ORGANIC LETTERS

2010
Vol. 12, No. 7
1377−1379

Enantioselective Total Synthesis of Otteliones A and B

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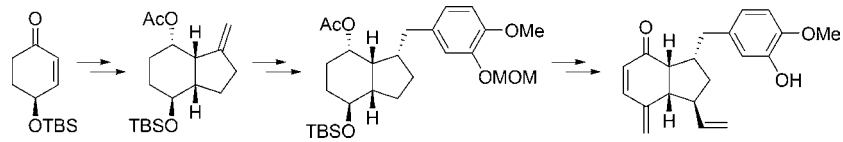
Received December 2, 2009

ABSTRACT



Enantioselective total synthesis of otteliones A and B was accomplished. The key steps are radical cyclization of an alpha-iodoketone to construct the *cis*-hydrindanone skeleton and Suzuki−Miyaura coupling to incorporate the aromatic group. (+)-Ottelione A was converted to (−)-ottelione B on treatment with NaOH in THF.

Ayyad and Hoye et al. isolated otteliones A (**1**) and B (**2**) from the freshwater plant *Ottelia alismoides* collected in the Nile Delta (Figure 1).[1] These natural products exhibit remarkable biological activities, including antitumor and antitubercular activities.[1,2] Upon screening against a panel of 60 human tumor cell lines at the National Cancer Institute in Bethesda, MD,[1] these compounds were found to inhibit tubulin polymerization into microtubules similarly to the well-known alkaloids colchicine, vincristine, and vinblastine.[3] Scientists from Rhone-Poulenc Rorer (now Sanofi-Aventis) independently isolated compound RPR112378, which was identical to ottelione A (**1**). They determined the relative stereochemistry with extensive NMR experiments and also investigated their biological activities.[3] Because of the powerful anticancer activities and scarcity of these natural products, otteliones A (**1**) and B (**2**) have attracted much attention from the synthetic community.

Mehta and co-workers reported the first total synthesis of racemic otteliones A (**1**) and B (**2**) and confirmed the relative stereochemistry of their structures.[4a] They subsequently achieved an enantioselective total synthesis and determined the absolute configurations of **1** and **2**.[4b] Katoh et al.

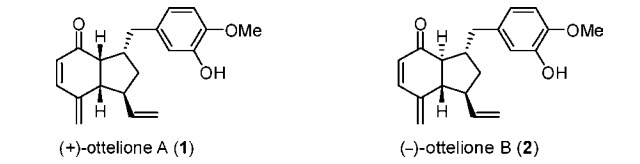


Figure 1. Structures of otteliones A and B.

independently achieved an enantioselective total syntheses of otteliones A (**1**) and B (**2**) and confirmed their absolute configuration.[5] Clive and co-workers reported an elegant synthesis of (+)-ottelione A (**1**) and (−)-ottelione B (**2**) utilizing a ring-closing metathesis to construct the hydrindane skeleton.[6] A formal total synthesis of ottelione A (**1**) was also described using an asymmetric Diels−Alder reaction

(1) Ayyad, S.-E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102.

(2) (a) Li, H.; Qu, X.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi (Chin. J. Chin. Mater. Med.)* **1995**, *20*, 128. (b) Leboul, J.; Provost, J. French Patent WO96/00205 1996. *Chem. Abstr.* **1996**, *124*, 242296.

(3) Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharmacol.* **2000**, *57*, 553.

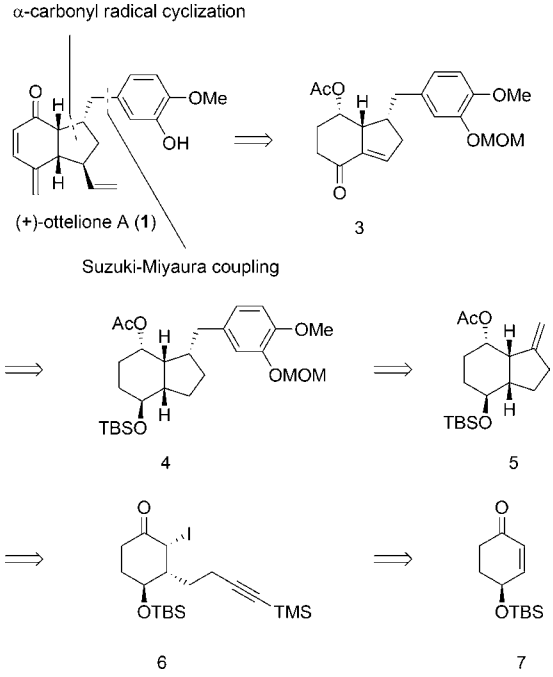
(4) (a) Mehta, G.; Islam, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2396. (b) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 6733.

(5) (a) Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903. (b) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem.—Eur. J.* **2007**, *13*, 9866.

10.1021/ol902776d
Published on Web 03/11/2010

by Ryu et al.[7] We found that only two distinct approaches, the Diels−Alder reaction and the ring-closing metathesis, were employed in these total syntheses.

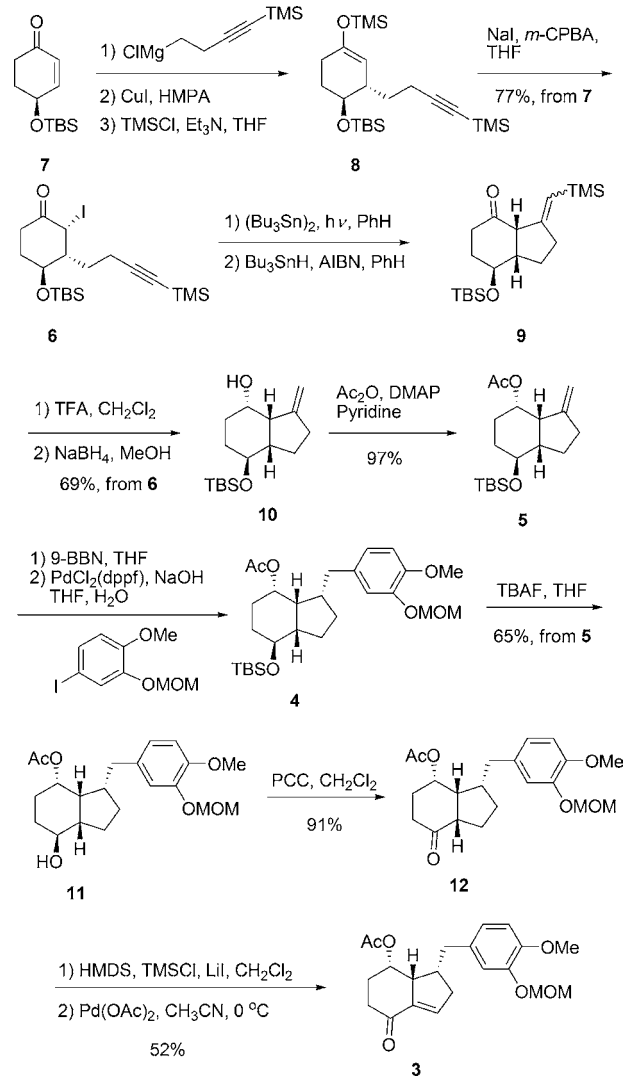
Scheme 1. Retrosynthetic Analysis of (+)-Ottelione A



In our laboratory, we envisaged that a radical cyclization of an α-iodocycloalkanone[8] might serve as a key step to construct the hydridanone skeleton with the desired stereochemistry. The retrosynthetic analysis is shown in Scheme 1. Conjugated addition of a vinyl group to compound **3** followed by Wittig reaction and introduction of the enone moiety would provide (+)-ottelione A (**1**). Compound **3** could be prepared from **4** via deprotection and oxidation steps. Compound **4** would be obtained from **5** via hydroboration and Suzuki−Miyaura coupling. Key intermediate **5** could be synthesized via radical cyclization of α-iodoketone **6** followed by hydrodesilylation, reduction of the carbonyl group, and protection of the resulting OH group. α-Iodoketone **6** would be prepared according to our method from chiral enone **7**.[9]

Our synthesis, shown in Scheme 2, began with optically active (−)-4-*tert*-butyldimethylsilyloxy-2-cyclohexen-1-one (**7**) prepared from commercially available (−)-quinic acid according to Danishefsky's procedure.[9] Treatment of enone **7** with 4-(trimethylsilyl)-3-butynylmagnesium chloride in the presence of CuI, followed by trapping the enolate with chlorotrimethylsilane, furnished trimethylsilylenol ether **8**. Without purification, crude compound **8** was treated with a solution of NaI/*m*-CPBA in THF to give α-iodoketone **6** as a single stereoisomer.[10] Stereochemistry of **6** was determinated by single crystal X-ray analysis.[11]

Scheme 2. Total Synthesis of Otteliones A and B



Photolysis of α-iodoketone **6** with a sunlamp in the presence of hexamethylditin,[8] followed by reduction with tributyltin hydride, gave compound **9**. Hydrodesilylation of compound **9** with trifluoroacetic acid followed by reduction with sodium borohydride cleanly afforded alcohol **10** as a single diastereomer. Alcohol **10** was treated with acetic

(6) (a) Clive, D. L. J.; Liu, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 3738. (b) Clive, D. L. J.; Liu, D. *J. Org. Chem.* **2008**, *73*, 3078.

(7) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. H.; Hwang, G.-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965.

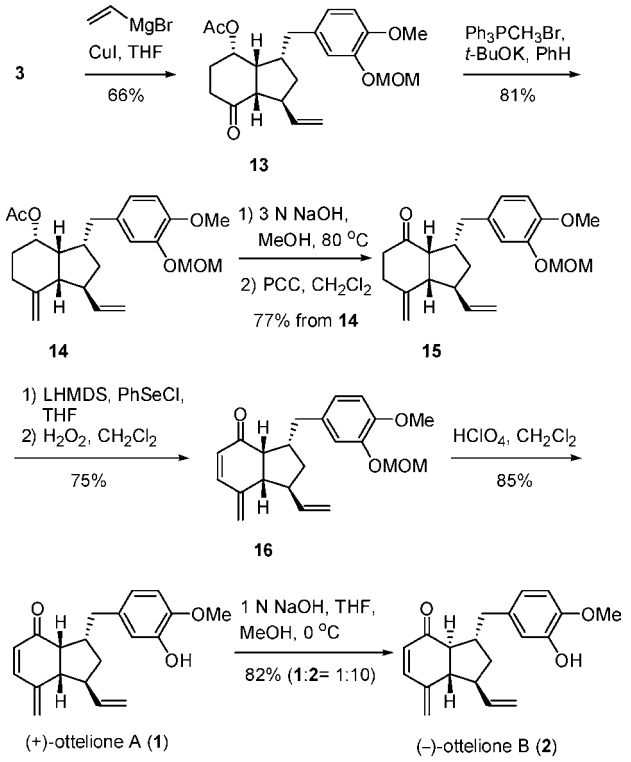
(8) (a) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130. (b) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1988**, *63*, 2699. (c) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875. (d) Sha, C.-K.; Ho, W.-Y. *Chem. Commun.* **1998**, *24*, 2709. (e) Sha, C.-K.; Liao, H.-W.; Cheng, P.-C.; Yen, S.-C. *J. Org. Chem.* **2003**, *68*, 8704. (f) Jiang, C.-H.; Bhattacharyya, A.; Sha, C.-K. *Org. Lett.* **2007**, *9*, 3241. (g) Liu, K.-M.; Chau, C.-M.; Sha, C.-K. *Chem. Commun.* **2008**, *1*, 91. (h) Kuo, Y.-L.; Dhanasekaran, M.; Sha, C.-K. *J. Org. Chem.* **2009**, *74*, 2033.

(9) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.

(10) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919.

(11) The molecular drawings and X-ray data of **6** are presented in the Supporting Information.

Scheme 3



anhydride in the presence of pyridine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to afford compound **5**. Hydroboration of the exocyclic double bond of **5** with 9-BBN,[12] followed by Suzuki−Miyaura coupling with 4-iodo-1-methoxy-2-(methoxymethoxy)benzene,[13] gave compound **4**. Treatment of **4** with tetrabutylammonium fluoride (TBAF) afforded alcohol **11**. Oxidation of **11** with PCC gave ketone **12.** Reaction of **12** with a mixture of 1,1,1,3,3,3-hexamethyldisilazane (HMDS), TMSCl, and LiI generated the corresponding trimethylsilylenol ether. Saegusa oxidation of the trimethylsilylenol ether intermediate with $Pd(OAc)_2$ gave compound **3**.[13]

Conjugate addition of vinylmagnesium bromide to compound **3** afforded compound **13**. Wittig reaction of **13** with methyltriphenylphosphonium bromide and *t*-BuOK gave compound **14**. Deprotection of **14** followed by PCC oxidation afforded compound **15**. Treatment of **15** with LHMDS and PhSeCl followed by oxidative elimination delivered compound **16**. Removal of the MOM protecting group eventually gave (+)-ottelione A (**1**), $[\alpha]_D^{25}$ +18.9 (*c* 0.60, $CHCl_3$).

Furthermore, we found that treatment of ottelione A (**1**) with NaOH in THF at 0 °C afforded (+)-ottelione A (**1**) and (−)-ottelione B (**2**) in a 1:10 mixture with 82% yield.[15] Ottelione B (**2**) was isolated by silica gel column chromatography and recrystallized $[\alpha]_D^{25}$ −327.3 (*c* 0.55, $CHCl_3$). The structure of ottelione B was confirmed by single-crystal X-ray analysis.[16] This method of epimerization of **1** to **2** is more effective than the DBU[4b] or the *t*-BuOK[5a] method.

In conclusion, we achieved enantioselective total syntheses of otteliones A and B in 3.8% and 2.8% overall yields. Using the α-carbonyl radical cyclization and the Suzuki−Miyaura coupling as the key steps, our total synthesis provides a new access to this important class of anticancer natural products. Our synthetic scheme is adaptable to prepare analogues of otteliones. The synthesis of such analogues according to our strategy for anticancer study is under current investigation.

Acknowledgment. We thank the National Science Council of the Republic of China (Taiwan) for financial support.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902776D

(12) (a) Suzuki, A.; Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Danishefsky, S. J.; Chemler, S. R.; Trauner, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(13) Feldman, K. S. *J. Org. Chem.* **1997**, *62*, 4983.

(14) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(15) The ratio of the mixture was determined with a HPLC column (DAICEL CHIRALPAK AD-H); see ref 5a.

(16) The molecular drawings and X-ray data of **2** are presented in the Supporting Information.