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Ancistrolikokine D, a 5,8′-coupled naphthylisoquinoline alkaloid, and related natural products from *Ancistrocladus likoko*☆

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In memoriam Professor Jeffrey B. Harborne, who passed away 21 July 2002.

Abstract

A new naphthylisoquinoline alkaloid, ancistrolikokine D, and the likewise 5,8′-coupled alkaloid ancistroealaine A, as well as two further, biosynthetically related, but nitrogen-free natural products, ancistronaphthoic acid B and *cis*-isoshinanolone, have been isolated from *Ancistrocladus likoko* J. LÉONARD (Ancistrocladaceae). The 5,8′-coupling of the new alkaloids and of the alkaloids isolated earlier hints at a close phylogenetic relationship of *A. likoko* to other Central African *Ancistrocladus* species. The compounds show moderate activities against *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei rhodesiense*.

Keywords: *Ancistrocladus likoko*; Ancistrocladaceae; Structural elucidation; Naphthylisoquinoline alkaloids; Ancistrolikokine D; Ancistroealaine A; Ancistronaphthoic acid B; Isoshinanolone; Antiprotozoal activity

1. Introduction

Ancistrocladus likoko J. LÉONARD (Ancistrocladaceae) (Léonard, 1949), a tropical liana indigenous to the rainforests of Central Africa, belongs to the small monogeneric family Ancistrocladaceae, which consists of ca. 20 species (Gereau, 1997). The main secondary metabolites of these plants and of the closely related Dioncophyllaceae (Bringmann et al., 1998a) are mono- and dimeric naphthylisoquinoline alkaloids (Bringmann and Pokorny, 1995), the first known tetrahydroisoquinoline natural products of polyketide origin (Bringmann et al., 2000c, Bringmann and Feineis, 2001). These remarkable natural biaryls are characterized by their intriguing chemotaxonomic implications (Meimberg et al., 2000) and their promising antiprotozoal, in particular antimalarial activities (Bringmann and Feineis, 2000). These activities and the discovery of anti-HIV active *dimeric* naphthylisoquinoline alkaloids, named michellamines (Boyd et al., 1994) have triggered the search for new, less cytotoxic natural analogs.

First phytochemical investigations on *A. likoko* revealed the presence of naphthylisoquinoline alkaloids (Bringmann et al., 1999b), of which the new alkaloid ancistrolikokine A (**1**; Fig. 1) and the known (Hallock et al., 1994) korupensamine A (**4**) were isolated from the roots, while the leaf extracts were found to contain the new compounds ancistrolikokines B (**2**) and C (**3**) (Bringmann et al., 2000a). In this paper, we describe the isolation and structural elucidation of several further secondary metabolites from this productive plant: the new bioactive naphthylisoquinoline alkaloid ancistrolikokine D (**5**), the already known ancistroealaine A (**6**), previously isolated from *Ancistrocladus ealaensis* (Bringmann et al., 2000b), the structurally related naphthoic acid derivative ancistronaphthoic acid B (**7**), and the tetralone isoshinanolone (**8**).

☆ Part 152 in the series "Acetogenic isoquinoline alkaloids". For part 151, see Bringmann et al. (2003).

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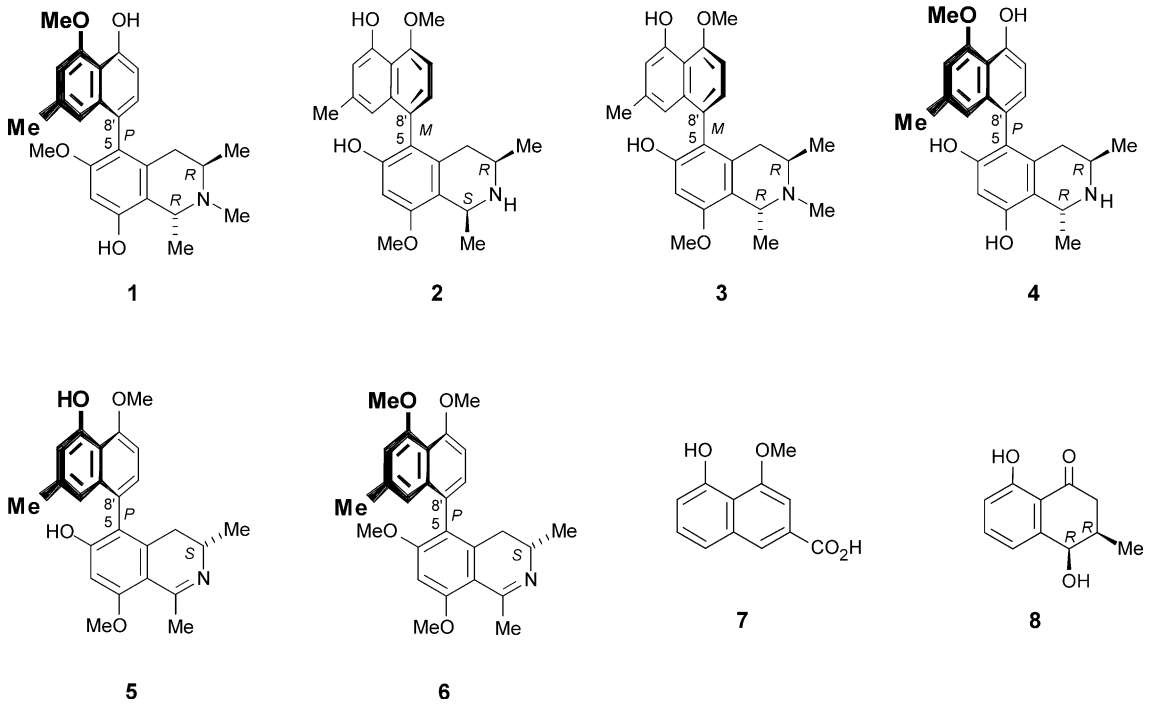


Fig. 1. Natural products from *A. likoko*: ancistrolikokines A–C (**1**–**3**), korupensamine A (**4**), ancistrolikokine D (**5**), ancistroealaine A (**6**), ancistronaphthoic acid B (**7**), and *cis*-isoshinanolone (**8**).

2. Results and discussion

A. likoko was collected in the Democratic Republic of Congo. Roots were air dried, powdered and successively extracted with petrol, CH_2Cl_2, and MeOH. The methanolic extract was perforated with $CHCl_3$ and subsequently fractionated by high-speed countercurrent chromatography (HSCCC). The obtained crude fractions were further purified by repeated normal-phase flash chromatography cycles using deactivated silica particles, permitting the isolation of four pure natural products.

The first compound displayed proton NMR signals typical of naphthylisoquinoline alkaloids. The high resolution electron impact mass spectrum (HREIMS) revealed the molecular peak at m/z 391 to correspond to a molecular formula of $C_{24}H_{25}NO_4$. In the aliphatic region of the proton NMR spectrum (Fig. 2a), two prominent singlets (δ 3.94 and 4.06 ppm) integrating to three protons each, hinted at the presence of aromatic methoxy groups. Their relatively low, not high-field shifted resonances indicated the OMe groups to be located far from the biaryl axis, i.e. in the 8- and 4′- or 5′-positions, with the biaryl axis being at C-5 of the isoquinoline moiety and at C-1′ or C-8′ of the naphthalene portion. A characteristic high-field singlet at δ 2.73 ppm, and the lack of a 1-H proton signal suggested the presence of a naphthyl-3,4-dihydroisoquinoline alkaloid. In the aromatic part of the ^{1}H NMR spectrum, resonances of five individual protons were observable,

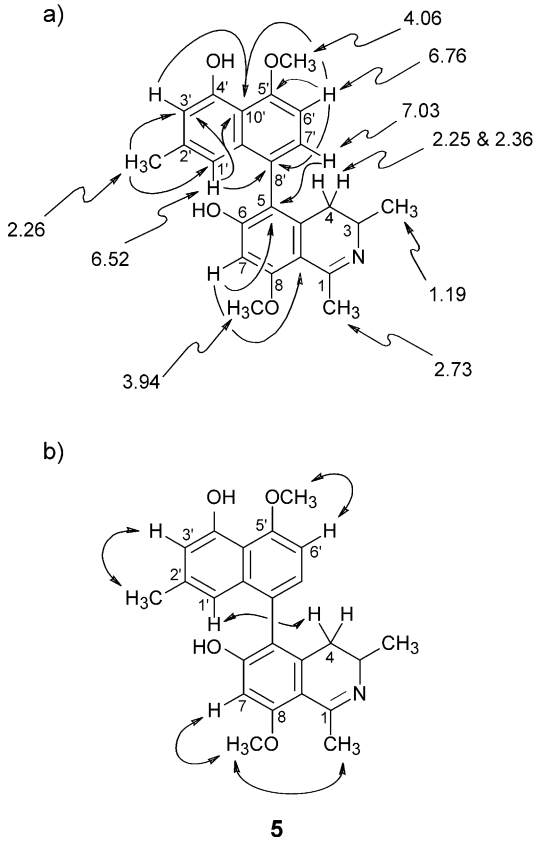


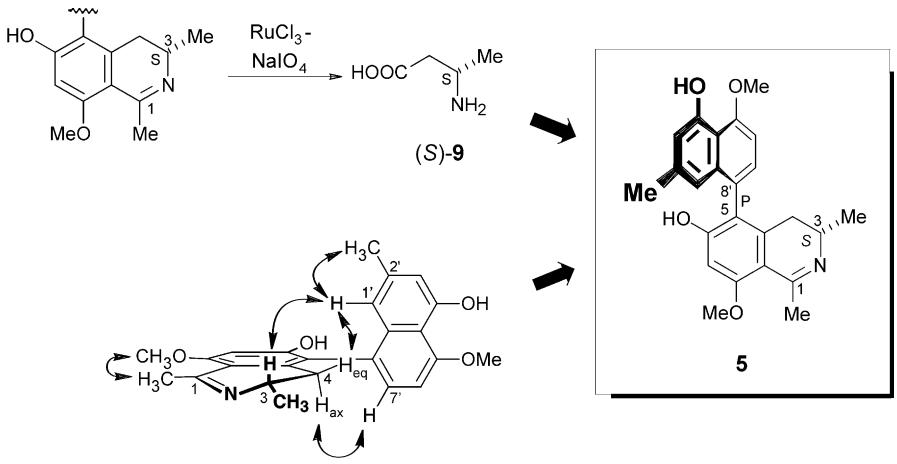
Fig. 2. Elucidation of the constitution of the alkaloid **5**, by (a) selected chemical shifts and HMBC correlations and (b) ROESY interactions.

three singlets and two doublets. Two of the singlets and the two doublets were assigned to belong to the naphthalene part. The remaining singlet was attributed to a proton in the isoquinoline moiety, with the two oxygen functions located at C-6 and C-8, and the naphthalene substituent either at C-5 or C-7 of the isoquinoline portion. The high-field shifted signals of the diastereotopic methylene protons at C-4 (δ 2.25 and 2.36 ppm) gave a clear hint for the axis to be located at C-5. As to the naphthalene part, the chemical shift of the 2′-CH_3 signal (δ 2.26 ppm) indicated that the biaryl axis is not adjacent to that methyl group, leaving only C-6′ or C-8′ as the remaining possible coupling sites. To clarify this, but also to confirm the constitution deduced so far, the structural elucidation was extended to Rotating Frame Overhauser Enhancement Spectroscopy (ROESY) and Heteronuclear Multiple Bond Correlation (HMBC) investigations. Thus, a 5,8′-coupling pattern could be firmly deduced from strong HMBC interactions between the aromatic 1′-H (δ 6.52 ppm) and C-8′, which in turn showed an interaction with 6′-H (δ 6.76 ppm, Fig. 2a). ROESY interactions between one of the diastereomeric protons at C-4 of the isoquinoline moiety and the proton attached to carbon C-1′ of the naphthalene part (Fig. 2b) as well as HMBC interactions between 7′-H (δ 7.03 ppm) and C-5 (Fig. 2a) supported these conclusions. One of the methoxy groups was assigned to be located at C-5′ by ROESY interactions to 6′-H, and the other one as positioned at C-8 by interactions with both, 7-H and with the methyl group at C-1. Fig. 2 summarizes the constitution of the alkaloid thus established.

The absolute configuration at the stereocenter in the isoquinoline moiety was determined by ruthenium-mediated oxidative degradation (Bringmann et al., 1996). The (*S*)-3-aminobutyric acid [(*S*)-**9**] thus obtained (Scheme 1, top) unequivocally established the alkaloid to be *S*-configured at C-3. The configuration at the rotationally hindered and thus stereogenic axis as deduced from stereochemically relevant ROESY interactions between the axial proton at C-4 in the isoquinoline part and 7′-H in the naphthalene portion (Scheme 1, bottom) revealed a situation where these protons are located on the same side of the isoquinoline plane, viz. both underneath. In agreement with this assignment, the dipolar coupling of 1′-H, both with 3-H and with the equatorial proton at C-4, can be explained by the fact that these hydrogen atoms must again be *syn* to each other, now jointly lying above the isoquinoline moiety. With the known absolute configuration at C-3, this nicely complementary spatial information allows to assign the (*P*)-configuration to the axis. This is in agreement with the CD spectrum of the compound, which is very similar to that, e.g., of korupensamine A (**4**) and opposite to that of ancistrolikokine B (**2**). Scheme 1 summarizes the complete structure **5** of the isolated alkaloid, which was thus new and henceforth named ancistrolikokine D.

The second pure compound isolated from the plant extract again showed Dragendorff activity and the proton NMR spectrum suggested the presence of a naphthylisoquinoline alkaloid, which, by its chromatographic behavior on TLC, should be somewhat less polar than **5**. This alkaloid, corresponding to a molecular formula of $C_{26}H_{29}NO_4$ ($M^+ = 419$ m/z) according to HREIMS, showed similar ^1H NMR peak patterns and chemical shifts as **5**, yet with a higher *O*-methylation degree, chromatographically identical with the likewise 5,8′-coupled, but known antileishmanial naphthylisoquinoline alkaloid ancistroealaine A (**6**; Fig. 1) previously isolated from *A. ealaensis* (Bringmann et al., 2000b). One- and two-dimensional NMR experiments, high-resolution mass spectrometry, CD spectra as well as physical properties (like melting points and optical rotation) unequivocally confirmed the identity of this second isolated alkaloid as ancistroealaine A (**6**).

The third compound, a nitrogen-free carbocylic acid corresponding to the molecular formula $C_{12}H_{10}O_4$,



Scheme 1. Assignment of the full absolute configuration of **5**, by oxidative degradation and stereochemically diagnostic ROESY interactions.

turned out to be the likewise known ancistronaphthoic acid B (**7**; Fig. 1). This compound had previously been found only in *A. ealaensis* (Bringmann et al., 2000b), again emphasizing the close phylogenetic relationship of that plant with *A. likoko* investigated in this paper.

In contrast to **7**, the fourth substance isolated is a far more wide-spread natural product, the likewise nitrogen-free naphthalene-derived isoshinanolone (**8**) (Tezuka et al., 1973), whose absolute stereostructure has been firmly established recently (Bringmann et al., 1999a). It is an acetate-derived tetralone (Bringmann et al., 1998b), apparently arising from the same polyketidic precusor as both molecular halves of the naphthylisoquinoline alkaloids, probably via 1,8-dihydroxy-3-methylnaphthalene, which can then be oxidatively coupled to an isoquinoline portion to give, e.g., **5** or **6**, or side-chain oxygenated to give the naphthoic acid **7**, or core-oxidized to give the naphthoquinone plumbagin (Durand and Zenk, 1971) and then reduced to give isoshinanolone (**8**).

The structures of the alkaloids thus isolated from *A. likoko* are chemotaxonomically significant in several respects: Firstly, the two alkaloids described in the paper, **5** and **6**, both represent 'Ancistrocladaceae-type' alkaloids, i.e. with *S*-configuration at C-3 and with an oxygen substituent at C-6, as found throughout, in all Asian and East African Ancistrocladaceae species. By contrast, **1**–**4** belong to the 'Dioncophyllaceae-Ancistrocladaceae hybrid type' (again with an oxygen substitutent at C-6, but now with *R* at C-3), as frequently found in Central African species like also in *A. guineensis* and *A. korupensis*, while 'Dioncophyllaceae-type' alkaloids (*R* at C-3 and no oxygen function at C-6) occur in West-African species like *A. abbreviatus* (Bringmann et al., 1992) and in Dioncophyllaceae plants themselves (Bringmann et al., 1998a). Secondly, it is noteworthy that *all* of the alkaloids identified so far from *A. likoko* are based on the same coupling type, viz. with the biaryl axis between C-5 and C-8′, in contrast to the other *Ancistrocladus* species so far investigated, which normally show even more than two different coupling types. After the relatively late discovery of the first 5,8′-coupled naphthylisoquinoline alkaloid, ancistrobrevine B (Bringmann et al., 1992), this coupling type has meanwhile become the most frequent one identified in nature—but never as complete and exclusive as now in *A. likoko*! The reason for the high coupling regioselectivity in the biosynthetic origin of the alkaloids in this plant remains to be investigated.

The new alkaloid ancistrolikokine D (**5**) was found to exhibit moderate activity against the malaria parasite *Plasmodium falciparum* in vitro, both against the strains K1 ($IC_{50} = 0.79$ μg/ml; standard: chloroquine, $IC_{50} = 0.053$) and NF54 ($IC_{50} = 1.16$; standard: chloroquine, $IC_{50} = 0.004$). Its activity against L-6 cells (rat myoblasts) was distinctly weaker ($IC_{50} = 36.6$). This result is consistent with ongoing structure–activity relationship investigations (Bringmann and Rummey, 2003) revealing that in naphthylisoquinoline alkaloids the presence of at least one or two free aromatic hydroxy functions is essential for high antiplasmodial activity (François et al., 1996). In view of the promising other antiprotozoal activities of some naphthylisoquinoline alkaloids (Bringmann and Feineis, 2000), compound **5** was also tested in vitro against *Leishmania donovani*, which causes the widespread tropical disease visceral leishmaniasis, *Trypanosoma cruzi* (pathogen of Chagas disease), and *T. brucei rhodesiense* (African sleeping sickness). It likewise showed activities against *T. cruzi* ($IC_{50} = 12.7$; standard: benznidazole, $IC_{50} = 0.33$), *T. b. rhodesiense* ($IC_{50} = 2.71$; standard: melarsoprol, $IC_{50} = 0.0026$), and *L. donovani* ($IC_{50} = 5.9$; standard: pentamidine, $IC_{50} = 5.5$).

The results show that naphthylisoquinoline alkaloids continue to be structurally intriguing and pharmacologically promising natural products. Further work aiming at the isolation and pharmacological evaluation of further alkaloids present in the plants, is in progress.

3. Experimental

3.1. General

Mps: uncorr. IR spectra were taken on a Jasco FT/IR-410 spectrometer, CD spectra on a Jasco J-715 spectropolarimeter, and optical rotations on a Perkin-Elmer 241MC polarimeter. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) were recorded on a Bruker DMX 600 in $CDCl_3$ with the solvent as the internal standard (δ 7.26 and δ 77.01). Proton-detected, heteronuclear correlations were analyzed using HMQC (optimized for $^1J_{HC} = 145$ Hz) and HMBC (optimized for $^nJ_{HC} = 7$ Hz) techniques. ROE effects were measured using ROESY pulse sequences from the standard Bruker pulse program library. EIMS (70 eV) and HREIMS (70 eV) were determined on Finnigan MAT 8200 and Finnigan MAT 90 instruments. CC: silica gel (60–200 mesh, Merck) deactivated with 5% conc. NH_3. HSCCC: 'Triple coil', 1.68 mm×106.5 m (large coil, flow 2.0 ml min^{-1}, 850 min^{-1}), (H)→T, lower phase as mobile phase, forward elution mode.

3.2. Plant material

Plant material of *A. likoko* was collected and identified by one of us (V. M.) in the Yangambi area, Democratic Republic of Congo, in August 1996. A voucher specimen has been deposited at Herb. Bringmann, University of Würzburg (No. 16).

3.3. Extraction and isolation

The air-dried and powdered roots (1.5 kg) were successively extracted with petrol, dichloromethane, and

methanol. 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 perforated 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], yielding eleven HSCCC fractions. From fractions 4 and 2, alkaloids **5** and **6**, resp., were isolated by repeated CC (MeOH–CH_2Cl_2 99:01→97:03). From fraction 7, compound **7** was isolated by CC (MeOH–CH_2Cl_2 99:01→90:10) and from fraction 1, tetralone **8** was gained (EtOAc–petrol 9:1).

3.4. Ancistrolikokine D (*5*)

Colorless solid. Mp 122–124 °C. $[\alpha]_D^{25}$ + 191.6° ($CHCl_3$; *c* 0.15). CD: $\Delta\varepsilon_{214}$ 4.2, $\Delta\varepsilon_{231}$ 7.2, $\Delta\varepsilon_{250}$ −1.6, $\Delta\varepsilon_{311}$ 2.5, $\Delta\varepsilon_{321}$ 1.4, $\Delta\varepsilon_{336}$ 2.2, $\Delta\varepsilon_{355}$ 0.9, $\Delta\varepsilon_{363}$ 1.8, $\Delta\varepsilon_{375}$ 1.1, $\Delta\varepsilon_{381}$ 2.3 (EtOH; *c* 0.012). IR ν_{max}^{KBr} cm^{-1}: 3413 (*m*, O–H), 2929 (*m*), 1678 (*m*), 1633 (*m*), 1587 (*s*), 1387 (*m*), 1328 (*m*), 1201 (*s*), 1129 (*m*), 1126 (*m*), 1088 (*s*), 836 (*m*), 718 (*m*), 588 (*m*). ^1H NMR (600 MHz, $CDCl_3$): δ 1.19 (3H, *d*, *J* = 6.7 Hz, CH_3-3), 2.25 (1H, *dd*, *J* = 16.6, 10.6 Hz, H_{ax}-4), 2.26 (3H, *s*, CH_3-2′), 2.36 (1H, *dd*, *J* = 16.8, 5.5 Hz, H_{eq}-4), 2.73 (3H, *s*, CH_3-1), 3.62 (1H, m_c, H-3), 3.94 (3H, *s*, OCH_3-8), 4.06 (3H, *s*, OCH_3-5′), 6.52 (1H, *s*, H-1′), 6.72 (1H, *s*, H-3′), 6.76 (1H, *d*, *J* = 7.9 Hz, H-6′), 6.80 (1H, *s*, H-7), 7.03 (1H, *d*, *J* = 7.8 Hz, H-7′). ^{13}C NMR (150.9 MHz, $CDCl_3$): *δ* 17.36 (CH_3-3), 21.86 (CH_3-2′), 24.18 (CH_3-1), 32.09 (C-4), 47.69 (C-3), 56.09 (OCH_3-8), 56.21 (OCH_3-5′), 98.57 (C-7), 102.98 (C-6′), 107.76 (C-9), 113.29 (C-3′), 113.57 (C-10′), 115.03 (C-1′), 119.97 (C-5), 123.13 (C-8′), 128.93 (C-7′), 135.11 (C-9′), 139.34 (C-2′), 140.31 (C-10), 154.93 (C-4′), 156.91 (C-5′), 163.67 (C-8), 164.64 (C-6), 173.53 (C-1). The ^{13}C attributions were achieved by HMQC and HMBC experiments. EIMS *m*/*z* (rel. int.): 391 $[M]^+$ (100), 376 $[M-CH_3]^+$ (40), 188 $[M-CH_3]^{2+}$ (16). HREIMS *m*/*z* 391.1779 $[M]^+$ ($C_{24}H_{25}NO_4$ requires 391.1784).

3.5. Ancistroealaine A (*6*)

Amorphous solid. Mp 92 °C; 94–96 °C (Bringmann et al., 2000b). $[\alpha]_D^{25}$ −38.3° (EtOH, *c* 0.45); −34.3° (EtOH, *c* 0.55) (Bringmann et al., 2000b). Spectroscopic data are identical to those of an authentic sample from previous isolation work from *A. ealaensis* (Bringmann et al., 2000b).

3.6. Ancistronaphthoic acid B (*7*)

Colorless solid. Mp 233 °C; 238 °C (Bringmann et al., 2000b). Spectroscopic data in full agreement with those of an authentic sample from *A. ealaensis* (Bringmann et al., 2000b).

3.7. cis-Isoshinanolone (*8*, *3R,4R*)

Oil. $[\alpha]_D^{25}$ + 46.7° ($CHCl_3$, *c* 0.60); + 22.2° ($CHCl_3$, *c* 1.0) (Bringmann et al., 1999a). Identical with an authentic sample from *Dioncophyllum thollonii* (Bringmann et al., 1999a) in all spectroscopic details.

3.8. Oxidative degradation

The degradation, the derivatization of the amino acids, and the subsequent GC–MSD analysis were carried out as described previously (Bringmann et al., 1996).

3.9. Biological experiments

Antiplasmodial (*P. falciparum*), antitrypanosomal (*T. cruzi* and *T. brucei rhodesiense*), and antileishmanial (*L. donovani*) activities as well as was cytotoxicities (rat skeletal myoblast L-6 cells) were assessed as described earlier (Bringmann et al., 2000b).

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