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Edulisones A and B, two epimeric benzo[*b*]oxepine derivatives from the bark of *Aglaia edulis*

Soyoung Kim,[a,b] Bao-Ning Su,[b] Soedarsono Riswan,[c] Leonardus B. S. Kardono,[d] Johar J. Afriastini,[c] Judith C. Gallucci,[e] Heebyung Chai,[a,b] Norman R. Farnsworth,[a] Geoffrey A. Cordell,[a] Steven M. Swanson[a] and A. Douglas Kinghorn[b,*]

[a]*Program for Collaborative Research in the Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, USA*
[b]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*
[c]*Herbarium Bogoriense, Research and Development Center for Biology, Indonesian Institute of Science, 16122 Bogor, Indonesia*
[d]*Research and Development Chemistry, Indonesian Institute of Science, Serpong, 15310 Tangerang, Indonesia*
[e]*Department of Chemistry, The Ohio State University, Columbus, OH 43210, USA*

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Abstract—Two benzo[*b*]oxepine derivatives, edulisones A (**1**) and B (**2**), were isolated from the bark of *Aglaia edulis*, collected in Indonesia. The relative stereochemistry of **1** was determined by single-crystal X-ray diffraction analysis. Treatment of compounds **1** and **2** with lithium hydroxide produced the same hydrolysis products, **1a** and **1b**, as a result of cleavage of the pyrrolidine ring to an alkylated amide mixture in each case, which demonstrated that these substances are epimeric at their 2-aminopyrrolidine moiety.

Since the first cyclopenta[*b*]benzofuran derivative, rocaglamide, was isolated from *Aglaia elliptifolia* in 1982,[1] many other representatives of this interesting group of secondary metabolites have been obtained from plants of the genus *Aglaia* (Meliaceae).[2] These compounds exhibit both potent insecticidal activity[2,3] and cytotoxicity against human cancer cell lines.[4,5] In addition to the cyclopenta[*b*]benzofurans, two structurally related groups of constituents, the benzo[*b*]oxepines and benzo[*b*]pyrans, are also considered as characteristic compounds of the genus *Aglaia*.[2] Most of these benzo[*b*]oxepines and benzo[*b*]pyrans have been reported to possess a 2-aminopyrrolidine moiety as a side chain.[3,6–9] However, the determination of the configuration of the 2-aminopyrrolidine moiety of these compounds is quite challenging. For several compounds in this series, the stereochemistry of this substituent has been left unresolved[3,8] or has been determined tentatively as *R* or *S* on the basis of NOESY correlations.[7,9]

Thus far, the structure and stereochemistry of only one *Aglaia* benzo[*b*]oxepine has been supported by X-ray crystallography, namely, forbaglin A.[6] In the present study, edulisones A (**1**) and B (**2**), two new benzo[*b*]oxepine derivatives possessing a 2-aminopyrrolidine side chain were isolated from the bark of *Aglaia edulis* (Roxb.) Wall. collected in Indonesia.[10] By interpretation of their HRMS and NMR spectroscopic data, edulisones A (**1**) and B (**2**) were suggested to be C-13 epimers at their respective 2-aminopyrrolidine moiety. The structures and relative stereochemistry of these two new compounds were determined by single-crystal X-ray analysis of **1**, and by alkaline hydrolysis of both **1** and **2**, from which unusual ring cleavage products were obtained and characterized.

The MeOH extract of the bark of *Aglaia edulis* was partitionated in turn with *n*-hexane and chloroform against water. Edulisones A (**1**)[11] and B (**2**)[12] were isolated from the chloroform-soluble partition by open silica gel column chromatography and HPLC.

Compound **1** was obtained as colorless needles, mp 215–218 °C, $[\alpha]_D^{20}$ +55 (*c* 0.2, $CHCl_3$). Its HRESIMS

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* Corresponding author. Tel.: +1 614 247 8094; fax: +1 614 247 8642; e-mail: kinghorn.4@osu.edu

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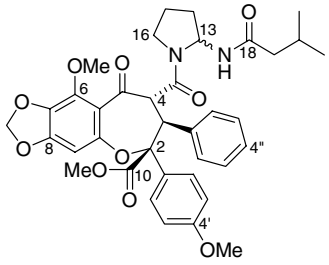
Table 1. NMR spectroscopic data of compounds **1**, **2**, **1a**, and **1b** in CD_3OD[a]

Position	**1**		**2**		**1a**		**1b**	
	δ_C	δ_H (J Hz)	δ_C	δ_H (J Hz)	δ_C	δ_H (J Hz)	δ_C	δ_H (J Hz)
1a	155.2		156.7		155.7		155.8	
2	92.2		92.1		92.3		92.4	
3	51.6	5.23 d (9.4)	53.3	4.97 d (10.3)	52.0	5.00 d (10.4)	52.0	5.01 d (10.3)
4	65.8	4.75 d (9.4)	64.3	4.74 d (10.3)	67.2	4.33 d (10.4)	67.3	4.33 d (10.3)
5	194.7		191.8		193.8		194.1	
5a	118.7		118.4		118.9		118.8	
6	142.2		142.6		142.5		142.6	
7	134.4		135.2		135.0		134.8	
8	154.5		154.1		154.1		154.1	
9	98.7	6.69 s	100.0	6.69 s	99.5	6.66 s	99.4	6.67 s
10	172.0		172.0		172.3		172.3	
11	168.8		169.0		169.2		169.2	
13	64.2	5.28 d (4.6)	63.9	5.30 d (4.9)	39.9	3.00–3.03 m	39.9	3.08 m, 2.97 m
14	34.6	1.94 m, 1.66 m	35.1	1.30 m	25.8	1.30 m	25.6	1.30 m
15	22.1	1.89 m	22.5	1.84 m	32.8	1.40–1.29 m	32.7	1.43 m, 1.30 m
16	47.1	3.38 m	47.2	3.46 m, 3.12 m	81.9	4.88 m	82.0	4.88 m
18	174.2		174.0		176.0		176.2	
19	46.0	1.94 m, 1.77 m	45.6	1.65 m, 1.40 m	46.4	2.07 m	46.5	2.12 m
20	27.4	1.91 m	27.0	1.62 m	27.3	2.05 m	27.3	2.09 m
21	23.1	0.84 d (6.2)	23.1	0.78 d (6.5)	22.8	0.96 d (6.0)	22.9	0.97 d (6.2)
22	22.5	0.88 d (6.3)	22.2	0.75 d (6.4)	22.8	0.94 d (5.4)	22.9	0.96 d (6.2)
1′	128.2		128.4		128.3		128.4	
2′,6′	130.7	7.31 d (8.7)	130.6	7.33 d (8.8)	130.7	7.34 d (8.9)	130.8	7.34 d (8.9)
3′,5′	114.8	6.74 d (8.9)	114.7	6.75 d (8.9)	114.7	6.76 d (9.0)	114.8	6.76 d (8.9)
4′	161.5		161.4		161.4		161.5	
1″	141.3		140.8		140.8		140.9	
2″,6″	131.0	7.55 m	130.8	7.66 br d (8.9)	130.6	7.54 br d (6.8)	130.7	7.55 br d (7.0)
			129.4	7.21–7.32 m				
3″,5″	129.3	7.27 m	129.0	7.21–7.32 m	129.3	7.28 m	129.3	7.28 m
4″	128.8	7.27 m	129.3	7.21–7.32 m	128.9	7.28 m	128.9	7.28 m
MeO-6	61.0	3.81 s	61.3	3.67 s	61.2	3.73 s	61.2	3.73 s
MeO-10	52.7	3.12 s	52.6	3.01 s	52.6	3.11 s	52.7	3.11 s
MeO-16					55.7	3.24 s	55.8	3.24 s
MeO-4′	55.7	3.72 s	55.7	3.71 s	55.7	3.70 s	55.8	3.72 s
OCH_2O	103.5	6.01 s	103.5	5.95 s	103.6	5.98 s	103.6	5.98 s
		5.96 s		5.92 s		5.93 s		5.93 s

[a] ^1H and ^{13}C NMR spectra were acquired at 400 and 100 MHz, respectively; TMS was used as internal standard; assignments are based on ^1H–^1H COSY, HMQC, HMBC, and NOESY spectra.

exhibited a sodiated molecular ion peak at m/z 695.2554, consistent with a molecular formula of $C_{37}H_{40}N_2O_{10}$. The ^1H NMR spectroscopic data of compound **1** in CD_3OD (Table 1) showed characteristic signals for three methoxy groups at δ_H 3.81 (3H, s, MeO-6), 3.72 (3H, s, MeO-4′), and 3.12 (3H, s, MeO-10), for a *para*-substituted aromatic ring at δ_H 7.31 (2H, d, $J = 8.7$ Hz, H-2′,6′), and 6.74 (2H, $J = 8.9$ Hz, H-3′,5′), and for a mono-substituted aromatic ring at δ_H 7.55 (2H, m, H-2″,6″) and 7.27 (3H, m, H-3″,4″,5″). In addition, resonances for a methine pair appeared at δ_H 5.23 (1H, d, $J = 9.4$ Hz, H-3) and 4.75 (1H, d, $J = 9.4$ Hz, H-4), and were mutually coupled in the ^1H–^1H COSY spectrum. Based on the observed HMQC correlations, these two signals were found to correspond to the ^{13}C NMR signals at δ_C 51.6 (C-3) and 65.8 (C-4), respectively. Characteristic signals of a pyrrolidine-type bisamide unit in **1** were apparent, with two carbonyl groups at δ_C 168.8 (C-11) and 174.2 (C-18). The ^{13}C NMR spectrum of **1** also exhibited a conjugated keto signal at δ_C 194.7 (C-5). All the above-mentioned NMR observations suggested that compound **1** is a benzo[*b*]oxepine derivative



1 13*R*
2 13*S*

Figure 1. Structures of compounds **1** and **2**.

containing a bisamide side chain (Fig. 1).[6,7] HMBC correlations from two methine protons, δ_H 5.23 (H-3) and 4.75 (H-4), to δ_C 168.8 (C-11), and from the proton at δ_H 5.23 (H-3) to δ_C 131.0 (C-2″,6″) of the monosubstituted aromatic ring, indicated that the locations of the pyrrolidine-type bisamide unit and the aromatic ring are at C-4 and C-3, respectively (Fig. 2a). NOESY

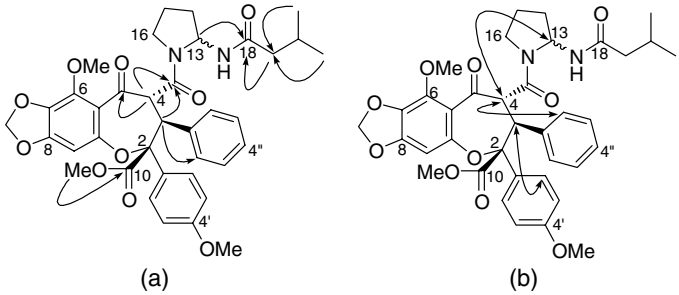


Figure 2. Selected (a) HMBC and (b) NOESY correlations of compounds **1** and **2** (CD_3OD).

NMR correlations were used to establish the relative configurations at all chiral centers in **1** except for C-13 (Fig. 2b).

Compound **2**, $[\alpha]_D^{20}$ +48.5 (*c* 0.2, $CHCl_3$), was isolated as an amorphous powder. A molecular formula of $C_{37}H_{40}N_2O_{10}$, the same as that of **1**, was determined for **2** by HRESIMS. Both the ^1H and ^{13}C NMR spectroscopic data of compound **2** (Table 1) were closely comparable to those of **1**, and suggested this to be also a benzo[*b*]oxepine derivative possessing a pyrrolidine-type bisamide side chain. The gross structure of compound **2** was assigned as being the same as that of compound **1**, based on the observed correlations in its 2D ^1H–^1H COSY, HMQC, and HMBC spectra. The chemical shifts of H-3, H-4, C-3, and C-4 of **1** and **2** (Table 1) were very similar. This information, in combination with the observed NOESY correlations from H-3 to H-2′ and H-6′, and from H-4 to H-2″ and H-6″ (Fig. 2b), was used to establish that the configurations of C-2, C-3, and C-4 of **2** are the same as those of **1**. Therefore, edulisone B (**2**) is the C-13 epimer of edulisone A (**1**).

The configuration at C-13 of several previously reported benzo[*b*]oxepine derivatives has been proposed based on certain NOESY correlations (e.g., H-20,21/H-2″,6″ for 13*R*, and H-22/MeO-6 for 13*S*).[6,7] However, in the present study, NOESY cross peaks H-21/H-2″,6″ and H-22/MeO-6 were not observed for either compound **1** or **2**, possibly due to the free rotation of their respective bisamide side chain. Accordingly, a suitable single crystal was obtained for one of the epimers, edulisone A (**1**), and X-ray crystallographic analysis was used to establish its relative stereochemistry at C-13 as *R* (Fig. 3).[13] Thus, compound **2** could be assigned with the 13*S* configuration. To confirm this, compounds **1** and **2** were separately hydrolyzed under the same conditions, by refluxing for 4 h in MeOH–1 N LiOH (1:1). Both edulisones A (**1**) and B (**2**) gave the same hydrolysis products, **1a** and **1b** (Fig. 4 and Table 1), which confirmed that the parent compounds are epimeric isomers with different configurations at C-13 in their side chain.

As shown in Table 1, most of ^1H and ^{13}C NMR spectroscopic data of **1** and **2** are very similar. However, several protons close to the epimeric site (C-13) of these two compounds have different ^1H NMR chemical shifts. For example, H-14a and H-14b of the 13*R* epimer (**1**)

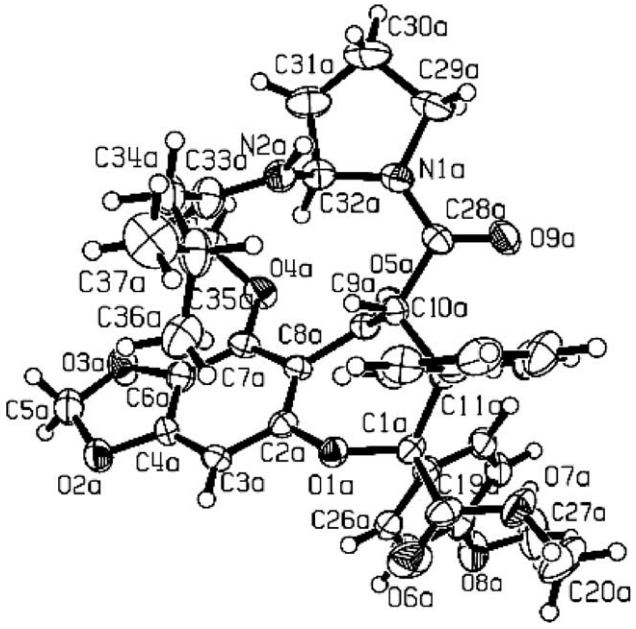
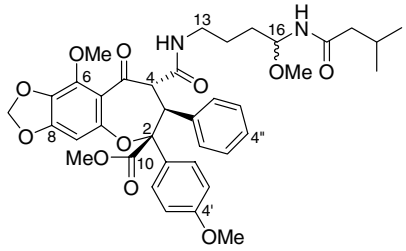


Figure 3. ORTEP plot of the X-ray crystallographic structure of compound **1**.



1a (16*S* or 16*R*)

1b (16*R* or 16*S*)

Figure 4. Structures of compounds **1a** and **1b**.

were displayed at δ_H 1.94 and 1.66, respectively, while these two protons in the 13*S* epimer (**2**) were overlapped in a relatively upfield region at δ_H 1.30. Similarly, H-16a and H-16b of **1** were almost magnetically equivalent and showed an overlapping signal at δ_H 3.38, while these two protons of **2** were separately displayed at δ_H 3.46 and 3.12, respectively. The relative stereochemistry of the pyrrolidine-type bisamide side chains of other structurally

similar benzo[*b*]oxepine derivatives may thus be assigned by comparison of their ^{1}H NMR data with those of edulisones A (**1**) and B (**2**), described herein.

The cytotoxic activities of compounds **1** and **2** were evaluated in a small panel of human cancer cell lines, but neither compound exhibited discernible activity.[14]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.107.

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10. The bark of *Aglaia edulis* was collected in October, 2001 from Senaru village, Bayan District, West Lombok Island, Indonesia. A voucher specimen has been deposited at the Herbarium Bogoriense, Bogor, Indonesia, and Research Center for Chemistry, Indonesian Institute of Science, Serpong, Tangerang, Indonesia (collection number SR-022), and at the University of Illinois Pharmacognosy Field Station, Downers Grove, Illinois, USA (assession number A5242).
11. Physical data for edulisone A (**1**) {(+)-(2*R*)-1-[(2*R*,3*S*,4*R*)-2,3,4,5-tetrahydro-2-methoxycarbonyl-2-(4-methoxyphenyl)-6-methoxy-7,8-methylenedioxy-5-oxo-3-phenyl-1-benzoxepine-4-carbonyl]-2-(3-methylbutanoylamino)-pyrrolidine}: colorless needles, mp 215–218 °C; $[\alpha]_D^{20}$ +55 (*c* 0.2, $CHCl_3$), UV (EtOH) λ_{max} (log ε) 208 (4.20), 278 (3.47), 329 (3.06) nm; IR (film) ν_{max} 3343, 2956, 1758, 1673, 1471, 1256, 1105 cm^{-1}; HRESIMS *m*/*z* 695.2554 $[M+Na]^+$ (calcd for $C_{37}H_{40}N_2O_{10}Na$, 695.2575); ^{1}H and ^{13}C NMR, see Table 1.
12. Physical data for edulisone B (**2**) {(+)-(2*S*)-1-[(2*R*,3*S*,4*R*)-2,3,4,5-tetrahydro-2-methoxycarbonyl-2-(4-methoxyphenyl)-6-methoxy-7,8-methylenedioxy-5-oxo-3-phenyl-1-benzoxepine-4-carbonyl]-2-(3-methylbutanoylamino)-pyrrolidine}: an amorphous powder; $[\alpha]_D^{20}$ +48.5 (*c* 0.2, $CHCl_3$), UV (EtOH) λ_{max} (log ε) 212 (4.31), 277 (3.72), 332 (3.33) nm; IR (film) ν_{max} 3443, 2956, 1758, 1626, 1471, 1227, 1103 cm^{-1}; HRESIMS *m*/*z* 695.2585 $[M+Na]^+$ (calcd for $C_{37}H_{40}N_2O_{10}Na$, 695.2575); ^{1}H and ^{13}C NMR, see Table 1.
13. Crystal data for edulisone A (**1**): Compound **1** was recrystallized from MeOH–H_2O (~2:3). $2(C_{37}H_{40}N_2O_{10})+H_2O$; $M_r = 1363.44$; Crystal size $0.12 \times 0.27 \times 0.31$ mm^3; monoclinic, space group $P2_1$, $a = 10.692(2)$ Å, $b = 13.987(2)$ Å, $c = 23.208(4)$ Å, $\beta = 97.450(6)°$, $V = 3441.4(10)$ Å^3, $Z = 2$, $D_{calcd} = 1.316$ Mg/m^3, $\lambda = 0.71073$ Å, $\mu = 0.097$ mm^{-1}, $F(000) = 1444$, $T = 150(2)$ K. The structure was solved by the direct methods procedure in SHELXD[15,16] and full matrix least-squares refinements based on F^2 were performed in SHELXL-97,[17] as incorporated in the WinGX package.[18] There are two molecules in the asymmetric unit, which are labeled as A and B. There is also a water molecule disordered over two sites. The final refinement cycle was based on 8885 intensities and 901 variables and resulted in agreement factors of $R1(F) = 0.0488$ and $wR2(F^2) = 0.0956$. For the subset of data with $I > 2\sigma(I)$, the $R1(F)$ value is 0.0379 for 7697 reflections. The final difference electron density map contains maximum and minimum peak heights of 0.164 and −0.199 e/Å^3. These data have been deposited (CCDC 284779) at the Cambridge Crystallographic Data Centre, Cambridge, UK. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail deposit@ccdc.cam.ac.uk].
14. Performed according to standard protocols: Seo, E.-K.; Kim, N.-C.; Mi, Q.; Chai, H.; Wall, M. E.; Wani, M. C.; Navarro, H. A.; Burgess, J. P.; Graham, J. G.; Cabieses, F.; Tan, G. T.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1483–1485. The ED_{50} values (μg/mL) of compounds **1** and **2** were >5 μg/mL for all the tested cell lines: (Lu1 = human lung cancer; LNCaP = hormone-dependent human prostate cancer; MCF-7 = hormone-dependent human breast cancer; HUVEC = human umbilical vein endothelial cells).
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