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ARYLTETRALIN LIGNANS FROM *PODOPHYLLUM HEXANDRUM* AND *PODOPHYLLUM PELTATUM*

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Key Word Index—*Podophyllum hexandrum*; *P. peltatum*; Podophyllaceae; aryltetralin; lignans; podophyllotoxin.

Abstract—Roots of *Podophyllum hexandrum* and *P. peltatum* contain the same range of ten aryltetralin lignans: podophyllotoxin, 4′-demethylpodophyllotoxin, α-peltatin, β-peltatin, desoxypodophyllotoxin, podophyllotoxone, isopicropodophyllone, 4′-demethyldesoxypodophyllotoxin, 4′-demethylpodophyllotoxone and 4′-demethylisopicropodophyllone, although the relative proportions are markedly different. The latter two compounds are previously unreported natural products, but 4′-demethylisopicropodophyllone may well be an artefact resulting from epimerization of 4′-demethylpodophyllotoxone. The peltatins have not previously been isolated from *P. hexandrum*.

INTRODUCTION

The aryltetralin lignans of *Podophyllum* species have acquired considerable importance because of their cytotoxic and/or antitumour activity [1], and the successful conversion of the major lignan, podophyllotoxin (**1**), into the clinically-useful anticancer drugs etoposide and teniposide [2]. The biosynthetic origins of lignans in general, and the *Podophyllum* lignans in particular are essentially unknown despite long-standing speculations about their production [3]. Most hypotheses involve phenolic oxidative coupling of two phenylpropane units, and initial studies [4–6] offer some support for this. As a preliminary to a detailed study of the biosynthesis of the *Podophyllum* lignans, we report here a phytochemical examination of the lignans present in Indian *Podophyllum* (*Podophyllum hexandrum*)* and American *Podophyllum* (*P. peltatum*). Earlier work on these plants has established the presence of podophyllotoxin (**1**) [8, 9], 4′-demethylpodophyllotoxin (**2**) [10, 11], desoxypodophyllotoxin (**3**) [12, 13], podophyllotoxone (**7**) [13] and isopicropodophyllone (**9**) [13] in the roots of both species. α-Peltatin (**6**) [14], β-peltatin (**5**) [15] and dehydropodophyllotoxin (**11**) [16] have also been reported in *P. peltatum*, and glucosides of various lignans are present in both species [17]. The results reported here have been published briefly in abstract form [18].

RESULTS AND DISCUSSION

Ethanol extracts of powdered commercial *P. hexandrum* and *P. peltatum* root material were partitioned between ethyl acetate and water, and the non-glycosidic fraction was further purified by TLC (silica gel, $CHCl_3$–MeOH, 25:1). In each sample, eight clearly defined chromatographic zones were observed. These were eluted, purified further by TLC, and where possible, crystallized prior to characterization.

Zone 1 (R_f 0.9)

This zone contained a mixture of desoxypodophyllotoxin (**3**) and podophyllotoxone (**7**) as reported previously [13]. The two compounds could not be separated by TLC alone, but were satisfactorily resolved by gel filtration (Sephadex LH-20, EtOH) or by HPLC (Partisil-10 ODS2, MeOH–H_2O, 3:2) [13].

Zone 2 (R_f 0.8)

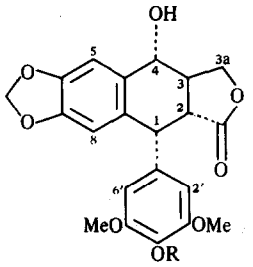
A minor band present in both species was identified as the 1α,2α,3α-isomer [13] of podophyllotoxone (**7**), i.e. isopicropodophyllone (**9**) [13]. Although this compound has been reported as a constituent of *P. pleianthum* [19], observations [13] that this isomer was formed by heating podophyllotoxone suggest it may be in artefact resulting from **7** by the drying and extraction procedures used. Isopicropodophyllone contains the less-strained *cis*-fused lactone ring as opposed to the severely-strained *trans*-fused system of podophyllotoxone, and this presumably accounts for the facile C-3 epimerization.

Zone 3 (R_f 0.7)

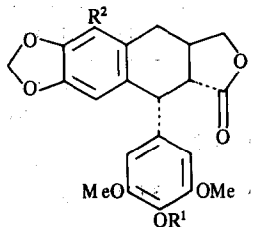
This minor zone possessed similar UV spectral characteristics to the desoxypodophyllotoxin–podophyllotoxone mixture comprising zone 1, i.e. main absorbances at 278 and 315 nm, and minor bands/shoulders at 290–300 nm, suggesting a mixture of 4-keto/methylene derivatives. Mass spectral analysis gave $[M]^+$ peaks at *m/z* 384 and 398, consistent with a mixture of demethyldesoxypodophyllotoxin and demethylpodophyllotoxone, most probably the 4′-demethyl derivatives. High resolution ^1H NMR spectroscopy of the mixture showed characteristic sets of signals for the alicyclic protons of these two series of compounds.

^1H NMR spectroscopy (250 MHz) is of particular value in the structural elucidation of the aryltetralin lactone lignans of *Podophyllum*. From observations of a range of natural and semisynthetic compounds, the chemical shifts and coupling constants relating to the alicyclic protons are

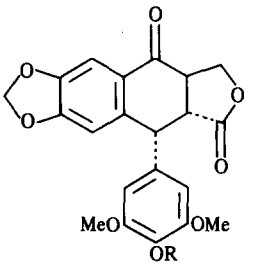
*P. *hexandrum* is now regarded as the preferred name rather than the more commonly used *P. emodi* [7].



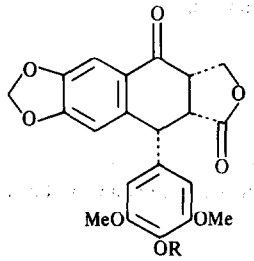
	R
1	Me
2	H



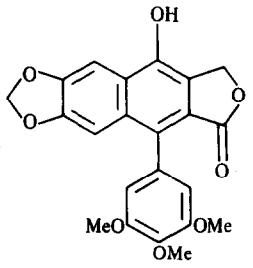
	R^1	R^2
3	Me	H
4	H	H
5	Me	OH
6	H	OH



	R
7	Me
8	H



	R
9	Me
10	H



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markedly dependent on substitution patterns and stereochemistry, such that easily recognisable sets of signals may be correlated with particular series of compounds. The signals are not fully interpretable in all cases, but are of very characteristic appearance (Table 1). The *Podophyllum* lignans fall into three main categories, the 4-desoxy series, e.g. desoxypodophyllotoxin (**3**) and the peltatins (**5** and **6**), the 4-hydroxy series, e.g. podophyllotoxin (**1**) and the 4-keto series, e.g. podophyllotoxone (**7**). With the exceptions of **9** and **10**, these all appear to have the same stereochemistry at C-1, C-2 and C-3 namely (1*R*,2*R*,3*R*) or (1α,2α,3β) [13], although absolute configurations could not be confirmed for the minor lignans because of lack of optical rotation data. Changes in stereochemistry, such as epimerization at C-2 to give the *picro*-series, or at C-3 in the 4-ketones giving the *isopicro*-compounds, are immediately reflected in the NMR spectrum, and further characteristic spectral patterns are produced. Substitution patterns in the aromatic rings may readily be assigned from the chemical shifts of the remaining signals (Table 2).

Confirmation of the presence of 4′-demethyldesoxypodophyllotoxin (**4**) and 4′-demethylpodophyllotoxone (**8**) was obtained by comparison with authentic synthetic material. 4′-Demethyldesoxypodophyllotoxin was prepared either by catalytic hydrogenation [20] of 4′-demethylpodophyllotoxin (**2**) or by acid-catalysed demethylation [21] of desoxypodophyllotoxin (**3**) using gaseous HBr. 4′-Demethylpodophyllotoxone was synthesized from **2** by manganese dioxide oxidation [22] of the benzyloxycarbonyl-protected [23] compound, followed by phase transfer catalytic hydrogenation to

Table 1. 250 MHz ^{1}H NMR data* for *Podophyllum* lignans: alicyclic protons

Lignan	H-4α	H-4β	H-1	H-3aα	H-3aβ	H-2	H-3
Podophyllotoxin (1)†	—	4.75 *d* *J* = 8.8	4.59 *m*	4.59 *m*	4.07 *t* *J* = 9.5	*ca* 2.9–2.7 *m*	
4′-Demethylpodophyllotoxin (2)‡	—	4.80 *d* *J* = 9.7	4.55 *m*	4.55 *m*	4.17 *dd* *J* = 10.4, 8.7	3.05 *dd* *J* = 14.2, 4.9	2.87 *m*
Desoxypodophyllotoxin (3)	3.10 *m*	2.76 *m*	4.61 *br s*	4.47 *dd* (*ca*) *J* = 8.5, 6.4	3.93 *dd* *J* = 10.1, 8.5	2.76 *m*	
4′-Demethyldesoxypodophyllotoxin (4)	3.07 *m*	2.76 *m*	4.60 *br s*	4.45 *dd* (*ca*) *J* = 8.5, 6.1	3.92 *dd* *J* = 10.1, 8.5	2.76 *m*	
β-Peltatin (5)	3.22 *m*	*ca* 2.50 *m*	4.61 *d* *J* = 3.7	4.48 *dd* (*ca*) *J* = 8.5, 6.4	3.96 *dd* *J* = 10.4, 8.5	*ca* 2.70 *m*	
α-Peltatin (6)	3.20 *m*	*ca* 2.50 *m*	4.60 *d* *J* = 3.7	4.48 *dd* (*ca*) *J* = 8.6, 6.2	3.95 *dd* *J* = 10.5, 8.6	*ca* 2.70 *m*	
Podophyllotoxone (7)	—	—	4.85 *d* *J* = 4.3	4.57 *dd* *J* = 9.2, 7.6	4.36 *dd* *J* = 10.4, 9.2	3.28 *dd* *J* = 15.6, 5.4	3.53 *ddd* *J* = 15.6, 10.4, 7.6
4′-Demethylpodophyllotoxone (8)	—	—	4.84 *d* *J* = 4.2	4.55 *dd* *J* = 9.1, 7.7	4.35 *dd* *J* = 10.3, 9.1	3.26 *dd* *J* = 15.5, 4.2	3.52 *ddd* *J* = 15.6, 10.3, 7.7
Isopicropodophyllone (9)	—	—	4.57 *d* *J* = 5.5	*ca* 4.53 *m*	*ca* 3.84 *m*	*ca* 3.7–3.5 *m*	
4′-Demethylisopicropodophyllone (10)	—	—	4.56 *d* *J* = 5.8	*ca* 4.50 *m*	*ca* 3.84 *m*	*ca* 3.7–3.5 *m*	

*Chemical shifts in ppm (δ) relative to internal standard TMS in $CDCl_3$ solution, except as indicated. Coupling constants (*J*) in Hz.
†$CDCl_3$–D_2O.
‡Acetone-d_6–D_2O.

Table 2. 250 MHz ^{1}NMR data* for *Podophyllum* lignans: aromatic and substituent protons

Lignan	H-5	H-8	H-2′, H-6′	OCH_2O	4′-OMe	3′,5′-OMe	OH
1	7.12	6.51	6.37	5.99 *d*, *J* = 1.2 5.97 *d*, *J* = 1.2	3.81	3.75	
2	7.18	6.49	6.43	5.99 *d*, *J* = 0.9 5.97 *d*, *J* = 0.9	—	3.72	
3	6.67	6.53	6.35	5.96 *d*, *J* = 1.2 5.94 *d*, *J* = 1.2	3.81	3.75	—
4	6.67	6.53	6.36	5.96 *d*, *J* = 1.5 5.93 *d*, *J* = 1.5	—	3.79	5.40
5	—	6.24	6.36	5.95 *d*, *J* = 1.5 5.94 *d*, *J* = 1.5	3.81	3.76	5.19
6	—	6.24	6.37	5.96 *d*, *J* = 1.4 5.94 *d*, *J* = 1.4	—	3.79	5.41 5.16
7	7.56	6.71	6.39	6.11 *d*, *J* = 1.2 6.09 *d*, *J* = 1.2	3.83	3.76	—
8	7.56	6.70	6.39	6.10 *d*, *J* = 1.2 6.08 *d*, *J* = 1.2	—	3.79	5.47
9	7.43	6.69	6.28	6.09 *d*, *J* = 1.2 6.07 *d*, *J* = 1.2	3.80	3.73	—
10	7.43	6.69	6.28	6.08 *d*, *J* = 1.2 6.07 *d*, *J* = 1.2	—	3.76	5.46

*See Table 1.

remove the protecting group. The analytical data for these compounds were in all ways identical to those observed in the zone 3 mixture, and a mixture of the compounds behaved identically to zone 3. In addition, analytical HPLC of zone 3 give two fractions with identical retention times as **4** and **8**.

4′-Demethyldesoxypodophyllotoxin-β-D-glucoside has been isolated previously from both *P. hexandrum* and *P. peltatum* [24], but this represents the first reported isolation of the free lignan from these species, although it

also occurs in *Polygala paenea* [25]. 4'-Demethylpodophyllotoxone has not been reported either naturally or synthetically.

Zone 4 (R_f 0.6)

The ready isomerization of podophyllotoxone (**7**) to isopicropodophyllone (**9**) suggested that 4'-demethylpodophyllotoxone (**8**) might behave similarly, and the corresponding 1α,2α,3α-isomer may be present in dried plant material. Zone 4 from both plant species was again a minor band, but indeed, had mass spectral ($[M]^+$ *m/z* 398) and ^{1}H NMR characteristics consistent with 4'-demethylisopicropodophyllone (**10**). All NMR signals were analogous to those for **9**, apart from loss of the 4'-methoxyl and appearance of a hydroxyl. Mild heating (60–70°) of synthetic **8** gave partial conversion to a compound chromatographically identical to **10**. Thus, although **10** is undoubtedly present in the dried root of *P. hexandrum* and *P. peltatum*, it could well be an artefact.

Zone 5 (R_f 0.5)

The major chromatographic band from *P. peltatum* was readily identified as the previously reported lignan β-peltatin (**5**) [15], differing from desoxypodophyllotoxin only in the presence of the additional 5-hydroxyl group. The corresponding zone in *P. hexandrum* is very weak, but comparison of UV, IR, ^{1}H NMR, mass spectral and TLC behaviour with the authentic material obtained from *P. peltatum* confirmed its structure. β-Peltatin has not been reported previously in *P. hexandrum*.

Zone 6 (R_f 0.3)

Again, this is a major zone in *P. peltatum* and material was confirmed to be the known α-peltatin (**6**) [14]. In *P. hexandrum*, a very weak zone is apparent, although this may sometimes be masked by the very large podophyllotoxin (**1**) (zone 7) band. Again, comparison of UV, IR, ^{1}H NMR, mass spectral and TLC data confirmed its identity as α-peltatin, which also has not been reported previously in *P. hexandrum*.

Zone 7 (R_f 0.25)

This zone is by far the major band in *P. hexandrum* and one of the three major ones in *P. peltatum*. Comparison with authentic material confirmed its identity as podophyllotoxin (**1**).

Zone 8 (R_f 0.2)

The second major zone in *P. hexandrum* was identified as 4'-demethylpodophyllotoxin (**2**) from literature data [10] and particularly by comparison with the spectral data for podophyllotoxin. In *P. peltatum* this zone is a minor one, but the presence of **2** was confirmed. Prior to this report, evidence for the existence of the free 4'-demethylpodophyllotoxin in *P. peltatum* has been indirect, although the glucoside is present [26]. The presence of **2** was assumed [11] following the isolation of diacetyl-4'-demethylpicropodophyllin via a technique involving the use of basic reagents (promoting C-2 epimerization) and acetic anhydride.

The compounds isolated, and their approximate content in the dried roots, are listed in Table 3. Of particular significance is the observation that all 10 lignans are present in both species, although the relative proportions are markedly different. The peltatins, previously regarded as being absent in *P. hexandrum*, are in fact present in small amounts. It is also evident from the range of structures identified, that there are two series of compounds differing in the level of methylation in the pendent aryl ring. Quantitative estimation shows that in general, the trimethoxy series of lignans is present in greater amounts than the corresponding 4'-demethyl analogues. The relevance of these observations in the biosynthesis of the *Podophyllum* lignans is discussed in a subsequent paper [27].

EXPERIMENTAL

General. Dried *P. hexandrum* (United Chemical and Allied Products, Calcutta) and *P. peltatum* (Joseph Flach, London) roots were obtained commercially. TLC was carried out using 0.5 mm layers of silica gel (Merck TLC-Kiesel gel 60 GF_{254}) and Me_2CO (Analar) was used for elution of TLC zones. HPLC was carried out using a UV detector (291 nm) and a Partisil-10 ODS2 column (250 × 4.6 mm) with a solvent (MeOH–H_2O, 3:2) flow rate of 2 ml/min.

Isolation of Podophyllum *lignans.* Powdered dried root material (30 g) was stirred with hot EtOH (4 × 100 ml) for 10 min.

Table 3. Lignan content* of *Podophyllum hexandrum* and *P. peltatum* roots

Lignan	*P. hexandrum*	*P. peltatum*
Podophyllotoxin (**1**)	1280	75
4'-Demethylpodophyllotoxin (**2**)	135	2†
Desoxypodophyllotoxin (**3**)	5	7
4'-Demethyldesoxypodophyllotoxin (**4**)	3†	2†
β-Peltatin (**5**)	3†	100
α-Peltatin (**6**)	2†	75
Podophyllotoxone (**7**)	17	6
4'-Demethylpodophyllotoxone (**8**)	4†	2†
Isopicropodophyllone (**9**)	10	2†
4'-Demethylisopicropodophyllone (**10**)	2†	1†

*Lignan content expressed as mg/30 g dried root material, and except where indicated, represents recrystallized product.

†Calculated from UV absorbance of chromatographically pure material.

The filtered extracts were combined, evapd, treated with H_2O (100 ml), then extracted with EtOAc (5 × 100 ml). The combined extracts were evapd and separated by TLC ($CHCl_3$–MeOH, 25:1). The eight clearly-defined zones were located by UV and separately eluted.

Zone 1 (R_f 0.9). After further TLC and gel filtration or HPLC as described [13], this yielded desoxypodophyllotoxin (**3**) and podophyllotoxone (**7**). Full analytical data have been reported previously [13]. HPLC R_t: **3**, 21.2 min; **7**, 13.4 min.

Zone 2 (R_f 0.8). This band was purified by TLC ($CHCl_3$–*iso*-PrOH, 10:1) and recrystallization from EtOH to give isopicropodophyllone (**9**). Full analytical data have been reported previously [13].

Zone 3 (R_f 0.7). After further TLC ($CHCl_3$–*iso*-PrOH, 10:1; Et_2O–CH_2Cl_2, 6:1), the mixture of 4′-demethyldesoxypodophyllotoxin (**4**) and 4′-demethylpodophyllotoxone (**8**) was characterized by ^1H NMR and MS, and by comparison with semisynthetic material (see below). HPLC R_t: **4**, 7.4 min; **8**, 5.6 min.

Zone 4 (R_f 0.6). Further TLC purification ($CHCl_3$–*iso*-PrOH, 10:1; Me_2CO–petrol (60–80°), 1:1) gave 4′-demethylisopicropodophyllone (**10**). EIMS (probe) 70 eV, *m/z* (rel. int.): 398 ([M]$^+$ 100%), 354 (10), 353 (40), 299 (14), 283 (13), 188 (19), 149 (20).

Zone 5 (R_f 0.5). After further TLC ($CHCl_3$–*iso*-PrOH, 10:1), followed by recrystallization from EtOH, this zone gave β-peltatin (**5**), mp 232–235° (dec) (lit. [26] 238–241°); UV λ_{max}^{EtOH} nm: 271; IR ν_{max}^{KBr} cm^{-1}: 3600–3100, 1770, 1628, 1595, 1510; EIMS (probe) 70 eV, *m/z* (rel. int.): 414 ([M]$^+$ 100%), 246 (28), 201 (22), 189 (41), 181 (38), 168 (17).

Zone 6 (R_f 0.3). This band was purified by TLC (hexane–Me_2CO, 1:1), then recrystallized from EtOH to give α-peltatin (**6**), mp 230–232° (dec.) (lit. [26] 243–246°); UV λ_{max}^{EtOH} nm: 272, 280 sh; IR ν_{max}^{KBr} cm^{-1}: 3450, 3310, 1730, 1650, 1612, 1522; EIMS (probe) 70 eV, *m/z* (rel. int.): 400 ([M]$^+$ 100%), 246 (19), 201 (20), 189 (17), 167 (15), 154 (12).

Zone 7 (R_f 0.25). Recrystallization from EtOH gave podophyllotoxin (**1**), mp 182–184° (lit. [28] 183–184°); UV λ_{max}^{EtOH} nm: 287 (log ε 3.63), 291 (3.64), 295 sh; IR ν_{max}^{KBr} nm: 3515, 3480, 1770, 1590, 1508; EIMS (probe) 70 eV, *m/z* (rel. int.): 414 ([M]$^+$ 100%), 399 (3), 189 (3), 181 (3), 168 (6).

Zone 8 (R_f 0.2). Band 8 was purified further by TLC (Me_2CO–petrol (60–80°), 1:1), and 4′-demethylpodophyllotoxin (**2**) recrystallized from EtOH, mp 250–251° (lit. [26] 250–252°); UV λ_{max}^{EtOH} nm: 282 (log ε 3.64), 291 (3.61), 296 sh; IR ν_{max}^{KBr} cm^{-1}: 3610, 3535, 1755, 1615, 1520; EIMS (probe) 70 eV, *m/z* (rel. int.): 400 ([M]$^+$ 100%), 201 (10), 200 (11), 189 (8), 167 (10), 155 (9), 154 (38).

4′-Demethyldesoxypodophyllotoxin (**4**). A gentle stream of H_2 was passed into a stirred soln of 4′-demethylpodophyllotoxin (50 mg) in HOAc (10 ml) containing Pd–C catalyst (10%, 50 mg) at 95° for 1 hr. After cooling the mixture was diluted with EtOH–H_2O (1:1, 50 ml), filtered and the filtrate evapd to dryness. The residue of **4** (30 mg) was recrystallized from MeOH. Mp 234–237° (lit. [25] 244–248°); UV λ_{max}^{EtOH} nm (rel. int.): 282 (99%), 287 (100), 293 (98), 297 sh; IR ν_{max}^{KBr} cm^{-1}: 3600–3200, 1760, 1610, 1520, 1503; EIMS (probe) 70 eV *m/z* (rel. int.): 384 ([M]$^+$ 100%), 230 (10), 185 (17), 173 (14), 167 (14), 154 (10).

Alternatively, dry HBr gas was bubbled into a soln of desoxypodophyllotoxin (14 mg) in dry 1,2-dichloroethane (10 ml) at 0° until satd (*ca* 10 min). The flask was then sealed and left at room temp for 24 hr. Following evapn, **4** (5 mg) was obtained by TLC ($CHCl_3$–*iso*-PrOH, 10:1) and recrystallization.

4′-Demethylpodophyllotoxone (**8**). Dry pyridine (40 μl) was added to a stirred soln of 4′-demethylpodophyllotoxin (100 mg) in dry THF–1,2-dichloroethane (1:1, 5 ml), which was then cooled to −6°. Benzyloxychloroformate (95%, 50 μl) in dry 1,2-dichloroethane (2 ml) was added dropwise over 20 min. After 30 min, a further portion of benzyloxychloroformate (10 μl) in 1,2-dichloroethane (1 ml) was slowly added and the stirring was continued for a further 20 min. The mixture was poured into 1,2-dichloroethane (40 ml), washed with HCl (10%, 50 ml), H_2O (2 × 50 ml) and the solvent removed. 4′-Benzyloxycarbonyl-4′-demethylpodophyllotoxin was isolated by TLC ($CHCl_3$–MeOH, 25:1) and recrystallized from EtOH, yield 97 mg, mp 108–112° (lit. [23] 113–114°). 4′-Benzyloxycarbonyl-4′-demethylpodophyllotoxin (20 mg) in $CHCl_3$ (1 ml) was stirred and heated under reflux with freshly prepared MnO_2 (50 mg) for 1 hr. The mixture was cooled, filtered and the evapd filtrate purified by TLC ($CHCl_3$–MeOH, 25:1) to give 4′-benzyloxycarbonyl-4′-demethylpodophyllotoxone (11 mg), recrystallized EtOH, mp 105–108°. This lignan (10 mg) was stirred and heated under reflux in EtOH (2 ml) with $Pd(OH)_2$–C catalyst (10%, 20 mg) and cyclohexene (1 ml) for 30 min. The mixture was filtered and 4′-demethylpodophyllotoxone (6 mg) isolated from the filtrate by TLC ($CHCl_3$–*iso*-PrOH, 10:1) and recrystallized from EtOH. Mp 173–185° (slow heating); UV λ_{max}^{EtOH} nm (rel. int.): 273 (100%), 313 (75); IR ν_{max}^{KBr} cm^{-1}: 3600–3400, 1778, 1680, 1615, 1520, 1505; EIMS (probe) 70 eV *m/z* (rel. int.): 398 ([M]$^+$ 100%), 354 (11), 353 (35), 321 (11), 244 (9), 188 (9), 167 (19), 154 (49).

Note. Mps for podophyllotoxin and related lignans are unreliable criteria for identity and purity. Wide variation in mp has been attributed to the existence of solvates and polymorphic forms [28].

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