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# Synthesis of 1-acetyl-2-silyoxycycloheptane derivatives via highly stereoselective formal [5+2] cycloaddition reaction



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#### ABSTRACT

A stereoselective [5+2] cycloaddition reaction using a new five-carbon unit, that has a dicobalt acetylene complex moiety and an enol silyl ether moiety, was developed. In the presence of a Lewis acid, the five-carbon unit reacted with an enol triisopropylsilyl ether to give a 1-acetyl-2-silyoxycycloheptane derivative, in which the three contiguous substituents on the seven-membered ring arrange *cis* to each other. © 2014 Elsevier Ltd. All rights reserved.

There are a number of natural compounds containing a cycloheptane ring with various kinds of substituents. The [4+3] cycloaddition reaction<sup>1</sup> of dienes or furan derivatives with allyl cationic species represents an efficient method for constructing sevenmembered carbocycles, but much less attention has been paid to the [5+2]-type reactions.<sup>2</sup> We have developed dicobalt acetylene complex **1** and its analogues as useful five-carbon units in the formal [5+2] cycloaddition reaction with enol silyl ethers<sup>3a,b</sup> or silyloxyallenes<sup>3c</sup> (Scheme 1).

The reaction proceeds through intermolecular addition of cationic species **A** with an enol silyl ether followed by the intramolecular cyclization of silyloxonium ion **B** to give cycloheptanone derivative  $2^4$  in a stereoselective fashion.<sup>5</sup> These results led us to develop a new synthetic method for polysubstituted cycloheptane derivatives through another type of formal [5+2] cycloaddition reaction (Scheme 2).

Thus, the use of dicobalt acetylene complex **3** as a five-carbon unit would afford cycloheptane derivative **4** through the stepwise addition reaction involving cationic intermediates **C** and **D**.<sup>6</sup> It should be noted that cycloadduct **4** possesses the ketone moiety as one of the three substituents on the seven-membered ring, while the ketone moiety of the cycloadduct **2** in Scheme 1 is incorporated in the carbocycle. Therefore, the utility of the new [5+2]-type reaction depends on the stereoselectivity at the three contiguous stereogenic centers in cycloadduct **4**. We report herein

\* Corresponding author. E-mail address: ktanino@sci.hokudai.ac.jp (K. Tanino). the highly stereoselective formal cycloaddition reaction of five-carbon unit **3** and its analogue with enol silyl ethers.

The new five-carbon unit was synthesized in only two steps as shown in Scheme 3. Methyl vinyl ketone was subjected to the conjugate addition reaction with organocopper reagent **5**,<sup>7</sup> which was prepared by successive treatment of methyl propargyl ether with butyllithium and copper(I) thiocyanate, in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). The resulting enol silyl ether **6** was then reacted with Co<sub>2</sub>(CO)<sub>8</sub> to afford the desired dicobalt acetylene complex **7**.<sup>8</sup> Although both of the enol silyl ethers **6** and **7** were found to readily undergo



**Scheme 1.** Cycloheptanone synthesis via a formal [5+2] cycloaddition reaction of dicobalt acetylene complex **1**.

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**Scheme 2.** Formal [5+2] cycloaddition reaction of a new five-carbon unit leading to substituted cycloheptanes.



Scheme 3. Preparation of the new five-carbon unit 7.

autooxidation of the allylic methylene group, addition of a small amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) effectively reduced the side reaction.

The reactions of dicobalt acetylene complex **7** and enol silyl ethers derived from the corresponding aldehydes were examined under the influence of ethylaluminum dichloride (Table 1).<sup>9</sup> Gratifyingly, the formal [5+2] cycloaddition reaction proceeded at 0 °C in good yield, and the desired products were obtained in a highly stereoselective manner. The stereochemistry of the cycloheptane derivative was determined by <sup>1</sup>H NMR spectra. Thus, the very small vicinal coupling constants<sup>10</sup> between the  $\alpha$ -protons of the three substituents indicated that these substituents are all *cis* to each other (entries 1–5). The reaction of **7** with the enol silyl ether derived from isobutyraldehyde also occurred smoothly to afford a cycloheptane derivative **4f** having a quaternary carbon atom as a single diastereomer (entry 6).

The stereochemical outcome of the cycloaddition reaction can be rationalized by the transition state models which correspond to the intramolecular cyclization step of the silyloxonium ion intermediate **D** in Scheme 2. Taking into account the rigidity as well as the bulkiness of the cobalt complex moiety,<sup>11</sup> transition state models in which the R group occupies an equatorial position can be depicted (Fig. 1). In these models, **D-2** would suffer from the serious steric repulsion between the two bulky silyl groups, while **D-3** having the enol silyl ether at the pseudo axial position would also be disfavored. Therefore, the diastereomer with all-*cis* substituents is formed through transition state **D-1**.

As was reported previously, the cyclic dicobalt acetylene complexes can be transformed into useful compounds in one step (Scheme 4). For example, cycloaddition product **4b** underwent

#### Table 1

Stereoselective synthesis of cycloheptane derivatives by formal [5+2] cycloaddition reactions  $^{\rm a,b}$ 



<sup>a</sup> The general procedure is described in Ref. 9.

<sup>b</sup> Minor diastereomers were not detected by proton NMR spectra.



Figure 1. Suggested transition state models for the cyclization step.



Scheme 4. Transformation of the cyclic dicobalt acetylene complex.



**Scheme 5.** Synthesis and reactions of dicobalt acetylene complexes with a cyclic enol silyl ether moiety.

reductive decomplexation<sup>12</sup> by refluxing with tributyltin hydride in benzene to afford the corresponding cycloheptene **8**. On the other hand, oxidation of **4b** with cerium(IV) ammonium nitrate resulted in the formation of maleic anhydride **9** in high yield.<sup>3,13</sup>

Next, the formal [5+2] cycloaddition reaction was applied to the synthesis of bicyclic compounds. New five-carbon units **10** and **11** having a cyclic enol silyl ether moiety were prepared from the corresponding 2-cycloalken-1-ones through a similar method for the synthesis of **7** (Scheme 5).<sup>7</sup>

In these cases, the use of 2,6-lutidine instead of BHT was found to give better results, because the enol silyl ethers tend to undergo hydrolysis rather than autooxidation.

The enol silyl ether derived from isobutyraldehyde was chosen as the coupling partner with cobalt complex **10**, so as to avoid the formation of the product as a mixture of four diastereomers. The reaction under the previous conditions using ethylaluminum dichloride at 0 °C (Method A) gave the desired bicyclic ketone 12 in moderate yield along with by-product 13 which arose from desilylation of the silyloxonium ion intermediate. We found, however, that the reaction under the influence of titanium(IV) chloride proceeds even at -78 °C (Method B), giving rise to the desired product 12 in 93% yield as a single diastereomer. The reaction of six-membered substrate 11 by adopting Method B resulted in the formation of bicyclic ketone 14 in good yield. Judging from the coupling constants in the <sup>1</sup>H NMR spectra, compound **12** possessed a cis-fused 5-7 skeleton, and the configuration of the 6-7 bicyclic system of 14 was suggested to be trans. Although the origin of the different stereochemical outcome depending on the ring size of the substrates is not clear, the present cycloaddition reaction shows promise for constructing highly substituted bicyclic systems in short steps.

In summary, we have developed an efficient method for the synthesis of substituted cycloheptane derivatives on the basis of a formal [5+2] cycloaddition reaction. The five-carbon unit **7**, a dicobalt acetylene complex possessing a leaving group and an enol silyl ether moiety, was prepared from commercially available compounds in only two steps. Under the influence of a Lewis acid, the cobalt complex reacted with enol triisopropylsilyl ethers to afford cycloheptane derivatives having three substituents as a single diastereomer. The formal [5+2] cycloaddition reaction was applied to construct bicyclic skeleton, and applications in total synthesis of polycyclic natural compounds are under investigation.

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### **References and notes**

- For reviews on [4+3] cycloaddition strategy, see: (a) Rigby, J. H.; Pigge, F. C. In Organic Reactions; Paquette, L. A., Ed.; ; John Wiley & Sons: New York, 1997; 51, pp 351–476; (b) Harmata, M. Chem. Commun. 2010, 8886–8903; (c) Harmata, M. Chem. Commun. 2010, 8904–8922.
- 2. For a recent review on [5+2] cycloaddition strategy: Pellissier, H. Adv. Synth. Catal. 2011, 353, 189–218.
- The authors reported another type of [5+2] cycloaddition strategy: (a) Tanino, K.; Shimizu, T.; Miyama, M.; Kuwajima, I. J. Am. Chem. Soc. 2000, 124, 6116– 6117; (b) Tanino, K.; Kondo, F.; Shimizu, T.; Miyashita, M. Org. Lett. 2002, 4, 2217–2219; (c) Mitachi, K.; Yamamoto, T.; Kondo, F.; Shimizu, T.; Miyashita, M.; Tanino, K. Chem. Lett. 2010, 39, 630–632.
- For a review on seven-membered dicobalt acetylene complexes, see: Green, J. R. Synlett 2012, 1271–1282.
- 5. This type of transformation is classified as 'time and space integration of reactions' where all reaction components are mixed at once to perform a sequence of reactions in one-pot Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. Synlett 2011, 1189–1194.
- 6. Since the silyloxonium ion intermediate **D** should survive without desilylation during the stepwise reaction, enol silyl ethers with a bulky TIPS group were employed as the two-carbon units. In contrast, the R<sub>3</sub>Si group of five-carbon unit **3** should be smoothly removed after the cyclization step, which led us to use a TBS group for preparing the five-carbon unit.
- 7. Similar conjugate addition reactions using a zinc acetylide were reported: Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627–7630.
- 8. Preparation of five-carbon unit 7: To a solution of methyl propargyl ether (2.55 mL, 30.0 mmol) in THF (80 mL) was added *n*-BuLi (11.0 mL, 30 mmol, 2.77 M solution in hexane) at -78 °C. After being stirred for 10 min at room temperature, the solution of lithium acetylide was added via cannula to a suspension of CuSCN (3.65 g, 30.0 mmol) in ether (80 mL) at -78 °C. After being stirred for 2 h, the resulting heterogeneous mixture was added via cannula to a solution of *tert*-butyldimethylsilyl triflate (5.0 mL, 22.0 mmol) and methyl vinyl ketone (1.63 mL, 20.0 mmol) in ether (80.0 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 2 h, and to this was added 28% aqueous NH<sub>3</sub> solution. The mixture was separated, and the aqueous layer was extracted three times with ether. The combined organic layer was washed with brine and dried over MgSO<sub>4</sub>. Concentration under reduced

pressure followed by purification by silica gel column chromatography gave enol silyl ether 6 (2.92 g, 11.5 mmol, 57%) as a pale yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) *E* isomer:  $\delta$  4.38 (t, *J* = 6.9 Hz, 1H), 3.98 (s, 2H), 3.26 (s, 3H), 2.86 (dd, J = 6.9, 1.1 Hz, 2H), 1.68 (d, J = 1.1 Hz, 3H), 0.95 (s, 9H), 0.15 (s, 6H). With the peaks due to a small amount of Z isomer at:  $\delta$  4.58 (t, J = 7.5 Hz, 1H), 4.07 (s, 2H), 3.30 (s, 3H), 2.77 (d, J = 7.5 Hz, 2H), 1.62 (s, 3H), 0.92 (s, 9H), 0.13 (s, 6H). To a solution of  $Co_2(CO)_8$  (4.12 g, 12.1 mmol) and BHT (0.13 g, 0.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (37 mL) was added a solution of 6 (2.92 g, 11.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (35 mL) at room temperature. After being stirred for 1 h, the mixture was filtered through a pad of celite. Concentration under reduced pressure followed by purification by silica gel column chromatography afforded cobalt complex **7** (6.20 g, 11.5 mmol, 100%) as a dark brown oil. <sup>1</sup>H NMR (500 MHz,  $CDCI_3$ ) *E* isomer:  $\delta$  4.59 (s, 2H), 4.55 (t, *J* = 6.9 Hz, 1H), 3.56 (d, *J* = 6.9 Hz, 2H), 3.50 (s, 3H), 1.80 (s, 3H), 0.91 (s, 9H), 0.16 (s, 6H). With the peaks due to a small amount of Z isomer at: δ 4.65 (s, 2H), 4.80 (t, J = 6.3 Hz, 1H), 4.59 (s, 2H), 3.50 (s, 3H), 3.49 (d, J = 6.3 Hz, 2H), 1.80 (s, 3H), 0.91 (s, 9H), 0.16 (s, 6H) With the peaks due to a small amount of Z isomer at:  $\delta$  4.65 (s, 2H), 4.80 (t, J = 6.3 Hz, 1H), 4.59 (s, 2H), 3.50 (s, 3H), 3.49 (d, J = 6.3 Hz, 2H), 1.80 (s, 3H), 0.91 (s, 9H), 0.16 (s, 6H).

 General procedure: To a mixture of EtAlCl<sub>2</sub> (1.04 M solution of hexane, 0.96 mL, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added a solution of an enol triisopropylsilyl ether (0.50 mmol) and cobalt complex **7** (270 mg, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) via cannula at 0 °C. After being stirred for about 10 min at 0 °C, the reaction mixture was quenched with a saturated aqueous Roschell's salt solution. The mixture was stirred at room temperature vigorously for 1 h under argon atmosphere. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried over MgSO<sub>4</sub>. Concentration under reduced pressure followed by purification by silica gel column chromatography gave the [5+2] cycloaddition product as a dark brown oil. The data for **4e**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.10 (t, J = 7.1 Hz, 1H), 3.72 (s, 1H), 3.41 (dd, J = 16.1, 13.2 Hz, 1H), 3.15 (d, J = 16.1 Hz, 1H), 2.29 (dd, J = 15.5, 13.2 Hz, 1H), 2.47 (d, J = 12.1 Hz, 1H), 2.28 (m, 2H), 2.25 (s, 3H), 2.19 (m, 1H), 1.73 (s, 3H), 1.61 (s, 3H), 1.05 (m, 21H).

- In general, the α-methyne proton of the silyloxy group in the <sup>1</sup>H NMR spectra of cycloaddition products appears as a singlet. For example, see the data for 4e in Ref. 6.
- 11. Cotton, F. A.; Jamerson, J. D.; Stults, B. R. J. Am. Chem. Soc. 1976, 98, 1774–1779.
- 12. Hosokawa, S.; Isobe, M. Tetrahedron Lett. 1998, 39, 2609–2612.
- Mitachi, K.; Shimizu, T.; Miyashita, M.; Tanino, K. Tetrahedron Lett. 2010, 51, 3983–3986.