New Insecticidal Rocaglamide Derivatives from the Roots of *Aglaia duperreana*

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Bioassay-guided fractionation of an extract obtained from roots of *Aglaia duperreana* led to the isolation of 17 1*H*-cyclopenta[*b*]benzofurans of the rocaglamide type. Of the compounds isolated, four rocaglamide derivatives (**2**, **6**, **11**, and **16**) were obtained as new natural products, and their structure elucidation was conducted by spectral methods. For bioassay-guided fractionation and determination of LC_{50} and EC_{50} values, neonate larvae of *Spodoptera littoralis* were employed. The results of chronic feeding assays have shown new aspects of the structure−activity relationship of rocaglamide derivatives. The substitution of a hydroxyl group at C-8b by a methoxyl substituent leads to a loss of insecticidal activity in a manner not previously documented in this compound class.

The genus *Aglaia* (Meliaceae) comprises more than 100 species that occur in tropical rainforests of the Indo-Malaysian region.[1] *Aglaia* species accumulate unusual 1*H*-cyclopenta[*b*]benzofurans of the rocaglamide type that are known to be powerful natural insecticides. Some of the most active rocaglamide congeners are comparable to azadirachtin from the Neem tree[2−5] with regard to their insecticidal activity, and thus represent interesting lead structures for plant protection. Rocaglamide derivatives are also known for their cytostatic effects on cancer cells[6−9] and have been shown to inhibit protein synthesis.[10] The insecticidal activity of the rocaglamide-type compounds seems to be linked primarily to the integrity of the furan ring system, for aglain-type compounds, which differ from the rocaglamides in the nature of the heterocyclic ring (pyran vs furan ring), were recently shown to be inactive.[2] However, the substitution pattern of rocaglamide derivatives, especially the nature of the substituents at C-1, C-2, and C-3′, has also been suggested to be important for the insecticidal activity of the respective derivatives.[2−5] Thus, preliminary structure−activity relations among this group of natural insecticides are emerging. For a deeper understanding of the structural parameters that influence insecticidal activity of rocaglamide congeners, though, a larger number of derivatives has to be included in these comparative studies. As part of our ongoing screening efforts within the genus *Aglaia*, we have now investigated the rocaglamide constituents obtained from the roots of *Aglaia duperreana* Pierre (Meliaceae) collected in Vietnam and report on the isolation of 17 rocaglamide congeners, of which four (**2**, **6**, **11**, and **16**) are new natural products. The insecticidal activity of the new compounds was evaluated using larvae of the polyphagous pest insect *Spodoptera littoralis*, which were also employed in previous investigations within this group of compounds.[2−5,11]

Results and Discussion

A crude methanolic extract from roots of *A. duperreana* exhibited significant insecticidal activity when incorporated into an artificial diet and tested against neonate larvae of the polyphagous pest insect *S. littoralis* at an arbitrarily chosen concentration of 2600 ppm. None of the insects was found to survive after 6 days of exposure to the treated diet (data not shown). Bioassay-guided chromatographic separation resulted in the isolation of 17 compounds (**1**−**14**, **16**−**18**). When roots were separated into bark and woody pith, no tissue-specific differences of the resulting rocaglamide patterns were observed. Based on their spectral characteristics and comparison with published data,[2−6,12,13] 13 of the isolated compounds could be readily identified as known rocaglamide derivatives previously reported from *A. elliptica* (**1**, **9**, and **10**),[4,6] *A. duperreana* (**1**, **3**−**5**, **12**, and **18**),[3,16] *A. odorata* (**1**, **3**, **4**, **7**, **8**, **10**, **13**, **14**, **15**, and **17**),[2,5,12,13] or other *Aglaia* species. Compounds **2**, **6**, **11**, and **16** were isolated as new natural products.

The structures of two of the new compounds (**2** and **6**) were characterized by the presence of an acetate substituent. Compound **2** proved to be a new C-1-*O*-acetyl derivative of rocaglamide (**1**), as suggested by the molecular weight of 547 (42 amu higher than that of **1**) and the loss of 60 amu under EIMS conditions, which is indicative of the presence of acetic acid. Inspection of the ^1H and ^{13}C NMR spectra of **2** allowed the assignment of an acetate unit at C-1 (Tables 1 and 2). The H-1 (6.10 ppm) resonance in the ^1H NMR spectrum of **2** exhibited a large downfield shift compared to the corresponding signal in the ^1H NMR spectrum of rocaglamide (**1**) (5.01 ppm).[3]

O-Acetylation at C-1 was also a characteristic structural feature of compound **6**. The mass spectral and NMR data showed similar differences in diagnostic signals of **6** when compared to the deacetylated parent compound desmethylrocaglamide (**5**), as discussed above for compound **2** and

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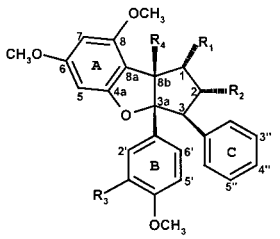
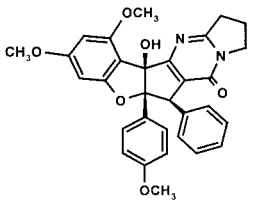


	R_1	R_2	R_3	R_4
1	OH	$CON(CH_3)_2$	H	OH
2	$OCOCH_3$	$CON(CH_3)_2$	H	OH
3	OH	$CON(CH_3)_2$	OH	OH
4	$OCOCH_3$	$CON(CH_3)_2$	OH	OH
5	OH	$CONHCH_3$	H	OH
6	$OCOCH_3$	$CONHCH_3$	H	OH
7	OH	$CONHCH_3$	OH	OH
8	$OCOCH_3$	$CONHCH_3$	OH	OH
9	OH	$CONH_2$	H	OH
10	OH	$COOCH_3$	H	OH
11	OH	$COOCH_3$	H	OCH_3
12	$OCOCH_3$	$COOCH_3$	H	OH
13	OH	$COOCH_3$	OH	OH
14	$OCOCH_3$	$COOCH_3$	OH	OH
15	OH	H	H	OH
16	OH	H	H	OCH_3



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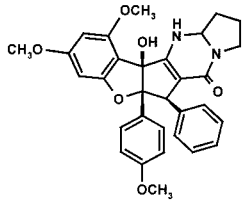

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its deacetylated congener rocaglamide (**1**). These diagnostic spectroscopic features include particularly the loss of 60 amu in the mass spectrum of **6** and the downfield shift of H-1 in the ^{1}H NMR spectrum of **6**.

The mass spectra of compounds **11** and **16** showed a characteristic pair of fragments at *m*/*z* 314 and 327, respectively, compared to fragments at *m*/*z* 300 and *m*/*z* 313 that arise from their demethylated congeners **10**[6,12] and **15**[12] under EIMS conditions. Plausible structures of these fragments are given in Figure 1 and indicate an exchange of the regularly observed hydroxyl group at C-8b (for example, in compounds **10**[6,12] and **15**[12]) by a methoxyl substituent in the new derivatives **11** and **16**. This assumption was corroborated by inspection of HREIMS data and the ^{1}H and ^{13}C NMR spectra of **11** and **16** (Tables 1 and 2). The ^{1}H NMR spectra of **11** and **16**, when compared to those of **10**[6,12]and **15**,[12] showed additional three-proton singlets with unusually high-field shifts at 2.39 and 2.41 ppm, respectively, that could be assigned to methoxyl substituents. The observed downfield shift of ca. 8 ppm of the C-8b signals (compared, for example, to the ^{13}C NMR spectra of **2** and **6** in Table 2) is only compatible with the presence of a methoxyl substituent at this position. These findings were further corroborated from long-range correlations in the HMBC spectrum of **11**, where the ^{1}H NMR signal at 2.41 ppm correlated with the ^{13}C NMR signal at 101.4 ppm, and by comparison with data reported in the literature.[7]

The absolute configurations of compounds **2**, **6**, **11**, and **16** were deduced by comparing their CD spectral data to those of rocaglamide (**1**).[3] The absolute configuration of **1** is known through enantioselective synthesis.[14]

In a recent monograph on the genus *Aglaia*, *A. duperreana* is considered to be the same species as *A. odorata*.[1] Phytochemically, however, both taxa are clearly different. For example, rocaglamide congeners exhibiting an methoxyl substituent at position C-8b like **11** and **16** have never been described for *A. odorata*.[2,5,10,12,13] Aglain derivatives, which differ from rocaglamide-type compounds by the nature of their heterocycle (bridged benzopyran vs benzofuran ring), are absent in *A. duperreana*[3] but occur in *A. odorata*.[2] Thus, the true taxonomic position of *A. duperreana* remains open and requires further investigation.

The insecticidal activities of the new rocaglamide derivatives **2**, **6**, **11**, and **16** was studied by incorporating the

Table 1. ^{1}H NMR Data of Compounds **2**, **6**, **11**, and **16**[a]

	compound			
proton	**2**	**6**	**11**	**16**
1	6.10 (m)	6.04 (d, 5.8)	5.00 (d, 7.0)	4.85 (d, 6.6)
2A				2.79 (ddd, 6.9, 14.1, 14.2)
2B	4.35 (m)	3.99 (dd, 5.8, 14.5)	3.94 (dd, 7.0, 14.4)	1.91 (dd, 6.4, 13.8)
3	4.35 (m)	4.25 (d, 14.5)	4.10 (d, 14.4)	3.81 (dd, 6.4, 14.5)
5	6.32 (d, 1.9)	6.31 (d, 2.1)	6.39 (d, 1.8)	6.39 (d, 2.0)
7	6.17 (d, 1.9)	6.17 (d, 1.9)	6.28 (d, 2.0)	6.30 (d, 2.0)
2′[b]	7.22 (d, 9.0)	7.23 (d, 9.0)	7.20 (d, 7.5)	7.21 (d, 9.0)
3′[b]	6.68 (d, 9.0)	6.67 (d, 9.0)	6.72 (d, 8.6)	6.71 (d, 9.0)
5′[b]	6.68 (d, 9.0)	6.67 (d, 9.0)	6.72 (d, 8.6)	6.71 (d, 9.0)
6′[b]	7.22 (d, 9.0)	7.23 (d, 9.0)	7.20 (d, 7.5)	7.21 (d, 9.0)
2″	6.95 (m)	6.96 (m)	6.82 (m)	6.88 (m)
3″	7.05 (m)	7.04 (m)	7.05 (m)	7.07 (m)
4″	7.05 (m)	7.04 (m)	7.05 (m)	7.07 (m)
5″	7.05 (m)	7.04 (m)	7.05 (m)	7.07 (m)
6″	6.95 (m)	6.96 (m)	6.82 (m)	6.88 (m)
CH_3O-6	3.79 (s)	3.79 (s)	3.90 (s)	3.94 (s)
CH_3O-8	3.87 (s)	3.87 (s)	3.91 (s)	3.89 (s)
CH_3O-12	3.70 (s)	3.71 (s)	3.74 (s)	3.74 (s)
CH_3O-8b			2.41 (s)	2.39 (s)
$N-CH_3$	3.41 (s)	2.63 (d, 4.6)		
$N-CH_3$	2.84 (s)			
$OCOCH_3$	1.86 (s)	1.89 (s)		
$-COOCH_3$			3.62 (s)	

[a] All compounds recorded in MeOD. [b] In all compounds H-2′, H-3′, H-5′ and H-6′ appear as an AA′BB′ spin system.

Table 2. ^{13}C NMR Data of Compounds **2**, **6**, **11**, and **16**[a]

carbon	compound			
	2	**6**	**11**	**16**
1	79.3 (d)	80.8 (d)	80.9 (d)	80.7 (d)
2	49.0 (d)	51.5 (d)	51.6 (d)	37.0 (t)
3	58.2 (d)	57.4 (d)	55.5 (d)	56.2 (d)
3a	102.4 (s)	102.4 (s)	100.6 (s)	102.1 (s)
4a	161.9 (s)	161.7 (s)	162.7 (s)	162.8 (s)
5	89.5 (d)	89.5 (d)	90.3 (d)	90.4 (d)
6	165.5 (s)	165.4 (s)	165.9 (s)	165.8 (d)
7	92.7 (d)	92.7 (d)	93.1 (d)	93.0 (d)
8	159.7 (s)	159.7 (s)	159.7 (s)	159.5 (s)
8a	108.5 (s)	109.0 (s)	104.7 (s)	104.9 (s)
8b	94.0 (s)	93.8 (s)	101.4 (s)	102.3 (s)
1′	129.5 (s)	129.3 (s)	128.9 (s)	127.4 (s)
2′	130.2 (d)	130.2 (2d)	129.2 (2d)	129.3 (2d)
3′	113.3 (d)	113.2 (2d)	113.6 (2d)	113.4 (2d)
4′	159.9 (s)	159.9 (s)	160.2 (s)	160.1 (s)
5′	113.3 (d)	113.2 (2d)	113.6 (2d)	113.4 (2d)
6′	130.2 (d)	130.2 (2d)	129.2 (2d)	129.3 (2d)
1″	139.1 (s)	138.7 (s)	138.4 (s)	139.5 (s)
2″/6″	129.0 (2d)	129.1 (2d)	129.1 (2d)	129.3 (2d)
3″/5″	128.6 (2d)	128.5 (2d)	128.5 (2d)	128.5 (2d)
4″	127.2 (d)	127.4 (d)	127.5 (d)	127.4 (d)
C=O	171.2 (s)	171.6 (s)	172.2 (s)	-
O*C*=*O*−CH_3	170.3 (s)	171.3 (s)		
OC=O−*CH_3*	20.8 (q)	20.9 (q)		
COO−*CH_3*			52.3 (q)	
Ar−O−*CH_3*	56.1, 55.8, 55.5 (3 x q)	56.1, 55.7, 55.4 (3 x q)	56.7, 56.2, 56.1 (3 x q)	56.2, 55.5, 55.2 (3 x q)
C−8b−O−*CH_3*			52.2 (q)	52.1 (q)
N−CH_3	37.7, 36.0 (q)	26.3 (q)		

[a] All compounds recorded in MeOD.

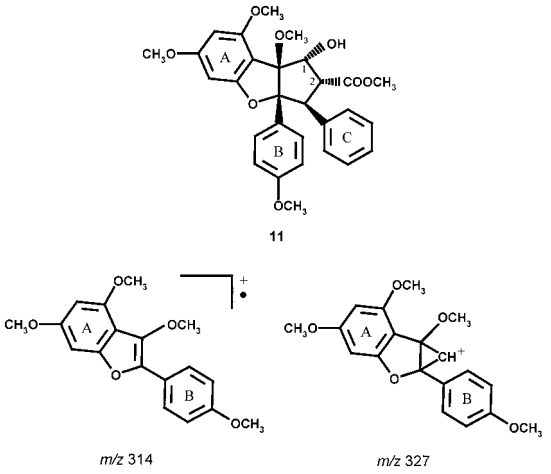

Figure 1. Plausible structures of the ions *m*/*z* 314 and 327 arising from fragmentation of compound **11** under EIMS conditions.

compounds into artificial diets over a range of concentrations and offering these to neonate larvae of *S. littoralis* in a long-term feeding assay (duration: 7 days). The known rocaglamide derivatives **1**, **5**, **10**, and **15**, which differ from the new compounds **2**, **6**, **11**, and **16** by only one substituent, were included in the assays for comparison purposes. As a positive control, the well-known natural insecticide azadirachtin was employed. The LC_{50} and EC_{50} values of each compound were calculated by probit analysis from the respective dose−response curves (Table 3). The acetylated compounds **2** and **6** showed very similar LC_{50} (7.1 and 8.1 ppm) and EC_{50} values (0.43 and 0.23 ppm). As expected from previous studies,[3−5] both compounds were approximately sevenfold less active than their corresponding deacetyl derivatives **1** and **5** (Table 3). The most remarkable finding, however, was the complete lack of insecticidal activity observed for compounds **11** and **16**, even when tested at concentrations of 100 ppm. Compounds **10** and **15**, which differ from **11** and **16** by having a hydroxyl substituent at position C-8b instead of a methoxyl group, exhibited LC_{50} values of 1.3 and 17.4 ppm, respectively, as expected for rocaglamide derivatives (Table 3).[2−5] Previously, the complete inactivation of rocaglamide derivatives has only been found upon replacement of the furan heterocycle by a pyran system as present in aglain derivatives.[2]

Table 3. Insecticidal Activity of the Rocaglamide Derivatives **1**, **2**, **5**, **6**, **10**, **11**, **15**, and **16**[a]

compound	EC_{50} (ppm)	LC_{50} (ppm)
1	0.08	0.9
2	0.43	7.1
5	0.27	1.3
6	0.23	8.1
10	0.18	1.3
11	n.a.[b]	n.a.[b]
15	0.76	17.4
16	n.a.[b]	n.a.[b]
azadirachtin[c]	0.06	0.7

[a] Determined in a chronic feeding assay (7 days) with neonate larvae of *S. littoralis*. [b] n.a. = not active up to a concentration of 100 ppm. [c] Positive control.

The results obained in this study suggest that the nature and especially the regiospecific position of substituents in the rocaglamide skeleton (in the present case hydroxyl vs methoxyl at C-8b) are likewise important structural features with considerable impact on the insecticidal activity of these benzofuran derivatives.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin−Elmer 241 MC polarimeter. CD spectra were measured in EtOH on an Yvon Dichrograph CD 6 spectrometer. ^1H and ^{13}C NMR spectra were recorded in CD_3-OD on Bruker AM 300 or ARX 400 NMR spectrometers. EIMS spectra (70 eV, direct inlet) were recorded on a Finnigan MAT

8430 mass spectrometer. HREIMS data were determined by peak matching at a resolution of approximately 10 000 (10% valley).

Plant Material. Roots of *Aglaia duperreana* Pierre (Meliaceae) were collected at a plantation near Ho Chi Minh City, Vietnam, in December 1997. A voucher specimen is on file in the J.-v.-Sachs-Institut für Biowissenschaften, Universität Würzburg.

Extraction and Isolation. Air-dried roots of *A. duperreana* (580 g dry wt) were ground and exhaustively extracted with MeOH and acetone. After evaporation of the solvent, the extract was partitioned between petroleum ether−MeOH−H_2O (90:10) and EtOAc−H_2O. Each fraction was submitted to a bioassay with neonate larvae (see below). From this bioassay, the insecticidal activity was found to reside in the EtOAc extract. Bioassay-guided fractionation of the EtOAc extract was achieved using vacuum-liquid chromatography (VLC) [Si gel (Merck, Darmstadt, FRG), CH_2Cl_2−*i*-PrOH gradient mixtures], repeated column chromatography employing Si gel (mobile phase: hexanes−EtOAc, 30:70), and passage over Sephadex LH-20 (Sigma, Deisenhofen, FRG) (mobile phase: MeOH). Final purification was obtained using RP_{18} Lobar columns (Merck, Darmstadt, FRG) (mobile phase: mixtures of MeOH and H_2O) and by preparative HPLC. The separatory column (7 or 10 μm, 300 × 8 mm, i.d.) was pre-filled with Eurospher RP_{18} (Knauer, Berlin, FRG). Solvents were distilled prior to use, and spectral grade solvents were used for spectroscopic measurements. Fractions were monitored by TLC on precoated TLC plates with Si gel 60 F_{254} (Merck, Darmstadt, FRG) (mobile phase: CH_2Cl_2−*i*-PrOH, 95:5 or CH_2Cl_2−MeOH, 95:5). Rocaglamide derivatives were detected by their dark absorbance under UV_{254} nm or after spraying the TLC plates with anisaldehyde reagent. The known compounds **1**, **3**−**5**, **7**−**10**, **12**−**14**, **17**, and **18** were identified by their HPLC retention times (co-chromatography with reference substances) as well as by EIMS and 1D ^{1}H NMR and comparison with literature data.[2−6,12,13] Yields of compounds were **1**, 10.0 mg; **2**, 5.0 mg; **3**, 1.6 mg; **4**, 2.8 mg; **5**, 2.3 mg; **6**, 3.6 mg; **7**, 0.6 mg; **8**, 0.9 mg; **9**, 1.9 mg; **10**, 13.5 mg; **11**, 4.1 mg; **12**, 1.5 mg; **13**, 0.7 mg; **14**, 1.4 mg; **16**, 35.2 mg; **17**, 11.0 mg; and **18**, 1.9 mg.

1-*O*-Acetylrocaglamide (2): white amorphous residue; $[\alpha]^{20}_D$ −100.1° (*c* 3.1, $CHCl_3$); CD 218 nm ($\Delta\epsilon$ −13), 243 nm (sh) ($\Delta\epsilon$ +1), 276 nm ($\Delta\epsilon$ −1); ^{1}H NMR, see Table 1; ^{13}C NMR see Table 2; EIMS (70 eV) *m*/*z* 547 $[M]^+$ (19), 529 (20), 487 (53), 469 (33), 442 (46), 415 (30), 390 (21), 333 (25), 313 (63), 300 (100), 285 (49), 205 (36), 181 (53), 135 (21); HREIMS *m*/*z* found 547.2195 (calcd for $C_{31}H_{33}O_8N$, 547.2206).

1-*O*-Acetyldesmethylrocaglamide (6): white amorphous residue; $[\alpha]^{20}_D$ −53.0° (*c* 4.5, $CHCl_3$); CD 217 nm ($\Delta\epsilon$ −13), 242 nm (sh) ($\Delta\epsilon$ +5), 272 nm ($\Delta\epsilon$ −1); ^{1}H NMR, see Table 1; ^{13}C NMR see Table 2; EIMS (70 eV) *m*/*z* 533 [M]+ (11), 473 (51), 442 (23), 415 (28), 390 (20), 319 (21), 313 (68), 300 (100), 285 (58), 181 (40), 162 (24), 135 (26); HREIMS *m*/*z* found 533.2039 (calcd for $C_{30}H_{31}O_8N$, 533.2050).

8b-*O*-Methyl−methylrocaglate (11): white amorphous residue; $[\alpha]^{20}_D$ −37.3° (*c* 3.2, $CHCl_3$); CD 218 nm ($\Delta\epsilon$ −26), 233 nm (sh) ($\Delta\epsilon$ +6), 275 nm ($\Delta\epsilon$ −2); ^{1}H NMR, see Table 1; ^{13}C NMR see Table 2; EIMS (70 eV) *m*/*z* 506 $[M]^+$ (6), 475 (2), 404 (2), 373 (2), 340 (6), 327 (17), 314 (100), 299 (30), 177 (13), 161 (9), 149 (9), 135 (8), 121 (5); HREIMS *m*/*z* found 506.1931 (calcd for $C_{29}H_{30}O_8$, 506.1941), *m*/*z* found 327.1227 (calcd for $C_{19}H_{19}O_5$, 327.1232), *m*/*z* found 314.1148 (calcd for $C_{18}H_{18}O_5$, 314.1154).

8b-*O*-Methylrocaglaol (16): white amorphous residue; $[\alpha]^{20}_D$ −43.7°(*c* 6.4, $CHCl_3$); CD 218.5 nm ($\Delta\epsilon$ −25), 233.5 nm (sh) ($\Delta\epsilon$ +5), 275 nm ($\Delta\epsilon$ −4); ^{1}H NMR, see Table 1; ^{13}C NMR see Table 2; EIMS (70 eV) *m*/*z* 448 $[M]^+$ (11), 416 (6), 373 (3), 327 (9), 314 (100), 299 (35), 284 (9), 269 (5), 135 (10); HREIMS *m*/*z* found 448.1879 (calcd for $C_{27}H_{28}O_6$, 448.1886), *m*/*z* found 327.1227 (calcd for $C_{19}H_{19}O_5$, 327.1232), *m*/*z* found 314.1148 (calcd for $C_{18}H_{18}O_5$, 314.1154).

Insect Bioassays. The chronic feeding assays were carried out with larvae of the polyphagous pest insect *Spodoptera littoralis* (Noctuidae, Lepidoptera). The larvae were from a laboratory colony reared on artificial diet under controlled conditions at 26 °C as described previously.[15] Feeding studies were conducted with neonate larvae (n = 20 for each treatment) that were kept on a diet containing extracts or compounds under study. After a 7-day exposure, survival and weights of surviving larvae were recorded and compared with controls that had been exposed to diet treated with solvent (MeOH) only. LC_{50} (calculated concentration of pure compounds in the artificial diet leading to a 50% lethality of the larvae) and EC_{50} (calculated concentration of pure compounds in the artificial diet leading to a reduction of 50% in weight gain of the larvae compared to control) values were calculated from dose−response curves by probit-analysis (concentrations: 0.2−11.0 ppm). Azadirachtin from the neem tree, which was used as a positive control, was obtained from Roth (Karlsruhe, F.R.G.).

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References and Notes

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