Aglacins A−D, First Representatives of a New Class of Aryltetralin Cyclic Ether Lignans from *Aglaia cordata*

Bin-Gui Wang,[†] Rainer Ebel,[†] Bambang W. Nugroho,[‡] Djoko Prijono,[‡] Walter Frank,[§] Klaus G. Steube,[⊥] Xiao-Jiang Hao,[∥] and Peter Proksch*[,†]

Institut für Pharmazeutische Biologie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, Geb. 26.23, D-40225 Düsseldorf, Germany, Department of Plant Pests and Diseases, Faculty of Agriculture, Bogor Agricultural University, Jl. Raya Pajajaran-Bogor 16144, Indonesia, Institut für Anorganische Chemie und Strukturchemie II, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, Geb. 26.42, D-40225 Düsseldorf, Germany, Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany, and Laboratory of Phytochemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China

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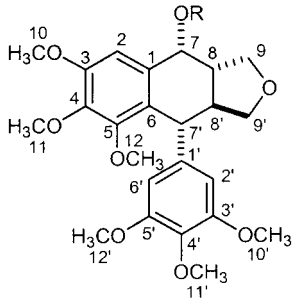
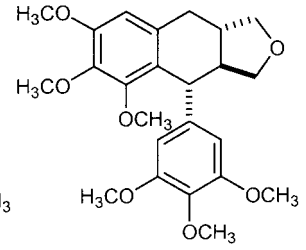
Four new metabolites, aglacins A−D (**1**−**4**), were identified from the methanol extract of the stem bark of *Aglaia cordata*. These compounds represent a new class of aryltetralin cyclic ether lignan. The structure of aglacin A (**1**) including the absolute configuration was elucidated by interpretation of spectral data, X-ray crystal structure determination, and employing the modified Mosher's method. In addition, three other derivatives, aglacins B−D (**2**−**4**), were isolated and identified by spectral means.

The plant genus *Aglaia* (Meliaceae), which is mainly distributed in the tropical rain forests of the Indo-Malaysian region,[1] has attracted considerable attention in recent years due to the accumulation of highly insecticidal cyclopenta[*b*]tetrahydrobenzofurans,[2−12] the so-called rocaglamides, as well as other representatives of different classes of compounds with interesting structures and biological activities.[13−18]

As part of our continuing studies directed toward the discovery of novel naturally occurring insecticidal rocaglamide derivatives and related compounds from the genus *Aglaia*,[2−6,8−10] we recently focused our attention on the species *Aglaia cordata* Hiern collected in Kalimantan (Indonesia). The HPLC−UV profiles of the methanol extract of *A. cordata* showed two prominent components together with small amounts of related derivatives. On the basis of their UV spectra and their retention values, these compounds were at first assumed to be rocaglamide derivatives. However, the result of subsequent insecticidal assays showed that the crude methanol extract of the stem bark of *A. cordata* displayed no activity against the test insect, *Spodoptera littoralis* (Lepidoptera, Noctuidae), which was also used in our previous studies. This phenomenon prompted us to examine the constituents of this species, resulting in the isolation of four highly oxygenated lignans, namely, aglacins A−D (**1**−**4**), which represent a new class of aryltetralin cyclic ether lignan. The structures and stereochemistries of these metabolites were elucidated on the basis of comprehensive spectral analyses (^{1}H, ^{13}C, ^{1}H−^{1}H COSY, HMQC, HMBC, and ROESY NMR, as well as low- and high-resolution EIMS experiments), chemical means, and X-ray crystal structure determination.



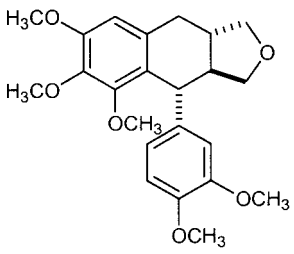


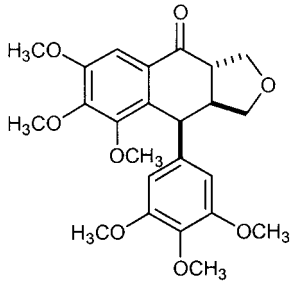
1: R = $COCH_3$ **2**

1a: R = H

1b: R = (*R*)-MTPA

1c: R = (*S*)-MTPA





3 **4**

Results and Discussion

A methanolic extract of the air-dried stem bark of *Aglaia cordata* was partitioned between water and cyclohexane, EtOAc, and *n*-butanol, respectively. The EtOAc-soluble fraction was subjected to silica gel VLC (vacuum liquid chromatography), Sephadex LH-20, and reversed-phase HPLC chromatographic steps, yielding four novel compounds, aglacins A−D (**1**−**4**). Aglacins A and B were the major components, comprising 0.16% and 0.20% of the EtOAc fraction, while aglacins C and D represented only 0.02% and 0.04% of the EtOAc fraction, respectively.

The first major metabolite, aglacin A (**1**), obtained as colorless needle crystals, showed a molecular ion peak at *m*/*z* 488 in the low-resolution EIMS, which in conjunction with 1D NMR data (Table 1) suggested the empirical formula $C_{26}H_{32}O_9$. This result was subsequently confirmed by the high-resolution EIMS. The ^{1}H NMR spectrum

* To whom correspondence should be addressed. Tel: 0049-211-8114163. Fax: 0049-211-8111923. E-mail: proksch@uni-duesseldorf.de.
[†] Institut für Pharmazeutische Biologie, Heinrich-Heine-Universität Düsseldorf.
[‡] Bogor Agricultural University.
[§] Institut für Anorganische Chemie und Strukturchemie II, Heinrich-Heine-Universität Düsseldorf.
[⊥] Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH.
[∥] Chinese Academy of Sciences.

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Table 1. NMR Spectral Data of Aglacins A and B (**1** and **2**)[a]

	aglacin A (**1**)			aglacin B (**2**)		
	δ_H	δ_C	HMBC (H to C)	δ_H	δ_C	HMBC (H to C)
1		131.2 s			133.0 s	
2	6.77 s	109.1 d	1, 3, 4, 6, 7,	6.49 s	107.5 d	1, 3, 4, 6, 7
3		152.6 s			152.3 s	
4		143.1 s			140.8 s	
5		152.5 s			152.6 s	
6		126.8 s			125.5 s	
7α		68.3 d		2.73 dd (15.1, 11.7)	33.5 t	1, 2, 6, 8, 8′
7*β*	6.11 d (2.5)		1, 2, 6, 8, 8′,9, 13	2.91 dd (15.5, 4.1)		1, 6, 8
8	2.25 m	44.6 d	1, 7, 7′, 9, 9′	2.11 m	41.7 d	1, 7, 7′, 9, 9′
9α	4.06 br t (7.9)	68.1 t	8, 9′	4.16 br t (7.6)	72.7 t	7, 8, 8′, 9′
9*β*	3.48 dd (10.7, 7.9)		7, 8, 8′	3.49 dd (10.1, 7.9)		7, 8
10	3.86 s	55.9 q	3	3.86 s	55.8 q	3
11	3.76 s	60.4 q	4	3.73 s	60.4 q	4
12	3.15 s	59.5 q	5	3.15 s	59.4 q	5
13		170.8 s				
14	2.12 s	21.2 q	13			
1′		143.5 s			144.1 s	
2′	6.32 s	104.0 d	1′, 3′, 4′, 6′, 7′	6.27 s	103.8 d	1′, 3′, 4′, 6′, 7′
3′		153.2 s			153.1 s	
4′		136.3 s			136.1 s	
5′		153.2 s			153.1 s	
6′	6.32 s	104.0 d	1′, 2′, 4′, 5′, 7′	6.27 s	103.8 d	1′, 2′, 4′, 5′, 7′
7′	3.77 d (8.0)	46.4 d	1, 1′, 2′, 5, 6, 6′, 8, 8′	3.82 d (7.7)	46.9 d	1, 1′, 2′, 6, 6′, 8, 8′, 9′
8′	2.60 m	44.8 d	6, 7, 9, 9′	2.02 m	52.8 d	1′, 6, 7, 8, 9′
9′α	3.94 br t (7.6)	72.2 t	8′, 9	3.91 br t (7.6)	72.6 t	8, 8′, 9
9′*β*	3.59 dd (10.4, 7.6)		8′	3.60 dd (10.1, 7.6)		7′, 8′
10′	3.79 s	56.2 q	3′	3.77 s	56.2 q	3′
11′	3.81 s	60.9 q	4′	3.81 s	60.9 q	4′
12′	3.79 s	56.2 q	5′	3.77 s	56.2 q	5′

[a] Recorded in $CDCl_3$ at 500 and 125 MHz, respectively.

disclosed the presence of three aromatic protons, two of which are part of an A_2 spin system, six methoxyl groups, one acetyl methyl group, four oxymethylene protons, one oxymethine proton, and three methine protons. The ^{13}C NMR and DEPT spectra confirmed the presence of the above functionalities in **1**. These NMR data were indicative of two highly substituted phenyl groups. Since nine out of eleven degrees of unsaturation were already accounted for, compound **1** was inferred to contain two further rings.

Detailed interpretation of 1D, 2D NMR and HREIMS spectral data resulted in the elucidation of three substructures for aglacin A (**1**) as follows. Protons 2′ and 6′ appeared as a singlet (δ 6.32) and displayed HMBC correlations to C-1′, C-3′/5′, and C-4′, thus indicating a symmetrical 1,3,4,5-tetrasubstituted phenyl ring system. This was confirmed by an intense fragment ion peak at *m*/*z* 181.0899 in the HREIMS characteristic of the 3′,4′,5′-trimethoxylbenzyl partial structure in **1**.[19] Careful inspection of the HMBC spectrum (see Table 1) allowed for a complete assignment of all signals in this partial structure.

The $^1H-^1H$ COSY spectrum revealed that all aliphatic methine and methylene protons were part of a continuous spin system comprising H-7, H-7′, H-8, H-8′, H_2-9, and H_2-9′ in the final structure of **1**. This was also supported by HMBC correlations from H-7 to C-8′ and C-9, from H-8 to C-7′ and C-9′, from H-9*β* to C-7 and C-8′, and from H-8′ to C-7 and C-9 (see Table 1). The observed long-range correlations from H-7 and H-14 to C-13 indicated the connection of the acetoxyl group to C-7. The presence of a furan ring was revealed by two significant ^3J HMBC cross-peaks from the oxymethylene proton H-9α to C-9′ and from H-9′α to C-9. Besides the above deduced substructures in compound **1**, the remaining signals suggested the presence of a 5-fold substituted aromatic unit, with three of the substituents being methoxyl groups.

Connectivities of the substructures of compound **1** were established by interpretation of the HMBC spectrum

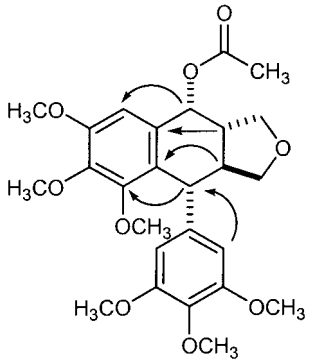

Figure 1. Selected HMBC correlations for aglacin A (**1**).

(Figure 1) as follows. The ^3J HMBC cross-peaks from H-7′ to C-2′/C-6′, as well as from H-2′/H-6′ to C-7′, indicated the connection between C-1′ and C-7′. This deduction was further confirmed by the observation of a ^2J HMBC correlation from H-7′ to the quaternary aromatic carbon C-1′. Two strong ^3J HMBC cross-peaks, from H-2 to C-7 and from H-7 to C-2, and a weak but nevertheless diagnostic correlation from H-8 to C-1 suggested further linkage through C-1 and C-7. This was corroborated by the observation of a ^2J correlation between H-7 and C-1. Moreover, a connection between C-6 and C-7′ was indicated by correlations from H-7′ to C-1, C-5, and C-6. The positions of the other functional groups were assigned by $^1H-^1H$ COSY, HMQC, HMBC, and ROESY correlations, which resulted in the assignment of all proton and carbon signals of **1** (Table 1).

The relative stereochemistry of **1** was determined primarily on the basis of *J* values obtained from the ^1H NMR spectrum and from the observed ROESY correlations. The large coupling constant observed between H-7′ and H-8′ (J = 8.0 Hz) implied a *trans*-orientation (axial−axial) for this proton pair. In contrast, the small coupling constant

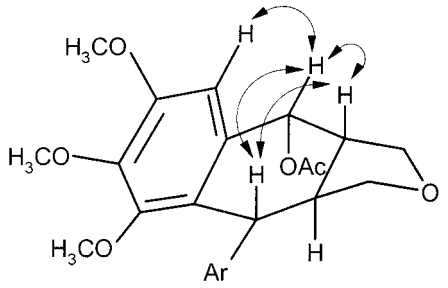

Figure 2. Selected ROESY correlations for aglacin A (**1**).

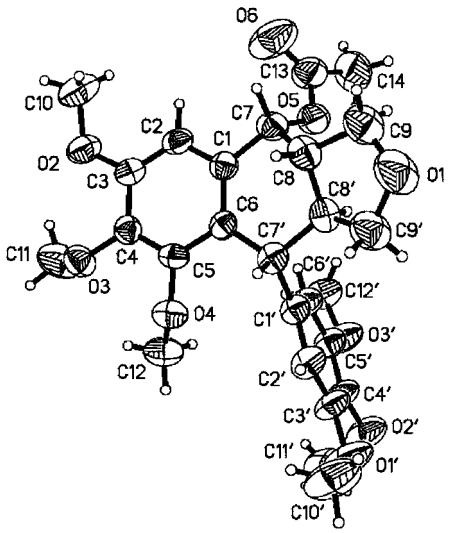

Figure 3. Diagram of **1**. Displacement ellipsoids are drawn at the 50% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity.

observed for H-7 and H-8 (J = 2.5 Hz) clearly corresponded to the *cis*-configuration of the two protons. This assignment was further corroborated by ROESY cross-peaks between H-7 and H-8 as well as H-7′, and between H-8 and H-7′ (Figure 2).

Crystallization of aglacin A (**1**) from methanol yielded colorless crystals, which were subjected to X-ray crystal structure determination. This provided unambiguous proof for the structure of **1** initially deduced from 1D and 2D NMR data. As shown in Figure 3, the X-ray structure demonstrated also the relative H-7β, H-8β, H-8′α, and H-7′β configurations in the molecule.

The absolute configuration of aglacin A (**1**) was determined using the modified Mosher's method.[20,21] Compound **1** was hydrolyzed under mild conditions with $NaHCO_3$ at room temperature, yielding the corresponding alcohol **1a**, which was subsequently treated with (*R*)- and (*S*)-(+)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to obtain the corresponding (*S*)-(**1a**)-ester and (*R*)-(**1a**)-ester, respectively. Analysis of the $\Delta\delta_{H(S-R)}$ data (Table 2) showed a negative difference in chemical shift for the protons in the aliphatic moiety, indicating that the absolute configuration at C-7 in compound **1** was *S*. Hence the absolute configurations at C-8, C-8′, and C-7′ were deduced as *S*, *R*, and *S*, respectively.

Aglacin B (**2**), the second major component, showed a molecular ion peak at *m*/*z* 430 in the low-resolution EIMS. Together with the consideration of ^{1}H and ^{13}C NMR data (Table 1) $C_{24}H_{30}O_7$ was assigned as molecular formula, which was confirmed by high-resolution EIMS. The ^{1}H and ^{13}C NMR data of compound **2** as well as the 2D NMR correlations were very similar to those of aglacin A (**1**). Detailed comparison of the NMR data for compounds **2** and

Table 2. Partial ^{1}H NMR Data of the (*S*)- and (*R*)-MTPA Ester Derivatives of **1a**[a]

proton	δ_H *S*-isomer	δ_H *R*-isomer	$\Delta\delta_{S-R}$
2	6.87	6.84	+0.03
7	6.34	6.42	−0.08
8	2.36	2.38	−0.02
9α	4.09	4.09	0
9β	3.49	3.49	0
7′	3.79	3.80	−0.01
8′	2.54	2.59	−0.05
9′α	3.94	3.94	0
9′β	3.60	3.60	0

[a] Recorded in $CDCl_3$ at 500 MHz.

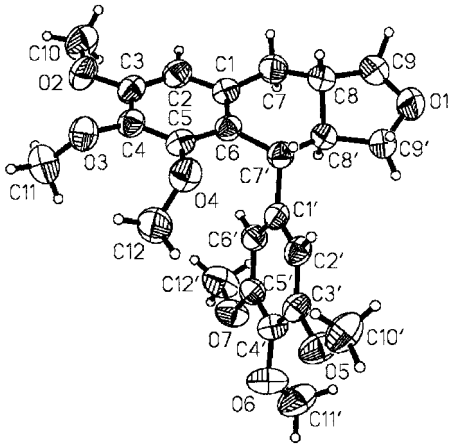

Figure 4. Diagram of **2**. Displacement ellipsoids and further details as described for Figure 3.

1 prompted us to conclude that the aromatic units as elucidated for **1** were also present in **2**. Significant differences in their ^{1}H NMR spectra, including the disappearance of the acetoxyl methyl signal at δ 2.12 and the one-proton doublet oxymethine signal at δ 6.11 observed in **1**, but the appearance of two one-proton double doublets at δ 2.73 and 2.91 for **2** attributable to H-7α and H-7β, respectively, suggested that compound **2** was the deacetoxyl derivative of **1**. This conclusion was confirmed by comparison of the ^{13}C NMR spectra, in which the signals for the acetoxyl methyl at δ 21.2 and the acetoxyl carbonyl at δ 170.8 observed for **1** were absent, while the oxygen-bearing methine signal at δ 68.3 (C-7) in **1** was replaced by a methylene signal at δ 33.5 in **2**.

The relative stereochemistry of **2** was also determined on the basis of J values obtained from the ^{1}H NMR spectrum and from ROESY correlations. The large coupling constant observed between H-7α and H-8 (J = 11.7 Hz) and between H-7′ and H-8′ (J = 7.7 Hz) implied a *trans*-orientation (axial−axial) for the respective proton pairs. As expected, significant cross-peaks observed in the ROESY spectrum between H-7α and H-8′ and between H-7′ and H-8 agreed with the relative stereochemistries assigned from the J values. Unambiguous confirmation of the structure and relative stereochemistry of **2** was afforded by X-ray crystal structure determination (Figure 4).

Aglacin C (**3**), obtained as a minor component, whose molecular formula was determined to be $C_{23}H_{28}O_6$ by high-resolution EIMS and 1D NMR experiments, displayed ^{1}H and ^{13}C NMR chemical shifts (see Table 3) very similar to those of **2**. However, the symmetrical ^{1}H NMR resonance pattern for the A_2 spin system of the 3′,4′,5′-trimethoxyphenyl group in compound **2** changed to an ABC spin system in **3**, with one *meta* coupling proton at δ 6.58, one

Table 3. NMR Spectral Data of Aglacins C and D (**3** and **4**)[a]

	aglacin A (**3**)		aglacin B (**4**)			
	δ_H	δ_C	δ_H	δ_C	δ_H[b]	HMBC (H to C)
1		133.1 s		130.0 s		
2	6.48 s	107.5 d	7.43 s	105.1 d	7.67 s	1, 3, 4, 6, 7
3		152.2 s		151.2 s		
4		140.9 s		140.2 s		
5		152.6 s		148.1 s		
6		126.0 s		127.5 s		
7α	2.73 dd (15.1, 12.0)	33.5 t		197.7 s		
7*β*	2.90 dd (15.1, 4.4)					
8	2.10 m	41.7d	2.02 m	45.9 d	2.88 m	8′
9α	4.16 br t (7.6)	72.8t	4.29 br d (8.8)	73.1 t	4.60 dd (8.5, 1.3)	7, 8, 9′
9*β*	3.49 br t (9.5)		3.98 dd (8.8, 6.3)		3.81 dd (8.5, 6.3)	7
10	3.87 s	55.8q	3.94 s	56.0q	3.27 s	3
11	3.74 s	60.4q	3.93 s	60.8q	3.81 s	4
12	3.10 s	59.4q	3.53 s	60.8q	3.42s	5
1′		141.0 s		140.2 s		
2′	6.58 br s	111.2 d	6.24 s	104.7 d	6.34 s	1′, 3′, 4′, 6′, 7′
3′		147.0 s		153.4 s		
4′		148.8 s		136.7 s		
5′	6.76 d (8.2)	110.2 d		153.4 s		
6′	6.61 br d (8.2)	118.7 d	6.24 s	104.7 d	6.34 s	1′, 2′, 4′, 5′, 7′
7′	3.86 d (8.0)	46.1 d	4.52 br s	37.3 d	4.57 d (1.6)	1′, 2′, 5, 6, 6′, 8, 8′, 9′
8′	2.02 m	53.1 d	2.02 m	46.9 d	2.76 m	6, 8
9′α	3.88 br t (7.6)	72.6 t	4.19 br t (8.8)	71.9 t	4.00 br t (8.5)	8′, 9
9′*β*	3.59 dd(10.1, 7.6)		3.45 br t (9.5)		3.53 dd (9.5, 8.5)	8
10′	3.81 s	56.0 q	3.75 s	56.2 q	3.36 s	3′
11′	3.85 s	55.9 q	3.80 s	60.9 q	3.64 s	4′
12′			3.75 s	56.2 q	3.36 s	5′

[a] Recorded in $CDCl_3$ at 500 and 125 MHz, respectively, unless stated otherwise. [b] Measured in C_6D_6 at 500 MHz.

ortho coupling proton at *δ* 6.76, and one *ortho* and *meta* coupling proton at *δ* 6.61. The chemical shift values and the coupling pattern agreed with a loss of the 5′-methoxyl substituent in **3** as compared to **2**. Correspondingly, an intense fragment ion peak at *m*/*z* 151.0773 in the high-resolution EIMS was observed, indicative of the 3′,4′-dimethoxybenzyl partial structure in **3**.[22]

The ^1H and ^{13}C NMR signals in the aliphatic region of compound **3**, including both the chemical shift values and the coupling constants, were essentially identical to those of aglacin B (**2**), indicating the same relative stereochemistry as in compound **2**.

Aglacin D (**4**), a further minor constituent, was shown to have the molecular formula $C_{24}H_{28}O_8$, as indicated by high-resolution EIMS and 1D NMR experiments. The ^1H and ^{13}C NMR spectral data (Table 3) resembled those of aglacin B (**2**) in many aspects. Detailed inspection of the overall ^1H and ^{13}C NMR data, together with the analysis of $^1H-^1H$ COSY, HMQC, and HMBC spectra, suggested the presence of the same aromatic units in **4** as already elucidated for **2**. However, the two one-proton double doublet signals in the ^1H NMR spectrum of **2** ascribable to H-7α and H-7*β* were absent in **4**. The disappearance of the methylene carbon signal at *δ* 33.5 observed for C-7 in compound **2** and the appearance of a signal at *δ* 197.7 in the ^{13}C NMR spectrum of **4** strongly suggested the presence of a ketone group in **4**. The significant ^3J HMBC cross-peaks from the aromatic proton H-2 and the aliphatic protons H-9α and H-9*β* to the carbonyl signal at *δ* 197.7 allowed the positioning of the keto group at C-7.

Detailed analysis of the ^1H, ^{13}C, $^1H-^1H$ COSY, HMQC, and HMBC spectral data led to the elucidation of the complete structure of aglacin D (**4**). However, the relative configuration at the chiral centers of **4** was still unclear since the proton signal of H-7′ appeared as a broad singlet and not as a doublet as in the case of aglacins A−C (**1**−**3**). On the other hand, the protons of H-8 and H-8′ overlapped in the ^1H NMR spectrum of **4** recorded in $CDCl_3$. However, measuring the ^1H NMR spectrum of **4** in C_6D_6 gave a satisfactory resolution of the proton signals of H-7′, H-8, and H-8′ (Table 3). This result encouraged us to further record the $^1H-^1H$ COSY and ROESY spectra of **4** in C_6D_6, which subsequently led to the complete assignment of the relative stereochemistry of aglacin D. The small coupling constant observed for H-7′ and H-8′ ($J = 1.6$ Hz) indicated a *cis*-configuration of the two protons. This assumption was corroborated by a cross-peak between H-7′ and H-8′ in the ROESY spectrum. No cross-peak was observed from H-8 either to H-7′ or to H-8′, implying a *trans*-orientation between H-8 and H-7′ as well as H-8′. Therefore, the relative stereochemistry of aglacin D (**4**) was assigned as H-8*β*, H-7′α, and H-8′α.

In *in vitro* assays with the human leukemia cell line HL-60 and the human carcinoma cell line HELA, aglacins A−D (**1**−**4**) exhibited no cytotoxity, while aglacins A (**1**) and B (**2**) showed only weak inhibitory activity toward KB cells.

Although several types of lignans have been reported from *Aglaia* species, e.g., (+)-methylarctigenin, a dibenzylbutyrolactone-type lignan from *A. tomentosa*,[7] (+)-yangambin, a tetrahydrofurofuran-type lignan (containing a dioxabicyclo[3.3.0]octane skeleton) from *A. grandis*,[7] *trans*-3,4-bis(3,4,5-trimethoxybenzyl)tetrahydrofuran and *trans*-2,3-bis(3,4,5-trimethoxybenzyl)-1,4-butanediol diacetate, two substituted dibenzylbutane lignans from *A. elaeagnoidea*,[23] the (+)-acetyl ester of lariciresinol,[7] (+)-grandisin and epigrandisin,[17] three substituted tetrahydrofuran-type lignans from *A. elaeagnoidea* and *A. leptantha*, respectively, aglacins A−D (**1**−**4**) represent the first example of a new class of aryltetralin cyclic ether lignan hitherto unknown from nature. It is interesting to note that structurally related cyclic ethers have been synthesized previously[24,25] in the course of investigations on structure−activity relationships of the well-known aryltetralin lactone lignan, podophyllotoxin, which eventually led to the development of commercially marketed drugs such as etoposide or teniposide.

Experimental Section

General Experimental Procedures. Melting points were measured on a Leitz Wetzlar Biomed Type 020-507.010 apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer Model 341 LC polarimeter. UV spectra were obtained in methanol using a BECKMAN MODEL 25 spectrophotometer. Low- and high-resolution EIMS were measured with a Finnigan MAT 311A mass spectrometer at 70 eV. ESIMS analysis was performed on a Finngan LCQ DECA spectrometer. ^{1}H, ^{13}C, and DEPT NMR spectral data and ^{1}H−^{1}H COSY, HMQC, HMBC, and ROESY experiments were performed on a Bruker DRX-500 MHz NMR spectrometer. X-ray crystal structure determination was carried out on a Stoe imaging plate diffraction system. HPLC−UV analyses were conducted with a Dionex system coupled to a photodiode array detector using a 5 μm Eurospher-100 C18 column (4 mm i.d. × 150 mm; Knauer, Berlin, Germany). Semipreparative HPLC was performed on a Merck-Hitachi instrument (pump L-7100, detector L-7400) using a 7 μm Eurospher-100 C18 column (8 mm × 300 mm; Knauer, Berlin, Germany). Vacuum liquid chromatography (VLC) and column chromatography were performed on silica gel (0.040−0.063 mm; Merck, Darmstadt, Germany), Sephadex LH-20 (Sigma-Aldrich, Steinheim, Germany), or RP-18 (Merck, Darmstadt, Germany), and TLC analyses were carried out using aluminum sheet precoated silica gel 60 F_{254} (Merck, Darmstadt, Germany). All solvents used were distilled prior to use.

Plant Material. The plant material was collected in September 1999 in Central Kalimantan (Indonesia) and identified at the Botanical Garden at Bogor, Indonesia. A voucher specimen was deposited there.

Extraction and Isolation. The dried stem bark of *Aglaia cordata* (1000 g) was ground and stirred with methanol three times at room temperature (5 h each time), filtered, and concentrated in a vacuum to give a residue (122 g), which was then partitioned between cyclohexane and water, between EtOAc and water, and between *n*-butanol (water saturated) and water, respectively, to afford cyclohexane- (39.0 g), EtOAc- (25.0 g), and *n*-butanol-soluble (19.0 g) residues. The EtOAc fraction was primarily separated through VLC, using *n*-hexane and *n*-hexane−EtOAc mixtures of increasing polarity. The fraction that was eluted with *n*-hexane−EtOAc (100:40) which contained the major components was subjected to repeated Sephadex LH-20 and silica gel column chromatographic steps. Final purification was by semipreparative RP-HPLC (MeOH−H_2O, 52:48), yielding pure compounds aglacins A (**1**, 40 mg), B (**2**, 50.0 mg), C (**3**, 5.0 mg), and D (**4**, 10.0 mg).

Aglacin A (1): obtained as colorless needles (MeOH); mp 155−156 °C; $[\alpha]^{20}_D$ +55.6° (*c* 0.52, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (4.92) nm; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 488 $[M]^+$ (40), 428 $[M - HOAc]^+$ (6), 181 (25), 81(65), 43 (100); HREIMS *m*/*z* 488.2054 (calcd for $C_{26}H_{32}O_9$, 488.2046), 181.0899 (calcd for $C_{10}H_{13}O_3$, 181.0865).

Hydrolysis of Compound 1. Saturated aqueous $NaHCO_3$ (0.5 mL) was added to a solution of **1** (10.0 mg in 1 mL of MeOH), and the mixture was stirred at room temperature for 7 h to yield 8 mg of a reaction product, which on purification by preparative TLC (CH_2Cl_2−MeOH, 30:1) afforded 5 mg of deacetylated compound **1a**. Compound **1a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (1H, s, H-2), 6.31 (2H, br s, H-2′/H-6′), 4.85 (1H, d, J = 1.9 Hz, H-7β), 4.10 (1H, t, J = 7.7 Hz, H-9α), 3.95 (1H, t, J = 7.4 Hz, H-9′α), 3.92 (3H, s, H-10), 3.88 (1H, dd, J = 10.5, 7.9 Hz, H-9β), 3.83 (3H, s, H-11′), 3.79 (6H, s, H-10′, H-12′), 3.77 (3H, s, H-11), 3.75 (1H, d, J = 10.1 Hz, H-7′), 3.62 (1H, dd, J = 10.4, 7.6 Hz, H-9′β), 3.16 (3H, s, H-12), 2.62 (1H, m, H-8′), 2.18 (1H, m, H-8); EIMS *m*/*z* 446 $[M]^+$ (100), 182 (25), 181 (48), 151(10); ESIMS *m*/*z* 470 $[M + Na + 1]^+$ (28), 469 $[M + Na]^+$ (72), 447 $[M + H]^+$ (19), 429 $[M + H - H_2O]^+$ (100).

Preparation of (*R*)- and (*S*)-MTPA Ester Derivatives of 1a. To a stirred solution of **1a** (2.0 mg) in $CHCl_3$ (0.5 mL) and pyridine (0.3 mL) were added 4-(dimethylamino)pyridine (1.0 mg) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20 mg).[20,21] The mixture was heated at 50 °C for 4 h and then passed through a disposable pipet packed with silica gel and eluted with CH_2Cl_2 and MeOH (50:1, 5 mL). The solvents were removed in reduced pressure to afford the respective *R*-Mosher ester of **1a**. Treatment of **1a** (2 mg) with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride as described above afforded the *S*-Mosher ester of **1a**.

Aglacin B (2): obtained as colorless needles (MeOH); mp 138−139 °C; $[\alpha]^{20}_D$ +45.0° (*c* 0.38, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (4.81) nm; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 430 $[M]^+$ (100), 182 (23), 181 (30), 151(5); HREIMS *m*/*z* 430.1991 (calcd for $C_{24}H_{30}O_7$, 430.1992), 181.0847 (calcd for $C_{10}H_{13}O_3$, 181.0865).

Aglacin C (3): obtained as colorless waxy solid; $[\alpha]^{20}_D$ +25.6° (*c* 0.60, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 211 (4.67) nm; ^{1}H and ^{13}C NMR data, see Table 3; EIMS *m*/*z* 400 $[M]^+$ (100), 165 (12), 151 (21), 81(22); HREIMS *m*/*z* 400.1876 (calcd for $C_{23}H_{28}O_6$ 400.1886), 151.0773 (calcd for $C_9H_{11}O_2$ 151.0759).

Aglacin D (4): obtained as colorless waxy solid (MeOH); $[\alpha]^{20}_D$ −87.2° (*c* 0.58, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (4.69), 229 (sh) (4.54), 282 (4.05) nm; ^{1}H and ^{13}C NMR data, see Table 3; EIMS *m*/*z* 444 $[M]^+$ (33), 256 (9), 195 (5), 181 (8), 83 (45); HREIMS *m*/*z* 444.1778 (calcd for $C_{24}H_{28}O_8$, 444.1784), 181.0846 (calcd for $C_{10}H_{13}O_3$, 181.0865).

Crystal Structure Determinations of Compounds 1 and 2. Crystals of **1** and **2** suitable for X-ray study were selected by means of a polarization microscope. They were investigated on a Stoe imaging plate diffracton system using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 8000 strong reflections, distributed equally in reciprocal space. For the crystals of **1** and **2** the orthorhombic space group type $P2_12_12_1$ was uniquely determined. Crystal data of **1**: $M_r(C_{26}H_{32}O_9)$ = 488.52, a = 9.5896(6) Å, b = 12.3842(11) Å, c = 21.1146(14) Å, V = 2507.6(3) Å^3, Z = 4, D_x = 1.294 g cm^{-3}, μ = 0.098 mm^{-1}, T = 293 K, colorless crystal of dimensions 0.4 mm × 0.3 mm × 0.3 mm. Crystal data of **2**: $M_r(C_{24}H_{30}O_7)$ = 430.48, a = 6.8133(4) Å, b = 11.6291(9) Å, c = 28.1522(6) Å, V = 2230.6(3) Å^3, Z = 4, D_x = 1.282 g cm^{-3}, μ = 0.094 mm^{-1}, T = 293 K, colorless crystal of dimensions 0.5 mm × 0.2 mm × 0.2 mm. In the case of **1** 35 831 intensity data (θ_{min} = 2.33°, θ_{max} = 25.93°) and in the case of **2** 15 155 intensity data (θ_{min} = 1.90°, θ_{max} = 25.00°) were collected, and *Lp* corrections were applied. The structures were solved by direct methods,[26] and approximate positions of all the hydrogen atoms were found. Refinements (**1**: 323 parameters; all of 4827 unique reflections used; **2**: 286 parameters, all of 3913 unique reflections used) by full-matrix least-squares calculations on F^2 [27] converged to the following final indicators. **1**: $R_1[F_o^2 > 2\sigma(F_o^2)] = 0.035$, $wR_2 = 0.076$ (all data), $w = 1/[\sigma^2(F_o^2) + (0.035P)^2 + 0.2P]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.010,[27] largest peak and hole in the final difference map are 0.192 and − 0.091 e/Å^2, respectively. **2**: $R_1[F_o^2 > 2\sigma(F_o^2)] = 0.036$, $wR_2 = 0.080$ (all data), $w = 1/[\sigma^2(F_o^2) + (0.025P)^2 + 0.5P]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.016,[27] largest peak and hole in the final difference map are 0.147 and − 0.139 e/Å^2, respectively. The absolute structures could not be determined reliably.[28] Anisotropic displacement parameters were refined for all non-hydrogen atoms. All H atoms were treated with fixed idealized C−H distances. The H atoms of methyl groups were allowed to move collectively around the neighboring C−C axis; for all the other H atoms the riding model was applied. The isotropic displacement parameters of the H atoms were kept equal to 120%, 130%, and 150% of the equivalent isotropic displacement parameters of the parent tertiary (or "aromatic"), secondary, and primary carbon atom, respectively. Scattering factors, dispersion corrections, and absorption coefficients were taken from International Tables for Crystallography (1992, Vol. C, Tables 6.114, 4.268, and 4.2.4.2).

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

Cytotoxicity Testing. The antiproliferative activity was examined using the human leukemia cell line HL-60, the human carcinoma cell line HELA, and the cell line KB. Assays were conducted at a concentration range from 2 mg/mL to 10 ng/mL and carried out in triplicate, by use of the MTT-assay, as described recently.[29]

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Supporting Information Available: Table 4: Atomic coordinates (estimated standard deviations) and equivalent isotropic displacement parameters for aglacin A (**1**). Table 5: Atomic coordinates (estimated standard deviations) and equivalent isotropic displacement parameters for aglacin B (**2**). Table 6: Crystal data and summary of intensity data collection and structure refinement details for aglacins A and B (**1** and **2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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