Asymmetric total synthesis of (−)-podophyllotoxin

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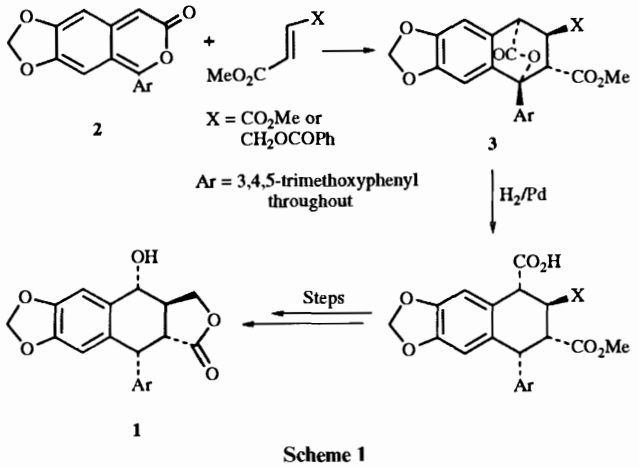
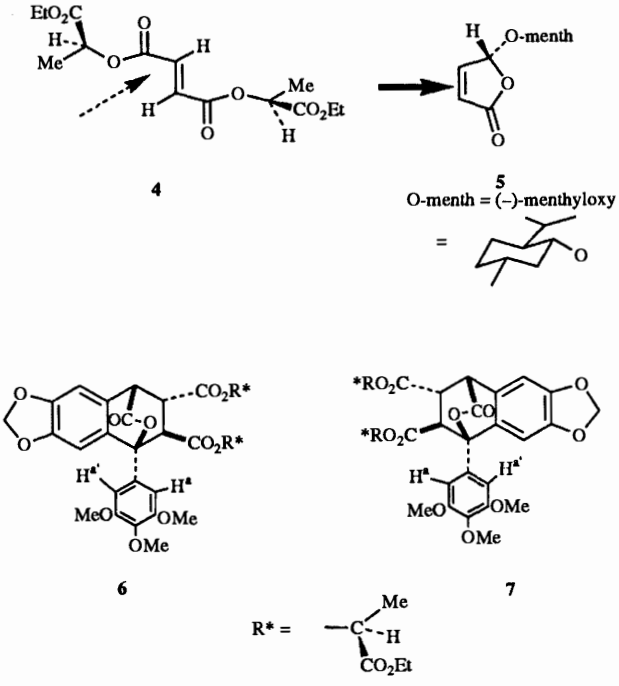
(−)-Podophyllotoxin of 98% optical purity has been synthesized in eight steps and in 15% overall yield. The key step, Diels–Alder addition of the *o*-quinonoid pyrone 2 [6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-2-benzopyran-3-one] to the chiral dienophile 5 [5-(−)-menthyloxyfuran-2(5*H*)-one], proceeds with very high regio-, *endo*- and facial selectivity.

Although the use of podophyllotoxin derivatives in cancer chemotherapy has prompted much synthetic work [1] there has appeared only one asymmetric total synthesis of (−)-podophyllotoxin **1**.[2] There is also a much shorter synthesis of (−)-4-*epi*-podophyllotoxin [3] which can be considered a formal synthesis of **1** in 14 steps. Both these syntheses have key steps based on carbanion chemistry.† We have previously shown [4] that the isolable *o*-quinonoid pyrone **2** is a useful building block for the synthesis of (±)-podophyllotoxin *via* cycloaddition as shown in Scheme 1. Addition of **2** to fumarate or ω-substituted



Scheme 1

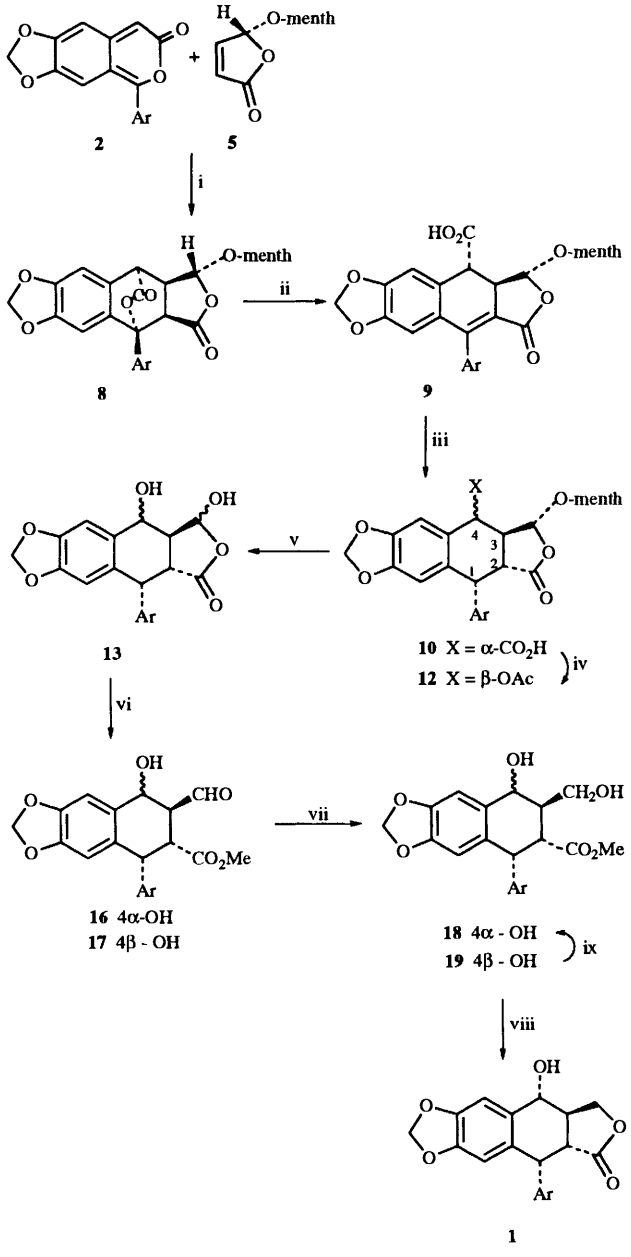
crotonates is regioselective in the required sense and the α-aryl group of **2** induces preferred *exo*-orientation of the methoxycarbonyl at C-2 (see **3**, Scheme 1). We sought to use this work as the basis of a synthesis of homochiral (−)-podophyllotoxin. Since we had been unable to observe Lewis acid catalysis of additions to 2-benzopyran-3-ones,[5] we selected dienophiles known to show good facial selectivity in uncatalysed Diels–Alder reactions. Examples of such dienophiles are the Helmchen fumarate ester **4**[6] and the Feringa dienophile **5**.[7] These dienophiles show preferred addition to dienes at the faces indicated by arrows in **4** and **5**. Because it appeared to more closely resemble our route to (±)-podophyllotoxin using fumarate we first tested the addition of **4** to **2**. Four adducts were formed indicating both incomplete facial, and *endo*–*exo* selectivity. The two major products were partially separated by careful short-column chromatography. On the basis that only adducts with an *exo* substituent at C-2 show different (and frequently) broadened resonances for H^a and $H^{a'}$ (see **6**), the major adducts from **4** are *exo*-adducts **6** and **7** produced *via* poorly selective addition to the faces of the



pyrone **2**. In contrast, we observed a highly facially selective addition of the more rigid dienophile **5** to **2**. Accordingly this became the corner stone of our route to (−)-podophyllotoxin.[8]

Addition of **2** to **5** at 50 °C in acetonitrile in base-washed glassware gave **8** (Scheme 2) as the only observed adduct in high yield. The expected high facial selectivity [7] is accompanied by very high regioselectivity which probably arises from the aryl group of the pyrone and the carbonyl group of the dienophile; methyl acrylate adds less selectively to 2-benzopyran-3-one itself. The addition of **2** and **5** is also remarkably *endo*-selective. For compact dienophiles, *e.g.* maleimides and cyclopropene, the effect of an α-aryl group in promoting *exo* addition is diminished [9] in favour of *endo* addition. In addition, for **5** the *O*-menthyl moiety appears to exert an important but poorly understood enhancement of *endo*-selectivity as furan-2(5*H*)-one itself adds to **2** to give both *endo* and *exo* adducts (ratio 4.2 : 1). If the Diels–Alder reaction is conducted in glassware that has not been base-washed the olefinic acid **9** accompanies the adduct **8**, and **9** can be produced from **8** in high yield merely by heating **8** in glacial acetic acid at 50 °C. The *O*-menthyl group also exerts an important influence upon the hydrogenation of **9**; addition of hydrogen to the β-face of **9** to give mostly the 2,3-*trans* lactone **10** contrasts with almost exclusive hydrogen addition to the α-face of related lactones lacking the *O*-menthyl group. A slight preference for β-hydrogen addition is shown by the related hydroxy acids, *e.g.* **11** and this has been used

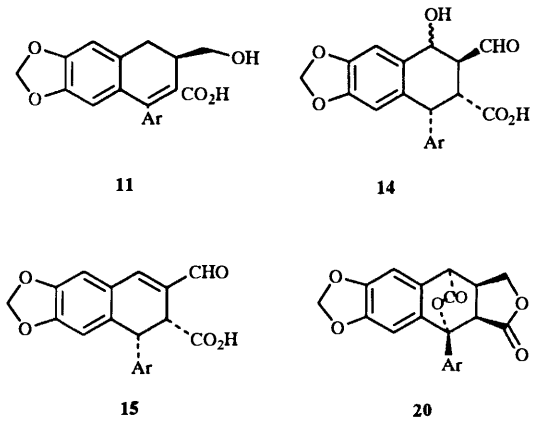
† A neat synthesis of (−)-neopodophyllotoxin by cycloaddition to a photo enol has been described (J. L. Charlton and K. Koh, *J. Org. Chem.*, 1992, **57**, 1514).



Scheme 2 *Reagents and conditions* (*with yields*): i, 50 °C (internal), MeCN, 29 h, Ar, base-washed glassware, 79%, 1.2 g scale; ii, 49 °C (internal), HOAc, 13 h, 87%; iii, 22 °C, EtOAc, 10% Pd–C, H_2, 40 h, 71% (77% on recovered **9**); iv, 20 °C, HOAc–THF (1:5), $Pb(OAc)_4$, Ar, 3 h, 80%; v, 41–43 °C (internal), dioxane–0.6 mol dm^{-3} hydrochloric acid (3:1), 51 h, 39% **4**α, 32.1% **4**β; vi, CH_2N_2, Et_2O–MeOH (24:1), 0 °C, 86% **16**, 85% **17**; vii, −78 °C, THF, Ar, $LiEt_3BH$ (2.2 equiv.), 1 h; $NaHCO_3$–H_2O quench, boil MeOH–silica gel (10 min); 84% **18**, 83% **19**; viii, 64 °C, THF, $ZnCl_2$, 4 Å molecular sieves, 2.5 h, 85%; ix, THF–4 mol dm^{-3} hydrochloric acid (1:1.5), 20 °C, 3.5 h, 63%, ref. 4

synthetically.[10] Addition to the β-face of **9** is also favoured by the presence of the α-carboxyl group.

The acid **10** with the correct stereochemistry at C-1, C-2 and C-3 was cleanly converted by lead tetraacetate oxidation[4] into the acetate **12**. The pseudo ester **12** was hydrolysed under carefully controlled acidic conditions (Scheme 1) to give the epimeric lactols **13**, readily separated by chromatography; these arise by acid-catalysed epimerisation at C-4 as observed in the conversion of **19** into **18** (Scheme 2). The absence of a C*H*O resonance in the NMR spectra of these lactols show that they and not the aldehydes **14** are the predominant ring-chain tautomers. Importantly, only a minor quantity (7.5%) of the enal **15** produced by β-elimination of water in **14** was formed under the proper hydrolysis conditions. Brief treatment of the individual lactols **13** with diazomethane in ether–methanol gave



the aldehydo esters **16** and **17** which were efficiently reduced to methyl podophyllate **18** and methyl epipodophyllate **19**. The former compound was lactonised using our $ZnCl_2$–4 Å molecular sieves procedure[4] to give (−)-podophyllotoxin **1** identical with an authentic sample. Methyl epipodophyllate **19** is readily converted into methyl podophyllate (Scheme 2). Accordingly (−)-podophyllotoxin can be prepared in 15% overall yield from the pyrone **2** with an optical yield of 98%.

Experimental

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Philips PU 8706 infrared spectrophotometer, and referenced to a peak at 1601 cm^{-1} of polystyrene. UV and visible spectra were recorded on a Pye-Unicam PU 8800 UV/VIS spectrophotometer; log ε values are in parentheses. Unless otherwise stated ^1H NMR spectra were determined, with tetramethylsilane as internal standard; 400 MHz spectra were measured on a Bruker WH-400 instrument, and 300 MHz spectra on a General Electric Nicolet QE 300 spectrometer. Coupling constants are in Hz. Mass spectra were obtained on an Autospec mass spectrometer. Chromatography on silica refers to short-column chromatography[11] over Kieselgel G60 (Merck). Ether refers to diethyl ether and light petroleum to the fraction bp 60–80 °C. 'Base-washed glassware' was soaked in 2 mol dm^{-3} aqueous potassium hydroxide (18 h), washed with water, washed with acetone and oven-dried (120 °C, 16 h). Optical rotations were obtained using an Optical Activity AA-1000 polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}.

Diels–Alder addition of 4 to the pyrone 2

The pyrone **2** (67 mg, 0.19 mmol) and the fumarate **4** (0.6 g, 1.9 mmol) were dissolved in acetonitrile (2.7 cm^3) and heated at 50 °C (internal temperature) in base-washed glassware (see general instructions) (20 h). NMR spectra of the total adduct mixture indicated the presence of four adducts in the ratio 6:6:1:1. Chromatography of the evaporated product on silica (60 g) in benzene–ether (22:3) gave, partially separated, the two major products: **6** or **7** (34 mg) (Found: M^+, 672.2047. $C_{33}H_{36}O_{15}$ requires M^+, 672.2054); $\nu_{max}(CH_2Cl_2$ film)/cm^{-1} 1750; δ_H(300 MHz) 1.19 (3 H, t, *J* 7.1, CH_2Me), 1.26 (3 H, t, *J* 7.0, CH_2Me), 1.33 (3 H, d, *J* 7.0, C*H*Me), 1.54 (3 H, d, *J* 7.0, C*H*Me), 3.88 (8 H, m, 2-H, 3-H and 3′,5′-OMe), 3.92 (3 H, s, 4′-OMe), 4.11 (2 H, m, CH_2Me), 4.21 (2 H, q, *J* 7.0, CH_2Me), 4.53 (1 H, d, *J* 2.4, 3-H), 4.89 (1 H, q, *J* 7.0, C*H*Me), 5.07 (1 H, q, *J* 7.0, C*H*Me), 5.93 (1 H, apparent s, OCH_2O), 5.95 (1 H, apparent s, OCH_2O), 6.21 (1 H, s, 8-H), 6.68 (1 H, s br, ArH), 6.95 (1 H, s br, ArH) and 6.98 (1 H, s, 5-H); *m*/*z* 672 (M^+), 629, 628, 482, 366, 365, 357, 356, 338 and 182 (11.5, 11.8, 33.0, 26.6, 25.9, 100.0, 13.3, 62.4, 14.2 and 10.4%); $[\alpha]_D^{22}$ −69.2 (*c* 3.4 in $CHCl_3$).

Further elution of the column gave either **6** or **7** (11 mg) (Found: M^+, 672.2042); $\nu_{max}(CH_2Cl_2$ film)/cm^{-1} 1750; δ_H(300 MHz) 1.07 (3 H, d, *J* 7.0, CH*Me*), 1.21 (3 H, t, *J* 7.0, CH_2*Me*), 1.24 (3 H, t, *J* 7.0, CH_2*Me*), 1.53 (3 H, d, *J* 7.0, CH*Me*), 3.88–3.97 (11 H, m, 1-H, 2-H and 3′,4′,5′-OMe), 4.12 (2 H, q, *J* 7.0, C*H*$_2$Me), 4.17 (2 H, q, *J* 7.0, C*H*$_2$Me), 4.43 (1 H, d, *J* 1.3, 3-H), 4.86 (1 H, q, *J* 7.0, C*H*Me), 5.02 (1 H, q, *J* 7.0, C*H*Me), 5.94 (1 H, d, *J* 1.0, OCH_2O), 5.97 (1 H, d, *J* 1.0, OCH_2O), 6.37 (1 H, s, 8-H), 6.70 (1 H, s br, ArH), 6.80 (1 H, s, 5-H) and 6.94 (1 H, s br, ArH); *m*/*z* 672 (M^+), 628, 483, 482, 366, 365, 356, 338, 334 and 323 (1.5, 23.5, 11.0, 34.6, 25.6, 100.0, 10.2, 10.4, 9.0 and 8.1%); $[\alpha]_D^{22}$ 7.64 (*c* 1.1 in $CHCl_3$).

When the pyrone **2** (39.5 mg, 0.11 mmol) and the fumarate **4** (0.35 g, 1.1 mmol) were dissolved in acetonitrile (1.6 cm^3) and heated at 50 °C (internal temperature) (72 h) in a flask that had not been pre-treated with base the reaction gave mainly two carboxylic acids related to **9**. The reaction mixture was concentrated and then dissolved in methanol and cooled to 0–5 °C (ice–water bath) and treated with diazomethane (1 min). The reaction flask was heated on a steam-bath to remove the excess of diazomethane and concentrated to give an oil. Chromatography of the residue on silica (35 g) eluting with benzene–ether (3:2) gave a 1:1 mixture of acids (57 mg, 76%) (Found: M^+, 686.2211. $C_{34}H_{38}O_{15}$ requires M^+, 686.2240); ν_{max}(film)/cm^{-1} 1740; δ_H(400 MHz) 0.74 (3 H, t, *J* 7, CH_2*Me*), 0.75 (3 H, t, *J* 7, CH_2*Me*), 0.87 (3 H, t, *J* 7, CH_2*Me*), 0.88 (3 H, t, *J* 7, CH_2*Me*), 0.96 (3 H, d, *J* 7, CH*Me*), 1.01 (3 H, d, *J* 7, CH*Me*), 1.20 (3 H, d, *J* 7, CH*Me*), 1.36 (3 H, d, *J* 7, CH*Me*), 3.18–3.90 (20 H, m, 4 × C*H*$_2$Me and 2 × 3′,5′-OMe), 3.27 (3 H, s, OMe), 3.30 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.86 (3 H, s, OMe), 4.46 (1 H, d, *J* 1.5), 4.63 (1 H, d, *J* 1.5), 4.88 (1 H, q, *J* 7.0, C*H*Me), 4.97 (1 H, q, *J* 7, C*H*Me), 5.04–5.14 (6 H, m, 2 × OCH_2O and 2 × C*H*Me), 5.09 (1 H, d, *J* 1.5), 5.20 (1 H, d, *J* 1.5), 6.46 (1 H, s br, ArH), 6.55 (1 H, s br, ArH), 6.73 (1 H, s, ArH), 6.89 (1 H, s br, ArH), 6.85 (2 H, s, ArH), 6.95 (1 H, s, ArH) and 7.08 (1 H, s br, ArH); *m*/*z* 686 (M^+), 509, 423, 84, 83, 69, 57, 55, 44 and 41 (23.6, 67.0, 100.0, 63.8, 59.9, 49.1, 50.4, 73.6, 58.8 and 68.7%).

Addition of the pyrone 2 to 5-(−)-menthyloxyfuran-2(5*H*)-one

The pyrone (1.28 g, 3.60 mmol) and furanone (8.0 g, 33.6 mmol) were combined in acetonitrile (65 cm^3) and the mixture stirred at 50 °C (internal temperature) in an argon atmosphere (29 h) using base-washed glassware (see general instructions). Chromatography of the evaporated product on silica (300 g) in benzene–ether (95:5) gave the *adduct* **8** (1.68 g, 79%), mp 167–170 °C (from CH_2Cl_2–light petroleum) (Found: C, 66.4; H, 6.5. $C_{33}H_{38}O_{10}$ requires C, 66.7; H, 6.4%); ν_{max}(Nujol)/cm^{-1} 1750 and 1790; λ_{max}(EtOAc)/nm 283 (4.31); δ_H(400 MHz, $CDCl_3$) 0.7–2.03 (18 H, m, menthyl-H), 3.25 (1 H, d br, *J* 9, 3-H), 3.41 (1 H, td, *J* 10.5 and 3.5, menthyl HCO), 3.90 (6 H, s), 3.92 (3 H, s), 4.07 (1 H, d br, *J* 2.0, 4-H), 4.30 (1 H, d br, *J* 9.0, 2-H), 5.12 (1 H, s, 11-H), 5.97 and 6.00 (2 H, two strong lines of OCH_2O AB-system), 6.41 (1 H, s, 8-H), 6.89 (1 H, s, 5-H) and 7.15 (2 H, s, 2′,6′-H); *m*/*z* 594 (M), 550, 548, 393, 366, 365, 323, 308, 307 and 97 (12.5, 65.0, 67.1, 52.4, 100.0, 53.5, 77.8, 54.3, 47.1 and 100%); $[\alpha]_D^{22}$ −102 (*c* 3.22 in $CHCl_3$).

Reaction of the adduct 8 with acetic acid

The foregoing adduct (1.27 g, 2.14 mmol) in acetic acid (56 cm^3) was heated at 49 °C (internal temperature) with stirring in an argon atmosphere (13 h). The precipitated acid **9** was filtered off and washed with ether (1.03 g). The combined mother liquor and washings were evaporated under reduced pressure and the residue chromatographed on silica (45 g) in benzene–ether–acetic acid (92:6:2) to give a *decarboxylated product* (0.10 g, 8.5%), mp 234–236 °C (from CH_2Cl_2–EtOH) (Found: C, 69.6; H, 6.9. $C_{32}H_{38}O_8$ requires C, 69.8; H, 6.9%); ν_{max}(Nujol)/cm^{-1} 1770; λ_{max}(EtOH)/nm 342 (3.58); δ_H(400 MHz, $CDCl_3$) 0.8–2.3 (18 H, m, menthyl-H), 2.99 (1 H, dd, *J* 14.5 and 6.0, 4-H), 2.83 (1 H, dd, *J* 16.0 and 14.5, 4-H), 3.14 (1 H, dt, *J* 16.0 and 6.0, 3-H), 3.65 (1 H, td, *J* 10.5 and 4.5, menthyl HCO), 3.84 (6 H, s vbr, 3′,5′-OMe), 3.92 (3 H, s), 5.46 (1 H, d, *J* 6, 11-H), 5.96 (2 H, apparent s, OCH_2O), 6.47 (1 H, s, 8-H) and 6.75 (1 H, s, 5-H); the 2′- and 6′-H were not observed presumably due to slow rotation about the C-aryl bond and associated breadth of the signals; *m*/*z* 551, 550 (M), 367, 366, 365, 335, 307, 149, 86 and 84 (35.4, 100.0, 17.9, 35.2, 29.2, 17.4, 9.1, 28.8, 11.6 and 20.3%); $[\alpha]_D^{22}$ −24.5 (*c* 0.816 in $CHCl_3$). Continued elution of the column gave the *acid* **9** (0.08 g) (total yield 87%), mp 262–264 °C (From CH_2Cl_2–EtOH) (Found: C, 66.95; H, 6.6. $C_{33}H_{38}O_{10}$ requires C, 66.7; H, 6.4%); ν_{max}(Nujol)/cm^{-1} 3220 (sharp), 1780 and 1735 cm^{-1}; λ_{max}(EtOH)/nm 337 (4.16); δ_H(400 MHz, $CDCl_3$) 0.83–2.30 (18 H, m, menthyl-H), 3.50 (1 H, dd, *J* 15.5 and 5.5, 3-H), 3.63 (1 H, td, *J* 11 and 4, menthyl HCO), 3.84 (6 H, s br, 3′,5′-OMe), 3.92 (3 H, s), 3.99 (1 H, d, *J* 15.5, 4-H), 5.62 (1 H, d, *J* 5.5, 11-H), 5.98 (1 H, d, *J* 1, OCH_2O), 6.02 (1 H, d, *J* 1, OCH_2O), 6.53 (1 H, s, 8-H) and 6.80 (1 H, s, 5-H); the 2′,6′-H signals were not observed owing to restricted rotation of the aryl group and associated breadth and the CO_2H signal was not recorded; *m*/*z* 594 (M^+), 549, 548, 409, 394, 393, 366, 365, 55 and 44 (38.6, 35.3, 94.5, 30.4, 34.6, 69.4, 41.1, 100.0, 31.0 and 27.5%); $[\alpha]_D^{22}$ 16.0 (*c* 0.749 in $CHCl_3$).

The tetrahydronaphthalene 10

The foregoing acid (0.50 g, 0.84 mmol) in ethyl acetate (125 cm^3) containing 10% palladium-on-charcoal catalyst (0.58 g) was stirred in a hydrogen atmosphere at 22 °C (40 h). The reaction mixture was filtered and evaporated and the residue was chromatographed on silica (65 g) in benzene–ether–acetic acid (92:6:2) to give the *acid* **10** (356 mg, 71%), mp 148.5–151 °C (from benzene–light petroleum) (Found: C, 66.2; H, 6.8. $C_{33}H_{40}O_{10}$ requires C, 66.4; H, 6.7%); ν_{max}(Nujol)/cm^{-1} 3600–2600, 1770 and 1710; λ_{max}(EtOH)/nm 288 (4.34); δ_H(400 MHz, $CDCl_3$) 0.70–2.15 (18 H, m, menthyl-H), 2.87 (1 H, dd, *J* 14.5 and 4.5, 2-H), 2.96 (1 H, ddd, *J* 14.5, 10.5 and 7.5, 3-H), 3.48 (1 H, td, *J* 10.5 and 4.0, menthyl HCO), 3.75 (6 H, s), 3.83 (3 H, s), 3.90 (1 H, d, *J* 10.5, 4-H), 4.58 (1 H, d, *J* 4.5, 1-H), 5.51 (1 H, d, *J* 7.5, 11-H), 5.95 and 5.96 (2 H, strong inner lines of OCH_2O AB-system), 6.48 (2 H, s, 2′,6′-H), 6.54 (1 H, s, 8-H) and 6.76 (1 H, s, 5-H); *m*/*z* 597, 596 (M), 414, 339, 313, 312, 83, 69, 55 and 41 (41.9, 100.0, 34.6, 56.7, 40.4, 34.1, 89.7, 52.5, 71.5 and 34.4%); $[\alpha]_D^{22}$ −140.8 (*c* 0.90 in $CHCl_3$).

Continued elution of the column with the same solvent mixture gave the C-1, C-2 invertomer of the *carboxylic acid* **10** (52 mg, 10.4%), mp 210–212 °C (from CH_2Cl_2–light petroleum) (Found: C, 66.45; H, 6.55%); $\nu_{max}(CH_2Cl_2$ film)/cm^{-1} 3000 and 1735; λ_{max}(EtOH)/nm 284 (3.46); δ_H(300 MHz, $CDCl_3$) 0.72–2.14 (18 H, m, menthyl-H), 3.45 (2 H, m, 3-H and menthyl HCO), 3.63 (1 H, dd, *J* 8.3 and 3.5, 2-H), 3.83 (6 H, s, 3′,5′-OMe), 3.88 (3 H, s), 3.83–3.88 (1 H, d, 4-H obscured), 4.33 (1 H, d, *J* 3.5, 1-H), 5.30 (1 H, s, 11-H), 5.92 and 5.94 (2 H, apparent singlets, OCH_2O), 6.50 (1 H, s, 8-H) and 6.80 (3 H, s, 5-H and 2′,6′-H); *m*/*z* 597, 596 (M), 441, 440, 339, 197, 83, 69, 55 and 43 (39.5, 100.0, 27.7, 75.2, 27.0, 25.8, 53.8, 34.5, 48.5 and 26.1%); $[\alpha]_D^{22}$ −146.2 (*c* 1.867 in $CHCl_3$).

Unchanged starting material (45 mg, 9%) was recovered from the first eluted acid by crystallisation from CH_2Cl_2–EtOH in which its solubility is limited.

Reaction of the acid 10 with $Pb(OAc)_4$

The title acid (268 mg, 0.45 mmol) in acetic acid–thf (1:5; 20 cm^3) was degassed by boiling under reflux whilst argon was bubbled through the solution (15 min). Lead tetra-acetate (220 mg, 0.50 mmol) was added to the mixture which was then stirred at 20 °C (3 h). After dilution of the mixture with water (20 cm^3) the product was extracted into dichloromethane. The extract was washed with saturated aqueous sodium hydrogen

carbonate, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica with benzene–ether–acetic acid (93:5:2) as eluent gave starting material (26 mg, 9.7%) and the *acetate* **12** (221 mg, 80.5%), mp 155–156 °C (from methanol) (Found: C, 66.65; H, 6.85%; M^+, 610.2771. $C_{34}H_{42}O_{10}$ requires C, 66.9; H, 6.9%; M^+, 610.2778); ν_{max}(CH_2Cl_2 film)/cm^{-1} 1780 and 1735; λ_{max}(EtOH)/nm 285 (3.77); δ_H(300 MHz, $CDCl_3$), 0.7–2.18 (18 H, m, menthyl-H), 2.14 (s, 3 H, CH_3CO), 2.65 (1 H, ddd, *J* 14.4, 7.7 and 3.4, 3-H), 3.35 (1 H, dd, *J* 14.4 and 5.3, 2-H), 3.50 (1 H, dt, *J* 4 and 10.5, menthyl HCO), 3.76 (6 H, s), 3.83 (3 H, s), 4.65 (1 H, d, *J* 5.3, 1-H), 5.54 (1 H, d, *J* 7.7, 11-H), 5.96 and 5.99 (2 H, strong inner lines of OCH_2O AB-system), 6.27 (2 H, s, 2′,6′-H), 6.34 (1 H, d, *J* 3.4, 4-H), 6.52 (1 H, s, 8-H) and 6.98 (1 H, s, 5-H); *m/z* 611, 610 (M), 552, 548, 393, 367, 339, 83, 69 and 55 (37.3, 100.0, 71.3, 39.3, 28.3, 50.4, 70.1, 65.4, 46.8 and 80.9%); $[\alpha]_D^{22}$ −240.7 (*c* 0.85 in EtOH).

Hydrolysis of the acetate 12 to the lactols 13

The foregoing acetate (273 mg, 0.448 mmol) was dissolved in 1,4-dioxane (14 cm^3) and 0.6 mol dm^{-3} hydrochloric acid (4.7 cm^3) and the mixture heated at 41–43 °C (internal temperature) (51 h). After dilution of the mixture with water (20 cm^3) the product was isolated in dichloromethane in the usual way. The crude product (274 mg) was chromatographed on silica (65 g) in ether–benzene acetic acid (55:43:2) to give in order of elution: one isomer of the *lactol* **13** (4β-OH) (76.1 mg, 39.5%) (Found: M^+, 430.1256. $C_{22}H_{22}O_4$ requires M^+, 430.1264); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3420, 2840 and 1785–1705vbr; λ_{max}(EtOH)/nm 276 (3.70); δ_H(300 MHz, $CDCl_3$), 2.73 (1 H, m, 3-H), 3.48 (1 H, m, 2-H), 3.73 (6 H, s), 3.79 (3 H, s), 4.53 (1 H, d, *J* 3.7, 1-H), 5.03 (1 H, s, 4-H), 5.96 (2 H, apparent s, OCH_2O), 6.20 (2 H, s, 2′,6′-H), 6.47 (1 H, s, 8-H) and 6.84 (1 H, s, 5-H); *m/z* 430 (M), 412, 394, 367, 366, 312, 168, 149, 57 and 43 (1.0, 89.2, 46.4, 54.9, 70.9, 37.7, 47.3, 100.0, 45.7 and 42.5%); $[\alpha]_D^{22}$ −78.8 (*c* 1.92 in $CHCl_3$).

Continued elution of the column gave a second isomer of the *lactol* **13** (4α-OH) (61.8 mg, 32.1%) (Found: M^+, 430.1263. $C_{22}H_{22}O_9$ requires M^+, 430.1264); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3450, 2850 and 1800–1700vbr; λ_{max}(EtOH)/nm 276 (4.49); δ_H(300 MHz, $CDCl_3$) 2.71 (1 H, m, 3-H), 3.11 (1 H, dd, *J* 13.5 and 4.3, 2-H), 3.69 (6 H, s), 3.77 (3 H, s), 4.53 (1 H, d, *J* 4.3, 1-H) 4.95 (1 H, d, *J* 9.5, 4-H), 5.94 and 5.95 (2 H, two strong inner lines of OCH_2O AB-system), 6.33 (2 H, s, 2′,6′-H), 6.44 (1 H, s, 8-H) and 7.10 (1 H, s, 5-H); *m/z* 430 (M), 412, 367, 366, 299, 151, 149, 81, 43 and 41 (2.8, 70.4, 40.5, 54.1, 55.1, 82.4, 83.3, 100.0, 40.2 and 53.0%); $[\alpha]_D^{22}$ −30.3 (*c* 0.57 in $CHCl_3$).

The early eluate from the column gave the *aldehyde* **15** (13.9 mg, 7.5%) (Found: M^+, 412.1147. $C_{22}H_{20}O_8$ requires M^+, 412.1158); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3700–2900, 2820, 1725 and 1710; λ_{max}(EtOH)/nm 256 (4.62); δ_H(300 MHz, $CDCl_3$) 3.82 (6 H, s), 3.88 (3 H, s), 3.97 (1 H, d, *J* 7.3, 2-H), 4.42 (1 H, d, *J* 7.3, 1-H), 6.01 (3 H, m including OCH_2O), 6.53 (2 H, s, 2′,6′-H), 6.62 (1 H, s), 6.88 (1 H, s) and 9.61 (1 H, s, CHO); *m/z* 412 (M), 382, 368, 367, 366, 351, 324, 308, 168 and 153 (86.5, 42.1, 41.5, 93.1, 100.0, 47.9, 32.1, 35.3, 52.4 and 35.6%).

Methylation of the lactols 13 with diazomethane

To the chromatographically less polar lactol **13** (4β-OH) (35 mg) in ether (4.8 cm^3) and methanol (0.2 cm^3) cooled to 0–5 °C was added ethereal diazomethane to achieve a pale yellow colour. The excess of reagent was immediately destroyed by the addition of acetic acid (3 drops). The product was diluted with ether and washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica in ether–benzene–acetic acid (60:38:2) to give the *aldehydo ester* **17** (31 mg, 86%) (Found: M^+, 444.1429. $C_{23}H_{24}O_9$ requires M^+, 444.1420); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3450, 2860 and 1730; λ_{max}(EtOH)/nm 272 (4.00); δ_H(400 MHz, $CDCl_3$) 3.29 (1 H, ddd, *J* 12.5, 3.5 and 1.0, 3-H), 3.55 (3 H, s), 3.73 (6 H, s), 3.77 (1 H, dd, *J* 12.5 and 6.5, 2-H), 3.79 (3 H, s), 4.54 (1 H, d, *J* 6.5, 1-H), 5.27 (1 H, t, *J* 3.5, 4-H), 5.96 and 5.97 (2 H, strong inner lines of AB-system, OCH_2O), 6.05 (2 H, s, 2′,6′-H), 6.45 (1 H, s, 8-H), 6.85 (1 H, s, 5-H) and 9.85 (1 H, d, *J* 1, CHO); *m/z* 444 (M), 427, 426, 398, 395, 367, 366, 339, 313 and 312 (56.9, 70.0, 100.0, 43.9, 40.9, 64.8, 42.8, 55.2, 49.0 and 59.3%); $[\alpha]_D^{22}$ −160.9 (*c* 4.00 in $CHCl_3$).

In a similar way the more polar lactol **13** (4α-OH) from the preceding experiment (51 mg) gave after chromatography the *aldehydo ester* **16** (45 mg, 85%) (Found: M^+, 444.1415. $C_{23}H_{24}O_9$ requires M^+, 444.1420); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3470, 2860 and 1735; λ_{max}(EtOH)/nm 271 (4.16); δ_H(400 MHz, $CDCl_3$) 3.31 (1 H, ddd, *J* 12.5, 8 and 1, 3-H), 3.37 (1 H, dd, *J* 12.0 and 5.0, 2-H), 3.61 (3 H, s), 3.76 (6 H, s), 3.81 (3 H, s), 4.45 (1 H, d, *J* 5, 1-H), 4.96 (1 H, dd, *J* 8 and 3.5, 4-H), 5.94 (2 H, apparent s, OCH_2O), 6.22 (2 H, s, 2′,6′-H), 6.41 (1 H, s, 8-H), 7.05 (1 H, s, 5-H) and 9.99 (1 H, d, *J* 1, CHO); *m/z* 444 (M), 426, 368, 367, 366, 365, 339, 338, 252 and 217 (31.1, 39.0, 31.2, 100.0, 46.4, 51.5, 36.8, 34.3, 51.8 and 38.3%); $[\alpha]_D^{22}$ −62.8 (*c* 1.23 in $CHCl_3$).

(−)-Methyl podophyllate 18

The aldehyde **16** (38 mg, 0.0856 mmol) in dry distilled THF (2.0 cm^3) was cooled to −78 °C under argon and lithium triethylborohydride (1 mol dm^{-3} solution in THF; 0.193 cm^3, 2.2 mol equiv.) was added to it. The mixture was stirred at −78 °C for 1 h after which it was treated with saturated aqueous sodium hydrogen carbonate (10 drops) and allowed to reach 20 °C. The mixture was then diluted with water and extracted with ether and the extract dried ($MgSO_4$) and evaporated. The resulting boron complex (45 mg), silica gel (45 mg) and methanol (30 cm^3) were boiled and stirred under reflux for 10 min after which it was evaporated. The product was chromatographed on silica (18 g) in ethyl acetate–ether (85:15) to give methyl podophyllate (32 mg, 84%); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3460 and 1735; δ_H(300 MHz, $CDCl_3$) 2.46 (1 H, m, 3-H), 3.01 (1 H, dd, *J* 12 and 5.5, 2-H), 3.56 (3 H, s), 3.70 (1 H, partly obscured, 11-H), 3.76 (6 H, s), 3.80 (3 H, s), 4.06 (1 H, dd, *J* 10 and 3, 11-H), 4.31 (1 H, d, *J* 5.5, 1-H), 4.78 (1 H, d, *J* 8, 4-H), 5.92 (2 H, apparent s, OCH_2O), 6.22 (2 H, s, 2′,6′-H), 6.38 (1 H, s, 8-H) and 7.08 (1 H, s, 5-H); *m/z* 446 (M^+), 414, 398, 351, 340, 339, 338, 324, 308 and 252 (76.5, 24.0, 81.4, 49.2, 25.8, 100.0, 23.2, 33.0, 39.9 and 23.8%); $[\alpha]_D^{22}$ −186.1 (*c* 3.10 in $CHCl_3$) [lit.,[12] $[\alpha]_D^{20}$ −199.1 (*c* 0.725 in $CHCl_3$)]. The IR spectrum (CH_2Cl_2 film) and 300 MHz ^1H NMR spectrum were identical with those of a purified authentic sample of (±)-methyl podophyllate.

Methyl epipodophyllate 19

In a similar way to that described in the preceding experiment, reduction of the aldehyde **17** (9.0 mg) gave (−)-methyl epipodophyllate (7.5 mg, 83%), mp 182–183.5 °C (from CH_2Cl_2–diethyl ether) (Found: C, 61.75; H, 5.7. $C_{23}H_{26}O_9$ requires C, 61.9; H, 5.8%); ν_{max}(CH_2Cl_2 film)/cm^{-1} 3330 and 1725; δ_H(400 MHz, $CDCl_3$) 2.42 (1 H, m, 3-H), 3.57 (1 H, dd, *J* 12.5 and 6.0, 2-H), 3.58 (3 H, s), 3.73 (6 H, s), 3.80 (3 H, s), 3.97 (1 H, dd, *J* 11.0 and 5.5, 11-H), 4.04 (1 H, dd, *J* 11 and 3, 11-H), 4.46 (1 H, d, *J* 6, 1-H), 5.0 (1 H, d, *J* 3.5, 4-H), 5.93 and 5.95 (2 H, strong inner lines of AB-system, OCH_2O), 6.05 (2 H, s, 2′,6′-H), 6.42 (1 H, s, 8-H) and 6.82 (1 H, s, 5-H); *m/z* 446 (M), 428, 399, 398, 340, 339, 338, 324, 308 and 252 (7.7, 21.9, 31.2, 92.8, 33.9, 100.0, 28.6, 39.9, 50.0 and 33.7%); $[\alpha]_D^{22}$ −103.2 (*c* 0.52 in $CHCl_3$).

(−)-Podophyllotoxin 1

Methyl podophyllate (14.8 mg, 0.033 mmol) in dry THF (2.0 cm^3) was mixed with freshly fused zinc chloride (28 mg) and freshly ground 4 Å molecular sieves (75 mg) and the mixture boiled under reflux with stirring under argon (2.5 h). The mixture was treated with saturated brine (1 cm^3), stirred (5 min) and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$)

and evaporated under reduced pressure. The residue was chromatographed on silica (17 g) in benzene–ethyl acetate (3:2) to give (−)-podophyllotoxin (11.7 mg, 85%). The unrecrystallised chromatographed product showed $[\alpha]_D^{22}$ −122.4 (*c* 1.17 in $CHCl_3$) indicating an enantiomeric excess of 94%. The crystalline material from CH_2Cl_2–Et_2O had mp 159.5–160.5 °C (lit.,[2] mp 158–159.5 °C) and $[\alpha]_D^{24}$ −136.9 (*c* 0.529 in $CHCl_3$) and −102.1 (*c* 0.529 in EtOH) [lit.,[2] $[\alpha]_D^{28}$ −130 (*c* 1.0 in $CHCl_3$) and −104 (*c* 0.36 in EtOH)]. The IR spectrum (Nujol) and 400 MHz ^1H NMR spectra were identical with those of a purified authentic sample of (−)-podophyllotoxin obtained from Aldrich Chemical Company Limited.

Addition of the pyrone 2 to furan-2(5*H*)-one

The pyrone (120 mg, 0.34 mmol), acetonitrile (0.7 cm^3) and furan-2(5*H*)-one (0.7 cm^3) were added to a base-washed flask and stirred and heated (internal temp. 64–65 °C) for 8.5 h. The crude mixture was then chromatographed on silica (22 g), eluting initially with benzene–ether (17:3) and then benzene–ether (1:1) to give in order of elution the endo-*adduct* (102.4 mg, 68%), mp 177.5–180.0 °C (from dichloromethane–petroleum) (Found: C, 62.7; H, 4.4. $C_{23}H_{20}O_9$ requires C, 62.7; H, 4.6%); ν_{max}(Nujol)/cm^{-1} 1770 and 1755; λ_{max}(EtOH)/nm 282 (4.64); δ_H(300 MHz, C_6D_6) 2.39 (1 H, m, 3-H), 3.03 (1 H, dd, *J* 2.7 and 9.5, 11-H), 3.22 (1 H, d, *J* 2.2, 4-H), 3.35 (1 H, t, *J* 9.5, 11-H), 3.4–3.45 (1 H, m, 2-H signal obscured by a signal at 3.47), 3.47 (6 H, s, 3′,5′-OMe), 3.92 (3 H, s, 4′-OMe), 4.97 (1 H, s, OCH_2O), 5.16 (1 H, s, OCH_2O), 6.30 (1 H, s, 8-H), 6.59 (1 H, s, 5-H) and 7.30 (2 H, s, 2′,6′-H); δ_H(300 MHz, $CDCl_3$) 4.24 (1 H, d, *J* 10.0, 2-H); *m*/*z* 440 (M^+), 397, 396, 395, 394, 381, 379, 365, 319 and 168 (41.4, 24.9, 100.0, 22.9, 30.0, 19.5, 20.6, 21.4, 15.4 and 17.7%).

Continued elution of the column gave the exo-*adduct* (24.3 mg, 16%), mp 189.0–190.8 (from EtOH) (Found: C, 62.7; H, 4.4%); ν_{max}(Nujol)/cm^{-1} 1775; λ_{max}(EtOH)/nm 282 (3.34); δ_H(300 MHz) 3.28 (1 H, m, 3-H), 3.61 (1 H, d, *J* 10.5, 2-H), 3.89 (6 H, br s, 3′,5′-OMe), 3.94 (3 H, s, 4′-OMe), 4.00 (1 H, d, *J* 2.4, 4-H), 4.35 (1 H, dd, *J* 10.0 and 3.4, 11-H), 4.57 (1 H, t, *J* 10.0, 11′-H), 5.96 (1 H, s, OCH_2O), 5.99 (1 H, s, OCH_2O), 6.28 (1 H, s, 8-H), 6.62 (1 H, br s, ArH), 6.86 (1 H, s, 5-H) and 6.92 (1 H, br s, ArH); *m*/*z* 440 (M^+), 397, 396, 394, 381, 365, 356, 338, 323 and 44 (8.7, 29.6, 100.0, 16.4, 19.1, 14.1, 19.6, 22.1, 17.0 and 19.2%).

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