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Synthesis of 1-Hydroxybicyclo[n.1.0]alkanes (n = 3 and 4) and Their Silyl Ethers from Olefinic Esters *via* Tandem Intramolecular Nucleophilic Acyl Substitution and Intramolecular Carbonyl Addition Reactions Mediated by $Ti(OPr\text{-}i)_4$ / 2 *i*-PrMgCl Reagent

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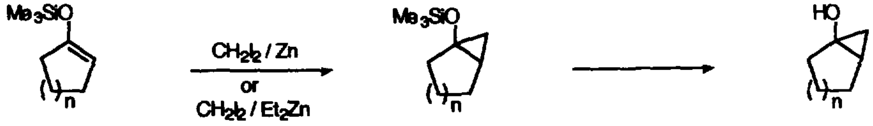
Abstract *: Treatment of olefinic esters with $Ti(OPr\text{-}i)_4$ / 2 i-PrMgCl reagent resulted in intramolecular nucleophilic acyl substitution and successive intramolecular carbonyl addition reactions providing 1-hydroxybicyclo[n.1.0]alkanes (n = 3 and 4) in high yields.*

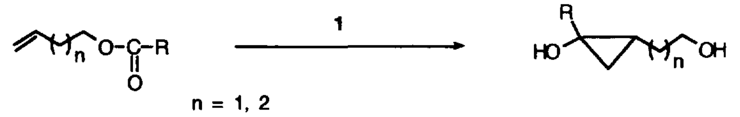
1-Hydroxybicyclo[n.1.0]alkanes and their silyl ethers have been widely accepted as useful starting materials or intermediates in organic synthesis.[2] 1-Siloxybicyclo[n.1.0]alkanes can be most conveniently obtained by Simmons-Smith reaction of the corresponding enol silyl ethers.[3] Upon treatment with acids or bases under mild conditions, they can be converted into 1-hydroxybicyclo[n.1.0]alkanes (Scheme 1).[3a-e,4]



Scheme 1

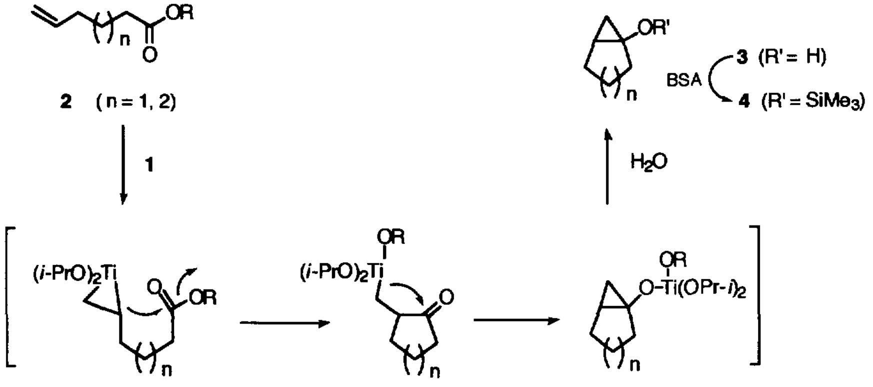
Although the methodology shown in Scheme 1 is highly efficient and potentially general, some kinds of 1-siloxy- and consequently 1-hydroxybicycloalkanes are actually difficult to prepare because the corresponding starting enol silyl ethers are not easily obtainable.[5] We have succeeded in developing a new general method for synthesis of 1-hydroxybicyclo[n.1.0]alkanes where n = 3 and 4, including those which are difficult to obtain by the method shown in Scheme 1.

Recently, we have reported that the reaction of $Ti(OPr\text{-}i)_4$ with 2 equiv of *i*-PrMgX (X = Cl, Br) provides (η^2-propene)$Ti(OPr\text{-}i)_2$ (1) in essentially quantitative yield, and it works as a versatile $Ti(OPr\text{-}i)_2$ equivalent, thus opening up synthetically useful Ti(II)-chemistry.[6] In the course of the research work for applications of 1 in organic synthesis, we have revealed that its reaction with homoallyl or bis-homoallyl esters affords 1,2-disubstituted cyclopropanols in excellent yields *via* tandem intramolecular nucleophilic acyl substitution (INAS) and intramolecular carbonyl addition reactions (eq 1).[6c]



(eq 1)

These findings prompted us to carry out the reaction of **1** with olefinic esters **2** in anticipation of getting 1-hydroxybicyclo[n.1.0]alkanes (**3**) *via* Ti(OPr-*i*)$_2$-mediated INAS reaction and the successive intramolecular carbonyl addition reaction of the resulting β-titanated cyclic ketones as shown in Scheme 2.[7] The reaction was found to proceed as we anticipated. Thus, to a solution of Ti(OPr-*i*)$_4$ and **2** in ether was added *i*-PrMgCl; the mixture was allowed to react at -45 ~ -40 °C and warmed up to 0 °C to afford the corresponding 1-hydroxybicycloalkanes **3** as summarized in Table 1 (entries 1-8).[8] The alcohols **3** thus obtained can be readily converted into the corresponding trimethylsilyl ethers **4** by treatment with N,O-bis(trimethylsilyl)acetamide (BSA)[9] (see entries 5 and 8).

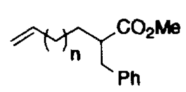
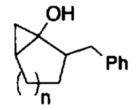
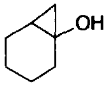
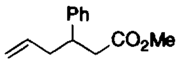
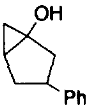
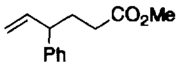
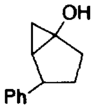
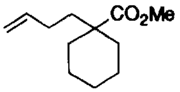
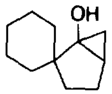
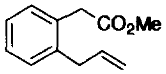
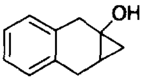
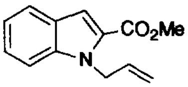
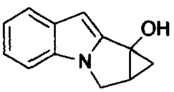
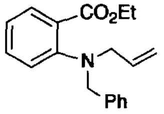
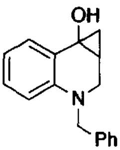


Scheme 2

As revealed in Table 1, a variety of 1-hydroxybicyclo[3.1.0]- and 1-hydroxybicyclo[4.1.0]alkanes can be readily obtained in good to excellent yields. Especially noteworthy is the easy access to the compounds such as **3d**, **3g** (entries 5, 8), since preparation of these compounds might be difficult using the method shown in Scheme 1 because of the problem involved to generate regioselectively the corresponding starting enol silyl ethers.[5,10] It should be noted, however, the olefinic substrates containing a disubstituted double bond (such as methyl *cis*-2-benzyl-5-octenoate) or those in which the double bond and an ester group are separated by more than four carbons (such as methyl 2-benzyl-7-octenoate) did not afford the expected bicyclic products.[11]

The reaction can be also applicable to the synthesis of N-heterocyclic compounds as represented by entries 9 and 10. Preparation of other N-heterocyclic compounds and their application in organic synthesis are now underway in our laboratory.

Table 1. Synthesis of 1-Hydroxybicyclo[n.1.0]alkanes (n = 3 and 4) from Olefinic Esters Using $Ti(OPr\text{-}i)_4$ / 2 i-PrMgCl Reagent[a]

Entry	Substrate **2**	Product **3**		Yield, %[b] (ds)[c]
1			**3a** (n = 1)	77 (66 : 34)
2			**3b** (n = 2)	73 (89 : 11)
3			**3c**	57 [R = Me]
4				52 [R = Et]
5			**3d**[d]	83 (61 : 39)
6			**3e**	76 (55 : 45)
7			**3f**	88
8			**3g**[d]	98
9[e]				75
10[e]				94

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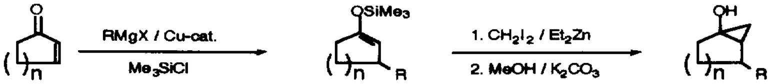
[a] The reactions were carried out using 2.0 equiv of $Ti(OPr\text{-}i)_4$ and 4.0 equiv of i-PrMgCl at -45 ~ -40 °C (1 h), then the reaction mixture was warmed up to 0 °C for 2.5 h unless stated otherwise. [b] Isolated yields based on starting olefinic esters. [c] Diastereoselectivity according to ^{1}H NMR data; related stereochemistry was not determined. [d] The product **3** was converted to the corresponding silyl ether **4** by treatment with BSA in acetonitrile (20 °C, 1 h) in more than 90% yield. [e] i-PrMgCl was added at -78 °C, then the reaction mixture was warmed up to 20 °C for 2 h.

References and Notes

1. On leave from Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences.
2. (a) Murai, S.; Ryu, I.; Sonoda, N. *J. Organometal. Chem.* **1983**, *250*, 121. (b) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. (c) Ito, Y.; Fujii, S; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth. Coll. Vol. 6*, **1988**, 327. (d) Ryu, I.; Matsumoto, K.; Kameyama, Y.; Ando, M.; Kusumoto, N.; Ogawa, A.; Kambe, N.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 12330. (e) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 6907 and references cited therein.
3. For cyclopropanation with CH_2I_2 by using Zn-Cu couple, see: (a) Le Goaller, R.; Pierre, J.-L. *Bull. Soc. Chim. Fr.* **1973**, 1531. (b) Rubottom, G. M.; Lopez, M. I. *J. Org. Chem.* **1973**, *38*, 2097. (c) Murai, S.; Aya, T.; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354. By using Zn-Ag couple, see: (d) Conia, J. M.; Girard, C. *Tetrahedron Lett.* **1973**, 2767. (e) Girard, C.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3327. By using Et_2Zn, see: (f) Ryu, I.; Murai, S.; Sonoda, N *Tetrahedron Lett.* **1977**, 4611. (g) Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *Synthesis* **1977**, 700.
4. One pot synthesis of 1-hydroxybicyclo[n.1.0]alkanes from cyclic ketones *via* cyclopropanation of the corresponding Li-enolates by using CH_2I_2 / SmI_2 has been also reported, see: Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, *28*, 1307.
5. For regioselective synthesis of enol silyl ethers from various ketones under conditions of either kinetic or thermodynamic control, see reviews: Rasmussen, J. K. *Synthesis* **1977**, 91. Brownbridge, P. *Synthesis* **1983**, 1 and 85. Taylor, R. J. K. *Synthesis* **1985**, 364.
6. (a) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Kasatkin, A.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6075. (c) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079, see also references cited therein.
7. Oxidation of 1-hydroxybicyclo[n.1.0]alkanes **3** or their silyl ethers **4** to ω-alkenoic acids **2** (R = H) was reported; Rubottom, G. M.; Marrero, R.; Krueger, D. S.; Schreiner, J. L. *Tetrahedron Lett.* **1977**, 4013. Rubottom, G. M.; Beedle, E. C.; Kim, C.-W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230. See also ref. 2e.
8. A typical procedure is as follows; To a stirred solution of methyl 2-benzyl-5-hexenoate (0.218 g, 1.00 mmol) and $Ti(OPr\text{-}i)_4$ (0.568 g, 2.00 mmol) in ether (12 mL) was added *i*-PrMgCl (3.08 mL, 1.30 M in ether, 4.00 mmol) at -45 °C. The mixture was stirred for 1 h at -45 °C ~ -40 °C and warmed up to 0 °C over 2.5 h. After addition of THF (3.0 mL) and H_2O (1.3 mL), the resulting white suspension was stirred for 0.5 h at 20 °C. The organic layer was separated by decantation, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (Wako C-200, hexane / AcOEt, 5 : 1) to give 1-hydroxy-2-benzylbicyclo[3.1.0]hexane (**3a**) (0.145 g, 77% yield) as a mixture (66 : 34) of diastereomers.
9. Klebe, J. F.; Finkbeiner, H.; White, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 3390.
10. Substituted 1-hydroxybicyclo[n.1.0]alkanes of the type **3e** (entry 6) were prepared according to the following scheme; see, for example: Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Narasaka, K. *Chem. Lett.* **1993**, 545. Booker-Milburn, K. I. *Synlett*, **1992**, 809.



11. Complicated mixtures of unidentified products along with 20-30% of the starting materials were isolated in both reactions.

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