Nucleophilic Substitution Reaction of Optically Pure Chloroselenurane with Active Methylene Compounds. Formation of Optically Pure Selenonium Ylides

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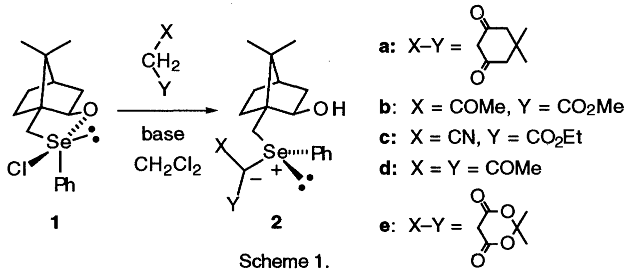
Nucleophilic substitution reaction of (R_{Se})-chloroselenurane **1** with active methylene compounds proceeded in highly stereoselective manner with retention of configuration to give (S_{Se})-selenonium ylides **2**. (S_{Se})- and (R_{Se})-Ylides, **2** and **3**, were stereospecifically formed from the reaction of (R_{Se})- and (S_{Se})-selenoxides, **4** and **5**, with active methylene compounds.

Studies on the synthesis and stereochemistry of organoselenium compounds are limited in contrast to those on organosulfur compounds.[1] We have quite recently reported the facile synthesis of optically pure haloselenuranes and selenoxides by using 2-*exo*-hydroxy-10-bornyl group as a chiral ligand.[2] We have also demonstrated that the formation of haloselenuranes from selenoxides is stereoselective and the nucleophilic substitution reactions of haloselenuranes with metal halides proceed with retention of configuration.

We report here that the reaction of optically pure chloroselenurane **1** with active methylene compounds proceeds in a highly stereoselective manner to give optically pure selenonium ylide **2** with retention of configuration. We also present that the same reaction of optically pure selenoxides, **4** and **5**, proceeds stereospecifically to yield the ylides, **2** and **3**, with retention of configuration.

First, we examined nucleophilic substitution reaction of chloroselenurane **1** with active methylene compounds to compare the stereochemical course of the reaction with that of interconversion reaction of haloselenuranes. Reaction of chloroselenurane **1**[2] with dimedone gave selenonium ylide **2a**[3] as a single isomer (93% yield) after being stirred in the presence of a base (Et$_3$N) in CH$_2$Cl$_2$ at room temperature for 1 h. Under the similar reaction conditions, the selenonium ylides **2b**-**e**[3] were obtained as a single diastereomer (70-100% yield) from the reaction of **1** with methyl acetoacetate, ethyl cyanoacetate, acetylacetone, and Meldrum's acid, respectively (Scheme 1 and Table 1).



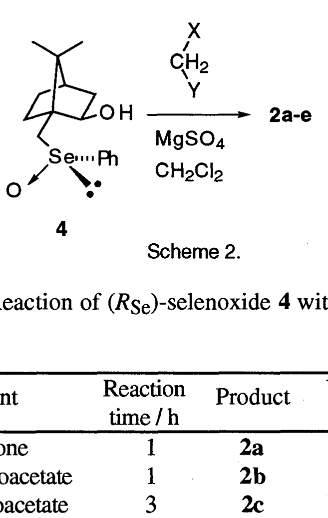
Scheme 1.

Table 1. Nucleophilic substitution reaction of chloroselenurane **1** with active methylene compounds[a]

Reagent	Base	Product	Yield / %	De / %
Dimedone	Et$_3$N	**2a**	93	>99
Methyl acetoacetate	Et$_3$N	**2b**	100	>99
Ethyl cyanoacetate	Et$_3$N	**2c**	96	>99
Acetylacetone	Et$_3$N	**2d**	94	>99
Meldrum's acid	LiH	**2e**	70	>99

[a] Reaction time was 1 h.

Next, we undertook the reaction of (R_{Se})-selenoxide **4**[2] with active methylene compounds. Reaction of (R_{Se})-selenoxide **4** with dimedone, methyl acetoacetate, ethyl cyanoacetate, acetylacetone, and Meldrum's acid gave selenonium ylide **2a**-**e**[3] as a single isomer (82-99% yield) after being stirred in the presence of anhydrous MgSO$_4$ in CH$_2$Cl$_2$ at room temperature (Scheme 2 and Table 2).



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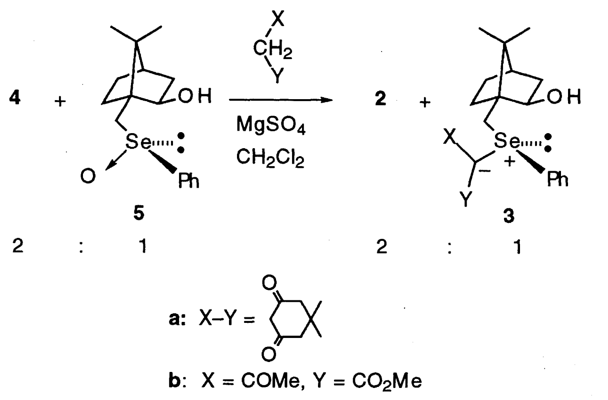
Scheme 2.

Table 2. Reaction of (R_{Se})-selenoxide **4** with active methylene compounds

Reagent	Reaction time / h	Product	Yield %	De / %
Dimedone	1	**2a**	99	>99
Methyl acetoacetate	1	**2b**	88	>99
Ethyl cyanoacetate	3	**2c**	93	>99
Acetylacetone	1	**2d**	84	>99
Meldrum's acid	24	**2e**	82	>99

When a 2 : 1 mixture[2] of **4** and **5** was treated with dimedone under similar conditions as described above, a 2 : 1 diastereomeric mixture of selenonium ylides, **2a** and **3a**, was formed in quantitative yield (Scheme 3 and Table 3). Similar results were obtained from the reaction of a 2 : 1 mixture of **4** and **5** with methyl acetoacetate. These results showed that the ratio of the diastereomeric ylides, **2** and **3**, reflected that of **4** and **5**, implying that the formation of ylides from selenoxides, **4** and **5**, is stereospecific.

To reveal the stereochemical aspects of these reactions, the absolute configuration of the ylide **3b** was determined by X-ray crystallographic analysis. Figure 1 shows a stereoscopic view of the molecular structure of **3b**.[4] It was established that **3b** has *R* configuration[5] at the selenium center. Accordingly, the configuration of the other diastereomer **2b** was *S* at the selenium center. The absolute configurations of **2a**,**c**-**e** and **3a**,**c**-**e** were suggested



Scheme 3.

Table 3. Stereospecific formation of (S_{Se})- and (R_{Se})-selenonium ylides, **2** and **3**, from (R_{Se})- and (S_{Se})-selenoxides, **4** and **5**

4 : 5	Reagent	Reaction time / h	Yield %	2 : 3^a
68 : 32	Dimedone	0.25	100	67 : 33
68 : 32	Methyl acetoacetate	0.5	98	66 : 34

^{a} The ratio of **2** : **3** was determined by ^{1}H NMR spectra.

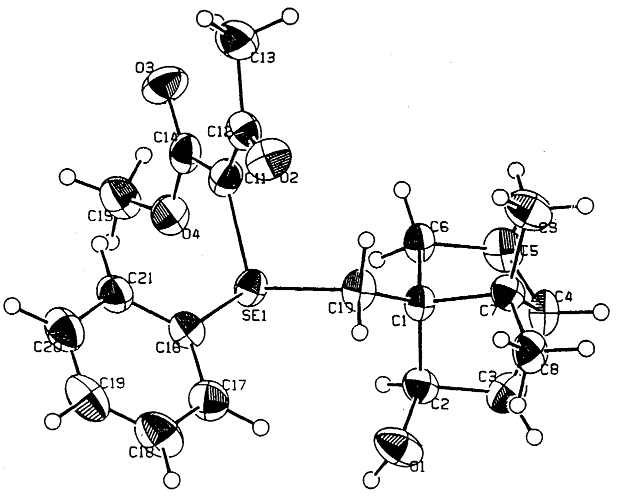
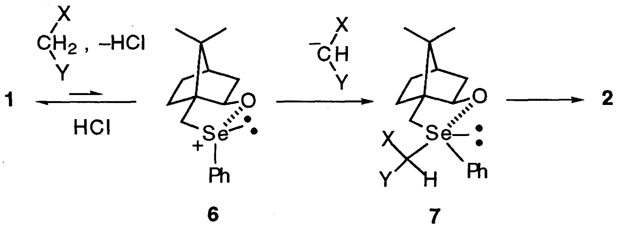


Figure 1. Perspective structure of **3b**.

by analogy with those of **2b** and **3b**, respectively. The bond lengths and bond angles of **3b** are similar to those of {4'-[(-)-menthyloxycarbonyl]phenyl}(methyl)selenonium 4,4-dimethyl-2,6-dioxocyclohexylide.[6]

From these results, it is established that nucleophilic substitution reaction of chloroselenurane **1** and the reaction of selenoxide, **4** and **5**, with active methylene compounds proceeded with retention of configuration yielding optically pure selenonium ylides, **2** and **3**, in high yield. There have been only a few reports concerning optically active selenonium ylides: Sakaki and Oae demonstrated an asymmetric synthesis of some selenonium ylides but they did not refer to optical purity of the ylides[7]; Kamigata *et al.* obtained an optically pure selenonium ylide by optical resolution of a diastereomeric mixture.[6] We have thus developed the first practical method of chiral synthesis of optically pure selenonium ylides.

Detailed mechanistic studies of the nucleophilic substitution reactions are now in progress in order to confirm the intermediate formation of oxyselenonium ion **6**[2] as shown in Scheme 4.



Scheme 4.

References and Notes

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1 a) C. Paulmier, "Selenium Reagents and Intermediates in Organic Synthesis," Pergamon Press, Oxford (1986); b) "The Chemistry of Organic Selenium and Tellurium Compounds," ed by S. Patai and Z. Rappoport, Wiley, New York (1987), Vol. 2.

2 T. Takahashi, N. Kurose, S. Kawanami, Y. Arai, T. Koizumi, and M. Shiro, *J. Org. Chem.*, **59**, 3262 (1994).

3 Satisfactory analytical (combustion and high resolution mass) and spectral (IR, ^{1}H NMR, ^{13}C NMR, Mass) data were obtained for all new compounds.

4 Ylide **3b** was prepared by the reaction of (R_{Se})-selenoxide **4** (100 mg, 0.31 mmol) with methyl acetoacetate (36.5 μL, 0.34 mmol) in dry ether (6 mL) in the presence of Ac$_2$O (32 μL, 0.34 mmol) at room temperature for 1 day. Filtration of the reaction mixture gave a mixture (23 mg, 18%) of ylides **2b** and **3b** (1 : 3.1). Concentration of the mother liquor and filtration gave crude **3b** (23 mg, 18%). After several recrystallization of the crude **3b** from ether were obtained colorless prisms which were suitable for X-ray crystallographic analysis: mp 185-186 °C, $[\alpha]_D^{25}$ -96.3° (*c* 1.93, CHCl$_3$). Crystal data for **3b**: C$_{21}$H$_{28}$O$_4$Se, M_w 423.41, triclinic, space group, $P1$ with a = 10.520 (2) Å, b = 11.396 (3) Å, c = 10.230 (2) Å, α = 109.27 (2)°, β = 107.31 (2)°, γ = 64.00 (2)°, V = 1023.5 (4) Å^3, and Z = 2 (D_c = 1.374 gcm^{-3}), μ (CuKα) = 154.18 cm^{-1} absorption corrected by ω scans; 3030 unique reflections; 2685 with $I > 3.00\sigma(I)$ were used in refinement; R = 3.2%, R_w = 4.4%.

5 Designation of absolute configuration at tetracoordinate selenium(IV) was followed by an extension of the Cahn, Ingold, Prelog (CIP) *R-S* nomenclature proposed by Martin and Balthazor, see: J. C. Martin and T. M. Balthazor, *J. Am. Chem. Soc.*, **99**, 152 (1977).

6 a) N. Kamigata, Y. Nakamura, H. Matsuyama, and T. Shimizu, *Chemistry Lett.*, **1991**, 249; b) N. Kamigata, Y. Nakamura, K. Kikuchi, I. Ikemoto, T. Shimizu, and H. Matsuyama, *J. Chem. Soc., Perkin Trans. 1.*, **1992**, 1721.

7 K. Sakaki and S. Oae, *Tetrahedron Lett.*, **1976**, 3703.