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Preparation of Bridgehead Substituted Bicyclo[3.3.0]octane Derivatives by the $BF_3{\bullet}OEt_2$-Catalyzed Rearrangement of Bicyclo[3.2.1]oct-6-en-8-ols

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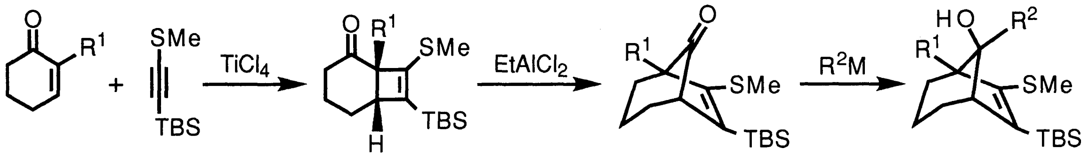
6-*t*-Butyldimethylsilyl-7-methylthiobicyclo[3.2.1]oct-6-en-8-ol derivatives prepared from the [2+2] cycloadducts of 1-*t*-butyldimethylsilyl-2-methylthioacetylene and 2-cyclohexenones are rearranged by the treatment with $BF_3{\bullet}OEt_2$ into two types of bicyclo-[3.3.0]octane compounds, bicyclo[3.3.0]oct-3-en-2-one or 2-methylenebicyclo[3.3.0]oct-3-ene derivatives selectively, depending on the substituent at C-1 position.

By the use of Lewis acid, [2+2] cycloaddition reaction between alkenyl and alkynyl sulfides with electron deficient olefins proceeds smoothly giving cyclobutane and cyclobutene derivatives.1) In the previous paper,2) we reported that bicyclo[4.2.0]octenone derivatives **1** prepared from the cycloadducts of 2-cyclohexenones and 1-*t*-butyldimethylsilyl-2-methylthioacetylene were readily rearranged to 6-*t*-butyldimethylsilyl-7-methylthio-bicyclo[3.2.1]oct-6-en-8-one derivatives **2** by the $EtAlCl_2$-catalyzed Cargill rearrangement (Eq. 1). Since the bicyclo[3.2.1]octenones **2** thus can be readily available, the further transformation of **2** has been investigated by applying Lewis acid catalyzed Wagner-Meerwein rearrangement.3)

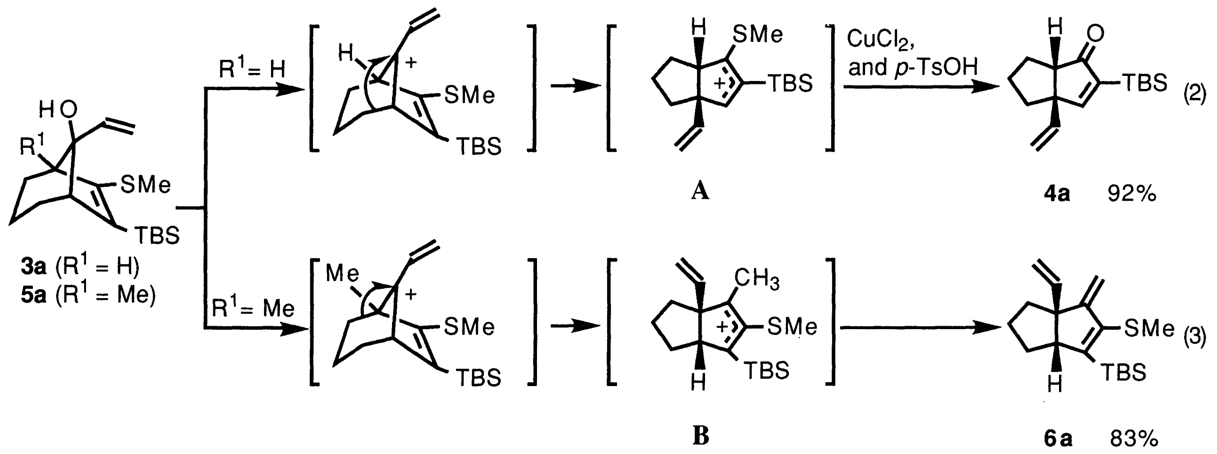


1 **2** **3** (R^1 = H) **5** (R^1 = Me) (1)

M = MgBr, Li
TBS = *t*-Butyldimethylsilyl

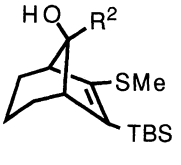
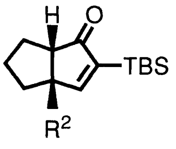
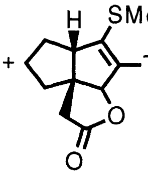
Various bicyclo[3.2.1]oct-6-en-8-ols **3** and the 1-methyl derivatives **5** were prepared by the reaction of the bicyclic octenones **2** with organo lithium and magnesium compounds (Eq. 1),4) and the rearrangement of **3** and **5** was examined by the use of acid catalysts. After screening the reaction conditions, $BF_3{\bullet}OEt_2$ was found to catalyze the rearrangement5) and two types of bicyclo[3.3.0]octenes were obtained, depending on the substituent at C-1 position (R^1 group in the compounds **3** and **5**). For example, when 6-*t*-butyldimethylsilyl-7-methylthio-8-vinylbicyclo[3.2.1]oct-6-en-8-ol (**3a**) which has no substituent at C-1 position (R^1 = H) was treated with $BF_3{\bullet}OEt_2$ for 10 min at rt in acetonitrile and then with $CuCl_2{\bullet}2H_2O$ and *p*-$TsOH{\bullet}H_2O$,6) the rearranged product was obtained as a conjugate enone **4a** in 92% yield (Eq. 2). On the other hand, the rearrangement of the 1-

methyl derivative **5a** (R^1= Me) proceeded in an alternative mode. The treatment of **5a** with $BF_3•OEt_2$ at rt in acetonitrile, followed by quenching with aq. $NaHCO_3$, yielded a triene derivative **6a** in 83% yield without the rearranged product corresponding to the enone **4a** (Eq. 3).



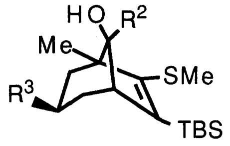
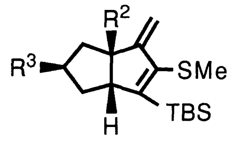
In Tables 1 and 2 are listed the examples of the $BF_3•OEt_2$-catalyzed rearrangement of various bicyclo-[3.2.1]oct-6-en-8-ols **3** and **5**. The course of the rearrangement is completely governed by the substituent R^1 in bicyclo[3.2.1]octenol derivatives. The substrates **3** with hydrogen at C-1 position are rearranged to bicyclo-[3.3.0]oct-3-en-2-one derivatives **4** by the migration of the C4-C5 bond (Table 1), whereas the substrates **5** with methyl group at this position are rearranged to 2-methylenebicyclo[3.3.0]oct-3-ene derivatives **6** by the migration of the C1-C2 bond (Table 2).

Table 1. The $BF_3•OEt_2$ catalyzed rearrangement of **3**a)

Substrate **3**	R^2	Product **4**	Yield/%
			
3a	$CH=CH_2$	**4a**	92
3b	Me	**4b**	89
3c	*n*-Bu	**4c**	89
3d	Ph	**4d**	99
3e	C≡CTBS	**4e**	95
3f b)	CH_2COOCH_3	**4f** +  **4f'**	86 10

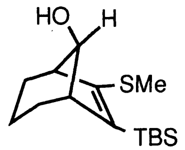
a) The reaction was performed in the presence of $BF_3•OEt_2$ in 10 min in CH_3CN at rt and was quenched with $CuCl_2•2H_2O$ and *p*-$TsOH•H_2O$, unless otherwise noted.
b) The reaction temperature was 82 °C.

Table 2. The $BF_3{\bullet}OEt_2$ catalyzed rearrangement of **5**[a)]

Substrate **5**	R^2	R^3	Product **6**	Yield/%
				
5a	$CH=CH_2$	H	**6a**	83
5b	Me	H	**6b**	67
5c	$CH=CH_2$	$C(Me)=CH_2$	**6c**	quant.
5d	$C{\equiv}CTBS$	$C(Me)=CH_2$	**6d**	86

a) The reaction was performed in the presence of $BF_3{\bullet}OEt_2$ in 10 min in CH_3CN at rt and was quenched with aq. $NaHCO_3$.

The rearrangement exhibits wide generality with regard to the substituent at C-8 position of the bicyclo[3.2.1]octenol derivatives **3** and **5**. That is, the rearrangement proceeds smoothly by the use of the substrates having not only vinyl group **3a**, **5a**, **5c** at C-8 position but also alkyl **3b**, **3c**, **5b**, aryl **3d**, alkynyl **3e**, **5d**, and methoxycarbonylmethyl **3f** substituents. In the reaction of the secondary alcohol **7** (**3**, R^2 = H), however, the rearranged product was not obtained with the recovery of the starting material **7**.



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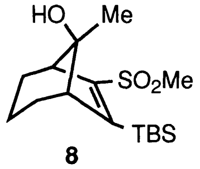

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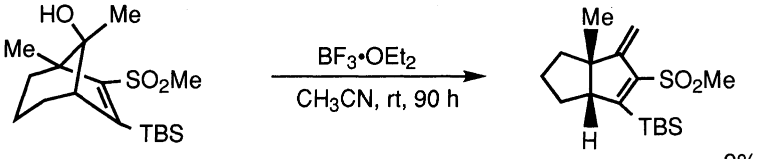
Methylsulfonyl compounds **8** and **9**, the sulfonyl analogous of **3b** and **5b**, were found to be hardly rearranged under the same reaction conditions: The reaction of **8** did not occur at room temperature. The rearrangement of **9** proceeded very slowly to afford the rearranged product **10** in 9% yield after 90 h (Eq. 4). Accordingly, methylthio group accelerates the rearrangement. In the rearrangement of **3**, the regioselective migration of the C4-C5 bond occurred by the generation of the cationic intermediates **A** (Eq. 2), while 1-methyl derivatives **5** are rearranged selectively to form the carbocations **B** (Eq. 3).



9 **10** 9% (4)

Although this-type of skeletal rearrangement has been observed in the solvolysis of bicyclo[3.2.1]octyl-8-tosylates[7)] and utilized in the biogenetic-like synthesis of hirsutene,[8)] the synthetic utility of this rearrangement has not been revealed with a systematic study. By the present investigation, it was noted that the skeletal rearrangement occurs smoothly by employing the bicyclo[3.2.1]octenols **3** and **5** having methylthio group at C-7 position, affording the two kinds of bicyclo[3.3.0]octane derivatives which is one of the basic structures of many biologically active compounds.[9)] Furthermore, various substituents are able to be introduced at the bridgehead position of bicyclo[3.3.0]octane skeleton by choosing organometallic compounds.

A typical experimental procedure is as follows (Table 1, **3a**): To an acetonitrile solution (2.5 mL) of **3a** (310 mg, 1.00 mmol) was added a dichloromethane solution (0.67 mL) of $BF_3\bullet OEt_2$ (213 mg, 1.50 mmol) at room temperature under an argon atmosphere and the mixture was stirred for 10 min. The reaction was quenched by the addition of a mixture of $CuCl_2\bullet 2H_2O$ (255 mg, 1.50 mmol), *p*-$TsOH\bullet H_2O$ (285 mg, 1.50 mmol), and 0.3 mL of H_2O. Then, after the addition of a pH 9 NH_3-NH_4Cl buffer solution, reaction products were extracted with dichloromethane and purified by TLC to afford the desired product **4a** (271 mg, 92% yield).

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References

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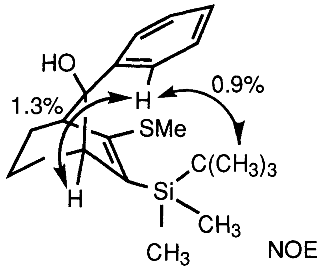
2) K. Narasaka, H. Shimadzu, and Y. Hayashi, *Chem. Lett.*, **1993**, 621.

3) Review, J. R. Hanson, "Wagner-Meerwein rearrangements," in "Comprehensive Organic Synthesis," ed by B. M. Trost et al., Pergamon Press, Oxford (1991), Vol. 3, p. 705.

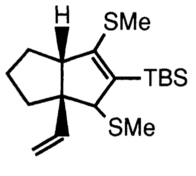
4) For instance, 6-*t*-butyldimethylsilyl-7-methylthio-8-phenylbicyclo[3.2.1]oct-6-en-8-ol (**3d**) was prepared quantitatively as a single isomer by the reaction of phenyl lithium and 6-*t*-butyldimethylsilyl-7-methylthiobicyclo[3.2.1]oct-6-en-8-one (**2**, R^1 = H) at 0 °C. The stereochemistry of **3d** was determined as (1*S**, 5*R**, 8*S**) by the analysis of NOESY spectrum which showed the indicated NOEs. The other alcohols **3a-c**, **3e-f** and **5a-d** were also obtained as a single isomer, and were assumed to have the same stereochemistry at C-8 position as that of **3d**.



3d

5) $TiCl_4$ or $EtAlCl_2$ did not promote the rearrangement and the starting material was recovered.

6) Without the treatment with $CuCl_2\bullet 2H_2O$ and *p*-$TsOH\bullet H_2O$, 2,4-bis(methylthio)bicyclo[3.3.0]oct-2-ene derivative **4a'** was obtained in a substantial amount. As for the hydrolysis of vinyl sulfide with $CuCl_2$, see; K. Narasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 3721 (1972); K. Narasaka, T. Shibata, and Y. Hayashi, *ibid.*, **65**, 2825 (1992).



4a'

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