Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 5, pp. 909-920, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)E0120-Y

An Asymmetric Synthesis of Isopodophyllotoxin

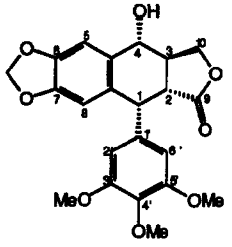
Andrew Pelter*, Robert S Ward*, Li Qianrong and Jaroslav Pis.

Chemistry Department, University of Wales, Swansea, Singleton Park, Swansea SA2 8PP UK

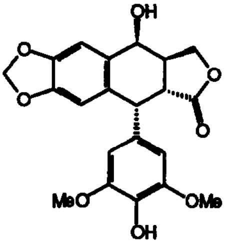
Abstract:

(-)-Isopodophyllotoxin has been synthesised by a route involving an asymmetric Diels Alder reaction between (5*R*)-menthyloxy-2(5*H*)-furanone and an arylisobenzofuran. Raney nickel reduction of the major adduct affords 10-menthyloxyisopicropodophyllin which is converted into (-)-isopodophyllotoxin.

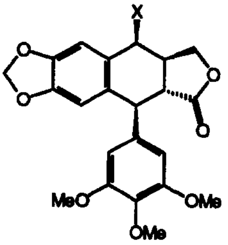
There is considerable interest in the synthesis of podophyllotoxin (1)[1] and related compounds[2,3] due to the useful biological activity associated with some of its derivatives[4,5]. In particular, glycoside derivatives of 4′-demethyl-4-epipodophyllotoxin (2) have found use in cancer chemotherapy[6,7].



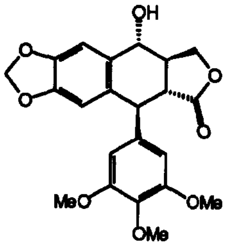
(1)



(2)

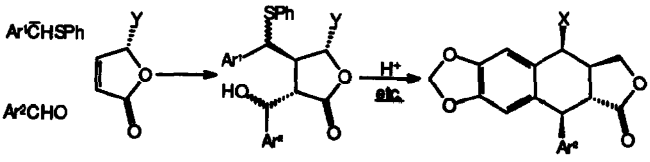


(3) X = OH
(4) X = H



(5)

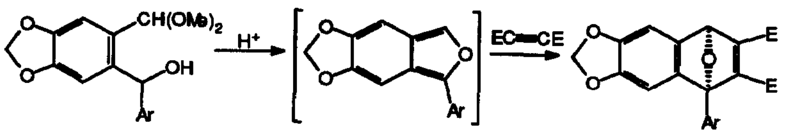
We have previously reported useful syntheses of racemic epiisopodophyllotoxin (3) and deoxyisopodophyllotoxin (4)[8], and have also reported asymmetric syntheses of deoxyisopodophyllotoxin (4) and a variety of other lignans including members of the dibenzocyclooctadiene series[9]. In addition to the tandem conjugate addition methodology employed in all of these syntheses we have now investigated the use of asymmetric Diels Alder reactions as an alternative approach to enantiomerically pure podophyllotoxin derivatives. The advantage of this approach compared with the tandem conjugate addition approach (Scheme 1) is that we anticipated that it might be possible to obtain the 1,2-*cis* stereochemistry present in (1) and (2).



Y = H or Omenthyl
X = H or OH
Ar² = 3,4,5-trimethoxyphenyl

Scheme 1

The major disadvantage of the tandem conjugate addition approach is that the 1,2-*trans* configuration present in isopodophyllotoxin (**5**) is obtained in the acid catalysed cyclisation step[1,8]. Our asymmetric Diels Alder strategy was based upon earlier work which had shown that the arylisobenzofuran (**6**) reacts with dimethyl butynedioate to give the adduct (**7**), which could then be converted in several steps to a variety of racemic podophyllotoxin stereoisomers. The arylisobenzofuran (**6**) was generated *in situ* by acid catalysed elimination from the hydroxyacetal (**8**) (eqn. 1)[10].

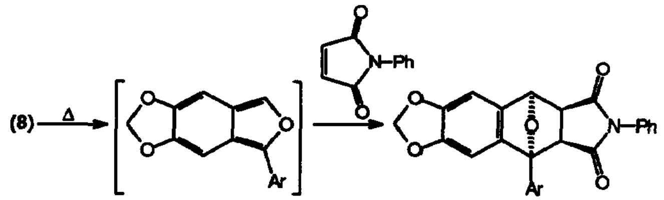


(eqn.1)

(**8**) (**6**) (**7**)

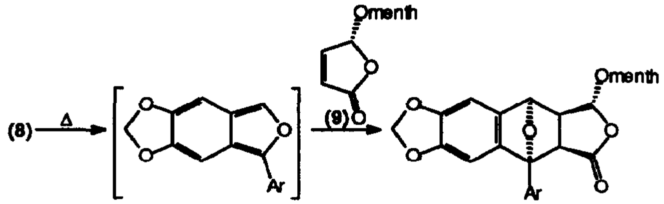
Ar = 3,4,5-trimethoxyphenyl
E = CO$_2$Me

The dienophile selected for our work was the (5*R*)-menthyloxy-2(5*H*)-furanone (**9**)[9,11] which can be readily prepared in homochiral form by reacting (-)-menthol with 5-hydroxy- or commercially available 5-methoxy-2(5*H*)-furanone. In order to avoid racemisation of (**9**), we needed to show that the arylisobenzofuran could be generated under non-acidic conditions, since we anticipated that the furanone (**9**) and also the Diels Alder adducts obtained would be highly sensitive to acid. We therefore demonstrated that hydroxyacetal (**8**) undergoes elimination of two molecules of methanol on thermolysis[12] and also that heating (**8**) in toluene in the presence of N-phenylmaleimide gave adduct (**10**) in 80% yield as a mixture of *endo* and *exo* isomers (eqn. 2).



(eqn. 2)

(**6**) (**10**) (major isomer)



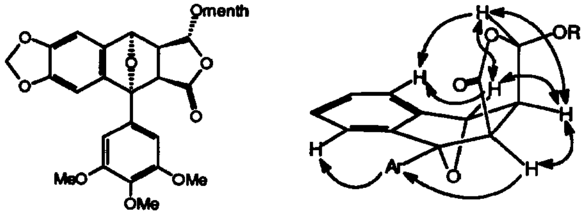
(eqn. 3)

(**6**) (**11**) (major isomer)

We had anticipated that the addition of (9) to (6) would give adducts with the lactone positioned as in podophyllotoxin as the major products. Treatment of hydroxyacetal (8)[10] with (9) in refluxing toluene gave a mixture of products from which the major product homochiral (11) could be readily isolated by crystallisation from methanol (eqn. 3). Four further adducts (12-15) could be isolated from the mother liquor by column chromatography. The structures of each of these compounds was established by a detailed analysis of their ^{1}H and ^{13}C n.m.r. spectra (Tables 1 and 2) and in particular by carrying out NOE experiments to determine the relative disposition of the hydrogen containing groups (Figure 1). It was clear that our expectations had been borne out, as there was a 61.4% yield of (11) - (13), with the lactone placed as in podophyllotoxin and only 13.3% of the reversed lactones (14) and (15), a ratio of 4.62:1.

11

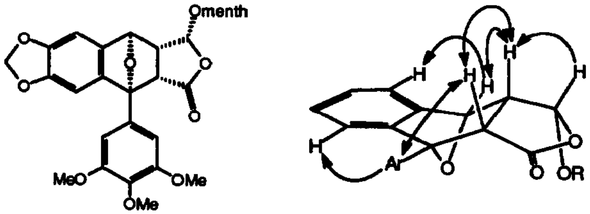
(37.5%)



$J_{3,10} = 1.03$ Hz
$J_{3,4} = 5.43$ Hz
$J_{2,3} = 9.22$ Hz

12

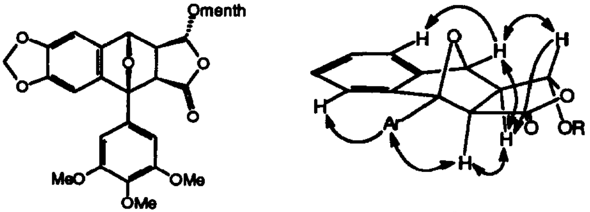
(5.1%)



$J_{3,10} = 6.75$ Hz
$J_{3,4} = 0$
$J_{2,3} = 7.79$ Hz

13

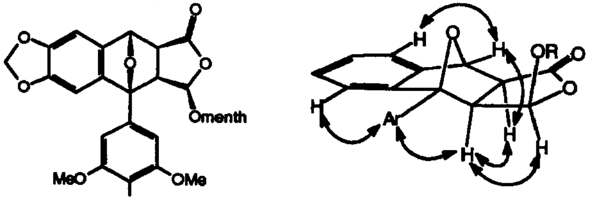
(18.8%)



$J_{3,10} = 1.87$ Hz
$J_{3,4} = 0$
$J_{2,3} = 7.41$ Hz

14

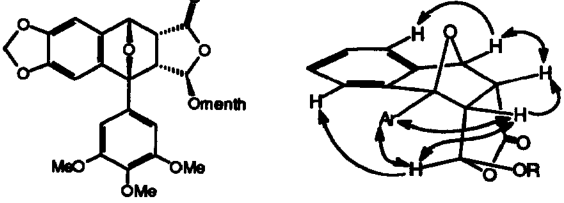
(8.5%)



$J_{2,9} = 1.85$ Hz
$J_{3,4} = 0$
$J_{2,3} = 7.60$ Hz

15

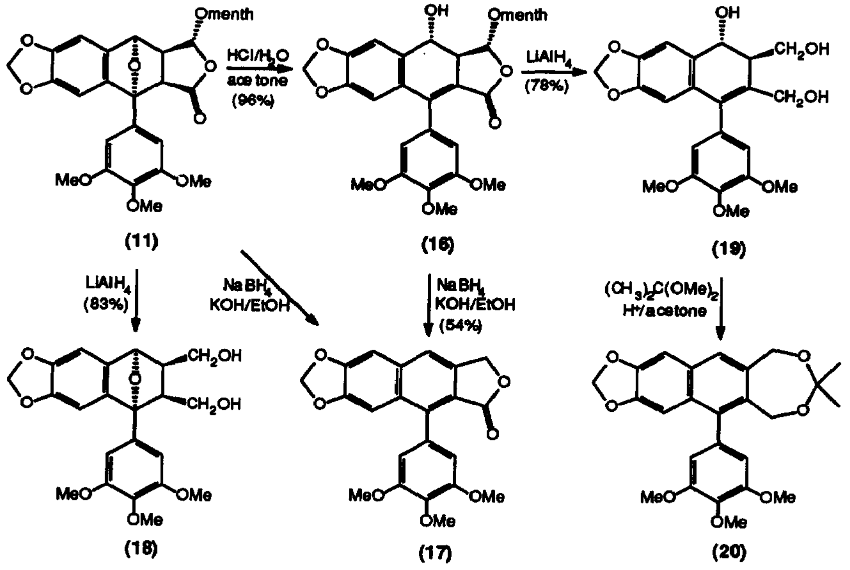
(4.8%)



$J_{2,9} = 1.18$ Hz
$J_{3,4} = 5.87$ Hz
$J_{2,3} = 9.29$ Hz

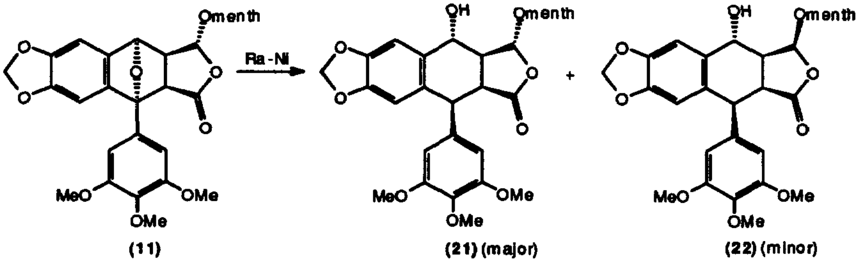
Figure 1

The major adduct (**11**) was readily available in pure crystalline form and we therefore decided to concentrate our efforts on this. Compound (**11**) readily underwent ring opening with aqueous acid to give an almost quantitative yield of the dehydropodophyllotoxin derivative (**16**) (Scheme 2). Hydrogenation of the double bond of (**16**) was anticipated to take us directly into the podophyllotoxin series. However hydrogenation of this compound could not be achieved under a wide variety of conditions. We therefore attempted to remove the menthyloxy substituent from both (**11**) and (**16**) using $NaBH_4/KOH$,[9,13] but only the arylnaphthalene (**17**) was obtained. Lithium aluminium hydride reduction of (**11**) gave the diol (**18**) while similar reduction of (**16**) gave (**19**). Protection of the latter compound with 2,2-dimethoxypropane in mild conditions favoured elimination to give the fully aromatic seven-membered ketal (**20**) (Scheme 2). Clearly there was a great tendency for the delicate hydroxydihydronaphthalene (**16**) to aromatise and we therefore reexamined (**11**) itself.

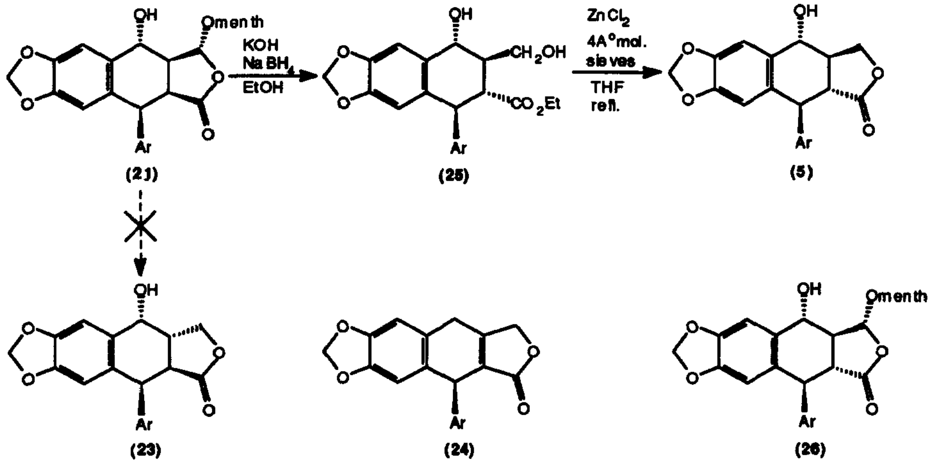


Scheme 2

Raney nickel reduction of (**11**) (Scheme 3) gave as the major product the required isopicropodophyllin derivative (**21**) along with a smaller amount of the C-10 epimer (**22**). The structures and stereochemistry of (**21**) and (**22**) were assigned on the basis of their ^1H and ^{13}C n.m.r. spectra, by comparison with the spectra of isopicropodophyllin[10] and on the basis of NOE experiments (Figure 2). At this point it was hoped that it would be possible to remove the menthyloxy group from (**21**) (and **22**) using the $NaBH_4/KOH$ procedure and at the same time induce epimerisation at C-3 leading directly to epipodophyllotoxin (**23**) (Scheme 4). However despite many variations in the reaction conditions this could not be achieved. Typically a mixture of products containing the fully aromatic product (**17**) and/or β-apopicropodophyllin (**24**) was obtained. The most useful transformation was achieved by carrying out the reaction in ethanol using either $NaBH_4$ alone or $NaBH_4/KOH$ which gave in addition to (**24**) the hydroxy ester (**25**) (Scheme 4). When $NaBH_4$ alone was used the C-2 epimer (**26**) of the starting material was also obtained showing that epimerisation at C-2 occurs very readily and prior to ring opening. Cyclisation of (**25**) using anhydrous $ZnCl_2$ and 4Å molecular sieves[14] gave (-)-isopodophyllotoxin (5). Thus under the conditions required to remove the menthyloxy substituent, epimerisation at C-2 is taking place leading to the all *trans* stereoisomer. Nevertheless the sequence described represents a short asymmetric synthesis of (-)-isopodophyllotoxin and may be amenable to further modification in due course.



Scheme 3



Scheme 4

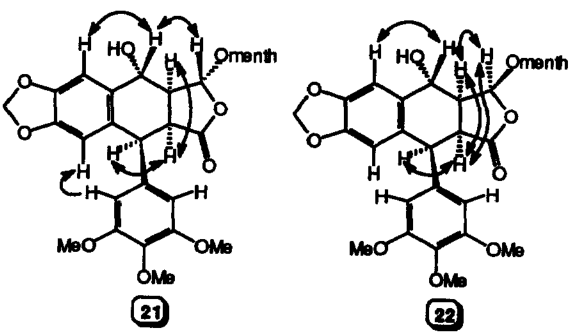


Figure 2

Table 1. ^{1}H n.m.r. spectra[a]

	10[b]	11	12[C]	13	14	15[c]	16	17
H - 1	-	-	-	-	-	-	-	-
H - 2	3.95d (8.28)	3.80d (9.22)	3.21d (7.87)	3.26d (7.41)	2.90dd (1.85, 7.60)	3.36dd (1.21, 9.28)	-	-
H - 3	4.12dd (5.70, 8.20)	3.48m	2.94dd (6.85, 7.72)	2.78dd (1.85, 7.41)	3.16d (7.60)	4.03dd (5.89, 9.30)	3.08dd (5.19, 14.36)	-
H - 4	5.83d (5.76)	5.53d (5.43)	5.85s	5.49s	5.66s	5.67d (5.86)	4.94d (14.55)	7.71s
H - 5	6.89s	6.89s	6.82s	6.83s	6.84s	6.88s	7.20s	7.21s
H - 8	6.54s	6.49s	6.67s	6.59s	6.52s	6.62s	6.48s	7.11s
9/10	-	4.94 d (1.03)	5.77d (6.75)	5.64d (1.89)	5.19d (1.86)	5.29d (1.16)	5.72d (5.23)	5.38s
	-	-	-	-	-	-	-	-
2′6′	7.22s	7.12s	6.77s	6.76s	6.69s	6.76s	6.50br.	6.55s
OCH_2O	(5.88d (1.13) (5.98d (1.13)	5.98d (1.43) 5.95d (1.43)	5.93s	5.93ABq (1.55)	5.93s	6.02ABq (0.95)	5.99d (1.31) 5.98d (1.31)	6.09s
OMe	(3.92s (3.90s	3.90s 3.88s	3.89s 3.88s	3.89s 3.86s	3.90s 3.88s	3.88s 3.77s	3.91s 3.83br.	3.97s 3.85s
Omenth[e]	-	3.34dt(4.22, 10.70)	3.36dt(4.17, 10.70)	3.55dt(4.21, 10.66)	3.35dt(4.25, 10.61)	3.36dt(4.25, 10.60)	3.68dt(4.13, 10.69)	-
OH	-	-	-	-	-	-	-	-

	18[c]	19	20[d]	21	22	24	25[f]	5	26
H - 1	-	-	-	4.62d(5.41)	4.63d(6.13)	4.82 (M)	4.15d(11.13)	4.05d(10.96)	4.11d(11.08)
H - 2	3.26m	-	-	3.47dd(10.32, 5.45)	3.25dd(12.17, 6.12)	-	2.81t(11.51)	2.64dd(14.11, 10.96)	2.75dd(11.40, 14.00)
H - 3	2.81m	3.15m	-	2.79dt(10.29, 4.78)	2.92ddd(12.14, 8.05, 6.42)	-	2.20m	2.51m	2.40m
H - 4	5.28d(4.0)	5.0br	7.37s	4.87d(4.84)	5.34d(7.92)	3.75	4.90d(9.14)	4.88d(10.15)	5.00d(10.60)
H - 5	6.92s	6.41s	7.02s	7.07s	7.72s	6.72s	7.08s	7.12s	7.12s
H - 8	6.59s	6.32s	6.66s	6.63s	6.72s	6.63s	6.16s	6.32s	6.36s
9/10	4.22t (5.35)	3.6-4.1m	4.73s	5.15d(4.47)	5.66d(6.42)	4.84m	3.7-4.0m	4.66dd(8.95, 6.65)	5.70d(4.64)
	4.15dd (4.12, 6.19)		4.99s	-	-	-	-	4.14dd(8.95, 10.45)	-
2′6′	6.94s	6.79s	6.43s	6.50s	6.29s	6.37s	6.30s	6.37s	6.28s
OCH_2O	5.92s	5.86br.s	5.95s	5.96d (1.37) 5.97d(1.37)	6.00d(1.39) 5.99d(1.39)	5.96ABq(1.32)	5.90s	5.92ABq(1.30)	5.92s
OMe	3.84s 3.77s	3.81s 3.87s	3.81s 3.95s	3.77s 3.83s	3.71s 3.82s	3.79s 3.78s	3.83s 3.80s.	3.84s 3.81s	3.84s 3.80s
Omenth[e]	-	-	-	3.45dt(4.23, 10.67)	3.30dt(4.08, 9.20)	-	-	-	
OH	-	5.0br.	-				4.8br		

[a] solvent $CDCl_3$ unless otherwise indicated.

[b] major isomer only listed. Solvent d_6-DMSO. NPh not included.

[c] solvent d_6-acetone.[d] Me_2C at 1.49s.

[e] H-1″only listed.

[f] OEt 4.01q (6.08), 1.04t (7.15).

Table 2. ^{13}C n.m.r. spectra[a]

	10[b]	11	12[c]	13	14	15[c]	16	17	18[c]	19	20[e]	21	22	24	25[f]	26	5
C - 1	91.29	92.07	92.84	92.90	92.40	92.78	149.74	130.36	91.87	146.72	128.83	46.62	45.93	42.74	46.48	46.48	47.79
C - 2	50.47	51.40	50.91	51.76	52.49	51.56	119.19	118.71	47.52	127.71	128.98	44.37	45.17	157.28	50.50	46.04	47.02
C- 3	52.56	52.99	53.23	53.91	53.31	54.11	49.93	130.42	48.05	46.56	132.06	51.96	49.31	128.13	49.61	51.33	46.26
C - 4	78.26	78.81	79.59	81.49	81.69	79.94	71.95	119.19	80.34	68.58	123.86	77.87	82.16	77.23	71.41	78.41	71.92
C - 5	102.08	102.01	102.28	101.59	101.71	103.43	101.98	103.70	103.35	106.30	102.60	104.42	104.19	107.75	106.07	104.56	105.32
C - 8	102.72	103.26	102.84	101.86	102.07	103.66	104.78	103.77	103.60	107.21	103.25	106.42	104.98	109.54	106.20	105.38	106.52
C - 6	147.04	147.62	147.36	147.12		148.27	147.06	148.74	147.33	147.65	147.30	147.59	146.89	147.03	146.96	146.05	147.18
C - 7	147.04	147.68	147.68	147.20	147.18	148.33	147.15	150.03		152.94	147.59	147.18	152.82	147.24	146.77	146.43	147.60
C - 4a	137.93	138.83	142.57	141.15	140.65	139.30	128.89	134.65	134.04	133.27	134.39	133.63	134.45	129.62	138.47	135.96	138.17
C - 8a	131.43	132.21	131.42	129.07	130.27	133.63	129.18	137.77	138.80	130.42	134.72	137.03	136.71	138.28	131.19	131.14	132.79
C- 1′	134.87	134.21	140.14	137.27	137.51	137.07	135.91	139.86	139.15	136.83	136.21	131.48	130.39	136.00	131.89	131.84	133.09
C - 2′/6′	103.67	103.57	104.66	103.54	102.95	104.60	109.72	107.24	106.28	107.69	106.48	106.69	106.27	105.54	108.35	108.22	109.48
C – 3′/5′	137.17	137.68	138.39	137.65	137.74	139.42	138.35	140.42	140.33	136.92	136.97	131.56	134.06	123.74	136.92	137.20	137.12
C - 4′	152.84	153.33	154.01	153.15	153.71	154.60	152.62	153.00	154.07	153.36	153.42	153.06	153.06	153.21	153.18	152.14	153.22
C - 9	172.99	173.71	171.21	171.79		101.05	165.04	169.73	60.64	61.16	63.13	175.20	176.62	172.21	173.21	170.60	174.66
C - 10	173.78	99.16	98.34		174.79	173.53		68.07	60.87	61.85	65.09	108.71	108.92	71.00	60.63	101.64	70.20
OCH_2O	101.60-	101.69-	102.28-		101.58-	102.63-	101.73	101.92	102.14	101.24	101.01	101.28	101.22	101.32	100.97	100.30	101.30
OMe	55.67	56.14	56.35	56.17	56.20	56.65	56.19	56.17	56.46	56.20	56.05	56.16	55.96	56.16	56.12	55.12	56.21
	59.91	60.84	60.49	60.86	60.93	60.67	60.96	61.08	60.52	60.90	60.96	60.87	60.87	60.79	60.83	59.83	60.86
Omenth[d]	-	76.79	78.34	76.90	77.72	77.37	78.28	-	-	-	-	-	69.43	65.28	-	-	69.65

[a] solvent $CDCl_3$ unless otherwise indicated.

[b] Major isomer only listed. Solvent d_6-DMSO. NPh not included

[c] solvent d_6-acetone. [d] *C-1″ only listed.*

[e] Me_2C 23.79 and 102.10.

[f] OEt 63.59 and 140.04

EXPERIMENTAL

IR spectra were recorded on a Pye Unicam SP1050 spectrometer. UV spectra were recorded on a Phillips PU8720 scanning spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 WM spectrometer at 250 MHz and 62.5 MHz respectively. All spectra used tetramethylsilane as the internal standard and were run in deuteriated chloroform unless otherwise indicated. Mass spectra were recorded on a VG-12-250 low resolution quadrupole spectrometer whilst accurate mass measurements were obtained on a ZAB-E high resolution double focusing instrument. M.p.s. were recorded on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotation values were obtained on a Perkin Elmer 141 polarimeter using a sodium lamp at 589nm and values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

Analytical HPLC was carried out using an LDC 3100 Spectromonitor, 3000 Constametric pump, CI-4100 integrator, and an Apex ODS II 5μ column. Thin layer chromatography was carried out on Merck 5735 Kieselgel 60F$_{254}$ fluorescent plates. Flash chromatography was performed with silica gel (Merck 9385, Kieselgel 60, 230-400 mesh). Small scale purifications were conducted on a Chromatotron 7924 using 1, 2 or 4 mm plates prepared from silica gel (Merck 7749, Kieselgel 50 F$_{254}$ gipshaltig).

Reactions carried out under an inert atmosphere were conducted using argon and 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran was dried by stirring overnight over calcium hydride, passing down a dry alumina column and distillation from sodium wire and benzophenone. Diethyl ether and dichloromethane were dried by passage down a dry alumina column and then distillation from calcium hydride. Dry toluene was prepared by distillation from calcium hydride and stored over sodium wire. Lithium aluminium hydride was used as a solid or as a solution in dry tetrahydrofuran, estimated as described by Brown.[14]

Diels Alder reaction of arylisobenzofuran (6) with N-phenylmaleimide. - The hydroxyacetal (**8**)[10] (262mg, 0.667 mmol) and N-phenylmaleimide (150mg, 0.868 mmol) were dissolved in toluene (50ml) and heated under reflux so that the condensing toluene passed through a Soxhlet thimble containing $LiAlH_4$ (2g). After 9 hr all of the starting material had reacted as indicated by t.l.c.. The toluene was removed by distillation *in vacuo* to give a yellow oil which was triturated with ether and the solid recrystallised from diethyl ether to give the pure product (**10**) (273mg, 81%) as white crystals m.p. 129-136°C, 196-210°C. See Tables 1 and 2 for ^{1}H and ^{13}C NMR spectra. ν_{max} (KBr) 1712, 1591cm^{-1}. *m/z* (EI) 328 (100), 313 (35), 173 (20%). *m/z* (CI) 502 (M+1, 10), 329(100), 314 (15), 313 (15), 173 (20%). Found: M+H, 502.1510. $C_{28}H_{24}NO_8$ requires 502.1502.

Diels Alder reaction of arylisobenzofuran (6) with 5-menthyloxy-2(5H)-furanone (9). - The hydroxyacetal (**8**)[10] (5.08g, 12.95mmol) and the furanone (**9**)[9,11] (4.63g, 19.4mmol) were dissolved in toluene (700ml) and heated under reflux using a Soxhlet extractor charged with $LiAlH_4$ (1g). After 9 hr the solvent was removed by distillation *in vacuo* and the resulting yellow oil (11.0g) was crystallised from methanol to give (**11**) as white crystals (2.75g, 37.5%), m.p. 213-4°C. The mother liquor was evaporated *in vacuo* to give a yellow oil (5.54g) which was separated by repeated column chromatography on silica eluting with diethyl ether-petroleum ether (1:2) followed by crystallisation from methanol to give (**12**)-(**15**). See Tables 1 and 2 for ^{1}H and ^{13}C NMR data.

Compound (**11**): yield 2.75g, 37.5% m.p. 213-4°C. ν_{max} ($CHCl_3$) 1750 (C=O), 2960, 1580 cm^{-1}. *m/z* (EI) 328 (100), 313 (51), 285 (7%). *m/z* (CI) 567 (M+1, 8), 329 (100%). Found: M+H, 567.2590. $C_{32}H_{39}O_9$ requires 567.2594.

Compound (**12**): yield 0.37g, 5.1% amorphous solid. ν_{max} ($CHCl_3$) 1750 (C=O), 2940, 1580 cm^{-1}. *m/z* (EI) 567 (M+1, 3), 328 (100), 313 (33%). *m/z* (CI) 567 (M+1, 48), 329 (100%). Found: M+H, 567.2590. $C_{32}H_{39}O_9$ requires 567.2594.

Compound (**13**): yield 1.38g, 18.8% amorphous solid. ν_{max} ($CHCl_3$) 1750 (C=O), 2960, 1580 cm^{-1}· *m/z* (EI) 567 (M+1, 1), 328 (100), 313 (61%). *m/z* (CI) 567 (M+1, 18), 329 (100), 313 (18%). Found: M+H, 567.2590. $C_{32}H_{39}O_9$ requires 567.2594.

Compound (**14**): yield 0.62g, 8.5% m.p. 148-150°C. ν_{max} ($CHCl_3$) 1750 (C=O), 2950, 1580 cm^{-1}. *m/z* (EI) 567 (M+1, 3), 522 (3), 411 (2), 384 (4), 328 (100), 313 (28%). *m/z* (CI) 567 (M+1, 48), 385 (14), 329 (100), 314 (20%). Found: M+H, 567.2590. $C_{32}H_{39}O_9$ requires 567.2594.

Compound (**15**): yield 0.35g, 4.8% m.p. 201-203°C. ν_{max} ($CHCl_3$) 1750 (C=O), 2940, 1580 cm^{-1}. *m/z* (EI) 393 (10), 328 (100), 313 (60%). *m/z* (CI) 567 (M+1, 10), 411 (2), 355 (10), 329 (100), 313 (8%). Found: M+H, 567.2590. $C_{32}H_{39}O_9$ requires 567.2594.

Acid catalysed ring opening of (11) to give (16). The Diels Alder adduct (**11**) (50mg, 0.088 mmol) was dissolved in acetone (5ml) and dilute aqueous HCl (0.2ml, 1N, 0.2 mmol) was added. After 3 hr the product started to crystallise out and after 5.5 hr the reaction was complete (HPLC). The solvent was removed by distillation *in vacuo* and the residue dissolved in chloroform (30ml) and washed with water (3 x 0.5ml). The chloroform solution was dried over anhyd. $MgSO_4$, filtered and evaporated and the residue was crystallised from acetone to give (**16**) (48mg, 96%). m.p. 238-241°C. ν_{max} ($CHCl_3$) 3560, 3400 (O-H), 1780 (C=O) cm^{-1}. *m/z* (EI) 566 (M+1, 23), 548 (60), 393 (27), 365 (100%). *m/z* (CI) 567 (M+1, 100). 549 (57), 429 (26), 411 (87), 393 (41), 365 (35%). Found: M$^+$, 566.2516. $C_{32}H_{38}O_9$ requires 566.2516. See Tables 1 and 2 for ^{1}H and ^{13}C NMR data.

$NaBH_4$ reduction of (16).- Compound (**16**) (65mg, 0.115mmol) was dissolved in THF (4ml) and ethanol (3ml) and $NaBH_4$ (31mg, 0.81mmol) was added. A solution of KOH in ethanol (0.5ml, 0.4M, 0.2mmol) was then added and the reaction mixture was stirred for 3hr. The reaction mixture was then acidified by 1M HCl to pH 4 and extracted with chloroform (3 x 15ml). The combined chloroform extracts were dried over anhyd.$MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was dissolved in chloroform and left to stand overnight (no change by HPLC) and the chloroform again evaporated. The residue was treated with ethanol (0.2ml) and THF (0.2ml) to give (**17**) (25.6mg, 54%) m.p. 277-9°C. υ_{max} ($CHCl_3$) 2980, 1750 (C=O), 1560cm^{-1}. For ^{1}H and ^{13}C NMR data see Tables 1 and 2. *m/z* (EI) 394 (M$^+$, 100) 379 (400), 351 (12%). *m/z* (CI) 412 (M+ NH_4, 13), 395 (M + H, 100), 379 (8), 351 (5%). Found: M$^+$, 394.1053. $C_{22}H_{18}O_7$ requires 394.1052)

$NaBH_4$ reduction of (11).- Compound (**11**) (208mg, 0.368mmol) was dissolved in THF (5ml) and cooled to -10°C. A solution of $NaBH_4$ in DMF (0.68ml, 1M, 0.68mmol) was added followed by a solution of KOH in ethanol (0.97ml, 0.4M, 0.388mmol), which was added over a period of 5hr. After 6.5hr no starting material was left (HPLC), the reaction mixture was allowed to warm up to room temperature and aqueous HCl (1.4ml, 1N) was added. The mixture was partitioned between chloroform (50ml) and water (8ml). The water layer was extracted with chloroform (2 x 50ml) and the combined chloroform extracts were dried over anhyd. $MgSO_4$. The volume was reduced to 1ml and left overnight (no change by HPLC). Column chromatography of the residue silica gel and elution with ether afforded compound (**17**) (34.5mg) along with menthol (52.6mg) and a third product (27.6mg) which was not identified. (**17**) was identical to the compound prepared above. Eluting the column with methanol gave a mixture of the 3 products (74.8mg).

$LiAlH_4$ reduction of (11).- Compound (**11**) (101mg, 0.178mmol) was dissolved in THF (2ml) and added to a solution of $LiAlH_4$ (7.6mg, 0.2 mmol) in THF (3ml) at room temperature. The reaction mixture was stirred for 4hr. Aqueous NaOH (15ml, 4%) was added and the mixture stirred for 1hr when it was filtered. The filtrate was evaporated *in vacuo* to give a colourless oil (82.2mg). Column chromatography on silica gel and elution with chloroform gave menthol (20mg) and with chloroform-methanol (9:1) gave the product (61.8mg, 83%) which was recrystallised from ether to give (**18**), m.p. 138-146°C. See Tables 1 and 2 for ^{1}H

and ^{13}C NMR spectra. υ_{max} ($CHCl_3$) 3600, 3400, 3000, 2900, 1580cm^{-1}. *m/z* (EI) 416(M$^+$, 27), 398 (8), 345(20), 328(100), 313(32), 177(48%). *m/z* (CI) 417(M + 1, 100), 399(10), 381(15), 329(15%). Found: M$^+$, 416.1471. $C_{22}H_{24}O_8$ requires 416.1471.

LiAlH$_4$ reduction of (16). - Compound (**16**) (104mg, 0.184mmol) in THF (2ml) was added to a stirred solution of $LiAlH_4$ (10.2mg, 0.269mmol) in THF (1ml) at room temperature. The reaction mixture was stirred for 4hr. Aqueous NaOH (11ml, 4%) was added and the mixture stirred for 1hr and then filtered. The filtrate was evaporated to give a yellow oil (80.6mg) which was purified by column chromatography on silica gel. Elution with chloroform-methanol (9:1) gave (**19**) as an unstable amorphous solid (60.2mg, 78%). See Tables 1 and 2 for ^1H and ^{13}C NMR data. *m/z* (EI) 398 (M-H_2O, 100), 380 (M-2H_2O, 35), 368 (40%). *m/z* (CI) 416 (M$^+$, 2) 398 (10), 381 (100), 351 (50%). Found: M-H_2O, 398.1365. $C_{22}H_{22}O_7$ requires 398.1365.

Attempted ketal formation from (19). - Compound (**19**) (79mg, 0.189mmol) was dissolved in acetone (5ml) and 2,2-dimethoxypropane (1ml) and p-toluenesulphonic acid (1mg) were added. The reaction mixture was stirred at room temperature for 1hr. Addition of anhyd. K_2CO_3 followed by filtration and removal of the solvent gave the crude product which was crystallised from ether-petroleum ether to give (**20**) (54mg, 63%) m.p. 218-226°C. υ_{max} ($CHCl_3$) 2990, 2920, 1570 cm^{-1}. For ^1H and ^{13}C NMR data see Tables 1 and 2. *m/z* (EI) 438 (M$^+$, 100), 380 (85), 337 (65%). *m/z* (CI) 438 (M$^+$, 2), 381 (100%). Found: M$^+$, 438.1679. $C_{25}H_{26}O_7$ requires 438.1678.

Preparation of 10-menthyloxyisopicropodophyllin (21) and (22): Diels Alder adduct (**12**) (1.5g, 2.65mmol) was dissolved in dry ethyl acetate (250ml) and freshly prepared W-2 Raney nickel (7g) was added. The mixture was hydrogenated using a Parr 3911 hydrogenator under 60psi hydrogen pressure at room temperature for 15hr. The catalyst was filtered and the solvent removed *in vacuo* to give an amorphous white solid (1.53g). Purification by repeated chromatography on silica using a Chromatotron (eluent $CHCl_3$-MeOH, 98:2, 92:8, 90:10) gave the stereoisomers (**21**) and (**22**) (total yield 1.24g, 82%). See Tables 1 and 2 for ^1H and ^{13}C NMR data.

Compound (**21**): yield of pure isomer 708mg, 47%, white solid. υ_{max} (KBr) 3460cm^{-1}. *m/z* (EI) 568(M$^+$, 20), 550(M-H_2O, 100), 412 (100%). *m/z* (CI) 586(M+NH_4, 7), 568(M$^+$, 30), 551(40), 413(100%). Found: M$^+$, 568.2670. $C_{32}H_{40}O_9$ requires 568.2672.

Compound (**22**): yield of pure isomer 53mg, 3.5%, white solid. υ_{max} (KBr) 3450cm^{-1}. *m/z* (EI) 568(M$^+$, 15), 550(M-H_2O, 5), 412(100%). *m/z* (CI) 586(M+NH_4, 10), 569(M+1, 20), 413(100%). Found: M$^+$, 568.2671. $C_{32}H_{40}O_9$ requires 568.2672.

NaBH$_4$ reduction of (21).- Compound (**21**) (0.20g, 0.35mmol) was dissolved in dry ethanol (5ml) under argon and the solution cooled to 0°C. A solution of KOH in ethanol (0.88ml, 0.60M, 0.53mmol) was then added with stirring over 15min. followed by $NaBH_4$ (0.053g, 1.4mmol) and the stirring continued for another 2$^1/_2$hr. at 0°C. The reaction was then quenched by the addition of aqueous 5% HCl until pH3. An equal volume of water was then added and the mixture extracted with CH_2Cl_2 (3 x 10ml). The organic extracts were combined and allowed to stand overnight before being washed with water (3 x 10ml), dried ($MgSO_4$), filtered and evaporated to give a transparent green oil (150mg) which was dissolved in methanol and allowed to crystallise yielding a yellow product (**24**) (28mg, 20%). The mother liquor was evaporated and purified by chromatography or silica using a chromatotron, eluent CH_2Cl_2-ethyl acetate, to give a white powder (**25**) (59mg, 41%).

Compound (**24**): $[\alpha]^{22}_{D}$ - 97.6(c = 0.540, $CHCl_3$), lit.[15]+92 (C 0.85, $CHCl_3$); See Tables 1 and 2 for ^1H and ^{13}C NMR spectra. *m/z* (EI) 396(M$^+$, 65), 351(10), 337(10), 321(10), 229(15), 199(13), 185(22), 168(100),

153(80%). *m/z* (CI) 414 (M+18, 90), 397 (M+1, 23), 246(80), 229(100), 186(13), 169(40%). Found: M^+, 396.1209. $C_{22}H_{20}O_7$ requires 396.1209)
Compound (**25**): $[\alpha]_D^{22}$ 17.06(c = 0.85, $CHCl_3$); See Tables 1 and 2 for ^1H and ^{13}C NMR spectra. *m/z* (EI) 460(M^+, 7), 442(35), 425(63), 424(68), 351(100%). *m/z* (CI) 443(5), 425(100%). υ_{max} ($CHCl_3$) 3462(O-4), 1723(C=O)cm^{-1}. Found: M^+, 460.1730. $C_{24}H_{28}O_9$ requires 460.1733.

$NaBH_4$ reduction of (21).- Compound (**21**) (0.182g, 0.32mmol) was dissolved in dry ethanol (4ml) under argon and the solution cooled to 0°C. $NaBH_4$ (6mg, 0.16mmol) was added to the stirred solution and stirring was continued for 20hr at room temperature. The reaction was then quenched by addition of water (3ml) and the mixture extracted with CH_2Cl_2 (3 x 10ml). The organic extracts were combined, washed with water (3 x 10ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a colourless transparent oil (173mg) which was dissolved in methanol and allowed to crystallise. White crystals of (**26**) (80mg, 44%) were collected and the mother liquor evaporated and purified by chromatography on silica using a Chromatotron, eluent CH_2Cl_2-ethyl acetate, to give (**25**) (76mg, 52%), identical to the compound obtained in the previous experiment.

Compound (**26**): $[\alpha]_D^{22}$ - 119.0(c = 0.200, $CHCl_3$); See Tables 1 and 2 for ^1H and ^{13}C NMR data. *m/z* (EI) 568(M^+, 80), 413(15), 367(20), 339(35), 181(30%). *m/z* (CI) 568(M^+, 7), 431(10), 413(60), 313(100%). Found: M^+, 568.2670. $C_{32}H_{40}O_9$ requires 568.2672.

Preparation of (-)-isopodophyllotoxin (5).- Compound (**25**) (11mg, 0.024mmol) was dissolved in dry THF (4ml) and freshly ground 4Å molecular sieves (60mg) and zinc chloride (31mg, 0.142mmol) were added. The mixture was stirred under reflux under argon for 40min. More molecular sieves (50mg) were then added and the reflux continued for a further 6hr. The mixture was cooled and brine (15ml) added. Extraction with ethyl acetate (3 x 15ml) followed by removal of the solvent *in vacuo* gave a pale yellow residue (15mg) which was purified on silica using a chromatotron eluting with CH_2Cl_2-ethyl acetate, to give (-)-isopodophyllotoxin (**5**) (9mg, 91%) identified by comparison with the spectral data of the racemic compound. υ_{max} 1775 (C=O), 3433 (OH)cm^{-1}. $[\alpha]_D^{22}$ - 143(c 0.056, $CHCl_3$), lit.[15] - 187(C 0.70, pyridine); See Tables 1 and 2 for ^1H and ^{13}C NMR spectra. *m/z* (EI) 414(M^+, 100), 399 (14), 168 (10%). *m/z* (CI) 432(M+18, 100), 415(M+1, 65%). Found: M^+, 414.1314. $C_{22}H_{22}O_8$ requires 414.1315.

ACKNOWLEDGEMENTS

We are grateful to the Royal Society for a Fellowship to JP and to the British Council for a Fellowship to QL. We are also grateful to Dr. O. W. Howarth (SERC Highfield n.m.r. service University of Warwick) for providing 360 MHz ^1H n.m.r. spectra and carrying out NOE experiments.

REFERENCES

1. For a review of the synthesis of podophyllotoxin and its isomers see Ward, R. S. *Synthesis*, **1993**, 719.
2. Pelter, A.; Ward, R. S.; Li Qianrong, *J. Nat. Prod.*, **1993**, *56*, 2204.
3. *cf* Pelter, A. ; Ward, R. S.; Ma Weiyong, unpublished results.
4. Pelter, A. in "The Shikimic Acid Pathway" (ed. Conn, E. E.), Plenum Press, New York, **1986**, p.201.
5. Ayres, D. C.; Loike, J. D. "Lignans", Cambridge University Press, **1990**, Chapters 3 and 4.
6. Jardine, I. in "Anticancer Agents based on Natural Products"(ed. Cassady, M. M.; Douros, J. D. Academic Press, **1980**, Chapter 9.

7. Issell, B. F.; Rudolph, A. R.; Louie, A. C.; Doyle, T. W. in "Etoposide (VP-16) Current Status and New Developments" (ed. Issell, B. F.; Muggia, F. M.; Carter, S. K. Academic Press, **1984**, Chapters 1 and 2.
8. Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1603 and 1615.
9. Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. *ibid*, **1993**, 2621 and 2631.
10. Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.*, **1989**, *54*, 4280.
11. Feringa, B. L.; de Lange, B. *Tetrahedron*, **1988**, *44*, 7213.
12. Galletti, G. C.; Ward, R. S.; Pelter, A.; Goubet, D. *J. Anal. Appl. Pyrol*, **1992**, *24*, 139.
13. Speybroeck, R. V.; Guo, H.; Eycken, J. V. D.; Vandervalle, M. *Tetrahedron*, **1991**, *47*, 4675.
14. Brown, H. C. "Organic Syntheses via Boranes", 1975, Wiley, New York p.241
15. Aiyar, V. N.; Chang, F. C. *J. Org. Chem.*, **1977**, *42*, 246.

(*Received in UK* 23 *March* 1994)