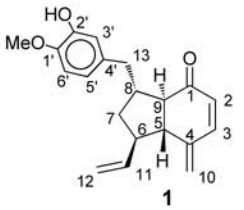
Total Synthesis of (±)-Otteliones A and B**

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



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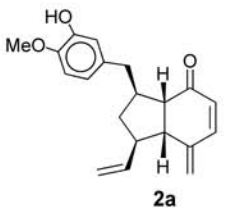
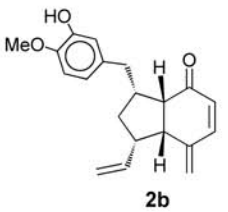
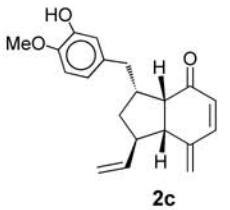


2a



2b



2c

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

[*] Prof. G. Mehta, K. Islam
Department of Organic Chemistry, Indian Institute of Science
Bangalore-560012 (India)
Fax: (+91) 80-360-0936
E-mail: gm@orgchem.iisc.ernet.in

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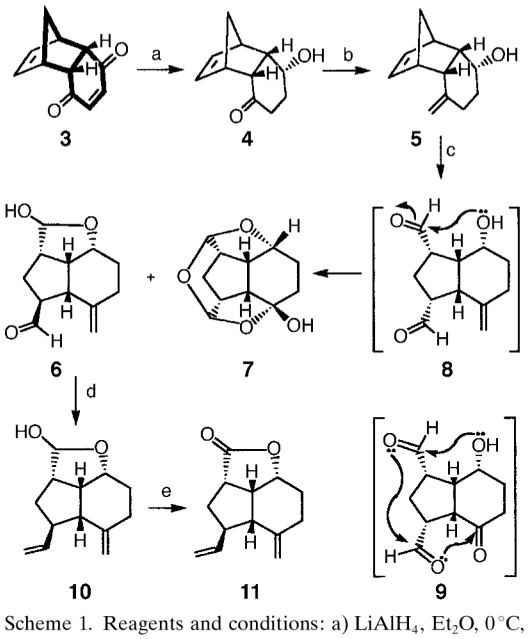
the unique electrophilic 4-methylenecyclohex-2-enone moiety that engages the sulfhydryl groups of the cysteine residues on the tubulin and disrupts the microtubule dynamics; this suggests a mechanism of action similar to that of T138067, a cytotoxic molecule with antitumor activity that reacts specifically 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]

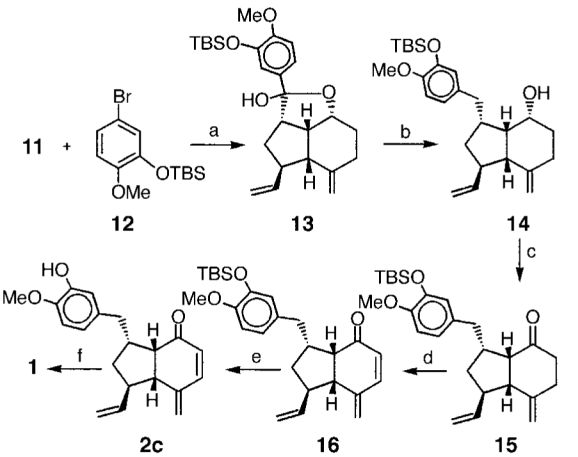
The key to our synthetic strategy towards otteliones **1** and **2** was the choice of the readily available Diels–Alder adduct **3** of cyclopentadiene and benzoquinone as the starting point (Scheme 1).[10] We recognized that **3** embodies a readily



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-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).



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.

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,

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

[1] S. E. N. Ayyad, A. S. Judd, W. T. Shier, T. R. Hoye, *J. Org. Chem.* **1998**, *63*, 8102.

[2] C. Combeau, J. Provost, F. Lanceli, Y. Tournoux, F. Prod'homme, F. Herman, F. Lavelle, J. Leboul, M. Vuilhorgne, *Mol. Pharm*. **2000**, *57*, 553.

[3] H. Li, H. Li, X. Qu, Y. Shi, L. Guo, Z. Yuan, *Zhongguo Zhongyao Zazhi (Chin. J. Chin. Mater. Med.)* **1995**, *20*, 115, 128.

[4] J. Leboul, J. Prevost, French Patent WO96/00205, **1996** [*Chem. Abstr.* **1996**, *124*, 242296].

[5] The 4-methylenecyclohex-2-enone moiety has been rarely reported,[6] and therefore the interaction of this electrophilic chromophore with biological systems has remained unexplored.

[6] a) D. F. Murray, M. W. Baum, M. Jones, *J. Org. Chem*. **1986**, *51*, 1; b) M. E. Jung, H. L. Rayle, *Synth. Commun*. **1994**, *24*, 197; c) H. Wild, *J. Org. Chem*. **1994**, *59*, 2748.

[7] For the details of the interaction of tubulin with drugs and alkylating agents, see: a) R. Kuriyama, H. Sakai, *J. Biochem. (Tokyo)* **1974**, *76*, 651; b) R. F. Luduena, M. C. Roach, *Biochemistry* **1981**, *20*, 4444; c) B. Shan, J. C. Medina, E. Shanta, W. P. Franckmoelle, T. C. Chau, R. M. Learned, M. R. Narbut, D. Stott, P. Wu, J. C. Jean, T. Rosen, P. B. Timmermans, H. Beckmann, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 5686.

[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).

[9] a) G. Mehta, D. S. Reddy, *Chem. Commun*. **1999**, 2193; b) G. Mehta, K. Islam, *Synlett* **2000**, 1473; for other approaches to the otteliones, see: L. Trembleau, L. Patiny, L. Ghosez, *Tetrahedron Lett.* **2000**, *41*, 6377.

[10] a) O. Diels, J. M. Blom, W. Koll, *Justus Liebigs Ann. Chem.* **1925**, *443*, 247; b) R. C. Cookson, E. Crundwell, R. R. Hill, J. Hudec, *J. Chem. Soc*. **1964**, 3062.

[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).

[12] L. Lombardo, *Tetrahedron Lett.* **1982**, *23*, 4293.

[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.