New Insecticidal Rocaglamide Derivatives and Related Compounds from *Aglaia oligophylla*

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Organic-soluble extracts of the twigs of *Aglaia oligophylla* collected in Vietnam yielded four insecticidal cyclopentatetrahydrobenzofurans of the rocaglamide type including one new natural product (compound **4**). Moreover, two cyclopentatetrahydrobenzopyran derivatives, belonging to the aglain and aglaforbesin types, respectively, were also isolated. The aglaforbesin derivative **6** proved likewise to be a new natural product. All isolated rocaglamide, aglain, and aglaforbesin derivatives have a characteristic methylenedioxy substituent linked to C-6 and C-7 or to C-7 and C-8, respectively. Structure elucidation of the new natural products and the determination of the absolute configuration of compound **1** by calculation of its CD spectrum with molecular dynamics simulation are described. All isolated rocaglamide derivatives exhibited strong insecticidal activity toward neonate larvae of the polyphageous pest insect *Spodoptera littoralis* when incorporated into an artificial diet, with LC_{50} values varying between 2.15 and 6.52 ppm.

The genus *Aglaia* (Meliaceae), which occurs in the tropical rain forests of the Indo-Malaysian region, is characterized phytochemically by the presence of cyclopentatetrahydrobenzofurans of the rocaglamide type.[1−9] Rocaglamide derivatives are known to be powerful natural insecticides, and some of the most active rocaglamide congeners are comparable in their insecticidal potency to azadirachtin, from the Neem tree, *Azadirachta indica*.[4] Thus, rocaglamide derivatives are of considerable interest in that they may afford novel lead structures for agrochemicals.

The insecticidal activity of rocaglamide-type compounds seems to be largely linked to the integrity of the furan ring system since aglain-type compounds, which differ from the rocaglamides by the nature of their heterocyclic unit (bridged pyran vs furan ring), were recently shown to be inactive.[4] However, the substitution pattern, especially the nature of the substituents at C-1, C-2, C-3′, and C-8b, was also suggested to be important for the insecticidal activity of the resulting congeners. For example, recently we have reported that replacement of the OH-group at C-8b, which is a characteristic structural feature of most known rocaglamide congeners, by an OCH_3- or OC_2H_5- substituent, results in a total loss of insecticidal activity.[5,6]

In our continuing search for new insecticidal compounds we have investigated the twigs of *Aglaia oligophylla* Miq. collected in Vietnam, and we report on the isolation of four rocaglamide congeners (**1**−**4**) including one new natural product (**4**) as well as an aglain (**5**) and a new aglaforbesin-like derivative (**6**). The absolute configuration of compound **1** was elucidated unequivocally for the first time by calculation of its CD spectrum using molecular dynamics (MD) simulations. The insecticidal activity of compounds **1**−**6** was evaluated using neonates of the polyphageous pest insect *Spodoptera littoralis*.

Results and Discussion

A crude methanolic extract of the twigs of *A. oligophylla* exhibited significant insecticidal activity when incorporated into an artificial diet and tested against neonate larvae of the polyphagous pest insect *S. littoralis* at the arbitrarily chosen concentration of 1000 ppm. None of the insects were found to survive after 6 days of exposure to the treated diet (data not shown). Bioassay-guided fractionation of the crude extract resulted in the isolation of four rocaglamide compounds (**1**−**4**, Chart 1) and an aglain (**5**) and aglaforbesin derivative (**6**), respectively.

For the structural determination of all compounds (**1**−**6**) careful comparison of the ^1H and ^{13}C NMR data with previously published values[2−9] allowed substituent chemical shifts to be readily interpreted. The four rocaglamide derivatives (**1**−**4**) are characterized by a methylenedioxy substituent linked to C-6 and C-7 instead of the more common C-6 methoxyl unit. Compound **1** proved to be the C-6-demethoxy-C-6,C-7-methylenedioxy derivative of rocaglamide (also known as the flavagline, aglaroxin A) (Chart 1), which was previously isolated from *Aglaia roxburghiana*.[10] Compound **2** was identified as the 3′-methoxyl derivative of compound **1**, which has been isolated previously from the stem bark of *A. roxburghiana* (syn. *Aglaia elaeagnoidea*).[10] Compound **3** could be readily identified as a known rocaglamide derivative, namely, C-6-demethoxyl-C-6,C-7-methylenedioxymethylrocaglate, which had previously been isolated from *A. elaeagnoidea* (**3**).[7] Compound **4**, however, was a new natural product.

Compound **4** had a molecular ion peak in the EIMS at *m*/*z* 628, which is unusually high for rocaglamide deriva-

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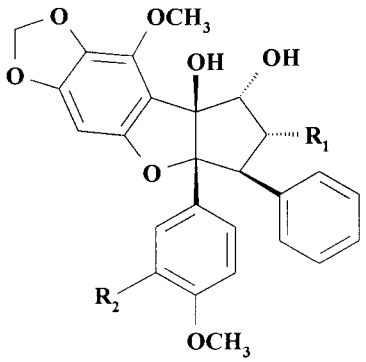
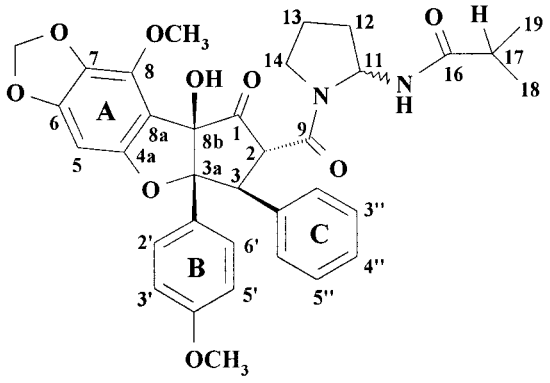
Chart 1. Structures of Compounds **1**−**6**



	R_1	R_2
1	$CON(CH_3)_2$	H
2	$CON(CH_3)_2$	OCH_3
3	$COOCH_3$	H



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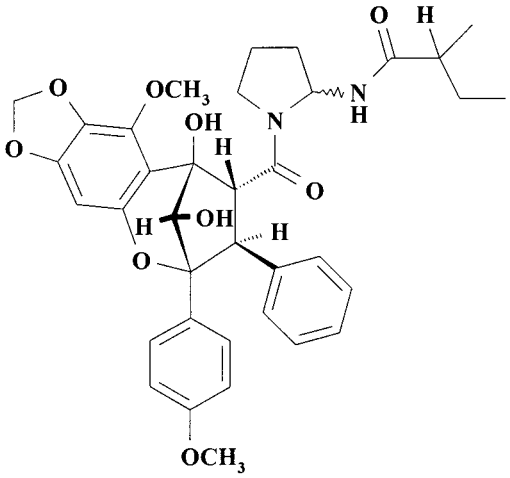

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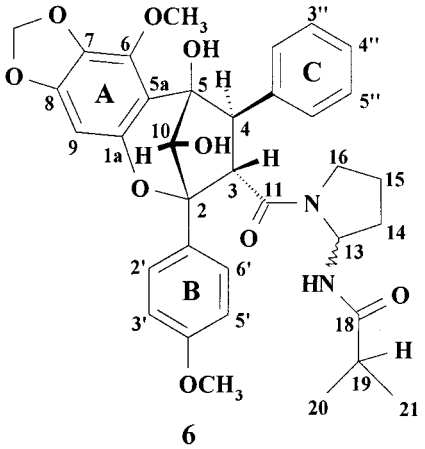

6

tives, and resulted from a substituent at C-2 that is similar to piriferine.[9] The molecular formula was determined to be $C_{35}H_{36}O_9N_2$ by HREIMS. This new compound was identified as a C-1-oxo, C-2-piriferine derivative of **1**. This assumption is corroborated by inspection of the ^1H and ^{13}C NMR spectra of **4** (Table 1). In the ^1H NMR spectrum of **4** the proton resonance at C-1 was missing because of the new ketone substituent, and there was a substantial shift for H-2 of 0.55 ppm which was now a doublet. The structure elucidation of the piriferine-like substituent was confirmed by comparison to known aglain derivatives which possess similar substituents[4,8] and from data from the HMBC and $^1H-^1H$ COSY NMR spectra. Further support for the assignment of a ketone group at C-1 was evident from the ^{13}C NMR spectrum of **4** (Table 1). The observed extreme downfield shift of the C-1 signal was indicative of the presence of a ketone substituent at position C-1. These findings were corroborated by inspection of the HMBC spectrum of **4**. The stereochemistry at C-11 remains uncertain since no significant NOEs could be observed.

Compound **5** is comparable with the aglain congeners described previously,[4,8] which possess a cyclopentatetrahydrobenzopyran skeleton. On the basis of the data obtained for the isolated compound and comparison with ^1H NMR data for aglain B isolated by Dumontet et al. (1996),[8] **5** was identified as C-8-demethoxy-C-7,C-8-methylenedioxyaglain (also known as homothapsakin A), which was isolated previously from *Aglaia edulis*.[9]

The structure of compound **6** is similar to those of the previously described aglaforbesin derivatives.[8] Although its molecular weight is similar to those of aglaforbesin A and B (all 630 amu) isolated by Dumontet et al. (1996),[8] there were a few differences in the ^1H and ^{13}C NMR spectra. The molecular formula was determined to be $C_{35}H_{38}O_9N_2$ by HREIMS. The ^1H NMR spectrum of **6** showed similarities to that of **5** (Table 1). In comparison with **5** the ^1H NMR signal of the methyl group at position 21 was absent, and hence **6** could be assigned with the same piriferine-like substituent as found in **4**. However, the HMBC experiment clearly indicated that the substituents at C-3 and C-4 were mutually exchanged. The correlations of the protons H-2″ and H-6″ with C-4 established the phenyl ring to be affixed to C-4 in **6**. The piriferine-like substituent was therefore attached to C-3. The assignment of the relative stereochemistry in **6** followed the same principles as outlined by Dumontet et al. (1996).[8] The absence of any NOESY

Table 1. ^{1}H and ^{13}C NMR Data of Compounds **4** and **6**[a]

compound **4**			compound **6**		
position	δ_H (J Hz)	δ_C	position	δ_H (J Hz)	δ_C
1		206.5 (s)	1a		148.9 (s)
2	4.72 (d, 13.4)	56.9 (d)	2		87.8 (s)
3	4.43 (d, 13.4)	51.8 (d)	3	4.48 (d, 6.9)	62.4 (d)
3a		101.1 (s)	4	4.30 (d, 6.9)	62.1 (d)
4a		156.2 (s)	5		82.0 (s)
5	6.48 (s)	89.8 (d)	5a		117.0 (s)
6		154.4 (s)	6		140.2 (s)
7		132.5 (s)	7		132.4 (s)
8		142.9 (s)	8		150.0 (s)
8a		111.0 (s)	9	6.28 (s)	94.1 (d)
8b		90.4 (s)	10	4.21 (s)	83.8 (d)
9		166.9 (s)	11		171.8 (s)
11	6.68 (d, 6.7)	64.3 (d)	13	4.99 (d, 5.5)	64.6 (d)
12	A 2.36 (m)	22.3 (t)	14	A 1.40 (m)	21.3 (t)
	B 1.94 (m)			B 1.18 (m)	
13	A/B 2.10 (m)	34.7 (t)	15	A 1.73 (m)	35.4 (t)
14	A/B 3.45 (m)	47.1 (t)		B 1.73 (m)	
16		179.1 (s)	16	A 3.20 (m)	47.2 (t)
17	2.48 (h, 6.9)	36.0 (d)		B 3.46 (m)	
18	1.19 (d, 7.0)	20.6 (q)	18		178.4 (s)
19	1.12 (d, 6.7)	20.6 (q)	19	1.98 (h, 6.9)	35.6 (d)
1′		127.6 (s)	20	0.92 (d, 6.8)	19.0 (q)
2′/6′	7.06 (m)	129.6 (d)	21	0.89 (d, 7.1)	20.0 (q)
3′/5′	6.77 (m)	114.1 (d)	1′		131.9 (s)
4′		160.2 (s)	2′/6′	8.08 (m)	129.6 (d)
1″		138.0 (s)	3′/5′	7.05 (m)	114.4 (d)
2″/6″	6.84 (m)	129.4 (d)	4′		160.9 (s)
3′/5	7.06 (m)	114.4 (d)	1″		141.9 (s)
4″	7.06 (m)	127.9 (d)	2″/6″	7.52 (m)	131.7 (d)
OCH_3-8	3.99 (s)	60.2 (q)	3″/5″	7.32 (m)	129.3 (d)
OCH_3-4′	3.74 (s)	55.5 (q)	4″	7.22 (m)	127.5 (d)
O-CH_2-O	5.96 (s)	102.8 (t)	OCH_3-6	4.06 (s)	60.9 (q)
			OCH_3-4′	3.88 (s)	55.5 (q)
			O-CH_2-O	A 5.93 (d, 1.1)	102.4 (t)
				B 5.95 (d, 1.2)	

[a] All spectra were recorded in CD_3OD.

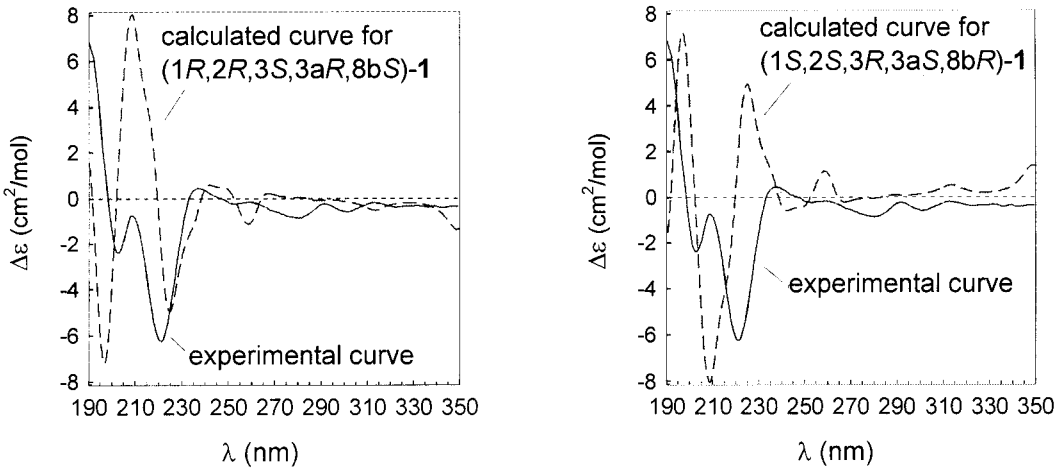

Figure 1. Boltzmann weighting based calculated CD spectra of both enantiomers of **1** (- - -) and comparison with experimental data (—).

relationships of H-10 to H-3 or H-4, respectively, in conjunction with the chemical shift of the C-6-methoxyl group (δ 4.06), indicated the relative configurations at C-3, C-4, and C-10 as shown in Chart 1. The stereochemistry at C-11 remains uncertain since no significant NOEs could be observed.

The absolute configuration of rocaglamide-related compounds has so far been deduced only by chiroptical comparison with rocaglamide itself,[1,3,12] (Chart 1) whose stereostructure was elucidated by enantioselective synthesis. To establish a second independent stereochemical standard for rocaglamides, we have performed the first quantum chemical CD calculations in this field of natural products.

As a result of the great number of substituents with rotatable bonds connected to the rigid framework, **1** is quite a flexible compound. This is the reason our previous approach of calculating the CD spectra of all AM1[14] conformers below an energetic cutoff and adding them up (by Boltzmann weighting), followed by a "UV-correction" as described earlier,[15] was unsuccessful: None of the calculated CD spectra—neither for "1*R*,2*R*,3*S*,3a*R*,8b*S*" nor for "1*S*,2*S*,3*R*,3a*S*,8b*R*"—showed a sufficiently good fit with the experimental data (Figure 1) to allow an unambiguous assignment.

A more detailed investigation of the dependence of the chiroptical properties from the molecular structure of **1**

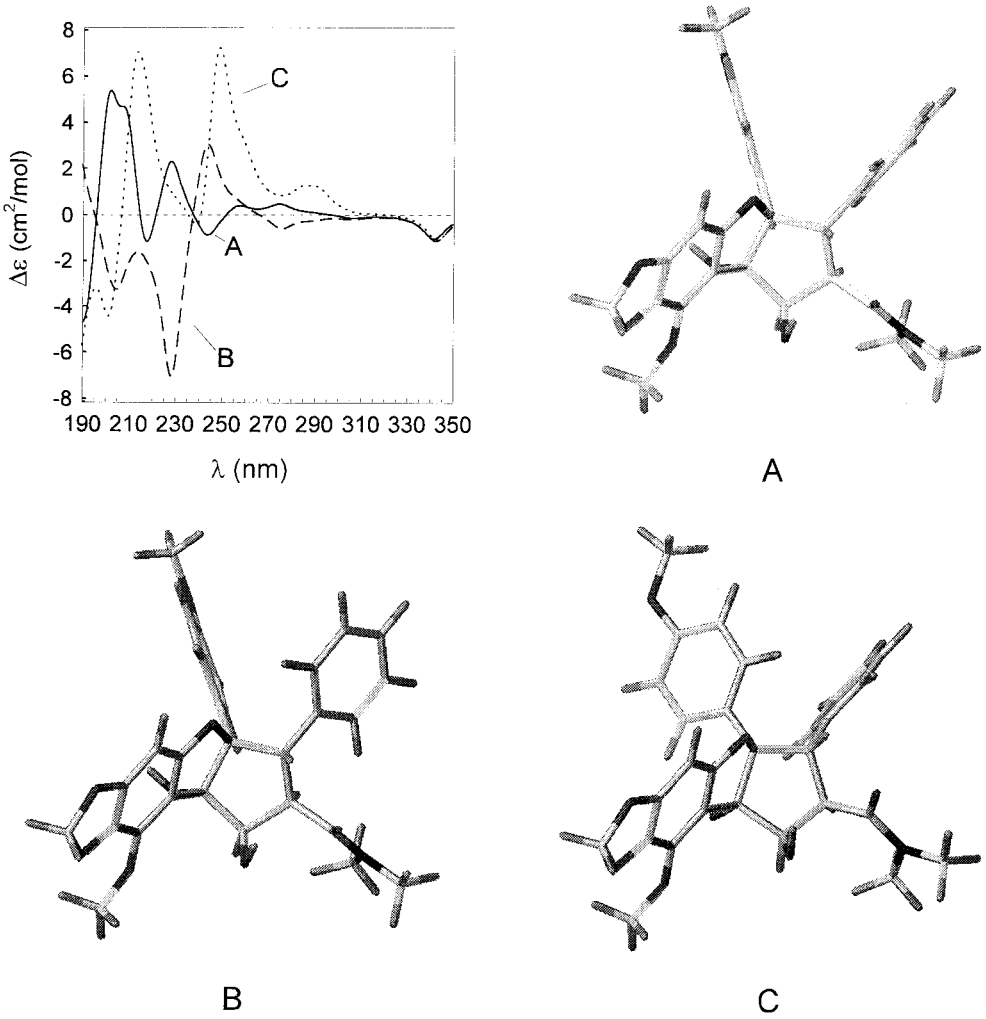

Figure 2. Dependence of the calculated CD curve shapes (A−C) from the rotational positions of the two aromatic substituents of **1**.

showed that even the smallest conformational changes of the two aromatic substituents will result in drastic changes of the corresponding single CD spectrum (Figure 2). Therefore, a conclusive attribution of the absolute configuration of **1** by means of a Boltzmann weighting based conformational analysis is not possible in this particular case. As a consequence, we then combined the calculation of the CD spectrum with molecular dynamics (MD) simulations as recently introduced by our group.[16] The simulation was carried out for a total period of 500 ps, recording the structure every 0.5 ps for further calculations. For the 1000 structures thus collected, single CD spectra were calculated. The computed spectra were—in contrast to the conventional method mentioned above—averaged *arithmetically* over the trajectory to give a now MD-based theoretical overall CD spectrum for **1** as presented in Figure 3. The now excellent agreement of the calculated overall spectrum for the (1*R*,2*R*,3*S*,3a*R*,8b*S*)-configured enantiomer with the experimental one permitted an unequivocal attribution of the absolute configuration of **1** as 1*R*,2*R*,3*S*,3a*R*,8b*S*. This shows that for such flexible molecules the use of the (more CPU-intensive) MD approach is indeed superior to the "statistical" Boltzmann-based procedure. This first quantum chemical CD calculation in the field of rocaglamides paves the way for further work on similar compounds, as a rational, time-saving alternative to sometimes tedious enantioselective syntheses. This work is in progress.

By comparison of the CD spectrum of the now stereochemically clearly attributed metabolite **1** with the CD spectra of **2** and **3**, also their absolute configurations could be established. The conclusions obtained are in agreement also with a comparison with the CD behavior of rocaglamide itself.[1,12] Note that the stereochemistry given for compound **4** depicts only the relative configuration. The absolute stereochemistry could not be determined by the method outlined above since its CD spectrum exhibits significant differences from the CD spectra of compounds **1**−**3** (Figure 4). The additional peak at 323 nm in the CD spectrum of **4** might be due to the oxo functionality at C-1 and to the piriferine-like substituent at C-2, which are only present in **4**.

The insecticidal activities of compounds **1**−**6** were studied by incorporating the compounds into an artificial diet over a range of concentrations and offering them to neonate larvae of *S. littoralis* in a long-term feeding assay (duration 8 days). As positive controls, the parent compound rocaglamide and the known natural insecticide azadirachtin were employed. The LC_{50} and EC_{50} values of each compound were calculated by probit analysis from the respective dose−response curves (Table 2). The rocaglamide derivatives **1**−**4** showed strong insecticidal activities with LC_{50} values between 2.15 and 6.52 ppm and EC_{50} (concentrations that reduce larval growth by 50%) values between 0.11 and 0.99 ppm, respectively. The methylenedioxy substituent linked to C-6 and C-7 in compounds **1**−**3**,

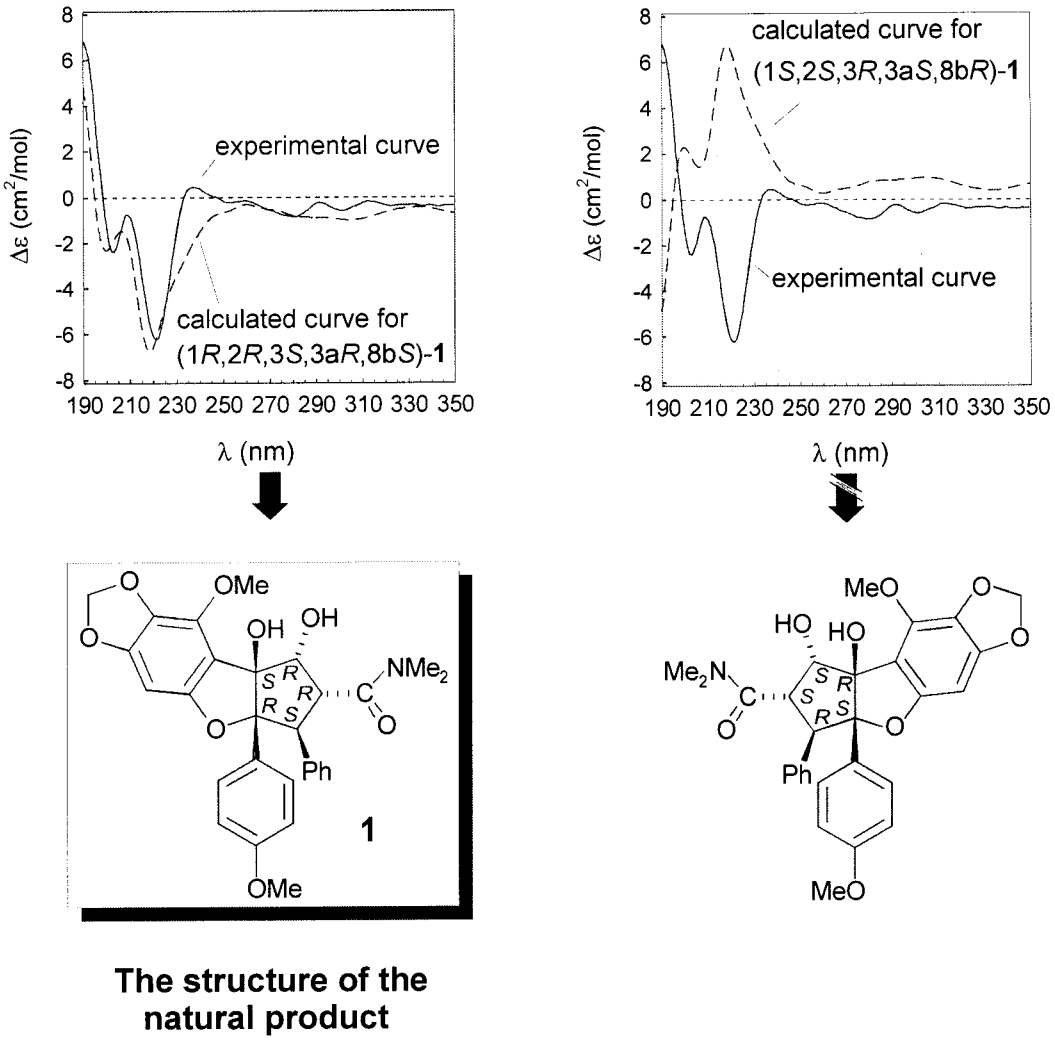

Figure 3. MD-based calculated CD spectrum of **1** (- - -) and comparison with experimental data (—).

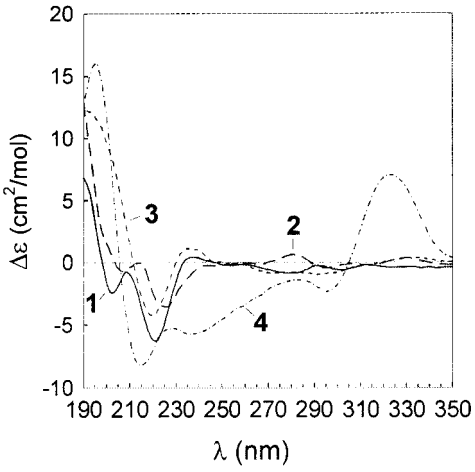

Figure 4. Comparison of the experimental CD spectrum of **1** with the CD spectra of **2**—**4**.

however, renders them less active in comparison to the parent compound rocaglamide, which bears OCH_3 substituents at C-6 and C-8, respectively (Table 2). Compound **4** was found to be approximately 3-fold less active when compared to **1** (Table 2), probably due to the large piriferine-like substituent at C-2 even though the as yet unknown effect of the chiral center at C-1 that is absent in **4** also has to be taken into consideration when discussing insecticidal structure—activity relationships. Compounds **5** and **6** showed no insecticidal activity. These findings provide additional circumstantial evidence for the importance of the benzofuran versus a benzopyran moiety for the biological activity of the class of compounds under study.

Table 2. Insecticidal Activities of Compounds **1**—**6**[a]

compound	LC_{50} (ppm)	EC_{50} (ppm)
1	2.34	0.49
2	2.15	0.20
3	3.97	0.11
4	6.52	0.99
5	n.a[b]	n.a[b]
6	n.a[b]	n.a[b]
rocaglamide[c]	0.90	0.08
azadirachtin[c]	0.70	0.06

[a] Determined in a chronic feeding assay (8 days) with neonate larvae of *Spodoptera littoralis*. [b] n.a.= not active up to a concentration of 100 ppm. [c] Positive control.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 241 MC instrument. CD spectra were measured in EtOH on an Yvon Dichrograph CD 6 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in CD_3OD on Bruker AMX 300 or ARX 400 NMR spectrometers in the 1D (^1H and ^{13}C, including DEPT) and 2D (COSY, long-range ^{13}C—^1H correlations) mode. EIMS (70 eV, direct inlet) were recorded on a Finnigan MAT 8430 mass spectrometer. HREIMS data were determined on a Finnigan

MAT 91 instrument by peak matching at resolution of approximately 10 000 (10% valley). Solvents were distilled prior to use, and spectral grade solvents were used for spectroscopic measurements.

Plant Material. Twigs of *A. oligophylla* were collected at Nui Sam, near Chau Doc, Vietnam, in January 1998, and identified by L.C.K. A voucher specimen (LCK 98-001) is on file in the Department of Botany, College of Natural Science, Vietnam National University, Ho Chi Minh City, Vietnam.

Extraction and Isolation. Air-dried twigs of *A. oligophylla* (1.3 kg) were ground and exhaustively extracted with MeOH and acetone. Following evaporation of the solvent, the extract was partitioned between MeOH/hexane, H_2O/CH_2Cl_2, and H_2O/EtOAc. Each crude extract obtained was subjected to bioassay with neonate larvae (see below). In this bioassay, insecticidal activity was found to reside in the CH_2Cl_2 fraction. Bioassay-guided fractionation of the CH_2Cl_2 fraction was conducted by vacuum-liquid chromatography (Si gel, Merck, Darmstadt, Germany, mixtures of CH_2Cl_2−*i*-PrOH) and repeated column chromatography separation employing Si gel [mobile phase: CH_2Cl_2−*i*-PrOH, 90:10 and 95:5, or hexane−$(CH_3)_2CO$, 1:1]. Final purification was obtained using RP-18 lobar columns (Merck, Darmstadt, Germany) (mobile phase: mixtures of MeOH and H_2O) and by preparative HPLC. The separation column (7 μm, 300 × 8 mm, i.d.) was prefilled with Eurospher RP-18 (Knauer, Berlin, Germany). Solvents were distilled prior to use, and spectral grade solvents were used for spectroscopic measurements. Fractions were monitored on precoated TLC plates with Si gel 60 F_{254} (Merck, Darmstadt, Germany) (mobile phase: CH_2Cl_2−*i*-PrOH, 90:10, or hexane−*i*-PrOH/EtOAc, 8:1:1). Rocaglamide derivatives were detected by their UV absorbance at 254 nm or after spraying the TLC plates with anisaldehyde reagent. Yields of compounds were **1**, 13.6 mg; **2**, 2.4 mg; **3**, 4.5 mg; **4**, 3.7 mg; **5**, 3.3 mg; and **6**, 8.0 mg. The known compounds **1**−**3** and **5** were identified by their EIMS and 1D ^{1}H NMR data and by comparison with literature data.[1−8]

Compound 4: white amorphous residue; $[\alpha]^{20}_D$ +12.2° (*c* 1.0, EtOH); CD 217 ($\Delta\epsilon$ −12.67), 283 ($\Delta\epsilon$ −2.04), 295 ($\Delta\epsilon$ −2.67), 322 ($\Delta\epsilon$ +4.96); ^{1}H and ^{13}C NMR data, see Table 1; EIMS (70 eV) *m*/*z* 628 $[M]^+$ (2), 610 (9), 523 (3), 472 (8), 454 (6), 428 (14), 325 (21), 314 (100), 299 (26), 254 (3), 200 (5), 135 (6), 131 (8), 85 (3); HREIMS *m*/*z* 628.2418 (calcd for $C_{35}H_{36}O_9N_2$, 628.2421).

Compound 6: white amorphous residue; $[\alpha]^{20}_D$ −22.7° (*c* 6.0, EtOH); CD 219.5 ($\Delta\epsilon$ −7.95), 230.5 ($\Delta\epsilon$ +0.07), 240 ($\Delta\epsilon$ −3.01), 261 ($\Delta\epsilon$ −0.11), 295.5 ($\Delta\epsilon$ −1.18); ^{1}H and ^{13}C NMR data, see Table 1; EIMS (70 eV) *m*/*z* 630 $[M]^+$ (1), 524 (3), 464 (8), 456 (25), 430 (3), 376 (11), 327 (100), 313 (13), 299 (14), 280 (9), 200 (30), 168 (8), 131 (21), 70 (6); ESIMS *m*/*z* $[M + H]^+$ 631.4, $[M + Na]^+$ 653.6, $[2M + Na]^+$ 1284.0; HREIMS *m*/*z* 630.2572 (calcd for $C_{35}H_{38}O_9N_2$, 630.2577).

Computational Methods. **Conformational Analysis**. The conformational analysis of **1** was performed on Silicon Graphics OCTANE (R10000) workstations by means of the AM1[14] parametrization as implemented in the program package VAMP6.5,[17] starting from preoptimized geometries generated by the TRIPOS[18] force field using the Random Search algorithm implemented in SYBYL.[18]

Molecular Dynamics (MD). The MD simulation was performed on Silicon Graphics OCTANE (R10000) workstations using the TRIPOS[18] force field as implemented in the molecular modeling package SYBYL.[18] The molecule was weakly coupled to a thermal bath at $T = 400$ K,[19] with a temperature relaxation time $\tau = 0.1$ ps.

CD Calculations. The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by a CNDO/S-CI[20,21] calculation, in which the CI expansion[20,21] takes into account the ground state and all n and π orbitals. These calculations were carried out on Linux *i*PII workstations using the BDZDO/MCDSPD[20] program package. For a better comparison of the theoretical CD spectrum with the experimental one, a Gaussian band shape function was generated over the calculated rotational strength values.

Insect Bioassays. The chronic feeding assays were carried out with larvae of the polyphagous pest insect *S. littoralis* (Noctuidae, Lepidoptera). The larvae were from a laboratory colony reared on artificial diet under controlled conditions at 26 °C as described previously.[13] Feeding studies were conducted with neonate larvae ($n = 20$ for each treatment), which were kept on a diet containing extracts or compounds under study. After an 8-day exposure, survivals and weights of surviving larvae were recorded and compared with controls that had been exposed to diet treated with solvent (MeOH) only. LC_{50} and EC_{50} values were calculated from dose−response curves by probit analysis. Azadirachtin, which was used as a positive control, was obtained from Roth (Karlsruhe, Germany).

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