Pergamon

Tetrahedron 55 (1999) 1731–1740

TETRAHEDRON

Octadehydromichellamine, a Structural Analog of the Anti-HIV Michellamines without Centrochirality[1]

Gerhard Bringmann* and Matthias Wenzel

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

T. Ross Kelly

Boston College, Eugene F. Merkert Chemistry Center, Department of Chemistry, Chestnut Hill, MA 02467-3860, USA

Michael R. Boyd and Robert J. Gulakowski

Laboratory of Drug Discovery Research and Development, National Cancer Institute, Building 1052, Room 121, Frederick, MD 21702-1201, USA

Ronald Kaminsky

Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland

Received 12 November 1998; accepted 10 December 1998

Abstract: The synthesis of octadehydromichellamine (**4**), as the fully dehydrogenated structural analog of the naturally occurring michellamines (**1**), is described. This derivative is the first michellamine-type quateraryl without centrochirality and thus constitutes a distinctly simplified structural michellamine analog. Key step of the total synthesis is the twofold coupling of a bis-*O*-triflate activated central binaphthalene building block **9** with 2 eq. of the isoquinoline boronic acid **8**, to give the quateraryl **11**, whose deprotection delivers the target molecule **4**, in an apparently stereochemically pure form. Octadehydromichellamine (**4**) shows a good order of anti-HIV activity and, compared with natural michellamines, enhanced antimalarial activity against *Plasmodium falciparum*.

INTRODUCTION

Michellamines A-C (**1a-c**)[2,3] constitute a structurally novel type of dimeric naphthylisoquinoline alkaloid,[4] isolated from the 'new' Cameroonian liana, *Ancistrocladus korupensis*.[5] In particular, michellamine B (**1b**) shows a high anticytopathic activity against HIV-1 and -2.[2,3] Its development as a potential novel anti-AIDS drug, however, has been hampered by toxicity,[3] necessitating further design, preparation, and testing of structural analogs of michellamines. The synthetic goal is the identification of less toxic analogs, hopefully with an increased antiviral activity, and if possible based on simplified structures. We have recently described

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01195-8

first syntheses of (probably non-natural) dimers of natural, well available naphthylisoquinolines like jozimine A (**2**) (*i.e.* dimeric dioncophylline A),[6] which has an additional (moderately stable) element of axial chirality in the center of the molecule and shows an unexpectedly high antimalarial activity, and jozimine C (**3**) (*i.e.* dimeric dioncophylline C), the first unnatural dimer of a naphthylisoquinoline alkaloid with a high anti-HIV activity.[7] Recently, additional, in part simplified analogs of michellamines have been prepared.[8-12] Here we report on the total synthesis of the fully dehydrogenated close structural analog **4** of the michellamines (**1**), which is simplified by the absence of stereocenters in the isoquinoline parts.

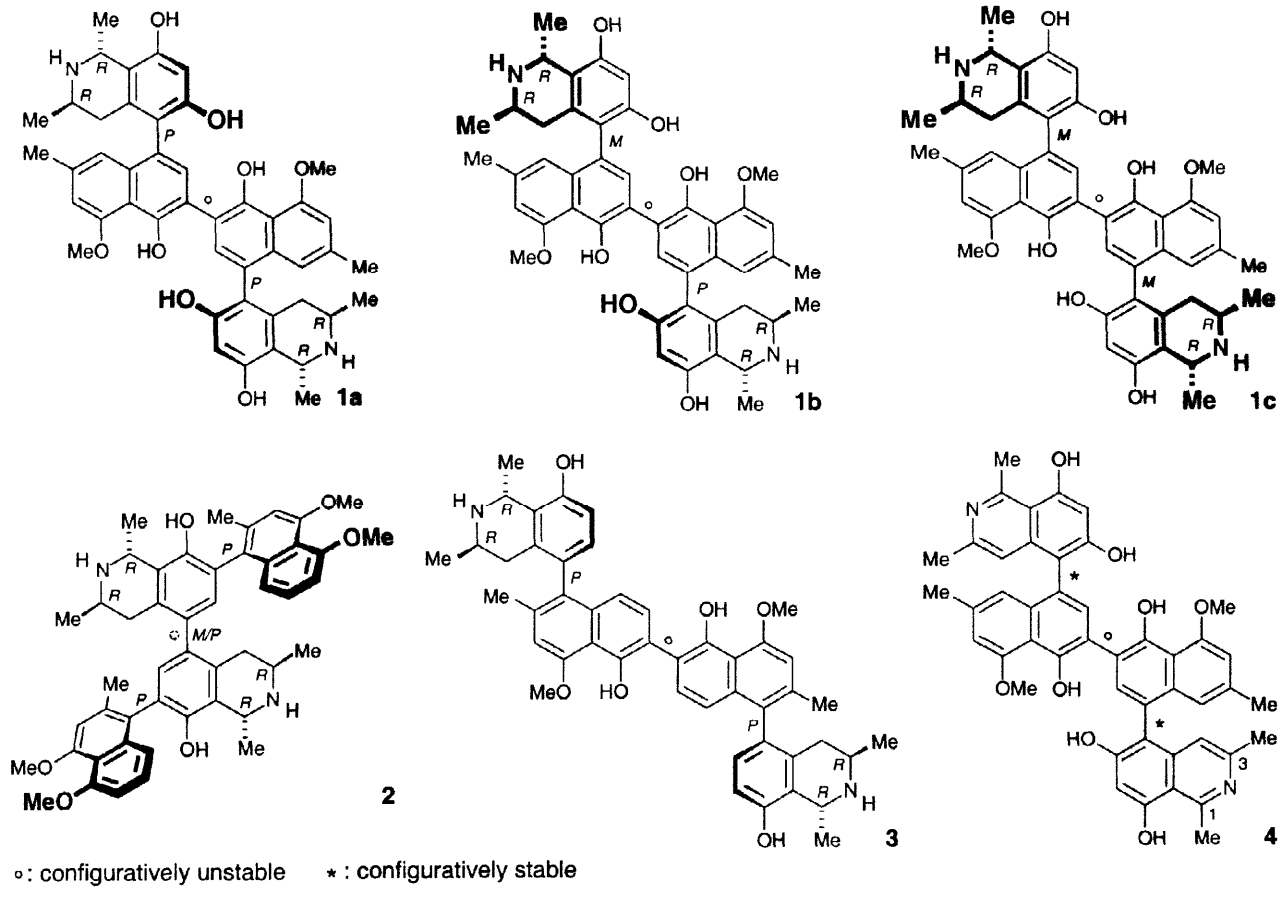


Fig. 1. Antiviral michellamines (**1a-c**) and some synthetic structural analogs.

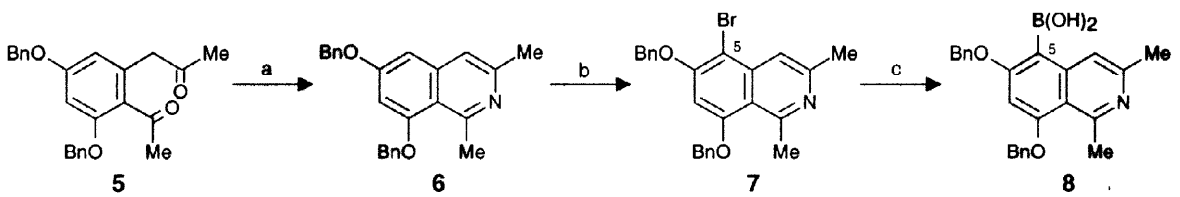
RESULTS AND DISCUSSION

The preparation of a dehydrogenated analog **4** seemed attractive, since such a compound still shows a close structural similarity to michellamines, but is simultaneously characterized by the absence of all the four stereogenic centers, due to the sp^2-character of C-1 and C-3 of both of the isoquinoline parts. A simple

possibility for the rational preparation of **4** should be the catalytic dehydrogenation of natural michellamines, which, however, gave complex product mixtures.

For the - hence required - directed *total* synthesis of **4**, two principal synthetic approaches - as also applied in our first syntheses of authentic michellamines[13-17] - were imaginable: to first build up the outer biaryl axes of **4** to give of the corresponding fully aromatic monomeric naphthylisoquinoline, and then the inner one, by its oxidative dimerization - or, *vice versa*, to construct the inner axis first, and then the outer ones.

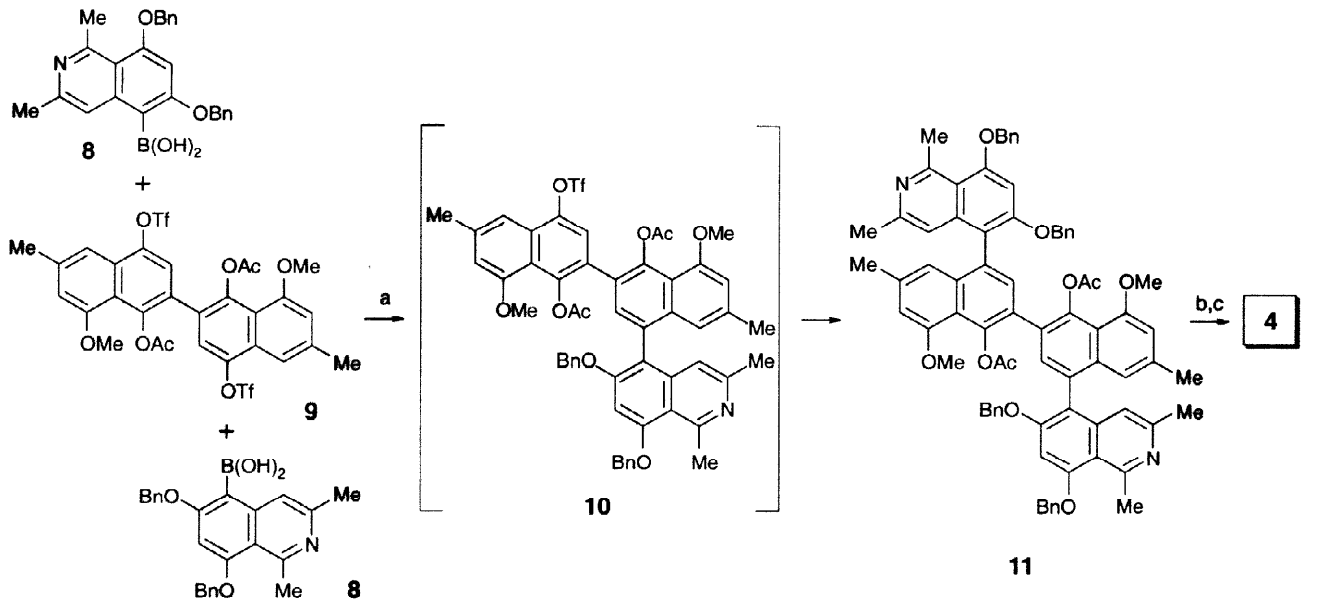
Of these two strategies, we chose the latter, given the availability of the required inner binaphthalene fragment **9** (Scheme 2) from one of our previous michellamine syntheses.[16,17] As the starting material for the preparation of the likewise required fully aromatic isoquinoline building block **8** (Scheme 1), we chose the diketone **5**[18] - in its non-protected form a postulated biosynthetic precursor to naphthylisoquinoline alkaloids.[19] Biomimetic incorporation of ammonia[20] into **5** to give the isoquinoline **6** and subsequent bromination exclusively in the 5-position, led to **7** in good yields. Conversion into the corresponding boronic acid **8** proved to be difficult, but finally succeeded using *t*-butyllithium in THF at -100 °C for the lithiation step, followed by reaction with trimethylborate to form **8**.



Scheme 1. Reagents and conditions: a) NH_4OAc, EtOH, 4 °C, 79%; b) Br_2, NaOAc, CH_2Cl_2, 25 °C, 93%; c) *t*-BuLi, THF / Et_2O (4:1), $B(OMe)_3$, -100 °C, 48%.

Palladium-catalyzed coupling experiments (Scheme 2) initially gave the desired quateraryl **11** in extremely low, but detectable yields (3%). First hints at the existence of the required structure were obtained from the correct mass spectrum (M^+ 1192 amu). Further optimization (*i.a. in situ* boronation → Suzuki coupling using the same catalyst and solvent but *t*-BuOK as a stronger base as $Ba(OH)_2$ used before) allowed a significant improvement of the yield, albeit on a still relatively low basis (12%). One of the by-products occasionally observed, was the monocoupled mono-*O*-triflate teraryl **10**, which opens the principal option of preparing *mixed* michellamine analogs, *e.g.* a hybrid of **1** and **4**.[21]

Deacylation of **11** was achieved by refluxing in methanolic HCl and led to the corresponding dihydroxy species. Removal of the benzyl groups by hydrogenation over palladium on carbon gave a complex mixture, in which the expected product **4** was initially not detectable. The deprotection of **11** finally succeeded by hydrogenolysis using formic acid in methanol as a hydrogen source and palladium black as the catalyst,[22] to afford **4** in a pure form.



Scheme 2. Reagents and conditions: a) $Pd(PPh_3)_4$, *t*-BuOK, H_2O / DME (1:3), 85 °C, 12%; b) HCl_g, MeOH, reflux; c) palladium black, MeOH / HCO_2H (2:3), reflux, 71%.

On account of an expected free rotation of the central axis and the presence of two stereogenic 'outer' axes and the symmetric constitution, **4** might consist of three stereoisomeric forms, two C_2-symmetric enantiomers, **4a** (*P,P*) and **4c** (*M,M*), and a *meso*-form **4b** (*M,P*). In contrast, the three atropisomeric forms of the michellamines, **1a**, **1b**, and **1c**, are all diastereomeric to each other, due to the additional presence of four (homochiral) stereocenters, so that **1a** and **1c** are likewise C_2-symmetric, but not enantiomeric to each other, and **1b** is not a *meso*-compound.

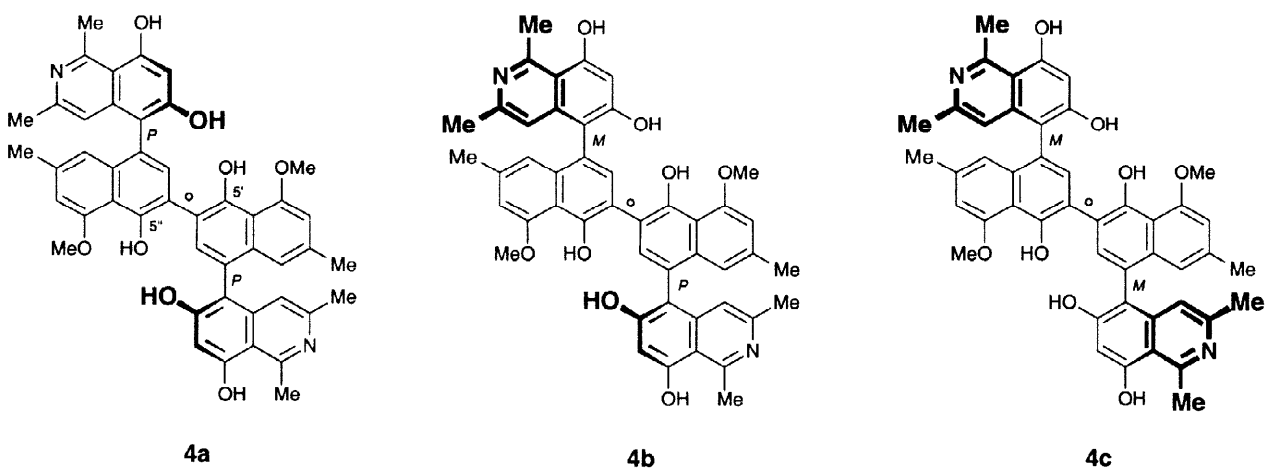


Fig. 2. Possible stereoisomeric forms of octadehydromichellamines (**4**).

If formed statistically, without any atropselectivity, **4** should constitute a 1:2:1 mixture of **4a**:**4b**:**4c**. In NMR, it should thus appear as a 1:1 mixture of **4a** + **4c** and **4b**. It does, however, exhibit a single set of NMR

signals. This is all the more astonishing since its precursor, **11**, does show the expected peak doubling in NMR, although likewise behaving like a single substance chromatographically. Given the configurative stability of the 'outer' biaryl axes of michellamines (**1**)[14,16] and a series of other 5,8'-coupled naphthylisoquinoline-alkaloids,[4] the corresponding axes of **4** and **11** should likewise be configurationally stable. The peak doubling of **11**, which gets lost through deprotection to give **4**, should result from a reduced free rotation around the *central* biaryl axis of **11**, which is neighbored by two OAc (instead of OH) groups at C-5' and C-5", giving rise to the differentiation into additional atropoisomers that are stable at least on the NMR time scale, while **4**, with its smaller OH groups at C-5' and C-5", should not show such a discrimination at room temperature. A low-temperature experiment on **4**, however, does reveal a peak decoalescence, starting with the 1-Me group at 233 K and resulting in a near-complete peak doubling at 180 K - as for **11** at room temperature.

If peak doubling through blocking of the central axis is observed, it allows conclusions on the stereostructure of the product **4** formed in that unexpected stereochemical purity. Blocking the rotation about the central axis of a *meso*-compound **4b** (*M,P*) - by lowering the temperature or by increasing the size of the *ortho*-substituents - should result in the formation of an enantiomeric mixture, *M,M,P* and *M,P,P* (= *P,P,M*) and thus should not give any peak doubling. By contrast, **4a** (*P,P*) or **4c** (*M,M*) or mixtures thereof should deliver diastereomeric mixtures when freezing the central axis, leading to the formation of ***P,P,P*** and ***P,M,P*** from **4a** (plus their enantiomers, *M,M,M* and *M,P,M*, from **4c**). The peak doubling of **4** (upon cooling) and of its precursor **11** (already at room temperature) suggest octadehydromichellamine to have the C_2-symmetric structure **4a/4c**. The reason for the high diastereoselectivity of its formation is as yet unknown.[23]

Octadehydromichellamine (**4**) showed antiviral (HIV-1) activity (EC_{50} = 29 μM), comparable to michellamine B (**1**) (EC_{50} = 11 μM). The cytotoxicity of **4** (IC_{50} = 104 μM) was also similar to that of michellamine B (142 μM). Octadehydromichellamine (**4**) thus represents the first synthetic[24] highly anti-HIV active michellamine analog without centrochirality.

In addition to these anticytopathic properties, octadehydromichellamine (**4**) shows antimalarial activities *in vitro* against both chloroquine resistant (IC_{50} [K1-strain] = 0.848 μM) and susceptible (IC_{50} [NF54-strain] = 1.26 μM) strains of *Plasmodium falciparum*, distinctly higher than *e.g.* michellamine B (**1b**) itself (3.03 and 5.70 μM, respectively). This activity is specific and not due to a non-specific basal cytotoxicity as also evidenced by the lack of cytotoxic activity against rat muscle myoblast cells at the highest concentration tested (440.6 μM). These results prompt further investigations including *in vivo* studies to evalutate the potential of octadehydromichellamine as an antimalarial compound. The design, synthesis, and biotesting of further michellamine analogs are in pogress.

EXPERIMENTAL

Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. NMR spectra were recorded with a Bruker AC 200, a Bruker WM 400, a Bruker AC 250, and a Bruker DMX 600 spectrometer. The chemicals shifts δ are given in parts per million (ppm) with the proton signals in the deuterated solvent as internal reference for ^{1}H and ^{13}C NMR. The coupling constants, *J*, are given in Hertz. HPLC separations: combination of a Waters 600E pump, a Nova-Pak C_{18} (Waters, 200 x 25 mm, 6 μm, integrated guard pak) column, and a Waters 996 photodiode array detector. MPLC separations: combination of a LATEK P400 pump, a reversed phase C_{18} column (MERCK LiChroprep RP-18 (40-63 μm), size B (310-25), and a LATEK VISI-6 UV detector (254 nm). IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer, and are reported in wave numbers (cm^{-1}). Mass spectra were obtained on a Finnigan MAT 8200 mass spectrometer at 70 eV in the EI mode. LC/MS: separation on a reversed phase C_{18} column (Waters RP-18, 5 μM, 150 x 2.1 mm); mass spectra were obtained using a Tripel-Quadrupol-TSQ 7000 mass spectrometer with a Finnigan MAT ESI-interface.

6,8-Dibenzyloxy-1,3-dimethylisoquinoline (6). To a cooled (4 °C) solution of 1-(2'-acetyl-3',5'-dibenzyloxyphenyl)-2-propanone (**5**)[18] (400 mg, 1.03 mmol) in ethanol (200 ml), a solution of NH_4OAc (200 mg, 2.57 mmol) in cooled (4 °C) ethanol (20 ml) was added and the mixture was stirred. The reaction was monitored by TLC, after 32 h the diketone **5** had vanished completely. After removal of the solvent the crude yellow product was purified by column chromatography on silica gel. Finally, the product was crystallized from petroleum ether / *t*-butylmethyl ether (1:1), to give **6** (276 mg, 79%) as colorless crystals: mp 137 °C; IR (KBr): $\tilde{\nu}$ 3000, 2960, 2780, 2720, 1600, 1540, 1390, 1350, 1250, 1170; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (s, 3H, 3-CH_3), 2.91 (s, 3H, 1-CH_3), 5.06 (s, 4H, OCH_2Ph at C-6 and C-8), 6.50 (d, *J* = 1.8, 1H, 7-H), 6.56 (d, *J* = 1.8, 1H, 5-H), 7.03 (s, 1H, 4-H), 7.27-7.55 (m, 10H, Ar-H); ^{13}C NMR (63.25 MHz, $CDCl_3$): δ = 24.06 (CH_3 at C-3), 28.76 (CH_3 at C-1), 70.16 (OCH_2Ph), 70.98 (OCH_2Ph), 98.41, (C-5), 99.89 (C-7), 116.61 (C-8a), 118.27 (C-4), 129.01, 129.13, 129.31, 129.46, 129.87, 130.33, 137.73, 138.01, 142.64 (C-4a), 152.57 (C-3), 159.02 (C-1), 160.16 (C-8), 161.59 (C-6); MS: *m/z* (%) = 369 (11) [M^+], 278 (2) [M^+ - C_7H_7], 91 (50) [$C_7H_7^+$]; Anal. calcd. for $C_{25}H_{23}NO_2$ (369.5): C, 81.28; H, 6.27; N, 3.79. Found: C, 80.63; H, 6.45; N, 3.77.

5-Bromo-6,8-dibenzyloxy-1,3-dimethylisoquinoline (7). To a cooled (0 °C) solution of **6** (100 mg, 271 μmol) in $CHCl_3$ (100 ml) containing 186 mg (227 mmol) NaOAc, a solution of Br_2 (0.05 ml, 273 μmol) in $CHCl_3$ (100 ml) was added and the mixture was stirred for 10 min. After addition of 5% aqueous $Na_2S_2O_3$ solution (12 ml), the aqueous layer was extracted with $CHCl_3$. The organic extract was washed with brine and dried ($MgSO_4$). After of removal of the solvent, the crude product was chromatographed on silica gel [petroleum ether / *t*-butylmethyl ether (1:2)] and recrystallized from *t*-butylmethyl ether / THF (1:1), to give **7**

(112 mg, 83%) as colorless crystals: mp 148-150 °C; IR (KBr): $\tilde{\nu}$ 3010, 1600, 1540, 1390, 1370, 1340; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.65 (s, 3H, 3-CH_3), 3.03 (s, 3H, 1-CH_3), 5.13 (s, 2H, OCH_2Ph), 5.26 (s, 2H, OCH_2Ph), 6.67 (s, 1H, 7-H), 7.69 (s, 1H, 4-H), 7.25-7.50 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.12 (CH_3 at C-3), 28.92 (CH_3 at C-1), 71.25 (OCH_2Ph), 71.50 (OCH_2Ph), 97.46, (C-7), 99.11 (C-5), 115.36 (C-4), 115.64 (C-9), 127.10, 127.77, 128.24, 128.49, 128.59, 128.77, 128.88, 135.70, 136.29, 138.75 (C-10), 152.24 (C-3), 155.93 (C-6), 158.07 (C-1), 158.34 (C-8); MS: *m/z* (%) = 447/449 (3/3) [M^+], 368 (1) [M^+ - Br], 91 (100) [$C_7H_7^+$]; Anal. calcd. for $C_{25}H_{22}BrNO_2$ (448.4): C, 66.97; H, 4.94; N, 3.12. Found: C, 66.61; H, 5.20; N, 2.93.

6,8-Dibenzyloxy-1,3-dimethylisoquinoline-5-boronic acid (8). To a cooled (-100 °C) solution of *t*-BuLi (1.7 M in *n*-hexane, 92 µl, 156 µmol) in diethyl ether (1 ml), a cooled solution (-100 °C) of the bromo-isoquinoline **7** (30 mg, 67 µmol) in a mixture of THF / diethyl ether (2:1, 1.5 ml) was added dropwise *via* a syringe. The mixture was stirred for 10 min at -100 °C, then 30 µl (243 µmol) trimethylborate (freshly distilled from Na) was added and the resulting suspension was allowed to warm up to room temperature over a period of 1h. On TLC, **8** appeared as a slowly eluting, light-blue fluorescent spot [R_f = 0.1, petroleum ether / *t*-butylmethyl ether (1:1)] besides the hydrodehalogenation product **6** (R_f = 0.8). The boronic acid was purified by preparative MPLC on RP_{18} material (methanol / water 95:5) to yield pure **8** (13.3 mg, 48%) as a colorless powder: mp 102-105 °C; IR (KBr): $\tilde{\nu}$ 3400-3100, 2360, 1620, 1570, 1330, 1240, 1190, 1110; ^{1}H NMR (200 MHz, MeOH-d_4): δ = 2.58 (s, 3H, 3-CH_3), 2.98 (s, 3H, 1-CH_3), 5.18 (s, 2H, OCH_2Ph), 5.20 (s, 2H, OCH_2Ph), 6.63 (s, 1H, 7-H), 7.26-7.61 (m, 10H, Ar-H), 8.13 (s, 1H, 4-H); ^{11}B NMR (100 MHz, CH_3OH; C_6D_6 as internal standard): δ = 18.21; MS: *m/z* (%) = 369 (16) [M^+ - BO_2H], 368 (5) [M^+ - $B(OH)_2$], 278 (3) [M^+ - BO_2H - C_7H_7], 91 (100) [$C_7H_7^+$]. Anal. calcd. for $C_{25}H_{24}BNO_4$ (414.3): C, 72.48; H, 5.84; N, 3.38. Found: C, 72.78; H, 6.22; N, 3.38. For the coupling reaction (see below), **8** was used without further purification, after evaporation of the solvent under reduced pressure. Furthermore, 9.16 mg (24.8 µmol, 37%) **6** were reisolated.

1,2,3,4,1‴,2‴,3‴,4‴-Octadehydro-6,8,6‴,8‴-tetra-*O*-benzyl-5',5''-di-*O*-acetylmichellamine (11). To a solution of the boronic acid **8** (13.3 mg, 32.2 µmol) in 3 ml H_2O / DME (1:3), 15 mg (19.9 µmol) of the bistriflate **9**,[17] 1.5 mg (1.3 µmol) tetrakis(triphenylphosphine)palladium(0), and 10 mg (88.5 µmol) *t*-BuOK were added. The solution was heated at 85 °C for 2 h until **8** had completely disappeared, and was then cooled to room temperature. After evaporation of the solvent *in vacuo*, the crude product was purified in three steps, by preparative TLC with petroleum ether / *t*-butylmethyl ether (1:3, three times developed, R_f = 0.46), preparative MPLC on RP_{18} material (methanol / water 95:5, isocratic), and finally by preparative HPLC on RP_{18} material [H_2O-CF_3COOH buffer (pH = 2.5) / MeOH (3:7), isocratic] to yield 4.6 mg (3.86 µmol, 12%) of the fully dehydrogenated michellamine derivative **11**: mp dec. ≥ 260 °C; IR (KBr): $\tilde{\nu}$ 3020, 2935, 2820, 2720, 1640, 1620, 1330, 1290, 1160; ^{1}H NMR (200.1 MHz, $CDCl_3$, two partly resolved sets of signals) : δ =

1.87 / 2.07 (2s, 6H, 2' and 2"-CH_3), 2.21 / 2.40 (2s, 6H, 3 and 3'"-CH_3), 2.27 (s, 6H, 5'- and 5"-OAc), 3.04 / 3.06 (2s, 6H, 1- and 1'"- CH_3), 3.90 / 3.91 (2s, 6H, 4'- and 4"-OCH_3), 5.00 (2d, 4H, 6- and 6"- OCH_2Phe), 5.20 (s, 4H, 8 and 8"-OCH_2Phe), 6.69 - 7.25 (5s, 10H, 4-H, 4'"-H, 7-H, 7'"-H, 1'-H, 1"-H, 3'-H, 3"-H, 7'-H, 7"-H), 7.38 - 7.46 (m, 20 H, Ar-H); MS: *m/z* (%) = 1192 (0.5) [M^+], 1101 (8) [M^+ - C_7H_7], 368 (4) [$C_{25}H_{22}NO_2^+$], 91 (100) [$C_7H_7^+$]. Exact mass calcd. for $C_{78}H_{68}O_{10}N_2$ (M^+) 1192.487. Found: 1192.486.

5',5"-Diacetoxy-8'-[5-(6,8-dibenzyloxy-1,3-dimethylisoquinolyl)]-4',4"-dimethoxy-2',2"-dimethyl-8"-trifluoromethanesulfonyloxy-6',6"-bisnaphthalene (10).[25] Preparative HPLC on RP_{18} material [H_2O-CF_3COOH buffer (pH = 2.5) / MeOH (3:7), isocratic] of the above produced coupling mixture yielded 0.877 mg (0.901 μmol, 2.8%) of the monocoupled product **10**: mp dec. ≥ 189°C. IR (CCl_4): $\tilde{\nu}$ = 3500-3400, 3000, 2900, 2835, 2720, 1590, 1340, 1300, 1160, 1090; ^{1}H NMR (200.1 MHz, $CDCl_3$): δ = 1.99 and 2.13 (2s, 6H, 2'- and 2"-CH_3), 2.28 (s, 3H, 3-CH_3), 2.37 (s, 6H, 5'- and 5"- OAc), 3.06 (s, 3H, 1-CH_3), 3.87 and 3.95 (2s, 6H, 4'- and 4"-OCH_3), 5.01 (2d, 2H, 6-OCH_2Phe), 5.19 (s, 2H, 8-OCH_2Phe), 6.68, 6.72, 6.76, 6.78 (4s, Ar-H), 6.98, 6.99 (2s, 2H, Ar-H), 7.38-7.43 (m, 12H, Ar-H); ^{19}F-NMR (376.5 MHz, $CDCl_3$): δ = -73.5 (s); MS: *m/z* (%) = 973 (0.5) [M^+], 931 (8) [M^+ - CH_3O + H], 840 (3) [$C_{25}H_{22}NO_2^+$], 91 (100) [$C_7H_7^+$].

1,2,3,4,1'",2'",3'",4'"-Octadehydromichellamine (4). The octadehydromichellamine derivative **11** (10.8 mg, 9.06 μmol) was refluxed with 10 ml of methanol that had been saturated with HCl gas at room temperature, for 1 h. The mixture was cooled to room temperature and the solvent was evaporated. The resulting product was diluted in 5 ml of 60% HCOOH in MeOH and 10 mg Pd black was added. The mixture was refluxed for 1 h, then the catalyst was filtered off, and the solvent was removed under reduced pressure. The crude product was purified first by preparative MPLC [H_2O-CF_3COOH buffer (pH = 2.5) / MeOH (3:7), isocratic], then by preparative HPLC [H_2O-CF_3COOH buffer (pH = 2.5) / MeOH (2:8), isocratic] to yield 4.8 mg (6.42 μmol, 71%) of octadehydromichellamine (**4**) as a greenish amorphous solid: mp dec. ≥ 200 °C; IR (CCl_4): $\tilde{\nu}$ 3410, 3100, 1640, 1600, 1400, 1350, 1250, 1175, 1080; ^{1}H NMR (600 MHz, MeOH-d_4): δ = 2.26 (s, 6H, 2'- and 2"-CH_3), 2.40 (s, 6 H, 3- and 3'"-CH_3), 3.32 (s, 6H, 1- and 1'"-CH_3), 4.10 (s, 6H, 4'- and 4"-OCH_3), 6.56 (s, 2H, 1'- and 1"-H), 6.84 (s, 2H, 3'- and 3"-H), 6.88 (s, 2H, 7- and 7'"-H), 6.95 (s, 2H, 4- and 4'"-H), 7.36 (s, 2H, 7'- and 7"-H). ^{13}C NMR (150 MHz, MeOH-d_4): δ = 16.82 (CH_3 at C-3 and C-3'"), 20.86 (CH_3 at C-2' and C-2"), 21.61 (CH_3 at C-1 and C-1'"), 55.54 (4' and 4"-OCH_3), 103.43 (C-4 and C-4'"), 106.78 (C-3' and C-3"), 112.26 (C-8a and C-8a'"), 112.82 (C-5 and C-5'"), 113.95 (C-4a and C-4a'"), 117.0 (C-1' and C-1"), 117.51 (C-7 and C-7'"), 118.88 (C-8a' and C-8a"), 120.29 (C-8' and C-8"), 134.41 (C-7' and C-7"), 135.43 (C-6' and C-6"), 136.56 (C-2' and C-2"), 140.0 (C-3 and C-3'"), 151.60 (C-5' and C-5"), 156.33 (C-4' and C-4"), 156.81 (C-1 and C-1'"). ESI/MS: *m/z* (%) = 749 (18) [M + H]$^+$, 375.4 (100) [M + 2H]$^{++}$.

Biological Experiments. The antiviral activity (HIV-I) was determined *in vitro* using CEM-SS cells and an RF-strain of HIV-I.[26] The results were expressed as EC_{50} values, cytotoxicities are given as IC_{50}'s (both μM). Activity against *P. falciparum* was tested by the semiautomated microdilution assay against intraerythrocytic forms derived from asynchronous stock cultures as previously described[27] with minor modifications.[28] The strains used were K1 (Thailand; resistant to chloroquine and pyrimethamine) and NF54 (an airport strain of unknown origin; susceptible to standard antimalarials). The activities are given as IC_{50} values (μM). Chloroquine was used as a standard (IC_{50} [K1] = 0.125 μM, IC_{50} [NF54] = 0.011 μM).

ACKNOWLEDGEMENTS

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Graduiertenkolleg "NMR *in vivo* und *in vitro* für die biologische und medizinische Grundlagenforschung), and the U.S. National Institutes of Health (grant CA65095 to TRK). Experimental help by Markus Rückert, Kristina Wolf and Martin Welter and technical assistance by Manuela Michel (née Schäffer) and Andrea Luginbühl is gratefully acknowledged.

REFERENCES AND NOTES

1. "Acetogenic Isoquinoline Alkaloids", part 123; for part 122, see Bringmann, G.; Teltschik, F.; Michel, M.; Busemann, S.; Rückert, M.; Haller, R.; Bär, S.; Robertson, A.; Isahakia, M. *Phytochemistry*, submitted. - "HIV-Inhibitory Natural Products", part 56; for part 55, see Yang, F.; Bewley, C. A.; Bax, A.; Louis, J. M.; Clore, G. M.; Gronenborn, A.; Gustafson, K. R.; Boyd, M. R.; Wlodawer, A. *J. Molec. Biol.*, submitted.
2. Manfredi, K. P.; Blunt, J. W.; Cardellina II, J. H.; McMahon, J. B.; Pannell, L. K.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 3402-3405.
3. Boyd, M. R.; Hallock, Y. F.; Carellina II, J. H.; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit Jr., R. W.; Bringmann, G; Schäffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740-1745.
4. Bringmann, G.; Pokorny, F. in *The Alkaloids*; Cordell G. ed.; Academic Press: New York, Vol. 46, 1995, pp. 127-271.
5. Thomas, D. W.; Gereau, R. E. *Novon* **1993**, *3*, 494-498.
6. Bringmann, G.; Saeb, W.; Koppler, D. *Tetrahedron* **1996**, *52*, 13409-13418.
7. Bringmann, G.; Holenz, J.; Weirich, R.; Rübenacker, M.; Funke, C.; Boyd, M. R.; Gulakowski, R. J.; François, G. *Tetrahedron* **1998**, *54*, 497-512.
8. Bringmann, G. *Bull. Soc. Chim. Belg.* **1996**, *105*, 601-613.

9. Bringmann, G.; Saeb, W.; François, G.; Schlauer, J. *Pharm. Pharmacol. Lett.* **1998**, *8*, 8-10.
10. Bringmann, G.; Götz, R.; François, G. *Tetrahedron* **1996**, *52*, 13419-13426.
11. Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.; Bowden, B.; Crase, J. L.; Thomas, D. W.; Pandey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocyclic Chem.* **1996**, *33*, 1371-1384.
12. Zhang, H.; Zembower, D. E.; Chen, Z. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2687-2690.
13. Bringmann, G.; Götz, R.; Keller, P. A.; Walter, R.; Henschel, P.; Schäffer, M.; Stäblein, M.; Kelly, T. R.; Boyd, M. R. *Heterocycles* **1994**, *39*, 503-512.
14. Bringmann, G.; Harmsen, S.; Holenz, J.; Geuder, T.; Götz, R.; Keller, P. A.; Walter, R. *Tetrahedron* **1994**, *50*, 9643-9648.
15. Bringmann, G.; Götz, R.; Harmsen, S.; Holenz, J.; Walter, R. *Liebigs Ann.* **1996**, 2045-2058.
16. Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J.; Bhaskar, K. V.; Boyd, M. R.; Götz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 7621-7624.
17. Bringmann, G.; Götz, R.; Keller, P. A.; Walter, R.; Boyd, M.R.; Lang, F.; Garcia, A.; Walsh, J.J.; Tellitu, I.; Bhaskar, K. V.; Kelly, T. R. *J. Org.Chem.* **1998**, *63*, 1090-1097.
18. Bringmann, G.; Pokorny, F.; Wenzel, M.; Wurm, K.; Schneider, C. *J. Lab. Compd. Radiopharm.* **1997**, *39*, 29-38.
19. Bringmann, G.; François, G.; Aké Assi, L.; Schlauer, J. *Chimia* **1998**, *52*, 18-28.
20. Bringmann, G. *Liebigs Ann. Chem.* **1985**, 2116-2125.
21. Interestingly, such a mono-coupled product was never observed in the synthesis of authentic michellamines by a similar double coupling of **9** with two eq. of the corresponding *tetrahydro*isoquinoline boronic acid.[16,17]
22. El Amin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3443-3444.
23. Compare also the likewise astonishingly high atropselectivity in the related michellamine synthesis by an analogous double coupling of **9** with two eq. of the tetrahydroisoquinoline building block related to **8** but with two stereocenters, by which only michellamines A (**1a**) and B (**1b**) - but no michellamine C (**1c**) - were formed.[16,17]
24. Although **4** has not yet been found in michellamine-producing plants, its occurrence as a natural product is not quite improbable; a search for **4** in various *Ancistrocladus* species is under investigation.
25. For reason of easier spectral comparison, the numbering of **10** was done as for michellamines (**1**).
26. Gulakowski, R. J.; McMahon, J. B.; Staley, P. G.; Moran, R. A.; Boyd, M. R. *J. Virol. Methods* **1991**, *33*, 87-100.
27. Desjardins, R. E.; Canfield, C. J.; Haynes, D.; Chulay, J. *Antimicrob. Agents Chemother.* **1979**, *16*, 710-718.
28. Ridley, R. G.; Hofheinz, W.; Matile, H.; Jaquet, C.; Dorn, A.; Masciadri, R.; Jolidon, S.; Richter, W. F.; Guenzi, A.; Girometta, M. A.; Urwyler, H.; Huber, W.; Thaithong, S.; Peters, W. *Antimicrob. Agents Chemother.* **1996**, *40*, 1846-1854.