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Shuangancistrotectorines A–E, Dimeric Naphthylisoquinoline Alkaloids with Three Chiral Biaryl Axes from the Chinese Plant *Ancistrocladus tectorius*

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Abstract: Five novel dimeric naphthylisoquinoline alkaloids, shuangancistrotectorines A (**3a**), B (**3b**), C (**4**), D (**5a**), and E (**5b**), have been isolated from the twigs of the Chinese plant *Ancistrocladus tectorius*. Their absolute stereostructures were determined by spectroscopic and chiroptical methods in combination with quantum chemical CD calculations. In contrast to all other known dimeric naphthylisoquinoline alkaloids, in which the central binaphthalene axis is 6′,6″-coupled and thus not rotationally hindered, the dimers described here are linked via the sterically more hindered 3′,3″- or 1′,1″-positions of the naphthalene units. They are thus the first such dimers—and even the very first natural products at all—that have three consecutive stereogenic axes. Hence, including the stereogenic centers, they have up to seven stereogenic units in total. Some of the compounds, in particular shuangancistrotectorines A, B, and D (**3a**, **3b**, and **5a**) exhibit very good, and specific, antiplasmodial activities.

Keywords: alkaloids · circular dichroism · density functional calculations · natural products · structure elucidation

Introduction

Naphthylisoquinoline alkaloids are structurally, biosynthetically, and pharmacologically remarkable natural products from tropical lianas of the Ancistrocladaceae and Dioncophyllaceae families.[1–3] Stereochemically, they are characterized by the presence of stereogenic centers (mostly at C1 and C3) and, in particular, by the (usually) rotationally hindered biaryl axis (C,C- or N,C-coupled)[1,4] between the isoquinoline and the naphthalene portions. Besides their unique biosynthetic origin from polyketide precursors,[5] they have pronounced anti-infective activities against protozoic pathogens of severe tropical diseases like malaria, trypanosomiasis, and leishmaniasis.[6,7] But only some of the few known dimeric representatives, in particular michellamine B (**1**), display high anti-HIV activities,[8,9] while other dimers, such as ancistrogriffithine A (**2**), show significant antiplasmodial activities.[10] All of these dimers have in common that they are coupled via C6′ of both naphthalene portions, and thus the central biaryl axis is not an additional element of chirality, neither in michellamines like **1** (both monomeric naphthylisoquinoline portions: 5,8′-coupled) nor in **2** (twofold 7,8′-linked), nor in korundamine A (a mixed, 5,8′–7,8′-bonded "dimer", not shown). Their promising pharmacological properties have triggered extensive synthetic work towards natural dimers and unnatural analogues,[11–15] including the development of methods for the directed search for such dimers in crude extracts.[16] Despite systematic screening in crude extracts of many other *Ancistrocladus* species, dimeric naphthylisoquinoline alkaloids have, until recently, been known only from one African Ancistrocladaceae species, namely, *Ancistrocladus korupensis* (seven

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representatives[8,9]), and the South-East Asian species *Ancistrocladus griffithii* (only one single dimer, viz. ancistrogriffithine A (**2**)[10]). A species belonging to the same plant family, *Ancistrocladus tectorius*, is distributed over a wide area of South-East Asia and isolation work by different groups[17–21] led to the reported occurrence of 14 different monomeric naphthylisoquinoline alkaloids with various coupling types (5,1′, 5,8′, 7,1′, and 7,3′), and also free, noncoupled (i.e., naphthalene-devoid) isoquinolines, but no dimers. Here we report on the first isolation of five novel dimeric naphthylisoquinolines, shuangancistrotectorines A–E (**3a**, **3b**, **4**, **5a**, and **5b**, respectively; Figure 1), from this plant species, which is only seemingly well investigated. All of them are 1′,1″- or 3′,3″-coupled and thus the first representatives whose central biaryl axis between the two identical naphthylisoquinoline portions is rotationally hindered. This leads to an unprecedented array of three consecutive chiral biaryl axes, which was found for the first time in any natural products.

Results and Discussion

Due to the broad structural diversity of the naphthylisoquinolines that have so far been isolated from *Ancistrocladus tectorius* from different locations,[17–21] and because of more

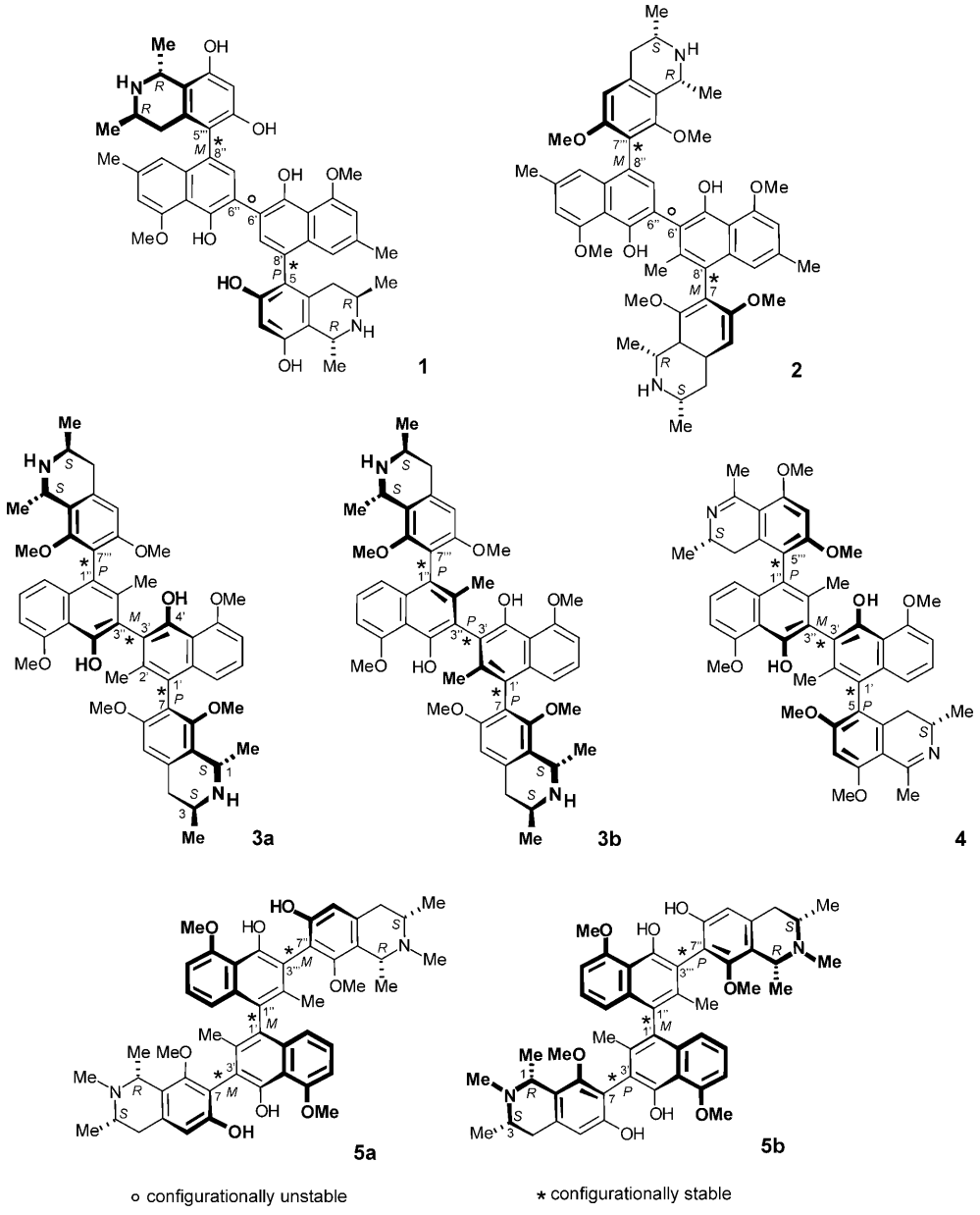

Figure 1. Structures of two "conventional" dimeric naphthylisoquinoline alkaloids, michellamine B (**1**) and ancistrogriffithine A (**2**), and of the new dimers isolated from *A. tectorius*, shuangancistrotectorines A–E (**3a**, **3b**, **4**, **5a**, and **5b**), with three stereogenic axes each.[22]

recent genetic investigations on the *Ancistrocladus tectorius* complex which hint at the existence of different local types,[23] it seemed interesting to reinvestigate the chemical constituents, exemplarily for *A. tectorius* from the Chinese island Hainan, from which previously four different monomeric naphthylisoquinolines had been isolated.[21] In the course of these investigations, we found several further trace alkaloids having novel structures. Of particular interest were those compounds whose MS data hinted at the presence of dimeric alkaloids, because no dimers had so far been reported for this plant species from any location.

One of the major peaks of these trace dimers, upon further purification, could be resolved into two very similar compounds, the more polar of which was found to have the molecular formula $C_{50}H_{58}N_2O_8$, as deduced from HRESIMS (407.2091 $[M+2]^{2+}$, calcd 407.2091), which is typical of diprotonated naphthylisoquinoline dimers,[10] while MALDI-TOF MS showed the "full-size" (since only mono-ionized) molecular peak at 812.385 ($[M]^+$). The reduced set of signals of ^{1}H and ^{13}C NMR spectra revealed that the molecule is symmetric, which suggests that the two molecular portions should be homomorphous to each other, or enantiomorphous, whereby the latter case (i.e., a *meso* compound) was clearly excluded by its optical activity and its chiroptical properties. The ^{1}H NMR spectrum showed the presence of four aromatic protons, one at $\delta=6.74$ ppm (s, H5) and a three-proton spin system with signals at $\delta=6.89$ (dd, $J=8.2$, 1.0 Hz, H6′), 7.18 (dd, $J=8.2$, 8.6 Hz, H7′), and 6.86 ppm (dd, $J=8.6$, 1.0 Hz, H8′), which is consistent with a dimer built up from two 7,1′-coupled monomers (Figure 2a). The HMBC correlations of H5 with C4 ($\delta=34.8$ ppm, t), C7 ($\delta=121.4$ ppm, s), and C9 ($\delta=119.8$ ppm, s) confirmed the 7,1′-type coupling (Figure 2b). In the aliphatic region, the signals at $\delta=1.67$ ppm (d, $J=6.9$ Hz, 1-CH_3) and $\delta=1.53$ ppm (d, $J=6.7$ Hz, 3-CH_3) suggested the presence of a 1,3-dimethyltetrahydroisoquinoline portion. But the extremely upfield shifted methyl signal at $\delta=1.86$ ppm (s, 2′-CH_3), which is the lowest δ value ever reported for a naphthylisoquinoline alkaloid, indicated the immediate proximity of even two aryl substituents, and hence the presence of yet another biaryl axis at C3′, and 3′,3″-coupling between the two identical molecular halves. This was corroborated by a ROESY correlation of the proton signal of 2′-CH_3 ($\delta=$ 1.85 ppm) with that at $\delta=9.72$ ppm (4′-OH, both obtained only in $CDCl_3$), which is possible only in the case of a 3′,3″-linkage. Moreover, the three methoxyl groups at $\delta=3.64$ (s, 6-OCH_3), 3.32 (s, 8-OCH_3), and 4.07 ppm (s, 5′-OCH_3) were assigned by further HMBC and ROESY correlations (Figure 2b), also in accordance with the presence of 7,1′-coupling in the monomeric half.

From a ROESY correlation between 1-CH_3 and H3 (Figure 2c), the relative configuration of the stereocenters was determined to be *trans*. The coupling constants for the 4-CH_2 methylene protons ($J_{H4eq,H3}=18.0$, 5.0 Hz and $J_{H4ax,H3}=$ 18.0, 11.8 Hz) indicated H3 to be axial. Hence the methyl group at C3 was deduced to be equatorial, and thus that at C1 axial. The absolute configurations at the stereocenters were determined as 1*S* and 3*S* by oxidative degradation[24] giving L-alanine and (*S*)-3-aminobutyric acid, respectively, which thus simultaneously confirms the above-determined relative *trans* configuration between C3 and C1. The degradation results clearly excluded the possibility that the two molecular halves might be enantiomorphous to each other, which would have led to racemic degradation products.

The configuration of the axis in the monomeric half relative to the centers was assigned on the basis of the ROESY correlations between H8′ and 1-CH_3, and between 2′-CH_3 and H1 (Figure 2c). This, together with the absolute config-

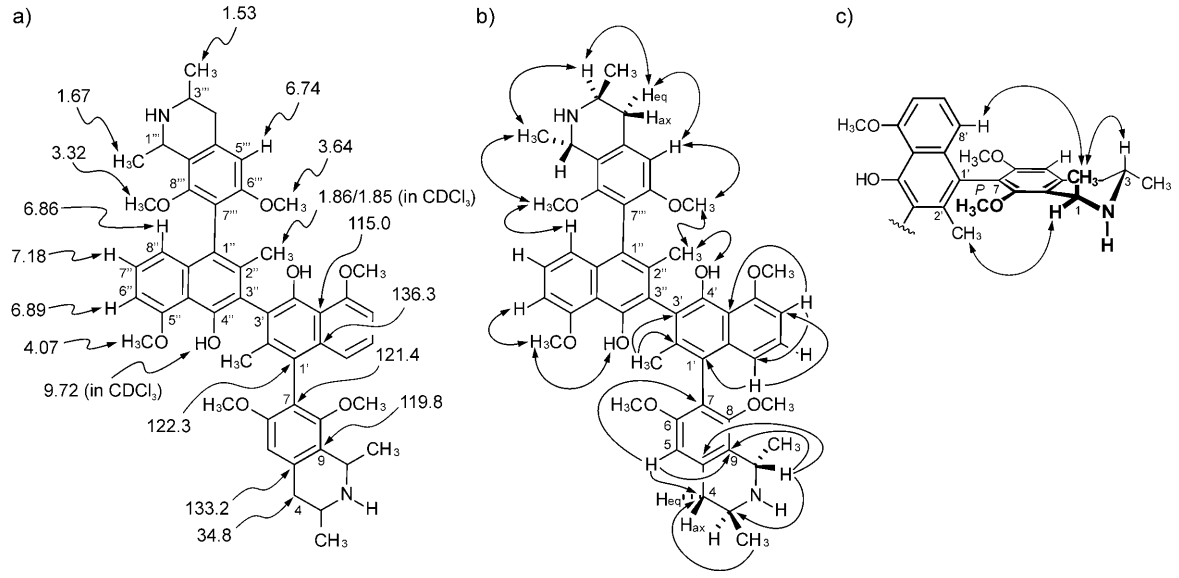

Figure 2. Selected NMR data of **3a**. a) ^{1}H and ^{13}C NMR shifts (δ in ppm). b) ROESY (double arrows) and HMBC interactions (single arrows) indicative of the constitution (including the position of the central axis and the outer ones). c) ROESY interactions defining the relative configurations at centers versus axes and among the stereogenic axes in the monomeric half.

uration at the two stereogenic centers, as determined by oxidative degradation (see above), evidenced the "outer" axes, that is, the naphthalene–isoquinoline linkages, to be *P*-configured. Given the C_2-symmetric structure of the dimer, both molecular halves should thus be *S*,*S*,*P*-configured.

The HRESIMS of the second of the two peaks, 813.4109 ($[M+1]^+$, calcd 813.4109) again gave a molecular formula of $C_{50}H_{58}N_2O_8$, that is, the same as that of the first compound. The very similar ^{1}H and ^{13}C NMR spectra, together with the ROESY and HMBC correlations as well as the proton coupling constants, indicated that both compounds had the same symmetric constitution and also the same relative configurations at all of the stereogenic centers and naphthylisoquinoline axes. Even the absolute configurations were identical, as again evidenced by the degradation experiment. Nonetheless, the CD spectra of the two dimers were nearly opposite to each other (Figure 3).

The only structural element that might be responsible for this striking chiroptical difference should thus be the central biaryl axis. In contrast to all other naphthylisoquinoline dimers known so far, natural or unnatural,[8–15] it is flanked not just by two but by four *ortho* substituents. Consequently, it is rotationally hindered and hence constitutes an additional stable stereogenic element. The fact that it even dominates the CD spectrum over all other six stereogenic elements (the two other axes and the four centers) is understandable because it fixes the two main chromophores (the substituted naphthalene moieties) in the given spatial orientation to each other.

Based on the C_2-symmetric structure of the dimers, the Cotton effects at 240 nm (Figure 3) should be suitable for assignment of the configuration at this central axis by application of the exciton chirality[25] approach. Accordingly, the first compound, which has a negative couplet, should be *M*-configured at the central axis, and thus should have the stereostructure **3a**, while the second dimer, with its positive couplet, should have the *P* configuration and thus structure **3b**. However, it is already known that the exciton chirality method may lead to the assignment of wrong absolute configurations for such chiroptically complex structures.[26] Therefore, and because of the unprecedented molecular frameworks of **3a** and **3b** and the unique array of three consecutive biaryl axes, an unambiguous, independent stereochemical assignment by quantum chemical CD calculations[27,28] seemed to be required.

For this purpose, by using PM3,[29] a conformational analysis was performed on **3a** and **3b**. The global minima thus found were used as the basis for ZINDO/S-CIS[30] calculations to finally provide the theoretically predicted CD spectra (see Computational Details). The spectrum calculated for **3b**, that is, with *P*,*P*,*P* configuration, was in very good agreement with the CD curve measured for the later-eluting peak, whereas the spectrum computed for *P*,*M*,*P*, that is, for structure **3a**, matched well with the earlier-eluting one (see the Supporting Information). To further corroborate this assignment, the global minima for **3a** and **3b**, as found in the PM3 analysis, were further optimized with B3LYP/6-31G*,[31,32] and the resulting structures were then used to calculate the excited states by TD-B3LYP/6-31G* (TD = time-dependent). Shifting the CD spectrum calculated for **3b** (Figure 3, right), that is, with *P*,*P*,*P* configuration, by a "UV-correction"[28] value of 8 nm again provided a good fit with the experimental CD curve of the later-eluting peak, and a shift of 5 nm for that computed for **3a** (*P*,*M*,*P*) gave good accordance with the spectrum of the earlier-eluting peak (Figure 3, left). This configurational assignment based on quantum chemical calculations proved to be in agreement with the above-described tentative assignment made by applying the exciton chirality method.

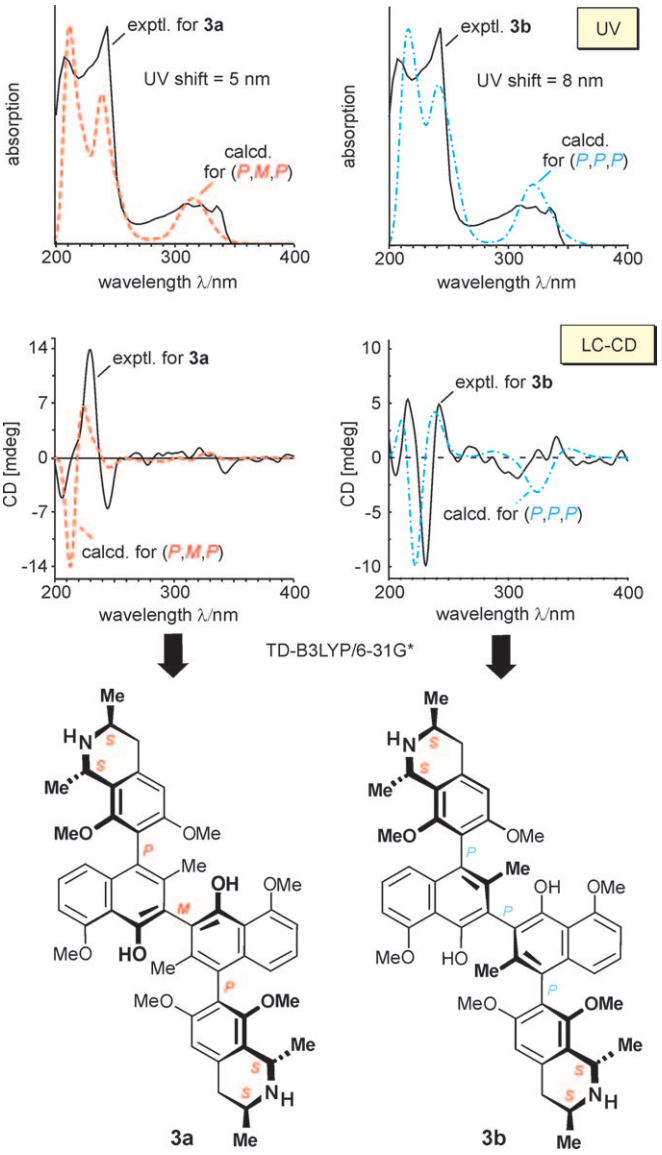

Figure 3. Assignment of the absolute configurations to **3a** (left) and its atropo-diastereomer **3b** (right) by comparison of the experimental LC-CD spectra (stopped-flow mode) with the spectra calculated for the *P*,*M*,*P* and *P*,*P*,*P* atropisomers by using TD-B3LYP/6-31G*. Similar experimental spectra were obtained offline, after isolation of pure **3a** and **3b** (see the Supporting Information).

Thus, the two atropo-diastereomeric naphthylisoquinoline dimers have the full absolute stereostructures **3a** and **3b**, that is, both with *S*,*S*,*P* configuration in each of the monomeric naphthylisoquinoline units, but once with *M* and once with *P* configuration at the central axis that links these units. These novel threefold axially chiral quateraryl alkaloids were named shuangancistrotectorines A and B, respectively, according to the name of the plant (*Ancistrocladus tectorius*) and the Chinese word *shuang*, meaning pair, couple.

Under "normal" conditions (ambient temperature, neutral pH), **3a** and **3b** were found to be configurationally stable at the central axis. On warming to 40 °C in the presence of acid, however, or upon storage in $CDCl_3$ as the NMR solvent, a pure sample of **3a**, that is, with *P*,*M*,*P* configuration, was converted to a mixture of two atropo-diastereomers **3a** and **3b** over several days. Therefore, **3a** and **3b** were again purified by HPLC, but then further treated under very mild conditions, that is, at room temperature avoiding light, and dried by lyophilization, which led to stereochemically homogeneous material.

Under such mildest-possible conditions for the isolation process, only **3a** was obtained from the plant extract, that is, this atropo-diastereomer is a true natural product, and at present it remains open whether **3b** is only an artifact or an authentic (minor) natural product, too.

The third compound gave MALDI-TOF-MS and HRESIMS signals at *m/z* 809.3 and 405.2022, respectively, in accordance with the mono- and diprotonated molecular ions $[M+1]^+$ and $[M+2]^{2+}$ of a substance with molecular formula $C_{50}H_{52}N_2O_8$. This again suggested the presence of a dimeric naphthylisoquinoline alkaloid, also in agreement with the lack of the ^{1}H NMR resonance of one of the aromatic protons present in the respective monomers. From the half-number of NMR signals expected for the molecular formula, the two moieties of the compound were equivalent, which, in combination with the (chir)optical activity of the compound, showed that the molecule was again C_2-symmetric. The ^{1}H NMR chemical shifts of the methyl groups at C1 and C3 were typical of a dihydroisoquinoline [$\delta = 2.82$ (s, C1) and $\delta = 1.19$ ppm (d, $J = 6.8$ Hz, C3)]. The double doublets at $\delta = 6.96$, 7.26, 6.83 ppm were attributed to the three neighboring protons at C6′, C7′, and C8′ (Figure 4a). The HMBC correlations of the aromatic proton at C7 ($\delta =$ 6.90 ppm, s) with C6 ($\delta = 168.7$ ppm), C8 ($\delta = 166.4$ ppm), C9 ($\delta = 109.1$ ppm), and C5 ($\delta = 122.9$ ppm) (Figure 4b) showed the two methoxy groups to be located at C6 and C8, that is, the monomeric halves are 5,1′-coupled, leaving the 3′,3″-linkage as the only possible connection between the two halves. Key HMBC correlation observed from 2′-CH_3, from H7, and from 4-CH_2 to C5 confirmed the 5,1′-coupling between the monomeric halves (Figure 4b). Another HMBC correlation from 2′-CH_3 to the neighboring quaternary carbon C3' ($\delta = 121.6$ ppm) finally established the two identical monomeric portions to be connected via a central 3′,3″-bond.

The absolute configurations of the two stereocenters C3 and C3‴ were determined as *S* by formation of (*S*)-3-aminobutyric acid on oxidative degradation, which again proves the existence of a homo-dimer with two identical (i.e., homomorphous) monomeric halves. The configuration at the axes in the monomeric portions relative to the stereogenic centers was determined by the ROESY correlations of $H_{eq}4$ ($\delta = 2.49$ ppm, dd, $J = 16.9$, 5.5 Hz) with H8′ ($\delta = 6.83$ ppm, dd, $J = 8.6$, 1.0 Hz) and $H_{ax}4$ ($\delta = 2.32$ ppm, dd, $J = 16.9$, 10.4 Hz) with 2′-CH_3 ($\delta = 1.74$ ppm, s) (Figure 4c). This, in combination with the absolute configuration at C3 from the degradation results, led to a *P* configuration at the axis of the 5,1′-coupled monomer.

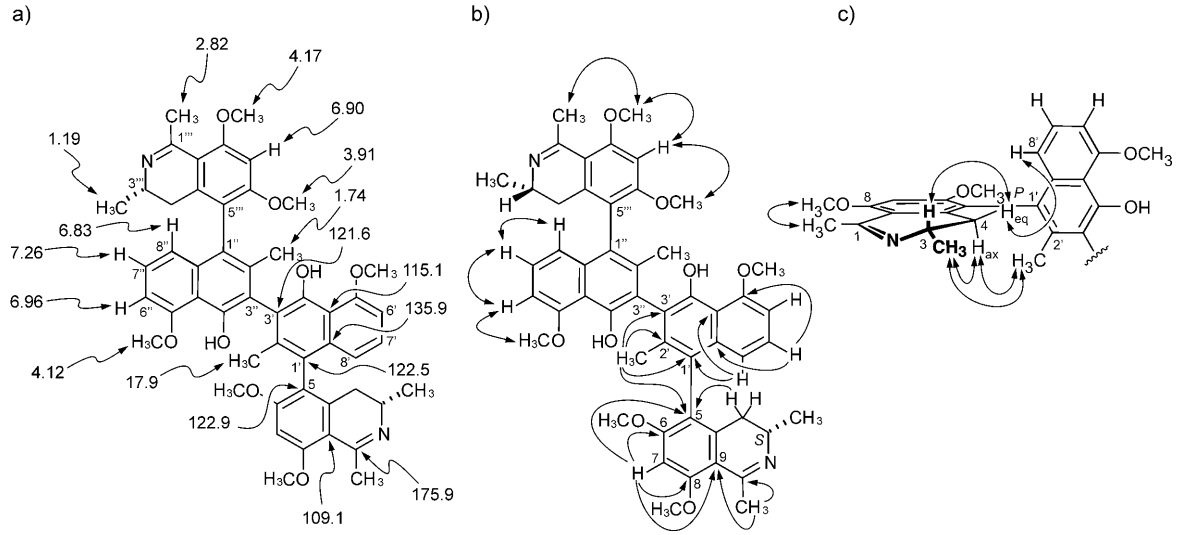

Figure 4. Selected NMR data of **4**. a) ^{1}H and ^{13}C NMR shifts (δ in ppm). b) ROESY (double arrows) and HMBC (single arrow) interactions indicative of the constitution (including the position of the central axis and the outer ones). c) ROESY interactions defining the relative configuration at centers versus axis within the monomeric half.

Compound **4** was also subjected to a PM3-based conformational analysis. Since the configurations at the outer axes and at the stereocenters C3 and C3‴ were known from the above experiments, only two configurations had to be considered for this analysis: *P,M,P* and *P,P,P*. The found global minima were further optimized with B3LYP/6-31G*, and subsequent TDB3LYP/6-31G* calculations of these structures yielded CD spectra, which were compared with those obtained experimentally. Thus, the absolute configuration of the axes of **4** was unequivocally assigned as *P,M,P* (Figure 5).

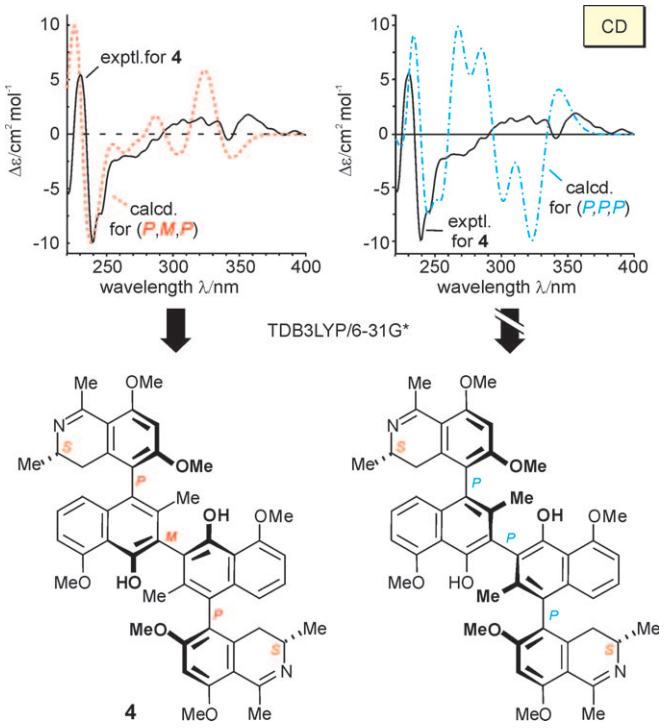

Figure 5. Assignment of the absolute configurations of **4** by comparison of the experimental CD spectra with the spectra calculated for the *P,M,P* and *P,P,P* atropo-diastereomers by using TD-B3LYP/6-31G*.

This assignment was, at first view, again in agreement with that obtained applying the exciton chirality method for this C_2-symmetric new compound. At the wavelength of the main UV band at 235 nm (see the Supporting Information), the CD spectrum showed a negative couplet, that is, a first negative Cotton effect at higher wavelength followed by a positive second one confirming that the central axis must be *M*-configured. However, in the CD curve calculated for the *P,P,P*-configured atropo-diastereomer of **4**, that is, with the central axis *P*-configured, the CD curve had a negative exciton couplet, too. According to the exciton chirality method, this would have led to the (wrong!) assumption that the configuration at the central axis would be *M*, which clearly shows that this approach is not unambiguous for this type of compounds and that only quantum chemical calculations will give reliable results. Thus, the correct assignment of the configuration at the central axis in **3a** and **3b** by this method may have been correct only by accident, and this emphasizes, once again, the importance of quantum chemical CD calculations. Interestingly (and in contrast to **3a** and **3b**), no other stereoisomers of **4** were identified in the extract, and this hints at a possibly high specificity of the coupling enzyme. New compound **4** was named shuangancistrotectorine C.

From a more polar fraction, yet another naphthylisoquinoline alkaloid was isolated, apparently again a dimer. This was evident from the MALDI-TOF-MS signal at *m/z* 813.4 $[M+1]^+$ and the HRESIMS peak at 407.2091 $[M+2]^{2+}$ (calcd for $C_{50}H_{58}N_2O_8$: 407.2091), leading to a molecular formula of $C_{50}H_{57}N_2O_8$. In support of this, the ^{1}H NMR spectrum displayed an upfield-shifted signal for 2′-CH_3 (δ = 1.72 ppm, s), which was even lower than in the cases of **3a** and **3b** (see above), and four aromatic protons, and is thus consistent with a *meso*-configured or a C_2-symmetric dimer, the latter being evident from the results of oxidative degradation and the (chir)optical activity of the compound. By detailed analysis of the ^{1}H NMR spectrum, in particular of the spin system at δ = 6.92 (dd, J = 7.7, 1.0 Hz, H6′), 7.14 (dd, J = 8.8, 7.7 Hz, H7′), 6.82 ppm (dd, J = 8.8, 1.0 Hz, H8′) (Figure 6a), and from an HMBC correlation between H5 (δ = 6.62 ppm, s) and C4 (δ = 35.2 ppm, t) (Figure 6b), the monomeric entity was identified as a 7,3′-coupled naphthylisoquinoline, leaving C1′–C1″ as the only possible coupling position between the monomeric halves. The isoquinoline moiety showed three methyl signals, including two doublets (δ = 1.75 ppm, d, J = 6.8 Hz, 1-CH_3; δ = 1.58 ppm, d, J = 6.8 Hz, 3-CH_3) and one singlet (δ = 3.03 ppm, s, NCH_3), in agreement with an *N*-methyltetrahydroisoquinoline portion. Based on ROESY and HMBC correlations, the protons of the remaining methoxyl groups were deduced to be located at C-8 in the isoquinoline part and at C-5′ in the naphthalene portion. With respect to the linkage between the two halves, an unexpected ROESY correlation between 2′-CH_3 (δ = 1.72 ppm, s) and H8″ (δ = 6.82 ppm, s) (Figure 6b) was observed, which unequivocally confirmed the central axis to be 1′,1″-coupled.

The ROESY correlation between H1 and H3 established the relative configuration at the stereogenic centers C1 and C3 as *cis* (Figure 7a). The absolute configurations were assigned as 1*R* and 3*S* by ruthenium-mediated oxidative degradation,[24] which yielded *N*-methyl-D-alanine and *N*-methyl-(*S*)-3-aminobutyric acid, and thus simultaneously confirmed the above-assigned relative *cis* configurations. This also corroborated that the two monomeric portions were identical, including the absolute configuration. The configuration at the axis relative to the stereogenic centers was determined by a ROESY interaction between 2′-CH_3 and H1 (Figure 7a), which, together with the absolute *R* configuration at C1, evidenced the absolute configuration at the outer axes to be *M*. In view of the symmetric structure of the dimer, both monomeric halves were thus assigned as *R,S,M*-configured, so that only the absolute configuration of

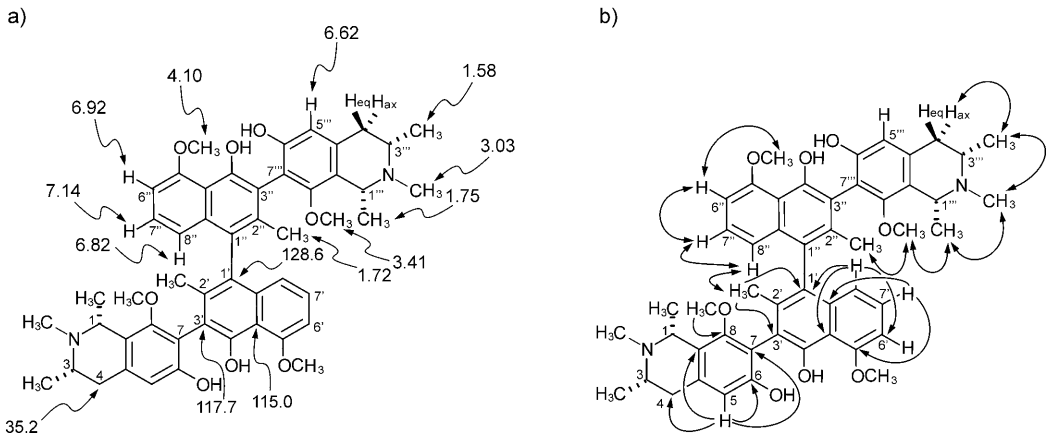

Figure 6. Selected NMR data of **5a**. a) ^{1}H and ^{13}C NMR shifts (δ in ppm).; b) ROESY (double arrows) and HMBC (single arrow) interactions indicative of the constitution (including the positions of the central axis and the outer ones).

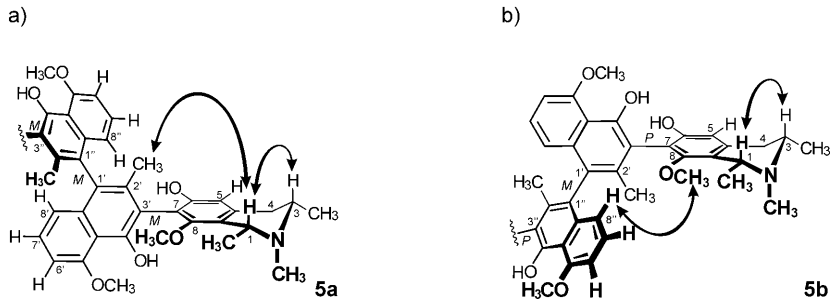

Figure 7. Selected ROESY correlations in **5a** (a) and **5b** (b).

the central axis remained to be determined, and the biaryl axes of **5a** could only be *M*,*M*,*M*- or *M*,*P*,*M*-configured.

Another dimer, less polar than the previous one, was found to have the same molecular formula as **5a**, $C_{50}H_{58}N_2O_8$, by its HRESIMS $[M+2]^{2+}$ signal with *m/z* 407.2120 (calcd for $C_{50}H_{58}N_2O_8$: 407.2091). The very similar ^{1}H and ^{13}C NMR spectra, together with the HMBC correlations, showed that the compound had the same constitution as that described above, including the absolute configuration at the stereocenters, as evidenced from the oxidative degradation,[24] which revealed the presence of atropo-diastereomers. In contrast to the opposite CD spectra of **3a** versus **3b**, however, the CD spectra of the two new dimers were almost identical.

Detailed analysis of the ROESY spectra revealed a strong diastereomer-specific ROESY interaction between H8″ and 8-CH_3O, which was absent in the other of the two dimers (Figure 7b). This interaction evidenced that both spin systems of this second dimer were on the same side of the naphthalene part (i.e., both above or both below). In view of the C_2 symmetry of **5b**, it could thus only be *P*,*M*,*P*- or *M*,*P*,*M*-configured.

For the final stereochemical assignment of **5a** and **5b**, in view of the fact that the CD spectra of these two atropo-diastereomers were so similar, it seemed rewarding to investigate them by quantum chemical CD calculations. The global minima of the remaining potential stereostructures of **5a** and **5b** (see above), that is, with *M*,*M*,*M*, *P*,*M*,*P*, and *M*,*P*,*M* configuration (each with 1*R*,3*S* at the stereogenic centers) were determined with the PM3 Hamiltonian, and the resulting lowest-energy conformers were further optimized by the B3LYP/6-31G* method. The excited states of these structures were calculated with TDB3LYP/6-31G* (Figure 8). From the above described experimental results, **5a** could only be *M*,*M*,*M*- or *M*,*P*,*M*-configured, and thus the experimental CD spectrum had to be compared with those calculated for these atropo-diastereomers. By this means the absolute configuration for **5a** was unambiguously elucidated as *M*,*M*,*M*, because only the cal-

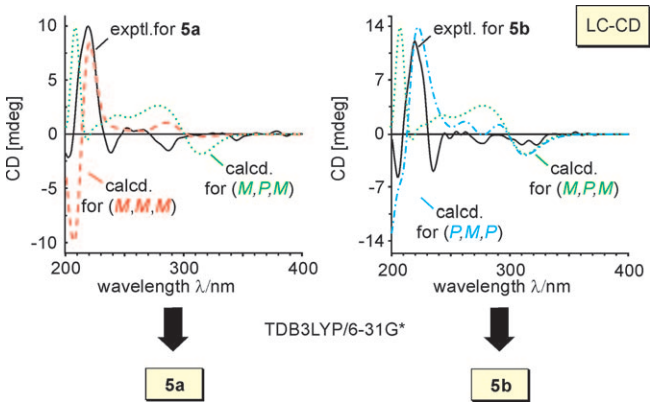

Figure 8. Assignment of the absolute configuration at the central axis of the earlier-eluting atropo-diastereomer **5a** (left), and of the later-eluting one **5b** (right), by comparison of the experimental CD spectra with the spectra calculated for *M*,*M*,*M*, *M*,*P*,*M*, and *P*,*M*,*P* by using TDB3LYP/6-31G*.

culated spectrum of the *M*,*M*,*M* isomer matched the experimental one. In the case of the two possible isomers of **5b**, with *P*,*M*,*P* or the *M*,*P*,*M* configuration, only the curve computed for *P*,*M*,*P* was in agreement with the measured CD spectrum, and thus **5b** had to be configured as shown in Figure 1.

In conclusion, the absolute configurations of the two naphthylisoquinoline dimers were fully elucidated as **5a** and **5b** (Figure 1). Accordingly, both compounds have an *M*-configured central axis, and the two homomorphous monomeric portions of **5a** and **5b** were assigned to be *R*,*S*,*M*- and *R*,*S*,*P*-configured, respectively. Both diastereomers were shown to occur in plant extracts prepared under mildest-possible conditions and thus were evidenced to be genuine natural products. These two novel dimers were henceforth named shuangancistrotectorines D and E, respectively.

Shuangancistrotectorines A–E (**3a**, **3b**, **4, 5a**, and **5b**) are the first representatives of a structurally unique type of dimeric naphthylisoquinoline alkaloids that have three consecutive configurationally stable and thus chiral axes. They are all C_2-symmetric and at first sight seem to be prime examples of structures ideally suited for application of the exciton chirality method.[25] A detailed analysis by quantum chemical calculations, however, revealed that for all these compounds the Cotton effects originate from mixtures of several excited states, so that no exciton couplet could be unambiguously determined. This was the case in particular for the *M*,*M*,*M* and *M*,*P*,*M* atropo-diastereomers of shuangancistrotectorine **5**, which have, independent of the configuration at the central axis, quite similar predicted CD curves, and thus the exciton chirality method is not safely and unambiguously applicable here. Therefore, we strongly recommend not to use this approach for such complex molecules.

Bioactivities of shuangancistrotectorines A–E: Given the high antimalarial activity of some other naphthylisoquinoline dimers, either of synthetic origin like jozimine A,[12] jozimine B,[13] and pindikamine A,[15] or the natural dimer ancistrogriffithine,[10] the dimers **3a**, **3b**, **4**, **5a**, and **5b** were evaluated for their activity against the chloroquine-resistant strain K1 of *Plasmodium falciparum*. Three of the compounds, **3a**, **3b**, and **5a**, showed very good antiplasmodial activities (IC_{50} = 0.05, 0.08, and 0.09 μM, respectively), which were even stronger than that of the standard drug chloroquine. Shuangancistrotectorine E (**5b**) was significantly less active (1.05 μM) than **5a**, and this shows the importance of axial chirality for the bioactivity.

Shuangancistrotectorine A (**3a**) and (to a smaller degree) also B (**3b**) furthermore exhibited good activity against *T. brucei rhodesiense* (IC_{50} = 0.32 μM) but only weak activity against *Trypanosoma cruzi* (IC_{50} = 3.80 μM), while the bioactivities of the other dimers against these pathogens were significantly lower (Table 1). Although the cytotoxicities against rat skeletal myoblast (L6) cells of **3a** and **3b** were higher than those of **4**, **5a**, and **5b**, these toxicities were much lower than the antiplasmodial activities, in the case of **4** and **5a** even by two to three orders of magnitude (for all indexes, see the Supporting Information). A further hint at the significant specificity of the antiplasmodial activity of the new dimers **3**–**5** is that they simultaneously show very weak activities against the (likewise protozoan) pathogen of visceral leishmaniasis, *L. donovani*, with indexes of up to approximately 1000 (in the case of **5a**), which makes these dimers promising candidates for in vivo tests, but also for total synthesis.

Table 1. Bioactivities of **3a**, **3b**, **4**, **5a**, and **5b** against *Plasmodium falciparum* (strain: K1), *Trypanosoma cruzi*, *T. brucei rhodesiense*, *T. brucei brucei*, and *Leishmania donovani*, and cytotoxicities against rat skeletal myoblast (L6) cells.

Compound	IC_{50} [μM]					
	P. falciparum	*T. cruzi*	*T. brucei rhodesiense*	*T. brucei brucei*	*L. donovani*	L6 cells (cytotoxicity)
standard	0.259[a]	1.98[b]	0.007[c]	0.003[d]	0.351[e]	0.017[f]
3a	0.052	3.80	0.318	–[g]	26.6	5.68
3b	0.076	15.7	1.24	–[g]	21.4	7.59
4	0.234	84.0	13.0	>40	79.7	59.9
5a	0.085	42.5	5.29	7.17	76.0	51.9
5b	1.05	>90	19.6	18.1	107	>90

[a] Chloroquine. [b] Benznidazole. [c] Melarsoprol. [d] Pentamidin. [e] Miltefosine. [f] Podophyllotoxin. [g] Not measured.

Conclusion

The above-described discovery of five novel naphthylisoquinoline dimers from *Ancistrocladus tectorius* shows that this Chinese plant species is a particularly rich source of unprecedented alkaloids. The dimers are unprecedented in that they are not based on a 6′,6″- or 8′,8″-coupled binaphthalene core, but are linked through sterically more constrained positions in the naphthalene moiety, so that now even the central axis is sterically hindered, giving rise to three consecutive stereogenic biaryl axes, that is, the highest number ever found not only in naphthylisoquinoline alkaloids, but also in natural products in general, which pose particular stereo-analytical challenges. This makes it rewarding to further investigate the natural variation of the coupling types of such dimers and their stereostructures, and will simultaneously contribute to the phytochemical and taxonomic classification of Asian *Ancistrocladus* species. In addition, the pronounced pharmacological properties of these naphthylisoquinoline alkaloids make them promising potential lead compounds against severe tropical infectious diseases.

Experimental Section

General experimental procedures: UV/Vis spectra were obtained on a Cary 50 Conc spectrometer (Varian). The IR spectra were recorded on a JASCO FT-IR-410 spectrometer. Optical rotations were measured on a JASCO P-1020 polarimeter. CD spectra were taken on a J-715 spectropolarimeter (JASCO, Gross-Umstadt, Germany) at room temperature by using a 0.1 cm standard cell and spectrophotometric-grade MeOH, and are reported in $\Delta\varepsilon$ values [$cm^2 mol^{-1}$] at the given wavelength λ [nm]. For HPLC-CD coupling experiments, the J-715 CD spectrometer was equipped with a PU-1580 pump (JASCO), an LG-980-02S ternary gradient unit, a 7725i Rheodyne injector valve, an ERC-7215 UV detector hyphenated to a J-715 spectropolarimeter with a 5 mm standard flow cell, and the Bowin chromatographic software (Jasco, Germany). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 and DMX 600 (400 and 600 MHz) instruments in CD_3OD with the solvent as the internal standard (CD_3OD, $\delta = 3.31$ and 49.15 ppm, respectively). HRESIMS spectra were obtained on a microTOF-focus mass spectrometer (Bruker Daltonik GmbH). FCPC separations were performed on a Kromaton apparatus with a 1000 mL rotor. Preparative HPLC was carried out on a Symmetry C_{18} column (Waters, 19×300 mm, 7 μm), flow 10 mL min^{-1}, UV detection (210 nm). Organic solvents were analytical grade or distilled prior to use. Column chromatography was performed on silica gel 60 (particle size 0.040–0.063 mm).

Plant material: The specimen of *Ancistrocladus tectorius* was collected in the region Ledong, Hainan Province, People's Republic of China, in August, 2006. A voucher of *A. tectorius* has been deposited at the the State Key Laboratory of Natural and Biomimetic Drugs, Peking University, P. R. China, with the individual number HN-033.

Extraction and isolation: Air-dried twigs from *A. tectorius* (1,500 g) were ground and extracted with 95% EtOH at room temperature. The extract was concentrated under vacuum to give around 30 g of residue, which was dissolved in MeOH and filtered, subsequently subjected to fast centrifugal partition chromatography (FCPC) with a two-phase solvent system consisting of *n*-heptane/EtOAc/MeOH/H_2O (1:9:1:9). The lower phase served as the stationary phase (flow rate 10 mL min^{-1}, rotational speed 800 min^{-1}, ascending mode) to eliminate high-polarity impurities. The total alkaloid part was eluted first with the mobile phase, and then concentrated under reduced pressure to give a fraction of 10 g. After about 60 min, the stationary phase was flushed out in reversed mode by using MeOH. This raw extract (10 g) was subjected to chromatography on an open silica gel column with a CH_2Cl_2/MeOH gradient (40:1 to 5:1).

Fraction 17 (300 mg) was eluted with CH_2Cl_2/MeOH (10:1), then purified by Sephadex LH-20 with MeOH and resolved on a Lobar Rp-18 column with 50% MeOH (0.05% trifluoroacetic acid) and 50% H_2O (0.05% trifluoroacetic acid) to afford several subfractions consisting of naphthylisoquinoline alkaloids, as evidenced by their UV profiles. Subfraction 17-2 (256 mg) was further resolved by twofold preparative HPLC, first with the following gradient: H_2O (0.05% trifluoroacetic acid) (A)/CH_3CN (0.05% trifluoroacetic acid) (B): 0 min 35% B, 22 min 48% B, then with the solvent system H_2O (0.05% trifluoroacetic acid) (A)/MeOH (0.05% trifluoroacetic acid) (B′): 0 min 40% B′, 30 min 70% B′, finally giving pure **3a** (5 mg). During evaporation of the solvent, **3a** was converted to a mixture of **3a** and **3b**. These two atropo-diastereomers were again separated by HPLC by using the solvent gradient: H_2O (0.05% trifluoroacetic acid) (A)/CH_3CN (0.05% trifluoroacetic acid) (B): 0 min 35% B, 20 min 50% B. The alkaloids **3a** (1.5 mg) and **3b** (2.0 mg) were collected at retention times of 15.7 and 18.5 min, respectively. From the same subfraction 17-2, compound **4** (1 mg) was isolated at a later retention time by using the same HPLC method.

Fraction 20 (200 mg) was subjected to column chromatography on silica gel, eluted with CH_2Cl_2/MeOH (8:1), and resolved on a Lobar Rp-18 column (MeOH/H_2O 3:2, with 0.05% trifluoroacetic acid). Subfraction 20-2, which showed the characteristic UV spectrum of naphthylisoquinolines, was purified by preparative HPLC by using the following solvent system: H_2O (0.05% trifluoroacetic acid) (A)/CH_3CN (0.05% trifluoroacetic acid) (B): 0 min 30% B, 30 min 60% B, to afford six subfractions. From the last one compounds **5a** (1 mg) and **5b** (2 mg) were collected at retention times of 14.7 and 18.6 min, respectively, by applying the following gradient: H_2O (0.05% trifluoroacetic acid) (A)/MeOH (0.05% trifluoroacetic acid) (B′): 0 min 40% B′, 30 min 70% B′.

Shuangancistrotectorine A (3a): White amorphous powder; $[\alpha]_D^{20} = +28.0$ ($c = 0.26$ in MeOH); UV/Vis (MeOH): λ_{max} ($\log\varepsilon$) = 335, 323, 311, 243, 207 nm; CD (MeOH): $\Delta\varepsilon_{341} = -1.8$, $\Delta\varepsilon_{323} = +1.3$, $\Delta\varepsilon_{245} = -6.9$, $\Delta\varepsilon_{230} = +15.7$, $\Delta\varepsilon_{209} = -4.8$ $cm^2 mol^{-1}$; IR ($CHCl_3$): $\tilde{\nu} = 2925, 2854, 1683, 1577, 1457, 1362, 1272, 1201, 1136$ cm^{-1}; ^{1}H NMR and ^{13}C NMR data: see Tables 2 and 3; EIMS: *m/z* (%): 813.4 (100) $[M+1]^+$; HRMS (TOF): *m/z*: calcd for $C_{50}H_{58}N_2O_8$: 407.2091; found: 407.2091.

Shuangancistrotectorine B (3b): White amorphous powder; $[\alpha]_D^{20} = -14.5$ ($c = 0.30$ in MeOH); UV/Vis (MeOH): λ_{max} ($\log\varepsilon$) = 335, 323, 311, 243, 207 nm; CD (MeOH): $\Delta\varepsilon_{341} = +2.3$, $\Delta\varepsilon_{307} = -1.9$, $\Delta\varepsilon_{244} = +5.6$, $\Delta\varepsilon_{231} = -10.6$, $\Delta\varepsilon_{209} = -3.5$ $cm^2 mol^{-1}$; IR ($CHCl_3$): $\tilde{\nu} = 2938, 2846, 1670, 1605, 1576, 1455, 1385, 1354, 1266, 1197, 1134$ cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; HRMS (TOF): *m/z*: calcd for $C_{50}H_{57}N_2O_8$: 813.4109; found: 813.4109.

Shuangancistrotectorine C (4): White amorphous powder; $[\alpha]_D^{20} = -12.8$ ($c = 0.05$ in MeOH); UV/Vis (MeOH): λ_{max} ($\log\varepsilon$) = 335, 323, 311, 239, 203 nm; CD (MeOH): $\Delta\varepsilon_{356} = +1.7$, $\Delta\varepsilon_{316} = +1.1$, $\Delta\varepsilon_{270} = -2.0$, $\Delta\varepsilon_{239} = -9.3$, $\Delta\varepsilon_{230} = +5.1$, $\Delta\varepsilon_{221} = -5.2$, $\Delta\varepsilon_{208} = +10.3$ $cm^2 mol^{-1}$; IR ($CHCl_3$): $\tilde{\nu} = 2927, 2851, 1683, 1558, 1540, 1570, 1456, 1207, 1133$ cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; EIMS: *m/z* (%): 809.3 (100) $[M+1]^+$; HRMS (TOF): *m/z*: calcd for $C_{50}H_{54}N_2O_8$: 405.1935; found: 405.2022.

Table 2. ^{1}H NMR (600 MHz) data of shuangancistrotectorines A (**3a**), B (**3b**), C (**4**), D (**5a**), and E (**5b**) in [D_4]methanol.[a]

Atom no.	3a	3b	4	5a	5b
1/1‴	4.77 (q, 6.7)	4.76 (q, 6.8)	–	4.63 (q, 6.8)	4.64 (q, 6.7)
3/3‴	3.93 (m)	3.94 (m)	3.76 (m)	3.39 (m)	3.39 (m)
4/4‴	3.27 (dd, 18.0, 5.0)	3.28 (dd, 18.0, 5.1)	2.49 (dd, 16.9, 5.5)	3.00 (m)	3.00 (m)
	2.93 (dd, 18.0, 11.8)	2.94 (dd, 18.0, 11.8)	2.32 (dd, 16.9, 10.4)	2.98 (m)	–
5/5‴	6.74 (s)	6.77 (s)	–	6.62 (s)	6.60 (s)
7/7‴	–	–	6.90 (s)	–	–
6′/6″	6.89 (dd, 8.2, 1.0)	6.92 (m)	6.96 (dd, 8.1, 1.0)	6.92 (dd, 7.7, 1.0)	6.90 (brd, 7.3)
7′/7″	7.18 (dd, 8.6, 8.2)	7.21 (dd, 8.8, 8.6)	7.26 (dd, 8.6, 8.1)	7.14 (dd, 8.8, 7.7)	7.10 (dd, 8.8, 7.3)
8′/8″	6.86 (dd, 8.6, 1.0)	6.90 (dd, 8.8, 1.0)	6.83 (dd, 8.6, 1.0)	6.82 (dd, 8.8, 1.0)	6.69 (dd, 8.8, 1.0)
1/1‴-CH_3	1.67 (d, 6.9)	1.65 (d, 6.8)	2.82 (s)	1.75 (d, 6.8)	1.78 (d, 6.8)
NCH_3	–	–	–	3.03 (s)	3.03 (s)
3/3‴-CH_3	1.53 (d, 6.7)	1.53 (d, 6.4)	1.19 (d, 6.8)	1.58 (d, 6.8)	1.58 (d, 6.8)
6/6‴-OCH_3	3.64 (s)	3.68 (s)	3.91 (s)	–	–
8/8‴-OCH_3	3.32 (s)	3.18 (s)	4.17 (s)	3.41 (s)	3.51 (s)
2′/2″-CH_3	1.86 (s)	1.82 (s)	1.74 (s)	1.72 (s)	1.74 (s)
5′/5″-OCH_3	4.07 (s)	4.09 (s)	4.12 (s)	4.10 (s)	4.10 (s)

[a] Multiplicities and coupling constants *J* [Hz] are shown in parentheses, and δ values are given in ppm.

Table 3. ^{13}C NMR (600 MHz) data of shuangancistrotectorines A (**3a**), B (**3b**), C (**4**), D (**5a**), and E (**5b**) in [D_4]methanol.[a]

Atom no.	3a	3b	4	5a	5b
1/1‴	49.9 (d)	49.7 (d)	175.9 (s)	62.4 (d)	62.4 (d)
3/3‴	45.2 (d)	45.2 (d)	49.5 (d)	60.9 (d)	60.9 (d)
4/4‴	34.8 (t)	34.7 (t)	32.6 (t)	35.2 (t)	35.2 (t)
5/5‴	107.0 (d)	107.4 (d)	122.9 (s)	111.1 (d)	111.0 (d)
6/6‴	159.9 (s)	160.0 (s)	168.7 (s)	157.47 (s)	157.6 (s)
7/7‴	121.4 (s)	121.6 (s)	96.0 (d)	119.0 (s)	119.2 (s)
8/8‴	157.1 (s)	157.0 (s)	166.4 (s)	157.54 (s)	157.4 (s)
9/9‴	119.8 (s)	119.8 (s)	109.1 (s)	117.9 (s)	118.0 (s)
10/10‴	133.2 (s)	133.3 (s)	141.2 (s)	134.2 (s)	134.2 (s)
1′/1″	122.3 (s)	122.4 (s)	122.5 (s)	128.6 (s)	128.4 (s)
2′/2″	138.5 (s)	138.0 (s)	138.0 (s)	137.8 (s)	137.0 (s)
3′/3″	121.9 (s)	121.6 (s)	121.6 (s)	117.7 (s)	117.97 (s)
4′/4″	152.0 (s)	152.3 (s)	152.6 (s)	152.6 (s)	152.5 (s)
5′/5″	157.8 (s)	157.8 (s)	158.2 (s)	157.9 (s)	157.6 (s)
6′/6″	104.6 (d)	104.7 (d)	105.1 (d)	105.0 (d)	104.9 (d)
7′/7″	126.5 (d)	126.7 (d)	127.5 (d)	127.2 (d)	127.1 (d)
8′/8″	120.7 (d)	120.7 (d)	119.2 (d)	121.0 (d)	120.5 (d)
9′/9″	136.3 (s)	136.4 (s)	135.9 (s)	137.1 (s)	137.1 (s)
10′/10″	115.0 (s)	115.0 (s)	115.1 (s)	115.0 (s)	115.0 (s)
1/1‴-CH_3	19.3 (q)	19.3 (q)	24.9 (q)	20.8 (q)	20.8 (q)
NCH_3	–	–	–	42.0 (q)	42.1 (q)
3/3‴-CH_3	19.4 (q)	19.5 (q)	18.1 (q)	18.3 (q)	18.3 (q)
6/6‴-OCH_3	56.3 (q)	56.3 (q)	57.05 (q)	–	–
8-OCH_3	60.6 (q)	60.5 (q)	57.06 (q)	60.6 (q)	60.7 (q)
2′/2″-CH_3	18.5 (q)	18.4 (q)	17.9 (q)	18.0 (q)	18.0 (q)
5′/5″-OCH_3	56.8 (q)	56.9 (q)	56.9 (q)	56.9 (q)	56.9 (q)

[a] Multiplicities are shown in parentheses, and δ values are given in ppm.

Shuangancistrotectorine D (5a): White amorphous powder; $[\alpha]_D^{20}=+38.4$ ($c=0.09$ in MeOH); UV/Vis (MeOH): λ_{max} ($\log\varepsilon$)=339, 323, 311, 283, 231, 195 nm; CD (MeOH): $\Delta\varepsilon_{344}=-1.67$, $\Delta\varepsilon_{287}=-4.1$, $\Delta\varepsilon_{252}=+1.3$, $\Delta\varepsilon_{238}=-4.6$, $\Delta\varepsilon_{219}=+25.5$, $\Delta\varepsilon_{202}=-5.9\ cm^2mol^{-1}$; IR ($CHCl_3$): $\tilde{\nu}=2979$, 2851, 1681, 1613, 1456, 1205, 1134 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 3; EIMS: *m/z* (%): 813.4 (100) $[M+1]^+$; HRMS (TOF): *m/z*: calcd for $C_{50}H_{58}N_2O_8$: 407.2091; found: 407.2091.

Shuangancistrotectorine E (5b): White amorphous powder; $[\alpha]_D^{20}=-77.8$ ($c=0.09$ in MeOH); UV/Vis (MeOH): λ_{max} ($\log\varepsilon$)=339, 323, 311, 283, 231, 195 nm; CD (MeOH): $\Delta\varepsilon_{340}=-1.41$, $\Delta\varepsilon_{286}=-1.2$, $\Delta\varepsilon_{240}=-4.8$, $\Delta\varepsilon_{222}=+12.0$, $\Delta\varepsilon_{205}=-5.5\ cm^2mol^{-1}$; IR ($CHCl_3$): $\tilde{\nu}=2979$, 2846, 1682, 1613, 1456, 1205, 1134 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2 and Table 3; EIMS: *m/z* (%): 813.4 (100) $[M+1]^+$; HRMS (TOF): *m/z*: calcd for $C_{50}H_{58}N_2O_8$: 407.2091; found: 407.2120.

Oxidative degradation: Ruthenium(III)-catalyzed periodate degradation, derivatization of the resulting amino acids with MeOH/HCl and then with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(*R*)-MTPA-Cl, prepared from (*S*)-MTPA], and subsequent GC-MSD analysis were carried out as described previously.[24]

Biological experiments: Antiparasitic activities against the pathogens *P. falciparum* (K1 strain), *Trypanosoma cruzi*, *T. brucei rhodesiense*, *L. donovani* (all tested in Basel), and *T. brucei brucei* (tested in Würzburg) and the cytotoxicities against host cells (rat skeletal myoblast L-6 cells, J774.1 macrophages) were assessed as described earlier.[33]

Computational details: All optimizations with PM3[29] or B3LYP/6-31G*[31,32] and the TD-DFT calculations were done with Gaussian 03.[34] To identify the found structures as minima, frequency calculations were performed, and it was checked that there were no imaginary frequencies. For the ZINDO/S-CIS[30] calculations, the ab initio software package Orca[35] was used. Oscillator and rotational strength values were computed by the length formalism. To form the UV and CD curves, Gaussian functions were summed up centered at the wavelength of the respective electronic transitions and multiplied by the corresponding oscillator strength or rotational strength values. The CD spectra thus obtained were UV-corrected[28] and compared with the experimental ones. For the generation of Gauss curves, the calculation of UV shifts, and all comparisons of calculated results with experimental spectra, SpecDis was used.[36]

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