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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7537–7540

Ti(II)-mediated domino cyclization of 2-functionalized 1-halo-2,*n*-enynes (*n* = 7, 8) to bicyclic compounds

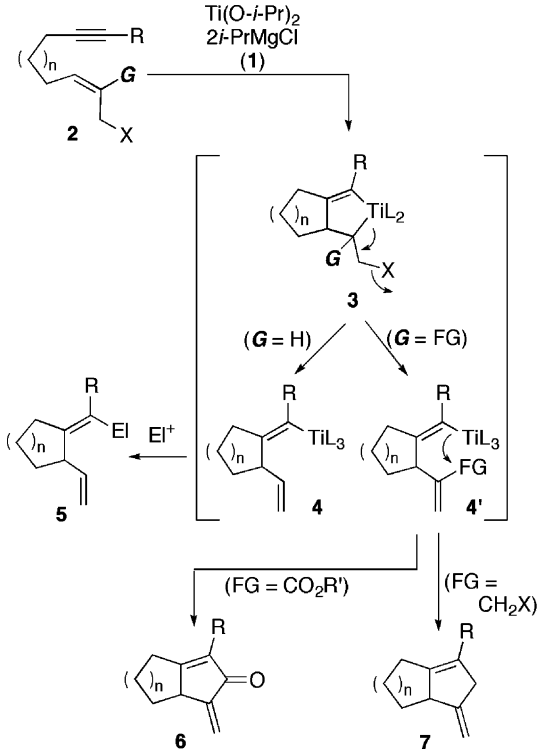
Sentaro Okamoto,[a,*] Hidemoto Ito,[a] Shogo Tanaka[b] and Fumie Sato[b]

[a]*Department of Material and Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan*
[b]*Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan*

Received 21 July 2006; revised 22 August 2006; accepted 24 August 2006

Abstract—The reaction of 2-functionalized 1-halo-2,*n*-enynes ($n = 7$ or 8) with a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, proceeded in a domino fashion to afford bicyclic compounds in good yields.

We have recently developed a divalent titanium reagent-mediated cyclization of 2,7- and 2,8-enyn-1-ol derivatives. Thus, the reaction of enyn-1-ol derivatives **2** (G = H) with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**1**)[1] proceeded through β-elimination of the leaving group X from a titanacyclic intermediate **3** (G = H) to give alkenyltitanium compound **4** (Scheme 1).[2] The resulting alkenyltitaniums **4** could act as a nucleophile and reacted with various electrophiles to give **5**. With these results in hand, we thought that further intramolecular cyclization of the resulting alkenyltitaniums of the type **4** to bicyclic compounds might occur in a domino fashion[3] when the starting enynes have a functional group (FG), which can react with the alkenyltitanium moiety, as a substituent G at a C-2 position (Scheme 1). Herein reported is the realization of this idea by introducing $-CO_2R'$ or $-CH_2Cl$ as the FG at a C-2 position of 2,7- and 2,8-enyn-1-ol derivatives, the reaction of which produced the corresponding bicyclic products **6** and **7**, respectively.[4]



Scheme 1. Plan for domino reaction.

First, we investigated the **1**-mediated reaction of **2a**, which has a methoxycarbonyl group as the substituent G (Table 1). Thus, enynol derivative **2a** was treated with 1.4 equiv of **1** at −40 to −20 °C for 2 h and the mixture was quenched by addition of H_2O. However, the expected dienone **6a** was not produced but 29% of enone compound **8** was produced with 37% of the recovered **2a** (Table 1, entry 1).

Therefore, we carried out the reaction using 2.3 equiv of **1** and found that the reaction provided **8** [diastereomeric ratio (dr) = 95:5] in 84% yield (Table 1, entry 2).[5,6]

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

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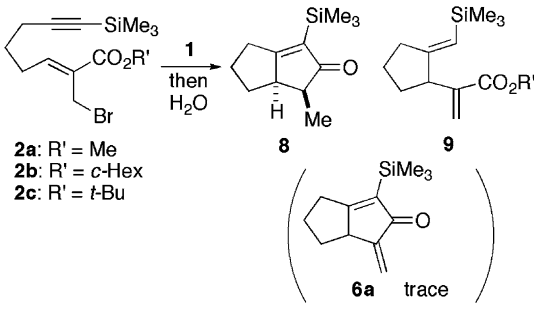
doi:10.1016/j.tetlet.2006.08.099

Table 1. Reactions of **5** with **1**

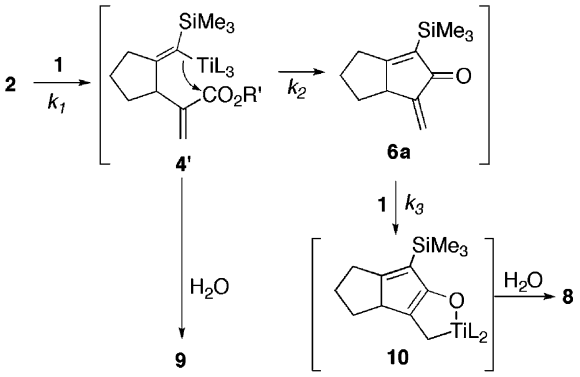


Entry	2	Equiv of 1	Yield (%)		
			8	9	Recovered 2
1	2a	1.4	29	Trace	37
2	2a	2.3	84	Trace	Trace
3	2b	1.4	35	60	Trace
4	2c	1.4	Trace	93	Trace

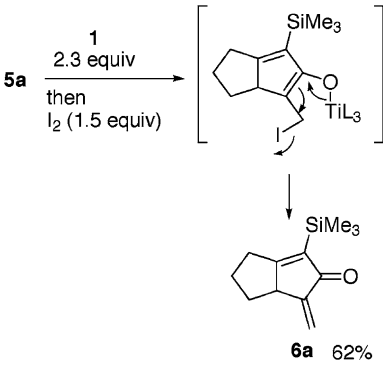
Enynes **2** having a more sterically demanding ester group reacted smoothly with 1.4 equiv of **1** but afforded mono-cyclic compounds **9**[5] as a major product (entries 3 and 4).

The results can be explained by assuming that the reaction of **2a** with **1** provided dienone **6a** via **4′a** as expected, however, the resulting **6a** further reacted with **1** fast to afford the corresponding oxatitanacyclic compound **10**, hydrolysis of which gave **8** (the order of reaction rates: k_2, $k_3 > k_1$) (Scheme 2). Introduction of a cyclohexyl group into an ester moiety relatively decreased the reaction rate from the corresponding **4′** to **6a** (k_2) and, therefore, the reaction provided a mixture of **8** and **9** (k_1, $k_3 > k_2$). The *t*-Bu group may be so bulky that the intramolecular acyl substitution reaction of the corresponding **4′** could not be undergone.

The presence of an intermediate **10** was confirmed by iodolysis of the reaction mixture derived from **2a** and 2.3 equiv of **1** (Scheme 3): The reaction mixture was treated with I_2 to give **6a** in 62% yield.[5] Thus, Ti(II)-mediated domino cyclization could provide bicyclic compounds **6a** and **8** having a cyclopentene and methylenecyclopentene structures, respectively, from the acyclic enyne starting compound.



Scheme 2. A Possible explanation for the formation of **8** and **9**.

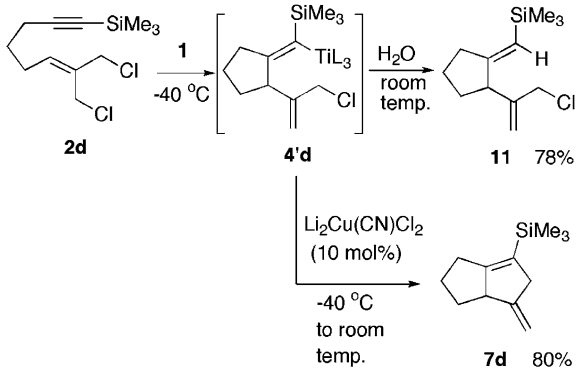


Scheme 3. Formation of **6a** by the reaction of **10** with I_2.

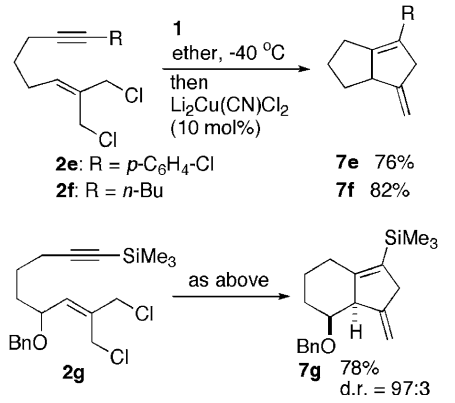
We next prepared enyne **2d** as a substrate, which has a chloromethyl moiety as the substituent G at the C-2 position, expecting that the corresponding titanium compound **4′d** could undergo an intramolecular allylic substitution giving **7d** (Scheme 4). Treatment of **2d** with 1.2 equiv of **1**, however, resulted in the production of mono-cyclic compound **11** after hydrolysis. The results indicate that generated alkenyltitanium **4′d** could not undergo allylic substitution. It was found that the addition of a catalytic amount of $Li_2Cu(CN)Cl_2$ to the reaction mixture of **4′d** could effect intramolecular allylic substitution to produce 1,2-annulated fuluvenes **7d** in 80% yield.[5,7]

Under similar reaction conditions, analogous compounds **2e–g** reacted smoothly with a divalent titanium reagent **1** and then $Li_2Cu(CN)Cl_2$ catalyst to afford the corresponding 1,2-annulated fuluvenes **7e–g**, respectively, in good yield (Scheme 5). A high 1,2-diastereoselectivity was observed in the reaction of **2g**.[6]

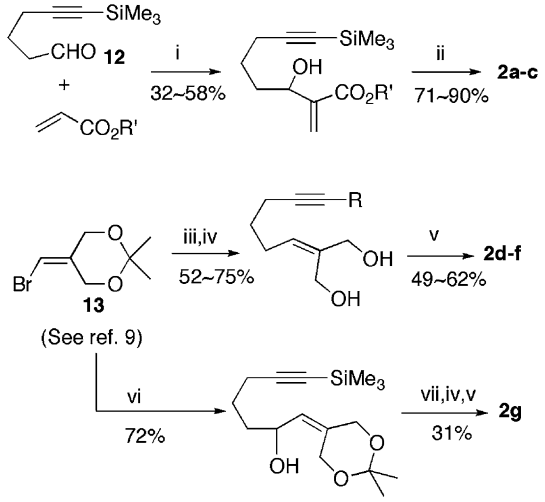
Scheme 6 illustrates the preparation of substrates **2** for the present cyclization reactions. Thus, compounds **2a–c** were synthesized by the Baylis–Hillman reaction[8] of acrylic esters with 6-trimethylsilylhex-5-ynal (**12**) followed by the bromination of the resulting alcohols, where the bromination reaction proceeded stereoselectively to yield the corresponding bromoesters as a *Z* isomer. While, compounds **2d–f** were prepared from the known 5-bromomethylene-2,2-dimethyl-[1,3]dioxane



Scheme 4. Reaction of **2d** with **1** and the following Cu-catalyzed cyclization.



Scheme 5. Domino Ti(II)-mediated and Cu-catalyzed bicyclization reactions.



Scheme 6. Preparation of **5**. Reagents and conditions: (i) PhOH (0.2 equiv), *n*-Bu_3P (0.2 equiv), THF, 50 °C; (ii) NBS (2 equiv), Me_2S (2 equiv), CH_2Cl_2, rt, 12 h; (iii) R–C≡CCH_2CH=CH_2 (1.5 equiv), 9-BBN (1.5 equiv), THF, rt, 12 h then **13**, cat. $PdCl_2$(dppf) (0.05 equiv), K_3PO_4 (3 equiv), reflux, 2 h; (iv) *p*-TsOH (0.05 equiv), THF–H_2O, rt, 2.5 h; (v) MsCl (2.5 equiv), Et_3N (5.4 equiv), CH_2Cl_2, rt, 12 h; (vi) *t*-BuLi (2 equiv), ether, −78 °C then **12**; (vii) BnBr (1.2 equiv), NaH (1.4 equiv), THF, rt, 12 h.

(**13**)[9] by the Suzuki–Miyaura coupling reaction and the following cleavage of ketal and chlorination of the resulting diols.[10] Compound **2g** was obtained via the lithiation of **13** and the reaction with aldehyde **12**.

In summary, we have demonstrated that a divalent titanium reagent could effectively cyclize 2-functionalized 2,7- and 2,8-enyn-1-ol derivatives in a domino fashion to provide bicyclic compounds. The synthetic application of the present method is now underway in our laboratory.

Acknowledgement

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

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5. Compound **8**: To a solution of **2a** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (2.3 mmol) in ether (10 mL) was added *i*-PrMgCl (4.6 mmol, 0.97 M in ether) at −40 °C and the mixture was stirred for 2 h at this temperature. After the addition of aqueous 1 M HCl, usual extractive work-up was followed; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39–2.70 (m, 3H), 2.18 (dt, $J = 12$, 6.6 Hz, 1H), 1.83–2.11 (m, 4H), 1.19 (d, $J = 7.2$ Hz, 3H), 0.18 (s, 9H). Compound **9c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.12 (br s, 1H), 5.43 (br s, 1H), 5.20 (q, $J = 2.1$ Hz, 1H), 3.36–3.43 (m, 1H), 2.33–2.46 (m, 2H), 1.40–1.97 (m, 4H), 1.47 (s, 9H), 0.08 (s, 9H). Compound **6a**: To the reaction mixture derived from **2a** (1.0 mmol) and **1** (2.3 mmol) prepared above was added a solution of I_2 (2.3 mmol) in ether at −20 °C. After the addition of aqueous 1 M HCl, usual extractive work-up was followed; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (br s, 1H), 5.26 (br s, 1H), 3.27–3.37 (m, 1H), 2.50–2.75 (m, 2H), 1.90–2.25 (m, 2H), 1.08–1.30 (m, 2H), 0.21 (s, 9H). Compound **7d**: To a solution of **2d** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (1.2 mmol) in ether (10 mL) was added *i*-PrMgCl (2.4 mmol, 0.97 M in ether) at −40 °C and the mixture was stirred for 3 h at −40 °C. To the mixture was added $Li_2Cu(CN)Cl_2$ (0.1 mmol, 1.0 M in THF) and the mixture was gradually warmed to room temperature over 2 h. After the addition of water (0.3 mL), NaF (1 g) and Celite (1 g), the mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography on silica gel; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 and 4.75 (2br s, each 1H), 3.37–3.52 (m, 2H), 3.16 (d, $J = 18.6$ Hz, 1H), 2.16–2.25 (m, 2H), 1.90–2.05 (m, 3H), 1.08–1.25 (m, 1H), 0.08 (s, 9H). Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29 (br s, 2H), 5.05 (s, 1H), 4.04 and 3.99 (2d,

each $J = 12.6$ Hz, each 1H), 3.26 (t, $J = 6.3$ Hz, 1H), 2.14–2.54 (m, 2H), 1.51–2.03 (m, 4H), 0.08 (s, 9H).

6. Stereochemistries of compounds **8** and **7g** were determined by ^{1}H–^{1}H COSY and NOESY experiments. Explanation of these stereoselectivities must await further study.
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10. Although bromination of the intermediate diol was carried out, the resulting dibromides were relatively unstable to be stored.