Phytochemical Investigation of *Aglaia rubiginosa*

S. Weber, J. Puripattanavong, V. Brecht, and A. W. Frahm*

Department of Pharmaceutical Chemistry, Institute of Pharmacy, University of Freiburg, Hermann-Herder-Strasse 9, 79104 Freiburg, Germany

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The phytochemical investigation of a methanolic leaf extract of *Aglaia rubiginosa* furnished 15 isoprenoid constituents, eight of which represented new natural entities. Two androstane derivatives (**1** and **2**), previously synthesized, and also obtained by microbiological transformations; an extraordinary 17-octanor-cycloartane-ring-A-*seco* acid (**3**); four cycloartane-type triterpenes (**4**−**7**); and three unusual cholesterol derivatives (**8**−**10**) were isolated, along with two known dammaranes (**11** and **12**), a stigmastandiol (**13**), and β-sitosterol and its β-D-glucoside. Spectroscopic structure elucidation of the new natural products (**1**−**3**, **6**, **7**, **8**−**10**) is described.

With more than 100 species, *Aglaia* represents the largest genus in the family Meliaceae and constitutes an important part of the tropical forest in Indochina. The taxonomic species delimitation proved to be troublesome and had to be revised several times. Based on the dehiscence of the fruit and the flower characters, a taxonomic monograph of the genus *Aglaia* recognizes two sections within this family, the section *Aglaia* (88 species) and the section *Amoora* (16 species).[1] Some species are used in traditional medicine against different diseases, including cancer,[2] heart problems,[3] fever,[3] inflammation,[4] and cough.[4]

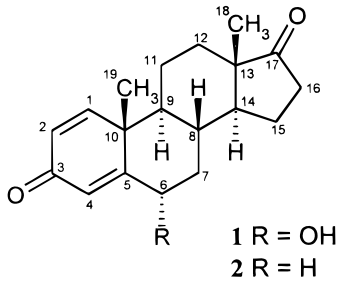
So far only representatives of the section *Aglaia* have been investigated phytochemically. Various triterpenes (e.g., limonoids,[5−7] cycloartanes,[2,8,9] and tirucallanes[10,11]) and cyclopenta[*b*]benzofurans (flavaglines[12]) were isolated. In particular, some of the benzofuran derivatives show interesting phamacological properties: antileukemic,[13] antiviral,[14] and insecticidal[15] activities have been found. As part of our studies on the constituents of *Aglaia* species from Thailand, we have examined the leaves of *A. rubiginosa* (Hiern) Pannell, belonging to the section *Amoora* with dehiscent fruits, which are dispersed by birds. It seemed interesting from the phytochemical and taxonomic point of view to establish whether the above-mentioned classes of compounds discriminate the section *Amoora* from the section *Aglaia*. This prompted us to direct our search toward structurally differentiating compounds.

Results and Discussion

Repeated chromatographic separation of the methanolic leaf extract from *A. rubiginosa* resulted in the isolation of eight new steroid and triterpenoid compounds. The structures were elucidated by means of spectroscopic methods, such as EIMS, HREIMS, ESIMS, ^{1}H NMR, ^{13}C NMR, and 2D NMR techniques (gs-COSY, gs-HSQC, gs-HMQC, NOESY).

The identification of 6α-hydroxyandrosta-1,4-diene-3,17-dione (**1**) was carried out spectroscopically and finally confirmed by comparing the ^{1}H spectral data with literature values[16] and with those of a synthetic reference sample (Schering AG, Berlin). The ^{13}C NMR data have been assigned for the first time by means of DEPT and gs-HMQC spectra. Seven indicative low-field signals out of 19 were assigned to two carbonyl carbons at δ 219.5, typical of a five-membered ring ketone (C-17), and at δ 186.1, characteristic of a cross-coupled dienone-moiety (C-3), four olefinic carbons at δ 169.6 (one quaternary carbon, C-5) and at δ 155.1, 127.7, and 119.8 (three methine carbons, C-1, C-2, and C-4), together with one oxygenated methine carbon at δ 68.0, identified as C-6 because it showed long-range coupling to H-4. The α-position of the C-6 hydroxyl group was proven by positive NOE effects between H-6β→H-8 and H-6β→H-19, respectively.

Compared with that of **1**, the ^{13}C NMR spectrum of compound **2** showed broad similarities. Only the downfield-shifted signal at δ 68.0 assigned to C-6 was missing. The HREIMS exhibited a molecular ion peak at *m*/*z* 284.1775 against *m*/*z* 300.1725 for **1**, with the former corresponding to the supposed elemental formula $C_{19}H_{24}O_2$ and leading to the identification of **2** as androsta-1,4-diene-3,17-dione,[16] the non-hydroxylated parent compound of **1**.



The androstane derivatives **1** and **2** represent a very unusual type of steroid in plants with the characteristic ring A-cyclohexadienone structure, well-known from synthetic corticosteroid compounds. They were obtained previously from hyodeoxycholic acid[17] by microbiological transformation reactions.[16] Their synthesis is described in the patent literature,[18] but they have never been isolated from any plant until now.

A reduced number of ^{13}C NMR signals for 18 carbons excluded a normal triterpenoid structure for compound **3**. The IR spectrum exhibited absorptions in the hydroxyl region (3400 cm^{-1}) and for two carbonyl functions (1721 and 1683 cm^{-1}) with a shoulder (1710 cm^{-1}), pointing to the presence of a third carbonyl group. The ^{1}H NMR spectrum of **3** showed the presence of only two singlets for methyl groups (δ 0.83, 1.14) and two 1H-doublets at δ 0.96 and 1.68 (J = 5.7 Hz) characteristic of geminal cyclopropane ring protons. On the basis of 2D NMR results

* To whom correspondence should be addressed. Tel.: +49-761-203-6335. Fax: +49-761-203-6351. E-mail: awfrahm@ruf.uni-freiburg.de.

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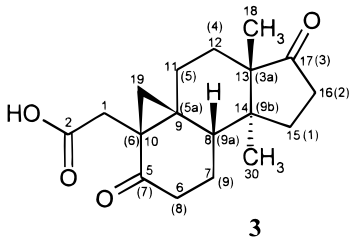

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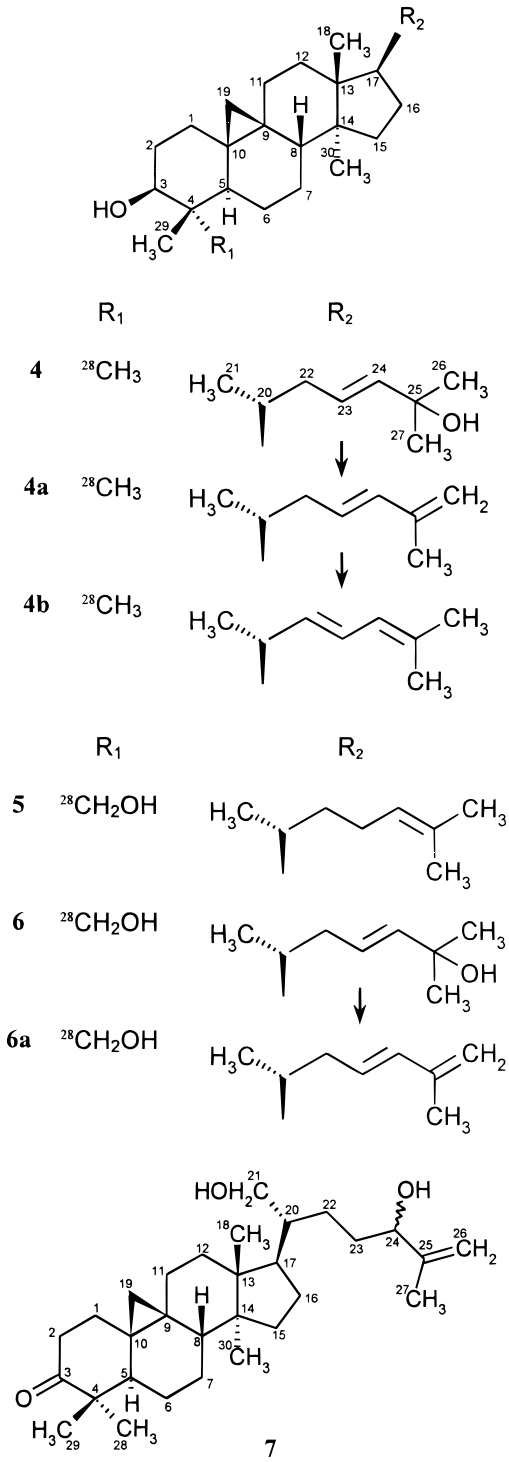
(^{1}H−^{1}H COSY and NOESY), the signal groups at δ 2.68 and 2.74 (each 1H, d, J = 16.6 Hz) were assigned to the C-1 methylene group. The ^{13}C NMR spectrum gave evidence of three carbonyl signals, at δ 218.8 (five-membered ring ketone), 209.7 (six-membered ring ketone), and 176.5 (carboxylic acid). The carboxylic acid structural element was confirmed by the ^{1}H NMR spectrum in DMSO-d_6 with a singlet at δ 11.8 integrating for one exchangeable proton. The HREIMS showed the molecular ion peak at m/z 304.1685 and confirmed the proposed elemental formula $C_{18}H_{24}O_4$. These data allowed us to identify the skeleton of **3** as a 17-octanor-cycloartane-ring-A-*seco* acid. To the best of our knowledge this is the first report of a *seco*-compound in the genus *Aglaia*. So far only very few structurally related ring A *seco*-cycloartanes have been isolated from other natural sources,[19,20] with structures substantially different from that of **3**.

The number of publications on cycloartane-type triterpenes in *Aglaia* species clearly indicates that this class of compounds may be regarded as a distinctive chemotaxonomic feature. Cycloartane-type triterpenes possess a cyclopropane bridge between C-9 and C-10, and protons attached to cyclopropyl rings characteristically appear as a pair of doublets in the high-field ^{1}H NMR region with a geminal coupling constant (J = 4.3 Hz). From the leaves of *A. rubiginosa* we have isolated four such cycloartane derivatives (**4**−**7**), which have not been isolated previously from any *Aglaia* species. Two of them (**6** and **7**) proved to be new compounds.

Based on its spectral characteristics and comparison with published data,[21] compound **4** was identified as cycloart-23-ene-3β,25-diol, disregarding the (*E*)- or (*Z*)-configuration of the double bond at C-23. When the ^{1}H NMR spectrum was recorded in benzene-d_6, the narrow multiplet at δ 5.60 ppm observed in the $CDCl_3$ spectrum was separated into an AB-pattern with $\Delta\delta$ = 13.2 Hz and $^3J_{(23/24-H)}$ = 16 Hz, from which the (*E*)-configuration was unequivocally deduced. This contradicts the literature data for cycloart-(23*Z*)-ene-3β,25-diol.[21]

In the ^{1}H NMR spectrum of **5**, when compared to that of **4**, one of the three methyl singlets below 1 ppm was missing, whereas a pair of doublets (1H each) appeared downfield shifted to δ 3.50 and 3.75, respectively, the latter overlapping with the H-3 multiplet. However, the coupling constant (J = 10.5 Hz) confirmed a geminal relationship, and the gs-HMQC spectrum indicated that the hydroxymethyl substituent is attached to C-4 either in the β- (C-29) or in the α-position (C-28). A decision in favor of C-28 followed from the observation of the high-field chemical shift of C-29 from δ 14.0 in **4** to 10.1 in **5**. From a detailed comparison of all spectral data with literature values,[22] the structure of **5** was deduced as cycloart-24-ene-3β,28-diol.

The NMR experiments indicated that **6** has the same basic skeleton as **5**, with hydroxyl groups at C-3 and C-28, but with a structurally different side chain at position 17. The side-chain moiety consisted of an OH-substituted quaternary carbon (C-25, δ 70.8), two geminal methyl groups (C-26 and C-27, δ 1.30, 6H, δ 30.0 and 29.9), and a



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double bond (C-23 and C-24, δ 5.59, 2H, δ 125.6 and 139.3). The only structural feature capable of deshielding such geminal methyl groups is an oxygen-bearing carbon atom. Unfortunately, cycloart-23-ene-3β,25,28-triol **(6)** decomposed during the NMR experiments in $CDCl_3$. The precise interpretation of these corresponding spectra proved that H_2O had been eliminated from the side chain. The reaction might have been catalyzed by traces of hydrochloric acid from the $CDCl_3$ solvent. Compound **6** has not yet been reisolated from the plant. The NMR data of **6** and of the resulting artifact **6a** is given (see Table 1). These findings have been proven via compound **4**, with an identical side chain. After dissolving **4** in the same impure $CDCl_3$ solvent, the regularly recorded ^{1}H NMR spectra showed analogous changes within 24 h at room temperature. The resulting

Table 1. ^{13}C NMR Data for Cycloartane Triterpenes **4**−**7** (75 MHz, $CDCl_3$, δ/ppm, mult)

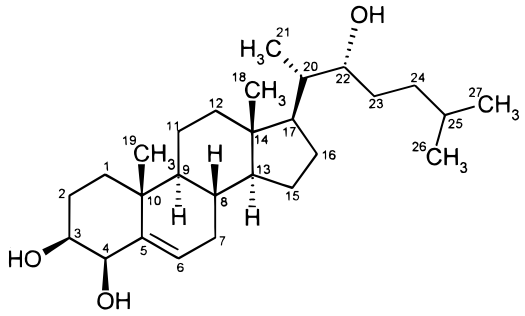
position	4	5	6	6a	7
1	32.0 t	31.7 t	31.7 t	31.7 t	33.4 t
2	30.4 t	30.2 t	30.1 t	30.2 t	37.4 t
3	78.8 d	77.0 d	77.0 d	77.1 d	216.5 s
4	40.5 s	43.7 s	43.6 s	43.7 s	50.2 s
5	47.1 d	42.5 d	42.4 d	42.5 d	48.4 d
6	21.1 t	21.0 t	21.0 t	21.0 t	21.4 t
7	26.0 t	25.7 t	25.7 t	25.7 t	25.8 t
8	48.0 d	47.9 d	47.9 d	47.9 d	47.8 d
9	20.0 s	20.0 s	19.9 s	19.9 s	21.0 s
10	26.1 s	25.4 s	25.3 s	25.3 s	26.0 s
11	26.5 t	26.4 t	26.3 t	26.4 t	26.6 t
12	32.8 t	32.9 t	32.7 t	32.7 t	32.1 t
13	45.3 s	45.2 s	45.2 s	45.3 s	45.1 s
14	48.8 s	48.8 s	48.7 s	48.7 s	48.8 s
15	35.6 t	35.6 t	35.5 t	35.6 t	35.4 t
16	28.1 t	28.1 t	28.0 t	28.2 t	27.5 t
17	52.0 d	52.3 d	52.0 d	52.2 d	46.4 d
18	18.1 q	18.0 q	18.1 q	18.1 q	18.3 q
19	29.9 t	30.0 t	29.8 t	30.0 t	29.5 t
20	36.4 d	35.9 d	36.3 d	36.8 d	42.4 d
21	18.3 q	18.2 q	18.3 q	18.3 q	62.5 t
22	39.0 t	36.3 t	39.0 t	39.7 t	25.0 t
23	125.6 d	24.9 t	125.6 d	129.6 d	30.7 t
24	139.4 d	125.3 d	139.3 d	134.4 d	76.2 d
25	70.7 s	130.9 s	70.8 s	142.2 s	147.6 s
26	30.0 q	17.6 q	30.0 q	114.0 t	110.9 t
27	29.9 q	25.7 q	29.9 q	18.8 q	17.7 q
28	25.4 q	71.1 t	71.1 t	71.2 t	22.2 q
29	14.0 q	10.1 q	10.1 q	10.1q	20.7 q
30	19.3 q	19.3 q	19.3 q	19.3 q	19.4 q

product was identified as cycloarta-23,25-diene-3β,28-diol (**4a**), which, after a further 10 days under these conditions, rearranged its conjugated double-bond system to form the more stable cycloarta-22,24-diene-3β,28-diol (**4b**). This reaction has not been observed previously in cycloartanes.

In contrast to the substances **4**−**6**, compound **7** contained a carbonyl group (δ 216.5) instead of a β-OH group at C-3. Furthermore, the ^1H NMR spectrum showed a pattern of a hydroxymethyl substituent instead of the methyl doublet, besides a new lowfield-shifted multiplet (δ 4.03) of another methine proton together with two broad singlets (δ 4.81 and 4.93), the characteristic pattern of an sp^2 methylene group. The 2D NMR experiments justified the location of the hydroxyl groups at C-21 and C-24. The methylene carbon was assigned to C-26. Duplication of most of the signals for the side chain and some of the signals of the basic skeleton in its ^{13}C NMR spectrum indicated that **7** was a mixture of epimers. In fact, the doubling of the resonances associated with C-24 and its adjacent carbons was consistent with the presence of a mixture of C-24 epimers in the ratio of about 6:4. Therefore, compound **7** was assigned the structure 21,24(*RS*)-dihydroxycycloart-25-en-3-one.

According to NMR studies of ^{13}C-enriched cycloartenol biosynthesized from [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]-acetate,[23] and from our own results, some of the ^{13}C NMR spectral assignments of cycloartenol derivatives in the literature require revision, namely, C-7, C-11, C-16, C-18, C-21, and C-28. Thus, ^{13}C NMR data of all four cycloartanes (**4**−**7**) are presented in Table 1.

In addition, compounds (**8**−**10**) were isolated with 27 carbon atoms and a steroid skeleton, representatives of a class of compounds not yet reported from *Aglaia* species. The basic structure of steroid **8** was revealed by ^{13}C NMR and DEPT experiments, with five methyl, nine methylene, 10 methine, and three quaternary carbons detected, inclusive of one quaternary olefinic (δ 142.8), one tertiary olefinic



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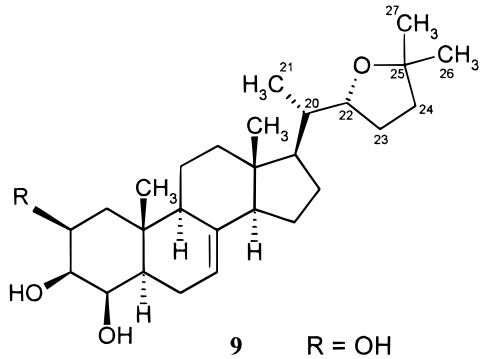


9 R = OH
10 R = H

(δ 128.7), and three oxygenated methine carbons (δ 77.3, 74.1 and 72.5). These data were in good agreement with a cholesterol-type triterpene structure with the chemical shifts of the olefinic carbons pointing to the Δ^5-cholesterol series. In addition to the expected methyl (three doublets and two singlets) and methylene proton signals, the ^1H NMR spectrum of **8** showed resonances for one olefinic proton at δ 5.68 (dd, H-6), one 1H doublet at δ 4.14 (H-4α), and a multiplet integrating for two protons at δ 3.59 (H-3α, H-22) (Table 2). $^1H-^1H$ COSY and long-range 2D NMR experiments (gs-HMQC) allowed us to locate three hydroxyl groups at C-3, C-4, and C-22, respectively. The configuration at C-22 was deduced from the magnitude of the observed β-effects on the chemical shift. According to the literature,[24] **8** is the (22*R*)-epimer, because of a strong β-effect on C-20. The β-positions of the hydroxyls at C-3 and C-4 are based on the coupling constants of the attached methine protons and proven by NOE experiments. A NOE was observed between H-3 and H-4, whereas no NOE was identified between H-3/H-4 and H_3-19.

A more polar part of the methanolic extract yielded compound **9**, with ^{13}C NMR spectral data (Table 3) similar to those of cholest-5-ene-3β,4β,22(*R*)-triol (**8**), but differing in the shift data for the olefinic carbons (δ 138.0, C-8 and 119.2, C-7) and with a broad proton singlet at δ 5.36, both indicating a double bond shift to position C-7/C-8. One of the five observed oxygenated carbons was quaternary, bearing two methyl groups identified by two singlets at δ 1.25 (H_3-26) and 1.26 (H_3-27), respectively. Therefore, C-25 must be oxygenated. A long-range coupling between H_3-21 and C-22 (δ 80.6) identified the second oxygenated carbon atom. The downfield shift of the C-22 (δ 80.6) and C-25 (δ 79.6) signals in comparison to those of the 22,25-dihydroxy derivative (δ 74 and δ 70, respectively) could be explained by a tetrahydrofuran ring structure in the C-17 side chain.[25] This was confirmed by the HREIMS showing the molecular ion peak at *m/z* 432.3218 and leading to the elemental formula $C_{27}H_{44}O_4$ with only four oxygen atoms instead of five for the respective open side-chain compound. The absolute configuration of C-22 was derived from NOE

Table 2. ^{1}H NMR Data for Cholesterol Derivatives **8**−**10** (300 MHz, $CDCl_3$, δ/ppm, TMS, *J* Hz, mult[a])

position	**8**	**9**[b]	**10**
1	1.05/1.83	1.40 (m) 2.45 (dd, 3.3, 14.1)	1.08/1.83
2	1.64/1.88	4.49 (br s)	1.6−1.8
3	3.59 (m)	3.79 (br s)	3.57 (m)
4	4.14 (d, 3.4)	4.21 (br s)	3.81 (t, 2.6)
5		1.50	1.33
6	5.68 (dd, 1.6, 4.8)	1.90/2.85	1.78/2.36
7	2.08 (2H)	5.36 (br s)	5.24 (m)
8	1.54		
9	0.89	1.74	1.62
11	1.46 (2H)	1.59 (2H)	1.48 (2H)
12	1.17/2.01	1.26/2.08	1.20/2.03
14	0.98	1.85	1.74
15	1.11/1.60	1.4−1.7 (2H)	1.4−1.6 (2H)
16	1.38/1.70	1.44/1.90	1.44/1.78
17	1.12	1.25	1.16
18	0.72 (s)	0.58 (s)	0.54 (s)
19	1.20 (s)	1.59 (s)	1.01 (s)
20	1.68	1.90	1.81
21	0.94 (d, 6.4)	1.00 (d, 6.7)	0.91 (d, 6.7)
22	3.59 (m)	4.09 (ddd, 4, 7, 7)	4.04 (ddd, 3.5, 7, 7)
23	1.20/1.32	1.68 (2H)	1.68 (2H)
24	1.16/1.40	1.65 (2H)	1.66 (2H)
25	1.55		
26	0.92 (d, 6.4)	1.25 (s)	1.22 (s)
27	0.91 (d, 6.6)	1.26 (s)	1.23 (s)

[a] All ^{1}H NMR shifts given without multiplicities consist of nonresolved overlapping multiplets; their correct values and assignments were determined by 2D hetero-techniques. [b] Spectrum recorded in pyridine-d_5.

Table 3. ^{13}C NMR Data for Cholesterol Derivatives **8**−**10** (75 MHz, $CDCl_3$ δ/ppm, TMS, mult)

position	**8**	**9**[a]	**10**
1	36.9 t	45.1 t	37.3 t
2	25.4 t	73.0 d	25.6 t
3	72.5 d	72.7 d	72.6 d
4	77.3 d	76.0 d	73.2 d
5	142.8 s	45.9 d	44.4 d
6	128.7 d	27.2 t	26.0 t
7	32.1 t	119.2 d	117.9 d
8	31.9 d	138.0 s	139.0 s
9	50.2 d	52.8 d	50.7 d
10	36.1 s	34.4 s	34.2 s
11	20.6 t	21.3 t	21.0 t
12	39.7 t	39.8 t	39.4 t
13	42.7 s	44.2 s	43.9 s
14	56.5 d	54.9 d	54.6 d
15	24.4 t	23.6 t	23.1 t
16	27.4 t	27.6 t	27.3 t
17	53.2 d	54.3 d	53.7 d
18	11.9 q	12.1 q	11.8 q
19	21.0 q	18.5 q	15.2 q
20	42.3 d	39.2 d	38.5 d
21	12.4 q	13.0 q	12.4 q
22	74.1 d	80.6 d	80.2 d
23	27.7 t	25.7 t	24.8 t
24	36.0 t	39.1 t	38.9 t
25	28.2 d	79.6 s	79.7 s
26	22.5 q	28.2 q	28.0 q
27	22.9 q	29.0 q	28.6 q

[a] Recorded in pyridine-d_5.

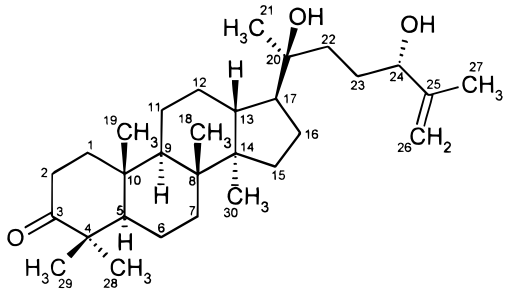
experiments in combination with the analysis of the coupling constants of the H-22 signal group, based on the configurational and conformational arrangement of the CH_3-18−C-13−CH-17−CH-20−CH_3-21 structural fragment, in which H-17 is antiperiplanar to H-20 at the (*S*)-configured C-20. Inspecting the Dreiding model of compound **9**, we discovered the crucial NOE effects between H-17 and H_2-23 as well as between H-20 and H-22, together with the missing NO enhancements between H-22 and H_3-21 are compatible only with the (*R*)-configuration of C-22. In the adopted conformation of the cyclic C-17 side chain, H-17 is spatially close to H_2-23, with dihedral angles between H-22 and H-20 of about 25° and between H-22 and H-23a+b of about 25° and 120°, respectively. The corresponding coupling constants of 7, 7, and 4 Hz are found in the splitting pattern of H-22. Independent evidence for the (22*R*)-configuration is derived from the ^{13}C NMR chemical shift of C-23 (δ 25.7), which is shielded compared to the (22*S*)-epimer (around 30 ppm).[25] The hydroxylation pattern of ring A was again settled by ^{1}H−^{1}H COSY and gs-HMQC experiments. The NOESY spectrum revealed indirectly the β-position of all three hydroxyl groups in ring A. The structure of compound **9** was established accordingly as (22*R*,25)-epoxy-cholest-7-ene-2β,3β,4β-triol.

The ^{1}H and ^{13}C NMR spectra of **10** were similar to those of compound **9**. The only difference was the number of downfield-shifted methine protons with three (instead of four) multiplets observed in the region δ 3.5−4.5 in the ^{1}H NMR spectrum and only four, instead of five, carbon resonances between δ 72 and 81 in the ^{13}C NMR spectrum. Accordingly, one secondary hydroxyl group was absent in **10**. An unusual 4-hydroxyl substitution was supported unambiguously by ^{1}H−^{1}H COSY relations between H-4 (δ 3.81)→H-3 and H-4→H-5 and by strong long-range cross-peaks between H-4→C-2, H-4→C-6, and H-4→C-10, respectively. Further comparison with the spectral data of compound **9** revealed **10** to contain the identical cyclized C-17 side chain. Taking into account all available data, compound **10** proved to be the new (22*R*,25)-epoxy-cholest-7-ene-3β,4β-diol. It is interesting to note that **9** and **10** display the same side chain as some ecdysteroids,[26] the well-known insect molting hormones with an (*R*)-configured C-22.

The first compound isolated from an *Aglaia* species was aglaiol,[3] a tetracyclic triterpene with a dammarane skeleton. We have now isolated two more dammaranes from *A. rubiginosa*, which were identified as the known (20*S*,24*S*)-dihydroxydammar-25-en-3-one (**11**) and (20*S*,25)-dihydroxydammar-23-en-3-one (isofouquierone) (**12**).[27,28] Furthermore, three stigmasterol derivatives were identified as the ubiquitous β-sitosterol, its glucoside, and stigmast-5-ene-3β,7α-diol (**13**).[29] The NMR data and the spectral properties of these compounds were consistent with those in the literature.[27−29]

The accumulation of cycloartanes, dammaranes, cholesterol derivatives, and even the biogenetically more advanced androstanes in one single species, gives rise to the supposition that the biogenesis of these different structural types is closely connected. The androstanes **1** and **2** represent a novel group of steroids from plants. Related pregnane derivatives without the characteristic A-ring dienone have been isolated from species in the Meliaceae (*Melia*[30] and *Trichilia*[31] species), the Simaroubaceae,[32] and the Burseraceae.[33] Due to their rarity, these steroids may be regarded as significant chemotaxonomic evidence supporting the proposed link between these three families that all belong to the order Rutales. We did not isolate any of the insecticidal flavaglines or related cyclopenta[*b*]benzofurans from *A. rubiginosa*. The absence of flavonoids, which represent important biosynthetic precursors of the flavaglines,[5] corroborates these results.

On the other hand the hydroxylated cholesterol derivatives show a structural relationship to the ecdysteroids,[26,34] and the A-ring dienone structure of the androstanes is also present in the insecticidal petuniasterones,[35] pointing to



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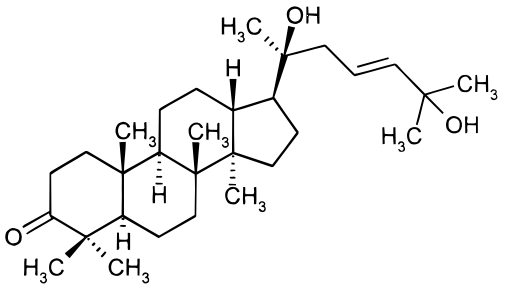
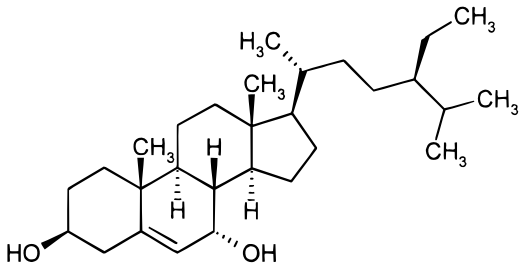


12



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different mechanisms and active principles with a significance in the chemical plant-insect interactions.

It is hypothesized that these significant deviations observed in the secondary metabolism might represent important differences between the section *Amoora* and the section *Aglaia*. Further phytochemical investigations may help to establish a final chemotaxonomic classification.

Experimental Section

General Experimental Procedures. Melting points were determined on a Mel-Temp II apparatus (Laboratory Devices, Holliston, MA) and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were obtained on a Perkin-Elmer 1605 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 300 (^{1}H NMR at 299.95 MHz, ^{13}C NMR at 75.4 MHz) using TMS as internal standard. With a Finnigan MAT 312 apparatus, mass spectra were obtained at 70 eV. Column chromatography was performed on Sephadex LH-20 (Pharmacia, Freiburg, Germany); Si 60 (63−200 μm) (Merck, Darmstadt, Germany), and Lobar A (240 × 10 mm), B (310 × 25 mm), and C (440 × 37 mm) Lichroprep Si 60 (40−63 μm) (Merck), respectively. TLC spots (Si gel 60 F_{254}, Merck) were detected with a UV_{254} lamp and by 40% H_2SO_4 followed by heating at 120 °C for 5 min.

Plant Material. The leaves of *A. rubiginosa* (Hiern) Pannell (Meliaceae) were collected from a peat swamp forest in Narathiwat Province (Thailand) in May 1994. A voucher specimen (no. ES-94051) is deposited at the herbarium of the Department of Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

Extraction and Isolation. Air-dried leaves of *A. rubiginosa* (10 kg) were ground and exhaustively extracted with methanol. The methanolic extract (550 g) was evaporated to dryness under reduced pressure. A part of the residue (94 g) was preadsorbed on Kieselgur (Seitz-Filter-Werke, Bad Kreuznach, Germany) and successively eluted with *n*-hexane, ethyl acetate, and methanol, respectively. The EtOAc fraction (37 g) and the MeOH fraction (10 g) were roughly separated by column chromatography on Sephadex LH-20 with MeOH (600 fractions of 10 mL and 200 fractions of 15 mL, respectively) followed by repeated chromatography on Si gel with different eluents. The *n*-hexane residue (47 g) was directly chromatographed on Si gel using a cyclohexane−EtOAc gradient (1000 fractions of 15 mL). Lobar column chromatography (UV detection, 254 nm) was used to finally purify the compounds.

***n*-Hexane Extract.** Fractions 166−300 of the chromatographic separation of the *n*-hexane extract directly yielded 1 g of β-sitosterol. Si gel chromatography of fractions 301−485 (5 g) with cyclohexane−EtOAc (2:1) yielded **4** (100 mg) and that of the following fractions 486−670 (4 g) with cyclohexane−EtOAc (1:1), compound **10** (10 mg). Fractions 671−900 (11.5 g) were separated by Si gel rechromatography with cyclohexane−EtOAc (2:1), which led to the isolation of **5** (20 mg) (fractions 533−750), **11** (20 mg) (fractions 751−920), and **13** (30 mg) (fractions 980−1119). Fractions 921−979 (1 g) were further purified by repeated Lobar column chromatography (2% MeOH in CH_2Cl_2) to yield finally 10 mg of **2** as an oily substance and 10 mg of **12**.

EtOAc Extract. Fractions 76−117 (16 g) of the chromatographic separation of the EtOAc extract on Sephadex LH-20 were further separated by Si gel chromatography (cyclohexane−EtOAc gradient). Fractions 417−500 (930 mg) were eluted with cyclohexane−EtOAc (1:1) and afforded 80 mg of **8**, while fractions 1037−1056 contained β-sitosterol-β-D-glucoside (20 mg). Fractions 566−1025 (6 g), were further purified by repeated Lobar column chromatography (3% MeOH in CH_2Cl_2), which led to the isolation of **7** (15 mg) (fractions 29−50), an additional amount of **13** (8 mg) (fractions 51−61), and **6** (5 mg) (fractions 62−88), respectively. Lobar column chromatography of a portion (5 g) of fractions 118−148 (7.6 g) from the EtOAc extract, using CH_2Cl_2−EtOAc (4:1), afforded 100 mg of **3** and 20 mg of **1**, respectively.

MeOH Extract. The MeOH extract was chromatographed on a Sephadex LH-20 column with MeOH to yield 30 mg of **9** (fractions 54−70) as an amorphous powder.

6α-Hydroxyandrosta-1,4-diene-3,17-dione (1): mp 240−242 °C; $[\alpha]^{20}_D$ +96.6° (*c* 0.11, MeOH); UV (MeOH) λ_{max} (ϵ) 240 (11 506) nm; CD (MeCN) λ (θ) 298 (7484), 258 (−2753), 236 (13 309) nm; IR (KBr) ν_{max} 3480 (OH), 1738 (17-C=O), 1655 (3-C=O), 1613 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, d, *J* = 10.0 Hz, H-1), 6.22 (1H, t, *J* = 1.8 Hz, H-4), 6.48 (1H, dd, *J* = 1.9, 10.3 Hz, H-2), 4.49 (1H, ddd, *J* = 1.7, 5.5, 11.7 Hz, H-6), 2.45 (1H, dd, *J* = 9.0, 19.0 Hz, H-16b), 2.33 (1H, ddd, *J* = 3.7, 5.5, 12.0 Hz, H-7b), 2.07 (1H, dd, *J* = 10.0, 19.0 Hz, H-16a), 1.96 (1H, m, H-15b), 1.85 (2H, m, H-8, H-12b), 1.83 (1H, m, H-11b), 1.65 (1H, m, H-11a), 1.59 (1H, m, H-15a), 1.29 (1H, m, H-14), 1.26 (1H, m, H-12a), 1.21 (3H, s, H-19), 1.10 (1H, m, H-7a), 1.07 (1H, m, H-9), 0.91 (3H, s, H-18); ^{13}C NMR ($CDCl_3$) δ 219.5 (s, C-17), 186.1 (s, C-3), 169.6 (s, C-5), 155.1 (d, C-1), 127.7 (d, C-2), 119.8 (d, C-4), 68.0 (d, C-6), 52.1 (d, C-9), 50.2 (d, C-14), 47.7 (s, C-13), 43.5 (s, C-10), 41.1 (t, C-7), 35.6 (t, C-16), 33.6 (d, C-8), 31.1 (t, C-12), 22.0 (t, C-11), 21.9 (t, C-15), 19.1 (q, C-19), 13.8 (q, C-18); EIMS (70 eV) *m*/*z* 300 $[M]^+$ (12), 282 $[M - H_2O]^+$ (4), 255 (17), 228 (10), 171 (10), 159 (11), 147 (17), 138 (55), 121 (31), 107 (72), 91 (64), 79 (92), 67 (47), 55 (81), 41 (100); HREIMS *m*/*z* 300.1725 (calcd for $C_{19}H_{24}O_3$, 300.1726).

Androsta-1,4-diene-3,17-dione (2): oil, $[\alpha]^{20}_D$ +66.7° (*c* 0.14, MeOH), UV (MeOH) λ_{max} (ϵ) 240 (7652) nm [242−243 nm];[36] CD (MeOH) λ (θ) 331 (−1607), 295 (5564), 260 (−4694), 230 (10 444) nm; ^{1}H and ^{13}C NMR data were coincident with those from the literature;[37] HREIMS *m*/*z* 284.1775 (calcd for $C_{19}H_{24}O_2$, 284.1776).

Ring A *seco*-17-octanor-5,17-dioxo-cycloartane-1-carboxylic acid (5a,6-methano-3a,9b-dimethyl-3,7-dioxo-cyclopentano[a]naphthalene-6-yl-ethanoic acid) (3): mp 198 °C; $[\alpha]^{20}_D$ +60.8° (*c* 0.11, MeOH); UV (MeOH) λ_{max} (ϵ) 280 (69) nm; CD (MeOH) λ (θ) 302 (2048), 271 (−2475), 214 (9168) nm; IR (KBr) ν_{max} 3400 (OH), 2934, 1721 (C=O), 1710 (sh, C=O), 1683 (C=O), 1457, 1377, 1113, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (2H, d, J = 7.6, H-1a, H-1b), 2.40 (2H, m, H-6b, H-16b), 2.35 (1H, m, H-8), 2.32 (1H, m, H-6), 2.23 (1H, dt, J = 9.0, 19.5, H-16a), 1.96−1.97 (2H, m, H-7b, H-11b), 1.73−1.82 (2H, m, H-15a, H-15b), 1.80 (1H, m, H-7a), 1.68 (1H, d, J = 5.7, H-19b), 1.65 (1H, m, H-12b), 1.56 (1H, m, H-11a), 1.49 (1H, m, H-12a), 1.14 (3H, s, H-30), 0.96 (1H, d, J = 5.7, H-19a), 0.83 (3H, s, H-18); ^{13}C NMR ($CDCl_3$) δ 218.8 (s, C-17), 209.7 (s, C-5), 176.5 (s, COOH), 53.5 (s, C-13), 44.3 (s, C-14), 38.4 (s, C-10), 38.3 (d, C-8), 34.0 (s, C-9), 33.8 (t, C-1), 33.6 (t, C-6), 33.6 (t, C-16), 30.9 (t, C-15), 27.1 (t, C-11), 24.8 (t, C-12), 24.0 (t, C-19), 19.7 (q, C-30), 19.4 (t, C-7), 17.8 (q, C-18); EIMS (70 eV) *m/z* 304 $[M]^+$ (18), 286 $[M - H_2O]^+$ (71), 271 $[M - H_2O - CH_3]^+$ (42), 258 (15), 243 (16), 229 (12), 201 (9), 187 (7), 173 (8), 161 (10), 133 (9), 105 (31), 91 (68), 79 (72), 55 (100), 41 (89); HREIMS *m/z* 304.1685 (calcd for $C_{18}H_{24}O_4$, 304.1675).

Cycloart-23-ene-3β,25,28-triol (6): Physical data for **6** could not be obtained because of decomposition during NMR analysis (H_2O-elimination, which led to **6a**); ^1H NMR ($CDCl_3$) δ 5.59 (2H, m, H-23, H-24), 3.74 (1H, dd, J = 5.0, 10.7, H-3), 3.71 (1H, d, J = 10.5, H-28b), 3.50 (1H, d, J = 10.5, H-28a), 2.16 (1H, m, H-22b), 1.98 (1H, m, H-11b), 1.90 (1H, m, H-16b), 1.70 (1H, m, H-22a), 1.74 (1H, m, H-2b), 1.6 (3-H, m, H-2a, H-12a, H-12b), 1.56 (1H, m, H-17), 1.5 (1H, m, H-1b), 1.48 (1H, m, H-8), 1.44 (1H, m, H-20), 1.44 (1H, m, H-5), 1.40 (1H, m, H-6b), 1.36 (1H, m, H-7b), 1.30 (6H, s, H-26, H-27), 1.29 (1H, m, H-16a), 1.28 (2H, m, H-15a, H-15b), 1.22 (1H, m, H-1a), 1.12 (1H, m, H-11a), 1.06 (1H, m, H-7a), 0.96 (3H, s, H-18), 0.91 (3H, s, H-29), 0.87 (3H, s, H-30), 0.85 (3H, d, J = 6.3, H-21), 0.80 (1H, m, H-6a), 0.59 (1H, d, J = 4.3, H-19b), 0.35 (1H, d, J = 4.3, H-19a); ^{13}C NMR ($CDCl_3$), see Table 1.

Cycloarta-23,25-diene-3β,28-diol (6a): ^1H NMR ($CDCl_3$) δ 6.13 (1H, m, H-24), 5.60 (1H, m, H-23), 4.85 (2H, br s, H-26a, H-26b), 3.75 (1H, dd, J = 4.9, 10.7, H-3), 3.74 (1H, d, J = 10.4, H-28b), 3.52 (1H, d, J = 10.4, H-28a), 2.24 (1H, m, H-22b), 1.97 (1H, m, H-11b), 1.88 (1H, m, H-16b), 1.84 (3H, s, H-27), 1.81 (1H, m, H-22a), 1.72 (1H, m, H-2b), 1.6 (3-H, m, H-2a, H-12a, H-12b), 1.56 (1H, m, H-17), 1.53 (1H, m, H-1b), 1.48 (1H, m, H-8), 1.47 (1H, m, H-20), 1.44 (1H, m, H-5), 1.40 (1H, m, H-6b), 1.29 (1H, m, H-7b), 1.27 (1H, m, H-16a), 1.26 (2H, m, H-15a, H-15b), 1.22 (1H, m, H-1a), 1.12 (1H, m, H-11a), 1.06 (1H, m, H-7a), 0.96 (3H, s, H-18), 0.94 (3H, s, H-29), 0.89 (3H, s, H-30), 0.85 (3H, d, J = 6.1, H-21), 0.80 (1H, m, H-6a), 0.59 (1H, d, J = 4.2, H-19b), 0.38 (1H, d, J = 4.2, H-19a); ^{13}C NMR ($CDCl_3$), see Table 1.

(21,24*RS*)-Dihydroxycycloart-25-en-3-one (7): solid, epimeric mixture (6:4); ^1H NMR ($CDCl_3$) δ 4.93 (1H, br s, H-26b), 4.81 (1H, br s, H-26a), 4.03 (1H, m, H-24), 3.73 (1H, dd, J = 3.2, 11.2, H-21b), 3.53 (1H, dd, J = 6, 11.2 H-21a), 2.68 (1H, m, H-2b), 2.28 (1H, ddd, J = 1.7, 2.7, 4.4, H-2a), 2.01 (1H, m, H-11b), 1.87 (1H, m, H-16b), 1.86 (1H, m, H-17), 1.80 (1H, m, H-1b), 1.71 (3H, s, H-27), 1.68 (1H, m, H-5), 1.65 (1H, m, H-23b), 1.62 (2H, m, H-12a, H-12b), 1.60 (1H, m, H-22b), 1.57 (1H, m, H-8), 1.55 (1H, m, H-20), 1.54 (1H, m, H-6b), 1.50 (1H, m, H-1a), 1.46 (1H, m, H-22a), 1.43 (1H, m, H-23a), 1.36 (1H, m, H-7b), 1.33 (1H, m, H-16a), 1.30 (2H, m, H-15a, H-15b), 1.14 (1H, m, H-11a), 1.11 (1H, m, H-7a), 1.07 (3H, s, H-29), 1.02 (3H, s, H-28), 0.99 (3H, s, H-18), 0.92 (1H, m, H-6a), 0.89 (3H, s, H-30), 0.77 (1H, d, J = 4.3, H-19b), 0.55 (1H, d, J = 4.3, H-19a); ^{13}C NMR ($CDCl_3$), see Table 1; EIMS (70 eV) *m/z* 456 $[M]^+$ (6), 438 $[M - H_2O]^+$ (24), 423 (11), 423 $[M - 2H_2O]^+$ (9), 352 (15), 313 (20), 297 (10), 271 (8), 245 (11), 201 (27), 175 (32), 173 (32), 147 (53), 95 (100); HREIMS *m/z* $[C_{30}H_{48}O_3 - H_2O]^+$ 438.3514 (calcd for $C_{30}H_{46}O_2$, 438.3498).

Cholest-5-ene-3β,4β,22(*R*)-triol (8): mp 176 °C; $[\alpha]^{20}_D$ −59.8° (*c* 0.11, MeOH); IR (KBr) ν_{max} 3344 (OH), 2943 (OH), 2869 (OH), 1462 and 1382 (C=C), 1045 cm^{-1}; ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS (70 eV) *m/z* 418 $[M]^+$ (52), 403 $[M - CH_3]^+$ (48), 400 $[M - H_2O]^+$ (24), 374 (100), 361 (16), 329 (16), 302 (17), 289 [M − side chain $C_8H_{17}O]^+$ (9) 285 (21), 274 [M − CH_3 − side chain $C_8H_{17}O]^+$ (26), 271 [M − H_2O − side chain $C_8H_{17}O]^+$ (20), 243 (13), 229 (14), 173 (13), 147 (16), 131 (13), 105 (18), 83 (27), 69 (15), 55 (19); HREIMS *m/z* 418.3454 (calcd for $C_{27}H_{46}O_3$, 418.3447).

(22*R*,25)-Epoxycholest-7-ene-2β,3β,4β-triol (9): mp >250 °C (dec); $[\alpha]^{20}_D$ +23.1° (*c* 0.1, MeOH); IR (KBr) ν_{max} 3386 (OH), 3306 (OH), 2964 (OH), 1443 and 1379 (C=C), 1142 and 1096 (C−O−C) cm^{-1}; ^1H NMR (pyridine-d_5) and ^{13}C NMR (pyridine-d_5), see Tables 2 and 3; EIMS (70 eV) *m/z* 432 $[M]^+$ (20), 414 $[M - H_2O]^+$ (9), 334 (6), 185 (6), 171 (7), 152 (14), 145 (13), 131 (14), 105 (27), 100 (47), 99 (100), 81 (100); HREIMS *m/z* 432.3218 (calcd for $C_{27}H_{44}O_4$, 432.3239).

(22*R*,25)-Epoxycholest-7-ene-3β,4β-diol (10): mp 230 °C; $[\alpha]^{20}_D$ +23.5° (*c* 0.1, MeOH); IR (KBr) ν_{max} 3422 (OH), 2964 (OH), 1455 and 1375 (C=C), 1146 and 1047 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS (70 eV) *m/z* 416 $[M]^+$ (3), 398 $[M - H_2O]^+$ (2), 185 (3), 171 (3), 152 (9), 145 (7), 131 (10), 105 (14), 100 (20), 99 (100), 81 (100); ESIMS *m/z* 439 $[M + Na]^+$ (100) $\{M^+ = 416\}$.

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