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Highly Stereoselective Cationic Cyclization Assisted by a Sulfenyl Group

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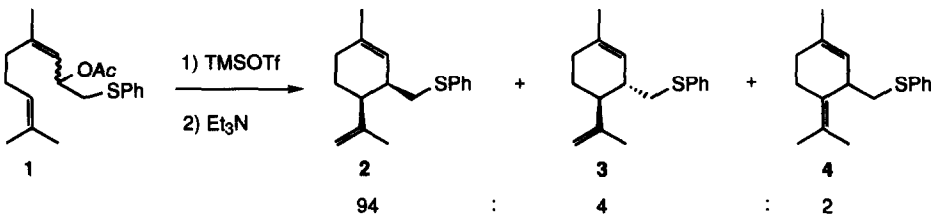
Abstract: When 8-acetoxy-2,6-dimethyl-9-phenylthio-2,6-nonadiene was successively treated with TMSOTf and Et_3N in CH_2Cl_2 at room temperature, an alkylative cyclization proceeded with high diastereoselectivity to give *cis*-4-isopropenyl-1-methyl-3-phenylthiomethyl-1-cyclohexene. A ^1H NMR study of the reaction suggested that a cyclic sulfonium ion was formed as an intermediate. The sulfenyl group-assisted reaction could be applied for the cyclization of secondary alcohol derivatives.

Alkylative cationic cyclization is one of the attractive methods used for carbocycle construction, and has been widely applied for terpene syntheses.[1] Among them, the simplest reaction is the biomimetic synthesis of limonene/terpinolene by a cyclization of a nerol derivative. For such a type of cyclization, the stereoselectivity concerning the newly formed stereogenic center is of interest. In this regard, an enantioselective version of the cyclization has been demonstrated by Yamamoto's group using a chiral leaving group and a suitably designed aluminum reagent.[2] On the other hand, in the case that the electrophile part in a substrate is secondary, the reaction generates two vicinal chiral centers; the diastereoselectivity of the reaction becomes a problem. However, there has been no report concerning the diastereoselectivity for such a 6-exo mode of an alkylative cationic cyclization.[3]

We recently reported on the regioselective allylation of (α-sulfenylmethyl)allyl acetates, which proceeded via an episulfonium ion intermediate.[4] We then tried to apply this reaction to an intramolecular reaction, i.e., a cationic cyclization, with the expectation that a diastereoselective process would be realized.

When substrate **1** (which could be easily synthesized from citral as a 3:2 mixture of stereoisomers) was treated with 1.1 equiv. of TMSOTf in CH_2Cl_2 at room temperature, the starting material was quickly consumed to give no cyclized product, but a very polar species. The species slowly decomposed upon standing at room temperature to form a mixture of much less polar cyclized products **2**, **3**, and **4**. The reaction conditions were then thoroughly examined for the conversion of the polar compound into the cyclized products. As a result, it was found that the decomposition was enhanced by treatment of the polar product with a base. When a reaction mixture of **1** and TMSOTf was treated with excess Et_3N, the cyclized products were obtained in 79% yield; cis isomer **2** was obtained with very high selectivity in spite of the stereochemical heterogeneity of **1** (Scheme 1).[5]



Scheme 1.

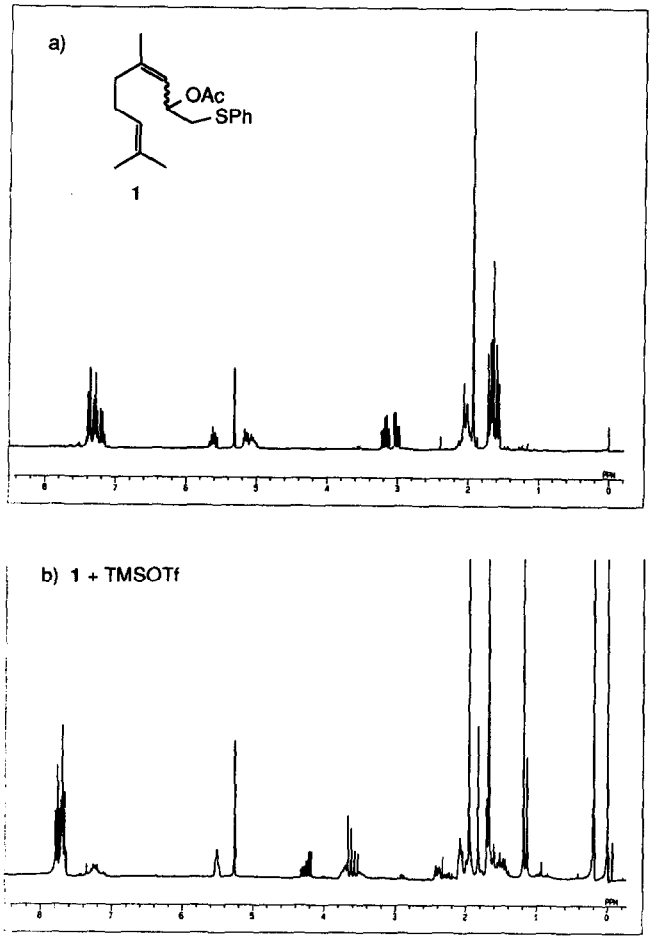
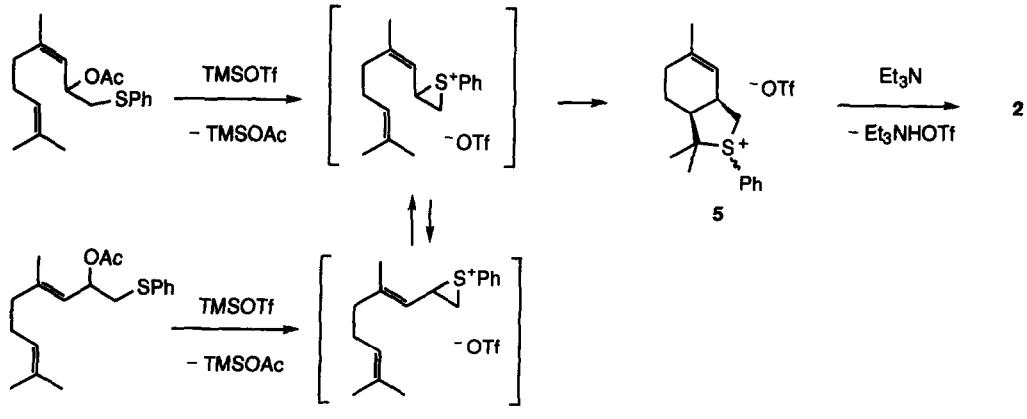


Fig. 1. ^1H NMR of a) **1** and b) **1** + TMSOTf in CD_2Cl_2.



Scheme 2.

We tried to identify the intermediate using ^1H NMR (Fig. 1). The signal of **1** quickly faded upon the addition of TMSOTf, and new peaks appeared. A precise investigation of the spectra led us to conclude the intermediate being a 1:2 mixture of two diastereomeric sulfonium salts **5** shown in Scheme 2. Irrespective of the ratio of the diastereomers, a very high cis-selectivity was attained in the present reaction. This fact indicates that the diastereoselectivity for the cyclization is governed by the stereochemistry of the initially formed six/five fused ring system of **5**.

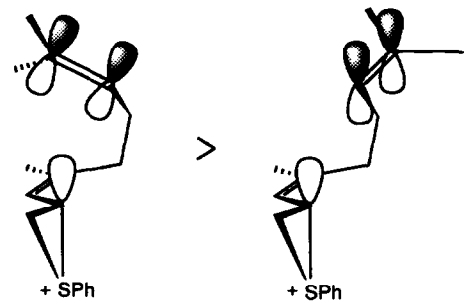
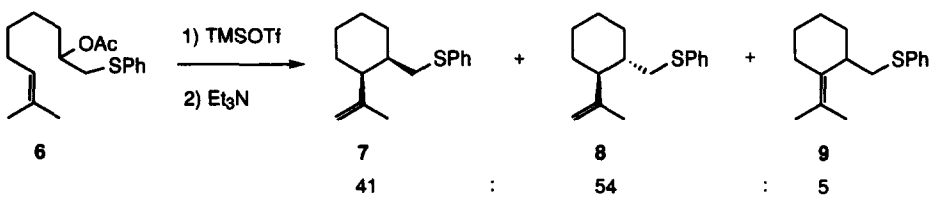


Fig. 2. Possible transition states for the cyclization of **1**.

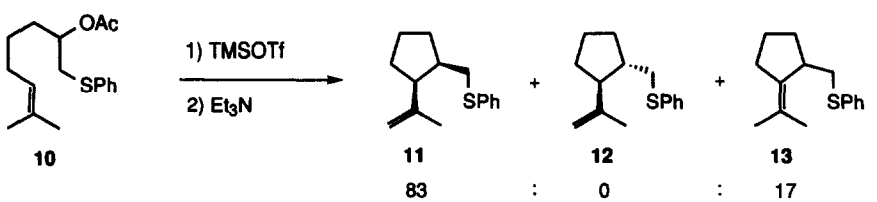
In this reaction, an isomerization of the double bond would take place in analogy with that in the intermolecular reaction of (α-sulfenylmethyl)allyl acetate.[4] Moreover, it is known that an electrophilic attack toward a double bond occurs from the direction where the π-electron of the double bond is maximally overlapped with the vacant lobe of the electrophile.[6] Taking these considerations into account, the mechanism for the present reaction would be as shown in Fig. 2.

We next applied the present cationic cyclization to simple secondary acetates. The reaction of **6** with TMSOTf also gave a five-membered sulfonium intermediate. Treatment of the intermediate with Et_3N gave a mixture of cyclized products in 85% yield (Scheme 3). However, in this case, the stereoselectivity for the cyclized products was very low. On the other hand, the reaction of substrate **10** with TMSOTf, followed by treatment with Et_3N, gave a mixture of cyclized products in 70% yield; the formation of the trans-isomer was completely suppressed (Scheme 4).[5,7] Thus, the cationic cyclization of secondary alcohol derivatives was proved to be successful with the aid of the neighboring group participation of a sulfenyl group.

Judging from 1) the low reaction rates for **6** and **10**, 2) the non-selectivity for the reaction of **6**, and 3) the fact that the formation of an episulfonium salt from a simple secondary β-sulfenylalkyl acetate does not occur under the present reaction conditions,[8] the mechanism for the cyclization of **6** and **10** might be slightly different from that of **1**; the intermediate sulfonium salt would be formed through a concerted mechanism. In the reaction of **6**, since the energy difference between cis- and trans-six/five fused ring systems would be small, the intermediate was obtained as a mixture of diastereomers concerning two newly formed stereogenic carbons.



Scheme 3.



Scheme 4.

However, in the case of a five/five fused ring system, the trans-fused isomer is considerably more strained than the cis isomer. Therefore, the cyclization of **10** resulted in an exclusive formation of the cis-isomer.

An experimental procedure for the cyclization is as follows: To a solution of the substrate (0.35 mmol) in CH_2Cl_2 (2 ml) was added a CH_2Cl_2 solution of TMSOTf (1.2 M, 0.32 ml, 0.38 mmol) at room temperature, and the resulting mixture was stirred until no starting material was detected by TLC analysis (2 min for **1**, 1 day for **6** and **10**). During this period, the reaction mixture turned black. Then, triethylamine (0.5 ml, 3.6 mmol) was added to the mixture, and the resulting pale-brown solution was stirred for 8 h. After addition of saturated aqueous NH_4Cl (10 ml), the mixture was partitioned between CH_2Cl_2 and aqueous layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 ml), and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the crude material was purified by preparative TLC (eluent: hexane) to give a mixture of the cyclized compounds. The identification was carried out by GC-MS and ^{1}H-NMR.

Lewis acid-mediated alkylative cationic cyclizations to form cycloalkanes have usually been limited for tertiary or allylic alcohol derivatives;[3,9] these cyclizations have a drawback that the substrate structure is restricted. Our method provides a novel example for the cyclization of secondary alcohol derivatives. The product of the present reaction is 1,2-disubstituted carbocycles, which have easily functionalizable moieties, a sulfenyl group and a isopropenyl group. Moreover, thermodynamically less-favorable cis-isomers were predominantly obtained in the cyclizations to cyclohexene and cyclopentane derivatives, which make this reaction synthetically useful.

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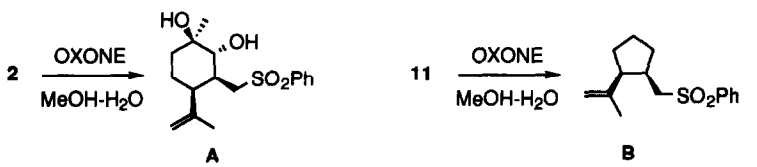
5. The stereochemistries of **2** and **11** were unambiguously determined by the single crystal X-ray structural analyses of sulfones **A** and **B**. Crystal data for **A**: $C_{17}H_{24}O_4S$, orthorhombic, *Pcnb*, a = 17.559(2) Å, b= 18.894(3) Å, c = 10.478(2) Å, V = 3476.3(9) Å^3, Z = 8, D_{calc} = 1.24 g cm^{-3}, R = 0.071, R_w = 0.082 for 2741 reflections and 272 variables. **B**: $C_{15}H_{20}O_2S$, orthorhombic, $P2_12_12_1$, a = 10.869(3) Å, b= 16.352(4) Å, c = 8.006(2) Å, V = 1423.0(6) Å^3, Z = 4, D_{calc} = 1.23 g cm^{-3}, R = 0.051, R_w = 0.055 for 1222 reflections and 243 variables.



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7. Related to the cyclization of **10**, the $Tl(ClO_4)_3$-mediated reaction of geraniol to give 3-oxabicyclo[3.3.0]-octane derivative has been reported; Yamada, Y.; Sanjoh, H.; Iguchi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 997.
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