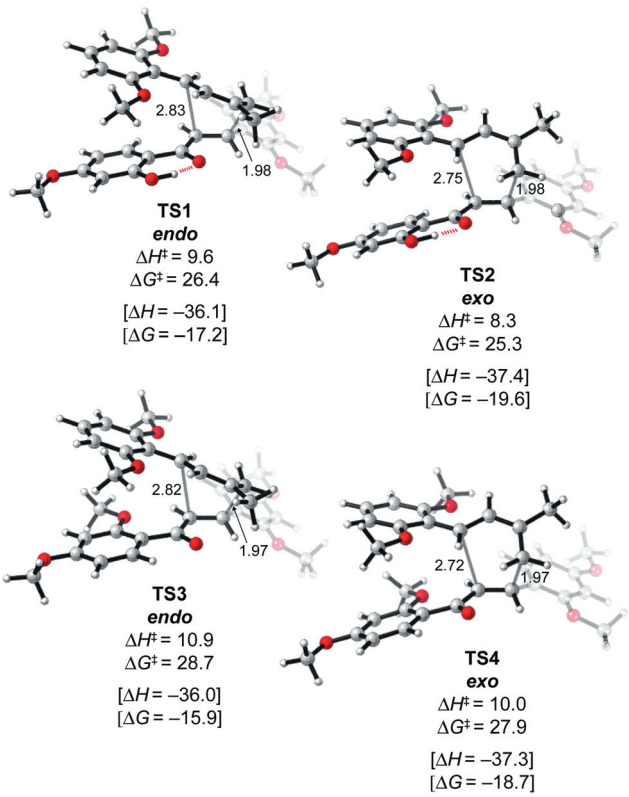


Fig. 4 Calculated transition structures for Diels–Alder reactions of diene **38** with chalcones **24** and **12** (B3LYP geometries, distances in Å). M06-2X activation and reaction energies are shown (kcal mol^{-1}).

Geometries of reactants, transition states, and products were optimized at the B3LYP/6-31G(d) level, and single-point energies were then computed at the M06-2X/6-311+G(d,p) level. The *endo* and *exo* transition structures are shown in Fig. 4, together with their activation energies and the overall reaction energies. The transition states are concerted, but highly asynchronous. The bond to the more electrophilic β carbon of the chalcone is 0.75–0.85 Å shorter than the bond forming at the α carbon. The major geometrical difference between the transition

states for the two chalcones is that the carbonyl oxygen is hydrogen-bonded to OH in chalcone **24** (**TS1**/**TS2**), while there is no possibility for hydrogen bonding in the chalcone **12** (**TS3**/**TS4**) which has its OMe group positioned *anti* to C═O to minimize electrostatic repulsion.

The values of $\Delta G^{\ddagger}$ for **TS1–TS4** predict *exo* selectivities of approximately 1 kcal mol^{-1}, but this value is lowered by inclusion of other low-lying TS conformers. Experimentally, little *exo*/*endo* selectivity was detected. The OH group lowers the activation energy ($\Delta G^{\ddagger}$) by 2.3–2.6 kcal mol^{-1} compared to OMe. This corresponds to a 13–18-fold larger rate constant at 180 °C, in agreement with the yields of 40% and <5% obtained from the Diels–Alder reactions of arylbenzofuran diene **7** with the OH- and OMe-substituted chalcones **24** and **12**, respectively (Schemes 5 and 6).

As mentioned above, the diene **32** (Schemes 9–11), which bears a pendant OMe-substituted chalcone, could undergo Diels–Alder reaction with a second molecule of itself. However, no self-reaction adduct was detected and we surmise that the diene simply prefers to combine with the faster-reacting OH-substituted chalcone **27**. The overall energetics for OH *versus* OMe favour this explanation. There is only a ~1 kcal mol^{-1} difference in the thermodynamic stabilities of the two chalcone products, which would require the self-reaction product to be present in a 1 : 3 ratio if an equilibrium had indeed been reached. This suggests that the reaction is subject to kinetic control under the conditions used.

The enhancement of reactivity by the *ortho* OH group can be traced to two features. During the reaction of diene **38** with OH-substituted chalcone **24**, less energy is required to distort the diene to its TS geometry, and the interaction between the diene and the chalcone in the TS is stronger. An analysis[44] of the OH and OMe transition states **TS2** and **TS4** shows that each of these factors contributes ~1 kcal mol^{-1} to the overall difference in barriers ($\Delta E^{\ddagger}$, M06-2X). The smaller diene distortion for the OH reaction reflects a better coplanarity between the diene and its aryl substituent (Ar[3]) in the TS.[45] The stronger chalcone–diene interaction reflects the LUMO-lowering effect of the OH–carbonyl hydrogen bond. Charge transfer from diene to dienophile is 0.14 e greater in the OH-substituted **TS2** than in the OMe-substituted **TS4**.[46]

Conclusions

A number of thermal Diels–Alder reactions between dehydroprenyl dienes and chalcones to afford the methyl ether derivatives **2**, **4** and **6** of the mulberry Diels–Alder adducts chalcomoracin (**1**) and mulberrofuran C (**3**) and kuwanon J (**5**), respectively, as well as mulberrofuran J hexamethylether (**25**), mongolicin F hexamethylether (**30**), and kuwanon I heptamethylether (**35**), are reported. The success of the [4 + 2]-cycloaddition was dependent on the presence of the H-bonded phenol in the chalcone dienophile and density functional theory calculations suggest that the acceleration of the cycloaddition reaction by the OH group arises both from the LUMO-lowering effect of the OH–carbonyl hydrogen bond and from better coplanarity between the diene and its aryl substituent in the TS. The high temperature conditions utilised above by no means mirror those found in Nature, however the current results do not discount the possibility that a concerted [4 + 2]-cycloaddition reaction is involved in the biogenesis of this family of natural products.

Experimental

General

High resolution mass spectra (HRMS) were run using electrospray ionisation (ESI). Proton nuclear magnetic resonance (^{1}H NMR, 400 and 500 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 100 and 125 MHz) were recorded for deuteriochloroform solutions with residual chloroform as internal standard unless otherwise stated. Analytical thin layer chromatography (TLC) was conducted on aluminium backed 2 mm thick silica gel GF254. Compounds were visualized with solutions of 20% w/w phosphomolybdic acid in ethanol, 20% w/w potassium permanganate in water or under UV (365 nm). Anhydrous tetrahydrofuran (THF) and diethyl ether were dried using a Glass Contour cartridge solvent dispensing system. Petrol refers to the fraction boiling at 40–60 °C. All other commercial reagents were used as received. All air and moisture sensitive reactions were performed in glassware that was either flame dried under an atmosphere of dry argon or oven dried at 150 °C.

5-Ethynyl-2-iodo-1,3-dimethoxybenzene (14)

To a solution of aldehyde **16** (1.50 g, 5.08 mmol) in distilled methanol (10 mL) were added K_2CO_3 (1.41 g, 10.2 mmol) and Bestmann–Ohira reagent[28] (1.23 g, 6.36 mmol). The reaction mixture was stirred at r.t. for 16 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography eluting with 30% EtOAc–petrol to afford **14** (108 mg, 98%) as a yellow crystals; m.p. 127–130 °C; IR ν_{max} (film): 3016, 2970, 2945, 1738, 1435, 1366, 1229, 1217, 120 cm^{-1}; δ_H (500 MHz) 6.62 (s, 2H), 3.88 (s, 6H), 3.11 (s, 1H); δ_C (100 MHz) 159.4, 123.6, 107.8, 83.4, 77.82, 77.80, 56.7; HRMS (ESI) calcd for $C_{10}H_9IO_2Na$ $[M + Na]^+$: 310.95394. Found 310.95394.

2-((4-Iodo-3,5-dimethoxyphenyl)ethynyl)5-methoxyphenyl acetate (17)

To a flame-dried 2-neck round bottom flask, under an argon atmosphere were added tetrakis(triphenylphosphine)palladium(0) (20 mg, 17.4 μmol), copper iodide (4.96 mg, 26.1 μmol), iodide **15** (77.3 mg, 0.26 mmol) and dry DMF (1 mL). The mixture was degassed for 15 min and a solution of alkyne **14** (50 mg, 0.1736 mmol) in dry DMF (1 mL) was added dropwise at 0 °C. The reaction mixture was degassed for 15 min before the addition of cesium carbonate (84.9 mg, 0.26 mmol). The reaction mixture was then stirred at r.t. for 4 h, then filtered through a pad of celite. To the filtrate was added water and the mixture was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The

crude residue was purified by flash chromatography with 30%–40% ether–petrol as eluent to give tolan **17** as a yellow amorphous solid (51 mg, 65%); ν_{max} (film): 3016, 2971, 2946, 1738, 1441, 1366, 1229, 1217, 1206, 1157, 1119, 896 cm^{-1}; δ_H (500 MHz) 7.48 (d, J = 8.5 Hz, 1H), 6.78 (dd, J = 2.5, 8.5 Hz, 1H), 6.68 (d, J = 2.5 Hz), 6.61 (s, 2H), 3.89 (s, 6H), 3.83 (s, 3H), 2.35 (s, 3H); δ_C (125 MHz) 168.7, 160.9, 159.4, 152.9, 133.74, 124.8, 112.3, 109.2, 108.5, 107.2, 92.5, 85.0, 78.8, 56.78, 56.75, 21.0; HRMS (ESI): calculated for $C_{19}H_{17}INaO_5$ $[M + Na]^+$ 475.0018, found: 475.0014.

2-(4-Iodo-3,5-dimethoxyphenyl)-6-methoxybenzofuran (13)

To a solution of acetate **17** (37 mg, 0.08 mmol) in distilled methanol (5 mL) was added K_2CO_3 (20 mg, 0.14 mmol). The reaction mixture was stirred at r.t.for 3 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography with 40% ether–petrol as eluent to afford phenol **18** (26 mg, 78%) a light yellow amorphous solid; ν_{max} (film): 3457, 3016, 2971, 2946, 1738, 1563, 1441, 1366, 1229, 1217, 1206, 1119, 899.5 cm^{-1}; δ_C (500 MHz) 7.33 (d, J = 8.5 Hz, 1H), 6.64 (s, 2H), 6.54 (d, J = 2.5 Hz, 1H), 6.49 (dd, J = 2.5, 8.5 Hz, 1H), 3.92 (s, 6H), 3.82 (s, 3H); δ_C (125 MHz) 162.0, 159.5, 158.2, 132.6, 124.2, 107.7, 107.1, 101.6, 100.3, 95.0, 83.9, 79.1, 56.8, 55.6; HRMS (ESI): calculated for $C_{17}H_{14}IO_4$ $[M - H^+]^-$ 408.9937, found: 408.9940.

To a solution of phenol **18** (29 mg, 0.07 mmol) in THF (5 mL) TBAF (44.6 mg, 0.14 mmol) was added. The reaction mixture was refluxed for 3 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography with 30% ether–petrol as eluent to give benzofuran **13** (24 mg, 82%) as a pale yellow solid; m.p. 191–192 °C; ν_{max} (film): 3000, 2939, 2837, 1623, 1597, 1578, 1558, 1492, 1455, 1405, 1277, 1237, 1207, 1151, 1121, 1021, 962, 821 cm^{-1}; δ_H (500 MHz) 7.44 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 7.02 (d, J = 1.0 Hz, 1H), 6.95 (s, 2H), 6.88 (dd, J = 2.5, 8.5 Hz, 1H), 3.99 (s, 6H), 3.88 (s, 3H); δ_C (125 MHz) 159.8, 158.5, 156.0, 154.5, 132.6, 122.5, 121.2, 112.3, 102.2, 100.4, 96.0, 56.8, 55.8; HRMS (ESI): calculated for $C_{17}H_{15}INaO_4$ $[M + Na]^+$ 432.9913, found: 432.9908.

(*E*)-4,4,5,5-Tetramethyl-2-(3-methylbuta-1,3-dienyl)-1,3,2-dioxaborolane (20)

To a solution of pinacolborane (325 mg, 2.54 mmol) in distilled pentane (4 mL), under an argon atmosphere, was added 2-methyl-1-buten-3-yne **19** (139 mg, 2.10 mmol) dropwise at 0 °C. The reaction mixture was heated under reflux for 17 h and allowed to cool to r.t. The mixture was filtered through a pad of celite and the filtrate was concentrated to provide **20** (296 mg, 73%) as a colourless oil which was used in the next step without further purification. δ_H (500 MHz) 7.08 (d, J = 18.0 Hz, 1H), 5.54 (d, J = 18.0 Hz, 1H), 5.15 (s, 2H), 1.85 (s, 3H,), 1.25 (s, 12H); δ_C (125 MHz) 152.3, 143.1, 120.2, 83.3, 24.92, 24.69, 17.8.

(*E*)-2-(3,5-Dimethoxy-4-(3-methylbuta-1,3-dienyl)phenyl)-6-methoxybenzofuran (7)

To a flame-dried 2-neck round bottom flask containing a solution of arylbenzofuran iodide **13** (20 mg, 0.05 mmol) and dienylboronate **20** (39.7 mg, 0.20 mmol) in DMF (2 mL), were added $Pd_2(dba)_3$ (3.29 mg, 3.59 μmol) and $AsPh_3$ (2.20 mg, 7.19 μmol) under an argon atmosphere. The reaction mixture was degassed for 15 min before the addition of a solution of K_3PO_4 in water (3 M, 170 μL, 0.51 mmol). The reaction mixture was stirred at 50 °C for 16 h, then filtered through a pad of celite. To the filtrate was added water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography with 10% ether–petrol (1% Et_3N) as eluent to provide diene **7** (14 mg, 82%) as a light yellow amorphous solid; ν_{max} (film): 2922, 2853, 1745, 1655, 1621, 1599, 1556, 1492, 1456, 1412, 1357, 1338, 1278, 1204, 1151, 1120, 1028, 962, 975, 878, 821, 765, 697; δ_H (500 MHz) 7.43 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 16.5 Hz, 1H), 7.08 (d, J = 1.5 Hz, 1H), 7.01 (s, 2H), 6.97 (d, J = 0.5 Hz, 1H), 6.86 (d, J = 16.5 Hz, 1H), 6.86 (dd, J = 2.5, 8.5 Hz), 5.10 (br s, 1H), 5.05 (br s, 1H), 5.03, 3.97 (s, 6H), 3.88 (s, 3H), 2.01 (s, 3H); δ_C (125 MHz, d_6-acetone) 159.7, 159.5, 156.8, 155.7, 144.5, 136.2, 131.1, 129.8, 129.2, 122.0, 120.6, 116.7, 113.2, 103.0, 101.0, 96.4, 56.3, 56.0, 23.3; HRMS (ESI) calculated for $C_{22}H_{23}O_4$ $[M + H]^+$ 351.1596, found: 351.1582.

Mulberrofuran C hexamethyl (26) ether mulberrofuran J hexamethyl ether (25)

Diene **7** (13 mg, 0.0371 mmol) and dienophile **24** (14 mg, 0.0445 mmol) were dissolved in distilled toluene (2 mL) in a sealed tube. The mixture was degassed for 15 min and heated at 180 °C for 16 h. The reaction mixture was concentrated and separated by column chromatography with 30% ether–petrol as eluent to give a mixture of diastereoisomers **25** and **26** as a yellow solid (12 mg, 40%). The mixture of diastereoisomers was separated by preparative HPLC (5 micron Spherex 5 silica 250 × 10 mm column, 40% EtOAc–petrol as an eluent, flow rate: 2 mL min^{-1}).

Endo-isomer **26** (R_t = 11.03 min) was obtained as a pale yellow a light yellow amorphous solid; ν_{max} (film): 2956, 2837, 1740, 1624, 1609, 1563, 1506, 1492, 1462, 1412, 1374, 1358, 1278, 1235, 1207, 1152, 1124, 1033, 962, 823; δ_H (500 MHz, d_6-acetone) 12.6 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 0.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.95 (s, 2H), 6.86 (dd, J = 2.5, 8.5 Hz, 1H), 6.51 (dd, J = 2.5, 8.5 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 6.31 (dd, J = 2.5, 8.5 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 5.40 (br s, 1H), 4.63 (br s, 2H), 4.24 (br d, J = 5.5 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.65 (br s, 6H), 2.35 (dd, J = 6.5, 18.0 Hz, 1H), 2.18 (dd, J = 10.0, 18.0 Hz, 1H), 1.77 (s, 3H); δ_C (125 MHz, d_6-acetone) 207.1, 166.3, 166.2, 165.9, 165.6, 159.9, 159.3, 159.2, 156.6, 156.0, 133.3, 133.1,

131.1, 123.3, 122.9, 121.9, 119.0, 115.8, 113.0, 107.1, 105.2, 102.3, 101.32, 101.27, 101.22, 101.20, 99.5, 96.4, 56.0, 55.93, 55.91, 55.8, 55.3, 49.3, 38.3, 35.6, 23.7; HRMS (ESI): calculated for $C_{40}H_{40}NaO_9$ $[M + Na]^+$ 687.2570, found: 687.2565.

Exo-isomer **25** (R_t = 11.95 min) was obtained as a yellow amorphous solid; ν_{max} (film): 2999, 2970, 2938, 2836, 1738, 1609, 1563, 1506, 1492, 1454, 1439, 1412, 1371, 1277, 1230, 1207, 1151, 1111, 1031, 960, 937, 922, 822, 736 cm^{-1}; δ_H (500 MHz, d_6-acetone) 13.1 (s, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 7.08 (br s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.87 (br s, 1H), 6.86 (dd, J = 2.0, 9.0 Hz, 1H), 6.36 (s, 1H), 6.26 (dd, J = 2.0, 8.0 Hz, 1H), 6.15 (dd, J = 2.0, 9.0 Hz, 1H), 6.05 (br s, 1H), 5.25 (s, 1H), 4.93 (br s, 1H), 4.51 (br d, J = 10 Hz, 1H), 4.06 (br s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.70 (br s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 2.15 (br s, 1H), 1.74 (s, 3H); δ_C (125 MHz, d_6-acetone) 209.8, 166.5, 165.8, 160.7, 160.2, 159.3, 159.2, 159.0, 156.6, 155.8, 132.9, 132.3, 131.0, 125.1, 123.2, 121.9, 120.6, 116.0, 113.0, 107.1, 105.1, 102.4, 101.9, 101.3, 100.7, 99.3, 96.4, 56.6, 56.4, 56,0, 55.7, 55.3, 42.0, 38.8, 36.9, 36.8, 23.4; HRMS (ESI): calculated for $C_{40}H_{41}O_9$ $[M + H]^+$ 665.2751, found: 665.2700.

Mulberrofuran C heptamethyl ether (4)

To a solution of mulberrofuran C hexamethyl ether **26** (2 mg, 3.125 mmol) in acetone (2 mL) under an argon atmosphere were added anhydrous K_2CO_3 (4.3 mg, 31.25 mmol) and MeI (4.43 mg, 31.25 mmol). The reaction mixture was heated under reflux for 16 h and water and CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated to afford a yellow amorphous solid **4** (2 mg, 98%); ν_{max} (film): 2925, 2851, 1716, 1663, 1603, 1562, 1504, 1492, 1462, 1413, 1361, 1279, 1252, 1231, 1207, 1152, 1121, 1030, 962, 936, 824, 737 cm^{-1}; δ_H (500 MHz, d_6-acetone) 7.46 (d, J = 8.5 Hz, 1H), 7.14 (s, 1H), 7.13 (s, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.88 (br s, 2H), 6.86 (dd, J = 2.5, 9.0 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.42 (d, J = 2.5 Hz, 1H), 6.31 (dd, J = 2.0, 8.5 Hz, 2H), 5.32 (br s, 1H), 4.77 (dd, J = 8.0, 11.5, 1H), 4.75 (br s, 1H), 4.29 (dd, J = 6.3, 10.5 Hz, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H), 3.61 (br s, 6H), 2.34 (dd, J = 6.0, 18.3 Hz, 1H), 2.07 (d, J = 6.5 Hz, 1H), 1.73 (s, 3H); δ_C (125 MHz, d_6-acetone) 199.8, 164.5, 161.3, 159.5, 159.3, 159.2, 156.6, 156.3, 133.2, 132.6, 160.6, 129.2, 123.6, 123.5, 123.4, 121.8, 120.3, 112.9, 105.9, 105.2, 102.0, 99.4, 98.5, 96.4, 56.2, 56.0, 55.88, 55.82, 55.81, 55.4, 53.6, 38.8, 33.5, 32.6, 23.8; HRMS (ESI): calculated for $C_{41}H_{42}O_9$ $[M + H]^+$ 679.2907, found: 679.2897.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-(4-methoxy-2-(3-methylbut-2-enyloxy)phenyl)prop-2-en-1-one (28)

To a solution of chalcone **24** (200 mg, 0.64 mmol) in acetone (5 mL) were added K_2CO_3 (220 mg, 1.59 mmol) and prenyl chloride (325 mg, 3.10 mmol). The reaction mixture was heated under reflux for 16 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography with 40% ether–petrol as eluent to provide chalcone **28** (206 mg, 84%) as a yellow oil; ν_{max} (film): 3016, 2971, 2949, 1738.6, 1600, 1440, 1366, 1229, 1217, 1206 cm^{-1}; δ_H (500 MHz) 7.99 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 16.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 6.56 (dd, J = 2.5, 8.5 Hz, 1H), 6.50 (dd, J = 2.5, 8.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 5.52 (t of sept, J = 1.5, 6.5 Hz, 1H), 4.60 (d, J = 6.5 Hz, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H); δ_C (125 MHz) 190.9, 163.8, 162.6, 160.2, 159.8, 137.2, 133.0, 129.7, 125.7, 123.2, 119.6, 118.0, 105.5, 105.4, 100.0, 98.4, 65.9, 55.7, 55.6, 25.9, 18.4; HRMS (ESI): calculated for $C_{23}H_{27}O_5$ $[M + H]^+$ 383.1858, found 383.1852.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)phenyl)prop-2-en-1-one (27) and (*E*)-3-(2,4-dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-5-(3-methylbut-2-enyl)phenyl)prop-2-en-1-one (29)

To a solution of prenyl chalcone **28** (206 mg, 0.54 mmol) in distilled toluene (3 mL) was added 60–100 mesh Florisil® (800 mg). The reaction mixture was stirred at 100 °C for 16 h, then filtered through a pad of celite and the filtrate was concentrated. The crude residue was purified by flash chromatography eluting with 50% CH_2Cl_2–petrol to give **27** (R_f = 0.5) (60 mg, 28%) as a yellow oil; ν_{max} (film): 2963, 2922, 2840, 1680, 1626, 1606, 1557, 1505, 1494, 1458, 1438, 1417, 1372, 1314, 1297, 1266, 1235, 1210, 1161, 1072, 1031, 986, 835, 790 cm^{-1}; δ_H (500 MHz) 13.58 (s, 1H), 8.11 (d, J = 15.5 Hz, 1H), 7.79 (d, J = 9.5 Hz, 1H), 7.63 (d, J = 15.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 6.54 (dd, J = 2.0, 8.5 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 5.24 (t of sept, J = 1.5, 7.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.38 (d, J = 7.5 Hz, 2H), 1.79 (s, 3H), 1.68 (s, 3H); δ_C (125 MHz) 193.0, 163.2, 163.1, 160.6, 139.9, 131.8, 131.2, 129.2, 122.3, 118.8, 117.5, 117.3, 115.0, 105.6, 102.0, 98.6, 55.8, 55.7, 55.6, 25.9, 21.9, 17.9; HRMS (ESI): calculated for $C_{23}H_{27}O_5$ $[M + H]^+$ 383.1858, found: 383.1851.

Further elution provided the [1,5]-rearrangement product **29** (R_f = 0.4) as a yellow oil (45 mg, 22%); IR ν_{max} (film): 2929, 1629, 1608, 1558, 1503, 1457, 1440, 1362, 1294, 1256, 1210, 1160, 1130, 1032, 995, 834 cm^{-1}; δ_H (500 MHz) 13.63 (s, 1H), 8.09 (d, J = 15.5 Hz, 1H), 7.63 (d, J = 15.5 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.5 Hz, 1H), 6.55 (dd, J = 2.5, 9.0 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H), 6.43 (s, 1H), 5.31 (t of sept, J = 1.5, 7.0, 1H), 3.92 (s, 3H), 3.874 (s, 3H), 3.870 (s, 3H), 3.25 (d, J = 7 Hz, 2H), 1.78 (s, 3H), 1.73 (s, 3H); δ_C (125 MHz) 192.5, 165.2, 163.8, 163.0, 160.5, 139.9, 132.8, 131.5, 129.6, 122.3, 121.3, 118.8, 117.2, 105.4, 99.3, 98.5, 55.6, 55.5, 55.4, 27.8, 25.8, 17.8; HRMS (ESI): calculated for $C_{23}H_{27}O_5$ $[M + H]^+$ 383.1858, found 383.1851.

Chalcomoracin hexamethyl ether (31) and mongolicin F hexamethyl ether (30)

Diene **7** (14 mg, 0.04 mmol) and dienophile **27** (20 mg, 0.052 mmol) were dissolved in distilled toluene (2 mL) in a

sealed tube. The mixture was degassed for 15 min and heated at 180 °C for 16 h. The reaction mixture was concentrated and separated by column chromatography with 60% CH_2Cl_2–petrol as eluent to give a mixture of diastereoisomers **30** and **31** as a yellow solid (16 mg, 55%). The mixture was separated by preparative HPLC (5 micron Spherex 5 silica 250 × 10 mm column, 40% EtOAc–petrol as an eluent, flow rate: 2 mL min^{-1}).

Endo-isomer **31** (R_t = 9.75 min) was obtained as a yellow solid; ν_{max} (film): 2926, 2837, 1737, 1608, 1562, 1492, 1454, 1413, 1358, 1277, 1238, 1206, 1150, 1109, 1071, 1033, 962, 936, 821, 789, 735, 703; δ_H (500 MHz, d_6-acetone) 12.7 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 1.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.93 (s, 2H), 6.86 (dd, J = 2.5, 8.5 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.31 (dd, J = 2.5, 8.5 Hz, 1H), 5.40 (s, 1H), 5.08 (t, J = 1.5, 7.0 Hz, 1H), 4.65 (dd, J = 7.0, 10.0 Hz, 1H), 4.58 (br s, 1H), 4.26 (br d, J = 6.0, 10.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.56 (br s, 6H), 3.18 (d, J = 7 Hz, 2H), 2.40 (dd, J = 18.0, 6.0 Hz, 1H), 2.17 (dd, J = 10.0, 16.0 Hz, 1H), 1.77 (s, 3H,), 1.64 (s, 3H), 1.58 (s, 3H); δ_C (125 MHz, d_6-acetone) 207.4, 163.2, 162.1, 159.7, 159.2, 159.1, 156.5, 155.9, 133.3, 131.3, 130.8, 123.2, 122.8, 121.9, 118.7, 116.7, 116.1, 112.9, 105.1, 102.5, 102.3, 99.3, 96.2, 56.1, 55.9, 55.8, 55.7, 55.2, 49.2, 35.7, 25.8, 23.7, 22.0, 17.7; HRMS (ESI): calculated for $C_{45}H_{48}NaO_9$ $[M + Na]^+$ 755.3196, found: 755.3191.

Exo-isomer **30** (R_t = 10.60 min) as a yellow amorphous solid; ν_{max} (film): 2999, 2927, 2837, 1738, 1611, 1563, 1492, 1454, 1438, 1414, 1366, 1276, 1206, 1150, 1109, 1068, 1032, 962, 936, 820, 792, 736 cm^{-1}; δ_H (500 MHz, d_6-acetone) 13.1 (s, 1H, OH), 7.49 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.11 (s, 2H), 7.07 (br s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.86 (dd, J = 2.5, 8.5 Hz, 1H), 6.79 (br s, 1H), 6.36 (s, 1H), 6.26 (dd, J = 2.5, 8.5 Hz, 1H), 6.25 (d, J = 9.0 Hz, 1H), 5.26 (s, 1H), 4.98 (t, J = 1.3, 7.0 Hz, 1H), 4.91 (br s, 1H), 4.45 (br d, J = 10.0 Hz, 1H), 4.07 (br s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.66 (br s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.08 (d, J = 7.0 Hz, 2H), 2.51 (br s, 1H), 2.14 (br d, J = 16.0 Hz, 1H), 1.74 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H); δ_C (125 MHz, d_6-acetone) 210.1, 163.5, 162.0, 160.6, 160.2, 159.3, 159.0, 156.6, 155.9, 132.2, 131.2, 131.0, 130.9, 125.1, 123.3, 123.2, 121.9, 120.7, 116.6, 116.3, 113.0, 105.2, 102.3, 102.0, 101.1, 99.4, 96.4, 56.4, 56.0, 55.7, 55.9, 55.3, 46.9, 39.0, 25.7, 23.4, 22.0, 17.7; HRMS (ESI): calculated for $C_{45}H_{49}O_9$ $[M + H]^+$ 733.3377, found: 733.3373.

Chalcomoracin heptamethyl ether (2)

To a stirred solution of chalcomoracin hexamethyl ether **31** (7 mg, 9.88 μmol) in acetone (2 mL) under an argon atmosphere were added anhydrous K_2CO_3 (10 mg, 0.072 mmol) and MeI (500 mg, 3.52 mmol). The reaction mixture was heated under reflux for 16 h and water and CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by preparative HPLC (5 micron Spherex 5 silica 250 × 10 mm column, 40% EtOAc–petrol as eluent, flow rate: 2 mL min^{-1}) to provide **2** (4 mg, 56%) as a yellow amorphous solid (R_t = 9.81 min); ν_{max} (film): 2934, 2835, 1737, 1673, 1608, 1587, 1562, 1491, 1454, 1411, 1359, 1276, 1232, 1206, 1151, 1109, 1032, 962, 936, 822, 735; δ_H (500 MHz, d_6-acetone) 7.46 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 9.0 Hz, 1H), 7.136 (d, J = 2.0 Hz, 1H), 7.134 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.87 (dd, J = 2.5, 9.0 Hz, 1H), 6.86 (s, 2H), 6.60 (d, J = 9.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.36 (dd, J = 2.5, 8.5 Hz, 1H), 5.32 (s, 1H), 5.10 (t, J = 6.5 Hz, 1H), 4.59 (s, 2H), 4.29 (br s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.61 (br s, 6H), 3.38 (s, 3H), 3.30 (dd, J = 7.5, 14.0 Hz, 1H), 3.19 (dd, J = 6.5, 14.0 Hz, 1H), 2.39 (dd, J = 6.0, 17.5 Hz, 1H), 2.18 (br, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 1.63 (s, 3H); δ_C (125 MHz, d_6-acetone) 200.6, 161.7, 160.2, 159.8, 159.4, 159.3, 159.2, 156.6, 156.3, 132.4, 131.2, 130.8, 130.6, 129.6, 129.3, 128.6, 127.4, 124.2, 123.6, 123.4, 121.8, 119.9, 112.9, 106.4, 105.2, 102.0, 101.0, 99.3, 96.4, 62.9, 56.2, 56.0, 55.8, 55.7, 55.4, 52.2, 37.8, 34.2, 25.8, 23.8, 23.4, 17.9; HRMS (ESI): calculated for $C_{46}H_{51}O_9$ $[M + H]^+$ 747.3533, found 747.3528.

Methylation of an authentic sample of chalcomoracin (1)

To a stirred solution of authentic sample of impure chalcomoracin **1** (6 mg, 9.25 μmol) in acetone (2 mL) were added anhydrous K_2CO_3 (12.7 mg, 92.5 μmol) and MeI (500 mg, 3.52 mmol). The reaction mixture was refluxed for 16 h before and water and CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was separated by column chromatography with 50% ether–petrol as eluent to give the crude product (4 mg) which was subjected to purification using preparative HPLC (5 micron Spherex 5 silica 250 × 10 mm column, 40% EtOAc–petrol as eluent, flow rate: 2 mL min^{-1}) to give chalcomoracin heptamethyl ether **31** as a yellow solid (1 mg, 14%).

1-(2-Hydroxy-3-iodo-4-methoxyphenyl)ethanone 32 and 1-(2-hydroxy-5-iodo-4-methoxyphenyl)ethanone

To a solution of acetophenone **23** (100 mg, 0.59 mmol) in distilled MeOH was added iodosuccinimide (224 mg, 0.90 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 16 h before the addition of a solution of $Na_2S_2O_3$ and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with 20% EtOAc–petrol to provide a yellow solid (R_f = 0.6) (66 mg, 38%) as 5-iodo-2-hydroxy-4-methoxymethylacetophenone; m.p. 151–152 °C; ν_{max} (film): 2938, 1621, 1564, 1484, 1464, 1440, 1411, 1362, 1322, 1278, 1250, 1226, 1205, 1176, 1070, 1042, 950, 893, 818, 715 cm^{-1}; δ_H (500 MHz) 12.6 (s, 1H), 8.07 (s, 1H), 6.40 (s, 1H). 3.91 (s, 3H), 2.55 (s, 3H); δ_C (125 MHz) 201.7, 165.2, 163.7, 141.0, 115.8, 99.9, 73.2, 56.7, 26.3; HRMS (ESI): calculated for $C_9H_{10}IO_3$ $[M + H]^+$ 292.96691, found 292.96688.

Further elution provided the 3-iodo-2-hydroxy-4-methoxymethyl acetophenone **32** as a yellow solid (R_f = 0.4) (90 mg, 52%); m.p. 150–151 °C; ν_{max} (film): 2970, 1738, 1632, 1551, 1490, 1402, 1370, 1276, 1228, 1217, 1163, 1087, 1056, 976, 938, 825, 793, 749 cm^{-1}; δ_H (500 MHz) 13.5 (s, 1H), 7.74

(d, J = 9.0 Hz, 1H), 6.45 (d, J = 9.0 Hz, 1H), 3.97 (s, 3H), 2.60 (s, 3H); δ_C (125 MHz) 202.4, 164.5, 163.4, 132.7, 114.7, 102.4, 76.9, 56.8, 26.1; HRMS (ESI): calculated for $C_9H_{10}IO_3$ $[M + H]^+$ 292.96691, found 292.96689.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-(3-iodo-2,4-dimethoxyphenyl)-prop-2-en-1-one (34)

To a solution of acetophenone **33** (1.16 g, 3.97 mmol) and benzaldehyde **22** (550 mg, 3.31 mmol) in distilled EtOH (20 mL) was added KOH (3.71 g, 66.2 mmol). The reaction mixture was refluxed for 16 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography eluting with 60% CH_2Cl_2–petrol to afford the chalcone (1.08 g, 61%) as a yellow solid; m.p. 175–177 °C; ν_{max} (film): 2837, 1626, 1607, 1549, 1504, 1487, 1461, 1402, 1297, 1266, 1224, 1175, 1157, 1149, 1073, 1029, 987, 949, 824, 790, 750 cm^{-1}; δ_H (500 MHz) 8.16 (d, J = 15.0 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 15.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 6.55 (dd, J = 8.5, 2.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H); δ_C (125 MHz) 192.2, 164.6, 164.1, 163.5, 160.7, 141.3, 131.6, 131.5, 117.5, 116.8, 115.2, 105.6, 102.2, 98.4, 77.1, 56.7, 55.6; HRMS (ESI): calculated for $C_{18}H_{18}IO_5$ $[M + H]^+$ 441.01934, found 441.01926.

To a solution of the chalcone (1.0 g, 2.27 mmol) in acetone were added K_2CO_3 (627 mg, 4.54 mmol) and CH_3I (644 mg, 4.54 mmol). The reaction mixture was refluxed for 18 h before the addition of water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine solution and dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography eluting with 15% EtOAc–petrol to give chalcone **34** (862 mg, 83%) as a yellow solid; m.p. 130–131 °C; ν_{max} (film): 2970, 2940, 2838, 1738, 1649, 1583, 1503, 1456, 1421, 1385, 1329, 1276, 1267, 1228, 1209, 1161, 1120, 1079, 1029, 919, 823, 799, 734 cm^{-1}; δ_H (500 MHz) 8.05 (d, J = 15.5 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 15.5 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 6.51 (dd, J = 2.5, 8.5 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H); δ_C (125 MHz) 191.1, 163.1, 162.0, 160.3, 139.5, 132.3, 130.3, 130.2, 127.4, 117.1, 106.7, 105.4, 98.4, 85.0, 62.7, 56.8, 55.6, 55.5; HRMS (ESI): calculated for $C_{19}H_{20}IO_5$ $[M + H]^+$ 455.03510, found 455.03499.

(*E*)-1-(2,4-Dimethoxy-3-((*E*)-3-methylbuta-1,3-dienyl)phenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (32)

To a flame-dried 2-neck round bottom flask containing a solution of chalcone iodide **34** (95.0 mg, 0.21 mmol) and dienylboronate **20** (81 mg, 0.42 mmol) in DMF (3 mL) were added $Pd_2(dba)_3$ (9.55 mg, 10.5 µmol) and $AsPh_3$ (6.4 mg, 20.9 µmol) under an argon atmosphere. The reaction mixture was degassed for 15 min before the addition of a solution of K_3PO_4 in water (3M, 0.65 mL, 2.09 mmol). The reaction mixture was stirred at 50 °C for 16 h, the filtered through a pad of celite. To the filtrate were added water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2×). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography with 40% ether–petrol as eluent to provide diene **32** (30.0 mg, 18%) as a yellow oil; ν_{max} (film): 3470.7, 2968.2, 2939.2, 1739.0, 1619.3, 1562.8, 1504.7, 1455.3, 1399.7, 1353.2, 1300.0, 1233.2, 1165.8, 1119.8, 1017.5, 829.9, 751.1, 732.6, 696.7 cm^{-1}; δ_H (500 MHz) 7.97 (d, J = 16.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 16.0 Hz, 1H), 7.34 (d, J = 17.0, 1H), 6.77 (d, J = 16.5 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 2.5, 8.5 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H), 5.12 (br s, 1H), 5.09 (br s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 2.01 (s, 3H); δ_C (125 MHz) 192.6, 163.0, 161.1, 160.3, 158.9, 143.4, 139.0, 137.0, 130.2, 130.1, 127.4, 124.8, 120.0, 119.4, 117.4, 106.8, 105.5, 98.5, 62.4, 56.0, 55.68, 55.62, 18.4; HRMS (ESI): calculated for $C_{24}H_{27}O_5$ $[M + H]^+$ 395.18530, found 395.18539.

Kuwanon J heptamethyl ether (31) and kuwanon I heptamethyl ether (30)

Diene **32** (30.0 mg, 0.07 mmol) and dienophile **27** (34.8 mg, 0.09 mmol) was dissolved in distilled toluene (3 mL) in a sealed tube. The mixture was degassed for 15 min and heated at 180 °C for 16 h. The reaction mixture was concentrated and separated by column chromatography with 50% ether–petrol as eluent to a mixture of diastereoisomers as a yellow oil (22 mg, 37%). The mixture was separated by preparative HPLC (5 micron Spherex 5 silica 250 × 10 mm column, 40% EtOAc–petrol as an eluent, flow rate: 2 mL min^{-1}).

Endo-isomer **31** (R_t = 14.80 min) was obtained as a yellow solid; ν_{max} (film): 2935.0, 2838.5, 1587.5, 1504.5, 1463.6, 1438.6, 1416.7, 1330.8, 1293.2, 1266.4, 1238.6, 1112.7, 1209.9, 1033.4, 939.2, 834.3, 795.6 cm^{-1}; δ_H (500 MHz, d_6-acetone) 12.8 (s, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 16.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 16.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 2.5 Hz), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 6.61 (d, J = 8.5 Hz), 6.58 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 2.5 Hz), 6.31 (dd, J = 8.5 and 2.5 Hz, 1H), 5.49 (br s, 1H), 5.06 (t, J = 7.0 Hz, 1H), 4.71 (br s, 1H), 4.57 (br s, 1H), 4.27 (br d, J = 7.5 Hz, 1H), 3.923 (s, 3H), 3.920 (s, 3H), 3.89 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.48 (s, 3H), 3.39 (s, 3H), 3.18 (d, J = 6.0 Hz, 2H), 2.41 (br s, 1H), 2.30 (br d, J = 18.0 Hz, 1H), 1.81 (s, 3H), 1.65 (s, 3H), 1.53 (s, 3H); δ_C (125 MHz, d_6-acetone) 207.6, 192.7, 164.1, 163.4, 162,4, 161.2, 160.0, 159.3, 139.1, 133.7, 131.3, 130.9, 127.7, 125.3, 123.4, 123.2, 123.0, 117.8, 117.0, 116.9, 116.3, 106.8, 105.3, 102.6, 99.6, 99.1, 63.2, 56.2, 56.1, 55.9, 55.5, 55.3, 48.9, 42.1, 37.7, 36.0, 34.4, 31.2, 25.7, 23.8, 22.8, 22.1, 17.8; HRMS (ESI): calculated for $C_{47}H_{52}O_{10}Na$ [M + Na] 799.34527, found 799.34586.

Exo-isomer **30** (R_t = 16.77 min) was obtained as a 3 : 2 mixture of atropisomers; ν_{max} (film): 2960.1, 2930.2, 1727.5, 1611.4, 1588.8, 1504.8, 1463.7, 1416.7, 1380.5, 1272.1, 1209.6, 1160.1, 1119.8, 1073.1, 742.7 cm^{-1}; δ_H (500 MHz) 12.9 (s, 1H), 12.8 (s, 1H), 8.01 (d, J = 15.5 Hz, 1H), 7.93 (d, J = 16.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.33

(t, J = 5.0 Hz, 1H), 7.29 (d, J = 9.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 6.57 (dd, J = 2.0, 8.5 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.43 (s, 1H), 6.34 (s, 1H), 6.30 (d, J = 8.5 Hz, 1H), 6.26 (dd, J = 2.0, 9.0 Hz, 1H), 6.06 (d, J = 9.5 Hz, 1H), 6.02 (d, J = 9.0 Hz, 1H), 5.34 (s, 1H), 5.26 (s, 1H), 5.01 (t, J = 7.0 Hz, 1H), 4.95 (t, J = 7.0 Hz, 1H), 4.86 (br s, 1H), 4.74 (br s, 1H), 4.47 (d, J = 7.5 Hz, 1H), 4.43 (d, J = 7.5 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 3.12 (d, J = 7.0 Hz, 2H), 3.09 (d, J = 4.0 Hz, 1H), 3.05 (d, J = 5.5 Hz, 1H), 2.25 (d, J = 18.5 Hz, 1H), 2.17 (d, J = 18.0 Hz, 1H), 1.75 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H); δ_C (125 MHz) 209.2, 208.8, 192.6, 192.2, 163.1, 162.5, 162.1, 161.5, 161.2, 160.6, 160.4, 160.2, 159.0, 158.3, 138.9, 138.1, 132.4, 131.8, 131.4, 130.5, 130.3, 129.8, 129.5, 126.9, 125.3, 124.7, 124.6, 124.2, 123.8, 123.6, 122.5, 122.3, 117.5, 117.4, 116.5, 116.06, 116.01, 107.4, 105.8, 105.6, 105.4, 104.4, 101.2, 99.0, 98.6, 98.5, 63.7, 63.2, 56.0, 55.9, 55.6, 55.5, 55.3, 47.8, 46.0, 38.9, 38.7, 29.8, 29.5, 25.8, 25.7, 23.4, 23.3, 21.6, 17.8; HRMS (ESI): calculated for $C_{47}H_{52}O_{10}Na$ [M + Na] 799.34527, found 799.34590.

Computational methodology

Density functional theory calculations were performed in Gaussian 09.[47] Geometry optimizations and frequency calculations were performed at the B3LYP/6-31G(d) level.[48] Conformational searching at this level was performed to identify the lowest-energy conformer of each species. Stationary points were identified as minima or transition states by frequency analyses, and transition states were further verified by IRC calculations.[49] Single-point energies were then calculated at the M06-2X/6-311+G(d,p) level[50] and used in conjunction with the unscaled B3LYP zero-point energies and thermochemical corrections to obtain enthalpies and free energies at 298.15 K. A standard state of 1 mol L^{-1} was used. For comparison, energies were also calculated with the dispersion-corrected B3LYP-D method,[51] which gave similar predictions of reactivity to the M06-2X results (see ESI†). The effect of solvent was explored by means of CPCM calculations[52] (M06-2X/6-31G(d), toluene, UAKS radii). Solvation was found to lower $\Delta G^{\ddagger}$ for **TS1–TS4** quite uniformly by 3.2–3.3 kcal mol^{-1} and lowered ΔG by 4.4–5.4 kcal mol^{-1}. Distortion–Interaction analyses[44] on **TS2** and **TS4** were performed at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level. Calculations were also performed to estimate the barrier to rotation about the C–Ar[3] bond in the products resulting from cycloaddition of **24** with **38**. The B3LYP-optimized cycloadduct geometry was subjected to a torsional scan in 10° steps, using MMFF94 optimization followed by an M06-2X/6-31G(d) single-point calculation at each step;[53] the computed barriers for the *endo* and *exo* cycloadducts were 18 and 25 kcal mol^{-1}, respectively.

Acknowledgements

We thank the Australian Research Council Discovery Grants Scheme (DP110100112 to M.A.R. and DP0985623 to E.H.K.) and the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology for funding. Computational resources were provided by the National Computational Infrastructure National Facility (Australia) and by the University of Melbourne School of Chemistry.

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