Graphical Abstract

Stereoselective construction of 3a-methylhydrindanes starting from 2,7-enynol derivatives based on Ti(II)-mediated cyclization and Ru-catalyzed ring-closing metathesis

Mutsumi Ohkubo, Wataru Uchikawa, Hitomi Matsushita, Aiko Nakano, Takayuki Shirato and Sentaro Okamoto*
Department of Applied Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686

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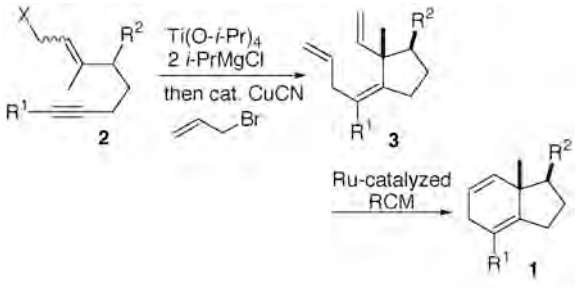

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Stereoselective construction of 3a-methylhydrindanes starting from 2,7-enynol derivatives based on Ti(II)-mediated cyclization and Ru-catalyzed ring-closing metathesis

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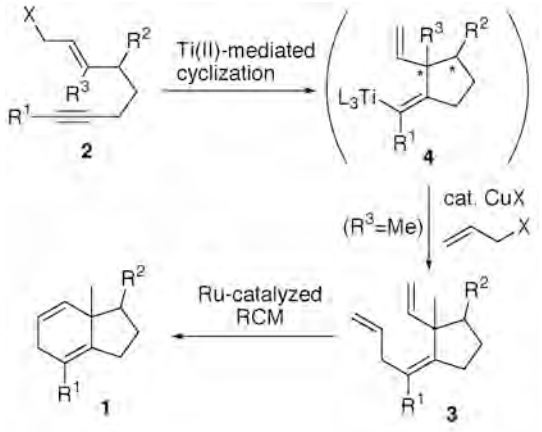
Abstract—The Ti(II)-mediated cyclization of 3-methyloct-2-en-7-yn-1-ol derivatives **2** proceeded stereoselectively to afford 1-methyl-2-(1-alkylbut-3-enylidene)-1-vinylcyclopentanes **3** after treatment of the resulting alkenyltitaniums with allylbromide in the presence of CuCN, which was readily converted to 3a-methyl-2,3,3a,6-tetrahydro-1*H*-indenes **1** by the Ru-catalyzed ring-closing metathesis.

Construction of the 3a-methylhydrindane skeleton that is widely present in natural compounds such as steroids, vitamin D, higher terpenes and related natural products has received a great deal of attetion.[1] Recently, metal-promoted or –catalyzed reactions have attracted interest as a selective means for synthesis of 3a-methylhydrindane from acyclic starting compound(s).[2] Herein we report an efficient two-step method for the synthesis from acyclic unsaturated starting compounds.

Our synthetic plan for synthesizing 3a-methyl-2,3,3a,6-tetrahydro-1H-indene (**1**) is summarized in Scheme 1 (R^2 = Me), which involves divalent titanium-mediated enyne-cyclization (intramolecular allyltitanation of alkyne) of enyne **2** followed by copper-catalyzed allylation of the resulting alkenyltitanium compound **4** and the subsequent Ru-catalyzed ring-closing metathesis reaction of the resulting triene **3**. Regarding the first step of Scheme 1, we already reported that the reaction of **2** (R^3 = H) with a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl,[3] proceeds in an intramolecular allyltitanation pathway to provide the corresponding cyclized product type **4** (R^3 = H) in excellent yield.[4] With the results, we expected that we could find appropriate conditions to control 1,2-diastereoselection of the reaction of compound **2** (R^3 = Me) with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl.[5]



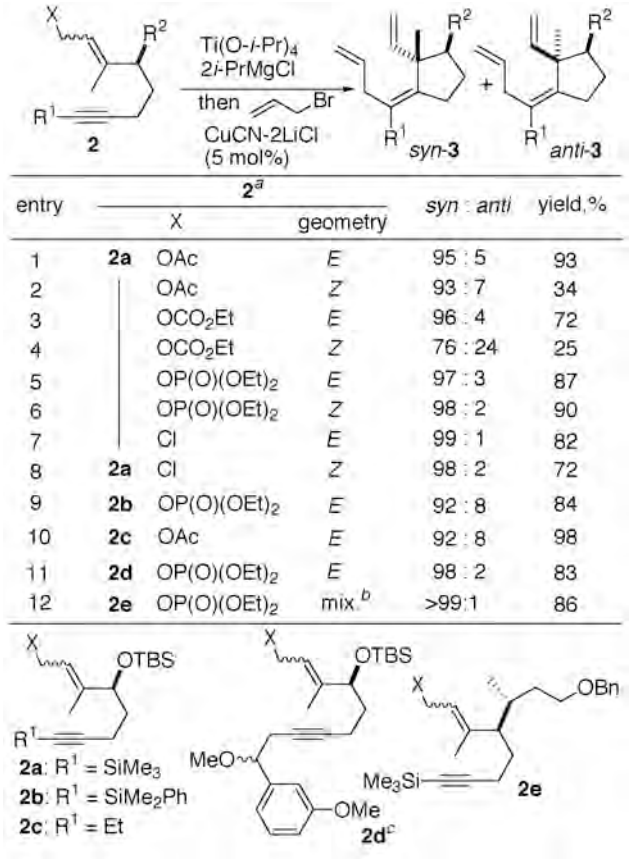
Scheme 1. Synthetic plan.

First, we carried out the Ti(II)-mediated cyclization of enynes **2** (R^3 = Me) having a different leaving group X such as OAc, OP(O)(OEt)$_2$, OCO$_2$Et, or Cl and the following copper-catalyzed allylation of the resulting alkenyltitanium **4** to see the efficiency. Thus, to a solution of **2** (1.0 equiv) and Ti(O-*i*-Pr)$_4$ (1.3 equiv) in ether was added dropwise *i*-PrMgCl (2.6 equiv, 1.3 M in ether) at –40 °C. After being stirred for 1.5 h at this temperature, to the resulting solution of alkenyltitanium **4** were added

* Corresponding author. Tel.: +81-45-481-5661; fax: +81-45-413-9770; e-mail: okamos10@kanagawa-u.ac.jp

allylbromide (1.5 equiv) and a THF solution of CuCN-2LiCl (5 mol%) at –40 °C.[4i] After warming to room temperature over 3 h, usual aqueous work-up afforded **3**. As can be seen from Table 1 summarizing the results, all reactions predominantly produced the cyclized compound **3** with *syn* configuration regarding the methyl and R^2 groups.[6] Although the reaction of *Z*-**2a** having an OAc or OCO_2Et moiety as a leaving group resulted in poor yield and/or low stereoselectivity (entries 2 and 4), high selectivity and good yield of *syn*-**3a** was attained by using **2a** having $OP(O)(OEt)_2$ or Cl, irrespective of the olefin geometry of the starting **2a** (entries 5-8). Similarly, the reaction of enynes **2b-d** having other alkyne substituents yielded the corresponding triene *syn*-**3** selectively. The enynol derivative **2e** with a secondary alkyl group as R^2 could also be converted to *syn*-**3e** with nearly complete selectivity, where a mixture of *E*- and *Z*-isomers was employed as the substrate.

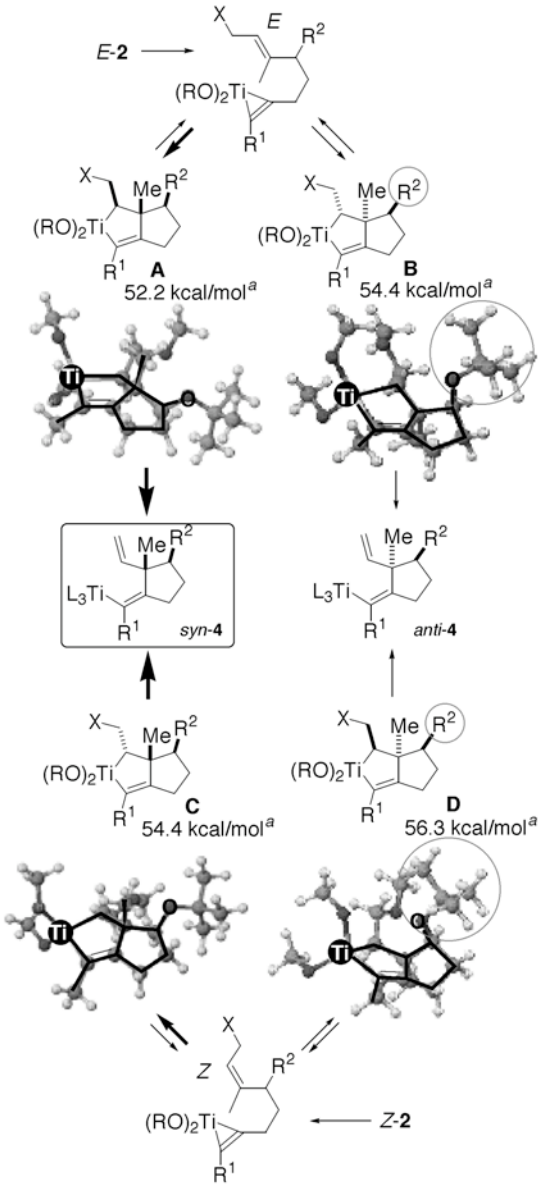
Table 1. Ti(II)-mediated cyclization and the following allylation of **2** to **3**.



entry	2[a]	X	geometry	*syn* : *anti*	yield,%
1	**2a**	OAc	*E*	95 : 5	93
2		OAc	*Z*	93 : 7	34
3		OCO_2Et	*E*	96 : 4	72
4		OCO_2Et	*Z*	76 : 24	25
5		$OP(O)(OEt)_2$	*E*	97 : 3	87
6		$OP(O)(OEt)_2$	*Z*	98 : 2	90
7		Cl	*E*	99 : 1	82
8	**2a**	Cl	*Z*	98 : 2	72
9	**2b**	$OP(O)(OEt)_2$	*E*	92 : 8	84
10	**2c**	OAc	*E*	92 : 8	98
11	**2d**	$OP(O)(OEt)_2$	*E*	98 : 2	83
12	**2e**	$OP(O)(OEt)_2$	mix[b]	>99:1	86

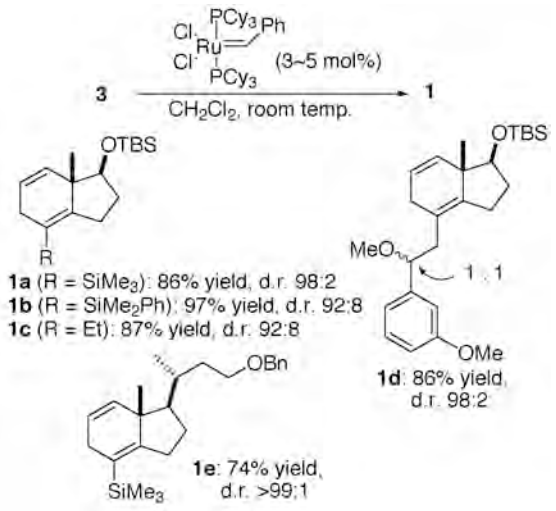
[a]The structure is shown above. [b]*E*:*Z* = 90:10. [c]A 1:1 mixture of diastereoisomers.

To explain the diastereoselectivity observed in Table 1, we carried out MM2 calculations[7] using simplified models **A**-**D** for the possible titanacyclopentene intermediates derived from (*E*)- and (*Z*)-**2**, where R^2, X, R^1 in **2** and O-*i*-Pr moieties on the titanium atom were replaced by O-*t*-Bu, OMe, Me, and OMe groups, respectively (Scheme 2). As shown in Scheme 2, it was revealed that models **A** and **C** which can provide the product of the type *syn*-**4**, i.e. *syn*-**3**, are more stable in ~2 kcal/mol than the corresponding isomers **B** and **D**. The pseudo-axial orientation of the R^2 group (O-*t*-Bu) in models **B** and **D** (indicated by gray circles in Scheme 2) may cause their instability. Use of a better leaving group (X) enhanced the rate of the β-elimination reaction of the titanacycle intermediates. Accordingly, it could increase the overall reaction rate and efficiency of the formation of **4**. The rate enhancement of the β-elimination reaction from **A** or **C** by use of the better leaving group may be larger than that for **B** or **D**, respectively, and it may favorably effect predominant formation of *syn*-**4.**



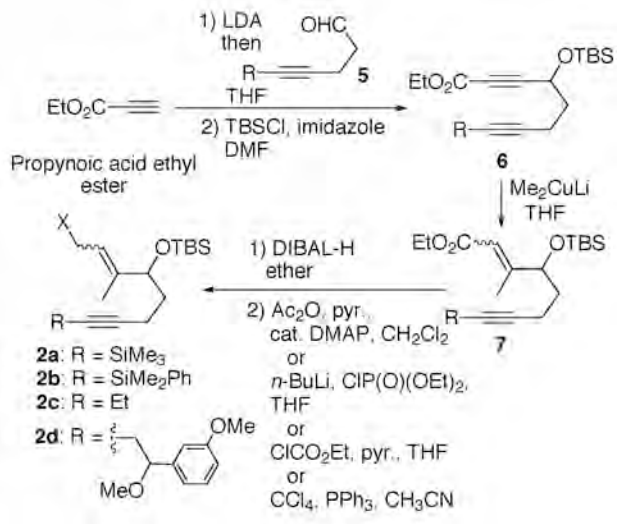
Scheme 2. Postulated reaction mechanism and MM2 calculation of models of titanacycle intermediates: [a]Energy calculated as RO, R^1, R^2 and X are MeO, Me, O-*t*-Bu and MeO, respectively.

With these results in hand, we next carried out the Ru-catalyzed ring-closing metathesis reaction[8,9] of the resulting triene **3** to **1** (Scheme 3). Thus, the triene **3** was treated with the first-generation Grubbs catalyst, $Cl_2(Cy_3P)_2Ru{=}CHPh$, (3~5 mol%) in CH_2Cl_2 at room temperature and the following purification by column chromatography to provide **1**[6] in good isolated yield.



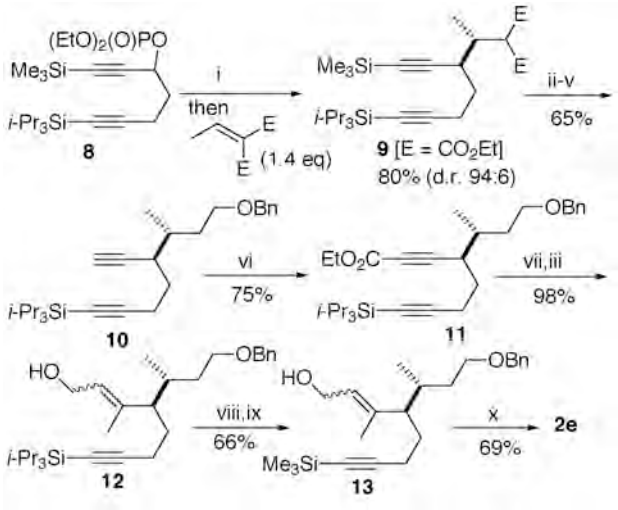
Scheme 3. Ru-catalyzed ring-closing metathesis of **3** to **1**.

2,7-Enynol derivatives **2a-d** (R_2 = Me, R_3 = OTBS) thus utilized were synthesized according to the procedure summarized in Scheme 4. Thus, diynes **8** were obtained by the reaction of the alkynyllithium compound derived from the propynoic acid ethyl ester and LDA with the corresponding alkynylaldehydes **5** and the following silylation of the resulting alcohols. Treatment of **6** with Me_2CuLi provided **7**, [10] which were converted to **2** by the reduction with DIBAL and the following esterification or halogenation.



Scheme 4. Preparation of **2a-2d**.

Meanwhile, **2e** was prepared by the procedure depicted in Scheme 5. Thus, diynol derivative **8** was treated with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl to generate the corresponding allenyltitanium,[3] addition of ethylidene malonate to which provided the Michael addition product **9** in 80% yield with a high diastereomeric ratio (94:6).[11] The resulting diester **9** was converted to benzyl ether **10** by decarboxylation and the following reduction, desilylation and benzylation. The 1-alkyne **11** was carboxylated by treatment with *n*-BuLi and then $ClCO_2Et$ to give **11**, which was isolated as a single diastereomer. After methylation of **11** was performed by treatment with Me_2CuLi, reduction of the resulting β-methyl-α,β-unsaturated ester with DIBAL afforded alcohol **12**, the TIPS group of which was replaced by a TMS moiety to give **13**. Esterification of **13** with $ClP(O)(OEt)_2$ provided **2e** (*E*:*Z* = 90:10). Although compound **2e** thus synthesized was racemic, an optically active compound can be prepared by starting from optically active **9**.[11]

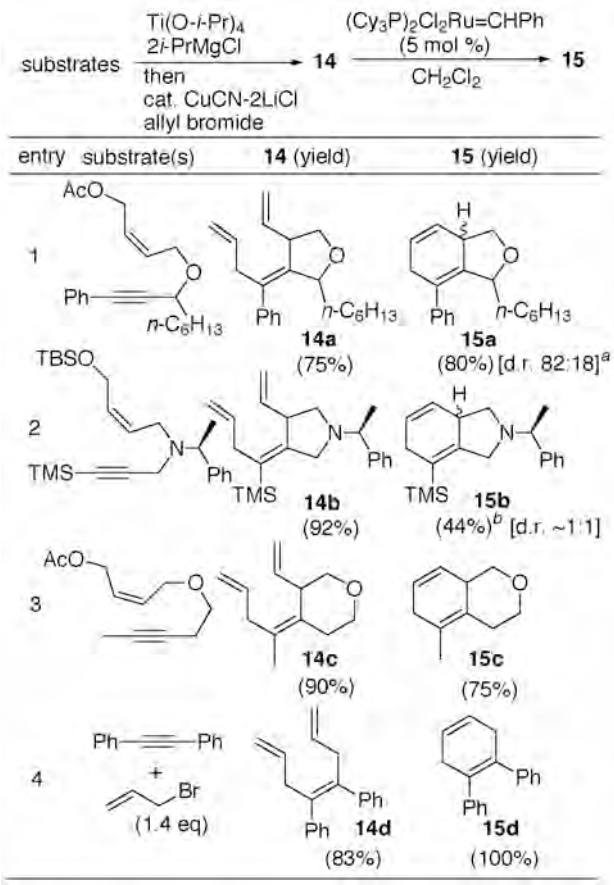


Scheme 5. Preparation of **2e**. *Reagents*: (i) Ti(O-*i*-Pr)$_4$ (1.5 eq), *i*-PrMgCl (3.0 eq), ether, -40 °C, 3 h; (ii) LiCl (2.7 eq), DMSO-H_2O, 135 °C, 10 h; (iii) DIBAL (2 eq), ether, -20 °C, 1 h; (iv) cat. K_2CO_3, MeOH, rt, 2 h; (v) BnBr (1.5 eq), NaH (1.5 eq), THF-DMF, rt, 10 h; (vi) *n*-BuLi (1.5 eq) then $ClCO_2Et$ (1.8 eq), THF, -78 °C, 0.5 h; (vii) CuI (1.4 eq), MeLi (2.8 eq), THF, -40 °C, 3 h; (viii) TBAF (1.5 eq), THF, rt, 3 h; (ix) *n*-BuLi (2.3 eq) then TMSCl (2.3 eq), THF, 0 °C and then 1M HCl-MeOH, rt, 0.5 h; (x) $ClP(O)(OEt)_2$ (2 eq), pyridine, rt, 0.5-1 h.

Closely related reaction conditions to those for the synthesis of 3a-methylhydrindanes **2** were subsequently utilized for synthesis of a variety of 1,4-cyclohexadienes (Table 2), which are useful intermediates as a precursor of the arene ligand in organometallic compounds,[12] a substrate of ene and/or Diels-Alder reactions[13] and oxidation to the corresponding benzene derivatives. Table 2 summarizes representative results of the synthesis of 1,4-cyclohexadienes **15** from acyclic unsaturated starting materials by the intra- or intermolecular Ti(II)-mediated cyclization/Cu-catalyzed allylation and the following Ru-catalyzed ring-closing metathesis reactions of the resulting trienes **14**. Entry 4 exemplified preparation of disubstituted

1,4-cyclohexadienes through the intermolecular Ti(II)-mediated bis-allylation of alkynes.

Table 2. Other representative results of synthesis of cyclic compounds having a 1,4-cyclohexadiene structure



[a]Stereochemistry was not confirmed. [b]Reaction was carried out in toluene at 70 °C for 3 days.

In summary, we have developed an efficient two-step method for diastereoselective construction of 3-substituted 3a-methyl-2,3,3a,6-tetrahydro-1*H*-indenes from acyclic unsaturated compound by the tandem Ti(II)-mediated cyclization/Cu-catalyzed allylation and Ru-catalyzed ring-closing metathesis reactions. Further investigation including preparation of optically active compounds[11] of the type **1** and their application to natural product synthesis is in progress.

Acknowledgments

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