Ancistrolikokines A−C: New 5,8′-Coupled Naphthylisoquinoline Alkaloids from *Ancistrocladus likoko*[1]

Gerhard Bringmann*,[†] Christian Günther,[†] Wael Saeb,[†] Jan Mies,[†] Anura Wickramasinghe,[‡] Virima Mudogo,[§] and Reto Brun[⊥]

Institut für Organische Chemie der Universität, Am Hubland, D-97074 Würzburg, Germany, Department of Chemistry, University of Peradeniya, Peradeniya, Sri Lanka, Faculté des Sciences, Université de Kinshasa, B.P. 202, Kinshasa XI, Democratic Republic of Congo, and Schweizerisches Tropeninstitut, Socinstrasse 57, CH-4002 Basel, Switzerland

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Three new naphthylisoquinoline alkaloids, ancistrolikokines A−C (**1**−**3**), have been isolated and structurally assigned from *Ancistrocladus likoko*, as well as the known compound korupensamine A (**4**). Their 5,8′-coupling hints at a close biogenetic relationship of *A. likoko* to other Central African *Ancistrocladus* species. Compounds **1**−**4** showed good to moderate antimalarial activities when evaluated in vitro against the NF54 and K1 strains of *Plasmodium falciparum*.

Plants in the family Ancistrocladaceae are intriguing targets for phytochemical investigation, not only because of the great structural variability, but also due to the diverse biological activities of their characteristic secondary metabolites, the naphthylisoquinoline alkaloids.[2] During the past few years, West and Central African *Ancistrocladus* species, in particular, have received increasing attention in the search for less cytotoxic analogues of the anti-HIV active michellamines[3] and their antimalarial "halves", the korupensamines.[4] One of these tropical lianas is *Ancistrocladus likoko* J. Léonard,[5] the root extracts of which have as yet been analyzed only in situ, by HPLC NMR. This analysis led to the identification and elucidation of the constitutions of three naphthylisoquinoline alkaloids, but without any assignments of their relative and absolute configurations.[7] For the elucidation of the latter and for the analysis of their potential biological activities, a more in-depth study on this plant seemed worthwhile. In this paper, we report the isolation and the elucidation of the complete stereostructures of three new 5,8′-coupled naphthylisoquinoline alkaloids, ancistrolikokines A−C (**1**−**3**), together with the identification of the known compound korupensamine A (**4**), from *A. likoko* (Figure 1) and the in vitro antimalarial activities of these four compounds.

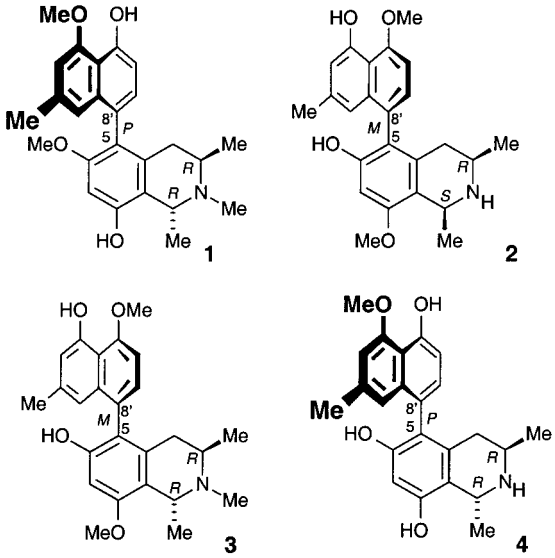

Figure 1. Naphthylisoquinoline alkaloids from *A. likoko.*

Results and Discussion

The MeOH extract of the root bark of *A. likoko* was perfused with chloroform. The organic layer was then resolved by high-speed countercurrent chromatography (HSCCC)[7] yielding two compounds, the known alkaloid korupensamine A (**4**)[4] and a new one (**1**). The M^+ peak of the latter, together with HRMS, indicated a molecular formula of $C_{25}H_{29}NO_4$. The ^1H NMR spectrum exhibited the typical signals of a naphthyl-1,3-dimethyltetrahydroisoquinoline alkaloid. The ^1H NMR spectrum was closely comparable to that of an *N*-methylated, 5,8′-coupled naphthylisoquinoline previously analyzed in situ by HPLC NMR, in the root extract of *A. likoko*, so that the same molecular framework was to be expected for the compound now isolated in a pure form. In fact, the singlets at 4.01 and 3.51 ppm, each corresponding to three protons, indicated the presence of two methoxy groups (Figure 2a). The latter had previously[6] been shown to be connected to C-6 of the isoquinoline moiety by its ROESY interaction to H-7 measured in situ; this assumption was confirmed by an HMBC interaction of the OCH_3-6 group to C-6. Further HMBC and ROESY correlations, in particular between the methoxy group at 4.01 ppm and C-4′ and between that methoxy group and H-3′ (Figures 2a and b), proved the other methoxy group to be located at C-4′. The high-field shift of the CH_3-3 protons (0.90 ppm) resulted from the anisotropic effect caused by the naphthyl substituent and hence provided clues for a coupling position at C-5 of the isoquinoline portion of the molecule. This assumption was supported by an HMBC interaction of H-7′ and C-5 (Figure 2a). Because of the "normal", (i.e., not high-field-shifted) position of the CH_3-2′ protons (2.22 ppm), the naphthalene part must be coupled in the "methyl-free" isocyclic ring (i.e., at C-8′ or C-6′). The coupling site at C-8′ could be deduced unambiguously from HMBC correlations between H-1′ and C-8′ as well as from a ROESY cross-peak connecting H_{ax}-4 and H-1′.

Because no naphthylisoquinoline alkaloids with this constitution were known previously, compound **1** was given

* To whom correspondence should be addressed. Tel.: +49-931-888-5323. Fax: +49-931-888-4755. E-mail: bringman@chemie.uni-wuerzburg.de.
† Institut für Organische Chemie.
‡ Department of Chemistry.
§ Faculté des Sciences.
⊥ Schweizerisches Tropeninstitut.

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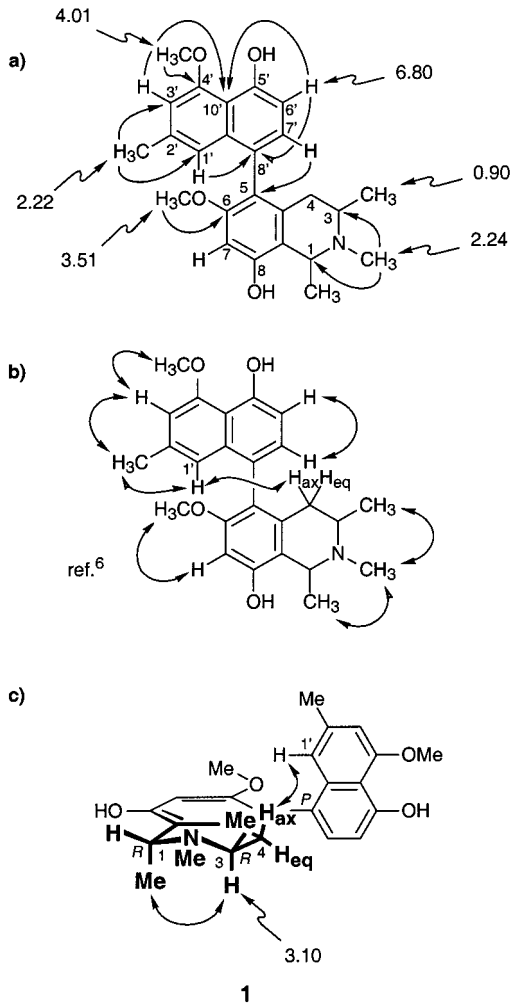


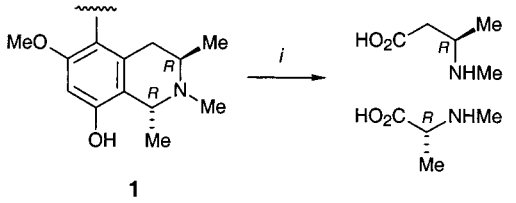
Figure 2. Constitution of **1** (a) by chemical shifts (δ values) and HMBC interactions; (b) by ROESY correlations; (c) relative configuration (and additional proof of constitution) of the new alkaloid by further ROESY measurements.

a new trivial name, ancistrolikokine A. The relative configuration of the two methyl groups in the isoquinoline part of **1** was assigned as trans from the chemical shift of the H-3 signal at 3.10 ppm (Figure 2c), which was observed in the region typical[9] of trans-configured 1,3-dimethyltetrahydroisoquinolines. This assumption was corroborated by a ROESY interaction between H-3 and CH_3-1 (Figure 2c).

For the elucidation of the absolute configuration at these two centers, a ruthenium-catalyzed oxidative degradation procedure[9] was applied (Scheme 1), ultimately leading to the Mosher derivatives of (*R*)-*N*-methylalanine and (*R*)-*N*-methyl-3-aminobutyric acid and establishing an 1*R*,3*R* configuration.

The last problem to be solved was the stereoarray of the two molecular halves of **1**, that is, the absolute axial configuration. A ROESY interaction between the axial proton at C-4 and H-1′ indicated a close spatial proximity of these atoms (i.e., both atoms are above the isoquinoline "plane") and thus hinted at a *P*-configuration at the axis. This conclusion was further confirmed by CD comparison of the new compound with the likewise 5,8′-coupled and *P*-configured very similar alkaloid korupensamine A (**4**),[4] which had previously been assigned stereochemically by spectroscopic methods and total synthesis.[10] Ancistrolikokine A has, therefore, the full absolute stereostructure **1** as depicted in Figure 2c and can also be regarded as *N*-methyl-6-*O*-methylkorupensamine A.

Scheme 1. Oxidative Degradation of **1** and Analysis of the Resulting Amino Acids[a]



(i) $RuCl_3$, $NaIO_4$; analysis by subsequent gas chromatography with mass selective detection (GC−MSD) of the Mosher derivatives of the methyl esters.

For the isolation of further alkaloids of *A. likoko*, the MeOH−H_2SO_4 extract—this time of the leaves—was perfused with chloroform. Subsequently, the organic layer was resolved by HSCCC and rotation chromatography, yielding two compounds. The mass peak of the first one (**2**), together with the HRMS, suggested a molecular formula of $C_{24}H_{27}NO_4$, and the ^{1}H NMR spectrum again exhibited the typical signals of a naphthylisoquinoline alkaloid. As for **1**, two methoxy groups were observed, but their "normal" chemical shifts (3.85 and 4.10 ppm) indicated that they were not close to a biaryl axis. The 5,8′-coupling type was attributed tentatively from data similar to those described for **1** (see above), by the chemical shifts of CH_3-2′ (2.30 ppm) and CH_3-3 (1.04 ppm), and by the HMBC and ROESY interactions shown in Figure 3a,b. By virtue of an NOE interaction with H-7 (and because it is not adjacent to the axis and thus cannot be located at C-6), the methoxy group at 3.85 ppm must be located at C-8. The other methoxy function (4.10 ppm) must, therefore, be attached to C-4′ or C-5′; an NOE interaction from this group to H-6′ (Figure 3b) provided evidence for a 4′-hydroxy-5′-methoxy substitution. In contrast to ancistrolikokine A (**1**), the H-3 signal appeared at 2.75 ppm (Figure 3c), which is indicative of a cis-array of the methyl groups at C-1 and C-3. This was confirmed by an NOE interaction between H-1 and H-3. The cis-configuration of this compound is remarkable because of the known[8] instability of such cis-configured *N*-unsubstituted-1,3-dimethyltetrahydroisoquinolines, which may be the reason that only a few such alkaloids have as yet been reported as natural products.[2,8,11]

The absolute configuration of **2** was again deduced from the oxidative degradation: the formation of (*R*)-3-aminobutyric acid indicated unambiguously a 3*R* configuration. For the configuration at C-1 of cis-configured 1,3-dimethyltetrahydroisoquinolines, however, this degradation is not as reliable as for the trans-isomers.[11] From the *R* configuration at C-3 and the above-mentioned NOE interaction, a 1*S* configuration could be concluded. As for **1**, the configuration at the biaryl axis was finally derived by ROESY interactions between H_{ax}-4 and H-7′, on the one hand, and between H-3 and H-1′, on the other. The isolated compound must thus have stereostructure **2** (Figure 3c). Because no naphthylisoquinoline alkaloid with this structure was known, the compound was recognized as new and named ancistrolikokine B. It may be regarded as a C-1-epi derivative of korupensamine E (**5**, Figure 4), a compound isolated previously from the Cameroonian liana *A. korupensis*.[12] The close similarity of the CD spectra of these two compounds supported the axial *M* configuration attributed to **2** above.

The second compound (**3**) isolated from the leaves of *A. likoko* exhibited a ^{1}H NMR spectrum similar to that of **2**, but the mass peak at *m*/*z* 407 indicated a molecular formula of $C_{25}H_{29}NO_4$, corresponding to a naphthylisoquinoline alkaloid with one more methyl group compared to **2**. The additional ^{1}H NMR signal at 2.31 ppm, corresponding to

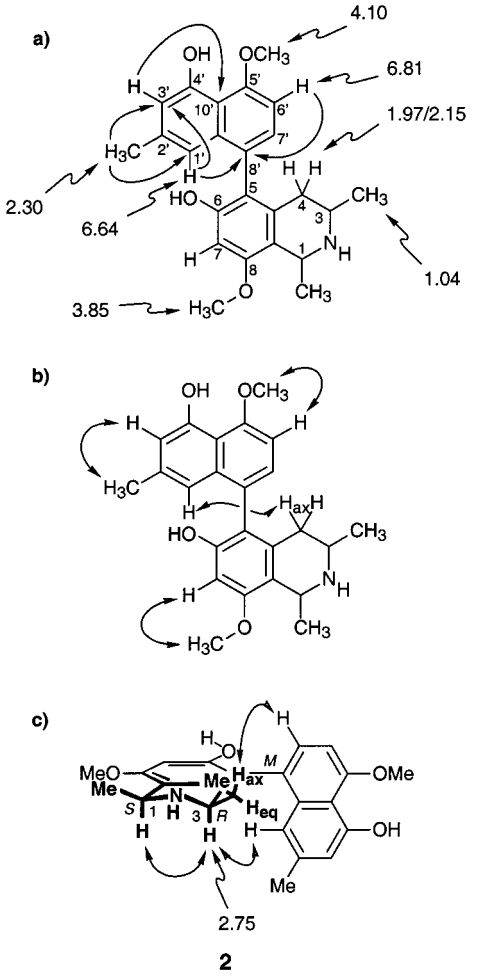


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Figure 3. Constitution of **2** (a) by chemical shifts (δ values) and HMBC interactions; (b) by ROESY correlations; (c) relative configuration (and additional proof of constitution) of the new alkaloid by further ROESY measurements.

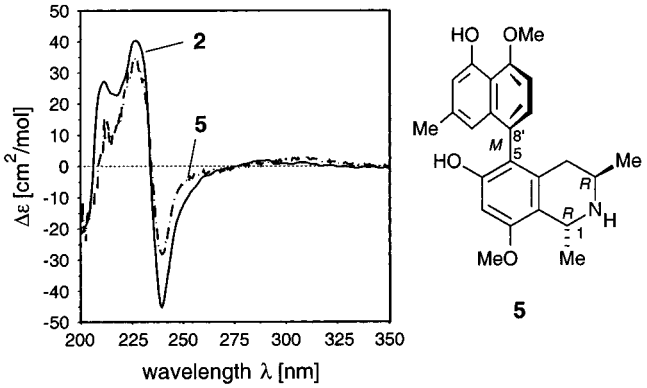

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Figure 4. Absolute axial configuration of **2** as derived from CD comparison with korupensamine E (**5**).

three protons, indicated the presence of an *N*-methyl group, with this attribution being corroborated by HMBC correlations to C-1 and C-3 (Figure 5a,b). The complete structure elucidation led to the constitution of an *N*-methylated derivative of **2**, but this new alkaloid is trans-configured, as was seen from the chemical shift of the H-3 (3.15 ppm) and, as for **1**, from the NOE interaction between CH_3-1 and H-3. From its NMR and CD spectra, the axial configuration was shown also to be *M*, as described above for **2**, leading to the stereostructure **3**. This new naphthylisoquinoline alkaloid, named ancistrolikokine C, is closely related to korupensamine E (**5**), being its *N*-methyl derivative.

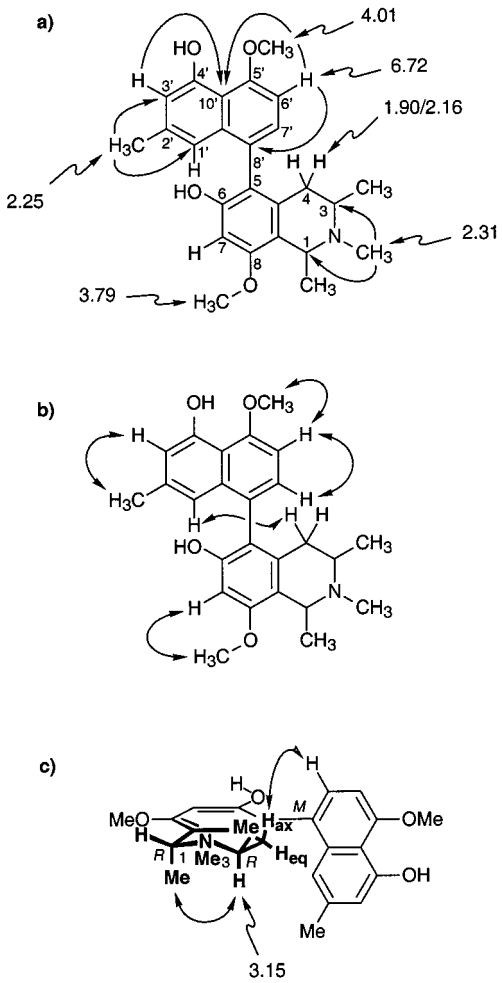

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Figure 5. Constitution of **3** (a) by chemical shifts (δ values) and HMBC interactions; (b) by ROESY correlations; (c) relative configuration (and additional proof of constitution) of the new alkaloid by further ROESY measurements.

Table 1. Activities against *P. falciparum* and Cytotoxicities of Compounds **1**−**4**

compound	NF54 strain IC_{50} (ng mL^{-1})	K1 strain IC_{50} (ng mL^{-1})	MIC L-6 (μg mL^{-1})
1	191 (4.0[a])	140 (53[a])	90
2	538 (3.6[a])	208 (81[a])	30
3	6232 (3.2[a])	924 (71[a])	n.d.[b]
4	24 (18[a])	72 (42[a])	100

[a] Respective value for chloroquine in the same test series. [b] Not determined.

The alkaloids described here were tested for their in vitro antiplasmodial activities against the malaria parasite *Plasmodium falciparum*. Whereas korupensamine A (**4**) was again found to be highly active, in accordance with literature findings,[4,13] the new, less polar compounds **1**−**3** exhibited only moderate antimalarial activities. This fact accords with our previous observation[14] that the presence of free hydroxy groups is essential for potent antiplasmodial effects of naphthylisoquinoline alkaloids.

In this work, the isolation and structure elucidation of three new (**1**−**3**) and one known (**4**) naphthylisoquinoline alkaloids have been described. Apart from the additional *N*-methyl group in **3**, ancistrolikokines B (**2**) and C (**3**) are C-1 epimers, while ancistrolikokine A (**1**) has the opposite axial configuration and an *O*-methylation pattern completely different from the other alkaloids. Interestingly, the

alkaloids of other *Ancistrocladus* species, such as *A. abbreviatus* and *A. barteri*, are frequently *N*-methylated for cis and *N*-unsubstituted for trans, and thus exhibit opposite characteristics to the new alkaloids described here.[2] Compound **1** may thus be regarded as a derivative of korupensamine A (**4**), known from *A. korupensis*[4] and now also found in *A. likoko*. To our knowledge, **1** is the first 5,8′-coupled naphthylisoquinoline alkaloid with a 6-methoxy-8-hydroxy substitution pattern.

The absolute configuration at C-3 is of chemotaxonomical interest because, for Asian and East African *Ancistrocladus* species (for example, *A. heyneanus* and *A. robertsoniorum*), only 3*S*-configured naphthylisoquinoline alkaloids are known, whereas both 3*S*- and 3*R*-configured alkaloids occur in West African species, as in *A. guineënsis* and *A. korupensis*.[2] The Central African liana *A. likoko*, with four 3*R*-configured alkaloids, seems to be closely related to the latter ones. Furthermore, the 5,8′-coupling type of its constituents classifies the plant as a typical African member of this family. Interestingly, the 4′-hydroxy-5′-methoxy substitution pattern is quite a rare feature that has until now been found exclusively in one other 5,8′-coupled naphthylisoquinoline alkaloid, viz. korupensamine E (**5**, Figure 4) from *A. korupensis*.

Experimental Section

General Experimental Procedures. Melting points were determined on a Reichert-Jung Thermovar hot-plate and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter (25 °C, 10 cm cell); IR spectra, on a Perkin-Elmer 1429 spectrophotometer; and CD spectra (25°, EtOH, 0.1 cm cell), on a JASCO J-715 spectropolarimeter. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were measured on a Bruker DMX 600 instrument using $CDCl_3$ or CD_3OD as solvents and internal standards (δ 7.26 and δ 77.01, respectively, as well as δ 3.30 and δ 49.01 ppm, respectively). Proton-detected, heteronuclear correlations were measured using HMQC (optimized for $^1J_{HC}$ = 145 Hz) and HMBC (optimized for $^nJ_{HC}$ = 7 Hz). EIMS and HRMS were determined on Finnigan MAT 8200 and Finnigan MAT 90 instruments (70 eV). For TLC, precoated Si gel 60 F_{254} plates (Merck, 5 × 10 cm), deactivated with concentrated NH_3, were used. Spots were detected under UV light. Column chromatography was carried out using Si gel 60 (60−200 mesh, Merck), deactivated with 5% concentrated NH_3. A PC, Inc. high-speed countercurrent chromatograph was used ["Tripple Coil", 1.7 × 106 500 mm (large coil), TLC detection (see above), flow 2.0 mL min^{-1}, 850 min^{-1}]. Rotation chromatography was performed using a Harrison Research Chromatotron with Si gel 60 PF_{254} containing $CaSO_4$.

Plant Material. Leaves and roots of *A. likoko* were collected and identified by one of us (V. M.) in the Yangambi area, Democratic Republic of Congo, in August 1996. A voucher specimen is deposited at the Institut für Organische Chemie (no. 16).

Extraction and Isolation. The air-dried and ground root bark (1.5 kg) of *A. likoko* was extracted successively with petroleum ether, dichloromethane, and methanol using a Soxhlet apparatus. A solution of the methanol extract (20 g) and $NaHCO_3$ (8 g) in water (1 L) was stirred for 24 h. This solution was perfused with chloroform until the aqueous layer was free of alkaloids (72 h). Evaporation of the organic layer under vacuum gave a brown solid (8.7 g), which was partitioned using HSCCC [$CHCl_3$-MeOH-1 N HCl, 100:80:60, mobile phase: lower phase, (H) → T]. Eleven fractions were obtained, of which fractions 5 (0.85 g) and 6 (0.23 g) were combined and chromatographed over Si gel deactivated with 5% NH_3 (CH_2Cl_2−MeOH, gradient 49:1 to 9:1). A compound containing a yellow impurity was eluted from this column using CH_2Cl_2−MeOH (20:1). This fraction was evaporated to dryness, and the colored impurity was removed by washing with MeOH to yield **1** (13.7 mg, 33.6 μmol, 0.00090%). HSCCC fraction 7 (0.29 g) was chromatographed over Si gel deactivated with 5% NH_3 using CH_2Cl_2−CH_3OH (gradient 49:1 to 9:1). Another compound was eluted using CH_2Cl_2−CH_3OH (9:1). A colored impurity was again removed by washing with CH_2Cl_2 to yield **4** (7.2 mg, 18.9 μmol, 0.00048%).

The air-dried and ground leaves were extracted exhaustively with 1 N H_2SO_4−MeOH (5:1) at room temperature. After removal of MeOH, the aqueous solution was prefractionated by liquid−liquid partition using CH_2Cl_2. Evaporation of the solvent furnished a residue, which was subjected to HSCCC [$CHCl_3$−MeOH−0.1 N HCl, 100:85:60, mobile phase:lower phase, (H) → T], yielding two brownish crude fractions. The first HSCCC fraction was resolved by rotation chromatography using CH_2Cl_2−MeOH−triethylamine (gradient 99:1:0.1 to 90:10:0.1), yielding **2** (11.9 mg, 30.2 μmol, 0.0024%). Likewise by rotation chromatography (CH_2Cl_2−MeOH−triethylamine, gradient 99:1:0.2 to 70:30:0.2), the second HSCCC fraction was resolved yielding **3** (13.5 mg, 33.1 μmol, 0.0024%).

Ancistrolikokine A (1): colorless solid; mp 230−231 °C; $[\alpha]^{25}_D$ +79.6° (*c* 0.25, MeOH); CD (EtOH) $\Delta\epsilon_{194}$ 21.0, $\Delta\epsilon_{227}$ −22.16, $\Delta\epsilon_{239}$ 15.5, $\Delta\epsilon_{259}$ 1.93, $\Delta\epsilon_{263}$ 3.86, $\Delta\epsilon_{311}$ 3.57; IR (KBr) ν_{max} 3395 (m, NH), 2959 (m), 1619 (m), 1588 (s), 1424 (m), 1329 (m), 1254 (m), 1198 (m), 1126 (m), 1078 (s), 1038 (m), 954 (m), 819 (m), 736 (m), 675 (m), 600 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, d, J = 6.5 Hz, CH_3-3), 1.36 (3H, d, J = 6.6 Hz, CH_3-1), 1.82 (1H, dd, J = 17.9, 11.2 Hz, H_{ax}-4), 2.15 (1H, dd, J = 17.9, 4.5 Hz, H_{eq}-4), 2.22 (3H, s, CH_3-2′), 2.24 (3H, s, NCH_3), 3.10 (1H, m_c, H-3), 3.51 (3H, s, OCH_3-6), 4.01 (3H, s, OCH_3-4′), 4.09 (1H, q, J = 6.5 Hz, H-1), 6.37 (1H, s, H-7), 6.56 (1H, s, H-3′), 6.61 (1H, s, H-1′), 6.80 (1H, d, J = 7.8 Hz, H-6′), 7.06 (1H, d, J = 7.8 Hz, H-7′), 9.37 (1H, s, OH-5′); ^{13}C NMR ($CDCl_3$) δ 16.78 (CH_3-1), 18.95 (CH_3-3), 21.96 (CH_3-2′), 30.88 (C-4), 35.65 (*N*-CH_3), 46.23 (C-3), 55.40 (C-1), 55.77 (OCH_3-6), 56.01 (OCH_3-4′), 97.50 (C-7), 106.21 (C-3′), 109.31 (C-6′), 113.43 (C-10′), 116.00 (C-9), 118.29 (C-1′), 119.91 (C-5), 125.13 (C-8′), 129.55 (C-7′), 134.88 (C-10), 135.48 (C-9′), 135.61 (C-2′), 153.33 (C-5′), 153.74 (C-8), 156.20 (C-4′), 156.62 (C-6) (^{13}C attributions achieved by HMQC and HMBC experiments); EIMS *m/z* 407 $[M]^+$ (3), 392 $[M - CH_3]^+$ (99), 362 $[M - 2CH_3]^+$ (26), 188 $[M - 2CH_3]^{2+}$ (12); HRMS *m/z* 392.186 $[M - CH_3]^+$ (calcd for $C_{24}H_{26}NO_4$, 392.185).

Ancistrolikokine B (2): amorphous solid; $[\alpha]^{25}_D$−166.4° (*c* 0.11, EtOH); CD (EtOH) $\Delta\epsilon_{210}$ +20.6, $\Delta\epsilon_{217}$ +8.0, $\Delta\epsilon_{224}$ +21.5, $\Delta\epsilon_{226}$ +20.8, $\Delta\epsilon_{228}$ +21.16, $\Delta\epsilon_{239}$ −43.6, $\Delta\epsilon_{310}$ +1.5; IR (KBr) ν_{max} 3400 (m, NH), 2980 (m), 1635 (m), 1590 (s), 1460 (m), 1395 (m), 1340 (m), 1270 (m), 1170 (m), 1120 (m), 1100 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, d, J = 6.3 Hz, CH_3-3), 1.54 (3H, d, J = 6.2 Hz, CH_3-1), 1.97 (1H, dd, J = 16.4, 2.2 Hz, H_{eq}-4), 2.15 (1H, dd, J = 16.1, 11.3 Hz, H_{ax}-4), 2.30 (3H, s, CH_3-2′), 2.75 (1H, m_c, H-3), 3.85 (3H, s, OCH_3-8), 4.10 (3H, s, OCH_3-5′), 4.38 (1H, q, J = 6.2 Hz, H-1), 6.50 (1H, s, H-7), 6.64 (1H, s, H-1′), 6.76 (1H, s, H-3′), 6.81 (1H, d, J = 7.9 Hz, H-6′), 7.22 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR ($CDCl_3$) δ 21.57 (CH_3-3), 21.88 (CH_3-2′), 22.56 (CH_3-1), 36.89 (C-4), 48.62 (C-3), 49.89 (C-1), 55.13 (OCH_3-8), 56.14 (OCH_3-5′), 96.53 (C-7), 103.36 (C-6′), 113.14 (C-3′), 113.64 (C-10′), 115.44 (C-1′), 117.19 (C-5), 120.00 (C-9), 124.67 (C-8′), 130.01 (C-7′), 135.52 (C-9′), 136.58 (C-10), 139.16 (C-2′), 152.55 (C-6), 154.78 (C-4′), 156.56 (C-5′), 157.63 (C-8) (^{13}C attributions achieved by HMQC and HMBC experiments); EIMS *m/z* 393 $[M]^+$ (10), 392 $[M - H]^+$ (22), 391 $[M - H_2]^+$ (67), 378 $[M - CH_3]^+$ (100), 376 $[M - CH_3 - H_2]^+$ (37), 363 $[M - 2CH_3]^+$ (9), 348 $[M - 3CH_3]^+$ (21), 188 $[M - CH_3 - H_2]^{2+}$ (28), 181.5 $[M - 2CH_3]^{2+}$ (19), 174 $[M - 3CH_3]^{2+}$ (18); HRMS *m/z* 378.1704 $[M - CH_3]^+$ (calcd for $C_{23}H_{24}NO_4$, 378.1705).

Ancistrolikokine C (3): amorphous solid; $[\alpha]^{20}_D$−54.86° (*c* 0.11, EtOH); CD (EtOH) $\Delta\epsilon_{211}$ +26.9, $\Delta\epsilon_{218}$ +22.8, $\Delta\epsilon_{227}$ +40.2, $\Delta\epsilon_{240}$ −44.7, $\Delta\epsilon_{288}$ +1.8; IR (KBr) ν_{max} 3390 (s, OH), 2960 (m, C−H), 1627 (m), 1580 (s), 1440 (m), 1883 (s), 1330 (m), 1160 (m), 1120 (m), 1090 (s), 745 (m); ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6.5 Hz, CH_3-3), 1.39 (3H, d, J = 6.6 Hz, CH_3-1), 1.90 (1H, dd, J = 17.8, 4.6 Hz, H_{eq}-4), 2.16 (1H, dd, J = 17.9, 11.3 Hz, H_{ax}-4), 2.25 (3H, s, CH_3-2′), 2.31 (3H, s, *N*-CH_3), 3.15 (1H,

m_c, H-3), 3.79 (3H, s, OCH_3-8), 4.01 (3H, s, OCH_3-5′), 4.15 (1H, q, J = 6.6 Hz, H-1), 6.46 (1H, s, H-7), 6.66 (2H, s, H-1′ and H-3′), 6.72 (1H, d, J = 7.9 Hz, H-6′), 7.05 (1H, d, J = 7.9 Hz, H-7′); ^{13}C NMR ($CDCl_3$) δ 17.17 (CH_3-1), 18.84 (CH_3-3), 21.72 (CH_3-2′), 31.32 (C-4), 35.59 (N-CH_3), 46.33 (C-3), 55.06 (OCH_3-8), 55.52 (C-1), 55.91 (OCH_3-5′), 96.51 (C-7), 103.14 (C-6′), 112.66 (C-3′)[a], 113.47 (C-10′)[a], 115.41 (C-1′)[a], 117.09 (C-5), 118.36 (C-9), 125.33 (C-8′)[a], 128.94 (C-7′), 133.60 (C-9′)[a], 135.56 (C-10)[a], 138.44 (C-2′), 153.00 (C-6), 154.40 (C-4′), 156.04 (C-5′), 156.67 (C-8) (^{13}C attributions achieved by HMQC and HMBC experiments, except for those marked[a], which have been attributed by analogy to those of **3**); EIMS m/z 407 $[M]^+$ (1), 406 $[M - H]^+$ (3), 392 $[M - CH_3]^+$ (100), 377 $[M - 2CH_3]^+$ (4), 362 $[M - 3CH_3]^+$ (26), 196 $[M - CH_3]^{2+}$ (7), 188.6 $[M - 2CH_3]^{2+}$ (18), 181 $[M - 3CH_3]^{2+}$ (14); HRMS m/z 392.1869 $[M - CH_3]^+$ (calcd for $C_{24}H_{26}NO_4$, 392.1862).

Korupensamine A (4): colorless solid; mp 170−172 °C; $[\alpha]^{20}_D$ +20.68° (*c* 0.10, $CHCl_3$); spectroscopic data in accordance to those of authentic samples from previous synthetic[10,15] and isolation work.[4]

Oxidative Degradation of 1−3. The degradation, the derivatization of the amino acids, and the subsequent GC-MSD analysis were carried out for **1**−**3** as described previously.[9]

Biological Experiments. Antiplasmodial activity was determined using the NF54 strain of *P. falciparum* (sensitive to all known antimalarial drugs) and the K1 strain (resistant to chloroquine and pyrimethamine). A modification of the [^{3}H]-hypoxanthine incorporation assay[16] was used.[17] Briefly, infected human red blood cells were exposed to serial drug dilutions in microtiter plates for 48 h at 37 °C in a gaseous mixture with reduced oxygen and elevated CO_2. [^{3}H]-Hypoxanthine was added to each well, and, after further incubation for 24 h, the wells were harvested on glass fiber filters and counted in a liquid scintillation counter. From the sigmoidal inhibition curve the IC_{50} value was calculated. The assays were run in duplicate and repeated at least once. Cytotoxicity was assessed using rat skeletal myoblast (L-6) cells and microscopic determination of the MIC after 72 h.

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