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New methoxylated aryltetrahydronaphthalene lignans and a norlignan from *Aglaia cordata*

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Abstract—Four novel lignans, aglacins E–H (**1**–**4**), were isolated and identified from the methanolic extract of the stem bark of *Aglaia cordata* collected in Indonesia. All of these metabolites contain two unusual contiguous trimethoxylated phenyl systems. While two of these compounds (**1** and **2**) are aryltetralin cyclic ether lignans, a third lignan (**3**) exhibits an unusual formyl group whereas compound (**4**) is a rare norlignan. The structures of all compounds were elucidated by interpretation of 1D and 2D NMR, as well as by low- and high-resolution EIMS. The absolute configurations of aglacins E and F (**1** and **2**) were determined by the modified Mosher's method. © 2002 Elsevier Science Ltd. All rights reserved.

Plants of the genus *Aglaia* (Meliaceae) have recently been the subject of intense studies due to the occurrence of a structurally unique group of cyclopenta[*b*]-benzofurans (rocaglamide derivatives) as well as cyclopenta[*bc*]benzopyrans (aglain and aglaforbesin derivatives) which to date have exclusively been isolated from this genus.[1,2] Rocaglamide and most of its numerous naturally occurring congeners are characterized by strong insecticidal properties and by a pronounced antiproliferative activity towards human cancer cells.[2,3] During our continuing phytochemical investigation of *Aglaia* species,[4] we recently isolated four novel lignans, aglacins A–D, from *Aglaia cordata* Hiern collected in Kalimantan (Indonesia) which proved to be the first representatives of a new class of aryltetralin cyclic ether lignans.[4j] This prompted us to analyze the more polar fraction of *A. cordata* for further lignans. Here we report on the isolation and structural elucidation of three new lignans (**1**–**3**) and a new norlignan (**4**) from *A. cordata*.

The EtOAc-soluble fraction of the MeOH extract of *Aglaia cordata* was subjected to silica gel vacuum liquid chromatography (VLC) and the fraction eluted with *n*-hexane:EtOAc (1:1) was further subjected to Sephadex LH-20 (MeOH) and reversed phase HPLC chromatographic separation (RP-18, with a gradient starting from 32% to 50% methanol in water). Four novel compounds, aglacins E (**1**, 10.5 mg), F (**2**, 4.5 mg), G (**3**, 8.2 mg), and H (**4**, 4.2 mg) were obtained in yields of 0.042%, 0.018%, 0.033%, and 0.017%, respectively, based on the weight of the EtOAc-soluble fraction.

Aglacin E (**1**) was obtained as a colorless waxy solid which showed a molecular ion peak at m/z 446 in the EI mass spectrum. The molecular formula was established as $C_{24}H_{30}O_8$ from the HREI MS $[M]^+$ m/z 446.1924 (calcd 446.1941).[5] The carbons and functional groups present in **1** were determined from 1D and 2D NMR data (Table 1) as three aromatic methines (δ_H 7.05 and 6.23 with relative intensities 1:2; δ_C 104.0 and 103.7 with relative intensities 1:2), six methoxyl groups (δ_H 3.91, 3.81, 3.77 (6H), 3.75, and 3.15; δ_C 60.9, 60.4, 59.5, 56.2 (2C), and 55.9), two oxymethylenes (δ_H 4.32, 3.92, 3.74, and 3.66; δ_C 72.4 and 72.1), one oxymethine (δ_H 4.76; δ_C 73.3), and three methines (δ_H 3.86, 2.16, and 2.16; δ_C 50.1, 49.8, and 47.1), respectively. Comparison of the ^1H and ^{13}C NMR data of **1** with literature data suggested that aglacin E (**1**) is a new member of the aryltetrahydronaphthalene lignans.[4j,6] The ^1H–^1H COSY spectrum of **1** indicated that all aliphatic methine and methylene protons were part of a contiguous spin system comprising H-7, H-7′, H-8, H-8′, H_2-9, and H_2-9′. The presence of a furan ring was revealed by significant long-range C–H correlations from the oxygen-bearing methylene protons H-9α and

Keywords: aglacin; aryltetrahydronaphthalene; lignan; norlignan; *Aglaia cordata*; structure elucidation.

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Table 1. ^1H and ^{13}C NMR spectral data of aglacins E (1) and F (2)[a]

Atom	Aglacin E (**1**)				Aglacin F (**2**)		
	^1H	^{13}C	^1H[b]	HMBC (H to C)	^1H	^{13}C	HMBC (H to C)
1		137.4 s				135.1 s	
2	7.05 s	104.0 d	7.08 s	1,3,4,6,7	6.71 s	108.3 d	3,4,6,7
3		152.9 s				152.8 s	
4		141.7 s				142.7 s	
5		151.8 s				152.7 s	
6		125.9 s				126.1 s	
7	4.76 t (9.0)	73.3 d	4.51 br s	8′	4.83 d (3.2)	67.3 d	1,2,6,8′
8	2.16 m	50.1 d	1.88 m		2.18 m	46.1 d	
9	α 4.32 t (7.4) β 3.74 t (7.9)	72.1 t	α 4.30 t (7.7) β 3.67 dd (10.5, 7.3)	8′,9′	α 4.09 t (7.7) β 3.87 dd (10.5, 7.7)	68.2 t	8′,9′
10	3.91 s	55.9 q	3.27 s	3	3.91 s	55.9 q	3
11	3.75 s	59.5 q	3.82 s	4	3.76 s	60.4 q	4
12	3.15 s	60.9 q	3.45 s	5	3.15 s	59.5 q	5
1′		143.4 s				143.5 s	
2′/6′	6.23 s	103.7 d	6.32 s	3′/5′,4′,7′	6.30 s	103.9 d	1′,3′/5′,4′,7′
3′/5′		153.2 s				153.2 s	
4′		136.3 s				136.2 s	
7′	3.86 d (9.2)	47.1 d	3.90 d (11.1)	1,1′,6,8,8′	3.74 (d, 9.5)	46.9 d	1′,2′/6′,6,8′,9′
8′	2.16 m	49.8 d	2.13 m		2.61 m	43.8 d	
9′	α 3.92 t (7.1) β 3.66 dd (9.8, 7.9)	72.4 t	α 4.02 t (7.5) β 3.65 dd (10.4, 7.6)	9	α 3.94 t (7.6) β 3.61 dd (10.4, 7.6)	72.5 t	8,9
10′/12′	3.77 s	56.2 q	3.38 s	3′/5′	3.78 s	56.2 q	3′/5′
11′	3.81 s	60.4 q	3.69 s	4′	3.82s	60.9 q	4′

[a] ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 500 and 125 MHz, respectively. All proton and carbon signals were assigned by detailed analysis of ^1H–^1H COSY, HMQC, HMBC, and ROESY spectral data.
[b] Measured in C_6D_6 at 500 MHz, proton signals were assigned from the analysis of ^1H–^1H COSY and ROESY spectra.

H-9′α to the oxymethylene carbons C-9′ and C-9 in the HMBC spectrum, respectively. The position of one aromatic proton at C-2 and of the hydroxyl group at C-7 were determined by analysis of the HMBC spectrum, which featured cross peaks from H-2 to C-1, C-3, C-4, C-6 and C-7. The relative stereochemistry of **1** was based on the *J* values measured in the ^1H NMR spectrum. The coupling constants observed between H-7 and H-8 ($J=9.0$ Hz) and between H-7′ and H-8′ ($J=9.2$ Hz) confirmed a *trans*-orientation (axial–axial) of the respective proton pairs. This assignment was corroborated by a ROESY experiment (spectrum recorded in C_6D_6) which showed cross peaks between H-7 and H-8′ as well as between H-7′ and H-8. The absolute configuration of the four asymmetric centers in **1** was unambiguously determined using the modified Mosher's method.[7] Treatment of **1** with (*R*)- or (*S*)-MTPACl gave the (*S*)- or (*R*)-MTPA esters **1s** and **1r**, respectively.[8] The ^1H NMR signals of the two MTPA esters were assigned on the basis of their ^1H–^1H COSY spectra, and the $\Delta\delta_{H(S-R)}$ values were then calculated (Table 2). The results indicated that the absolute

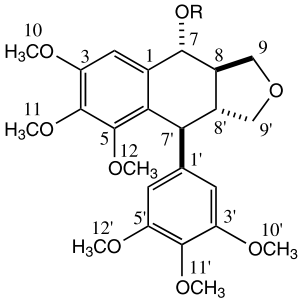
Table 2. Partial ^1H NMR data of the (*S*)- and (*R*)-MTPA esters of aglacins E (**1**) and F (**2**)[a]

Proton	Aglacin E (**1**)			Aglacin F (**2**)		
	(*S*)-Isomer	(*R*)-Isomer	$\Delta\delta_{S-R}$	(*S*)-Isomer	(*R*)-Isomer	$\Delta\delta_{S-R}$
2	6.46	7.05	−0.59	6.87	6.84	+0.03
7	6.32	6.28	+0.04	6.34	6.42	−0.08
8	2.38	2.37	+0.01	2.36	2.38	−0.02
9α	3.98	4.02	−0.04	4.08	4.09	−0.01
9β	3.72	3.85	−0.13	3.49	3.49	0
7′	3.86	3.87	−0.01	3.78	3.80	−0.02
8′	2.30	2.34	−0.04	2.53	2.58	−0.05
9′α	3.92	3.93	−0.01	3.94	3.94	0
9′β	3.66	3.68	−0.02	3.59	3.60	−0.01

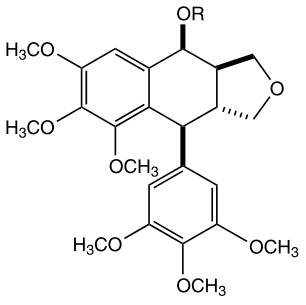
[a] Recorded in $CDCl_3$ at 500 MHz.

configuration of C-7 was *R*, and therefore the absolute configurations at C-8, C-8′, and C-7′ were *R*, *R*, and *S*, respectively.

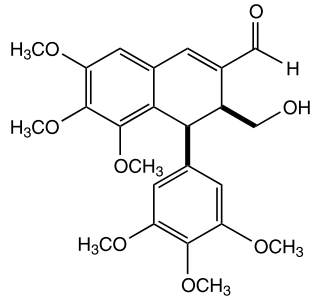
The high-resolution EI MS of **2** gave the molecular formula $C_{24}H_{30}O_8$ for aglacin F ($[M]^+$ m/z 446.1947, calcd 446.1941). The ^1H and ^{13}C NMR data (Table 1) as well as 2D correlations revealed that both the functional groups and the general substitution pattern present in **2** were similar to those observed in **1** suggesting that **2** was a stereoisomer of **1**. The only difference between **2** and **1** was observed with regard to the configuration of the hydroxyl group at C-7. Compared to **1**, the signal of H-7 in **2** appeared at a slightly lower field (δ_H 4.83) with a smaller coupling constant ($J=3.2$ Hz) indicating a *cis*-orientation of H-7 and H-8 in **2** as compared to the *trans*-orientation in **1**. The relative stereochemistry for the other chiral centers in **2** (C-7′, C-8, and C-8′) were the same as in **1** based on the characteristic *J*-values and on a ROESY experiment. It should be mentioned that compound **2** had previously already been obtained as a hydrolysis product during the absolute stereochemistry determination of aglacin A, the first lignan of the aryltetralin cyclic ether series.[4j] Both the NMR and EIMS data of compound **2** were identical to those of deacetylated aglacin A thus supporting the proposed structure of aglacin F (**2**). Similarly as described for **1**, the absolute configuration of **2** was determined by the modified Mosher's method which proved the *S*-configuration for C-7 (Table 2). Consequently, the absolute configurations at C-8, C-8′, and C-7′ were *R*, *R*, and *S*, respectively, the same as previously reported for aglacin A.[4j]



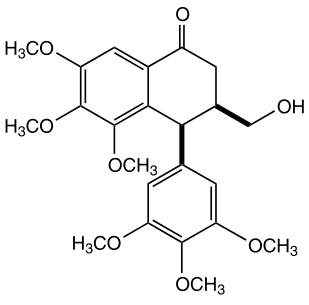
1 R = H
1r R = (*R*)-MTPA
1s R = (*S*)-MTPA



2 R = H
2r R = (*R*)-MTPA
2s R = (*S*)-MTPA



3



4

Aglacin G (**3**) was obtained as a colorless waxy solid with the molecular formula of $C_{24}H_{28}O_8$ (HREIMS $[M]^+$ m/z 444.1796, calcd 444.1784). Careful inspection of the NMR data for compound **3** (Table 3) indicated that the aromatic units were the same as those of **1** and **2**. Significant differences in the ^1H NMR spectrum of **3** compared to those of **1** and **2** included the absence of the signal for the methine proton H-8, the oxymethine proton H-7, and the oxymethylene protons H_2-9 in the spectrum of **3**. Instead one olefinic proton singlet at δ_H 7.30 and one proton singlet at δ_H 9.59 indicative of an aldehyde moiety were present in the ^1H NMR spectrum of **3**. This observation was confirmed by comparison of the ^{13}C NMR spectra of **1** and **3** in which the signals for the methine carbon C-8, the oxymethine carbon C-7, and the oxymethylene carbon C-9 were absent in the spectrum of **3**, while an olefinic quaternary carbon (δ 137.2, C-8), an olefinic methine carbon (δ 146.1, C-7), and an aldehyde carbon (δ 193.0, C-9), were observed. The ^1H–^1H COSY spectrum of **3** revealed one spin system which only included H-7′, H-8′, and H-9′, implying that the additional olefinic proton was attached to C-7, while C-9 was oxidized to an aldehyde group. This assumption was confirmed by C–H correlations from H-7 to C-1, C-2, and C-9, and from H-9 to C-7 and C-8′ in the HMBC spectrum.[5] H-7′ and H-8′ were oriented *cis*, since the signal of proton H-7′ appeared as a broad singlet, but not as a doublet as

Table 3. ^1H and ^{13}C NMR spectral data of aglacins G (**3**) and H (**4**)[a]

Atom	Aglacin G (**3**)		Aglacin H (**4**)	
	^1H	^{13}C	^1H	^{13}C
1		125.1 s		130.2 s
2	6.76 s	108.3 d	7.44 s	104.5 d
3		152.8 s		152.8 s
4		145.3 s		147.9 s
5		152.2 s		151.5 s
6		127.0 s		128.0 s
7	7.30 s	146.1 d		196.4 s
8		137.2 s	α 2.46 dd (17.6, 1.9) β 2.77 dd (17.6, 5.7)	36.3 t
9	9.59 s	193.0 d		
10	3.92 s	56.1 q	3.94 s	56.0 q
11	3.91 s	60.9 q	3.92 s	60.8 q
12	3.60 s	60.8 q	3.49 s	60.7 q
1′		139.4 s		139.5 s
2′/6′	6.20 s	104.6 d	6.25 s	105.3 d
3′/5′		153.0 s		153.2 s
4′		136.6 s		136.7 s
7′	4.66 br s	38.0 d	4.63 d (2.6)	39.7 d
8′	3.30 m	42.0 d	2.53 m	44.6 d
9′	α 3.60 dd (8.8, 6.7) β 3.39 dd (10.4, 8.6)	63.9 t	3.66 d (6.3, 2H)	65.0 t
10′/12′	3.71 s	56.0 q	3.74 s	56.2 q
11′	3.76 s	60.9 q	3.81 s	60.9 q

[a] ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 500 and 125 MHz, respectively. Proton and carbon signals were assigned by analysis of COSY, HMQC, HMBC, and ROESY spectral data.

observed for aglacins E (**1**) and F (**2**). This interpretation was confirmed by a ROESY experiment which showed a correlation between H-7′ and H-8′.

Aglacin H (**4**), obtained as a colorless waxy solid, had the molecular formula $C_{23}H_{28}O_8$ as shown by HREI MS ($[M]^+$ m/z 432.1766, calcd 432.1784). The same aromatic units were present in **4** as in **1**–**3**. However, **4** contained only 23 carbons compared to **1**–**3**, suggesting that **4** was a norlignan. Detailed analysis of the ^1H and ^{13}C NMR data (Table 3), as well as of the ^1H–^1H COSY, HMQC and HMBC [5] spectra led to the conclusion that the tetrahydrofuran ring present in **1** and **2** had been opened, and that carbon C-9 was absent in **4**. Accordingly, two *gem*-methylene protons (H-8α and H-8β) were observed in the ^1H NMR spectrum of **4** at δ_H 2.77 (dd, $J=17.6$, 5.7 Hz) and 2.46 (dd, $J=17.6$, 1.9 Hz). Furthermore, instead of the H-7 and C-7 signals observed in the ^1H and ^{13}C NMR spectra of compounds **1**–**3**, a keto signal was detected (δ_C 196.4) in the ^{13}C NMR spectrum of **4**. As in the case of **4**, the H-7′ and H-8′ were oriented *cis*, since as H-7′ was observed as a doublet at δ_H 4.63 with only a small vicinal coupling constant ($J=2.6$ Hz). This was confirmed by a ROESY experiment which revealed a correlation between both protons.

All of the above compounds, aglacins E–H (**1**–**4**), belong to the aryltetrahydronaphthalene lignans featuring two trimethoxyl substituted phenyl ring systems, which, to the best of our knowledge, have not been reported for this type of lignan in nature to date. Taken in combination with our previously reported data on the occurrence of aglacins A–D in *A. cordata*,[4j] it is obvious that this species is an exceedingly rich source of highly methoxylated aryltetralin cyclic ether lignans.

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5. Aglacin E (**1**): Colorless waxy solid; $[\alpha]_D^{20}$ +17 (c 0.69, $CHCl_3$), ^1H and ^{13}C NMR ($CDCl_3$), see Table 1; EI MS m/z 446 ($[M]^+$, 100), 182 (18), 181 (26), 71 (36); HREI MS m/z $[M]^+$ 446.1924 (calcd for $C_{24}H_{30}O_8$: 446.1941), 181.0882 (calcd for $C_{10}H_{13}O_3$: 181.0865). Aglacin F (**2**): Colorless waxy solid; $[\alpha]_D^{20}$ −1 (c 0.41, $CHCl_3$), ^1H and ^{13}C NMR ($CDCl_3$), see Table 1; EI MS m/z 446 ($[M]^+$, 100), 182 (11), 181 (17); HREI MS m/z $[M]^+$ 446.1947 (calcd for $C_{24}H_{30}O_8$: 446.1941), 181.0840 (calcd for $C_{10}H_{13}O_3$: 181.0865). Aglacin G (**3**): Colorless waxy solid; $[\alpha]_D^{20}$ −42 (c 0.78, $CHCl_3$), ^1H and ^{13}C NMR ($CDCl_3$), see Table 2; HMBC: H-2 to C-1, 3, and 4, H-7 to C-1, 2, 8′, and 9, H-9 to C-7, 8, and 8′, H-2′/6′ to C-3′/5′, 4′, and 7′, and H-7′ to C-1, 1′, 2′/6′, 5, 6, and 8; EI MS m/z $[M]^+$ 444 ($[M]^+$, 100), 181 (12), 84 (15), 71 (14); HREI MS m/z $[M]^+$ 444.1796 (calcd for $C_{24}H_{28}O_8$: 444.1784), 181.0856 (calcd for $C_{10}H_{13}O_3$: 181.0865). Aglacin H (**4**): Colorless waxy solid; $[\alpha]_D^{20}$ −40 (c 0.57, $CHCl_3$), ^1H and ^{13}C NMR ($CDCl_3$), see Table 2; HMBC: H-2 to C-1, 3, 4, 6, and 7, H-8α to C-7 and 8′, H-8β to C-7 and 7′, H-2′/6′ to C-1′, 3′/5′, 4′, and 7′, and H-7′ to C-1, 1′, 2′/6′, 5, and 6; EI MS m/z $[M]^+$ 432 ($[M]^+$, 100), 181 (15), 84 (27), 71 (14); HREI MS m/z $[M]^+$ 432.1766 (calcd for $C_{23}H_{28}O_8$: 432.1784), 181.0847 (calcd for $C_{10}H_{13}O_3$: 181.0865).

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8. Preparation of (*R*)- and (*S*)-MTPA ester derivatives of aglacins E **1** and F **2**:[7] To a stirred solution of **1** (1.0 mg) in $CHCl_3$ (1.0 mL) and pyridine (100 μL) was added 4-(dimethylamino)pyridine (0.5 mg) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (10 mg). 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). The solvents were removed under reduced pressure to afford a residue which was further purified by prep. TLC (CH_2Cl_2:MeOH, 40:1) to give the respective (*R*)-Mosher ester **1r**. Treatment of **1** (1.0 mg) with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride as described above afforded the (*S*)-Mosher ester **1s**. Treatment of aglacin F **2** with (*S*)- and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride afforded the respective Mosher esters **2r** and **2s**.