Oxyselenation of Diolefins with Phenyl Selenocyanate and Copper(II) Chloride. Synthesis of Cyclic Ethers

Akio Toshimitsu, Toshiaki Aoai, Sakae Uemura,* and Masaya Okano

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

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A general route for cyclic ethers by oxyselenation of diolefins is described. Reaction of *cis,cis*-1,5-cyclooctadiene with phenyl selenocyanate in the presence of copper(II) chloride in various alcohols, aqueous tetrahydrofuran, or aqueous acetonitrile produces an isomeric mixture of 2,6-bis(phenylseleno)-9-oxabicyclo[3.3.1]nonane (**1a**) and 2,5-bis(phenylseleno)-9-oxabicyclo[4.2.1]nonane (**1b**) in a good to excellent yield. The isomer ratio depends on the solvent utilized, and a suitable choice of solvent results in a selective formation of each isomer. Similar treatment of 5-methoxy- and 5-hydroxycyclooctenes also gives an isomeric mixture of 2-(phenylseleno)-9-oxabicyclo[3.3.1]nonane (**4a**) and its [4.2.1] isomer (**4b**). ^{13}C NMR spectral data reveal that all phenylseleno groups are on an endo position of the bicyclic ring system in **1a,b** and **4a,b**, consistent with the trans stereospecificity of the oxyselenation reaction. The application to other diolefins such as 1,5-hexadiene, diallyl ether, diallyl sulfide, or 4-vinylcyclohexene in aqueous acetonitrile as solvent results in the formation of monocyclic and bicyclic ethers bearing two phenylseleno groups (**5-8**) in good to excellent yields. The reaction proceeds through alkoxy- or hydroxyselenation of one double bond, followed by a transannular attack of the alkoxyl or hydroxyl group on the episelenonium ion which is formed at the other double bond by the attack of another phenyl selenocyanate.

The chemistry of organoselenium compounds is of current interest owing to its fertile and easily manipulated nature.[1] For utilization in organic syntheses, one of the key reactions is the introduction of selenium into organic molecules. We have previously reported the oxyselenation of monoolefins using phenyl selenocyanate and copper(II), copper(I), or nickel(II) halide in alcohol, acetic acid, or water.[2] It has now been found that the application of this reaction to certain diolefins resulted in the construction of cyclic ether frameworks accompanied by the introduction of two phenylseleno groups,[3,4] providing a further method for organic synthesis using the easily accessible aryl selenocyanates.[5,6,7a] Since the introduced phenylseleno group can be easily substituted by hydrogen[1,8] and eliminated by oxidation to give a double bond,[1] the reaction should be valuable for syntheses of compounds possessing tetrahydrofuran or tetrahydropyran systems, which exist in many naturally occurring substances of biological interest. We describe here the details of this reaction as one of our series of studies on organoselenium chemistry.[2,7]

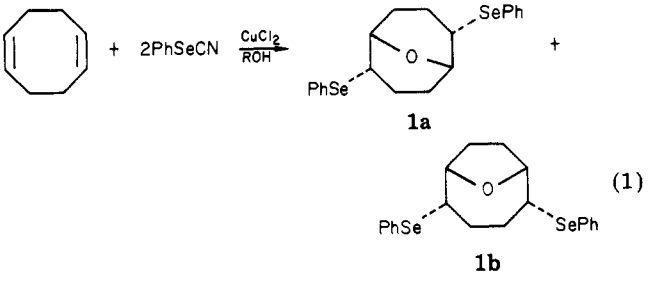
Table I. Yield and Isomer Ratio of 1a and 1b in Various Solvents[a]

solvent (vol, mL)	temp, °C	time, h	% yield[b] of 1a + 1b	ratio[c] of 1a/1b
MeOH (10)	64	5	62	95:5
EtOH (10)	78	5	62	90:10
i-PrOH (10)	67	5	73	82:18
t-BuOH (10)	82	5	44	38:62
THF-H_2O (18 + 2)	60	5	68	0:100
MeCN-H_2O (15 + 3)	76	5	88	56:44[d]
MeCN-H_2O (3 + 0.6)[e]	76	24	87[d]	89:11[d]
MeCN-H_2O (15 + 3)	30	96	88	12:88[d]

[a] 1,5-cod (5 mmol), PhSeCN (10 mmol), and $CuCl_2$ (5 mmol). [b] Isolated yield. [c] Determined by comparison of peak intensities of the ^{13}C NMR signals due to carbon atoms attached to oxygen or selenium. [d] Determined by liquid chromatography. [e] 1,5-cod (1 mmol), PhSeCN (2 mmol), and $CuCl_2$ (1 mmol).

Results and Discussion

When an alcoholic solution of *cis,cis*-1,5-cyclooctadiene (1,5-cod) and phenyl selenocyanate (2 molar equiv) was heated in the presence of copper(II) chloride, an isomeric mixture of **1a** and **1b** was formed in a good yield (eq 1).



(1)

The assignment of [3.3.1] and [4.2.1] ring systems for **1a** and **1b** was based on their respective ^{13}C and ^1H NMR spectra. It has been well established that a bridgehead carbon in the [4.2.1] ring system is deshielded by ca. 10 ppm compared with that in the [3.3.1] ring system[9] by ^{13}C NMR and also that a bridgehead proton in the former is

(1) For review, see: Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049-1132. Reich, H. J. "Oxidation in Organic Chemistry, Part C"; Trahanovsky, W.; Ed.; Academic Press: New York, 1978; pp 1-130. Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22-30.

(2) (a) Toshimitsu, A.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1977**, 166-167. (b) Toshimitsu, A.; Aoai, T.; Uemura, S.; Okano, M. *J. Org. Chem.* **1980**, *45*, 1953-1958.

(3) Preliminary communications: Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1979**, 610-611. Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *Chemistry Lett.* **1979**, 1359-1360.

(4) Independently, synthesis of cyclic ethers from diolefins using different selenium reagents has been reported: Scarborough, R. M., Jr.; Smith, A. B., III; Barnette, W. E.; Nicolaou, K. C. *J. Org. Chem.* **1979**, *44*, 1742-1744. Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704-3706.

(5) Sharpless, K. B., Young, M. W. *J. Org. Chem.* **1975**, *40*, 947-949.

(6) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486. Grieco, P. A.; Yokoyama, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5210-5211.

(7) (a) Uemura, S.; Toshimitsu, A.; Okano, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1925-1928. (b) Toshimitsu, A.; Kozawa, Y.; Uemura, S.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1273-1278. (c) Toshimitsu, A.; Uemura, S.; Okano, M. *Ibid.* **1979**, 1206-1210. (d) Esaki, N.; Tanaka, H.; Uemura, S.; Suzuki, T.; Soda, K. *Biochemistry* **1979**, *18*, 407-410. (e) Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *Tetrahedron Lett.* **1980**, 1533-1536. (f) Toshimitsu, A.; Aoai, T.; Owada, H.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1980**, 412-413. (g) Toshimitsu, A.; Aoai, T.; Uemura, S.; Okano, M. *Ibid.* **1980**, 1041-1042.

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(9) Barrelle, M.; Apparu, M.; Gey, C. *Can. J. Chem.* **1978**, *56*, 85-92.

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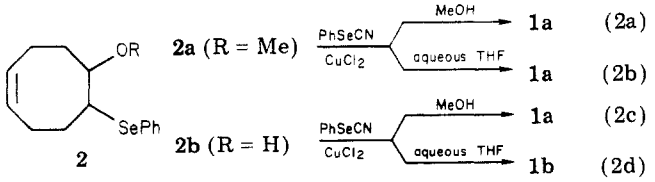
deshielded by ca. 0.5 ppm compared to that in the latter by ^{1}H NMR.[10,11] Thus, in the ^{13}C NMR, signals due to bridgehead carbons appeared at δ 69.1 for **1a** and δ 81.0 for **1b** both as doublets, and in the ^{1}H NMR, signals due to bridgehead protons appeared at δ 3.8–4.0 for **1a** and δ 4.5–4.7 for **1b** (see Experimental Section). The assignment was supported by the absorption at 1496 cm^{-1} in the IR spectrum of **1a** which was attributed to the twin-chair conformation of [3.3.1] ring system.[12] The assignment was further confirmed by the replacement of phenylseleno groups in **1a** and **1b** by hydrogen,[8] leading to known oxabicyclo[3.3.1]- and -[4.2.1]nonanes.[13] Later, we will discuss the signal assignments in ^{13}C NMR spectra in more detail. The isomer ratio of **1a**/**1b** depended on the alcohol utilized; i.e., **1a** was produced almost exclusively in methanol, and the ratio of **1b** to **1a** increased by the use of more substituted alcohols, **1b** being the major product in *tert*-butyl alcohol. Furthermore, when aqueous tetrahydrofuran (THF/H_2O ratio of 9:1) was used as solvent, **1b** became the sole product. This seems to be the first example of a solvent-controlled preparation of each isomer which has never been achieved in reactions of 1,5-cod with other electrophiles such as mercury,[14,15] iodine,[11,14] or a proton.[10] When this reaction was carried out in aqueous acetonitrile (MeCN/H_2O, 5:1) as solvent, both **1a** and **1b** were produced in excellent yields even at room temperature. In this solvent and at reflux temperature the ratio of **1a** to **1b** increased with longer reaction time, the total yield of both being almost unchanged. This clearly indicates the isomerization of **1b** to **1a** under these conditions. Typical results are summarized in Table I.

If this reaction is comparable with oxyselenation of monoolefins,[2] it should proceed through alkoxy- or hydroxyselenation of one double bond, followed by transannular attack of the alkoxyl or hydroxyl group on the episelenonium ion which is formed at the other double bond by the attack of another phenyl selenocyanate. In order to confirm this, we have prepared 5-methoxy- and 5-hydroxy-6-(phenylseleno)cyclooctenes, **2a** and **2b**, respectively, and treated them with phenyl selenocyanate (1 molar equiv) and copper(II) chloride in methanol or aqueous THF under reflux for 5 h. Consistent with the results described above, **1a** was the major product obtained (62% isolated yield, >95% purity) from **2a** by using methanol as solvent, and **1b** was the sole product obtained (81% isolated yield) from **2b** by using aqueous THF as solvent. Interestingly, on the other hand, in "cross" reactions (**2a** in aqueous THF or **2b** in methanol) **1a** was the major product in both cases (>95% purity, 65% and 52% isolated yields, respectively, eq 2). As we confirmed



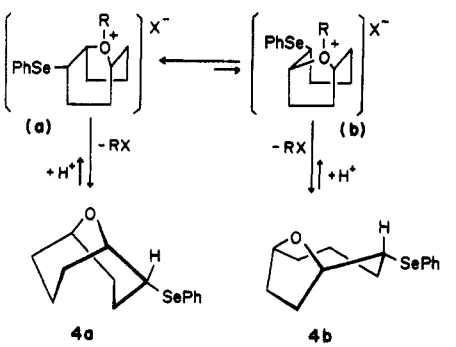
separately that isomerization of **1b** to **1a** occurred only very slowly in methanol even in the presence of acid catalyst (>90% of **1b** was recovered unchanged after reflux for 5 h in methanol containing 1 molar equiv of HCl; see Experimental Section), these results show that both solvent and leaving group (R in **2**) affect the course of transannular reaction, giving the [3.3.1] or [4.2.1] isomer.

Table II. Yield and Isomer Ratio of 4a and 4b[a]

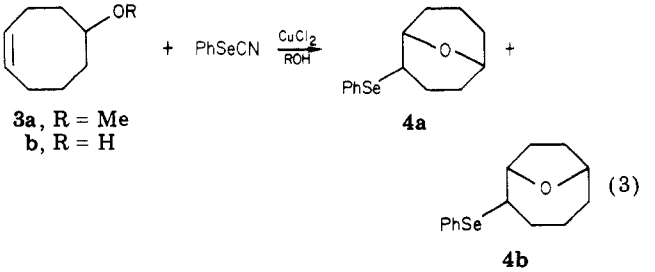
expt	R in 3	solvent (vol, mL)	% yield of 4[b]	ratio[c] of 4a/4b
1	Me	MeOH (10)	68	4a[d]
2[e]	Me	MeOH (10)	80	89:11[f]
3	Me	THF-H_2O (18 + 2)	39	4a[d]
4[e,g]	Me	THF-H_2O (9 + 1)	79	91:9[f]
5	H	MeOH (10)	81[h]	88:12[f]
6[g]	H	MeOH-H_2O (9 + 1)	72[h]	59:41
7[g]	H	THF (4)	86[h]	82:18
8	H	THF-H_2O (18 + 2)	99	19:81[f]
9	H	*t*-BuOH (10)	56[h]	54:46
10	H	MeCN (10)	73[h]	82:18

[a] **3** (5 mmol), PhSeCN (5 mmol), and $CuCl_2$ (5 mmol); at reflux for 5 h. [b] Determined by GLC analysis. [c] Determined by ^{1}H NMR spectra from the integration of signals due to H atoms attached to C adjacent to Se or O atoms. [d] Although the precise ratio could not be estimated, **4a** was formed almost exclusively. [e] Reaction time 24 h. [f] Determined by ^{13}C NMR (see footnote *c* in Table I). [g] **3** (2 mmol), PhSeCN (2 mmol), and $CuCl_2$ (2 mmol). [h] Isolated yield.

Scheme I



In order to exclude the possibility of an exchange between the methoxyl and hydroxyl groups in **2** by the assistance of selenium, we investigated the effect of the solvent and leaving group on the course of reaction using 5-methoxy- and 5-hydroxycyclooctene, **3a** and **3b**, respectively, as starting materials. In the reaction of **3** with phenyl selenocyanate (1 molar equiv) in various solvents containing copper(II) chloride an isomeric mixture of 2-(phenylseleno)-9-oxabicyclo[3.3.1]nonane (**4a**) and 2-(phenylseleno)-9-oxabicyclo[4.2.1]nonane (**4b**) was produced in a good to excellent yield (eq 3). The structure



of the products was unambiguously determined by ^{13}C and ^{1}H NMR spectra (vide supra). Typical results in various solvents are summarized in Table II. As expected, when the leaving group is methyl, the [3.3.1] isomer was formed almost exclusively irrespective of the nature of solvent,

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(11) Labows, J. N., Jr.; Swern, D. *J. Org. Chem.* **1972**, *37*, 3004–3006.
(12) Eglinton, G.; Martin, J.; Parker, W. *J. Chem. Soc.* **1965**, 1243–1251. Weil, E. D.; Smith, K. J.; Gruber, R. J. *J. Org. Chem.* **1966**, *31*, 1669–1679.
(13) Cope, A. C.; Anderson, B. C. *J. Am. Chem. Soc.* **1957**, *79*, 3892–3895. Cope, A. C.; Fournier, A., Jr. *Ibid.* **1957**, *79*, 3896–3899.
(14) Cope, A. C.; McKervey, M. A.; Weinshenker, N. M. *J. Org. Chem.* **1969**, *34*, 2229–2231.
(15) Stetter, H.; Meissner, H. J. *Tetrahedron Lett.* **1966**, 4599–4602.

Table III. Chemical Shifts in ^{13}C NMR Spectra of 1 and 4

compd	chemical shifts, δ							
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
1a	69.1	44.5	27.8	26.8	69.1	44.5	27.8	26.8
4a	69.4	45.1	27.8	31.4	66.2	29.2	19.0	25.2
9-oxabicyclo[3.3.1]nonane[a]	66.6	29.4	18.9	29.4	66.6	29.4	18.9	29.4
1b	81.0	40.1	30.2	30.2	40.1	81.0	28.4	28.4
4b	81.1	48.6	34.8	24.0	35.8	76.1	31.8	25.0
9-oxabicyclo[4.2.1]nonane[a]	77.7	36.2	24.4	24.4	36.2	77.7	31.6	31.6

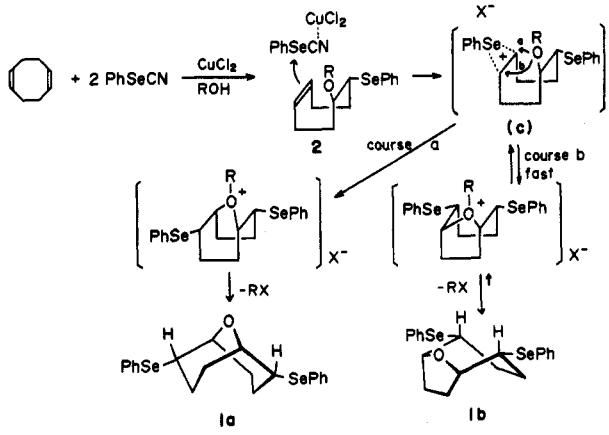
[a] Reference 9.

while the course of transannular reaction depended very much on solvent utilized when the leaving group is hydrogen. Namely, in the reaction of **3b** the effect of water added to the solvent is remarkable (expt 5 and 6 or expt 7 and 8), the formation of the [4.2.1] isomer being favored by the addition of water. On consideration of the product yield, it is clear that cyclization of **3b** is faster than that of **3a** (expt 1 and 5 or expt 3 and 8). A longer reaction time was required for **3a** to produce 4 in good yield (expt 2 and 4). These results are consistent with the reaction mechanism through the intermediate a or b in Scheme I. In the transannular reaction, the formation of five-membered ring is kinetically favored to give b.[11,16] When R is not a good leaving group (R = Me), b is isomerized to a thermodynamically more stable intermediate a from which **4a** is formed. When R is hydrogen, the removal of a proton from b to form **4b** and the isomerization of b to a compete, the course of the reaction being determined by the nature of solvent. The effect of water described above seems to be due to the increase of the basicity of solvent which facilitates the removal of a proton from b to form **4b**.

The slightly lower selectivity for 4 (expt 2 and 8) compared to that for 1 (see Table I) was attributed to isomerization between **4a** and **4b**. In fact, we observed the isomerization of **4b** to **4a** catalyzed by mineral acid; i.e., almost pure **4b** was isomerized to a mixture of **4a** and **4b** (**4a**/**4b** ratio of ca 4:1) when it was heated in methanol containing HCl (1 molar equiv) for 5 h. This isomerization reaction was much faster than that of **1b** to **1a** (vide supra). It should be noted that under our reaction conditions the reaction mixture finally became acidic presumably due to the formation of hydrogen chloride (the hydrogen cyanide formed can react with copper(II) chloride to produce hydrogen chloride and copper(II) cyanide).

The discussion above supports the mechanism for selective formation of **1a** and **1b** from 1,5-cod. As shown in Scheme II, the first step of this reaction is the oxyselenation of one double bond to produce **2**. In the transannular reaction of an alkoxyl or hydroxyl group with the episelenonium ion formed at the other double bond, the formation of an oxonium ion having [4.2.1] framework is kinetically favored (course b). In the case where R is hydrogen, R is removed prior to the isomerization in the solvent utilized (aqueous THF) to give **1b** as a sole product. When R is reluctant to be removed (Me > Et > *i*-Pr > *t*-Bu), an isomerization to a thermodynamically more stable intermediate having a [3.3.1] framework (course a) occurs to give **1a** as major product. This interpretation agrees well with the results shown in Table I where the isomer ratio of **1b** to **1a** is increased when R is changed from methyl to *tert*-butyl. It should be noted here that the monocyclic compound 1,5-bis(phenylseleno)-2,6-dimethoxycyclooctane (or its regioisomer) was not obtained from 1,5-cod irrespective of solvent. This indicates that

Scheme II

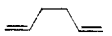
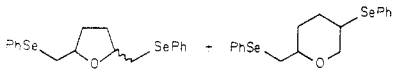
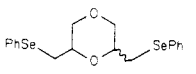
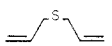
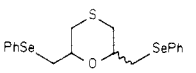
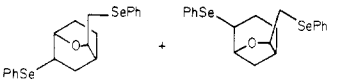


the intramolecular process predominates at stage c in Scheme II.

Here we discuss briefly the results of assignment of signals of the ^{13}C NMR spectra of 1 and 4. The observed data are summarized in Table III together with the data reported for 9-oxabicyclo[3.3.1]- and -[4.2.1]nonanes. Signal assignments are based on the shielding effects by steric interactions between the substituted group and hydrogen in bicyclic nonanes reported by Barrelle et al.[9] and the inductive effect of the phenylseleno group which is reported[2b] to be 13 ppm for α-carbons and 6 ppm for β-carbons in linear compounds. The chemical shifts of C_2, C_3, and C_4 in **4a** are well explained by the inductive effect of phenylseleno group on C_2. The inductive effect on the γ-carbon (C_4, 2 ppm) can also be ascribed to the same reason. The β-inductive effect on bridgehead carbon (C_1) is very small (2.8 ppm), consistent with many precedents in substituted 9-oxabicyclo[3.3.1]nonanes.[9] C_8 is shielded by 4.2 ppm as a result of a through-space interaction of the phenylseleno group and the hydrogen on C_8 (about −6 ppm) which is compensated by the γ-inductive effect of phenylseleno group (2 ppm). A shielding effect of the same magnitude (−6 to −7 ppm) has been reported by Barrelle et al.[9] These results indicate that phenylseleno group is in the endo position of the bicyclic ring system or in the equatorial position in the tetrahydropyran ring. The same reasoning stands for the chemical shifts of **1a**, again confirming that both phenylseleno groups are in the endo position. In the chemical shifts of **4b**, γ steric interaction is also observed. Thus, C_8 is shielded 6.6 ppm as compared with that for nonsubstituted compounds, suggesting endo substitution of the phenylseleno group. On the other hand, the chemical shifts of **1b** show different features from those of other compounds. Thus, the inductive effect of the phenylseleno group on the α-carbon is canceled by other factors by 9–12 ppm and that on β-carbon by 3–5 ppm. Similarly, C_7 and C_8 are shielded 3.2 ppm as compared to the nonsubstituted compound. These shielding effects can best be explained by assuming the C_2-H···H-C_5 and C_3/C_4-H···H-C_7/C_8 interactions in the conformer which has

(16) Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993–999.

Table IV. Synthesis of Cyclic Ethers by Oxyselenation of Diolefins[a]

diolefin	temp, °C	time, h	products	yield, %[b] (isomer ratio)[b]
	76 30	8 96	 5a 5b	86 (91:9) 49 (90:10)
	76	24	 6	64
	76	24	 7	42
	76	8	 8a 8b	43 (96:4)[c]

[a] Diolefin (1 mmol), PhSeCN (2 mmol), $CuCl_2$ (1 mmol), and aqueous MeCN (3.6 mL; MeCN/H_2O ratio of 5:1). [b] Determined by liquid chromatography. [c] Assignment for **8a** and **8b** might be reversed.

two phenylseleno groups in the equatorial position (see Scheme II). The result that **1a,b** and **4a,b** each consist of one stereoisomer and are all endo-substituted compounds agrees well with the trans stereospecificity of oxyselenation reactions.[2]

Attempts to apply this cyclization reaction to linear diolefins by using alcohols as solvents gave unsatisfactory results. For instance, in the reaction of 1,5-hexadiene or diallyl ether with phenyl selenocyanate (2 molar equiv) in the presence of copper(II) chloride in methyl alcohol as solvent a cyclic ether was not formed, and, instead, methoxyselenated products of both double bonds were obtained in 63% and 60% yields, respectively. When *tert*-butyl alcohol was used as the solvent, the cyclization reaction did occur, but the yields of cyclic ethers were low (at most 27% and 25% yield, respectively) because of the formation of resinous byproducts.

It was eventually found that aqueous acetonitrile (MeCN/H_2O, 5:1) was the best solvent for the synthesis of cyclic ethers from these diolefins. Thus, when the aqueous acetonitrile solution of 1,5-hexadiene and phenyl selenocyanate (2 molar equiv) was heated in the presence of copper(II) chloride, an isomeric mixture of 2,5-bis[(phenylseleno)methyl]tetrahydrofuran (**5a**) and 2-[(phenylseleno)methyl]-5-(phenylseleno)tetrahydropyran (**5b**) was formed in 86% yield (**5a**/**5b**, 91:9). In the ^{13}C NMR spectrum of a mixture of **5a** and **5b** (9:1), signals due to the carbons attached to oxygen were well separated from other signals, appearing at δ 78.4 (d) and 79.0 (d) for major component **5a** and at δ 71.4 (t) and 76.9 (d) for minor component **5b**. The assignment of the products to **5a** and **5b** was based on the splitting pattern of these signals. Nearly equivalent intensities of the signals at δ 78.4 and 79.0 indicate that **5a** consists of almost equal amounts of two stereoisomers, presumably cis and trans with respect to two (phenylseleno)methyl groups. The ratio of both stereoisomers was further confirmed by liquid chromatographic analysis to be 52:48 cis/trans.

Similar reaction of diallyl ether and diallyl sulfide afforded 2,6-bis[(phenylseleno)methyl]-1,4-dioxane (**6**) and 2,6-bis[(phenylseleno)methyl]-1,4-oxathiane (**7**) in 64% and 42% yields, respectively. These 1,6-dienes required longer reaction times than the 1,5-dienes to give the cyclic ethers in good yields, reflecting the slow reaction for the formation of a six-membered ring compared to that of a five-membered one. Similar to **5a**, both **6** and **7** contained almost equal amounts of two stereoisomers.

This reaction also proceeded with 4-vinyl-1-cyclohexene to give an isomeric mixture of 3-[(phenylseleno)methyl]-6-(phenylseleno)-2-oxabicyclo[2.2.2]octane (**8a**) and 4-(phenylseleno)-7-[(phenylseleno)methyl]-6-oxabicyclo[3.2.1]octane (**8b**) in a yield of 43%. Although ^{13}C NMR revealed that the products were not contaminated by the other possible isomers such as bicyclo[3.2.2]- or -[3.3.1]nonanes, we could not distinguish between **8a** and **8b** by ^{13}C NMR analysis. We therefore tentatively assigned the major product as **8a**. Typical results are summarized in Table IV.

Experimental Section

IR spectra were recorded with Hitachi EPI-S2 and Perkin-Elmer 521 spectrometers. ^1H NMR spectra were taken with Varian EM-360 and JEOLCO JNM-PFT-100 instruments on solutions in $CDCl_3$ with Me_4Si as an internal standard. ^{13}C NMR spectra were taken at 25.1 MHz with a JEOLCO ^{13}C Fourier transform NMR system (JNM-PFT 100) and were recorded on solutions in $CDCl_3$ after 200–1750 pulses with intervals of 3 s. GLC analyses were carried out with a Shimadzu 4CMPF apparatus by using EGSS-X (15%)–Chromosorb W (1 m) and PEG 6000 (25%)–Shimalite (3 m) columns (N_2 as carrier gas; 1,4-diphenylbutadiene or allyl phenyl ether as an internal standard). Liquid chromatographic analyses were carried out with a Waters HPLC system equipped with a 6000A solvent delivery system, a Model 440 absorbance detector (at 254 nm), and a μ-Porasil (3.9 mm × 0.3 m) column.

Materials. Phenyl selenocyanate was prepared by a reported method from a phenyldiazonium salt and potassium selenocyanate;[17] bp 90–97 °C (3 torr) [lit.[18] bp 134 °C (10 torr)]. 5-Methoxycyclooctene (**3a**) was prepared by methoxymercuration of 1,5-cod followed by demercuration using sodium borohydride;[19] bp 91 °C (37 torr) [lit.[11] bp 43 °C (1.5 torr)]. 5-Hydroxycyclooctene (**3b**) was prepared by the reported method.[20] 5-Hydroxy-6-(phenylseleno)cyclooctene (**2b**) was prepared by the known method[21] from 1,5-cod monoxide[20] (2.48 g, 20 mmol), phenyl selenocyanate (3.64 g, 20 mmol), and sodium borohydride (0.909 g, 24 mmol) in ethanol (40 mL) (under N_2, reflux 2 h). Triphenyltin hydride was prepared by reduction of commercial triphenyltin

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chloride with lithium aluminum hydride in diethyl ether under N_2[22] and was used without purification such as distillation or recrystallization.

5-Methoxy-6-(phenylseleno)cyclooctene (2a). To a solution of 1,5-cod (1.08 g, 10 mmol) and phenyl selenocyanate (0.911 g, 5 mmol) in methanol (10 mL) was added solid copper(I) cyanide (0.448 g, 5 mmol) and the resulting mixture was stirred under reflux for 5 h. Water (20 mL) was added, and an inorganic precipitate thus formed was filtered off. The benzene extract (3 × 20 mL) of the filtrate was washed with brine and dried over $MgSO_4$. After evaporation of solvent in vacuo, distillation of a residual yellow-brown oil gave pure **2a**: 0.735 g (2.49 mmol, 50%) bp 148–149 °C (4 torr); IR (film) 3060, 2930, 1650, 1580, 1473, 1432, 1096, 738, 690 cm^{-1}; ^1H NMR δ 1.6–2.6 (m, 8 H), 3.35 (s, 3 H), 3.4–4.0 (m, 2 H), 5.4–5.8 (m, 2 H), 7.1–7.7 (m, 5 H). Anal. Calcd for $C_{15}H_{18}OSe$: C, 61.01; H, 6.83. Found: C, 61.24; H, 6.73.

All other organic and inorganic materials were commercial products.

2,6-Bis(phenylseleno)-9-oxabicyclo[3.3.1]nonane (1a). To a solution of 1,5-cod (0.541 g, 5 mmol) and phenyl selenocyanate (1.82 g, 10 mmol) in methyl alcohol (10 mL) was added solid copper(II) chloride (0.672 g, 10 mmol), and the resulting mixture was stirred under reflux for 5 h. Water (100 mL) was added, and a pale blue precipitate thus formed was filtered off. The filtrate was extracted with benzene (3 × 30 mL), and the organic layer was washed with water and dried over $MgSO_4$. Evaporation of solvent in vacuo left a yellow oil, which was subjected to column chromatography (silica gel) to give diphenyl diselenide [0.151 g, 0.48 mmol, 19%; hexane–chloroform (5:1) as eluent] and a mixture of **1a** and **1b** [1.36 g, 3.11 mmol, 62%; hexane–ethyl acetate (5:1) as eluent] as a white solid. The ^{13}C NMR spectrum of the mixture revealed that the isomer ratio (**1a**/**1b**) was 95:5 by comparison of peak intensities of the signals due to carbon atoms attached to oxygen or selenium. Recrystallization of this solid from hexane gave pure **1a** as white needles: mp 84.0–85.0 °C; IR (KBr) 3080, 2940, 1588, 1496, 1485, 1445, 1032, 1023, 743, 691 cm^{-1}; ^1H NMR (100 MHz) δ 1.8–2.3 (m, 8 H), 3.6–3.8 (m, 2 H), 3.8–4.0 (m, 2 H), 7.1–7.7 (m, 10 H). Anal. Calcd for $C_{20}H_{22}OSe_2$: C, 55.06; H, 5.08. Found: C, 55.16; H, 5.23.

2,5-Bis(phenylseleno)-9-oxabicyclo[4.2.1]nonane (1b). A homogeneous mixture of 1,5-cod (0.541 g, 5 mmol), phenyl selenocyanate (1.82 g, 10 mmol), and copper(II) chloride (0.672 g, 5 mmol) in aqueous THF (20 mL; H_2O/THF, 1:9) was stirred under reflux for 5 h. After the workup procedure as described above a pale yellow oil was subjected to column chromatography (silica gel) to give diphenyl diselenide [0.514 g, 1.60 mmol, 32%; hexane–chloroform (5:1) as eluent] and **1b** [1.48 g, 3.40 mmol, 68%; hexane–ethyl acetate (5:1) as eluent] as a white solid. Recrystallization from hexane gave **1b** as white needles: mp 97.5–98.5 °C; IR (KBr) 3070, 2940, 1585, 1484, 1475, 1444, 1045, 1024, 925, 918, 745, 695 cm^{-1}; ^1H NMR (100 MHz) δ 1.9–2.1 (m, 8 H), 3.5–3.7 (m, 2 H), 4.5–4.7 (m, 2 H), 7.1–7.7 (m, 10 H). Anal. Calcd for $C_{20}H_{22}OSe_2$: C, 55.06; H, 5.08. Found: C, 55.22; H, 5.22.

Triphenyltin Hydride Reduction of 1a and 1b. A homogeneous toluene (15 mL) solution of **1a** (0.436 g, 1 mmol) and triphenyltin hydride (1.06 g, 3 mmol) was heated at reflux for 4 h. The GLC analysis of the cooled solution showed that the product was identical with oxabicyclo[3.3.1]nonane prepared by the reported method[16] [retention time 6.20 min on PEG-6000 (25%)–Shimalite column at 180 °C; N_2 flow rate 60 mL/min]. The yield was found to be 61% with allyl phenyl ether as an internal standard. By the same procedure with **1b** as starting material, oxabicyclo[4.2.1]nonane (retention time 6.12 min under the same conditions) was produced in a yield of 45%.

2-(Phenylseleno)-9-oxabicyclo[3.3.1]nonane (4a). To a solution of 5-methoxycyclooctene (**3a**; 0.631 g, 5 mmol) and phenyl selenocyanate (0.911 g, 5 mmol) in methanol (10 mL) was added copper(II) chloride (0.672 g, 5 mmol), and the resulting mixture was stirred under reflux for 24 h. After the workup procedure as described above, a yellow oil was analyzed by GLC to show the presence of 4 (4.0 mmol, 80%). After removal of diphenyl diselenide and resinous byproducts by column chromatography [silica gel; hexane–chloroform (5:1) and hexane–ethyl acetate as eluents], ^{13}C NMR measurement revealed that the isomer ratio of **4a** to **4b** was 89:11 by comparison of peak intensities of signals due to carbon atoms attached to oxygen or selenium. This mixture was again subjected to column chromatography [silica gel; hexane–ethyl acetate (10:1) as eluent] to give pure **4a** and a small amount of a mixture of **4a** and **4b**. For **4a**: yellow oil; IR (film) 3060, 2940, 1575, 1480, 1440, 1030, 900, 860, 740, 695 cm^{-1}; ^1H NMR δ 1.3–2.4 (m, 10 H), 3.5–4.1 (m, 3 H), 7.1–7.7 (m, 5 H). Anal. Calcd for $C_{14}H_{18}OSe$: C, 59.78; H, 6.45. Found: C, 59.77; H, 6.27.

2-(Phenylseleno)-9-oxabicyclo[4.2.1]nonane (4b). A solution of 5-hydroxycyclooctene (**3b**; 0.631 g, 5 mmol), phenyl selenocyanate (0.911 g, 5 mmol), and copper(II) chloride (0.672 g, 5 mmol) in aqueous THF (20 mL; H_2O/THF, 1:9) was stirred under reflux for 5 h. A yellow oil thus obtained by a workup procedure as described above was analyzed by GLC to show the presence of 4 (4.95 mmol, 99%). After removal of diphenyl diselenide and quite a little amount of resinous byproducts by column chromatography [silica gel; hexane–chloroform (5:1) and hexane–ethyl acetate (5:1) as eluents], ^{13}C NMR measurement of the residue showed that the isomer ratio of **4a** to **4b** was 19:81 (vide supra). This mixture was again subjected to column chromatography [silica gel; hexane–ethyl acetate (10:1) as eluent] to give pure **4b** and a mixture of **4a** and **4b**. For **4b**: yellow oil; IR (film) 3060, 2940, 1580, 1480, 1440, 1050, 935, 910, 740, 690 cm^{-1}; ^1H NMR δ 1.1–2.4 (m, 10 H), 3.3–3.7 (m, 1 H), 4.2–4.7 (m, 2 H), 7.1–7.7 (m, 5 H). Anal. Calcd for $C_{14}H_{18}OSe$: C, 59.78; H, 6.45. Found: C, 60.19; H, 6.52.

2,5-Bis[(phenylseleno)methyl]tetrahydrofuran (5a) and 2-[(Phenylseleno)methyl]-5-(phenylseleno)tetrahydropyran (5b). To a solution of 1,5-hexadiene (0.083 g, 1 mmol) and phenyl selenocyanate (0.364 g, 2 mmol) in aqueous acetonitrile (3.6 mL; H_2O/CH_3CN, 1:5) was added copper(II) chloride (0.135 g, 1 mmol), and the resulting mixture was stirred under reflux for 8 h. Water (10 mL) was added, and the products were extracted with chloroform (3 × 10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give a yellow oil. Liquid chromatographic analysis [hexane–dichloromethane (1:1) as eluent, benzophenone as internal standard] showed the presence of **5a** (0.786 mmol, 79%; isomer ratio 52:48) and **5b** (0.076 mmol, 8%). Pure **5a** and a mixture of **5a** and **5b** were isolated by column chromatography of this oil obtained from the reaction on a 5-times greater scale [silica gel; hexane–chloroform (5:1, to remove diphenyl diselenide) and hexane–ethyl acetate (20:1) as eluents]. For **5a**: yellow oil; IR (film) 3060, 2940, 1580, 1480, 1435, 1075, 1025, 740, 695 cm^{-1}; ^1H NMR δ 1.4–2.3 (m, 4 H), 2.7–3.3 (m, 4 H), 3.8–4.4 (m, 2 H), 7.1–7.7 (m, 10 H); ^{13}C NMR δ 31.0 (t), 31.9 (t), 33.0 (t),[23] 78.4 (d), 79.0 (d), phenyl signals. For **5b** (identified as a mixture with **5a**): ^{13}C NMR δ 71.4 (t), 76.9 (d) (other signals were not distinguished from those of **5a**). Anal. (for a mixture of **5a** and **5b**). Calcd for $C_{18}H_{20}OSe_2$: C, 52.70; H, 4.91. Found: C, 52.42; H, 4.94.

2,5-Bis[(phenylseleno)methyl]-1,4-dioxane (6). The reaction and workup procedures were analogous to those described above (diallyl ether; 0.098 g, 1 mmol). Liquid chromatographic analysis [hexane–chloroform (4:1) as eluent, *p*-nitroanisole as internal standard] of the oil showed the presence of **6** (0.645 mmol, 64%; isomer ratio 43:57). Pure **6** was isolated in a same way as described above: yellow oil; IR (film) 3050, 2860, 1580, 1475, 1435, 1240, 1100, 895, 740, 695 cm^{-1}; ^1H NMR δ 2.7–3.2 (m, 4 H), 3.2–4.1 (m, 6 H), 7.1–7.7 (m, 10 H); ^{13}C NMR δ 27.7 (t), 28.1 (t), 68.8 (t), 69.7 (d), 70.0 (t), 74.9 (d), phenyl signals. Anal. Calcd for $C_{18}H_{20}O_2Se_2$: C, 50.72; H, 4.73. Found: C, 51.17; H, 4.69.

2,5-Bis[(phenylseleno)methyl]-1,4-oxathiane (7). The reaction and workup procedures were analogous to those described above (diallyl sulfide, 0.115 g, 1 mmol). Liquid chromatographic analysis [hexane–chloroform (5:1) as eluent, *m*-dinitrobenzene as internal standard] showed the presence of **7** (0.420 mmol, 42%; isomer ratio 48:52). Pure **7** was isolated in a same way as described above: yellow oil; IR (film) 3060, 2920, 1580, 1475, 1435, 1410, 1075, 1025, 740, 690 cm^{-1}; ^1H NMR δ 2.3–2.7 (m, 4 H), 2.7–3.3 (m, 4 H), 3.5–4.3 (m, 2 H), 7.1–7.7 (m, 10 H); ^{13}C NMR δ 29.6 (t), 30.1 (t),[23] 32.8 (t), 70.4 (d), 78.4 (d), phenyl signals. Anal. Calcd for $C_{18}H_{20}OSSe_2$: C, 48.88; H, 4.56. Found: C, 49.44; H, 4.78.

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(23) Two signals overlapped.

3-[(Phenylseleno)methyl]-6-(phenylseleno)-2-oxabicyclo-[2.2.2]octane (8a) and 4-(Phenylseleno)-7-[(phenylseleno)-methyl]-6-oxabicyclo[3.2.1]octane (8b). The reaction and workup procedures were analogous to those described above (4-vinylcyclohexene, 0.109 g, 1 mmol; reflux 8 h). Liquid chromatographic analysis [hexane–chloroform (9:1) as eluent, benzophenone as internal standard] showed the presence of **8a** (0.415 mmol, 42%) and **8b** (0.018 mmol, 2%). A mixture of **8a** and **8b** was isolated in a same way as described above: yellow oil; IR (film) 3060, 2950, 1589, 1475, 1435, 1210, 1070, 1025, 980, 890, 740, 690 cm^{-1}; ^1H NMR δ 1.3–2.4 (m, 7 H), 2.6–3.3 (m, 2 H), 3.3–3.9 (m, 1 H), 3.9–4.6 (m, 2 H), 7.1–7.7 (m, 10 H); ^{13}C NMR δ 25.5 (t), 26.8 (t), 31.9 (t), 32.5 (t), 38.7 (t), 44.7 (d), 68.9 (d),[24] 79.0 (d), 81.0 (d), phenyl signals. Anal. Calcd for $C_{20}H_{22}OSe_2$: C, 55.06; H, 5.08. Found: C, 55.27; H, 5.11.

Acid-Catalyzed Isomerization of 1b to 1a. To a solution of **1b** (0.436 g, 1 mmol) and phenyl selenocyanate (0.364 g, 2 mmol) in methanol (20 mL) containing hydrogen chloride (36.5% aqueous HCl, 0.1 mL; 1 mmol as HCl) was added copper(II) chloride (0.314 g, 1 mmol), and the resulting mixture was stirred under reflux for 5 h. Water (50 mL) was added, and the products were extracted with chloroform (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a yellow oil. After removal of phenyl selenocyanate by column chromatography [silica gel; hexane–chloroform (3:1) and chloroform as eluents], ^1H NMR measurement revealed that the product contained more than 90% of **1b** and less than 10% of **1a** by integration of signals due to methine protons.

Acid-Catalyzed Isomerization of 4b to 4a. To a solution of **4b** (0.141 g, 0.5 mmol) in methanol (2 mL) was added hydrogen chloride (36.5% aqueous HCl, 0.05 mL; 0.5 mmol as HCl), and the resulting solution was stirred under reflux for 5 h. After the workup procedure as described above, the yellow oil obtained was purified by column chromatography [silica gel; hexane–ethyl acetate (20:1) as eluent] to give **4** (0.111 g, 0.39 mmol, 79%). The **4a**/**4b** isomer ratio was estimated to be 80:20 by integration of the signals due to the methine protons in ^1H NMR spectrum. The same reaction of **4b** in methanol containing phenyl selenocyanate (2 molar equiv) and copper(II) chloride (1 molar equiv) as well as hydrogen chloride gave the same result, indicating that hydrogen chloride worked as a catalyst in this isomerization reaction.

(24) Attributed to minor component.

Registry No. **1a**, 75494-81-4; **1b**, 70187-90-5; **2a**, 72695-46-6; **2b**, 72695-47-7; **3a**, 32160-45-5; **3b**, 4277-34-3; **4a**, 77552-07-9; **4b**, 77552-08-0; *cis*-**5a**, 72991-21-0; *trans*-**5a**, 72991-22-1; **5b**, 72991-23-2; *cis*-**6**, 72991-24-3; *trans*-**6**, 72991-25-4; *cis*-**7**, 72991-26-5; *trans*-**7**, 72991-27-6; **8a**, 72991-28-7; **8b**, 72991-29-8; (*Z*,*Z*)-1,5-cyclooctadiene, 1552-12-1; phenyl selenocyanate, 2179-79-5; copper(II) chloride, 7447-39-4; 9-oxabicyclo[3.3.1]nonane, 281-05-0; 9-oxabicyclo[4.2.1]-nonane, 284-20-8; 1,5-hexadiene, 592-42-7; diallyl ether, 557-40-4; diallyl sulfide, 592-88-1; 4-vinylcyclohexene, 100-40-3.

Rearrangements of Penicillin Sulfoxides. 2.[1] Spectral Data and X-ray Crystallography of the Novel Imidazo[5,1-*c*][1,4]thiazine Ring System

Abraham Nudelman*

Chemistry Department, Bar-Ilan University, Ramat-Gan, Israel

Tali E. Haran and Zippora Shakked*

Department of Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel

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The novel imidazo[5,1-*c*][1,4]thiazine ring system has been obtained by rearrangement of penicillin sulfoxide esters upon treatment with ethoxycarbonyl isocyanate. The unexpected structure of the rearrangement product **4b** was established by X-ray analysis. A mechanism involving C_5–S cleavage and the formation of an episulfonium ion, D, is postulated.

Penicillin sulfoxides undergo numerous rearrangements to a variety of ring systems.[2] A number of publications[3] have described the attempted synthesis of the elusive penicillin sulfilimines. In the course of our investigation we treated penicillin sulfoxide esters **1**[4] with ethoxycarbonyl isocyanate[5] with the aim of preparing the corresponding sulfilimines.[6] This paper describes the physical, spectroscopic, and X-ray data, which establish the structure of the novel products produced in the course of the investigation.

The reaction took place (Scheme I) when a tetrahydrofuran solution of a penicillin sulfoxide ester, **1**,[4] was heated with 2 mol of ethoxycarbonyl isocyanate **2**[5] for 17 h. A major product was isolated in yields of 54% (**1a** → **3a**), 31% (**1b** → **3b**) and 40% (**1c** → **3c**).[7]

Elemental analysis of the products **3a–c** indicated that the elements of carbon and nitrogen had been incorporated and that one hydrogen had been lost from the empirical formula of the respective starting materials. High-reso-

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