Ancistrotanzanine A, the First 5,3′-Coupled Naphthylisoquinoline Alkaloid, and Two Further, 5,8′-Linked Related Compounds from the Newly Described Species *Ancistrocladus tanzaniensis*[#,1]

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The first phytochemical investigation of the recently discovered East African liana *Ancistrocladus tanzaniensis* is described, resulting in the isolation and structural elucidation of two new naphthylisoquinoline alkaloids, ancistrotanzanines A (**5**) and B (**6**), and the known compound ancistrotectoriline A (**7**). Ancistrotazanine A (**5**) represents a hitherto unprecedented 5,3′-coupling type between the naphthalene and isoquinoline portions, while **6** and **7** are 5,8′-coupled. The structures of the compounds were determined by spectroscopic, chemical, and chiroptical methods. Compounds **5** and **6** showed good activities against the pathogens of leishmaniasis and Chagas' disease, *Leishmania donovani* and *Trypanosoma cruzi*, while **5**−**7** displayed moderately potent antiplasmodial activities against *Plasmodium falciparum* parasites.

Ancistrocladus, the only genus of the tropical plant family Ancistrocladaceae, comprises about 25 species indigenous to the tropical rainforests of West, Central, and East Africa and of Southeast Asia.[2] Like the closely related Dioncophyllaceae,[3] the Ancistrocladaceae are characterized phytochemically by the presence of naphthylisoquinoline alkaloids.[4] Some of these structurally and biosynthetically unique secondary metabolites display highly potent in vitro and in vivo antiplasmodial activities, like dioncopeltine A (**1**) and dioncophyllines B (**2**) and C (**3**),[5−7] while other representatives of this novel class of acetogenic isoquinoline alkaloids[8] show remarkable antileishmanial activities, such as ancistroealaine A (**4**),[9] or antitrypanosomal properties,[10] making the search for further new compounds of this type potentially rewarding. The broad structural variety within the naphthylisoquinoline alkaloids arises from the fact that, due to their probable biosynthetic formation through oxidative phenolic coupling,[11] their two molecular portions can be linked either in *ortho*- or in *para*-positions relative to the phenolic oxygen functions, i.e., in positions 1′, 3′, 6′, or 8′ of the naphthalene portion and at C-5 or C-7 of the isoquinoline part. Of the eight possible different coupling types, six have so far been identified in nature (viz., 5,1′, 5,8′, 7,1′, 7,3′, 7,6′, and 7,8′, see for example, structures **1**−**4**).

In this paper, we report on the first phytochemical investigation of the newly described East African *Ancistrocladus* species *A. tanzaniensis*,[12] leading to the discovery of a novel 5,3′-coupling type, present in the new alkaloid ancistrotanzanine A (**5**). In addition, the new ancistrotanzanine B (**6**) and the known[13] ancistrotectoriline A (**7**), both 5,8′-coupled, were also isolated.

Results and Discussion

A. tanzaniensis was collected in Tanzania in the Uzungwa mountains at 1200 m above sea level, in contrast to all the other *Ancistrocladus* species, which so far have been found in habitats of less than 800 m altitude.[12] Repeated column chromatography and preparative HPLC of a CH_2Cl_2 extract of the air-dried and ground leaves of *A. tanzaniensis* afforded three alkaloids (**5**−**7**), the UV spectra of which suggested that they are naphthylisoquinoline alkaloids.

The M^+ peak of the first compound (**5**), together with HRMS data, indicated a molecular formula of $C_{25}H_{27}NO_4$. The ^{1}H NMR spectrum exhibited signals typical of a naphthyl-1,3-dimethyldihydroisoquinoline alkaloid with the significant lack of the H-1 quartet at ca. 4 ppm and the downfield shifted CH_3-1 signal at 2.81 ppm (Figure 2a). This assumption was corroborated by the chemical shift of the C-1 peak (δ 175.6) in the ^{13}C NMR spectrum. The signals at 3.90, 4.05, and 4.13 ppm (three protons each) showed the presence of three methoxy groups. Two of them were attached to C-6 and C-8 in the isoquinoline moiety by NOESY correlations (Figure 2b) between H-7 and OCH_3-8 and OCH_3-6. HMBC investigations showed significant cross-peaks from OCH_3-8 to C-8, from OCH_3-6 to C-6, and from H-7 to C-6 and C-8, which confirmed the above assignment. The third methoxy group was located at C-5′ in the naphthalene portion because of a NOESY interaction with H-6′ and an HMBC correlation to C-5′. This assignment was confirmed by the HMBC interaction between H-7′ and C-5′. When recording the ^{1}H NMR spectrum in $CDCl_3$ instead of CD_3OD, an additional OH signal was identified at 9.51 ppm. This hydroxy group was located at C-4′, because both its proton and the protons of the aromatic methyl group showed HMBC correlations to C-3′. While the signals of H-7′ and H-8′ overlapped in the ^{1}H NMR spectrum recorded in CD_3OD, measurement in $CDCl_3$ revealed the aromatic protons to form the coupling pattern of a triplet, two doublets, and two singlets, which

[#] Dedicated to Prof. Werner Hanke on the occasion of his 60th birthday.

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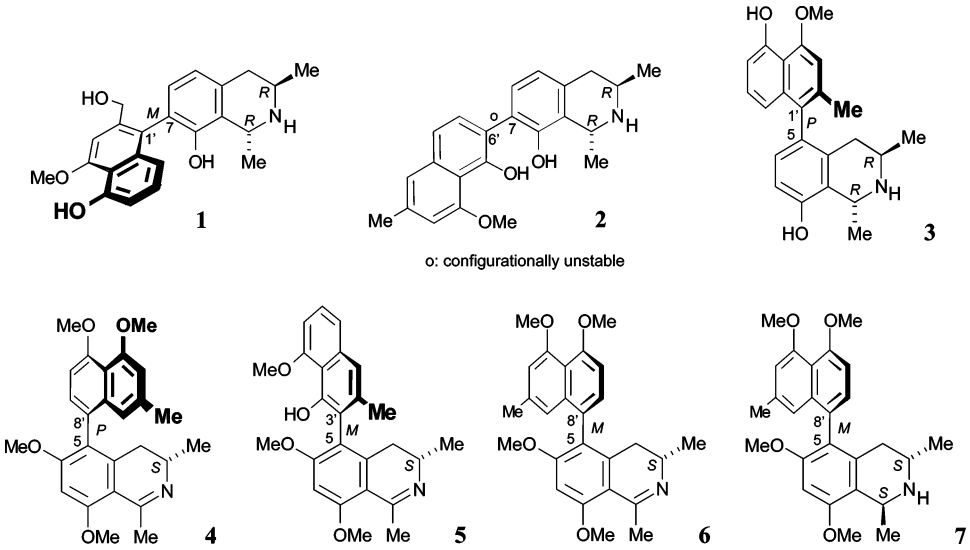


Figure 1. Structures of naphthylisoquinoline alkaloids of different coupling types. Compounds **5**−**7** have been isolated from *A. tanzaniensis*.

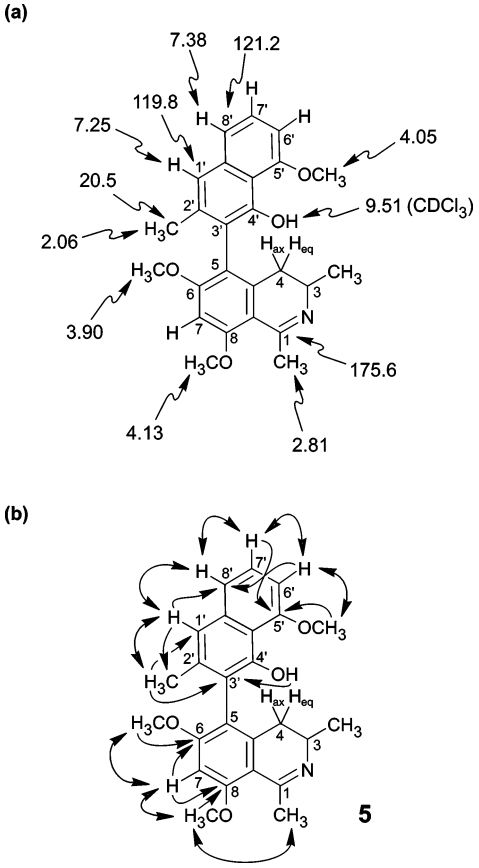


Figure 2. Selected NMR data of ancistrotanzanine A (**5**): (a) ^{1}H NMR and ^{13}C NMR shifts (CD_3OD, δ in ppm) and (b) NOESY and HMBC interactions relevant for the constitution.

excluded the biaryl axis from being located at C-6′ or C-8′, leaving only C-3′ or C-1′ for the coupling position. Of these, the latter was excluded by NOESY interactions of H-1′ (δ 7.25) with H-8′ (δ 7.38) and CH_3-2′ (δ 2.06). HMBC correlations from H-1′ and H-6′ to C-8′ (δ 121.2), from H-1′ to CH_3-2′ (δ 20.5), and vice versa from the protons of the aromatic methyl group to C-1′ (δ 119.8) corroborated the assumption that the biaryl axis is located at C-3′ in the naphthalene moiety. The high-field ^{1}H NMR shifts of CH_3-2′ and OCH_3-6 finally determined the position of the biaryl axis to correspond to an as yet unknown 5,3′-coupled naphthylisoquinoline alkaloid **5**, for which the trivial name ancistrotanzanine A is proposed.

The absolute configuration at C-3 of **5** was determined by ruthenium-mediated oxidative degradation[14] followed by stereochemical analysis of the degradation products by gas chromatography with mass selective detection (GC-MSD) after derivatization with the *R*-enantiomer of Mosher's chloride. The formation of (*S*)-3-aminobutyric acid clearly showed the alkaloid to be *S*-configured at C-3.

Attempts to assign the configuration at the biaryl axis relative to the now known absolute configuration at C-3 by specific NOESY interaction between H_{eq}-4 and CH_3-2′ (Figure 2c) failed because of the overlap of the two diastereotopic, but unfortunately largely isochronous protons at C-4.[15]

Therefore, the absolute axial configuration of ancistrotanzanine A (**5**) was established by circular dichroism (CD) investigations. However, since an empirical comparison of its CD spectrum with that of a configurationally known similar alkaloid was not possible due to the presence of a novel coupling type, the experimental CD spectrum of **5** was interpreted by quantum chemical CD calculations, a highly efficient, most useful tool in the stereoanalysis of chiral natural products, further developed and frequently used by our group.[16−18] To take into account the possibly different chiroptical behavior of a large number of hypothetical conformational species, ancistrotanzanine A (**5**) was submitted to a conformational analysis using the Tripos force field and further refined using the semiempirical AM1[19] method as implemented in the program package Vamp 6.5.[20] These calculation were arbitrarily started with the (*M*,*S*)-atropo-diastereomer. For each of the 48 conformers thus identified (all appearing within 3 kcal/mol above the global minimum), the corresponding CD spectrum was calculated by applying the semiempirical CNDO/2S[21] approach. With respect to the different occurrence of these conformers according to their energetic contents, the 48 calculated single CD spectra were then added up according to the Boltzmann statistics to give the overall calculated CD spectrum for the (*M*,*S*)-isomer of ancistrotanzanine A (**5**), which was subsequently submitted to a "UV-correction"[22] (Figure 3, top left). In a similar way, the theoretical spectrum for the *P*-atropisomer was also computed (Figure 3, top right). Comparison of the calculated CD spectra with the experimental one showed a good agreement in the case of the (*M*,*S*)-isomer, whereas the

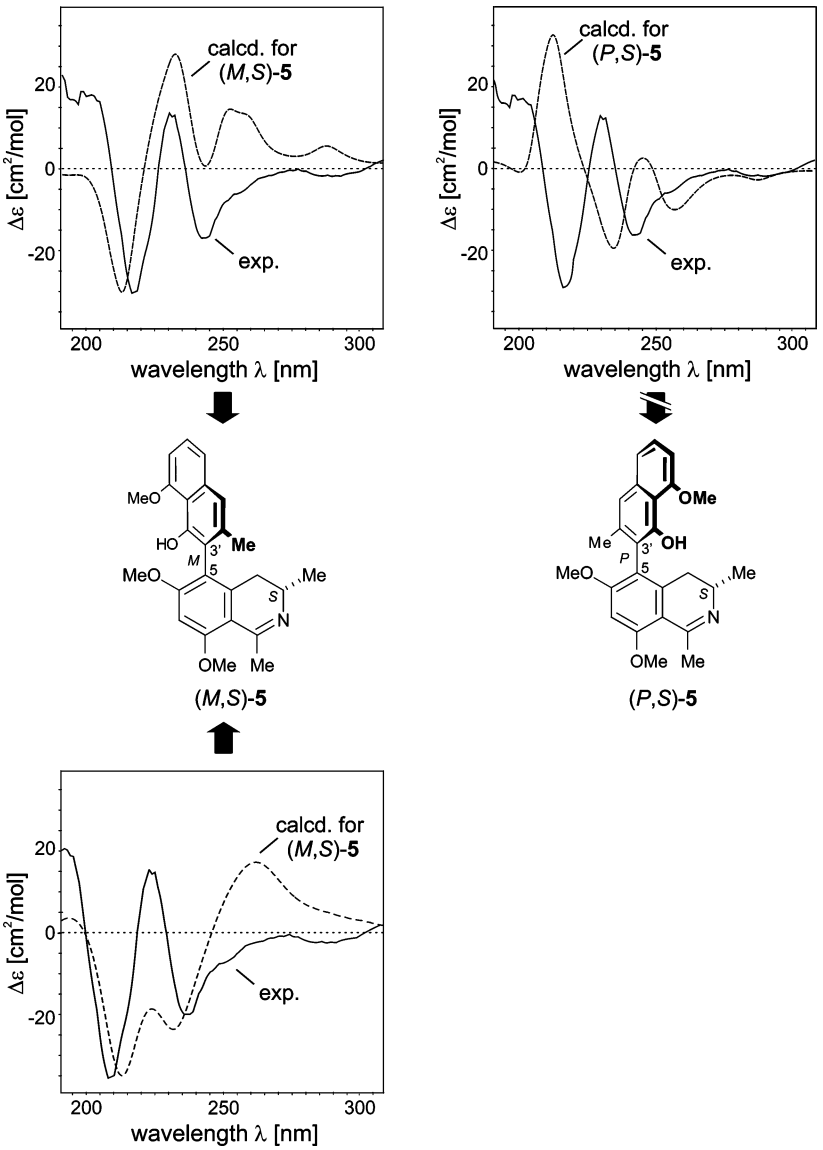


Figure 3. Attribution of the absolute axial configuration of ancistrotanzanine A (**5**) by comparison of the CD spectra calculated for (*M*,*S*)-**5** and (*P*,*S*)-**5** (top left and right: AM1-Boltzmann; bottom left: MM3-MD) with the experimental one (in MeOH).

theoretical spectrum predicted for the (*P*,*S*)-diastereomer was almost opposite, which helped assign the axial configuration of **5** as *M*, thus establishing ancistrotanzanine A (**5**) as having the (*M*,*S*)-configuration as shown in Figure 3. For the confirmation of the absolute axial configuration of ancistrotanzanine A (**5**), the molecule was submitted to a molecular dynamics (MD) simulation,[16,23,24] which was carried out at a virtual temperature of 500 K using the MM3[25] force field. From the 500 ps trajectory of motion, 1000 structures were extracted, for which the single CD spectra were calculated with the semiempirical CNDO/2S[21] method as mentioned earlier. In the next step, the 1000 single CD spectra were added up arithmetically to give the theoretical overall CD spectrum. The spectrum calculated for (*M*,*S*)-**5** again revealed a good agreement with the measured one (Figure 3, bottom left), thus permitting the assignment of the absolute configuration of the chiral axis of ancistrotanzanine A (**5**) as *M*.

The second alkaloid (**6**) was deduced to correspond to the molecular formula of $C_{26}H_{29}NO_4$, from its HRMS and from the ^{13}C NMR spectral data. Its ^1H NMR spectrum (see Figure 4a) revealed a three-proton singlet at low field for CH_3-1 (δ 2.86), which, when combined with the absence of both a three-proton doublet at ca. δ 1.5 and a H-1 signal at ca. δ 4 (as typical of naphthyl-1,3-methyltetrahydroisoquinolines), hinted at the presence of a naphthyldihydroisoquinoline alkaloid.[4] This assumption was confirmed by the chemical shift of the C-1 peak (δ 173.9) in the ^{13}C NMR spectrum.

From the "normal", not high-field-shifted signal of CH_3-2′ (δ 2.33), and the aromatic spin pattern system of three singlets and two doublets, the biaryl axis was excluded from being located at C-1′ or C-3′, leaving only C-8′ or C-6′ for the positioning of the biaryl axis. Of these, the latter could be eliminated by NOESY interactions between H-6′ (a doublet at δ 6.84) and the (normal-shifted) methoxy group (δ 4.00) at C-5′ (Figure 4b), revealing that the coupling position in the naphthalene moiety was located at C-8′.

Since only one out of four methoxy groups (δ 3.80) was found to be high-field-shifted (in contrast to those at δ 3.98, 4.00, and 4.06), the axis had to be located at C-5 of the isoquinoline unit, which was confirmed by NOESY interactions between H-7 (δ 6.54) and the protons of OCH_3-6 and OCH_3-8. In conclusion, the second compound was a

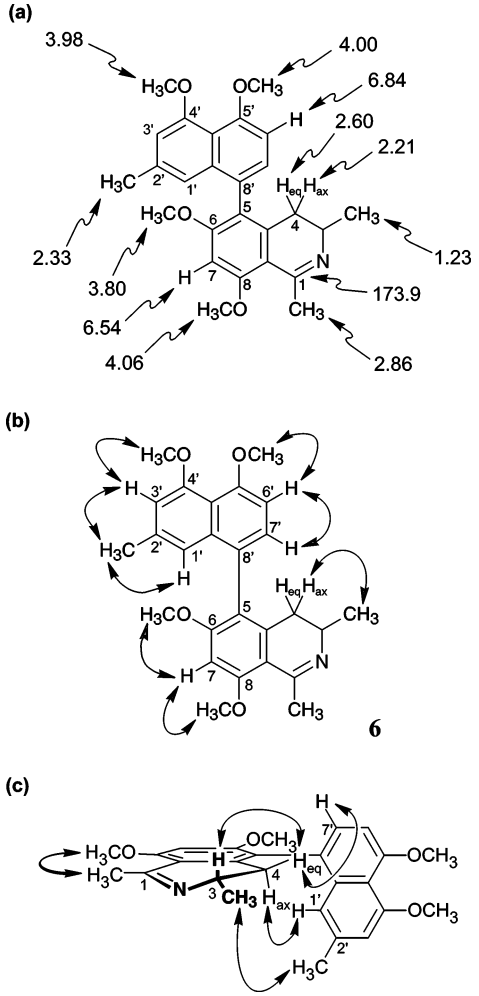


Figure 4. Selected NMR data of ancistrotanzanine B (**6**): (a) ^{1}H and ^{13}C NMR shifts (δ in ppm); (b) NOESY interactions indicative of the constitution; (c) configuration at the biaryl axis relative to the stereogenic center through NOESY interactions.

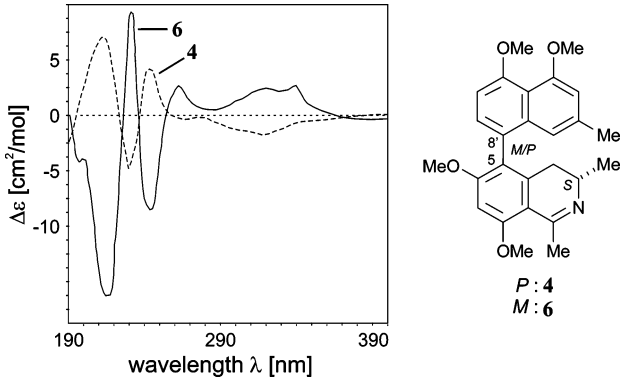


Figure 5. CD spectra of ancistrotanzanine B (**6**) and ancistroealaine A (**4**).

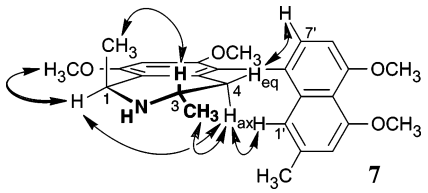
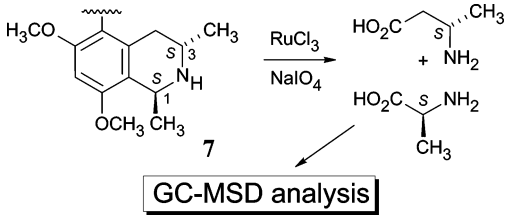


Figure 6. Selected NOESY interactions of **7** relevant for the configuration at the biaryl axis relative to the stereogenic center.

Scheme 1. Oxidative Degradation of **7** and Analysis of the Resulting Amino Acids



5,8′-coupled naphthyldihydroisoquinoline with the constitution **6**, as shown in Figure 4b.

Compound **6** has two stereogenic elements, the center at C-3 and the rotationally hindered biaryl axis between C-5 and C-8′. The absolute configuration at the stereocenter was assigned by a ruthenium-catalyzed oxidative degradation procedure,[14] ultimately leading to the Mosher derivative of (*S*)-3-aminobutyric acid, thus establishing the configuration at C-3 to be *S*.

The configuration at the biaryl axis relative to that of the stereogenic center at C-3 was deduced from NOESY interactions between the protons of the aromatic methyl group (CH_3-2′) and H-1′ with those of the methyl group at C-3 and with H-4_{ax}, which are both below the isoquinoline plane, indicating a close spatial proximity of these atoms, and a similar specific interaction was found between H-4_{eq} and H-7′. Given the known absolute *S*-configuration at the C-3 stereogenic center, these interactions clearly indicated an absolute *M*-configuration at the axis as shown in Figure 4c.

This conclusion that the biaryl axis has the *M*-configuration was confirmed by the CD spectrum of **6** (Figure 5), which was opposite to that of the likewise 5,8′-coupled, but *P*-configured alkaloid ancistroealaine A (**4**).[9]

This naphthylisoquinoline alkaloid **6** was thus a new compound and was named ancistrotanzanine B. With its constitution identical to that of **4** and the same configuration at C-3, it can also be addressed as 5-*epi*-ancistroealaine A.

The NMR, CD, and mass spectra of the third compound and its optical rotation were very similar to those published for ancistrotectoriline A (**7**), an alkaloid from the Asian liana *A. tectorius*,[13] but with some differences in the ^{1}H NMR and ^{13}C NMR shifts.[26] Still, our one- and two-dimensional NMR experiments led to the conclusion that the compound isolated here is the same as that isolated by Ye's group, with the constitution and relative configuration as shown in Figure 1. The identity of compound **7** with ancistrotectoriline A was finally proven by chromatographic and spectroscopic comparison with an authentic sample kindly provided by Dr. Ye.

The absolute configuration at C-1 and C-3 of **7**, however, had been assigned only tentatively in the literature.[13] Ruthenium(III)-catalyzed periodate oxidation of our compound afforded L-alanine and (*S*)-3-aminobutyric acid (Scheme 1), confirming the configuration at the two stereogenic carbons as 1*S*,3*S*, as previously assumed.[13]

This result was in agreement with NOESY interactions between H-3 and CH_3-1 on one hand and between H-4_{ax} and CH_3-3 and H-1 on the other (Figure 6), indicating a relative *trans*-configuration at C-1 versus C-3, which had previously been deduced only from chemical shifts.[13] The relative stereoarray at the biaryl axis in **7** was established by NOESY interactions between H-7′ and H-4_{eq} (hence both were above the isoquinoline "plane") and between H-1′ and H-4_{ax} (both below this "plane"), from which, in conjunction with the absolute *S*-configuration at C-1 and C-3 estab-

Table 1. ^{1}H and ^{13}C NMR Spectral Data of Compound **5** and **6**

	5[a,b]		**6**[a,c]	
C/H no.	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1		175.6		173.9
3	3.82 m	48.0	3.79 m	47.6
4	2.62 m	29.2	2.21 dd (17.1, 8.4), 2.60 dd (17.1, 5.7)	31.5
5		119.3		122.7
6		167.0		165.9
7	6.81 s	95.0	6.54 s	94.0
8		165.1		163.5
9		108.4		108.4
10		141.2		140.2
1′	7.25 s	119.8	6.51 s	123.4
2′		137.7		137.1
3′		117.1	6.70 s	108.9
4′		155.7		157.7
5′		157.1		157.5
6′	6.91 dd (6.8, 1.9)	105.2	6.84 d (7.9)	105.0
7′	7.34 t (8.5)	126.8	7.06 d (7.9)	128.8
8′	7.38 dd (7.6, 1.3)	121.2		116.1
9′		137.2		135.8
10′		113.3		123.3
CH_3-1	2.81	24.9	2.86 s	24.5
CH_3-3	1.33 d (6.8)	18.3	1.23 d (8.8)	17.2
OCH_3-6	3.90 s	55.3	3.80 s	56.3
OCH_3-8	4.13	55.2	4.06 s	56.2
CH_3-2′	2.06 s	20.5	2.33 s	22.1
OCH_3-4′			3.98 s	56.4
OCH_3-5′	4.05 s	55.6	4.00 s	56.6

[a] Signals were assigned by H,H-COSY, HMQC, HMBC, and NOESY spectra. [b] Spectra recorded in CD_3OD. [c] Spectra recorded in $CDCl_3$. [d] The signals are partly overlapped resulting in a pseudo triplet.

Table 2. Bioactivities of Compounds **5**−**7**

	IC_{50} [μg/mL]		
	5	**6**	**7**
P. falciparum (strain: K1)[a]	0.3	0.3	0.5
standard: chloroquine 0.055[b]			
P. falciparum (strain: 3D7)[c]	n.d.[d]	5	14
standard: chloroquine 0.01[b]			
T. cruzi	1.7	1.5	17.8
standard: benznidazole 0.42[b]			
T. b. rhodesiense	0.7	0.7	2.1
standard: melarsoprol 0.001[b]			
L. donovani	1.8	1.6	>10
standard: miltefosin 0.305[b]			
cytotoxicity L6 (MIC)	6.4	8.1	6.5

[a] Basel. [b] All values in μg/mL. [c] Copenhagen. [d] Not determined.

lished above, the *M*-configuration at the biaryl axis was deduced. This absolute axial configuration of **7** was confirmed by the close resemblance of its CD spectrum with that of the related *M*-configured ancistrobrevine B[27] (not shown) and was in agreement with the likewise CD-based assignment in the literature,[13] allowing a full stuctural assignment for ancistrotectoriline (**7**), occurring in both *A. tectorius* and *A. tanzaniensis*.

Because of the already mentioned promising antiprotozoal activities of several naphthylisoquinoline alkaloids,[3,5,6] the compounds **5**−**7** were tested for their in vitro antiplasmodial activity (see Table 2). All three alkaloids exhibited moderate antiplasmodial activities against the K1 strain (Basel) of *P. falciparum* (resistant to chloroquine and pyrimethamine), less than that of the standard chloroquine, but showed virtually no antiplasmodial activity against the chloroquine-sensitive 3D7 strain (Copenhagen) of *P. falciparum*. These results give an important contribution to our ongoing structure−activity relationship investigations within this compound class.[28] The most significant activity was found against *Leishmania donovani*, the pathogen of visceral leishmaniasis. In comparison to the highly active naphthylisoquinoline alkaloid ancistroealaine A (**4**, 4.1 μg/mL),[9] its atropo-diastereomer ancistrotanzanine B (**6**) was more active by a factor of 2.5 (1.6 μg/mL), and a similar high antileishmanial activity was found for ancistrotanzanine A (**5**). Weak antitrypanosomal activities were exhibited by compounds **5**−**7** against the pathogen of African sleeping sickness, *T. b. rhodeniense*, while **5** and **6** were some 4 times less active than the standard against *T. cruzi* (Chagas' disease) and showed only weak cytotoxicity.

From a chemotaxonomic point of view, all of the compounds isolated in this work, **5**−**7**, have an oxygen function at C-6 and the *S*-configuration at C-3. They are thus representatives of the so-called "Ancistrocladaceae-type" alkaloids. With these phytochemical characteristics, *A. tanzaniensis* closely resembles the only other known East African *Ancistrocladus* species, *A. robertsoniorum*,[29,30] and also the Southeast Asian members of the Ancistrocladaceae (among them, the ancistrotectoriline A producing *A. tectorius*).[4,13,31] It is clearly different from Central and West African *Ancistrocladus* species, many of which produce typical "Dioncophyllaceae-type" alkaloids such as **1**−**3** (*R*-configurated at C-3 and devoid of an oxygen function at C-6[4]) and also mixed, hybrid types (e.g., *R* at C-3 and oxygenated at C-6).[32]

In addition to these relationships with other plants, which help to define the chemotaxonomic position of *A. tanzaniensis*, the discovery of ancistrotanzanine A (**5**), with its previously unknown 5,3′-linkage, makes this "new" plant species unique within the tropical plant families Ancistrocladaceae and Dioncophyllaceae from a phytochemical point of view.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter (25 °C, 10 cm cell). UV spectra were recorded with a Varian Cary 50 Conc UV−visible spectrophotometer, IR spectra on a JASCO FT/IR-410 spectrometer, and CD spectra (25 °C, CH_3CN unless otherwise stated, 0.1 cm cell) on a JASCO J-715 spectropolarimeter. ^{1}H NMR (400 MHz, 600 MHz) and ^{13}C NMR (100 MHz, 150 MHz) spectra were measured on Bruker AMX 400 and DMX 600 instruments, respectively, using $CDCl_3$ (δ 7.26 and 77.0) and CD_3OD (δ 3.31 and 49.2) as solvents and internal ^{1}H and ^{13}C standards. Proton-detected, heteronuclear correlations were measured using HMQC (optimized for $^1J_{HC}$ = 145 Hz) and HMBC (optimized for $^nJ_{HC}$ = 7 Hz) pulse sequences. EIMS and HRMS were determined on JEOL JMS-HX/HX 110A and Finnigan MAT 90 instruments (70 eV), respectively. Analytical HPLC was carried out on a Bondapak C_{18} column (Waters, 3.9 × 300 mm, 5 μm); flow 1 mL min^{-1}; UV detection (307 nm); solvent, CH_3CN−H_2O (0.1% trifluoroacetic acid) (3:7 and 4:6), or on a Symmetry C_{18} column (Waters, 4.6 × 250 mm, 5 μm); flow 1 mL min^{-1}; UV detection (233 nm); solvent (A) CH_3CN (0.05% trifluoroacetic acid), (B) H_2O (0.05% trifluoroacetic acid); linear gradient, 0 min 5% A, 30 min 70% A. Preparative HPLC was carried out on a Discovery C_{18} column (Supelco, 21.2 × 250 mm, 5 μm) and on a silica gel 60 column (Knauer, 18.5 × 327 mm, 5 μm); flow, 6 mL min^{-1}, UV detection (307 nm), or on a Symmetry C_{18} column (Waters, 19 × 300 mm, 7 μm); flow 11 mL min^{-1}, UV detection (233 nm); solvent (A) CH_3CN (0.05% trifluoroacetic acid), (B) H_2O (0.05% trifluoroacetic acid); linear gradient, 0 min 20% A, 25 min 55% A. (*R*)-MTPA-Cl was prepared from (*S*)-MTPA (Fluka Chemie AG, Deisenhofen, Germany) as described earlier.[29] Organic solvents were dried and distilled prior to use.

Plant Material. Leaves of *A. tanzaniensis* were collected by two of us (H.N. and F.M.) in the Uzungwa Mountains in Tanzania, in February 2000, and identified by C. Frimodt-Møller, University of Copenhagen, and Dr. H. Rischer, University of Würzburg. Voucher specimens are deposited at the Department of Medicinal Chemistry, Pharmaceutical University of Denmark, and at Herbarium Bringmann (no. 42), University of Würzburg, Germany.

Extraction and Isolation. The air-dried material (500 g leaves) was ground and sequentially extracted with petroleum ether, CH_2Cl_2, and MeOH. The CH_2Cl_2 extract was concentrated in vacuo to give 29.6 g of a residue, 2 g of which were dissolved in methanol and directly resolved using preparative HPLC with the Symmetry C_{18} column and (a) CH_3CN (0.05% trifluoroacetic acid), (b) H_2O (0.05% trifluoroacetic acid) as the solvents, using a linear gradient (0 min 20% A, 25 min 55% A) to give 4.3 mg of compound **5** (t_R = 23.52 min). The rest of the extract was fractionated by vacuum-liquid chromatography on silica gel 60H (1 kg, 90% < 45 μm, Merck) using CH_2Cl_2–MeOH–diethylamine (90:10:3, 1.5 L; 80:20:3, 1 L; 60:40:3, 1 L) as the eluent. The fraction eluting between 2 and 4 L was further fractionated by column chromatography on silica gel 60 (650 g, 60–200 mesh, Merck) using petroleum ether–EtOAc–diethylamine (90:10:3, followed by 80:20:3, 70:30:3, 60:40:3, 50:50:3, and 40:60:3, each 1.5 L). The fraction eluted by petroleum ether–EtOAc–diethylamine (70:30:3) was concentrated to give 910 mg of a residue, while the fraction eluted by petroleum ether–EtOAc–diethylamine (50:50:3) yielded 710 mg of a residue. The former fraction was purified by preparative HPLC on silica gel 60 using CH_2Cl_2–MeOH–diethylamine (195:4:1) as the eluent, to give 3.2 mg of compound **6** (t_R = 7 min). The latter fraction was purified by preparative HPLC on silica gel 60 with CH_2Cl_2–MeOH–diethylamine (195:4:1) as the eluent, to give 17.7 mg of compound **7** (t_R = 10 min).

Ancistrotanzanine A (5): pale yellow powder; $[\alpha]_D^{25}$ +69.5° (*c* 0.1, EtOH); UV (MeOH) λ_{max} (log ϵ) 231 (1.87), 307 (1.43) nm; CD (MeOH) $\Delta\epsilon_{216}$ −29.7, $\Delta\epsilon_{230}$ +12.9, $\Delta\epsilon_{243}$ −16.6, $\Delta\epsilon_{338}$ +14.4; IR (NaCl) ν_{max} 3371, 2957, 2924, 2853, 2359, 2335, 1739, 1681, 1201, 1088, 654 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1; ESIMS *m*/*z* 406 $[M + H]^+$; EIMS *m*/*z* 405 $[M]^+$ (100), 390 $[M - CH_3]^+$ (29), 374 $[M - OCH_3]^+$ (10), 202.6 $[M]^{2+}$ (9); HRMS *m*/*z* 405.1937 (calcd for $C_{25}H_{27}NO_4$, 405.1940).

Ancistrotanzanine B (6): yellow oil; $[\alpha]_D^{25}$ +44.0° (*c* 0.01, MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (1.89), 305 (1.42) nm; CD (CH_3CN) $\Delta\epsilon_{215}$ −17.1, $\Delta\epsilon_{230}$ +9.5, $\Delta\epsilon_{245}$ −8, $\Delta\epsilon_{259}$ +3.2, $\Delta\epsilon_{320}$ +3.0; IR (NaCl) ν_{max} 2962, 2921, 2855, 1583, 1261, 1116, 801 cm^{-1};^1H NMR and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 419 $[M]^+$ (100), 404 $[M - CH_3]^+$ (50), 388 $[M - OCH_3]^+$ (13), 209.5 $[M]^{2+}$ (7); HRMS *m*/*z* 419.2099 (calcd for $C_{26}H_{29}NO_4$, 419.2097).

Ancistrotectoriline A (7): yellow oil; $[\alpha]_D^{25}$ +5.67° (*c* 0.1, MeOH) (lit. +1.34°, *c* 0.75, $CHCl_3$);[13] UV (MeOH) λ_{max} (log ϵ) 231 (1.86), 305 (1.43) nm; CD (CH_3CN) $\Delta\epsilon_{202}$ −12.6, $\Delta\epsilon_{209}$ 0, $\Delta\epsilon_{229}$ +32, $\Delta\epsilon_{240}$ −17.9; IR (NaCl) ν_{max} 2962, 2923, 2851, 1260, 1207, 1115, 800 cm^{-1}; apart from some minor differences (see ref 26), spectroscopic data were identical to those previously published.[13]

Oxidative Degradation of 6 and 7. Ruthenium(III)-catalyzed periodate degradation, derivatization of the resulting amino acids, and subsequent GC-MSD analysis were carried out as described previously.[14]

Biological Experiments. Antiparasitic activities against the pathogens *P. falciparum*, *T. cruzi*, *T. brucei rhodesiense*, and *L. donovani* as well as cytotoxicity (rat skeletal myoblast L-6 cells) were assessed as described earlier.[9]

Computational Methods. The conformational analyses of the (*M*,*S*)- and the (*P*,*S*)-atropo-diastereomers of ancistrotanzanine A (**5**) were performed on Silicon Graphics OCTANE R10000 workstations by means of the semiempirical AM1[19] method as implemented in the program package VAMP6.5,[20] starting from preoptimized geometries generated by the TRIPOS[33] force field.

The molecular dynamics simulations of **5** were performed at a virtual temperature of 500 K using the MM3[25] force field as implemented in the molecular modeling package SYBYL 6.7,[34] with a time step of 2 fs. Bond lengths were constrained using the SHAKE algorithm.[33] The overall simulation time was 500 ps, and every 0.5 fs single geometries of ancistrotanzanine A (**5**) were extracted.

The wave functions required for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/2S-CI[21] calculations with a CI expansion including 400 singly occupied configurations and the ground state determinant. These calculations were carried out with Linux Pentium III workstations by the use of the BDZDO/MCDSPD[35] program package. All of the single CD spectra received in this way for all of the single conformational species were added up by Boltzmann weighting, according to the respective heats of formation, to give the calculated overall CD spectrum. For a better visualization, the rotational strengths were transformed into $\Delta\epsilon$ values and superimposed with a Gaussian band shape function.

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References and Notes

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