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Revision of the Structures of Citrifolinin A, Citrifolinoside, Yopaaoside A, Yopaaoside B, and Morindacin, Iridoids from *Morinda citrifolia* L. and *Morinda coreia* Ham.

Jan Schripsema,*[†,‡] Geisa P. Caprini,[†] and Denise Dagnino[§]

Grupo Metabolômica, Laboratório de Ciências Químicas, Centro de Ciência e Tecnologia, Universidade Estadual do Norte Fluminense, Av. Alberto Lamego 2000, Campos dos Goytacazes, RJ BR-28015-620, Brazil, Laboratório de Biotecnologia, Centro de Biociências e Biotecnologia, Universidade Estadual do Norte Fluminense, Av. Alberto Lamego 2000, Campos dos Goytacazes, RJ BR-28015-620, Brazil, and Department of Analytical Biotechnology, Technical University Delft, Julianalaan 67, 2628 BC Delft, The Netherlands

jan@uenf.br

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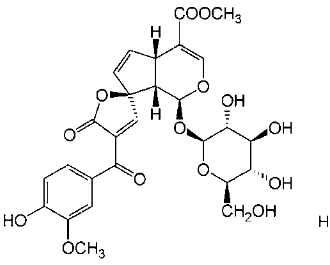
ABSTRACT



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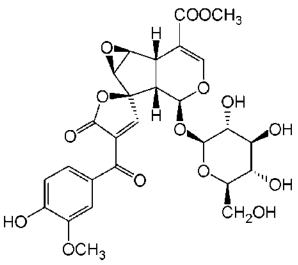

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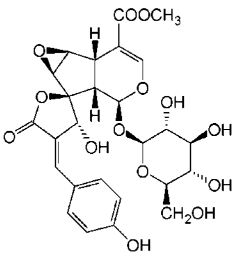

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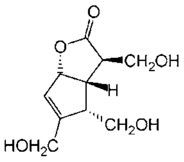

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Citrifolin A was revised to dehydromethoxygaertneroside (2). Citrifolinoside and yopaaoside A were found to be identical, and their structures were revised to the new structure dehydroepoxymethoxygaertneroside (5). Yopaaoside B was revised to citrifolinoside A (9), and morindacin was revised to borreriagenin (11).

In our recent investigation of *Pentas lanceolata* (Forssk.) Deflers, a plant from the family Rubiaceae, a number of iridoid glucosides were isolated with structures similar to those found in *Morinda* species. Especially *M. citrifolia*, a plant originating from Southeast Asia, has been quite well studied because it is extensively cultivated for its fruits (Noni).[1] A thorough investigation of the literature data of the iridoids from *Morinda* revealed that the structures from citrifolinin A (**1**),[2] citrifolinoside (**3**),[3] yopaaoside A (**4**),[4] yopaaoside B (**6**),[4] and morindacin (**10**)[5] would need to berevised. Citrifolinin A was found to be identical to dehydromethoxygaertneroside (**2**)).[6] Citrifolinoside was found to be identical to yopaaoside A; however, the configuration

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[†] Laboratório de Ciências Quimicas, UENF.
[‡] Department of Analytical Biotechnology, TU Delft.
[§] Laboratório de Biotecnologia, UENF.

[1] Chan-Blanco, Y.; Vaillant, F.; Perez, A. M.; Reynes, M.; Brillouet, J.-M.; Brat, P. *J. Food Comp. Anal.* **2006**, *19*, 645.

[2] Sang, S.; He, K.; Liu, G.; Zhu, N.; Wang, M.; Jhoo, J.-W.; Zheng, Q.; Dong, Z.; Ghai, G.; Rosen, R. T.; Ho, C.-T. *Tetrahedron Lett.* **2001**, *42*, 1823.

[3] Sang, S.; He, K.; Liu, G.; Zhu, N.; Cheng, X.; Wang, M.; Zheng, Q.; Dong, Z.; Ghai, G.; Rosen, R. T.; Ho, C.-T. *Org. Lett.* **2001**, *3*, 1307.

[4] Kanchanapoom, T.; Kasai, R.; Yamasaki, K. *Phytochemistry* **2002**, *59*, 551.

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of the C-8 of yopaaoside A was incorrectly assigned and both structures were revised to the new structure dehydroepoxymethoxygaertneroside (**5**). Also, in yopaaoside B (**8**), the configuration of C-8 should be inverted, and the compound was shown to be identical to citrifolinoside A (**9**).[7] Morindacin (**10**), an iridoid aglycone recently isolated from *M. citrifolia*,[5] was found to be identical to borreriagenin (**11**).[8]

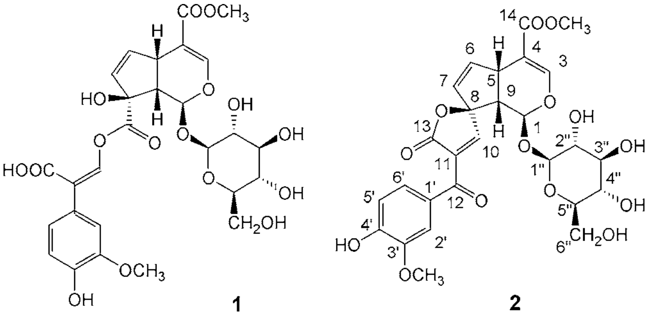

Figure 1. Citrifolinin A (**1**) was revised to dehydromethoxygaertneroside (**2**).

Citrifolinin A (Figure 1) (**1**) and citrifolinoside (**3**) were presented in separate papers as being new unusual iridoids, with a rearranged ferulic acid moiety.[2,3] Careful examination of the reported data revealed a number of inconsistencies. The ^{13}C chemical shift of δ 187.0 for C-9″, the carbon of a carboxylic acid, was high; in fact, even supposing the presence of a hydrogen bond, this chemical shift is outside the expected range. The two four-bond HMBC correlations, which should be present between C-9″ and both H-2″ and H-6″ are also remarkable. It is not common to see such correlations. Furthermore, during acetylation the hydroxyl which is supposed to be present at C-8 was not acetylated. It seemed improbable that the proposed weak intramolecular H-bond could avoid this.

The comparison with the literature data (Table 1) did show that the NMR data of citrifolinin A are essentially identical to those of dehydromethoxygaertneroside (**2**), an iridoid glucoside from *M. morindoides*.[6] This structure takes away all the inconsistencies mentioned above, and the δ 187.0 carbon should be a ketone, explaining much better the high chemical shift. The reported HMBC correlations are now all two- or three-bond correlations, and furthermore, the oxygen at C-8 forms part of a lactone ring, explaining its impossibility to be acetylated. The rather constant deviation of the ^{13}C NMR values of about 1.1 ppm must be explained by the incorrect setting of the internal standard value by Sang et al.[2]

Table 1. Comparison of the ^{13}C NMR Spectra Reported for Citrifolinin A (**1**) and Dehydromethoxygaertneroside (**2**)[a]

C	citrifolinin A (**1**)	dehydromethoxygaertneroside (**2**)	difference (**2** − **1**)
1	92.6	94.05	1.45
3	151.2	152.48	1.28
4	109.9	111.09	1.19
5	39.2	40.62	1.42
6	141.8	142.35	0.55
7	128.3	129.12	0.82
8	96.7	97.79	1.09
9	50.2	51.40	1.20
10	158.1	159.00	0.90
11	130.5	131.62	1.12
12	169.0	169.96	0.96
13	187.0	188.11	1.11
14	167.0	168.32	1.32
1′	128.1	128.74	0.64
2′	111.6	112.63	1.03
3′	146.1	149.75	3.65
4′	153.8	155.50	1.70
5′	115.2	116.91	1.71
6′	125.9	127.26	1.36
1″	98.9	100.02	1.12
2″	73.8	74.59	0.79
3″	76.8	77.75	0.95
4″	70.7	71.65	0.95
5″	77.8	78.70	0.90
6″	61.9	62.87	0.97
3′-OMe	55.4	56.47	1.07
COOMe	51.0	51.97	0.97

[a] The numbering of **1** was adapted.

The only remaining doubt could be the mass found by APCI-MS for citrifolinin A of *m/z* 609, but the lack of additional data indicates that this might have been a presupposed mass supported by some experimental peak.

The NMR data of citrifolinoside (**3**) were found to be identical to those of yopaaoside A (**4**)[4] (Table 2, Figure 2), considering again the about 1.1 ppm deviation of the ^{13}C values reported by Sang et al.[3] Remarkable about the structure of yopaaoside A (**4**) in relation to dehydromethoxygaertneroside (**2**) is the opposite stereochemistry at C-8. Also, for citrifolinoside (**3**), a stereochemistry opposite to that for citrifolinin A was reported.[3] Both Sang et al.[3] and Kancha-

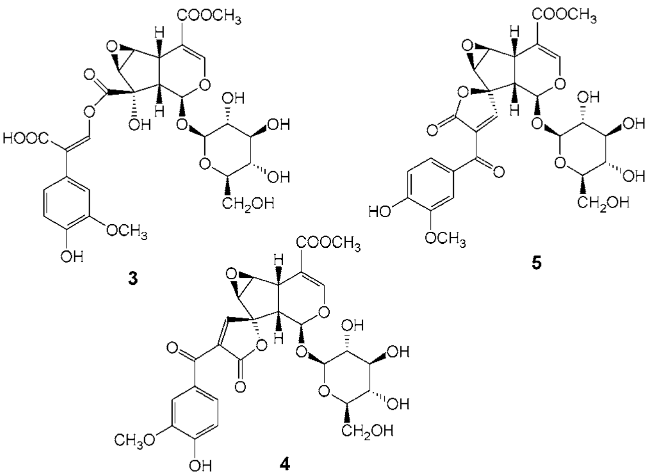

Figure 2. Citrifolinoside (**3**) and yopaaoside A (**4**) were revised to dehydroepoxymethoxygaertneroside (**5**).

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(5) Kamiya, K.; Tanaka, Y.; Endang, H.; Umar, M.; Satake, T. *Chem. Pharm. Bull.* **2005**, *53*, 1597.

(6) Cimanga, K.; Hermans, N.; Apers, S.; Van Miert, S.; Van den Heuvel, H.; Claeys, M.; Pieters, L.; Vlietinck, A. *J. Nat. Prod.* **2003**, *66*, 97.

(7) Sang, S.; Cheng, X.; Zhu, N.; Wang, M.; Jhoo, J.-W.; Stark, R. E.; Badmaev, V.; Ghai, G.; Rosen, R. T.; Ho, C.-T. *J. Nat. Prod.* **2001**, *64*, 799.

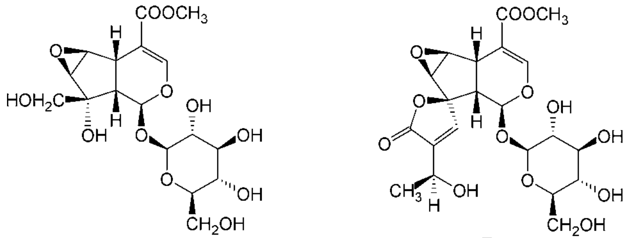
(8) Vieira, I. J. C.; Mathias, L.; Braz-Filho, R.; Schripsema, J. *Org. Lett.* **1999**, *1*, 1169.

Table 2. Comparison of the ^{13}C NMR Spectra (CD_3OD) Reported for Citrifolinoside (**3**) and Yopaaoside A (**4**) with the Spectrum Calculated for Dehydroepoxymethoxygaertneroside (**5**)

C	citrifolinoside **3**	yopaaoside A **4**	difference (**4** − **3**)	calcd[a] **5**
1	91.9	92.7	0.8	93.1
3	152.4	153.6	1.2	154.0
4	107.2	108.5	1.3	108.3
5	31.9	33.1	1.2	32.8
6	57.0	58.0	1.0	57.1
7	58.1	59.2	1.1	60.2
8	91.9	92.7	0.8	92.7
9	43.6	44.2	0.6	44.6
10	155.6	156.2	0.6	155.9
11	127.9	129.1	1.2	128.6
12	169.2	169.3	0.1	169.4
13	186.4	187.7	1.3	188.2
14	167.0	167.8	0.8	167.9
1′	132.6	133.9	1.3	134.8
2′	111.9	113.0	1.1	112.6
3′	148.0	149.2	1.2	149.8
4′	154.0	154.8	0.8	155.5
5′	115.6	116.2	0.6	116.9
6′	125.7	126.8	1.1	127.3
1″	98.2	99.6	1.4	100.0
2″	73.9	74.4	0.5	74.3
3″	76.9	77.8	0.9	77.6
4″	70.2	71.5	1.3	71.7
5″	77.7	78.5	0.8	78.8
6″	61.9	62.7	0.8	62.6
3′-OMe	55.3	56.5	1.2	56.5
COOMe	51.0	52.1	1.1	52.1

[a] The ^{13}C NMR spectrum from **5** was calculated by adding the shifts on carbons 1−14 and 1″−6″, due to the introduction of the 6*β*,7*β*-epoxy group in plumieride, to the ^{13}C NMR spectrum of **2**.

napoom et al.[4] based their assignment of the C-8 configuration on the low ^{13}C chemical shift of C-9, such as that observed in 6*β*,7*β*-epoxysplendoside (**6**).[9,10] However, a much better model compound would be plumiepoxide (**7**) (Figure 3).[11] By comparison with plumieride, the effect of the 6*β*,7*β*-epoxy group can be seen in a compound with a spiro-lactone ring at C-8.

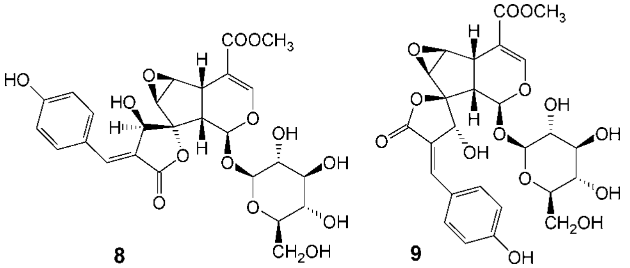


6 **7**

Figure 3. 6*β*,7*β*-Epoxysplendoside (**6**) and plumiepoxide (**7**).

After calculation of the shifts of the individual carbons due to the 6*β*,7*β*-epoxy group, these were used to calculate the ^{13}C NMR spectrum of dehydroepoxymethoxygaertneroside (**5**), an iridoid glucoside not reported before, starting from the spectrum of **2** (Table 2). The calculated spectrum is nearly identical to the spectra of **3** and **4**, thus showing that C-10 should be in an α-configuration relative to C-8, as depicted in **5**.

As additional proof, a NOESY spectrum was recorded for epoxygaertneroside obtained from *Pentas lanceolata*. This compound was previously reported from *M. morindoides*.[6] In the NOESY spectrum, H-10 did show a strong correlation with H-1 and H-7, thus leaving no doubt about the stereochemistry at C-8. Both citrifolinoside and yopaaoside A thus need to have their structure revised to the new structure dehydroepoxymethoxygaertneroside (**5**).



8 **9**

Figure 4. Yopaaoside B (**8**) was revised to citrifolinoside A (**9**).

Also for yopaaoside B (**8**), a *β*-orientation of C-10 was reported.[4] In this case, the literature data were identical to those reported for citrifolinoside A (**9**) (Figure 4),[7] with an α-orientation of C-10 (Table 3). In the latter case, this was confirmed by ROESY correlations, especially a strong cross peak between H-1 and H-10, which provides strong support for the α-orientation. The NMR data were also in full accordance with this orientation in a manner similar to that explained before for **5**.

Table 3. Comparison of the ^{13}C NMR Spectra (CD_3OD) Reported for Yopaaoside B (**8**) and Citrifolinoside A (**9**)

C	**8**	**9**	C	**8**	**9**
1	92.8	92.6	1′	126.2	126.3
3	153.3	153.3	2′	134.8	134.8
4	108.0	108.1	3′	117.0	117.0
5	33.2	33.3	4′	162.1	162.2
6	58.1	58.2	5′	117.0	117.0
7	58.2	58.2	6′	134.8	134.8
8	92.6	92.8	1″	99.3	99.3
9	45.1	45.2	2″	74.3	74.4
10	69.1	69.1	3″	77.6	78.1
11	123.9	124.0	4″	71.1	71.2
12	172.7	172.9	5″	77.9	77.6
13	144.0	144.0	6″	62.3	62.3
14	168.0	168.1	COOMe	52.0	51.9

Morindacin (**10**), recently reported from fruits of *Morinda citrifolia*,[4] did show ^{1}H NMR data, recorded in CD_3OD, identical to those of borreriagenin (**11**) (Figure 5),[8] an iridoid aglycone isolated from *Borreria verticillata*. These NMR

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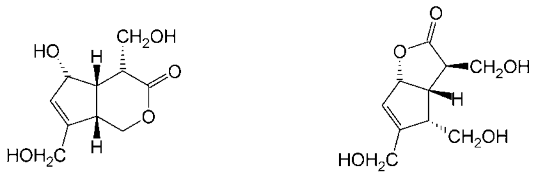
(9) Jensen, S. R.; Nielsen, B. J. *Phytochemistry* **1982**, *21*, 1623.

(10) Damtoft, S.; Jensen, S. R.; Nielsen, B. J. *Phytochemistry* **1981**, *20*, 2717.

(11) Abe, F.; Mori, T.; Yamauchi, T. *Chem. Pharm. Bull.* **1984**, *32*, 2947.



10 **11**

Figure 5. Morindacin (**10**) was revised to borreriagenin (**11**).

data were supplied in the Supporting Information of the publication (Table 4). The only difference between the two structures is the way the lactone ring is formed. In morindacin, a lactone bond was supposed between C-3 and C-1, whereas in borreriagenin, the lactone bond was between C-3 and C-6. Kamiya et al.[5] did not provide any evidence for the presence of the lactone bond at the supposed position, and for borreriagenin, it was confirmed by HMBC correlations. Furthermore, the high chemical shift of the carbonyl group indicates it forms part of a five-ring lactone.

Acknowledgment. This work was supported by CNPq and FAPERJ.

Table 4. Comparison of the ^{1}H NMR Spectra (CD_3OD) Reported for Morindacin (**10**) and Borreriagenin (**11**)

H	morindacin (**10**)		borreriagenin (**11**)	
1a	3.79	dd (11.4; 4.5)	3.78	dd (11.3; 4.4)
1b	3.72	dd (11.4; 6.7)	3.71	dd (11.3; 6.7)
3a	3.90	dd (10.8; 4.7)	3.89	dd (10.8; 4.6)
3b	3.84	dd (10.8; 3.7)	3.83	dd (10.8; 3.9)
4	2.96	ddd (6.0; 4.7; 3.7)	2.95	ddd (6.1; 4.6; 3.9)
5	3.33	dt (7.7; 6.0)	3.32	ddd (8.3; 7.8; 6.1)
6	5.40	dbr (7.7)	5.39	ddddd (7.8; 2; 1.5; 1.5; 1)
7	5.84	quintlike	5.83	dddd (2; 2; 1.5; 1.5)
9	3.10	m	3.10	m
10a	4.22	ddd (15.0; 2.4; 1.2)	4.21	dddd (14.9; 1.5; 1; 1)
10b	4.16	ddd (15.0; 2.8; 1.7)	4.15	dddd (14.9; 1.5; 1.5; 1.5)

Supporting Information Available: A table with the ^{1}H NMR spectra of the discussed compounds (**1**−**4**, **8**, and **9**). ^{1}H NMR, NOESY, and HMBC spectrum of epoxygaertneroside. This material is available free of charge via the Internet at http://pubs.acs.org.

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