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Total synthesis of the antimalarial naphthylisoquinoline alkaloid 5-*epi*-4′-*O*-demethylancistrobertsonine C by asymmetric Suzuki cross-coupling

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ABSTRACT

The first total synthesis of the antimalarial naphthylisoquinoline alkaloid 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its—as yet unnatural—atropo-diastereomer, **1b**, is described. The key step of the synthesis is the construction of the rotationally hindered and thus stereogenic biaryl axis, which was built up by a Suzuki reaction. The use of chiral ligands in the palladium-catalyzed cross-coupling permitted to increase the low internal asymmetric induction up to a diastereomeric ratio of 74:26. The assignment of the axial configurations of the atropo-diastereomers was achieved by 2D NMR experiments and corroborated by quantum chemical CD calculations.

1. Introduction

Tropical lianas belonging to the plant families Dioncophyllaceae and Ancistrocladaceae are the only plants known to produce naphthylisoquinoline alkaloids,[1,2] a rapidly growing class of remarkable secondary metabolites: biosynthetically, since these are the only acetogenic tetrahydroisoquinoline alkaloids,[3–5] pharmacologically, because of their pronounced bioactivities (among them antimalarial,[6,7] antileishmanial,[8] and antitrypanosomal[9] effects), and structurally, due to the presence of a usually rotationally hindered and thus stereogenic biaryl axis.[1,10] One of the alkaloids of this type, 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**, Scheme 1), which has recently been isolated from a Congolese *Ancistrocladus* species related to *Ancistrocladus congolensis*,[11] has been found to exhibit promising activities (IC_{50}=0.27 μg/mL) against *Plasmodium falciparum*, the pathogen of malaria tropica. For more detailed structure–activity relationship (SAR) investigations, in particular with respect to the influence of the configuration at the biaryl axis, the availability of the other atropo-diastereomer, **1b**, would be of importance. Since **1b** has so far not yet been found in nature, both **1a**, with its proven activity, and **1b** constitute rewarding synthetic targets. In this paper, we report on the total synthesis, stereochemical analysis, and bioactivities of 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its atropo-diastereomer, **1b**.

2. Results and discussion

The stereoselective construction of a stereogenic biaryl axis has, over the past years, attracted a lot of interest, making use of both intramolecular and intermolecular C–C coupling reactions.[12–14] One of the most successful concepts that have, finally, proven applicable to the total synthesis of concrete natural products, is the 'lactone method',[15–17] which permits the directed synthesis of either of the two atropisomers in excellent chemical and optical yields and asymmetric inductions.[18] This concept has been successfully applied to the total synthesis of a broad number of naphthylisoquinoline alkaloids (also including representatives with large steric hindrance at the axis).[19] A certain drawback is the required presence of a C_1 unit next to the coupling position. Although examples have been described that succeeded in circumventing the problem, such solutions may prolong the synthesis of target molecules that lack an *ortho*-C_1 substituent. For this reason, alternatives involving intermolecular cross-coupling reactions with different metal catalysts have been used for the total synthesis of such particular naphthylisoquinoline alkaloids, too, examples being korupensamines A and B[20–24] and dioncophylline B.[25] These intermolecular alternatives are, however, less generally applicable, due to their sensitivity toward major steric hindrance. Moreover, they usually lack any significant stereocontrol (or even atropodiastereodivergence) because of the use of achiral catalysts, thus restricting any asymmetric induction to the influence of the inherent chirality as resulting from stereogenic centers present in the isoquinoline portion.[26] After some early pioneering work in

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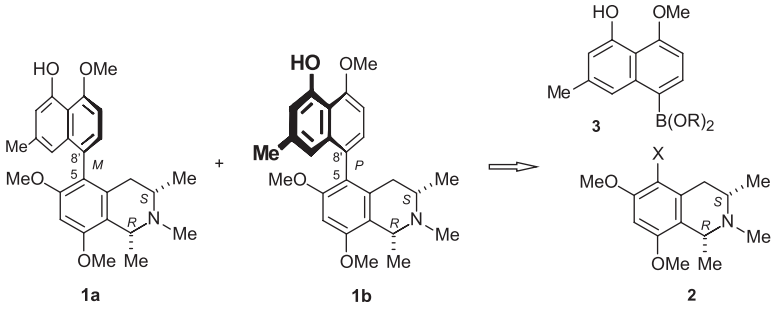


Scheme 1. Retrosynthetic disconnection of the alkaloid **1a** and its atropo-diastereomer **1b**.

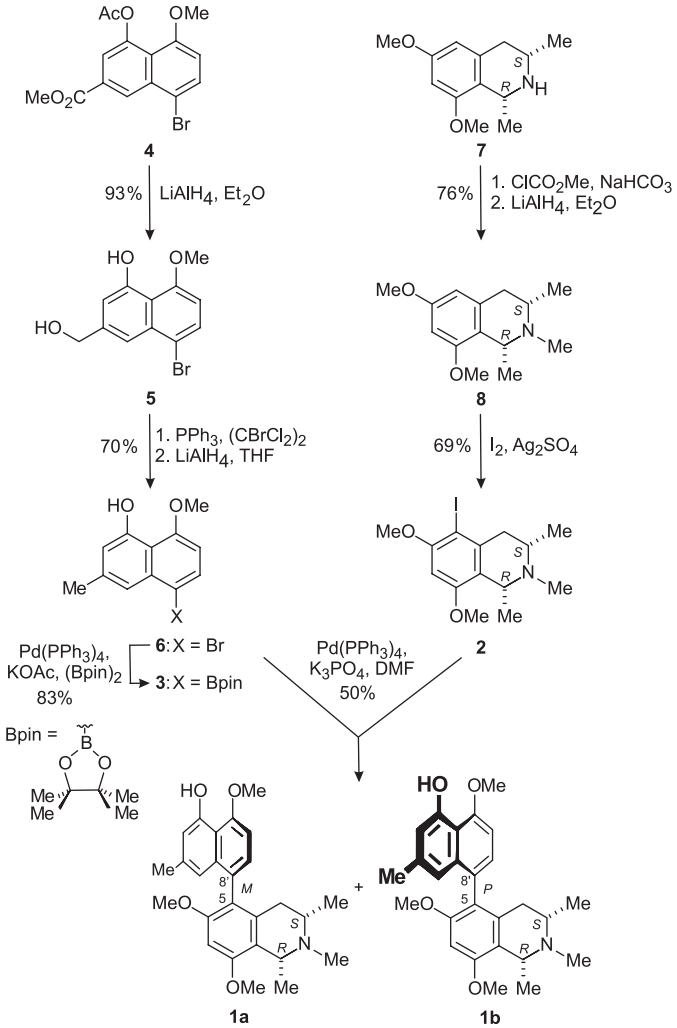
enantioselective biaryl Suzuki coupling,[27–29] the first efficient examples of atropo-enantioselective Suzuki couplings were reported in 2000 by Cammidge and Buchwald,[30,31] but still only few applications of this concept to the total synthesis of natural products are known,[32] among them the synthesis of the naphthylisoquinoline alkaloids ancistroealaine A and ancistrotanzanine B.[33] Like in that case, the presence of a 5,8′-linkage (i.e., only three *ortho*-substituents next to the axis, in particular without a C_1 unit) in **1a** and **1b** should offer the possibility to construct the stereogenic biaryl axis by a Suzuki cross-coupling. Before evaluating the use of chiral ligands in the asymmetric construction of the biaryl axis, however, achiral catalysts were utilized to gain a rapid access to both atropo-diastereomers for biological testing.

In order to keep the synthesis as short and efficient as possible and to further explore the scope and limitations of the method,[34] the use of any protective groups was avoided. For this purpose, the naphthalene moiety was activated as a boronic ester, which would permit both, boronation and cross-coupling by palladium-catalyzed reactions in the presence of the free phenolic function at C-4′. Thus, the known[35] naphthalene bicycle **4** was built up by a Wittig reaction with subsequent ring closure (Scheme 2),[35] then both ester groups were reduced with lithium aluminum hydride, and deoxygenation of the benzylic alcohol (by hydroxy–halogen exchange followed by renewed $LiAlH_4$ reduction) eventually furnished the brominated naphthalene **6**, which was further converted into the pinacol boronic ester **3** following the conditions reported by Miyaura.[36]

The isoquinoline portion, in turn, was iodinated, since it was known from previous work on a similar system[33] that the use of a less reactive brominated derivative leads to much lower yields in the cross-coupling step.[33] Therefore, the tetrahydroisoquinoline **7**, with its quite sensitive cis-configuration, was prepared as described before[37] and was then *N*-methylated by reaction with methyl chloroformate and subsequent reduction of the carbamate with lithium aluminum hydride to give **8**[38] in 76% yield. Despite its electron-rich character, iodination of **8** turned out to be difficult. After careful optimization of the reaction conditions, treatment of **8** with I_2 and Ag_2SO_4[39] gave **2** in 69% yield. Attempts to perform the iodination under less rigorous conditions (e.g., by using NIS and TFA[40]) gave no reaction or resulted in mixtures of difficult-to-separate regioisomers.

With the two building blocks available, a first Suzuki cross-coupling of the two moieties was achieved in DMF with K_3PO_4 as the base (see Table 2, entry 1), which (according to ^1H NMR) resulted in a 62:38 mixture of the two expected atropisomers in 50% yield. Although the two diastereomers showed a very similar chromatographical behavior on reversed-phase HPLC, they were easily separable by simple silica gel column chromatography, in contrast to more difficult previous separations of other, related atropo-diastereomers (which could only be resolved on a chiral phase, as if they were enantiomers).[33,41] Similar to related other cases,[42–44] this atropisomer-differentiating chromatographical behavior is presumably due to interactions of the free phenolic group at C-4′ with the silica gel. The more rapidly eluting isomer proved to be identical in all spectroscopic, chromatographical, and physical properties with the authentic natural product, 5-*epi*-4′-*O*-demethylancistrobertsonine C, thus confirming the structure previously published,[11] in all details.

The assumption that the two obtained products were really atropo-diastereomers, was demonstrated by their mirror-shaped circular dichroism (CD) curves (Fig. 1b), as measured offline. The spectrum of the more rapidly eluting isomer (peak A) perfectly matched the one of the natural product and was also in a good agreement with that of the structurally related, likewise 5,8′-



Scheme 2. Synthetic pathway to 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its atropo-diastereomer **1b**.

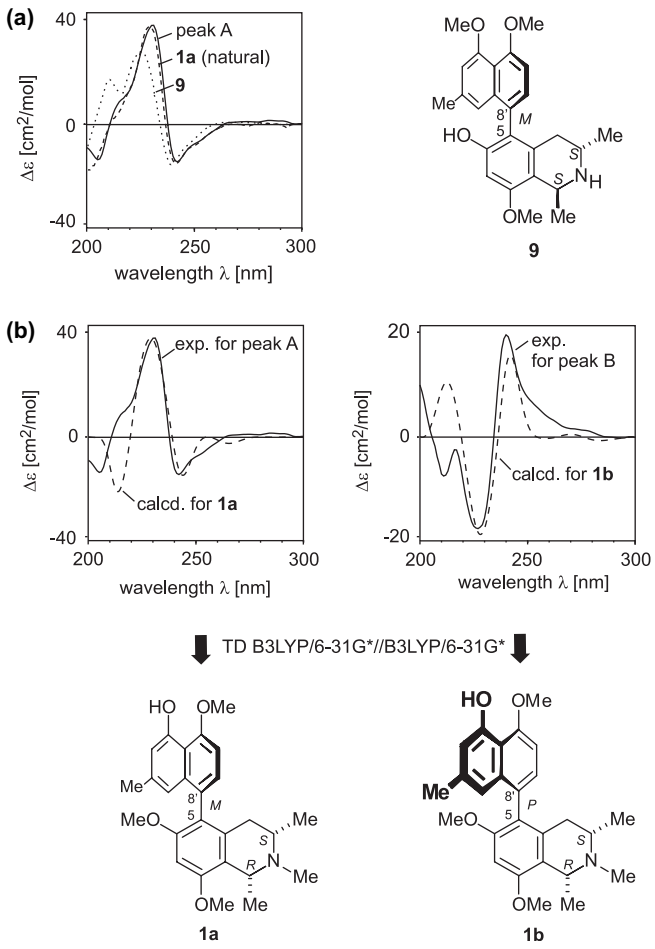


Figure 1. CD spectra of the more rapidly eluting isomer (peak A, —), of natural **1a** (- - -), and of **9**, i.e., the (*M*)-configured ancistrobrevine B (···) (a); CD spectra quantum chemically calculated for **1a** and **1b**, and their comparison with the experimental CD spectra of peak A and peak B, respectively (b).

coupled and (*M*)-configured alkaloid ancistrobrevine B (**9**, Fig. 1a),[45] thus again evidencing an *M*-configuration at the axis. The more slowly eluting isomer (peak B) should thus be *P*-configured. This assumption was further corroborated by quantum chemical CD calculations. Using B3LYP/6-31G(d),[46,47] a potential energy surface scan was performed, yielding two minimum energy conformers for each diastereomer within an energy range of 3 kcal/mol, which should contribute to a relevant part to the corresponding overall CD spectra. For the conformers thus obtained, time-dependent (TD) DFT calculations were performed, using the same combination of hybrid functional and basis set. The single spectra received were added following the Boltzmann statistics to give the overall UV and CD spectra predicted for the diastereomers **1a** and **1b**.[48] A comparison of the calculated UV spectra with the ones experimentally obtained resulted in a UV shift of 20 nm for **1a** and of 18 nm for **1b**, revealing that the energies of the excited states were slightly overestimated in both cases. To take into account this systematic mistake, the CD curves were shifted by these amounts, too, and were compared with the experimental spectra of peak A (more rapidly eluting) and peak B (more slowly eluting). The comparison revealed a good agreement between the spectrum calculated for the (*M*,*R*,*S*)-configuration (i.e., for **1a**) and the experimental spectrum for peak A (Fig. 1b, left) on the one hand, and between the one predicted for the (*P*,*R*,*S*)-configuration (i.e., for **1b**) and that of peak B (Fig. 1b, right) on the other, thus unambiguously establishing the absolute configurations of the two atropo-diastereomers as *M* and *P*, respectively.

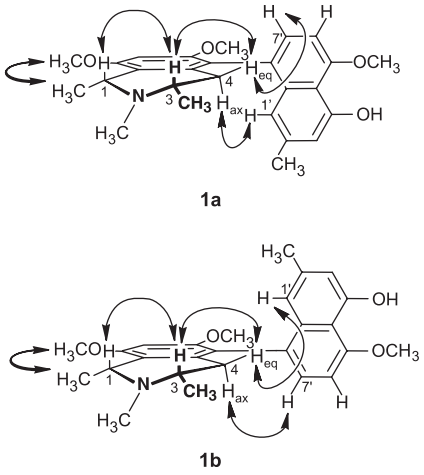


Figure 2. NOESY correlations decisive for the determination of the relative—and thus absolute—axial configurations of **1a** and **1b**.

An unequivocal final confirmation of the attribution of the axial configurations thus obtained was achieved by NOESY measurements. In the case of **1a**, correlations in the series {H-1–H-3–H-4_{eq}–H-7′} and an interaction of H-4_{ax} with H-1′ confirmed the *M*-configuration (as already established for the natural **1a**),[11] whereas couplings in the series {H-1–H-3–H-4_{eq}–H-1′} and a correlation of H-4_{ax} with H-7′ proved the *P*-configuration for **1b** (Fig. 2).

For a direct comparison of their antiprotozoal effects, the two atropo-diastereomeric products thus synthetically obtained, **1a** and **1b**, were tested for their activities against pathogens belonging to the genera of *Plasmodium*, *Leishmania*, and *Trypanosoma* (Table 1).

For both atropo-diastereomers, only weak activities were observed against *Leishmania donovani*, which causes the visceral leishmaniasis, against the pathogen of African sleeping sickness, *Trypanosoma brucei rhodesiense*, and against *Trypanosoma cruzi* (pathogen of the Chagas' disease). Interestingly, the non-natural *P*-isomer **1b** was more than twice as active as **1a** against the K1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine), and thus, in comparison with chloroquine as the positive control, less active only by a factor of 3 (Table 1).

These results demonstrated the value of the availability of the non-natural **1b** by the total synthesis now achieved, and made it even more rewarding to perform the cross-coupling step in a more stereocontrolled manner by an additional *external* asymmetric induction using chiral catalysts.

As a first step in this direction, the coupling conditions were further optimized. Although no product was formed with DME as the solvent and with fluoride as a mild base (Table 2, entry 2),[30] yields were improved to 72% by changing the solvent system to toluene/water and by employing K_2CO_3 as the base (Table 2, entry 3).

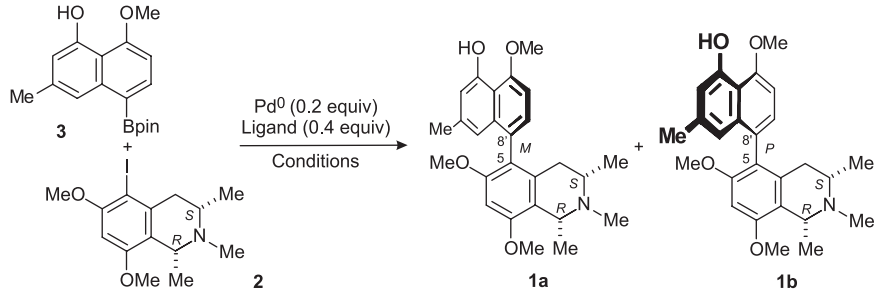
This did not change substantially when (R_c,S_p)-**10** was used as the first chiral ligand (Table 2, entry 4), but (as in other cases)[32] the use of this diphosphine led to almost no preference for any diastereomer.[49] A change to (R_c,S_p)-**11** as a monodentate ligand,

Table 1
Bioactivities of compounds **1a** and **1b**

	IC_{50}[a]	
	1a	**1b**
P. falciparum (strain: K1) standard: chloroquine 0.0425[a]	0.27	0.111
Trypanosoma b. rhodesiense standard: melarsoprol 0.006[a]	3.38	3.25
T. cruzi standard: benznidazole 0.87[a]	6.20	16.70
Leishmania donovani standard: miltefosine 0.08[a]	12.6	20.2
Cytotoxicity (strain: J774.1 macrophages) standard: podophyllotoxin 0.005[a]	30.94	29.58

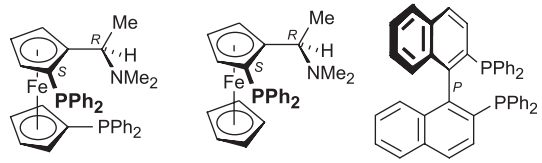
[a] All values in μg/mL.

Table 2
Coupling conditions, chemical yields, and diastereomeric ratios (dr) in the asymmetric Suzuki cross-coupling reactions



Entry	Catalyst	Ligand	Conditions	Yield[a] (%)	dr[b] (*M*/*P*)
1	$Pd(PPh_3)_4$	—	DMF, K_3PO_4, 90 °C	50	38:62
2	$Pd(PPh_3)_4$	—	DME, KF, 90 °C	—	—
3	$Pd(PPh_3)_4$	—	Toluene/H_2O, Na_2CO_3, 90 °C	72	41:59
4	$Pd_2(dba)_3$	(R_c,S_p)-**10**	Toluene/H_2O, Na_2CO_3, 80 °C	69	50:50
5	$Pd_2(dba)_3$	(R_c,S_p)-**11**	Toluene/H_2O, Na_2CO_3, 80 °C	85	66:34
6	$Pd_2(dba)_3$	(S_c,R_p)-**11**	Toluene/H_2O, Na_2CO_3, 80 °C	69	48:52
7	$Pd_2(dba)_3$	(*P*)-**12**	Toluene/H_2O, Na_2CO_3, 80 °C	17	74:26
8	$Pd_2(dba)_3$	(*M*)-**12**	Toluene/H_2O, Na_2CO_3, 80 °C	24	46:54
9	$Pd_2(dba)_3$	(*P*)-**12**	Toluene/H_2O, $Ba(OH)_2$, 80 °C	—	—

[a] Combined yield of **1a** and **1b** after resolution by column chromatography.
[b] Diastereomeric ratio determined by ^{1}H NMR.



which had already successfully been used in similar cases,[32,33] resulted in a high chemical yield of 85% and in an atropo-diastereomeric ratio of 66:34 (Table 2, entry 5), but this time in favor of the *M*-diastereomer **1a**—thus inverting the stereochemical ratio obtained with achiral catalysts (see above). The catalyst derived from the (S_c,R_p)-enantiomer of **11**, however, did not give the stereochemically expected 'matched' case (which should strongly favor the formation of the *P*-isomer, **1b**), but led to an almost 1:1 ratio of the two diastereomers (Table 2, entry 6). Similar results were obtained with the chiral BINAP ligands (*P*)-**12** and (*M*)-**12**, although in much lower yields (Table 2, entries 7 and 8): construction of the biaryl axis in the presence of (*P*)-**12** increased the diastereomeric ratio to 74:26 in favor of **1a**, while (*M*)-**12** inverted the selectivity toward the formation of **1b** with a dr of 46:54. Attempts to increase the low yields of 17% and 24% (entries 7 and 8, respectively) by using $Ba(OH)_2$ as the base,[50] resulted in decomposition.

3. Conclusion

In summary, the first and efficient, total synthesis of 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) was achieved by an effective, high-yield Suzuki cross-coupling as the decisive step, remarkably without the need for protective groups. The absolute configurations of the two diastereomers were unambiguously established by a combination of spectroscopic and computational methods. The use of chiral catalysts in the Suzuki cross-coupling led to quite good asymmetric inductions in favor of **1a** (up to 74:26), although the application of the other ligand enantiomers did not lead to a complete chirality reversal. The total synthesis described here provides a plant-independent access to **1a**, but also to its as yet unknown atropo-diastereomer **1b**, which was found to exhibit even better antiplasmodial activities against *P. falciparum*.

4. Experimental

4.1. General

Melting points were obtained on a Reichert-Jung Thermovar hot plate and are uncorrected. UV spectra were taken on a Varian Cary 50 spectrophotometer, IR spectra on a Jasco FT/IR-410 spectrometer, and optical rotations on a Jasco P-1020 polarimeter. ^{1}H NMR (600 MHz, 400 MHz) and ^{13}C NMR (150 MHz, 100 MHz) were recorded on a Bruker DMX 600 or on an AMX 400, using $CDCl_3$ (δ 7.26 and 77.01) and CD_3OD (δ 3.30 and 49.15) as solvents and internal ^{1}H and ^{13}C standards. EIMS (70 eV), HREIMS (70 eV), and HRESIMS were determined on Finnigan MAT 8200, Finnigan MAT 90, and Bruker microTOF instruments, respectively. CD spectra were recorded on a J-715 spectrometer (JASCO Deutschland, Gross-Umstadt, Germany) at room temperature using a 0.1 cm standard cell and spectrophotometric-grade MeOH. For analytical TLC silica gel precoated glass plates (60 F_{254}, Merck) were used and flash chromatography was carried out on silica gel (0.063 mm, Merck). Deactivated silica gel was prepared by mixing silica gel with 7.5 vol% NH_3. All reagents were reagent grade and solvents were dried and distilled prior to use.

4.2. Synthesis of 5-*epi*-4′-*O*-demethylancistrobertsonine C (1a) and its atropo-diastereomer, 1b

*4.2.1. 5-Bromo-8-methoxy-3-hydroxymethyl-1-naphthol (**5**)*

The ester **4** (1.00 g, 2.83 mmol, 1.0 equiv) was placed under argon in a flame-dried flask and dissolved in Et_2O (50 mL). After addition of $LiAlH_4$ (215 mg, 5.66 mmol, 2.0 equiv), the reaction mixture was stirred for 5 h at room temperature and then cautiously quenched with 2 N HCl. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$. Removal of all volatiles under reduced pressure gave **5** as a white powder (743 mg, 2.62 mmol, 93%); mp 117 °C (petroleum ether/ethyl acetate); IR (KBr) ν_{max} 3407, 3385, 2921, 2844, 1633, 1603, 1572, 1386, 1358, 1273, 1228, 1159, 1083, 976, 958 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.40 (s, 1H, HO-1), 7.67 (d, ^4J=1.5 Hz, 1H, H-4), 7.61 (d, ^3J=8.3 Hz, 1H, H-6), 6.96 (d, ^4J=1.5 Hz, 1H, H-2), 6.64 (d, ^3J=8.3 Hz, 1H, H-7), 4.81 (s, 2H, CH_2-3), 4.06 (s, 3H, OCH_3-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (C-1), 155.1 (C-8), 142.2 (C-3), 134.3 (C-10), 129.7 (C-6), 115.8 (C-4), 115.3 (C-5 or C-9), 115.0 (C-5 or C-9), 110.3 (C-2), 104.3 (C-7), 65.2 (CH_2-3), 56.3 (OCH_3-8); EIMS (70 eV) *m*/*z* (rel int.) 284.0/282.0 (98/100) $[M]^+$, 268.9/266.9 (24/21) $[M^+-CH_3]$. Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92. Found: C, 51.31; H, 4.05.

4.2.2. 5-Bromo-8-methoxy-3-methyl-1-naphthol (**6**)

Under argon, a solution of **5** (250 mg, 0.88 mmol, 1.0 equiv), PPh_3 (695 mg, 2.65 mmol, 3.0 equiv), and $(CBrCl_2)_2$ (863 mg, 2.65 mmol, 3.0 equiv) in CH_2Cl_2 (25 mL) was stirred for 4 h at room temperature. After removal of the solvent in vacuo, the residue was dissolved in THF (20 mL), $LiAlH_4$ (134 mg, 3.52 mmol, 4.0 equiv) was carefully added, and the reaction mixture was stirred for 2 h at room temperature. After acid hydrolysis, the aqueous layer was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure, followed by purification by column chromatography on silica gel, using petroleum ether/ethyl acetate (5:1) as the eluent, afforded **6** as white crystals (164 mg, 0.61 mmol, 70%); mp 105 °C (petroleum ether/ethyl acetate); lit.[51] mp 104–105 °C (acetone/petroleum ether). All spectroscopic and physical data were in accordance with those reported.[51]

4.2.3. 8-Methoxy-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthol (**3**)

A suspension of **6** (55.0 mg, 0.20 mmol, 1.0 equiv), KOAc (121 mg, 1.23 mmol, 6.0 equiv), and bis(pinacolato)diboron (77.0 mg, 0.30 mmol, 1.5 equiv) in DMF (10 mL) was degassed for 10 min, then $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol, 0.1 equiv) was added and the reaction mixture was stirred (after renewed degassing) for 2 h at 90 °C. After removal of the solvent under reduced pressure and purification of the remaining residue by column filtration on silica gel, using petroleum ether/ethyl acetate (6:1) as the eluent, **3** was obtained as fine white crystals (54.1 mg, 0.17 mmol, 83%); mp 89–90 °C (petroleum ether/ethyl acetate); IR (KBr) ν_{max} 3421, 2924, 1654, 1459, 1022, 484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H, HO-1), 8.02 (d, ^4J=1.4 Hz, 1H, H-4), 7.90 (d, ^3J=7.8 Hz, 1H, H-6), 6.74 (d, ^4J=1.4 Hz, 1H, H-2), 6.70 (d, ^3J=7.8 Hz, 1H, H-7), 4.06 (s, 3H, OCH_3-8), 2.45 (s, 3H, CH_3-3), 1.40 (s, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C-1), 154.7 (C-8), 140.9 (C-9), 138.7 (C-3), 136.9 (C-6), 119.4 (C-4), 113.3 (C-10), 112.6 (C-7), 103.0 (C-2), 83.9 (C-5), 56.3 (OCH_3-8), 30.1 [*C*(CH_3)$_2$], 25.3 [C(*C*H_3)$_2$], 22.5 (CH_3-3); EIMS (70 eV) *m*/*z* (rel int.) 314.1 (100) $[M]^+$, 241.1 (37), 129.1 (40). Anal. Calcd for $C_{18}H_{22}BO_4$: C, 68.81; H, 7.38. Found: C, 67.67; H, 7.11.

4.2.4. (1S,3S)-N-Methyl-5-iodo-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**2**)

Ag_2SO_4 (167 mg, 0.53 mmol, 2.5 equiv) and I_2 (101 mg, 0.40 mmol, 1.9 equiv) were added to a solution of **8** (50.0 mg, 0.21 mmol, 1.0 equiv) in EtOH (20 mL) under argon and the reaction mixture was stirred for 2 h at 0 °C, then for further 3 h at room temperature. Filtration and evaporation of the solvent led to a crude residue, which was further purified by flash column chromatography on deactivated SiO_2, using petroleum ether/ethyl acetate (4:1) as the eluent, to yield **2** as a yellow oil (53.0 mg, 0.14 mmol, 69%); $[\alpha]_D^{20}$ +67.5 (*c* 1.0, MeOH); IR (KBr) ν_{max} 3430, 2929, 1638, 1590, 1458, 1324, 1206, 1073, 494, 474, 423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 1H, H-7), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.62 (q, ^3J=6.3 Hz, 1H, H-1), 2.82 (dd, ^2J=16.0 Hz, ^3J=3.2 Hz, 1H, H-4), 2.52 (dd, ^2J=16.0 Hz, ^3J=10.3 Hz, 1H, H-4), 2.43 (s, 3H, *N*-CH_3), 2.35–2.40 (m, 1H, H-3), 1.32 (d, ^3J=6.2 Hz, 3H, CH_3-1), 1.25 (d, ^3J=6.1 Hz, 3H, CH_3-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (C-6 or C-8), 157.2 (C-6 or C-8), 140.7 (C-4a), 123.7 (C-8a), 94.3 (C-7), 81.9 (C-5), 60.7 (C-1), 57.4 (NCH_3), 56.0 (OCH_3), 55.7 (OCH_3), 44.7 (C-4), 41.3 (C-3), 22.9 (CH_3-1), 21.4 (CH_3-3); EIMS (70 eV) *m*/*z* (rel int.) 361.0 (1) $[M]^+$, 346.0 (100) $[M^+-CH_3]$, 218.1 (8), 158.0 (8), 102.1 (10). Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 43.39; H, 5.17; N, 3.89.

4.2.5. Suzuki cross-coupling of **2** and **3**

4.2.5.1. Using $Pd(PPh_3)_4$ as an achiral catalyst. A solution of **2** (53.0 mg, 0.14 mmol, 1.0 equiv), **3** (60.0 mg, 0.19 mmol, 1.3 equiv), and K_3PO_4 (135 mg, 0.63 mmol, 5.0 equiv) in DMF (8 mL) was degassed. After addition of $Pd(PPh_3)_4$ (15.0 mg, 0.01 mmol, 0.1 equiv), the reaction mixture was stirred under argon for 2.5 h at 90 °C. The mixture was filtered through a short pad of Celite and all volatiles were removed under reduced pressure. The remaining residue was extracted with CH_2Cl_2, the solvent was evaporated in vacuo, and column chromatography on deactivated SiO_2 (eluent: petroleum ether/ethyl acetate 2:1) yielded **1a** (12.0 mg, 28.2 μmol, 19%) and subsequently **1b** (19.0 mg, 45.0 μmol, 31%), both as pale yellow solids, which were recrystallized from MeOH to give white solids.

4.2.5.2. Asymmetric Suzuki cross-coupling reactions with chiral ligands. A typical experimental procedure is given for the use of chiral ligands in the cross-coupling step: a mixture of $Pd_2(dba)_3$ (1.0 mg, 1.4 μmol, 0.2 equiv) and (R_c,S_p)-**11** (5.0 mg, 6.0 μmol, 0.4 equiv) in degassed toluene (2 mL) was stirred at 25 °C for 15 min. After addition of **2** (5.0 mg, 14.0 μmol, 1.0 equiv), **3** (6.0 mg, 18.0 μmol, 1.3 equiv), and 2 N aqueous Na_2CO_3 solution (0.75 mL), the reaction mixture was stirred for 20 h at 80 °C. All volatiles were removed under reduced pressure and the products purified by column chromatography (eluent: petroleum ether/ethyl acetate 2:1) to give a mixture of **1a** and **1b** (5.0 mg, 11.8 μmol, 85%) in a ratio of 41:59.

*4.2.5.3. 5-epi-4′-O-Demethylancistrobertsonine C (**1a**).* Mp 92 °C (MeOH); lit.[11] not obtained in a crystalline form; $[\alpha]_D^{20}$ +51.8 (*c* 1.0, MeOH); lit[11] $[\alpha]_D^{20}$ +15.7 (*c* 0.12, MeOH). Identical with the natural product (isolated from a Congolese *Ancistrocladus* species related to *A. congolensis*)[11] by TLC, HPLC coelution, ^1H and ^{13}C NMR, HRESIMS, and CD.

*4.2.5.4. Atropo-diastereomer **1b** (4′-O-demethylancistrobertsonine C).* Mp 93 °C (MeOH); $[\alpha]_D^{20}$ +52.0 (*c* 1.0, MeOH); IR (KBr) ν_{max} 3400, 2957, 2926, 2849, 1690, 1610, 1597, 1453, 1416, 1385, 1266, 875 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.07 (d, ^3J=7.9 Hz, 1H, H-6′), 6.91 (d, ^3J=7.9 Hz, 1H, H-7′), 6.76 (d, ^4J=1.3 Hz, 1H, H-1′), 6.64 (d, ^4J=1.3 Hz, 1H, H-3′), 6.45 (s, 1H, H-7), 4.68 (q, ^3J=6.6 Hz, 1H, H-1), 4.10 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.16–3.20 (m, 1H, H-3), 3.03 (s, 3H, *N*-CH_3), 2.58 (dd, ^2J=17.3 Hz, ^3J=11.5 Hz, 1H, H-4), 2.24 (dd, ^2J=17.3 Hz, ^3J=2.9 Hz, 1H, H-4), 2.22 (s, 3H, CH_3-2′), 1.72 (d, ^3J=6.6 Hz, 3H, CH_3-1), 1.26 (d, ^3J=6.5 Hz, 3H, CH_3-3); ^{13}C NMR (150 MHz, CD_3OD) δ 158.4 (C-8), 156.4 (C-6), 156.1 (C-4′), 154.6 (C-5′), 137.6 (C-4a), 135.5 (C-2′), 133.0 (C-9′), 128.4 (C-7′), 126.1 (C-8′), 119.9 (C-8a), 115.1 (C-1′), 113.6 (C-5), 113.1 (C-10′), 111.7 (C-3′), 102.8 (C-6′), 94.2 (C-7), 60.6 (C-1), 58.9 (C-3), 55.3 (OCH_3-2′), 54.9 (OCH_3-6), 54.8 (OCH_3-8), 40.0 (*N*-CH_3), 32.5 (C-4), 20.4 (CH_3-2′), 18.3 (CH_3-1), 16.4 (CH_3-3); ESIMS *m*/*z* (rel int.) 422.2 (100) $[M^+H]$; HRESIMS 422.2325 ($[M+H]^+$, 422.2325 calcd for $C_{26}H_{32}NO_4$); UV/vis (MeOH): λ_{max} 307 (0.44), 230 (1.17); CD (MeOH): $\Delta\varepsilon_{211}$ −8.2, $\Delta\varepsilon_{216}$ −3.2, $\Delta\varepsilon_{227}$ −18.2, $\Delta\varepsilon_{240}$ +18.6.

5. Computational

All calculations were performed using the software package Gaussian 03. For both, DFT and TDDFT, the B3LYP[46] hybrid functional together with Pople's basis set 6-31G(d)[47] were applied.

Frequency calculations corroborated the found conformers as minima on the potential energy surface and were also used for a zero-point correction of the found energies. The conformers thus obtained were used for excited-states calculations by TDDFT to give oscillator and rotational strength values. These were multiplied with the sums of Gaussian functions centered at the wavelengths of the corresponding electronic transitions to form absorption and CD curves, respectively. These single UV and CD spectra were subsequently added up following the Boltzmann statistics,[48] using the zero-point corrected energies from the DFT calculations. Eventually, the UV-corrected CD spectra were compared with the ones experimentally obtained after fitting the intensity of the curves to the measured data.

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra for **1a**, **1b**, **2**, **3**, and **5**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.087.

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