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Two-Directional Olefinic-Ester Ring-Closing Metathesis using Reduced Ti Alkylidenes. A Rapid Entry into Polycyclic Ether Skeletons

Yuan Zhang and Jon D. Rainier*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112

rainier@chem.utah.edu

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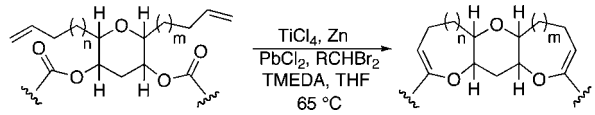
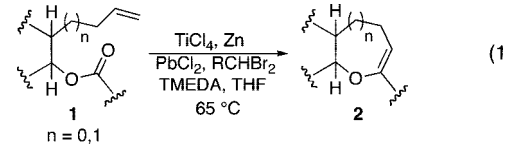
ABSTRACT



The use of a reduced titanium ethylidene reagent in an efficient two-directional approach to polycyclic ether skeletons is described.

Although the majority of the polycyclic ether containing natural products of the brevetoxin/ciguatoxin class bind and activate voltage-gated sodium channels (VGSCs),[1,2] others either inhibit the binding of known VGSC agonists and/or do not bind to VGSCs at all.[3] This apparently disparate behavior has led many to propose that polycyclic ethers might be interesting tools to study ion channels.[4]

Holding back their use in the context mentioned above are the relatively small quantities of polyether natural products that have traditionally been isolated from natural sources or that are generated from synthesis programs.[5] In our opinion, a solution to this problem will come from the development of improved synthetic approaches that enable the rapid construction of polyether skeletons from simple starting materials.[6] Outlined in this manuscript is our attempt to address this through the use of a reduced titanium reagent to effect two-directional olefinic-ester cyclizations.



(1)

In studies that were driven by our polycyclic ether natural product total synthesis program,[7] we recently discovered that titanium ethylidene reagents were capable of inducing olefinic ester cyclization and diene ring closing metathesis reactions (eq 1).[8] When compared to reagents

(1) Catterall, W. A.; Cestéle, S.; Yarov-Yarovoy, V.; Yu, F. H.; Konoki, K.; Scheuer, T. *Toxicon* **2007**, *49*, 124.

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(3) (a) Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469. (b) LePage, K. T.; Rainier, J. D.; Johnson, H. W. B.; Baden, D. G.; Murray, T. F. *J. Pharm. Exp. Ther.* **2007**, *323*, 174. (c) Cuypers, E.; Abdel-Mottaleb, Y.; Kopljar, I.; Rainier, J. D.; Raes, A. L.; Snyders, D. J.; Tytgat, J. *Toxicon* **2008**, *51*, 974.

(4) Torikai, K.; Oishi, T.; Ujihara, S.; Matsumori, N.; Konoki, K.; Murata, M.; Aimoto, S. *J. Am. Chem. Soc.* **2008**, *130*, 10217.

(5) (a) A 1100 L fermentation of *G. toxicus* was needed to isolate 1.2 mg of gambiero. Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361. (b) A total of 1100 kg of eel was needed to isolate 1.3 mg of ciguatoxin. Tachibana, K.; Nukina, M.; Joh, Y.-G.; Scheuer, P. J. *Biol. Bull.* **1987**, *172*, 122. (c) Our 44 step synthesis of gambierol generated 7.5 mg (see ref 7).

(6) (a) Marmsater, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8* (19), 4346. (b) Sasaki, M. *Top. Heterocycl. Chem.* **2006**, *5*, 149. (c) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314.

(7) (a) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1747. (b) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1736. (c) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

(8) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604.

(9) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

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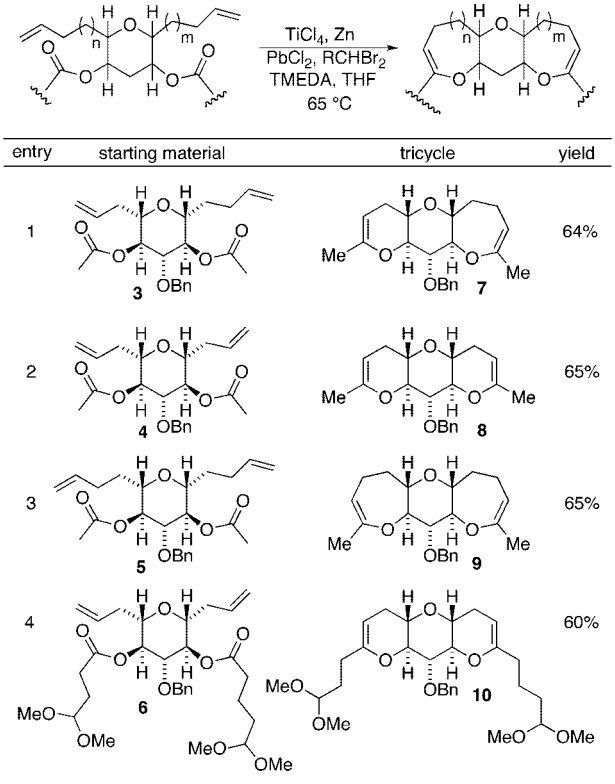
that carry out related transformations, the titanium reagent is advantageous because of its low cost, its in situ preparation, and its general applicability to the olefinic ester cyclization problem.[9−11]

It occurred to us that the reduced titanium cyclization approach to polycyclic ether frameworks would be even more efficient if it were amenable to a two-directional reaction sequence where two olefinic esters would undergo cyclization in the same reaction flask. To a significant degree this work was inspired by the symmetrical nature of the natural products and the elegant two-directional approaches that have been carried out by the groups of Nicolaou, Martín, Nakata, and especially Clark.[12] The Clark work is closest to that proposed here in that it involves two-directional ring-closing metathesis reactions. Clark's reactions differ from those proposed here in that his precursors were dienes or ene-ynes and in the nature of the reagent used to carry out the cyclizations (Ru or Mo (Clark) versus Ti (this work)).

We initially chose to test whether olefinic ester cyclizations were amenable to a two-directional approach with readily available dienyl diester **3**[13] and were delighted to find that **3** gave tricycle **7** in 64% yield when exposed to the titanium ethylidene reagent (Table 1, entry 1). Equally pleasing were

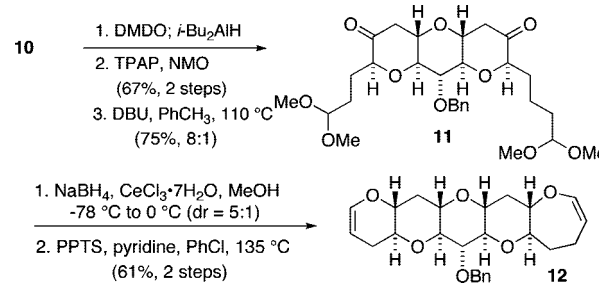
Table 1. Two-Directional Olefinic Ester Cyclizations



the reactions to give the symmetrical tricyclic substrates **8** and **9** from *C*-glycosides **4** and **5**, respectively (entries 2 and 3). As demonstrated by the cyclization of **6** to give **10**, esters other than acetates can be employed in these reactions (entry 4).

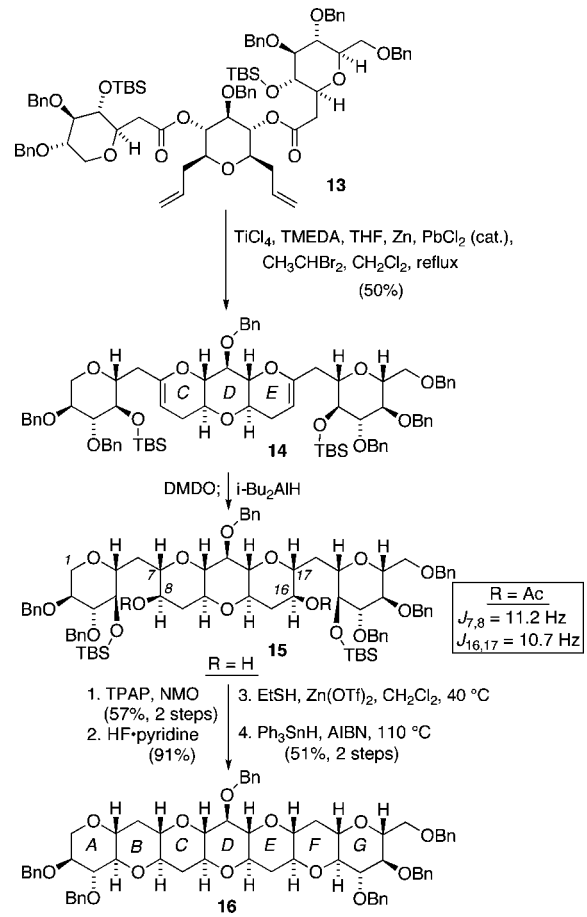
From an interest in exploiting the products from the cyclization chemistry, we decided to examine the conversion of tricyclic bis-acetal **10** into the corresponding pentacycle (Scheme 1). Oxidation of both enol ethers with DMDO followed by

Scheme 1



reduction of the resulting epoxides with *i*-Bu_2AlH gave the corresponding secondary alcohols as a mixture of diastereomers. Oxidation and equilibration of the resulting ketones using DBU resulted in the generation of **11** as the major diastereomer. Reduction of the ketone and cyclization/elimination gave pentacycle **12** as a single diastereomer in only six synthetic transformations from monocyclic *C*-glycoside **6**.[13]

Scheme 2



Illustrative of our ability to use this chemistry to generate even more elaborate polycyclic ether architectures is the synthesis of heptacycle **16** from *C*-glycoside precursor **13** in six synthetic transformations (Scheme 2). Readily available dienyl diester **13**[13] served as the precursor to a two-directional cyclization reaction leading to **14** in 50% yield. Oxidation of both enol ethers with DMDO and in situ reduction of the resulting anhydrides with *i*-Bu_2AlH gave the corresponding secondary alcohols as a single diastereomer. The relative stereochemistry at C7, C8, C16, and C17 was determined after the conversion of **15** into the corresponding C8 and C16 acetates. The $J_{7,8}$ and $J_{16,17}$ values revealed that **15** had the desired *trans-syn-trans* stereochemistry at the C, D, and E-ring junctions. Oxidation, removal of the silyl ethers, *O*,*S*-acetal formation, and reduction provided heptacycle **16** in good overall yield.[14]

In summary, this communication has outlined a two-directional olefinic-ester cyclization strategy to polycyclic ethers that results in the rapid construction of tri-, penta-, and heptacyclic skeletons. We are continuing to examine the scope of these transformations and to utilize the products as tools in the study of ion channels.

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

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(10) Olefinic ester cyclizations were known prior to the work described in ref 8. See: (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 380. (d) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (e) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (f) Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209.

(11) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.

(12) (a) Nicolaou, K. C.; McGarry, D. G.; Sommers, P. K. *J. Am. Chem. Soc.* **1990**, *112*, 3696. (b) Ravelo, J. L.; Regueiro, A.; Martín, J. D. *Tetrahedron Lett.* **1992**, *33*, 3389. (c) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372. (d) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374. Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157.

(13) See Supporting Information for the synthesis of **3**, **4**, **5**, **6**, and **13**.

(14) See ref 7 and Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.