Olefin Metathesis in Cyclic Ether Formation. Direct Conversion of Olefinic Esters to Cyclic Enol Ethers with Tebbe-Type Reagents

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The olefin metathesis reaction[1] is rapidly emerging as a powerful tool in organic synthesis.[2] Of particular interest are ring forming metathesis reactions catalyzed by transition metal complexes, several elegant examples of which have recently appeared.[3] Despite the successes of this general approach to ring construction, much remains to be improved in terms of scope, convenience, and generality. In this communication we report a new strategy, based on the olefin metathesis reaction, for the generation of cyclic enol ethers directly from olefin esters[4] using the Tebbe[5] or the Petasis reagents.[6]

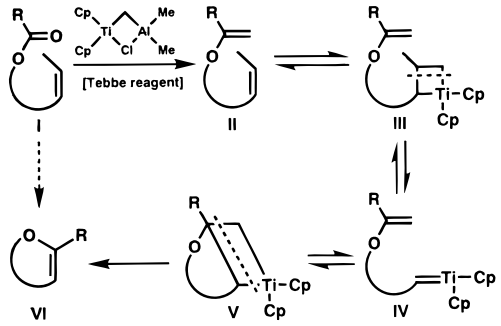
Scheme 1 shows the general concept[7] for the envisioned Tebbe-reagent-mediated transformation of olefinic esters of type **I** to cyclic enol ethers of type **VI**. Thus it was anticipated that the initially formed enol ether **II** would react with a second molecule of the Tebbe reagent to afford the titanacyclobutane **III**, fragmentation of which would then lead to titanium alkylidene **IV**. Intramolecular reaction of **IV** was then expected to lead to titanacyclobutane **V**, whose regioselective fragmentation as shown should allow an entry to the desired cyclic enol ethers **VI** via olefin metathesis.

Implementation of this strategy using olefinic ester **1** leads to the formation of cyclic enol ether **3** via the initially formed methylenation product **2** in 71% overall yield (Scheme 2). The intermediacy of compound **2** was proven by isolation and full spectral characterization followed by conversion to **3** under the influence of the Tebbe reagent.

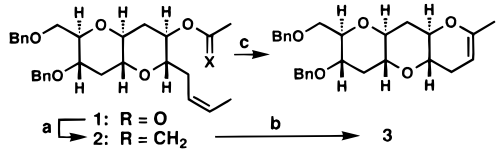
The generality and scope of this new process was investigated by employing a variety of substrates. As illustrated in Table 1, the reaction can deliver a series of six- and seven-membered cyclic enol ethers in good yields (entries 1−3 and 10−12, respectively). In addition to these findings, the important observation of the open-chain products shown in entries 6−9 (Table 1) was made. These hydroxy exomethylenic compounds are presumably obtained by sequential hydrolysis and olefination of the initially formed cyclic enol ethers.[8] Apparently the lability of the enol ether products depends on their precise environment and the reaction conditions, a circumstance that allows the direct elaboration of these intermediates to further compounds of considerable synthetic utility in organic synthesis. The use of dimethyltitanocene (Cp_2TiMe_2), a reagent popularized by Petasis,[6] instead of the Tebbe reagent allows the isolation of labile cyclic enol ethers (entries 4 and 6). The structure of **9** was confirmed by an X-ray crystallographic analysis (see Figure 1).

The applicability of this strategy to the synthesis of complex polyether frameworks has also been demonstrated as shown in Schemes 3 and 4. Scheme 3 shows the assembly of hexacycle **25** and demonstrates that the reaction is tolerant of other olefins in the system, at least trisubstituted ones, as in the case of **24**. Scheme 4 outlines the synthesis of a second hexacycle (**30**) reminiscent of the structures of the marine neurotoxins bre-

Scheme 1. Titanium-Mediated Metathesis Strategy for the Conversion of Olefinic Esters to Cyclic Enol Ethers

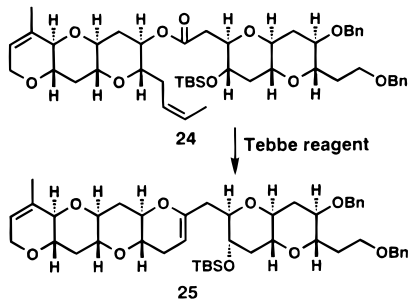


Scheme 2[a]



[a] Reagents and conditions: (a) Tebbe reagent (1.3 equiv), THF, 25 °C, 20 min, 77%; (b) Tebbe reagent (2 equiv), THF, reflux 3 h, 65%; (c) Tebbe reagent (4 equiv), THF, 25 °C, 20 min; then reflux, 5 h, 71%.

Scheme 3. Synthesis of Hexacyclic Polyether **25**[a]



[a] Reagents and conditions: Tebbe reagent (4.0 equiv), THF, 25 °C, 20 min; then reflux, 5 h, 61%.

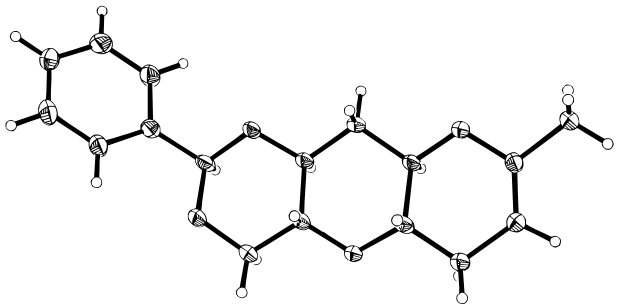


Figure 1. ORTEP drawing of compound **9**.

(1) (a) Katz, T. J .; Lee, S. J.; Shippey, M. A. *J. Mol. Catal.* **1980**, *8*, 219. (b) Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.

(2) For recent reviews on olefin metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon; New York, 1991; Vol. 5, Chapter 9.3.

(3) (a) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855. (b) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943. (c) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169. (d) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801.

(4) For related work, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (b) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029.

(5) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

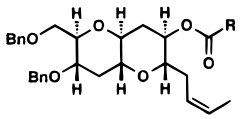
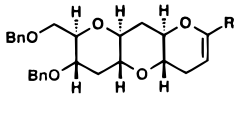
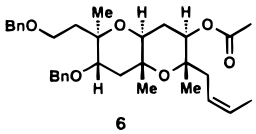
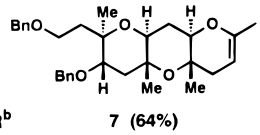
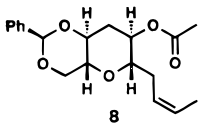
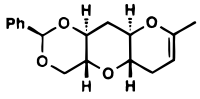
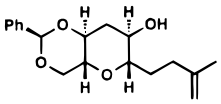
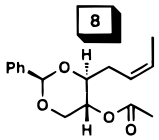
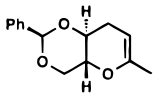
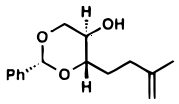
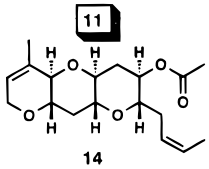
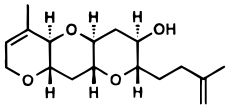
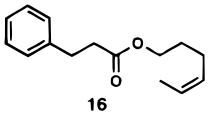
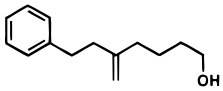
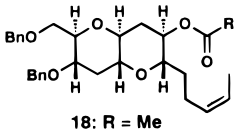
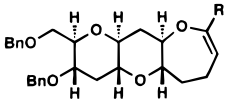
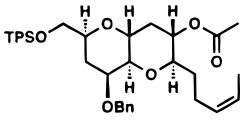
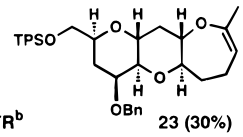
(6) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(7) For a related, but mechanistically different, closure, see: (a) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (b) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855.

(8) Buffering the reaction with pyridine or 2,6-di-*tert*-butyl-4-methylpyridine did not stop this, presumably, Lewis-acid-catalyzed reaction.

0002-7863/96/1518-1565$12.00/0

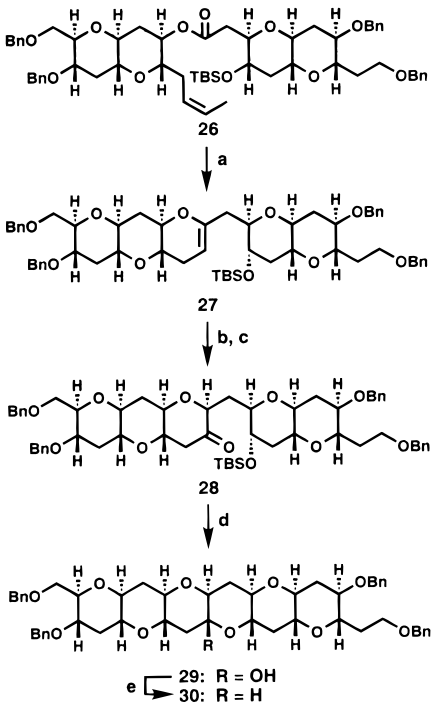
Table 1. Synthesis of Cyclic Enol Ethers and Hydroxy Olefins from Olefinic Esters[a]

Entry	Substrate	Reagent	Product (%Yield)
1	 1: R = Me	TR[b]	 3: R = Me (71%)
2	4: R = Ph	TR[b]	5: R = Ph (70%)
3	 6	TR[b]	 7 (64%)
4	 8	DT[c]	 9 (60%)
5		TR[b]	 10 (41%)
6	 11	DT[c]	 12 (30%)
7		TR[b]	 13 (41%)
8	 14	TR[b]	 15 (77%)
9	 16	TR[b]	 17 (71%)
10	 18: R = Me	TR[b]	 19: R = Me (45%)
11	20: R = Ph	TR[b]	21: R = Ph (32%)
12	 22	TR[b]	 23 (30%)

[a] Reactions were carried out on a 0.1−0.2 mmol scale with 3−6 equiv of reagent and were complete in 2−15 h. [b] TR = Tebbe reagent ($Cp_2TiCH_2ClAlMe_2$). [c] DT = dimethyltitanocene (Cp_2TiMe_2).

vetoxin B,[9,10] ciguatoxin,[11] and maitotoxin.[12] The latter compound (**30**) was constructed rapidly and efficiently via a convergent strategy made possible by this reaction. Thus treatment of **26** with excess Tebbe reagent in THF (25 °C → reflux) led to **27** in 71% yield. Regioselective hydroboration

Scheme 4. Synthesis of Hexacyclic Polyether **30**[a]



[a] Reagents and conditions: (a) Tebbe reagent (4.0 equiv), THF, 25 °C, 0.5 h; then reflux, 10 h, 71%; (b) BH_3 (5 equiv), THF, 0 °C; then 3 N NaOH (20 equiv), H_2O_2 (20 equiv); (c) Dess−Martin reagent (3.0 equiv), 60% for two steps; (d) TBAF (1.5 equiv), 25 °C, 8 h, 60%; (e) Et_3SiH (200 equiv), $BF_3{\cdot}Et_2O$ (5 equiv), CH_2Cl_2 0 °C, 1 h, 91%.

of **27** followed by oxidative workup and further oxidation of the resulting alcohol with Dess−Martin reagent furnished ketone **28** in 63% overall yield. Finally, removal of the silicon protecting group from **28** followed by exposure of the resulting lactol (**29**) to $Et_3SiH-BF_3{\cdot}Et_2O$ provided the hexacyclic, all-*trans*-fused framework **30** in 55% overall yield from **28**.

The reported process represents a powerful tool for the construction of complex polycyclic frameworks and/or extended hydroxy olefins using simple functional groups as coupling partners in ring closure reactions and allows convergency in target-oriented synthesis. Applications of the present technology to the total synthesis of natural and designed molecules of the marine biotoxin family are in progress.[13,14]

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Supporting Information Available: Listing of selected data for compounds **1**−**9**, **14**−**19**, and **24**−**30** (22 pages). This material is contained in many libraries on micofiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Structure determination: (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.

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(11) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380.

(12) (a) Satake, M.; Ishida, S.; Yasumoto, T.; Murata, M.; Utsumi, H.; Hinomoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 7019. (b) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem Soc.* **1994**, *116*, 7098.

(13) For a palladium-catalyzed approach to maitotoxin-type fragments, see: Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. Submitted for publication.

(14) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.