149.13 (each s, =C), 200.13 (s, C=O); HREIMS, m/z 182.0950, calcd for $C_{10}H_{14}O_3$ 182.0943; EIMS, m/z (relative intensity) (M^+ not appeared), 167 (2), 139 (24), 137 (21), 67 (9), 55 (10), 43 (100).

2-Methoxy-5-methyl-1,4-benzoquinone (13): mp 158–160 °C; UV 203 nm (log ϵ 3.74), 260 (4.30); IR ν 1675, 1655, 1605 cm^{-1}; ^1H NMR (400 MHz) δ 2.07 (d, J = 2 Hz, 3 H), 3.85 (s, 3 H), 5.93 (s, 1 H), 6.55 (q, J = 2 Hz, 1 H); HREIMS, m/z 152.0471, calcd for $C_8H_8O_3$ 152.0474; EIMS, m/z (relative intensity) 152 (M^+) (52), 122 (24), 69 (100), 66 (24), 39 (20).

5,6,7,8-Tetrahydro-8-isopropyl-2,5-dimethyl-1,4-naphthoquinone (22): mp 52–53 °C; $[\alpha]_D$ -77.8° (c 2.38); UV 205 nm (log ϵ 3.60), 260 (4.04); IR ν 1650 cm^{-1}; ^1H NMR (100 MHz) δ 0.87 (d, J = 7 Hz, 6 H, C_8 isopropyl Me), 1.05 (d, J = 7 Hz, 3 H, C_5 Me), 1.98 (d, J = 2 Hz, 3 H, C_2 Me), 2.70 (m, 1 H, H-8), 2.90 (m, 1 H, H-5), 6.42 (q, J = 2 Hz, H-3); ^{13}C NMR (100 MHz) δ 15.9, 20.5, 21.1, 21.9 (each q, Me), 18.7, 25.4 (each, t, CH_2), 26.4, 31.8, 36.6 (each, d, CH), 133.3 (d, Ph CH), 144.5, 145.6, 147.1 (each s, Ph C), 187.3, 188.5 (each s, C=O); HREIMS, m/z 232.1467, calcd for $C_{15}H_{20}O_2$ 232.1463; EIMS, m/z (relative intensity) 232 (M^+) (46), 205 (21), 189 (100), 175 (76), 161 (40), 149 (61), 91 (30), 43 (40).

5,6,7,8-Tetrahydro-5-isopropyl-3,8-dimethyl-1,2-naphthoquinone (23): mp 84–85 °C; $[\alpha]_D$ -87.5° (c 0.33); UV 212 nm (log ϵ 4.09), 430 (3.10); IR ν 1680, 1660, 1650 cm^{-1}; ^1H NMR (400 MHz) δ 0.88, 1.07, 1.08 (each d, J = 6.6 Hz, C_5 isopropyl Me and C_8 Me), 1.94 (br s, 3 H, C_3 Me), 2.85 (m, 1 H, H-8), 6.70 (s, 1 H, H-4); ^{13}C NMR (100 MHz) δ 15.1, 19.3, 20.6, 21.9 (each q, Me), 18.5, 26.5 (each t, CH_2), 26.6, 30.6, 44.0 (each d, CH), 135.4, 140.6, 150.2 (each s, Ph C), 140.4 (d, Ph CH), 180.0, 181.6 (each s, C=O); HREIMS, m/z 232.1455, calcd for $C_{15}H_{20}O_2$ 232.1463; EIMS, m/z (relative intensity) 232 (M^+) (5), 204 (13), 191 (36), 161 (100).

8-Methoxy-7-hydroxycalamenene (28): mp 62–63 °C; $[\alpha]_D$ +23° (c 0.21); UV 220 nm (log ϵ 3.78), 270 (4.11), 280 (3.15); IR ν 3550, 1420, 1060 cm^{-1}; ^1H NMR (400 MHz) δ 0.80, 0.96, 1.20 (each d, J = 7 Hz, C_4 isopropyl Me and C_1 Me), 2.21 (s, 3 H, C_6 Me), 3.06 (td, J = 6.5, 2.9 Hz, 1 H, H-1), 3.78 (s, 3 H, C_8 OMe), 5.54 (br s, 1 H, C_7 OH), 6.69 (s, 1 H, H-5); ^{13}C NMR (100 MHz) δ 15.5, 19.3, 22.0, 23.3 (each q, Me), 15.5, 27.5 (t, CH_2), 27.9, 33.0, 42.8 (each d, CH), 60.9 (q, OMe), 121.4, 131.6, 132.9, 144.7, 145.1 (each s, Ph C), 127.1 (d, Ph CH), HREIMS, m/z 248.1787, calcd for $C_{16}H_{24}O_2$ 248.1776; EIMS, m/z (relative intensity) 248 (M^+) (9), 223 (26), 205 (100), 173 (21).

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Antiinsectan Aflavinine Derivatives from the Sclerotia of *Aspergillus flavus*

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Four natural products with the aflavinine ring system (1 and 3–5) have been isolated as major components of the sclerotia (key survival structures) produced by several isolates of the common fungus *Aspergillus flavus*. These metabolites are selectively allocated to the sclerotia and exhibit antifeedant activity against fungivorous insects which commonly encounter sclerotia in nature. All four compounds were characterized and identified by NMR and mass spectral analysis, and three of them (3–5) have not been previously reported, despite extensive chemical studies of *Aspergillus* spp.

Many species of higher fungi produce specially adapted propagules called sclerotia as a means of surviving harsh climates or nutrient-poor conditions.[1] These relatively large resting bodies can survive for several months to several years in the soil, but the factors that permit the long-term survival of sclerotia are not fully understood. It has been suggested that sclerotial metabolites that would prevent or reduce predation by detritivorous, fungivorous insects could make a significant contribution to sclerotial longevity.[2-4] Some sclerotium-producing species of the widespread genus *Aspergillus* are known to produce significant amounts of a variety of important mycotoxins, including aflatoxins.[5] However, to our knowledge, *Aspergillus* sclerotia have not been specifically surveyed for unique bioactive metabolites.

Our studies of the sclerotia of a non-aflatoxigenic strain of *Aspergillus flavus* have led to the isolation of four sclerotial metabolites that deter feeding by the fungivorous beetle *Carpophilus hemipterus* (nitidulidae), a common crop insect that encounters *A. flavus* sclerotia under natural conditions. The antiinsectan activity of one of these compounds, 20,25-dihydroxyaflavinine (1), has been described earlier.[4] We report here details of the characterization of these metabolites.

Results and Discussion

Sclerotia of a non-aflatoxigenic isolate of *A. flavus* (NRRL 6541) produced in solid-substrate fermentation

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0022-3263/88/1953-5457$01.50/0

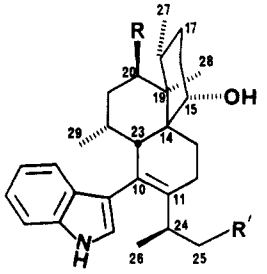
Table I. Proton NMR Data for Compounds 1 and 3–5 (360 MHz, CD_3OD)

position	1	3	4	5
2	6.91 (s)	6.89 (s)	7.06 (s)	7.00 (s)
5	7.44 (br d; 7.8)[a]	7.39 (br d; 7.8)[c]	7.46 (br d; 7.8)[e]	7.46 (br d; 7.8)[g]
6	7.03 (dd; 7.8, 6.4)[b]	7.08 (dd; 7.8, 6.3)[d]	6.98 (dd; 7.8, 6.3)[f]	7.02 (dd; 7.8, 6.1)[h]
7	7.14 (dd; 8.0, 6.4)[b]	7.18 (dd; 8.3, 6.3)[d]	7.06 (dd; 8.1, 6.3)[f]	7.09 (dd; 8.0, 6.1)[h]
8	7.40 (br d; 8.0)[a]	7.36 (br d; 8.3)[c]	7.30 (br d; 8.1)[e]	7.36 (br d; 8.0)[g]
10	–	–	3.66 (dd; 13, 6)	4.17 (d; 5)
11	–	–	3.22 (ddd; 13, 12, 6)	–
12	2.34 (m)	2.31 (m)	1.95 (m)	5.66 (br d; 5.6)
	2.16 (m)	2.21 (m)	1.65 (m)	
13	2.02 (m)	1.99 (m)	2.17 (m)	2.63 (dd; 13.5, 5.6)
	1.75 (m)	1.67 (m)	1.78 (m)	2.29 (m)
15	4.54 (br s)	4.44 (br s)	4.64 (br s)	4.29 (br s)
16	2.11 (m)	2.04 (m)	1.96 (m)	2.19 (m)
	1.78 (m)	1.63 (m)	1.17 (m)	1.80 (m)
17	1.86 (m)	1.79 (m)	1.85 (m)	1.81 (m)
	1.09 (m)	1.11 (m)	1.27 (m)	1.26 (m)
18	2.09 (m)	2.12 (m)	2.23 (m)	2.22 (m)
20	3.94 (dd; 10, 2)	3.99 (dd; 12.8, 2.7)	3.92 (dd; 12.9, 2.7)	3.95 (dd; 12.8, 3)
21	1.91 (m)	1.95 (m)	1.95 (ddd; 13, 12, 5.5)	1.78 (m)
	1.42 (dd; 12, 2)	1.46 (m)	1.21 (m)	1.32 (m)
22	2.21 (m)	2.10 (m)	1.55 (m)	1.49 (m)
23	2.56 (br d; 6)	2.47 (br d; 5.5)	2.67 (dd; 5, 6)	2.53 (dd; 5.3, 5.0)
24	2.61 (br q; 7)	2.61 (septet; 6.8)	–	2.71 (septet; 6.8)
25	3.51 (dd; 11, 7)	0.82 (d; 6.8)	4.81 (br s)	1.10 (d; 6.8)
	3.25 (dd; 11, 7)			
26	0.81 (d; 7)	0.96 (d; 6.8)	1.50 (br s)	0.72 (d; 6.8)
27	0.95 (d; 7)	0.99 (d; 6.6)	1.03 (d; 6.6)	1.02 (d; 6.6)
28	1.19 (s)	1.24 (s)	1.28 (s)	1.24 (s)
29	1.15 (d; 8)	1.16 (d; 7.6)	1.32 (d; 7.3)	1.14 (d; 7.1)

[a–h] Assignments denoted by superscript letters are interchangeable.

culture were avoided by *C. hemipterus* in controlled feeding studies.[4] Reversed-phase flash chromatography of the chloroform extract of the sclerotia, followed by reversed-phase HPLC, afforded several pure metabolites, which displayed varying degrees of insect feeding deterrence. Analysis of the most potent antifeedant component (**1**) by HREIMS suggested a molecular formula of $C_{28}H_{39}NO_3$ (M^+ 437.2931; Δ = 0.2 mmu). ^1H NMR, ^{13}C NMR, and MS data indicated that it contained a 3-substituted indole moiety, three hydroxyl groups, a tetrasubstituted double bond, four methyl groups, and numerous aliphatic methine and methylene units. Assignment of the ^1H NMR signals for **1** (Table I) was accomplished through a series of homonuclear decoupling experiments. The structure of this component was determined as 20,25-dihydroxyaflavinine (**1**)[6] by comparison of its spectral, physical, and chromatographic properties to those of an authentic standard. Compound **1** and aflavinine itself (**2**)[7] are the only two naturally occurring representatives of this ring system that have been previously reported, and they were first isolated from whole *A. flavus* solid-substrate fermentation mixtures. Both structures, including relative stereochemistry, were originally assigned by X-ray diffraction analysis.[6,7] There has been recent synthetic interest in the aflavinine ring system,[8a–c] and 3-desmethylaflavinine has been prepared.[8c]

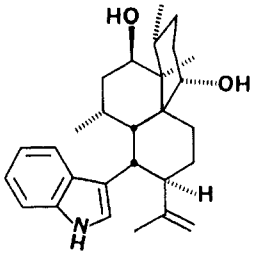
Three new antifeedant aflavinine derivatives closely related to **1** were also isolated. HREIMS and ^{13}C NMR data indicated that all three compounds possess the molecular formula $C_{28}H_{39}NO_2$. The most abundant metabolite (**3**) afforded ^1H NMR data nearly identical with those of **1** except for the presence of an additional methyl doublet at 0.95 ppm and the absence of the hydroxymethylene resonances (Table I), suggesting that this metabolite is a monohydroxylated aflavinine derivative containing a methyl group in place of the hydroxymethyl substituent in **1**. The ^1H and ^{13}C NMR spectra of the third metabolite lacked signals for the hydroxymethylene substituent and the tetrasubstituted olefin found in **1** and indicated the presence of an isopropenyl group in place of the isopropyl group, suggesting structure **4**. NMR data



1 R = R′ = OH

2 R = R′ = H

3 R = OH, R′ = H



4

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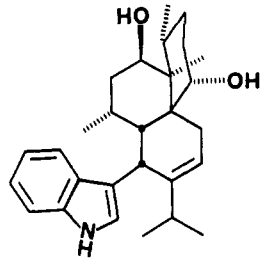
for the final metabolite indicated the presence of a vinylic isopropyl group, a new olefinic proton allylically coupled to the isopropyl methine proton, and a new doubly allylic methine proton. This metabolite was assigned structure **5**, a double-bond isomer of **3** with the ring double bond moved out of conjugation with the indole nucleus. ^{1}H NMR decoupling experiments for **3–5** were correlated with analogous results for **1**, providing further support for assignment of the structures as shown.



5

Despite the close correlation of the NMR spectra of **3–5** with those of **1**, additional NMR experiments were conducted to verify the connectivity of the ring system for one of the new metabolites (**4**). Individual carbon signals for **4** were correlated with proton signals through heteronuclear decoupling experiments, permitting assignment of proton-bearing carbon signals of interest. Irradiation of proton signals using a selective INEPT pulse sequence[9] provided relevant two- and three-bond C–H correlations. The proton signal corresponding to C-27 showed long-range correlations with C-17 (28.5, t), C-18 (32.6, d), and a quaternary carbon (C-19; 45.5, s). The resonance for the methyl protons at C-28 was correlated with C-18, C-19, C-20 (72.6, d), and the only other aliphatic quaternary carbon (C-14; 47.4, s), while the signal for H-20 was correlated with C-14, C-18, C-19, and C-28 (13.8, q). Irradiation at H-23 showed it to be coupled to C-14, C-19, C-15 (69.1, d), C-29 (23.1, q), and C-13 (25.8, t). These results, in conjunction with the proton spin systems known to be present, confirmed the proposed gross structure for **4**. The NMR spectral data for **3** and **5** were completely consistent with the presence of the same ring system.

The relative stereochemistry shown for structures **3–5** was assigned by analogy to the known relative configurations in **1**.[6,7] Compound **4** has two additional chiral centers at C-10 and C-11. The strong coupling between H-10 and H-11 (J = 13 Hz) in the ^{1}H NMR spectrum of **4** suggests that they possess a trans-diaxial relationship, but H-23 and H-10 are not trans diaxial (J = 5 Hz). Thus, if C-23 has the S^* configuration (by analogy to structures **1** and **2**), C-10 and C-11 would have to possess S^* and R^* configurations, respectively. The S^* configuration shown for C-10 in structure **5** is proposed on the basis of a similar coupling involving H-23 and H-10. These assignments are supported by the results of difference NOE experiments conducted on **4** (Figure 1). Molecular models suggest that H-15 and H-10 would be quite close in the structure proposed for **4**. Irradiation at H-15 enhanced the signal for H-10 by 15%, and the complementary experiment showed an enhancement of 13% for H-15. Relatively little enhancement was observed for H-11 when H-15 was irradiated, or in the converse experiment (observed values 3% and 1%, respectively). Finally, irradiation of the C-29 methyl proton resonance caused a significant enhancement (12%) of the signal for H-11, as expected if C-11 has the proposed stereochemistry with H-11 assuming an axial position.

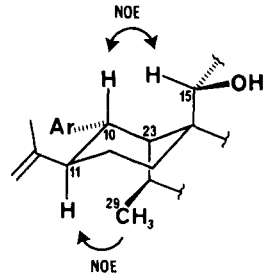


Figure 1.

Compound **1** causes complete inhibition of feeding by *C. hemipterus* at a 100 ppm dry weight dietary level.[4] This compound also exhibits entomotoxicity to the crop pest *Heliothis zea* comparable to that of rotenone. Prior to our studies, no biological activity had been described for **1** or **2**. Structurally related compounds such as aflatrem and paspalinine possess tremorgenic properties,[5] but **1** is nontoxic and nontremorgenic to 1-day-old chickens at 300 mg/kg.[6] Compounds **3–5** are inactive against *C. hemipterus* at 100 ppm, but show significant feeding deterrence when tested at the levels found in sclerotia (400–1100 ppm). Compounds **1** and **3–5** also exhibit mild activity against *Bacillus subtilis* in standard disk assays at 100 μg/disk, but show no toxicity toward brine shrimp at 250 μg/mL.

Comparative assays of *A. flavus* sclerotia and mycelia have previously indicated that **1** is present only in sclerotia.[2] We have found that all four metabolites are almost exclusively allocated to the sclerotia. Also, sclerotia are not produced in liquid fermentation cultures of *A. flavus*, and only small traces of these metabolites can be detected in such cultures. Thus, the biosynthetic processes leading to the production of these aflavinine derivatives are closely tied to sclerotium production. This correlation is analogous to the selective allocation of ergot alkaloids to the ergot (sclerotium) of *Claviceps* spp.[10] Furthermore, we have found these compounds to be abundant in the sclerotia of all eleven different isolates of *A. flavus* and *Aspergillus parasiticus* that we have examined. Selective allocation of secondary metabolites to important physiological structures is a generally accepted mechanism of chemical defense in higher plants,[11] but such phenomena have not been commonly explored among the fungi. Clearly, conclusions about any significance of these compounds to sclerotium survival in soil must await field trials.

A. flavus has been widely studied for many years, largely because of its capacity for aflatoxin production. The discovery of new, apparently common major metabolites from *A. flavus* sclerotia suggests that previously undetected bioactive metabolites can be found through studies of such important fungal structures. Further chemical and biological studies of sclerotial metabolites produced by *Aspergillus* spp. and other fungi are currently underway in our laboratories.

Experimental Section

General. General procedures, details of bioassays, preparation of sclerotia, and isolation and quantitation procedures employed in these studies have been described elsewhere.[4,12,13] The original

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isolate of *A. flavus* used in this work (NRRL 6541) was obtained from the ARS culture collection of the USDA Northern Regional Research Center, Peoria, IL.

Hexane and $CHCl_3$ extracts of milled sclerotia (21.8 g) were subjected to reversed-phase flash chromatography followed by reversed-phase HPLC (5-μm C_{18} column, 250 × 10 mm, 70:30 MeOH-H_2O, 2.0 mL/min, monitored at 215 nm) to afford 1 (10.1 mg), **3** (7.1 mg), **4** (15.6 mg), and **5** (6.8 mg). Since some loss was involved, actual concentrations in the sclerotia were determined by direct HPLC quantitation of fresh sclerotial extracts.[4] Sclerotia from 10 other isolates of *A. flavus* and *A. parasiticus* contained comparable or higher concentrations of these compounds. Submerged shake cultures of NRRL 6541 grown in corn steep liquor or glucose-yeast extract media failed to produce sclerotia, and only traces of 1 and **3-5** (range, 0-80 μg/L) could be detected in these cultures by HPLC.

20,25-Dihydroxyaflavinine (1) was identified by analysis of spectral data and by comparison to an authentic sample. Earlier reports have not provided complete physical and spectral properties for 1, and this information is included here. Compound 1 (concentration in sclerotia, 470 ppm): mp 255-257 °C; $[\alpha]_D$ +22.9° (*c* 0.50, MeOH); HPLC retention time 14.4 min under the above conditions; UV (MeOH) 224 (ϵ 20190), 283 (3850), 291 nm (3670); ^1H NMR, Table I; ^{13}C NMR (CD_3OD) 138.5 (s), 137.7 (s), 129.9 (s), 128.4 (s), 123.2 (d), 122.2 (d), 120.0 (d), 119.6 (d), 118.0 (s), 112.2 (d), 72.6 (d), 71.0 (d), 67.3 (t), 49.9 (d), 45.9 (s), 44.7 (s), 40.4 (d), 35.9 (t), 32.5 (d), 31.3 (t), 31.2 (d), 28.6 (t), 23.1 (t), 22.8 (t), 20.1 (q), 19.6 (q), 15.6 (q), 13.6 ppm (q); EIMS (70 eV), 437 (M^+; relative intensity 12.5), 419 (3.5), 328 (3.0), 302 (5.4), 288 (5.4), 260 (18), 234 (31), 218 (44), 194 (47), 180 (45), 167 (49), 154 (30), 144 (40), 130 (100), 117 (85); HREIMS obsd 437.2931, calcd for $C_{28}H_{39}NO_3$ 437.2936.

20-Hydroxyaflavinine (3): concentration 1100 ppm; mp 174-176 °C dec; $[\alpha]_D$ +23.8° (*c* 0.56, MeOH); retention time 34.2 min; UV (MeOH) 224 (ϵ 14920), 283 (2760), 290 nm (2520); ^1H NMR, Table I; ^{13}C NMR (CD_3OD) 141.8 (s), 137.7 (s), 128.5 (s), 127.2 (s), 122.8 (d), 122.1 (d), 120.0 (d), 119.5 (d), 112.2 (d), 112.0 (s), 72.6 (d), 71.0 (d), 49.8 (d), 46.0 (s), 44.7 (s), 36.0 (t), 32.5 (d), 32.0 (d), 31.5 (t), 31.2 (d), 28.6 (t), 23.2 (t), 22.1 (t), 21.5 (q), 21.1 (q), 19.9 (q), 19.6 (q), 13.6 ppm (q); EIMS (70 eV), 421 (M^+; 20), 403 (2.0), 378 (3.1), 360 (3.1), 342 (4.3), 288 (4.4), 234 (12), 220 (26), 206 (22), 194 (35), 180 (28), 168 (62), 154 (25), 144 (26), 130 (100), 117 (50); HREIMS obsd 421.2981, calcd for $C_{28}H_{39}NO_2$ 421.2980.

24,25-Dehydro-10,11-dihydro-20-hydroxyaflavinine (4): concentration 440 ppm; mp 259-262 °C; $[\alpha]_D$ +0.9° (*c* 0.34, MeOH); retention time 25.8 min; UV (MeOH) 227 (ϵ 26260), 284 (6060), 291 nm (5720); ^1H NMR, Table I; ^{13}C NMR (CD_3OD) 151.7 (s), 137.7 (s), 128.6 (s), 124.6 (d), 122.0 (d), 119.3 (d), 118.7 (d), 116.2 (s), 112.3 (d), 111.6 (t), 72.6 (d), 69.1 (d), 47.4 (s), 45.5 (s), 44.8 (d), 39.5 (d), 38.9 (t), 35.7 (d), 32.6 (d), 32.3 (d), 31.1 (t), 29.2 (t), 28.5 (t), 25.8 (t), 23.1 (q), 19.7 (q), 18.4 (q), 13.8 ppm (q); EIMS (70 eV), 421 (M^+; 23), 406 (1.5), 403 (1.7), 388 (1.0), 330 (4.3), 302 (2.4), 288 (1.2), 248 (2.0), 220 (4.0), 210 (10), 196 (28), 184 (14), 168 (28), 143 (13), 130 (100), 117 (16); HREIMS obsd 421.2975, calcd for $C_{28}H_{39}NO_2$ 421.2980.

10,11-Dihydro-11,12-dehydro-20-hydroxyaflavinine (5): concentration 530 ppm; mp 276-278 °C; $[\alpha]_D$ +1.7° (*c* 0.1, MeOH); retention time 35.5 min; UV (MeOH) 224 (ϵ 20030), 251 (3600), 285 nm (3380); ^1H NMR, Table I; ^{13}C NMR (CD_3OD) 144.7 (s), 137.5 (s), 129.5 (s), 124.5 (d), 122.2 (d), 121.6 (d), 120.0 (s), 119.6 (d), 118.3 (d), 112.3 (d), 73.1 (d), 70.7 (d), 46.1 (s), 44.9 (s), 40.1 (d), 37.9 (t), 37.1 (d), 31.5 (d), 31.4 (d), 30.9 (t), 30.2 (d), 29.0 (t), 28.7 (t), 23.4 (q), 21.1 (q), 19.7 (q), 17.9 (q), 13.6 ppm (q); EIMS (70 eV), 421 (M^+; 2.8), 403 (0.6), 388 (0.8), 342 (1.6), 274 (3.1), 260 (4.4), 246 (7.7), 232 (8.9), 220 (14), 210 (24), 196 (30), 180 (32), 168 (100), 143 (32), 130 (95), 117 (81); HREIMS obsd 421.2990, calcd for $C_{28}H_{39}NO_2$ 421.2980.

Activity against *C. hemipterus*. Antifeedant activity was measured by incorporating each metabolite into a plug of pinto bean diet and evaluating the extent of feeding by *C. hemipterus* after 7 days.[4] Compound 1 prevented any feeding damage to the plug when incorporated at 100 ppm. Compounds **3-5** were tested at their normal sclerotial concentrations. Compounds **4** and **5** allowed only slight penetration of the diet plug, while **3** permitted some penetration and fragmentation, but control plugs were completely pulverized by insect feeding.

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High Pressure Mediated Diels-Alder Reaction of Furan with Dialkyl (Acetoxymethylene)malonate

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The Diels-Alder reaction of furan with dialkyl (acetoxymethylene)malonates 1 did not proceed even in the presence of Lewis acid catalysts under conventional conditions. However, the reaction under high pressure (1.1 GPa) gave the expected cycloadducts, dialkyl 3-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2,2-dicarboxylates **2**. The bis-, tris-, and tetrakisadducts **3-6** were also produced in some amounts. Similar high-pressure reactions in the presence of zinc iodide as a catalyst yielded dialkyl 2-furfurylidenemalonate **8**, and none of the adducts were obtained.

Substituted 7-oxabicyclo[2.2.1]heptanes have been used as key intermediates in the syntheses of a variety of natural products.[1] Construction of a 7-oxabicyclo[2.2.1]hept-5-ene moiety should be achieved by the Diels-Alder reaction of furan with an appropriate dienophile. However, this strategy is in many cases not feasible because of the low reactivity of furan toward dienophiles, or thermal instability of adducts (retro Diels-Alder reactions). In fact, the reported Diels-Alder reactions of furan have been limited within those with very reactive dienophiles. In some instances, Lewis acid catalysts,[2] chelation by metal,[3] or high

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