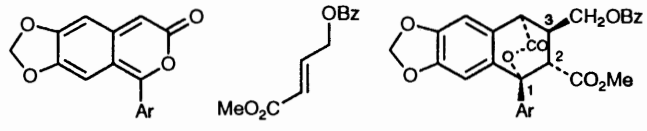
Synthesis of (±)-4-Deoxypodophyllotoxin, (±)-Podophyllotoxin and (±)-Epipodophyllotoxin

David W. Jones* and Adrian M. Thompson
School of Chemistry, The University, Leeds LS2 9JT, UK

6,7-Methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-2-benzopyran-3-one **1** and dimethyl fumarate in acetonitrile give mostly the C-2 *exo*-CO_2Me adduct **4** which is transformed in four steps into epipodophyllotoxin **10a**. Attempted addition of dimethyl maleate to **1** proceeds with decarboxylation of the putative *endo*-adduct **11** to a transient *o*-quinodimethane which undergoes a highly regioselective 1,5-hydrogen shift to the dihydronaphthalene **14**. The alternative 1,5-shifts are shown for the model *o*-quinodimethane **22** [**22** and **22a** (arrows)] it being suggested that the shift in **22a** is disfavoured by the steric clash shown therein. The product **14** is converted into 4-deoxypodophyllotoxin in an efficient sequence of reactions having as a key step a high-yield epimerisation of the aldehyde **26** to **27**. The dihydronaphthalene **14** is also converted into podophyllotoxin **10b** (seven steps, 24% overall yield); novel steps include the epimerisation of **35** to **36** and selective oxidation of **34** to **35** using $(Bu_3Sn)_2O$–I_2.

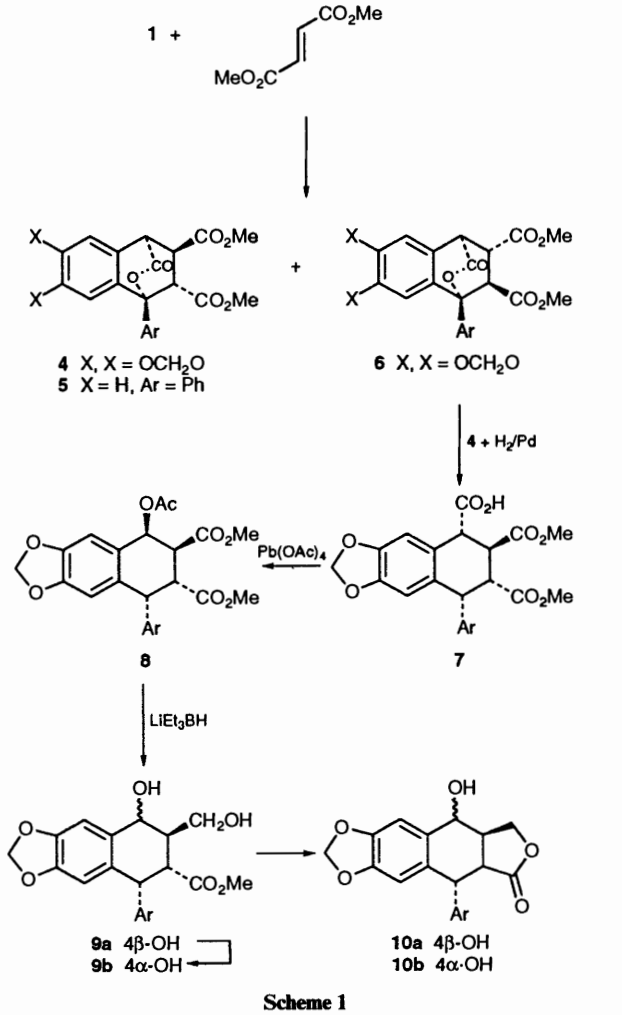
In the foregoing paper[1] we described how (±)-podophyllotoxin could be synthesised by Diels–Alder addition of the isolable pyrone **1** and methyl 4-benzoyloxycrotonote **2**. The resulting adduct **3** with a *trans* C(1)–C(2) stereochemistry is the result of preferred *exo*-addition of the dienophile CO_2Me group. We argued[1] that improved *exo*-selectivity at C-2, and *endo*-selectivity at C-3, would be expected upon addition of dimethyl fumarate to **1**. There was every prospect that the resulting adduct **4** (Scheme 1) could be converted into (±)-epipodophyllotoxin using reactions already developed in the preceding paper. The main potential problem with this proposal appeared to be the necessity for selective reduction of the 3-CO_2Me group in the conversion of **8** into **9**.



1 **2** **3**

Unless otherwise specified Ar = 3,4,5-trimethoxphenyl

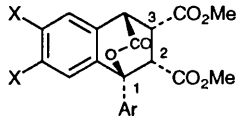
Reaction of **1** with dimethyl fumarate in boiling benzene gave the adducts **4** and **6** in a ratio of *ca.* 3.5:1. As in the addition of **2** to **1**[1] the ratio of the 2-*exo*-adduct **4** to 2-*endo*-adduct **6** increased (to *ca.* 5:1) when adduct formation was carried out in acetonitrile at 50 °C; pure **4** was then isolated (76%) by crystallisation of the adduct mixture from ethanol. Hydrogenolysis of **4** over palladium (HOAc, 50 °C) proceeded with predominant inversion at C-1 to give **7** in 50% recrystallised yield. Oxidative decarboxylation of **7** [$Pb(OAc)_4$ in THF–HOAc (5:1), 20 °C] gave **8** in 61% yield by crystallisation of the crude product from ether. After some experimentation, **8** and lithium triethylborohydride in dry THF at −20 °C, was induced to give methyl epipodophyllate **9a** in 65% yield. Using our $ZnCl_2$ 4 Å molecular sieves/THF procedure this was lactonised in 81% yield to (±)-epipodophyllotoxin **10a**. Methyl epipodophyllate **9a** was readily epimerised at C-4 by HCl–H_2O–THF to give methyl podophyllate **9b** (63%).[1] This was lactonised to podophyllotoxin **10b** using $ZnCl_2$ and molecular sieves (75% yield). Thus, both epipodophyllotoxin **10a** and podophyllotoxin **10b** are available from the fumarate adduct **4** of the pyrone **1**.



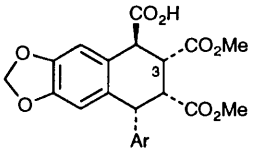
Scheme 1

It was further pointed out in the preceding paper that addition of dimethyl maleate to **1** should be *endo*-selective giving mostly the adduct **11** with the *cis* C(1)–C(2) stereochemistry appropriate for podophyllotoxin synthesis. Since **11** should give **13** by reduction over Raney nickel (retention at C-1) a further route to podophyllotoxin would be

available if epimerisation at C-3 could be contrived. In the event, addition of dimethyl maleate to **1** proceeded sluggishly at lower temperatures whilst at ~ 140 °C in boiling xylene addition was accompanied by decarboxylation, the main product, isolable in 71% yield being the dihydronaphthalene **14**. The *cis*-stereochemistry of **14** follows from the coupling constant (8.0 Hz) between the C-1 and C-2 protons. With 1,5-diazabicyclo[4.3.0]non-5-ene(DBN) in boiling benzene, **14** was cleanly epimerised to the *trans*-isomer **16** in which the coupling between the 1-H and 2-H is reduced to 3.0 Hz. These



11 X, X = OCH_2O
12 X = H, Ar = Ph



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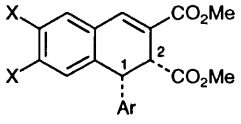
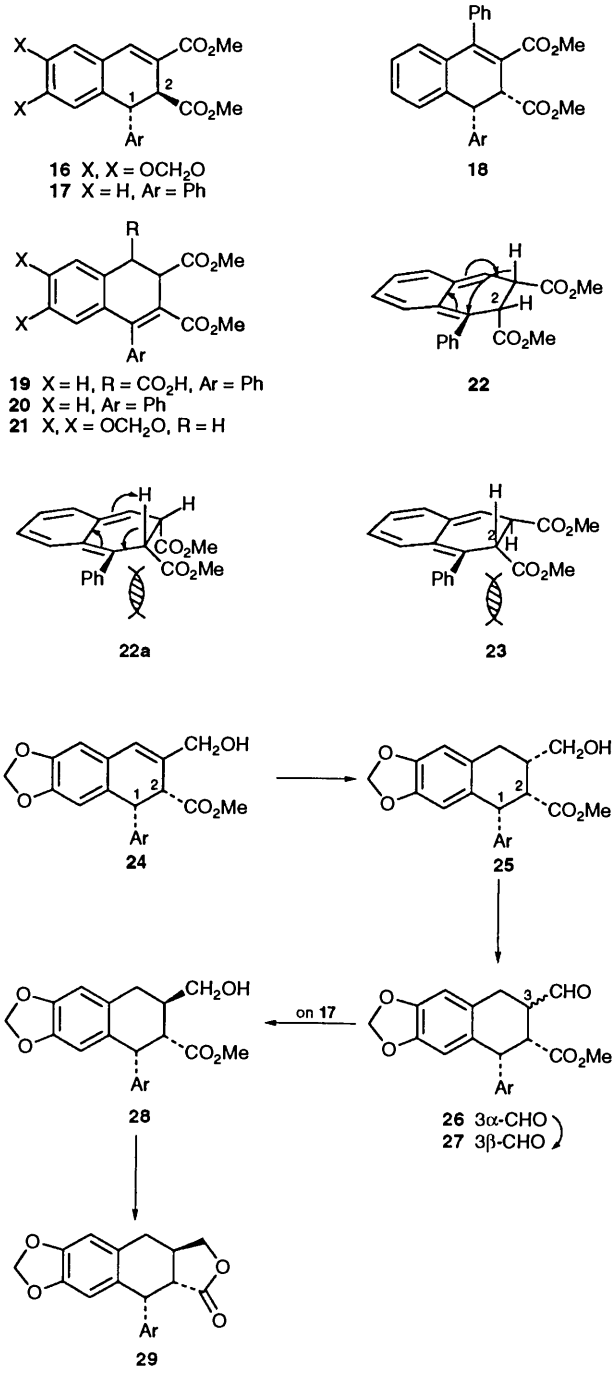


14 X, X = OCH_2O
15 X = H, Ar = Ph

observations agree with literature data[2,3] for related *cis*- and *trans*-dihydronaphthalenes, *e.g.* the *cis*-isomer **18** shows a vicinal coupling of 7 Hz whereas its *trans*-isomer has J_{vic} of 4.0 Hz.[2] The formation of **14** requires easier decarboxylation of the putative intermediate adduct **11** than of the isolable *endo*-adduct **12** prepared at 140 °C. There is some evidence that oxygen substituents speed up the decarboxylation of isochroman-3-ones.[4] Indeed, at a higher temperature (183 °C), **12** undergoes smooth decarboxylation to an analogous *cis*-dihydronaphthalene **15** (88% yield). This compound was cleanly isomerised by DBN to the *trans*-isomer **17**. Thermolysis of **12** in C_6D_6 in a sealed NMR tube with monitoring by 400 MHz ^1H NMR failed to reveal a significant quantity of any other product. If thermolysis of **12** is conducted in glassware that has not been base washed a competing β-elimination leading to **19** may become important. Formation of **15** from **12** presumably involves decarboxylation to an *o*-quinodimethane **22** which undergoes the indicated 1,5-sigmatropic hydrogen shift. This shift is presumably favoured over the shift shown in **22a** because the transition state for the rearrangement depicted in **22a** is like the ground-state structure **22a**, destabilised by near eclipsing of the phenyl and 2-CO_2Me groups. In contrast, the transition state corresponding to the shift in **22** has an axial-like 2-CO_2Me and is of lower energy. In agreement with this explanation, thermolysis of the fumarate adduct **5** (220 °C, 6 h) gave both the *trans*-dihydronaphthalene **17** and the isomer **20** (ratio 2:1). For the *trans*-*o*-quinodimethane **23** formed by decarboxylation of **5** the transition states for both possible 1,5-shifts are related to the same destabilised ground-state conformer shown in **23**. Consequently, there is little preference for either 1,5-shift and both occur. The *trans*-adduct **4** behaved similarly when heated at a lower temperature (170 °C) (see Experimental section). In agreement with suprafacial 1,5-shifts, the *cis*-dihydronaphthalenes **14** and **15** were absent from these thermolyses of fumarate adducts.

The readily available dihydronaphthalene **14** is an attractive intermediate for lignan synthesis. We have used it to prepare both 4-deoxypodophyllotoxin and podophyllotoxin itself. Selective reduction of the less-hindered methoxycarbonyl group at C-3 of **14** was achieved with lithium triethylborohydride in

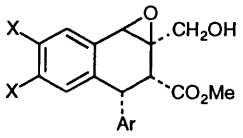


16 X, X = OCH_2O
17 X = H, Ar = Ph
18
19 X = H, R = CO_2H, Ar = Ph
20 X = H, Ar = Ph
21 X, X = OCH_2O, R = H
22
22a
23
24
25
26 3α-CHO
27 3β-CHO
28
29

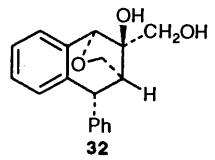
Scheme 2

THF at −70 °C to give **24** (Scheme 2) in high yield (64–76%). Hydrogenation of **24** over rhodium–alumina at 20 °C in benzene avoided hydrogenolysis of the allylic alcohol that was important with a palladium catalyst, and gave **25** by hydrogen addition to the less-hindered face of the double bond. Oxidation using the Swern procedure gave the aldehyde **26** which was epimerised selectively at C-3 with 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) (THF, 25 °C, 24 h) to give **27** in excellent yield. Catalytic reduction over palladium then gave the hydroxy ester **28** which was lactonised in high yield (80%) using $ZnCl_2$–molecular sieves to 4-deoxypodophyllotoxin **29**. The crucial selective epimerisation of aldehyde **26** at C-3 was also efficiently carried out by adsorption of **26** on chromatographic silica gel.

Our first conceived route to podophyllotoxin from **24** involved epoxidation on the less-hindered β-face of the double bond to give **30**. By analogy with the sodium bis(methoxy-



30 X, X = OCH_2O
31 X = H, Ar = Ph



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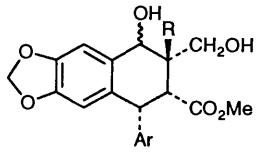
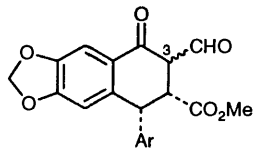
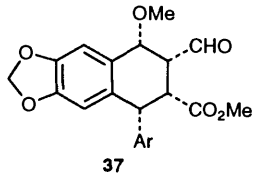


33 R = Br
34 R = H



35 3α-CH_2OH
36 3β-CH_2OH



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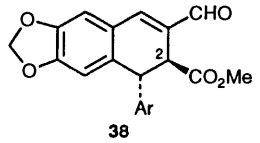

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ethoxy)aluminium hydride(Red-Al) reduction of the epoxides of allylic alcohols[6] regio- and stereo-selective hydride delivery to the α-face of C-3 in **30** should give methyl epipodophyllate **9a**. Although the β-epoxide **30** was readily prepared by reaction of **24** with *m*-chloroperbenzoic acid in the presence of sodium hydrogen carbonate, attempts to obtain **9a** by reduction of **30** with Red-Al were fruitless. The course of the Red-Al reduction was explored using the similarly prepared but more accessible epoxide **31**. Reduction of **31** gave the ether **32** which, presumably, arises by reduction of the methoxycarbonyl group of **31** and nearside attack of the resulting alkoxide at C-4 of the epoxide. The 400 MHz ^1H NMR spectrum of **32** fully supports the assigned structure (Experimental section). In view of this failure, the following revised strategy for conversion of **24** into podophyllotoxin was adopted. Reaction of **24** with *N*-bromosuccinimide in wet dimethyl sulphoxide gave the stereoisomeric bromohydrins **33** (72%) (4α-OH:4β-OH ratio 4:1). Debromination of the mixture with tributyltin hydride proceeded in high yield (96%) when initiated photochemically to give a mixture of diols **34**. Initial attempts to effect selective oxidation of the benzylic alcohol in **34** with either manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the ketone **35** in poor yield (~40%). Remarkably, work-up of the debromination reaction of **33** with iodine and sodium fluoride by stirring with water–CH_2Cl_2 in air gave **35** (52%) rather than the expected diol **34**. Reasoning that this selective oxidation during work-up was related to the known[8] selective oxidation of benzylic (and secondary) alcohols by $(Bu_3Sn)_2O$–Br_2 we found $(Bu_3Sn)_2O$–I_2 in CH_2Cl_2 (20 °C) to be an effective oxidant for the conversion of the alcohols **34** into ketone **35**; the 4α-OH epimer gave **35** in 72% recrystallised yield and the 4β-OH epimer gave **35** in 60% recrystallised yield. Selective inversion at C-3 of **35** was achieved in quantitative yield by treatment with DBU, and the product **36** was reduced with lithium triethylborohydride to give methyl podophyllate **36** (89%). This was lactonised to podophyllotoxin **10b** as previously described. In this way the alkene **14** obtained directly from the reaction of dimethyl maleate with the pyrone **1** is converted into (±)-podophyllotoxin **10b** in seven steps and 24% overall yield.

The route from **24** to deoxypodophyllotoxin (Scheme 2) has as key-step epimerisation of the aldehyde **26**. An attempt to effect related epimerisation of the methoxy compound **37** gave instead the enal **38** by β-elimination of methanol and epimerisation at C-2. Accordingly, the key step in the conversion of **24** into podophyllotoxin became epimerisation at C-3 in the ketone **35**. The ability to effect epimerisation at C-3 in the ways described here may be generally useful in lignan synthesis.

Experimental

For general details see the preceding paper. Experiments marked with an asterisk were performed in base-washed glassware. All coupling constants are in Hz. Light petroleum had a b.p. in the range 60–80 °C.

Diels–Alder Addition of the Pyrone **1** *with Dimethyl Fumarate**.—The pyrone **1** (1 g) and dimethyl fumarate (2.5 g) in acetonitrile (40 cm^3) were heated in an oil-bath at 52–54 °C (internal temperature 47–48 °C) with stirring under argon (37 h). The product obtained by evaporation of the reaction mixture was chromatographed on silica in benzene–ether (4:1) to give a mixture of the adducts **4** and **6** (1.35 g, 92%) which was crystallised from ethanol to give the adduct **4** (1.10 g, 76%), m.p. 175–184 °C (decomp. to a yellow melt) (Found: C, 59.65; H, 4.8. $C_{25}H_{24}O_{11}$ requires C, 60.0; H, 4.8%); ν_{max}(Nujol)/cm^{-1} 1725 and 1752; δ(400 MHz, $CDCl_3$) 3.5 (3 H, s), 3.71 (3 H, s), 3.73 (1 H, dd, *J* 4.5 and 3.0, 3-H), 3.80 (1 H, d, 4.5, 2-H), 3.89 (6 H, br, 3′5′-OMe), 3.91 (3 H, s), 4.38 (1 H, d, *J* 3.0, 4-H), 5.94 (1 H, d, $J \approx 1$, OCH_2O), 5.96 (1 H, d, $J \approx 1$, OCH_2O), 6.29 (1 H, s, 8-H), 6.8 (1 H, s, 5-H) and 6.62–6.98 (2 H, vbr, 2′,6′-H). The minor fumarate adduct was not isolated; the following NMR signals due to **6** are useful in determining the **4**:**6** ratio: δ(400 MHz, $CDCl_3$), 3.06 (1 H, dd, *J* 6.5 and 2.5, 3-H), 3.98 (1 H, d, *J* 6.5, 2-H), 4.23 (1 H, d, *J* 2.5, 4-H), 6.0 (2 H, AB-system, $J \approx 1$, OCH_2O). Similar formations of adducts were performed in hexamethylphosphoric triamide at 47–48 °C (**4**:**6** ratio *ca.* 2), in benzene at 80 °C (**4**:**6** ratio ~3.5) and in acetonitrile at 80 °C when a new product appeared to be forming from the less-abundant adduct **6**.

Hydrogenolysis of Adduct **4** *over Palladium.*—The foregoing adduct **4** (1.10 g), 10% palladium on charcoal (1.6 g), and acetic acid (70 cm^3) were stirred under hydrogen in an oil-bath at 52–54 °C (19 h). The reaction mixture was filtered and evaporated under reduced pressure and the residue crystallised from ethyl acetate (2×) to give the *acid* **7** (0.47 g), m.p. 205–218 °C; the m.p. of an analytical sample, 222–224 °C, was reached only after several crystallisations and extensive drying at 77 °C in high vacuum (Found: C, 59.8; H, 5.2. $C_{25}H_{26}O_{11}$ requires C, 59.8; H, 5.2%); δ(400 MHz, $CDCl_3$) 3.36 (1 H, dd, *J* 5.2 and 13, 2-H), 3.66 (1 H, dd, *J* 11.5 and 13, 3-H), 3.93 (1 H, d, *J* 11.5, 4-H), 4.47 (1 H, d, *J* 5.2, 1-H), 5.94 (2 H, AB-system, $J \approx 1$, OCH_2O), 6.32 (2 H, s, 2′,6′-H), 6.48 (1 H, s, 8-H), 6.78, (1 H, s, 5-H), and sharp methoxy resonances at 3.61 (3 H), 3.71 (3 H), 3.76 (6 H) and 3.80 (3 H). The NMR spectrum of the total hydrogenolysis product indicated a mixture of **7** (3.5 parts) and a compound (1.1 parts) tentatively assigned as the C-1 epimer of **7** showing the following proton resonances: δ(400 MHz, $CDCl_3$) 3.10 (1 H, t, *J* 11), 4.19 (1 H, br d, *J* 11), 4.27 (1 H, d, *J* 10), 5.91 (1 H, AB-system, $J \approx 1$), 6.24 (1 H, s), 6.31 (2 H, s) and 6.87 (1 H, s). The mother liquors obtained by recrystallisation of the acid **7** were chromatographed on silica in benzene–acetic acid (9:1) to give a further quantity (150 mg) of **7** (total yield 56%) also of purity sufficient for the next step of the synthesis.

Oxidative Decarboxylation of the Acid **7**.—The acid **7** (350 mg) in degassed THF–HOAc (5:1) (17.5 cm^3) was stirred under argon at 20 °C and lead tetraacetate (340 mg) added to it. The yellow colour that was produced faded over 90 min. After addition of ethylene glycol (*ca.* 10 drops) to the mixture stirring

was continued (5 min) followed by dilution with dichloromethane and washing with water, and saturated aqueous sodium hydrogen carbonate (2×), drying ($MgSO_4$) and evaporation. Crystallisation of the crude product from ether gave the *acetate* **8** (0.22 g, 61%), m.p. 174–177 °C (after drying at 77 °C *in vacuo*) (Found: C, 60.2; H, 5.45. $C_{26}H_{28}O_{11}$ requires C, 60.5; H, 5.4%); δ($CDCl_3$, 400 MHz) 2.0 (3 H, s, MeCO), 3.40 (1 H, dd, *J* 13 and 4, 3-H), 3.74 (1 H, dd, *J* 13 and 6.5, 2-H), 4.52 (1 H, d, *J* 6.5, 1-H), 5.94 (2 H, AB-system, $J \approx 1$, OCH_2O), 6.03 (2 H, s, 2',6'-H), 6.42 (1 H, s, 8-H), 6.45 (1 H, d, *J* 4, 4-H), 6.86 (1 H, s, 5-H), methoxy resonances at 3.51 (3 H), 3.66 (3 H), 3.73 (6 H) and 3.79 (3 H); *m/z* 516 (M), 456, 397, 396, 365, 338, 312, 257, 60, 59, and 43 (7.2, 63.3, 91.4, 100, 99, 19, 31, 8.9, 14.8, 11.5, and 23%).

Methyl Epipodophyllate **9a** *by* $LiEt_3BH$ *Reduction of* **8**.—The triester **8** (50 mg) in dry THF (ex. $LiAlH_4$) (1.25 cm^3) was stirred at −20 °C under a nitrogen atmosphere and lithium triethylborohydride (0.84 mol dm^{-3} solution in THF; 0.52 cm^3, 4.5 equiv.) was added to it. After 1.5 h further reagent (0.2 cm^3) was added to the mixture and stirring at −20 °C continued (30 min). Aqueous ammonium chloride (1 cm^3) and distilled water (1 cm^3) were added at −20 °C to the mixture which was then stirred vigorously (5 min). After the mixture had reached room temperature the product was extracted into ethyl acetate and the extract dried ($MgSO_4$) and evaporated. The crude product was boiled in methanol containing chromatography silica ≈10 mg to decompose boron complexes and the mixture then evaporated. The residue was chromatographed on silica in benzene–ethyl acetate (1:2) to give methyl epipodophyllate (28 mg, 65%) that crystallised from methanol, m.p. 217 °C (lit.,[1] m.p. 217 °C). The product has ^1H NMR characteristics identical with those described previously.[1]

Reaction of the Pyrone **1** *with Dimethyl Maleate to give the Dihydronaphthalene* **14***.—The pyrone **1** (200 mg) and dimethyl maleate (100 mg) in xylene (5 cm^3) was boiled under reflux under an argon atmosphere (3.5 h). The mixture was then evaporated under reduced pressure on a water-bath and the residue chromatographed on silica in ether–CH_2Cl_2 (7.5:92.5) when the olefin **14** was eluted first. Crystallisation from ethanol gave the pure *dihydronaphthalene* **14** (183 mg, 71% yield), m.p. 129–130 °C (Found: C, 62.85; H, 5.3. $C_{24}H_{24}O_9$ requires C, 63.2; H, 5.3%); ν_{max}(Nujol)/cm^{-1} 1715 and 1740; δ(400 MHz, $CDCl_3$) 3.94 (1 H, d, *J* 8, 2-H), 4.44 (1 H, d, *J* 8, 1-H), 5.96 (2 H, AB-system $J \approx 1$, OCH_2O), 6.44 (2 H, s, 2'6'-H), 6.57 (1 H, br, s), 6.81 (1 H, s), 7.59 (1 H, s), and methoxy resonances at 3.40 (3 H), 3.78 (3 H), 3.80 (6 H) and 3.85 (3 H); *m/z* 456 (M), 424, 396, 365, 338, 312, 257, 213, 168, 81, 59, 44 (100, 14.7, 64.4, 73.4, 28.2, 48.1, 13.9, 15.2, 18.8, 13.5, 58.0 and 25%). The yield was 67% when reaction was conducted with 1.1 g of **1**.

Preparation of the Allylic Alcohol **24**.—To the foregoing dihydronaphthalene **14** (900 mg) in dry THF (4 cm^3) at −70 °C was added a solution of $LiEt_3BH$ in THF (0.8 mol dm^{-3} solution; 7.65 cm^3) with stirring under nitrogen. After the mixture had been stirred at −70 °C for 3 h saturated aqueous NH_4Cl (18 cm^3) was added to it and the whole allowed to warm to 20 °C. The product was extracted with ethyl acetate and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The resulting oil in methanol (100 cm^3) was boiled under reflux (10 min) with silica (0.9 g) and then evaporated. The product was chromatographed on silica in ethyl acetate–light petroleum to give the *allylic alcohol* **24** (640 mg, 76% yield), m.p. 165–167 °C (from methanol) (Found: C, 64.55; H, 5.7. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.6%); ν_{max}(Nujol)/cm^{-1} 3520br and 1740; δ(400 MHz, $CDCl_3$) 2.16 (1 H, t, br, *J* 6, OH), 3.52 (3 H, s, OMe), 3.70 (1 H, dd, *J* 7 and 0.5, 2-H), 3.80 (6 H, s, OMe), 3.84 (3 H, s, OMe), 4.26 (2 H, d, *J* 6, CH_2), 4.35 (1 H, d, *J* 7, 1-H), 5.92 (2 H, AB-system), $J \approx 1$, OCH_2O), 6.50 (2 H, s, 2',6'-H), 6.54 (2 H, m, 8-H and 4-H) and 6.67 (1 H, s, 5-H).

Preparation of the Epoxide **30**.—To a solution of the allylic alcohol **24** (100 mg, 0.23 mmol) in dry dichloromethane (12 cm^3) was added $NaHCO_3$ (aq., 5%; 5 cm^3). The mixture was then stirred vigorously while *m*-CPBA (60 mg, 1.5 equiv.) was added directly; vigorous stirring was maintained for 1.75 h. The reaction mixture was then poured into ether and the whole shaken with Na_2SO_3 (sat., aq) and then brine and finally dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product (105 mg) which was triturated with dry ether (5 cm^3). The supernatant layer was pipetted off, and the crystalline residue dried *in vacuo* to afford **30** (100 mg. 96%), m.p. 175–182 °C (Et_2O); δ_H(400 MHz, C_6D_6) 3.10 (3 H, s, OMe), 3.46 (6 H, s, 2 × OMe), 3.62 (1 H, dd, *J* 8 and 12.5, CH_2), 3.71 (1 H, d, *J* 6, 2-H), 3.82 (1 H, dd, *J* 5.5 and 12.5, CH_2), 3.85 (1 H, s, 4-H), 3.90 (3 H, s, OMe), 4.52 (1 H, dd, *J* 0.5 and 6, 1-H), 5.31 (2 H, m, OCH_2O), 6.42 (2 H, s, 2',6'-H), 6.82 (1 H, s, 5-H) and 6.90 (1 H, br s, 8-H); ν_{max}(Nujol)/cm^{-1} 3600–3300 and 1730; *m/z* 444 (M^+, 52) and 394 (100%) (Found: M^+, 444.1419. $C_{23}H_{24}O_9$ requires *M*, 444.1420).

Reduction of the Epoxide **30**.—To the solid epoxide (12 mg, 0.03 mmol) contained in a dry round-bottomed flask was added a 0.34 mol dm^{-3} solution of Red-Al in THF (0.16 cm^3, 2 equiv.) and the solution stirred at 20 °C for 1 h. The solution was diluted with ether and washed with saturated NH_4Cl (aq.). The organic phase was separated and shaken with brine before being dried ($MgSO_4$). Rotary evaporation of the solvent gave the crude product (10 mg), the 90 MHz ^1H NMR spectrum of which showed several products, none of which corresponded to methyl epipodophyllate.

Rhodium-catalysed Hydrogenation of **24** *to* **25**.—The allylic alcohol **24** (20 mg, 0.05 mmol) in benzene (5 cm^3) was hydrogenated at 1 atm over 5% rhodium on alumina at 20 °C for 22 h, when UV analysis of an aliquot showed the absence of starting material (λ_{max} 317 nm, EtOH). The crude mixture was filtered by gravity, and the residue washed well with hot ethyl acetate. Evaporation of the filtrate gave the crude product (25 mg) which was recrystallised from methanol to afford **25** (15.5 mg, 40%), m.p. 200–203 °C (MeOH); δ_H(400 MHz; $CDCl_3$) 1.70 (1 H, br t, *J* 5, OH), 2.45 (1 H, m, 3-H), 2.71 (1 H, dd, *J* 5.5 and 16.5, 4-H), 2.93 (1 H, br dd, *J* 13 and 16.5, 4-H), 3.35 (1 H, dd, *J* 4 and 5.5, 2-H), 3.42 (3 H, s, OMe), 3.52 (1 H, m, CH_2O), 3.72 (1 H, m, CH_2O), 3.79 (6 H, br s, 2 × OMe), 3.85 (3 H, s, OMe), 4.22 (1 H, br d, *J* 5.5, 1-H), 5.88 (1 H, d, *J* 1.5, OCH_2O), 5.90 (1 H, d, *J* 1.5, OCH_2O), 6.42 (3 H, br s, 2',6'-ArH, and 8-H) and 6.62 (1 H, s, 5-H); ν_{max}(Nujol)/cm^{-1} 3470br and 1735; *m/z* 430 (M^+, 47) and 398 (M^+ − MeOH, 100%) (Found C, 64.1; H, 6.05. $C_{23}H_{26}O_8$ requires C, 64.2; H, 6.05%).

Preparation of the Aldehyde **26**.—To a pre-cooled solution of DMSO (18 mm^3, 2.2 equiv.) in dry dichloromethane (1 cm^3) was added a solution of oxalyl chloride (11 mm^3, 1.1 equiv.) in dichloromethane (1.5 cm^3), and the solution stirred at −70 °C for 10 min. The alcohol **25** (50 mg, 0.1 mmol) in dichloromethane (3 cm^3) was added dropwise to the mixture so that the temperature did not exceed −70 °C. The reaction mixture was then stirred at −70 °C for 50 min after which triethylamine (40 mm^3, 2.5 equiv.) was added to it and stirring continued for 10 min. The mixture was then allowed to warm to 20 °C over 1 h after which it was poured into ether and the whole washed with water and brine and dried ($MgSO_4$). Evaporation afforded the crude aldehyde (49 mg, 100%), m.p. 185–190 °C. Recrystallis-

ation of the latter from ether–light petroleum afforded pure material (40 mg), m.p. 189–190 °C; δ_H(400 MHz; $CDCl_3$) 2.93 (1 H, dd, *J* 6.5 and 17, 4-H), 3.05 (1 H, m, *J* 4, 6.5, and 8, 3-H), 3.54 (1 H, dd, *J* 4 and 6, 2-H), 3.54 (1 H, dd, *J* 8 and 17, 4-H), 3.55 (3 H, s, OMe), 3.76 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 4.44 (1 H, d, *J* 6, 1-H), 5.90 (1 H, d, *J* 1.5, OCH_2O), 5.91 (1 H, d, *J* 1.5, OCH_2O), 6.25 (2 H, s, 2′,6′-ArH), 6.41 (1 H, s, 8-H), 6.70 (1 H, s, 5-H) and 9.61 (1 H, s, CHO); ν_{max}(Nujol)/cm^{-1} 2720w, and 1725; *m/z* 428 (M^+, 100) and 410 (M^+ − CO, 17%) (Found C, 64.3; H, 5.6. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.6%).

Preparation of the Aldehyde **27** *with DBU.*—To the aldehyde **27** (16 mg, 0.04 mmol) in dry THF (0.8 cm^3) was added DBU (5 mm^3, 1 equiv.) and the mixture stirred for 23 h. It was then diluted with water (1 cm^3), vigorously stirred for 5 min and then extracted with ether. The combined extracts were washed with brine dried ($MgSO_4$) and evaporated to give the crude product (18 mg). Recrystallisation of this afforded the pure aldehyde **27** (15 mg, 94%), m.p. 155–156 °C (CH_2Cl_2–Et_2O); δ_H(400 MHz; C_6D_6) 2.23 (1 H, dd, *J* 12 and 17, 4-H), 2.50 (1 H, dd, *J* 6 and 17, 4-H), 3.13 (1 H, dd, *J* 5.5 and 12, 2-H), 3.20 (3 H, s, OMe), 3.22 (1 H, m, *J* 1.5, 6, and 12, 3-H), 3.34 (6 H, s, 2 × OMe), 3.79 (3 H, s, OMe), 4.35 (1 H, d, *J* 5.5, 1-H), 5.23 (1 H, d, *J* 1.5, OCH_2O), 5.28 (1 H, d, *J* 1.5, OCH_2O), 6.20 (2 H, s, 2′,6′-ArH), 6.38 (1 H, s, 8-H), 6.45 (1 H, s, 5-H) and 9.60 (1 H, d, *J* 1.5, CHO); ν_{max}(Nujol)/cm^{-1} 2720w, 1730 and 1720; *m/z* 428 (M^+, 100%) (Found: M, 428.1475. $C_{23}H_{24}O_8$ requires *M*, 428.1471).

Preparation of the Aldehyde **27** *with* SiO_2.—The aldehyde **26** (5 mg, 0.01 mmol) was adsorbed on Kieselgel G (Merck) (20g) in ethyl acetate–light petroleum (3:2) and left for 3 h. Elution of the adsorbent gave crystalline material (5 mg) which 90 MHz ^{1}H NMR spectroscopy showed to be composed of the aldehydes **27** and **26** in a ratio of *ca.* 9:1. Recrystallisation afforded the pure compound **27** (4.5 mg, 90%) identical with a sample prepared above.

Preparation of the Alcohol **28**.—The aldehyde **27** (17 mg, 0.04 mmol) in ethyl acetate (2.5 cm^3) was hydrogenated at atmospheric pressure for 14 h at 20 °C over 10% Pd-C (6 mg). Further catalyst (5 mg) was then added and the mixture hydrogenated for a further 24 h. The suspension was filtered by gravity and the residue washed well with hot ethyl acetate. Evaporation of the combined filtrates under reduced pressure gave the crude product (18 mg), m.p. 187–192 °C. Purification by chromatography afforded **28** (17 mg, 100%), m.p. 189–191 °C (lit.,[9] m.p. 190 °C). The 400 MHz ^{1}H NMR spectrum was identical with that published.[9]

Preparation of (±)-*Deoxypodophyllotoxin* **29**.—The alcohol **28** (15 mg, 0.03 mmol) in dry THF (2 cm^3) was refluxed with fused $ZnCl_2$ (24 mg) and freshly ground 4AMS (100 mg) for 35 min. The reaction mixture was cooled and diluted with brine (1 cm^3). The mixture was extracted with ethyl acetate and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (15 mg). Chromatography (ethyl acetate–light petroleum, 3:2) of the latter afforded (±)-deoxypodophyllotoxin (11 mg, 80%), m.p. 232–236 °C, which, on recrystallisation from dichloromethane–ether, gave **29** (8 mg) with a m.p. and 400 MHz ^{1}H NMR spectrum similar to those published;[9] ν_{max}(Nujol)/cm^{-1} 1765; *m/z* 398 (M^+, 100%).

Preparation of the Aldehyde **37**.—(i) To a solution of the allylic alcohol **24** (20 mg, 0.05 mmol) in dry methanol (0.5 cm^3) and dry dichloromethane (0.25 cm^3) at 0 °C was added NBS (8.5 mg, 1.3 equiv.) and the solution stirred for 30 min. The mixture was diluted with water (2 cm^3) and then extracted with ether. The combined extracts were shaken with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (30 mg). This was redissolved in CCl_4 and the residual succinimide filtered off. Re-evaporation of the filtrate afforded the bromo methoxy compound (25 mg, 99%), m.p. 118 °C (decomp); (Et_2O–light petroleum); δ_H(400 MHz; C_6D_6) 2.60 (1 H, dd, *J* 6 and 8, OH), 3.05 (3 H, s, OMe), 3.15 (3 H, s, OMe), 3.35 (6 H, s, 2 × OMe), 3.75 (1 H, d, *J* 6, 2-H), 3.84 (3 H, s, OMe), 4.23 (1 H, dd, *J* 5.5 and 12.5, CH_2), 4.29 (1 H, dd, *J* 9 and 12.5, CH_2), 4.48 (1 H, br s, 4-H), 4.94 (1 H, d, *J* 6, 1-H), 5.30 (2 H, m, OCH_2O), 6.71 (2 H, br s, 2′,6′-ArH), 6.73 (1 H, s, ArH) and 6.97 (1 H, s, ArH); ν_{max}(Nujol)/cm^{-1} 3600–3300, 1740 and 1720; *m/z* 429 (M + 1 − Br − OMe, 30) and 428 (M^+ − OMe − Br, 100%).

(ii) To a solution of the foregoing bromo methyl ether (50 mg, 0.09 mmol) and Bu_3SnH (34 mm^3, 1.1 equiv.) in dry oxygen-free benzene (2.5 cm^3) under argon was added AIBN (2 mg; cat.). The solution was then irradiated with UV light from a well-cooled 100-W medium-pressure mercury-vapour lamp (with SiO_2 jacket) for 5 min. Filtration of the mixture and evaporation of the filtrate under reduced pressure gave the crude product (86 mg). This was dissolved in benzene and the solution shaken with 10% aqueous KF for 15 min and then brine, dried ($MgSO_4$) and evaporated under reduced pressure to a volume of *ca.* 5 cm^3. With time the product crystallised and was filtered off and dried *in vacuo* at 20 °C to afford the debrominated product (21 mg, 49%), m.p. 257–259 °C (decomp.). Chromatography of the mother liquors eluting with ethyl acetate–petroleum (3:1) afforded a γ-lactone (15 mg) followed by the desired diol (12 mg, 28%), m.p. 255–259 °C (decomp.); δ_H(400 MHz; $CDCl_3$) 2.25 (1 H, dd, *J* 5.5 and 7, OH), 2.60 (1 H, septet, *J* 3.5–4, 3-H), 3.24 (1 H, dd, *J* 3.5 and 5.5, 2-H), 3.51 (3 H, s, OMe), 3.54 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe), 3.90–4.05 (2 H, m, CH_2), 4.15 (1 H, br d, *J* 5.5, 1-H), 4.32 (1 H, d, *J* 4, 4-H), 5.94 (2 H, m, OCH_2O), 6.59 (3 H, m, ArH) and 6.89 (1 H, s, ArH); ν_{max}(Nujol)/cm^{-1} 3600–3300 and 1735; *m/z* 428 (M^+ − MeOH, 100%) (Found: M^+, 460.1718. $C_{24}H_{28}O_9$ requires *M*, 460.1721).

(iii) Oxalyl chloride (7.6 mm^3, 2 equiv.) in dry dichloromethane (1 cm^3) was added dropwise to a pre-cooled (−70 °C) solution of dry DMSO (12.3 mm^3, 4 equiv.) in dichloromethane (0.5 cm^3) and the solution stirred for 10 min. The foregoing, debrominated product (15 mg, 0.03 mmol, 1 equiv.) in dichloromethane (1 cm^3) was added to the mixture dropwise over 20 min so as not to exceed −65 °C. After a further 5 min triethylamine (27 mm^3, 4.5 equiv.) was added to the mixture which was then stirred for 10 min before being allowed to warm to 20 °C over 1 h. The reaction mixture was poured into ether and the solution shaken with water and then brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude *aldehyde* **37** (15 mg, 100%). Recrystallisation from benzene–ether–hexane gave the pure compound (10 mg), m.p. 145–150 °C (decomp.); δ_H(400 MHz; C_6D_6) 2.56 (1 H, m, 3-H), 3.12 (3 H, s, OMe), 3.14 (3 H, s, OMe), 3.27 (1 H, dd, *J* 4 and 5.5, 2-H), 3.43 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 3.96 (1 H, d, *J* 5.5, 1-H), 4.22 (1 H, d, *J* 4, 4-H), 5.30 (2 H, m, OCH_2O), 6.71 (2 H, s, 2 × ArH), 6.85 (2 H, br s, 2 × ArH) and 9.93 (1 H, d, *J* 1.5, CHO); ν_{max}(Nujol)/cm^{-1} 1730vbr; *m/z* 458 (M^+, 5) and 426 (M^+ − MeOH, 100%) (Found: M^+, 458.1565. $C_{24}H_{26}O_9$ requires *M*, 458.1565).

Preparation of the Aldehyde **38**.—The aldehyde **37** (5 mg, 0.01 mmol) was added to a solution of DBU (1.6 mm^3, 1 equiv.) in dry THF (0.5 cm^3) at 20 °C. The initially intense yellow colour faded with time. After 24 h water (1 cm^3) was added to the mixture which was then stirred vigorously for 2 min. After this it was extracted with ether and the extract dried ($MgSO_4$)

and evaporated under reduced pressure to give the crude product (5 mg). The 90 MHz ^{1}H NMR spectrum of this material indicated formation of the *trans*-aldehyde **38**; δ_H(90 MHz; C_6D_6) 3.47 (3 H, s, OMe), 3.57 (6 H, s, 2 × OMe), 3.93 (3 H, s, OMe), 4.60 (1 H, d, *J* 4, 1-H), 4.97 (1 H, br d, *J* 4, 2-H), 5.40 (2 H, s, OCH_2O), 6.54 (2 H, s, 2',6'-ArH), 6.72 (1 H, s), 6.77 (1 H, s), 6.87 (1 H, s) and 9.67 (1 H, s, CHO). This compound was not further characterised.

Preparation of the Bromohydrins **33**.—To a solution of the allylic alcohol **24** (75 mg, 0.18 mmol) in DMSO (1 cm^3) containing water (3 mm^3, 1 equiv.) was added NBS (31.5 mg, 1 equiv.), and the solution stirred at 20 °C for 30 min. The reaction was quenched with the addition of water (1 cm^3) to the mixture which was then extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a mixture of **33** (4α-OH and 4β-OH) (79 mg). The co-polar bromohydrins were cleanly separated by crystallisation. Thus, crystallisation from ether–light petroleum gave **33** (4β-OH) (15 mg, 16%), double m.p. 120 °C (decomp.) and 145–148 °C; δ_H(400 MHz; $CDCl_3$) 2.11 (1 H, dd, *J* 4.5 and 10, 1-OH), 2.80 (1 H, d, *J* 5, 4-OH), 3.33 (3 H, s, OMe), 3.78 (1 H, dd, *J* 10 and 13.5, CH_2), 3.80 (6 H, br s, 2 × OMe), 3.85 (3 H, s, OMe), 3.98 (1 H, d, *J* 6.5, 2-H), 4.32 (1 H, dd, *J* 4.5 and 13.5, CH_2), 4.37 (1 H, br d, *J* 6.5, 2-H), 5.92 (1 H, d, *J* 1.5, OCH_2O), 5.95 (1 H, d, *J* 1.5, OCH_2O), 5.99 (1 H, br d, *J* 5, 4-H), 6.36 (2 H, br s, 2',6'-ArH), 6.37 (1 H, d, *J* < 1, 8-H) and 7.20 (1 H, d, *J* 1, 5-H); ν_{max}(Nujol)/cm^{-1} 3600–3300 and 1735; *m/z* 476 (21), 474 (17) and 410 (100%). Compound **33** (4α-OH) (64 mg, 70%) remained in the mother liquors. It could be crystallised with difficulty from benzene–ether, m.p. 152 °C (decomp.); δ_H(400 MHz; $CDCl_3$) 2.81 (1 H, t, *J* 7, 1-OH), 3.30 (3 H, s, OMe), 3.51 (1 H, dd, *J* 1 and 6.5, 2-H), 3.65–4.00 (6 H, vbr s, 2 × OMe), 3.86 (3 H, s, OMe), 4.11 (1 H, dd, *J* 8 and 12.5, CH_2), 4.22 (1 H, dd, *J* 6.5 and 12.5, CH_2), 4.75 (1 H, d, *J* 6.5, 1-H), 4.92 (1 H, d, *J* 12, 4-H), 5.00 (1 H, br d, *J* 1 and 12, 4-H), 5.93 (1 H, d, *J* 1.5, OCH_2O), 5.98 (1 H, d, *J* 1.5, OCH_2O), 6.10–6.30 (1 H, vbr s, ArH), 6.40–6.70 (1 H, vbr s, ArH), 6.49 (1 H, s, 8-H) and 6.97 (1 H, s, 5-H); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3600–3300, 1730 and 1710; *m/z* 564 (M^+, 9), 566 (M^+, 9) and 394 (54%) (Found: M^+, 524.0689. $C_{23}H_{25}{}^{79}BrO_9$ requires *M*, 524.0682) (Found: M^+, 526.0654. $C_{23}H_{25}{}^{81}BrO_9$ requires *M*, 526.0663).

Preparation of the Diol **34** (4β-OH).—To a solution of the bromohydrin **33** (9.5 mg, 0.02 mmol) and Bu_3SnH (5 mm^3, 1 equiv.) in dry oxygen-free benzene (4.5 cm^3) was added AIBN (2 mg; cat.). The solution was irradiated with UV light from a well-cooled medium-pressure 100-W, Hanovia lamp (SiO_2 jacket) for 5 min. Removal of the solvent under reduced pressure followed by chromatography on silica in ethyl acetate–light petroleum (4:1) gave the *diol* **34** (4β-OH) (7 mg, 84%), m.p. 205–210 °C (decomp.) CH_2Cl_2–Et_2O); δ_H(400 MHz; $CDCl_3$), 2.25–2.30 (2 H, m, 3-H and OH), 2.37 (1 H, d, *J* 7.5, 4-OH), 3.25 (1 H, dd, *J* 4 and 6, 2-H), 3.37 (3 H, s, OMe), 3.79 (6 H, br s, 2 × OMe), 3.80–3.86 (1 H, m, CH_2), 3.85 (3 H, s, OMe), 3.96 (1 H, m, CH_2), 4.33 (1 H, br d, *J* 6, 1-H), 5.15 (1 H, br dd, *J* 7.5 and 8, 4-H), 5.92 (2 H, m, OCH_2O), 6.36 (2 H, br s, 2',6'-ArH), 6.33 (1 H, br s, ArH) and 7.12 (1 H, br s, ArH); ν_{max}(Nujol)/cm^{-1} 3560br, 3460br and 1735; *m/z* 446 (M^+, 11), 414 (M^+ – MeOH, 82) and 240 (100%) (Found: M^+, 446.1573. $C_{23}H_{26}O_9$ requires *M*, 446.1577).

Preparation of the Diol **34** (4α-OH).—To a stirred solution of the bromohydrin **33** (4α-OH) (49 mg, 0.09 mmol) and Bu_3SnH (24 mm^3, 1.1 equiv.) in dry oxygen-free benzene (2.6 cm^3) under argon was added AIBN (2 mg; cat.). The solution was irradiated with UV light from a 100-W Hanovia medium-pressure mercury lamp (with SiO_2 jacket) for 5 min. Removal of the solvent from the mixture on a rotary evaporator at 20 °C gave the crude product (86 mg). Chromatography of this on silica using ethyl acetate–light petroleum (4:1) as eluent gave the impure diol **34** (4α-OH) (45 mg). This was recrystallised from ether–dichloromethane to afford the pure *compound* (37 mg, 89%), m.p. 185–189 °C (decomp.); δ_H(400 MHz; $CDCl_3$) 2.33 (1 H, m, 3-H), 2.50 (1 H, vbr s, OH), 3.23 (1 H, dd, *J* 4 and 6.5, 2-H), 3.35 (3 H, s, OMe), 3.80 (6 H, vbr s, 2 × OMe), 3.86 (3 H, s, OMe), 3.92 (1 H, m, CH_2), 4.02 (1 H, m, CH_2), 4.20 (1 H, br d, *J* 6.5, 1-H), 4.57 (1 H, d, *J* 11.5, 4-OH), 4.80 (1 H, dd, *J* 5 and 11.5, 4-H), 5.94 (2 H, m, OCH_2O), 6.42 (1 H, d, *J* 1, ArH), 6.30–6.50 (2 H, vbr s, 2',6'-ArH) and 7.02 (1 H, s, ArH); ν_{max}(Nujol)/cm^{-1} 3460br, 3400br, 1760s (absent in $CDCl_3$) and 1710; *m/z* 446 (M^+, 2) and 414 (M^+ – MeOH, 100%) (Found: M^+, 446.1580. $C_{23}H_{26}O_9$ requires *M*, 446.1577).

Preparation of the Ketone **35** *with* MnO_2.—To the diol **34** (4α-OH) (15 mg, 0.03 mmol) in acetone (1.5 cm^3; AnalaR) was added freshly prepared and powdered MnO_2 (71 mg). The suspension was stirred at 20 °C for 3 h. Further MnO_2 (71 mg) was then added and the mixture stirred overnight. After 20 h, the reaction mixture was filtered by gravity and the residue washed well with hot ethyl acetate. Evaporation of the filtrate gave a crude product (14 mg). Chromatography on silica using ethyl acetate–light petroleum (3:2) as eluent afforded the crystalline ketone **35** (6 mg, 40%), m.p. 190–193 °C (decomp.); δ_H(400 MHz; $CDCl_3$), 2.90 (1 H, vbr m, OH), 3.05 (1 H, dt, *J* 4.5 and 7, 3-H), 3.40 (3 H, s, OMe), 3.40 (1 H, dd, *J* 4.5 and 5.5, 2-H), 3.80 (6 H, vbr s, 2 × OMe), 3.80–3.85 (1 H, m, CH_2), 3.87 (3 H, s, OMe), 3.95–4.01 (1 H, m, CH_2), 4.57 (1 H, dd, *J* 1 and 5.5, 1-H), 6.01 (2 H, m, OCH_2O), 6.30–6.50 (2 H, vbr s, 2',6'-ArH), 6.45 (1 H, d, *J* 1, 8-H) and 7.54 (1 H, s, 5-H); λ_{max}(EtOH) nm 316, 273 and 233; ν_{max}(Nujol)/cm^{-1} 3480br, 1735 and 1680; *m/z* 444 (M^+, 23) and 426 (M^+ – H_2O, 100%) (Found: C, 62.0; H, 5.45. $C_{23}H_{24}O_9$ requires C, 62.2; H, 5.4%).

Preparation of the Ketone **35** *with Tributyltin Hydride and Iodine*.—To a solution of the chromatographed bromohydrins **33** (4α-OH and 4β-OH) (185 mg, 0.35 mmol) and Bu_3SnH (90 mm^3, 1 equiv.) in dry oxygen-free benzene (5 cm^3) was added AIBN (2 mg; cat.). The solution was then irradiated with UV light from a 100-W Hanovia medium-pressure mercury lamp (with SiO_2 jacket) for 5 min. The benzene was removed from the mixture on a rotary evaporator and the crude product redissolved in dichloromethane (20 cm^3). This solution was stirred vigorously in a stoppered flask with a saturated solution of NaF (aq., 20 cm^3) and iodine in dichloromethane (20 cm^3) for 15 h at 20 °C. The reaction mixture was then filtered through a sinter and the filtrate shaken with 0.1 mol dm^{-3} $Na_2S_2O_3$ (aq.), water, and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (350 mg). This was chromatographed using ethyl acetate–light petroleum (4:1) as eluent to afford the desired ketone (81 mg, 52%), m.p. 190–193 °C decomp.

Oxidation of the Diols **34** *with* $(Bu_3Sn)_2O$–I_2.—The diol **34** (4α-OH) (48 mg), bis(tributyltin) oxide (87 mg) and iodine (254 mg) were combined in CH_2Cl_2 (2 cm^3) at 20 °C. TLC in ethyl acetate–light petroleum (4:1) showed complete oxidation over 10 min. Chromatography of the product on silica in the same solvent system gave the crude ketone **35** (48 mg), m.p. 194–197 °C from CH_2Cl_2–Et_2O (36 mg, 72% recrystallised yield). Oxidation of **34** (4β-OH) in a similar way but using 12 cm^3 of CH_2Cl_2 for 33 mg of diol was complete in 10 min and gave the ketone **35** (20 mg, 60% recrystallised yield), m.p. 193–196 °C.

Preparation of the Ketone **36**.—DBU (34 mm^3, 1 equiv.) was

added to a solution of the ketone **35** (100 mg, 0.2 mmol) in dry THF (10 cm^3) and the solution stirred at 20 °C for 7 h. The reaction mixture was diluted with water (20 cm^3) and ether (10 cm^3) and after being stirred vigorously for 5 min was extracted (×6) with ether. The combined extracts were shaken with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (100 mg). Recrystallisation of the latter from dichloromethane–ether afforded the pure *ketone* **36**, m.p. 143–144 °C; δ_H(400 MHz; $CDCl_3$) 2.50 (1 H, vbr t, *J* 7, OH), 3.07 (1 H, td, *J* 3, 5 and 13, 3-H), 3.62 (1 H, dd, *J* 5.5 and 13, 2-H), 3.66 (3 H, s, OMe), 3.73 (6 H, s, 2 × OMe), 3.73–3.77 (1 H, m, CH_2), 3.80 (3 H, s, OMe), 4.22 (1 H, m, CH_2), 4.59 (1 H, d, *J* 5.5, 1-H), 6.04 (2 H, m, OCH_2O), 6.11 (2 H, s, 2′,6′-ArH), 6.58 (1 H, s, 8-H) and 7.53 (1 H, s, 5-H); ν_{max}(Nujol)/cm^{-1} 3460 br, 1730w and 1660; *m/z* 444 (M^+, 83), 414 ($M^+ - CH_2O$, 24) and 367 (100%) (Found: C, 62.25; H, 5.45. $C_{23}H_{24}O_9$ requires C, 62.2; H, 5.4%).

Preparation of Methyl Podophyllate from the Ketone **36**.—To a solution of the ketone **36** (49 mg, 0.11 mmol) in dry THF (5 cm^3) was added a 1 mol dm^{-3} solution of $LiEt_3BH$ in THF (0.45 cm^3; 4 equiv.) and the solution stirred for 3 h at −76 °C (bath temp.). The reaction was quenched by the addition of saturated NH_4Cl (aq., 5 cm^3) to the mixture which was then allowed to warm to 20 °C with vigorous stirring. It was then extracted (×6) with ether and the combined extracts were shaken with water and brine, dried ($MgSO_4$) and evaporated on a rotary evaporator to give the crude boronate ester. This was heated in refluxing methanol (10 cm^3) containing flash silica (50 mg) for exactly 10 min after which the mixture was evaporated under reduced pressure. Chromatography of the residue in ethyl acetate–light petroleum gave (±) methyl podophyllate (44 mg, 89%), m.p. 187–190 °C identical with samples prepared earlier.[1]

Thermolysis of the Adduct **12***.—The *endo*-adduct **12** (110 mg) in diphenyl ether (1 cm^3) was heated at 183 °C (internal temperature) for 45 min in an argon atmosphere. Chromatography of the mixture on silica in benzene–ether (95:5) gave the *dihydronaphthalene* **15** (85 mg, 88%) as a gum (Found: C, 74.55; H, 5.65. $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%); δ_H(400 MHz; C_6D_6) 3.05 (3 H, s), 3.44 (3 H, s), 4.14 (1 H, d, *J* 8, 2-H), 4.33 (1 H, d, *J* 8, 1-H), 6.8–7.2 (9 H, m, ArH) and 7.74 (1 H, s, 4-H); λ_{max}(EtOH)/nm 297; ν_{max}(film)/cm^{-1} 1700–1750. A similar thermolysis* conducted at 183 °C in C_6D_6 in a sealed and evacuated (3 freeze–pump–thaw cycles) NMR tube showed the absence of the *trans*-dihydronaphthalene **17**, and no more than a trace of the isomer **20**.

Conversion of the cis-*Dihydronaphthalenes* **14** *and* **15** *into* trans-*Dihydronaphthalenes* **16** *and* **17**.—The foregoing *cis*-dihydronaphthalene **15** (50 mg), DBN (300 mg) and benzene (4 cm^3) were boiled under reflux under an argon atmosphere (4 h). The mixture was then diluted with ether and washed with hydrochloric acid (2 mol dm^{-3}) and water, dried ($MgSO_4$), and evaporated to give a crude product **17**. This was purified by chromatography on silica in benzene–ether (19:1), m.p. 130–132 °C (from ethanol) (35 mg) (Found: C, 74.45; H, 5.55%); δ_H(400 MHz, C_6D_6) 3.19 (3 H, s), 3.33 (3 H, s), 4.42 (1 H, d, *J* 3, 2-H), 4.92 (1 H, d, *J* 3, 1-H), 6.8–7.2 (9 H, m, ArH) and 7.79 (1 H, s, 4-H). In a similar way, the dihydronaphthalene **14** (50 mg) gave the trans-*dihydronaphthalene* **16** (36 mg), m.p. 155–158 °C (from ethanol) (Found: M^+, 456.1416. $C_{24}H_{24}O_9$ requires *M*, 456.1420); ν_{max}(Nujol)/cm^{-1} 1715, 1740 and 1600; δ_H(400 MHz; $CDCl_3$) 3.64 (3 H, s, OMe), 3.74 (6 H, s, OMe), 3.77 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.99 (1 H, d, *J* 3, 2-H), 4.50 (1 H, d, *J* 3, 3-H), 5.98 (2 H, AB-system, $J \approx 1$, OCH_2O), 6.22 (2 H, s, 2′,6′-H), 6.64 (1 H, s, ArH), 6.82 (1 H, s, ArH) and 7.64 (1 H, s, 4-H).

Thermolysis of the Fumarate Adducts **4** *and* **5***.—When heated in C_6D_6 in a sealed (3 freeze–pump–thaw cycles) NMR tube at 170 °C (2 h) with ^1H NMR monitoring compound **4** gave a mixture of the foregoing *trans*-dihydronaphthalene **16** (1 part) and the isomer **21** (1.5 parts) which was not isolated but characterised by the following signals in the NMR spectrum of the mixture: δ_H(400 MHz; $CDCl_3$) 3.13 (1 H, dd, *J* 16 and 7, 4-H), 3.22 (1 H, dd, *J* 16 and 5.5, 4-H), 3.49 (3 H, s, OMe), 3.68 (3 H, s, OMe), 3.82 (6 H, vbr s, OMe), 3.91 (3 H, s, OMe), 3.85 (1 H, dd, *J* 7 and 5.5, 3-H), 5.91 (2 H, AB-system, $J \approx 1$, OCH_2O), 6.33 (1 H, s, ArH), 6.37–6.56 (2 H, vbr s, 2′,6′-H) and 6.70 (1 H, s, ArH).

In a similar pyrolysis the adduct **5** in C_6D_6 at 220 °C (6 h) gave the dihydronaphthalene **17** (2 parts) and the isomer **20** (1 part) as indicated by the 400 MHz ^1H NMR spectrum in $CDCl_3$. While the signals due to **17** were similar to those recorded above for the pure compound in C_6D_6 the following signals serve to characterise the isomer **20**: δ 3.25 (1 H, d, *J* 16 and 7, 4-H), 3.36 (1 H, dd, *J* 16 and 5.5; 4-H), 3.47 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.98 (1 H, dd, *J* 7 and 5.5, 3-H) and 6.7–7.5 (9 H, m, ArH).

Selective Reduction of **15** *with* $LiEt_3BH$.—The diester **15** (460 mg) in THF (15 cm^3) was cooled in a bath at −76 °C and lithium triethylborohydride in THF (1 mol dm^{-3} solution; 7.5 cm^3) added with stirring over 10 min under an argon atmosphere. The mixture was stirred for 20 min at −76 °C and then quenched by addition of aqueous ammonium chloride (*ca.* 10 cm^3). After 20 min the mixture was allowed to warm to 20 °C when it was diluted with water and extracted with ethyl acetate (5×). The extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated. The crude product was boiled with methanol (5 min) and the allylic alcohol isolated by chromatography over silica gel in benzene–ether (3:1) to give the pure allylic alcohol (290 mg, 69%) (Found: M^+, 294.1255. $C_{19}H_{18}O_3$ requires *M*, 294.1256); δ_H(90 MHz; $CDCl_3$) 3.44 (1 H, s, OH), 3.46 (3 H, s, OMe), 3.76 (1 H, d, *J* 7.7, 2-H), 4.25 (2 H, s, CH_2), 4.55 (1 H, d, *J* 7.7, 1-H), 6.69 (1 H, br s, 4-H) and 6.8–7.4 (9 H, m, ArH); *m/z* 294, 276, 262, 234, 218, 205, 178, 127, 91, 77 (14.1, 24.2, 13.0, 18.6, 20.1, 100.0, 21.1, 19.8, 18.2 and 14.2%).

Preparation of the Epoxide **31**.—The allylic alcohol **24** (36 mg, 0.12 mmol) was dissolved in dry dichloromethane (1.5 cm^3) and the solution cooled in an ice-bath. A solution of *m*-CPBA (25 mg, 1.1 equiv.) in dichloromethane (1 cm^3) was added with stirring to the solution which was then allowed to warm to 20 °C. Stirring was continued for a total of 2 h, when further *m*-CPBA (12 mg) was added. After 2.25 h, the reaction mixture was poured into ether and washed with saturated Na_2SO_3 (aq.). The organic phase was dried ($MgSO_4$) and evaporated to give a mixture of epoxides (36 mg, 94%). The 90 MHz ^1H NMR showed *ca.* 10% α-epoxidation.

The β-epoxide. δ_H(90 MHz), $CDCl_3$) 2.1–2.5 (1 H, br s, exch. D_2O, OH), 3.40 (3 H, s, OMe), 3.55 (1 H, d, *J* 6, 2-H), 3.75 (1 H, d, *J* 13, CH_2), 4.0 (1 H, d, *J* 13, CH_2), 4.15 (1 H, s, 4-H), 4.45 (1 H, d, *J* 6, 1-H) and 6.85–7.05 (9 H, m, ArH); ν_{max}(Nujol)/cm^{-1} 3600–3100 and 1730; *m/z* 310 (M^+, 5), 280 ($M^+ - CH_2O$, 67) and 178 (100%) (Found: M^+, 310.1216. $C_{19}H_{18}O_4$ requires 310.1205).

Preparation of the Ether **32** *with Red-Al*.—To a cooled solution of the epoxy alcohol **31** (18 mg, 0.06 mmol) in dry THF (1 cm^3) was added a 3.4 mol dm^{-3} solution of Red-Al in toluene (20 mm^3, 1.2 equiv.), and the solution allowed to warm to 20 °C over 2 h. The reaction was quenched by addition of saturated NH_4Cl (aq., 1 cm^3) to the mixture. 2 mol dm^{-3} HCl (aq., 1 cm^3) was then added to dissolve the alkoxyaluminium precipitate, and the mixture extracted with ethyl acetate. The

combined extracts were washed with $NaHCO_3$ (aq., 5%), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product (18 mg), the 90 MHz ^1H NMR spectrum of which showed no methoxy signals. The crude product was chromatographed (benzene–ethyl acetate, 1:2) to afford **32** (4 mg, 25%) as an oil, and an uncharacterised compound (3 mg).

Compound **32**. δ_H(400 MHz; $CDCl_3$) 2.44 (1 H, dd, *J* 3.5, 4.5, 2-H), 3.68 (1 H, ddd, *J* 1.5, 5.5, and 10, CH_2O bridge), 3.84 (1 H, d, *J* 11, CH_2OH), 3.93 (1 H, d br, *J* 9.5–10, CH_2O bridge), 3.99 (1 H, d, *J* 11, CH_2OH), 4.55 (1 H, s, 4-H), 4.92 (1 H, br d, *J* 3.5, 1-H) and 7.15–7.35 (9 H, m, ArH); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3600–3100 (OH); *m/z* 282 (M^+, 2), 252 ($M^+ - HCHO$, 23) and 251 ($M^+ - CH_2OH$, 100%) (Found: M^+, 282.1250. $C_{18}H_{18}O_3$ requires *M*, 282.1256).

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