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Convergent Total Synthesis of the Michellamines[1]

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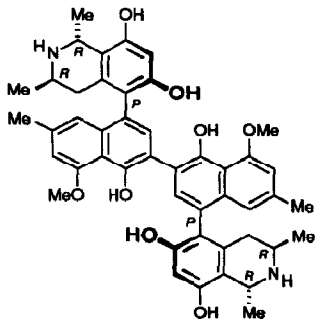
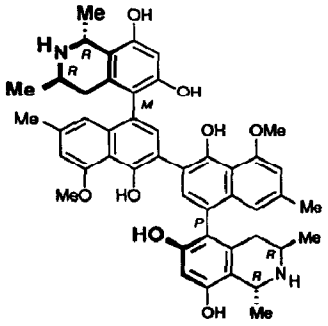
Abstract: The total synthesis of both michellamine A (**1a**) and B (**1b**), by consecutive construction first of the inner (non-stereogenic) axis and subsequently the two outer (stereogenic) axes in a highly convergent manner, is described. The michellamines are of considerable interest due to their pronounced anti-HIV activity.

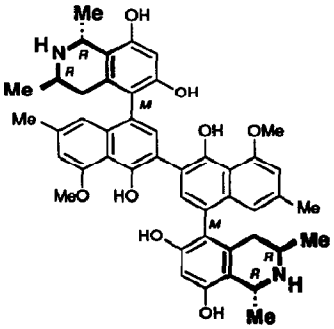
The lack of effective drugs for the treatment of AIDS led the United States National Cancer Institute to initiate in the late 1980's a major effort to discover novel anti-AIDS agents from natural sources.[2] One of the results of that program was the isolation and characterization of michellamines A and B (**1a** and **1b**), structurally unprecedented, highly polar, dimeric naphthylisoquinoline alkaloids from the rare tropical liana *Ancistrocladus korupensis*, which grows only in some parts of Cameroon.[3-5] In 1992, the National Cancer Institute encouraged the research community to pursue synthetic and/or other studies aimed at the production of michellamine B (**1b**).[6]



1a



1b



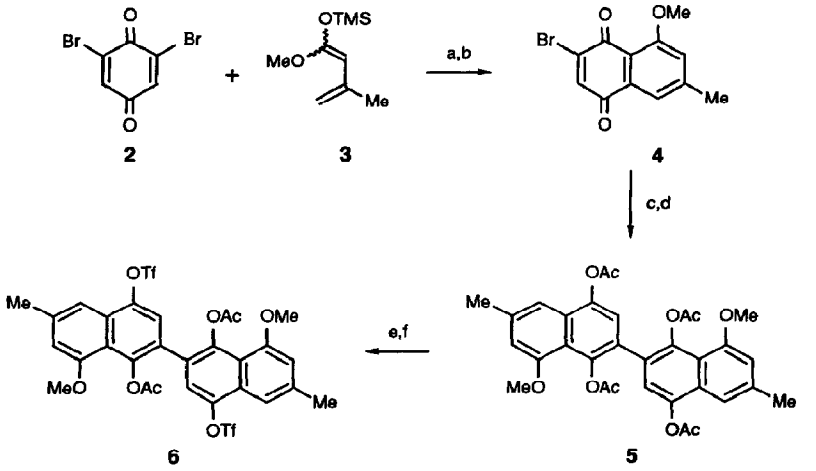
1c

Michellamines A and B both have identical, 1*R*,3*R*-configured tetrahydroisoquinoline parts, but differ with respect to the configurations at the biaryl axes.[4,7,8] Curiously, the third possible atropoisomer, michellamine C

(**1c**), does not appear to co-occur naturally, although equilibration of **1a** or **1b** produces a mixture of **1a** - **1c**.[4] Since the central axis is not configurationally stable, michellamines A - C constitute the complete series of atropodiastereomers with respect to the stereogenic axes between the isoquinoline and the naphthalene parts. Some of us have recently described a first total synthesis of michellamine A (**1a**) by oxidative coupling of the appropriately protected corresponding 'monomeric' naphthylisoquinoline alkaloid, named korupensamine A,[9] which itself had also been synthesized.[10] We now report the first non-biomimetic total synthesis of both michellamines A and B by a complementary stepwise construction of the biaryl axes, forming first the (configurationally unstable) central axis and then, simultaneously, the two (stereogenic) outer ones. Besides the convergent and regiospecific character of this route, it is also sufficiently flexible to be easily modified for the preparation of analogs.

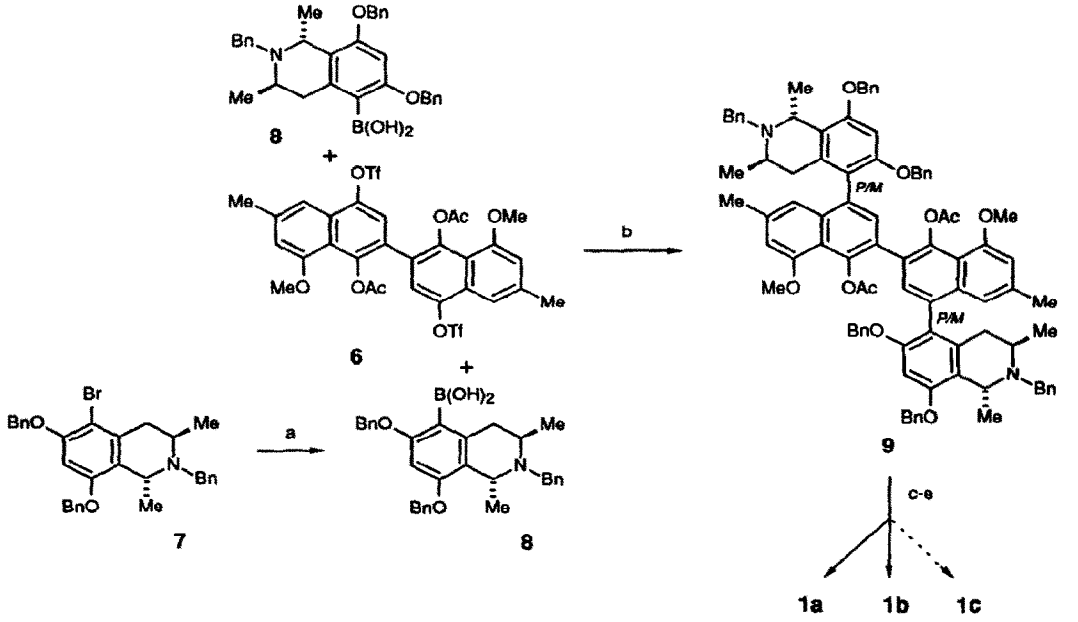
Given the constitutionally symmetric structure of the michellamines and our desire to synthesize all three, combined with the fact that the most promising stereoisomer, michellamine B (**1b**), is axially heterochiral, we chose as the key step of the synthesis the double intermolecular coupling of a central binaphthalene fragment with two equivalents of an appropriately protected, enantiomerically pure tetrahydroisoquinoline building block. For the required binaphthalene unit **6**, we envisaged acetate groups for the protection of the *O*-functionalities and triflate groups for the activation of the coupling positions.

The synthesis of **6** starts with the known[11,12] diene **3**, available in one step from methyl 3,3-dimethylacrylate by successive treatment with lithium diisopropylamide and trimethylsilyl chloride. The Diels-Alder reaction of **3** with 2,6-dibromobenzoquinone[13] (**2**) proceeded regiospecifically, as expected from the work of Brassard,[12] to give, after aromatization of the adduct, a hydroxynaphthoquinone, which was converted to its methyl ether **4**. This was then dimerized using copper bronze[14] and reductively acetylated[15] to afford tetraacetate **5**.[16] The two less-hindered acetate groups in **5** were selectively cleaved by treatment with diazabicycloundecene (DBU) in methanol[17] to generate a diol, which was converted to ditriflate **6**.[18]



Scheme 1. Preparation of the central binaphthalene unit **6**. Reaction conditions: a) 0 °C, THF, 2 h; stand on silica gel at rt 24 h, 70 %; b) MeI, Ag_2O, reflux 1 h, 97 %; c) DMF, copper bronze, $Pd(PPh_3)_4$, 1.5 h, 130 °C (convert crude directly to **5**); d) Zn, Ac_2O, NaOAc, DMAP, CH_2Cl_2, rt, 10 h, 43 % overall from **4**; e) CH_2Cl_2/MeOH, DBU, rt, 15 min, 70 %; f) CH_2Cl_2, 2,6-lutidine, Tf_2O, rt, 30 min, 79 %.

With the central biaryl axis established and the required coupling positions activated by *O*-triflate substituents, the construction of the outer biaryl axes could be approached. As a suitable building block for the heterocyclic tetrahydroisoquinoline system, we chose the correctly configured, enantiomerically pure boronic acid **8**,[18] with benzyl group protection for the *O*- and the *N*-functionalities. It was prepared from the known[10] corresponding bromo compound **7**, by lithiation and treatment with $B(OMe)_3$, followed by aqueous workup. Reaction of **6** and **8** in the presence of $Pd(PPh_3)_4$ and $Ba(OH)_2$, in DME/H_2O as a solvent,[19,20] gave the quateraryl **9**, with all the ring systems correctly linked to each other, as a mixture of atropodiastereomers. Removal of all *O*- and *N*-protecting groups finally gave a mixture of the atropodiastereomeric michellamines **1a** and **1b**, which was resolved as described previously.[3,4] The synthetic **1a** and **1b** were shown to be identical, by direct comparision, to authentic, naturally derived materials. By contrast, we were unable to detect any **1c** in the synthetic mixture even though we had a sample of **1c** as a TLC/HPLC standard. The question of why **1c** is so far not detectable as a natural or synthetic product is intriguing.



Scheme 2. Completion of the total synthesis. Reaction conditions: a) *n*-BuLi, THF, $B(OMe)_3$, -78°C to rt, aqueous workup, 89 %; b) $Pd(PPh_3)_4$, DME/H_2O, $Ba(OH)_2$, 80°C, 8 h, 74 %; c) H_2, EtOH, Pd/C (10 %), 3 d, 1 atm; d) MeOH/HCl, 85 % from **9**; e) atropoisomer separation as reported previously.[3,4]

In conclusion, this total synthesis of michellamines A and B is of importance not only for the preparation of the natural products themselves, but also as a vehicle for access to modified analogs for structure-activity investigations. This work is in progress.

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[18] Mp, $[\alpha]_D$ and ^1H NMR ($CDCl_3$) data for selected new compounds. **4**: mp 175-177°C, ^1H NMR δ 7.54 (s, 1 H), 7.41 (s, 1 H), 7.10 (s, 1 H), 4.01 (s, 3 H), 2.49 (s, 3 H); **5**: obtained as a gum, ^1H NMR δ 7.22 (s, 2 H), 7.12 (br, 2 H), 6.72 (s, 2 H), 3.89 (s, 6 H), 2.49 (s, 6 H), 2.43 (s, 6 H), 2.12 (br, 6 H); **6**: mp 190-191°C, ^1H NMR δ 7.47 (s, 2 H), 7.40 (br, 2 H), 6.82 (s, 2 H), 3.92 (s, 6 H), 2.55 (s, 6 H), 2.07 (s, br, 6 H); **8**: mp 106-108°C, $[\alpha]_D$ = + 49.3 (c= 1.5 in MeOH), ^1H NMR δ 7.31-7.19 (m, 15 H), 6.42 (s, 1 H), 5.92 (s, br, 2 H), 5.04 (s, 2 H), 5.02 (s, 2 H), 4.08 (q, J = 6.7 Hz, 1 H), 3.85 (d, J = 14.1 Hz, 1 H), 3.56-3.45 (m, 1 H), 3.33 (d, J = 14.1 Hz, 1 H), 3.13 (dd, J = 18.0, 4.6 Hz, 1 H), 2.79 (dd, J = 18.0, 11.3 Hz, 1 H), 1.35 (d, J = 6.7 Hz, 3 H), 1.30 (d, J = 6.6 Hz, 3 H).

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