J. Am. Chem. Soc. **1996,** *118,* 8729−8730 8729

A Novel Tandem Cyclization of 2,7- or 2,8-Bis-Unsaturated Esters Mediated by (η^2-Propene)TiX$_2$ (X = Cl or O-*i*-Pr). A Facile Construction of Bicyclo[3.3.0]octane, -[4.3.0]nonane, and -[3.1.0]hexane Skeletons

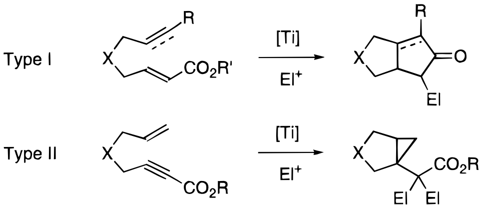
Ken Suzuki, Hirokazu Urabe, and Fumie Sato*

Department of Biomolecular Engineering
Tokyo Institute of Technology, 4259 Nagatsuta-cho
Midori-ku, Yokohama, Kanagawa 226, Japan

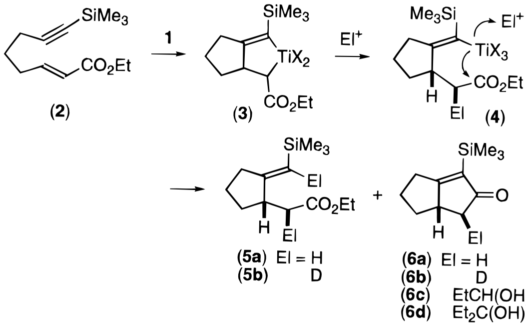
Received June 10, 1996

Two consecutive cyclizations of acyclic precursors should be useful for the preparation of bicyclic systems. Herein described is a novel type of such transformations consisting of two different kinds of cyclizations in tandem, starting from the title unsaturated compounds. The first step is based on the titanium-mediated cyclization of dienes and enynes reported earlier by us,[1] which is followed by the second ring closure via the addition of the resulting carbon−titanium bond to an electron-deficient moiety in the same molecule with concomitant incorporation of an electrophile(s). The overall outcome of the reaction is formulated in Scheme 1 ([Ti], a low-valent titanium; El$^+$, electrophile). The patterns of reactions are, simply dependent upon the substrates: type I occurs with α,*β-olefinic* esters, and type II involves the reactions of α,*β-acetylenic* esters.[2,3]

Scheme 1



Scheme 2



Treatment of a mixture of 2-en-7-ynoate **2** (1 equiv) with (η^2-propene)TiX$_2$ (X = Cl or *i*-PrO) (**1**), generated *in situ* from Ti(O-*i*-Pr)$_3$Cl (1.2 equiv) and *i*-PrMgCl (2.4 equiv) in ether,[4] at −78 → −20 °C followed by aqueous workup afforded the cyclized product **5a** together with unexpected bicyclic ketone **6a** always in good to excellent combined yields, but in varying product ratios (**5a**/**6a**) from run to run (*ca*. 6:4−3:7) (Scheme 2). The structure of **6a**, a product of the type I reaction, was unambiguously assigned in comparison with an authentic sample.[5] We soon became aware that the poor reproducibility of the product ratios would arise from the competing reactions of the titanium intermediate **4** generated during the aqueous workup. Thus, the titanacycle **3**,[6] formed by the titanium-mediated cyclization of **2**,[1] underwent the fast and selective protonation to its more reactive enolate moiety[7,8] to give **4** (El = H in Scheme 2). Then the resulting alkenyltitanium **4** suffered further protonation to afford **5a**, or it underwent the intramolecular nucleophilic acyl substitution reaction to give **6a**, both of which competed with each other under the workup conditions. In order to suppress the second proton delivery to **4**, we tried to terminate the reaction with a limited amount of the proton source (1.1 equiv of *s*-BuOH to **2**), which, in fact, led to a selective formation of the ketone **6a** uniformly in good yields (80% in isolation or 90% determined by ^{1}H NMR) (entry 1 in Table 1).[9] Deuterolysis of the same reaction mixture with 1.1 equiv of *i*-PrOD gave cleanly **6b** (Scheme 2 and entry 2 in Table 1). More importantly, the electrophile is not limited to proton (or deuterium) but also involves carbonyl compounds. Thus, the titanabicycle **3** could be trapped with a slight excess of propionaldehyde or diethyl ketone to promote the second ring closure as described above to give the products **6c** and **6d** in good yields (entries 3 and 4). In all of these reactions, the electrophiles were introduced to the convex face of the bicyclo[3.3.0]octene system in high selectivities.

Additional results of the cyclization of type I starting from a variety of substrates are summarized in entries 5−10 in Table 1. 2-En-7-ynoates (**7** and **8**) and a homologous 2-en-8-ynoate **10** underwent the same reactions to give the bicyclic ketones in good yields (entries 5−7). The stereochemical integrity of the olefinic portion of the starting materials **2** and **7** was completely lost in the (deuterated) products most likely through the formation of a planar enolate form of **3**.[10] 2,7-Dienoates behaved similarly as did 2-en-7-ynoates (entries 8−10). It should be noted that the trapping of the titanabicycle, generated *in situ* from **14**, with 1.5 equiv of propionaldehyde afforded the aldol product **15b** virtually as a single isomer; although the stereochemistry of its ring junction could be determined to be *cis*, that of the aldol moiety has not been assigned yet (entry 10). From the synthetic point of view, this reaction demonstrated a one-pot preparation of an aldol of the *defined* regiochemistry. Although several transition metal-mediated transformations involving cyclization and carbonylation of dienes or enynes may serve for the preparation of the parent ketone **15a** itself,[11] further extension of a carbon chain is not

---

[1] (a) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 4261. (b) Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett*. **1996**, *37*, 1253.

[2] The cyclization of these substrates with other early transition metal species such as Cp$_2$Zr or Cp$_2$Ti complexes has not been mentioned before; see: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev*. **1988**, *88*, 1047. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1163. Negishi, E.; Takahashi, T. *Acc. Chem. Res*. **1994**, *27*, 124. See also: Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259.

[3] Preparation of bicyclic ketone(or imine)−zirconium complexes via zirconium-mediated cyclization and carbonylation of dienes and enynes was reported; see: Probert, G. D.; Whitby, R. J.; Coote, S. J. *Tetrahedron Lett*. **1995**, *36*, 4113. Barluenga, J.; Sanz, R.; Fañanás, F. J. *J. Chem. Soc., Chem. Commun*. **1995**, 1009.

[4] The use of TiCl(O-*i*-Pr)$_3$ instead of Ti(O-*i*-Pr)$_4$ gave somewhat better results in the reactions of type I and II. For choice of these titanium salts in a few relevant reactions, see: Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc*. **1994**, *116*, 9345. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc*. **1995**, *117*, 3881. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198.

[5] Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc*. **1989**, *111*, 3336.

[6] Although the structure of **3** is tentatively drawn as in a C−Ti form, its exact nature is unknown, and accordingly, it may be the corresponding titanium enolate.

[7] For the general reactivity of carbon−titanium bonds, see: Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 116.

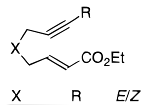
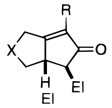
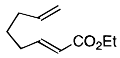
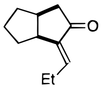
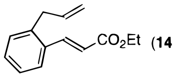
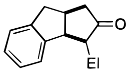
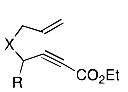
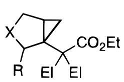
[8] For some regioselective reactions of Cp$_2$-zirconacycles with electrophiles, see: Aoyagi, K.; Kasai, K.; Kondakov, D. Y.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1994**, *220*, 319. Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem*. **1994**, *59*, 5643.

[9] Experimental details are described in supporting information.

[10] Cf.: Negishi, E.; Choueiry, D.; Nguyen, T. B.; Swanson, D. R. *J. Am. Chem. Soc*. **1994**, *116*, 9751.

S0002-7863(96)01928-2 CCC: $12.00

Table 1. Tandem Cyclization of Bis-Unsaturated Esters and Subsequent Reactions with Electrophiles[a]

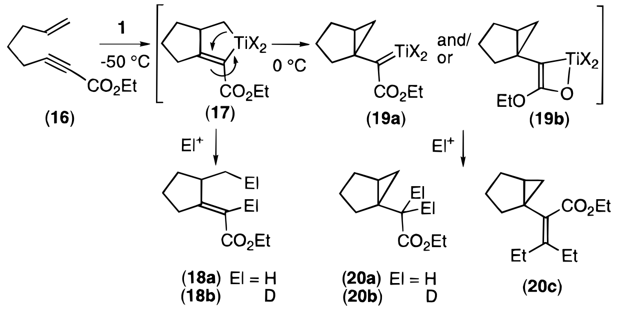
Entry	Unsaturated Ester				Electrophile[b] (El⁺)	Product		Yield (%)[c] [Ratio]
								
	X	R	E/Z			El		
1	CH_2	$SiMe_3$	*E*	(**2**)	H^+	H	(**6a**)	80
2				(**2**)	D^+	D	(**6b**)	79 [*d*]
3				(**2**)	EtCHO	EtCH(OH)-	(**6c**)	78 [63:37[e]]
4				(**2**)	Et_2CO	$Et_2C(OH)$-	(**6d**)	65
5	CH_2	$SiMe_3$	*Z*	(**7**)	D^+	**6b**		66 [*d*]
6	CH_2	C_5H_{11}	*E*	(**8**)	H^+	H	(**9**)	73
7	$(CH_2)_2$	$SiMe_3$	*E*	(**10**)	H^+	H	(**11**)	54
8				(**12**)	EtCHO		(**13**)[f]	53
9				(**14**)	H^+	 El = H	(**15a**)	74
10					EtCHO	EtCH(OH)-	(**15b**)	69 [single[g]]
								
	X	R				El		
11	CH_2	H		(**16**)	H^+	H	(**20a**)	74
12				(**16**)	D^+	D	(**20b**)	78 [99%d_2]
13				(**16**)	Et_2CO	**20c**		58
14	BnN	H		(**21**)	H^+	H	(**22**)	76
15	O	C_5H_{11}		(**23**)	H^+	H	(**24**)	53 [3:1[h]]

[a] See Schemes 2 and 3. [b] In entries 1−10, H^+ or D^+ refers to 1.1 equiv of *s*-BuOH or *i*-PrOD. In entries 11−15, H^+ or D^+ stands for excess aqueous 1 N HCl (or H_2O in entry 14) or 1 N DCl in D_2O. [c] Isolated yields. [d] Exclusively deuterated. [e] With respect to the CO-CHCH(OH) moiety. [f] After dehydration of the aldol product (TsOH, C_6H_6, reflux). [g] See text. [h] In the major isomer, the pentyl and acetate side chains are *cis*.

usually possible, and even a successive aldol reaction will not guarantee the regioselection, particularly in the case of nearly symmetrical **15a**.

In contrast to the aforementioned reactions, α,*β*-acetylenic esters underwent another type of cyclization (type II in Scheme 1). A 7-en-2-ynoate **16** afforded the normal cyclization product **18a** (91%) after the reaction under the standard conditions[1] followed by aqueous workup (Scheme 3). However, at a higher temperature up to 0 °C, the monocyclic **18a** completely disappeared and a new product **20a** having an additional cyclopropane ring (its structure was confirmed in comparison with an authentic sample) was obtained in good yield (entry 11 in Table 1).[9] The formation of the latter is most likely rationalized as follows. The alkyl−titanium bond of the titanacycle **17**, the presence of which was confirmed by the isolation of **18b** (>99% d_2) after deuterolysis, attacks the proximate terminus of the electron-deficient carbon−carbon double bond to give the new titanium compound **19**, which, upon hydrolysis, afforded the observed product **20a**.[12] The intermediacy of the titanium−carbene complex **19a**[13] and/or bis-titanated species **19b**[14] was, in fact, verified by the treatment of the reaction mixture with excess DCl/D_2O, which gave **20b** with virtually complete deuterium incorporation (>99% d_2) in place of both hydrogens α to the ester group (Table 1, entry 12).[15] The intermediate **19** underwent smooth alkylidenation of diethyl ketone at around 0 °C to give **20c** (entry 13), which demonstrated the titanium−carbene complex-like behavior of this bimetallic species.[13] The cyclization seems to be reasonably general so that a heteroatomic tether of the enyne moiety could tolerate the reaction conditions to give heterocyclic compounds (entries 14 and 15).

Scheme 3



Supporting Information Available: Typical procedures for the preparation of **6a**, **6c**, **20a**, and **20c**, physical properties of all starting materials and products, and structural determination of several compounds (14 pages). See any current masthead page for ordering and Internet access instructions.

JA961928N

---

[11] An alternative approach to the preparation of the cyclic ketones in type I involves transition metal-catalyzed or -mediated cyclization of dienes and enynes followed by carbonylation with carbon monoxide or isonitriles. For the Pauson−Khand reaction, see: Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1037. Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793. Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761. For cyclization and carbonylation with Cp_2Zr complex, see: Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633. Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424. With Cp_2Ti complex, see: Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593. With $(i\text{-PrO})_2Ti$ complex, see ref 1a. With Rh complex, see: Matsuda, I.; Ishibashi, H.; Ii, N. *Tetrahedron Lett.* **1995**, *36*, 241. With Ni complex, see: Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286.

[12] A similar flow of electrons is described in the isomerization of palladacyclopentenes to cyclopropylalkylidene−Pd complex; see: Trost, B. M.; Hashmi, S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183.

[13] The presence of a titanium−carbene complex is invoked in several synthetic reactions; see: Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 1276. Hartner, F. W.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4979. Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733. Okazoe, T.; Takai, K.; Oshima, K. Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410. Takai, K.; Fujimura, O.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 211.

[14] Some compounds of a similar structure were characterized or have even found applications in organic synthesis; see: Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 5393. Lee, S. Y.; Bergman, R. G. *Tetrahedron* **1995**, *51*, 4255. McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485.

[15] Cyclization of enynes with certain metal−carbene complexes afforded a similar class of compounds. However, a metallic moiety is not involved in the products, which is again in marked contrast to the reaction reported herein. For these reactions and also some synthetic utility of the products, see: Katz, T. J.; Yang, G. X.-Q. *Tetrahedron Lett.* **1991**, *32*, 5895. Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082. Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268.