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Trimethylgermyl group in Pauson–Khand reaction

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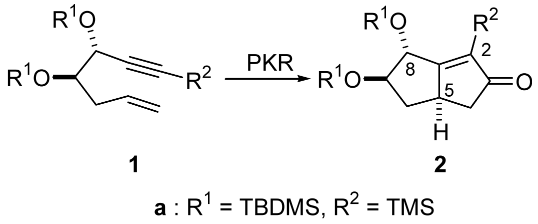
Abstract—The Pauson–Khand reaction of enynes possessing the trimethylgermyl group at the alkyne terminus stereoselectively afforded the corresponding bicyclo[3.3.0]octenone and bicyclo[4.3.0]decenone skeletons. The formed trimethylgermyl group of the bicyclic compound was then converted to the iodo group, which was used for further elaboration. Thus the trimethylgermyl group at the triple bond terminus was shown to become a precursor for other appendages. © 2002 Elsevier Science Ltd. All rights reserved.

Recent efforts in this laboratory[1,2] have led to the development of the highly stereoselective Pauson–Khand reaction (PKR)[3] of enynes *ent*-**1** leading to the formation of the bicyclo[3.3.0]octenone derivative *ent*-**2**[1] possessing two distinguishable hydroxy groups. The exclusive formation of *ent*-**2** was recorded when both substituents (R^1 and R^2) were sterically bulky silyl groups (such as **2a**: R^1 = TBDMS and R^2 = TMS). During the course of our program[4] directed toward application of the newly developed stereoselective PKR to the total synthesis of bioactive compounds, the bicyclo[3.3.0]octenone derivatives **2** with a suitable carbon appendage at the C_2-position were required as a core carbon framework. However, the PKR of the corresponding **1** gave only a mixture of **2** and its C_5-epimer in a moderately stereoselective manner or nonstereoselectively (Scheme 1).[1]

We required a method for the stereoselective preparation of **2** with a suitable carbon side chain at the C_2-position. The silyl group can generally be replaced under electrophilic substitution and can thus be considered as a latent functional group. Therefore, compound **2a**, obtained from **1a** in a stereocontrolled manner, could become a versatile intermediate for our purpose if efficient transformation of the TMS group at C_2-position into the iodo functionality could be realized. Treatment of **2a** under typical conditions using I_2[5] or NIS,[6] however, showed no reaction at all and the starting **2a** was completely recovered intact. Negishi's procedure[7] with ICl or ICl/$AlCl_3$ system was also found not to be effective in this case. Thus, our endeavor turned to examine the PKR of **1** having the stannyl or germyl group instead of the silyl group at the triple bond terminus and transformation of the resulting **2** into the corresponding iodo derivatives in line with the above considerations. In this paper, we describe the successful use of the trimethylgermyl group as a latent functional group in PKR.



Scheme 1.

At the inception of this study, we investigated the PKR of the stannyl compounds, derived from **3**. Treatment of **3** with tributyltin chloride under basic conditions afforded the corresponding enyne with the tributylstannyl functionality at the triple bond terminus. Because of its instability, the stannylated compound was directly converted to the cobalt complex, which was heated at 50–55°C in acetonitrile[8] to provide **4a** in 47% yield in a stereoselective manner along with the nonstereoselective formation of **5**. The bicyclic compound **4a** was stable enough under the Pauson–Khand conditions, thereby the formation of **5** could be rationalized by destannylation before the ring closure reaction occurred. When the ring closure reaction was carried out in the presence of 4 Å molecular sieves, **4a** was obtained in 65% yield as the sole product without the detection of **5**. Changing the tributyl group on the tin atom to trimethyl and

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Keywords: Pauson–Khand reaction; enyne; trimethylgermyl group; latent functional group; NIS.

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triphenyl groups did not improve the chemical yield of **4**. For the trimethylstannyl group, a small amount of the dimer **6** was detected. These results were summarized in Table 1. Upon exposure to I_2[5] in THF at room temperature, **4a** underwent electrophilic displacement to provide the iodo derivative **7** in 97% yield.

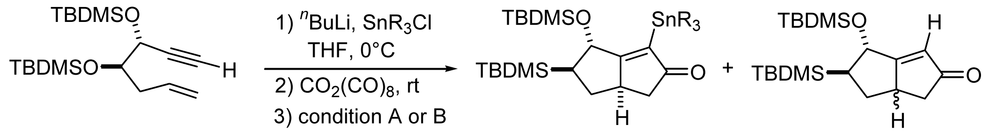
Although we succeeded in the transformation of the stannyl derivative **3** into the iodo compound **7** in a stereoselective manner (Table 1, entry 2), the reproducibility of this procedure (exclusive formation of **4a** without the detection of **5** and **6**) was poor due to the easy destannylation during cyclization. Therefore, a more reliable method was mandatory for our purpose. To this end, we introduced the trimethylgermyl group to the alkyne terminus of **3** hoping that (i) the germyl group would be more reactive toward electrophilic substitution than the silyl group, and (ii) the C–Ge bond would be stronger than the C–Sn bond under the ring closure conditions employed. The acetylide, generated from **3**, was trapped by treatment with trimethylgermanium bromide to give **8** in 88% yield, which was subsequently exposed to $Co_2(CO)_8$, and the resulting cobalt complex was heated in acetonitrile[8] to exclusively produce **9** in 85% overall yield. No formation of **5** or **6** could be detected in the reaction mixture. The 4 Å molecular sieves were found not to be required in this case. Furthermore, it should be emphasized that this procedure is reproducible. Conversion of **9** into **7** in 90% yield was realized when heated with NIS[5] in refluxing 1,2-dichloroethane for 36 h.

With the required iodo derivative **7** in hand, we initially examined the introduction of some side chains at the C_2-position of **7**. The representative results are shown in Scheme 2. The palladium-mediated coupling reactions of **7** with suitable counterparts easily proceeded under the typical coupling conditions to furnish the corresponding coupling products **10**, **11**, **12** with high yields. The unsubstituted one **5**, which had previously been nonstereoselectively prepared by the PKR of **3**,[1] could be exclusively obtained upon exposure of **7** to Bu_3SnH (Scheme 2).

The final step in this program was to confirm the generality of this newly developed procedure. The examples we investigated are summarized in Scheme 3. The PKR of enynes possessing the trimethylgermyl functionality provided the corresponding bicyclic frameworks with reasonable yields. In the cases of **16**, **19**, **27**, a high stereoselectivity was observed as anticipated. Transformation of the trimethylgermyl group into the iodo one could be attained without difficulty in most cases except for a relatively prolonged reaction time. Conversion of **20** into **22** occurred under the standard conditions, but it took 2 weeks to complete. Adjustment of the protecting group of **20** from the bulky silyl group to the less sterically hindered acetyl group (compound **21**)[9] made its reaction time fairly shorter (24 h) with a similar chemical yield. In addition, **28** could be converted into **30** in 95% yield with long heating (72 h). Thus, the similar scenario described in the case of **20** was applied to **28**. The bulky silyl protecting group of **28** was removed to afford the hydroxy derivative **29**, which was then reacted with NIS[6] in refluxing 1,2-dichloroethane leading to the complete consumption of the starting material within 5.5 h to provide **31** in 83% yield.

In summary, we developed the PKR of enynes having a trimethylgermyl group at the alkyne terminus. The trimethylgermyl moiety at α to the carbonyl functionality of the resulting bicyclic frameworks could be converted into an iodo functionality by simple treatment with NIS in refluxing 1,2-dichloroethane. Thus, this procedure provides a new utilization of the

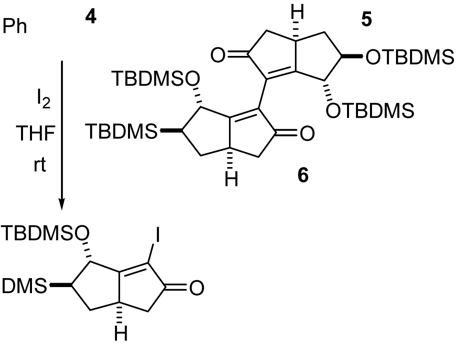
Table 1.



3 **4** **5**

a : R = Bu, **b** : R = Me, **c** : R = Ph

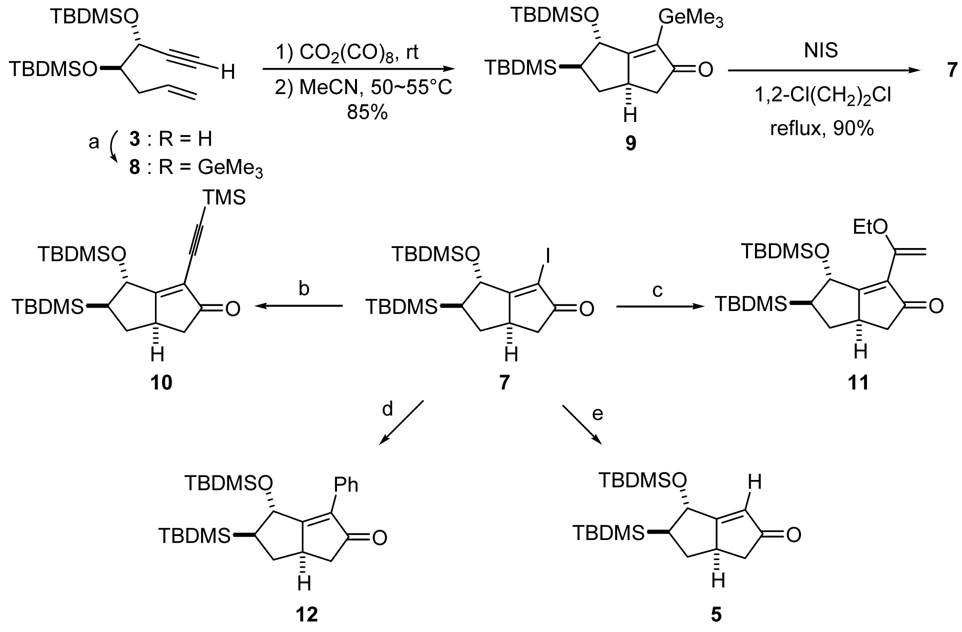
entry	R	condition	Yield (%) 4	5	6
1	Bu	A	47	14	—
2	Bu	B	65	—	—
3	Me	A	26	21	8
4	Me	B	24	24	9
5	Ph	A	27	17	—
6	Ph	B	48	trace	—



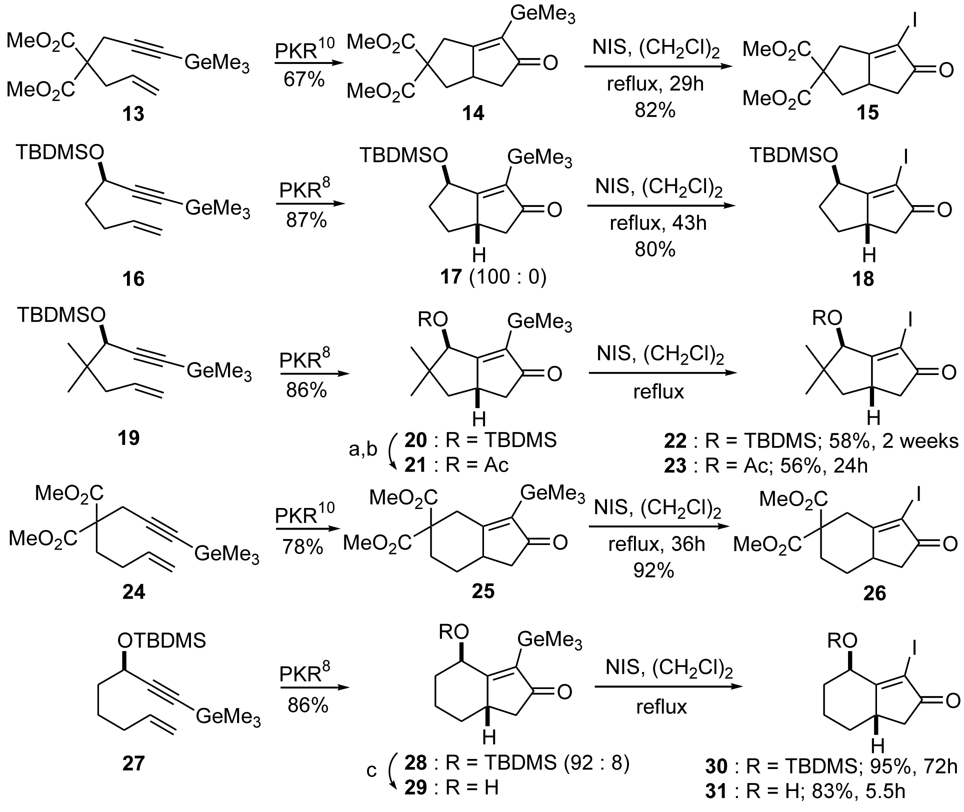
6

7

Condition A: heated in CH_3CN at 50-55°C; Condition B: heated in CH_3CN at 50-~55°C in the presence of 4ÅMS.



Scheme 2. *Reagents and conditions*: (a) ^{n}BuLi, Me$_3$GeCl, THF, 0°C, 88%; (b) Pd(PPh$_3$)$_2$Cl$_2$, TMSC≡CH, ^{i}Pr$_2$NH, CuI, THF, rt, 98%; (c) Pd(PPh$_3$)$_2$Cl$_2$, (α-ethoxyvinyl)SnMe$_3$, THF, 65°C, 84%; (d) Pd(PPh$_3$)$_2$Cl$_2$, PhSnBu$_3$, THF, reflux, 76%; (e) Bu$_3$SnH, THF, 55°C, 83%.



Scheme 3. *Reagents and conditions*: (a) TBAF, AcOH, THF, 0°C, 77%; (b) Ac$_2$O, DMAP, CH$_2$Cl$_2$, rt, 94%; (c) TBAF, THF, 0°C, 87%.

trimethylgermyl group in PKR as a latent functional group, which requires future elaboration.

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