tors, $GOF = 1.081$, $R_1 = 0.0463 \ [I > 2\sigma(I)]$, $wR_2 = 0.1350$, min./max. residual electron density $-0.989/0.599 \ \text{e} \ \text{Å}^{-3}$. Crystal structure determination of $3\sim4$: $C_7H_8Fe(NO)O_2$, $M = 252.05 \ (3)$, $C_9H_9Fe(NO)O_2$, $M = 392.24 \ (4)$; orange crystals of $3$ and $4$ (molar ratio 1:1; chromatographic work-up of the product mixture of the reaction of [Fe( CO)]$_2$ with $\text{Me}_3N\overset{\text{C}}{\text{C}}\text{NMe}_2$ containing the complexes $2$, $3$, $4$ and [Fe( CO)]$_2(\mu$-$\text{CNMe}_3)$) led to a fraction containing $3$ and $4$ from which the coocrystals were grown from a pentane solution upon cooling from $20 \sim -30^\circ C$. Triclinic, space group $P\bar{1}$, $a = 8.831(2), b = 8.944(2), c = 21.354(5) \ \text{Å}, \ \alpha = 97.26(3), \ \beta = 95.31(3), \ \gamma = 113.20(3) \ \text{°}$, $V = 1519.0(7) \ \text{Å}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.409 \ \text{g} \ \text{cm}^{-3}$, $T = 160(2) \ \text{K}$, $2\theta_{\text{max}} = 52.48^\circ$, $\mu = 1.005 \ \text{mm}^{-1}$, $F(000) = 672$, $13771$ 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 $-0.504/0.524 \ \text{e} \ \text{Å}^{-3}$. Crystal structure determination of $5$: $C_9H_9Fe(NO)O_2$, $M = 362.17$; violet crystals from pentane upon cooling from $20 \sim -78^\circ C$. Triclinic, space group $P\bar{1}$, $a = 8.6326(12), b = 10.222(2), c = 11.114(3) \ \text{Å}, \ \alpha = 113.15(2), \ \beta = 105.499(17), \ \gamma = 99.58(3) \ \text{°}$, $V = 8272.2(3) \ \text{Å}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.454 \ \text{g} \ \text{cm}^{-3}$, $T = 180(2) \ \text{K}$, $2\theta_{\text{max}} = 53.9^\circ$, $\mu = 0.936 \ \text{mm}^{-1}$, $F(000) = 376$, $5758$ 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 $-0.631/0.685 \ \text{e} \ \text{Å}^{-3}$. Crystal structure determination of $6$: $C_9H_9F_4Fe(NO)O_2S$, $M = 430.14$; yellow crystals upon diffusion of diethyl ether in THF at $20^\circ C$. Triclinic, space group $P\bar{1}$, $a = 6.6594(17), b = 10.490(3), c = 12.9884(4) \ \text{Å}, \ \alpha = 102.87(4), \ \beta = 100.02(3), \ \gamma = 95.78(3) \ \text{°}$, $V = 861.84(4) \ \text{Å}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.638 \ \text{g} \ \text{cm}^{-3}$, $T = 180(2) \ \text{K}$, $2\theta_{\text{max}} = 50.48^\circ$, $\mu = 1.062 \ \text{mm}^{-1}$, $F(000) = 436$, $5674$ reflections, $2892$ unique reflections, $226$ parameters, $GOF = 1.095$, $R_1 = 0.0776[I > 2\sigma(I)]$, $wR_2 = 0.2197$, min./max. residual electron density $-0.725/0.778 \ \text{e} \ \text{Å}^{-3}$. Instruments: STOE STADI-4 four-circle diffractometer with scintillation counter ($2$ and $5$) and STOE-IPDS diffractometer with area detector ($3$ and $6$) at $l(MoK\alpha) = 0.71073 \ \text{Å}$. CCDCC-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 CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).


[13] Additional evidence for the Lewis acidic character of 2 is the formation of adducts with Lewis bases such as PMe$_5$. The resulting octahedral ferracyclobutenones mer/[Fe(CO)$_2$]PMe$_5$(η$^2$-C(NMe$_2$)$_2$(OC)C) are isolated to 1: T. Rosenauer, A. C. Filippou, unpublished results.


**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-ene 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 stereostereo 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 Rorer 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 alismoides*, 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.[5] The cytotoxicity of otteliones can be attributed to the presence of...
the unique electrophilic 4-methylene cyclohex-2-ene moiety that engages the sulphydryl 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.[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-hydridane moiety with side chains at C6 and C8, and the rare and sensitive 4-methylene cyclohex-2-ene 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 extractable cis-hydridane 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 hydridane moiety. Controlled ozonolysis of 5 delivered 6 and 7 (8:1).[13] 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 stereochemistry corresponded to the revised[2] formulation 2c of ottelone A and was fully secured through single-crystal X-ray structure determination.

We next focused on the introduction of the benzyl 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-methylene cyclohex-2-

![Scheme 1](image1)

![Scheme 2](image2)

Scheme 1. Reagents and conditions: a) LiAlH₄, Et₂O, 0 °C, 78%; b) Zn – TiCl₄ – CH₂Br₂, CH₂Cl₂, 0 °C, 71%; c) 1) O₃, MeOH, −78 °C; 2) MeS, room temperature, 70%; d) Ph₂PCH₂Br, nBuLi, THF, 0 °C, 89%; e) PCC, CH₂Cl₂, 0 °C, 91%. PCC = pyridinium chlorochromate.

Scheme 2. Reagents and conditions: a) nBuLi, THF, −78 °C → RT, 82%; b) Li, liquid NH₃, THF, −33 °C, 63%; c) PCC, CH₃Cl, 0 °C, 89%; d) 1) LHMDS, PhSeCl, THF, −78 °C; 2) H₂O₂ (30%), CH₂Cl₂, 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 1,1,3,3,3-hexamethyldisilazane, TBAF = tetrabutylammonium fluoride.
Although the plant O. 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. [13]


[5] The 4-methylencyclohex-2-enone moiety has been rarely reported, and therefore the interaction of this electrocrophile with biological systems has remained unexplored.


[8] Our synthetic efforts towards the otteliones began towards the end of 1998, and were initially targeted towards 2a. In January 2001, we became aware of the alternate formulation 2b. In January 2001, we became aware of the alternate formulation 2c, and efforts were directed towards this target. We have completed the total synthesis of 2a, b 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).


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


[13] Although the plant Ottelia 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.

Polynoxometalates, often considered as soluble metal oxides, have long attracted interest because of their large field of applications, especially in the domain of heterogeneous catalysis. The famous Keggin ion [α-PMo12O40]3− was isolated nearly 200 years ago. Isomerization formally results from successive 60° rotations of the four basic MoO3 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 PMo12O40 have been structurally characterized to date. However, the ε-Keggin structure has been encountered in related compounds which are either polyoxometalates, with an AlII core and a central tetrahedral AlIII, or GaIII, or Ge[VI] center, or polyoxoanions with MoV and V[IV] cores. In the case of MoV and V derivatives[4] the highly negatively charged structure is stabilized by electrophilic capping groups. The MoII12−O40 skeleton has been crystallographically characterized in four polyoxometalates: the [(C6H5)4RhIII]2(−PMo12O36(OH)4{La(H2O)4.25Cl0.75}4][H2Mo16(OH)12O40] complex[7] has a central MoVI2− tetrahedron and eight RhIII capping centers, the [NaMo12(OH)12O40]3−[8, 9] and [H2Mo16(OH)12O40]6−[8, 9] polyoxometalates are stabilized by four capping MoVO4 units and have a central cavity encapsulating a sodium cation and two protons, respectively. Finally, the most recent example is the [Mo12O36(OH)3H2[Ni(H2O)5]6]4+ cluster[10] with two central protons and four NiIII capping centers. These compounds highlight the capacity of the ε-[Mo12O36] 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(H2O)12]6−capping groups. This cation was isolated in the three different salts 1, 2, and 3:

[ε-PMo12O36(OH)4{La(H2O)4}4]15−: The First ε-PMo12O40 Keggin Ion and Its Association with the Two-Electron-Reduced α-PMo12O40 Isomer

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Dedicated to Professor Dr. Gilbert Herve

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