ters, GOF = 1.081, $R_1 = 0.0463$ [$I > 2\sigma(I)$], w$R_2 = 0.1350$, min./max. residual electron density -0.989/0.599 e Å^{-3}. Crystal structure determination of **3**+**4**: $C_9H_{12}FeN_2O_3$, $M_r = 252.05$ (**3**), $C_{16}H_{24}FeN_4O_4$, $M_r = 392.24$ (**4**); orange cocrystals of **3** and **4** (molar ratio 1/1: chromatographic work-up of the product mixture of the reaction of $[Fe_2(CO)_9]$ with $Me_2N{-}C{\equiv}C{-}NMe_2$ containing the complexes **2**, **3**, **4** and $[Fe_2(CO)_6(\mu\text{-}CNMe_2)_2]$ led to a fraction containing **3** and **4** from which the cocrystals were grown from a pentane solution upon cooling from 20 → −30 °C), triclinic, space group $P\bar{1}$, $a = 8.831(2)$, $b = 8.944(2)$, $c = 21.354(5)$ Å, $\alpha = 97.26(3)$, $\beta = 95.31(3)$, $\gamma = 113.20(3)°$, $V = 1519.0(7)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.409$ g cm^3, $T = 160(2)$ K, $2\theta_{max} = 52.48°$, $\mu = 1.005$ mm^{-1}, $F(000) = 672$, 13 771 reflections, 5573 unique reflections, 361 parameters, GOF = 1.008, $R_1 = 0.0461[I > 2\sigma(I)]$, $wR_2 = 0.1311$, min./max. residual electron density −0.504/0.524 e Å^{-3}. Crystal structure determination of **5**: $C_{14}H_{18}FeN_4O_4$, $M_r = 362.17$; violet crystals from pentane upon cooling from 20 → −78 °C, triclinic, space group $P\bar{1}$, $a = 8.6326(12)$, $b = 10.222(2)$, $c = 11.114(3)$ Å, $\alpha = 113.15(2)$, $\beta = 105.499(17)$, $\gamma = 99.58(3)°$, $V = 827.2(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.454$ g cm^{-3}, $T = 180(2)$ K, $2\theta_{max} = 53.9°$, $\mu = 0.936$ mm^{-1}, $F(000) = 376$, 5758 reflections, 3512 unique reflections, 209 parameters, GOF = 1.068, $R_1 = 0.0451[I > 2\sigma(I)]$, $wR_2 = 0.1324$, min./max. residual electron density −0.631/0.685 e Å^{-3}. Crystal structure determination of **6**: $C_{11}H_{13}F_3FeN_2O_7S$, $M_r = 430.14$; yellow crystals upon diffusion of diethyl ether in THF at 20 °C, triclinic, space group $P\bar{1}$, $a = 6.6594(17)$, $b = 10.490(3)$, $c = 12.988(4)$ Å, $\alpha = 102.87(4)$, $\beta = 100.02(3)$, $\gamma = 95.78(3)°$, $V = 861.8(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.658$ gcm^{-3}, $T = 180(2)$ K, $2\theta_{max} = 50.48°$, $\mu = 1.062$ mm^{-1}, $F(000) = 436$, 5674 reflections, 2892 unique reflections, 226 parameters, GOF = 1.109, $R_1 = 0.0776[I > 2\sigma(I)]$, $wR_2 = 0.2197$, min./max. residual electron density −0.725/1.778 e Å^{-3}. Instruments: STOE STADI-4 four-circle diffractometer with scintillation counter (**2** and **5**) and STOE-IPDS diffractometer with area detector (**3** and **6**) at $\lambda(Mo_{K\alpha}) = 0.71073$ Å. CCDC-181665 – 181668 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[13] Additional evidence for the Lewis acidic character of **2** is the formation of adducts with Lewis bases such as PMe_3. The resulting octahedral ferracyclobutenones *mer*/*fac*-$[Fe(CO)_3PMe_3(\eta^1{:}\eta^1\text{-}C(NMe_2)C(NMe_2)C(O))]$ are related to **1**: T. Rosenauer, A. C. Filippou, unpublished results.

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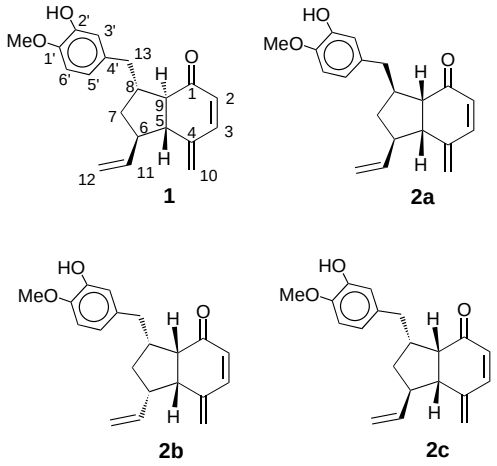
Total Synthesis of (±)-Otteliones A and B**

Goverdhan Mehta* and Kabirul Islam

The isolation of the two diastereomeric otteliones A and B from the widely occurring but little studied fresh water plant *Ottelia alismoides*, and the determination of their structures, which include a unique 4-methylenecyclohex-2-enone substructure, was reported in 1998.[1] Collaborative efforts between US and Egyptian scientists, who employed high-field NMR spectroscopy techniques and modeling studies, led to the stereostructure **1** for ottelione B. However, the



structure of ottelione A could not be assigned unambiguously, and both **2a** and **2b** were considered as likely formulations, the former being more likely.[1] In 2000, scientists at Rhône-Poulenc Rohrer reinterpreted[2] the NMR spectroscopic data and proposed an alternate stereostructure **2c** for ottelione A (RPR 112378). Otteliones have attracted much attention as they exhibit remarkable, broad-ranging biological activity.[1–4] Chinese scientists have reported the antitubercular effect of extracts of *Ottelia alismoid*es, which is rich in otteliones, and have shown in clinical trials that two cases of bilateral tuberculosis of the cervical lymph gland were cured in three months.[3] At the National Cancer Institute, in vitro screening against a panel of 60 human cancer cell lines showed that otteliones exhibited cytotoxicity at nM – pM levels.[1, 4] More recent results have shown that ottelione A is an efficient inhibitor of tubulin polymerization ($IC_{50} = 1.2$ μM) and is able to disassemble preformed microtubules in a manner reminiscent of the colchicines, vinblastine, and vincristine.[2] The cytotoxicity of otteliones can be attributed to the presence of

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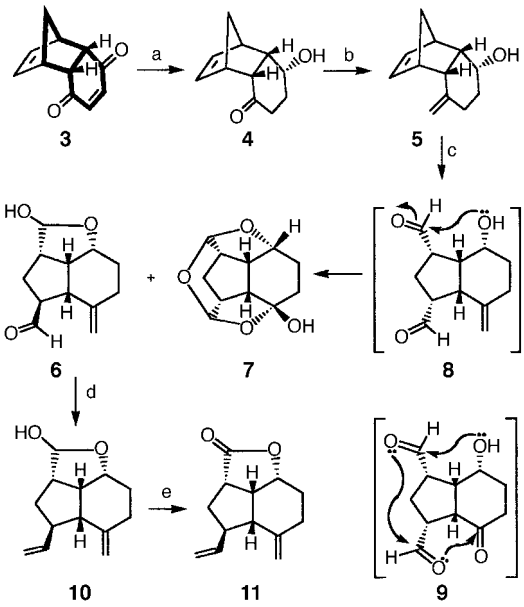
the unique electrophilic 4-methylenecyclohex-2-enone moiety that engages the sulfhydryl groups of the cysteine residues on the tubulin and disrupts the microtubule dynamics; this suggests a mechanism of action similar to that of T138067, a cytotoxic molecule with antitumor activity that reacts specifically with cysteine residue 239 in β-tubulin and is proposed to bind in the close vicinity of the colchicine-binding site.[2, 5–7] In view of the structural ambiguity and complexity, exceptional therapeutic potential, and the desirability to access analogues, otteliones have aroused considerable synthetic interest. The presence of four contiguous stereogenic centers, the *cis*-hydrindane moiety with side chains at C6 and C8, and the rare and sensitive 4-methylenecyclohex-2-enone functionality make otteliones challenging synthetic targets. We report herein the first total synthesis of racemic otteliones A and B through a short and flexible strategy that fully secures their structure and has potential for accessing diverse analogues.[8, 9]

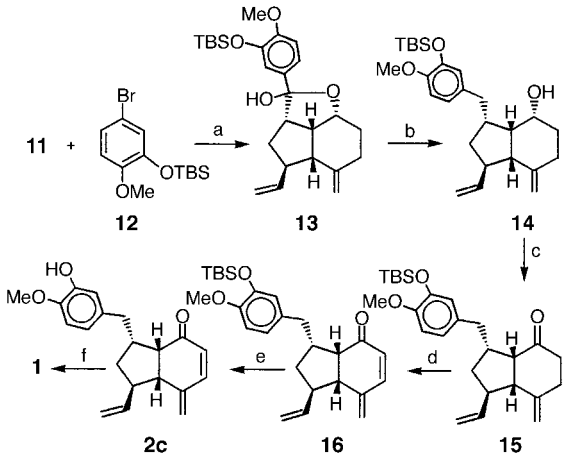
The key to our synthetic strategy towards otteliones **1** and **2** was the choice of the readily available Diels–Alder adduct **3** of cyclopentadiene and benzoquinone as the starting point (Scheme 1).[10] We recognized that **3** embodies a readily



Scheme 1. Reagents and conditions: a) $LiAlH_4$, Et_2O, 0 °C, 78 %; b) Zn–$TiCl_4$–CH_2Br_2, CH_2Cl_2, 0 °C, 71 %; c) 1) O_3, MeOH, −78 °C; 2) Me_2S, room temperature, 70 %; d) $Ph_3PCH_3{}^+I^-$, *n*BuLi, THF, 0 °C, 89 %; e) PCC, CH_2Cl_2, 0 °C, 91 %. PCC = pyridinium chlorochromate.

extractable *cis*-hydrindane framework (see bold lines in **3**) whose functionalities can be differentiated and elaborated in a regio- and stereoselective manner to the substitution and functionalization pattern of the natural products. Lithium aluminum hydride reduction of **3** led to both 1,4- and 1,2-reduction to furnish the tricyclic hydroxy ketone **4**.[11] Lombardo methylenation[12] of **4** smoothly delivered **5** and set the stage for unraveling the hydrindane moiety. Controlled ozonolysis of **5** delivered **6** and **7** (8:1).[11] The major product of the reaction, the lactol aldehyde **6** originated through the intramolecular capture of one of the aldehyde moieties of the intermediate dialdehyde **8** by the appropriately positioned α-hydroxy group and concomitant epimerization of the second aldehyde group to the thermodynamically more stable *exo* orientation. The minor product of the ozonolysis reaction, the dome-shaped pentacyclic ether **7**, was derived through a cascade intramolecular acetalization process in the intermediate keto dialdehyde **9**, which is formed through the oxidative cleavage of both olefinic bonds of **5** (Scheme 1). Wittig olefination of **6** installed the vinyl side chain of **10** with the correct stereochemistry. PCC oxidation of lactol **10** delivered the crystalline lactone **11** whose stereostructure corresponded to the revised[2] formulation **2c** of ottelione A and was fully secured through single-crystal X-ray structure determination.

We next focused on the introduction of the benzylic side chain at C8 by utilizing the lactone functionality of **11**. The organolithium reagent derived from **12** readily added to **11** to furnish **13**, which was further deoxygenated through lithium/ammonia reduction (Scheme 2). This protocol also released the hydroxy group at C1 to yield **14**. PCC oxidation of **14** to the cyclohexanone **15** was straightforward and set the stage for the generation of the crucial 4-methylenecyclohex-2-



Scheme 2. Reagents and conditions: a) *n*BuLi, THF, −78 °C → RT, 82 %; b) Li, liquid NH_3, THF, −33 °C, 63 %; c) PCC, CH_2Cl_2, 0 °C, 89 %; d) 1) LHMDS, PhSeCl, THF, −78 °C; 2) H_2O_2 (30 %), CH_2Cl_2, 0 °C, 61 % over two steps; e) TBAF, THF, 0 °C, 68 %; f) DBU, benzene, 65 °C, 83 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LHMDS = lithium 1,1,1,3,3,3-hexamethyldisilazane, TBAF = tetrabutylammonium fluoride.

enone moiety, which was produced through the phenylselenation–selenoxide elimination sequence to give **16** (Scheme 2). Finally, fluoride-mediated cleavage of the TBS protecting group in **16** furnished ottelione A (**2c**), whose spectra are identical to those of the natural product.[1, 2] Synthetic **2c** smoothly underwent epimerization at C9 on exposure to base (DBU) to give ottelione B (**1**), whose spectra match those of the natural product (Scheme 2).

To summarize, we have delineated an 11-step, regio- and stereocontrolled synthesis of the biologically potent natural products otteliones A and B from commercially available starting materials in 5.4 % overall yield, and have thus fully secured their structures. Our approach is concise and flexible,

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amenable to scale-up, geared to provide access to analogues, and involves only one protecting-group manipulation. [13]

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[8] Our synthetic efforts towards the otteliones began towards the end of 1998, and were initially targeted towards **2a**,[9a] the then favored structure[1] of ottelione A, and subsequently towards the other possible formulation **2b**.[9b] In January 2001, we became aware[2] of the alternate formulation **2c**, and efforts were directed towards this target. We have completed the total synthesis of **2a**–**c** and several other diastereomers of otteliones A and B. Spectral data of **2a**,**b** did not match those of the natural product ottelione A (K. Islam, unpublished results).

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[11] All new compounds reported herein are racemic and fully characterized on the basis of IR and ^{1}H and ^{13}C NMR spectroscopic data, mass spectrometry, and elemental analyses (see Supporting Information).

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[13] Although the plant O*ttelia alismoides* is regarded as a weed and is widely distributed along irrigation canal linings and rice fields in the Afro-Asian region, otteliones A and B are present only at ppm levels; thus synthetic access through practical routes is necessary to evaluate their biological potential.

$[\varepsilon\text{-}PMo_{12}O_{36}(OH)_4\{La(H_2O)_4\}_4]^{5+}$: The First $\varepsilon\text{-}PMo_{12}O_{40}$ Keggin Ion and Its Association with the Two-Electron-Reduced $\alpha\text{-}PMo_{12}O_{40}$ Isomer

Pierre Mialane, Anne Dolbecq, Laurent Lisnard, Alain Mallard, Jérôme Marrot, and Francis Sécheresse*

Dedicated to Professor Dr. Gilbert Hervé

Polyoxometalates, often considered as soluble metal oxides, have long attracted interest because of their large field of applications, especially in the domain of heterogeneous catalysis.[1] The famous Keggin ion $[\alpha\text{-}PMo_{12}O_{40}]^{3-}$ was isolated nearly 200 years ago. Isomerization formally results from successive 60° rotations of the four basic Mo_3O_{13} groups. Although the five isomers α, β, γ, δ, and ε of the Keggin structure have been postulated, only the α[2] and β[3] isomers of $PMo_{12}O_{40}$ have been structurally characterized to date. However, the ε-Keggin structure has been encountered in related compounds which are either polyoxocations, with an Al^{III}_{12} core and a central tetrahedral Al^{III},[4] Ga^{III}, or Ge^{III}[5] center, or polyoxoions with Mo^{V}_{12} and V^{V}_{12} cores. In the case of Mo and V derivatives,[6] the highly negatively charged structure is stabilized by electrophilic capping groups. The $Mo^{V}_{12}O_{40}$ skeleton has been crystallographically characterized in four polyoxometalates: the $[(C_5Me_5Rh^{III})_8(Mo^{V}_{12}O_{36})(Mo^{VI}O_4)]^{2+}$ complex[7] has a central $Mo^{VI}O_4^{2-}$ tetrahedron and eight Rh^{III} capping centers, the $[NaMo_{16}(OH)_{12}O_{40}]^{7-}$[8, 9] and $[H_2Mo_{16}(OH)_{12}O_{40}]^{6-}$[8] polyoxometalates are stabilized by four capping $Mo^{VI}O_3$ units and have a central cavity encapsulating a sodium cation and two protons, respectively. Finally, the most recent example is the $[Mo_{12}O_{30}(OH)_{10}H_2\{Ni(H_2O)_3\}_4]$ cluster[10] with two central protons and four Ni^{II} capping centers. These compounds highlight the capacity of the ε-$\{Mo_{12}O_{40}\}$ core to encapsulate various guests. We report here the synthesis and characterization of the first ε-Keggin cation with a central phosphorous atom, stabilized by four $\{La(H_2O)_4\}^{3+}$ capping groups. This cation was isolated in the three different salts **1**, **2** and **3**:

$[\varepsilon\text{-}PMo_{12}O_{36}(OH)_4\{La(H_2O)_4\}_4]Br_5\cdot 16H_2O$ **1**

$[\varepsilon\text{-}PMo_{12}O_{36}(OH)_4\{La(H_2O)_{2.5}Cl_{1.25}\}_4]\cdot 27H_2O$ **2**

$K_3[\varepsilon\text{-}PMo_{12}O_{36}(OH)_4\{La(H_2O)_{4.25}Cl_{0.75}\}_4][\alpha\text{-}PMo_{12}O_{40}]\cdot 28H_2O$ **3**

Compound **1** is the bromide salt of the $[\varepsilon\text{-}PMo_{12}O_{36}(OH)_4\{La(H_2O)_4\}_4]^{5+}$ polyoxocation. Compounds **2** and **3** have chloride ions directly bound to the capping La^{3+} centers; **2** is a neutral compound while **3** has an $[\alpha\text{-}PMo_{12}O_{40}]^{5-}$ ion as the counterion.

Compounds **1** and **2** were characterized by ^{31}P NMR, IR, and UV/Vis spectroscopy, elemental analysis, potentiometric

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