Intramolecular Cyclization of 2,7- or 2,8-Bis-unsaturated Esters Mediated by (η^2-Propene)Ti(O-*i*-Pr)$_2$. Facile Construction of Mono- and Bicyclic Skeletons with Stereoselective Introduction of a Side Chain. A Synthesis of *d*-Sabinene

Hirokazu Urabe, Ken Suzuki, and Fumie Sato*

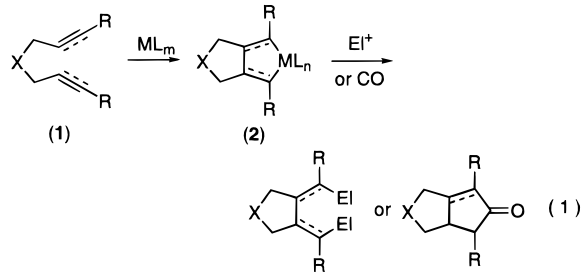
Contribution from the Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226, Japan

Received May 19, 1997[⊗]

Abstract: *tert*-Butyl 2-en-7-ynoate **6** was treated with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**3**), generated *in situ* from Ti(O-*i*-Pr)$_4$ or Ti(O-*i*-Pr)$_3$Cl and *i*-PrMgCl, in ether at −50 to −20 °C to afford the product **8** in good yield. The presence of the intermediate titanabicycle **7** was verified by bis-deuterolysis with excess D_2O. When the titanabicycle **7** was treated with 1.1 equiv of *i*-PrOD and then worked up as usual, the monodeuterated product **10** was obtained with high site selectivity and stereoselectivity. Other electrophiles such as aldehydes and ketones also reacted with the titanabicycle in a highly stereoselective manner to give cyclopentanes having a stereo-defined side chain. On the contrary, treatment of the corresponding ethyl ester, ethyl 8-(trimethylsilyl)-(*E*)-2-octen-7-ynoate (**28**), with **3** under the same conditions followed by the addition of 1.1 equiv of *s*-BuOH afforded 2-(trimethylsilyl)-1-bicyclo[3.3.0]-octen-3-one (**32**) in 80% yield. Quenching the same reaction mixture with *i*-PrOD, EtCHO, and Et_2CO in place of *s*-BuOH gave 4-deuterio (with exclusive deuterium incorporation), 4-(1-hydroxypropyl), and 4-(1-ethyl-1-hydroxypropyl) derivatives of the above bicyclic ketone (**34**, **35**, and **36**) in good yields. These electrophiles were always introduced from the convex face of the bicyclic skeleton. The stereochemistry of the cyclization could be controlled by an allylic substituent such as (*tert*-butyl)dimethylsiloxy or butyl group to a high degree yet with a reversal diastereoselection to give **45** or **47**. The reaction of ethyl 7-octen-2-ynoate (**56**) and **3** at −50 to 0 °C took place in a quite different way to afford 1-[(ethoxycarbonyl)methyl]bicyclo[3.1.0]hexane (**64**) in 74% yield after hydrolysis. If the simple hydrolysis is replaced by deuterolysis or the action of diethyl ketone, 1-[(ethoxycarbonyl)dideuteriomethyl] (with 99% deuterium incorporation), or 1-[(ethoxycarbonyl)(3-pentylidene)methyl] derivative of the above product (**65** or **66**) was obtained in good yields. A 7-en-2-ynoate having an internal *Z*-double bond such as **80** afforded a single stereoisomer **82** with the substituent at the *endo* position of the bicyclic skeleton, suggesting that the stereochemical integrity of the *Z*-double bond of the starting material was retained in the product. An alkyl substituent at the allylic position of the substrates like **74** and **76** nicely controlled the stereochemistry of the cyclization to afford single products **75** and **77** with the substituent being placed in the *exo* orientation of the bicyclic structure. This high diastereoselectivity was successfully applied to an enantioselective synthesis of *d*-sabinene from an optically active enynoate via nearly complete chirality transfer.

Introduction

Intramolecular cyclizations of olefins and acetylenes have been achieved by a variety of transition metal complexes in either a catalytic or a stoichiometric manner with respect to the metal.[1,2] Broad and easy availability of the open-chain, bis-unsaturated precursors **1** (eq 1) makes this method very attractive for the preparation of cyclic compounds. Particularly, the stoichiometric reactions usually leave metallabicycles **2** as the intermediate, which can be utilized for further synthetic elaboration. Frequently encountered are the titana- or zirconabicycles generated with low-valent Cp_2Ti or Cp_2Zr complexes, and their applications to carbon−carbon bond formation or functionalization with second reagents such as an electrophile (El^+) or carbon monoxide (or equivalent isonitriles) have been amply demonstrated as shown in eq 1 (ML_n = $TiCp_2$ or $ZrCp_2$).[1]



Recently, we reported that a low-valent titanium alkoxide, (η^2-propene)Ti(O-*i*-Pr)$_2$ (**3** = ML_m in eq 1) prepared *in situ* from Ti(O-*i*-Pr)$_4$ or Ti(O-*i*-Pr)$_3$Cl and 2 equiv of *i*-PrMgCl,[3−5] also promotes the above bicyclization.[6] This cyclization proved to

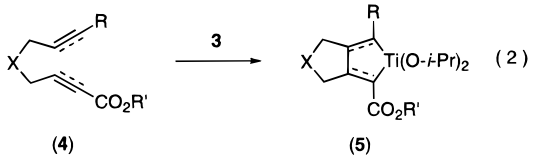
[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

(1) For reviews on early transition metal-mediated cyclizations, see: (a) Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120. (b) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (c) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 1163. (d) Negishi, E.; Takahashi, T. *Acc. Chem. Res*. **1994**, *27*, 124. (e) Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burkalov, V. V.; Rosenthal, U. *Synlett* **1996**, 111. (f) Sato, F.; Urabe, H. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996, p 23.

(2) For recent reviews for general survey, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev*. **1996**, *96*, 635. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49. Cyclization with Co: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 539; Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 1037. With Fe: Takacs, J, M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc*. **1987**, *109*, 2542. Knölker, H.-J.; Heber, J. *Synlett* **1993**, 924. With Mo or W: Jeong, N.; Lee, S. J.; Lee, B. Y.; Chung, Y. K. *Tetrahedron Lett.* **1993**, *34*, 4027. With Nb: Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem*. **1992**, *57*, 1615. With Ni−Cr: Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc*. **1987**, *109*, 5268. With Ni: Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539. With Pd: Trost, B. M. *Acc. Chem. Res*. **1990**, *23*, 34. With Ru or Rh: Chatani, N.; Murai, S. *Synlett* **1996**, 414. With Ta: Takai, K.; Yamada, M.; Odaka, H.; Utimoto, K. *J. Org. Chem*. **1994**, *59*, 5852. With Pt: Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901.

S0002-7863(97)01616-8 CCC: $14.00

be quite general with respect to the substrates. To broaden the scope, we were interested in the cyclization of substrates having a functionalized unsaturated bond. So far, only vinyl and alkynyl ethers or halides (R = OR′ or halogen in eq 1) have been examined as the reaction partner in early transition metal-mediated cyclizations.[7] Keeping the idea in mind that electron-deficient olefins may be prone to interact with a low-valent, hence electron-rich, metal center, we undertook to verify the feasibility of the intramolecular cyclization of substrates like **4** having an α,β-unsaturated ester moiety (eq 2).[8] Gratifyingly,

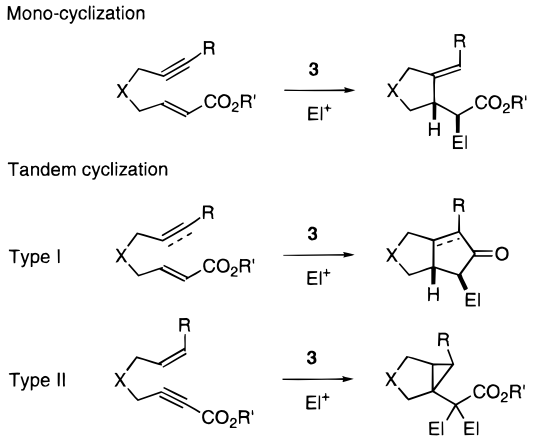


(4) (5) (2)

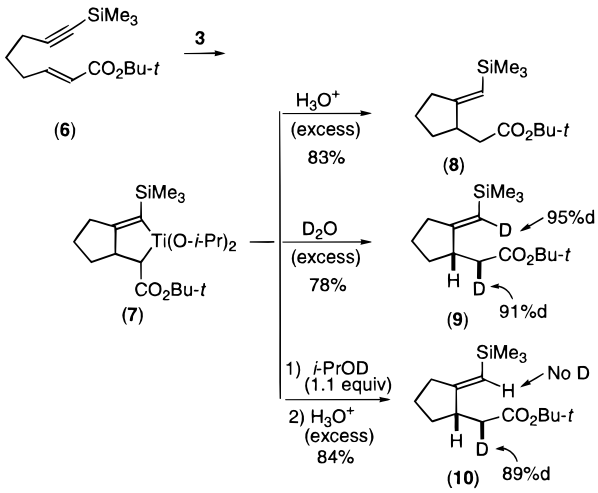
the cyclization proceeds smoothly with the ester group remaining intact to give the titanabicycle **5**[9] as a reasonably stable species. In some cases, the cyclization of **4** was followed by some novel transformations that were more than what we had expected.[10]

Scheme 1 illustrates such representative reactions. The reaction patterns are simply classified according to the structure of the substrates. The first type is a monocyclization, which is observed for α,β-*olefinic* esters having a *hindered* ester group. The intermediate titanabicycles generated herein have an alkenyl−titanium bond as well as a titanium enolate moiety, the latter of which preferentially reacts with an electrophile (El^+) in a highly diastereoselective manner to provide a potential method for the stereoselective construction of the side chain in addition to the cyclization. The same esters, yet having *a less hindered ester group such as methyl or ethyl*, underwent the monocyclization as well, but it is followed by a second ring closure initiated by the reaction with an electrophile, giving eventually bicyclic ketones (Scheme 1, type I of the tandem cyclization).[11] α,β-*Acetylenic* esters experienced another type of tandem cyclization (type II), which led to the formation of a cyclopropane ring via the addition of the alkyl−titanium bond

Scheme 1



Scheme 2



of the titanabicycle to an electron-deficient carbon in the same molecule. An appropriate substituent in the tether portion of these bis-unsaturated esters can favorably regulate the stereochemistry of the cyclization, serving for substrate-controlled asymmetric cyclization.

Results and Discussion

Monocyclization and Diastereoselective Extension of the Side Chain. *tert*-Butyl 2-en-7-ynoate **6** was treated with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**3**), generated *in situ* from Ti(O-*i*-Pr)$_4$ (1.2 equiv) and *i*-PrMgCl (2.4 equiv) in ether, first at −78 °C and finally at −20 °C to ensure the complete cyclization. This procedure is an adaptation of our standard reaction conditions reported previously.[6] After aqueous workup, a virtually sole product **8** was obtained in good yield (Scheme 2). The *E* geometry of its double bond was confirmed by NOE study of ^{1}H NMR spectroscopy. The presence of the intermediate titanabicycle **7** was verified by the bis-deuterolysis with excess D_2O to give **9**. Alternatively, the titanabicycle **7** was first treated with 1.1 equiv of *i*-PrOD and then worked up as above to afford the monodeuterated product **10**, indicating the higher reactivity of the titanated ester portion of **7** toward the proton as compared to its alkenyltitanium moiety.[12,13] This difference in the reactivities between both carbon−titanium bonds is the key in the following reactions.

In addition to this site selectivity, another important feature is that the deuterium is exclusively incorporated in place of one

(3) The generation of olefin (derived from the added Grignard reagent)−titanium complexes from Ti(OR)$_4$ and Grignard reagents was first reported by Kulinkovich *et al*. They utilized this complex as 1,2-bis-anionic species, see: Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. See also: de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem*. **1993**, *58*, 502. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, 117, 9919. Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc*. **1994**, *116*, 9345.

(4) A similar titanium species having aryloxy groups in place of the alkoxy group is known. Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc*. **1993**, *115*, 1581. Balaich, G. J.; Rothwell, I. P. *Tetrahedron* **1995**, *51*, 4463.

(5) For the initial reports on the use of (η^2-propene)Ti(O-*i*-Pr)$_2$ prepared *in situ* from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl as a divalent titanium reagent, see: Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 3203. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc*. **1995**, *117*, 3881. See also: Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc*. **1996**, *118*, 2208. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198.

(6) (a) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 4261. (b) Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett*. **1996**, *37*, 1253. (c) Urabe, H.; Sato, F. *J. Org. Chem*. **1996**, *61*, 6756.

(7) Nugent, W. A.; Thorn D. L.; Harlow, R. L. *J. Am. Chem. Soc*. **1987**, *109*, 2788. Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc*. **1995**, *117*, 5871.

(8) To our best knowledge, early transition metal-mediated bicyclization of α,β-unsaturated ester and another olefin or acetylene has not been reported. However, reductive homocoupling of dimethyl acetylenedicarboxylate or α,β-unsaturated aryl ketones with $Cp_2Ti(CO)_2$ has been reported. Demerseman, B.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun*. **1981**, 665. Schobert, R.; Maaref, F.; Dürr, S. *Synlett* **1995**, 83.

(9) Although the structure of **5** (and the relevant species hereafter) is tentatively drawn in the form of α-titana ester for simplicity, its exact nature is unknown and, accordingly, it may be the corresponding titanium enolate (for example, see Scheme 3).

(10) Portions of this work have been communicated. Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1996**, *118*, 8729.

(11) For reviews on tandem reactions, see: Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev*. **1996**, *96*, 195.

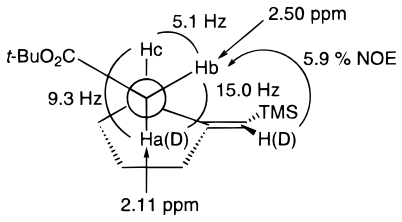


Figure 1. ^{1}H NMR analysis on the structure of **10**.

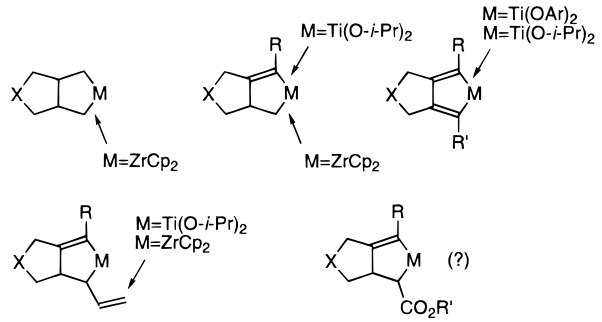


Figure 2. Carbon−metal bond reacting with aldehydes and ketones.

particular hydrogen of the two α-protons of the ester group. The stereochemical assignment to the deuterated position as depicted in Scheme 2 was unambiguously made by the following ^{1}H NMR analysis. Figure 1 shows a Newman projection (view from ester α-carbon to ring carbon) of the most stable conformer **8**−**10**. Both protons Ha and Hb α to the ester group (δ 2.11 and δ 2.50 ppm) were distinguished from each other on the basis of following: (i) the downfield shift for Hb as compared to Ha owing to the deshielding effect of the nearby olefinic bond, (ii) the fact that the coupling constants observed between Ha/Hc and Hb/Hc shown in the figure satisfy the calculated values by the Karplus equation based on a molecular model, and (iii) the NOE observed for the proton Hb and the vinylic proton, but not between Ha and the vinylic proton. On deuterolysis, proton Ha (δ 2.11 ppm) was exclusively exchanged to deuterium to give **9** or **10**.

Reaction of metallacycles with carbon electrophiles such as carbonyl and related compounds should provide a straightforward method for the side-chain extension after the cyclization. These reactions have been documented for representative types of metallabicycles of early transitions metals. Figure 2 summarizes the position where the carbon−metal bond is cleaved with aldehydes. The titanacyclo*pentenes* and *-pentadienes* react with aldehydes at their *alkenyl*−titanium bond,[6c,14] while Cp_2-zirconacyclo*pentanes* and *-pentenes* afford adducts at their *alkyl*−zirconium bond.[1b,15] Both titana- and zirconabicycles having an α-vinyl group are known to attack carbonyl compounds at the terminal carbon of the vinyl group.[1b,6b,16] The degrees of the site selectivity generally fall within a very high range.

In relation to the above discussion, reaction of the new titanabicycle **7** with carbonyl compounds should be of interest in the synthetic point of view. The titanacycle **7** and formaldehyde afforded a nearly single product **11** (eq 3). Only a small amount of a byproduct which may be the minor diastereoisomer of **11** was detected. The reaction took place at the titanated ester in **7** without any complication, and no adduct arising from the alkenyl−titanium moiety was observed under these reaction conditions.[17] The shown stereochemistry of **11** stems from its cyclization to tetrahydrofuran **12** (eq 3), the structure of which was determined by NOE study on ^{1}H NMR spectroscopy to have the (thermodynamically less stable) *endo*-ester group (Figure 3).

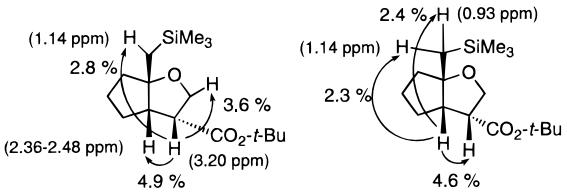
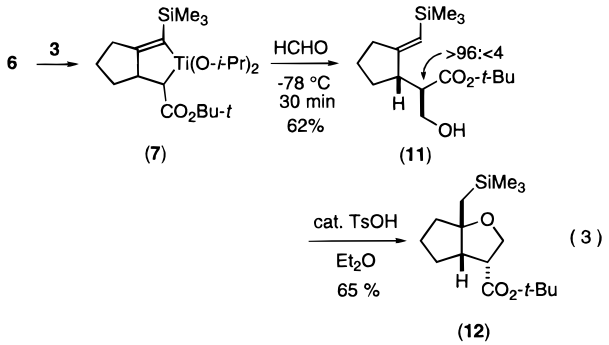


Figure 3. NOE study on the structure of **12**.



It is noteworthy that the high diastereoselectivity found for the deuterolysis (Scheme 2) was preserved in the carbonyl addition, which means that the stereogenic centers with respect to the cyclopentane ring and the ester α-carbon could be efficiently created.[18] This type of highly 1,2-diastereoselective construction of the side chain from the metallacycles is the first demonstration in the early transition metal-mediated cyclizations, which complements the previously reported 1,3-[15] or 1,4-stereoselectivities[6c] involving the orientation of the hydroxy group arising from the aldehyde addition. Other results are summarized in Table 1. The same reactions of the titanabicycles generated from **6**, (*Z*)-**6**, **15**, and **17** with a few carbonyl compounds always realized the stereoselective extension of the side chains (entries 2, 3, 5, 6, and 9). The depicted structures of these products were deduced provided that the reaction took place in the same sense as **10** and **11**. It should be emphasized that the stereochemical integrity of the olefinic portion of the starting materials **6** and (*Z*)-**6** was completely lost during the

(12) For the general reactivity of carbon-titanium bonds, see: Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 116. See also the following: Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 1, p 139. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, U.K., 1994; p 195.

(13) Cf. For regioselection in protonation of other metallacyclopentenes of early transition metal, see: (a) Aoyagi, K.; Kasai, K.; Kondakov, D. Y.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1994**, *220*, 319. (b) Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem*. **1994**, *59*, 5643.

(14) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911.

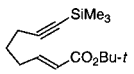
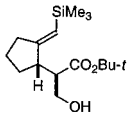
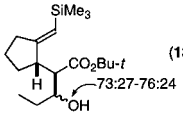
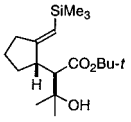
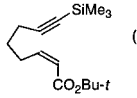
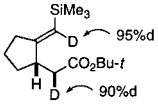
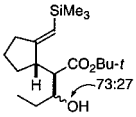
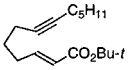
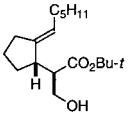
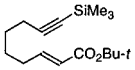
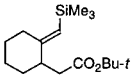
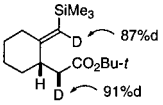
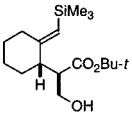
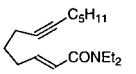
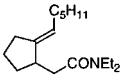
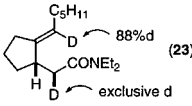
(15) Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett*. **1994**, *35*, 695.

(16) Negishi, E.; Miller, S. R. *J. Org. Chem*. **1989**, *54*, 6014. Dimmock, P. W.; Whitby, R. J. *J. Chem. Soc., Chem. Commun*. **1994**, 2323. Hanzawa, Y.; Harada, S.; Nishio, R.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 9421. Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 9465.

(17) Ordinary alkenyltitanium species were reported to react with aldehydes. Boeckman, R. K., Jr.; O'Connor, K. J. *Tetrahedron Lett*. **1989**, *30*, 3271. Schick, H.; Spanig, J.; Mahrwald, R.; Bohle, M.; Reiher, T.; Pivnitsky, K. K. *Tetrahedron* **1992**, *48*, 5579.

(18) 1,2-Diastereoselective introduction of a side chain to a ring structure is often necessary transformation. With aldol reactions: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 181. With 1,4-additions: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992; p 137. With sigmatropy rearrangements: Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 785. Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 827. Wilson, S. R. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1993; Vol. 43, p 93. With radical reactions: Curran, D. P. *Synthesis* **1988**, 417.

Table 1. Monocyclization of Bis-unsaturated Esters and Amides and Subsequent Reactions with Electrophiles[a]

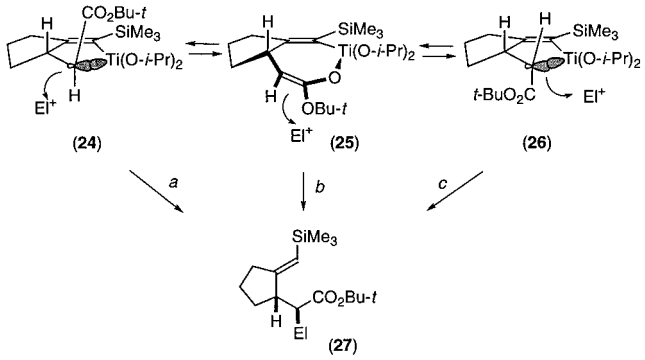
Entry	Unsaturated Ester		Electrophile	Product		Yield (%)	D.S.[b]
1		(**6**)	HCHO		(**11**)	62	>96:<4
2	**6**		EtCHO		(**13**)	63	single
3	**6**		Me_2CO		(**14**)	34	single
4		(*Z*-**6**)	D_2O		(**9**)	78	single
5	*Z*-**6**		EtCHO		(**13**)	61	single
6		(**15**)	HCHO		(**16**)	78	>93:<7
7		(**17**)	H_3O^+		(**18**)	52	--
8	**17**		D_2O		(**19**)	50	single
9	**17**		HCHO		(**20**)	25	single
10		(**21**)	H_3O^+		(**22**)	80	--
11	**21**		D_2O		(**23**)	82	single

[a] See Scheme 2 and eq 3. [b] Diastereoselectivity with respect to bold lines. "Single" refers to a case wherein the minor isomer could not be identified even after careful analysis.

reaction to give the same deuterated and aldol-type products (cf. Scheme 2 and entry 4 in Table 1, and entries 2 and 5),[19] which is to be discussed afterward. The monocyclization was the exclusive path also for an *N*,*N*-dialkylamide **21** as exemplified in entries 10 and 11. The highly stereoselective deuterolysis of the titanated amide was again observed, and the structure of **23** was assigned in an analogous way to that of **10** (Figure 1) by ^{1}H NMR analysis.

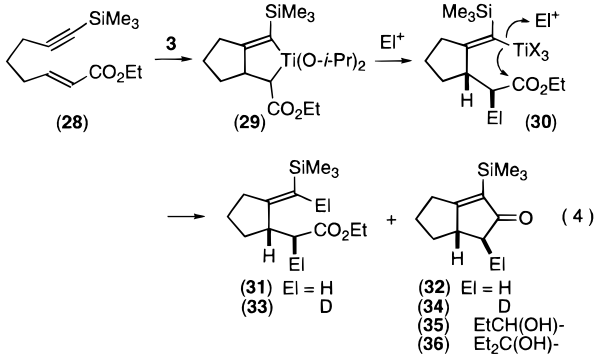
The stereochemical outcome may be explained by the three likely models of electrophilic attack to the titanabicycle, which include an α-titana ester and/or titanium enolate[12] and are illustrated in Scheme 3. In path *a*, the sterically demanding *tert*-butoxycarbonyl group of **24** occupies the equatorial position and an electrophile must attack the carbon-titanium bond with inversion of configuration[20] to give the observed product **27**.

Scheme 3



Contrarily, path *c* assumes an electrophilic addition to the carbon−titanium bond with retention of configuration.[21] To accommodate the *tert*-butoxycarbonyl group to this reaction course, it should be located in axial direction in the reacting species, although this position is considerably encumbered. Finally, the most plausible path among the three would be path *b* because one side of the π-plane of the titanium enolate in **25** may be effectively blocked owing to the seven-membered oxatitanacycloheptadiene structure similar to those of enolates of medium-ring ketones or lactones.[22] This could reasonably account for (i) the observed sense of the addition irrespective of the kind of electrophiles, (ii) the uniformly high diastereoselectivities, and (iii) the loss of the geometrical integrity of the starting α,*β*-unsaturated ester (*E* or *Z*) after the reaction.

Tandem Cyclization of α,*β*-Olefinic Esters (Type I). Although we had successfully carried out the cyclization of the *tert*-butyl enynoates as described above, we were rather confused to encounter difficulties when we attempted to obtain the same products starting from the corresponding ethyl esters. Ethyl 2-en-7-ynoate **28** (1 equiv) was treated with **3** (1.2 equiv, prepared from $Ti(O\text{-}i\text{-}Pr)_3Cl$) under the standard reaction conditions to afford the desired cyclized product **31**, but together with a more polar product in varying ratios from run to run (*ca.* 6:4−3:7) after aqueous workup (eq 4).



(4)

The structure of this byproduct was deduced by spectroscopic analysis, which disclosed the lack of the ester moiety yet revealed the presence of a cyclopentenone skeleton with a vinylic trimethylsilyl group. Finally, the proposed structure **32** (El = H) was firmly established in comparison with an authentic

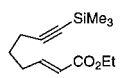
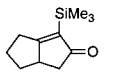
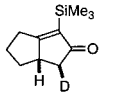
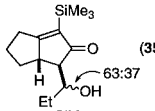
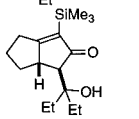
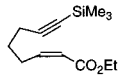
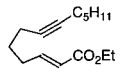
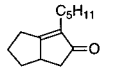
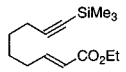
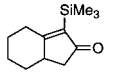
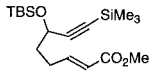
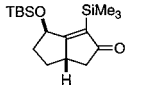
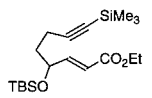
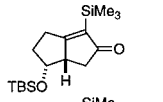
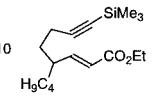
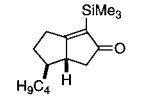
(19) For the issue on transmission of olefin geometry to the product, see and compare: Negishi, E.; Choueiry, D.; Nguyen, T. B.; Swanson, D. R. *J. Am. Chem. Soc.* **1994**, *116*, 9751. Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450.

(20) Even though we intensively searched the literature, we could not find any dependable data on the stereochemistry of the electrophilic attack to a titanium−carbon bond adjacent to an ester group.

(21) This stereochemistry was proposed for other early transition metal complexes. Four-membered transition state was given in the reaction of a zirconacyclopentene with aldehydes to rationalize the stereochemical result (ref 15). Deuteration of a zirconacyclopentene most likely proceeded with retention of configuration. See ref 13b.

(22) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, p 73. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

Table 2. Type I Tandem Cyclization of Enynoates and Subsequent Reactions with Electrophiles[a]

Entry	Unsaturated Ester	Electrophile[b]	Product[c]	Yield (%)	D.S.[d]
1	 (28)	H^+	 (32)	80	--
2	**28**	D^+	 (34[e])	79	single
3	**28**	EtCHO	 (35)	78	single
4	**28**	Et_2CO	 (36)	65	single
5	 (37)	D^+	**34**[e]	66	single
6	 (38)	H^+	 (39)	73	--
7	 (40)	H^+	 (41)	54	--
8	 (42)	H^+	 (43)	52	60:40
9	 (44)	H^+	 (45)	69	90:10
10	 (46)	H^+	 (47)	89	97: 3

[a] See eq 4. [b] H^+ or D^+ refers to 1.1 equiv of *s*-BuOH or *i*-PrOD. [c] Major isomer is shown. [d] Diastereoselectivity with respect to bold or dotted lines. "Single" refers to a case wherein the minor isomer could not be identified even after careful analysis. [e] Exclusively deuterated.

sample.[23] At this stage, we became aware that the ketone **32** was formed via intramolecular attack of the alkenyltitanium moiety of **30** to its ester group, both of which were generated through the fast and selective protonation to the titanabicycle **29** as described in the preceding section. The shaky product ratios should reflect the subtle change in the noncontrolled workup conditions which allow the following two reactions to compete with each other: the resulting alkenyltitanium **30** suffered further protonation to afford **31**, or it underwent the intramolecular attack to the ester group to give **32**. To suppress the second proton delivery to **30**, we terminated the reaction with a limited amount of the proton source (1.1 equiv of *s*-BuOH to **28**), which, in fact, enabled a selective formation of the ketone **32** uniformly in good yields (80% in isolation or 90% determined by ^{1}H NMR spectroscopy) (entry 1 in Table 2). If the titanium reagent **3** prepared from Ti(O-*i*-Pr)$_3$Cl was replaced by the one prepared from Ti(O-*i*-Pr)$_4$, the yield of **32** determined by ^{1}H NMR dropped to 81%. Deuterolysis of the same reaction mixture of **29** with excess D_2O afforded a mixture of **33** (97% D in place of one particular hydrogen α to the ester group and 89% D at the vinylic position) and **34**, but 1.1 equiv of *i*-PrOD gave cleanly **34** (eq 4 and entry 2 in Table 2). Gratifyingly, the electrophile involves not only proton (or deuterium) but also carbonyl compounds. Thus, the titanabicycle **29** could be trapped with propionaldehyde or diethyl ketone to promote the second ring closure as described above to give the products **35** and **36** in good yields. In all of these reactions, the electrophiles were introduced to the convex face of the bicyclo[3.3.0]octene system in high selectivities. This stereochemical outcome, which apparently originates at the stage of the initial electrophilic attack to the titanabicycle and is, of course, consistent with the observation of **10** and **11** (Scheme 2 and eq 3), was independently determined on the basis of the coupling constants and/or NOE studies of ^{1}H NMR spectroscopy.

Additional results of the cyclization of type I starting from a variety of substrates are summarized in entries 5−10 in Table 2.[24,25] The reaction has broad applicability to 2-en-7-ynoates and also a 2-en-8-ynoate. The stereochemical integrity of the olefinic portion of the starting materials **28** and **37** was again lost in the (deuterated) products (entries 2 and 5) in accord with the observation discussed in the monocyclization. Control of the stereochemistry of the cyclization by an appropriate substituent in the substrate is often a necessary operation in conjunction with an asymmetric cyclization via chirality induction.[26,27] The siloxy substituent at the propargylic position in **42** showed a moderate effect on the ratio of the diastereoisomers **43** (entry 8), which were separable by routine flash chromatography. The same substrate having a benzyloxy group in place of the siloxy substituent did not improve this selectivity. In contrast, an allylic substituent of α,β-unsaturated ester **44** or **46** nicely controlled the direction of the cyclization to give the products **45** and **47** in high selectivities. Pure samples of **45** and **47** free of the minor isomers could be easily obtained by chromatography on silica gel. The prevailing influence of nearby 1,2-interaction of the diastereomeric centers (**45** and **47**) over that of remote 1,3-relationship (**43**) would account for the higher degree of diastereoselectivities in the former. ^{1}H NMR analysis revealed that the stereochemistry of cyclization controlled by the siloxy or the alkyl group is in reverse to each other. It is also noteworthy that the siloxy group-directed cyclization of **44** took place with the opposite orientation to the carbonylative cyclization of a similar substrate **48** (eq 5), which placed the benzyloxy group at the *exo* position to give **49**.[24a,25b] Thus, these methods could be used complementarily to prepare the oxygenated bicyclic structures, although the origin

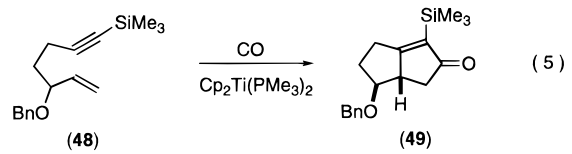
(23) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

(24) 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 a comprehensive survey, see refs 1 and 2. For recent reports on early transition metal-promoted carbonylation, see: with Cp_2Ti complex: (a) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116*, 8593. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11688. With (*i*-PrO)$_2$Ti complex: (c) reference 6a. Preparation of bicyclic ketone (or imine)−zirconium complexes via zirconium-mediated cyclization and carbonylation of dienes and enynes and their reactions with electrophiles were reported, see: (d) Probert, G. D.; Whitby, R. J.; Coote, S. J. *Tetrahedron Lett*. **1995**, *36*, 4113. (e) Barluenga, J.; Sanz, R.; Fañanás, F. J. *J. Chem. Soc., Chem. Commun*. **1995**, 1009.

(25) For application of these bicyclic ketones as starting materials for the synthesis of naturally occurring products, see: (a) Trost, B. M. *Chem. Soc. Rev*. **1982**, *11*, 141. (b) Agnel, G.; Negishi, E, *J. Am. Chem. Soc*. **1991**, *113*, 7425. (c) Agnel, G.; Owczarczyk, Z.; Negishi, E. *Tetrahedron Lett*. **1992**, *33*, 1543. (d) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem*. **1994**, *59*, 5633. (e) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem*. **1987**, *52*, 1483. (f) Jeong, N.; Lee, B. Y.; Lee, S. M.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett*. **1993**, *34*, 4023. (g) Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett*. **1997**, *38*, 465.

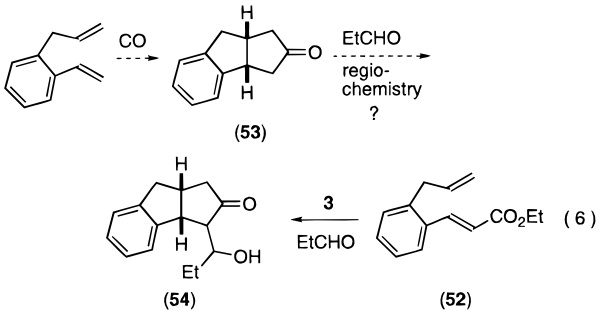
(26) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307.

(27) Diastereoselectivities in substrate-controlled, early transition metal-mediated ring closure were extensively studied. See ref 1c and the following recent reports: RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc*. **1988**, *110*, 7128. Taber, D. F.; Louey, J. P. *Tetrahedron* **1995**, *51*, 4495. Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421. Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A, *Tetrahedron Lett*. **1996**, *37*, 9059.



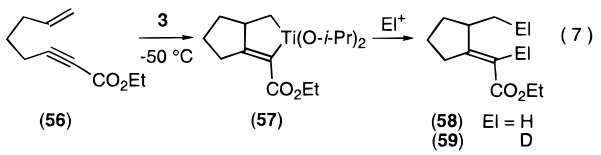
of the unusual role of the allylic siloxy group in the present cyclization can not be explained.

2,7-Dienoates **50** and **52** having a terminal double bond behaved in a way similar to 2-en-7-ynoates (Table 3). We were able to isolate only *cis*-fused bicyclic ketone as the product of the tandem cyclization. Neither its *trans*-isomer nor the *trans*-substituted monocyclic product that may be reluctant to undergo the second ring closure could be seen. These facts could be attributed to the good *cis*-selectivity in the first cyclization step, which is in contrast to the cyclization of unfunctionalized 1,6-dienes affording a *trans*-disubstituted cyclopentane as the major product.[6a] The unsaturated ester having another internal olefin such as **55** only resulted in a complicated reaction (entry 4). We emphasize that the trapping of the titanabicycle, generated from **52**, with 1.5 equiv of propionaldehyde afforded the aldol product **54** virtually as a single isomer (entry 3). While the stereochemistry of its ring junction could be determined to be *cis*, that of the aldol moiety has not been assigned yet. From the synthetic point of view, this reaction demonstrated a one-pot preparation of an aldol of *the defined regiochemistry* (eq 6). Although several transition metal-mediated transformations



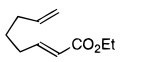
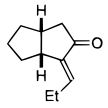
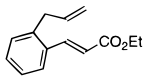
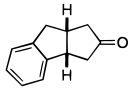
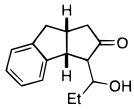
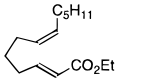
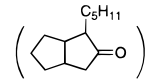
involving cyclization and carbonylation of dienes or enynes may serve for the preparation of the parent ketone **53** itself,[24] further extension of a carbon chain is not usually possible and even a successive aldol reaction will not guarantee the regioselection, particularly in the case of nearly symmetrical **53**.

Tandem Cyclization of α,*β*-Acetylenic Esters (Type II). In contrast to the aforementioned reactions starting from an α,*β*-olefinic ester, α,*β*-acetylenic esters underwent another type of cyclization (type II in Scheme 1). 7-En-2-ynoate **56** afforded the monocyclization product **58** (91%) after the reaction with **3** under the standard conditions (−50 °C, 2 h)[6] followed by aqueous workup (eq 7). The intermediate titanabicycle **57** was confirmed by the isolation of **59** (>99% D_2) after deuterolysis.

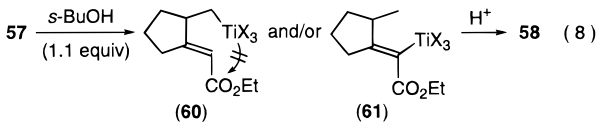


No other isolable byproducts were found under these reaction conditions. The monocyclic **58** was again produced in 80% yield even when the reaction mixture of **57** was treated with 1.1 equiv of *s*-BuOH at −50 to 0 °C followed by aqueous workup as shown in the foregoing section (eq 8). This experiment clearly shows that the possible monotitanated intermediate **60** and/or **61** does not undergo any subsequent reactions.

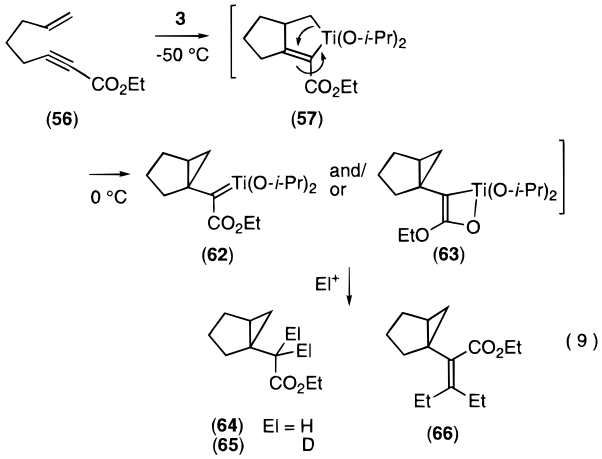
Table 3. Type I Tandem Cyclization of 2,7-Dienoates and Subsequent Reactions with Electrophiles[a]

Entry	Unsaturated Ester		Electrophile[b]	Product		Yield (%) [Ratio]
1		(**50**)	EtCHO		(**51**)[c]	53
2		(**52**)	H^+		(**53**)	74
3	**52**		EtCHO		(**54**)	69 [single[d]]
4		(**55**)	H^+			0

[a] See eq 4. [b] H^+ refers to 1.1 equiv of *s*-BuOH. [c] After dehydration of the aldol product (TsOH, C_6H_6, reflux). [d] See text.

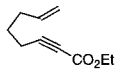
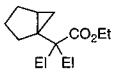
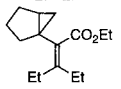
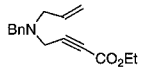
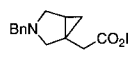
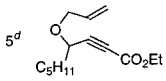
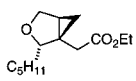
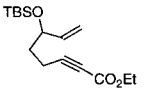
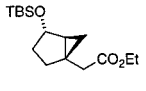
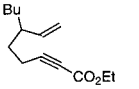
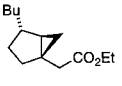
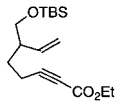
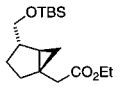
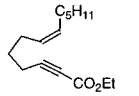
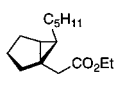


However, when the titanabicycle generated at −50 °C was simply allowed to warm to a higher temperature up to 0 °C, the above product **58** completely disappeared and a new product **64** was obtained in good yield (eq 9). Its structure having a



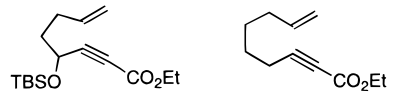
cyclopropane ring was first suggested by NMR and IR spectroscopy and was eventually confirmed in comparison with an authentic sample. As in type I reactions, **3** generated from $Ti(O\text{-}i\text{-}Pr)_3Cl$ was again the reagent of choice, which increased the yield of **64** by 10−20% as compared to the one prepared from $Ti(O\text{-}i\text{-}Pr)_4$. Formation of this new compound is most likely rationalized as follows. The alkyl−titanium bond of the titanacycle **57**, the presence of which was confirmed by the deuterolysis shown in eq 7, attacks the proximate terminus of the electron-deficient carbon−carbon double bond to give the new titanium compound **62**/**63**, which, upon hydrolysis, afforded the observed product **64**. The intermediary of the titanium−carbene complex **62**[28] and/or bis-titanated species **63**[29] was, in fact, verified by the treatment of the reaction mixture with excess DCl/D_2O, which gave **65** with virtually complete deuterium incorporation (>99% D_2) in place of both hydrogens α to the ester group (eq 9 and entry 2 in Table 4).[30] The intermediate **62**/**63** underwent smooth alkylidenation of diethyl ketone at around 0 °C to give **66**, which demonstrated the titanium−carbene complex-like behavior of this bimetallic species.[28]

Table 4. Type II Tandem Cyclization of 7-En-2-ynoates and Subsequent Reactions with Electrophiles[a]

Entry	Unsaturated Ester		Electrophile	Product[b]		Yield (%)	D.S.[c]
1		(56)	H^+		El = H (64)	74	--
2			D^+		D (65)	78 (99%d_2)	--
3	56		Et_2CO		(66)	58	--
4		(67)	H^+		(68)	76	--
5[d]		(69)	H^+		(70)	53	3:1
6		(72)	H^+		(73)	70	62:38
7		(74)	H^+		(75)	63	single
8		(76)	H^+		(77)	78	single
9		(80)	H^+		(82)	51	single

[a] See eq 9. [b] Major isomer is shown. [c] Diastereoselectivity with respect to bold or dotted lines. "Single" refers to a case wherein the minor isomer could not be identified even after careful analysis. [d] The reaction was finally performed at room temperature.

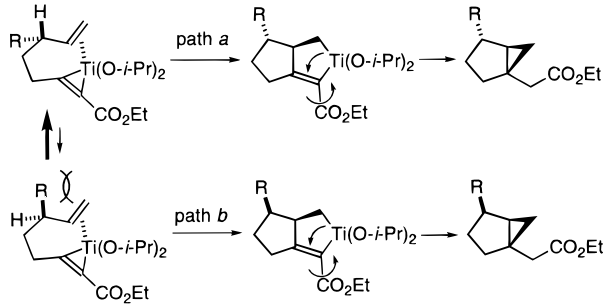
This cyclization proved to be general to a variety of 7-en-2-ynoates having a substituent (Table 4). A heteroatomic moiety in the tether of the enynoate could tolerate the reaction conditions to give heterocyclic compounds **68** and **70** (entries 4 and 5). A substitution to the propargyl position showed a retarding effect on the progress of the second cyclization,



(71) (83)

Figure 4. Substrates unsuitable for type II cyclization.

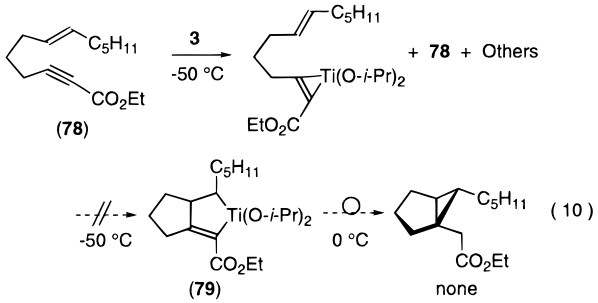
Scheme 4



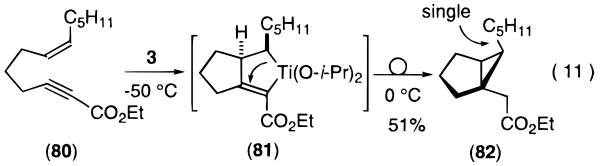
although the first cyclization giving a titanabicycle was, in fact, proved to be completed as evidenced by the hydrolysis of the intermediate. For example, the cyclopropane formation from **69** did not proceed well at 0 °C so that it requires more forcing conditions involving room temperature, at which the desired product **70** could be obtained in an acceptable yield and with moderate diastereoselectivity (entry 5). However, another substrate **71** with a siloxy group (Figure 4) no longer afforded the expected product (<20%) even at room temperature.

On the contrary, an allylic substituent does not seem to have a detrimental effect on the cyclopropane cyclization. Enynoate **72** having an allylic siloxy group afforded a 62:38 mixture of the diastereoisomers **73** in good yield under the standard reaction conditions (entry 6). To our satisfaction, switching the substituent from the siloxy to an alkyl such as butyl or $TBSOCH_2-$ group nearly completely controls the stereochemistry of the cyclization to afford virtually a single product **75** or **77** carrying the *exo*-substituent (entries 7 and 8). The less sterically hindered path *a* prevailing over path *b* as shown in Scheme 4 would rationalize the stereoselection observed herein. This highly diastereoselective cyclopropane formation was subsequently applied to a synthesis of *d*-sabinene (*vide infra*).

Equation 10 shows that enynoate **78** having an internal *E*-double bond failed in the *first cyclization* to give any titanabicycle **79** at all, as judged by the hydrolysis of the reaction



mixture, which gave ethyl (2*Z*,7*E*)-tridecadienoate as the main product. However, enynoate **80** having a *Z*-disubstituted double bond did undergo the cyclization eventually to give the substituted cyclopropane **82** as a single stereoisomer (eq 11).

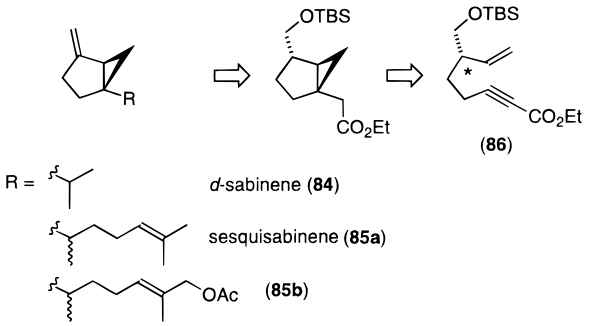


(28) The presence of a titanium−carbene complex is invoked in several synthetic reactions, see: Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. Yoshida, T.; Negishi, 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. Petasis, N. A.; Hu, Y.-H. *J. Org. Chem.* **1997**, *62*, 782. For a relevant review, see: Beckhaus, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 687.

(29) 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.

(30) Cyclization of enynes with certain metal−carbonyl or −carbene complexes afforded a similar class of compounds. However, a bimetallic 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. Watanuki, S.; Mori, M. *Organometallics* **1995**, *14*, 5054. Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268. Lee, J. E.; Hong, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1997**, *38*, 1781. For other representative methods for the synthesis of cyclopropanes, see the following. By alkylation: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; Vol. 2, p 181. By addition−elimination sequence: Chapdelaine, M.; Hulce, M. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1990; Vol. 38, p 225. By carbene or carbenoid addition: Helquist, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, p 951. Nair, V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 999. Davies, H. M. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, p 1031.

Scheme 5

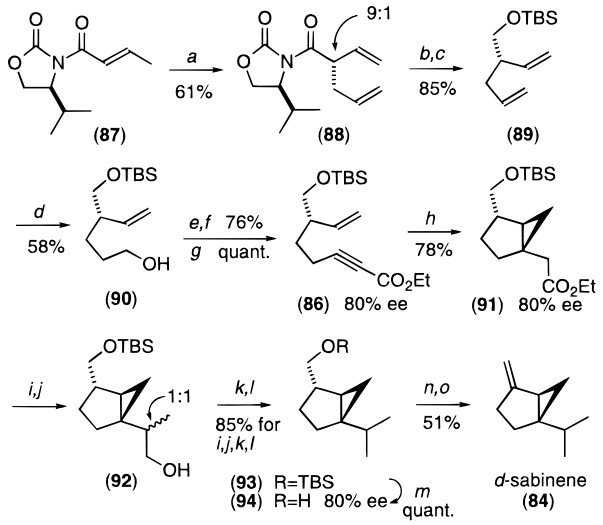


The observed stereochemical outcome, which obviously does not arise from a thermodynamically controlled cyclization, should reflect the initial geometry of the double bond in **80** via the reaction with retention of configuration of the carbon−titanium bond in **81**.[19] The attempted cyclization of an 8-enynoate **83** (Figure 4) afforded an intractable mixture of several products, in which the desired bicyclic product is a very minor constituent.

A Synthesis of *d*-Sabinene. *d*-Sabinene (**84**), widely distributed in essential oils from plants, is a monoterpene having a chiral cyclopropane moiety.[31] Sesquisabinene and its derivative (**85a**,**b**) also belong to the same class.[31] A few racemic syntheses of sabinene have been reported in the past 30 years.[32] A synthetic plan taking advantage of the substrate-controlled chirality transfer and starting from **86** (optically active form of **76**) is shown in Scheme 5.

The optically active 2-vinyl-1-alkanol moiety in **86** was readily prepared by deconjugative allylation of the known Evans amide **87**,[33a] which gave a 9:1 mixture of the diastereoisomers **88** (Scheme 6).[33] We did not attempt to seek optimal conditions for achieving better selectivity. The structure of the major isomer was assigned by consideration of the precedents and finally was certified by the completion of the synthesis of **84**. After removal of the chiral auxiliary by a reductive method, the resultant alcohol was protected with the TBS group to give **89**. 9-BBN was able to recognize a subtle difference between the two terminal olefins in **89** (9:1 selectivity by a qualitative estimation) in its hydroboration to give the alcohol **90**, which was converted to the acetylene ester **86** by standard methods.[34,35] The ee of the sample **86** was determined to be 80%, reflecting the isomeric ratio of **88**. The cyclization was carried out under standard conditions as above to give **91** in 78% yield and 80% ee determined by chiral shift study ((+)-Eu(hfc)$_3$) on ^{1}H NMR spectroscopy. Thus, the highly effective chirality transfer was achieved. Methylation and reduction afforded the 1:1 mixture of diastereomeric alcohols **92**. It is interesting to note that these alcohols showed significantly different R_f values on silica gel, which is informative observation for the synthesis of **85**, in which the separation of diastereoisomers at this stage will be crucial. Deoxygenation of the alcohol via its tosylate[36] and deprotection of the TBS ether afforded the alcohol **94**, the enantiopurity of which is again 80% ee. Dehydration of the alcohol with a selenium reagent[37] completed the synthesis of *d*-sabinene (**84**): $[\alpha]_D^{23}$ +75.8 (*c* 0.65, *n*-pentane) for a sample of 80% ee; lit. $[\alpha]_D^{20}$ +107 ± 3 (in substance) for a 99% pure sample;[38a] $[\alpha]_D$ +89.[38b]

Scheme 6[a]



[a] Key: (a) LDA-HMPA, allyl bromide; (b) $LiAlH_4$; (c) TBS-Cl, imidazole; (d) 9-BBN, H_2O_2; (e) DMSO, SO_3·py, NEt_3; (f) CBr_4, PPh_3; (g) BuLi, $ClCO_2Et$; (h) see text; (i) LDA, MeI; (j) Dibal-H; (k) TsCl, py; (l) $LiEt_3BH$; (m) TBAF; (n) 2-$(O_2N)C_6H_4SeCN$, PBu_3; (o) H_2O_2, K_2CO_3.

Conclusion

The low-valent titanium-mediated cyclization of bis-unsaturated compounds having a conjugated ester moiety was found to be a versatile method to obtain mono- and bicyclic compounds. The diastereoselective reaction of carbonyl compounds with the intermediate titanium species allows facile stereoselective extension of side chains from the cyclization product. Alternatively, the stereoselective cyclization controlled by an appropriate substituent in the substrate is also a useful tool for construction of the ring structure of the defined stereochemistry. In addition to these points, this transformation circumvents the use of carbon monoxide in the preparation of bicyclic ketones and provides an opportunity for regioselective aldol formation from a nearly symmetrical ketone (in type I reaction). All of these advantages make this method very attractive in the preparation of stereogenic centers involving a cyclic structure, a part of which is illustrated in the synthesis of *d*-sabinene.

Experimental Section

General Procedure. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively. $CDCl_3$ was used as the solvent unless otherwise noted. Chemical shifts

(31) (a) Croteau, R. B. *ACS Symp. Ser.* **1992**, *490*, 8. (b) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. II, pp 30−31. (c) Glasby, J. S. *Encyclopaedia of the Terpenoids*; Wiley: Chichester, U.K., 1982. (d) Hanson, J. R., Ed. *Terpenoids and Steroids*; The Royal Society of Chemistry: London, 1981; Vol. 10, p 17.

(32) For racemic synthesis, see: (a) Rousseau, G.; Slougui, N. *J. Am. Chem. Soc*. **1984**, *106*, 7283. (b) Vig, O. P.; Bhatia, M. S.; Gupta, K. C.; Matta, K. L. *J. Ind. Chem. Soc*. **1969**, *46*, 991. (c) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1968**, *33*, 1656. A synthetic sample of optically active sabinene has been recorded, but no details are given. See ref 31b and the references cited therein.

(33) For a review, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737. (c) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem*. **1993**, *58*, 2725.

(34) Tidwell, T. T. *Synthesis* **1990**, 857. Tidwell, T. T. In *Organic Reactions*; Wiley: New York, 1990; Vol. 39, p 297.

(35) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, 3769.

(36) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.

(37) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem*. **1976**, *41*, 1485. Sharpless, K. B.; Young, M. W. *J. Org. Chem*. **1975**, *40*, 947. Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1996**, *118*, 7108.

(38) (a) *Fluka Chemika-BioChemika*; Fluka Chemie AG: Buchs, Switzerland, 1995; Vol. 1995/96. (b) Padmanabhan, R.; Jatkar, S. K. K. *J. Am. Chem. Soc*. **1935**, *57*, 334.

(39) Screttas, C. G.; Smonou, I. C. *J. Organomet. Chem*. **1988**, *342*, 143. Barluenga, J.; Alvarez, F.; Concellon, J.; Yus, M. *Synthesis* **1986**, 654.

(40) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

are reported in parts per million (δ value) from Me_4Si ($\delta = 0$ ppm for ^1H) or based on the middle peak of the solvent ($CDCl_3$) ($\delta = 77.00$ ppm for ^{13}C NMR) as an internal standard. When ^1H NMR spectra were taken in C_6D_6, the peak of the residual proton of the solvent is the internal standard ($\delta = 7.20$ ppm). Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz. Infrared (IR) spectra were recorded on a JASCO FT/IR-230 spectrometer. Broad or shoulder peaks were specified as br or sh. Optical rotation was measured on JASCO DIP-370 digital polarimeter. All reactions were performed under nitrogen or argon. Solvents and chemicals were purified or dried in a standard manner.

Starting Materials. Preparation and characterization data of all starting materials are placed in the Supporting Information.

Typical Procedure for the Monocyclization. *tert*-Butyl [2-[(*E*)-(Trimethylsilyl)methylene]cyclopent-1-yl]acetate (8). To a stirred solution of Ti(O-*i*-Pr)$_4$ (0.070 mL, 0.24 mmol) in Et_2O (2 mL) were successively added **6** (53.3 mg, 0.20 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.30 mL, 1.60 M solution in Et_2O, 0.48 mmol) in this order at −78 °C under an argon atmosphere. The solution was gradually allowed to warm to −20 °C over 1 h and kept at this temperature for an additional 2 h. Then the reaction was terminated by the addition of 1 N HCl and Et_2O. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to give the title compound (44.5 mg, 83%) as an oil: ^1H NMR δ 0.07 (s, 9H), 1.18−1.39 (m, 1H), 1.45 (s, 9H), 1.50−1.68 (m, 1H), 1.68−1.83 (m, 1H), 1.87−2.01 (m, 1H), 2.11 (dd, $J = 9.3$, 15.0 Hz, 1H), 2.21−2.50 (m, 2H), 2.50 (dd, $J = 5.1$, 15.0 Hz, 1H), 2.63−2.79 (m, 1H), 5.26 (q, $J = 2.3$ Hz, 1H). Irradiation of the proton at δ 5.26 ppm (vinylic-H) showed 5.9% NOE enhancement to that at δ 2.50 ppm ($CHCO_2$-*t*-Bu). Therefore, the stereochemistry of the olefin moiety was assigned to be *E*. The assignment to the protons α to the ester group (δ 2.11 and δ 2.50 ppm) was described in the text. ^{13}C NMR: δ −0.35, 24.31, 28.15, 32.25, 32.52, 40.55, 43.71, 80.03, 117.63, 164.35, 172.58. IR (neat): 2950, 2870 (sh), 1730, 1620, 1370, 1320, 1250, 1150, 870, 840, 690 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 66.96; H, 10.66.

***tert*-Butyl (*RS*)-Deuterio-[(1*RS*)-2-[(*E*)-Deuterio(trimethylsilyl)-methylene]cyclopent-1-yl]acetate (9):** ^1H NMR δ 0.07 (s, 9H), 1.18−1.39 (m, 1H), 1.45 (s, 9H), 1.50−1.68 (m, 1H), 1.68−1.83 (m, 1H), 1.87−2.01 (m, 1H), 2.28−2.52 (m, 2H), 2.47 (dt, $J = 5.3$, 2 Hz, 1H), 2.65−2.75 (m, 1H). The peaks at δ 2.11 ppm ($CHCO_2$-*t*-Bu) and at δ 5.26 ppm (vinylic-H) of **8** disappeared to show 91% and 95% deuterium incorporation, respectively.

***tert*-Butyl (*RS*)-Deuterio-[(1*RS*)-2-[(*E*)-(trimethylsilyl)methylene]-cyclopent-1-yl]acetate (10):** ^1H NMR δ 0.07 (s, 9H), 1.18−1.39 (m, 1H), 1.45 (s, 9H), 1.50−1.68 (m, 1H), 1.68−1.83 (m, 1H), 1.87−2.01 (m, 1H), 2.28−2.52 (m, 2H), 2.47 (m, 1H), 2.65−2.75 (m, 1H), 5.26 (q, $J = 2.3$ Hz, 1H). The peak at δ 2.11 ppm ($CHCO_2$-*t*-Bu) of **8** disappeared to show 89% deuterium incorporation.

***tert*-Butyl (2*RS*)-3-Hydroxy-2-[(1*SR*)-2-[(*E*)-(trimethylsilyl)methylene]cyclopent-1-yl]propanoate (11).** A >96:<4 mixture of diastereoisomers. An ether solution of freshly cracked formaldehyde (ca. 3 equiv) was used as the electrophile according to the typical procedure (*vide infra*).

Major Diastereoisomer: ^1H NMR δ 0.07 (s, 9H), 1.47 (s, 9H), 1.32−1.62 (m, 2H), 1.63−1.85 (m, 2H), 2.12−2.29 (m, 2H), 2.30−2.47 (m, 2H), 2.74 (ddd, $J = 3.5$, 5.5, 8.9 Hz, 1H), 2.78−2.90 (m, 1H), 3.60 (ddd, $J = 3.5$, 7.4, 11.1 Hz, 1H), 3.81 (ddd, $J = 5.5$, 8.6, 11.1 Hz, 1H), 5.34−5.40 (m, 1H); ^{13}C NMR δ −0.37, 24.61, 28.13, 28.50, 33.10, 46.26, 50.47, 60.52, 81.10, 118.77, 162.20, 174.58; IR (neat) 3450 (br), 2950, 2900 (sh), 1730, 1620, 1460, 1390, 1370, 1250, 1160, 1040, 870, 840 cm^{-1} for a >96:<4 mixture of the above diastereoisomers. Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.13; H, 10.27 for a >96:<4 mixture of the above diasteroisomers. The stereochemistry of the major isomer was unambiguously determined by the derivatization to **12.**

Minor Diastereoisomer: ^1H NMR δ (only characteristic peaks are shown) 1.45 (s, 9H), 3.86 (dd, $J = 7.5$, 11.0 Hz, 1H).

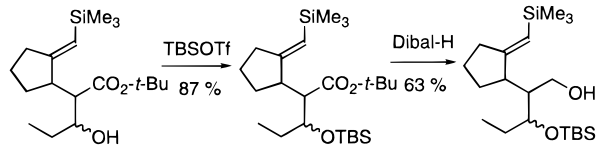
Structural Determination of the Major 11. (1*RS*,4*SR*,5*RS*)-4-(*tert*-Butoxycarbonyl)-2-oxa-1-[(trimethylsilyl)methyl]bicyclo[3.3.0]-octane (12). To a stirred solution of the alcohol **11** (10.1 mg, 0.034 mmol) in Et_2O (0.3 mL) was added a crystal of TsOH·H_2O (1.3 mg, 0.0068 mmol) at room temperature. After 2 days, the mixture was poured into aqueous $NaHCO_3$ solution. The organic layer was separated off, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to afford the title compound (6.6 mg, 65%): ^1H NMR δ 0.04 (s, 9H), 0.93 (d, $J = 14.6$ Hz, 1H), 1.14 (d, $J = 14.6$ Hz, 1H), 1.44 (s, 9H), 1.48−1.80 (m, 5H), 1.82−1.94 (m, 1H), 2.36−2.48 (m, 1H), 3.20 (dt, $J = 9.6$, 8.5 Hz, 1H), 3.90 (t, $J = 8.5$ Hz, 1H), 3.94 (t, $J = 8.5$ Hz, 1H). Irradiation of the proton at δ 3.20 ppm ($CHCO_2$-*t*-Bu) showed 4.9% NOE enhancement to δ 2.36−2.48 ppm (bridgehead-CH) and 2.8% NOE enhancement to δ 1.14 ppm (TMS-CH). And irradiation of the proton at δ 2.36−2.48 ppm (bridgehead-H) showed 2.4% NOE enhancement to δ 0.93 ppm (TMS-CH) and 2.3% NOE enhancement to δ 1.14 ppm (TMS-CH). These facts support the structural assignment shown in the text. ^{13}C NMR: δ −0.01, 25.66, 27.74, 28.06, 29.39, 40.87, 48.60, 53.31, 67.56, 80.60, 95.47. IR (neat): 2950, 2900, 2870, 1730, 1390, 1370, 1320, 1250, 1220, 1160, 1060, 690 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.35; H, 10.04.

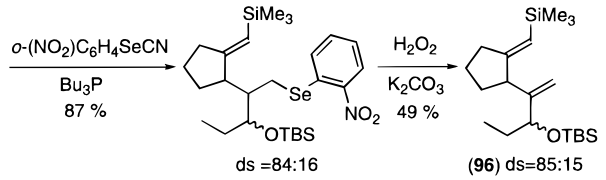
Typical Procedure for the Monocyclization and Subsequent Reaction with Carbonyl Compounds. *tert*-Butyl (2*RS*)-3-Hydroxy-2-[(1*SR*)-2-[(*E*)-(trimethylsilyl)methylene]cyclopent-1-yl]pentanoate (13). To a stirred solution of Ti(O-*i*-Pr)$_4$ (0.070 mL, 0.24 mmol) in Et_2O (2 mL) were added **6** (53.3 mg, 0.20 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.30 mL, 1.60 M solution in Et_2O, 0.48 mmol) in this order at −78 °C under an argon atmosphere. The solution was stirred for 30 min at −78 °C, gradually allowed to warm to −20 °C over 1 h, and kept at this temperature for an additional 2 h. Then propionaldehyde (0.021 mL, 0.30 mmol) was added at −78 °C. After the mixture was stirred for 0.5 h, the reaction was terminated by the addition of 1 N HCl and Et_2O at −78 °C. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil, ^1H NMR analysis of which showed the formation of diastereoisomers in a ratio of 73:27, was purified on silica gel (hexane−ether) to give the title compound (41.2 mg, 63%) as a 73:27 mixture of the diastereoisomers with respect to the alcohol moiety. Careful chromatography on silica gel enabled partial separation of the diastereoisomers in isomerically pure forms.

Major Diastereoisomer: ^1H NMR δ 0.06 (s, 9H), 0.96 (t, $J = 7.4$ Hz, 3H), 1.46 (s, 9H), 1.33−1.98 (m, 6H), 2.20−2.44 (m, 2H), 2.30 (dd, $J = 2.3$, 9.8 Hz, 1H), 2.82−2.95 (m, 1H), 3.33 (d, $J = 10.2$ Hz, 1H), 3.50−3.63 (m, 1H), 5.32 (br s, 1H); ^{13}C NMR δ −0.29, 10.62, 23.99, 28.21, 29.58, 29.71, 32.26, 47.07, 52.57, 72.40, 81.55, 119.38, 163.12, 174.83; IR (neat) 3510 (br), 2960, 2890, 1730, 1700, 1620, 1450, 1390, 1370, 1250, 1150, 1120, 1050, 970, 870, 840, 770, 750, 690 cm^{-1}.

Minor Diastereoisomer: ^1H NMR δ 0.08 (s, 9H), 0.99 (t, $J = 7.3$ Hz, 3H), 1.46 (s, 9H), 1.27−1.69 (m, 4H), 1.73−1.90 (m, 2H), 2.09 (d, $J = 6.7$ Hz, 1H), 2.21−2.50 (m, 2H), 2.63 (t, $J = 6.4$ Hz, 1H), 2.68−2.80 (m, 1H), 3.74−3.85 (m, 1H), 5.35 (br s, 1H); ^{13}C NMR δ −0.35, 10.40, 24.40, 27.95, 28.12, 29.40, 32.70, 46.40, 54.45, 72.91, 80.92, 118.78, 164.23, 173.16; IR (neat) 3500 (br), 2960, 2890, 1730, 1710 (sh), 1620, 1460, 1390, 1370, 1250, 1150, 970, 870, 840, 750, 690 cm^{-1}. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 65.92; H, 10.47 for the 73:27 mixture of the above diastereoisomers.

The following derivatization of **13** to **96** established that the shown diastereomeric ratio refers to that corresponding to the hydroxy group, but not the one between the cyclopentane carbon and the ester α-carbon. Thus, a 76:24 mixture of the diastereoisomers of **13** was silylated to give an 84:16 mixture of **95**. In this reaction, the minor isomer of **13** somewhat resisted the silylation so that a part of the minor isomer was recovered unchanged, which is the reason why the composition of the major diastereoisomer increased before and after the silylation. The rest of the transformation was carried out in a standard manner to give the dehydrated product **96**, which still showed the same diastereomeric ratio of 85:15, verifying the aforementioned point.





***tert*-Butyl (2*RS*)-3-Methyl-3-hydroxy-2-[(1*SR*)-2-[(*E*)-(trimethylsilyl)methylene]cyclopent-1-yl]butanoate (14):** ^{1}H NMR δ 0.06 (s, 9H), 1.21 (s, 3H), 1.28 (s, 3H), 1.44 (s, 9H), 1.51−1.68 (m, 1H), 1.68-1.93 (m, 3H), 2.21−2.41 (m, 2H), 2.38 (d, J = 6.4 Hz, 1H), 2.76−2.88 (m, 1H), 3.66 (s, 1H), 5.35−5.45 (m, 1H); ^{13}C NMR δ −0.24, 24.28, 28.16, 28.26, 29.84, 32.17, 32.84, 46.86, 58.38, 71.91, 81.19, 121.12, 162.52, 174.53; IR (neat) 3490 (br), 2990, 2980, 1700, 1620, 1380, 1360, 1310, 1250, 1210, 1140, 870, 840. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 65.88; H, 10.60.

***tert*-Butyl (2*RS*)-3-Hydroxy-2-[(1*SR*)-2-[(*E*)-1-hexylidene]cyclopent-1-yl]propanoate (16).** A >93:<7 mixture of diastereoisomers.

Major Diastereoisomer: ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 1.17−1.59 (m, 8H), 1.46 (s, 9H), 1.63−1.82 (m, 2H), 1.88−2.19 (m, 3H), 2.20−2.40 (m, 2H), 2.65 (ddd, J = 3.6, 6.3, 8.4 Hz, 1H), 2.75−2.87 (m, 1H), 3.57−3.69 (m, 1H), 3.75−3.87 (m, 1H), 5.18−5.27 (m, 1H); ^{13}C NMR δ 13.94, 22.46, 24.09, 28.02, 29.13, 29.24, 29.38, 31.49, 43.28, 50.85, 60.82, 81.00, 121.73, 142.86, 174.78; IR (neat) 3450 (br), 2960, 2930, 2870, 2860, 1730, 1460, 1390, 1370, 1250, 1160, 1040, 850 cm^{-1} for the >93:<7 mixture of the above diastereoisomers. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.93; H, 10.81 for the >93:<7 mixture of the above diastereoisomers.

Minor Diastereoisomer: ^{1}H NMR δ (only characteristic peaks are shown) 1.45 (s, 9H), 2.51 (dt, J = 4.0, 7.8 Hz, 1H).

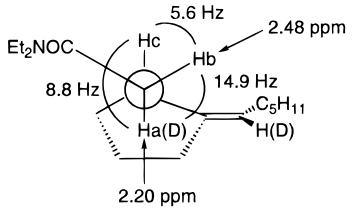
***tert*-Butyl [2-[(*E*)-(Trimethylsilyl)methylene]cyclohex-1-yl]acetate (18):** ^{1}H NMR δ 0.07 (s, 9H), 1.14−1.28 (m, 1H), 1.32−1.59 (m, 2H), 1.42 (s, 9H), 1.62−1.85 (m, 3H), 2.04 (ddd, J = 3.5, 10.2, 13.5 Hz, 1H), 2.17 (m, 1H), 2.38−2.58 (m, 3H), 5.03 (br s, 1H); ^{13}C NMR δ 0.19, 24.85, 28.01, 28.68, 34.25, 34.48, 39.27, 43.34, 79.98, 118.08, 161.02, 172.67; IR (neat) 2960, 2930, 2860, 1730, 1610, 1450, 1370, 1290, 1250, 1150, 1130, 890, 870, 840, 690 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.90; H, 10.69.

***tert*-Butyl (*RS*)-Deuterio[(1*RS*)-2-[(*E*)-deuterio(trimethylsilyl)methylene]cyclohex-1-yl]acetate (19):** ^{1}H NMR δ 0.07 (s, 9H), 1.14−1.28 (m, 1H), 1.32−1.59 (m, 2H), 1.42 (s, 9H), 1.62−1.85 (m, 3H), 2.04 (ddd, J = 3.5, 10.2, 13.5 Hz, 1H), 2.38−2.58 (m, 2H), 2.43 (m, 1H). The peaks at δ 2.17 ppm ($CHCO_2$-*t*-Bu) and at δ 5.03 ppm (vinylic-H) of **18** disappeared to show 91% and 87% deuterium incorporation, respectively.

***tert*-Butyl (2*RS*)-3-Hydroxy-2-[(1*SR*)-2-[(*E*)-(trimethylsilyl)methylene]cyclohex-1-yl]propanoate (20):** ^{1}H NMR δ 0.08 (s, 9H), 1.42 (s, 9H), 1.17−1.72 (m, 6H), 2.12−2.38 (m, 3H), 2.58 (dt, J = 10.2, 4.9 Hz, 1H), 2.77 (ddd, J = 3.5, 6.8, 10.2 Hz, 1H), 3.68−3.87 (m, 2H), 5.18 (br s, 1H); ^{13}C NMR δ 0.21, 22.51, 28.03, 28.50, 30.03, 32.27, 46.31, 48.32, 61.53, 80.97, 121.60, 159.60, 174.87; IR (neat) 3440 (br), 2950, 2930, 2860, 1730, 1620, 1450, 1370, 1250, 1160, 1060, 870, 840, 690 cm^{-1}. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.21; H, 10.19.

***N*,*N*-Diethyl-[2-[(*E*)-1-hexylidene]cyclopent-1-yl]acetamide (22):** ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 1.11 (t, J = 7.7 Hz, 3H), 1.16 (t, J = 7.7 Hz, 3H), 1.20−1.39 (m, 7H), 1.47−1.83 (m, 2H), 1.87−2.00 (m, 3H), 2.20 (dd, J = 8.8, 14.9 Hz, 1H), 2.11−2.35 (m, 2H), 2.48 (dd, J = 5.6, 14.9 Hz, 1H), 2.80−2.93 (m, 1H), 3.20−3.50 (m, 4H), 5.14 (m, 1H). In a Newman projection analogous to Figure 1, the assignment to the protons α to the amide group was made on the basis of the following: (i) the downfield shift for Hb as compared to Ha owing to the deshielding effect of the nearby olefinic bond (ii) the fact that the coupling constants observed between Ha/Hb and cyclopentyl-Hc shown in the following figure satisfy the calculated values by the Karplus equation based on a molecular model. On deuteration (*vide infra*), the proton at δ 2.20 ppm was exchanged to deuterium.

^{13}C NMR: δ 13.12, 14.05, 14.49, 22.58, 24.01, 29.06, 29.30, 29.42, 31.60, 33.34, 38.09, 40.19, 41.00, 42.09, 120.48, 145.47, 171.70. IR (neat): 2960, 2930, 2870, 2860, 1640, 1460, 1430, 1380, 1360, 1270, 1220, 1150, 1100 cm^{-1}. Anal. Calcd for $C_{17}H_{31}ON$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.52; H, 11.59; N, 5.09.

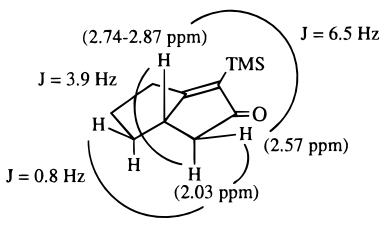


***N*,*N*-Diethyl-(*RS*)-deuterio[(1*RS*)-2-[(*E*)-1-deuterio-1-hexylidene]-cyclopent-1-yl]acetamide (23):** ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 11.1 (t, J = 7.7 Hz, 3H), 1.16 (t, J = 7.7 Hz, 3H), 1.20−1.39 (m, 7H), 1.47−1.83 (m, 2H), 1.85−2.04 (m, 3H), 2.12−2.35 (m, 2H), 2.46 (br d, J = 5.1 Hz, 1H), 2.80−2.93 (m, 2H), 3.20−3.50 (m, 4H). The peaks at δ 2.20 ppm ($CHCONEt_2$) and at δ 5.14 ppm (vinylic-H) of **22** disappeared to show ca. 100% and 88% deuterium incorporation, respectively.

Ethyl [2-(*E*)-(Trimethylsilyl)methylenecyclopent-1-yl]acetate (31): ^{1}H NMR δ 0.09 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.19−1.37 (m, 1H), 1.49−1.67 (m, 1H), 1.68−1.83 (m, 1H), 1.89−2.02 (m, 1H), 2.18 (dd, J = 9.4, 15.0 Hz, 1H), 2.21−2.46 (m, 2H), 2.57 (dd, J = 5.2, 15.0 Hz, 1H), 2.67−2.81 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 5.25 (br s, 1H); ^{13}C NMR δ −0.37, 14.27, 24.29, 32.34, 32.49, 39.36, 43.55, 60.14, 117.84, 164.10, 173.18; IR (neat) 2950, 2870 (sh), 1740, 1620, 1370, 1320, 1240, 1170, 1100, 1030, 870, 840 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.91; H, 10.07.

Typical Procedure for Type I Tandem Cyclization. 2-(Trimethylsilyl)-1-bicyclo[3.3.0]octen-3-one (32). To a stirred solution of Ti(O-*i*-Pr)$_3$Cl (0.12 mL, 2 M solution in Et_2O, 0.24 mmol) in Et_2O (1.6 mL) were added **28** (47.7 mg, 0.20 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.31 mL, 1.53 M solution in Et_2O, 0.48 mmol) in this order at −78 °C under an argon atmosphere. The solution was stirred for 30 min at −78 °C, gradually allowed to warm to −20 °C over 1 h, and kept at this temperature for an additional 2 h. Then 2-butanol (0.12 mL, 2 M solution in Et_2O, 0.24 mmol) was added. After the mixture was stirred for 15 min at −20 °C, the reaction was terminated by the addition of 1 N HCl and Et_2O. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to give the title compound (31.2 mg, 80%): ^{1}H NMR δ 0.19 (s, 9H), 1.10 (dq, J = 7.9, 11.9 Hz, 1H), 1.87−2.20 (m, 3H), 2.03 (dd, J = 3.9, 17.6 Hz, 1H), 2.54 (dt, J = 19.4, 8.9 Hz, 1H), 2.57 (ddd, J = 0.8, 6.5, 17.6 Hz, 1H), 2.66 (ddd, J = 3.0, 10.7, 19.4 Hz, 1H), 2.74−2.87 (m, 1H). The assignments to the *exo* and *endo* protons α to the ketone group were made on the basis of the following facts: (i) the coupling constants shown in the following figure satisfy the calculated values by the Karplus equation based on a molecular model and (ii) a long-range coupling (J = 0.8 Hz) was observed for the *exo* proton at δ 2.57 ppm. This differentiation between two α protons to the ketone group is crucial to determine the stereochemistry of the deuteration (*vide infra*).

^{13}C NMR: δ 1.11, 25.74, 27.54, 30.98, 43.14, 48.51, 135.16, 198.84, 214.70; IR (neat) 2970, 2920 (sh), 2870, 1690, 1610, 1420, 1250, 1230, 1140, 930, 870, 860 (sh), 840, 760, 690 cm^{-1}. Anal. Calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.34. Found: C, 67.62; H, 9.28. These spectral properties were in good agreement with those of an authentic sample.[23]



Ethyl (*RS*)-Deuterio-[(1*RS*)-2-[(*E*)-deuterio(trimethylsilyl)methylene]cyclo-pent-1-yl]acetate (33): ^{1}H NMR δ 0.09 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.19−1.37 (m, 1H), 1.49−1.67 (m, 1H), 1.68−1.83 (m, 1H), 1.89−2.02 (m, 1H), 2.27 (ddt, J = 2.1, 17.0, 8.4 Hz, 1H), 2.40 (ddd, J = 4.5, 8.7, 17.0 Hz, 1H), 2.56 (dt, J = 5.0, 2.3 Hz, 1H), 2.73 (br q, J = 7.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H). The peaks at δ 2.18 ppm ($CHCO_2Et$) and at δ 5.25 ppm (vinylic-H) of **31** disappeared to show 97% and 89% deuterium incorporation, respectively.

(4*RS*,5*RS*)-2-(Trimethylsilyl)-4-deuterio-1-bicyclo[3.3.0]octen-3-one (34): ^{1}H NMR δ 0.19 (s, 9H), 1.10 (dq, J = 7.9, 11.9 Hz, 1H), 1.87−2.20 (m, 3H), 1.98−2.04 (m, 1H), 2.54 (dt, J = 19.1, 9.1 Hz, 1H), 2.66 (ddd, J = 3.3, 10.6, 19.1 Hz, 1H), 2.74−2.87 (m, 1H). Note that the proton at δ 2.57 ppm (*exo*-CH_2C=O) of **32** was exclusively deuterated.

Typical Procedure for Type I Tandem Cyclization and Subsequent Reaction with Carbonyl Compounds. (4*RS*,5*SR*)-4-(1-Hydroxypropyl)-2-(trimethylsilyl)-1-bicyclo[3.3.0]octen-3-one (35). To a stirred solution of Ti(O-*i*-Pr)$_3$Cl (0.12 mL, 2 M solution in Et_2O, 0.24 mmol) in Et_2O (1.6 mL) were added **28** (47.7 mg, 0.20 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.31 mL, 1.53 M solution in Et_2O, 0.48 mmol) in this order at −78 °C under an argon atmosphere. The solution was stirred for 30 min at −78 °C, gradually allowed to warm to −20 °C over 1 h, and kept at this temperature for an additional 2 h. Then propionaldehyde (0.021 mL, 0.30 mmol) was added. After the mixture was stirred at −20 °C for 1 h, the reaction was terminated by the addition of 1 N HCl and Et_2O. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to give the title compound (39.2 mg, 78%) as a 63:37 mixture of the diastereoisomers with respect to the alcohol moiety.

Major Diastereoisomer: ^{1}H NMR δ 0.20 (s, 9H), 1.01 (t, J = 7.3 Hz, 3H), 1.22 (dq, J = 10.0, 12.0 Hz, 1H), 1.37−1.74 (m, 2H), 1.87−2.03 (m, 1H), 2.03−2.19 (m, 2H), 2.08 (dd, J = 4.5, 10.0 Hz, 1H), 2.42−2.61 (m, 2H), 2.66 (ddd, J = 3.0, 10.1, 19.8 Hz, 1H), 3.72 (ddd, J = 2.8, 7.6, 10.0 Hz, 1H), 4.86 (br s, 1H). The coupling constant (J = 4.5 Hz) observed for the α proton to the ketone (δ 2.08 ppm) and the bridgehead proton (δ 2.42−2.61 ppm) suggests that the CH(OH)-Et group occupies the *exo* position. The observed NOE (4% peak enhancement at the peak of δ 2.42−2.61 ppm (bridgehead-H) by irradiation of the one at δ 3.72 ppm (CHOH)) also confirmed the stereochemical assignment. ^{13}C NMR: δ 1.31, 9.03, 26.01, 27.69, 28.73, 30.73, 52.13, 58.96, 73.03, 134.53, 198.32, 218.38. IR (neat): 3450 (br), 2970, 2930 (sh), 2880, 1670, 1610, 1420, 1250, 970, 840 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.14; H, 9.58. Found: C, 65.89; H, 9.51 for a mixture of the above diastereoisomers.

Minor Diastereoisomer: ^{1}H NMR δ 0.19 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H), 1.29 (dq, J = 7.9, 11.7 Hz, 1H), 1.42−1.88 (m, 3H), 1.89−2.20 (m, 3H), 2.22 (dd, J = 2.8, 4.0 Hz, 1H), 2.54 (dt, J = 19.3, 8.2 Hz, 1H), 2.66 (ddd, J = 3.4, 10.2, 19.3 Hz, 1H), 2.91 (m, 1H), 4.13 (ddd, J = 2.8, 5.7, 8.3 Hz, 1H). The coupling constant (J = 4.0 Hz) observed for the α proton to the ketone (δ 2.22 ppm) and the bridgehead proton (δ 2.91 ppm) suggests that the CH(OH)Et group occupies the *exo* position. The observed NOE (0.7% peak enhancement at the peak of δ 4.13 ppm (CHOH) by irradiation of the one at δ 2.91 ppm (bridgehead-CH)) also confirmed the stereochemical assignment. ^{13}C NMR: δ −1.20, 10.47, 26.15, 27.71, 28.21, 31.03, 48.94, 60.85, 70.52, 134.62, 198.75, 215.34. IR (neat): 3450 (br), 2970, 2950 (sh), 2880, 1680, 1610, 1250, 1150, 840 cm^{-1}. Thus, both diastereoisomers have the hydroxyethyl group at the *exo* position α to the ketone so that the relative stereochemistries of the hydroxy groups should be different.

(4*RS*,5*SR*)-4-(1-Ethyl-1-hydroxypropyl)-2-(trimethylsilyl)-1-bicyclo-[3.3.0]octen-3-one (36): ^{1}H NMR δ 0.17 (s, 9H), 0.86 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 1.20 (dq, J = 7.7, 11.8 Hz, 1H), 1.25−1.54 (m, 3H), 1.64−1.81 (m, 1H), 1.86−2.19 (m, 3H), 2.38 (d, J = 4.4 Hz, 1H), 2.44−2.63 (m, 2H), 2.66 (ddd, J = 2.8, 10.5, 19.7 Hz, 1H), 4.45 (br s, 1H). The coupling constant (J = 4.4 Hz) observed for the proton α to the ketone (δ 2.38 ppm) and the bridgehead proton (δ 2.44−2.63 ppm) suggests that the CEt_2(OH) group occupies the *exo* position. ^{13}C NMR: δ 1.27, 7.55, 7.79, 25.88, 27.58, 29.92, 30.61, 31.15, 51.85, 59.91, 75.36, 135.52, 198.51, 218.69. IR (neat): 3440 (br), 2870, 2850 (sh), 2780, 1670, 1610, 1470, 1420, 1250, 1230, 1150, 960, 850 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.08; H, 10.29.

2-Pentyl-1-bicyclo[3.3.0]octen-3-one (39): ^{1}H NMR δ 0.87 (t, J = 7.0 Hz, 3H), 1.04 (dq, J = 8.3, 11.6 Hz, 1H), 1.17−1.51 (m, 6H), 1.89−2.28 (m, 5H), 2.02 (dd, J = 3.1, 17.6 Hz, 1H), 2.45−2.66 (m, 2H), 2.61 (dd, J = 6.2, 17.6 Hz, 1H), 2.67−2.81 (m, 1H); ^{13}C NMR δ 13.95, 22.38, 23.79, 25.12, 25.71, 27.66, 31.32, 31.69, 41.73, 44.35, 136.30, 186.60, 210.68; IR (neat) 2960, 2930, 2850, 1710, 1670, 1480, 1460 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.87; H, 10.83.

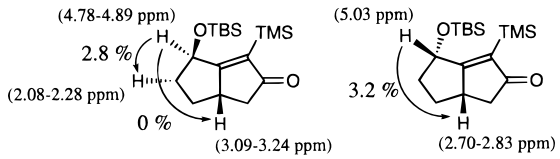
9-(Trimethylsilyl)-9-bicyclo[4.3.0]nonen-8-one (41): ^{1}H NMR δ 0.21 (s, 9H), 1.11 (dq, J = 3.5, 13.0 Hz, 1H), 1.36 (tq, J = 3.5, 13.0 Hz, 1H), 1.51 (tq, J = 3.5, 13.0 Hz, 1H), 1.76−1.87 (m, 1H), 1.91 (dd, J = 1.7, 18.1 Hz, 1H), 1.96−2.07 (m, 1H), 2.10−2.25 (m, 2H), 2.50 (dd, J = 6.9, 18.1 Hz, 1H), 2.53−2.64 (m, 1H), 2.95−3.05 (m, 1H); ^{13}C NMR δ 0.34, 25.46, 27.53, 31.68, 35.60, 42.85, 43.60, 136.17, 191.66, 212.91; IR (neat) 2950, 2860, 1690, 1600, 1450, 1270, 1250, 1200, 870 (sh), 850, 770 cm^{-1}. Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.17; H, 9.67. Found: C, 68.75; H, 9.63.

8-[(*tert*-Butyl)dimethylsiloxy]-2-(trimethylsilyl)-1-bicyclo[3.3.0]octen-3-one (43).

Major (5*RS*,8*SR*)-Diastereoisomer: ^{1}H NMR δ 0.09 (s, 3H), 0.12 (s, 3H), 0.21 (s, 9H), 0.87 (s, 9H), 1.00−1.16 (m, 1H), 1.79-1.94 (m, 1H), 1.99 (dd, J = 3.5, 17.7 Hz, 1H), 2.08−2.28 (m, 2H), 2.62 (dd, J = 6.6, 17.7 Hz, 1H), 3.09−3.24 (m, 1H), 4.78−4.89 (m, 1H); ^{13}C NMR δ −4.30, −3.67, 0.96, 17.91, 25.77, 27.89, 36.54, 43.34, 43.82, 68.99, 135.82, 194.62, 215.42; IR (neat) 2950, 2930, 2900, 2860, 1700, 1620, 1470, 1250, 1070, 1030, 930, 840, 780, 700 cm^{-1}.

Minor (5*RS*,8*RS*)-Diastereoisomer: ^{1}H NMR δ 0.14 (s, 3H), 0.15 (s, 3H), 0.22 (s, 9H), 0.91 (s, 9H), 1.29−1.47 (m, 1H), 1.91-1.20 (m, 3H), 2.10 (dd, J = 3.9, 17.6 Hz, 1H), 2.57 (dd, J = 6.6, 17.6 Hz, 1H), 2.70−2.83 (m, 1H), 5.03 (dd, J = 2.7, 7.6, 1H); ^{13}C NMR δ −3.50, −3.13, −0.52, 18.37, 26.32, 28.38, 37.11, 43.36, 46.13, 71.11, 137.81, 198.12, 214.24; IR (neat) 2960, 2930, 2900, 2860, 1700, 1610, 1470, 1250, 1140, 1060, 840, 780 cm^{-1}. Anal. Calcd for $C_{17}H_{32}O_2Si_2$: C, 62.90; H, 9.94. Found: C, 62.92; H, 9.92 for a mixture of the above diastereoisomers.

Irradiation of the proton at δ 4.78−4.89 ppm (CH-OTBS) of the major isomer showed no NOE enhancement to that at δ 3.09−3.24 ppm (bridgehead-CH), while irradiation of the proton at δ 5.03 ppm (CH-OTBS) of the minor isomer showed 3.2% NOE enhancement to that at δ 2.70−2.83 ppm (bridgehead-CH). These facts support the above structural assignments to both isomers.



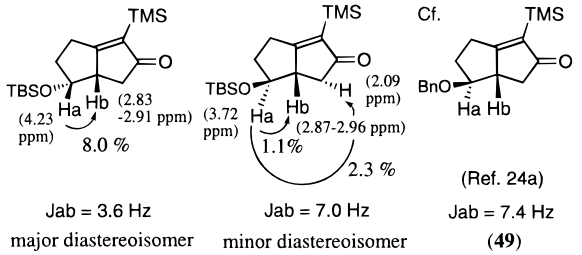
6-[(*tert*-Butyl)dimethylsiloxy]-2-(trimethylsilyl)-1-bicyclo[3.3.0]octen-3-one (45).

Major (5*RS*,6*SR*)-Diastereoisomer: ^{1}H NMR δ 0.01 (s, 3H), 0.03 (s, 3H), 0.18 (s, 9H), 0.79 (s, 9H), 1.98 (br ddd, J = 3.6, 6.7, 13.6 Hz, 1H), 2.12 (ddt, J = 3.6, 13.6, 9.8 Hz, 1H), 2.30 (d, J = 5.4 Hz, 2H), 2.57−2.67 (m, 2H), 2.83−2.91 (dt, J = 3.6, 5.4 Hz, 1H), 4.23 (br t, J = 3.6 Hz, 1H); ^{13}C NMR δ −5.15, −4.78, −1.40, 17.90, 25.40, 25.54, 36.01, 37.50, 54.27, 70.50, 136.54, 196.87, 215.50; IR (neat) 2950, 2930, 2900, 2860, 1690, 1610, 1250, 1230, 1120, 1080, 1050, 980, 890, 840, 800, 780, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{32}O_2Si_2$: C, 62.90; H, 9.94. Found: C, 63.11; H, 10.05.

Minor (5*RS*,6*RS*)-Diastereoisomer: ^{1}H NMR δ 0.06 (s, 6H), 0.18 (s, 9H), 0.89 (s, 9H), 1.96 (ddt, J = 11.7, 12.9, 9.2 Hz, 1H), 2.09 (dd, J = 3.8, 17.8 Hz, 1H), 2.15−2.26 (m, 1H), 2.48−2.62 (m, 1H), 2.57 (dd, J = 6.6, 17.8 Hz, 1H), 2.73−2.96 (m, 2H), 3.72 (br dt, J = 7.0, 9.2 Hz, 1H). Decoupling experiments determined the coupling constant between CHOTBS and allylic bridgehead-CH is 7.0 Hz, consistent with the previously reported value (7.4 Hz) for a similar structure in **49**.[24a] ^{13}C NMR: δ −4.75, −4.72, −1.32, 17.96, 25.71, 26.64, 35.01, 41.66, 55.43, 77.27, 137.75, 194.27, 214.01. IR (neat): 2950, 2930, 2900, 2860, 1700, 1610, 1470, 1250, 1210, 1130, 1100, 840, 780 cm^{-1}.

Irradiation of the proton at δ 4.23 ppm (CH-OTBS) of the major diastereoisomer showed 8.0% NOE enhancement to δ 2.83−2.91 ppm

(bridgehead-CH), while irradiation of the proton at δ 3.72 ppm (CH-OTBS) of the minor diastereoisomer showed 1.1% NOE enhancement to δ 2.87−2.96 ppm (bridgehead-CH) in addition to a 2.3% NOE enhancement to the *endo* α-carbonyl proton. These facts support the above structural assignments to both diastereoisomers.

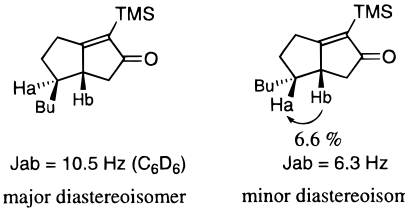


6-Butyl-2-(trimethylsilyl)-1-bicyclo[3.3.0]octen-3-one (47).

Major (5*RS*,6*SR*)-Diastereoisomer: ^{1}H NMR δ 0.18 (s, 9H), 0.89 (t, J = 7.1 Hz, 3H), 1.21−1.64 (m, 7H), 2.02 (dd, J = 3.8, 16.8 Hz, 1H), 2.08−2.21 (m, 1H), 2.40−2.60 (m, 2H), 2.54 (dd, J = 6.5, 16.8 Hz, 1H), 2.69 (ddd, J = 2.1, 10.8, 19.2 Hz, 1H); ^{13}C NMR δ −1.31, 13.91, 22.83, 27.80, 30.29, 32.70, 34.66, 42.79, 44.98, 54.41, 135.11, 199.30, 214.78; ^{1}H NMR (C_6D_6) δ 0.39 (s, 9H), 0.91 (t, J = 7.1 Hz, 3H), 0.86−1.03 (m, 1H), 1.04−1.30 (m, 7H), 1.73 (ddt, J = 4.3, 12.9, 6.5 Hz, 1H), 1.87 (dd, J = 3.8, 16.8 Hz, 1H), 1.91−2.01 (ddd, J = 3.8, 6.5, 10.5 Hz, 1H), 2.18−2.27 (m, 2H), 2.44 (dd, J = 6.5, 16.8 Hz, 1H); ^{13}C NMR (C_6D_6) δ −1.14, 14.01, 23.05, 27.55, 30.41, 32.64, 34.73, 42.70, 44.85, 54.12, 135.13, 197.31, 212.49; IR (neat) 2960, 2930, 2860, 1700, 1610, 1460, 1410, 1290, 1250, 1230, 1150, 910, 840, 760, 700, 660 cm^{-1}. Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 71.80; H, 10.39.

Minor (5*RS*,6*RS*)-Diastereoisomer: ^{1}H NMR δ 0.18 (s, 9H), 0.87 (t, J = 7.5 Hz, 3H), 0.95−1.20 (m, 7H), 1.85−2.06 (m, 2H), 2.06−2.16 (m, 1H), 2.20 (dd, J = 4.3, 18.0 Hz, 1H), 2.38 (dd, J = 6.3, 18.0 Hz, 1H), 2.44−2.68 (m, 2H), 3.04 (br dt, J = 4.3, 6.3 Hz, 1H); IR (neat) 2960, 2930, 2890, 1690, 1610, 1460, 1250, 840, 760, 690 cm^{-1}.

Irradiation of the proton at δ 3.04 ppm (bridgehead-CH) of the minor diastereoisomer showed 6.6% NOE enhancement to δ 2.06−2.16 ppm (Bu-CH). This fact supports the above structural assignment to the minor diastereoisomer. The coupling constants observed for BuCH and the bridgehead proton in both isomers are also consistent with the proposed assignment.



(1*RS*,5*RS*)-2-[(*E*)-Propylidene]-3-bicyclo[3.3.0]octanone (51). The primary product, a mixture of the two diastereoisomers of β-hydroxyketones and **51**, was eventually converted to the title ketone by treatment with TsOH in refluxing benzene. ^{1}H NMR: δ 1.06 (t, J = 7.6 Hz, 3H), 1.31−1.50 (m, 2H), 1.50−1.74 (m, 2H), 1.84−1.90 (m, 1H), 2.02−2.26 (m, 4H), 2.58 (dd, J = 9.7, 18.4 Hz, 1H), 2.58−2.72 (m, 1H), 3.25 (br q, J = 7.4 Hz, 1H), 6.48 (dt, J = 2.5, 7.7 Hz, 1H). Irradiation of the angular allylic hydrogen at δ 3.25 ppm showed a 0.7% NOE enhancement to the acyclic allylic hydrogens at δ 2.02−2.26 ppm. Thus, the olefinic stereochemistry was assigned to be *E*. The shown stereochemistry of the ring junction was deduced based on the assignment to **54** (*vide infra*). ^{13}C NMR: δ 12.94, 22.78, 26.35, 34.08, 34.64, 36.68, 43.26, 44.63, 138.73, 144.26, 208.25. IR (neat): 2960, 2870, 1720, 1650, 1460, 1420, 1280, 1210, 1150, 1020 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.57; H, 9.98.

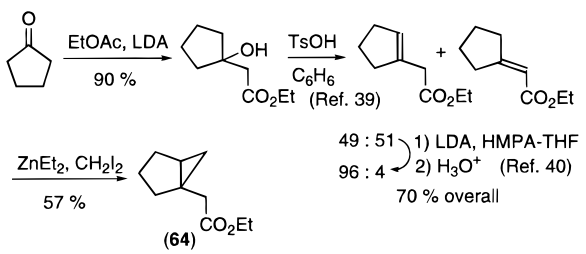
(1*RS*,5*SR*)-6,7-Benzo-3-bicyclo[3.3.0]octanone (53): ^{1}H NMR δ 1.96 (dd, J = 8.0, 18.5 Hz, 1H), 2.44−2.62 (m, 1H), 2.55 (dd, J = 3.4, 19.5 Hz, 1H), 2.70 (ddd, J = 1.5, 9.2, 19.5 Hz, 1H), 2.82 (br d, J = 15.2 Hz, 1H), 3.08−3.22 (m, 1H), 3.25 (dd, J = 7.4, 15.2 Hz, 1H), 3.78−3.93 (m, 1H), 7.10−7.28 (m, 4H); ^{13}C NMR δ 38.42, 39.41, 43.44, 43.78, 45.96, 124.59, 125.31, 126.96, 127.17, 142.24, 144.92, 218.92; IR (neat) 3060, 3010, 2940, 2900, 2850, 1740, 1480, 1460, 1450 (sh), 1400, 1330, 1250, 1150, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.23. Found: C, 83.72; H, 7.19. The shown stereochemistry of the ring junction was deduced on the basis of the assignment to **54** (*vide infra*).

(1*RS*,5*RS*)-7,8-Benzo-2-(1-hydroxypropyl)-3-bicyclo[3.3.0]-octanone (54): ^{1}H NMR δ 1.06 (t, J = 7.3 Hz, 3H), 1.61−1.89 (m, 2H), 2.19 (ddd, J = 1.2, 7.6, 18.5 Hz, 1H), 2.47 (ddd, J = 1.2, 4.4, 6.6, 1H), 2.60 (dd, J = 8.3, 18.5 Hz, 1H), 2.81 (dd, J = 3.1, 15.7 Hz, 1H), 3.07−3.20 (m, 1H), 3.25 (dd, J = 7.6, 15.7 Hz, 1H), 3.27 (br s, 1H), 3.68 (dd, J = 4.4, 7.7 Hz, 1H), 3.84 (ddd, J = 3.0, 6.6, 11.0 Hz, 1H), 7.15−7.30 (m, 4H). Irradiation of the proton at δ 3.68 ppm (benzylic-bridgehead-CH) showed 4% NOE enhancement to δ 3.07−3.20 ppm (another bridgehead-CH), which verified that the ring junction is *cis*. ^{13}C NMR: δ 9.34, 28.07, 38.24, 38.38, 44.84, 49.83, 58.39, 73.63, 124.56, 125.27, 126.99, 127.21, 142.05, 144.97, 211.46. IR (neat): 3400 (br), 2990, 2980, 2940, 2800, 1730, 1640, 1460, 1240, 1160, 1110, 1040, 970, 750, 640 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.25; H, 7.85.

1-[(*E*)-(Ethoxycarbonyl)methylene]-2-methylcyclopentane (58): ^{1}H NMR δ 1.12 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.17−1.34 (m, 1H), 1.50−1.70 (m, 1H), 1.76−1.98 (m, 2H), 2.44−2.60 (m, 1H), 2.73 (dtt, J = 19.8, 2.5, 8.6 Hz, 1H), 2.86−3.01 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.69 (q, J = 2.4 Hz, 1H); ^{13}C NMR δ 14.39, 18.20, 24.09, 32.89, 34.34, 41.53, 59.45, 111.01, 167.23, 173.21; IR (neat) 2990 (sh), 2950, 2890, 1700, 1650, 1450, 1380, 1310, 1250, 1210, 1160, 1040, 870 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: 71.21; H, 9.63.

1-[(*E*)-(Ethoxycarbonyl)deuteriomethylene]-2-(deuteriomethyl)-cyclopentane (59): ^{1}H NMR δ 1.11 (dt, J = 6.8, 1.8 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.17−1.34 (m, 1H), 1.50−1.70 (m, 1H), 1.76−1.98 (m, 2H), 2.44−2.60 (m, 1H), 2.73 (ddt, J = 2.3, 19.8, 8.7 Hz, 1H), 2.94 (dddd, J = 3.4, 5.0, 8.3, 19.8 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H). Both protons at δ 1.12 ppm (CH_3) and at δ 5.69 ppm (vinylic-H) of **58** disappeared to show 99% deuterium incorporation.

Typical Procedure for Type II Tandem Cyclization. 1-[(Ethoxycarbonyl)methyl]bicyclo[3.1.0]hexane (64). To a stirred solution of Ti(O-*i*-Pr)$_3$Cl (0.30 mL, 2 M solution in Et_2O, 0.6 mmol) in Et_2O (3.8 mL) were added **56** (119 mg, 0.5 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.86 mL, 1.40 M solution in Et_2O, 1.2 mmol) in this order at −78 °C under an argon atmosphere. The solution was stirred for 30 min at −78 °C, gradually allowed to warm to 0 °C over 1 h, and kept at this temperature for an additional 1 h. The reaction was terminated by the addition of 1 N HCl and Et_2O. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to give the title compound (60.3 mg, 72%): ^{1}H NMR δ 0.36 (dd, J = 4.8, 8.2 Hz, 1H), 0.45 (t, J = 4.8 Hz, 1H), 1.08−1.22 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.50−1.86 (m, 6H), 2.37 (d, J = 15.0 Hz, 1H), 2.47 (d, J = 15.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 12.09, 14.28, 21.37, 23.36, 25.23, 27.47, 31.77, 41.00, 59.99, 172.70; IR (neat) 2950, 2860, 1740, 1260, 1180, 1170, 1150, 1040 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.49. An authentic sample, prepared by the method illustrated in the following scheme, showed the same physical properties.



1-[(Ethoxycarbonyl)dideuteriomethyl]bicyclo[3.1.0]hexane (65): ^{1}H NMR δ 0.36 (dd, J = 4.8, 8.2 Hz, 1H), 0.45 (t, J = 4.8 Hz, 1H), 1.08−1.22 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.50−1.86 (m, 6H), 4.12 (q, J = 7.1 Hz, 2H). Note that the two protons at δ 2.37 and 2.47

ppm (d, J = 15.0 Hz, CH_2CO_2Et) of **64** disappeared to show 99% deuterium incorporation to both protons.

Typical Procedure for Type II Tandem Cyclization and Subsequent Reaction with Ketone. 1-[(Ethoxycarbonyl)(3-pentylidene)methyl]bicyclo[3.1.0]hexane (66). To a stirred solution of Ti(O-*i*-Pr)$_3$Cl (0.30 mL, 2 M solution in Et_2O, 0.6 mmol) in Et_2O (3.8 mL) were added **56** (119 mg, 0.5 mmol) in 1 mL of Et_2O and *i*-PrMgCl (0.86 mL, 1.40 M solution in Et_2O, 1.2 mmol) in this order at −78 °C under an argon atmosphere. The mixture was stirred for 30 min, gradually allowed to warm to 0 °C over 1 h, and kept at this temperature for 1 h. 3-Pentanone (0.075 mL, 0.75 mmol) was added at 0 °C. After the mixture was stirred at 0 °C for 3 h, the reaction was terminated by the addition of 1 N HCl and Et_2O. The organic layer was separated off, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. The crude oil was purified on silica gel (hexane−ether) to give the title compound (68.3 mg, 58%): ^{1}H NMR δ 0.47 (dd, J = 4.7, 8.3 Hz, 1H), 0.65 (t, J = 4.7 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H), 1.04 (t, J = 7.6 Hz, 3H), 1.17−1.23 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.54−1.93 (m, 6H), 2.17 (dq, J = 13.9, 7.5 Hz, 1H), 2.23 (dq, J = 13.9, 7.5 Hz, 1H), 2.27 (dq, J = 13.4, 7.6 Hz, 1H), 2.38 (dq, J = 13.4, 7.6 Hz, 1H), 4.15 (dq, J = 10.7, 7.1 Hz, 1H), 4.20 (dq, J = 10.7, 7.1 Hz, 1H); ^{13}C NMR δ 12.40, 13.31, 14.40, 14.45, 21.17, 24.28, 25.15, 27.66, 28.44, 33.57, 59.70, 130.47, 152.23, 170.42; IR (neat) 2970, 2940, 2870, 1720, 1640, 1220, 1200, 1070 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.13; H, 10.26.

3-Aza-3-benzyl-1-[(ethoxycarbonyl)methyl]bicyclo[3.1.0]hexane (68): ^{1}H NMR δ 0.42 (dd, J = 4.0, 8.0 Hz, 1H), 1.11 (t, J = 4.0 Hz, 1H), 1.23 (t, J = 7.7 Hz, 3H), 1.23 (m, 1H), 2.28 (d, J = 8.0 Hz, 1H), 2.35 (d, J = 15.0 Hz, 1H), 2.40 (dd, J = 2.5, 8.0 Hz, 1H), 2.52 (d, J = 15.0 Hz, 1H), 2.91 (d, J = 8.0 Hz, 1H), 3.03 (d, J = 8.0 Hz, 1H), 3.60 (s, 2H), 4.11 (q, J = 7.7 Hz, 2H), 7.18−7.38 (m, 5H); ^{13}C NMR δ 12.99, 14.28, 21.78, 23.70, 39.08, 54.70, 58.33, 58.99, 60.22, 126.70, 128.07, 128.46, 139.52, 172.23; IR (neat) 3080, 3050, 2980, 2930, 2800, 1745, 1470, 1380, 1350, 1260, 1220, 1160, 1040, 750, 710 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.04; H, 8.12, N, 5.16.

A 3:1 Mixture of (1*RS*,2*RS*)- and (1*RS*,2*SR*)-1-[(Ethoxycarbonyl)methyl]-3-oxa-2-pentylbicyclo[3.1.0]hexane (70).

Major Diastereoisomer: ^{1}H NMR δ 0.60 (dd, J = 4.6, 8.0 Hz, 1H), 0.70 (t, J = 4.6 Hz, 1H), 0.88 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H), 1.28 (m, 6H), 1.39 (m, 1H), 1.50 (m, 2H), 2.17 (d, J = 15.0 Hz, 1H), 2.88 (d, J = 15.0 Hz, 1H), 3.65 (d, J = 8.0 Hz, 1H), 3.79 (d, J = 8.0 Hz, 1H), 3.98 (br d, J = 11.0 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H). The following NOE experiment determined the assigned stereochemistry to the major diastereoisomer. Irradiation of the peak at δ 0.70 ppm (*endo*-cyclopropane-CH_2 of the major isomer) shows 2% and 4% enhancement of the peaks at δ 3.79 ppm (one of cyclopentane-CH_2) and δ 3.98 ppm (OC<u>H</u>-C_5H_{11}). Thus, the cyclopropane ring and the pentyl side chain should be *trans* in the major diastereoisomer. IR (neat): 2970, 2940, 2860, 1740, 1480, 1380, 1250, 1160, 1080, 1040 cm^{-1} for the above 3:1 mixture of diastereoisomers. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.71; H, 10.46 for the above 3:1 mixture of diastereoisomers.

Minor Diastereoisomer: ^{1}H NMR δ (only characteristic peaks are shown) 0.50 (dd, J = 4.6, 8.0 Hz, 1H), 0.68 (t, J = 4.6 Hz, 1H), 2.36 (d, J = 15.0 Hz, 1H), 2.66 (d, J = 15.0 Hz, 1H), 3.78 (m, 3H).

1-[(Ethoxycarbonyl)methyl]-4-[(*tert*-butyl)dimethylsiloxy]bicyclo-[3.1.0]hexane. A 62:38 Mixture of the (1*RS*,4*SR*,5*SR*)- and (1*RS*,4*RS*,5*SR*)-Diastereoisomers (73).

Major Isomer: ^{1}H NMR (C_6D_6) δ 0.10 (s, 3 H), 0.12 (s, 3 H), 0.23 (t, J = 4.6 Hz, 1 H), 0.46 (dd, J = 4.6, 7.5 Hz, 1 H), 1.00 (m, 12 H), 1.10−2.15 (m, 5 H), 2.23 (d, J = 14.6 Hz, 1 H), 2.59 (d, J = 14.6 Hz, 1 H), 4.02 (q, J = 7.5 Hz, 2 H), 4.10 (d, J = 6 Hz, 1 H). The stereochemistry of the major isomer was assigned based on negligible coupling constant (J = ca. 0 Hz) between tertiary cyclopropane-H and TBSOC<u>H</u> by analogy to the case of **77**.

Minor Isomer: ^{1}H NMR (C_6D_6) δ 0.04 (t, J = 4 Hz, 1 H), 0.12 (s, 3 H), 0.14 (s, 3 H), 0.37 (dd, J = 4, 7.5 Hz, 1 H), 1.00 (m, 12 H), 1.10−2.15 (m, 5 H), 2.19 (d, J = 15 Hz, 1 H), 2.25 (d, J = 15 Hz, 1 H), 3.98 (q, J = 7.5 Hz, 2 H), 4.58 (dt, J = 5, 7.7 Hz, 1 H).

The separation of peaks of the diastereoisomers is less pronounced in $CDCl_3$, but the following few characteristic signals would be useful to distinguish both isomers.

Major Isomer: ^{1}H NMR δ 0.30 (t, J = 4.6 Hz, 1 H), 0.46 (dd, J = 4.6, 7.5 Hz, 1 H), 2.28 (d, J = 15 Hz, 1 H), 2.64 (d, J = 15 Hz, 1 H).

Minor Isomer: ^{1}H NMR δ 0.41 (dd, J = 4.6, 7.5 Hz, 1 H), 2.37 (s, 2 H), 4.55 (dt, J = 5, 7.7 Hz, 1 H).

IR (neat): 3060, 2960, 2930, 2885, 2860, 1740, 1470, 1460, 1380, 1360, 1250, 1160, 1100, 1080, 1040, 840, 770 cm^{-1} for the 62:38 mixture of diastereoisomers. Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.51; H, 10.21 for the 62:38 mixture of diastereoisomers.

(1*RS*,4*SR*,5*RS*)-4-Butyl-1-(ethoxycarbonylmethyl)bicyclo[3.1.0]-hexane (75): ^{1}H NMR δ 0.39 (dd, J = 5.0, 8.4 Hz, 1 H), 0.44 (dd, J = 4.2, 5.0 Hz, 1 H), 0.88 (t, J = 7 Hz, 3 H), 1.00 (dd, J = 4.2, 8.4 Hz, 1 H), 1.26 (m, 8 H, alkyl-H), 1.26 (t, J = 7.5 Hz, 3 H), 1.70 (m, 2 H), 1.84 (br q, J = 6 Hz, 1 H), 2.38 (d, J = 15 Hz, 1 H), 2.43 (d, J = 15 Hz, 1 H), 4.10 (q, J = 7.5 Hz, 2 H). The stereochemistry was assigned based on negligible coupling constant (J = ca. 0 Hz) between tertiary cyclopropane-H and BuC<u>H</u> by analogy to the case of **77**. ^{13}C NMR: δ 13.42, 14.03, 14.19, 22.80, 25.02, 26.99, 28.65, 29.44, 29.98, 35.11, 40.27, 41.27, 60.06, 172.92. IR (neat): 3060, 2960, 2920, 2870, 1740, 1460, 1370, 1250, 1200, 1140, 1040 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.15; H, 10.98.

(1*RS*,4*SR*,5*RS*)-4-[((*tert*-Butyl)dimethylsiloxy)methyl]-1-[(ethoxycarbonyl)methyl]bicyclo[3.1.0]hexane (77). This is a racemic form of **91**. For physical properties, see those of **91**.

(5*RS*,6*SR*)-1-[(Ethoxycarbonyl)methyl]-6-pentylbicyclo[3.1.0]-hexane (82): ^{1}H NMR δ 0.67 (q, J = 7.5 Hz, 1 H), 0.86 (t, J = 7 Hz, 3 H), 1.16 (m, 1 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.26 (m, 8 H), 1.5−2.05 (m, 6 H), 2.26 (d, J = 15.4 Hz, 1 H), 2.47 (d, J = 15.4 Hz, 1 H), 4.11 (q, J = 7.5 Hz, 2 H). The stereochemical assignment to this product was made based on the following ^{1}H NMR NOE experiment. Irradiation of the peak at δ 0.67 ppm (cyclopropane H geminal to the pentyl side chain) effected a 3.5% enhancement to the peak at δ 2.26 ppm ($CHCO_2Et$) and 2.5% to the one at δ 2.47 ppm ($CHCO_2Et$). ^{13}C NMR: δ 14.07, 14.32, 22.70, 23.78, 25.36, 27.26, 27.54, 28.37, 28.71, 29.97 (two peaks), 31.90, 43.23, 59.97, 172.99. IR (neat): 2960, 2920, 2860, 1740, 1460, 1370, 1250, 1180, 1040 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 76.06; H, 10.98.

(1*R*,4*S*,5*R*)-4-[[(*tert*-Butyl)dimethylsiloxy]methyl]-1-[(ethoxycarbonyl)methyl]bicyclo[3.1.0]hexane (91). To a mixture of the enynoate **86** (250 mg, 0.806 mmol) and Ti(O-*i*-Pr)$_3$Cl (0.525 mL of a 2 M solution in ether, 1.05 mmol) in ether (8 mL) was added *i*-PrMgCl (1.31 mL of a 1.60 M in ether, 2.10 mmol) at −78 °C. After −78 °C for 30 min, the resulting brown solution was gradually warmed to 0 °C over 1.5 h and was kept at this temperature for another 1.25 h. The reaction was terminated by the addition of 1 N HCl. The organic phase was diluted with ether, separated off, washed successively with 1 N HCl and aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. Purification on silica gel (2.5% ether in hexane) afforded the title compound (195 mg, 78%) as a colorless oil. ^{1}H NMR analysis of the crude and purified samples revealed that the product had been formed virtually as a single diastereoisomer (>98−99% diastereoselectivity): ^{1}H NMR δ 0.04 (s, 6 H), 0.46 (d, J = 7.5 Hz, 1 H), 0.48 (d, J = 4.7 Hz, 1 H), 0.88 (s, 9 H), 1.05 (dd, J = 4.7, 7.5 Hz, 1 H), 1.25 (t, J = 7 Hz, 3 H), 1.27 (m, 1 H), 1.44−1.60 (m, 1 H), 1.60−1.80 (m, 2 H), 2.08 (q, J = 7.5 Hz, 1 H), 2.35 (d, J = 15.3 Hz, 1 H), 2.46 (d, J = 15.3 Hz, 1 H), 3.37 (dd, J = 7.7, 9.2 Hz, 1 H), 3.48 (dd, J = 7.0, 9.2 Hz, 1 H), 4.11 (q, J = 7 Hz, 2 H). The following NOE study determined the stereochemistry of this compound. Irradiation of the peaks at δ 0.46 and 0.48 ppm (*exo*- and *endo*-cyclopropane H) showed 9%, 5%, 5%, 2%, and 2% enhancements to the peaks at δ 1.05 (tertiary-cyclopropane H), 1.27 (cyclopentane CH), 2.08 (TBSOCH_2C<u>H</u>), 2.35 (C<u>H</u>CO_2Et), and 2.46 ppm (C<u>H</u>CO_2Et), respectively. The negligible coupling constant (J = ca. 0 Hz) between tertiary cyclopropane-H and TBSOCH_2C<u>H</u> also supports this stereochemical assignment. ^{13}C NMR: δ −5.30, 13.17, 14.30, 18.36, 23.97, 25.06, 25.80, 25.98, 29.73, 41.14, 43.57, 60.04, 66.36, 172.51. IR (neat): 3060, 2960, 2930, 2860, 1740, 1470, 1250, 1110, 1100, 840, 770 cm^{-1}. $[\alpha]^{23}_D$: −2.2 (*c* 2.1, $CHCl_3$) for a sample of 80% ee. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.34; H, 10.32. Found: C, 65.75; H, 10.60. The enantiopurity of this sample was determined by ^{1}H NMR chiral shift study with (+)-Eu(hfc)$_3$ to be 80% ee. The following peaks of the cyclopropane moiety were separated at 40 mol % of the Eu reagent: major enantiomer: δ 0.71 (t, J = 4.6 Hz, 1 H); minor enantiomer: δ 0.67 (t, J = 4.6 Hz, 1 H).

(1*S*,4*S*,5*R*)-4-[[(*tert*-Butyl)dimethylsiloxy]methyl]-1-[1-(ethoxycarbonyl)ethyl]bicyclo[3.1.0]hexane. To a solution of diisopropylamine (0.103 mL, 0.735 mmol) in 3 mL of THF was added BuLi (0.295 mL of a 2.40 M hexane solution, 0.708 mmol) at −78 °C. After 10 min, the ester **91** (192 mg, 0.615 mmol) in 2 mL of THF was added at −78 °C and the solution was stirred at that temperature for 1 h. Then methyl iodide (0.057 mL, 0.916 mmol) was added. After the mixture was stirred for 10 min at −78 °C, the solution was gradually warmed to room temperature over 20 min and was stirred at this temperature for 10 min. The reaction was terminated with aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution, and organic products were extracted with ether−hexane. Combined organic layers were dried (Na_2SO_4) and concentrated to give a spectroscopically pure title compound (213 mg) as a 1:1 mixture of diastereoisomers, which was directly used in the next step. ^{1}H NMR: δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.39 (dd, J = 4.3, 7.5 Hz, $^1/_2$H), 0.4−0.48 (m, $^1/_2$H × 2), 0.56 (dd, J = 4.5, 7.5 Hz, $^1/_2$H), 0.87 (s, 9 H), 0.98−1.08 (m, $^1/_2$H × 2), 1.13 (d, J = 7.5 Hz, $^1/_2$H × 3), 1.15 (d, J = 7.5 Hz, $^1/_2$H × 3), 1.23 (t, J = 7.5 Hz, $^1/_2$H × 3), 1.25 (t, J = 7.5 Hz, $^1/_2$H × 3), 1.40−1.75 (m, $^1/_2$H × 4), 2.07 (q, J = 7 Hz, 1 H), 2.19 (q, J = 7.5 Hz, $^1/_2$H), 2.22 (q, J = 7.5 Hz, $^1/_2$H), 3.25 (dd, J = 7, 9 Hz, $^1/_2$H), 3.34 (dd, J = 7, 9 Hz, $^1/_2$H), 3.43 (dd, J = 5.5, 9 Hz, $^1/_2$H), 3.46 (dd, J = 5.5, 9 Hz, $^1/_2$H), 4.10 (m, 2 H). IR (neat): 3060, 2960, 2930, 2860, 1730, 1470, 1380, 1250, 1180, 1160, 1100, 840, 780 cm^{-1} for a 1:1 mixture of the diastereoisomers.

2-[(1*R*,4*S*,5*R*)-4-[[(*tert*-Butyl)dimethylsiloxy]methyl]bicyclo[3.1.0]-hex-1-yl]propan-1-ol (92). The crude, methylated ester (213 mg) obtained above was reduced with Dibal-H (1.94 mL of a 0.95 M hexane solution, 1.84 mmol) in ether (10 mL) first at −78 °C and then at 0 °C for 30 min. Aqueous workup with 1 N HCl and extraction with ether−pentane afforded a crude sample of the title compound (180 mg) as a 1:1 mixture of diastereoisomers having rather different R_f values on analytical TLC (R_f = 0.53 and 0.37, Merck Cat. No. 1.05554, 20% EtOAc in hexane). This product was used in the next step without further purification. ^{1}H NMR: δ 0.05 (s, $^1/_2$H × 6), 0.10 (s, $^1/_2$H × 3), 0.11 (s, $^1/_2$H × 3), 0.20 (m, $^1/_2$H × 2), 0.41 (m, $^1/_2$H × 2), 0.88 (m, 12 H), 1.1−1.8 (m, 7 H), 2.07 (q, J = 7.5 Hz, 1 H), 3.3−3.75 (m, 4 H). IR (neat): 3400 (br), 3060, 2960, 2930, 2860, 1470, 1260, 1100, 1040, 1000, 840, 780 cm^{-1}.

(1*R*,4*S*,5*R*)-4-[[(*tert*-Butyl)dimethylsiloxy]methyl]-1-isopropylbicyclo[3.1.0]hexane (93). A mixture of the crude alcohol **92** (180 mg), *p*-toluenesulfonyl chloride (TsCl, 176 mg, 0.923 mmol), and a small amount of (dimethylamino)pyridine (7.5 mg) in pyridine (0.4 mL) was kept in a refrigerator (5 °C) overnight to give, after standard workup, a mixture of the desired tosylate and the unreacted sulfonyl chloride (1:0.35). This crude product was treated with $LiBHEt_3$ (1.85 mL of a 1 M THF solution, 1.85 mmol) in 5 mL of THF at room temperature for 3 h. At this stage, another 1 equiv of $LiBHEt_3$ (0.62 mL) was added. After the mixture was stirred at room temperature for 2 h, the starting material completely disappeared. To this solution were added water (0.5 mL), 3 N aqueous NaOH solution (1 mL), and aqueous 35% H_2O_2 solution (1 mL) in this order. After the mixture was vigorously stirred for 30 min at room temperature, extractive workup with ether−pentane (1:1) afforded a crude product, which was purified on silica gel to give the title compound (140 mg, 85% overall yield from **91**) as a colorless oil: ^{1}H NMR δ 0.04 (s, 6 H), 0.28 (d, J = 5 Hz, 1 H), 0.28 (d, J = 7 Hz, 1 H), 0.86 (d, J = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.91 (d, J = 7.5 Hz, 3 H), 1.0−1.6 (m, 6 H), 2.05 (q, J = 7.5 Hz, 1 H), 3.31 (dd, J = 8.0, 9.6 Hz, 1 H), 3.42 (dd, J = 7.3, 9.6 Hz, 1 H); ^{13}C NMR δ −5.43, 12.19, 18.30, 19.68, 20.18, 23.24, 24.78, 25.09, 25.91, 32.43, 33.52, 43.32, 66.51; IR (neat) 3060, 2960, 2930, 2860, 1470, 1380, 1360, 1250, 1100, 1080, 1020, 840, 770 cm^{-1}; $[\alpha]^{23}_D$ +4.1 (*c* 2.1, $CHCl_3$) for a sample of 80% ee. Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 72.00; H, 12.28.

(1*R*,4*S*,5*R*)-1-Isopropylbicyclo[3.1.0]hexane-4-methanol (94). A mixture of the silyl ether **93** (140 mg, 0.521 mmol) and TBAF (0.626 mL of a 1 M solution in THF, 0.626 mmol) in 1 mL of THF was stirred at room temperature for 3.5 h. The solution was diluted with ether−pentane (1:1) and was washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed on silica gel (ether−hexane) to give the title compound (80 mg, quant.): ^{1}H NMR δ 0.325 (d, J = 7.4 Hz, 1 H), 0.33 (d, J = 5 Hz, 1 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.92 (d, J = 7.2 Hz, 3 H), 1.20−1.70 (m, 7 H), 2.08 (q, J = 7.5 Hz, 1 H), 3.38 (dd, J = 7.5, 9 Hz, 1 H), 3.49 (dd, J = 7.5, 9 Hz. 1 H); ^{13}C NMR δ 12.40, 19.62, 20.19, 23.58, 24.69, 25.05, 25.54, 32.43, 43.40, 66.60; IR (neat) 3320 (br), 3060, 2960, 2920, 2870, 1470, 1380, 1360, 1050, 1020 cm^{-1}; $[\alpha]^{23}_D$ +7.9 (*c* 3.8, THF) for a sample of 80% ee. The enantiopurity of this sample was determined by the integration of the following peaks of the ^{1}H NMR spectrum of the (*S*)-MTPA ester prepared from (*R*)-(−)-MTPA-Cl. Major enantiomer: δ 4.03 (dd, J = 7.9, 10.6 Hz, 1 H, C$\underline{H}_2$OMTPA), 4.15 (dd, J = 7.6, 10.6 Hz, 1 H, C$\underline{H}_2$OMTPA). Minor enantiomer: δ 4.06 (dd, J = 7.9, 10.6 Hz, 1 H, C$\underline{H}_2$OMTPA), 4.13 (dd, J = 7.6, 10.6 Hz, 1 H, C$\underline{H}_2$OMTPA).

(1*R*,4*S*,5*R*)-1-Isopropyl-4-[[(2-nitrobenzene)selenenyl]methyl]-bicyclo[3.1.0]hexane. To a solution of the alcohol **94** (76 mg, 0.493 mmol) and (2-nitrophenyl)selenocyanate (134 mg, 0.591 mmol) in 3 mL of THF was added PBu_3 (0.147 mL, 0.590 mmol) at room temperature. After the dark solution had been stirred at room temperature for 2 h, the starting material still remained so that further portions of the selenocyanate (90 mg, 0.394 mmol) and PBu_3 (0.099 mL, 0.394 mmol) were added. Twenty minutes later, TLC analysis showed the complete consumption of the starting material. The solution was washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The resultant brown oil was roughly purified on silica gel (ether−hexane) to give the title compound (195 mg, contaminated with a small amount of byproducts) as a yellow oil, which was directly used in the next step: ^{1}H NMR: δ 0.36 (d, J = 6 Hz, 2 H), 0.91 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.09 (t, J = 6 Hz, 1 H), 1.30−1.96 (m, 5 H), 2.28 (q, J = 7.3 Hz, 1 H), 2.76 (dd, J = 8, 11 Hz, 1 H), 2.88 (dd, J = 6.9, 11 Hz, 1 H), 7.30 (t, J = 8 Hz, 1 H), 7.52 (m, 2 H), 8.28 (d, J = 8 Hz, 1 H).

(1*R*,5*R*)-(+)-1-Isopropyl-4-methylenebicyclo[3.1.0]hexane (*d*-Sabinene) (84). To a stirred solution of the above selenide (195 mg) in 1 mL of THF were added powdered K_2CO_3 (204 mg, 1.48 mmol) and 35% aqueous H_2O_2 (0.48 g, ca. 5 mmol) in this order at room temperature. After the stirring was continued for 30 min, 0.4 mL of THF, 70 mg of K_2CO_3, and water (0.4 mL) were added to the red solution. The mixture was stirred at room temperature for 40 h and eventually diluted with 4 mL of pentane. The pentane layer was washed seven times with 3 mL portions of water to remove the bulk of THF. The organic layer was dried over Na_2SO_4 and carefully concentrated to a red oil, which was subjected to purification on silica gel (pentane) to yield the pure title compound (34 mg, 51% overall from **93**) as a colorless oil: ^{1}H NMR δ 0.64 (d, J = 5.3 Hz, 2 H), 0.87 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.48 (quintet, J = 7 Hz, 1 H), 1.58 (t, J = 5.5 Hz, 1 H), 1.68 (m, 1 H), 1.76 (dd, J = 9.3, 12 Hz, 1 H), 1.99 (dtt, J = 16, 2.3, 9.3 Hz, 1 H), 2.16 (br dd, J = 8.6, 16 Hz, 1 H), 4.61 (br s, 1 H), 4.80 (br s, 1 H); ^{13}C NMR δ 15.92, 19.58, 19.68, 27.40, 28.88, 30.04, 32.49, 37.58, 101.55, 154.69; IR (neat) 3080, 3060 (sh), 2960, 2940, 2880, 1650, 1470, 1450, 1380, 1360, 1330, 1315, 1300, 1280, 1240, 1200, 1160, 1150, 1130, 1105, 1090, 1070, 1020, 990, 960, 930, 915, 860, 805, 780, 730 cm^{-1}. These spectral properties are in good agreement with those reported in the literature.[32b,c] $[\alpha]^{23}_D$: +75.8 (*c* 0.65, *n*-pentane) for a sample of 80% ee; lit. $[\alpha]^{20}_D$ +107 ± 3 (in substance) for a 99% pure sample;[38a] $[\alpha]_D$ +89.[38b]

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture (Japan) for financial support.

Supporting Information Available: Preparation and characterization data for all starting materials (12 pages). See any current masthead page for ordering and Internet access instructions.

JA9716160