C-5-Substituted Antifeedant Silphinene Sesquiterpenes from *Senecio palmensis*

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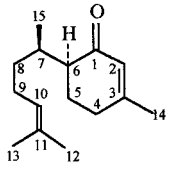
The new sesquiterpenes, 5α-senecioyloxysilphinen-3-one (**5**), 5α-tigloyloxysilphinen-3-one (**7**), and 3*β*-hydroxy-5α-angeloyloxysilphinene (**8**), and the known compounds (6*S*)-2,10-bisaboladien-1-one (**1**), 6,7-epoxy-3(15)-caryophyllene (**2**), 6,7-epoxy-2,9-humuladiene (**3**), 5α-angeloyloxysilphinen-3-one (**4**), and 5α-acetoxysilphinen-3-one (**6**) were isolated from bioactive fractions of *Senecio palmensis*. The structures of these compounds were established by spectroscopic analysis and chemical evidence. The semisynthetic analogues silphinen-3,5-dione (**9**), 5α-hydroxysilphinen-3-one (**10**), 5*β*-hydroxysilphinen-3-one (**11**), 5*β*-acetoxysilphinen-3-one (**12**), and 5*β*-isobutyryloxysilphinen-3-one (**13**) were generated to carry out a structure−activity study on the antifeedant action of these molecules against several divergent insect species.

Species belonging to the family Asteraceae are an important source of terpenes and alkaloids with biological activity.[1,2] Our previous work on endemic Asteraceae species found in the Canary Islands has resulted in the isolation of a tricyclopentanoid silphinene sesquiterpene, 11*β*-acetoxy-5α-angeloyloxysilphinen-3-one, from *Senecio palmensis* Chr. Sm., as well as related C-5/C-11-substituted derivatives that were found to be very efficient antifeedants against several divergent insect species.[3−6]

Given the importance of this class of molecules as model insect antifeedants and their potential as new GABA modulators,[6,7] we carried out additional chemical work on *S. palmensis*, resulting in the isolation of the known sesquiterpenes (6*S*)-2,10-bisaboladien-1-one (**1**), 6,7-epoxy-3(15)-caryophyllene (**2**), 6,7-epoxy-2,9-humuladiene (**3**), 5α-angeloyloxysilphinen-3-one (**4**), 5α-acetoxysilphinen-3-one (**6**), and the new silphinenes 5α-senecioyloxysilphinen-3-one (**5**), 5α-tigloyloxysilphinen-3-one (**7**), and 3*β*-hydroxy-5α-angeloyloxysilphinene (**8**). We have also generated a series of semisynthetic analogues, silphinen-3,5-dione (**9**), 5α-hydroxysilphinen-3-one (**10**), 5*β*-hydroxysilphinen-3-one (**11**), 5*β*-acetoxysilphinen-3-one (**12**), 5*β*-isobutyryloxysilphinen-3-one (**13**), and 5α-isobutyryloxysilphinen-3-one (**14**), to carry out a preliminary structure−activity study on the antifeedant action of these molecules against several divergent insect species, including the lepidopteran *Spodoptera littoralis*, the chrysomelid *Leptinotarsa decemlineata* (Colorado potato beetle, CPB), and five aphid species with diverse host adaptations.



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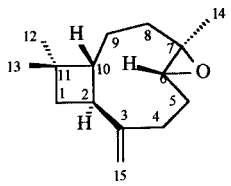

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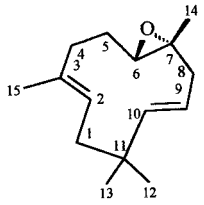


3

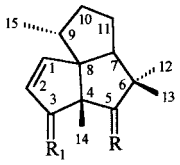
4 R= ·····Oang; R_1=O

5 R= ·····Osen; R_1=O

6 R= ·····OAc; R_1=O

7 R= ·····Otig; R_1=O

8 R= ·····Oang; R_1=OH



9 R= R_1= O

10 R= ·····OH; R_1=O

11 R= —OH; R_1=O

12 R= —OAc; R_1=O

13 R= —Oisobut; R_1=O

Results and Discussion

Compounds **1**−**3** were identified by comparison with previously published physical and NMR data.[3,11,12]

The molecular formulas of compounds **4**−**8** were derived from their HRMS and ^{13}C NMR spectral data. The ^1H NMR spectra of these compounds were similar to those of sesquiterpenes isolated from *Cineraria geifolia*.[8] Thus, compounds **4** and **6** were identified as 5α-angeloyloxysilphinen-3-one and 5α-acetoxysilphinen-3-one, respectively, with their ^{13}C NMR data being reported herein for the first time (Table 2).

Compounds **5** and **7** have the same molecular formula, $C_{20}H_{28}O_3$. Their ^1H NMR spectra were very similar, having proton signals characteristic of a tricyclopentanoid sesquiterpene silphinene skeleton with additional proton signals at δ_H 5.79 (H, br s), 1.92 (3H, s), and 2.20 (3H, s). These signals correlated with carbon resonances at δ_C 116.0 (d, C-2′), 27.4 (q, C-5′), and 20.3 (q, C-4), corresponding to a senecioyl group in compound **5**. The proton signals at δ_H

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Table 1. ^{1}H, ^{13}C, COSY, HMQC, and HMBC NMR Data of Compound **8**[a]

				(correlated carbon)	
proton	δ (J_{H-H} in Hz)	COSY		HMQC	HMBC
1	5.84 dd (5.7, 1.4)	H-2, H-3α,		140.5 d	C-2, C-3, C-4, C-8
2	5.62 dd (5.7, 2.0)	H-1, H-3α		129.6 d	C-1, C-3, C-4, C-8
3α	5.17 br d	H-1, H-2		80.7 d	
			C-4	57.5 s	
5β	5.12 br s			86.7 d	C-1′, C-3, C-6, C-13, C-14
			C-6	42.2 s	
7α	1.86 dd (11.4, 7.7)	H-11α, H-11β		28.8 t	C-1, C-4, C-5, C-6, C-8, C-13
			C-8	67.5 s	
9β	1.98 m	H-15		39.5 d	C-4, C-8, C-10, C-14
10α	1.17 m	H-9β, H-10β, H-11β		35.9 t	C-8, C-9
10β	1.81 m	H-9β, H-10α			C-7, C-8
11α	1.66 m	H-7, H-10β, H-11β		28.9 t	C-8, C-9
11β	1.32 dddd (12.2, 6.0, 5.4)	H-7, H-10α, H-11α			C-6, C-7
12	0.91 s			24.2 q	C-5, C-6, C-7, C-13
13	0.92 s			25.6 q	C-5, C-6, C-7, C-12
14	1.02 s			17.5 q	C-3, C-4, C-5, C-8, C-13
15	0.87 d (7.0)	H-9β		15.9 q	C-8, C-9, C-10
			C-1′	167.4 s	
			C-2′	126.8 s	
3′	6.07 dq (7.2, 1.4)	H-4′		138.1 d	C-1′, C-5′
4′	2.03 dd (7.2, 1.4)	H-3′		15.7 q	C-2′, C-3′
5′	1.94 quint. (1.4)	H-4′		20.7 q	C-1′, C-2′, C-3′

[a] Coupling constants (Hz) are shown in parentheses.

Table 2. ^{13}C NMR Assignments for Compounds **2**−**7**, **9**−**11**, and **13**[a]

carbon	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**13**
1	50.7	40.2	168.0	168.1	168.4	168.1	170.4	171.2	169.9	169.2
2	27.1	125.7	130.3	130.1	130.4	130.1	129.1	129.9	127.7	128.8
3	39.1	131.8	211.7	212.0	211.1	212.0	215.0	218.5	210.0	212.8
4	59.8	36.6	56.8	56.6	56.0	56.9	55.0	56.3	59.2	60.2
5	63.7	24.7	85.7	85.1	86.2	85.8	204.5	87.1	84.8	86.3
6	30.1	61.9	42.7	42.6	42.0	42.8	50.0	42.6	46.6	44.9
7	29.7	61.9	58.0	58.0	58.0	58.0	56.7	57.2	57.9	59.6
8	151.8	42.6	64.9	64.8	64.0	64.6	62.6	63.2	67.6	67.4
9	48.7	122.1	38.6	38.6	38.6	38.5	38.8	38.5	38.9	38.9
10	39.7	143.1	35.6	35.7	35.7	35.6	35.1	35.4	36.3	36.3
11	33.9	36.5	28.2	28.3	28.3	28.4	29.9	29.0	26.3	29.6
12	21.5	29.0	24.4	24.2	24.2	24.2	21.5	22.8	29.1	29.6
13	29.8	25.5	24.6	24.6	24.6	24.6	28.6	25.0	19.8	28.9
14	16.9	36.6	19.6	19.5	19.7	19.5	17.8	19.2	13.8	19.2
15	112.7	15.0	16.0	16.0	16.1	16.0	16.6	15.8	16.0	15.5
1′			167.3	168.3	170.5	167.6				164.0
2′			127.8	116.0	20.9	128.4				34.4
3′			138.7	157.1		137.9				21.3
4′			15.7	27.5		14.4				15.8
5′			20.5	20.3		11.9				

[a] Multiplicities were determined by DEPT data.

6.99 (H, qq, J = 7.0, 1.1 Hz), 1.80 (3H, dq, J = 7.0, 1.2 Hz), and 1.85 (3H, quint., J = 7.2 Hz) correlated with the corresponding carbon in the HSQC[9] experiment at δ_C 137.9 (d, C-3′), 11.9 (q, C-5′), and 14.4 (q, C-4′), corresponding to a tigloyl group in compound **7**. An HMBC experiment confirmed the positions of attachment of the acyl portions at C-5 in compounds **5** and **7**.

Compound **8** was isolated as an oil, and its HREIMS produced a molecular ion peak at *m*/*z* 318.2209 (2.2%) for $C_{20}H_{30}O_3$, with several significant fragment ions observed at *m*/*z* 300.2071, $C_{20}H_{28}O_2$ (calcd 300.2089), *m*/*z* 235.1685 (33%), $C_{15}H_{23}O_2$ (calcd 235.1698), *m*/*z* 217.1596 (71%), $C_{15}H_{21}O$ (calcd 217.1592), and the base peak seen at *m*/*z* 83 (100%). The spectroscopic data of compound **8** (Table 1) corresponded to those of compound **4**, with the exception of the carbonyl group signals on a pentacyclic ring (ν_{max} 1745 cm^{-1} and δ_C 210−212 ppm). The ^{1}H NMR spectra of **8** did not show proton signals for a conjugated five-membered ring ketone at δ_H 7.62 and 6.04, while two olefinic proton doublets were observed at δ_H 5.80 and 5.59. These proton signals were correlated in the HMBC spectrum with carbons at δ_C 140.5 (d, C-1) and 129.7 (d, C-2) and had long-range connectivities with the carbon resonances at δ_C 80.7 (d, C-3), 57.5 (s, C-8), and 67.5 (s, C-4). The broad proton doublet at δ_H 5.17 (J = 6.2 Hz), which correlated with the carbon at δ_C 80.7 (d) (HSQC experiment) and carbons at δ_C 140.5 (d) and 129.7 (d) in a HMBC experiment, could be attributed to a geminal proton of a hydroxyl group located at C-3. Oxidation of compound **8** with Cornforth's reagent afforded compound **4**. The stereochemistry was established by a GOESY 1D experiment with pulsed-field gradients (PFG).[10] A selective excitation at δ_H 5.17 (br d, H-3) gave a 1D spectrum with proton signals having a positive NOE effect at δ_H 5.62 (dd, H-2) and 0.91 (3H, s, H-12). Therefore, the structure proposed for compound **8** is 3β-hydroxy-5α-angeloyloxysilphinene.

The hydrolysis of **4** and **7** with a methanolic KOH solution (35%) afforded compounds **10** and **11** (ratio 3:1) resulting from solvolytic reaction. Their structures were established by 1D and 2D NMR, including a ROESY experiment. Thus, a selective excitation at δ_H 3.64 (H, s, H-5β) and δ_H 3.60 (H, s, H-5α) of compounds **10** and **11**,

Table 3. Effective Antifeedant Doses (EC_{50}) and 95% Confidence Limits (Lower, Upper) of the Test Compounds on *S. littoralis* L6 Larvae, Adult *L. decemlineata*, and Five Species of Apterous Adult Aphids

	EC_{50} (95% CL) (nmol/cm^2)						
compound	*S. littoralis*	*L. decemlineata*	*M. persicae*	*R. padi*	*S. avenae*	*M. dirhodum*	*D. noxia*
1	>200	66.5 (16.1, 274.5)	92.2 (74.5, 114.1)	110.0 (81.8, 147.5)	84.4 (38.5, 86.8)	57.8 (38.5, 86.8)	14.9 (9.9, 22.2)
2	159.1 (48.6, 523.2)	>200	>500	43.3 (23.7, 79.1)	>200	70.5 (43.7, 113.6)	38.4 (22.9, 64.3)
3	>200	28.7 (9.0, 92.0)	>200	>200	>200	>200	>180
4	>200	>150	>200	~190	31.6 (25.3, 41.7)	>150	>150
5	>100	6.3 (1.0, 38.2)	>180	>400	na[a]		>100
6	>200	2.81 (1.1, 7.1)	>500	>200	>200	~180	57.4 (8.6, 85.0)
7	>200	43.9 (13.7, 141.5)	29.1 (11.4, 73.7)	39.8 (17.4, 90.5)	>100	>150	29.8 (15.2, 56.8)
8	~100	22.1 (9.4, 51.9)	>200	na[a]	na[a]	na[a]	>150
9	>100	4.82 (2.2, 10.4)	>200	>150	>200	54.7 (31.9, 93.9)	25.6 (4.9, 48.6)
10	>100	6.06 (2.09, 23.0)	>200	38.0 (22.6, 64.5)	>200	>200	26.1 (12.8, 51.3)
11	>200	18.3 (5.7, 56.6)	>200	14.1 (2.6, 23.1)	23.1 (13.7, 39.3)	~256	32.0 (20.5, 49.6)
12	>100	2.4 (0.9, 6.1)	>500	>500	~181	>180	65.5 (38.4, 111.8)
13	18.7 (5.9, 58.2)	3.4 (1.4, 8.2)	>100	na[a]	na[a]	na[a]	35.8 (20.8, 61.6)

[a] na, insuficient compound available.

respectively, gave a positive NOE with proton signals at δ_H 0.96 (3H, s, H-13β) and 1.24 (3H, s, H-14) for compound **10** and δ_H 0.86 (3H, s, H-12) for compound **11**, clarifying the stereochemistry at C-5 for both compounds. Compound **10** was treated with isobutyric anhydride in pyridine to afford **14**. Furthermore, the hydrolysis of **14** under similar conditions gave compounds **10** and **11**.

An equimolecular amount of compounds **10** and **11** treated with Cornforth's reagent in pyridine for 48 h at room temperature gave compound **9**. Its spectra lacked the proton signal on C-5 (see ^{1}H and ^{13}C NMR data in the Experimental Section and Table 2). Additionally, compound **11** was acetylated with Ac_2O/pyridine to form **12** in order to further enhance the structure−activity study.

The antifeedant effects of compounds **1**−**13** were species-dependent (Table 3). The polyphagous *S. littoralis* was sensitive to silphinene **13**, while *L. decemlineata*, a specialist of some Solanaceae species,[13−15] responded to most of the sesquiterpenes (except **2** and **4**). In turn, *Myzus persicae* (with more than 40 host-plant families) was sensitive to compounds **1** and **7**. *Rhopalosiphum padi* (the most polyphagous among the cereal aphids[16]) was sensitive to **1**, **2**, **7**, **10**, and **11**, while *Sitobion avenae* and *Metopolophium dirhodum*, both specialists of grasses and cereals as secondary hosts,[16] were moderately sensitive to these compounds (*S. avenae* responded to **1**, **4**, and **11**; *M. dirhodum* to **1**, **2**, and **9**). *Diuraphis noxia*, with the most restricted host range (limited to wheat and barley[16]), was the most sensitive aphid to these silphinene derivatives (**1**, **2**, **6**, **7**, **9**−**13**). These results are consistent with a previous model suggesting that differences in taste sensitivity to deterrent compounds could account for the difference in host range.[17,18] These insects also responded to C-5/C-11-substituted silphinenes and the GABA modulators thymol and picrotoxinin,[6] supporting the hypothesis of a shared molecular mechanism for antifeedant taste chemoreception in divergent insect species.[5]

L. decemlineata responded to most of the compounds tested, as expected from their structural similarities with the C-5/C-11-substituted silphinenes and their possible biogenetic relationships with compounds **2** and **3**.[6,19,20] Compounds **6**, **12**, **13**, and **9** were the most active ones, followed by **10**, **5** (2−3 times less active), **11**, **8**, **3** (9−15 times less active), **7**, **1** (22−23 times less active), and **2** (>100 times less active) (Table 3). Most of the silphinenes were also active against *D. noxia* with lower potency than for CPB. Compounds **9**, **10**, and **7** were the most active, followed by **11**, **13**, **6**, and **12** (Table 3).

Among sesquiterpenes **1**−**3**, bisabolene **1** was the most active. This compound has been previously described as an effective antifeedant against *L. decemlineata* and *M. persicae*.[3,21] Bisabolene derivatives also play a role in insect behavior acting as sex pheromones.[22,23]

β-Caryophyllene epoxide (**2**) deterred three of the five aphid species. Previous studies have shown that β-caryophyllene oxide acts as an aphid alarm pheromone inhibitor with a similar role in ladybirds,[24] suggesting a strong molecular selectivity of action for this compound on aphids. Beetle mortality increased when injected with **2** (64% mortality at 72 h). This lack of correlation between antifeedant and toxic effects has been previously described for the toxicity of C-5/C-11 silphinenes on CPB.[4−6] This compound has phytotoxic effects.[25] Furthermore, structurally related β-caryophyllene derivatives have cytotoxic and antimalarial effects[26,27] that could explain the toxicity of **2** on CPB.

Humulene and derivatives exhibit phytotoxic and cytotoxic activities.[28] However, this is the first report on the antifeedant action of humuladiene epoxide (**3**).

Table 4 summarizes the comparative structure−activity relationships for the antifeedant effects of silphinenes on *L. decemlineata* and *D. noxia*. Esterification of C-5 with different substituents had a strong effect on the activity of these compounds on CPB (Ac as in **6** or isobut as in **13** > sen as in **5** > tig as in **7** > ang as in **4**) and a milder effect on *D. noxia* (tig as in **7**, **13** > Ac as in **6** and **12** > sen as in **5** and ang as in **4**). The comparison with the C-5/C-11-substituted silphinenes[6] showed that the presence of a β-Ac group in C-11 had varying effects on their activity on CPB, ranging from a significant to moderate increase depending on the type of C-5 substituent (258-fold for ang, 187-fold for tig, 4-fold for isobut, 3-fold for Ac). On the contrary, the presence of a β-Ac group in C-11 significantly decreased the activity on *D. noxia* except with an ang or isobut substituent in C-5 (Table 3). The hydrolysis (**10**, **11**) or oxidation (**9**) of the substituent in C-5 did not have a significant effect on the activity on CPB or *D. noxia*. However, the hydrolysis or oxidation at C-11 resulted in the loss of activity on *D. noxia* (both) or CPB (oxidation) (Table 3). Therefore, we can conclude that C-11 plays a key role in the antifeedant activity of silphinenes since its acetylation increased their action on *L. decemlineata* and decreased it on *D. noxia*.

Insufficient structural diversity was represented among the compounds listed to establish structure−activity relationships for the C-3 substituents of silphinenes. However, the presence of a hydroxyl group in this position increased the activity on *L. decemlineata* (>7-fold increase, **8** versus **4**) (Table 4).

Table 4. Antifeedant Structure−Activity Relationships of Silphinene Sesquiterpenes from *S. palmensis*

compound	substituents			EC_{50} (nmol/cm^2)	
	C-3	C-5	C-11	*L. decemlineata*	*D. noxia*
4	=O	α-ang	H	>150	>150
8	α-OH	α-ang	H	22	>150
11β-acetoxy-5α-angeloyloxysilphinen-3-one[a]	=O	α-ang	β-Ac	0.8	31
7	=O	α-tig	H	44	30
11β-acetoxy-5α-tigloyloxysilphinen-3-one[a]	=O	α-tig	β-Ac	0.17	>120
6	=O	α-Ac	H	2.8	57
12	=O	β-Ac	H	2.4	65
11β,5α-diacetoxysilphinen-3-one[a]	=O	α-Ac	β-Ac	1.0	≈100
13	=O	β-isobut	H	3.4	36
11β-acetoxy-5α-isobutyryloxysilphinen-3-one[a]	=O	α-isobut	β-Ac	0.08	8.0
9	=O	=O	H	4.8	25
silphinen-3,5,11-trione[a]	=O	=O	=O	>100	>200
10	=O	α-OH	H	6	26
11	=O	β-OH	H	18	32
11β,5α-dihydroxysilphinen-3-one[a]	=O	α-OH	β-OH	4.8	>200

[a] From ref 6.

The antifeedant mode of action of silphinenes remains unknown. However, the CPB antifeedants 11β-acetoxy-5α-angeloyloxysilphinen-3-one and 11β-hydroxy-5α-angeloyloxysilphinen-3-one are GABA antagonists at mammalian receptors.[7] These results paralleled their rootworm antifeedant action and their effects on excitation of galeal chemoreceptors,[5] supporting the hypothesis of GABA-mediated silphinene taste regulation in chrysomelid insects.[29]

In summary, C-5-substituted silphinenes such as **5**−**13** are more efficient Colorado potato beetle and aphid antifeedants than their biogenetic precursors (**2** and **3**). A comparative study of their activity with that of C-5/C-11-substituted analogues showed that esterification in C-5 and acetylation in C-11 are important structural requirements for the antifeedant action of these molecules.

Experimental Section

General Experimental Procedures. Optical rotations were determined at room temperature using a Perkin-Elmer 241 polarimeter. IR spectra were taken on a Perkin-Elmer 1600 FT spectrometer. NMR spectra were measured on a Bruker AMX2 500 MHz spectrometer with pulsed-field gradient, using the solvent as internal standard ($CDCl_3$, at δ_H 7.26 and δ_C 77.0). Exact mass measurements and EIMS were recorded on an Autospect instrument at 70 eV. HPLC were carried out on a Beckman System Gold equipped with a UV−visible diode array detector, model 168. Sephadex LH-20 (Pharmacia) and silica gel from Merck (15111, 7741, 5554, and 5715) were used for column chromatography, TLC, and preparative TLC. Sesquiterpenes were visualized on TLC with a 25% H_2SO_4 solution.

Plant Material. *Senecio palmensis* Chr. Sm. (Asteraceae) was collected in Boca Tauce, Tenerife, Spain, in July 1996 and identified by Dr. A. Santos. A voucher specimen has been deposited in the Botanical Garden in La Orotava, Tenerife, Spain (voucher number ORT 36393).

Insect Bioassays. Insects: *Spodoptera littoralis*, *Leptinotarsa decemlineata*, and aphid colonies (*Myzus persicae*, *Diuraphis noxia*, *Rhopalosiphum padi*, *Metopolophium dirhodum*, and *Sitobion avenae*) were reared on artificial diet[30] and their respective host plants (*Solanum tuberosum*, *Capsicum annuum*, and *Hordeum vulgare*) and maintained at 22 ± 1 °C, >70% relative humidity with a photoperiod of 16:8 h (L:D) in a growth chamber.

Choice Feeding Assays. These experiments were conducted with *S. littoralis* L6 larvae, adult *L. decemlineata*, and apterous aphid adults. Percent feeding inhibition (%FI) and percent settling inhibition (%SI) were calculated as described by Reina et al.[2] Compounds with an FR/SI > 50% were tested in a dose−response experiment to calculate their relative potency (EC_{50} values, the effective dose for 50% feeding reduction), which was determined from linear regression analysis (%FR or %SI on log dose).

Hemolymph Injection. DMSO solutions of the test compounds (10 μg/insect) were injected in 20 adult *L. decemlineata* beetles as described by Reina et al.[2] Beetle mortality was recorded up to 3 days after injection. Percent mortality was analyzed with contingency tables and corrected according to Abbott.[31]

Extraction and Isolation. Dried aerial parts of *S. palmensis* (2.8 kg) were exhaustively extracted with EtOH. The ethanolic extract (1000 g, 35.7% yield of dry plant weight) was chromatographed on a silica gel (Si gel) vacuum-liquid chromatography column (VLC) using a hexane−EtOAc−MeOH gradient (100:0−50:50) to give fractions A−G.

A portion (2.1 g) of fraction B (75.00 × 10^{-3}% yield) was purified by Si gel vacuum-liquid chromatography (hexane−EtOAc, 100:0−90:10) and by passage over Sephadex LH-20 (hexane−CH_2Cl_2−MeOH, 3:1:1) to give fractions B_1 (240 mg) and B_2 (400 mg). Fraction B_1 was chromatographed by preparative TLC (20 × 20 × 0.5 mm, Schleicher & Schuell G1500 plates, hexane−EtOAc, 96:4) to obtain 90 mg of compound **1** (3.00 × 10^{-3}% yield). Fraction B_2 was chromatographed over Sephadex LH-20 to afford 95 mg of a mixture of compounds **2**−**4**. These compounds were separated by semi-preparative normal-phase HPLC on a 250 × 20 mm silica column (Inertsil Prep-Sil, 10 μm particle size) at a flow rate of 10 mL min^{-1} and an isocratic mixture of hexane−EtOAc (96:4) to obtain 57.8 mg of **1** (2.00 × 10^{-3}% yield), 17.0 g of **2** (0.60 × 10^{-3}% yield), and 8.0 mg of **3** (0.28 × 10^{-3}% yield). Peaks were detected at 254 nm.

A portion (2.0 g) of fraction C (0.07%, hexane−EtOAc, 97:3) was chromatographed over Sephadex LH-20 and Si gel to obtain fractions C_1 (250 mg of a mixture of **4** and **7**), C_2 (50 mg of a mixture of **5** and **6**), and C_3 (24 mg of **8**). These fractions were further purified by semipreparative normal-phase HPLC on a 250 × 10 mm silica column (Ultrasphere, 5 μm particle size) at a flow rate of 3 mL min^{-1} with an isocratic mixture of hexane−EtOAc (94:6) to obtain 50 mg of **4** (2.00 × 10^{-3}% yield), 5.0 mg of **5** (0.17 × 10^{-3}% yield), 4.0 mg of **6** (0.14 × 10^{-3}% yield), 10.5 mg of **7** (0.36 × 10^{-3}% yield), and 7.0 mg of **8** (0.24 × 10^{-3}% yield). Peaks were detected at 254 nm.

(6*S*)-2,10-Bisaboladien-1-one (1): oil; $[\alpha]_D$ −34° (*c* 0.34, EtOH) {lit. $[\alpha]_D$ −37° ($CHCl_3$)};[15] EIMS *m*/*z* $[M]^+$ 220 (34), 205 (4), 151, (5), 137 (100), 135 (58), 123 (6), 121 (5), 110 (59), 109 (22), 121 (51), 95 (18), 82 (18) 69 (27), 67 (12), 55(22), 53 (9); HREIMS *m*/*z* $[M]^+$ 220.1820 (34), calcd for $C_{15}H_{24}O$ 220.1827); $[M - C_6H_{11}]^+$ 137.1013 (100), for $C_9H_{13}O$ (calcd 137.9066); ^1H and ^{13}C NMR data, see ref 3.

6,7-Epoxy-3(15)-caryophyllene (2): oil; $[\alpha]_D$ −40° (*c* 0.04, $CHCl_3$) {lit. $[\alpha]_D$ −66° ($CHCl_3$)};[14] ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.97 and 2.10 (H each, ddd, J = 13.2, 5.0, 5.0 Hz H-8β and

H-8α), 0.99 (3H, s, H-12), 1.08 (3H, s, H-13), 1.20 (3H, s, H-14), 1.32 and 2.24 (H each, m, H-5*β* and H-5α), 1.45 and 1.67 (H each, m, H-9α and H-9*β*), 1.65 and 1.69 (H each, m, H_2-1), 1.77 (H, t, J = 9.8 Hz, H-10), 2.10 and 2.34 (H each, m, H-4α and H-4*β*), 2.62 (H, q, J = 9.3 Hz, H-2α), 2.88 (H, dd, J = 10.6, 4.2 Hz, H-6), 4.86 and 4.98 (H, s, H-15a and H-15b); EIMS *m/z* 220 $[M]^+$ (20), 202 (46), 187 (49), 161 (62), 145 (30), 131 (40), 121 (50), 107 (64), 93 (97), 79 (100), 69 (64), 55 (66); HREIMS *m/z* $[M]^+$ 220.1827 (20), calcd for $C_{15}H_{24}O$ 220.1827; ^{13}C NMR data see Table 2.

6,7-Epoxy-2,9-humuladiene (3): oil; IR ($CHCl_3$) ν_{max} 3019, 1522, 1423, 1211, 1047, 929, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 1.08 (3H, s, H-13), 1.11 (3H, s, H-12), 1.31 (3H, s, H-14), 1.36 and 2.17 (H each, m, H-5α and H-5*β*), 1.55 (3H, s, H-15), 1.65 (H, t, J = 11.2 Hz, H-8α), 1.88 and 2.00 (H each, dd, J = 13.5, 9.2 Hz, H-1α and H-1*β*), 2.11 and 2.23 (H each, m, H-4*β* and H-4α), 2.53 (H, dd, J = 10.2, 3.9 Hz, H-6), 2.58 (H, dd, J = 12.3, 5.1 Hz, H-8*β*), 5.00 (H, br dd, J = 8.9, 5.9 Hz, H-2), 5.16 (H, d, J = 15.9 Hz, H-10), 5.29 (H, dddd, J = 15.5, 5.5, 5.5, 5.0 Hz, H-9); EIMS *m/z* 220 $[M]^+$ (1), 205 (16), 202 (46), 187 (49), 174 (20), 161 (63), 159 (40), 145 (30), 138 (38), 131 (40), 121 (51), 107 (64), 93 (97), 79 (100), 69 (76), 55 (66); HREIMS *m/z* $[M]^+$ 220.1836 (1), calcd for $C_{15}H_{24}O$ 220.1827; ^{13}C NMR data, see Table 2.

5α-Angeloyloxysilphinen-3-one (4): oil; $[\alpha]_D$ −59.2° (*c* 0.29, $CHCl_3$) {lit. $[\alpha]_D$ −69° ($CHCl_3$)};[5] IR ($CHCl_3$) ν_{max} 2950, 2878, 1707, 1590, 1457, 1233, 1157, 1130, 1084, 977 and 834 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.81 (3H, s, H-12), 0.89 (3H, d, J = 7,0 Hz, H-15), 0.91 (3H, s, H-13), 1.17 (3H, s, H-14), 1.33 (H, dddd, J = 12.3, 12.3, 5.7, 4.4 Hz, H-10α), 1.43 (H, dddd, J = 12.3, 12.3, 5.7 Hz, H-11*β*), 1.75 (H, m, H-11α), 1.91 (H, m, H-10*β*), 1.92 (H, t, J = 1.4 Hz, H-5′), 2.0 (3H, dd, J = 7.3, 1.4 Hz, H-4′), 2.10 (H, dd, J = 10.6, 7.9 Hz, H-7α), 2.16 (H, m, H-9*β*), 5.12 (H, s, H-5*β*), 5.97 and 7.53 (H each, d, J = 5.6 Hz, H-2 and H-1, respectively), 6.07 (H, dq, J = 7.2, 1,4 Hz, H-3′); EIMS *m/z* 316 $[M]^+$ (6), 307 (2), 245 (1), 233 (31), 218 (18), 217 (100), 83 (79), 55 (38); HREIMS *m/z* $[M]^+$ 316.2034, calcd for $C_{21}H_{30}O_5$ 316.2038; $[M - C_4H_7O]^+$ 245.1539, calcd for $C_{16}H_{21}O_2$ 245.1541; $[M - C_5H_7O]^+$ 233.1555, calcd for $C_{15}H_{21}O_2$ 233.1541; ^{13}C NMR data, see Table 2.

5α-Senecioyloxysilphinen-3-one (5): oil; $[\alpha]_D$ −7.1° (*c* 1.4 × 10^{-2}, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.83 (3H, s, H-12), 0.92 (3H, s, H-13), 0.92 (3H, d, J = 6.8 Hz, H-15), 1.19 (3H, s, H-14), 1.35 (H, dddd, J = 11.9, 11.9, 7.0, 5.2, Hz, H-10α), 1.45 (H, dddd, J = 11.5, 11.5, 5.6 Hz, H-11*β*), 1.77 (H, m, H-11α), 1.92, (3H, s, H-4′), 1.96 (H, m, H-10*β*), 2.13 (H, dd, J = 10.8, 8.0 Hz, H-7α), 2.19 (3H, s, H-5′), 2.20 (H, m, H-9), 5.10 (H, s, H-5*β*), 5.79 (H, br s, H-2′), 6.01 and 7.58 (H, d, J = 5.7 Hz, H-2 and H-1, respectively); EIMS *m/z* 316 $[M]^+$ (1), 288 (1), 279 (1), 233 (34), 217 (15), 163 (13), 97 (10), 83 (100), 55 (14); HREIMS *m/z* $[M]^+$ 316.2034, calcd for $C_{20}H_{28}O_3$ 316.2038; $[M - CO]^+$ 288.2101, calcd for $C_{19}H_{28}O_2$ 288.2089; $[M - C_5H_7O]^+$ 233.1552, calcd for $C_{15}H_{21}O_2$ 233.1541; ^{13}C NMR data, see Table 2.

5α-Acetoxysilfinen-3-one (6): oil; $[\alpha]_D$ −3 (*c* 4.2 × 10^{-2}, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.80 (3H, s, H-12), 0.89 (3H, s, H-13), 0.91 (3H, d, J = 7.0 Hz, H-15), 1.15 (3H, s, H-14), 2.12 (H, m, H-9), 5.00 (H, s, H-5*β*), 5.99 (H, d, J = 5.3 Hz, H-2), 7.54 (H, d, J = 5.6 Hz, H-2), 7.54 (H, d, J = 5.6 Hz, H-1); EIMS *m/z* 276 $[M]^+$ (4), 234 (31), 233 (40), 206 (19), 179 (31), 163 (100), 91 (20), 55 (24); HREIMS *m/z* $[M]^+$ 276.1720, calcd for $C_{17}H_{24}O_3$ 276.1725; $[M - C_2H_3O]^+$ 233.1542, calcd for $C_{15}H_{21}O_2$ 233.1542; $[M - C_9H_5]^+$ 163.1265, calcd for $C_8H_{19}O_3$ 163.1334; ^{13}C NMR data, see Table 2.

5α-Tigloyloxysilphinen-3-one (7): oil; $[\alpha]_D$ −67.2° (*c* 5.8 × 10^{-2}, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.82 (3H, s, H-12), 0.90 (3H, s, H-13), 0.91 (3H, d, J = 6.2 Hz, H-15), 1.14 (3H, s, H-14), 1.34 (H, dddd, J = 12.0, 12.0, 6.5, 5.0, Hz, H-10α), 1.43 (H, dddd, J = 12.2, 12.2, 6.5, 5.0 Hz, H-11*β*), 1.76 (H, m, H-11α), 1.80, (3H, dq, J = 7.0, 1.2 Hz, H-4′), 1.85 (3H, quint., J = 1.2 Hz, H-5′) 1.93 (H, m, H-10*β*), 2.10 (H, dd, J = 11.0, 7.9 Hz, H-7α), 2.17 (H, m, H-9), 5.09 (H, s, H-5*β*), 6.99 (H, qq, J = 7.0, 1.4 Hz, H-3′), 5.99 and 7.56 (H, d, J = 5.7 Hz, H-2 and H-1, respectively); EIMS *m/z*, 316 $[M]^+$ (24), 245 (4), 234 (29), 233 (100), 217 (22), 206 (7), 163 (8), 83 (64), 55 (16); HREIMS *m/z* $[M]^+$ 316.1986, calcd for $C_{20}H_{28}O_3$ 316.2038; $[M - C_5H_7O]^+$ 233.1503(100), calcd for $C_{15}H_{21}O_2$ 233.1541; $[M - C_5H_7O_2]^+$ 217.1530, calcd for $C_{15}H_{21}O$ 217.1592; ^{13}C NMR data, see Table 2.

3*β*-Hydroxy-5α-angeloyloxysilphinene (8): oil; $[\alpha]_D$ +3° (*c* 0.84 $CHCl_3$); IR (NaCl) ν_{max} 3049, 2931, 1734, 1654, 1458, 1264, 1189 cm^{-1}; EIMS *m/z* 318 $[M]^+$ (1.6), 300 (0.6), 235 (41), 218 (51), 217 (74), 203 (17), 190 (10), 189 (11), 123 (38), 83 (100), 55 (51); HREIMS *m/z* $[M]^+$ 318.2209, calcd for $C_{20}H_{30}O_3$ 318.2194); $[M - H_2O]^+$ 300.2071, calcd for $C_{20}H_{28}O_2$ 300.2089; $[M - C_5H_7O]^+$ 235.1685, calcd for $C_{15}H_{23}O_2$ 235.1698; $[M - C_5H_7O_2]^+$ 218.1672, calcd for $C_{15}H_{22}O$ 218.1670; $[M - C_5H_8O]^+$ 217.1596, calcd for $C_{15}H_{21}O$ 217.1592; ^1H and ^{13}C NMR data, see Table 1.

Silphinen-3,5-dione (9): oil; IR (NaCl) ν_{max} 1744 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.85 (3H, s, H-12), 0.95 (3H, d, J = 7.0 Hz, H-15), 1.00 (3H, s, H-13), 1.23 (3H, s, H-14), 1.21 (H, dddd, J = 12.0, 12.0, 5.6 Hz, H-11*β*), 1.39 (H, dddd, J = 12.0, 12.0, 5.2 Hz, H-10α), 1.87 (H, m, H-11α), 1.95 (H, m, H-10*β*), 2.16 (H, m, H-9*β*), 2.26 (H, dd, J = 11.5, 7.3 Hz, H-7α), 6.06 and 7.77 (H, d, J = 5.6 Hz, H-2 and H-1, respectively); EIMS *m/z* 232 $[M]^+$ (100), 215 (17), 204 (22), 189 (50), 162 (55), 147 (43), 91 (34), and 55 (44); HREIMS *m/z* $[M]^+$ 232.1466, calcd for $C_{15}H_{20}O_2$ 232.1463; ^{13}C NMR data, see Table 2.

5α-Hydroxysilphinen-3-one (10): oil; $[\alpha]_D$ +1° (*c* 2.25 × 10^{-1}, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.68 (3H, s, H-12), 0.94 (3H, s, H-13), 0.94 (3H, d, J = 7.0 Hz, H-15), 1.22 (3H, s, H-14), 1.26 (H, m, H-10α), 1.27 (H, m, H-11*β*), 1.72 (H, m, H-11α), 1.82 (H, m, H-10*β*), 2.00 (H, dd, J = 3.8, 10.7 Hz, H-7α), 2.01 (H, m, H-9*β*), 3.61 (H, s, H-5*β*), 5.99 and 7.65 (H, d, J = 5.6 Hz, H-2 and H-1, respectively); EIMS *m/z* 234 $[M]^+$ (100), 216 (9), 206 (19), 205 (56), 191 (16), 163 (45), 152 (23), 151 (21), 150 (18), 124 (87), 123 (67), 91 (20), 69 (34), 55 (20); HREIMS *m/z* $[M]^+$ 234.1625, calcd for $C_{15}H_{22}O_2$ 234.1619; ^{13}C NMR data, see Table 2.

5*β*-Hydroxysilphinen-3-one (11): oil; $[\alpha]_D$ −20.3° (*c* 0.118, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.86 (3H, s, H-12), 0.86 (3H, d, J = 7.0 Hz, H-15), 0.94 (3H, s, H-13), 1.14 (3H, s, H-14), 1.43 (H, ddddd, J = 12.1, 12.1, 7.0 Hz, H-10α), 1.64 (H, m, H-11*β*), 1.70 (H, m, H-11α), 1.96 (H, m, H-10*β*), 1.97 (H, d, J = 9.0 Hz, H-7α), 2.19 (H, m, H-9*β*), 3.60 (H, s, H-5*β*), 5.90 and 7.54 (H, d, J = 5.7 Hz, H-2 and H-1, respectively); EIMS *m/z*, 234 $[M]^+$ (12), 206 (21), 179 (20), 163 (100), 123 (25), 124 (35), 91 (13), 69 (14), 55(12); HREIMS *m/z* $[M]^+$ 234.1610, calcd for $C_{15}H_{20}O_2$ 234.1619; $[M - CO]^+$ 206.1669, calcd for $C_{14}H_{22}O$ 206.1670; $[M - C_4H_7O]^+$ 163.1118, calcd for $C_{11}H_{15}O$ 163.1122; ^{13}C NMR data, see Table 2.

Acetylation of 11. A mixture of compound **11** (5.0 mg), pyridine (0.2 mL), and acetic anhydride (0.1 mL) was kept at room temperature for 24 h. The reaction product was chromatographed over Si gel (hexanes−EtOAc, 85:15) to afford 5.1 mg (86.5%) of 5*β*-acetoxysilphinen-3-one (**12**): oil; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 0.82 (3H, s, H-12), 0.86 (3H, s, H-13), 0.92 (3H, d, J = 7.0 Hz, H-15), 1.02 (3H, s, H-14), 1.34 (H, ddddd, J = 12.2, 12.2, 5.7 Hz, H-10a), 1.53 (H, m, H-11b), 1.70 (H, m, H-11a), 1.92 (H, m, H-10b), 1.99 (H, dd, J = 10.7, 7.8 Hz, H-7a), 2.08 (3H, s, $COCH_3$), 2.20 (H, m, H-9b), 5.11 (H, s, H-5a), 6.0 and 7.59 (H, d, J = 5.6 Hz, H-2 and H-1, respectively); EIMS *m/z* 276 $[M]^+$ (9), 234 (59), 233 (19), 206 (26), 179 (35), 163 (100), 124 (21), 91 (9), 55 (11); HREIMS *m/z* $[M]^+$ 276.1723, calcd for $C_{17}H_{24}O_3$ 276.1725); $[M - C_2H_2O]^+$ 234.1581, calcd for $C_{15}H_{22}O_2$ 234.1619; $[M - C_3H_2O_2]^+$ 206.1698, calcd for $C_{14}H_{22}O$ 206.1670; $[M - C_6H_9O_2]^+$ 163.1148, calcd for $C_{11}H_{15}O$ 163.1122.

Hydrolysis of Compounds 4, 7, and 14. Compound **4** (54.1 mg) was treated with methanolic KOH (5 mL, 35%) and shaken for 4 h. The reaction was visualized over time by TLC. The reaction mixture was extracted at pH 7 with CH_2Cl_2 to give a crude product (35.7 mg, 89.25%). Purification by preparative TLC (two 20 × 20 × 0.25 cm plates) gave products **10** (20.9 mg, 54.7%) and **11** (6.7 mg, 17.5%). The hydrolysis of compounds **7** and **14** yielded similar amounts of **10** and **11**.

Synthesis of 5*β*-Isobutyryloxysilphinen-3-one (13). A mixture of compound **11** (3.0 mg), pyridine (0.2 mL), and isobutyric anhydride (0.1 mL) was kept at room temperature

for 48 h. The reaction product was chromatographed by Si gel column chromatography (hexane−EtOAc, 85:15) to give 3.4 mg (87.4%) of **13**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.60 (H, d, J = 5.8 Hz, H-1), 5.99 (H, d, J = 5.8 Hz, H-2), 5.13 (H, s, H-5), 2.60 (H, sept., H-2′), 2.20 (H, m, H-9), 1.22 (3H, s, H-14), 1.20 (3H, d, J = 6.6 Hz, H-4′), 1.01 (3H, s, H-13), 0.91 (3H, d, J = 6.6 Hz, H-3′), 0.83 (3H, d, J = 6.8 Hz, H-15), 0.82 (3H, s, H-12); EIMS m/z $[M]^+$ 304 (8), 233 (38), 217 (5), 206 (37), 179 (28), 163 (100), 124 (19), 123(11), 91 (11), 71 (33), and 55 (8); HREIMS m/z $[M]^+$ 304.2038, calcd for $C_{19}H_{28}O_3$ 304.2038; ^{13}C NMR data, see Table 2.

Synthesis of 5α-Isobutyryloxysilphinen-3-one (14). A mixture of compound **10** (2.8 mg), pyridine (0.2 mL), and isobutyric anhydride (0.1 mL) was heated at 80 °C for 6 h. The reaction product was chromatographed by Si gel column chromatography (hexane−EtOAc, 85:15) to provide 2.6 mg (72.2%) of **14**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.55 (H, d, J = 5.8 Hz, H-1), 5.98 (H, d, J = 5.8 Hz, H-2), 5.06 (H, s, H-5β), 2.60 (H, sept., J = 7.0 Hz, H-2′), 2.11 (H, m, H-9), 1.15 (3H, s, H-14), 1.20 (3H, d, J = 7.0 Hz, H-4′), 0.97 (3H, d, J = 7.0 Hz, H-3′), 0.93 (3H, d, J = 7.0 Hz, H-15), 0.91 (3H, s H-13), 0.81 (3H, s, H-12); EIMS m/z $[M]^+$ 304 (2), 233 (27), 217 (2), 206 (9), 191 (2), 179 (8), 163 (29), 71 (17), and 57 (29); HREIMS m/z $[M]^+$ 304.2091, calcd for $C_{19}H_{28}O_3$ 304.2038.

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Supporting Information Available: Table showing the antifeedant effects of C-5/C-11-substituted silphinenes against *S. littoralis*, *L. decemlineata*, and five aphid species (from González-Coloma et al.[6]). This material is available free of charge via the Internet at http://pubs.acs.org.

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