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# Two new iridoid glycosides from *Morinda morindoides* (Rubiaceae)

**Chardin Seri Seri, Harisolo Ramiarantsoa, Timothée Aboua Okpekon, Frederic Nana, Amadou Dicko and Léon Atoutou Djakouré**

**Abstract**
Studies on the chemical constituents of the leaves of *Morinda morindoides* led to the isolation of two new iridoid glycosides: methoxymorindic acid 1 and methyl methoxymorindoate 2. The structures were elucidated through spectral studies including 2D-NMR experiments (HSQC, HMBC, COSY, and NOESY). Their complete $^{1}H$ and $^{13}C$ resonance assignments were also carried out.

**Keywords:** *Morinda morindoides*, Rubiaceae; iridoid glycosides, methoxymorindic acid, methyl methoxymorindoate

## Introduction
*Morinda morindoides* is one of the most popular medicinal plants in many African countries. Its traditional use against diarrhoea, amoebiasis, rheumatic pains and fungus was well-known [1, 2]. In Côte d'Ivoire, the aqueous decoctions of the leaves or the roots are widely used in the treatment of malaria [3]. Many traditional uses were confirmed by biological studies [4-8]. The petroleum ether and ethyl acetate extracts showed significant antiplasmodial and antidiarrheal activities [6, 9-10]. Previously, *Morinda* species revealed the presence of flavonoids [11-12], anthraquinones [13], sterols [14-15] and iridoids [16-20]. From *Morinda morindoides*, nine iridoid glucosides containing spirolactone functionality have been reported [7, 21].
In this paper, we report the isolation and structural determinations of two new iridoid glycosides named methoxymorindic acid 1 and methyl methoxymorindoate 2, isolated from the leaves of the same plant.

## 2. Materials and methods
### 2.1. General
The melting points were determined with a Büchi B-545 melting point apparatus and were uncorrected. The optical rotations were measured on a Schmidt-Haensch POLARTRONIC HH8 polarimeter. The UV spectra were obtained by using a Philips PU 8720 spectrophotometer. The IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. The HREIMS were measured on a Micromass Q-TOF micro instrument (Manchester, UK). $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded in $CD_3OD$ on a Bruker Avance DRX-400 spectrometer with TMS as internal standard. Column chromatography and gel permeation were run on Merck silica gel 60. Analytical TLC was carried out on 0.25 mm thick layer of silica gel percolated on aluminium foil (Merck GF254). Spots on chromatograms were detected by observing under UV light (254 nm) and were further visualized by spraying with a vanillin solution (1g in 250 mL of MeOH, 10 mL of $H_2SO_4$ and 25 mL of $CH_3COOH$).

### 2.2. Plant material
Leaves of *Morinda morindoides* were collected in July 2009 in Saïoua, in the west of Côte d'Ivoire. The plant was identified by Prof. Aké Assi of the University of Félix Houphouët-Boigny, Abidjan; a voucher specimen (Z.G n°116) was deposited at the "Centre National Floristique" of the same university.

### 2.3. Extraction and isolation
Dried and powdered leaves of *Morinda morindoides* were extracted with 90% of ethanol in water three times. The combined extracts were concentrated under reduced pressure. The obtained residue was suspended in water and successively partitioned with petroleum ether, ethyl acetate and n-butanol.

The n-butanol extract (12.02 g) was fractionated on a silica gel column and eluted with EtOAc–MeOH (100:0, 90:10, 80:20 and 70:30) to give 4 fractions. The fraction (1200 mg) obtained with EtOAc-MeOH 90:10 was rechromatographed on a silica gel column using the mixture $CH_2Cl_2$-MeOH (90:10). Compound 1 was isolated as an orange amorphous powder (25.6 mg).

The ethyl acetate extract (12.08 g) was subjected to a silica gel chromatography column with $CH_2Cl_2$-EtOAc-MeOH mixtures (100:0:0, 70:30:0, 60:40:0, 0:100:0, 0:90:10 and 0:80:20) of increasing polarity to yield 6 fractions based on their TLC profiles. The fraction (3.01 g) obtained with the mixture (EtOAc-MeOH 90:10 to 80:20) was then separated on a silica gel column chromatography to give three sub-fractions. One of them (1460 mg), that obtained with the elution EtOAc-MeOH (90:10) was further purified on a silica gel column chromatography using a mixture of $CH_2Cl_2$-MeOH (90:10) to give compound 2 (33mg).

### 2.4. Spectral data

Methoxymorindic acid (1). Orange amorphous powder, $[\alpha]_D^{24}$ -21.4 (c 0.06, MeOH); mp 230-231 °C; UV $\lambda_{max}$ (MeOH) nm: 282, 240; IR bands (KBr): 3356, 2937, 1745, 1694, 1638, 1515, 1428, 1338, 1070, 1022 $cm^{-1}$; negative ion HRESI-MS *m/z*: $[M-H]^-$ 563.1376 for $C_{26}H_{28}O_{14}$ (calcd. 563.1401); $^1$H-NMR ($CD_3OD$, 400 MHz) and $^{13}$C-NMR ($CD_3OD$, 100 MHz) are shown in table 1.

Methyl methoxymorindoate (2). Yellow amorphous powder, $[\alpha]_D^{22}$-155 (c 0.05, MeOH); mp 232-233 °C; UV $\lambda_{max}$ (MeOH) nm: 285, 235; IR bands (KBr): 3356, 2946, 1747, 1700, 1640, 1605, 1516, 1438, 1017 $cm^{-1}$; negative ion HRESI-MS *m/z*: $[M-H]^-$ 577.1648 for $C_{27}H_{30}O_{14}$ (calcd. 577.1557); $^1$H-NMR ($CD_3OD$, 400 MHz) and $^{13}$C-NMR ($CD_3OD$, 100 MHz) are shown in table 2.

## 3. Results and discussion

The n-butanol and ethyl acetate extracts of the leaves of *Morinda morindoides* were subsequently purified by silica column chromatography to afford respectively the compounds 1 and 2 (Fig. 1).

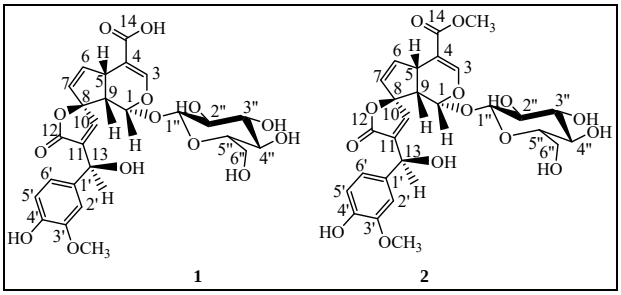

**Fig 1:** Chemical structure of compounds 1-2

Compound 1 was obtained as an orange amorphous powder. Its molecular formula was established to be $C_{26}H_{28}O_{14}$ by HRESI-MS (*m/z* 563.1376, calcd 563.1401 $[M-H]^-$). Its UV spectrum exhibited absorptions at $\lambda_{max}$ 282 and 240 nm, characteristic of aromatic chromophore. The IR spectrum showed the absorption bands due to a hydroxyl (3356 $cm^{-1}$), an $\alpha$, $\beta$-unsaturated $\gamma$-lactone (1745 $cm^{-1}$), an α, $\beta$-unsaturated acid (1694 $cm^{-1}$), an olefin and an aromatic groups (1638, 1515 $cm^{-1}$). The $^1$H-NMR spectrum showed three aromatic protons signals of an ABX system at $\delta_H$ 7.03(*d*, 1H, 2.0, H-2'), 6.92 (*dd*, 1H, 8.0, 2.0, H-6') and 6.80 (*d*, 1H, 8.0, H-5'), four olefinic methine protons signals at $\delta_H$ 7.52 (*d*, 1H,1.6, H-3), 7.37 (*d*, 1H, 1.2, H-10), 6.52 (*dd*, 1H, 5.6, 2.4, H-6) and 5.57 (*dd*, 1H, 5.6, 1.6, H-7), signals of an oxymethine proton at $\delta_H$ 5.39 (*d*, 1.2, H-13), those of an acetal proton at $\delta_H$ 5.14 (*d*, 1H, 3.6, H-1) and two methine protons respectively at $\delta_H$ 3.89 (*m*, 1H, H-5) and 2.90 (*dd*, 1H, 8.0, 3.6, H-9). The signal of an anomeric proton at $\delta_H$ 4.60 (*d*, 1H, 8.0, H-1") and that of methoxy protons at $\delta_H$ 3.91 (*s*, 3H) were also observed. The $^{13}$C-NMR data agreed with the results above. It displayed 26 carbon signals including those of olefinic, phenyl, carbonyl - at $\delta_C$ 172.4 (C-12) and $\delta_C$ 170.0 (C-14) -, acetal - at $\delta_C$ 93.7 (C-1) and $\delta_C$ 100.0 (C-1") - and oxymethine - $\delta_C$ 70.0 (C-13) - carbons in the aglycone moiety. The quaternary carbon signals at $\delta_C$ 98.0 (C-8), $\delta_C$ 138.1 (C-11) and $\delta_C$ 172.4 (C-12), and that of an olefinic carbon at $\delta_C$ 149.9 (C-10) are characteristic of a spiro-lactone ring corresponding to a plumieride type iridoid [22]. The HMBC correlations of the signals of C-10, C-2' and C-6' to that of the oxymethine proton signal at $\delta_H$ 5.39 (H-13) suggested the presence of a benzyl moiety attached to the spiro-lactone ring. The observed $^1$H-$^1$H COSY correlation between H-13 and H-10 due to their allylic coupling, confirmed the above hypothesis. The correlation of the methoxy protons signal at $\delta_H$ 3.91 to that of the carbon at $\delta_C$ 149.1 (C-3'), and the cross peaks between the signals of both H-5' ($\delta_H$ 6.80) and H-6' ($\delta_H$ 6.92) and that of C-4' ($\delta_C$ 147.62), justified the positions of the methoxy and the hydroxyl groups respectively at C-3' and C-4'. The HMBC correlations between both carbon signals at $\delta_C$ 170.0 (C-14) and $\delta_C$ 111.8 - attributed to C-4 - and the olefinic proton signal at $\delta_H$ 7.52 assigned to H-3, as well as the correlations between both C-8 and C-12 carbon signals and that of the olefinic proton at $\delta_H$ 7.37 (H-10), gave the locations of the double bonds respectively in positions 3(4) and 10(11). The $^1$H-$^1$H COSY correlations between the proton signals at $\delta_H$ 5.14 (*d*, H-1), $\delta_H$ 2.90 (*dd*, H-9), $\delta_H$ 3.89 (*m*, H-5), $\delta_H$ 6.52 (*dd*, H-6) and $\delta_H$ 5.57 (*dd*, H-7) gave the partial structure of the iridoid -CH(1)-CH(9)-CH(5)-HC(6)=CH(7)-. They also showed the location of the third double bond in position 6(7) and the correlation between H-3 (*J*=1.6 Hz) and H-5 because of their allylic coupling. Furthermore, the $^1$H-$^1$HCOSY correlations between the osidic protons signals at $\delta_H$ 4.60 (H-1"), $\delta_H$ 3.17 (H-2"), $\delta_H$ 3.38 (H-3", H-4"), $\delta_H$ 3.25 (H-5"), $\delta_H$ 3.77 (H-6"a) and $\delta_H$ 3.68 (H-6b) led to deduce the chemical nature of the sugar moiety as glucose; the antiperiplanar coupling constant between H-1" (*J*=8 Hz) and H-2" indicated more precisely that it was the $\beta$-D-glucose. These NMR data agreed with those of glucose reported in the literature [7]. The HMBC correlation of the anomeric carbon signal at $\delta_C$ 100.0 with that of the proton at $\delta_H$ 5.14 showed the attachment of the glucose moiety to the position 1 of the iridoid.

The relative proposed stereochemistry was confirmed by the NOESY spectrum correlations, in particular cross-peaks between H-5 and both H-1 and H-9 signals which meant their spatial proximities. The lack of correlations between H-13 and both H-1, H-5 and H-9 signals indicated its $\alpha$-orientation. These data were in accord with those 1α-plumieride and 1α-protoplumericin A isolated from *Plumeria acutifolia* [23-25]. The "R" absolute configuration of C-8 was deduced from the comparison of its chemical shift value with that related phenylpropanoid conjugated iridoïdes [19, 21]. Based on the above evidence, the structure of 1 was elucidated and named methoxymorindic acid. The NMR-data were listed in table 1.

**Table 1:** $^{1}H$ (400 MHz) and $^{13}C$ (100 MHz) NMR spectral data of Compound 1 in $CD_3OD$.

| Position | $\delta_C$ | $\delta_H$ (*m, J* in Hz) | COSY | HMBC |
|---|---|---|---|---|
| 1 | 93.7 | 5.14 (*d*, 3.6) | $H_9$ | $C_{1''}$, $C_3$, $C_5$, $C_9$ |
| 3 | 151.9 | 7.52 (*d*, 1.6) | $H_5$ | $C_1$, $C_4$, $C_5$, $C_{14}$ |
| 4 | 111.9 | | | |
| 5 | 39.8 | 3.89 (*m*) | $H_3$, $H_6$, $H_7$, $H_9$ | $C_4$, $C_9$ |
| 6 | 141.2 | 6.52 (*dd*, 5.6,2.4) | $H_5$, $H_7$ | $C_5$, $C_9$ |
| 7 | 130.0 | 5.57 (*dd*,5.6,1.6) | $H_5$, $H_6$ | $C_5$, $C_6$, $C_8$, $C_9$ |
| 8 | 98.0 | | | |
| 9 | 50.8 | 2.90 (*dd*,8.0,3.6) | $H_1$, $H_5$ | |
| 10 | 149.9 | 7.37 (*d*, 1.2) | $H_{13}$ | $C_8$, $C_{11}$, $C_{12}$, $C_{13}$ |
| 11 | 138.1 | | | |
| 12 | 172.4 | | | |
| 13 | 70.0 | 5.39 (*d*, 1.2) | $H_{10}$ | $C_{1'}$, $C_{2'}$, $C_{6'}$, $C_{10}$, $C_{11}$, $C_{12}$ |
| 14 | 170.0 | | | |
| 1’ | 133.9 | | | |
| 2’ | 111.6 | 7.03 (*d*, 2.0) | $H_{6'}$, $H_{13}$ | $C_{1'}$, $C_{3'}$, $C_{6'}$, $C_{13}$ |
| 3’ | 149.1 | | | |
| 4’ | 147.6 | | | |
| 5’ | 116.0 | 6.80 (*d*, 8.0) | $H_{6'}$ | $C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$ |
| 6’ | 121.2 | 6.92 (*dd*, 8.0, 2.0) | $H_{5'}$, $H_{13}$ | $C_{2'}$, $C_{4'}$, $C_{13}$ |
| 1’’ | 100.0 | 4.60 (*d*, 8.0) | $H_{2''}$ | $C_1$ |
| 2’’ | 74.4 | 3.17 (*m*) | $H_{1''}$, $H_{3''}$ | $C_{1''}$, $C_{3''}$ |
| 3’’ | 77.9 | 3.38 (*m*) | $H_{2''}$, $H_{4''}$ | $C_{2''}$, $C_{4''}$ |
| 4’’ | 70.8 | 3.38 (*m*) | $H_{3''}$, $H_{5''}$ | $C_{3''}$, $C_{5''}$ |
| 5’’ | 78.2 | 3.25 (*m*) | $H_{4''}$ | |
| 6’’a | 62.0 | 3.77 (*m*) | $H_{5''}$, $H_{6b''}$ | |
| 6’’b | | 3.68 (*m*) | $H_{5''}$, $H_{6a''}$ | |
| $OCH_3$ | 56.5 | 3.91 (*s*) | | $C_{3'}$ |

Compound 2 was obtained as yellow amorphous powder. Its molecular formula was established to be $C_{27}H_{30}O_{14}$ by HRESI-MS (*m/z* 577.1648, calcd 577.1557 $[M-H]^-$).The UV spectrum showed the same profile as that of compound 1. The IR spectrum exhibited absorption bands due to an hydroxyl (3356 $cm^{-1}$), an $\alpha$, $\beta$-unsaturated $\gamma$-lactone (1747$cm^{-1}$), an $\alpha$, $\beta$-unsaturated ester (1700 $cm^{-1}$), a double bond and aromatic groups (1640, 1605, 1516, 1438$cm^{-1}$). The $^{1}H$ and $^{13}C$ NMR spectra of 2 were rather similar to those of 1. The only differences were the presence of a singlet at $\delta_H$ 3.76 assigned to the oxymethyl protons of an ester function in the $^{1}H$ NMR spectrum of 2 and its corresponding carbon signal resonating at $\delta_C$ 51.9. The HMBC correlation between the signal at $\delta_C$ 168.4 (C-14) and the above singlet proved the attachment of the ester group to the olefinic carbon signal at $\delta_C$ 111.5 (C-4). The chemical structure of 2 was determined in the same way as for 1. The NMR spectral data were given in table 2. We designated this compound (2) methyl methoxymorindoate.

**Table 2:** $^{1}H$ (400 MHz) and $^{13}C$ (100 MHz) NMR spectral data of Compound **2** in $CD_3OD$

| Position | $\delta_C$ | $\delta_H$ (*m, J* in Hz) | COSY | HMBC |
|---|---|---|---|---|
| 1 | 93.7 | 5.15 (*d*, 3.6) | $H_9$ | $C_{1''}$ |
| 3 | 152.1 | 7.53 (*d*, 1.2) | $H_5$ | $C_1$, $C_4$, $C_5$, $C_{14}$ |
| 4 | 111.5 | | | |
| 5 | 39.6 | 3.90 (*m*) | $H_3$, $H_6$, $H_7$, $H_9$ | $C_9$ |
| 6 | 140.8 | 6.49 (*dd*, 5.6,2.8) | $H_5$, $H_7$ | |
| 7 | 130.3 | 5.59 (*dd*, 5.6,2.0) | $H_5$, $H_6$ | $C_6$, $C_8$, $C_9$ |
| 8 | 97.9 | | | |
| 9 | 50.8 | 2.99 (*dd*, 8.0, 3.6) | $H_1$, $H_5$ | |
| 10 | 149.8 | 7.35 (*d*, 1.6) | $H_{13}$ | $C_8$, $C_{12}$ |
| 11 | 138.2 | | | |
| 12 | 172.4 | | | |
| 13 | 70.0 | 5.39 (*d*, 1.2) | $H_{10}$ | $C_{2'}$, $C_{3'}$, $C_{5'}$, $C_{6'}$ ; $C_{10}$, $C_{11}$ |
| 14 | 168.4 | | | |
| 1’ | 133.9 | | | |
| 2’ | 111.6 | 7.03 (*d*, 1.6) | $H_{6'}$ | $C_{3'}$, $C_{6'}$, $C_{13}$ |
| 3’ | 149.1 | | | |
| 4’ | 147.6 | | | |
| 5’ | 116.0 | 6.79 (*d*, 8.0) | $H_{6'}$ | $C_{1'}$, $C_{3'}$ |
| 6’ | 121.2 | 6.91 (*dd*, 8.0,1.6) | $H_{2'}$, $H_{5'}$ | $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{13}$ |
| 1’’ | 100.1 | 4.59 (*d*, 8.0) | $H_{2''}$ | $C_1$ |
| 2’’ | 74.4 | 3.16 (*m*) | $H_{1''}$, $H_{3''}$ | $C_{1''}$, $C_{3''}$ |
| 3’’ | 77.9 | 3.37 (*m*) | $H_{2''}$ | $C_{2''}$, $C_{4''}$ |
| 4’’ | 70.8 | 3.37 (*m*) | $H_{5''}$ | $C_{3''}$, $C_{5''}$ |
| 5’’ | 78.3 | 3.24 (*m*) | $H_{4''}$, $H_{6''a}$, $H_{6''b}$ | |
| 6’’a | 62.0 | 3.72 (*m*) | $H_{5''}$, $H_{6''b}$ | |
| 6’’b | | 3.69 (*m*) | $H_{5''}$, $H_{6''a}$ | |
| $COOCH_3$ | 51.9 | 3.76 (*s*) | | $C_{14}$ |
| $OCH_3$ | 56.5 | 3.92 (*s*) | | $C_{3'}$ |

## 4. Conclusion

The chemical study of the leaves of *Morinda morindoides* resulted in the isolation of two new iridoids namely methoxymorindic acid (1) and methyl methoxymorindoate (2). Both compounds 1 and 2 have spirolactone functionality and their stereochemistry at position 1 are uncommon in iridoid glycosides.

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