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Isoeichlerianic acid from *Aglaia silvestris* and revision of the stereochemistry of foveolin B

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ABSTRACT

A new series of 20,24-epoxy (tetrahydrofuryl) type dammarane triterpenoids were established. So far two series were described, based on the stereochemistries of the tetrahydrofurane ring linked to the D ring of the triterpenoid skeleton. Eichlerianic acid was characterised by the absolute configuration (20*S*,24*S*) and shoreic acid by (20*S*,24*R*). Foveolins A and B were correlated with these compounds and published also as (20*S*,24*S*) and (20*S*,24*R*), respectively. ^{13}C NMR analysis of a further stereoisomer of the acids isolated from *Aglaia silvestris* allowed the conclusion that the new isoeichlerianic acid, its methyl ester and the known foveolin B belonged to the new stereochemical series (20*R*,24*S*).

From the root bark extract of *Aglaia silvestris* (M. Roemer) Merrill (Meliaceae) from Thailand a triterpenoid acid (**1**) with the molecular formula $C_{30}H_{50}O_4$ and its methyl ester (**2**) were isolated. First inspection of the ^{1}H and ^{13}C NMR data showed immediately that the acid was a closely related stereoisomer of the 3,4-seco-dammarane type triterpenes shoreic acid (**4**) and eichlerianic acid (**6**).

The first dammaranes characterised by a 20,24-epoxy ring closure were isolated about 30 years ago from different species of *Shorea*[1,2] and from *Cabralea eichleriana*.[3] Later an X-ray analysis was published confirming the 20*S*,24*R* configuration for methyl shoreate.[4] Eichlerianic acid was described as the C-24 epimer of shoreic acid with configuration 20*S*,24*S*. After some confusion, the stereochemistries of the dammaranes ocotillone (**5**) and cabraleone (**7**) were finally correlated with shoreic acid (**4**) and eichlerianic acid (**6**).[4] About 10 years ago similar 20,24-epoxy dammaranes were isolated from *Aglaia foveolata*.[5] Based on NMR arguments (see below) foveolin A (**8**) was assigned to the configuration of \eichlerianic acid (20*S*,24*S*) and foveolin B (**3**) to the stereochemistry of shoreic acid (20*S*,24*R*). The ^{13}C NMR data of Roux et al.[5] were often used as a reference, compare, for example, more recent publications on dammaranes from *Cabralea*[6] or *Aglaia*.[7] However, a thorough analysis of the ^{13}C NMR data of compounds **1** and **2** in comparison with relevant data from literature led to a revision of the stereochemistry of foveolin B (**3**).

The ^{1}H and ^{13}C NMR chemical shift values of the newly isolated acid (**1**) differed clearly from the ones of eichlerianic acid (**6**). Less, but still significant deviations from shoreic acid (**4**) were observed in the vicinity of the stereo centers C-20 and C-24. For the discrimination between the shoreic 20*S*,24*R* and the eichlerianic 20*S*,24*S* series ^{1}H and ^{13}C NMR properties were used in literature. In the ^{1}H NMR of eichlerianic acid the resonance for 24-H appeared as a clear dd with $J = 10/5.5$ Hz, in the case of shoreic acid it was a degenerated dd $J = 7/7$ Hz appearing as a triplet.[5] The same authors postulated a diagnostic ^{13}C chemical shift of ca. 83.2 ppm for 24*R* (shoreic acid) and ca. 86.5 for 24*S* (eichlerianic acid). In the case of compound **1** a slightly broadened triplet for 24-H with $J = 6.8$ Hz was observed. The ^{1}H resonance multiplicity was clearly in favour of a tetrahydrofuran ring conformation (not necessarily absolute configuration!) similar to the one of shoreic acid. The resonance for C-24 was found at 84.3 ppm, differing by 1.1 ppm from the corresponding resonance of shoreic acid. This seemed not dramatically at all, however, two further resonances C-21 and C-22 differed by about 2 ppm. Deviations like that are already significant and prompted us to compare the ^{13}C NMR data of important 20,24-epoxy dammaranes in order to make clear the distinct stereochemical series (Table 1, see also Ref. 8). The known compounds ocotillone (**5**) and cabraleone (**7**) were isolated from *Aglaia oligophylla* Miq.,[9] the data for compounds **3**, **4**, **6** and **8** were taken from Ref. 5.

Table 1 is divided into three groups. Compounds **1**–**3** belong to the newly postulated series, the stereochemistry of which has still to be discussed. Compounds **4** and **5** belong to the shoreic acid

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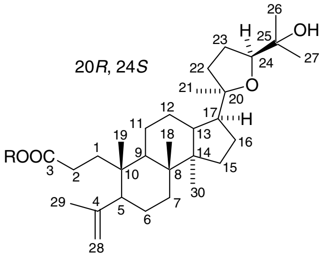
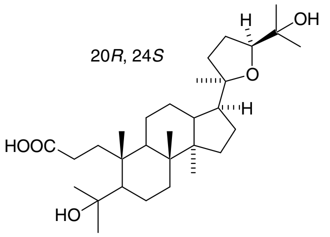
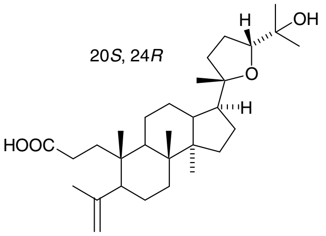
Table 1
^{13}C NMR data of 20,24-epoxydammaranes **1**–**8** (400 MHz, CDCl$_3$, δ/ppm)



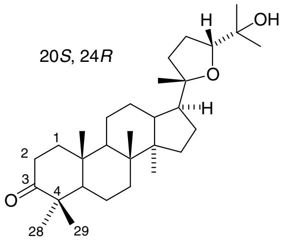
1 R = H isoeichlerianic acid
2 R = CH$_3$ methyl isoeichlerianate



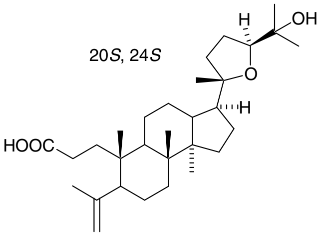
3 foveolin B



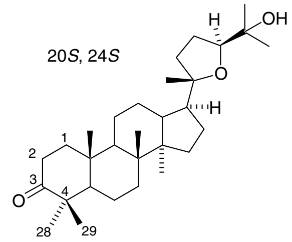
4 shoreic acid



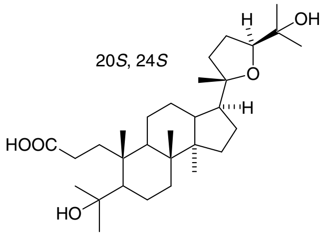
5 ocotillone



6 eichlerianic acid



7 cabraleone



8 foveolin A

No.	20*R*,24*S* (isoeichlerianic type)			20*S*,24*R* (shoreic type)		20*S*,24*S* (eichlerianic type)		
	1	**2**	**3**[5]	**4**[5]	**5**	**6**[5]	**7**	**8**[5]
1	36.1 t	34.5 t	34.9 t	34.0 t	39.9 t	34.1 t	39.9 t	34.7 t
2	31.8 t	28.4 t	27.8 t	28.1 t	34.1 t	28.1 t	34.1 t	29.1 t
3	182.0 s	174.6 s	179.7 s	179.5 s	218.1 s	179.5 s	218.1 s	179.7 s
4	148.1 s	147.6 s	76.8 s	147.2 s	47.4 s	147.3 s	47.4 s	76.5 s
5	50.4 d	50.8 d	53.3 d	50.5 d	55.3 d	49.7 d	55.3 d	49.9 d
6	24.9 t	24.6 t	22.7 t	24.3 t	19.7 t	24.4 t	19.7 t	22.5 t
7	34.0 t	33.9 t	34.9 t	33.6 t	34.6 t	33.7 t	34.6 t	34.7 t
8	40.0 s	40.0 s	40.2 s	39.8 s	40.3 s	39.9 s	40.3 s	40.0 s
9	40.9 d	41.0 d	42.5 d	40.9 d	50.1 d	41.0 d	50.2 d	42.5 d
10	39.1 s	39.1 s	41.5 s	38.8 s	36.9 s	38.9 s	36.9 s	41.2 s
11	22.0 t	22.0 t	21.4 t	22.9 t	22.1 t	22.2 t	22.3 t	21.4 t
12	26.8 t	27.0 t	27.2 t	27.0 t	27.4 t	26.7 t	27.0 t	27.0 t
13	43.1 d	43.0 d	43.2 d	42.7 d	43.1 d	42.8 d	43.0 d	42.9 d
14	50.3 s	50.3 s	50.4 s	50.1 s	50.0 s	50.2 s	50.0 s	50.3 s
15	31.2 t	31.2 t	31.3 t	31.2 t	31.4 t	32.0 t	31.4 t	31.4 t
16	25.8 t	25.8 t	26.0 t	25.4 t	25.7 t	25.6 t	25.8 t	25.8 t
17	50.1 d	50.1 d	51.9 d	49.2 d	49.5 d	49.6 d	49.8 d	49.7 d
18	15.4 q	15.3 q	16.1 q	16.1 q	15.1 q	16.1 q	15.2 q	16.2 q
19	20.4 q	20.2 q	20.7 q	19.9 q	16.0 q	20.0 q	16.1 q	19.7 q
20	86.6 s	86.5 s	86.6 s	86.1 s	86.4 s	86.4 s	86.5 s	86.5 s
21	21.7 q	21.7 q	22.0 q	23.9 q	23.6 q	27.0 q	27.2 q	27.0 q
22	37.0 t	37.5 t	37.5 t	35.5 t	35.7 t	34.6 t	34.8 t	34.8 t
23	26.0 t	25.8 t	26.0 t	25.9 t	26.1 t	26.2 t	26.4 t	26.4 t
24	84.3 d	84.5 d	84.5 d	83.1 d	83.3 d	86.2 d	86.4 d	86.3 d
25	71.4 s	71.1 s	71.6 s	71.4 s	71.4 s	70.2 s	70.3 s	70.3 s
26	27.6 q	27.7 q	27.8 q	27.1 q	27.5 q	27.6 q	27.8 q	27.7 q
27	23.9 q	24.3 q	24.5 q	24.3 q	24.3 q	23.9 q	24.1 q	24.2 q
28	113.0 t	113.4 t	34.6 q	113.2 t	26.7 q	113.3 t	26.6 q	34.2 q
29	23.7 q	23.3 q	27.4 q	23.2 q	21.0 q	23.1 q	21.0 q	27.4 q
30	16.5 q	16.0 q	15.5 q	15.0 q	16.4 q	15.2 q	16.3 q	15.3 q
Ester Me		51.6 q						

series 20*S*,24*R*, and **6**–**8** to the eichlerianic acid series 20*S*,24*S*. Interestingly enough, the ^{13}C chemical shifts of compound **1** in the stereochemically variable region of the tetrahydrofurofuran ring were almost identical with the corresponding data of foveolin B and differed systematically from the shoreic acid group. This implied that **1**, its methyl ester **2**, and foveolin B (**3**, Ref. 5) possess (i) the same stereochemistries, and (ii) the stereochemistries differ from the one of shoreic acid. However, foveolin B was originally described as 20*S*,24*R* like shoreic acid.[5] The arguments were based on the multiplicity of 24-H which was identical with shoreic acid and on the ^{13}C chemical shift of C-24 close to the value of 83.2 ppm which was considered to indicate 24*R* configuration. The ^{13}C chemical shifts of the newly postulated series **1**–**3** (including foveolin B) were 84.3-84.5, a small, but significant difference to 83.2. Further, the ^{13}C data for the methyl group C-21 and the neighbouring methylene group C-22 (both close to the stereochemically interesting C-20) differed systematically by ca. 2 ppm. The shift values for C-21 were 21.7-22.0 ppm for the postulated isoeichlerianic acid type (**1**–**3**), 23.6/23.9 for the shoreic acid type (**4**, **5**), and 27.0–27.2 for the eichlerianic type series (**6**–**8**). The corresponding values of C-22 were 37.0–37.5 (**1**–**3**), 35.5/35.7 (**4**/**5**) and 34.6–34.8 (**6**–**8**).

Comparisons within Table 1 clearly show that the data of **1**–**3** do neither match the ones of eichlerianic acid nor the ones of shoreic acid. There are some similarities between the series **1**–**3** and the shoreic acid series **4**/**5**. This includes the ^{1}H coupling pattern of 24-H (degenerated dd appearing as a t) and the only slightly different ^{13}C chemical shift of C-24. The most significant differences between **1**–**3** and **4**/**5** were observed for the chemical shifts of C-21 and C-22. This allows the conclusion that the stereochemistry at C-20 is different compared to shoreic acid. Compounds **1**–**3** should therefore possess 20*R* configuration with the methyl group 21 pointing downwards in the formula presentations (α Me-21). A strong Me-21↔24-H cross peak in the NOESY spectrum proves that 24-H is in α-position as well. The epoxide stereochemistry is therefore 20*R*,24*S*. This assumption explains all experimental findings. The conformation of the oxygen 5-ring in the case of 20*R*,24*S* configuration (isoeichlerianic acid) should be very similar to the one of shoreic acid 20*S*,24*R*. In both cases the bulky substituents, the polycyclic core of the triterpenoid rest at C-20 and the hydroxyisopropyl substituent at C-24 should adopt pseudo-equatorial positions in the typical envelope conformation of the oxygen-five-ring. This means that the less space demanding substituents methyl-21 and the proton at C-24 should occupy pseudo axial positions. This is supported by the strong NOESY cross peaks between 21-H_3 and 24-H in the case of shoreic and isoeichlerianic acid. The topology of the five ring in both series should be almost the same, the influence of the polycyclic bulk is rather low in the region near to C-24. This explains the identical ^{1}H coupling pattern for 24-H with the neighbouring 23-H_2 and the small (but still significant) difference in the ^{13}C chemical shift of C-24.

Based on the arguments outlined above we postulate 20*R*,24*S* configuration for the new compounds **1** and **2**. They were named isoeichlerianic acid (**1**) and methyl isoeichlerianate (**2**) since they are C-20 epimers of eichlerianic acid (**6**, 20*S*,24*S*). Foveolin B (**3**), previously described as 20*S*,24*R*[5,7] belongs also to the new series 20*R*,24*S*.

Structure elucidations of **1** and **2** were accomplished by extensive use of 2D NMR methods like HH-COSY, NOESY, HMQC and HMBC. Especially the long range contacts (HMBC) of the 7 methyl groups proved to be very efficient to assign the resonances of the bulk of the molecule. All expected contacts 18→8,7,9,14; 19→10,1,5,9; 21→20,17,22; 26→25,24,27; 27→25,24,26; 28→4,5,29; 29→4,5,28; and 30→14,8,13,15 showed rather strong cross peaks.

The plant material was collected in Khao Chong, Trang, south Thailand (February 1999). Voucher specimens (HG 719) are deposited at the Herbarium of the Institute of Botany, University of Vienna (WU), identified by Dr. Caroline M. Pannell, University of Oxford, UK. Dried root bark, 30 g, was ground and extracted with MeOH at room temperature for 3 days, filtered and concentrated. The $CHCl_3$ fraction (2000 mg) from the aqueous solution was evaporated to dryness under reduced pressure and roughly separated by column chromatography (Merk silica gel 60, 35–70 mesh) with increasing polarity of hexane, EtOAc and MeOH. The fraction eluted with 50% hexane in EtOAc (200 mg) was further separated by repeated MPLC (440 × 37 mm column, Merck LiChroprep Si 60, 40–63 μm) with 30% EtOAc in hexane to yield 15 mg of isoeichlerianic acid (**1**), $[\alpha]_D^{20}$ +28 (*c* 0.4, $CHCl_3$). The fraction eluted with 70% hexane in EtOAc (250 mg) was further separated by preparative MPLC starting with 5% EtOAc in hexane followed by preparative TLC (Merk silica gel 60, F_{254}) with 70% hexane in Et_2O to yield 4.5 mg of methyl isoeichlerianate (**2**), $[\alpha]_D^{20}$ +19 (*c* 0.3, $CHCl_3$).

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