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Asymmetric Synthesis of Bicyclic Ketones Having an Angular Substituent via Ti(II) Alkoxide-Mediated Tandem Cyclization of Trisubstituted Olefinic Substrates

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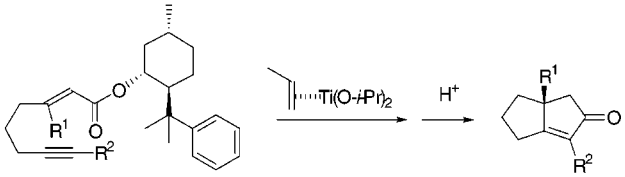
ABSTRACT



Angularly substituted, optically active bicyclic ketones of up to 94% ee were prepared by the Ti(II) alkoxide-mediated tandem cyclization of open-chain substrates, that is, 8-phenylmenthyl enynoates having a trisubstituted double bond.

Bicyclic ketones having a substituent at their angular position such as those shown in Figure 1 should be versatile

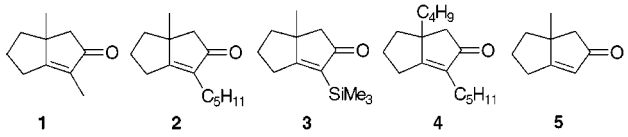


Figure 1.

compounds for the preparation of cyclic compounds.[1] In fact, some of these ketones were prepared in racemic form by an aldol-based method[1,2] and utilized as the starting material for the synthesis of naturally occurring products.[3] The increasing importance of asymmetric synthesis leads to a greater demand for chiral building blocks; however, the preparation of optically active ketones **1**−**5** has not yet been reported in the literature. In addition to the conventional methods, the recently introduced transition metal-catalyzed or -mediated carbonylative cyclization of enynes provides an attractive method for preparing a variety of bicyclic ketones,[4−7] including optically active ones.[4a,g,6b] However, this process does not appear to be suitable for the preparation of the above ketones, because the cyclization of 1,1-disubstituted olefinic substrates, which are precursors for the angularly substituted ketones, usually requires the presence

(1) For a review of the utility of five-membered bicyclic ketones, see: Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141−170. Paquette, L. A. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: Berlin, 1984; Vol. 119, pp 1−158. Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647−3692.

(2) Ramaiah, M. *Synthesis* **1984**, 529−570. Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284−290. Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467−1486.

(3) For the synthesis of (±)-isocomene and (±)-*β*-isocomene from (±)-**1**, see: Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1835−1838. Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898−899. For (±)-gymnomitrol and (±)-gymnomitrene from (±)-**5**, see: Welch, S. C.; Chayabunjonglerd, S. *J. Am. Chem. Soc.* **1979**, *101*, 6768−6769. Welch, S. C.; Chayabunjonglerd, S.; Rao, A. S. C. P. *J. Org. Chem.* **1980**, *45*, 4086−4093. See also: Dorsch, M.; Jäger, V.; Spönlein, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 798−799.

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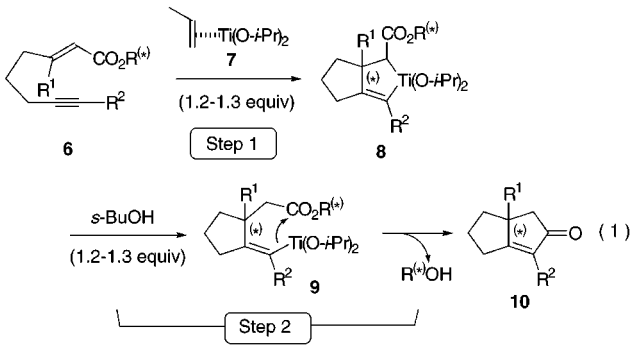
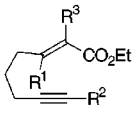
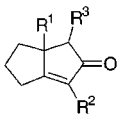
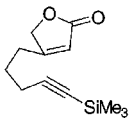
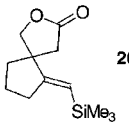
of substituents to the tether portion (i.e., steric promotion;[8] for example, the assistance by the Thorpe−Ingold effect) to achieve good yields.[4d,6] To find a viable solution, we reexamined our tandem cyclization of 2,7-enynoates with a titanium(II) alkoxide as shown in eq 1,[9] but this time, we chose substrates having a trisubstituted olefin. More importantly, the replacement of the ester portion of the substrate with an appropriate chiral auxiliary led us to develop an asymmetric synthesis of **1**−**5** with high enantiomeric purity.



The tandem cyclization shown in eq 1 consists of two steps: step 1 is the formation of titanacycle **8** from enynoates **6** and the titanium(II) reagent (η^2-propene)Ti(O-*i*-Pr)$_2$ (**7**) readily prepared in situ from Ti(O-*i*-Pr)$_3$Cl and *i*-PrMgCl.[10] Step 2 involves the regioselective protonation of **8** with *s*-BuOH giving alkenyltitanium species **9**, which undergoes intramolecular attack to the released ester group to give bicyclic ketone **10**.[9] As the Group 4 metal (Ti or Zr)-mediated intramolecular cyclization[5] of a *trisubstituted* olefin and other carbon−carbon multiple bonds is again a sluggish process,[11] the feasibility of the **7**-mediated cyclization to give titanacycle **8** was a matter of serious concern. Nonetheless, the tandem cyclization of ethyl esters **11**−**14** (entries 1−4 in Table 1) nicely proceeded according to eq 1 to give the desired bicyclic ketones **1**-**4** in good yields. The reactions of some other relevant substrates are also shown in Table 1. A trisubstituted olefin of a different pattern such as that in **15** also participated in the cyclization to afford bicyclic ketone **16** as a single stereoisomer (entry 5). Even tetrasubstituted olefinic ester **17** is a possible substrate for this tandem cyclization to give bicyclic ketone **18**, albeit in a moderate yield (entry 6). However, the cyclization of α,*β*-unsaturated lactone **19** stopped at step 1, most likely due to steric bias in the step-2 cyclization, to afford spirolactone **20** (entry 7). The favorable interaction between an electron-deficient olefin with the electron-rich, low-valent titanium center may account for the success of the step-1 cyclization, as the replacement of CO$_2$R(*) of **6** with an alkyl group completely halted the formation of the corresponding titanacycle.[7a]

Table 1. Preparation of Angularly Substituted Bicyclo[3.3.0]octenones and Related Reactions[a]

entry	substrate				product	yield (%)[b]
						
1	R^1 = Me	R^2 = Me	R^3 = H	**11**	**1**	69
2	Me	C_5H_{11}	H	**12**	**2**	80
3	Me	$SiMe_3$	H	**13**	**3**	73
4	C_4H_9	C_5H_{11}	H	**14**	**4**	66
5	H	C_5H_{11}	Me	**15**	**16**[c]	70
6	Me	C_5H_{11}	Me	**17**[d]	**18**[e]	36
7				**19**		**20** 54

[a]See eq 1. [b]Isolated yields. [c]A single stereoisomer, in which the angular H and the α-Me to ketone are *trans*, was obtained. [d]A 1:1 mixture of *E* and *Z* isomers. [e]Isolated as a single stereoisomer, the structure of which has not been assigned.

Considering the synthetic importance of the bicyclic ketones, we then turned our attention to an asymmetric version of the above process starting with optically active esters. After trials using several esters derived from chiral alcohols,[12] 8-phenylmenthyl esters[13] such as **21** in entry 1, Table 2, were found to give the best result. Under these conditions, the desired ketone (−)-**2** was isolated in good

(4) (a) Geis, O.; Schmalz, H.-G. *Angew. Chem*. **1998**, *110*, 955−958; *Angew. Chem., Int. Ed.* **1998**, *37*, 911−914. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev*. **1996**, *96*, 635−662. (c) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992** 539−546. (d) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1037−1064. (e) Schore, N. E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, pp 1−90. (f) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2801−2803. (g) Adrio J.; Carretero, J. C. *J. Am. Chem. Soc*. **1999**, *121*, 7411−7412.

(5) For a review on the Group 4 metal-mediated cyclization and carbonylative cyclization, see: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev*. **1988**, *88*, 1047−1058. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1163−1184. Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696−1701. Negishi, E.; Takahashi, T. *Acc. Chem. Res*. **1994**, *27*, 124−130. Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; pp 99−113. Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burkalov, V. V.; Rosenthal, U. *Synlett* **1996**, 111−118. Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 755−769.

(6) (a) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 5881−5898. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 7026−7033.

(7) (a) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 4261−4264. (b) Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 11295−11305.

(8) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205−1222.

(9) (a) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1996**, *118*, 8729−8730. (b) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 10014−10027.

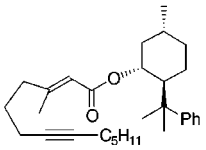
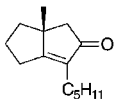
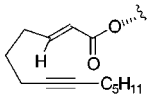
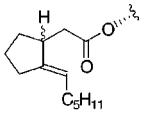
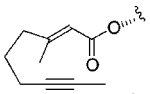
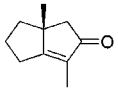
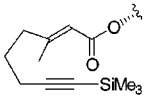
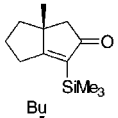
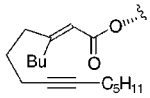
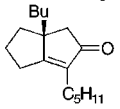
(10) Sato. F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem., Jpn*. **1998**, *56*, 424−432.

(11) The successful cases are so far limited to substrates having a nitrogen atom (coordination effect) or geminal substituents (Thorpe−Ingold effect) in their tether portion, which are not valid for **6**. For a survey on the outcome of the cyclization of polysubstituted olefins with Group 4 metal reagents, see: ref 6. Negishi, E.; Maye, J. P.; Choueiry, D. *Tetrahedron* **1995**, *51*, 4447−4462. Yamaura, Y.; Mori, M. *Tetrahedron Lett*. **1999**, *40*, 3221−3224.

(12) See Supporting Information.

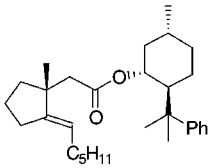
(13) Whitesell, J. K. *Chem. Rev*. **1992**, *92*, 953−964. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; p 513. Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357−373.

Table 2. Preparation of Optically Active Bicyclo[3.3.0]octenones[a]

entry	starting 8-phenylmenthyl ester	product[b]		yield (%)[c]	ee (%)
1		**21**		(-)-**2**	62	91-93
2		**22**		**23**	76	70[d]
3		**25**		(-)-**1**	66	93
4		**26**		(-)-**3**	62	91
5		**27**		(-)-**4**	49	94

[a]See eq 1. [b]In entry 2, a small amount of the bicyclic ketone (5%) was also produced. In entries 3 and 4, the mono-cyclic esters like **24** were separated in 26-29% yield and with 26-30% de (see text). [c]Isolated yields. [d]De.

yield and with high enantiopurity. This result deserves the following two comments. First, the step-2 cyclization of the relatively hindered ester **21** was notably promoted by the presence of the β-methyl group to the ester, because substrate **22** lacking the vinylic methyl group in **21** did not undergo the cyclization of step 2, merely giving monocyclic ester **23** (entry 2, Table 2). The latter observation is in accord with our earlier result that a similar *tert*-butyl ester does not undergo step 2 at all.[9b] Second, monocyclic ester **24** (Figure 2) was separated as a byproduct (30% yield) and its de value (42% de) was considerably lower than the ee of bicyclic ketone **2** (91−93% ee), suggesting that the kinetic resolution at step 2 should contribute to the further enhancement of the de value resulting from step 1. However, the forcing cyclization conditions in step 2 (a higher temperature and/or a longer reaction period) to promote the yield of **2** were totally ineffective. Thus, irrespective of a subtle change in the reaction conditions, the enantiopurity of the bicyclic ketone remains constant, the reproducibility being guaranteed.[14]



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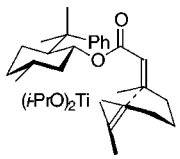

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Figure 2.

The preparation of a series of optically active bicyclic ketones **1**−**4** from the corresponding 8-phenylmenthyl esters **21** and **25**−**27** is summarized in Table 2. Silyl derivative (−)-**3** was smoothly desilylated with Bu_4NF to give (*R*)-**5** (Figure 1) without loss of the enantiopurity (80% yield). Subsequent hydrogenation of (*R*)-**5** (H_2, Pd/C) afforded the known (−)-(1*R*,5*S*)-1-methylbicyclo[3.3.0]octan-3-one (80% yield),[15] which unambiguously determined the absolute configuration of (−)-**3** to be *R*. The absolute stereochemistry of the other products was deduced by analogy based on the same sign of their optical rotations. The documented stereochemical control in 8-phenylmenthyl esters,[13] namely, that the phenyl ring blocks one side of the plane of the conjugated π-system of the α,β-unsaturated carbonyl moiety as illustrated with **28** in Figure 2, is consistent with the observed absolute stereochemistry of the products. The eliminated 8-phenylmenthol was recovered after the cyclization in a nearly quantitative yield (for instance, entry 1) and may be recycled. It should be noted that this method achieved the first preparation of the optically active bicyclic ketones **1**−**5** (Figure 1). The above results have brought about a novel phase of the **7**-mediated cyclization of bis-unsaturated compounds, and its further application to asymmetric synthesis will be reported in due course.

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture (Japan) and, in part, a Sankyo Award in Synthetic Organic Chemistry (to H.U.) for financial support.

Supporting Information Available: Procedure for the preparation of the starting material **21** and bicyclic ketone (−)-**2**, characterization data for the starting materials and products, and an addendum to Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Although the clear explanation needs more experimental support, the different site selectivities of the protonation (to vinyl-Ti vs α-ester-Ti bonds) dependent upon the diastereomeric titanacycles **8** (eq 1) may account for this phenomenon.

(15) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericás, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388−9389. Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525−5528.