Plant Anticancer Agents XXVII: Antileukemic and Cytotoxic Constituents of *Dirca occidentalis* (Thymelaeaceae)

MOHAMMED M. BADAWI, SUKHDEV S. HANDA, A. DOUGLAS KINGHORN[x], GEOFFREY A. CORDELL, and NORMAN R. FARNSWORTH

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Abstract □ Two antileukemic daphnane esters, Pimelea factor P_2 (I) and the new compound dircin (II), were isolated from the twigs and flowers of *Dirca occidentalis* A. Gray (Thymelaeaceae). Three lignans, (−)-medioresinol (III), (+)-syringaresinol (IV), and (−)-lariciresinol (V), as well as the coumarin daphnoretin (VI), were found to be additional cytotoxic constitents of this taxon.

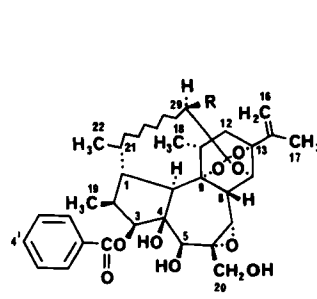
Keyphrases □ *Dirca occidentalis* (Thymelaeaceae)—isolation of antileukemic and cytotoxic constituents, daphnane esters and lignans, identification □ Daphnane esters—isolation from *Dirca occidentalis* (Thymelaeaceae), identification, antileukemic and cytotoxic potential □ Lignans—isolation from *Dirca occidentalis* (Thymelaeaceae), identification, antileukemic and cytotoxic potential □ Antileukemic agents—potential, daphnane esters and lignans isolated from *Dirca occidentalis* (Thymelaeaceae), cytotoxicity

Dirca occidentalis, one of two species representing a small genus in the family Thymelaeaceae indigenous to North America (1), is native to the Pacific States, where it is known by the colloquial name of western leatherwood (2). Although no laboratory studies appear to have been performed on either *D. occidentalis* or *Dirca palustris* L., the bark of *D. palustris* is highly vesicant to the skin and produces severe vomiting and purgation when ingested (3, 4).

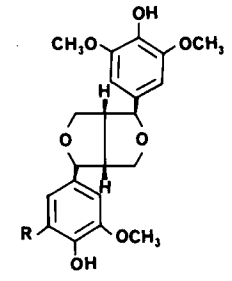
In a continuing search for anticancer agents of plant origin[1], our attention turned to *D. occidentalis* after a chloroform extract of a combined sample of the twigs and flowers was found to display significant *in vivo* and *in vitro* activity against the P-388 lymphocytic leukemia system[2] when tested according to standard protocols (6). In this paper, we report the isolation and identification of two antileukemic daphnane ester principles from this plant, Pimelea factor P_2 (I) and the novel compound dircin (II). In addition, four other cytotoxic constituents were isolated, namely, the lignans (−)-medioresinol (III), (+)-syringaresinol (IV), and (−)-lariciresinol (V) and the coumarin daphnoretin (VI).

DISCUSSION

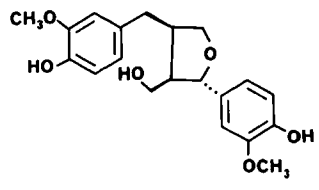
The molecular mass of dircin (II) was determined as 696 daltons by field-desorption mass spectrometry, a value consistent with a molecular formula of $C_{39}H_{52}O_{11}$. Comparison of the spectroscopic data (UV, IR, ^{1}H-NMR, MS) obtained for this isolate with those of Pimelea factor P_2 (I) and other 1α-alkyldaphnane derivatives (7–9), suggested that II is an acetoxy derivative of Pimelea factor P_2 (I). Thus, observations of



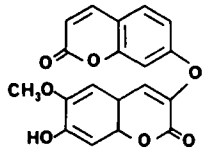
I: R = H
II: R = $OCOCH_3$



III: R = H
IV: R = OCH_3



V



VI

similar chemical shifts in the ^{1}H-NMR spectra of I and II permitted the assignment in the latter compound of methyl groups attached to C-2, C-11, and C-21; an isopropenyl group at C-13; a C-6α,C-7α-epoxide bridge; a C-9α,C-13α,C-14α-orthoester function; a 1α-alkyl chain; and a benzoate ester substituent at C-3. The remaining sites for possible esterification by an acetate group are at hydroxy groups attached to C-4, C-5, C-20, or at some other site in the molecule. The first of these alternatives was ruled out because esterification of this tertiary hydroxy group is unlikely, and no C-4-esterified tigliane or daphnane esters have been found as natural products to date (10). In addition, no resonance shifts in the ^{1}H-NMR spectrum of II relative to that of I for the protons adjacent to C-4 suggested such ester substitution. Likewise, a lack of esterification at either C-5 or C-20 in II was evident from the observation of resonances at δ 4.05 and 3.81 ppm, respectively (7–9). Since no signal assignable for a C-12 methine proton was present in the ^{1}H-NMR spectrum of II at ~δ 5.00 ppm (11, 12), such as that observed at δ 4.93 ppm in the ^{1}H-NMR spectrum of the positional isomer of II, linifolin a (12β-acetoxy-Pimelea factor P_2) (8), by a process of elimination the acetate group was placed in the alkyl chain of II. Similarities in the ^{1}H-NMR resonances assigned for the C-16 methylene protons in II(δ 4.88, 5.07 ppm) with those in the 29β-hydroxylated 1α-alkyldaphnane ester gnidimacrin (δ 4.85, 5.09) [a structure established by X-ray crystallography (9)] suggested the presence of a 29β-acetoxy function in II. In support of this the C-16 methylene protons in Pimelea factor P_2 (I), with no electronegative group substitution at C-29 on the alkyl chain, were found to resonate in a slightly upfield position at δ 4.85 and 4.96 ppm. The observation of the C-29 methine proton chemical shift at δ 5.28 ppm as a doublet in the ^{1}H-NMR spectrum of II suggested that coupling was apparent with only the *cis*-oriented C-28 methylene proton.

The structural assignment proposed here for dircin (II) is tentative, since the limited amounts of this isolate obtained in this investigation did not permit selective hydrolysis experiments to be performed to confirm the relative positions of ester substitution. However, support for our assignment of dircin as II may be gathered from the fact that all 3-esterified 1α-alkyldaphnane esters isolated to date from plants of the

[1] For the previous article in this series, see Ref. 5.

[2] Plant extracts, fractions, and isolates were tested under the auspices of the Drug Research and Development Program of the National Cancer Institute. A compound is considered active *in vivo* if it exhibits a prolongation of life in excess of 125% and is regarded as cytotoxic if the ED_{50} is ≤4 μg/ml. In *in vivo* testing, samples were administered intraperitoneally to six CD_2F_1 male tumor-bearing mice over a 10-day period. Evaluation was carried out by comparison of survival times with control tumor-bearing animal groups.

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Table I—Antileukemic and Cytotoxic Activity of *Dirca occidentalis* Isolates [a]

Compound	NSC Number	P-388 Screen *In Vivo* Dose, μg/kg	*In Vivo* % T/C	*In Vitro* ED_{50}, μg/ml
Pimelea factor P_2 (I)	334694	400	147	0.0000012
		200	127	
		100	110	
		50	116	
		25	110	
Dircin (II)	334696	125	156	0.00000025
		62.5	147	
		31.3	125	
(−)-Medioresinol (III)	329245	NT[b]		0.33
(+)-Syringaresinol (IV)	329246	2000	100	0.41
		1000	108	
		500	107	
		250	96	
(−)-Lariciresinol (V)	329247	NT[b]		0.23
Daphnoretin (VI)	291852	2000	107	3.5
		1000	100	
		500	95	
		250	100	

[a] Tested according to standard protocols (6). [b] NT = not tested.

Thymelaeaceae have been found to possess a benzoate group at C-3 (7–10). Dircin (II) is thus assigned as 29β-acetoxy-Pimelea factor P_2, being the 29β-acetate ester of the parent structure 1,2,6,7-tetrahydro-5,29-dihydroxy-21-methyl-6α,7α-epoxy-1α-nonylresiniferonol-30-oic acid (10).

Daphnane esters (8–14), lignans (15, 16), and coumarins (5, 15) have all been found previously as antileukemic and/or cytotoxic constituents of plants in the family Thymelaeaceae. It is pertinent to point out that while Pimelea factor P_2 (linifolin b) was determined in an earlier investigation to be devoid of activity against the P-388 lymphocytic leukemia system *in vivo* (8), this compound was shown to be active against this test system at the higher dose levels used in this study (Table I). Dircin (II), the most potent of the compounds isolated from *D. occidentalis* (Table I), exhibits somewhat less intense activity in the P-388 test system than demonstrated by the 1α-alkyldaphnane esters gnidimacrin and gnidimacrin 20-palmitate, which were isolated from *Gnidia subcordata* Meisn (9). However, the previously demonstrated skin-irritant and mouse skin tumor-promoting activities of Pimelea factor P_2 (I) and other daphnane esters (10) may very well act to restrict the development of I and II as clinically useful anticancer agents.

EXPERIMENTAL[3]

Plant Material—The twigs and flowers of *D. occidentalis* A. Gray (Thymelaeaceae) were collected in California in August 1977[4].

Extraction and Fractionation—The air-dried, milled plant material (12.5 kg) was defatted with petroleum ether (bp 60–80°), with the marc being extracted with methanol. On removal of solvent *in vacuo*, the residue was partitioned between water and chloroform. Biological activity was concentrated in both the petroleum ether extract, which was not examined further, and the chloroform extract, which was active against the P-388 lymphocytic leukemia test system both *in vivo* (T/C 144% at 1.87 mg/kg) and *in vitro* (ED_{50} 0.21 μg/ml).

A portion (90 g) of the dried chloroform extract was chromatographed on silica gel[5] (2 kg), with 2-liter fractions being collected and pooled on the basis of similar TLC profiles. Fraction F037 (17 g), obtained by elution with chloroform–methanol (9:1), exhibited an ED_{50} of 0.07 μg/ml in the P-388 cell culture system, while combined fractions F040–F042 (2.2 g), eluted with chloroform–methanol (19:1 and 17:3), were also found to be cytotoxic (P-388, ED_{50} 0.043, 0.18, 0.14 μg/ml, respectively).

Fraction F037 was rechromatographed on silica gel[5] (820 g), and eluted with chloroform and chloroform–methanol mixtures of increasing polarity, to afford 50 fractions (500 ml each). Crystals of daphnoretin (VI, 50 mg, 0.000092%), (−)-medioresinol (III, 6 mg, 0.000011%) and (+)-syringaresinol (IV, 18 mg, 0.000033%) were successively obtained during this separation on elution with chloroform–methanol (99:1). However, the more polar fractions F060–F064 (1.2 g) were highly cytotoxic (P-388, ED_{50} 1.9×10^{-4}–4.8×10^{-6} μg/ml), and were rechromatographed on silica gel[5] (40 g). Fractions eluted with chloroform–methanol (9:1) were pooled (0.9 g) and subjected to low-pressure column chromatography on octylsilyl silica gel contained in a prepacked column[6], using solvent systems composed of water–acetonitrile–methanol mixtures of decreasing polarity. Two daphnane esters were obtained as a result of this separation and were purified by preparative TLC on silica gel G plates[5], developed with benzene–ethyl acetate–hexane–ether (3:3:1:1), as follows: Pimelea factor P_2 (I, R_f 0.49, 3 mg, 0.000005%) and dircin (II, R_f 0.36, 4 mg). Further quantities of II were obtained by workup of other active fractions from the chloroform extract of *D. occidentalis*, in a manner similar to that described above, to produce a total of 32 mg (0.000059%) of this compound.

Fractions F040–F042 were similarly chromatographed on silica gel[5] eluted with chloroform–methanol mixtures. (−)-Lariciresinol (V, 10 mg, 0.000018%) was eluted with chloroform–methanol (19:1) and was purified by recrystallization from acetone–hexane (1:1).

Characterization of Biologically Active Isolates—The resinous Pimelea factor P_2 (I) exhibited the following spectral data. IR ν_{max} ($CHCl_3$): 3500, 1740, 1580, 1420, 1365, and 1235 cm^{-1}; UV λ_{max} (MeOH) (log ε): 229 (3.85) and 279 (3.10) nm; ^{1}H-NMR (60 MHz): δ 0.83 (d, 3, J = 6.4 Hz, 18-CH_3), 1.04 (d, 3, J = 6.5 Hz, 19-CH_3), 1.47 (d, 3, J = 3.5 Hz, 22-CH_3), 1.73 (bs, 3, 17-CH_3), 2.90 (d, 1, J = 2.7 Hz, 8-H), 3.11 (d, 1, J = 11.0 Hz, 10-H), 3.34 (s, 1, 7-H), 3.85 (bs, 2, 20-H_2), 4.10 (s, 1, H-5), 4.27 (d, 1, J = 2.7 Hz, 14-H), 4.85 and 4.96 (two bs, 1 each, 16-H_2), 5.09 (d, 1, J = 4.0 Hz, 3-H), and 7.45–8.05 ppm (m, 5, aromatic H); MS (20 eV): *m/z* 638 (M^+, 12%), 607 (11), 595 (24), 480 (11), 475 (13), 467 (16), 327 (11), 309 (10), 279 (13), 269 (15), 265 (10), 203 (11), 176 (19), 163 (16), 161 (41), 149 (22), 121 (16), and 105 (100). These data are in agreement with those reported for Pimelea factor P_2 (Daphnopsis factor R_1) (7) and linifolin b (8). Identity was established as Pimelea factor P_2 by direct comparison with an authentic sample[7] (^{1}H-NMR, MS, co-TLC).

The resinous isolate dircin (II), $[\alpha]_D^{25}$ + 9.0° (*c* 0.07, $CHCl_3$), exhibited the following spectral data. IR ν_{max} ($CHCl_3$): 3500, 1700, 1450, 1360, and 1270 cm^{-1}; UV λ_{max} (MeOH) (log ε): 228 (3.91) and 278 (3.10) nm; ^{1}H-NMR (400 MHz): δ 0.98 (d, 3, J = 7.5 Hz, 18-CH_3), 1.08 (d, 3, J = 7 Hz, 19-CH_3), 1.32 (d, 3, J = 7.5 Hz, 22-CH_3), 1.77 (bs, 3, 17-CH_3), 2.04 (s, 3, —OCOCH_3), 2.95 (d, 1, J = 12 Hz, 10-H), 2.96 (d, 1, J = 3 Hz, 8-H), 3.32 (s, 1, 7-H), 3.81 (ABq, 2, J_{AB} = 12 Hz, 20-H_2), 4.05 (s, 1, H-5), 4.19 (d, 1, J = 3 Hz, 14-H), 4.88 (d, 1, J = 6 Hz, H-3), 4.88 and 5.07 (two bs, 1 each, 16-H_2), 5.28 (d, 1, J = 8 Hz, 29-H), 7.50 (t, 2, J = 8 Hz, 3′- and 5′-H), 7.63 (t, 1, J = 7.5 Hz, 4′-H), and 8.06 ppm (dd, 2, J = 1.5 and 7.5 Hz, 2′- and 6′-H); MS (20 eV): *m/z* 696 (M^+, 2%), 678 (2), 647 (2), 592 (1), 561 (2), 556 (3), 533 (3), 467 (4), 403 (4), 368 (3), 363 (3), 345 (4), 327 (6), 309 (6), 299 (3), 297 (3), 281 (9), 205 (12), 203 (5), 189 (9), 188 (9), 177 (9), 176 (16), 161 (19), 148 (15), 147 (13), 133 (10), 123 (11), 122 (20), and 105 (100); field-desorption MS: MH^+ observed at *m/z* 697.

(−)-Medioresinol (III), mp 155–160°, $[\alpha]_D^{25}$−17.0° (*c* 0.14, $CHCl_3$) [lit. (17) (+)-medioresinol, mp 175–176°, $[\alpha]_D$ +57.4° ($CHCl_3$)], exhibited the following spectral data. IR ν_{max} (KBr): 3450, 3090, 1600, 1505, 1445, 1415, 1355, 1270, 1235, 1190, 1145, 1095, 1045, 945, and 780 cm^{-1}; UV λ_{max} (95% EtOH) (log ε): 220 sh (4.58), 232 (4.13), and 280 (3.58) nm; ^{1}H-NMR (60 MHz): δ 3.01–3.16 (m, 2, 8- and 8′-H), 3.88 (s, 9, 3 × —OCH_3), 3.76–3.98 and 4.13–4.30 (m, 4, 9- and 9′-H_2), 4.73 (dm, 2, J = 4.0 Hz, 7- and 7′-H), 5.48 (s, 1, phenolic OH), 5.59 (s, 1, phenolic OH), 6.58 (s, 2, 2- and 6-H), and 6.86 ppm (m, 3, 2′-, 5′-, and 6′-H); MS: *m/z* 388 (M^+, 100%), 358 (8), 235 (8), 210 (17), 206 (19), 193 (23), 182 (38), 181 (48), 180 (21), 167 (33), 163 (21), 161 (19), 154 (17), 151 (48), 137 (35), 124 (10), and 123 (10). These spectral data are in agreement with those published for (+)-medioresinol (17), and III exhibited identical TLC migration data to an authentic sample of (+)-medioresinol[8]. (−)-Medioresinol has not been isolated from a plant source previously.

[3] Melting points were determined by means of a Kofler hot-plate apparatus and are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. The UV spectra were obtained with a Beckman DB-G spectrophotometer and IR spectra on a Beckman model 18-A spectrophotometer, with polystyrene calibration at 1601 cm^{-1}. ^{1}H-NMR spectra were recorded in $CDCl_3$ with a Varian T-60A instrument operating at 60 MHz, equipped with a Nicolet Model TT-7 attachment. Tetramethylsilane was used as an internal standard, and chemical shifts are reported in δ (ppm). Low-resolution mass spectra were obtained with a Varian MAT-112S double-focusing spectrometer, operating at 70 eV.

[4] Plant material was collected and identified by staff of the Economic Botany Laboratory, BARC-East, U.S.D.A., Science and Education Administration, Beltsville, Md. A voucher specimen representing this collection has been deposited in the Herbarium of the National Arboretum, Washington, D.C.

[5] E. Merck, Darmstadt, W. Germany.

[6] Lobar, size B, containing LiChoprep RP-8 (40–63 μm); manufactured by E. Merck, Darmstadt, W. Germany.

[7] An authentic sample of Pimelea factor P_2 and a copy of its ^{1}H-NMR spectrum were kindly supplied by Professor E. Hecker.

[8] Authentic samples of (+)-medioresinol and (±)-syringaresinol were kindly provided by Dr. H. Fujimoto.

(+)-Syringaresinol (IV), mp 173–175°, $[\alpha]_D^{25}$+12.8° (*c* 0.05, $CHCl_3$) [lit. (17) mp 171–173°, $[\alpha]_D$ +19.0° ($CHCl_3$)], exhibited the following spectral data. IR ν_{max} (KBr): 3450, 3080, 1600, 1510, 1445, 1415, 1370, 1190, 1100, 980, 840, and 730 cm^{-1}; UV λ_{max} (95% EtOH) (log ϵ): 220 sh (4.16), 239 (4.05), and 273 (3.27) nm; ^{1}H-NMR (60 MHz): δ 3.07 (m, 2, 8- and 8′-H), 3.89 (s, 12, 4 × —OCH_3), 3.80–3.99 and 4.16–4.42 (m, 4, 9- and 9′-H_2), 4.73 (d,2, J = 4.0 Hz, 7- and 7′-H), 5.54 (s, 2, 4- and 4′-H), and 6.58 ppm (s, 4, 2-, 6-, 2′-, and 6′-H); MS: *m/z* 418 (M^+, 100%), 403 (3), 358 (3), 280 (4), 251 (5), 235 (11), 210 (16), 193 (25), 182 (41), 181 (65), 167 (56), 161 (18), 154 (17), and 151 (19). These spectral data are in agreement with those reported for (+)- and (±)-syringaresinol (17, 18), and the identification of IV as (+)-syringaresinol was confirmed by direct comparison (MS, co-TLC) with an authentic sample of (±)-syringaresinol.

(−)-Lariciresinol (V), mp 160–162°, $[\alpha]_D^{25}$−17.8° (*c* 1.4, acetone), exhibited the following spectral properties. IR ν_{max} (KBr): 3320, 3090, 1510, 1460, 1420, 1230, 1035, and 845 cm^{-1}; UV λ_{max} (MeOH) (log ϵ): 232 (4.17) and 283 (4.02) nm; ^{1}H-NMR (60 MHz): δ 2.2–3.0 (m, 4, 7-H_2, 8- and 8′-H), 3.5–4.1 (m, 4, 9- and 9′-H_2), 3.70 (s, 3, —OCH_3), 3.82 (s, 3, —OCH_3), 4.78 (d, 1, J = 6.2 Hz, 7′-H), 5.61 (m, 2, phenolic OH), and 6.70–6.83 ppm (m, 6, aromatic H); MS: *m/z* 360 (M^+, 62%), 345 (4), 329 (1), 252 (8), 236 (11), 194 (22), 180 (12), 175 (10), 167 (11), 153 (31), 151 (47), 137 (100), and 122 (17). These spectral data are similar to those expressed previously for (+)-lariciresinol (19), and V was closely comparable to an authentic sample[9] of (+)-lariciresinol (MS, co-TLC). The (−)-enantiomer of this lignan does not appear to have been obtained previously from a plant source.

Daphnoretin (VI), mp 243–244°, exhibited the following spectral data. IR ν_{max} (KBr): 3400, 3080, 1722, 1715, 1618, 1585, 1565, 1280, 1245, 1085, 840, and 757 cm^{-1}; UV λ_{max} (MeOH) (log ϵ): 230 (4.13), 267 (3.80), 325 (4.17), and 343 (4.22) nm; ^{1}H-NMR (60 MHz, DMSO-d_6): δ 3.83 (s, 3, —OCH_3), 6.35 (d, 1, J = 9.5 Hz, 3′-H), 7.03–7.78 (m, 5, aromatic H), 7.85 (s, 1, 4-H), and 8.01 (d, 1, J = 9.5 Hz, 4′-H); MS: *m/z* 352 (M^+, 100%), 337 (4), 324 (5), 309 (11), 262 (5), 179 (25), 167 (20), and 89 (18). Compound VI was identified as daphnoretin on the basis of consistency of the above data with published spectral data for this compound (15, 20–22), and confirmation of this identity was made by direct comparison with an authentic sample[10].

Biological Activity of the Isolates—The activities of isolates I–VI from *D. occidentalis* against the P-388 lymphocytic leukemia test system, *in vivo* and *in vitro*, are shown in Table I.

[9] An authentic sample of (+)-lariciresinol was donated by Dr. S. F. Fonseca.

[10] Daphnoretin was isolated in our laboratory previously from *Peddia fischeri* (5).

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