Two New Taxoids from European Yew (*Taxus baccata*) That Act as Pyrethroid Insecticide Synergists with the Black Vine Weevil (*Otiorhynchus sulcatus*)[1]

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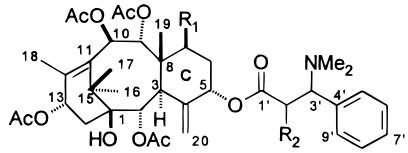
Received July 14, 1997[⊗]

Bioassay-guided fractionation of an extract of foliage of European yew (*Taxus baccata* L.) yielded two new (**1**−**2**) and a previously reported (**3**) taxoid that acted as pyrethroid insecticide synergists with the black vine weevil (*Otiorhynchus sulcatus* Fab.). Structures of the compounds were established by spectral methods.

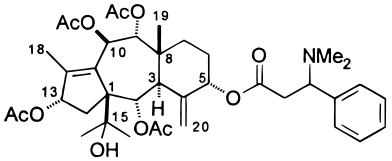
Black vine weevil, *Otiorhynchus sulcatus* Fab. (Curculionidae), is a serious pest of a number of food and ornamental crops in many temperate growing regions.[2] Control of this insect is difficult, as only a few insecticides are effective against it.[3] Among the insecticides registered for use against the black vine weevil are several pyrethroids (bioactive pyrethrin analogues[4]) including permethrin and fenvalerate. Registration of these materials was based, in part, on demonstration of their effectiveness against black vine weevil on *Taxus* x *media* Rehd. (Taxaceae),[3] a hybrid yew, which, like European yew (*T. baccata* L.), is an important ornamental host of the insect.

Interestingly, whereas fenvalerate was effective against black vine weevil on yew, it was ineffective in control of this insect on strawberry,[5] another important host plant. This difference in effectiveness was related to the presence of extractable materials present in yew foliage that acted as insecticide synergists.[5] We now report the structures of two new austrospicatine-type taxoids (**1**−**2**), one of which has an 11(15→1) *abeo* skeleton, and a previously reported one (**3**), whose isolation from European yew was based on their activity as pyrethroid synergists with the black vine weevil.



1 $R_1 = R_2 = H$

3 $R_1 = OAc$, $R_2 = OH$



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Results and Discussion

Crude EtOH or $CHCl_3$ extracts of foliage of several *Taxus* sp. exhibited synergist activity similar to that described previously.[5] Isolation of synergist compounds from European yew (*T. baccata*) required several chromatographic steps with fraction selection based on bioassay and TLC analysis (see Experimental Section). Three compounds (**1**−**3**) with synergist activity were obtained as glassy films.

The ^1H and ^{13}C NMR spectra of **1**−**3** were reminiscent of the austrospicatine class of taxoids,[6−8] which differ primarily in the number of and placement of hydroxy and acetoxy groups. A molecular formula of $C_{39}H_{53}NO_{11}$ for **1**, which is isomeric with three known austrospicatines,[7] was established by HRFABMS and NMR data. DEPT and HMQC NMR data indicated that **1** was comprised of 10 methyls, four methylenes, a vinyl group, a methine, five sp^2-hybridized methines, six heteroatom-substituted methines, five carboxyl groups, an oxygen-substituted quaternary, four sp^2-hybridized quaternary, and two quaternary carbons. Readily recognizable in the ^1H NMR spectrum were 10 methyl singlets, a vinyl function, and an aromatic ring. Five oxymethine proton signals were also observed, and their chemical shifts—5.42 (H-2), 5.21 (H-5), 5.90 (H-9), 6.00 (H-10), and 6.00 (H-13)—suggested that all five oxygens were acylated.

The presence of the Winterstein acid (3-(*N*,*N*-dimethylamino)-3-phenylpropanoyl) moiety in **1** was suggested by signals at δ 2.20 (br s), 2.83 (dd, J = 13.5, 6.0 Hz), 3.04 (dd, J = 13.5, 9.5 Hz), 3.77 (br t), and 7.25−7.35 in the ^1H and 40.2 (t), 42.8 (q), 68.0 (d), 127.4 (d), 128.3 (d), 128.4 (d), 138.4 (s), and 170.7 (s) in the ^{13}C NMR spectra, which were in good agreement with literature values.[9] Further support was provided by fragment ions in the FABMS at *m*/*z* 194 and 134 that analyzed for $C_{11}H_{16}NO_2$ and $C_9H_{12}N$ by HRFABMS, respectively, and $^1H-^1H$ COSY and HMBC data (Table 1).

Four spin systems, H-2 to H-3, H-5 to H_2-7, H-9 to H-10, and H-13 to H_2-14, were defined by $^1H-^1H$ COSY and HMQC-TOCSY NMR experiments. Cross-peaks

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⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1997.

S0163-3864(97)00335-2 CCC: $14.00

Table 1. NMR Data for **1** and **2** ($CDCl_3$)

	1			**2**		
position	^{13}C	^{1}H	HMBC	^{13}C	^{1}H	HMBC
1	79.5 (s)		H3, $H_2$14, H16, H17	68.6 (s)		H3, $H_2$14, H16, H17
2	74.1 (d)	5.42 (d, 7.0)	H3, $H_2$14	68.3 (d)	5.85 (d, 9.0)	H3, $H_2$14
3	46.9 (d)	3.22 (d, 7.0)	H2, H5, $H_2$7, H19, $H_2$20	44.8 (d)	3.10 (d, 9.0)	H2, H5, $H_2$7, H19, $H_2$20
4	141.9 (s)		H3, $H_2$20	141.8 (s)		H3, $H_2$20
5	78.0 (d)	5.21 (br t)	H3, H20a	76.6 (d)	5.13 (br overlapped)	H3, H20a
6α	28.4 (t)	1.03 (br d, 14.0)	$H_2$7	28.3 (t)	1.20−1.27 (m)	
6*β*		1.43 (tt, 14.0, 4.0)			1.50 (br t, 14.0)	
7α	27.1 (t)	1.32 (td, 13.0, 4.0)	H3, H5, H9, H19	27.0 (t)	1.20−1.27 (m)	H5, H9, H19
7*β*		1.55 (br d, 13.0)			1.40 (dd, 13.0, 4.0)	
8	44.2 (s)		H2, H3, $H_2$7, H9, H19	41.9 (s)		H2, H19
9	76.0 (d)	5.90 (d, 10.5)	H10, H19	76.6 (d)	5.79 (d, 10.5)	
10	71.7 (d)	6.00 (d, 10.5)	H9	68.5 (d)	6.15 (d, 10.5)	
11	133.4 (s)		H9, H10, H16, H17, H18	136.4 (s)		H9, H10, H13, H14*β*, H18
12	139.5 (s)		H10, H14*β*, H18	146.3 (s)		H10, H13, H14*β*, H18
13	70.7 (d)	6.00 (br t)	$H_2$14, H18	78.9 (d)	5.53 (bt, 7.0)	
14α	36.8 (t)	1.97 (dd, 15.5, 7.5)	H2	38.0 (t)	1.85 (dd, 15.0, 7.5)	H2
14*β*		2.30 (dd, 15.5, 9.5)			2.36 (dd, 15.0, 7.0)	
15	42.3 (s)		H2, H10, H14α, H16, H17	68.6 (s)		H2, $H_2$14, H16, H17
16	22.1 (q)	1.66 (s)	H17	27.6 (q)	1.17 (s)	
17	28.3 (q)	1.20 (s)	H16	25.2 (q)	1.18 (s)	
18	15.5 (q)	2.12 (s)		11.9 (q)	1.94 (s)	
19	17.9 (q)	0.82 (s)	H3, H7α, H9	17.0 (q)	0.88 (s)	H3, H9
20a	118.1 (t)	5.28 (s)	H3, H5	113.3 (t)	5.12 (s, overlapped)	H3
20b		4.68 (s)			4.68 (s)	
1′	170.7 (s)		H5, $H_2$2′	170.7 (s)		
2a′	40.2 (t)	2.83 (dd, 13.5, 6.0)		39.5 (t)	2.71 (dd, 13.5, 6.0)	
2b′		3.04 (dd, 13.5, 9.5)			2.95 (dd, 13.5, 9.5)	
3′	68.0 (d)	3.77 (br t)	H5′, H9′, $H_2$2′, NMe	67.2 (d)	3.77 (br t)	H5′, H9′, $H_2$2′, NMe
4′	138.4 (s)		H2b′	138.4 (s)[a]		
5′, 9′	128.3 (d)	7.25−7.35 (m)		128.3 (d)	7.23−7.39 (m)	
6′, 8′	128.4 (d)	7.25−7.35 (m)		128.4 (d)	7.23−7.39 (m)	
7′	127.4 (d)	7.25−7.35 (m)		127.4 (d)	7.23−7.39 (m)	
2-OAc	171.8 (s)		H2	171.8 (s)		H2
	21.2 (q)	2.05 (s)		20.6 (q)[b]	1.94 (s)[c]	
9-OAc	170.0 (s)		H9	170.0 (s)		H9
	20.8 (q)	2.05 (s)		20.8 (q)[b]	2.02 (s)[c]	
10-OAc	169.8 (s)		H10	169.8 (s)		H10
	21.0 (q)	2.03 (s)		20.9 (q)[b]	2.02 (s)[c]	
13-OAc	170.3 (s)		H13	170.3 (s)		H13
	21.3 (q)	2.10 (s)		21.7 (q)[b]	2.02 (s)[c]	
N-Me	42.8 (q)	2.20 (br s)	H3′	42.4 (q)	2.17 (br s)	

[a] Very weak, broad peak, detected by HMBC. [b,c] Values in column may be interchanged.

were observed in an HMBC experiment from a methyl singlet (H-19) to one carbon in each of three spin systems (C-3, C-7, C-9) and a quaternary carbon signal at δ 44.2 (C-8). Correlations from H-3 to olefinic carbons resonating at δ 141.9 (C-4) and 118.1 (C-20), a quaternary carbon at 79.5 (C-1), and C-2, C-5, C-7, C-8, and C-19, and from H_a-20 to C-5 completed the structure of ring C and a major portion of ring B. The methylene protons of the remaining spin system (H_2-14) displayed hetereonuclear coupling in the HMBC experiment to C-1 and C-2, allowing its connection at C-1. Cross-peaks were also observed from H_2-14 to C-13, from H_β-14 to a quaternary olefinic signal at δ 139.4 (C-12), and from H_α-14 to a quaternary methine at 42.3 (C-15). Two methyl singlets (1.66, H-16; 1.20, H-17) also showed correlations to C-15, as well as to the carbon atom to which the other was attached, and to C-1 and the remaining olefinic carbon signal at δ 133.4 (C-11). The remaining methyl group could be placed at C-12 due to HMBC correlations from H-18 to C-11, C-12, and C-13, which also allowed the connection of C-11 to C-12. Since the proton signals of H-10 and H-13 overlapped and were both expected to give HMBC correlations to C-11 and C-12, using these data to support the C-10 to C-11 bond would be tenuous. The necessary connection, however, was readily established by a three-bond correlation from H-9 to C-11. The placement of the Winterstein acid moiety at C-5 due to a cross-peak from H-5 to C-1′ completed the gross structure of **1**. Additional HMBC data (Table 1) further supported the proposed structure.

Relative stereochemistry of **1** was determined from chemical shifts, coupling constants, difference NOE, and ROESY data. A coupling constant between H-9 and H-10 of 10.5 Hz indicated that the B ring was in the chair−boat conformation. The NOE data (Table 2) unambiguously established the relative stereochemistry of **1** at all positions except at C-5 and, of course, could not relate the stereochemistry of the Winterstein acid moiety to the terpenoid portion. In known austrospicatines, H-5 is in a pseudoequatorial position, and its NMR signal is a broad triplet with a small coupling constant. This was the case for H-5 of **1**. ROESY correlations from H-5 to H_α-6 and H_β-6 but not to H_α-7 were consistent with the proposed relative stereochemistry at C-5. Thus, the relative stereochemistry of the terpenoid skeleton of **1** is the same as that found in other austrospicatines.

Compound **1** has appeared in the literature as a semisynthetic derivative,[10] but its spectral data were not reported and are unfortunately unavailable for comparison.[11]

NMR and HRFABMS data gave a molecular formula of $C_{39}H_{53}NO_{11}$ for **2**, identical with that of **1**, and the

Table 2. ROESY Correlations for the Terpenoid Portion of Compounds **1** and **2**

H	1	2
2	H9, H16, H19	H19
3	H7α, H10, H14α	H10 (w)[a]
5	H6α, H6β	H6α, H6β
6α	H5, H6β, H7α, H7β (w)	H5
6β	H5, 6α, H7α (w), H19	H5, H19
7α	H3, H6α (w), H6β (w), H7β	
7β	H6α (w), H6β (w), H7α, H19	H19
9	H16, H19	H19
10	H3	H3 (w)
13	H14β, H17	H14β
14α	H3, H14β	H3
14β	H13, H14α, H17	H13, H16, H17
16	H2, H9	H13, H14β
17	H13, H14β	H13, H14β
18		
19	H2, H6β, H7β, H9, H20b	H2, H6β, H7β, H9
20a	H20b	H20b
20b	H19 (w), H20a	H20a

[a] w = weak correlation.

DEPT data indicated it had the same number of methyls, methylenes, etc. HMBC and HMQC-TOCSY experiments established the presence of the Winterstein acid moiety and the same connectivities in **2** as in **1** for C-2 through C-14, C-18 to C-12, C-19 to C-8, and C-20 to C-4. Strong HMBC correlations of H-13 and H_β-14 to the same two olefinic carbons (C-11 and C-12) and the lack of cross-peaks from H-16 and H-17 to C-11, which were observed for **1**, were only consistent with **2** having an 11(15→1) *abeo*-austrospicatine carbon skeleton. Additional NMR data fully supported the structure (Table 1). A coupling constant between H-9 and H-10 of 10.5 Hz and the chemical shifts of H-9 and H-19 indicated that the B-ring of **2** was in the common chair−boat conformation instead of the rare chair−chair conformation, for which these values differ dramatically.[12] ROESY data (Table 2) led to the indicated relative stereochemistry for **2**, which is common to known 11(15→1) *abeo*-austrospicatines.

Compound **2** may be derived from **1** as an artifact of the extraction/isolation procedure, but circumstantial evidence suggests that the 11(15→1) *abeo* taxoids are indeed natural products.[12,13]

A third austrospicatine-type taxoid was isolated as a pesticide synergist. HRFABMS, ^{1}H, ^{13}C, HMQC, HMQC-TOCSY, HMBC, and ROESY NMR data identified the compound as previously reported **3**.[14] The chemical shifts were in excellent agreement with the published values.

The basis for the activity of the taxoid synergists with the black vine weevil are unknown. Paclitaxel (Taxol) was ineffective as a synergist.[15] Moreover, other taxoids obtained during the isolation of the synergists were not active. This suggests that the taxane skeleton alone is not sufficient for conferring synergist activity.

The taxoid synergists lack the (methylenedioxy)-phenyl group that characterizes the most well-studied class of insecticide synergists.[16] One of these compounds, piperonyl butoxide (PBO), which is widely used in insecticide formulations, was ineffective as a pyrethroid synergist with the black vine weevil. PBO, in contrast, was a potent synergist with the pyrethroid resistant Learn-PyR house fly strain,[17,18] whereas with such flies the taxoid synergists had no effect. It is possible that the synergism exhibited by these compounds is related to metabolic detoxification processes unique to the black vine weevil.

Experimental Section

General Experimental Procedures. NMR spectra were obtained on Bruker AMX 400 and DRX 600 MHz NMR spectrometers in $CDCl_3$ and referenced to residual $CHCl_3$ (δ 7.26) for ^{1}H and $CDCl_3$ (δ 77.0) for ^{13}C. A 300 ms mixing time was used for all ROESY experiments, and a 60 ms mixing time was used for all HMQC-TOCSY experiments.

Plant Material. Foliage from a mature specimen of *T. baccata* growing on the Oregon State University campus was used for extractions. A voucher specimen has been deposited in the Oregon State University Herbarium.

Extraction and Isolation. Fresh needles (1.0 kg) from *T. baccata* were extracted overnight (Soxhlet apparatus) with $CHCl_3$. The extract was concentrated in vacuo, resuspended/dissolved in 1 L of $CHCl_3$, filtered, and washed with water (4 × 500 mL). The residue (41.6 g) was fractionated by silica gel flash chromatography (FC), eluting with $CHCl_3$/MeOH (48:2). To identify the FC fractions containing synergists, subsamples were subjected to small-scale preparative TLC on silica gel using two solvent systems in sequence [hexane/EtOAC (8:92); hexane/2-propanol (1:1)]. Fractions were taken from the plates based on migration of synergists obtained previously from smaller scale isolations in marker lanes on the plate edges, which were removed, sprayed with H_2SO_4/MeOH (1:1), and heated until charred. Fractions obtained from the two rounds of preparative TLC and reference syntergists were subjected to TLC on silica gel using $CHCl_3$/MeOH (19:1), and FC fractions containing the compounds of interest were detected by charring and pooled to give 29.4 g of residue. The residue was chromatographed using silica gel FC [hexane/2-propanol (45:55)], and fractions containing synergists were identified and pooled to give 2.41 g of residue, which was further fractionated with silica gel FC [hexane/EtOAc (8:92)] to give 0.82 g of material containing the synergists. Low-pressure liquid chromatography (LPLC) [20 × 300 mm column, ODS, MeOH/H_2O (80:20)] of this material afforded 75 mg of residue. Preparative TLC [silica gel, $CHCl_3$/MeOH (95:5)] was used to separate the three synergists, which were each subjected to a final LPLC step [11 × 300 mm column, silica gel, $CHCl_3$/MeOH/HOAc (98.74:1.25:0.01)]. Yields of **1**, **2**, and **3** were 15, 4, and <1 mg, respectively. Purified compounds were bioassayed to confirm synergist activity.

Bioassay. Bioassays for synergist activity were conducted by applying 50 μL aliquots (25−50 μg) of a fraction in $CHCl_3$ or 100 μL of the crude $CHCl_3$ extract to 13 mm filter disks (Metricel DM-450, Gelman Instrument Co., Ann Arbor, MI) that had been pretreated with the phagostimulants sucrose and sitosterol (25 and 5 μg per disk, respectively) to stimulate black vine weevil feeding.[19,20] Disks were then divided into quarters. One adult weevil, reared on Totem strawberry plants as described,[21] was allowed to feed on each quarter of a treated disk or one treated with only the phagostimulants for approximately 48 h. Those that had fed were then transferred to fresh strawberry leaves that had been treated by dipping them in an 0.025% emulsion of

the pyrethroid pesticide fenvalerate (from Pydrin 2.4 EC, Shell Chemical Co.) or to untreated leaves. There were four replications of five weevils for each treatment for most bioassays. Knockdown of weevils, defined as an inability to walk, was recorded at hourly intervals for 8 h after transfer, and at 24 and 48 h.

(+)-2α-Acetoxy-2′,7-dideacetoxy-1-hydroxyaustrospicatine (1): colorless film; $[\alpha]^{22}_D$ +60° (*c* 0.52, $CHCl_3$); IR (film) 1737, 1371, 1237 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; FABMS (positive ion, 3-NBA matrix) *m/z* 712 (M + H), 194 (M − $C_{28}H_{37}O_9$), 134 (M − $C_{30}H_{41}O_{11}$); HRFABMS (positive ion, 3-NBA matrix) *m/z* 712.3693 (calcd for $C_{39}H_{54}NO_{11}$, 712.3697), 194.1180 (calcd for $C_{11}H_{16}NO_2$, 194.1181), 134.0970 (calcd for $C_9H_{12}N$, 134.0970).

(−)-2α-Acetoxy-2′,7-dideacetoxy-1-hydroxy-11(15→1)-*abeo*-austrospicatine (2): colorless film; $[\alpha]^{22}_D$ −46° (*c* 0.56, $CHCl_3$); IR (film) 1737, 1731, 1371, 1234 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; FABMS (positive ion, 3-NBA matrix) *m/z* 712 (M + H), 194 (M − $C_{28}H_{37}O_9$), 134 (M − $C_{30}H_{41}O_{11}$); HRFABMS (positive ion, 3-NBA matrix) *m/z* 712.3694 (calcd for $C_{39}H_{54}NO_{11}$, 712.3697).

2α-Acetoxy-2′-deacetyl-1-hydroxyaustrospicatine (3). ^1H and ^{13}C NMR spectral data were in excellent agreement with published data.[14] HRFABMS (positive ion, TSA/glycerol/3-NBA matrix) *m/z* 786.3699 (calcd for $C_{41}H_{56}NO_{14}$, 786.3700). Not enough material was available to obtain an optical rotation.

Acknowledgment. The authors thank X. Cascante, H. Throop, and J. K. Christian for technical assistance, Dr. C. A. Ishimaru for helpful suggestions, B. Arbogast for mass spectral measurements, and Professor S. J. Gould, Oregon State University, for preliminary contributions to this work. We also thank Professor J. G. Scott, Department of Entomology, Cornell University, Ithaca, NY, for providing a culture of the Learn-PyR house flies and Professor G. Appendino, Dipartimento di Scienza e Technologia del Farmaco, University of Torino, Italy, for clarifying for us some of the taxoid literature. The late Dr. M. Suffness, National Cancer Institute, Bethesda, MD, provided the sample of paclitaxel.

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NP9703353