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ACETYLATED LIGNANS FROM *JUNIPERUS SABINA*

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Key Word Index—*Juniperus sabina*; Cupressaceae; lignans; acetyl-epipodophyllotoxin; acetyl-epipicropodophyllotoxin.

Abstract—Two new natural products, the acetates of epipodophyllotoxin and epipicropodophyllotoxin, were isolated from the lignan fraction of a *n*-hexane extract of the leaves of *Juniperus sabina*, along with deoxypodophyllotoxin, deoxipicropodophyllotoxin, (−)-deoxypodorhizon, β-peltatin A methyl ether and picropodophyllotoxin.

As a continuation of our research into the lignans occurring in species of Cupressaceae [1], we have started work on the isolation and identification of the lignans of *Juniperus sabina* L., from whose *n*-hexane extract we have isolated deoxypodophyllotoxin (**1**), deoxypicropodophyllotoxin (**2**), (−)-deoxypodorhizon (**3**), β-peltatin A methyl ether (**4**), acetylepipodophyllotoxin (**5**), acetyl-epipicropodophyllotoxin (**6**) and picropodophyllotoxin (**7**).

Compounds **1**–**4** and **7** were identified by direct comparison with authentic samples [1] or by comparison of spectroscopic data published by other authors [2–5]. Compounds **5** and **6** were identical to the acetylation products of epipodophyllotoxin (**9**) and epipicropodophyllotoxin (**8**) [2, 3, 6–9] and have not been hitherto described as natural products.

Saponification of **5** with Na_2CO_3/MeOH–H_2O over 7 hr occurred with epimerization at C-2 yielding **8**. Upon saponification under gentler conditions ($NaHCO_3$/MeOH–H_2O; 7 hr at room temperature), a mixture of epipodophyllotoxin (**9**) and unreacted **5** was obtained. However, when the reaction time was extended to 46 hr only **8** was obtained.

EXPERIMENTAL

General experimental procedures. Mps: uncorr; Optical rotations: $CHCl_3$; UV: EtOH; IR: CH_2Cl_2 soln; ^1H NMR (200.13 MHz) and ^{13}C NMR (50.3 MHz): $CDCl_3$ with TMS as int. standard.

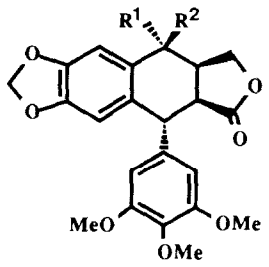
Collection of plant. Juniperus sabina was collected in Cardaño de Abajo (Palencia, Spain) in Oct 1986. The plant material was identified by Prof. M. Ladero (Salamanca) (voucher no. SALAF 15979).

Extraction and isolation. Dry ground leaves (7 kg) were extracted with *n*-hexane in a Soxhlet over 9 hr. After cooling overnight, the extract afforded an insoluble part (360 g) which following treatment with MeOH and urea-satd MeOH and later extraction with 4% NaOH yielded a neutral part (56 g). CC of 27 g of this fraction afforded **1** (530 mg), **2** (130 mg), **3** (1.1 g), **4** (70 mg), **5** (190 mg), **6** (40 mg) and **7** (30 mg).

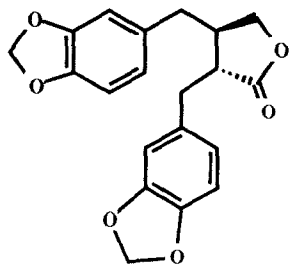
Acetyl epipodophyllotoxin (**5**). Eluted with *n*-hexane–Et_2O (1:4), mp 171° (EtOH); $[\alpha]^{24}$ (λ nm): −135.6° (589), −142.7° (578), −164.7° (546), −302.1° (436), −538.2° (365) ($CHCl_3$; *c* 1); UV λ_{max}nm, (ε): 216 (30700), 243 (11500), 291 (4200); IR $\nu_{max}cm^{-1}$: 1780, 1740, 1590, 1505, 1485, 1230, 1130, 1045, 1000, 950, 910, 850; ^1H NMR: δ2.12 (3H, *s*, OAc), 2.99 (1H, *dddd*, J_1 = 14.1 Hz, J_2 = 10.7 Hz, J_3 = 7.4 Hz and J_4 = 3.5 Hz, H-3), 3.25 (1H, *dd*, J_1 = 14.1 Hz, J_2 = 5.1 Hz, H-2), 3.74 (6H, *s*, MeO-3′ and MeO-5′), 3.79 (3H, *s*, MeO-4′), 3.91 (1H, *dd*, *J* = 10.7 Hz, J_2 = 8.8 Hz, Hβ-9), 4.34 (1H, *dd*, J_1 = 8.8 Hz, J_2 = 7.4 Hz, Hα-9), 4.65 (1H, *d*, *J* = 5.1 Hz, H-1), 5.95 (1H, *d*, *J* = 1.03 Hz, H-11), 5.98 (1H, *d*, *J* = 0.7 Hz, H-11), 6.15 (1H, *d*, *J* = 3.5 Hz, H-4), 6.29 (2H, *s*, H-2′ and H-6′), 6.55 (1H, *s*, H-8) and 6.89 (1H, *s*, H-5); ^{13}C NMR: δ20.7 (CH_3–COO-4), 36.7 (C-3), 41.4 (C-2), 43.7 (C-1), 56.2 (MeO-3′ and MeO-5′), 60.5 (MeO-4′), 67.3 (C-9), 68.0 (C-4), 101.5 (C-11), 108.5 (C-2′ and C-6′), 109.5 (C-5), 110.0 (C-8), 127.9 (C-4a), 132.9 (C-8a), 134.5 (C-1′), 137.6 (C-4′), 147.4 (C-7), 148.8 (C-6), 152.6 (C-3′ and C-5′), 170.3 (Me–COO-4) and 173.9 (C-10).

Compound **5** (83 mg) in 5 ml MeOH and 4 ml of a satd aq. soln of Na_2CO_3 was stirred for 7 hr to afford 74 mg of a reaction product which on purification by TLC afforded 46 mg epipicropodophyllotoxin (**8**). Compound **5** (210 mg) in 8 ml MeOH and 5 ml of a satd aq. soln of $NaHCO_3$ was stirred at room temp. for 7 hr to yield 175 mg of reaction product which on purification by flash chromatography gave 11 mg epipodophyllotoxin (**9**). After 46 hr under the same conditions, 120 mg of reaction product were obtained which on CC afforded 20 mg epipicropodophyllotoxin (**8**).

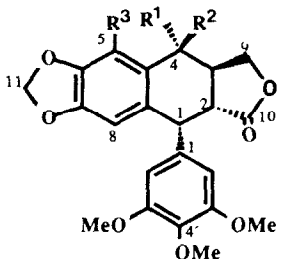
Acetyl epipicropodophyllotoxin (**6**). Eluted with CH_2Cl_2–EtOAc (19:1); $[\alpha]^{24}$ (λ mn): +2.3° (589), +3.0° (578), +3.1° (546) ($CHCl_3$; *c* 0.7); UV λ_{max}(ε): 240 (14 800), 288 (6300); IR $\nu_{max}cm^{-1}$: 1780, 1745, 1600, 1510, 1490, 1235, 1135, 1050, 945, 880; ^1H NMR: δ2.12 (3H, *s*, AcO-4), 3.34 (1H, *m*, H-3), 3.40 (1H, *dd*, J_1 = 3.9 Hz, H-2), 3.82 (6H, *s*, MeO-3′ and MeO-5′), 3.84 (3H, *s*, MeO-4′), 4.25 (1H, *dd*, J_1 = 9.8 Hz, J_2 = 3.1 Hz, Hβ-9), 4.39 (1H, *dd*, J_1 = 9.8 Hz, J_2 = 7.6 Hz, Hα-9), 4.40 (1H, *d*, *J* = 3.9 Hz, H-1), 5.94 (1H, *d*, *J* = 1.4 Hz, H-11), 5.96 (1H, *d*, *J* = 1.4 Hz, H-11), 6.00 (1H, *d*, *J* = 4.4 Hz, H-4), 6.43 (2H, *s*, H-2′ and H-6′), 6.52 (1H, *s*, H-8) and 6.85 (1H, *s*, H-5); ^{13}C NMR: δ20.8 (Me–COO-4), 38.0 (C-3), 44.6 (C-1), 45.2 (C-2), 56.3 (MeO-3′ and MeO-5′), 60.8 (MeO-4′), 68.1 (C-9), 70.7 (C-4), 101.3 (C-11), 105.6 (C-2′ and C-6′), 107.2 (C-8), 109.6 (C-5), 127.2 (C-4a), 131.5 (C-8a), 137.4 (C-4′), 137.6 (C-1′), 147.0 (C-6), 148.2 (C-7), 153.7 (C-3′ and C-5′), 170.1 (Me–COO-4) and 178.2 (C-10).



R^1	R^2		
H	H	deoxypicropodophyllotoxin	2
H	OAc	acetyl epipicropodophyllotoxin	6
OH	H	picropodophyllotoxin	7
H	OH	epipicropodophyllotoxin	8



(-) deoxypodorhizon 3



R^1	R^2	R^3		
H	H	H	deoxypodophyllotoxin	1
H	H	OMe	β-peltatin A methyl ether	4
H	OAc	H	acetyl epipodophyllotoxin	5
H	OH	H	epipodophyllotoxin	9

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