Synthesis of Podophyllum Lignans *via* an Isolable *o*-Quinonoid Pyrone

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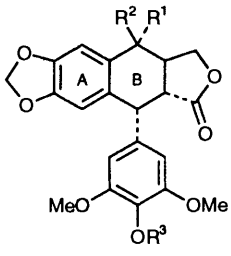
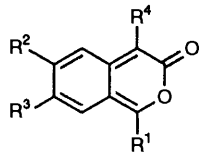
The 2-benzopyran-3-one **10** is a stable, isolable and useful Diels–Alder diene; its methyl 4-benzoyloxycrotonate adduct **23** formed regioselectively and stereoselectively in acetonitrile is reduced with H_2/Pd to give **31** with inversion of C-1-stereochemistry. The latter is readily converted into methyl podophyllate **34** (Scheme 2) which is directly lactonised to podophyllotoxin using $ZnCl_2$/4 Å molecular sieves in tetrahydrofuran. The factors leading to *exo*-selective additions to α-aryl-*o*-quinodimethanes are briefly discussed.

The synthesis of podophyllotoxin **1** and epipodophyllotoxin **2** is a subject of continuing interest.[1] This stems in part from the use of etoposide (VP-16) **3** and teniposide (VM-26) **4** in the treatment of bladder and lung cancer,[2] and in part from the fascinating problem of assembling efficiently, and maintaining the stereocentres in ring B.†

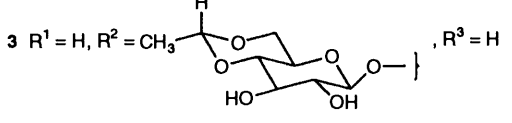
The 2-benzopyran-3-ones **5** and **6** generated as reactive intermediates by acetic anhydride dehydration of *o*-formylphenylacetic acid and 2-formyl-4-methoxyphenylacetic acid, respectively, are useful building blocks in the synthesis of aromatic steroids.[3] The pyrone **9**, similarly generated as a reactive intermediate, is useful in the synthesis of aklavinone.[4] Accordingly, the tetrahydronaphthalene units in **1** and **2** should



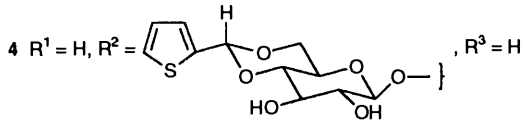


5 $R^1 = R^2 = R^3 = R^4 = H$
6 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
7 $R^1 = R^4 = Ph$, $R^2 = R^3 = H$
8 $R^1 = Ph$, $R^2 = R^3 = R^4 = H$

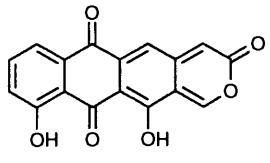
1 $R^1 = OH$, $R^2 = H$, $R^3 = Me$
2 $R^1 = H$, $R^2 = OH$, $R^3 = Me$



3 $R^1 = H$, $R^2 = CH_3$, $R^3 = H$



4 $R^1 = H$, R^2 = 2-thienyl, $R^3 = H$



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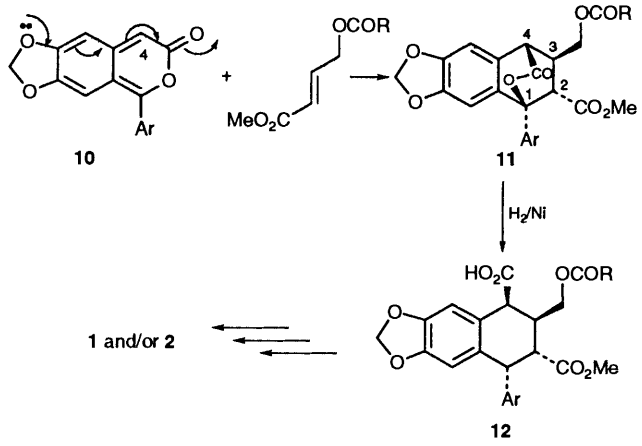
be accessible from the pyrone **10**. One approach is outlined in Scheme 1 where a regioselective and stereoselective Diels–Alder addition with a methyl 4-acyloxycrotonate is proposed as a way of setting up the required carbon skeleton and stereochemistry. The adduct **11** would be expected to undergo hydrogenolysis of

† Even very mild base epimerises **1** at C-2; see ref. 1(*a*) for the large number of steps commonly employed to assemble these lignans.



Ar = 3,4,5-trimethoxyphenyl throughout

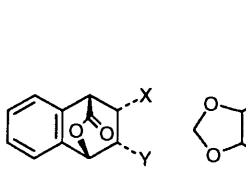
Scheme 1

the C(1)–oxygen bond with a Raney nickel catalyst to give **12** with retained stereochemistry at C-1.[5] The conversion of **12** into **1** and **2** involving replacement of CO_2H by OH and establishment of the *trans*-γ-lactone should involve simple manipulation of functional groups. There is flexibility regarding the stereochemistry at C-4 as **1** and **2** are interconvertible[6] and give the same β-glycosides (**3** or **4**).[7] The proposed Diels–Alder addition (Scheme 1) should proceed with the required regioselectivity for although methyl acrylate and the parent pyrone **5** give almost equal quantities of the regioisomers **13** and **14** the aryl group at C-1 would be expected to strongly favour the required *ortho* regioisomer. From the outset there was doubt about the stereochemistry of the addition for we had noted that α,α′-aryl substitution promoted *exo*-addition to the diphenylpyrone **7**.[8] The several factors that can influence *endo*-*exo*-selectivity in additions of the type shown in Scheme 1 are discussed later. In the meantime we note that hydrogenolysis using a palladium catalyst proceeds with predominant inversion.[5] Accordingly, *exo*-selectivity in the Diels–Alder addition of Scheme 1 could be followed by hydrogenolysis over palladium to give the required *cis* C(1)–C(2), *trans* C(2)–C(3) stereochemistry. The product would be the C-4 epimer of **12**. As noted above, the stereochemistry at C-4 can be adjusted at a late stage in the synthesis.

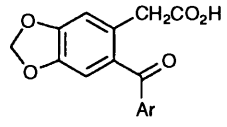
Synthesis and Reactivity of the Pyrone **10**.—The keto acid **15** required for preparation of **10** was obtained from the corresponding methyl ester, in turn prepared by Friedel–Crafts acylation of methyl 3,4-methylenedioxyphenylacetate with 3,4,5-trimethoxybenzoyl chloride in the presence of stannic chloride. Surprisingly, brief treatment of **15** with boiling acetic anhydride

led to quantitative conversion into the isolable pyrone **10** of good shelf-life. Previously, only the diphenylpyrone **7** had been isolated and it had shown reactivity to nucleophiles, *e.g.* MeOH[9] not shared by **10**. The special stability of **10** has been traced to the oxygen substituent at C-6 which is conjugated with the pyrone carbonyl group.[10] That **10** is isolable, allows the testing of its cycloadditions under a wide range of conditions and thus enhances its synthetic potential. The spectroscopic properties of **10** fully confirm the assigned structure (Experimental section). Moreover, reaction of **10** with dimethyl acetylenedicarboxylate gave the known[11] naphthalene **16** and with *N*-phenylmaleimide at 20 °C the adduct **17** was obtained. The *endo*-configuration assigned to **17** is supported by resonance of the *ortho*-protons of the phenyl group at higher field (δ 6.6–7.1) than the *meta* and *para* protons (δ 7.33–7.38) due to shielding by the aromatic ring A.[12] The oxygen substituents in the adduct **17** promote thermal loss of carbon dioxide to give the *o*-quinodimethane **18**. Thus, in boiling acetic anhydride containing an excess of *N*-phenylmaleimide, **15** gives the bis adduct **19**. This, presumably, arises by *endo*-addition of *N*-phenylmaleimide to **18**. In a similar fashion **17** and dimethyl acetylenedicarboxylate in boiling xylene gave the naphthalene **16** (70%). This may be formed by decarboxylation of **17** to **18**, addition of dimethyl acetylenedicarboxylate to give **20** and reverse Diels–Alder reaction **20** (arrows).

Diels–Alder Additions of **10** *to Crotonate Dienophiles.*—When heated together in boiling benzene, methyl crotonate and the pyrone **10** give a mixture of the *endo*-CO_2Me adduct **21** and *exo*-CO_2Me adduct **22** of the required regiochemistry in 30 and 20% yield, respectively. The 'undesired' regioisomer **24** with an *endo* 3-CO_2Me was obtained in only 10% yield. In a similar experiment, but without solvent, the reactants when heated in a bath at 90 °C gave **21** (38%), **22** (24%), **24** (12%), and a minor amount (4%) of a product **26** derived by decarboxylation. The latter probably arises by a 1,5-hydrogen shift **28** (arrows) or the equivalent protonation–deprotonation sequence. It is noteworthy that only in adducts with an *exo*-group at C-2 are the 2′,6′-proton resonances different and broadened. The effect extends to the 3′,5′-methoxy resonances which can be very broad. The enhanced rotational barrier for the *exo*-adducts can be appreciated by reference to **29**; rotation of the pendant aryl group must overcome simultaneous interaction of its 6′-H with 8-H and its 2′-H with the *exo*-group (X). This is more difficult if X = CO_2Me and N = H than for X = H and N = CO_2Me. In the latter case, the *endo*-substituent and the lactone oxygen comprise another joint barrier to aryl rotation but the small



13 X = H, Y = CO_2Me
14 X = CO_2Me, Y = H



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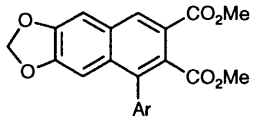

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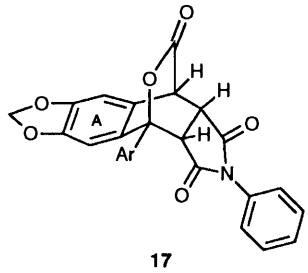

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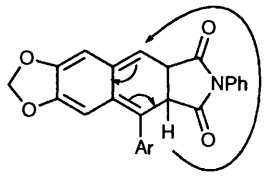

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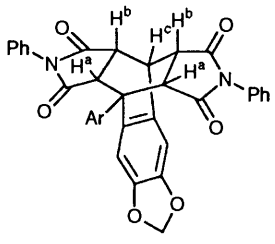

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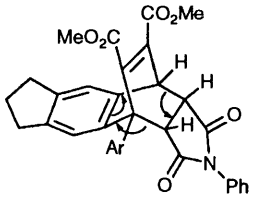

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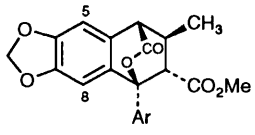

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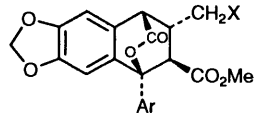
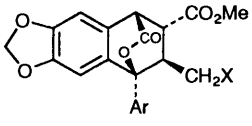
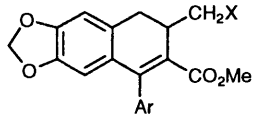


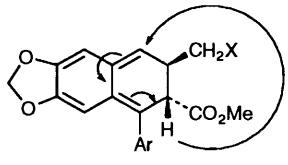
22 X = H
23 X = OBz



24 X = H
25 X = OBz



26 X = H
27 X = OBz



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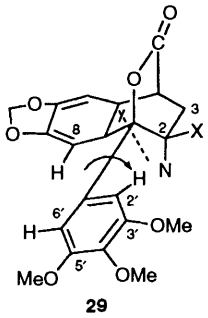

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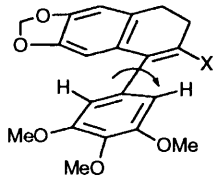

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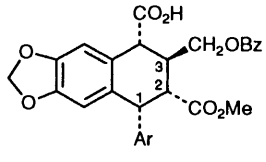

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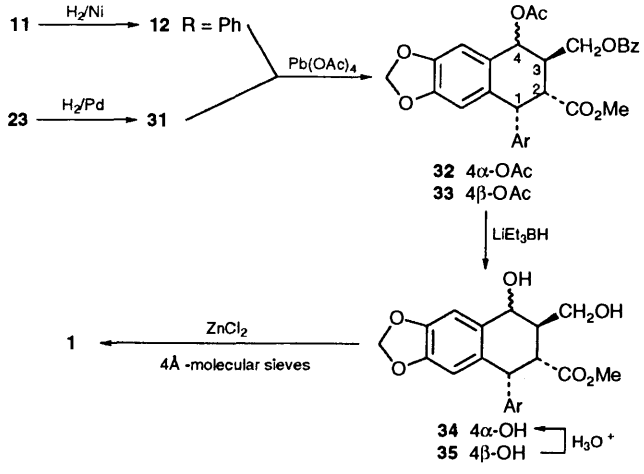
size of oxygen makes this a smaller barrier. For a similar reason, aryl rotation should be slow in structures of type **30**. Indeed, the 2',6'-and 3',5'-methoxy proton resonances are broad for **26** and related compounds. Adduct stereochemistry is assigned on the basis of greater shielding of *endo*- than *exo*-disposed groups, the presence or absence of slow aryl rotation, and a greater shielding of 8-H (see **29**) in *exo* than *endo* 2-substituted compounds, *e.g.* 8-H appears at δ 6.65 in **21**, 6.19 in **22** and 6.28 in **24**. Shielding of 8-H requires location of the pendant aryl ring in the plane shown by a dashed line in **29**. This rotamer whilst satisfactory for an *exo*-substituted compound would be disfavoured for its *endo*-isomer.[8]

The pyrone **10** and methyl 4-benzoyloxycrotonate were heated together in benzene in a bath at 90 °C. The products obtained **11** (R = Ph), **23**, **25** and **27** correspond to those from methyl acrylate but the *exo*-adduct **23** is now more abundant (30%) than the *endo*-adduct **11** (R = Ph) (25%). The *exo*-adduct **23** was also more abundant when addition was performed at very high pressure (10 kbar, 35 °C, CH_2Cl_2) [ratio **11** (R = Ph): **23**:**25**::0.66:1.0:0.1]. In this case no product derived by decarboxylation was detected. When addition of **10** and methyl 4-benzoyloxycrotonate was conducted in acetonitrile in a bath at 75 °C *exo*-addition became much more important the yield of *exo*-adduct **23** reaching 58% [ratio of products **11** (R = Ph):**23**:**25** + **27**::0.33:1: 0.19].

Synthesis of Podophyllotoxin.—Since several attempts, *e.g.* using Lewis acid catalysis, failed to increase the amount of *endo*-addition but the *exo*-adduct became readily available using acetonitrile as reaction solvent the synthesis of podophyllotoxin could use either both the *endo* and *exo* adducts or only the more abundant *exo*-adduct. The completion of a podophyllotoxin synthesis along these lines is outlined in Scheme 2. The



Scheme 2

proposed reductions with Raney nickel (retention of C-1 stereochemistry in the *endo*-adduct) and palladised charcoal (inversion of C-1 stereochemistry in the *exo*-adduct) gave predominantly the expected products but in both cases the C-1 epimers of the desired products were also formed (Experimental section). Oxidation of the resulting acids **12** and **31** with lead tetraacetate in HOAc–THF (1:5) proceeded rapidly at 20 °C to give in each case a 1:1 mixture of the 4α **31** and 4β **33** acetates. These were separately reduced with lithium triethylborohydride at −70 °C when selective reduction of the less hindered acetate and benzoate esters was readily achieved to give methyl podophyllate **34** (66%) and methyl epipodophyllate **35** (80% yield). The intermediate boron derivatives **36**[13] were found to be readily converted into the desired diols by treatment with chromatographic silica in boiling methanol (10 min). It was shown that methyl epipodophyllate could be converted into methyl podophyllate (63% yield).

Rajapaksa and Rodrigo developed an interesting strategy[13,14] for the conversion of **35** into epipodophyllotoxin **2**. This involved conversion of **35** into an acetonide which, unlike **35**, did not epimerise at C-2 during alkaline hydrolysis of the methyl ester. Removal of the 'protecting' acetonide group from the resulting acid gave epipodophyllic acid (CO_2H replacing CO_2Me in **35**) which readily lactonised to epipodophyllotoxin with dicyclohexylcarbodi-imide. Other lignan syntheses have followed this lead.[15,16] However, the protection–deprotection sequence is unnecessary, since **35** is found to undergo rapid, clean, and efficient (81%) direct lactonisation to epipodophyllotoxin **2** when heated with zinc chloride and 4 Å molecular sieves in THF. This procedure is based on the observation that $ZnCl_2$–MeOH equilibrates podophyllotoxin and methyl podophyllate (60% of the former and 16% of the latter) with only minor formation of neopodophyllotoxin (8%) and picropodophyllotoxin (4%).[17] Our $ZnCl_2$–4 Å molecular sieves procedure was designed to reduce the reaction time and give more complete reaction. Thus, some 18% of **35** survives after contact for 18 h with zinc chloride in boiling methanol but with $ZnCl_2$–4 Å molecular sieves in boiling THF **35** is completely consumed in 1 h. Under the same conditions **34** gives podophyllotoxin in high yield (75%). These direct lactonisations of methyl podophyllate and its C-4 epimer considerably simplify existing syntheses of podophyllum lignans.[14–16]

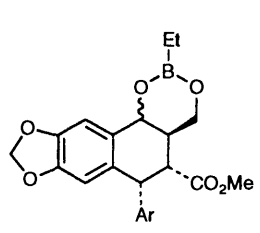
Role of α-Aryl Groups in Promoting exo-*Addition to* o-*Quinodimethanes.*—The presence of an *E*-aryl group at the terminus of an *o*-quinonoid diene favours *exo*-entry of an adjacent dienophile substituent. This effect is of considerable importance in the Diels–Alder route to podophyllium lignans, *e.g.* the potentially elegant route to podophyllotoxin by addition of the photo enol **37** to dimethyl fumarate gave instead the adduct **38** with C(1)–C(2) *trans*-stereochemistry leading to epi-isopodophyllotoxin.[16] As we proposed in 1973 the effect appears to arise through steric interaction involving the protons H^a and H^b (see **37**) and the *endo*-directed substituent of the dienophile. The effect shows the following features which may be useful in synthetic planning.

(i) A variety of dienophiles give mostly *exo*-adducts with the diphenylpyrone **7**[8] although the same dienophiles give mostly *endo*-adducts with the unsubstituted pyrone **5**.[18]

(ii) Compact dienophiles like cyclopropene, *N*-phenylmaleimide and furan do not show the effect, giving mostly *endo*-adducts with **7**. Similarly (*E*,*E*)-α,α'-diphenyl-*o*-quinodimethane gives mostly the *endo* adduct with *N*-phenylmaleimide.[19]

(iii) Unlike the diphenylpyrone **7** the 1-phenylpyrone **8** gave mostly the *endo*-adduct with dimethyl maleate.[8] Since the (*E*)-α-phenyl-*o*-quinodimethane **39** gives mostly *exo*-adduct with dimethyl maleate,[20] repulsion involving the pyrone CO–O moiety may favour *endo*-addition. Alternatively, the H^a–H^b interaction, *e.g.* see **37**, may be more severe in unbridged **39** than in the pyrones. When such interaction is reduced as in the 5-membered ring *o*-quinonoid diene **41** *endo*-addition is preferred.[8] The (*E*)-α-aryl-*o*-quinodimethane **40** gives mostly *endo*-adduct with maleic anhydride[21] in agreement with (ii) above.

(iv) Addition of dimethyl fumarate to the pyrone **8** gives the adducts **42** and **43** (ratio 3:1).[22] The major adduct **42** is favoured by *exo*-entry of the 2-CO_2Me group adjacent to the phenyl and unhindered *endo*-entry of the 3-CO_2Me group. A greater preference for C(2)-*exo*–C(3)-*endo* fumarate addition is also shown by the unbridged *o*-quinodimethanes **37**,[16] **39**[20] and **40**.[21] Predominance of the *endo*-adduct of the monophenylpyrone **8** with maleate is, therefore, favoured by *endo* entry of the 3-rather than the 2-CO_2Me group as well as avoidance of the CO–O bridge.



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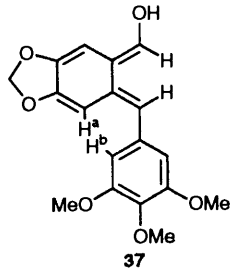

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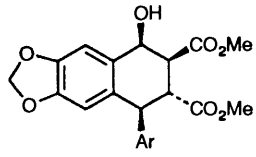

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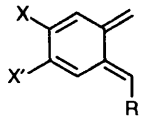
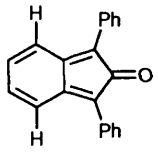


39 X = X' = H, R = Ph
40 X = X' = OCH_2O, R = Ar



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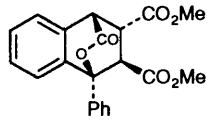

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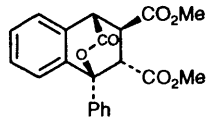

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(v) The somewhat reduced preference for C-2 *exo*-addition by crotonate compared to fumarate observed in the present work is consistent with reduced *endo*-preference of a methyl group compared to a CO_2Me group.

(vi) Remarkably, the photo enol **37** whilst giving the C-2 *exo*-adduct with dimethyl fumarate provides the C-2 *endo*-adduct with the fumarate of (*S*)-methyl mandelate. This addition is also facially selective and leads to an efficient synthesis of (−)-neopodophyllotoxin.[23]

Consideration of these features suggests several ways in which podophyllotoxin synthesis from the pyrone **10** might be improved. Thus, fumarates should add more stereoselectively than crotonates, and maleate should add *endo*-selectively to **10**. Both these approaches have been realised[24] and are described in the following paper. The use of compact dienophiles, *e.g.* butenolides should also be fruitful.

Experimental

^1H NMR spectra were recorded at 90 MHz on a JEOL FX 90Q or a Perkin-Elmer R32 instrument and 400 MHz spectra on a Bruker AM400 instrument. All coupling constants are in Hz. IR spectra were recorded on a Perkin-Elmer 1420 IR ratio recording spectrometer. UV spectra were obtained on Unicam SP800A and 8800 spectrophotometers. Low-resolution mass spectra were measured on a Kratos MS25 instrument. High-resolution mass spectra were obtained on a Kratos MS9/50 instrument. M.p.s were determined on a Reichart hot-stage apparatus and are uncorrected; the abbreviation decomp. refers to decomposition, as determined by TLC of the solidified material.

Chromatography refers to short-column chromatography on Kieselgel 60G (Merck).[25] A ratio of 40:1 silica to compound was used except for samples of less than 200 mg, when 25 g of silica was used. Flash chromatography was performed on Camlab (230–400 mesh) silica gel. Dichloromethane, ethyl acetate and light petroleum were distilled prior to use. Light petroleum refers to that of b.p. 60–80 °C. Thin layer chromatography was carried out using pre-coated aluminium-backed silica plates (Merck 5554), except prior to chromatography when dip plates made from Kieselgel 60G were employed. Preparative layer chromatography was conducted on pre-coated 2 mm (Merck 5717) silica plates.

All reactions were conducted under an atmosphere of dry oxygen-free nitrogen (Fieser's solution) unless otherwise specified. Temperatures were measured internally except where indicated.

Dry ether, tetrahydrofuran (THF) and oxygen-free benzene were freshly distilled from sodium–benzophenone ketyl under nitrogen. Benzene, xylene and toluene were dried over sodium wire prior to use. Chlorinated solvents were distilled from phosphorus pentoxide and stored over 4 Å molecular sieves. Amines were distilled from calcium hydride and stored over potassium hydroxide pellets. Dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves. Methanol was distilled from magnesium methoxide. All other reagents were used as received except where stated.

Methyl 3,4-*Methylenedioxy*-6-(3',4',5'-*trimethoxybenzoyl*)-*phenylacetate*.—Freshly distilled stannic chloride (3 cm^3, 26 mmol) was added to a well stirred ice-water cooled solution of methyl homopiperonylate (3 g, 15 mmol) in dry dichloromethane (45 cm^3) over 0.75 h. The cooling bath was removed and the mixture stirred for a total of 22 h. It was then poured into ice-cold water (300 cm^3), the organic phase was separated and the aqueous phase extracted with dichloromethane. The combined extracts were stirred overnight with saturated $NaHCO_3$ (aq.; 200 cm^3) and solid $NaHCO_3$ (20 g). The two layers were separated and the aqueous phase extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give crude product (6.5 g). This material was chromatographed on silica in ethyl acetate–light petroleum (1:2) to give starting material (0.67 g, 22%). Continued elution gave the *title compound* (2.30 g, 39%), m.p. 146–148 °C (EtOH); δ_H(90 MHz; $CDCl_3$) 3.63 (3 H, s, CO_2Me), 3.76 (2 H, s, CH_2), 3.88 (6 H, s, 2 × OMe), 3.95 (3 H, s, OMe), 6.05 (2 H, s, OCH_2O), 6.87 (1 H, s, ArH), 6.93 (1 H, s, ArH) and 7.04 (2 H, s, 2'-and 6'-ArH); *m/z* 388 (M^+, 95), 328 ($M^+ - HCO_2Me$, 100) and 193 ($ArCO^+$, 14%) (Found: C, 61.8; H, 5.0. $C_{20}H_{20}O_8$ requires C, 61.8; H, 5.1%).

3,4-*Methylenedioxy*-6-(3',4',5'-*trimethoxybenzoyl*)*phenylacetic Acid* **15**.—The foregoing ester (5.6 g, 14.4 mmol) was dissolved in ethanol (50 cm^3) and to the solution was added 2 mol dm^{-3} NaOH (50 cm^3). The reaction mixture was stirred at room temperature for 14 h. Acidification with 1 mol dm^{-3} HCl to pH 7, followed by removal of ethanol (rotary evaporator) and further acidification to pH 1, precipitated the crude acid. The mixture was extracted with ethyl acetate, and the extract dried ($MgSO_4$) and evaporated to give **15** (5.4 g, 100%). Recrystallisation of the latter gave the pure acid (4.5 g), m.p. 194–195 °C (MeOH); δ_H(90 MHz; $CDCl_3$) 3.73 (2 H, s, CH_2), 3.89 (6 H, s, 2 × OMe), 3.98 (3 H, s, OMe), 6.08 (2 H, s, OCH_2O), 6.97 (2 H, s, 2'- and 6'-ArH) and 7.09 (2 H, s, 2 × ArH); ν_{max}(Nujol)/cm^{-1} 3100–2500 br, 1700 and 1650; *m/z* 374 (M^+, 42) and 299 (100%) (Found: C, 60.85; H, 4.8. $C_{19}H_{18}O_8$ requires C, 61.0; H, 4.8%).

6,7-Methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-2-benzopyran-3-one **10**.—The acid **15** (3.51 g) was heated in refluxing acetic anhydride (20 cm^3) for 30 min, after which the reaction mixture was cooled in an ice-bath. The orange–yellow crystals were filtered off and washed with acetic anhydride (5 cm^3), followed by dry ether (30 cm^3). This and a second crop were dried *in vacuo* at 70 °C to give the *title compound* (3.17 g, 95%); m.p. 218.5–219.5 °C; δ_H(90 MHz; $CDCl_3$) 3.91 (6 H, s, 2 × OMe), 3.93 (3 H, s, OMe), 5.96 (2 H, s, OCH_2O), 6.16 (1 H, s, 8-H), 6.43 (1 H, s, 5-H), 6.81 (1 H, s, 4-H) and 6.89 (2 H, s, 2'- and 6'-ArH); ν_{max}(Nujol)/cm^{-1} 1740–1680 (C=O), and 1620; λ_{max}(Ac_2O) 260, 324sh and 445 nm (ε 39 700, 7500 and 11 600 dm^3 mol^{-1} cm^{-1}); *m/z* 356 (M^+, 100%), 341 (24), and 328 ($M^+ - CO$, 32%) (Found: C, 64.05; H, 4.45. $C_{19}H_{16}O_7$ requires C, 64.0; H, 4.5%).

Adduct **17**.—A solution of the pyrone **10** (20 mg, 0.06 mmol) and *N*-phenylmaleimide (10 mg, 1 equiv.) in dry dichloromethane (0.5 cm^3) was stirred at 20 °C for 7 h. Removal of the solvent under reduced pressure gave the crude adduct (30 mg, 100%). TLC and ^1H NMR showed no other products to be present. Recrystallisation of the crude material afforded the pure *compound*, m.p. 179–185 °C (EtOH, decomp.); δ_H(400 MHz; $CDCl_3$) 3.85 (1 H, dd, *J* 3 and 8.5, 3-H), 3.90 (6 H, s, 2 × OMe), 3.93 (3 H, s, OMe), 4.46 (1 H, d, *J* 8.5, 2-H), 4.50 (1 H, d, *J* 3, 4-H), 5.97 (1 H, d, *J* 1, OCH_2O), 6.01 (1 H, d, *J* 1, OCH_2O), 6.48 (1 H, s, 8-H), 6.6–7.1 (2 H, m, NPM *ortho* ArH), 6.90 (1 H, s, 5-H), 7.22 (2 H, s, 2'- and 6'-ArH) and 7.33–7.38 (3 H, m, NPM *meta* and *para* ArH); ν_{max}(Nujol)/cm^{-1} 1770 and 1715; *m/z* 488 ($M^+ - CO_2 - H_2$, 100%) (Found: C, 65.75; H, 4.3; N, 2.65. $C_{29}H_{23}NO_9$ requires C, 65.8; H, 4.35; N, 2.65%).

Diadduct **19**.—The acid **15** (100 mg, 0.27 mmol) and *N*-phenylmaleimide (NPM) (43 mg, 1 equiv.) were heated in refluxing acetic anhydride (2 cm^3) for 0.5 h, after which further dienophile (1 equiv.) was added. After 1 h further NPM (1 equiv.) was added to discharge all the yellow colour. Acetic anhydride was removed with a water pump at 100 °C. The product was triturated with chloroform–ether (1:1), and the white crystals (115 mg, 71%) filtered off at the pump, m.p. 179–185 °C; δ_H(400 MHz; $CDCl_3$) 3.53 (2 H, dd, *J* 3 and 8.5, H^b), 3.72 (2 H, d, *J* 8.5, H^a), 3.85 (6 H, br s, 2 × OMe), 3.91 (3 H, s, OMe), 4.33 (1 H, t, *J* 3, H^c), 5.95 (2 H, s, OCH_2O), 6.88 (1 H, s, ArH), 6.93 (2 H, br s, ArH), 6.77 (4 H, m, NPM ortho ArH), 7.26 (1 H, s, ArH), 7.30–7.35 (6 H, m, NPM *meta* and *para* ArH); ν_{max}(Nujol)/cm^{-1} 1770w and 1710; *m/z* 659 (M + 1, 45) and 658 (M^+, 100%) (Found: C, 69.3; H, 4.55; N, 4.1. $C_{38}H_{30}N_2O_9$ requires C, 69.3; H, 4.6; N, 4.3%).

Dimethyl 6,7-Methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-naphthalene-2,3-dicarboxylate **16**.—The pyrone **10** (60 mg, 0.17 mmol) was stirred in dry xylene (0.5 cm^3) in the presence of dimethyl acetylenedicarboxylate (DMAD) (1 cm^3) at 120 °C. After 15 min, excess of DMAD and xylene were removed with a water pump vacuum and steam-bath to give the crude product (111 mg). Recrystallisation of this afforded the pure naphthalene (68 mg, 89%) identical (90 MHz ^1H NMR, IR and UV) with earlier prepared material.[11]

Retro-Diels–Alder Formation of the Naphthalene **16**.—The adduct **17** (41 mg, 0.08 mmol) was stirred in xylene (0.5 cm^3) with DMAD (1 cm^3) at 140 °C (bath temp.) for 1 h. Xylene and most of the DMAD were removed with a water-pump vacuum and steam-bath to give a crude product (219 mg). The mixture was roughly separated by silica chromatography with chloroform. Recrystallisation of the first fraction from dichloromethane–ether gave **16** (24 mg, 70%), m.p. 217–219 °C (lit.,[11] m.p. 215–217 °C).

Diels–Alder Adduct Formation of the Pyrone **10** *with Methyl Crotonate in Benzene*.—To the pyrone **10** (150 mg, 0.42 mmol) suspended in dry benzene (2 cm^3) was added freshly distilled methyl crotonate (2 cm^3), and the mixture heated under reflux for 3 h. Benzene and methyl crotonate were removed under reduced pressure to give the crude product (190 mg). Part (160 mg) of this was chromatographed on silica eluting with benzene–ether (4:1) to give, in order of elution, the following compounds. Compound **24** (20 mg, 10%); m.p. 156–157 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 1.10 (3 H, d, *J* 7, 2-Me), 2.86 (1 H, dd, *J* 2.5 and 4, 3-H), 2.88 (1 H, dq, *J* 4, and 7, 2-H), 3.70 (3 H, s, OMe), 3.88 (3 H, vbr s, OMe), 3.90 (3 H, vbr s, OMe), 3.92 (3 H, s, OMe), 4.23 (1 H, d, *J* 2.5, 4-H), 5.91 (1 H, d, *J* 1.5, OCH_2O), 5.95 (1 H, d, *J* 1.5, OCH_2O), 6.28 (1 H, s, 8-H), 6.45 (1 H, vbr s, ArH), 6.80 (1 H, s, 5-H) and 6.97 (1 H, vbr s, ArH); ν_{max}(Nujol)/cm^{-1} 1765 and 1735; *m/z* 456 (M^+, 6), 412 ($M^+ - CO_2$, 75) and 353 (100%).

Compound **21** (60 mg, 31%); m.p. 140–141 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 1.38 (3 H, d, *J* 7, 3-Me), 2.17 (1 H, ddq, *J* 2, 6 and 7, 3-H), 3.13 (1 H, d, *J* 6, 2-H), 3.62 (3 H, s, OMe), 3.72 (1 H, d, *J* 2, 4-H), 3.85 (6 H, s, 2 × OMe), 3.89 (3 H, s, OMe), 5.97 (2 H, s, OCH_2O), 6.65 (1 H, s, 8-H), 6.74 (2 H, s, 2'- and 6'-ArH) and 6.82 (1 H, s, 5-H); ν_{max}(Nujol)/cm^{-1} 1760 and 1735; *m/z* 456 (M^+, 4) and 412 ($M^+ - CO_2$, 100%) (Found: C, 63.25; H, 5.45. $C_{24}H_{24}O_9$ requires C, 63.2; H, 5.3%).

Compound **22** (38 mg, 20%); m.p. 170–171 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 1.01 (3 H, d, *J* 7, 3-Me), 2.73–2.78 (2 H, m, 3 and 4-H), 3.52 (3 H, s, OMe), 3.74 (1 H, d, *J* 2, 2-H), 3.87 (6 H, br s, 2 × OMe), 3.90 (3 H, s, OMe), 5.94 (1 H, d, *J* 1.5, OCH_2O), 5.96 (1 H, d, *J* 1.5, OCH_2O), 6.19 (1 H, s, 8-H), 6.55 (1 H, vbr s, ArH), 6.83 (1 H, s, 5-H) and 6.91 (1 H, vbr s, ArH); ν_{max}(Nujol)/cm^{-1} 1750 br; *m/z* 456 (M^+, 4) and 412 ($M^+ - CO_2$, 100%) (Found: C, 63.10; H, 5.35%).

Diels–Alder Reaction of the Pyrone **10** *in Neat Methyl Crotonate*.—The pyrone (200 mg, 0.56 mmol) was stirred in methyl crotonate (2 cm^3) at 90 °C (bath temp.) for 1 h, when a further 1 cm^3 of dienophile was added to aid dissolution. After 3.75 h the reaction mixture was cooled to 20 °C. Removal of the dienophile with a water-pump vacuum and steam bath gave the crude adducts (269 mg). 400 MHz ^1H NMR showed **24**, **21**, **22** and a decarboxylation product to be present in a ratio of 1:3.1:4.3:0.4, respectively. Chromatography using benzene–ether (4:1) as eluent gave **24** (32 mg, 12%), **21** (98 mg, 38%), **22** (62 mg, 24%), and the decarboxylation product **26** (10 mg, 4%), m.p. 158–159 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 1.15 (3 H, d, *M* 7, 3-Me), 2.60 (1 H, dd, *J* 4.5 and 15, 4-H), 2.91 (1 H, m, 3-H), 3.09 (1 H, dd, *J* 6.5 and 15, 4-H), 3.50 (3 H, s, OMe), 3.82 (6 H, br s, 2 × OMe), 3.90 (3 H, s, OMe), 5.92 (2 H, s, OCH_2O), 6.34 (1 H, s, 8-H), 6.35 (2 H, br s, 2'- and 6'-ArH) and 6.71 (1 H, s, 5-H); ν_{max}(Nujol)/cm^{-1} 1730–1680 br; *m/z* 412 (M^+, 100%).

Methyl 4-Benzoyloxycrotonate.—Methyl 4-hydroxycrotonate[26] (1 g, 8.6 mmol) was stirred with triethylamine (1.43 cm^3, 1.2 equiv.) and DMAP (1 mol%) in dry dichloromethane (15 cm^3) at 0 °C and benzoyl chloride (1.2 cm^3, 1.2 equiv.) was added dropwise to the mixture over 15 min. After 45 min methanol (1 cm^3) was added to the reaction mixture and then after a further 30 min the solvent was removed under reduced pressure. The residue was taken up in ether and the solvent evaporated to give the crude product (2.6 g). ^1H NMR spectroscopy revealed the crude product to be contaminated with benzoic anhydride. Chromatography of the mixture eluting with benzene afforded the pure diester (1.77 g, 97%), m.p. 28–31 °C; δ_H(90 MHz; $CDCl_3$) 3.75 (3 H, s), 5.00 (2 H, dd, *J* 2 and 5), 6.15 (1 H, dt, *J* 2 and 16), 7.10 (1 H, dt, *J* 4.5 and 16), 7.30–7.70 (3 H, m) and 8.00–8.10 (2 H, m); ν_{max}(Nujol)/

cm^{-1} 1710 and 1660; *m/z* 220 (M^+, 3.6) and 105 (M^+ – PhCO, 100%) (Found: C, 65.5; H, 5.55. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.45%).

Preparation of the Adducts **11** (*R* = *Ph*), *and* **23**.—The pyrone (2.77 g, 7.78 mmol) and methyl 4-benzoyloxycrotonate (19.4 g, 11 equiv.) were mechanically stirred in benzene (15 cm^3) at reflux for 2.5 h, when further benzene (6 cm^3) was added to aid dissolution. After 5 h, the mixture was cooled, and Kieselgel G (Merck) (25 g) was added to it with dichloromethane (250 cm^3). The solvent was removed under reduced pressure to give a free-flowing powder. Elution of this material from Kieselgel G (Merck) (500 g) with benzene–ether (9:1) gave the dienophile (18.00 g), the crude adducts (2.95 g) and a mixture of the regioisomer **25** and the product of decarboxylation **27** (0.45 g). The crude C-2 *endo* and *exo* products **11** (R = Ph) and **23** were separated by chromatography using dichloromethane–ether (24:1) as eluent. This afforded **11** (R = Ph) (1.14 g, 25%), and **23** (1.33 g, 30%). The 1,5-shift product **27** and the adduct **25** were separated on Kieselgel G (Merck), eluting with benzene–ether (3:1) to yield **25** (0.30 g, 7%) and then **27** (150 mg, 3%). Recovery of the unchanged pyrone (0.84 g, 30%) from the first column was achieved by slowly changing the eluent to dichloromethane–ether (17:3). Data for **25**: m.p. 110–112 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 3.36 (1 H, dd, *J* 3 and 4, 3-H), 3.42 (1 H, dt, *J* 4 and 9, 2-H), 3.52 (3 H, s, OMe), 3.86 (3 H, vbr s, OMe), 3.93 (3 H, s, OMe), 3.98 (3 H, s, OMe), 4.04 (1 H, dd, *J* 9 and 11.5, CH_2), 4.33 (1 H, d, *J* 3, 4-H), 4.71 (1 H, dd, *J* 4 and 11.5, CH_2), 5.92 (1 H, d, *J* 1.5, OCH_2O), 5.95 (1 H, d, *J* 1.5, OCH_2O), 6.26 (1 H, s, 8-H), 6.75 (1 H, vbr s, ArH), 6.82 (1 H, s, 5-H), 6.96 (1 H, vbr s, ArH), 7.42 (2 H, t, *J* 8), 7.55 (1 H, t, *J* 8), 7.95 (2 H, dd, *J* 1 and 8); ν_{max}(Nujol)/cm^{-1} 1765, 1735 and 1720; *m/z* 532 (M^+ – CO_2, 9), 410 (56) and 105 (100%) (Found: C, 64.35; H, 4.85. $C_{31}H_{28}O_{11}$ requires C, 64.6; H, 4.9%).

Compound **11** (*R* = *Ph*). M.p. 165–166 °C (EtOH–CH_2Cl_2); δ_H(400 MHz; $CDCl_3$) 2.61 (1 H, qd, *J* 6.5 and 2), 3.45 (1 H, d, *J* 6.5, 2-H), 3.56 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 3.91 (3 H, s, OMe), 4.01 (1 H, d, *J* 2, 4-H), 4.52 (1 H, dd, *J* 6.5 and 11, CH_2), 4.56 (1 H, dd, *J* 6.5 and 11, CH_2), 6.00 (2 H, m, OCH_2O), 6.78 (2 H, s, 2′- and 6′-ArH), 6.90 (1 H, s, 8-H), 6.72 (1 H, s, 5-H), 7.45 (2 H, t, *J* 8), 7.58 (1 H, dt, *J* 1.5 and 7.5), 8.05 (2 H, dd, *J* 1.5 and 8); ν_{max}(Nujol)/cm^{-1} 1770, 1735 and 1720; *m/z* 532 (M^+ – CO_2, 6) and 410 (100%) (Found: C, 64.4; H, 4.9. $C_{31}H_{28}O_{11}$ requires C, 64.6; H, 4.9%).

Compound **23**. M.p. 192–194 °C (EtOH–CH_2Cl_2); δ_H(400 MHz; $CDCl_3$) 3.00 (1 H, d, *J* 5, 2-H), 3.18–3.25 (1 H, m, 3-H), 3.53 (3 H, s, OMe), 3.88 (6 H, br s, 2 × OMe), 3.91 (3 H, s, OMe), 3.99 (1 H, dd, *J* 8.5 and 11, CH_2), 4.10 (1 H, d, *J* 2.5, 4-H), 4.20 (1 H, dd, *J* 6.5 and 11, CH_2), 5.93 (1 H, d, *J* 1.5, OCH_2O), 5.94 (1 H, d, *J* 1.5, OCH_2O), 6.26 (1 H, s, 8-H), 6.50–7.05 (2 H, vbr s, 2′- and 6′-ArH), 6.83 (1 H, s, 5-H), 7.46 (2 H, t, *J* 8), 7.60 (1 H, t, *J* 1.5 and 8), 7.98 (2 H, dd, *J* 1.5 and 8); ν_{max}-(Nujol)/cm^{-1} 1765, 1735 and 1715; *m/z* 532 (M^+ – CO_2, 9) and 410 (56%) (Found: C, 64.7; H, 4.85%).

Compound **27**. M.p. 124–127 °C (EtOH); δ_H(400 MHz; $CDCl_3$) 2.99 (1 H, dd, *J* 2 and 16, 4-H), 3.20 (1 H, dd, *J* 9 and 16, 4-H), 3.34 (1 H, m, 3-H), 3.50 (3 H, s, OMe), 3.81 (6 H, br s, 2 × OMe), 3.90 (3 H, s, OMe), 4.30 (1 H, dd, *J* 9 and 11, CH_2), 4.52 (1 H, dd, *J* 5 and 11, CH_2), 6.31 (1 H, s, 8-H), 6.34 (2 H, vbr s, 2′- and 6′-ArH), 6.70 (1 H, s, 5-H), 5.88 (1 H, d, *J* 1.5, OCH_2O), 5.91 (1 H, d, *J* 1.5, OCH_2O), 7.42 (2 H, t, *J* 8), 7.55 (1 H, tt, *J* 1 and 8), 7.94 (2 H, dd, *J* 1 and 8); ν_{max}(Nujol)/cm^{-1} 1765–1740; *m/z* 532 (M^+, 11) and 410 (100%) (Found: C, 67.45; H, 5.25. $C_{30}H_{28}O_9$ requires C, 67.7; H, 5.3%).

High-pressure Diels–Alder Reaction.—The pyrone **10** (1.0 g) and methyl 4-benzoyloxycrotonate (2 g) were sent to Reading University high-pressure laboratories where they were dissolved in dichloromethane and subjected to a pressure of 10 kbar for 3 days at 35 °C. The product was returned in solution to Leeds. Preliminary TLC revealed more of the *exo* adduct **23** than the *endo* adduct **11** (R = Ph) to be present. The solvent was removed under reduced pressure and the crude product (1.03 g) flash chromatographed eluting with dichloromethane–ether (24:1) to afford the dienophile (0.84 g) followed by a mixture of adducts (200 mg). The 400 MHz ^1H NMR spectrum showed the adducts **25**, **11** (R = Ph), and **23** to be present in a ratio of 0.10:0.66:1.00.

Adduct Formation of the Pyrone **10** *in Acetonitrile.*—To a solution of the pyrone **10** (1 g, 2.8 mmol) in acetonitrile (AnalaR; 20 cm^3) was added methyl 4-benzoyloxycrotonate (6.15 g, 10 equiv.). The solution was heated at 75 °C (bath temp.) for 21.5 h, after which the solvent was removed on a rotary evaporator to give the crude product (6.89 g). Chromatography of this on silica using ethyl acetate–dichloromethane (1:24) as eluent gave in order of elution: recovered dienophile (5.08 g); a mixture of the regioisomer **25** and the product of decarboxylation **27** (175 mg); *endo* adduct **11** (R = Ph) (0.30 g, 19%), m.p. 164–166 °C and the *exo* adduct **23** (0.935 g, 58%), m.p. 192–194 °C. 400 MHz ^1H NMR of the crude product showed the adducts **23** and **11** (R = Ph) to be present in a ratio of 3.5:1.

The Acid **12** (*R* = *Ph*) *by Reduction with Raney Nickel.*—To a solution of the lactone **11** (R = Ph) (500 mg, 0.87 mmol) dissolved in warm ethanol–ethyl acetate (2:1; 150 cm^3) was added freshly prepared 'W-2' Raney nickel (suspension in ethanol; 4.2 g, 7 cm^3) and the mixture stirred mechanically under reflux, for 20 min. Water (100 cm^3) was added to the mixture and half the solvent removed under reduced pressure. The suspension was poured into a 1 dm^3 separating funnel containing 2 mol dm^{-3} HCl (aq., 500 cm^3). The mixture was simultaneously extracted with ether (**CARE!**), and the extracts were washed with water and filtered through anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product (518 mg), the 90 MHz ^1H NMR spectrum of which showed it to be a mixture of the acid **12** (R = Ph) and its C-1 epimer in a ratio of (2:1). This was chromatographed, using benzene–ether–acetic acid (32:16:0.5) as eluent, to give a mixture of the acids (368 mg, 73%). Recrystallisation gave pure **12** (R = Ph) (233 mg, 46%), m.p. 226–227 °C (EtOH–CH_2Cl_2); δ_H(400 MHz; $CDCl_3$) 2.97 (1 H, m, 3-H), 3.48 (3 H, s, OMe), 3.75 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 3.95 (1 H, dd, *J* 6.5 and 12.5, 2-H), 4.15 (1 H, d, *J* 5.5, 4-H), 4.31 (1 H, dd, *J* 9 and 11, CH_2), 4.48 (1 H, d, *J* 6.5, 1-H), 4.73 (1 H, dd, *J* 4 and 11, CH_2), 5.90 (1 H, d, *J* 1.5, OCH_2O), 5.93 (1 H, d, *J* 1.5, OCH_2O), 6.10 (2 H, s, 2′- and 6′-ArH), 6.42 (1 H, s, 8-H), 6.78 (1 H, s, 5-H), 7.42 2 H, t, *J* 8), 7.55 (1 H, tt, *J* 1.5 and 8) and 8.01 (2 H, dd, *J* 1.5 and 8); ν_{max}(Nujol)/cm^{-1} 3700–2500, 1740, 1715 and 1690; *m/z* 456 (M^+ – $PhCO_2H$, 100%) (Found: C, 64.1; H, 5.45. $C_{31}H_{30}O_{11}$ requires C, 64.4; H, 5.2%). The C-1 epimer of **12** (R = Ph) was obtained by recrystallising the combined mother liquors from several reactions: m.p. 183–185 °C (EtOH–CH_2Cl_2); δ_H(400 MHz; $CDCl_3$) 2.80 (1 H, m, 3-H), 3.48 (3 H, s, OMe), 3.59 (1 H, dd, *J* 11 and 12, 2-H), 3.72 (6 H, br s, 2 × OMe), 3.83 (3 H, s, OMe), 4.04 (1 H, d, *J* 5, 4-H), 4.25 (1 H, d, *J* 11, 1-H), 4.40 (2 H, m, CH_2), 5.91 (2 H, m, OCH_2O), 6.35 (1 H, d, *J* 0.5, 8-H), 6.39 (2 H, s, 2′- and 6′-ArH), 6.71 (1 H, s, 5-H), 7.40 (2 H, t, *J* 8), 7.54 (1 H, t, *J* 8) and 8.01 (2 H, m); ν_{max}(Nujol)/cm^{-1} 1725br and 1685; *m/z* 578.1778 ($C_{31}H_{30}O_{11}$ requires *M*, 578.1788); *m/z* 456 (M^+ – CO_2, 3), 122 ($PhCO_2H$, 81) and 105 (100%).

The Acid **31** *by Reduction with Hydrogen over Palladium*—To a solution of the adduct **23** (500 mg, 0.87 mmol) in acetic acid (50 cm^3) was added 10% palladium on charcoal (500 mg), and

the mixture stirred vigorously under hydrogen at 1 atm and 42 °C (bath temp.) for 24 h. Further catalyst (250 mg) was then added and the mixture hydrogenated for 4 h. The product was filtered through a Celite pad and the residue washed with hot ethyl acetate. Rotary evaporation of the filtrate followed by flash chromatography of the residue using ethyl acetate–acetic acid (99:1) as eluent gave a mixture of acid **31** and its C-1 epimer (505 mg, 100%). Recrystallisation from benzene and destruction of the solvate by drying *in vacuo* at 100 °C afforded the pure acid **31** as a glass (300 mg, 60%), m.p. 210–221 °C; δ_H(400 MHz; $CDCl_3$) 3.13 (1 H, dd, *J* 5 and 13, 2-H), 3.28 (1 H, m, 3-H), 3.62 (3 H, s, OMe), 3.74 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 3.99 (1 H, d, *J* 10, 4-H), 4.42 (1 H, d, *J* 5, 1-H), 4.46 (1 H, dd, *J* 6 and 11.5, CH_2), 4.51 (1 H, dd, *J* 3 and 11.5, CH_2), 5.90 (1 H, d, *J* 1, OCH_2O), 5.93 (1 H, d, *J* 1, OCH_2O), 6.38 (2 H, s, 2′- and 6′-ArH), 6.52 (1 H, s, 8-H), 6.90 (1 H, d, *J* 0.5, 5-H), 7.30 (2 H, tt, *J* 1.5 and 8), 7.45 (1 H, tt, *J* 1.5 and 8), 7.96 (2 H, dd, *J* 1.5 and 8); ν_{max}(Nujol)/cm^{-1} 3700–2500 (OH), 1730, 1725 and 1710; *m/z* 578 M^+, 1) and 436 (M^+ − $PhCO_2H$, 29%) (Found: C, 64.6; H, 5.25%).

C-1 Epimer of **31**. M.p. 221–225 °C (MeOH); δ_H(400 MHz; $CDCl_3$) 2.85 (1 H, br t, *J* 11.5, 2-H), 3.20 (1 H, m, 3-H), 3.41 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe), 4.00 (1 H, br d, *J* 9, 4-H), 4.25 (1 H, br d, *J* 11.5, 1-H), 4.34 (1 H, dd, *J* 5.5 and 12, CH_2), 4.39 (1 H, dd, *J* 5 and 12, CH_2), 5.88 (1 H, d, *J* 1.5, OCH_2O), 5.92 (1 H, d, *J* 1.5, OCH_2O), 6.24 (1 H, s, 8-H), 6.34 (2 H, s, 2′- and 6′-ArH), 6.84 (1 H, s, 5-H), 7.41 (2 H, t, *J* 8), 7.55 (1 H, tt, *J* 1.5 and 8) and 8.00 (2 H, dd, *J* 1.5 and 8); ν_{max}(Nujol)/cm^{-1} 3300br, and 1720br; *m/z* 456 (M^+ − $PhCO_2H$, 44) and 105 (100%) (Found: C, 64.1; H, 5.2%).

Preparation of the Triesters **33** *and* **32** *from the Acid* **12** (R = Ph).—To a solution of the acid **12** (R = Ph) (70 mg, 0.12 mmol) in a dry oxygen-free mixture of THF and AcOH (5:1) (3.5 cm^3) was added lead(IV) acetate (64 mg, 1.2 equiv.) and the mixture stirred at 20 °C for 27 min. Ethylene glycol (2 drops) was added to it to destroy the excess of reagent and the solution stirred for 5 min. Water (7 cm^3) was added to the mixture which was then stirred a further 5 min. Extraction of the mixture with ether and washing of the extracts with $NaHCO_3$ (aq., 5%) gave a residue (71 mg) after drying ($MgSO_4$) and removal of the solvent under reduced pressure. The 90 MHz NMR spectrum revealed this to be a 1:1 mixture of esters **32** and **33** together with 20 mol% of the starting acid. Careful chromatography using benzene–ether (9:1) as eluent gave, in order of elution: **33** (20 mg, 28%), m.p. 130–155 °C (decomp.; ether–hexanes); δ_H(400 MHz; $CDCl_3$), 1.96 (3 H, s, OAc), 2.93 (1 H, m, 3-H), 3.50 (3 H, s, OMe), 3.50 (1 H, dd, *J* 6.5 and 12, 2-H), 3.74 (6 H, s, 2 × OMe), 3.79 (3 H, s, OMe), 4.24 (1 H, t, *J* 10.5, CH_2), 4.49 (1 H, d, *J* 6.5, 1-H), 4.63 (1 H, dd, *J* 4 and 11, CH_2), 5.90 (1 H, d, *J* 1.5, OCH_2O), 5.93 (1 H, d, *J* 1.5, OCH_2O), 6.07 (2 H, s, 2′- and 6′-ArH), 6.40 (1 H, s, 8-H), 6.41 (1 H, d, *J* 4, 4-H), 6.99 (1 H, s, 5-H), 7.45 (2 H, t, *J* 8), 7.55 (1 H, tt, *J* 1.5 and 8) and 8.03 (2 H, dd, *J* 1.5 and 8); ν_{max}(Nujol)/cm^{-1} 1740, 1720 and 1715; *m/z* 592 (M^+, 7%), 532 (M^+ − AcOH), 12) and 410 (45%) (Found: C, 65.0; H, 5.4. $C_{32}H_{32}O_{11}$ requires C, 64.9; H, 5.4%). Continued elution gave **32** (20 mg, 28%), m.p. 80–81 °C (ether:hexanes, −40 °C); δ_H(400 MHz; $CDCl_3$) 2.17 (3 H, s, OAc), 2.82 (1 H, m, 3-H), 3.34 (1 H, dd, *J* 5 and 13, 2-H), 3.60 (3 H, s, OMe), 3.79 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 4.38 (1 H, dd, *J* 2.5 and 12, CH_2), 4.41 (1 H, d, *J* 5, 1-H), 4.58 (1 H, dd, *J* 3.5 and 12, CH_2), 5.93 (2 H, br s, OCH_2O), 6.27 (2 H, s, 2′- and 6′-ArH), 6.34 (1 H, d, *J* 8.5, 4-H), 6.45 (1 H, s, 8-H), 6.75 (1 H, s, 5-H), 7.42 (2 H, t, *J* 8), 7.55 (1 H, t, *J* 8) and 7.98 (2 H, d, *J* 8); ν_{max}(Nujol)/cm^{-1} 1735, 1705 and 1685; *m/z* 592 (M^+, 8), (M^+ − AcOH, 6) and 410 (24%) (Found: C, 64.65; H, 5.3%). Elution with ethyl acetate–acetic acid (99:1) gave the starting acid (25 mg, 36%).

Preparation of the Triesters **32** *and* **33** *from the Acid* **31**.—To a solution of the acid **31** (20.5 mg, 0.04 mmol) in a dry oxygen-free mixture of THF and acetic acid (5:1) (1 cm^3) was added lead(IV) acetate (18 mg; 1.1 equiv.) and the yellow solution stirred at 18 °C for 47 min. Ethylene glycol (2 drops) was added to the solution which was then stirred for 5 min; it was then diluted with water (2 cm^3). The mixture was extracted with ether, and the extracts were shaken with $NcHCO_3$ (aq., 5%), dried ($MgSO_4$) and evaporated to give the crude product (20 mg). Chromatography using benzene–ether (9:1) as eluent gave the triesters **33** (8.5 mg, 39%) and **32** (8.5 mg, 39%) identical with those prepared previously.

Preparation of the Diol **35** *from the Triester* **33**.—The triester **33** (100 mg, 0.17 mmol) was dissolved in dry THF (10 cm^3) and the solution cooled to −70 °C; a 1 mol dm^{-3} solution of lithium triethylborohydride in THF (3 cm^3) was then added dropwise to it with stirring. After 3.5 h at −70 °C further reagent (1 cm^3) was added to the mixture. After 4.75 h the reaction was quenched with saturated NH_4Cl (aq. 5 cm^3), and the mixture allowed to warm to 20 °C. It was then extracted with ether and the extract dried ($MgSO_4$) and evaporated to give an oily residue. This was heated under reflux in methanol (50 cm^3) containing a stirred suspension of flash silica (100 mg) for 5 min. Flash chromatography (benzene–ethyl acetate, 1:2) afforded (±)-methyl epipodophyllate (60 mg, 80%) which after recrystallisation (40 mg) had m.p. 208–211 °C (MeOH) (lit.,[14] m.p. 217 °C). IR and ^1H NMR spectra agreed with those published.[14]

Preparation of the Diol **34** *from the Triester* **32**.—The triester **34** (100 mg, 0.17 mmol) was dissolved in dry THF (2 cm^3) and the solution cooled to −76 °C (bath temp.). A 1 mol dm^{-3} solution of lithium triethylborohydride in THF (2 cm^3) was then added dropwise to it with stirring. After 3 h the reaction was quenched with saturated NH_4Cl (aq., 2 cm^3) and the mixture allowed to warm to 20 °C. The mixture was then diluted with a small amount of water to dissolve the precipitated NH_4Cl and extracted with ether. The extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator to give an oil. This was heated under reflux in methanol (50 cm^3) containing a stirred suspension of flash silica (100 mg) for 5 min. Removal of methanol under reduced pressure and chromatography of the residue using ethyl acetate–benzene (2:1) as eluent afforded the pure diol (50 mg, 66%); m.p. 188–190 °C (Et_2O–CH_2Cl_2); δ_H(400 MHz; $CDCl_3$) 2.40–2.50 (1 H, m, *J* 4, 8, 8 and 12, 3-H), 3.01 (1 H, dd, *J* 5.5 and 12, 2-H), 3.56 (3 H, s, OMe), 3.73 (1 H, dd, *J* 8 and 10.5, CH_2), 3.75 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 4.07 (1 H, br dd, *J* 4 and 10.5, CH_2), 4.30 (1 H, d, *J* 5.5, 1-H), 4.78 (1 H, d, *J* 8, 4-H), 5.92 (2 H, m, OCH_2O), 6.22 (2 H, s, 2′-and 6′-H), 6.38 (1 H, s, 8-H) and 7.08 (1 H, s, 5-H); the IR spectrum was identical with that published.[17]

Acid-catalysed Epimerisation of the Diol **35**.—To the diol **35** (10 mg, 0.02 mmol) dissolved in THF (1 cm^3) was added 4 mol dm^{-3} HCl (aq., 1.5 cm^3), and the mixture stirred at 20 °C for 3.5 h. The solution was carefully poured into $NaHCO_3$ (aq., 5%), and extracted with ethyl acetate. Filtration through anhydrous $MgSO_4$, and rotary evaporation of the filtrate afforded the crude mixture of epimers. The 90 MHz ^1H NMR spectrum showed the diols **34** and **35** to be present in a ratio of 3:1. The mixture was chromatographed, eluting with (benzene–ethyl acetate, 1:2) to give **35** (2.5 mg, 25%) and **34** (6.3 mg, 63%).

Lactonisation of Methyl Podophyllate with $ZnCl_2$-4 Å *Molecular Sieves* (4AMS).—To a solution of the diol **34** (20 mg, 0.04 mmol) in dry THF (2 cm^3) was added powdered, fused zinc chloride (23 mg), together with freshly ground 4AMS (100 mg).

The mixture was stirred at reflux for 1 h. Brine (1 cm^3) was added to the mixture which was then stirred vigorously for 2 min before extraction with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (28 mg). The 400 MHz ^1H NMR spectrum in [$^2H_6$]DMSO showed it to be a mixture of **1** (81%), **2** (12%) and neopodophyllotoxin (7%). Chromatography of this on silica in benzene–ethyl acetate (1:1) yielded epipodophyllotoxin (2 mg, 11%), (±)-podophyllotoxin (14.5 mg, 78%) and impure (±)-neopodophyllotoxin (2 mg). The ^1H NMR spectra were identical with those published.[17,27]

Lactonisation of Methyl Epipodophyllate with $ZnCl_2$-4 Å *Molecular Sieves* (4AMS).—To a solution of the diol **35** (10 mg, 0.02 mmol) in dry THF (2 cm^3) was added freshly ground 4AMS (100 mg) and zinc chloride (20 mg). The mixture was stirred under reflux for 25 min, when further 4AMS (75 mg) was added. After 1 h at reflux the mixture was cooled, and brine (1 cm^3) added with stirring. The mixture was then extracted with ethyl acetate (×5), and the extract dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (8 mg). Chromatography (ethyl acetate–benzene, 1:1) of this afforded pure (±)-epipodophyllotoxin **2** (7.5 mg, 81%). TLC and 90 MHz ^1H NMR spectroscopy of the crude product showed the absence of other compounds. The 400 MHz ^1H NMR spectrum of epipodophyllotoxin was identical with that published.[27]

Methanol–$ZnCl_2$ *Equilibration of Compounds* **35** *and* **2**.—To methyl epipodophyllate **35** (16 mg, 0.04 mmol) in dry methanol (1 cm^3) was added dry fused $ZnCl_2$ (20 mg). The mixture was stirred under reflux for 4.5 h, after which further methanol was added; the clear solution was then refluxed overnight. After 18 h, the solution was allowed to cool and brine (2 cm^3) was added to it. The aqueous layer was extracted with ethyl acetate and the extracts dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product (27 mg). The 400 MHz ^1H NMR spectrum in [$^2H_6$]DMSO showed the ratio of **2**:**35** to be 4.6:1.

Methanol–$ZnCl_2$ *Equilibration of Compounds* **34** *and* **1**.—To methyl podophyllate **34** (23 mg, 0.05 mmol) in dry methanol (1.5 cm^3) was added freshly fused zinc chloride (17 mg) and the mixture stirred under reflux for 24 h. Brine (1 cm^3) was added to the mixture which was then stirred vigorously for 2 min before extraction into ethyl acetate. Removal of solvent from the extract on a rotary evaporator gave a crude product (24 mg), the 400 MHz ^1H NMR spectrum of which showed that it contained podophyllotoxin, neopodophyllotoxin, epipodophyllotoxin and methyl podophyllate in a ratio of 76:15:5:3.

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