

A Tandem Enyne/Ring Closing Metathesis Approach to 4-Methylene-2-cyclohexenols: An Efficient Entry to Otteliones and Loloanolides

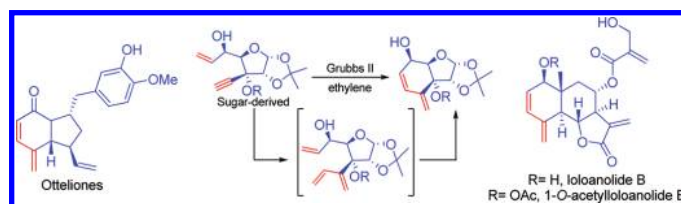
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ABSTRACT



A short and efficient approach to a 4-methylene-2-cyclohexenone substructure present in otteliones and loloanolides is described. This strategy involves a tandem enyne/ring closing metathesis as the key reaction to construct this labile core unit.

4-Methylene-2-cyclohexenone **1a** and 4-methylene-2-cyclohexenol **1b** are unique substructures present in a few biologically important natural products such as otteliones A (**2**) and B (**3**), loloanolides B (**4**), and 1-*O*-acetylloanolide B (**5**) (Figure 1). Otteliones isolated from the freshwater plant *Ottelia alismoides* collected in the Nile Delta^{1,2} show an impressive biological activity profile, such as antitubercular activity and cytotoxicity at nM–pM levels against a panel of 60 human cancer cell lines. Loloanolides have been isolated³ from the extract of aerial parts of *Camchaya loloana*, and they exhibit cytotoxicity against the HepG2 cell line, with GI₅₀ values at a nanomolar level. It is believed that the biological activity of these molecules is attributed to the presence of a unique 4-methylene-2-

cyclohexenone moiety.⁴ This moiety engages the sulfhydryl group of the cysteine residue on the tubulin and microtubule dynamics. Thus, the mechanism of action of these molecules resembles that of the cytotoxic molecule T13067, which reacts specifically with cysteine residue 239 in β -tubulin and binds in the close vicinity of the colchicine-binding site.^{5,6}

Such a promising biological activity profile and the presence of an unusual bicyclic/tricyclic framework with the sensitive 4-methylene-2-cyclohexenone moiety have made these molecules a new leads for the development of chemotherapeutic agents and also attractive targets for synthetic chemists. While considerable efforts have been addressed to synthesize otteliones A and B, loloanolides remain unexplored to date.

Mehta et al. reported the first total synthesis of racemic otteliones A and B and, thus, confirmed the relative

(1) Ayyad, S. E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102–8106.

(2) Incidentally, ottelione A (**2**) was identical to the compound named RPR112378 previously reported in the patent literature by a research group at Rhône-Poulenc Rorer (now Sanofi-Aventis); see: Leboul, J.; Provost, J. French patent WO96/00205, 1996 [*Chem. Abstr.* **1996**, *124*, 242296].

(3) Li, C. S.; Yu, H. W.; Chen, X. Z.; Wu, X. Q.; Li, G. Y.; Zhang, G. L. *Helv. Chim. Acta* **2011**, *94*, 105–110.

(4) Interaction of this electrophilic 4-methylene-2-cyclohexenone chromophore with biological systems remains unexplored as this moiety is rarely reported. (a) Murray, D. F.; Baum, M. W.; Jones, M. J. *Org. Chem.* **1986**, *51*, 1–7. (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197–203. (c) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748–2761.

(5) Combeau, C.; Provost, J.; Lanceli, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharmacol.* **2000**, *57*, 553–563.

(6) For the details of interaction of tubulin with drugs and alkylating agents, see: (a) Kuriyama, R.; Sakai, H. *J. Biochem. (Tokyo)* **1974**, *76*, 651–654. (b) Luduena, R. F.; Roach, M. C. *Biochemistry* **1981**, *20*, 4444–4450. (c) Shan, B.; Medina, J. C.; Shanta, E.; Franckmoelle, W. P.; Chau, T. C.; Learned, R. M.; Narbut, M. R.; Stott, D.; Wu, P.; Jean, J. C.; Rosen, T.; Timmermans, P. B.; Beckmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5686–5691.

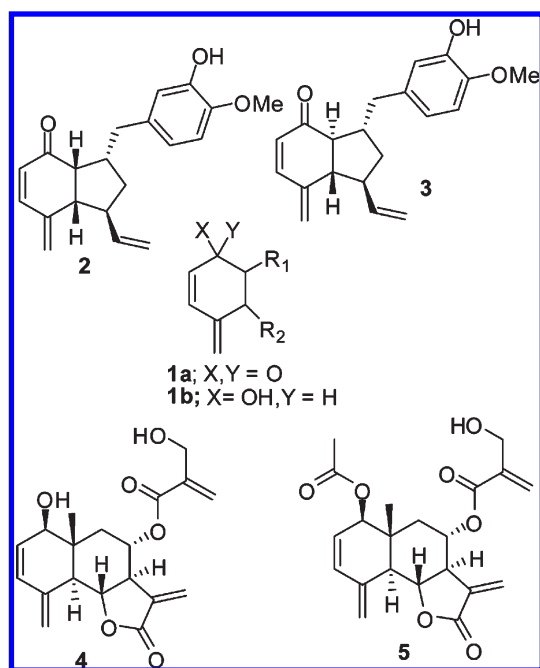
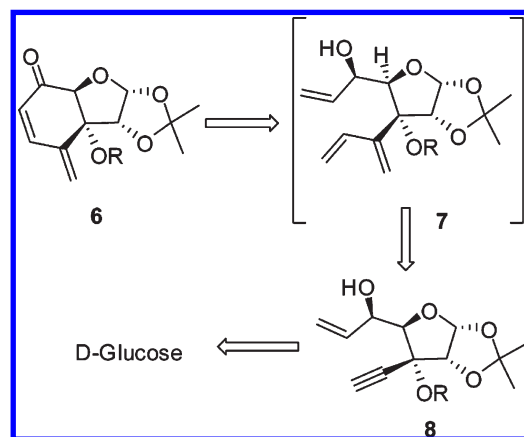


Figure 1. Otteliones A **2** and B **3**, loloanolide B **4**, and 1-*O*-acetylloanolide B **5**.

stereochemistry of these molecules.^{7a} Later, the same group reported an enantioselective total synthesis and, thus, determined the absolute configurations as well.^{7b} Since then, three more total syntheses^{8,9} and a few formal¹⁰ as well as partial syntheses¹¹ for otteliones have been reported.

Inspired by the biological and structural importance of these molecules from the preliminary reports, we became interested in the synthesis of these natural products. Though our main goal has been to accomplish total syntheses of these interesting natural products, our initial goal was to develop an efficient approach to the construction of the more sensitive 4-methylene-2-cyclohexenone framework. From our earlier reports on the synthesis of angularly fused dioxatriquinanes involving tandem

Scheme 1. Retrosynthesis



enyne/ring closing metathesis (RCM)¹² and synthesis of an AB ring of taxol¹³ and a taxa-oxa-sugar hybrid,¹⁴ using a tandem enyne/IMDA reaction, we realized that it was logical to use a tandem enyne/RCM¹⁵ to synthesize the 4-methylene-2-cyclohexenone moiety present in otteliones and loloanolides. This strategy, if successful, could pave the way to synthesize several simpler analogues of these interesting natural products, in addition to their total synthesis. It is also worth mentioning that the RCM approach involving the triene intermediate of type **7**⁹ has been utilized for the synthesis of otteliones and the present approach will be using acetylene as a 2-butadienyl equivalent. To check the feasibility of this approach, we initially designed a few sugar-derived 4-methylene-2-cyclohexenones **6**, where a broad diversity could be introduced at the sugar moiety. As per the retrosynthesis delineated in Scheme 1, the proposed target scaffold **6** could be derived from enyne **8** through a domino cross enyne metathesis with ethylene followed by RCM and oxidation. Further, enyne **8** could, in turn, be derived from D-glucose in a few steps.

Thus, our synthesis began with the stereoselective addition of lithium acetylide to the ketone **9**¹⁶ to afford tertiary alcohol **10** (Scheme 2).¹⁷ Methylation of this tertiary alcohol **10** with methyl iodide under basic conditions afforded ether **11a** in 96% yield. Selective removal of the more exposed acetone was carried out smoothly under mild acidic conditions at room temperature to afford

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(8) (a) Mehta, G.; Islam, K. *Org. Lett.* **2002**, *4*, 2881–2884. (b) Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903–3906. (c) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem.—Eur. J.* **2007**, *13*, 9866–9881. (d) Chen, C. H.; Chen, Y. K.; Sha, C. K. *Org. Lett.* **2010**, *12*, 1377–1379.

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(10) For formal synthesis of otteliones, see: (a) Suzuki, T.; Ghosati, K.; Katoh, T.; Sasai, H. *Org. Lett.* **2009**, *11*, 4286–4288. (b) Suzuki, T.; Ghosati, K.; Zhou, D. Y.; Katoh, T.; Sasai, H. *Tetrahedron* **2010**, *66*, 7562–7568. (c) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. Y.; Hwang, G. S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965–1967.

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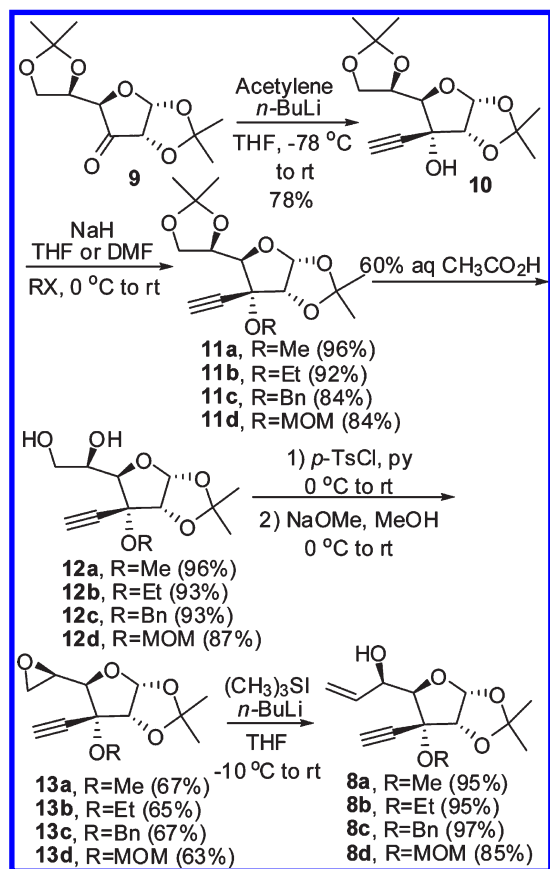
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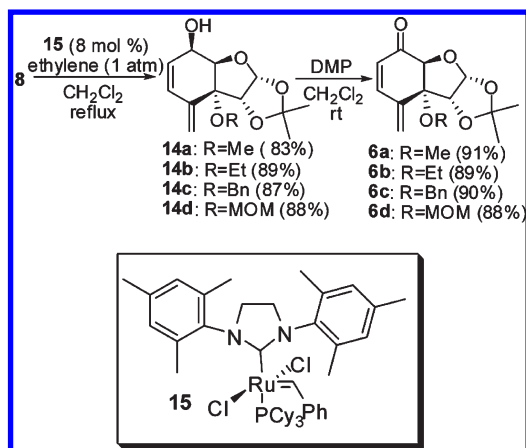
(16) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699–1702.

(17) Brimacombe, J. S.; Rollins, A. J.; Thompson, S. W. *Carbohydr. Res.* **1973**, *31*, 108–113.

Scheme 2. Synthesis of Enyne 8



Scheme 3. Tandem Enyne/RCM



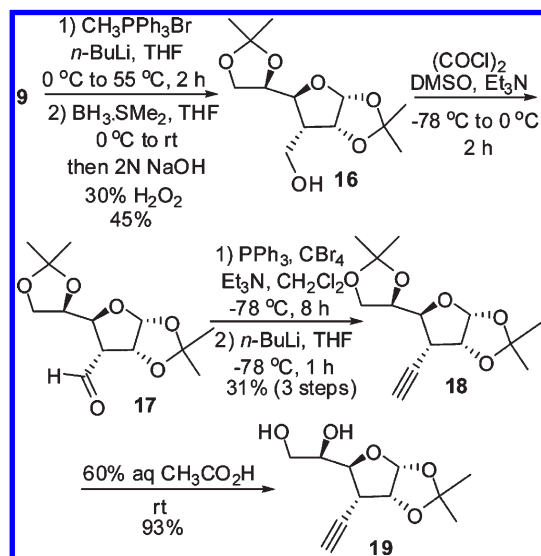
diol **12a**. Monotosylation of the primary alcohol using tosyl chloride, followed by treatment with NaOMe, provided the epoxide **13a** in good yield. The epoxide **13a** was then readily opened with trimethylsulfonium ylide¹⁸

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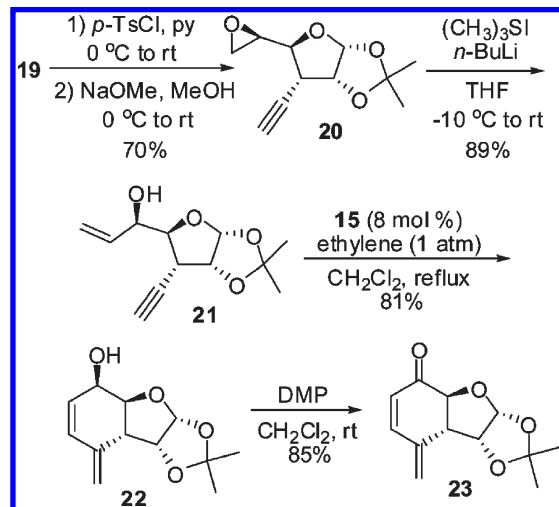
(generated *in situ* from Me_3SI by treatment with $n\text{-BuLi}$ in THF at $-10 ^\circ\text{C}$) to furnish enyne **8a**.

With a sufficient quantity of enyne **8a** in hand, the stage was now set for the execution of the key tandem enyne/RCM sequence. Accordingly, when enyne **8a** was subjected to cross enyne metathesis with ethylene gas (1 atm) in the presence of Grubbs' second generation catalyst **15** (8 mol %), in refluxing CH_2Cl_2 , pleasingly the desired enyne/RCM product was obtained in excellent yield through the triene intermediate **7**, which could not be isolated. Finally, oxidation of alcohol **14a** with Dess–Martin periodinane delivered the targeted 4-methylene-2-cyclohexenone derivative **6a** (Scheme 3). To show the diversity, alcohol **10** was protected with different alkylating agents under similar conditions to afford ethers **11b–d** in good yields. Further,

Scheme 4. Synthesis of Diol 19



Scheme 5. Tandem Enyne/RCM



the same sequence described for **6a** was extended to synthesize other scaffolds **6b–d**, starting from **11b–d** in good yields.

Having completed the construction of *cis*-fused 4-methylene-2-cyclohexenone frameworks **6a–d**, we then planned to extend this strategy to the synthesis of *trans*-fused scaffold **23**. To this end, the ketone **9** was subjected to Wittig olefination and hydroboration/oxidation to afford alcohol **16** (Scheme 4). Swern oxidation of **16** followed by homologation using the Corey–Fuchs protocol and subsequent treatment with *n*-BuLi afforded the alkyne **18**. Selective removal of the acetonide afforded the diol **19**.

Selective tosylation of the primary alcohol of **19** and subsequent base mediated intramolecular nucleophilic displacement afforded the epoxide **20** (Scheme 5). The epoxide opening with concurrent formation of a double bond furnished the key metathesis precursor **21**.

Following the same sequence of reactions involving a tandem cross enyne metathesis/RCM, the *trans*-fused

dienol **22** was obtained in very good yield. Subsequent oxidation of allylic alcohol with DMP afforded the key 4-methylene-2-cyclohexenone **23**.

In conclusion, we have outlined a simple and efficient strategy for the construction of the 4-methylene-2-cyclohexenone framework using a tandem enyne/RCM sequence. It is worth mentioning that the importance of this work lies in the fact that this strategy can be employed for the synthesis of a large number of analogues starting from diverse sugar units.

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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>.