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Lewis Acid-Mediated Intramolecular Cyclization of the Dienol Silyl Ether or Enol Silyl Ether and the Acetal for Medium-Sized Ring Formation

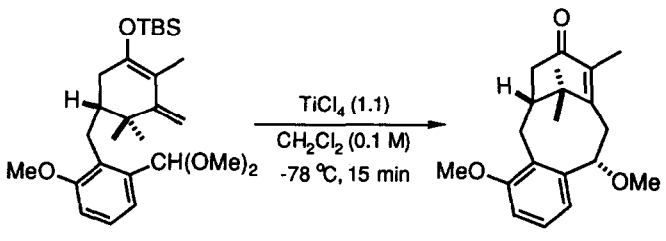
Yasuhiro Kataoka, Yusuke Nakamura, Koichiro Morihira, Hidehiro Arai, Yoshiaki Horiguchi, and Isao Kuwajima*

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152, Japan

Abstract: Lewis acid-mediated intramolecular cyclization of the dienol silyl ether or enol silyl ether and the acetal for medium-sized ring formation is described. Seven-, eight-, and nine-membered ring cyclization proceed in fairly good yields.

Numbers of biologically active natural products contain a medium-sized ring(s). Taxol,[1] esperamicin,[2] and brevetoxin[3] are the representative and syntheses of these classes of compounds have been being energetically studied. Construction of the medium-sized core is the key and strategy-determining for the syntheses of these classes of compounds. Although intramolecular medium-sized ring cyclization is one of the most desirable approach, it often suffers from intermolecular coupling reactions, and so results in poor yield. In this letter we describe highly efficient intramolecular cyclization of the dienol silyl ether or enol silyl ether and the acetal under Lewis acidic conditions for medium-sized ring formation.

We previously reported construction of the taxane ring system **2** *via* Lewis acid-mediated intramolecular coupling reaction of the dienol silyl ether and the acetal.[4] In spite that the eight-membered ring is highly strained owing to the bridgehead double bond, the cyclization proceeded rapidly even at -78 °C in good yield and no intermolecular coupling products formed. Though the dienol silyl ether moiety has two nucleophilic sites, α and γ-positions, the γ-cyclization product **2** exclusively formed.[5] In addition, **2** consists of all *endo* atropisomer.[6,7] We at first attributed such efficient cyclization both with high γ- and *endo*-selections to the coordination of the Lewis acid between 4- and 13-oxygen atoms (taxane numbering) (Figure 1). The chelation



1

2 (*endo*) 74%

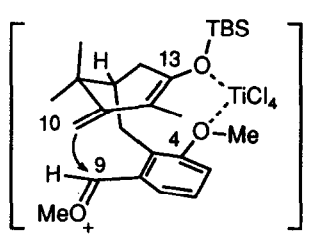
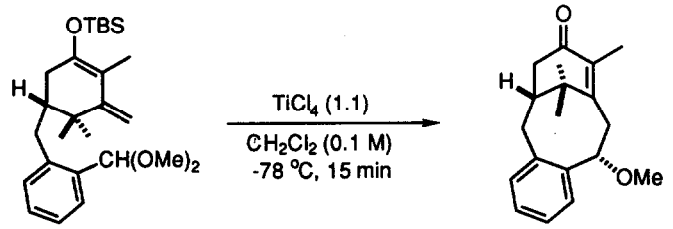


Figure 1

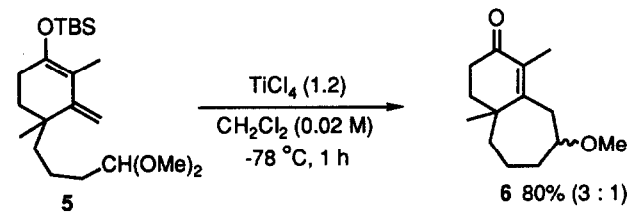
was expected to fold the whole molecule as *endo* conformation and fix the γ-position (C-10) close to the oxonium carbon (C-9). There was, however, a possibility that Lewis acid-mediated intramolecular cyclization of the dienol silyl ether and the acetal is generally efficient for medium-sized ring formation. We therefore investigated the general applicability of the cyclization. The regioselectivity of the cyclization is of additional interest as well as the efficiency.[5]

In order to verify the "enormous chelation effect", 4-deoxy derivative **3**[8] was subjected to the cyclization conditions. That **3** cyclized to the same extent with **1** affording **4**[9] suggested the generality of the medium-sized ring cyclization without such a specific conformational bias as the chelation.

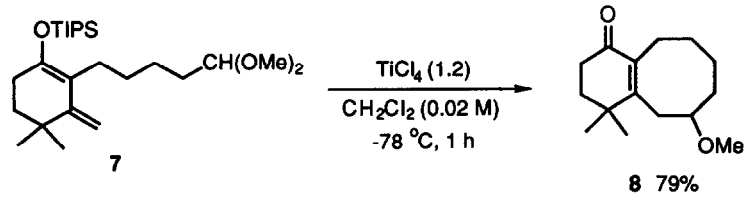


3 **4** (*endo*) 65%

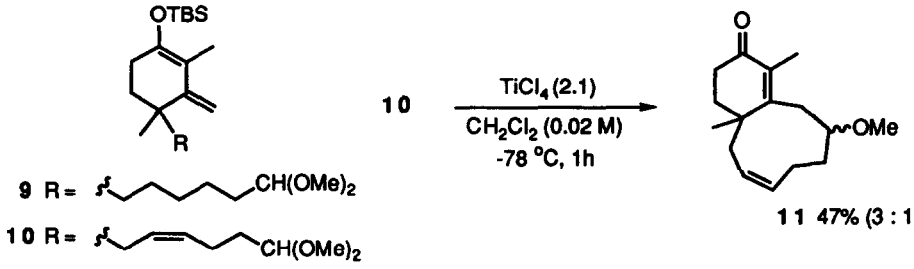
Then, cyclization of some other substrates[8] with a different substitution pattern and a ring size (seven to nine) was investigated. Without using high dilution and syringe pump technique the cyclization of seven- and eight-membered ring occurred in good yields (ca. 80%). It is noteworthy that **7** yields eight-membered product **8** instead of entropically favored six-membered ring formation *via* α-attack. Nine-membered ring cyclization is by far more difficult, as was revealed that **9** with a saturated side chain failed to cyclize even in highly diluted solution (0.001 M). However, introduction of a *cis* double bond on the side chain resulted in nine-membered ring cyclization in a fair yield (47%).



5 **6** 80% (3 : 1)

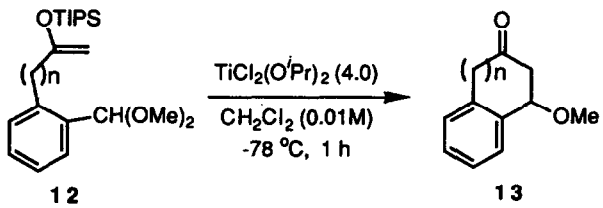


7 **8** 79%



Thus, it has appeared that the Lewis acid-mediated intramolecular cyclization of the dienol silyl ether and the acetal for medium-sized ring formation is of general applicability and of strong γ-preference, irrespective of the substitution pattern and the ring size.

A series of intramolecular Mukaiyama aldol reaction[10] was also investigated (**12** –> **13**). In the presence of $TiCl_2(O^iPr)_2$[11] seven-, eight-, and nine-membered ring cyclization occurred fairly well as in the case of cyclization of dienol silyl ethers.



12 13

n	Ring size	Yield
2	7	70%
3	8	80%
4	9	34%

Considering that some excellent methods for medium-sized ring cyclization which utilize acid-mediated reactions have emerged in recent years,[12] cationic reactions seem to be, in general, advantageous for medium-sized ring cyclization in comparison with anionic reactions. This may be due to that the unequivocally high reactivity of cationic species can manage to overcome the developing transannular repulsion during medium-sized ring closure.

Typical experimental procedure: To a methylene chloride (3.1 mL) solution of **7** (27 mg, 0.064 mmol) was added dropwise a methylene chloride solution of titanium chloride (1.6 M, 47 μL, 0.075 mmol) at -78 °C. After stirring for 1 h, saturated aqueous $NaHCO_3$ was added. The organic layer was separated and then the aqueous layer was extracted twice with ether. The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Chromatographic purification on silica gel (10% EtOAc/hexane) afforded **8** (11.9 mg, 79%) as a colorless oil.

REFERENCES and NOTES

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
2. Konishi, M.; Ohkuma, H.; Saitoh, K.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenwold, G.; Krishnan, B.; Doyle, T. W. *J. Antibiotics* **1985**, *38*, 1605.

3. Lin, Y.-Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
4. Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277.
5. Dienol silyl ethers, in intermolecular reactions, kinetically favour electrophilic attack at the γ-position. However, the regioselectivity depends upon the structure of the reactants and, in particular cases, it falls to ca. 1:1; Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319; Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *34*, 3205, 3209. Therefore, there has been no definite prediction for the regioselectivity of the intramolecular version.
6. It is known that the eight-membered B ring of C-aromatic taxanes has two stable conformations, that is *endo* and *exo* conformations. The rate of interconversion of these conformational isomers depends on the substitution pattern of the substrate. Our cyclization products **2** and **4** do not isomerize to the *exo* isomer at room temperature. Synthesis and conformation studies of C-aromatic taxanes, *see*: Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1984**, *25*, 2451; Shea, K. J.; Gilman, J. W. *J. Am. Chem. Soc.* **1985**, *107*, 4791; Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.
7. The stereochemistry of 9-methoxy group is controlled both by the *endo* cyclization and the orientation of the benzylic oxonium ion. Avoiding the *o*-methylene group, the benzylic oxonium ion should prefer the orientation depicted in Fig. 1.
8. The cyclization precursor was synthesized from the corresponding 1,3-diketone having the acetal side chain by two-step procedure: regioselective silylation (R_3SiCl, Et_3N/CH_2Cl_2) and Peterson olefination ($TMSCH_2Li$/THF, -78 °C, then ^tBuOK, room temperature).
9. We believe that the *endo* selectivity of **2** and **4** is originated by the electrostatic attraction between the electron deficient C-ring and the electron rich dienol silyl ether moiety.
10. Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. Cockerill *et al.* have reported a series of medium-sized ring cyclization *via* intramolecular Mukaiyama reaction, but the substrates investigated are rather specific; Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans I* **1985**, 2093. Until now systematic study on intramolecular Mukaiyama aldol reaction for medium-sized ring formation is lacking.
11. $TiCl_4$, $ZnCl_2$, BF_3-OEt_2, and TMSOTf gave lower yields. $TiCl_2(O^iPr)_2$ appeared the best and use of 4 equiv. of the Lewis acid is essential, otherwise the reaction results in incompletion.
12. For example: Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J Am. Chem. Soc.* **1986**, *108*, 3128; Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468; Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556; Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921; Gassman, P. G.; Riehle, R. J. *Tetrahedron Lett.* **1989**, *30*, 3275; Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851; Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386; Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.

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