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TOTAL SYNTHESIS OF MICHELLAMINES A-C: IMPORTANT ANTI-HIV AGENTS

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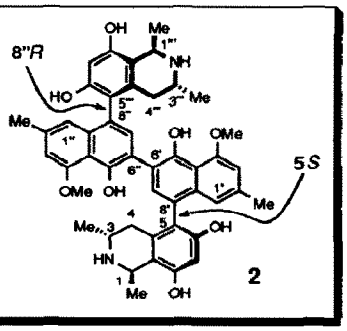
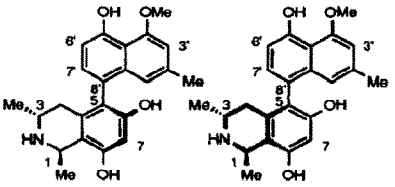
Abstract *Michellamines A-C have been prepared by total synthesis in 7 and 16 linear steps from known and commercial materials, respectively. Key steps include i) palladium(0)-mediated biaryl coupling, ii) silver oxide promoted oxidative 1-naphthol coupling to an atropisomeric mixture of cross-ring quinones (indigoids), and iii) simultaneous per-debenzylation/reductive bleaching to the central 2,2'-binaphthol.*

Michellamines A (**1**),[1,2] B (**2**),[1,2] and C (**3**)[2] constitute a family of anti-HIV, atropisomeric, naphthylisoquinoline alkaloids.[3] All are fully protective against both HIV-1 and HIV-2 in infected CEM-SS cells with EC_{50} values of 2-13 μM. Michellamine B, the most studied and most prevalent of the group, completely protects MT-2 cells from both AZT-resistant and pyridone-resistant strains of HIV-1. It possesses "a multilevel mode of action including both an inhibition of the viral reverse transcriptase as well as blockage of cellular fusion and synctium formation."[2] In light of these promising properties, as well as favorable initial toxicity evaluation,[2,4] michellamine B(**2**) has been selected by the National Cancer Institute for INDA-directed preclinical development.[2] The relative configurations of the stereogenic biaryl axes in each of **1-3** were cleverly determined by identification of NOE interactions between the peri-H(1') and -H(1") and one or the other of the diastereotopic protons at C(4) and C(4"').[1,2] The absolute configurations at C(1)/C(1"') and C(3)/C(3"') were assigned by degradation to *R*-alanine and *R*-3-aminobutyric acid, respectively.[5,2]

	Stereogenic Axis Configuration 5/8'	8"/5"'
1 Michellamine A	*S*	*S*
2 Michellamine B	*S*	*R*
3 Michellamine C	*R*	*R*



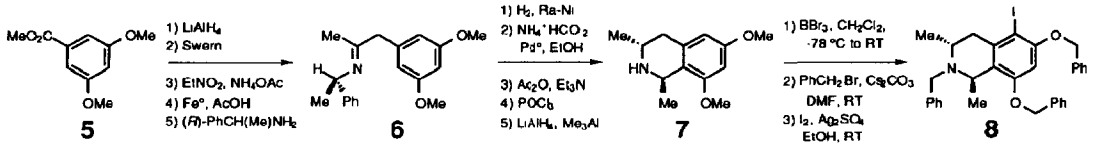


4 Korupensamine A

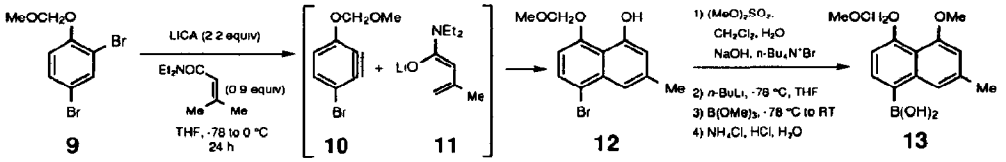
4' "Korupensamine C"

The first synthesis of michellamine A was very recently described.[6] An acyl derivative of a sample of the natural product korupensamine A (**4**), which co-exists with the michellamines in the plant,[7] was oxidatively coupled. Korupensamine A (**4**) itself has also been synthesized recently.[8] We have independently achieved a non-relay total synthesis of the michellamines A-C (as well as of korupensamine A) and are prompted to disclose our efforts here.

The non-racemic tetrahydroisoquinoline **7** was prepared from methyl 3,5-dimethoxybenzoate (**5**) via Raney nickel reduction of the non-racemic α-methylbenzylimine[9] **6** by the route pioneered by Bringmann.[10] Demethylation of **7** with excess boron tribromide gave a diphenol amine•HBr salt, which was tribenzylated with benzyl bromide and cesium carbonate in DMF at room temperature (85%, two steps). Regiospecific iodination with iodine and silver sulfate[11] gave C(5)-activated, benzyl protected **8** (66%).

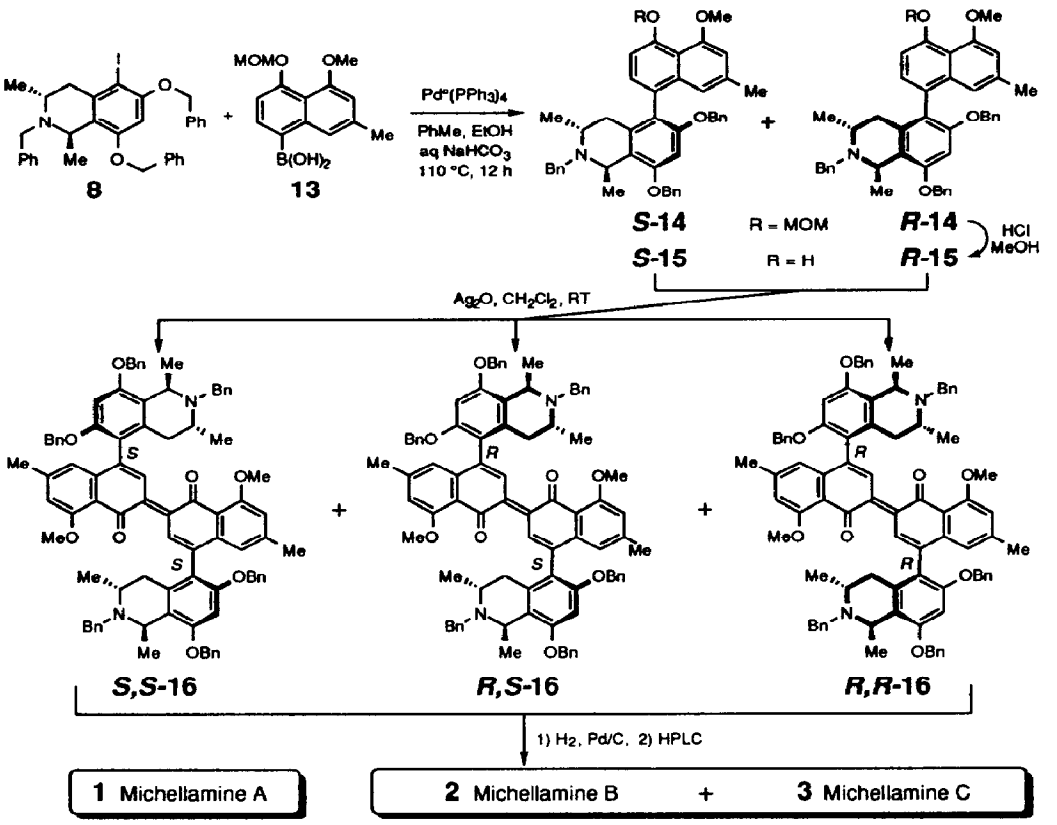


Boronic acid **13** was targeted as an ideal naphthalene building block. It was efficiently prepared from MOM-protected 2,4-dibromophenol (**9**) by a remarkably regiospecific benzyne annulation reaction. Treatment of **9** with an excess of lithium cyclohexylisopropylamide and N,N-diethyl seneciamide[12] gave **12**, presumably by way of benzyne **10** and lithium enolate **11**. Although the yield of this reaction was only 20%, the transformation was very reproducible and compares favorably with alternative, longer sequences we have investigated. O-Methylation and boronic acid synthesis followed standard protocols.



We were delighted to observe the palladium(0) catalyzed cross-coupling of **8** with **13**, which provided an ~4:3 ratio of the hindered atropisomers ***S*-14** and ***R*-14** (40-53%). Hydrolysis of the MOM ethers in **14** gave the naphthols **15** (75-100%), which could be separated by careful normal-phase HPLC. Hydrogenolysis of the benzyl groups in a mixture of the naphthols **15** provided an ~4:3 mixture of atropisomers **4** and **4'**.[13] This smooth deprotection was an encouraging harbinger.

The mixture of tribenzylated naphthols **15** underwent remarkably efficient oxidative coupling with excess silver oxide[14] in methylene chloride (or $CDCl_3$) at room temperature to give the purple indigoids ***R,S*-16**, ***S,S*-16**, and ***R,R*-16** in an ~2:1:1 ratio (~100%). The cross-ring quinones **16** could be reduced to the corresponding colorless binaphthols (sodium dithionite, H_2O, CH_2Cl_2 or $NaBH_4$, CH_2Cl_2, EtOH) and then perdebenzylated. More conveniently, *direct exposure of **16** to one atmosphere of hydrogen in methylene chloride/methanol over 10% Pd/C resulted in simultaneous reductive bleaching of the indigoid and complete hydrogenolysis of the six benzyl groups.* Michellamines A-C were cleanly (as judged from the crude ^1H NMR spectrum) produced with nearly quantitative mass recovery. Separation of a small portion on amino-bonded phase [7:1 CH_2Cl_2:0.1 weight % $(NH_4)_2CO_3$ in methanol][2] has thus far provided a pure sample of michellamine A (**1**) along with an ~2:1 mixture of michellamines B (**2**) and C (**3**).[15]



This synthesis consists of 7 and 16 linear steps from known and commercial materials, respectively. Optimization of this initial synthesis, identification of convenient intermediates for more efficient atropisomer separation, study of stereoselective coupling protocols, and michellamine analog preparation are now of high priority.

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13. This transformation was performed on a 1-2 mg scale; the crude mass recovery was nearly quantitative; and ^{1}H NMR spectrum consisted essentially only of resonances assigned to the mixture of **4** and **4'**: (500 MHz, CD_3OD, referenced to $C\underline{H}D_2OD$ @ 3.30 ppm) **4** (HCl salt): δ 7.09 [d, J = 7.5, H(7')], 6.79 [d, J = 7.5, H(6')], 6.78 [s, H(7)], 6.69 [s, H(1')], 6.43 [s, H(3')], 4.71 [q, J = 7.0, H(1)], 4.08 [s, OCH_3], 3.60 [ddq, J = 12.0, 4.5, 7.0, H(3)], 2.30 [s, CH_3(2')], 2.58 [dd, J = 18.0, 4.5, H(4eq)], 2.02 [dd, J = 18.0, 12.0, H(4ax)], 1.63 [d, J = 7.0, CH_3(1)], 1.17 [d, J = 7.0, CH_3(3)] and **4'** (HCl salt): δ 7.02 [d, J = 7.5, H(7')], 6.79 [s, H(7)], 6.78 [d, J = 7.5, H(6')], 6.69 [s, H(1')], 6.43 [s, H(3')], 4.70 [q, J = 7.0, H(1)], 4.08 [s, OCH_3], 3.56 [ddq, J = 10.0, 5.0, 7.0, H(3)], 2.34 [dd, J = ~18, ~10, H(4ax)], 2.33 [s, CH_3(2')], 2.20 [dd, J = 18.0, 5.0, H(4eq)], 1.65 [d, J = 7.0, CH_3(1)], 1.20 [d, J = 7.0, CH_3(3)]. Comparison with spectral data from natural korupensamine A awaits availability.
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15. Chemical shifts of the hydroacetate salt of synthetic michellamine A (**1**) closely match those reported for the hydrobromide salt of natural **1**.[1] All chemical shifts for the synthetic michellamine B (**2**) matched those we recorded for a sample of natural **2** to within ±0.01 ppm: ^{1}H NMR (500 MHz, CD_3OD, ~1% CH_3CO_2H, referenced to $C\underline{H}D_2OD$ @ 3.30 ppm) for michellamine A (**1**): δ 7.30 [s, H(7')], 6.85 [s, H(3')], 6.74 [s, H(1')], 6.44 [s, H(7)], 4.76 [q, J = 7.0, H(1)], 4.10 [s, OCH_3], 3.69 [ddq, J = 5, 12, 6, H(1)], 2.81 [dd, J = 18.0, 4.3, H(4eq)], 2.34 [s, CH_3(2')], 2.15 [dd, J = 18.0, 12.0, H(4ax)], 1.64 [d, J = 6.5, CH_3(1)], and 1.24 [d, J = 6.5, CH_3(3)]; michellamine B (**2** from the mixture of **2** and **3**) δ 7.31/7.26 [s, H(7')], 6.86/6.74 [s, H(3')], 6.85/6.83 [s, H(1')], 6.45/6.44 [s, H(7)], 4.76/4.72 [q, J = 7.0/6.7, H(1)], 4.10/4.09 [s, OCH_3], 3.71-3.60 [sym 10 line m, overlapping H(3) and H(3''') from **3**], 2.78 [dd, J = 18.0, 4.9, H(4eq)], 2.52 [dd, J = 18.0, 11.9, H(4ax)], 2.36/2.33 [s, CH_3(2')], 2.35-2.31 [dd, H(4eq), hidden by CH_3(2')], 2.11 [dd, J = 17.4, 11.3, H(4ax)], 1.68/1.64 [d, J = 6.7/7.0, CH_3(1)], and 1.26/1.22 [d, J = 6.4/6.4, CH_3(3)]; and michellamine C (**3** from the mixture of **2** and **3**) δ 7.28 [s, H(7')], 6.85 [two s's, H(1'), H(3')], 6.44 [s, H(7)], 4.74 [q, J = 6.7, H(1)], 4.10 [s, OCH_3], 3.71-3.60 [sym 10 line m, overlapping H(3) and H(3''') from **2**], 2.61 [dd, J = 18.0, 11.6, H(4ax)], 2.36 [s, CH_3(2')], 2.35-2.31 [dd, H(4eq), hidden by CH_3(2')], 1.68 [d, J = 6.7, CH_3(1)], and 1.30 [d, J = 6.1, CH_3(3)].

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