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Synthesis of Pindikamine A, a Michellamine-Related Dimer of a Non-Natural, 'Skew' Naphthylisoquinoline[1]

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Abstract: The synthesis of an unnatural dimeric naphthylisoquinoline, pindikamine A (**3**), as a 'skew' analog of antiviral michellamines, is described. Because of the unusual coupling positions, this C_2-symmetric quateraryl is the first michellamine analog without axial chirality. Key steps of the total synthesis are the preparation of the molecular precursor **9** by intermolecular biaryl coupling, followed by a highly efficient oxidative 'dimerization' to give **8**, which is transformed to **3**. Pindikamine A (**3**) and its monomeric 'half' **10** show good antimalarial activity against *Plasmodium falciparum in vitro*.

INTRODUCTION

Naphthylisoquinoline alkaloids[2,3] are a young, but rapidly growing class of natural biaryls. They are characterized by their unusual structures, remarkable biological activities, and an unprecedented biosynthetic origin. The recent isolation of novel 'dimeric' naphthylisoquinoline alkaloids named michellamines,[4,5] from the 'new' West African liana *Ancistrocladus korupensis*[6] has stimulated considerable further interest. Because of their strong antiviral activity against HIV-1 and HIV-2,[4,5] these naturally occurring quateraryls, among them michellamine A (**1**) and its atropodiastereomers, michellamines B and C, constitute a promising new lead structure. We have elaborated first synthetic pathways[7-9] to these interesting natural quateraryls, which simultaneously confirmed their absolute stereostructures as attributed earlier.[5,10] More recently, further total syntheses have been described.[11,12] Since michellamines do not only exhibit strong anti-HIV activity, but are also characterized by a certain cytotoxicity,[5] the availability of structural analogs of these new antiviral compounds is of great urgence. Besides the chemical modification of isolated natural michellamines themselves, another possibility for the preparation of novel michellamine-type quateraryls is the dimerization of

naturally occurring monomeric naphthylisoquinolines, as recently first achieved by the synthesis of jozimine A (**2**),[13] the unnatural dimer of the natural[14] monomeric naphthylisoquinoline alkaloid dioncophylline A. Still, these approaches will not give rise to more significantly modified, in particular simplified, structural analogs, which should thus best be attained by total synthesis. In this paper, we describe the first preparation of a non-natural ('skew', since 6,8'-coupled) naphthylisoquinoline and its oxidative coupling, to give the novel dimeric naphthylisoquinoline **3** ('pindikamine A'), the first michellamine analog without axial chirality.

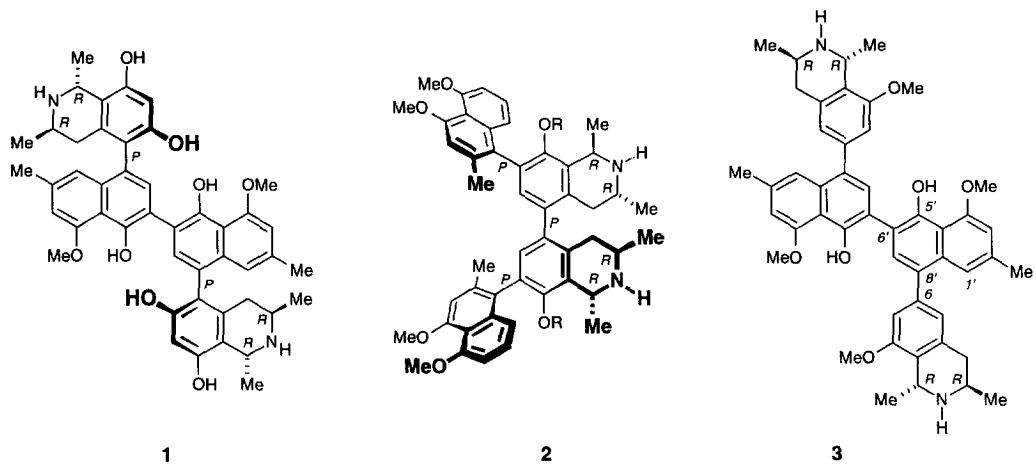
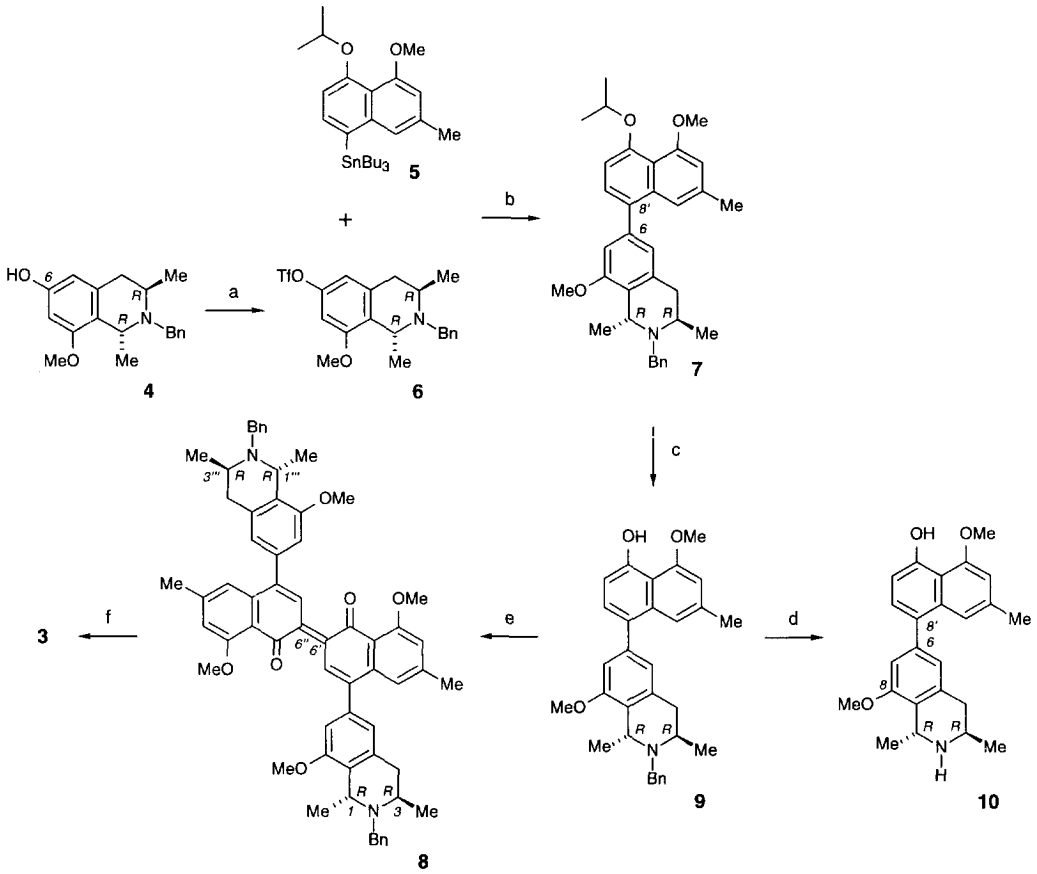


Figure 1. The naturally occurring antiviral michellamine A (**1**),[4,5] the non-natural dimer **2**[13] of natural[14] dioncophylline A (only the atropo-diastereomer with *P*-configuration at the stereogenic central biaryl axis is shown), and the artificial target molecule **3**.

RESULTS AND DISCUSSION

Given the C_2-symmetric structure of the target molecule **3** and our experience in the total synthesis of michellamine A (**1**) by oxidative dimerization of the corresponding monomeric 'half',[7,8] it seemed feasible to likewise build up **3** by such an oxidative phenolic coupling step, starting with the corresponding 'monomeric' naphthylisoquinoline precursor **10** or, even better, with its *N*-protected analog **9** (see Scheme 1). In **9** and **10**, the naphthalene substituent is located at C-6 of the isoquinoline part and thus *meta* to the oxygen function at C-8, not in an *ortho*- or *para*-position as in natural systems.[2,3] Consequently, this coupling type had to be built up by total synthesis. The introduction of the biaryl axis into the 6-position of the tetrahydroisoquinoline system was easily attained starting from the well-established synthetic building block **4**,[15] by transformation of the free phenolic oxygen function at C-6 into a triflate leaving group (see Scheme 1). Thus, reaction of **4** with trifluorsulfonic anhydride (Tf_2O) in the presence of thallium ethanolate as a base[16] gave the *O*-triflate **6.** Other bases (*e.g.* NaH or pyridine) resulted in most unsatisfying yields. As the naphthalene partner, we chose the

trialkylstannane **5**, which was present from previous synthetic work.[8,17] Subsequent palladium-catalyzed *C,C*-linkage of **5** and **6** in a Stille-type coupling, using reaction conditions initially described by Saá,[18] gave the required 6,8'-coupled naphthylisoquinoline **7**. Selective cleavage of the *O*-isopropyl protective group with BCl_3 in CH_2Cl_2 led to the key compound **9**, with the free phenolic oxygen function specifically located next to the scheduled coupling site.



Scheme 1. Reagents and conditions: a) TlOEt, Tf_2O, CH_2Cl_2, 87%; b) $PdCl_2(PPh_3)_2$, PPh_3, LiCl, CuBr, DMF, 135 °C, 63%; c) BCl_3, CH_2Cl_2, -15 °C, 96%; d) H_2, Pd/C (10%), CH_2Cl_2 / MeOH, 93%; e) Ag_2O, $CHCl_3$, Et_3N, 94%; f) H_2, Pd/C (10%), CH_2Cl_2 / MeOH, 98%.

Hydrogenolytic *N*-debenzylation of **9** gave the free naphthylisoquinoline **10**, which is closely related to several natural Dioncophyllaceae-type naphthylisoquinoline alkaloids,[3] but differs by its non-natural 6,8'-coupling type. For the oxidative dimerization to give michellamine-type quateraryls, the still *N*-protected analog **9** seemed ideal. Previous investigations[7,8,19] had shown that an ideal protective group for the aromatic position *para* to the free phenolic oxygen function in related naphthols is an aryl residue which, in **9**, is realized by the

isoquinoline part at C-8'. Indeed, oxidative coupling of **9** with Ag_2O in $CHCl_3/NEt_3$ delivered the deep-blue colored dione **8**, which was fully characterized. Subsequent reduction of the chromophor and cleavage of the *N*-protective group was achieved in a single step, by catalytic hydrogenation over Pd/C, to give the dimeric target molecule **3** in high yields.

The novel quateraryl **3**, subsequently named pindikamine A,[20] is the first artificial dimer of a non-natural, 6,8'-coupled naphthylisoquinoline. The most obvious structural difference between **3** and the michellamines is the position of the outer biaryl axes on the isoquinoline cores, which also has stereochemical consequences: **3** is the first structural analog of michellamines in which all of the biaryl systems show free, non-hindered rotation, hence all biaryl axes of **3** are non-stereogenic, which greatly facilitates its synthesis.

Regrettably, pindikamine A (**3**) does not show a particular antiviral activity comparable to that of michellamines.[21] Given the unexpectedly high antimalarial activity of jozimine A (**2**),[13] compared with its monomeric precursor, dioncophylline A, it seemed feasible to test the *in vitro* activity of the new mono- and dimeric naphthylisoquinoline against *Plasmodium falciparum*, the causative factor of the most dangerous *malaria tropica*. Indeed, quite good *in vitro* activities were found for both compounds, interestingly again the dimer **3** giving distinctly better results (IC_{50} = 1.23 µg/ml) than its monomeric analog **10** (IC_{50} = 3.49 µg/ml). This makes it rewarding to design and test further artificial dimers of natural or unnatural monomeric naphthylisoquinolines. This work is in progress.

EXPERIMENTAL

All reactions were run under an argon atmosphere unless otherwise stated. Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. NMR spectra were recorded with Bruker AC 200, Bruker AC 250, and Bruker WM 400 spectrometers. The chemicals shifts δ are given in parts per million (ppm) with the proton signals in the deuterated solvent as internal reference for ^1H NMR. The coupling constants, *J*, are given in Hertz. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer, and reported in wave numbers (cm^{-1}). Mass spectra were obtained on a Finnigan MAT 8200 mass spectrometer at 70 eV in the EI mode unless otherwise stated.

(1*R*,3*R*)-*N*-Benzyl-8-methoxy-1,3-dimethyl-6-trifluorsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (6). A solution of **4**[15] (238 mg, 802 µmol) in dry CH_2Cl_2 (5 ml) and thallium ethanolate[16] (299 mg, 1.20 mmol) was stirred for 15 min at room temperature. Trifluorosulfonic anhydride (339 mg, 1.20 mmol) was added with stirring. After 5 min, the pH value was adjusted to ca. 8 with concd. NH_3. The solvent was removed under reduced pressure and the residue was purified by column chromatography on deactivated (7.5% NH_3) silica gel with CH_2Cl_2 / MeOH (100:3) as the eluent, to afford **6** (300 mg, 87%) as a colorless oil, which was characterized as the HBr salt. This was recrystallized from CH_2Cl_2 / petroleum ether to give colorless crystals:

mp 93 °C; $[\alpha]_D^{23}$ = +25.3 (*c* = 0.60 in MeOH); IR (KBr): ν 3500-3400, 2910, 2800-2400, 1605, 1590, 1410, 1230, 1210, 1130, 1110; ^{1}H NMR (250 MHz, MeOH-d_4): δ = 1.46 (d, *J* = 6.7, 3 H, 3-CH_3), 1.51 (d, *J* = 6.8, 3 H, 1-CH_3), 2.89 (m_c, 2 H, 4-CH_2), 3.43 (d, *J* = 13.6, 1 H, NC*H*HPh), 3.67-3.78 (m, 1 H, 3-H), 3.96 (s, 3 H, OCH_3), 4.04 (d, *J* = 13.6, 1 H, NCH*H*Ph), 4.16 (q, *J* = 6.8, 1 H, 1-H), 6.91 (s, 2 H, 5-H and 7-H), 7.24-7.49 (m, 5 H, Ph-H); MS: *m/z* (%) = 429 (0.2) [M$^+$], 414 (41) [M$^+$ - CH_3], 281 (21) [414 - SO_2CF_3], 190 (5) [281 - C_7H_7], 91 (100) [$C_7H_7^+$]; Anal. calcd. for the HBr salt $C_{20}H_{23}BrF_3NO_4S$ (510.4): C, 47.07; H, 4.54; N, 2.74; S, 6.28. Found: C, 46.88; H, 4.36; N, 2.60; S,5.99.

(1*R*,3*R*)-*N*-Benzyl-6-(5'-isopropoxy-4'-methoxy-2'-methyl-8'-naphthyl)-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (7). To a solution of **6** as the free base (100 mg, 232 µmol), PPh_3 (18.4 mg, 69.6 µmol), $PdCl_2(PPh_3)_2$ (48.9 mg, 69.6 µmol), dry LiCl (76.0 mg, 1.79 mmol), CuBr (13.4 mg, 93.2 µmol), and three crystals of 2,6-di-*tert*-butyl-4-methylphenol in dry DMF (10 ml), the stannane **5**[8] (192 mg, 370 µmol) was added and the mixture was heated to 120 °C for 28 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on deactivated (7.5% NH_3) silica gel with CH_2Cl_2 as the eluent. The crude product was recrystallized from CH_2Cl_2 / petroleum ether, to give **7** (74.0 mg, 63%) as colorless crystals: mp 141 °C; $[\alpha]_D^{23}$ = +93.7 (*c* = 0.40 in $CHCl_3$); IR (KBr): ν 2980-2960, 1570, 1440, 1360, 1270, 1110; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.6, 3 H, 3-CH_3), 1.41 (d, *J* = 6.8, 3 H, 1-CH_3), 1.43 [d, *J* = 6.0, 6 H, CH(C*H*$_3$)$_2$], 2.40 (s, 3 H, 2'-CH_3), 2.66-2.71 (m, 2 H, 4-CH_2), 3.43 (d, *J* = 14.6, 1 H, NC*H*HPh), 3.65 (m_c, 1 H, 3-H), 3.72 (s, 3 H, 8-OCH_3), 3.89 (d, *J* = 14.6, 1 H, NCH*H*Ph), 3.96 (s, 3 H, 4'-OCH_3), 4.04 (q, *J* = 6.6, 1 H, 1-H), 4.56 [sept, *J* = 6.0, 1 H, C*H*(CH_3)$_2$], 6.69 (s, 1 H, 5-H or 7-H), 6.73 (s, 1 H, 5-H or 7-H), 6.77 (s, 1 H, 3-H), 6.90 (d, *J* = 8.1, 1 H, 6'-H), 7.24-7.45 (m, 7 H, 1'-H, 7'-H and Ph-H); MS: *m/z* (%) = 509 (4) [M$^+$], 494 (100) [M$^+$ - CH_3], 452 (10) [494 - C_3H_6], 422 (6) [452 - CH_2O], 361 (16) [452 - C_7H_7], 91 (39) [$C_7H_7^+$]; Anal. calcd. for $C_{34}H_{39}NO_3$ (509.7): C, 80.12; H, 7.71; N, 2.75. Found: C, 79.49; H, 7.84; N, 2.76.

(1*R*,3*R*)-*N*-Benzyl-6-(5'-hydroxy-4'-methoxy-2'-methyl-8'-naphthyl)-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (9). A solution of **7** (60.0 mg, 118 µmol) in dry CH_2Cl_2 (10 ml) was added dropwise during 15 min to a 1 M BCl_3 solution (236 µl, 236 µmol) in CH_2Cl_2 at -15 °C. After 30 min, MeOH (5 ml) was added and the solvent was removed under reduced pressure. Purification of the residue on deactivated (7.5% NH_3) silica gel with CH_2Cl_2 / MeOH (100:1) as eluent and subsequent recrystallization of the HBr salt from CH_2Cl_2 / petroleum ether gave **9** (53.0 mg, 96%) as colorless crystals: mp 144 °C; $[\alpha]_D^{23}$ = +59.9 (*c* = 0.50 in $CHCl_3$); IR (KBr): ν 3550-3100, 2940, 2920, 1600, 1440, 1420, 1250, 1120; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.4, 3 H, 3-CH_3), 1.42 (d, *J* = 6.8, 3 H, 1-CH_3), 2.41 (s, 3 H, 2'-CH_3), 2.67-2.72 (m, 2 H, 4-CH_2), 3.42 (d, *J* = 14.0, 1 H, NC*H*HPh), 3.57 (m_c, 1 H, 3-H), 3.73 (s, 3 H, 8-OCH_3), 3.90 (d, *J* = 13.8, 1 H, NCH*H*Ph), 4.06 (q, *J* = 6.4, 1 H, 1-H), 4.08 (s, 3 H, 4'-OCH_3), 6.66 (d, *J* = 1.2, 1 H, 5-H or 7-H), 6.72 (d, *J* = 1.2, 5-H or 7-H), 6.77 (s, 1 H, 3'-H), 6.86 (d, *J* = 7.8, 1 H, 6'-H), 7.32 (d, *J* = 7.8, 1 H, 7'-H), 7.23-7.46 (m, 6 H, 1'-H and Ph-H), 9.46 (s, 1 H, OH); MS: *m/z* (%) = 467 (29) [M$^+$], 452 (100) [M$^+$ - CH_3], 437 (9)

[452 - CH_3], 91 (50) [$C_7H_7^+$]; Anal. calcd. for the free base $C_{31}H_{33}NO_3$ (467.6): C, 79.63; H, 7.11; N, 3.00. Found: C, 79.34; H, 7.22; N, 2.94.

(1*R*,3*R*)-6-(5'-Hydroxy-4'-methoxy-2'-methyl-8'-naphthyl)-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (10). A mixture of **9** (36.0 mg, 77.0 µmol), dissolved in dry MeOH (4 ml), was hydrogenated in the presence of Pd/C (10%) (8.00 mg) for 14 h under normal pressure. The solvent was removed under reduced pressure and after filtration of the catalyst through silica gel, the residue was crystallized from ethanol to give **10** (27.0 mg, 93%) as a colorless microcrystalline powder: mp 115 °C; $[\alpha]_D^{23}$ = +10.6 (*c* = 1.27 in $CHCl_3$); IR (KBr): ν 3600-3150, 2920, 1600, 1570, 1440, 1250, 1120, 1100; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 6.3, 3 H, 3-CH_3), 1.79 (d, *J* = 6.9, 3 H, 1-CH_3), 2.40 (s, 3 H, 2'-CH_3), 2.96 (dd, *J* = 11.0, *J* = 4.1, 1 H, 4-H_{ax}), 3.18-3.23 (m_c, 1 H, 4-H_{eq}), 3.63 (m_c, 1 H, 3-H), 3.82 (s, 3 H, 8-OCH_3), 4.08 (s, 3 H, 4'-OCH_3), 4.89 (q, *J* = 6.3, 1 H, 1-H), 6.66 (s, 1 H, 5-H or 7-H), 6.75 (s, 1 H, 5-H or 7-H and 3'-H), 6.84 (d, *J* = 8.0, 1 H, 6'-H), 7.21 (d, *J* = 8.0, 1 H, 7'-H), 7.23 (s, 1 H, 1'-H), 9.46 (s, 1 H, OH); MS: *m/z* (%) = 377 (28) [M$^+$], 376 (68) [M$^+$ - H], 362 (100) [M$^+$ - CH_3], 347 (28) [362 - CH_3], 345 (7) [376 - OCH_3]; Anal. calcd. for $C_{24}H_{27}NO_3$ (377.5): C, 76.36; H, 7.21; N, 3.71. Found: C, 75.66; H, 7.00; N, 3.68.

(1*R*,3*R*)-*N*,*N'*-Diformyl-5',5''-di-*O*-dehydro-6-(5'-hydroxy-4'-methoxy-2'-methyl-8'-naphthyl)-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (8). To a solution of **9** (30.0 mg, 64.0 µmol) in $CHCl_3$ (6 ml) containing 0.2% Et_3N, Ag_2O (300 mg, 1.29 mmol) was added in the dark under air atmosphere. The reaction mixture was stirred for 6 h and the inorganic insolubles were filtered through silica gel. After removal of the solvent, **8** (28.0 mg, 94%) was obtained as a deep-blue colored microcrystalline solid from CH_2Cl_2 / petroleum ether: mp 115-116 °C; UV λ_{max} (EtOH) 232 nm (log ε 4.27), 386 (3.82), 565 (3.51); IR (KBr): ν 2900, 1640, 1620, 1620, 1570, 1450, 1240; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.3, 6 H, 3-CH_3 and 3'''-CH_3), 1.41 (d, *J* = 7.0, 6 H, 1-CH_3 and 1'''-CH_3), 2.34 (s, 6 H, 2'-CH_3 and 2''-CH_3), 2.71-2.74 (m, 4 H, 4-H and 4'''-H), 3.40 (d, *J* = 14.3, 2 H, 2 NC*H*HPh), 3.65-3.67 (m, 2 H, 3-H and 3'''-H), 3.76 (s, 6 H, 8-OCH_3 and 8'''-OCH_3), 3.91 (d, *J* = 14.6, 2 H, 2 NCH*H*Ph), 3.96 (s, 6 H, 4'-OCH_3 and 4''-OCH_3), 4.01-4.05 (m, 2 H, 1-H and 1'''-H), 6.75 (s, 2 H, 3'-H and 3''-H), 6.76 (s, 2 H, 5-H and 5'''-H or 7-H and 7'''-H), 6.78 (s, 2 H, 5-H and 5'''-H or 7-H and 7'''-H), 6.89 (s, 2 H, 1'-H and 1''-H), 7.31-7.46 (m, 10 H, Ph-H), 7.91 (s, 2 H, 7'-H and 7''-H); MS: *m/z* (%) = 932 (1) [M$^+$ + 2], 931 (1) [M$^+$ + 1], 930 (1) [M$^+$], 916 (29) [M$^+$ + 1 - CH_3], 915 (3) [M$^+$ - CH_3)], 841 (8) [M$^+$ - C_7H_7], 823 (8) [841 - H_2O], 91 (100) [$C_7H_7^+$]; Anal. calcd. for $C_{62}H_{62}N_2O_6$ (931.2): C, 79.97; H, 6.71; N, 3.01. Found: C, 79.27; H, 6.99; N, 2.97.

8',8''-Bis-(1*R*,3*R*)-(*N*-benzyl-8-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-yl)-4',4''-dimethoxy-2',2''-dimethyl-6',6''-binaphthylidene ('Pindikamine A')[20] (3). **8** (14.0 mg, 15.0 µmol) was hydrogenated in a mixture of dry CH_2Cl_2 (2 ml) and dry MeOH (2ml) in the presence of Pd/C (10%) (6.00 mg) for 17 h under normal pressure. After filtration of the catalyst through silica gel, the solvent was removed under reduced pressure and the residue was crystallized from MeOH / petroleum ether, which yielded **3** (11.0 mg,

98%) as an amorphous powder: mp dec. 210 °C; $[\alpha]_D^{23}$ = +1.2 (*c* = 1.22 in $CHCl_3$); IR (KBr): ν 3600-3200, 2920, 1570, 1440, 1420, 1250, 1120; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.8, 6 H, 3-CH_3 and 3'''-CH_3), 1.47 (d, *J* = 6.8, 6 H, 1-CH_3 and 1'''-CH_3), 2.39 (s, 6 H, 2'- CH_3 and 2''-CH_3), 2.45-2.49 (m, 2 H, 4-H_{ax} and 4'''-H_{ax}), 2.78 (dd, *J* = 17.8, *J* = 4.0, 2 H, 4-H_{eq} and 4'''-H_{eq}), 3.32-3.36 (m, 2 H, 3-H and 3'''-H), 3.80 (s, 6 H, 8-OCH_3 and 8'''-OCH_3), 4.04 (s, 6 H, 4'-OCH_3 and 4''-OCH_3), 4.40 (q, *J* = 6.8, 2 H, 1-H and 1'''-H), 6.66 (s, 2 H, 3'-H and 3''-H), 6.78 (s, 2 H, 5-H and 5'''-H or 7-H and 7'''-H), 6.80 (s, 2 H, 5-H and 5'''-H or 7-H and 7'''-H), 7.33 (s, 2 H, 7'-H and 7''-H), 7.42 (s, 2 H, 1'-H and 1'''-H), 9.88 (s, 2 H, 5'-OH and 5''-OH); MS (FAB; matrix: glycerine): *m/z* (%) = 753 (M^+ + 1), 737 (M^+ - CH_3). Anal. calcd. for $C_{48}H_{52}N_2O_6$ (753.0): C, 76.57; H, 6.96; N, 3.72. Found: C, 76.61; H, 6.98; N, 3.72.

Antiplasmodial activities of 10 and 3. Antiplasmodial assays were performed with *P. falciparum* (NF 54, clone A1A9)[22] asexual erythrocytic stages. Continuous parasite cultures were kept *in vitro*, essentially following the method of Trager and Jensen.[23,24] Parasite growth inhibition by **10** and **3** was determined measuring the incorporation of radiolabeled hypoxanthine.[25,26]

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