# Enol Ester as an Olefinic Partner in Enyne Cyclization. A Novel Tandem Cyclization to Stereodefined Bicyclo[3.3.0]octenes

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Preparation of a bicyclic carbon skeleton with stereodefined arrangement of functional groups is an attractive starting point to elaborate complex molecular architecture.[1] The metal-mediated enyne cyclization followed by a second ring closure with carbon monoxide or its equivalents is one of the most straightforward methods to prepare bicyclic compounds.[2–4] However, stereoselective functionalization of the newly formed carbon centers is usually performed in the subsequent transformations. Herein we describe a novel alternative of this method, which consists of a titanium alkoxide-based intramolecular cyclization of enol ester and acetylene as formulated in eq 1. The enol ester plays a dual role to effect the tandem ring closure and, at the same time, to impart stereocontrolled functional groups on the resulting bicyclo[3.3.0]octene framework.

$$\text{(1)}$$
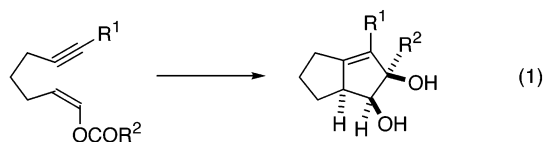
Acetylenic (E)- and (Z)-enol esters **2** and **4** (both >99% isomeric purity), which are readily and stereoselectively prepared by standard methods,[5,6] were treated with a titanium(II) alkoxide reagent, Ti-(O-i-Pr)₄/2i-PrMgCl (**1**),[3,7] to see the feasibility of the enyne cyclization.[8] Unfortunately, (E)-enol ester **2** afforded an intractable reaction mixture, which contained only a very small amount of cyclization product **3** after aqueous workup (eq 2). The corresponding (Z)-isomer **4** did not give **3** either (Scheme 1), but a more extensive survey of this reaction mixture revealed the formation of a polar compound, which was, to our surprise, bicyclic diol **5**. It should be emphasized that no other isomeric products were seen even after careful analysis by ¹H NMR spectroscopy. The 1,2-relative stereochemistry of **5** was determined by the coupling constant and nOe study between the two hydrogens (¹H NMR spectroscopy). The relationship of the 2,3-diol moiety was assigned on the basis of the stereochemistry of the homologous compound **20** (see eq 3).

$$\text{(2)}$$
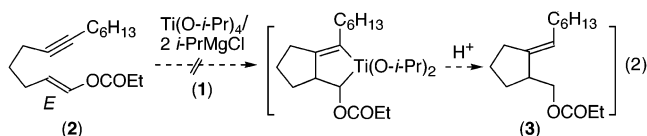
Considering the stereochemistry of the product, we propose the course of this bicyclization as shown in Scheme 1. The acetylene-titanium complex **6** undergoes the coupling with the double bond with retention of the olefin geometry to give stereodefined
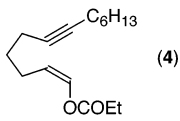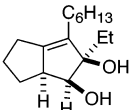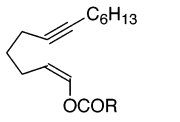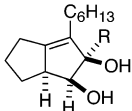
Scheme 1. Proposed Reaction Course
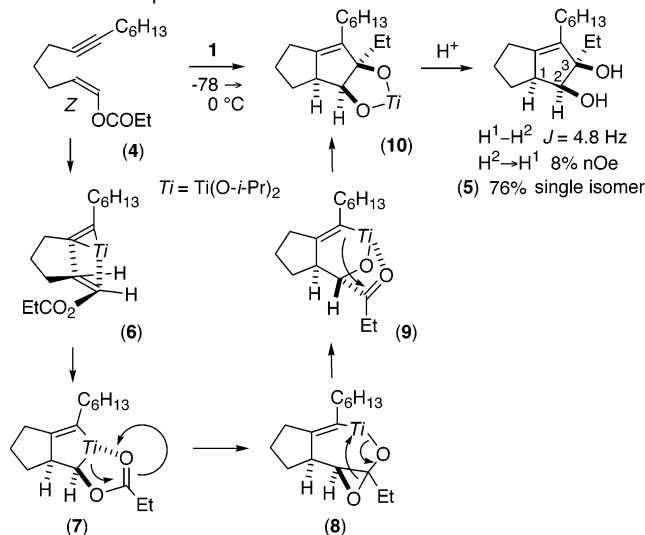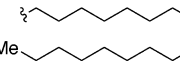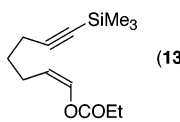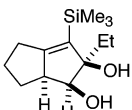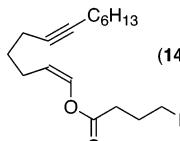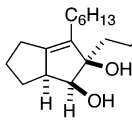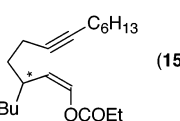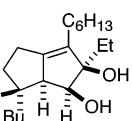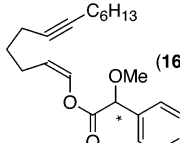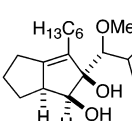
titanacycle **7**.[9] The sp³ carbon–titanium bond of **7** attacks the nearby carbonyl group again with retention of configuration to give **9** via **8**. The remaining vinyl–titanium bond in **9** then undergoes a second nucleophilic attack to the carbonyl group to give **10**, which, upon hydrolysis, gives **5**. Thus, the observed 1,2-stereochemistry of **5** most likely reflects the (Z)-olefin configuration of the initial enol ester **4**, and the cis-stereochemistry of the 2,3-diol moiety should arise from the intermediate formation of titanium-diolate chelate, respectively.

This cyclization appears to be reasonably general, and additional results are collected in Table 1. The enol esters of α-branched

$$\text{(3)}$$

$$\text{(4)}$$
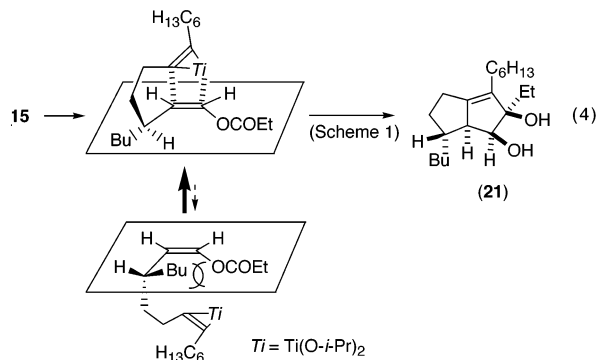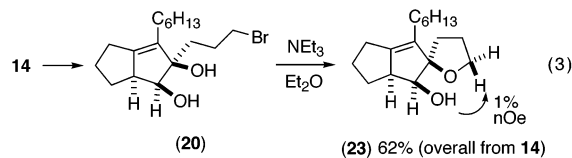
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Table 1. Preparation of Functionalized Bicyclo[3.3.0]octenes

Entry	Ynenyl Ester	Product	Yield (%)^{a,b} [d.s.]^c
1	(4)	(5)	76
2	R = i-Pr (11)	(17)	65
3	(12)	(18)	72
4	(13)	(19)	69
5	(14)	(20)	63
6	(15)	(21)	66 [>95:<5]
7	(16)	(22)	62 [67:33]

^{a} Isolated yield. ^{b} Unless otherwise stated, the product was obtained as a single stereoisomer. ^{c} Diastereoselectivity with respect to the chiral center (*) of the (racemic) starting material.

carboxylic acids **11** and **16** could be used equally well to give the desired compounds **17** and **22** (entries 2 and 7). When an enol ester was prepared from oleic acid (**12**), its acyl residue was transferred onto the bicyclic skeleton (**18**) with the cis double bond remaining unaffected (entry 3). A silylacetylene (**13**) is an acceptable substrate in place of alkyl acetylenes to give **19** having a vinylsilane moiety (entry 4). As shown in entry 5, an alkyl bromide survives these reductive conditions so that the ynenyl 4-bromobutyrate **14** gave the desired product **20** without any complication (entry 5). The produced 1,4-bromohydrin **20** is fairly unstable, and its treatment with Et₃N promoted spontaneous ring closure to give tricyclic compound **23** in good overall yield (eq 3). The structural analysis of this tricyclic compound by nOe study unambiguously determined the cis configuration of the original vicinal hydroxy groups of **20**, which should be valid for the diol moiety of other products. In all cases except for entry 7, each product was obtained as a single stereoisomer. This advantage combined with the stereocontrol by an allylic substituent of **15** made it possible to construct a total of four consecutive stereogenic centers in **21** in one pot and with virtually complete diastereoselectivity (entry 6).[6] Allylic strain between the cis-substituents as shown in eq 4 may account for this outcome. Alternatively, an attempted diastereoselective ring closure by a chiral carboxylate such as *O*-methylmandelate **16** so far afforded product **22** of moderate chiral induction (entry 7).

In conclusion, the titanium-mediated intramolecular cyclization of enol esters and acetylenes proceeded most likely with retention of the enol geometry of the starting material to give stereodefined, functionalized bicyclo[3.3.0]octenes. Further investigation on the utility of this tandem cyclization as well as the application of its products is now in progress.

Supporting Information Available: Experimental procedures, structural determinations, and physical properties of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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