# The Synthesis and Biological Activity of Two Analogs of the Anti-HIV Alkaloid Michellamine B



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Received November 1, 1995
Revised June 7, 1996

Two simplified analogs of the dimeric naphthalenyltetrahydroisoquinoline alkaloid michellamine B [4',4"-didesmethoxy-2',2"-didesmethylmichellamine B and 6,8-dihydroxy-5-(1',1"-dihydroxy-2',2"-binaphthalen-4'-yl)-1*R*,3*R*-dimethyl-1,2,3,4-tetrahydroisoquinoline] were synthesized using Suzuki palladium-catalyzed biaryl cross-coupling of 4-(2-benzyl-6,8-dibenzyloxy-1*R*,3*R*-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-1-benzyloxy-2-bromonaphthalene to its corresponding atropisomeric 2-naphthaleneboronic acid and 1-benzyloxy-2-naphthaleneboronic acid, respectively. These analogs inhibited recombinant HIV reverse transcriptase with $IC_{50}$ values of 62 μ*M* and 1000 μ*M*, respectively, whereas the $IC_{50}$ value for michellamine B was 33 μ*M*. Both michellamine B and the analogs inhibited the phosphorylation of histones by rat brain protein kinase C. The analogs were more active ($IC_{50}$ values of 36 μ*M* and 30 μ*M*, respectively) than michellamine B ($IC_{50}$ = 130 μ*M*).

*J. Heterocyclic Chem.*, **33**, 1371 (1996).

## Introduction.

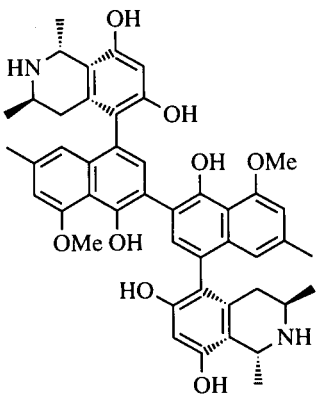
Michellamine B (**2**, Figure 1), a dimeric naphthalenyltetrahydroisoquinoline alkaloid isolated from the Cameroonian vine *Ancistrocladus korupensis*, along with its isomers, michellamines A **1** and C **3**, has shown *in vitro* activity against human immunodeficiency virus (HIV) strains in lymphocytes in culture [1-4]. Michellamine B has been reported to protect human lymphoblastoid CEM-SS cells against 11 strains of HIV-1, including six clinical isolates, with $EC_{50}$ values of 1 to 13 μ*M* and low toxicity to the cells [4]. Cytotoxic concentrations, as measured by 50% cell viability ($IC_{50}$ values), ranged from 40 to 120 μ*M*. Both the virus strain and cellular host influenced antiviral activity and cytotoxicity of michellamine B. The $EC_{50}$ value range for antiviral activity was 1 to 88 μ*M*, and the $IC_{50}$ value range for cytotoxicity was 42 to above 240 μ*M*. Complete inhibition of viral replication occurred at concentrations of 30 to 100 μ*M* [1]. Michellamine B also inhibited the replication of four HIV-2 strains in CEM-SS cells, with $EC_{50}$ values of 2 to 18 μ*M*, and protected MT-2 cells against 3'-azido-2',3'-dideoxythymidine-resistant HIV-1 (G910-6 strain) ($EC_{50}$ = 5 μ*M*). Michellamines A, B, and C had comparable activity against HIV-1 (RF) in CEM-SS cells ($EC_{50}$ = 10 to 13 μ*M*), as measured by their anticytopathic effects, but michellamine A was less active ($EC_{50}$ = 10 μ*M*) than michellamine B and C ($EC_{50}$ = 2 μ*M*) against HIV-2 (CBL-20) [4].

We undertook the syntheses of simplified analogs **4** and **5** of michellamine B to establish the pharmacophoric elements necessary for anti-HIV activity and to provide a source of antiviral drug that was more accessible than michellamine B obtained from natural sources. Analog **4**, which lacks the two methoxy and methyl groups of michellamine B on its central binaphthalene ring system, was designed both to assess the importance of these groups to antiviral activity and to simplify the synthetic sequence. Analog **5** has the dihydroxybinaphthalene ring of **4** but lacks the second tetrahydroisoquinoline group. The synthetic strategy used to construct these analogs employed Suzuki aryl bromide-arylboronic acid cross-coupling reactions [5-7] to introduce each biaryl bond. In this approach, the atropisomeric, fully protected naphthalenyltetrahydroisoquinoline intermediates were readily separated by chromatography on silica gel. The Suzuki reaction successfully introduced the central binaphthalenyl bond to provide the fully protected analogs as single isomers. We describe these syntheses below and then present the results of mechanism of action studies on **4**, **5**, and michellamine B.

## Results and Discussion.

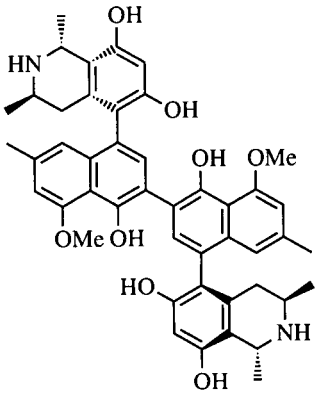
While analogs **4** and **5** were being evaluated, three syntheses of the michellamines were published as brief reports [8-10]. As with the syntheses reported here, all

Figure 1



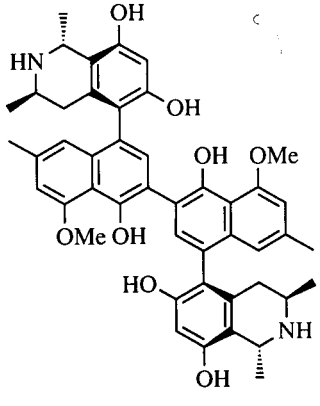
1

Michellamine A



2

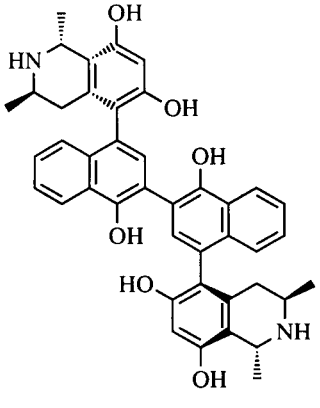
Michellamine B



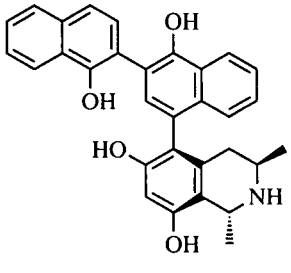
3

Michellamine C

Figure 2



4



5

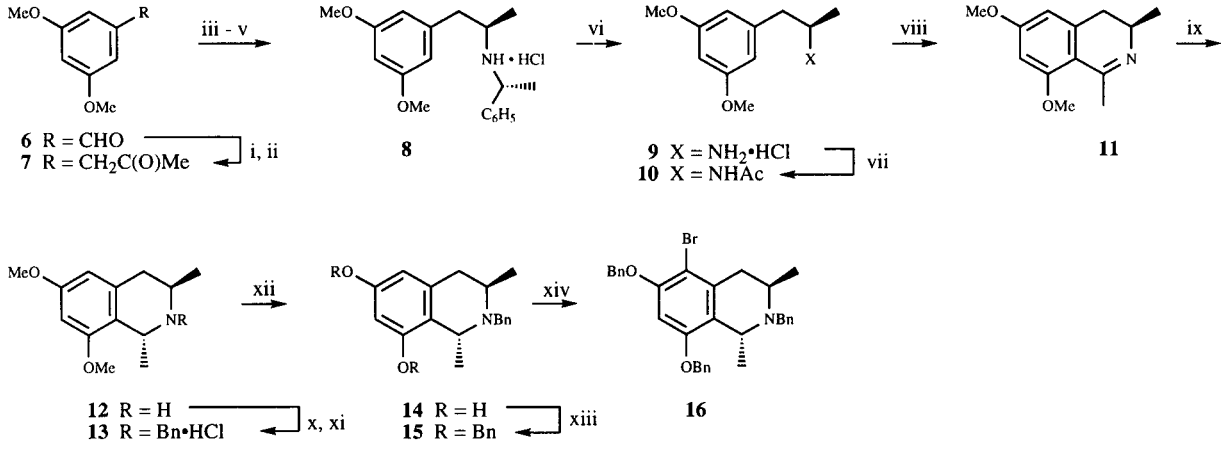
relied on palladium-catalyzed hetero-biaryl couplings to form the 5-8' bond between the tetrahydroisoquinoline and naphthalene rings. The Hoye group synthesis [8] was most similar in that it used the coupling of a benzyl group protected 5-iodotetrahydroisoquinoline with a naphthaleneboronic acid. The central 6'-6" binaphthalene bond was then constructed by oxidative coupling using silver oxide to give the cross-ring naphthoquinones, which on reduction-deprotection afforded a mixture of michellamines A, B, and C. The first synthesis by the Bringmann group [9] also employed oxidative coupling of the 6,8-diacetyl-2-formyl derivative of korupensamine A to construct the central 6'-6" binaphthalene bond of michellamine A. Korupensamine A, which has been isolated from *Ancistrocladus korupensis* also and could be considered a monomeric precursor to the dimeric michellamines, was also synthesized by a palladium-catalyzed coupling of the appropriately functionalized and protected 5-bromotetrahydroisoquinoline and the tri(*n*-butyl)stannylated naphthalene [11]. In the second michellamine synthesis by the Bringmann group [10], the binaphthalene bond was constructed first by using a Pd(0)-copper bronze homocoupling of 3-bromo-5-methoxy-7-methyl-1,4-naphthoquinone, followed by reductive acetylation of the product. The less hindered acetate groups on the binaphthalene ring system were then converted to triflates for cross-coupling with the benzyl group-protected tetrahydroisoquinoline-5-boronic acid in the presence of $Pd[P(C_6H_5)_3]_4$. Again, a mixture of michellamines A, B, and C was produced. These mixtures were separated after deprotection by high-performance liquid chromatography (hplc) on amine-bonded columns.

Because understanding the mechanism of action of each of the three michellamines and the differences in their antiviral activities would be facilitated by access to a reliable source of analogs of each isomer, we elected to use a stereoselective synthetic approach to analogs of michellamine A and B that relied on heterobiaryl couplings to form the 5-8' bond of the naphthalenyltetrahydroisoquinoline ring first, followed by separation of the two atropisomeric products, selective functionalization of each atropisomer, and a second heterobiaryl coupling to introduce the 6'-6" binaphthalene bond. Therefore, our strategy involved synthesizing the two naphthalenyltetrahydroisoquinoline atropisomers as a mixture by using palladium-catalyzed cross-coupling of (1*R*,3*R*)-2-benzyl-5-bromo-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydro-

isoquinoline **16** and 4-benzyloxynaphthalene-1-boronic acid **20**, followed by chromatographic separation of the atropisomers. Benzyl protecting groups were used on the precursors of the tetrahydroisoquinoline and naphthalene rings to facilitate transfer of the synthetic methodology to any subsequent stereoselective synthesis of the michellamines. In addition, benzyl protecting groups were suitable for the aromatic bromination and lithiation steps.

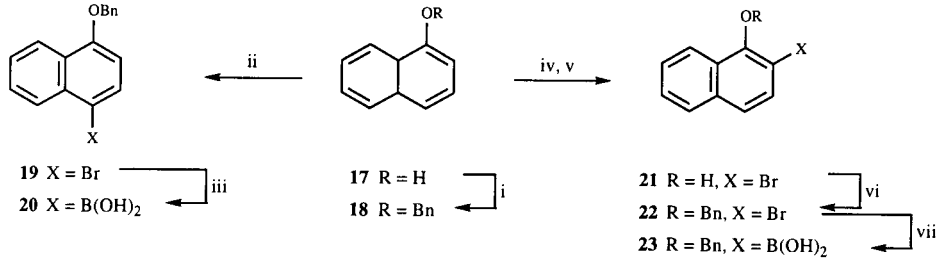
The construction of the tetrahydroisoquinoline ring system of **16** is outlined in Scheme 1 and was carried out by modifying the sequence for the synthesis of the 1*S*,3*S*-enantiomer developed by the Bringmann group [12]. 3,5-Dimethoxybenzaldehyde **6** was condensed with nitroethane (62% yield) and reduced with iron in acetic acid (90%) to provide the methyl benzyl ketone **7**. Reductive amination of **7** to introduce the chiral methyl group-which subsequently was to be found at the 3-position of the tetrahydroisoquinoline ring-was accomplished by a three-step procedure involving condensation with (*R*)-phenethylamine, hydrogenation of the resultant Schiff base over Raney nickel, and acidification to furnish the benzylamine hydrochloride salt **8** (61% overall yield). Hydrogenolysis of **8** over Pd(C) provided the primary amine hydrochloride salt **9** (98%), $[\alpha]_D^{20}$ = -14.4° (methanol). An optical rotation of $[\alpha]_D^{20}$ of +14.8° was reported for the 3*S*-enantiomer [12]. Acetylation of the amine group of **9** with acetyl chloride in the presence of triethylamine produced the acetamide **10**, which on Bischler-Napieralski cyclization with phosphorus oxychloride furnished the (*R*)-3-methyldihydroisoquinoline **11** (89%). Its optical rotation of $[\alpha]_D^{20}$ +140° (methanol) is in agreement with the $[\alpha]_D^{20}$ of -141° reported for the 3*S*-

Scheme 1




i: $NH_4OAc/EtNO_2/100°$, ii: Fe/HOAc, iii: (*R*)-$C_6H_5CH(Me)NH_2$/toluene/110°, iv: $H_2$/Ni(R)/EtOH, v: HCl(g)/MeOH/0°, vi: $H_2$/Pd(C)/MeOH/$H_2O$/45°, vii: AcCl/$Et_3N$/$CH_2Cl_2$/0°, viii: $POCl_3/CH_3CN$/82°, ix: $LiAlH_4$/THF/$AlMe_3$/toluene; aq. NaF, x: $C_6H_5CH_2Br/K_2CO_3$/THF, xi: HCl(g)/$Et_2O$, xii: 48% HBr/105°, xiii: $C_6H_5CH_2Br/K_2CO_3$/acetone/reflux, xiv: $Br_2$/HOAc/$CHCl_3$/0°.

Scheme 2




i: $C_6H_5CH_2Br/K_2CO_3$/acetone/reflux, ii: $C_5H_5NHBr_3$/HOAc, iii: *n*-BuLi/THF/78°; $B(OMe)_3$/aq. HCl, iv: (**17**) $Br_2/CH_2Cl_2$; v: *n*-BuLi (2.0 equiv.)/THF; aq. HCl, vi: $C_6H_5CH_2Br/K_2CO_3$/acetone/reflux, vii: *n*-BuLi/THF; $B(OMe)_3$; aq. HCl.

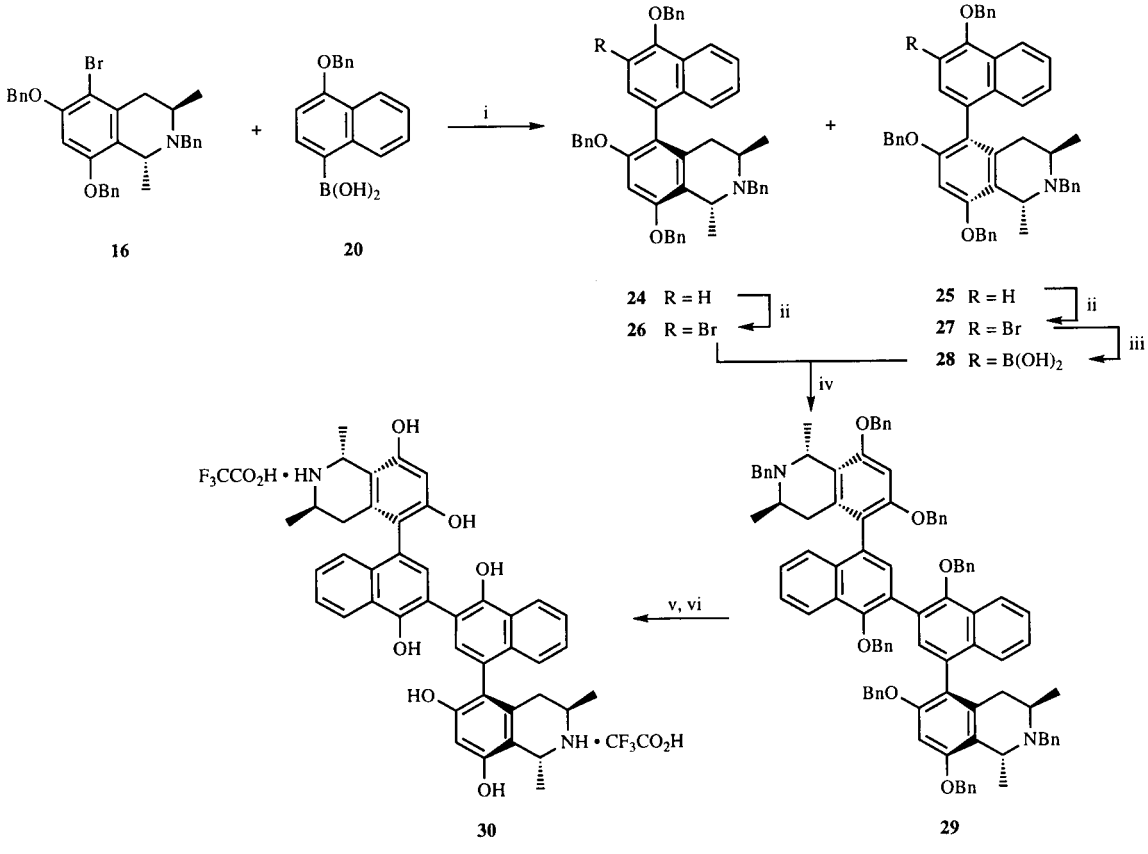
enantiomer [12]. The chiral methyl group at the 1-position of the tetrahydroisoquinoline ring was introduced by reduction of **11** with lithium aluminum hydride/trimethylaluminum (89%). The secondary amine of the resulting (1*R*,3*R*)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **12**, which was also isolated as the hydrochloride salt, was then protected by *N*-benzylation with benzyl bromide and potassium carbonate to give **13** (82%), $[a]_D^{22} = +78.4°$ (methanol).

Cleavage of the two methyl ether protecting groups from **13** with 48% hydrobromic acid by using the conditions (105°) of Grey and Dreiding [13] provided 2-benzyl-6,8-dihydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **14** in 80% yield. Dibenzylation under standard conditions occurred in 51% yield to give **15**. This material brominated almost exclusively at the 5-position upon treatment with bromine in acetic acid/chloroform at 0° to afford the 5-bromotetrahydroisoquinoline **16** (73%), which was characterized spectroscopically. The regioselective bromination at the 5-position was confirmed by $^1H$ nmr nOe studies, which showed that irradiation of the aromatic singlet at 6.43 ppm enhanced the signal for both *O*-benzyl methylene groups and was therefore assigned to the H-7 proton. The overall yield for this 14-step sequence from **6** was 6%.

The 4-benzyloxy-1-naphthaleneboronic acid **20** was easily prepared by the route outlined in Scheme 2. The benzyl-group-protected 1-naphthalenol **18** preferentially brominated at its 4-position to give **19** in 79% yield. Conversion of **19** to the aryllithium and treatment with trimethyl borate gave the dimethyl arylboronate, which was hydrolyzed with dilute acid to the arylboronic acid **20** in 96% yield. The overall yield for this four-step sequence was 55%.

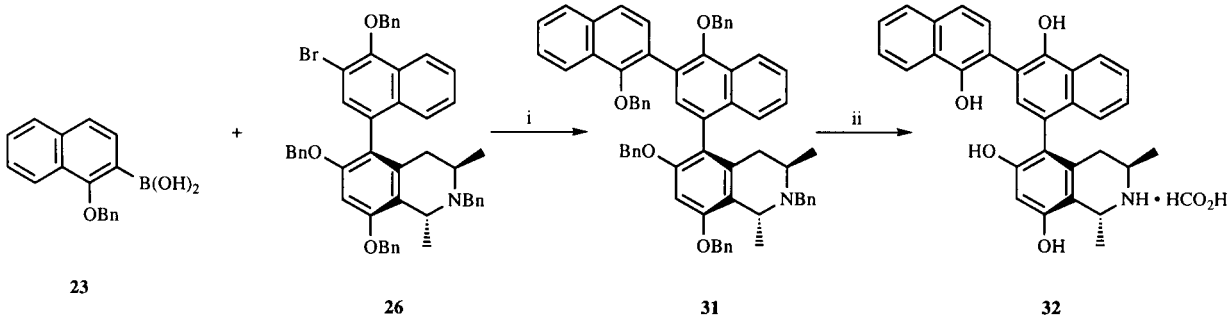
Model studies were first conducted to establish the optimal bromotetrahydroisoquinoline-naphthaleneboronic acid coupling conditions. Of these, the Suzuki coupling method under anhydrous conditions [5-7] proved the most satisfactory and therefore was used for the coupling of 5-bromotetrahydroisoquinoline **16** with 4-benzyloxy-1-naphthaleneboronic acid **20** as shown in Scheme 3. This coupling was effected with dichloro*bis*(diphenylphos-

Scheme 3




i: $PdCl_2(dppf)/K_3PO_4/DMF/65°$, ii: $C_5H_5NHBr_3/HOAc/CHCl_3$, iii: *n*-BuLi/THF/-78°; $B(OMe)_3$; aq. $NH_4Cl$, iv: $Pd[P(C_6H_5)_3]_4$/-2 *M* $Na_2CO_3$/DME/EtOH/80°, v: Pd, $HCO_2H$/MeOH, vi: $F_3CCO_2H$/MeOH

Scheme 4




i: $Pd[P(C_6H_5)_3]_4$/DME/EtOH/2 *M* $Na_2CO_3$/80°, ii: Pd black/$HCO_2H$/MeOH

phino)ferrocenepalladium(II) as the catalyst [14] and tribasic potassium phosphate as the base to give the two (1*R*,3*R*)-2-benzyl-5-(4'-benzyloxy-1'-naphthalenyl)-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolines, **24** and **25**, as a 1:1.7 atropisomeric mixture (82%) about the biaryl bond corresponding to the 5-8' biaryl bond of michellamine B. For comparison purposes, michellamine B ring numbering has been used to describe the biaryl bond linkages in this discussion, but compounds have been named using standard numbering.

After chromatographic separation of the atropisomers, **24** and **25** were characterized. The stereochemical assignments were made by comparing their $^1H$ nmr spectra with those of michellamines A, B, and C [2,4], and korupensamines A and B [15] for which structural and stereochemical assignments were made by the Bringmann and Boyd groups after extensive $^1H$-$^{13}C$ nmr heteronuclear coupling and $^1H$ nmr nOe experiments, with particular emphasis on the resonance signals of the 4- and 4'''-methylene groups on the tetrahydroisoquinoline rings of the michellamines. The relative stereochemistry of the tetrahydroisoquinoline unit of the michellamines [2,4] and korupensamines A and B [15], which Boyd and coworkers established by using $^1H$ nmr nOe experiments, indicated 1,3-diaxial geometry for the H-3 protons and the C-1 methyl groups. The coupling constants between the H-3 and the magnetically nonequivalent H-4 protons demonstrated that the H-3 proton and one H-4 proton (H-$4_a$) were *trans*-diaxial, and the other H-4 proton (H-$4_e$) was assigned to be equitorial position. The relative stereochemistry of the 5-8' biaryl bond was determined by comparing the $^1H$ nmr nOes between each of the H-4 protons and the H-1' and H-7' naphthalene protons. The absolute configurations at C-1 and C-3 were obtained by degradation of michellamine B [3] to (3*R*)-aminobutyric acid and D-alanine. The configurations of the atropisomeric 5-8' bonds of the symmetrical homodimeric michellamine A and the monomeric naphthalenyltetrahydroisoquinoline korupensamine A were assigned as 5*P*, and those for michellamine C and korupensamine B as 5*M*. Because $^1H$ nmr nOe enhancements of the resonances for both the H-1' and H-7' protons were observed on irradiation of both H-$4_a$ and H-$4_e$ signals of michellamine B and because of the two sets of proton signals displayed in the $^1H$ nmr spectrum, this isomer was determined to be the unsymmetrical dimer of both atropisomeric naphthalenyltetrahydroisoquinolines.

Separation of the two atropisomers permits ready access to each analog of michellamines A, B, or C, unlike reported prior syntheses of the michellamines, which afforded mixtures. Bromination at the 6'-position (michellamine B numbering) of the naphthalene rings of **24** and **25** with pyridinium bromide perbromide afforded the bromonaphthalenes **26** (64%) and **27** (68%), respectively. The location of the bromo group was verified by the disappearance of the 6'-proton signal in the $^1H$ nmr spectrum and the appearance of the 7'-proton as a singlet. Bromonaphthalene **27** was converted to the 1-benzyloxy-4-tetrahydroisoquinolinyl-2-naphthaleneboronic acid **28**. Heterobiaryl coupling of bromonaphthalene **26** with arylboronic acid **28**, with palladium tetrakis(triphenylphosphine) used as the catalyst and 2*M* sodium carbonate as the base, afforded the octabenzylated derivative **29** (58%) of analog **4**. Removal of the benzyl groups by hydrogenation of **29** over palladium on carbon led to reduction of the naphthalene ring. Deprotection by hydrogenation of the hydrochloride salt of **29** in methanol with palladium on carbon as the catalyst at 40 psi and ambient temperature for 16 hours gave three isomers with molecular ions (M + H) of 669. Analytical reversed-phase high-performance liquid chromatography showed these three isomers in a ratio of 2:2:1 [$t_R$ 8.9 (26.0%), 12.0 (25.9%), 16.5 minutes (12.5%)] and other products. Evidently isomerization occurred during the hydrogenolysis step. Deprotection by hydrogen-transfer catalysis using palladium black in formic acid/methanol afforded **4** as the *bis*(formic acid) salt (90%). This deprotected sample was analyzed

by high-performance liquid chromatography-thermospray mass spectral analysis (Zorbax $C_8$ 4.6 x 250-millimeters, 0.01*M* trifluoroacetic acid, in 55% methanol/45% water, 0.7 ml/min, 255 nm), which showed two isomers having molecular ions (M + H) of 669 [$t_R$ 9.5 (4.8%) and 12.1 minutes (**4**, 93.3%)], in agreement with the atropisomeric purity of the precursors. Therefore, the hydrogen-transfer deprotection method was satisfactory for quantitative cleavage of the eight benzyl protecting groups without further reduction or isomerization of the product. Because michellamine B is unstable to base but stable below *p*H 4.0 [16], the high-performance liquid chromatographic conditions used for analyses and the final purification of the deprotected analog **4** employed 0.01*M* trifluoroacetic acid (*p*H 2). Preparative high-performance liquid chromatography afforded **4** as the *bis*(trifluoroacetic acid) salt **30** (69%), which by analytical high-performance liquid chromatography showed two major peaks [$t_R$ 8.2 (1.2%) and 10.2 minutes (**30**, 98.5%)].

Analog **4** was further characterized from its high-resolution, fast-atom-bombardment mass spectrum, which showed a molecular mass of 669.2964 that indicated a molecular formula of $C_{42}H_{41}O_6N_2$ for the free base plus hydrogen. The ultraviolet spectrum of the *bis* salt **30** in methanol did show absorptions at 331 and 341 nm, which corresponded to those reported for michellamines A, B, and C at 331 and 344 nm, and additional absorptions at 225 and 278 nm, which differed from the 262-, 287-, and 312-nm absorptions reported for these natural products [2,4]. Interestingly, its optical rotation was low (2-8°) in methanol, in contrast to the negative rotations (-10.5°, -14.8°, -16.8°) reported for michellamines A, B, and C [2,4].

The heterodimeric nature of **30** was evident from the distinctive signals of the tetrahydroisoquinoline protons in its $^1$H nmr spectrum (Table 1), which more closely resembled those of michellamine B than those of the homodimers michellamine A and C. The signals for the four methyl groups at the C-1 and C-3 positions on the tetrahydroisoquinoline rings appeared as separate doublets, as they did in the spectrum of michellamine B, whereas in the spectra for michellamines A and C the 1-methyl and the 3-methyl proton signals are each coincident. Similarly, the four H-4$_a$ and H-4$_e$ signals each appeared as doublets of doublets, as they did in the spectrum for michellamine B, rather than as the two equivalent doublets of doublets found in the spectra for michellamines A and C. The signals for the H-1 and H-3 protons of **30** did not correspond to those of michellamine B but did to those of its *bis*(acetic acid) salt. The H-3 proton signal of **30** occurred as a complex multiplet at 3.58 ppm, and that for H-1 as a quartet at 4.66 ppm. The H-1 protons of michellamine B appeared as two quartets at 4.26 and 4.44

Table 1

$^1$H NMR Spectral Comparison of Analog **4** with Michellamines B, A, and C

| Compound | proton signal (ppm) [a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1,1'''-Me | 3,3'''-Me | 1,1''' | 3,3''' | 4a,4'''a | 4e,4'''e | 7,7''' | 1',1'' | 7',7'' |
| Analog **4** [b] | 1.54 d (6.7)<br>1.59 d (6.7) | 1.12 d (6.4)<br>1.15 d (6.4) | 4.66 q (6.7) | 3.58 m | 2.08 dd (17.9, 11)<br>2.43 dd (17.9, 11) | 2.33 dd (17.9, 4.8)<br>2.73 dd (17.9, 4.8) | 6.39 s | 8.26 d (8.4) | 7.14 s<br>7.18 s |
| Michellamine B [c] | 1.48 d (6.5)<br>1.52 d (6.5) | 1.01 d (6.5)<br>1.05 d (6.5) | 4.26 q (6.5)<br>4.44 q (6.5) | 3.21 ddq (11, 4.5, 6.5)<br>3.27 ddq (11,4.5, 6.5) | 1.86 dd (17.5, 11)<br>2.22 dd (17.5, 11) | 2.08 dd (17.5, 4.5)<br>2.49 dd (17.5, 4.5) | 6.34 s | 6.77 s<br>6.86 s | 7.24 s<br>7.28 s |
| Michellamine B•2 *bis*(acetate) [d] | 1.65 d<br>1.70 d | 1.20 d<br>1.22 d | 4.75 m | 3.65 m | 2.10 dd<br>2.50 dd | 2.25 dd<br>2.80 dd | 6.43 s | 6.75 s<br>6.85 s | 7.25 s<br>7.30 s |
| Michellamine A [c] | 1.57 d (6.5) | 1.16 d (6.5) | 4.64 q (6.5) | 3.54 ddq (11.8, 4.3, 6.5) | 2.05 dd (18.6, 11.8) | 2.69 dd (18.6, 4.3) | 6.40 s | 6.75 s | 7.30 s |
| Michellamine C [e] | 1.68 d (7.0) | 1.30 d (6.5) | 4.73 q (7.0) | 3.65 ddq (11.5, 5.9, 6.5) | 2.62 dd (17.5, 11.5) | 2.35 dd (17.5, 5.0) | 6.43 s | 6.84 s | 7.28 s |

[a] Michellamine B numbering is used. Coupling constants in Hertz appear in parentheses. [b] *Bis*(trifluoroacetate) salt. [c] Free base (Ref 2). [d] Spectrum provided by Dr. Ven Narayanan, NCI, Bethesda, MD. [e] Free base (Ref 4).

ppm, whereas those of michellamines A and C appeared as single quartets at 4.64 and 4.73 ppm, respectively. In the *bis*(acetic acid) salt of michellamine B, these protons appeared as complex multiplets that were shifted downfield to positions similar to those found in the spectrum of the *bis* salt **30**.

The signals for the 1-methyl and 3-methyl group protons of the the *bis*(acetic acid) salt of michellamine B were also shifted downfield to positions corresponding to those for the *bis* salt **30**. The H-7 proton signal of **30** appeared as a singlet at 6.39 ppm, which is in the vicinity of the signals for this proton in michellamines A, B, and C. The H-7' protons of **30** were upfield compared to these protons in the michellamines and, as in michellamine B, appeared as two singlets rather than as the single singlet of michellamines A and C. The spectrum of **30** also displayed a doublet at 8.03 ppm for the 1'-protons on the naphthalene rings, whereas that for michellamine B displayed discrete H-1' singlets.

The strategy for synthesizing the binaphthalenyltetrahydroisoquinoline analog **5** was similar to that employed for the synthesis of **4** and is outlined in Schemes 2 and 4. Functionality was introduced at the 2-position of the naphthalene ring by dibromination of 1-naphthalenol **17** followed by selective debromination at the 4-position (62%) (Scheme 2). Benzylation (90%), lithiation, treatment with trimethyl borate, and hydrolysis afforded 1-benzyloxy-2-naphthaleneboronic acid **23** (33%). The 2'-bromo atropisomer **26** was coupled to the 2-naphthaleneboronic acid **23** by using palladium tetrakis(triphenylphosphine) as the catalyst and 2*M* sodium carbonate as the base to afford the pentabenzylated derivative **31** of **5** (72%) (Scheme 4). Deprotection of **31** was achieved using palladium black in 5% methanolic formic acid to give **5** as the formic acid salt **32** (86%), $[a]_D^{23}$ -45.1° (methanol).

The structure of the formic acid salt **32** was supported by its spectral data. The mass spectrum had the appropriate molecular ion peak of 478 for the free base plus H, indicating a molecular formula of $C_{31}H_{27}NO_4$. In the $^1H$ nmr spectrum, the C-3 and C-1 methyl signals appeared as two broad singlets at 1.26 and 1.69 ppm and the H-$4_a$ and H-$4_e$ proton signals appeared as overlapped multiplets at 2.44 ppm. These signals contrast with those found in the spectrum of **30**, for which the former were doublets and the latter appeared as discrete signals. The H-7 tetrahydroisoquinolinyl proton of **32** occurred as a singlet at 6.50 ppm, and the aromatic proton on the naphthalene ring *ortho* to the tetrahydroisoquinoline ring had its singlet signal at 7.20 ppm. The characteristic naphthalene ring proton doublet occurred at 8.45 ppm. Hplc analysis (0.01*M* trifluoroacetic acid, in 70% methanol/30% water, 0.7 ml/min, 255 nm) showed two major peaks, with retention times of 8.9 (**32**, 96.7%) and 12.4 minutes (2.9%).

The mechanisms by which the michellamines inhibit HIV replication have not yet been determined, although it has been reported that these alkaloids do not inhibit the binding of the HIV coat glycoprotein gp120 to the T cell CD4 receptor [1,2]. A review of the literature on the antiviral activity of compounds having similar structures suggests that the michellamines and their analogs could exhibit their antiviral effects either by inhibiting HIV reverse transcriptase (RT), the enzyme required to produce viral DNA from the HIV RNA template, or by inhibiting protein phosphorylation. For example, the antiviral agent hypericin, which has a perylenequinone ring system, exerts its antiretroviral activity through an indirect mechanism that may involve interfering with RT activation during infection, perhaps by interfering with phosphorylation of an essential protein [17,18]. The perylenequinone shiraiachrome-A, which has an $EC_{50}$ value of 10 $\mu M$ against herpes simplex virus-1, inhibits protein kinase C [19], as does the related structure calphostin D [20]. At physiological *p*H, the michellamines interconvert about their atropisomeric 5-8' and 8"-5"' biaryl bonds and also readily undergo oxidation [16]. Therefore, the electron-rich 8,5'- and 5",8"'-dihydroxybiaryl or 5',5"'-dihydroxy-6',6"-binaphthalene ring systems of the michellamines could undergo oxidation in the plasma to produce a diphenoquinone system similar to those found in hypericin and shiraiachrome-A or, alternatively, the perylenequinone systems of these natural products could exhibit their antiviral effects after undergoing reduction to dihydroxybiaryl ring systems.

We undertook preliminary studies to probe the mechanism of action of the michellamines. The concentrations of michellamines B and A required to inhibit the level of supernatant HIV RT in HIV-2 (NIH-DZ)-infected MT-2 cells in culture by 50% ($EC_{50}$ value) were reported to be 30 $\mu M$ and 300 $\mu M$, respectively [4] and those required to reduce by 50% the lethal effects of the virus on these cells ($EC_{50}$ for anti-cytopathic effect) were also reported to be 30 $\mu M$ and 300 $\mu M$, respectively [4]. The dose-response curves for RT levels and anti-cytopathic effects were also similar. These results suggest a relationship between RT inhibition and antiviral activity because viral production is dependent on RT activity. There are no literature reports as to whether the michellamines directly inhibit HIV RT or whether inhibition occurs by an indirect mechanism involving other inhibitory processes. Therefore, the michellamine B *bis*(acetic acid) salt and analogs **4** and **5** were assayed for their ability to inhibit recombinant HIV RT. The $IC_{50}$ values are shown in Table 2. Analog **4** had 53% of the inhibitory activity of michellamine B, whereas analog **5** was a poor inhibitor, being 30-fold less active. The micromolar concentration range observed for inhibi-

tion of RT by analog **4** was similar to that required for inhibiting HIV-1 growth in cells. These results suggest that inhibition of HIV RT may be one mechanism by which the michellamines exert their anti-HIV effects.

Michellamine B and analogs **4** and **5** also inhibited the phosphorylation of histones by rat brain protein kinase C. The analogs were approximately fourfold more active than michellamine B as phosphorylation inhibitors. Additional studies using HIV protein kinases are necessary to clarify the role of these compounds in inhibiting phosphorylation of HIV proteins.

Table 2

Biological Activity of Michellamine B and Analogs **4** and **5**

| Compound | Inhibitory activities, $IC_{50}$ (μM) | |
|---|---|---|
| | HIV reverse transcriptase | Protein kinase C [a] |
| Michellamine B | 33 | 130 |
| **4** | 62 | 36 |
| **5** | 1000 | 30 |

[a] Inhibition of phosphorylation by rat brain protein kinase C.

These results suggest that the michellamines exert their anti-HIV effects by inhibiting HIV RT and may also inhibit viral protein phosphorylation.

## EXPERIMENTAL

All reactions were conducted under positive argon pressure unless otherwise noted. All solvents were purchased as hplc grade, and where appropriate, solvents were freshly distilled from calcium hydride or sodium/benzophenone ketyl (tetrahydrofuran) under reduced pressure or argon prior to storage over 4-Å molecular sieves. Unless otherwise stated, reagents were used as obtained. Flash chromatography with silica gel (60-240 mesh, E. Merck) was used for separations. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian 300 spectrometer using tetramethylsilane as the internal standard. Infrared (ir) spectra were obtained on a Perkin-Elmer FTIR 1600 spectrophotometer. Melting points are uncorrected. Mass spectra (ms) were obtained on LKB 9000 gcms (electron impact), Nermag R 10-10 C (chemical ionization), and Vestic 201 (LC-MS) spectrometers.

3,5-Dimethoxy-1-(2-nitro-1-propenyl)benzene.

The procedures of Bringmann *et al.* [12] were adapted for the preparation of **7** through **13**. A mixture of 150 g (0.90 mole) of 3,5-dimethoxybenzaldehyde **6** and 7.5 g (97 mmoles) of ammonium acetate in 750 g (10 moles) of nitroethane was stirred at 100° for 16 hours. Solvent was removed from the cooled solution by distillation at reduced pressure (40° head temperature). The pot residue was crystallized (hot methanol) to give 132 g (62%) of 3,5-dimethoxy-1-(2-nitro-1-propenyl) benzene as a yellow, crystalline solid, mp 88-89°; ir (potassium bromide): 1601, 1518, 1459, 1327, 1300, 1200, 1032, 947, 919, 676 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.45 (s, 3H, $CH_3C$), 3.80 (s, 6H, 2 $OCH_3$), 6.55 (m, 3H, HC=C, 2-H, 6-H), 8.0 (s, 1H, 4-H).

*Anal.* Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.21; H, 5.82; N, 6.21.

1-(3,5-Dimethoxyphenyl)-2-propanone **7.**

To a mechanically stirred mixture of 412 g (7.4 moles) of iron powder in 1.8 l of glacial acetic acid was added a solution of 132 g (0.6 mole) of 3,5-dimethoxy-1-(2-nitro-1-propenyl)benzene in 0.9 l of warm glacial acetic acid. The mixture was stirred at reflux temperature until hydrogen evolution slowed. The thick mixture was then diluted with glacial acetic acid (0.5 l), stirred at reflux for 3 hours, and allowed to cool to room temperature. Each 600-ml portion of the reaction mixture was diluted with water (3 l), and this aqueous mixture was extracted with dichloromethane (4 x 300 ml). The combined extracts were washed with 15% sodium hydroxide (300 ml), water (300 ml), and brine (300 ml), then dried (sodium sulfate) and concentrated to give an orange oil. This workup was repeated five times to give 103 g (90%) of **7** as an orange oil; ir (film): 2941, 2839, 1711, 1595, 1463, 1151 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.15 (s, 3H, $CH_3CO$), 3.60 (s, 2H, $ArCH_2$), 3.80 (s, 6H, $OCH_3$), 6.35 (m, 3H, 2-H, 4-H, 6-H).

*Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.89; H, 7.30.

(*R*,*R*)-*N*-[1-(3,5-Dimethoxyphenyl)-2-propyl]-α-methylbenzenemethanamine Hydrochloride **8**.

A solution of 110.1 g (567 mmoles) of **7** and 68.67 g (567 mmoles) of (*R*)-α-methylbenzylamine in 1.15 l of toluene was stirred at 110° under argon for 16 hours in the presence of a Dean-Stark trap. Removal of the solvent under vacuum gave 166 g of a hygroscopic, unstable brown oil, which contained 134 g (81%) of (*R*)-*N*-[1-(3,5-dimethoxyphenyl)-2-propylidene]-α-methylbenzenemethanamine as determined by integration of the relevant peaks in the $^1H$ nmr spectrum. This material was used immediately in the next step.

A solution of 166 g of this product, containing 134 g (446 mmoles) of (*R*)-*N*-[1-(3,5-dimethoxyphenyl)-2-propylidene]-α-methylbenzenemethanamine, as determined by $^1H$ nmr, in 300 ml of anhydrous ethanol was divided between two flasks, and 18 g of ethanol-washed 50% Raney nickel was added to each flask. The mixtures were shaken under 50 psi of hydrogen for 46 hours, then filtered through Celite (ethanol wash) and concentrated under vacuum. The resultant oil (165.5 g) was dissolved in anhydrous methanol (1 l), cooled to -15° (acetone/sodium chloride), and treated with an excess of anhydrous hydrogen chloride. The precipitated white solid was filtered and dried to give 97.73 g [51% from **7**] of **8**. Concentration of the mother liquors provided an additional 19.1 g (61% total yield) of **8**, mp 242-244°; ir (potassium bromide): 3460, 2940, 2750, 1594, 1458, 1432, 1293, 1206, 1155, 1063 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.45 (d, 3H, $H_\beta$), 2.00 (d, 3H, $CH_3CHAr$), 2.80 (dd, 1H, $H_\alpha$), 3.05 (m, 1H, $CH_2CHNH$), 3.35 (d, 1H, $H_\alpha$), 3.75 (s, 6H, $OCH_3$), 4.40 (br s, 1H, ArCHNH), 6.10 (m, 2H, 2-H, 6-H), 6.30 (m, 1H, 4-H), 7.60 (m, 5H, $C_6H_5$), 10.0 (br s, 2H,

$NH_2$).

*Anal.* Calcd. for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.95; H, 7.93; N, 4.28.

(*R*)-3,5-Dimethoxy-α-methylbenzeneethanamine Hydrochloride **9**.

To a solution of 30 g (89 mmoles) of **8** in 210 ml of 5% aqueous methanol at 0° was added 1.73 g of 5% palladium on carbon. The mixture was shaken at 45° under 50 psi of hydrogen for 18 hours, filtered through Celite, and concentrated under vacuum to give an off-white solid, which was triturated with ether. This procedure was repeated five times with a total of 216 g (643 mmoles) of **8** to give 146 g (98%) of **9** as a white solid, mp 149-150° (lit [12] mp of enantiomer 151.5°); $[\alpha]_D^{20}$ = -14.4° (c = 0.7, methanol) (lit $[\alpha]_D^{20}$ of enantiomer = 14.8° [12]); ir (potassium bromide): 3450, 2970, 1606, 1500, 1462, 1195, 1153, 1056 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.39 (d, 3H, $CH_3CH$), 2.80 (dd, 1H, $H_\alpha$), 3.19 (dd, 1H, $H_\alpha$, 3.60 (m, 1H, $CHNH_3$), 3.82 (s, 6H, $OCH_3$), 6.40 (m, 3H, 2-H, 4-H, 6-H), 8.44 (br s, 3H, $NH_3^+$).

*Anal.* Calcd. for $C_{11}H_{18}ClNO$: C, 57.02; H, 7.83; N, 6.04. Found: C, 56.78; H, 7.83; N, 6.15.

(*R*)-*N*-[1-(3,5-Dimethoxyphenyl)-2-propyl]acetamide **10**.

To a stirred solution of 47.51 g (205 mmoles) of **9** and 86 ml (615 mmoles) of triethylamine in 580 ml of dichloromethane at 0° under argon was added dropwise 25.7 g (328 mmoles) of acetyl chloride. The solution was warmed to 23°, stirred for 3 hours, poured into 340 ml of methylene chloride, washed with water (3 x 400 ml) and brine (400 ml), and dried (magnesium sulfate). Removal of the solvent gave a dark syrup that was shaken with 500 ml of pentane, filtered, and dried to give 45.84 g (94%) of **10** as a tan solid, mp 78-80°; ir (potassium bromide): 3340, 2980, 1643, 1539, 1460, 1371, 1270, 1206, 1180, 1057, 829 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.11 (d, 3H, J = 6.7 Hz, $CH_3CH$), 1.95 (s, 3H, $CH_3CO$), 2.63 (dd, 1H, J = 13.5, 7.3 Hz, $H_\alpha$), 2.80 (dd, 1H, J = 13.5, 5.6 Hz, $H_\alpha$), 3.78 (s, 6H, $OCH_3$), 4.25 (m, 1H, CHN), 5.45 (br s, 1H, NH), 6.32 (s, 3H, ArH).

*Anal.* Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.91; H, 8.01; N, 5.94.

(*R*)-3,4-Dihydro-6,8-dimethoxy-1,3-dimethylisoquinoline **11**.

A solution of 54.6 g (230 mmoles) of **10** and 54 ml (575 mmoles) of phosphoryl chloride in 550 ml of acetonitrile was stirred under argon at 82° for 8 hours and at 23° for 18 hours, then added dropwise to a solution of 366 g (3.45 moles) of sodium carbonate in 1 l of water. The mixture was washed with chloroform (3 x 500 ml), and the combined organic layers were washed with water (2 x 500 ml) and brine (800 ml), then dried (magnesium sulfate). Removal of the solvent under vacuum gave a dark gum, which was dissolved in ether and treated with excess hydrogen chloride in ether. The suspended solid was collected by filtration and dried (vacuum). This procedure was repeated twice with a total of 147.2 g (620.3 mmoles) of **10** to give 142.06 g (89%) of **11** as the hydrochloride as a light-tan solid, mp 190-191°.

A solution of 21.45 g (83.9 mmoles) of the hydrochloride of **11** in 250 ml of dichloromethane was washed with saturated sodium carbonate (100 ml). The organic layer was washed with brine (50 ml) and dried (magnesium sulfate). Removal of the solvent gave 18.31 g (quantitative) of **11** as a gum; $[\alpha]_D^{20}$ = 140° (c = 0.9, methanol) (lit $[\alpha]_D^{20}$ of enantiomer = -141° [12]); ir (potassium bromide): 3400, 2860, 1630, 1595, 1562, 1518, 1452, 1316, 1278, 1190, 1162, 1129, 1081, 1038, 868 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.52 (d, 3H, J = 6.7 Hz, 3-$CH_3$), 2.38 (dd, 1H, J = 16.6, 16.7 Hz, 4-$H_\alpha$), 2.95 (s, 3H, 1-$CH_3$), 3.08 (dd, 1H, J = 16.6, 15.7 Hz, 4-$H_\alpha$), 3.93 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$), 4.1 (br s, 1H), 6.41 (m, 2H, ArH).

*Anal.* Calcd. for the hydrochloride salt of **11** for $C_{13}H_{20}ClNO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.29; H, 7.90; N, 6.45.

(1*R*,3*R*)-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **12**.

To a mechanically stirred suspension of 22.21 g (59 mmoles) of lithium aluminum hydride in 350 ml of tetrahydrofuran at -78° under argon was added dropwise a solution of 18.31 g (84 mmoles) of **11** in 200 ml of tetrahydrofuran, followed dropwise over a 1.5 hour period by 292 ml of a 2*M* solution of trimethylaluminum (580 mmoles) in toluene. The mixture was stirred at -78° for 30 minutes, at -45° for 1 hour, at -25° for 1 hour, and at 0° for 1 hour, cooled to -45°, quenched by the dropwise addition of 200 ml of saturated sodium fluoride, warmed to 23°, stirred for 16 hours, concentrated to remove most of the tetrahydrofuran, and poured into 700 ml of ether. After filtration through a sintered-glass disk, the organic layer was washed with brine (300 ml) and dried (magnesium sulfate). Removal of the solvent gave 16.42 g (89%) of **12** as a gum; $[\alpha]_D^{20}$ = -7.7° (c = 0.6, methanol) (lit $[\alpha]_D^{20}$ 1*S*,3*S* enantiomer = 7.6° [12]); ir (potassium bromide): 3441, 2980, 1611, 1457, 1329, 1218, 1200, 1155, 1141, 1071 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.22 (d, 3H, J = 6.6 Hz, 3-$CH_3$), 1.38 (d, 3H, J = 6.0 Hz, 1-$CH_3$), 2.40 (dd, 1H, J = 14.6, 7.0 Hz, 4-H), 2.71 (dd, 1H, J = 14.6, 4.6 Hz, 4-H), 3.79 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 4.28 (m, 2H), 6.21 (d, 2H, J = 2.0 Hz), 6.3 (d, 1H, J = 2.0 Hz).

*Anal.* Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.72; H, 8.79; N, 6.42.

The hydrochloride salt of **12** was prepared as follows. A solution of 31.72 g (143 mmoles) of **12** in 300 ml of ether was filtered through Celite, cooled to 0°, and treated with excess ethereal hydrogen chloride. After 30 minutes, the suspended solid was filtered and dried to give 35.52 g (96%) of the salt as a white solid; ir (potassium bromide): 3430, 2990, 1595, 1460, 1329, 1204, 1153, 1111, 1054 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.70 (d, 3H, J = 6.5 Hz, $CH_3$) 1.74 (d, 3H, J = 6.5 Hz, $CH_3$), 2.90 (dd, 1H, J = 4, 17 Hz, 4-H), 3.16 (dd, 1H, J = 11.5, 17 Hz, 4-H), 3.6-3.75 (m, 1H, 3-H), 3.77 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 4.7-4.8 (m, 1H, 1-H), 6.20 (d, 1H, J = 2 Hz, ArH), 6.30 (d, 1H, J = 2 Hz, ArH).

*Anal.* Calcd. for $C_{13}H_{20}ClNO_2$: C, 60.58; H, 7.82; N, 5.43. Found: C, 60.36; H, 7.93; N, 5.34.

(1*R*,3*R*)-2-Benzyl-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride **13**.

In this benzylation, **12** was used directly or its stored hydrochloride salt was neutralized as follows. A solution of 35.52 g (138 mmoles) of (1*R*,3*R*)-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride in 300 ml of chloroform was shaken with a solution of 16 g (151 mmoles) of

sodium bicarbonate in 300 ml of water. The aqueous layer was washed with chloroform (200 ml), and the combined organic layers were washed with brine (200 ml) and dried (magnesium sulfate). Removal of the solvent gave 28.65 g (94%) of **12** as a dark oil, which was stirred for 24 hours with 20.5 ml (172 mmoles) of benzyl bromide and 39.6 g (287 mmoles) of potassium carbonate in 350 ml of tetrahydrofuran at 20° under argon, then poured into 300 ml of water and 300 ml of ether. The aqueous layer was washed with ether (200 ml), and the combined organic layers were washed with brine (200 ml) and dried (magnesium sulfate). Removal of the solvent gave a dark oil, which was stirred in 300 ml of hexanes for 2 hours, filtered, and concentrated to give an orange oil. The oil was dissolved in 400 ml of ether and treated with excess ethereal hydrogen chloride. The resultant suspended solid was collected by filtration and dried to give 39.06 g (82%) of **13** as a tan solid; $^1$H nmr (deuteriochloroform): δ 1.65 (d, 3H, J = 6.5 Hz, $CH_3$), 1.87 (d, 3H, J = 6.5 Hz, $CH_3$), 2.94 (dd, 1H, J = 12, 18.5 Hz, 4-H), 3.18 (dd, 1H, J = 6, 18.5 Hz, 4-H), 3.51 (dd, 1H, J = 9, 12.5 Hz, PhCH), 3.66 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.18-4.32 (m, 1H, 3-H), 4.38 (q, 1H, J = 6.5 Hz, 1-H), 4.54 (dd, 1H, J = 3.5, 12.5 Hz, PhCH), 6.32 (br s, 1H, ArH), 6.34 (br s, 1H, ArH), 7.32-7.48 (m, 5H, $C_6H_5$).

The crude free amine from another experiment was also chromatographed through silica gel with 5-25% ether/hexanes to give (1*R*,3*R*)-2-benzyl-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline as a colorless oil; $R_f$ 0.23 (10% ether/hexanes); $[\alpha]_D^{22}$ = 78.4° (c = 1.7, methanol) (lit $[\alpha]_D^{22}$ 1*S*,3*S* enantiomer = -78.8° [12]).

(1*R*,3*R*)-2-Benzyl-6,8-dihydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **14**.

A mechanically stirred slurry of 58.35 g (168 mmoles) of **13** in 400 ml of 48% hydrobromic acid was heated to 105° in an oil bath under argon for 4 days, poured into 1 l of 30% ammonium hydroxide, and washed with ethyl acetate (3 x 300 ml). The combined extracts were washed with brine (500 ml) and dried (magnesium sulfate). Removal of the solvent gave a dark oil, which was absorbed onto silica gel (90-200 mesh), then chromatographed (20-80% ethyl acetate/hexanes) to give 38 g (80%) of **14** as a purple oil; $R_f$ 0.27 (50% ethyl acetate/hexanes); $^1$H nmr (deuteriochloroform/dimethyl sulfoxide-$d_6$): δ 1.22 (d, 3H, J = 6.5 Hz, $CH_3$), 1.31 (d, 3H, J = 6.5 Hz, $CH_3$), 2.45-2.65 (m, 2H, $ArCH_2$), 3.32 (d, 1H, J = 14 Hz, PhCHN), 3.40-3.54 (m, 1H, 3-H), 3.80 (d, 1H, J = 14 Hz, PhCHN), 3.86 (q, 1H, J = 6.5 Hz, 1-H), 6.14 (d, 1H, J = 2 Hz, ArH), 6.22 (d, 1H, J = 2 Hz, ArH), 7.15-7.40 (m, 5H, $C_6H_5$), 7.55 (br s, 2H, OH).

(1*R*,3*R*)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **15**.

A mechanically stirred mixture of 38 g (134 mmoles) of **14**, 85 ml (715 mmoles) of benzyl bromide, and 85 g (615 mmoles) of potassium carbonate in 1 l of acetone was heated to 56° under argon for 6 hours, filtered, and concentrated to give a dark-yellow oil that was chromatographed (5-25% ether/hexanes) to give 31.9 g (51%) of **15** as a light yellow syrup, $R_f$ 0.27 (20% ether/hexanes); ir (film): 3062, 3030, 2965, 2928, 2870, 1604, 1495, 1454, 1432, 1372, 1304, 1270, 1148, 1072, 1029, 734, 696 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.25 (d, 3H, J = 6.5 Hz, $CH_3$), 1.34 (d, 3H, J = 6.5 Hz, $CH_3$), 2.50-2.70 (m, 2H, $ArCH_2$), 3.30 (d, 1H, J = 14 Hz, PhCHN), 3.45-3.60 (m, 1H, C3-H), 3.82 (d, 1H, J = 14 Hz, PhCHN), 4.02 (q, 1H, J = 6.5 Hz, 1-H), 4.98 (br s, 2H, $PhCH_2O$), 5.00 (s, 2H, $PhCH_2O$), 6.34 (d, 1H, J = 2.5 Hz, ArH), 6.42 (d, 1H, J = 2.5 Hz), 7.10-7.45 (m, 15H, $C_6H_5$). The product was contaminated with approximately 5% of (1*R*,3*R*)-2,5-dibenzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline, $R_f$ 0.32 (20% ether/hexanes); ir (film): 3061, 3027, 2968, 2930, 2871, 1592, 1494, 1453, 1305, 1122, 1100, 1070, 734, 697 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.22 (d, 3H, J = 6.5 Hz, $CH_3$), 1.35 (d, 3H, J = 6.5 Hz, $CH_3$), 2.42 (dd, 1H, J = 11, 16 Hz, ArCH), 2.56 (dd, 1H, J = 4.5, 16 Hz, ArCH), 3.26 (d, 1H, J = 14 Hz, PhCHN), 3.40-3.52 (m, 1H, 3-H), 3.77 (d, 1H, J = 14 Hz, PhCHN), 3.95-4.15 (m, 2H, $PhCH_2Ar$), 4.97 (br s, 4H, $PhCH_2O$), 6.47 (s, 1H, 7-H), 7.10-7.45 (m, 20H, 4 x $C_6H_5$); ms: (desorption chemical ionization-$NH_3$) 554 (M + H$^+$), 538, 478, 464.

(1*R*,3*R*)-2-Benzyl-5-bromo-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **16**.

To a stirred solution of 34.5 g (74.4 mmoles) of **15** in 100 ml of chloroform and 100 ml of acetic acid at 0° under argon was added dropwise over a 35 minute period a solution of 3.83 ml (74.4 mmoles) of bromine in 55 ml of acetic acid. After 1 hour, the solution was poured into 400 ml of water, and the aqueous layer was washed with chloroform (2 x 150 ml). The combined organic layers were washed with water (2 x 200 ml), 5% sodium bicarbonate (300 ml), and brine (200 ml), then dried (magnesium sulfate). Removal of the solvent gave a dark oil, which was chromatographed (5-30% ether/hexane) to give a tan solid. The solid was washed with hexanes (200 ml) and dried to give 29.4 g (73%) of **16** as a light-yellow solid, mp 99.5-100.5°; $R_f$ 0.35 (20% ether/hexanes), ir (film): 3062, 3028, 2969, 2930, 2871, 2830, 1592, 1572, 1452, 1328, 1308, 1175, 1063, 733, 696 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.31 (d, 3H, J = 6.5 Hz, $CH_3$), 1.34 (d, 3H, J = 6.5 Hz, $CH_3$), 2.45 (dd, 1H, J = 11.5, 17.5 Hz, 4-H), 2.74 (dd, 1H, J = 4.5, 17.5 Hz, 4-H), 3.22 (d, 1H, J = 14 Hz, PhCHN), 3.44-3.58 (m, 1H, 3-H), 3.82 (d, 1H, J = 14 Hz, PhCHN), 4.02 (q, 1H, J = 6.5 Hz, 1-H), 4.92 (d, 1H, J = 12.5 Hz, PhCHO), 4.98 (d, 1H, J = 14.5 Hz, PhCHO), 5.07 (s, 2H, $PhCH_2O$), 6.44 (s, 1H, 7-H), 7.15-7.50 (m, 15H, $C_6H_5$).

*Anal.* Calcd. for $C_{32}H_{32}BrNO_2$: C, 70.85; H, 5.95; Br, 14.73; N, 2.58. Found: C, 70.62; H, 6.02; Br, 14.52; N, 2.41.

1-Benzyloxynaphthalene **18**.

To a stirred solution of 10.2 g (0.071 mole) of 1-naphthol **17** in acetone (100 ml) was added 19.5 g (0.141 mole) of potassium carbonate, followed by 9.66 ml (0.0813 mole) of benzyl bromide. The mixture was heated at reflux (56°) for 10 hours, cooled, and filtered (acetone wash). The filtrate was concentrated to furnish a solid residue, which was chromatographed (5% dichloromethane/hexanes) to afford 12.8 g (78%) of 1-benzyloxynaphthalene **18** [21] as a white crystalline solid, mp 75-76°; ir (potassium bromide): 3449, 1576, 1507, 1456, 1400, 1269, 1238, 1093, 980, 918, 773 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 5.26 (s, 2H, $PhCH_2O$), 7.1 (dd, 1H, J = 7.5, 1.0 Hz, 2-H or 4-H), 7.34-7.58 (m, 9H, ArH), 7.8 and 8.35 (2 m, 2H, 5,8-ArH).

1-Benzyloxy-4-bromonaphthalene **19**.

To a stirred suspension of 8 g (0.03 mole) of **18** in 70 ml of acetic acid was added 11.5 g (0.036 mole) of pyridinium bro-

mide perbromide portionwise over 15 minutes. The reaction mixture was stirred for 30 minutes, poured into water (230 ml), and extracted with chloroform (3 x 100 ml). The combined organic extracts were washed with saturated sodium bicarbonate (100 ml), water (100 ml), and brine (80 ml), then dried (sodium sulfate). Concentration furnished a solid, which was recrystallized (ether) to afford 8.45 g (79%) of **19** as a white crystalline solid, mp 81-82°; ir (potassium bromide): 3033, 2939, 2878, 1955, 1815, 1616, 1587, 1500, 1452, 1369, 1236, 1070, 1150, 1070, 979, 762, 645 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.22 (s, 2H, $PhCH_2O$), 6.74 and 7.67 (2 d, 2H, J = 8.24 Hz, 2,3-ArH), 7.34-7.66 (m, 7H), 8.18 and 8.3 (2 d, 2H, J = 7.96 and 8.18 Hz, 5,8-ArH).

4-Benzyloxy-l-naphthaleneboronic Acid **20**.

To a stirred solution of 2.0 g (6.0 mmoles) of **19** in tetrahydrofuran (15 ml) at -78° under argon was added dropwise 4.78 ml of 1.6*M* *n*-butyllithium (7.66 mmoles) in hexane. After 15 minutes, 2.2 ml (19 mmoles) of trimethyl borate was added at once, and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was quenched with 5% hydrochloric acid (20 ml) and concentrated to a solid, which was suspended in water (10 ml) and extracted with chloroform (3 x 10 ml). The milky-white suspension of extracts was washed with brine (15 ml) and dried (sodium sulfate). The suspension was filtered to furnish 1.7 g (96%) of **20** as a white crystalline solid, mp 128-130°; ir (potassium bromide): 3283, 3036, 1578, 1509, 1405, 1366, 1305, 1263, 1161, 1079, 1027, 815, 762, 732, 694 $cm^{-1}$; $^1H$ nmr (acetone-$d_6$): δ 5.39 (s, 2H, $PhCH_2O$), 7.08 and 7.94 (2 d, 2H, J = 7.8 Hz, 2,3-ArH), 7.4-7.7 (m, 7H, ArH), 8.38 and 8.77 (2 dm, 2H, 5,8-ArH).

2-Bromo-1-hydroxynaphthalene **21**.

To a solution of 88.0 g (0.61 mole) of **17** in 800 ml of dichloromethane was added a solution of 205 g (1.282 moles) of bromine in 200 ml of dichloromethane at 0°. The mixture was stirred mechanically for 15 hours, then filtered through a sintered glass funnel. The collected crystals were washed with 20% dichloromethane/hexanes (100 ml) to give 92.2 g (50%) of 2,4-dibromo-1-hydroxynaphthalene as a white solid [22]. The filtrate was concentrated and chromatographed (15% dichloromethane/hexanes) to give another 41.85 g (23%) of 2,4-dibromo-1-hydroxynaphthalene, mp 109-111°; ir (potassium bromide): 3450, 1582, 1501, 1446, 1372, 1328, 1228, 1144, 1055 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.98 (s, 1H, OH), 7.59 (m, 2H, 6,7 ArH), 7.80 (s, 1H, 3-ArH), 8.13 and 8.26 (m, 2H, 5,8-ArH); ms: (electron impact) 300/302 ($M^+$), 195, 193, 192, 114, 113, 98, 97, 87, 63.

To a solution of 19.0 g (62.9 mmoles) of dibromonaphthaenol in 300 ml of tetrahydrofuran was added 83 ml of 1.6*M* *n*-butyllithium (0.132 mole) in hexanes at -78°. The yellow solution was stirred for 25 minutes, poured into 100 ml of 1% hydrochloric acid, and diluted with 500 ml of dichloromethane. The organic layer was washed with brine (500 ml), dried (magnesium sulfate), and concentrated to give a brown oil that was chromatographed (3% methylene chloride/hexanes) to give 11.83 g (84%) of **21** [23] as a white solid, mp 45°; $R_f$ 0.45 (3% methylene chloride/hexanes); ir (potassium bromide): 3460, 1583, 1502, 1449, 1398, 1373, 1328, 1231, 1146, 1054 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.97 (s, 1H, OH), 7.32 and 7.48 (d, 2H, J = 8.6 Hz, 3,4-ArH) 7.50-7.53 (m, 2H, 6,7-ArH), 7.78 and 8.24 (m, 1H, 5,8-ArH); ms: (electron impact) 222/224 ($M^+$), 195, 193, 115, 114, 113, 88, 63.

1-Benzyloxy-2-bromonaphthalene **22**.

To a solution of 10.95 g (49.1 mmoles) of **21** and 10.08 g (58.9 mmoles) of benzyl bromide in 100 ml of acetone was added 8.14 g (58.9 mmoles) of potassium carbonate. The mixture was heated at 56° for 3 hours. Another 10.08 g portion (58.9 mmoles) of benzyl bromide and 8.14 g (58.9 mmoles) of potassium carbonate were added to the reaction mixture, and heating at reflux was continued for 18 hours. The mixture was cooled and filtered through a sintered-glass funnel. The filtrate was concentrated to give a yellow oil that was chromatographed (10%, 20% dichloromethane/hexanes) to give 13.90 g (90%) of **22** as a white solid, mp 45°; $R_f$ 0.19 (10% dichloromethane/-hexanes); ir (potassium bromide): 3010, 1580, 1498, 1451, 1358, 1324, 1254, 1203, 1123, 1061, 956 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.14 (s, 2H, $CH_2$), 7.39-7.55 (m, 6H, ArH), 7.61-7.66 (m, 3H, ArH), 7.85 (m, 1H, ArH), 8.14 (m, 1H, ArH); ms: (electron impact) 312 ($M^+$), 233, 193, 114, 91.

1-Benzyloxy-2-naphthaleneboronic Acid **23**.

To a solution of 10.82 g (34.5 mmoles) of **22** in 120 ml of tetrahydrofuran was added 23.8 ml of 1.6*M* (38.0 mmoles) of *n*-butyllithium in hexanes at -78°. The mixture was stirred for 1 hour, then transferred using a cannula to a solution of 11.8 ml (0.104 mmole) of trimethyl borate in 50 ml of tetrahydrofuran cooled to -10°. The resultant mixture was warmed to 25°, stirred for 1 hour, poured into 100 ml of 1% hydrochloric acid, stirred for 30 minutes, and extracted with dichloromethane (2 x 300 ml). The organic layer was dried (magnesium sulfate) and concentrated to give 3.21 g (33%) of **23** as a white amorphous powder, mp 134-136°; $R_f$ 0.07 (dichloromethane); ir (potassium bromide): 3334, 1621, 1596, 1565, 1502, 1468, 1363, 1106, 1044, 952 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.12 (s, 2H, $CH_2$), 5.92 (br s, 2H, OH), 7.45-7.58 (m, 7H, ArH), 7.70 and 7.87 (2 d, 2H, J = 8.7 Hz, 3,4-ArH), 7.90 and 8.20 (2 m, 2H, 5,8-ArH); ms: (desorption chemical ionization) 296 ($M + NH_4^+$), 279 ($M + H^+$).

(1*R*,3*R*,5*M*)-2-Benzyl-5-(4-benzyloxy-1-naphthalenyl)-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **24** and (1*R*,3*R*,5*P*)-2-Benzyl-5-(4-benzyloxy-1-naphthalenyl)-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **25**.

To a stirred mixture of 3.3 g (13.0 mmoles) of **20**, 5.0 g (24.0 mmoles) of tribasic potassium phosphate, and 582 mg (0.79 mmole) of dichloro*bis*(diphenylphosphine)ferrocene palladium(II) [14] in 5 ml of freshly distilled dimethylformamide was added a solution of 4.3 g (7.96 mmoles) of **16** in 8 ml of dimethylformamide under argon. The reaction mixture was heated un-der argon at 65° with stirring for 14 hours, cooled to room temperature, diluted with water (10 ml) and ether (15 ml), and filtered. The filtrate was extracted with ether (3 x 10 ml), and the combined extracts were washed with brine (15 ml) and dried (sodium sulfate). Evaporation of the solvent furnished a brown solid, which was chromatographed (6% ethyl acetate/-hexanes) to afford 1.68 g (30%) of **24** as a white fluffy solid, mp 97°; $R_f$ 0.43 (15% ethyl acetate/10% dichloromethane/-hexanes); $[\alpha]_D^{23}$ = 60.6° (c = 1.0, chloroform); ir (potassium bro-

mide): 3060, 1583, 1509, 1454, 1372, 1320, 1232, 1096, 1066, 732, 696 $cm^{-1}$; $^1H$ nmr (chloroform): δ 1.04 (d, 3H, J = 6.5 Hz, 3-$CH_3$), 1.39 (d, 3H, J = 6.6 Hz, 1-$CH_3$), 1.95 (dd, 1H, J = 17.6, 4.3 Hz, 4-$H_e$), 2.28 (dd, 1H, J = 17.6, 11.3 Hz, 4-$H_a$), 3.35 (m, 2H, NCHPh, 3-H), 3.77 (d, 1H, J = 14.0 Hz, NCHPh), 4.13 (q, 1H, J = 6.6 Hz, 1-H), 4.81 (d, 1H, J = 17.6 Hz, PhCHO), 4.85 (d, 1H, J = 17.6 Hz, PhCHO), 4.98 (d, 1H, J = 17.6 Hz, PhCHO), 5.03 (d, 1H, J = 16.0 Hz, PhCHO), 6.52 (s, 1H, 7-H), 6.86 (m, 2H, ArH), 6.97 (d, 1H, J = 7.9 Hz, ArH), 7.0-7.62 (m, 17H, ArH), 8.44 (m, 1H, ArH); ms: (desorption chemical ionization) 696 (M + $H^+$, 100), 606 (12), 108 (28); hrms: Calcd. for $C_{49}H_{46}NO_3$ (M + $H^+$) 696.3477. Found: 696.3494.

Next was eluted 2.85 g (52%) of **25** as a white fluffy solid, mp 94-96°; $R_f$ 0.37 (15% ethyl acetate/10% dichloromethane/-hexanes); $[\alpha]_D^{23}$ = 82.1° (c = 1.0, chloroform); ir (potassium bromide): 2930, 1582, 1509, 1457, 1373, 1321, 1066, 733, 696 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.03 (d, 3H, J = 6.3 Hz, 3-$CH_3$), 1.43 (d, 3H, J = 6.5 Hz, 1-$CH_3$), 2.01 (dd, 1H, J = 17.5, 11.8 Hz, 4-$H_a$), 2.30 (dd, 1H, J = 17.5, 4.3 Hz, 4-$H_e$), 3.33 (d, 1H, J = 14.0 Hz, NCHPh), 3.40 (m, 1H, 3-H), 3.73 (d, 1H, J = 14.0 Hz, NCHPh), 4.14 (q, 1H, J = 6.5 Hz, 1-H), 4.87 (d, 1H, J = 19.2 Hz, PhCHO), 4.83 (d, 1H, J = 19.2 Hz, PhCHO), 5.02 (s, 2H, $PhCH_2O$), 5.30 (s, 2H, $PhCH_2O$), 6.53 (s, 1H, 7-H), 6.90 (m, 2H, ArH), 7.00 (d, 1H, J = 7.8 Hz, ArH), 7.10-7.62 (m, 17H, ArH), 8.46 (d, 1H, J = 8.0 Hz, ArH); ms: (desorption chemical ionization) 696 (M + $H^+$, 100), 606 (12), 337 (50), 141 (30), 108 (55); hrms: Calcd. for $C_{49}H_{46}NO_3$ (M + $H^+$) 696.3477. Found: 696.3454.

(1*R*,3*R*,5*M*)-2-Benzyl-5-(4'-benzyloxy-3'-bromo-1'-naphthalenyl)-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **26**.

To a solution of 650 mg (0.93 mmole) of **24** in 8 ml of chloroform was added a solution of 327 mg (1.02 mmoles) of pyridinium bromide perbromide in 30 ml of acetic acid at -2°. This mixture was stirred at ambient temperature for 24 hours, then poured into 100 ml of water. The organic layer was washed with saturated sodium bicarbonate (50 ml), dried (magnesium sulfate), and concentrated to give an oil that was chromatographed (8% ethyl acetate/hexanes) to give 492 mg (64%) of **26** as a white glass, mp 68-70°; $R_f$ 0.38 (20% ethyl acetate/hexanes); $[\alpha]_D^{23}$ = 55.8° (c = 1.0, chloroform); ir (potassium bromide): 2932, 1655, 1583, 1458, 1322, 1066, 732 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.09 (d, 3H, J = 6.6 Hz, 3-$CH_3$), 1.40 (d, 3H, J = 6.7 Hz, 1-$CH_3$), 1.91 (dd, 1H, J = 4.0, 17.5 Hz, 4-$H_a$), 2.29 (dd, 1H, J = 11.7, 17.5 Hz, 4-$H_e$), 3.37 (m, 2H, 3-H and NCHPh), 3.81 (d, 1H, J = 13.8 Hz, NCHPh), 4.13 (q, 1H, J = 6.7 Hz, 1-H), 4.83 (d, 1H, J = 20.8 Hz, PhCHO), 4.87 (d, 1H, J = 20.8 Hz, PhCHO), 5.02 (d, 1H, J = 16.0 Hz, PhCHO), 5.06 (d, 1H, J = 16.0 Hz, PhCHO), 5.20 (d, 1H, J = 12.8 Hz, PhCHO), 5.24 (d, 1H, J = 12.8 Hz, PhCHO), 6.53, (s, 1H, 7-H), 6.86 (m, 2H, ArH), 7.14 (m, 2H, ArH), 7.24-7.54 (m, 18H, ArH), 7.67 (m, 2H, ArH), 8.21 (d, 1H, J = 8.3 Hz, ArH); ms: (desorption chemical ionization) 774/776 (M + $H^+$, 80/80), 108 (100).

(1*R*,3*R*,5*P*)-2-Benzyl-5-(4'-benzyloxy-3'-bromo-1'-naphthalenyl)-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **27**.

To a stirred solution of 650 mg (0.93 mmole) of **25** in 8 ml of chloroform was added 329 mg (1.02 mmoles) of pyridinium bromide perbromide in 30 ml of acetic acid dropwise at ambient temperature. The reaction mixture was stirred for 24 hours, quenched with saturated sodium bisulfate (5 ml), and neutralized with saturated sodium bicarbonate. The organic phase was washed with water (10 ml) and brine (10 ml) and dried (sodium sulfate). Evaporation of the solvent furnished a solid that was chromatographed (8% ethyl acetate/hexanes) to afford 492 mg (68%) of **27** as a light-tan foam; $R_f$ 0.48 (15% ethyl acetate/10% dichloromethane/hexanes); $[\alpha]_D^{23}$ = 101.5° (c = 1.0, chloroform); ir (potassium bromide): 2930, 1589, 1458, 1354, 1205, 1066, 733, 696 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.04 (d, 3H, J = 6.5 Hz, 3-$CH_3$), 1.41 (d, 3H, J = 6.7 Hz, 1-$CH_3$), 1.97 (dd, 1H, J = 17.6, 11.0 Hz, 4-$H_a$), 2.27 (dd, 1H, J = 17.6 Hz, 4.2 Hz, 4-$H_e$), 3.32 (d, 1H, J = 14.0 Hz, NCHPh), 3.42 (m, 1H, 3-H), 4.13 (q, 1H, J = 6.7 Hz, 1-H), 4.84 (d, 1H, J = 21.8 Hz, PhCHO), 4.88 (d, 1H, J = 21.8 Hz, PhCHO), 5.04 (s, 2H, $PhCH_2O$), 5.17 (d, 1H, J = 12.9 Hz, PhCHO), 5.23 (d, 1H, J = 12.9 Hz, PhCHO), 6.53 (s, 1H, 7-H), 7.05 (m, 2H, ArH), 7.16 (m, 2H, ArH), 7.22-7.54 (m, 18H, ArH), 7.68 (m, 2H, ArH), 8.24 (d, 1H, J = 8.3 Hz, ArH); ms: (desorption chemical ionization) 774/776 (M + $H^+$, 100/100), 108 (90).

(1'*R*,3'*R*,5'*P*)-4-[2'-Benzyl-6',8'-dibenzyloxy-1',3'-dimethyl-1',2',3',4'-tetrahydro-5'-isoquinolinyl]-1-benzyloxy-2-naphthaleneboronic Acid **28**.

To a stirred solution of 600 mg (0.77 mmole) of **27** in 5 ml of dry tetrahydrofuran was added dropwise 0.53 ml of 1.6*M* *n*-butyllithium (0.85 mmole) in hexanes at -78°. After 30 minutes, 0.24 ml (2.3 mmoles) of trimethyl borate was added at once, and the mixture was stirred at ambient temperature for 10 hours. The reaction mixture was quenched with saturated ammonium chloride (5 ml) and diluted with ether (10 ml). The aqueous phase was extracted with ether (3 x 5 ml). The organic extracts were washed with brine (5 ml), dried (sodium sulfate), and concentrated to provide a solid that was chromatographed (2% methanol/dichloromethane) to afford 370 mg (64%) of **28** as a tan amorphous solid; $R_f$ 0.41 (6% methanol/dichloromethane); ir (potassium bromide): 3448, 3030, 2929, 1587, 1455, 1386, 1244, 1121, 1072, 734, 697 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.03 (d, 3H, J = 6.7 Hz, 3-$CH_3$), 1.41 (d, 3H, J = 6.6 Hz, 1-$CH_3$), 1.97 (dd, 1H, J = 17.8, 11.0 Hz, 4-$H_a$), 2.32 (dd, 1H, J = 4.4, 17.8 Hz, 4-$H_e$), 3.33 (d, 1H, J = 14.0 Hz, NCHPh), 3.42 (m, 1H, 3-H), 3.74 (d, 1H, J = 14.0 Hz, NCHPh), 4.83 (d, 1H, J = 20.0 Hz, PhCHO), 4.88 (d, 1H, J = 20.0 Hz, PhCHO), 5.04 (s, 2H, $PhCH_2O$), 5.20 (s, 2H, $PhCH_2O$), 5.89 [br s, 2H, $B(OH)_2$], 6.52 (s, 1H, 7-H), 6.88 (m, 2H, ArH), 7.14 (m, 2H, ArH), 7.24-7.62 (m, 21H, ArH), 7.73 (s, 1H, 2'-H), 8.28 (d, 1H, J = 8.2 Hz, ArH).

(1*R*,3*R*,5*M*,1'''*R*,3'''*R*,5'''*P*)-4'-(2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydro-5-isoquinolinyl)-4''-(2'''-benzyl-6''',8'''-dibenzyloxy-1'''-,3'''-dimethyl-1'''-,2''',3''',4'''-tetrahydro-5'''-isoquinolinyl)-1',1''-dibenzyloxy-2',2''-binaphthalene **29**.

The procedure of ElAmin *et al.* [24] was used. To a suspension of 44 mg (0.04 mmole) of palladium tetrakis(triphenyl)-phosphine in 1 ml of dimethoxyethane was added a solution of 300 mg (0.38 mmole) of **26** in 2 ml of dimethoxyethane, and the

mixture was stirred for 10 minutes at ambient temperature. To this solution were added sequentially a solution of 430 mg (0.58 mmole) of **28** in 2 ml of dimethoxyethane, 1 ml of ethanol, and 0.6 ml (1.16 mmoles) of 2*M* sodium carbonate. The reaction mixture was heated at 80° for 6 hours, cooled, diluted with ether (5 ml), and filtered. The filtrate was washed with brine (5 ml) and dried (sodium sulfate). Evaporation of the solvent furnished a solid that was chromatographed (6-10% ethyl acetate/hexanes) to afford 312 mg (58%) of **29** as a tan foam; $R_f$ 0.52 (35% ethyl acetate/hexanes); $[\alpha]_D^{23}$ = 101.5° (c = 1.0, chloroform); ir (potassium bromide): 3029, 2962, 2927, 1734, 1586, 1454, 1344, 1120, 1066, 1028, 733, 696 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.91 (br m, 6H, 3 $CH_3$, 3'''-$CH_3$), 1.47 (d, 6H, J = 6.5 Hz, 1-$CH_3$, 1'''-$CH_3$), 2.10 (m, 2H, 4-$H_a$, 4'''-$H_e$) 2.35 (m, 2H, 4-$H_e$, 4'''-$H_a$), 3.38 (m, 4H, NCHPh, 3-H, 3'''-H), 3.75 (m, 2H, NCHPh), 4.20 (m, 2H, 1-H, 1'''-H), 4.80-4.94 (m, 8H, $PhCH_2O$), 5.09 (br s, 4H, $PhCH_2O$), 6.60 (br s, 2H, 7-H, 7'''-H), 7.0-7.68 (m, 44H, ArH), 7.80 (m, 2H, ArH), 8.38 (m, 2H, ArH); ms: (thermospray) 1389 (M + $H^+$, 100), 1299 (30), 1209 (40), 695 (75), 606 (30); hrms: Calcd. for $C_{98}H_{89}O_6N_2$: (M + $H^+$) 1389.6720. Found: 1389.6730.

(1*R*,3*R*,5*M*,1'''*R*,3'''*R*,5'''*P*)-1',1'''-Dihydroxy-4'-(6,8-dihydroxy-1,3-dimethyl-1,2,3,4-tetrahydro-5-isoquinolinyl)-4'''-(6''',8'''-dihydroxy-1''',3'''-dimethyl-1''',2''',3''',4'''-tetrahydro-5'''-isoquinolinyl)-2',2''-binaphthalene *Bis*(trifluoroacetic acid) Salt **30**.

To a stirred suspension of 130 mg of palladium black in 5 ml of 4.4% formic acid in methanol was added 129 mg (0.093 mmole) of **29** in 1 ml of 4.4% formic acid in methanol, and the reaction mixture was stirred for 1 hour. The mixture was filtered under argon and washed with methanol (2 x 10 ml). The filtrate was concentrated to furnish 63 mg (90%) of the *bis* salt as a yellow-brown glass. This product was purified by reversed-phase preparative high-performance liquid chromatography (Waters, 6-μ Novapak $C_{18}$ column, 19 x 300 millimeters, 0.01*M* trifluoroacetic acid in 60% methanol/40% water, 3.0 ml/min, 285 millimeters) to afford 57.4 mg (69%) of **30** as an off-white solid, mp >270° dec; hplc (Zorbax $C_8$ column, 4.6 x 250 millimeters, 0.01*M* trifluoroacetic acid in 55% methanol/45% water, 0.7 ml/min, 255 nm): $t_R$ 8.2 (1.2%) and 10.2 minutes (98.5%); ir (potassium bromide): 3416, 1674, 1606, 1199, 840, 722 $cm^{-1}$; uv (methanol): $\lambda_{max}$ 341 (log ε 2.27), 332 (log ε 2.28), 278 (log ε 2.78), 225 nm (log ε 3.02); $^1H$ nmr (methanol-$d_4$): δ 1.12 and 1.15 (2 d, 6H, J = 6.4 Hz, 3-$CH_3$, 3'''-$CH_3$), 1.54 and 1.59 (2 d, 6H, J = 6.7 Hz, 1-$CH_3$, 1'''-$CH_3$), 2.08 (dd, 1H, J = 17.9, 11.5 Hz, 4-$H_a$), 2.33 (dd, 1H, J = 17.9, 5.0 Hz, 4'''-$H_e$), 2.43 (dd, 1H, J = 17.9, 11.0 Hz, 4'''-$H_a$) 2.73 (dd, 1H, J = 17.9, 4.8 Hz, 4-$H_e$), 3.58 (m, 2H, 3-H, 3'''-H), 4.66 (q, 2H, J = 6.7 Hz, 1 H, 1'''-H), 6.39 (s, 2H, 7-H, 7'''-H), 7.14 and 7.18 (2 s, 2H, 3'-H, 3''-H), 7.24-7.44 (m, 6H, Ar-H), 8.32 (d, 2H, J = 8.4 Hz, Ar-H); ms: (thermospray on free base) 783 (M + $H^+$ + trifluoroacetic acid, 10), 669 (M + $H^+$, 100), 335 (15); hrms: Calcd. for $C_{42}H_{41}O_6N_2$: (free base + $H^+$) 669.2964. Found: 669.2963.

(1*R*,3*R*,5*M*)-2-Benzyl-6,8-dibenzyloxy-5-(1',1''-dibenzyloxy-2',2''-binaphthalen-4-yl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **31**.

To a suspension of 18 mg (0.015 mmole) of palladium tetrakis(triphenylphosphine) in 1 ml of dimethoxyethane was added a solution of 120 mg (0.15 mmole) of **26** in 1 ml of dimethoxyethane. The mixture was stirred for 10 minutes at ambient temperature. To this solution were added sequentially a solution of 65 mg (0.23 mmole) of **23** in 1 ml of dimethoxyethane, 1 ml of ethanol, and 0.23 ml (0.46 mmole) of 2*M* sodium carbonate. This mixture was heated at 80° for 10 hours, cooled, diluted with ether (5 ml), and filtered. The filtrate was washed with brine (5 ml) and dried (sodium sulfate). Evaporation of the solvent furnished a foam that was chromatographed (6% acetone/-hexane) to afford 143 mg (72%) of **31** as a foam; $R_f$ 0.39 (25% ethyl acetate/hexanes); $[\alpha]_D^{23}$ = 94.7° (c = 1.0, chloroform); ir (potassium bromide): 2928, 1585, 1454, 1344, 1194, 1094, 1004, 733, 696 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 0.89 (m, 3H, 3-$CH_3$), 1.39 (d, 3H, J = 6.7 Hz, 1 $CH_3$), 2.01 (dd, 1H, J = 17.5, 4.4 Hz, 4-$H_e$), 2.26 (dd, 1H, J = 17.5, 11.4 Hz, 4-$H_a$), 3.28 (d, 1H, J = 14.0 Hz, NCHPh), 3.34 (m, 1H, 3-H), 3.66 (d, 1H, J = 14.0 Hz, NCHPh), 4.10 (q, 2H, J = 6.7 Hz, 1-H), 4.77 (s, 2H, $PhCH_2O$), 4.79 (s, 2H, $PhCH_2O$), 4.81 (s, 2H, $PhCH_2O$), 5.00 (d, 1H, J = 17.2 Hz, PhCHO), 5.04 (d, 1H, J = 17.2 Hz, PhCHO), 6.56 (s, 1H, 7-H), 6.81 (m, 2H, ArH), 7.0-7.90 (m, 32H, ArH), 8.22 (m, 1H, ArH), 8.37 (m, 1H, ArH); ms: (chemical ionization) 928 (M + $H^+$, 60), 838 (35), 748 (20), 370 (100), 342 (65), 325 (25); hrms: Calcd. for $C_{66}H_{58}O_4N$: (M + $H^+$) 928.4366. Found: 928.4379.

(1*R*,3*R*,5*M*)-6,8-Dihydroxy-5-(1',1''-dihydroxy-2',2''-binaphthalene-4-yl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline Formic Acid Salt **32**.

To a stirred suspension of 65 mg of palladium black in 3 ml of 5% formic acid in methanol was added 64 mg (0.07 mmole) of **31** in 3 ml of 5% formic acid in methanol at ambient temperature. The mixture was stirred for 35 minutes, filtered under argon, and washed with methanol (2 x 5 ml). The filtrate was concentrated to afford 31 mg (86%) of **32** as a tan solid, mp >280° dec; $[\alpha]_D^{23}$ = -45.1° (c = 1.0, methanol); ir (potassium bromide): 3422, 1602, 1499, 1344, 1094, 767 $cm^{-1}$; $^1H$ nmr (methanol-$d_4$): δ 1.26 (br s, 3H, 3-$CH_3$), 1.69 (br s, 3H, 1-$CH_3$), 2.44 (m, 2H, 4-H), 3.64 (m, 1H, 3-H), 4.80 (br s, 1H, 1-H), 6.50 (s, 1H, 7-H), 7.20 (s, 1H, 3'-H), 7.39-7.57 (m, 8H, Ar-H), 7.81 (m, 1H, ArH), 8.35 (m, 1H, ArH), 8.44 (d, 1H, J = 8.2 Hz, ArH); ms: (thermospray on free base) 478 (M + $H^+$, 100), 452 (3), 205 (5); hrms: Calcd. for $C_{31}H_{28}O_4N$: (M + $H^+$) 478.2018. Found: 478.2028.

Inhibition of Human Immunodeficiency Virus (HIV) Reverse Transcriptase Activity.

A reported procedure [25] was modified. Enzyme inhibition determinations were conducted in 100 μl of 50 m*M* Tris-hydrogen chloride, *p*H 8.0, with 6 m*M* magnesium chloride, 40 m*M* potassium chloride, 100 μg of bovine serum albumin/ml, 1 m*M* dithiothreitol, 0.1 m*M* polyadenylic acid (Pharmacia, Piscataway, NJ), 0.1 m*M* oligo(deoxythymidine)$_{12-18}$ (Pharmacia Uppsala, Sweden), 0.4 deoxythymidine triphosphate (dTTP, Sigma, St. Louis, MO), and 0.1 m*M* [$^3H$]deoxythymidine triphosphate (specific activity 93.5 Ci/mmoles, NEN, Boston, MA). Compounds were dissolved in methanol before serial dilution with buffer and addition in a volume of 10 μl. The final concentration of methanol in the assay mixture was below 2%. The assay time course was begun by the adding 10 units of recombinant HIV-1 reverse transcriptase (CalBiochem, La Jolla, CA) and incubating at 37°. Aliquots (10 μl) were removed as a

function of time and quenched in 20 µl of stop buffer [10 m*M* sodium pyrophosphate, containing 0.25 m*M* ethylenediamine tetraacetic acid and 0.5 mg/ml of yeast transfer ribonucleic acid (Sigma)]. The 30-µl samples were spotted onto Whatman 3-millimeter discs and batch-washed (10 ml/disc) in ice-cold 10% trichloroacetic acid and 1% sodium pyrophosphate for 10 minutes with agitation, followed by three 4 minute ice-cold 5% trichloroacetic acid washes and a 1 minute 95% ethanol rinse. Discs were dried and the radioactivity of the acid-insoluble product was determined by liquid scintillation counting. Assays were conducted in triplicate. Maximal enzyme activity was defined as that observed on the linear portion of the time-course curve of the enzyme-alone control. The concentration of compound that inhibited maximal reverse transcriptase activity by 50% was considered as the $IC_{50}$ value.

Inhibition of Protein Kinase C.

A modification of a reported protocol [26] was used. Rat brain protein kinase C (0.025 units, CalBiochem) and 6 x $10^4$ cpm of [$\gamma$-$^{32}$P]adenosine triphosphate ($^{32}$P-labeled, NEN; unlabeled diluent, Sigma) in 50 µl of 20 m*M* Tris·hydrogen chloride, *p*H 7.5, containing 0.5 µmole of magnesium acetate, 10 µg of histone III-S (Sigma), 4 µg of phosphatidyl serine (Sigma), 0.18 µg of diolein (Sigma), and 25 nmoles of calcium chloride was incubated at 30° for 5 minutes with various concentrations of the michellamine B analogs, which had been dissolved in methanol before serial dilution with buffer. The final concentration of methanol in the assay mixture was less than 1%. The enzyme reaction was stopped by adding 50 µl of 25% aqueous trichloroacetic acid. The acid-precipitable material was collected by filtration on filter paper (0.45-µm pore diameter, Millipore, Bedford, MA) (Tris·hydrogen chloride buffer wash). The amount of $^{32}$P label incorporated into histone was determined by scintillation counting of the filters. Assays were conducted in triplicate.

Acknowledgements.

The synthetic portion of this reseach was supported by the National Cancer Institute Contract N01-CM-17502. The suggestions of Project Officers Dr. Ven Narayanan and Dr. Ravi Varma, National Cancer Institute, Bethesda, MD, during the course of this research are gratefully acknowledged. The sample of michellamine B used for comparison purposes was kindly provided by Dr. Narayanan, who also arranged for antiviral evaluation by the National Cancer Institute.

## REFERENCES AND NOTES

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