A New Method for the Synthesis of Medium- and Large-Sized Carbocycles

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Received 19 February 1999

Abstract: A new synthetic method for medium and large-sized carbocycles has been developed. An acyclic compound having an olefin moiety and a 3-(methylthio)allyl acetate moiety at each of the terminal positions was designed as a cyclization precursor. The corresponding allyl cation intermediate, which was generated by treatment with EtAlCl₂, underwent cyclization via an intramolecular addition reaction. The ring size of the product, which depends on the reaction site of the allyl cation, can be controlled by changing the nucleophilicity of the terminal olefin moiety.

Key words: cyclization, allylcation, Lewis acid, vinyl sulfide, homoallylsilane

Medium- and large-sized carbocycles are an important class of compounds which occur in a range of natural and unnatural products, and an increasing number of cyclization techniques for these carbocycles have been developed. In the biosynthesis of terpenoids, an intramolecular addition reaction of a carbon-carbon double bond to an allyl cationic moiety is the most important process for constructing medium- and large-sized carbocycles.¹ From a synthetic viewpoint, however, use of this type of cyclization reaction may suffer from competition between the (n)-membered and (n+2)-membered rings.^{2,3}





On the other hand, we have reported a highly regioselective [3+2] cyclopentanone annulation reaction using a 3-(methylthio)-2-siloxyallyl cationic species (Scheme 2).⁴ It is noteworthy that the initial C-C bond formation between an olefin and the allyl cationic intermediate predominantly occurs at the γ -position of sulfur.⁵

The directing effect of sulfur in controlling the reaction site of an allyl cation led us to develop a new synthetic method for medium- and large-sized carbocyclic compounds. In order to estimate the directing effect of sulfur, allyl acetates **1a** and **1b** having a terminal olefin moiety were designed as cyclization precursors.⁶ Interestingly, the ring size of the products depends on the nature of the olefin moiety (Eq 1 and Eq 2). Thus, treatment of **1a** with EtAlCl₂ resulted in selective formation of eight-mem-







bered chloride **2**, while six-membered product **4** was predominantly obtained from allylsilane **1b**.

In order to understand the different behavior between 1a and 1b, PM3 calculations⁷ on the cationic intermediates were performed. The results indicated that eight-membered intermediate **B**, which involves the conjugation of the methylthio group and the double bond, is 9.6 kcal/mol more stable than six-membered intermediate **C**. Accordingly, an eight-membered compound would be produced under thermodynamic control, while cyclization to a six-membered ring is kinetically favored. Selective formation of six-membered product **4** from **1b** is, therefore, attributable to the high nucleophilicity of the allylsilane moiety.

Next, we designed cyclization precursors **1c**,⁸ **1d**,⁶ and **1e**⁶ with a view to increasing the chemical yield of the eightmembered product. We envisioned that the neighboringgroup participation of the internal acetoxy group would stabilize the eight-membered tertiary cation intermediate and control the stereochemistry of the product (Figure 2).



The Heat of Formation for Cyclization Intermediates ${\bf B}$ and ${\bf C}$ Calculated by PM3 Method







Although the reactions of **1d** and **1e** with $EtAlCl_2$ led to complex results, **1c** underwent smooth cyclization to give cyclooctene **5** as a single diastereomer in good yield (Eq 3). However, the *cis* relationship between the OAc group and chlorine, which was established by X-ray crystallographic structure determination, ruled out the possibility of neighboring-group participation as depicted in Figure 2.



In order to clarify the origin of the high yield as well as the complete stereoselection, we performed PM3 calculations⁷ on the allyl cationic species. The results suggested that an interaction between the internal acetoxy group and the terminal cationic carbon plays an important role in fixing the conformation by forming a seven-membered ring (Scheme 3). The axial orientation of the side chain, which is attributable to an allylic strain,⁹ would be advantageous for the cyclization reaction, and successive C-C bond formation and introduction of a chloride ion would give **5** stereoselectively.



Scheme 3

Since several attempts for constructing a nine-membered carbocycle from a homologue of **1c** proved fruitless, an aromatic ring was incorporated with an allyl cation precursor in order to facilitate a cyclization reaction.

Under the influence of EtAlCl_2 , **6a** underwent cyclization to afford nine-membered compound **7a** as a single isomer (Eq 4). Ten- to twelve-membered products **7b**, **7c**, and **7d** were also obtained, albeit in much lower stereoselectivities, from the corresponding diacetates **6**.⁸ In these cases, reactions in moderately dilute solutions led to better chemical yields.



Although the functional groups of the cyclization products would have advantages for natural product synthesis, a tertiary chloride moiety is not always suitable for further functionalization. We designed another type of cyclization precursor having a homoallylsilane moiety¹⁰ with a view to trapping a tertiary cation intermediate by 1,2-hydride shift promoted by a silyl group (Eq 5). Since a homoallylsilane has much lower nucleophilicity than the corresponding allylsilane, the reactions of **8a**⁶ and **8b**⁸ resulted in selective formation of eight-membered products.



In conclusion, a new synthetic method for medium- and large-membered carbocycles was developed by using intramolecular cyclization reaction of a 3-(methylthio)allyl cationic species. It is noteworthy that the reaction site of the allyl cation can be controlled by the nucleophilicity of the terminal olefin moiety. The functional groups of the cyclization products such as a vinyl sulfide moiety would have advantages for natural product synthesis.

Acknowledgement

This work was partially supported by Grants from the Ministry of Education, Science, Sports, and Culture of the Japanese Government. K.M. thanks JSPS for a predoctoral fellowship.

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Article Identifier:

1437-2096,E;1999,0,05,0647,0649,ftx,en;Y04499ST.pdf