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Note

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# Structure and in Vitro Antiparasitic Activity of Constituents of *Citropsis articulata* Root Bark

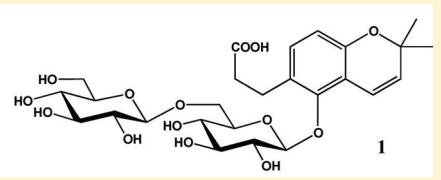
Damien Lacroix,[†] Soizic Prado,*[,†] Dennis Kamoga,[‡] John Kasenene,[‡] and Bernard Bodo*[,†]

[†]Molécules de Communication et Adaptation des Micro-Organismes, UMR 7245 CNRS, Muséum National d'Histoire Naturelle, 63 rue Buffon 75005 Paris, France

[‡]Department of Botany, P.O. Box 7062, Makerere University, Kampala, Uganda

Supporting Information

**ABSTRACT:** From the results of an ethnomedicinal investigation of plants from Uganda with antimalarial activity, *Citropsis articulata* was selected because of the antiplasmodial effect of an ethyl acetate extract of its root bark. Thus, from the cyclohexane, ethyl acetate, and methanol extracts, two new heterocyclic compounds, omubioside (**1**) and katimborine (**2**), were isolated in addition to five known coumarins (rutarin (**3**), seselin (**4**), suberosin (**5**), demethylsuberosin (**6**), and haploperoside (**7**)), two known alkaloids (5-hydroxynoracronycine (**8**) and 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (**9**)), trigonelline (**10**), and the limonoid 7$\alpha$-obacunyl acetate (**11**). The best growth inhibitors of *Plasmodium falciparum* were alkaloids **8** and **9**, with $IC_{50}$ values of 0.9 and 3.0 $\mu$g/mL.




In the course of our investigation of Ugandan medicinal plants, involving a field survey and screening of selected plant extracts for bioactivities, *Citropsis articulata* (Willd. ex Spreng.) Swingle & Kellerman (Rutaceae) was selected for the antimalarial activity of its extract. The root bark of *C. articulata* is used commonly in folk medicine for several purposes, but especially as an aphrodisiac.[1,2] In Southeast Uganda the tree is called "omuboro" or "katimboro", which literally means "sex tree". The dried and powered root bark is mixed with water and then drunk.[3] Antiplasmodial inhibition against *Plasmodium falciparum* FcB1 strain (77% at 10 $\mu$g/mL) was demonstrated for the EtOAc extract, associated with a low cytotoxicity (12%) against Vero cells. The parasite *P. falciparum* is mainly responsible for malaria around the world with close to 600 million cases, 90% of which occur in Africa. Malaria is the most common disease in Uganda with 20% of inpatient admissions, claiming the life of more than 200 children daily.[4] Acridone alkaloids have been isolated by Meva'a and associates from the stem bark of *C. articulata*.[5] The root bark has not yet been investigated, and this was done in order to characterize the compounds responsible for the observed in vitro antiplasmodial activity. This led to the isolation of two new compounds, omubioside (**1**) and katimborine (**2**), as well as five known coumarins (seselin (**4**),[6] suberosin (**5**),[7,8] demethylsuberosin (**6**),[9,10] rutarin (**3**),[11,12] and haploperoside (**7**)),[13] two known alkaloids (5-hydroxynoracronycine (**8**)[14] and 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (**9**)[15]), trigonelline (**10**),[16] and the limonoid 7$\alpha$-obacunyl acetate (**11**).[17]

The dried and powered root bark of *C. articulata* was extracted at room temperature successively with cyclohexane, EtOAc, and MeOH, and the extracts were purified by chromatography to yield **4** and **5** from the cyclohexane extract, **4**–**6** and **11** from the EtOAc extract, and the new phenylpropanoid omubioside (**1**) and the new alkaloid katimborine (**2**) together with **3** and **7**–**10** from the MeOH extract.

Compound **1** was obtained as an optically active amorphous solid with $[\alpha]_{546} = -26°$ (*c* 0.5, MeOH). Its HRESIMS data showed a protonated molecular ion $[M + H]^+$ at *m/z* 573.2176, corresponding to the molecular formula $C_{26}H_{36}O_{14}$ (calcd for $C_{26}H_{37}O_{14}$ 573.2181). Fragmentation of the $[M + H]^+$ ion provided two main fragments at *m/z* 411.1674 and 249.1142, corresponding to the successive loss of two *m/z* 162.05 fragments and suggesting that compound **1** is a diglycoside. Its IR spectrum showed strong absorptions at $\nu_{max}$ 1654 $cm^{-1}$ (carboxylic acid) and 3394 $cm^{-1}$ (hydroxy functionalities). The $^{13}C$ NMR spectrum exhibited 26 carbon resonances: 1 carboxylic acid at $\delta_C$ 178.0, 2 methyls, 2 methylenes, 8 $sp^2$ carbons, and 12 carbons characteristic of two glucose moieties. The $^1H-^1H$ COSY spectrum was indicative of the two spin systems **a** and **b**, assigned to the two glucose moieties, of one $-CH_2CH_2$ group, one cis carbon–carbon double bond, and two aromatic methines (Figure 1). These substructures were assembled from the HMBC data. The chemical shift of the quaternary carbon (C-9) at $\delta_C$ 76.5 indicated that it is linked to the heterocyclic oxygen and correlated to both the ethylenic methine H-10 ($\delta_H$ 5.68) and the two methyls at $\delta_H$ 1.36 and 1.42. The protons of the two methylenes (substructure **d**) were correlated to C-4 at $\delta_C$ 128.0 and to the C-1 carboxylic group. The C-8a resonance at $\delta_C$ 153.0 correlated with the anomeric proton (H-1′) of $Glc_b$, whereas the $-CH_2OH$ group (C-6′) of this $Glc_b$ was correlated to the anomeric proton (H-1″) of $Glc_a$. The structure was confirmed by analysis of the NOESY spectrum, showing strong NOEs between $CH_2$-3 and H-5, between H-1′ and H-11, H-3′

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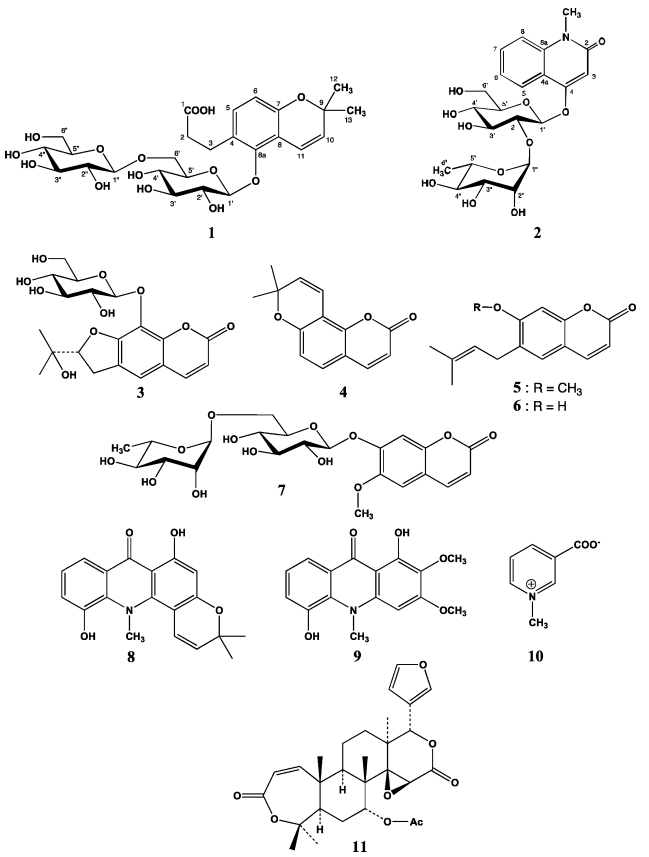


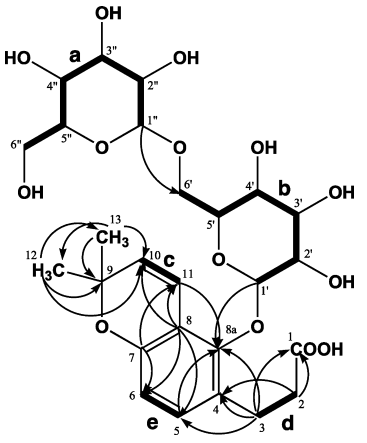


**Figure 1.** Key $^1$H−$^1$H COSY (bold bonds) and HMBC correlations (H→C) for omubioside (**1**).

and H-5′, and between H-1″ and $CH_2$-6′, H-3″, and H-5″. The vicinal coupling constants of the two anomeric protons ($^3J_{1'\text{-}2'}$ = 7.7 and $^3J_{1''\text{-}2''}$ = 7.8 Hz) indicated both glucose moieties to be $\beta$-axial. The chirality of both of these glucose units was determined as D, and they thus formed a $\beta$-gentiobioside moiety, in agreement with literature data.[18,19] The proposed structure for the glycoside **1**, 8a-(*O*-$\beta$-gentiobiosyloxy)-7,8-(9,9-dimethylpyrano)hydrocoumaric acid, is new, and it has been named omubioside. This hydrocoumaric acid derivative is related to seselin (**4**), from which it could derive by hydrolysis of the lactone ring and reduction of the carbon−carbon double bond.

Compound **2** was obtained as an optically active amorphous solid with $[\alpha]_{546} = -98°$ (*c* 0.5, MeOH). Its HRESIMS showed the protonated molecular ion $[M + H]^+$ at *m*/*z* 484.1826 corresponding to the formula $C_{22}H_{29}NO_{11}$ (calcd for $C_{22}H_{30}NO_{11}$ 484.1817), which implies nine degrees of unsaturation. The $^{13}$C NMR spectrum had 22 resonances, including 9 sp$^2$ carbons (among which one >C═O at $\delta_C$ 165.9 and four sp$^2$ methines (═CH−)), 10 oxymethines (−CH(O)−), 1 $-CH_2(O)$- group, and two $-CH_3$ groups. The molecule thus included four rings. The $^1$H−$^1$H COSY spectrum ($CD_3OD$) allowed the identification of the following substructures: an ortho-disubstituted benzene ring (**a**), a hexose (**b**), a desoxyhexose (**c**), an sp$^2$ proton at $\delta_H$ 6.27, together with two anomeric protons at $\delta_H$ 5.36 and 5.41, an *N*-methyl singlet at $\delta_H$ 3.71, and a methyl doublet at $\delta_H$ 1.11 (Figure 2).

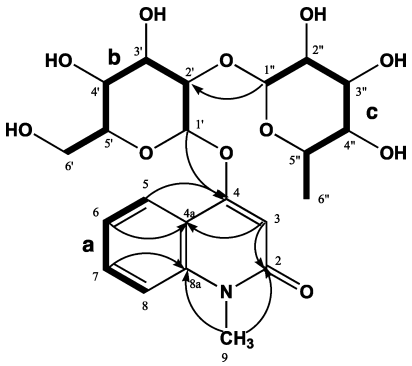


**Figure 2.** Key $^1$H−$^1$H COSY (bold bonds) and HMBC correlations (H→C) for katimborine (**2**).

From the coupling constant values and comparison of literature NMR data,[20] the first hexose was identified as a $\beta$-glucose and the second as an $\alpha$-rhamnose.

The HMBC spectrum of **2** showed that C-2 ($\delta_C$ 165.9), C-4 (162.2), and C-4a (117.5) were correlated to H-3 at $\delta_H$ 6.27, while C-2 and C-8a ($\delta_C$ 140.5) correlated to $CH_3$-9 at $\delta_H$ 3.71. Chemical shifts of $CH_3$-9 indicated that it is bonded to the nitrogen atom, and its HMBC correlations pointed out that, in turn, the nitrogen is linked to the quaternary C-2 at $\delta_C$ 165.9. Correlations of C-4a and C-8a with H-6 ($\delta_H$ 7.33) and H-7 (7.70), respectively, suggested the carbons located at the junction of the benzene and the 2-pyridone rings (Figure 2). The anomeric H-1′ ($\delta_H$ 5.41) of Glc was correlated to C-4, indicating that the glucose was linked to this position. Finally, the anomeric H-1″ ($\delta_H$ 5.36) of the rhamnose moiety was correlated to C-2′ ($\delta_C$ 80.2), indicative of a 1″→ 2′ junction of the two glycosides, and taking into account the vicinal coupling constants of the anomeric protons ($^3J_{1'\text{-}2'}$ = 7.7 for H-1′ and $^3J_{1''\text{-}2''}$ = 1.9 Hz for H-1″), an $\alpha$-rhamnopyranosyl-(1→2)$\beta$-glucopyranoside unit was defined. The chirality of the glucose was determined as D and that of the rhamnose as L. Thus, the diglycoside is a $\beta$-neohesperidose moiety, in agreement with literature data,[20] and is linked to C-4. The structure was confirmed from NOE data, in which strong correlations were seen in the NOESY spectrum between H-1′ and H-3, H-3′, and H-5′ and between H-1″ and H-2′ and H-2″. Compound **2** was thus proposed to be *N*-methyl-4-*O*-[$\alpha$-L-rhamnopyranosyl-(1→2)$\beta$-D-glucopyranosyl]-2-quinolone (*N*-methyl-4-*O*-$\beta$-neohesperidosyl-2-quinolone), a new alkaloid named katimborine.


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Table 1. Antiparasitical Activities of Compounds 1−11 against *P. falciparum*, *T. brucei brucei*, *L. donovani* and Cytotoxicity on Vero Cells

| compd | *Plasmodium falciparum* $IC_{50}$[a] (μg/mL) | *Trypanosoma brucei brucei* $EC_{50}$[b] (μg/mL) | *Leishmania donovani* $EC_{50}$ (μg/mL) | cytotoxicity Vero cells $IC_{50}$ (μg/mL) |
|---|---|---|---|---|
| **1** | >100 | >125 | >125 | >50 |
| **2** | >100 | >125 | >125 | >50 |
| **3** | 88.0 | >125 | >125 | >50 |
| **4** | >100 | >125 | >125 | >50 |
| **5** | >100 | >125 | >125 | >50 |
| **6** | 16.7 | >125 | 120 | >50 |
| **7** | >100 | >125 | >125 | >50 |
| **8** | 0.9 | 125 | 11.2 | 9.3 |
| **9** | 3.0 | 125 | 20.4 | 30.5 |
| **10** | >100 | >125 | >125 | >50 |
| **11** | 9.3 | >125 | 45.0 | >50 |
| chloroquine[c] | 0.1 | nd [d] | nd | nd |
| pentamidine[c] | nd | 1.4 | 3.1 | nd |
| bis(aminoethylthio)-4-melaminophenarsine[c] | nd | 1.0 | nd | nd |
| camptothecin [c] | nd | nd | nd | 0.6 |

[a]$IC_{50}$ = inhibitory concentration 50%. [b]$EC_{50}$ = efficacy concentration 50%. [c]Positive control substance. [d]nd = not determined.

The EtOAc extract of *C. articulata* root bark showed in vitro antiplasmodial activity with a 70% growth inhibition of *P. falciparum* at a 10 μg/mL concentration. The antiparasitic activities of the compounds purified from the extracts of *C. articulata* root bark were evaluated for their inhibition against *P. falciparum*, *Trypanosoma brucei brucei*, and *Leishmania donovani* and their cytotoxicity against Vero cells (Table 1). None of the compounds tested was active against *T. brucei brucei*. The most active compounds against *L. donovani* were **8** and **9**, with $EC_{50}$ values of 11.2 and 20.4 μg/mL, respectively. The best growth inhibitors for *P. falciparum* were also compounds **8** and **9**, with $IC_{50}$ values of 0.9 and 3.0 μg/mL, respectively, both having a selectivity index of around 10.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** Melting points were determined on a Büchi B-545 melting point apparatus. Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter, and the $[\alpha]_{546}^{22}$ values are given in deg cm$^2$ g$^{-1}$. IR spectra were recorded with a Shimatzu FTIR 8400S spectrometer, as films on NaCl plates. $^{13}$C NMR spectra were recorded on an Bruker AC 300 spectrometer operating at 75.47 MHz (for $^{13}$C) and $^1$H and 2D-NMR spectra on an Bruker Avance 400 spectrometer operating at 400.13 MHz. For HMBC experiments the delay ($^1/_2J$) was 70 ms, and for the NOESY experiments the mixing time was 150 ms. Mass spectra were recorded on an Applied Biosystems API Q-STAR PULSAR i instrument. For the CID spectra, the collision energy was 30 eV and the collision gas was nitrogen. Analytical HPLC was performed with a VWR L-2130 pump, a Dionex Ultimate 3000 injector, and a VWR L-2400 UV detector. The analytical column was a Dionex $C_{18}$ Acclain 120 (5 μm, 120 Å, 4.6 × 150 mm). UV detection was at 220 nm, with a flow rate of 1 mL/min, and the solvent was a $CH_3CN/H_2O$ (with 0.05% TFA) gradient. Preparative HPLC used a Merck-Hitachi L-6200 pump, an AS 2000 injector, and a Merck-Hitachi L-4250 UV−vis detector. The column was a Kromasil $C_{18}$ (5 μm, 100 Å, 10 × 250 mm). UV detection was at 220 nm, with a flow rate of 3 mL/min, and the solvent was a $CH_3CN/H_2O$ (containing 0.05% TFA) gradient.

**Plant Materials.** The roots of *Citropsis articulata* (Willd. ex Spreng.) Swingle & Kellerman were collected in the village of Kiohima, close to Kibale National Park (Uganda) in October 2008. Voucher specimens were deposited at the Herbarium of the Makerere University (Uganda) and identified by one of us (J.K.).

**Extraction and Isolation.** The dried and powdered root bark of *Citropsis articulata* (550 g) was extracted at room temperature with cyclohexane to give 27.8 g of dried extract and then with EtOAc (28 g of extract) and MeOH (19.9 g of extract). A part (3 g) of the cyclohexane extract was purified by silica gel column chromatography (CC) with a $CH_2Cl_2$/MeOH gradient (10/0 to 8/2) as eluent to yield suberosin (**4**; 2 g) and seselin (**5**; 50 mg). From 2 g of the EtOAc extract were obtained by CC on silica gel (elution with $CH_2Cl_2$/MeOH gradient from 1/0 to 0/1) nine fractions,: F-1−F-9. F-4 and F-5 contained suberosin (**4**) and seselin (**5**). From F-7 were obtained by CC on silica gel (elution with cyclohexane/EtOAc and 0.5% of $NH_4OH$ 1/0 to 0/1) demethylsuberosin (**6**; 7 mg) and 7α-obacunyl acetate (**11**; 16 mg). From 10 g of the MeOH extract were obtained by CC (elution $CH_2Cl_2$/MeOH from 1/0 to 0/1) 10 fractions: F′1−F′10. From fraction F′1 (1.62 g) by HPLC RP-$C_{18}$ with an acetonitrile/water gradient from 15/85 to 95/5 as eluent, trigonelline (**10**) was collected at $R_t$ = 4 min (34 mg). From fraction F′2 (3.01 g) by silica gel CC and elution with $CH_2Cl_2$/MeOH from 1/0 to 0/1 were obtained 15 subfractions: f1−f15. From f-11 by HPLC RP-18 Si gel with an acetonitrile/water gradient from 10/90 to 95/5 as eluent, haploperoside (**7**; 20 mg) and rutarin (**3**; 22 mg) were collected at $R_t$ = 7.8 and 13.6 min, respectively. From f-14 by the same process was collected omubioside (**1**; 12 mg) at $R_t$ = 19.0 min. From fraction F′3 (2.99 g) by silica gel and elution with $CH_2Cl_2$/MeOH from 1/0 to 0/1 were obtained 15 subfractions: f′1−f′15. From f′12 by HPLC RP-18 eluted with an acetonitrile/water gradient from 1/9 to 9/1, katimborine (**2**; 7 mg) was collected at $R_t$ = 8.2 min. From F′5 by CC on silica gel (elution with $CH_2Cl_2$/MeOH from 1/0 to 0/1), 5-hydroxynoracronycine (**8**; 4 mg) and 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (**9**; 5 mg) were obtained.

**Omubioside (1):** colorless amorphous solid; $[\alpha]_{546}^{22}$ = −26 (*c* 0.5, MeOH); IR (NaCl plate) $\nu_{max}$ 3394, 1654, 1627, 1203, 1060 cm$^{-1}$; $^{13}$C NMR ($CD_3OD$, 75.04 MHz) δ 178.0 (C-1), 36.0 (C-2), 26.4 (C-3), 128.0 (C-4), 130.4 (C-5), 114.0 (C-6), 155.0 (C-7), 116.3 (C-8), 153.0 (C-8a), 76.5 (C-9), 131.3 (C-10), 119.1 (C-11), 27.4 (C-12), 28.4 (C-13), 106.5 (C-1′), 75.7 (C-2′), 77.9 (C-3′), 71.5 (C-4′), 77.4 (C-5′), 69.8 (C-6′), 104.5 (C-1″), 75.1 (C-2″), 77.9 (C-3″), 71.6 (C-4″), 77.9 (C-5″), 62.8 (C-6″); $^1$H NMR ($CD_3OD$, 400.13 MHz) δ 2.66 (m, H-2a), 2.57 (m, H-2b), 2.96 (ddd, 8.6, 7.1, 1.6, H-3), 6.95 (d, 8.3, H-5), 6.52 (dd, 8.3, 0.7, H-6), 5.68 (d, 10.0, H-10), 6.99 (dd, 10.0, 0.7, H-11), 1.42 (s, H-12), 1.36 (s, H-13), 4.61 (d, 7.7, H-1′), 3.52 (dd, 9.2, 7.7, H-2′), 3.39 (dd, 9.2, 8.8, H-3′), 3.44 (dd, 8.8, 8.0, H-4′), 3.31 (m, H-5′), 4.08 (dd, 11.5, 2.1, H-6′a), 3.75 (dd, 11.5, 5.2, H-6′b), 4.26 (d, 7.8, H-1″), 3.15 (dd, 9.2, 7.8, H-2″), 3.25 (m, H-3″), 3.27 (m, H-4″), 3.24 (m, H-5″), 3.85 (dd, 12.0, 2.0, H-6″a), 3.66


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(dd, 12.0, 5.3, H-6″b) ; ESI-qTOF MS $m/z$ 573.2176 $[M + H]^+$ (calcd for $C_{26}H_{37}O_{14}$ 573.2181); ESI-qTOF MS/MS (CE 30 eV) $m/z$ 573 (39, $[M + H]^+$), 411 (100), 249 (42).

**Katimborine (2):** colorless amorphous solid; $[\alpha]_{546}^{22} = -98$ ($c$ 0.5, MeOH); IR (NaCl plate) $\nu_{max}$ 3340, 1635, 1577, 1450, 1234, 1134, 1072, 991 $cm^{-1}$; $^{13}C$ NMR ($CD_3OD$, 75.04 MHz) $\delta$ 29.8 (N-Me), 165.9 (C-2), 99.8 (C-3), 162.2 (C-4), 117.5 (C-4a), 125.0 (C-5), 123.5 (C-6), 133.0 (C-7), 115.8 (C-8), 140.5 (C-8a), 99.0 (C-1′), 80.2 (C-2′), 79.0 (C-3′), 71.1 (C-4′), 78.4 (C-5′), 62.1 (C-6′), 102.9 (C-1″), 72.3 (C-2″), 72.0 (C-3″), 74.0 (C-4″), 70.3 (C-5″), 18.5 (C-6″); $^1H$ NMR ($CD_3OD$, 400.13 MHz) $\delta$ 3.71 (s, N-Me), 6.27 (s, H-3), 8.10 (dd, 8.1, 1.5, H-5), 7.33 (ddd, 8.1, 7.1, 1.0, H-6), 7.70 (ddd, 8.5, 7.1, 1.5, H-7), 7.58 (dd, 8.5, 1.0, H-8), 5.41 (d, 7.7, H-1′), 3.83 (dd, 9.0, 7.7, H-2′), 3.67 (dd, 9.0, 8.8, H-3′), 3.48 (dd, 9.8, 8.8, H-4′), 3.54 (ddd, 9.8, 4.8, 2.2, H-5′), 3.88 (dd, 12.2, 2.2, H-6′a), 3.72 (dd, 12.2, 4.8, H-6′b), 5.36 (d, 1.9, H-1″), 3.98 (dd, 3.3, 1.9, H-2″), 3.59 (dd, 9.7, 3.3, H-3″), 3.31 (dd, 9.7, 9.5, H-4″), 3.69 (dq, 9.5, 6.2, H-5″), 1.11 (d, 6.2, H-6″); ESI-qTOF MS $m/z$ 484.1826 $[M + H]^+$ (calcd for $C_{22}H_{30}NO_{11}$ 484.1817); ESI-qTOF MS/MS (CE 30 eV) $m/z$ 484 (70, $[M + H]^+$), 338 (1), 176 (100).

**Determination of the Absolute Configuration of the Sugar Moieties in 1 and 2.** Omubioside (**1**; 2.4 mg) and katimborine (**2**; 2.0 mg) were treated with 1 N aqueous HCl (1 mL) at 100 °C for 3 h. For each, the acidic aqueous mixture was dried, $CH_2Cl_2$ (1 mL) was added, and the $CH_2Cl_2$ solution was extracted with $H_2O$ (3 × 1 mL). The aqueous fraction was evaporated and treated with pyridine (500 $\mu$L), DMAP (catalytic), and benzoyl chloride (30 $\mu$L) at room temperature for 24 h. After the addition of MeOH (200 $\mu$L), the reaction mixture was diluted with $CH_2Cl_2$ and washed successively with 1 N HCl, aqueous saturated $NaHCO_3$ solution, and brine. The organic layers were dried over $Na_2SO_4$ and evaporated to dryness. The sugar derivatives were subjected to chiral HPLC analysis using Chiralpak AD (Daicel Chemical Industry Ltd., 4.6 × 250 mm, cyclohexane−isopropyl alcohol 80/20, 0.5 mL/min; UV detection at 254 nm). The retention times of the *O*-benzoyl derivatives of the saccharide hydrolysis products of **1** and **2** were found to be identical with those of the synthetic benzoyl derivatives of D-glucose (26.4 min) and L-rhamnose (12.6 min).

**In Vitro Antiplasmodial Activity.** The antiplasmodial activity was evaluated against the chloroquine-resistant FcB1/Colombia strain of *P. falciparum*. The test was performed using the method of Desjardins et al.[21] Experiments were carried out in duplicate.

**In Vitro Antileishmanial Assay.** *L. donovani* (MHOM/ET/L82/LV9) promastigotes were kindly provided by Prof. S. L. Croft, from the WHO collection at the London School of Hygiene and Tropical Medicine. Assays were performed as previously described by M'Bongo.[22]

**In Vitro Antitrypanosomal Assay.** The antiparasitic activity was assessed using the method described by Loiseau et al.[23]

**Cytotoxicity Evaluation.** The Vero cell lines were seeded into 96-well microplates at 2 × $10^5$ cells per well. The cytotoxicity assays were performed in duplicate according to published procedures.[24]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Figures giving selected 1D and 2D NMR spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*Tel: 33-1-40793129. Fax: 33-1-40793135. E-mail: bodo@mnhn.fr (B.B.); sprado@mnhn.fr (S.P.).

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