Cyclorocaglamide, the First Bridged Cyclopentatetrahydrobenzofuran, and a Related "Open Chain" Rocaglamide Derivative from *Aglaia oligophylla*

Gerhard Bringmann,*[,†] Jörg Mühlbacher,[†] Kim Messer,[†] Michael Dreyer,[‡] Rainer Ebel,[‡] Bambang W. Nugroho,[‡,⊥] Victor Wray,[∥] and Peter Proksch*[,‡]

Institut für Organische Chemie der Universität, Am Hubland, D-97074 Würzburg, Germany, Institut für Pharmazeutische Biologie der Universität, Universitätsstrasse 1, D-40225 Düsseldorf, Germany, and Gesellschaft für Biotechnologische Forschung mbH, D-38124 Braunschweig, Germany

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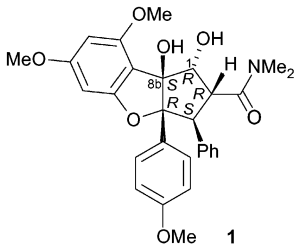
Two rocaglamide-related natural products, the previously known compound 6-demethoxy-10-hydroxy-11-methoxy-6,7-methylendioxyrocaglamide (**3**), and cyclorocaglamide (**4**), its 8b,10-anhydro analogue, have been isolated from the tropical plant *Aglaia oligophylla*. Compound **4** is the first bridged cyclopentatetrahydrobenzofuran natural product, and it exhibited a CD spectrum virtually opposite that of all the other rocaglamide natural products known so far, but it still has the same absolute configuration at all stereogenic centers of the basic molecular framework. This was shown unequivocally by quantum chemical CD calculations (here based on molecular dynamics-weighted force field structures) and was finally confirmed experimentally, by a "biomimetic-type" cyclization of **3** to give **4**, with the expected "inversion" of the CD spectrum. The opposite chiroptical properties of **3** and **4**, despite their homochiral character, underline the necessity of handling chiroptical data with the greatest care, e.g., by simulating them by quantum chemical CD calculations. Compound **3** exhibited an LC_{50} of 2.5 ppm when evaluated against neonate larvae of *Spodoptera littoralis*, while **4** was inactive in this assay up to 100 ppm.

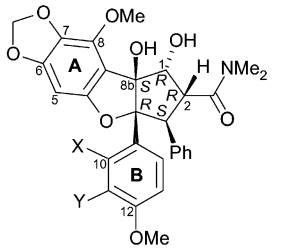
The genus *Aglaia* (Meliaceae), which occurs in the tropical rain forests of Southeast Asia, is characterized by the presence of cyclopentatetrahydrobenzofurans similar to rocaglamide (**1**).[1−11] These natural products, which are confined exclusively to *Aglaia* species, have recently attracted considerable attention due to their strong insecticidal activity[3−7] and their pronounced cytostatic effects against human cancer cells in vitro.[12−14]

Structure−activity studies with naturally occurring rocaglamide derivatives have proved the OH group at C-8b to be crucial for the insecticidal and cytostatic activities of these compounds. In contrast, all rocaglamide derivatives with methoxy or ethoxy substituents in this benzylic position were shown to be inactive.[7,13]

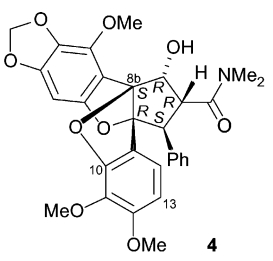
Whereas the absolute configuration of rocaglamide (**1**) itself was elucidated by enantioselective synthesis,[16] all of the stereostructures of the ca. 50 naturally occurring rocaglamide derivatives known to date have been published as configurationally analogous, and most of them have been assigned by CD comparison with the parent compound, rocaglamide (**1**), and some just arbitrarily.[2−7] Using 6-demethoxy-6,7-methylendioxyrocaglamide (**2**) as an example, we have recently achieved the first unambiguous elucidation of the absolute configuration of a rocaglamide derivative independent of a lengthy total synthesis, by quantum chemical calculation of its CD spectrum, based on a force-field-based molecular dynamics (MD) simulation, and comparison with the spectrum experimentally recorded.[11]

In the present contribution, we report on the discovery of cyclorocaglamide (6-demethoxy-8b,10-epoxy-11-methoxy-6,7-methylendioxyrocaglamide, **4**), an unprecedented rocaglamide derivative with an additional oxygen bridge between C-8b and C-10 of the aromatic ring B and showing a CD spectrum nearly opposite of all other rocaglamide analogues. Also described is the isolation of the related but open chain and thus "conventional" rocaglamide derivative **3**. This compound has already been reported earlier,[1] yet without any spectroscopic data supporting the postulated structure. It is the first and hitherto only rocaglamide derivative with three oxygen functions in the B ring; one of these is a free hydroxy function at C-10, a fundamental precondition for its probable S_N1-type biosynthetic ring closure to produce the cyclic ether **4**. MD-based CD calculations proved the stereochemical identity of the two new compounds, despite their nearly opposite CD spectra. This result was confirmed experimentally by the biomimetic cyclization of **3** to give chiroptically (and thus stereochemically) authentic **4**. The fact that compound **4** was isolated after mild extraction of the plant material utilizing only cold, acid-free solvents and the observation that **4** was not formed upon prolonged standing of purified **3** preclude cyclorocaglamide (**4**) as an isolation artifact.





2: X,Y = H
3: X = OH, Y = OMe



* To whom correspondence should be addressed. (G.B.) Tel: +49-931-8885323. Fax: +49-931-8884755. E-mail: bringman@chemie.uni-wuerzburg.de. (P.P.) Tel: +49-211-8114163. Fax: +49-211-8111923. E-mail: proksch@uni-duesseldorf.de.

† Universität Würzburg.

‡ Heinrich-Heine-Universität Düsseldorf.

∥ Gesellschaft für Biotechnologische Forschung mbH.

⊥ Permanent address: Department of Plant Pests and Diseases, Faculty of Agriculture, Bogor Agricultural University, Jl. Raya Pajajaran-Bogor 16144, Indonesia.

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Results and Discussion

Vacuum-liquid chromatography of the CH_2Cl_2 fraction of the MeOH extract of the twigs of *Aglaia oligophylla* Miq. yielded two new compounds. Compound **3**, the substance eluting first by reversed-phase HPLC, gave rise to an $[M + H]^+$ ion peak at *m*/*z* 566 on ESIMS, which, together with its ^{13}C NMR data for 30 carbons, suggested a molecular formula of $C_{30}H_{31}NO_{10}$. In the EIMS, a prominent peak at *m*/*z* 547 (base peak) was indicative of a loss of water, typical of rocaglamides.[3−7] An intense peak at *m*/*z* 176 revealed the nature of the amide substituent at C-2, which is cleaved together with ring C as a cinnamic acid derivative.[15] The presence of a methylenedioxy substituent at C-6 and C-7 was established by two additional doublets at 5.93 and 5.94 ppm (J = 1.1 Hz), a singlet for H-5 at 6.36 ppm, and the characteristic downfield shift for the methoxy group at C-8 (4.09 ppm) in the ^1H NMR spectrum. In addition, other evidence was obtained from a methylene carbon signal at 102.5 ppm in the ^{13}C NMR spectrum and by the pronounced upfield shifts of C-6 (153.2 ppm) and C-8 (141.7 ppm) as compared to rocaglamide congeners featuring a 6,8-dimethoxy substitution in ring A.[3−5] The spectral data for **3** were also in full agreement with rocaglamide derivatives such as **2** containing the same 8-methoxy-6,7-methylenedioxy substructure isolated from *Aglaia elaeagnoidea*.[8,10]

In the ^1H NMR spectrum, only two aromatic doublets were observed for ring B at 6.29 and 6.94 ppm (J = 9.1 Hz), thus indicating a tetrasubstituted phenyl ring system. The positions of the two methoxy substituents were assigned by HMBC correlations of signals at 3.71 and 3.74 ppm to C-11 at 137.6 ppm and C-12 at 153.4 ppm, respectively. With regard to the molecular formula, it was evident that the remaining substituent at C-10 had to be a free hydroxy group. This was in agreement with downfield shifts for C-10 and C-11 by 17.0 and 24.3 ppm, respectively, and with an upfield shift for C-9 by 10.9 ppm as compared to rocaglamide derivatives with only a *para*-methoxy substituent in ring B[3,4] and was further corroborated by HMBC correlations (see Supporting Information). Within the large number of rocaglamide derivatives described so far, **3** represents the first example bearing a free hydroxy group at C-10 as proven unequivocally in the present contribution.

The relative stereostructure of **3** was established by comparison of NMR chemical shifts and coupling constants and by CD spectral correlation with those published for other rocaglamides.[2−11,15]

The molecular formula of the new cyclic natural product **4** was determined to be $C_{30}H_{29}NO_9$ by ESIMS and ^{13}C NMR data, thus suggesting it to be an anhydro analogue of **3**. The EIMS data differed from those of other rocaglamide congeners in featuring an intense molecular ion at *m*/*z* 547 (base peak) while lacking most of the characteristic fragments in the lower mass region, indicating an unusually stable ring system. For example, the prominent peak at *m*/*z* 176, indicative of the amide substituent at C-2[15] for **3** (see above), was barely visible for **4**. The NMR spectral data for **4** showed an overall similarity to those of **3**, but with some pronounced differences: H-2 and H-14 displayed upfield shifts of 1.26 and 1.32 ppm, respectively, while C-10 and C-8b were shifted downfield by 6.5 and 12.2 ppm, and

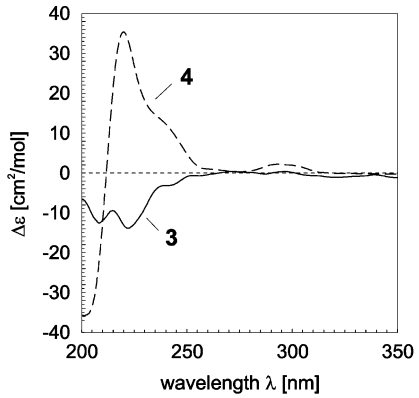

Figure 1. Experimental CD spectra of **3** (—) and **4** (- - -).

C-8a and C-1 were shifted upfield by 4.5 and 6.2 ppm, respectively. Since the ^1H NMR chemical shifts for H-2 and H-14 were inconsistent when compared to data published for other rocaglamide congeners,[2−11,15] assignments were verified by NOE difference experiments. Upon irradiation of H-13, a positive NOE of H-14 and the methoxy group at C-12 was observed, while a similar experiment involving H-2 led to enhancements of H-1 and H16/H-20 (see Supporting Information).

These findings were in agreement with the presence of an additional heterocycle resulting from loss of water between the hydroxy groups at C-8b and C-10, thus fixing the otherwise freely rotating ring B in a rigid position. Apart from the upfield chemical shift of H-2 and H-14, conformational changes in the cyclopentane ring were also involved, since the vicinal coupling constant between H-1 and H-2 amounts to 4.5 Hz in **4** in contrast to 7.1 Hz in nonbridged congeners such as **3**. By further NOE experiments (see Supporting Information), the relative configuration was assigned as depicted in the structure sheet.

Due to their structural similarity, all rocaglamide-related natural products that have so far been examined display CD spectra very similar to that of rocaglamide (**1**), itself. Since the absolute stereostructure of **1** has been elucidated by enantioselective total synthesis,[16] the absolute configurations of new rocaglamide-related compounds have as yet been assigned by chiroptical comparison with **1** as the "parent compound".[3−7] Indeed, as for all the other natural rocaglamides, compound **3** showed the expected CD curve (Figure 1), hinting at the presence of the usual rocaglamide-analogue absolute stereostructure, with (1*R*,2*R*,3*S*,-3a*R*,8b*S*)-configuration, as for all the other natural rocaglamides known so far (except for those exhibiting a pyrimidone unit linked to C-1 and C-2 of the rocaglamide skeleton[3]).

The novel cyclic natural product **4**, by contrast, displayed an intense marked CD curve, which was virtually opposite that of **3** for nearly the entire range of wavelength (Figure 1). Following the CD interpretation normally used for the attribution of the absolute configuration of rocaglamide derivatives,[3−7] this unusual behavior of **4** should lead to the conclusion that **4** is the first representative of this interesting class of compounds that has, at least for the major part of the molecule, an opposite overall stereostructure. Such a purely empirical interpretation of CD spectra, without a detailed analysis of the conformation of a molecule with flexible chromophores, is, however, generally critical, and all the more in the present case, because recent computational investigations of the compound **2**[11] have shown that the CD curve shape depends strongly on the conformational position of the two rotationally unstable (in

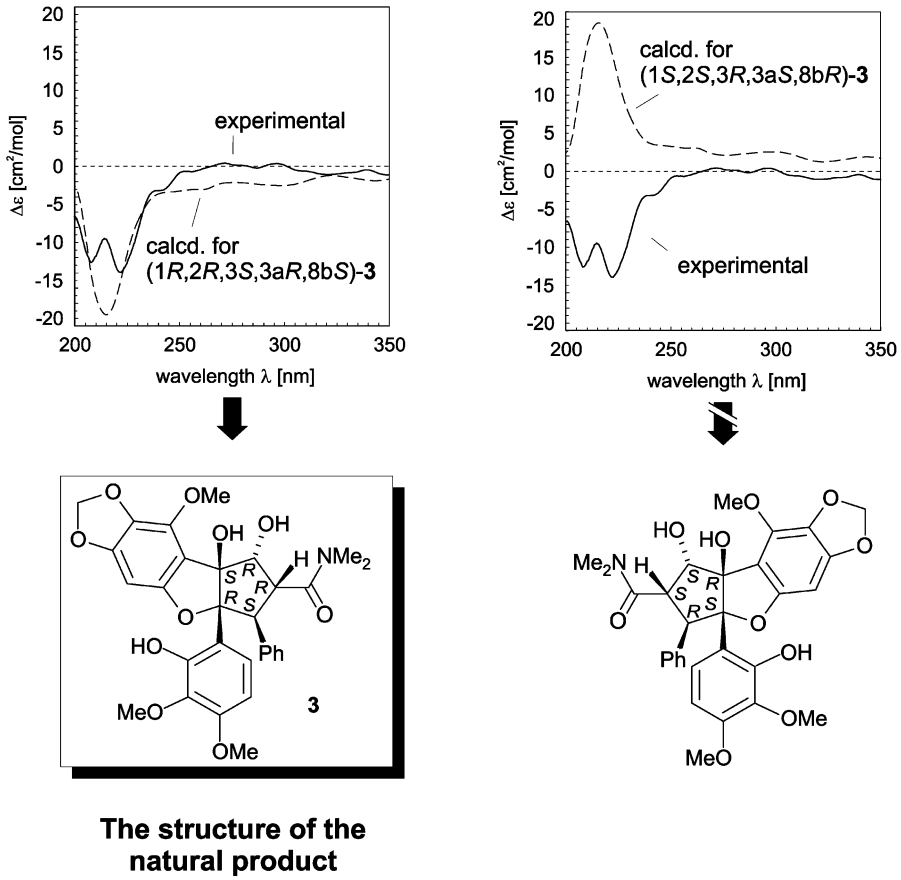

Figure 2. Attribution of the absolute configuration of **3** by MD-based calculated CD spectra of both enantiomers of **3** (- - -) and comparison with the experimental spectrum (—).

part oxygenated) phenyl substituents. In contrast to the rigid-looking tricyclic molecular framework to which these aryl groups are attached, the rotational barriers of these major chromophores of the molecule are quite low, so that, as for **2**, drastic changes in the CD behavior of such rocaglamide-related compounds during the rotational process are to be expected. If, as for **4**, this rotation is blocked by formation of a bridged compound, only this particular rotational conformer will contribute to the CD spectrum, which may happen to be one of those rotational arrays that deliver CD contributions opposite those of the majority of the conformational species, as in **3**.

For this reason, we performed comparative CD calculations for both **3** and **4** to see whether the opposite CD behavior of these two molecules is indeed due to an opposite configuration of the central tricyclic molecular core, or whether the two molecules do have the same stereochemical array, only with a fixed conformation for **4**. The CD calculations, as in a previous paper,[11] were based on MD simulations using the Tripos[17] force field. In both cases, the simulations were carried out for 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 averaged arithmetically over the trajectory to give the theoretical overall spectra. To take into account a systematic shift of the calculated CD spectra, a "UV correction" was carried out as introduced earlier.[18] The CD curve obtained for the (1*R*,2*R*,3*S*,3a*R*,-8b*S*)-enantiomer of **3** (Figure 2) showed an excellent agreement with the experimental CD spectrum, while that calculated for its (1*S*,2*S*,3*R*,3a*S*,8b*R*)-enantiomer was virtually opposite, thus permitting an unequivocal attribution of the absolute configuration of **3**.

For the cyclic compound **4**, by contrast, the CD spectrum calculated for the (1*R*,2*R*,3*S*,3a*R*,8b*S*)-enantiomer was now a near mirror-image of the one calculated for the stereochemically same (1*R*,2*R*,3*S*,3a*R*,8b*S*)-enantiomer of **3** and showed an agreement with the experimental one (Figure 3, left), while the one calculated for 1*S*,2*S*,3*R*,3a*S*,8b*R* was opposite (Figure 3, right). Consequently, both rocaglamide-related compounds, **3** and **4**, have the same absolute configuration, despite their near-opposite CD spectra.

This remarkable effect, despite the near-identical constitution and the fully identical configurations of **3** and **4** at each single stereogenic center, becomes understandable from an additional computational experiment. When comparing a timely average structure of **3** with that of **4**, the aryl substituents (rings B and C) adopt near-enantiomeric local arrays, roughly differing by dihedral angles of 50° (in the case of rings B) and 37° (for rings C). By comparing **3** with the mean structure of the (hypothetical) mirror image of **4**, i.e., *ent*-**4**, and subsequently "matching" these two structures, **3** and *ent*-**4**, by their chromophores, near-identical absolute conformations for the rotational arrays of the phenyl substituents were obtained, now varying only by a marginal difference of 4° and 15°, respectively (Figure 4). The cyclization does "freeze out" one of the conformations of **3** that has a near-enantiomeric array of the deciding chromophores.

To further confirm the stereochemical identity of **3** and **4**, a biomimetic ring closure of **3** to give **4** seemed worthwhile. Treatment of **3** (i.e., with its negative CD curve mainly in the region of 200−250 nm) with trifluoroacetic acid gave **4**, which, according to its in situ analysis by LC-CD, proved to be chiroptically identical with the natural product (i.e., with a *positive* CD curve between 220 and

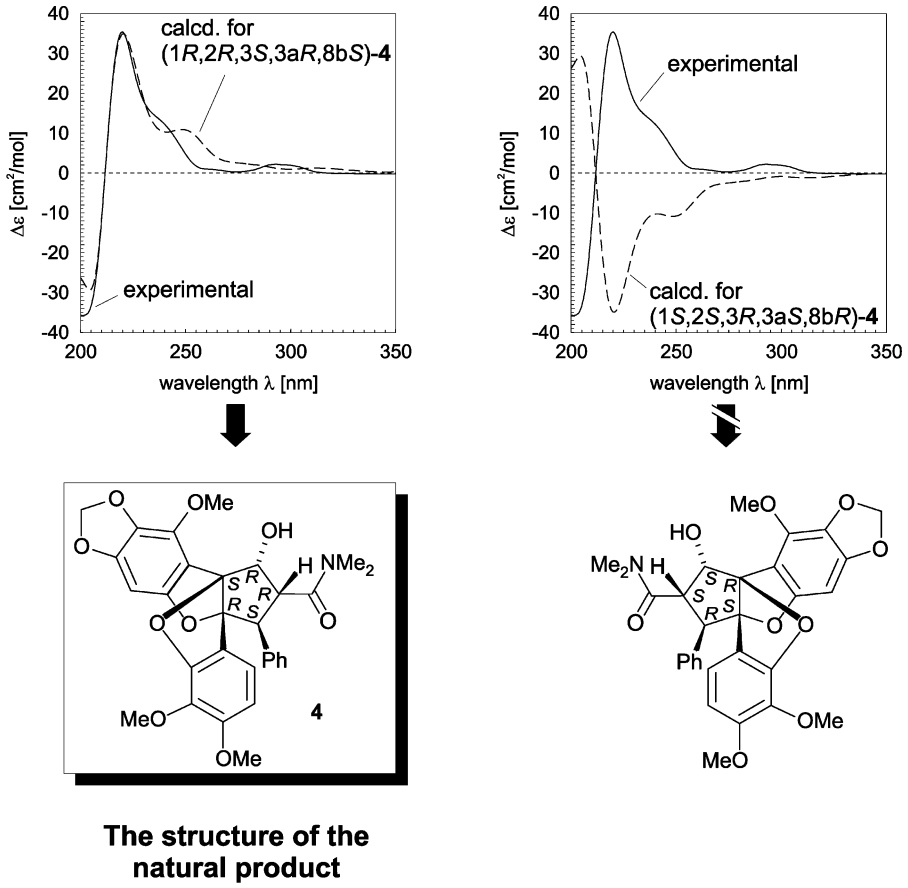

Figure 3. Assignment of the absolute stereostructures of **4** by comparison of its calculated CD spectra (- - -) with the experimental spectrum (—).

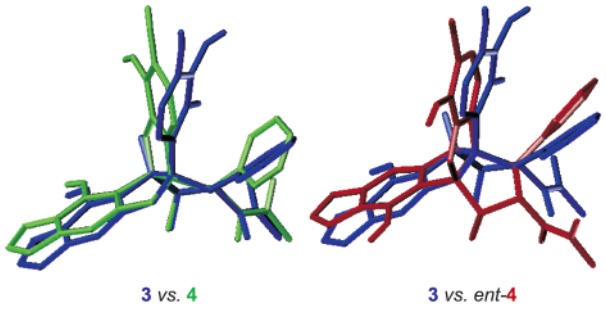

Figure 4. Matches of the "average" structures (H atoms are omitted for reasons of clarity) of **3** (blue) and **4** (green) (left side) and of **3** (blue) and *ent*-**4** (red) (right side).

250 nm). Besides confirming the stereochemical identity of **3** and **4**, this cyclization underlined the high reactivity of the benzylic oxygen function at C-8b. This OH group seems to be a precondition for the high insecticidal activity of rocaglamides,[3−7] since **4**, in contrast to **3**, was entirely devoid of this activity (see below).

Both rocaglamide derivatives, **3** and **4**, were tested against neonate larvae of the polyphagous pest insect *Spodoptera littoralis* following incorporation into artificial food at a range of concentrations. Larvae (n = 20) were kept on this diet or on a control diet. As a positive control the well-known natural insecticide azadirachtin was employed. After 8 days of exposure, surviving larvae were counted and compared to the controls. From the dose−response curve the LC_{50} of compound **3** was calculated to be 2.5 ppm, whereas the LC_{50} of azadirachtin amounted to 0.9 ppm. Compound **4** was completely inactive even at a concentration of 100 ppm. This finding essentially corroborates earlier studies[6,7] which had shown that substitution of the OH group at C-8b of rocaglamide congeners nullifies the insecticidal activity of the resulting derivatives, thereby identifying an unsubstituted OH group at this position as a prerequisite for biological activity of rocaglamide-derived compounds.

In summary, the first bridged rocaglamide, **4**, has been isolated, along with its open chain analogue, **3**. The cyclic compound **4** is, simultaneously, the first rocaglamide analogue with a virtually opposite CD spectrum but still is stereochemically identical to all of the normal, non-bridged natural products of this class. The reason for this chiroptical "inversion" is that in this case just a ring closure that does not involve any stereogenic center causes a near-enantiomeric preferential array of the chromophores and thus an inversion of the CD behavior. By freezing the rotation of one of the aromatic rings in **4**, the whole molecule is forced into a conformation whose chromophores are a near mirror-image of those of **3**.

This example points out the substantial value of quantum chemical CD calculations. A merely empirical interpretation of the CD behavior would have led to the erroneous assumption that the structurally so closely related compounds **3** and **4** had opposite stereostructures, and it is only from the CD calculations that their stereochemical identity was proven. The results furthermore underline the usefulness of the molecular dynamics simulations as a useful "building block" in quantum chemical CD calculations.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 241 MC instrument. CD spectra were recorded on an Jobin-Yvon CD6 Dichrograph in

EtOH. HPLC-CD measurements were performed on a JASCO J-715 spectropolarimeter (JASCO GmbH Deutschland) with a standard flow cell, using the stop-flow mode. HPLC conditions: Symmetry RP_{18} (Waters) 4.6 × 250 mm, MeCN−H_2O, 1:1 (0.1% TFA), 1 mL/min, 220 nm. ^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. Mass spectra (EI, CI, ESI) were recorded on a Finnigan MAT 8430 spectrometer or on an Intectra AMD 402 spectrometer. Solvents were distilled prior to use, and spectral grade solvents were used for spectroscopic measurements.

Plant Material. Twigs of *Aglaia oligophylla* Miq. were collected at Nui Sam, near Chau Doc, Vietnam, in January 1998 and identified by L. C. Kiet. A voucher specimen 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 *Aglaia oligophylla* (1.3 kg) were ground and exhaustively extracted with MeOH and acetone at room temperature. After evaporation of the solvent, the extract was partitioned between MeOH−H_2O (90:10) and *n*-hexane. The MeOH−H_2O phase was reduced to ca. 10% of its volume and extracted with CH_2Cl_2 and finally with EtOAc. Each crude fraction obtained was subjected to a bioassay with neonate larvae (see below). In this test, 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 and *i*-PrOH), repeated column chromatography separation employing Si gel using the same solvent system or using mixtures of *n*-hexane and acetone (e.g., 1:1). Final purification was achieved 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). 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 *n*-hexane−*i*-PrOH−EtOAc, 8:1:1). Rocaglamide derivatives were detected by their UV absorbance at 254 nm. For final HPLC separation of compounds **3** and **4**, methanol (LiChrosolv) and phosphoric acid (0.15%, pH 2) were used as the solvents. Compound **3** eluted at t_R = 26.93 min and compound **4** at t_R = 38.87 min. Yields of compounds: **3**, 6.1 mg; **4**, 2.0 mg.

Compound 3: white amorphous residue; CD (EtOH) 214 ($\Delta\epsilon$ −9.4), 222 ($\Delta\epsilon$ −13.8), 280 ($\Delta\epsilon$ +0.13) nm; ^1H NMR (CD_3-OD, 400 MHz) δ 7.03 (5H, m, H-16, H-17, H-18, H-19, H-20), 6.94 (1H, d, J = 9.1 Hz, H-14), 6.36 (1H, s, H-5), 6.29 (1H, d, J = 9.1 Hz, H-13), 5.94 and 5.93 (each 1H, d, J = 1.1 Hz, OCH_2O), 5.06 (1H, d, J = 7.1 Hz, H-1), 4.92 (1H, dd, J = 13.3, 7.1 Hz, H-2), 4.36 (1H, d, J = 13.4 Hz, H-3), 4.09 (3H, s, OCH_3-8), 3.74 (3H, s, OCH_3-12), 3.71 (3H, s, OCH_3-11), 3.37, 2.91 (each 3H, s, 2 × NCH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (s, C-21), 154.8 (s, C-4a), 153.4 (s, C-12), 153.2 (s, C-6), 147.5 (s, C-10), 141.7 (s, C-8), 140.0 (s, C-15), 137.6 (s, C-11), 132.0 (s, C-7), 129.0 (d, C-16/C-20), 128.3 (d, C-17/C-19), 127.1 (d, C-18), 125.2 (d, C-14), 118.5 (s, C-9), 112.2 (s, C-8a), 104.4 (s, C-13), 104.3 (s, C-3a), 102.5 (t, O-CH_2-O), 97.7 (s, C-8b), 88.8 (d, C-5), 81.0 (d, C-1), 61.0 (q, OCH_3-11), 60.4 (q, OCH_3-8), 58.8 (d, C-3), 56.1 (q, OCH_3-12), 48.2 (d, C-2), 37.3, 35.9 (q, 2 × NCH_3); EIMS m/z 565 $[M]^+$ (15), 547 (100), 529 (18), 502 (33), 457 (38), 432 (68), 373 (11), 360 (23), 355 (31), 335 (15), 257 (11), 195 (20), 176 (48), 131 (16); ESIMS (positive mode) m/z 588 $[M + Na]^+$, 566 $[M + H]^+$.

Compound 4: white amorphous residue; $[\alpha]^{20}_D$ +180.5° (*c* 1.25, EtOH); CD (EtOH) 220 ($\Delta\epsilon$ +35.4), 274 ($\Delta\epsilon$ +0.28), 293 ($\Delta\epsilon$ +2.18) nm; ^1H NMR (CD_3OD, 400 MHz) δ 7.31 (3H, m, H-17, H-18, H-19), 7.19 (2H, m, H-16, H-20), 6.26 (1H, d, J = 8.5 Hz, H-13), 6.17 (1H, s, H-5), 5.93 and 5.92 (each 1H, d, J = 1.0 Hz, OCH_2O), 5.62 (1H, d, J = 8.5 Hz, H-14), 4.96 (1H, d, J = 4.5 Hz, H-1), 4.52 (1H, d, J = 13.2 Hz, H-3), 4.15 (3H, s, OCH_3-8), 3.85 (3H, s, OCH_3-11), 3.76 (3H, s, OCH_3-12), 3.66 (1H, dd, J = 13.2, 4.5 Hz, H-2), 3.24, 2.90 (each 3H, s, 2 × NCH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 170.3 (s, C-21), 158.0 (s, C-4a), 155.3 (s, C-12), 154.0 (s, C-10), 153.8 (s, C-6), 141.7 (s, C-8), 138.4 (s, C-15), 134.1 (s, C-11), 131.2 (s, C-7), 129.0 (d, C-16/C-20), 127.8 (d, C-17/C-19), 127.8 (d, C-18), 122.4 (d, C-14), 119.9 (s, C-9), 109.9 (s, C-8b), 107.7 (s, C-8a), 106.1 (s, C-13), 105.1 (s, C-3a), 102.2 (t, O-CH_2-O), 88.3 (d, C-5), 74.8 (d, C-1), 60.7 (q, OCH_3-11), 59.9 (q, OCH_3-8), 56.5 (q, OCH_3-12), 55.0 (d, C-3), 50.9 (d, C-2), 37.3, 35.7 (q, 2 × NCH_3); EIMS m/z 547 $[M]^+$ (100), 502 (24), 484 (12), 457 (31), 432 (56), 372 (10), 355 (26), 335 (13), 267 (5), 176 (6), 168 (5), 131 (8), 103 (5); ESIMS (positive mode) m/z 570 $[M + Na]^+$, 548 $[M + H]^+$.

Computational Methods. The molecular dynamics simulations of **3** and **4** were performed on SGI Octane (R 10000) workstations using the Tripos[17] force field as implemented in the molecular modeling package Sybyl 6.4,[18] using a time step of 0.5 fs. The molecule was weakly coupled to a thermal bath at T = 400 K,[19] with a temperature relaxation time τ = 0.1 ps. The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI[20,21] calculations, in which the CI expansion takes into account the ground state and all n and π orbitals. These calculations were carried out on *i*PII- and *i*PIII-Linux 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.

Biomimetic Cyclization of 3. An aliquot (0.5 mg) of compound **3** was incubated with 400 μL of trifluoracetic acid for 1 h at room temperature followed by analysis of the reaction mixture by HPLC-CD, in comparison with the authentic compound **4**.

Insect Bioassays. Chronic feeding bioassays were conducted with neonate larvae of *Spodoptera littoralis* as previously described.[3] Larvae (n = 20) were kept on an artificial diet treated with different concentrations of compound **3** or **4**. After 8 days of exposure, surviving larvae were counted and compared with controls. From the dose−response curves LC_{50} values were calculated. The LC_{50} of compound **3** was 2.5 ppm, whereas compound **4** proved to be inactive even when tested at concentrations as high as 100 ppm.

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Supporting Information Available: Table of HMBC and NOESY or ROESY NMR data for compounds **3** and **4**. This information is available free of charge over the Internet at http://pubs.acs.org.

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