Diels–Alder Additions to 1-Phenyl-2-benzopyran-3-one and Transformations of the Adducts: Model Experiments for Podophyllotoxin Synthesis

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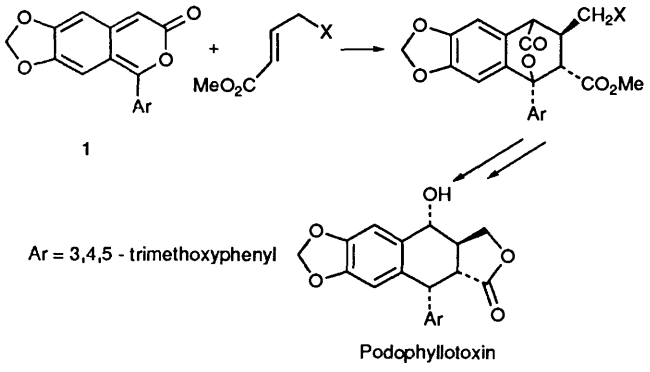
1-Phenyl-2-benzopyran-3-one **2** adds to a series of unsymmetrically substituted dienophiles (methyl acrylate, ethyl crotonate, methyl ω-bromocrotonate, and crotonaldehyde) with regioselectivity largely determined by the phenyl group but with little *endo*-*exo*-selectivity. Addition of **2** to dimethyl fumarate results in preferred *exo*-addition adjacent to the phenyl group. The stereochemistry of hydrogenolysis of the *endo* **15** and *exo* **16** maleate adducts of **2** appears to be governed by steric effects rather than the nature of the catalyst (Pd or Ni). Catalytic hydrogenation of the *cis* dihydronaphthalenes **23** and **24** gave **18** and **25**, respectively, which were different from the products obtained by addition of the *o*-quinodimethanes **11** and **12** to dimethyl maleate in agreement with preferred *exo*-addition in both Diels–Alder reactions. The steric course of catalytic hydrogenation of the *trans*-1,2-dihydronaphthalenes **26** and **28** and the carboxylic acid **31** is controlled by the 1-phenyl and 1-carboxy group, respectively, rather than by the 2-substituent.

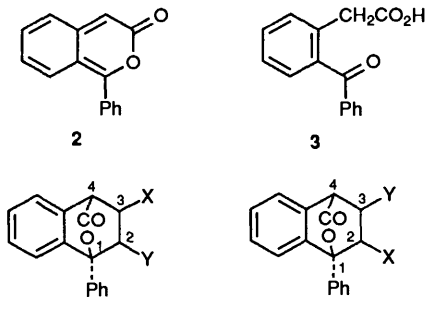
Possible syntheses of podophyllotoxin and its relatives[1] using Diels–Alder reactions of the 2-benzopyran-3-one **1**, as for example sketched in Scheme 1, raised several questions which at



Scheme 1

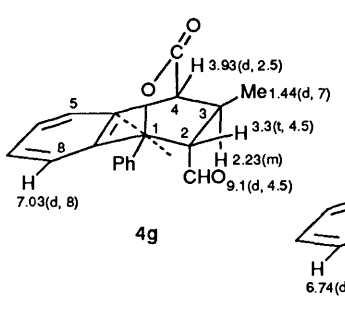
various stages of our work were addressed using the readily available pyrone **2** and its adducts. We were particularly interested in the regioselectivity and stereoselectivity of addition of unsymmetrical dienophiles to **2** and the course of hydrogenolysis and hydrogenation of the resulting adducts and related compounds. Our results serve to clarify contradictory reports[2,3] on the stereochemistry of the addition of dimethyl maleate to α-aryl-*o*-quinodimethanes.

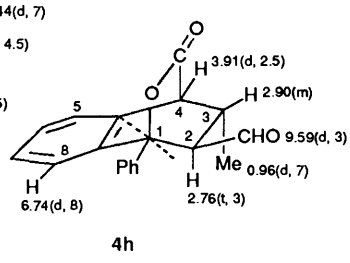
Although it cannot be isolated, the pyrone **2** is formed to the extent of *ca.* 50% from the readily available acid **3** in boiling acetic anhydride.[4a] We had previously shown that **2** generated in this way gave mostly the *endo* adduct with *N*-phenylmaleimide and a 5.9:1 mixture of *endo* and *exo* adducts with dimethyl maleate.[4c] The question whether **1** would show the synthetically useful regioselectivity in addition to dienophiles (Scheme 1), was answered in the affirmative when the model pyrone **2** was shown to add to methyl acrylate, ethyl crotonate, methyl ω-bromocrotonate, and crotonaldehyde to give more of the regioisomer type **4** than type **5**. For ethyl crotonate and methyl ω-bromocrotonate the regioisomers **5c** and **5e** were also obtained, but as minor products. The regioisomeric types **4** and **5** were readily distinguished by the multiplicities of the resonances of 4-H, 2-H and 3-H, even though in some cases signal overlap obscured one or more of these signals (Experimental section). In illustration, the NMR data for **4g**



a X = H, Y = α-CO_2Me
b X = H, Y = β-CO_2Me
c X = β-Me, Y = α-CO_2Et
d X = α-Me, Y = β-CO_2Et
e X = β-CH_2Br, Y = α-CO_2Me
f X = α-CH_2Br, Y = β-CO_2Me
g X = β-Me, Y = α-CHO
h X = α-Me, Y = β-CHO

and **4h** are appended to the perspective formulae **4g** and **4h** below in the form δ value (multiplicity, *J* values/Hz). The appearance of 2-H as a triplet for both these compounds shows they are of regioisomer type **4**, whilst the fact that they differ in having either an *endo* or *exo* directed CHO group is evident from the greater shielding of that group in **4g** and of the methyl group in **4h**. The greater shielding of the phenylene proton 8-H





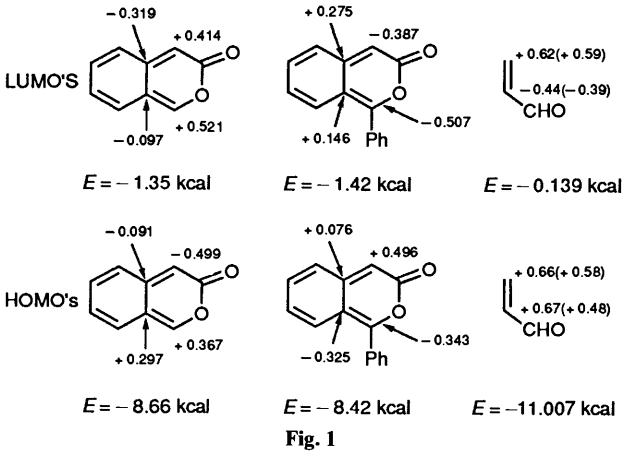
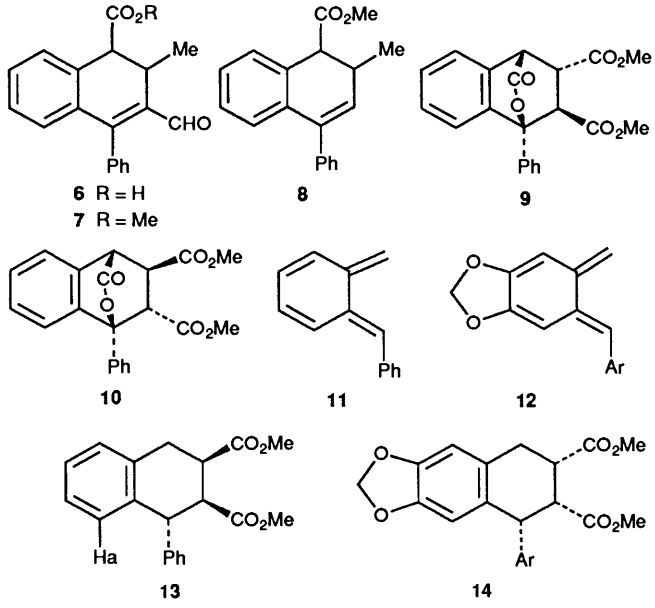


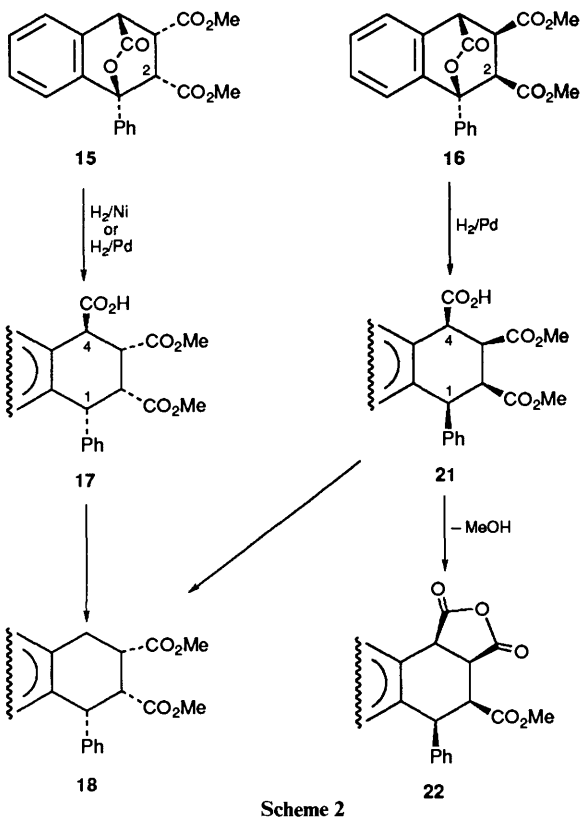
Fig. 1

when the C-2 group is *exo* directed is also illustrated by the spectra of **4g** and **4h**. We noted this effect previously and attributed it to reduced importance of the conformer with an aryl ring in the plane represented by a dashed line in **4g** and **4h** when the C-2 substituent is *endo*.[4c] These observations also allow assignment of adduct configuration at C-2. Preliminary experiments indicated a *ca.* 1:1 mixture of regioisomers from the addition of methyl acrylate to 2-benzopyran-3-one itself. The predominance of adducts of type **4** in additions to the 1-phenylpyrone **2** agrees with the well established and powerful '*ortho*'-directing effect of a 1-phenyl group in 1-phenyl substituted dienes.[5] A comparison of relevant characteristics of the frontier orbitals of the two pyrones and acrylaldehyde is presented in Fig. 1. These were mostly obtained using AM1 calculations but the coefficients of the acrylaldehyde orbitals from CNDO/2 calculations are also shown (in parentheses) as they better explain the dimerisation of acrylaldehyde.[6] From the orbital energies additions between either the parent pyrone or the 1-phenyl derivative and acrylaldehyde would be expected to be normal electron-demand additions controlled mainly by the pyrone HOMO–acrolein LUMO interaction. Accordingly, since introduction of the phenyl group increases the difference in size of the HOMO exponents at C-1 and C-4 the phenyl pyrone would be expected to show greater regioselectivity in its addition to acrylaldehyde and related systems. Although it subsequently transpired that either a C-2 *endo* or a C-2 *exo* adduct was suitable in the synthesis of podophyllotoxin[7] the addition of crotonaldehyde to **2** was tested in the hope of achieving greater C-2 *endo*-selectivity. Unfortunately, the adducts **4g** and/or **4h** underwent easy β-elimination under the reaction conditions to give the enal **6** which was characterised as the methyl ester formed with diazomethane; an attempt to directly convert the adducts **4g** and **4h** into **7** with methanolic hydrogen chloride gave instead the decarbonylated product **8**. Addition of crotonaldehyde to **2** under milder conditions gave the adducts **4g** and **4h** in a 1.4:1 ratio. However, even under these milder conditions β-elimination which might be expected to be easier for **4h** (*trans* relationship of eliminated hydrogen and carboxyl group) than **4g** is not excluded. The increased C-2 *endo* addition may, therefore, be more apparent than real. The generally more favourable C-2 *exo*-addition is, no doubt, induced by the phenyl group as has been observed in a number of related cases.[4c,8] Thus, we observed that addition of dimethyl maleate to 1,4-diphenyl-2-benzopyran-3-one gave more *exo* than *endo* adduct (ratio 2.3),[4c] and addition of dimethyl fumarate to **2** gave mostly the C-2 *exo*, C-3 *endo* adduct **9** (ratio **9**:**10** = 3.12),[9] although isolation of the individual adducts was not achieved. It has now been possible to isolate **9** in pure form and characterise it fully. Clearly, in this case the unimpeded C-3 *endo*- addition of a CO_2Me group accentuates C-2 *exo*-addition. This observation prompted our use of fumarate

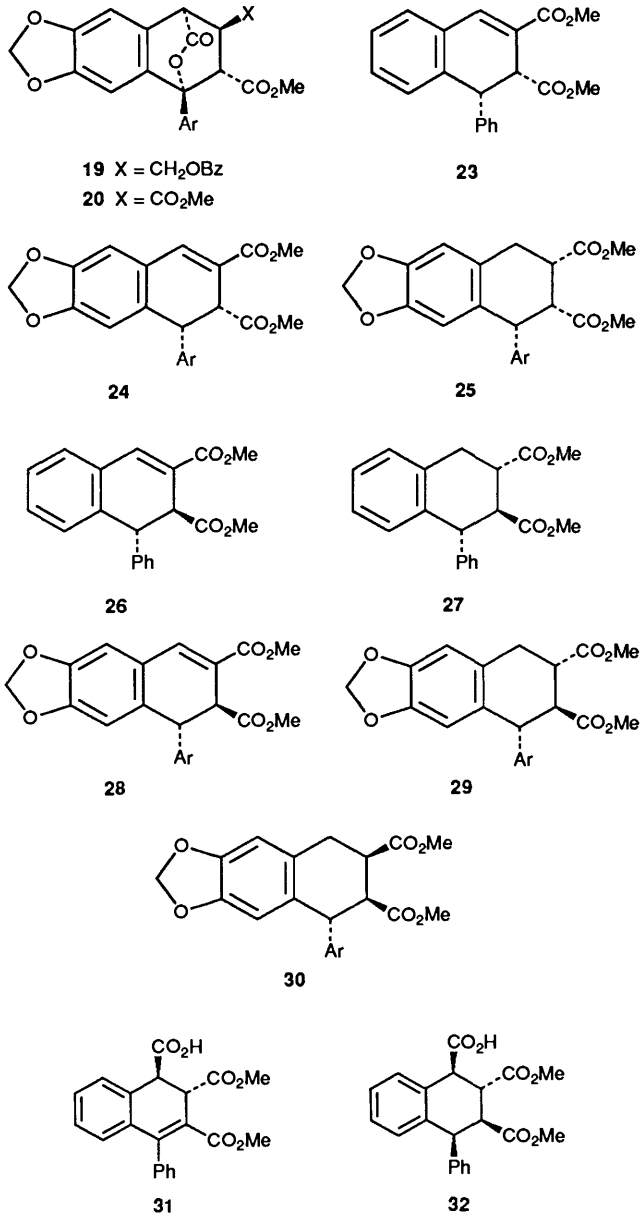


addition to **1** in a short synthesis of (±)-podophyllotoxin.[1a] Although it has both frustrated[10] and aided[1a] lignan synthesis the origin of the *exo*-selectivity induced by α-aryl substitution in *o*-quinodimethanes has not been precisely defined. As shown in Fig. 1 an aryl group is expected to increase the HOMO coefficient at C-8a of the pyrone thus enhancing secondary interaction and *endo* selectivity, contrary to observation. An electronic effect due to the phenyl substituent is, therefore, unlikely. Indeed other evidence[4c] points clearly to a steric effect.

Catalytic Hydrogenation of Adducts and Related Compounds.—These studies were undertaken to clarify the apparently conflicting observations regarding addition of dimethyl maleate to the *o*-quinodimethanes **11** and **12**,[2,3] as well as in connection with our podophyllotoxin syntheses.[1] Whilst Charlton and Durst report addition of dimethyl maleate to **11** gives the *exo* adduct **13**,[2] Mann and his collaborators formulate their product of addition of dimethyl maleate to **12** as the product of *endo* addition **14**.[3] We sought to prepare the unknown product of *endo* addition of maleate to **11** to confirm (or confound) the assignment of structure **13** which was made on the basis of modest shielding of the proton H_a in the product of Charlton and Durst. Our approach to this isomer is shown in Scheme 2 and begins with the known[4c] *endo* and *exo* maleate adducts **15** and **16**, respectively, of the pyrone **2**. These adducts were prepared and their configurations assigned on the basis of NMR evidence made more secure by the conformational rigidity of these adducts. Hydrogenolysis of **15** over Raney nickel would be expected to proceed with retention[11] to give the carboxylic acid **17**. Removal of the carboxyl from **17** using, for example, lead tetra-acetate oxidation followed by benzylic hydrogenolysis (H_2/PdC) of the intermediate acetate, would then be expected to give **18**. Some doubt about the steric course of the Raney nickel hydrogenolysis of **15** arose when hydrogenolysis over palladium charcoal was found to give the same acid **17**. We had previously observed predominant inversion of configuration upon hydrogenolysis of **19** and **20** over palladium.[1a,12] Inversion normally attends allylic and benzylic hydrogenolysis over palladium whilst retention is the general rule for hydrogenolysis over nickel.[11] In the case of **15** it appeared that the 2α-CO_2Me group might sufficiently inhibit hydrogen delivery from below to force hydrogenolysis over palladium with retention of configuration. Accordingly, we extended our study to the *exo* adduct **16** where both the inherent tendency of palladium to induce hydrogenolysis with inversion



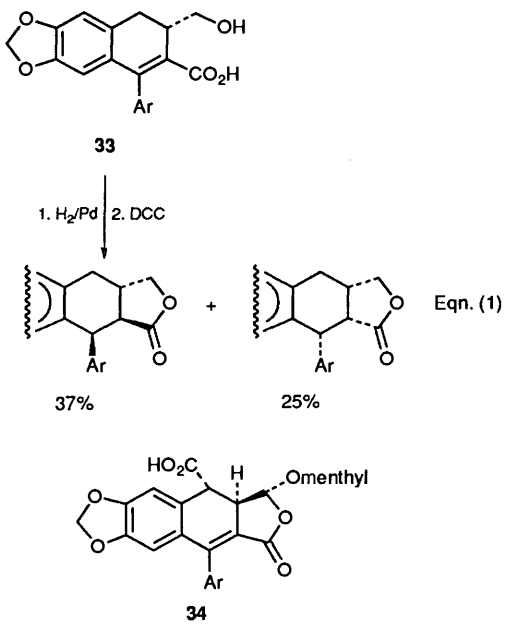
Scheme 2



and the steric effect of the 2β-CO_2Me group favour formation of **21**. In addition to **21** the anhydride **22** was produced in this reaction. The same anhydride was formed by treatment of **21** with a trace of toluene-*p*-sulfonic acid in boiling benzene. This observation confirms the *exo* configuration of the adduct **16** and, therefore, provides additional evidence for the *endo* configuration of **15**. In agreement with the configurations assigned to **17** and **21** and the steric course of the hydrogenolysis reactions, these compounds differ only in the configuration at C-4 for they afford the same product upon removal of the carboxyl group. The product **18** had properties different to those of the adduct from α-phenyl-*o*-quinodimethane and dimethyl maleate. Accordingly, that adduct is the *exo* product **13** claimed by Charlton and Durst. A further check on this assignment became available when we prepared[1b] the *cis*-dihydronaphthalene **23**. Hydrogenation of **23** over palladium gave the same all-*cis*-tetralin **18** by hydrogen delivery to the less hindered β-face. Similar hydrogenation of **24** gave a product to which we assign structure **14** though it has ^1H NMR characteristics quite different to those of the compound assigned structure **14** by Mann and his collaborators.[3] The true identity of the compound obtained by Mann and his collaborators must await the tedious but necessary repetition of their work. It appears safe to conclude that addition of dimethyl maleate to simple α-aryl-*o*-quinodimethanes proceeds with strong *exo* selectivity. This contrasts with the addition of more compact dienophiles, *e.g.* maleic anhydride, and additions to the pyrones **1** and **2** where repulsion between the pyrone COO moiety and *exo* directed groups aids preferred *endo* addition.

The *trans* isomers of **23** and **24** were readily prepared from these compounds by base-catalysed epimerisation.[1b] Hydrogenation of **26** involved preferred addition of hydrogen to the face opposite that of the phenyl group giving **27** and **13** in a 3.3:1 ratio. The major product **27** could be isolated by crystallisation of the mixture and the presence of **13** in the crude product determined from the NMR spectrum in which the resonances assigned to **13** by Koyuna and Charlton[2b] were clearly discerned. Similar reduction of the *trans*-dihydronaphthalene **28** gave mainly the isomer **29** identical with the fumarate adduct of **12** obtained by Mann and his collaborators.[3] The ^1H NMR spectrum of the crude product failed to reveal the presence of **30** which might have been the product observed by Mann and his collaborators[3] from maleate addition to **12**.

Initial experiments to study the thermal decarboxylation of the *endo* adduct **15** were conducted in glassware that had not been base-washed. Under these conditions the desired decarboxylation[1b] was superseded by β-elimination to give the dihydronaphthalene **31**. We studied the hydrogenation of this compound in the hope that the carboxyl group would induce hydrogen addition to the β-face, *cf.* the effect of the aryl group in the hydrogenation of **26** and **28**. Indeed reduction of **31** gave **32** and the previously prepared **17** in a ratio of 3.25:1. Thus, the carboxyl group in **31** induces reasonably strong preference for the synthetically desirable *cis*-1,2-*trans*-2,3 stereochemistry. Only a weak preference for such hydrogenation is shown by the compound **33** [eqn. (1)] and it is noteworthy that the γ-lactone related to **33** gives predominantly the *cis-cis* product[13] whereas hydrogenation of **34** proceeds by addition to the face opposite the carboxyl group to provide a synthesis of optically active podophyllotoxin.[1d]



Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Philips PU 8706 IR spectrophotometer, and referenced to a peak at 1601 cm^{-1} of polystyrene. ^1H NMR spectra were determined, with tetramethylsilane as internal standard; 400 MHz spectra were measured on a Bruker WH-400 instrument and 90 MHz spectra on a JEOL FX 90Q or a Perkin-Elmer R32 instrument. Coupling constants are in Hz. Mass spectra were obtained on a Kratos MS 9/50 instrument. Chromatography on silica refers to short-column chromatography over Kieselgel G60 (Merck).[14] Ether refers to diethyl ether and light petroleum (petroleum) to the fraction b.p. 60–80 °C.

Additions to 1-*Phenyl*-2-*benzopyran*-3-*one*.—(*a*) Methyl acrylate (1.5 cm^3), *o*-benzoylphenylacetic acid (250 mg) and acetic anhydride (6 cm^3) were heated in a sealed vessel in an oil-bath at 130–140 °C (16 h). The mixture was evaporated and the residue chromatographed on silica in benzene–ether (19:1) to give an adduct fraction (112 mg) which was rechromatographed on silica in benzene to give the endo *adduct* **4a** (25 mg), m.p. 152–154 °C (from benzene–petroleum) (Found: C, 74.1; H, 5.25. $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%); δ_H(60 MHz, $CDCl_3$) 1.88 (1 H, ddd, *J* 13, 3, 6, 3-H), 2.70 (1 H, ddd, *J* 13, 8, 3, 3-H), 3.52 (3 H, s), 3.70 (1 H, dd, *J* 6, 4, 2-H), 4.02 (1 H, t, *J* 3, 4-H) and 7.0–7.7 (9 H, m, H-Ar).

Continued elution gave the exo *adduct* **4b** (77 mg), m.p. 112–115 °C (from benzene–petroleum) (Found: C, 74.35; H, 5.35%); δ_H(60 MHz, $CDCl_3$) 2.1 (1 H, ddd, *J* 13, 10, 2.5–3.0, 3-H), 2.62 (1 H, ddd, *J* 13, 4, 3, 3-H), 3.35 (1 H, dd, *J* 10, 4, 2-H), 3.36 (3 H, s), 4.05 (1 H, t, *J* 3, 4-H), 6.6–6.8 (1 H, m, H-Ar) and 6.8–7.7 (8 H, m, H-Ar).

(*b*) Butadiene was bubbled through a red solution of the pyrone that had been formed by boiling *o*-benzoylphenylacetic acid in acetic anhydride (20 min). When the solution became yellow, the process was repeated (4 ×) and the acetic anhydride removed under reduced pressure on a boiling water-bath. The residue was chromatographed on silica in benzene to give first the exo *adduct*, m.p. 167–170 °C (from benzene–petroleum) (60 mg) (Found: C, 82.5; H, 5.8. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.8%); ν_{max}(Nujol)/cm^{-1} 1760; δ_H(60 MHz, $CDCl_3$) 2.0–2.5 (2 H, m), 3.1 (1 H, td, *J* 8.5, 6.0, 2-H), 3.96 (1 H, t, *J* 3, 4-H), 4.75–6.0 (3 H, m, vinyl-H), 6.5–6.9 (1 H, m, Ar-H) and 7.0–7.6 (8 H, m, Ar-H).

Continued elution of the column gave the endo *adduct* (30 mg), m.p. 177–179 °C (from benzene–petroleum) (Found: C, 82.55; H, 5.75%); ν_{max}(Nujol)/cm^{-1} 1755; δ_H(60 MHz, $CDCl_3$) 1.6 (1 H, dm *J* ≈ 14), 2.7 (1 H, ddd, *J* 14, 11, 3), 3.5 (1 H, m), 4.0 (1 H, t, *J* 3, 4-H), 5.1–5.3 (3 H, m, H-vinyl) and 6.9–8.0 (9 H, m, H-Ar).

(*c*) Ethyl crotonate (2 cm^3), acetic anhydride (2 cm^3), and *o*-benzoylphenylacetic acid (200 mg) were boiled under reflux in an argon atmosphere (3 h). Evaporation of the mixture under reduced pressure on a boiling water-bath and chromatography of the residue on silica in benzene–ether (19:1) gave the exo 2-*methyl adduct* **5c** (40 mg), m.p. 133–135 °C (from benzene–petroleum) (Found: C, 74.85; H, 5.9. $C_{21}H_{20}O_4$ requires C, 75.0; H, 5.95%); ν_{max}(Nujol)/cm^{-1} 1733 and 1760; δ_H(90 MHz, $CDCl_3$) 1.1 (3 H, d, *J* 7), 1.25 (3 H, t, *J* 7), 2.85–3.15 (2 H, m), 4.16 (2 H, q, *J* 7), 4.4 (1 H, d, *J* ≈ 2), 6.78 (1 H, d, *J* 7) and 7.1–8.0 (8 H, m).

Continued elution of the column gave the endo-2-CO_2Et *adduct* **4c** (87 mg), m.p. 131–132 °C (from benzene–petroleum) (Found: C, 75.1; H, 6.0%); ν_{max}(Nujol)/cm^{-1} 1725 and 1767; δ_H(90 MHz, $CDCl_3$) 1.11 (3 H, t, *J* 7), 1.46 (3 H, d, *J* 7), 2.25 (1 H, quintet br, *J* ≈ 7), 3.23 (1 H, d, *J* 7), 3.90 (1 H, d, *J* 2), 4.08 (2 H, q, *J* 7) and 7.1–7.75 (9 H, m).

Continued elution of the column gave the exo-2-CO_2Et *adduct* **4d** (127 mg), m.p. 134–136 °C (from benzene–petroleum) (Found: C, 75.0; H, 6.0%); ν_{max}(Nujol)/cm^{-1} 1730 and 1758; δ_H(400 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7), 0.98 (3 H, d, *J* 7), 2.76 (1 H, d, *J* 4.5), 2.88 (1 H, m, *J* 2.5, 4.5, 7.0), 3.85 (1 H, d, *J* 2.5), 3.90 (2 H, q, *J* 7), 6.75 (1 H, d, *J* 7.5), 7.20 (1 H, m), 7.35 (2 H, m), 7.41 (1 H, m), 7.48 (2 H, m) and 7.5–7.67 (2 H, very br, *ortho*-H's of Ph).

(*d*) Methyl ω-bromocrotonate (3 cm^3), acetic anhydride (3 cm^3) and *o*-benzoylphenylacetic acid (200 mg) were boiled under reflux (Ar) for 3 h. The product was evaporated under reduced pressure on a boiling water-bath and the residue chromatographed on silica in benzene–ether (39:1) to give first the 2-exo-*bromomethyl adduct* **5e** (47 mg), m.p. 185–186 °C (from benzene–petroleum); ν_{max}(Nujol)/cm^{-1} 1748 and 1773; δ_H(90 MHz, $CDCl_3$) 3.1–3.7 (4 H, m, unresolved), 4.4 (1 H, d, *J* 2), 6.77 (1 H, d, *J* 7) and 7.1–7.8 (8 H, m).

Continued elution of the column gave the 2-endo-CO_2Me-*adduct* **4e** (89 mg), m.p. 130–150 °C (decomp.) (Found: C, 59.95; H, 4.25. $C_{20}H_{17}BrO_4$ requires C, 59.85; H, 4.4%); ν_{max}(Nujol)/cm^{-1} 1740 and 1760; δ_H(90 MHz, $CDCl_3$) 2.65 (1 H, q, *J* 7 with further fine splitting), 3.34 (1 H, d, *J* 7), 3.61 (2 H, m, unresolved), 3.61 (3 H, s), 4.31 (1 H, d, *J* 3) and 7.15–7.75 (9 H, m).

Further elution of the column gave the 2-exo-CO_2Me-*adduct* **4f** (101 mg) which was meringue-like (Found: M^+, 400.0308 and 402.0285. $C_{20}H_{17}{}^{79}BrO_4$ and $C_{20}H_{17}{}^{81}BrO_4$ require 400.0311 and 402.0291, respectively); ν_{max}(CH_2Cl_2 film)/cm^{-1} 1735 and 1767; δ_H 2.98 (1 H, d, *J* 4), 3.08–3.9 (2 H, m), 3.5 (3 H, s), 4.39 (1 H, d, *J* 2), 6.9 (1 H, d, *J* 8) and 7.2–7.9 (8 H, m); *m*/*z* 321, 299, 292, 278, 277, 276, 275, 222, 217, 215, 194 and 165 (2.8, 1.0, 1.8, 1.6, 7.7, 10.8, 0.8, 100, 61.4, 21.5, 96 and 27.5%).

(*e*) Crotonaldehyde (distilled under Ar; 2 cm^3), *o*-benzoylphenylacetic acid (200 mg) and acetic anhydride (3 cm^3) were heated at 118 °C (internal temperature) under an argon atmosphere (30 min). Evaporation of the reaction mixture under reduced pressure at 100 °C gave a mixture of two adducts not separable by TLC as well as other products (^1H NMR spectrum). The mixture of adducts was obtained pure by chromatography on silica in benzene–ether (24:1) (86 mg) (Found: M^+, 292.1099. $C_{19}H_{16}O_3$ requires M^+, 292.1099); δ_H(90 MHz, $CDCl_3$) Major *endo*-CHO isomer **4g**: 1.44, (3 H, d, *J* 7), 2.23 (1 H, m), 3.3 (1 H, t, *J* 4.5), 3.93 (1 H, d, *J* 2.5), 7.03 (1 H, d, *J* ≈ 8), 7.2–8.0 (8 H, m) and 9.1 (1 H, d, *J* 4.5). Minor *exo*-CHO isomer **4h**: 0.96 (3 H, d, *J* 7), 2.76 (1 H, t, *J* 3), 2.90 (1 H,

m), 3.91 (1 H, d, $J \approx 2.5$), 6.74 (1 H, d, J 8), 7.2–8.0 (8 H, m), 9.59 (1 H, d, J 3); ratio of *endo*:*exo* isomers ≈ 1.4:1; *m/z* 292, 246, 222, 194, 178, 165, 105, 89 and 77 (17.1, 8.1, 79.3, 95.5, 8.3, 23.8, 11.7, 6.7 and 18.1%).

If the reaction time was increased to 6 h and the reaction mixture evaporated and the residue stored with methanol overnight, before brief treatment with diazomethane in ether, the major product (81 mg) was the *trans*-enal **7** formed by β-elimination and methylation, m.p. 120–123 °C (from benzene–petroleum) (Found: C, 78.4; H, 5.9. $C_{20}H_{18}O_3$ requires C, 78.6; H, 5.9%); δ_H(400 MHz, $CDCl_3$) 1.1 (3 H, d, J 7), 3.63 (3 H, s), 3.66 (1 H, qd, J 7 and 1.5), 3.69 (1 H, br s, partial overlap with 3.66 signal), 6.9 (1 H, d, J 8), 7.28–7.50 (8 H, m) and 9.50 (1 H, s); *m/z* 306.1256 (M^+ requires 306.1256), 291, 259, 247, 229, 202, 115, 101, 78 (18.3, 3.2, 7.8, 85.8, 36.7, 31.8, 4.1, 5.6 and 4.0%); ν_{max}(Nujol)/cm^{-1} 1661 and 1721.

When stored in methanol saturated with hydrogen chloride (16 h) the mixture of adducts produced in the first adduction described above gave the *decarbonylated enal* **8** (Found: M^+, 278.1309. $C_{19}H_{18}O_2$ requires *M*, 278.1307); ν_{max}(film)/cm^{-1} 1728 and 1740; δ_H(90 MHz, $CDCl_3$) 1.28 (3 H, d, J 7), 3.06 (1 H, quintet of d, $J \approx 7$ and 4), 3.65 (3 H, s), 3.8 (1 H, d, J 6), 5.79 (1 H, d, J 4) and 6.9–7.5 (9 H, m); *m/z* 278, 219, 218, 204, 203, 202, 178, 141, 115, 101, 91 and 59 (23.8, 94.8, 55.8, 33.1, 28.5, 26.6, 3.1, 5.5, 4.7, 7.9, 4.2 and 3.5%).

(*f*) Dimethyl fumarate (130 mg), *o*-benzoylphenylacetic acid (200 mg) and acetic anhydride (5 cm^3) were heated in an oil-bath at 150 °C under a nitrogen atmosphere. The product was evaporated at 100 °C using a water-pump and the residue examined by ^1H NMR which indicated an *exo*-2-CO_2Me adduct **9** to *endo*-2-CO_2Me adduct **10** ratio of 3.12:1. Chromatography of the mixture on silica in benzene–ether (9:1) gave the adduct mixture (315 mg) which resisted attempted crystallisation from several solvents but crystallised over a long period of time. Recrystallisation from ethanol gave the major adduct **9**, m.p. 150–151 °C (Found: C, 68.8; H, 5.0. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.9%); ν_{max}(Nujol)/cm^{-1} 1755 and 1730; δ_H(400 MHz, $CDCl_3$) 3.39 (3 H, s), 3.67 (3 H, s), 3.85 (2 H, m, unresolved), 4.49 (1 H, d, J 2), 6.83 (1 H, d, $J \sim 7.5$), 7.17–7.60 (7 H, m), 7.64 (1 H, br d, J 7). The following spectrum characterises the non-isolated *endo*-2-CO_2Me adduct: δ_H(400 MHz, $CDCl_3$) 3.14 (1 H, dd, J 6.5, 2.5), 3.58 (3 H, s), 3.83 (3 H, s), 4.05 (1 H, d, J 6.5) and 4.35 (1 H, d, J 2.5), aromatic proton resonances were not assignable for this isomer.

Hydrogenolysis of the endo-1-*Phenyl*-2-*benzopyran*-3-*one*–*Dimethyl Maleate Adduct*.—(*a*) 10% Palladium-on-charcoal catalyst (150 mg) in acetic acid (10 cm^3) containing the title compound (101 mg) were shaken under a hydrogen atmosphere and heated in a bath at 50 °C (20.5 h). The reaction mixture was filtered and evaporated and the residue was chromatographed on silica in benzene–ethyl acetate–acetic acid (9:1:0.5) to give the crude acid which upon trituration with ether (2 ×) gave 2,3-*dimethyl hydrogen* t-1-*phenyl*-1,2,3,4-*tetrahydronaphthalene*-t-2,t-3, r-4-*tricarboxylate* **17** (57.3 mg), m.p. 209–212 °C (Found: M^+, 368.1258. $C_{21}H_{20}O_6$ requires *M*, 368.1259); ν_{max}(Nujol)/cm^{-1} 1709, 1732, 1740 and 2500–3200; δ_H(400 MHz, $CDCl_3$) 3.33 (3 H, s), 3.65 (1 H, dd, J 5.5, 4.5), 3.71 (1 H, dd, J 11.5, 4.5), 3.73 (3 H, s), 4.59 (1 H, d, J 5.5), 4.79 (1 H, d, J 11.5), 6.95 (1 H, d, J 7.5), 7.10–7.36 (7 H, m) and 7.57 (1 H, d, J 7.5); *m/z* 368, 322, 308, 291, 290, 276, 262, 248, 232, 231, 205, 204, 203, 202, 178, 127, 101, 69 (13.2, 16.6, 21.2, 13.5, 39.7, 31.4, 100.0, 40.8, 22.9, 86.8, 85.2, 76.6, 90.8, 75.1, 62.5, 29.2, 19.9 and 66.0%).

(*b*) Similar reduction of the title compound (109 mg) in ethanol–ethyl acetate (2:1) (10 cm^3) with Raney nickel (suspension containing *ca.* 0.6 g cm^{-3} of settled material; 1.5 cm^3) at the b.p. (20 min) gave the same acid **17** (100 mg, crude), m.p. 210–211.5 °C (from ethyl acetate–petroleum).

Hydrogenolysis of the exo-1-*Phenyl*-2-*benzopyran*-3-*one Adduct*.—The adduct (50 mg), 10% palladium-on-charcoal catalyst (442 mg), and glacial acetic acid (30 cm^3) were stirred at 42 °C (internal temperature, bath at ≈50 °C) (24 h). Chromatography of the evaporated product on silica in benzene–acetic acid (9:1) gave 2,3-*dimethyl hydrogen* c-1-*phenyl*-1,2,3,4-*tetrahydronaphthalene*-c-2,c-3-r-4-*tricarboxylate* **21** (148 mg) (Found: M^+, 368.1249. $C_{21}H_{20}O_6$ requires *M*, 368.1259); ν_{max}(Nujol)/cm^{-1} 1706, 1732, 1745 and 2380–3200; δ_H(400 MHz, $CDCl_3$) 3.23 (3 H, s), 3.36 (1 H, dd, J 6.5 and 3.5), 3.57 (1 H, dd, J 6.5 and 3.5), 3.75 (3 H, s), 4.41 (1 H, d, J 6.5), 4.49 (1 H, d, J 6.5), 6.99 (1 H, d, J 8), 7.13–7.33 (7 H, m) and 7.52 (1 H, d, J 8); *m/z* 336, 264. 232, 205, 204, 178, 128, 101, 77, 59 and 44 (19.5, 15.9, 9.0, 75.1, 44.9, 16.0, 17.8, 13.4, 12.1, 8.4 and 11.1%).

The early fractions from the chromatography of the acid gave upon evaporation the *anhydride* **22** (85 mg), m.p. 204–206 °C (from CH_2Cl_2–petroleum) (Found: C, 71.6; H, 4.75. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%); ν_{max}(Nujol)/cm^{-1} 1720, 1780 and 1865; δ_H(400 MHz, $CDCl_3$) 3.51 (3 H, s), 3.52 partly obscured (1 H, dd, J 6.0 and 4.5), 3.87 (1 H, dd, J 10.5 and 6.0), 4.36 (1 H, d, J 10.5), 4.58 (1 H, d, J 4.5), 7.03 (1 H, d, J 7.5), 7.05–7.41 (7 H, m) and 7.82 (1 H, d, J 8); *m/z* 336.0994 (M^+), 264, 232, 205, 204, 203, 178, 128, 101, 89, 77, 59, 44 (22.4, 26.2, 14.8, 100, 59.9, 30.5, 20.8, 26.1, 18.3, 8.9, 14.3, 10.6 and 12.9%).

The same anhydride was readily produced by boiling the carboxylic acid **21** (70 mg) in benzene (10 cm^3) containing toluene-*p*-sulfonic acid (1 mg) (1.5 h) and isolated by triturating the evaporated product with ether and recrystallisation from CH_2Cl_2–petroleum.

Dimethyl r-1-*Phenyl*-1,2,3,4-*tetrahydronaphthalene*-c-2,c-3-*dicarboxylate* **14**.—(*a*) The acid **17** from hydrogenolysis of the *endo*-maleate adduct (70 mg) in THF–HOAc (5:1; 4 cm^3) that had been purged with a slow stream of argon at the b.p. was treated with lead tetraacetate (101 mg) with stirring at 20 °C (1 h) under an atmosphere of argon. The product was poured into water and isolated in ether in the usual way. Chromatography on silica in benzene–ether (9:1) gave first the previously prepared olefin[1b,c] (12 mg) identical (^1H NMR) with an authentic sample, and then the acetate (41 mg): δ_H(400 MHz, $CDCl_3$) 4.58 (1 H, d, J 5.5), 3.52 (1 H, dd, J 5.5, 4), 3.31 (1 H, dd, J 10, 4), 6.97 (1 H, d, J 10), 3.35 (3 H, s), 3.68 (3 H, s), 6.91 (1 H, d, J 8) and 6.99–7.42 (8 H, m). Without further characterisation this product (40 mg) and 10% palladium on charcoal catalyst (80 mg) is acetic acid (4 cm^3) was shaken under hydrogen at 20 °C (20 h). The product was diluted with ether, filtered, evaporated and the residue chromatographed on silica in benzene–ether (19:1) to give the tetrahydronaphthalene **18** (*ca.* 30 mg), m.p. 99–102 °C (from methanol) (Found: C, 73.9; H, 6.2. $C_{20}H_{20}O_4$ requires C, 74.1; H, 6.2%); ν_{max}(Nujol)/cm^{-1} 1729 and 1740; δ_H(400 MHz, $CDCl_3$), 3.12 (1 H, dd, J 16.5, 6.0), 3.19 (1 H, ddd, J 13.6, 6.4), 3.52 (1 H, dd, J 6.5, 4.0), 3.72 (1 H, dd, J 16.5, 13), 4.48 (1 H, d, J 6.5), 3.29 (3 H, s), 3.74 (3 H, s), 6.92 (1 H, d, J 8), 7.06 (1 H, td, J *ca.* 8.2) and 7.15–7.34 (7 H, m); irradiation of the δ 4.48 signal at its resonance frequency resulted in collapse of the δ 3.52 signal to a doublet (J *ca.* 4); *m/z* 324.1355 (M^+), 293, 292, 264, 205, 204, 178, 128, 101, 91, 77, 59 (14, 4.5, 5.9, 27.7, 85.1, 34.7, 20.7, 14.7, 5.6, 14.7, 7.2 and 8.8%).

(*b*) The olefin produced in the foregoing experiment and described elsewhere[1b,c] (110 mg) and 10% palladium-on-charcoal catalyst in ethyl acetate (4 cm^3) were shaken under hydrogen at 20 °C (10 h). Evaporation of the filtered product gave the title compound identical (^1H NMR) with the previously prepared sample.

(*c*) The acid **21** from hydrogenolysis of the *exo*-maleate adduct (70 mg containing *ca.* 25 mg of the anhydride) was treated with lead tetraacetate as described for the C-4 isomer in (*a*) above to give the olefin (8 mg) and the acetate (25 mg) both

compounds being identical (^{1}H NMR spectra) with those produced in (*a*) above.

Catalytic Reduction of trans 2,3-*Bis(methoxycarbonyl)*-1-*phenyl*-1,2-*dihydronaphthalene*.—The title compound (35 mg) and 10% palladium-on-charcoal catalyst (40 mg) in ethyl acetate (3 cm^3) was shaken under hydrogen at 20 °C (18 h). The 400 MHz ^{1}H NMR spectrum showed the presence of two stereoisomers of 2,3-bis(methoxycarbonyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene in a 3.3:1 ratio. The major product could be isolated pure by crystallisation from ethanol, m.p. 105–109 °C (13 mg); reported[2] for the *trans*-1,2-*trans*-2,3-isomer, m.p. 106–108 °C. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) 3.12 (1 H, t, *J* 11, 2-H), 3.12–3.29 (3 H, m), 3.44 (3 H, s), 3.71 (3 H, s), 4.29 (1 H, d, *J* 11, 1-H), 6.73 (1 H, d, *J* 8, 8-H), 7.04 (1 H, m) and 7.08–7.34 (7 H, m) identical with that reported.[2] By comparison with the spectrum of the mixture the following resonances can be assigned to the *trans*-1,2-*cis*-2,3-isomer; δ_H(400 MHz, $CDCl_3$) 2.98 (1 H, ddd, *J* 3.5, 6.0–6.5, 11.0, 3-H), 3.18 (1 H, m, 4-H_{eq}), 3.34 (1 H, dd, *J* 17, 11.0, 4-H_{ax}), 3.49 (1 H, t, *J* 3.0–3.5, 2-H), 3.65 (3 H, s), 3.67 (3 H, s) and 4.84 (1 H, d, *J* 3.0); these peaks are identical with those described[2] for this stereoisomer.

Catalytic Reduction of cis 2,3-*Bis(methoxycarbonyl)*-1-(3′,4′,5′-*trimethoxyphenyl*)-6,7-*methylenedioxy*-1,2-*dihydronaphthalene*.—The title compound[1b,c] (35 mg) and 10% palladium-on-charcoal catalyst in ethyl acetate (3 cm^3) was shaken in hydrogen at 20 °C (24 h). Evaporation of the filtered reaction mixture and crystallisation of the residue from ethanol gave the *cis*-1,2-*cis*-2,3-tetrahydronaphthalene **18**, m.p. 108–113 °C (Found: C, 62.75; H, 5.55. $C_{24}H_{26}O_9$ requires C, 62.9; H, 5.7%); ν_{max}(Nujol)/cm^{-1} 1738; δ_H(400 MHz, $CDCl_3$) 2.99 (1 H, dd, *J* 16.5, 5.5, 4-H_{eq}), 3.12 (1 H, ddd, *J* 13, 5.5, 4, 3-H), 3.36 (3 H, s), 3.45 (1 H, dd, *J* 6.5, 4, 2-H), 3.57 (1 H, dd, br, *J* 16–17 and 13–14, 4-H_{ax}), 3.72 (3 H, s), 3.78 (3 H, s), 3.84 (3 H, s), 4.27 (1 H, d br, *J* 6.5), 5.88 (AB-system, OCH_2O, *J ca.* 1.5), 6.38 (2 H, s, 2′,6′-H), 6.40 (1 H, s, 8-H) and 6.65 (1 H, s, 5-H); *m/z* 458.1581 (M^+), 427, 398, 367, 339, 308, 283, 252, 231, 199, 168, 115 and 59 (100, 9.8, 22.3, 9.8, 67.0, 13.0, 40.3, 23.3, 43.8, 22.2, 13.2, 9.4 and 19.1%).

Catalytic Reduction of trans 2,3-*Bis(methoxycarbonyl)*-1-(3′,4′,5′-*trimethoxyphenyl*)-6,7-*methylenedioxy*-1,2-*dihydronaphthalene*.—The title compound[1b] (36 mg) and 10% palladium-on-charcoal catalyst (40 mg) in ethyl acetate (3 cm^3) were shaken under hydrogen at 20 °C (16 h). Evaporation of the filtered reaction mixture and examination of the residue by 400 MHz ^{1}H NMR spectroscopy revealed the presence of the *trans*-1,2-*trans*-2,3-isomer **29** as the major product; δ_H(400 MHz, $CDCl_3$) 3.04 (1 H, t, *J* 10.5–11.0, 2-H), 3.05–3.10 (2 H, m, 4-H), 3.17 (1 H, td, *J* 10.5, 6.0, 3-H), 3.47 (3 H, s), 3.69 (3 H, s), 3.78 (6 H, s), 3.84 (3 H, s), 4.10 (1 H, d br, *J* 10.5, 1-H), 5.87 (2 H, AB-system *J* 1.5, OCH_2O), 6.24 (1 H, s, 8-H), 6.29 (2 H, s, 2′,6′-H) and 6.57 (1 H, s, 5-H). Apart from increased resolution expected at 400 MHz this spectrum is identical with that reported[3] at 200 MHz. No other isomer could be clearly discerned in the crude product of the hydrogenation and crystallisation from ethanol–dichloromethane gave the pure compound, m.p. 191–193 °C (lit.,[3] m.p. 193 °C).

trans 2,3-*Bis(methoxycarbonyl)*-1-*phenyl*-1,2-*dihydronaphthalene*-1-*carboxylic Acid*.—The *endo*-1-phenyl-2-benzopyrone–dimethyl maleate adduct **15** (100 mg) in a Pyrex test-tube (*not* base-washed) was heated in an oil-bath held at 190–200 °C (10 min) until bubbling ceased. Chromatography of the product on silica in benzene–acetic acid (9:1) gave first the previously described *cis*-2,3-bis(methoxycarbonyl)-1-phenyl-1,2-dihydronaphthalene (33 mg) and then the *title compound* (58 mg), m.p. 133–134 °C (benzene–petroleum) (Found: C, 69.0; H, 4.9. $C_{21}H_{20}O_6$ requires C, 68.85; H, 4.9%); ν_{max}(Nujol)/cm^{-1} 1700, 1725 and 2300–3200; δ_H(400 MHz, $CDCl_3$) 3.51 (3 H, s), 3.65 (3 H, s), 4.43 (1 H, d, *J* 1.5), 4.58 (1 H, d, *J* 1.5), 6.80 (1 H, dd, *J* 8 and *ca.* 1), 7.16 (1 H, td, *J* 7.5 and *ca.* 1), 7.29 (1 H, td, *J* 7 and *ca.* 1) and 7.33–7.45 (6 H, m); *m/z* 322.1197 (M^+), 290, 263, 262, 231, 204, 203, 202, 178, 155, 127, 101, 91, 77 and 59 (27.0, 52.1, 43.8, 58.0, 65.6, 94.1, 98.4, 100, 61.1, 13.9, 23.8, 16.4, 7.6, 12.8 and 36.8%).

Catalytic Hydrogenation of trans 2,3-*Bis(methoxycarbonyl)*-1-*phenyl*-1,2-*dihydronaphthalene*-1-*carboxylic Acid*.—The title compound (200 mg) and 10% palladium-on-charcoal catalyst (300 mg) in acetic acid (20 cm^3) were shaken under hydrogen in a bath at 50 °C. The reaction mixture was evaporated and filtered and the residue was chromatographed on silica in benzene–acetic acid (19:1) to give first an over-reduction product in which the phenyl ring is also reduced (6 mg) which was not further characterised. Continued elution gave material (69 mg) that crystallised on trituration with ether to give the *cis*-1,2-*cis*-2,3-*trans*-3,4-carboxylic acid **17** (43 mg) previously prepared by hydrogenolysis of the *endo*-1-phenyl-2-benzopyran-3-one–dimethyl maleate adduct. Continued elution of the column gave material (111 mg) that resisted crystallisation upon trituration with ether but crystallised upon storage and recrystallised from ethyl acetate–petroleum to give *dimethyl hydrogen* c-1-*phenyl*-1,2,3,4-*tetrahydronaphthalene*-c-2,t-3,r-4-*tricarboxylate* **32**, m.p. 175–177 °C (Found: C, 68.3; H, 5.5. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.4%); δ(400 MHz, $CDCl_3$) 3.44 (1 H, dd, *J* 5.5, 12.5), 3.58 (3 H, s), 3.68 (1 H, t, *J* 12), 3.71 (3 H, s), 4.06 (1 H, d br, *J* 10–12), 4.68 (1 H, d, *J* 5.5), 7.0–7.35 (7 H, m) and 7.40 (1 H, d, $J \approx 8$). Reduction proceeded very slowly in ethyl acetate *ca.* 25% of starting material remaining after 16 h at 20 °C. However, in acetic acid at 20 °C over 16 h reduction was complete. The 400 MHz ^{1}H NMR spectrum of the crude product indicated no over-reduction and the formation of the *trans*-2,3 and *cis*-2,3-products previously observed in a 3.25:1 ratio; no other products were present in significant quantities.

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