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'Biomimetic' Oxidative Dimerization of Korupensamine A: Completion of the First Total Synthesis of Michellamines A, B, and C[1]

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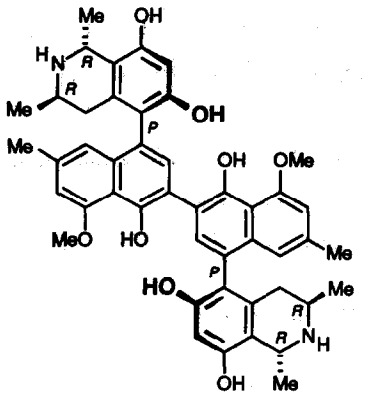
Abstract: A first synthetic access to michellamine A (1), a C_2-symmetric antiviral naturally occurring quateraryl, is described, by oxidative 'dimerization' of an appropriately protected 'monomeric' naphthylisoquinoline alkaloid, named korupensamine A (2). Due to the synthetic availability of 2 recently achieved and given the published interconversion of michellamines A - C, this coupling reaction simultaneously represents the completion of a first total synthesis of a representative and thus of all hitherto known michellamines.

INTRODUCTION

Michellamine A (1) is a representative of a new class of biologically important quateraryls with remarkable activity against human immunodeficiency viruses (HIV).[2,3] Structurally, it is characterized by the presence of no less than 6 free phenolic hydroxy groups and 2 secondary aminofunctions and, stereochemically, by the existence of 4 stereocenters and 3 axes, one of which is configuratively unstable, whereas the other 2 are stereogenic due to restricted rotation. Still, the molecule seems relatively simple, it is a C_2-symmetric 'dimer' consisting of 2 constitutionally and stereochemically identical halves, and both moieties of such 'monomeric' naphthylisoquinoline alkaloids are likely to be derived biogenetically from identical polyketide precursors,[4] as obvious from biomimetic cyclization reactions of ß-polycarbonyl compounds[5] and biosynthetic feeding experiments.[6] This suggests that also for a chemical synthesis, one might build up the michellamine framework biomimetically, *i.e.* by oxidative phenolic coupling[7] of the corresponding 'monomer' 2. This naphthylisoquinoline 2, named korupensamine A (2), has very recently become available as a natural product co-occurring with 1 in *Ancistrocladus korupensis*,[8] as well as by an efficient chemical total synthesis.[9] In this

paper, we report on a first directed synthesis of michellamine A (**1**) by an oxidative phenolic coupling of the appropriately protected derivative **3** of korupensamine A (**2**).



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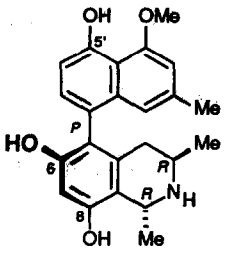

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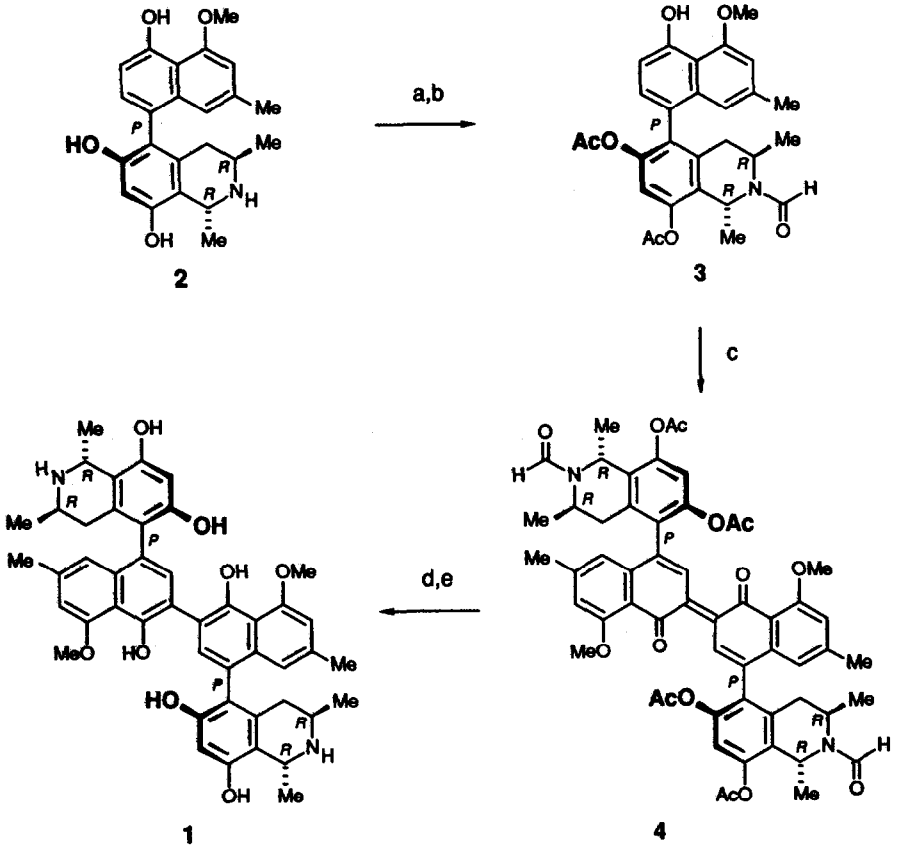
RESULTS AND DISCUSSION

From the structure of the given precursor **2**, with its phenolic oxygen functions and the secondary amino group, undesired by-products had to be expected for the oxidation step, besides the more difficult handling of such polar compounds. Consequently, it seemed plausible to guarantee selectivity for the coupling reaction already on the level of a specific protection of all these functionalities except 5'-OH,[10] *i.e.* the oxygen function next to the required coupling site. Thus, consecutive *N*-formylation with pivalic formic anhydride[11] and subsequent treatment with acetyl chloride clearly allowed to differentiate the 'free' hydroxy functions at C-6 and C-8 from the chelated one at C-5', specifically giving the partially protected monophenolic derivative **3** in most satisfactory yields (see Scheme 1). With this monomeric precursor **3** in hands, we could now start to investigate the crucial dimerization step, achieving optimum yields when using conditions elaborated by *Laatsch*[12] for the 'dimerization' of related naphthol precursors. Thus, treatment of **3** with Ag_2O in $CHCl_3$ in the presence of 0.2 % triethylamine led directly to the formation of the corresponding binaphthylidendione **4**,[13] without the necessity of stopping the reaction on the level of an intermediate binaphthol: The easy detection of the violet-colored diquinone **4** [UV/VIS λ_{max} (log ε) = 726 (5.15), 516 (5.22), 283 nm (5.48) in CH_2Cl_2] and its satisfying stability made this compound a convenient intermediate that could be fully characterized. Subsequent cautious reduction of **4** with sodium borohydride gave the corresponding substituted binaphthol, with the central biaryl axis now in the correct position and oxidation level. As expected, no complications by the formation of atropodiastereomeric products had to be taken into consideration, due to the

low isomerization barrier at this central axis. With the multifold derivatized michellamine A available, subsequent cleavage of all the 6 protective groups could be performed in a single step, by treatment with methanolic HCl.



Scheme 1. The oxidative 'dimerization' of korupensamine A (2) *via* its derivative 3. Reaction conditions: a) $(CH_3)_3CO_2CHO$, CH_2Cl_2, 20°C; b) CH_3COCl, Et_3N, cat. DMAP, CH_2Cl_2, 90 % from 2; c) Ag_2O, 0.2 % Et_3N in $CHCl_3$, 85 %; d) $NaBH_4$, *i*PrOH, 25 °C; e) MeOH/HCl, reflux, 67 % from 4.

The product 1 thus obtained was fully identical, according to its physical, spectroscopic and chromatographic data, with an authentic sample of michellamine A isolated from *A. korupensis*,[2,3] thus again confirming the absolute stereostructure of this natural product attributed by us earlier.[3]

CONCLUSIONS

This 'biomimetic dimerization' of korupensamine A (**2**) to give michellamine A (**1**) is of great importance for several reasons: It is a very rational first partial synthesis of a representative of this novel class of quateraryls from natural precursors. In addition, given the total synthesis of korupensamine A (**2**) recently achieved,[9] it is simultaneously the completion of the first total synthesis of a michellamine, and, moreover, given the reported[3,14] ready preparation of michellamines B and C from michellamine A (**1**), it is finally the first definitive total synthetic access to all of the currently known michellamines. Finally, the pathway described in this paper should easily be extended also to the preparation of related, natural or unnatural dimeric naphthylisoquinolines for biological evaluation. This work is in progress.

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, and a Bruker AC 250 spectrometer in $CDCl_3$. The chemicals shifts δ are given in parts per million (ppm) with the proton-signals of $CHCl_3$ in the deuterated solvent as internal reference for ^1H and ^{13}C NMR. The coupling constants, *J*, are given in Hertz. HPLC analysis: combination of a Waters 510 HPLC pump, a 6UK injector, and an amino-bonded phase column (Rainin Dynamax-60A). UV spectra were recorded on a Jobin Yvon Model CD6 spectrograph at room temperature within the range of 200 - 800 nm. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Mass spectra were determined with a Finnigan MAT 8200 mass spectrometer. IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer. The intensities of the vibrational absorptions are denoted by: s (strong), m (medium), w (weak) and br (broad).

6,8-Di-O-acetyl-N-formyl-korupensamine A (**3**): A mixture of 50.0 mg (132 µmol) korupensamine A (**2**), 26 µl (160 µmol) pivalic formic anhydride in 10 ml dry CH_2Cl_2 was stirred at 20°C for 2 h. Removal of the solvent in vacuum afforded a brown solid, which was dissolved in 10 ml dry CH_2Cl_2. After addition of 24 µl (330 µmol) acetyl chloride, 46 µl (330 µmol) Et_3N and a catalytic amount of DMAP, the reaction mixture was stirred for 5 h. After treatment with 5 ml 2 M aqueous NH_4Cl, the organic layer was filtered through deactivated (5 % NH_3) silica gel. Crystallization from CH_2Cl_2 / diethyl ether / petroleum ether afforded **3** (58.4 mg, 90%); mp 159 °C; $[\alpha]_D^{20} = +9.3°$ (*c* = 0.50 in $CHCl_3$); IR (KBr): ν 3363 (m), 2958 (w), 1755 (s), 1645 (s), 1605 (m), 1575 (m), 1425 (m), 1391 (m), 1359 (m), 1256 (m), 1204 (s), 1188 (s), 1167 (m), 1125 (m), 1080 (m), 1060 (m), 1046 (m), 1011 (m), 947 (w), 898 (w), 828 (w), 611 (w); ^1H NMR (main rotational isomer with respect to the *N*-formyl bond): δ = 1.06 (d, *J* = 8.4 Hz, 3 H), 1.43 (d, *J* = 8.4 Hz, 3 H), 1.71 (s, 3 H), 2.18 (dd, *J* = 7.1, 19.9 Hz, 1 H), 2.32 (s, 3 H), 2.39 (s, 3 H), 2.72 (dd, *J* = 5.6, 19.9 Hz, 1 H), 3.86 - 3.91 (m, 1 H), 4.08 (s, 3 H), 5.52

(q, J = 8.1 Hz, 1 H), 6.62 - 7.10 (m, 5 H), 8.22 (s, 1 H), 9.45 (s, 1 H); MS (70 eV): *m/z* (%) = 491 (40) [M^+], 476 (3) [M^+ - CH_3], 449 (18) [M^+ - C_2H_2O], 434 (35) [M^+ - C_3H_5O], 406 (14) [M^+ - $C_4H_5O_2$], 392 (100) [M^+ - $C_5H_7O_2$]; HR-MS (70 eV) *m/z* calcd. for $C_{28}H_{29}NO_7$: 491.194. Found: 491.194.

6,8,6‴,8‴-Tetra-O-acetyl-N,N'-diformyl-5',5"-di-O-dehydro-michellamine A (**4**): A solution of 40.1 mg (81.6 µmol) **3** in 50 ml dry $CHCl_3$ containing 0.2% NEt_3 was treated with 401 mg (1.73 mmol) Ag_2O. After 5 d stirring at 20°C, the solvent was removed and the residue purified by column chromatography on deactivated (5 % NH_3) silica gel with CH_2Cl_2 / methanol (95 : 5) as eluent. The crude product was crystallized from CH_2Cl_2 / petroleum ether, to give **4** (33.9 mg, 85%) as a deep-violet colored powder: mp dec. > 230 °C; $[\alpha]_D^{20}$ = + 31° (c = 0.0023 in $CHCl_3$); IR (KBr): ν 2970 (w), 1773 (s), 1654 (s, br), 1370 (m), 1198 (s); ^1H NMR (main rotational isomer): δ = 1.11 (d, J = 6.6 Hz, 6 H), 1.47 (d, J = 6.6 Hz, 6 H), 1.98 (s, 6 H), 2.25 (s, 6 H), 2.40 (s, 6 H), 2.54 (dd, J = 5.7, 16.2 Hz, 2 H), 3.16 (dd, J = 4.4, 16.2 Hz, 2 H), 3.87 - 4.07 (m, 2 H), 3.94 (s, 6 H), 5.55 (q, J = 6.3 Hz, 2 H), 6.18 (s, 2 H), 6.74 (s, 2 H), 7.06 (s, 2 H), 7.61 (s, 2 H), 8.27 (s, 2 H); MS (70 eV): *m/z* (%) = 980 (0.8) [M^+ + 2], 978 (0.3) [M^+], 938 (0.3) [M^+ + 2 - C_2H_2O], 896 (0.2) [M^+ + 2 - 2 C_2H_2O], 507 (5), 491 (4), 449 (6), 434 (7), 420 (4), 408 (9), 406 (7), 392 (21); Anal. calcd. for $C_{56}H_{54}N_2O_{14}$ (979.1): C, 68.70; H, 5.56; N, 2.86. Found: C, 68.16; H, 5.68; N, 2.88.

Michellamine A (**1**): A solution of 5.10 mg (5.20 µmol) **4** was treated with 1.00 mg (26.4 µmol) $NaBH_4$ in 1 ml dry *i*PrOH for 10 min at 20°C. The solvent was evaporated and the residue was dissolved in diethyl ether and extracted several times with water. The organic phases were dried over Na_2SO_4 and the solvent was evaporated in vacuum. A solution of the resulting oil in 2 ml dry methanol was treated with 1 ml portions of cold-saturated methanolic HCl over a period of 24 h while gently refluxing. After removal of the solvent, HPLC on a semipreparative amino-bonded phase column (Rainin Dynamax-60A) with CH_2Cl_2 / methanol / $(NH_4)_2CO_3$ (90 : 10 : 0.1) as eluent afforded **1** (2.64 mg, 67%), which is characterized as its diacetate salt: mp dec. > 220°C; (lit.:[14] 220°C); $[\alpha]_D^{20}$ = -10.6° (c = 0.13 in MeOH); [lit.:[2,14] -10.5° (c = 0.38 in MeOH)] spectroscopical and chromatographical data are fully identical with those obtained from authentic natural material.[2,3,14]

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