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Ring-Closure Reactions Initiated by the Peroxydisulfate Ion Oxidation of Diphenyl Diselenide

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The oxidation of diphenyl diselenide with ammonium peroxydisulfate proceeded cleanly to afford phenylselenium cations and sulfate anions. This is a very simple and efficient method to produce phenylselenium cations in the absence of nucleophilic counterions. This reaction was employed to effect selenium-induced ring closure reactions starting from alkenes containing internal nucleophiles. Thus, unsaturated alcohols and amides, β-diketones and β-keto esters gave the products of phenylselenoetherification. The same process occurred with dienes and unsaturated ketones when the reaction was carried out in the presence of water or methanol, respectively. Unsaturated acids, esters, and imides afforded the phenylselenolactonization products.

The facile addition of phenylselenium cations to unsaturated compounds has been largely used as a crucial step of many important synthetic transformations. The phenylseleno group is, in fact, a very useful and versatile functionality. It can be employed to direct further selective transformations of the molecule, and it can then be easily removed either by oxidation or by reduction.[1,2] The most common reagent employed to effect addition reactions to unsaturated compounds is the commercially available phenylselenenyl chloride. However, the presence of the nucleophilic halide anions is sometimes responsible for some undesirable processes such as addition of the halide ion and decrease in stereoselectivity. Moreover, the addition of PhSeCl to an alkene is sometimes complicated by further reaction of the formed alkyl phenyl selenides with PhSeCl, which affords the deselenenylation products; the two processes often proceed with comparable rates, and mixtures of products can thus be obtained.[3,4] The production of the electrophilic phenylselenium cations can also be effected by electrochemical oxidation of diphenyl diselenide, but this usually requires the use of halide anions as mediators.[5-7] Other selenenylating agents which do not suffer from these complications have been reported in the literature. The stable *N*-phenylselenophthalimide (NPSP) was employed to effect several types of selenenylation reactions.[8,9] Phenylselenenylating agents which have a nonnucleophilic counterion, such as SbF_6^-, PF_6^-,[10] or $CF_3SO_3^-$,[11,12] can be generated in situ and were introduced to effect conversions which did not take place with PhSeCl or NPSP. We have recently reported that electrophilic selenium species which act as phenylselenium cation equivalents can be easily produced from the oxidation of diphenyl diselenide with ammonium peroxydisulfate in several solvents.[13] This simple, unexpensive, and efficient method was employed to effect the methoxy- and hydroxyselenenylation of alkenes;[13] it also gives good results in the amido- and sulfonamidoselenenylation of the same substrates.[14] We report in this paper several examples of ring-closure reactions of alkenes, containing internal nucleophiles, initiated by the peroxydisulfate ion oxidation

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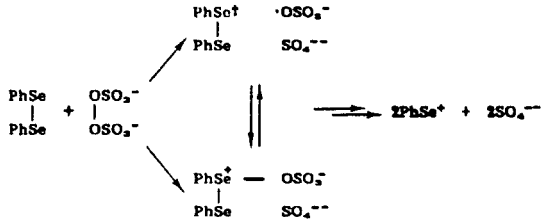
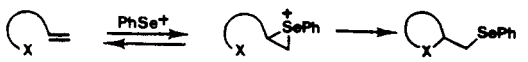
Table I

entry	alkene	R	R_1	method	time, h	temp, °C	product	yield, %
1	**1a**	H	H	A	0.5	25	**2a**	91
2	**1b**	H	Me	A	1	25	**2b**	68[a]
3	**1c**	Me	Me	A	1	25	**2c**	82
4	**3a**	H	Me	A	4	25	**4a**	90
5	**3b**	Me	Me	A	5	25	**4b**	65
6	**7**			A	0.5	25	**8**	78
7	**9**			B	12	70	**10**	77
8	**13a**	Me	COMe	B	6	70	**14a**	45
9	**13b**	Ph	COPh	B	2	70	**14b**	77
10	**13c**	Me	COOMe	B	2	70	**14c**	60
11	**13d**	Ph	CN	B	1	70	**14d**	70
12	**15**			B	1	70	**16**	58
13	**17**			B[b]	6	25	**18**	62[a]
14	**13c**			A	2	25	**20**	55[c]
15	**21**			B[d]	6	70	**22**	65
16	**24**			A	0.5	25	**25**	86
17	**26**			B	2	70	**27**	98
18	**28**			B	2	70	**29**	70
19	**30**			B	4	70	**31**	71[a]
20	**32**			B	2	25	**33**	84
21	**34**			B	1.5	70	**35**	97
22	**36**			B	1	25	**38**	70

[a] Mixture of two stereoisomers. [b] In methanol. [c] Mixture of stereoisomers. [c] In acetonitrile/water (5:1).

of diphenyl diselenide, which occurs according to the following general scheme:

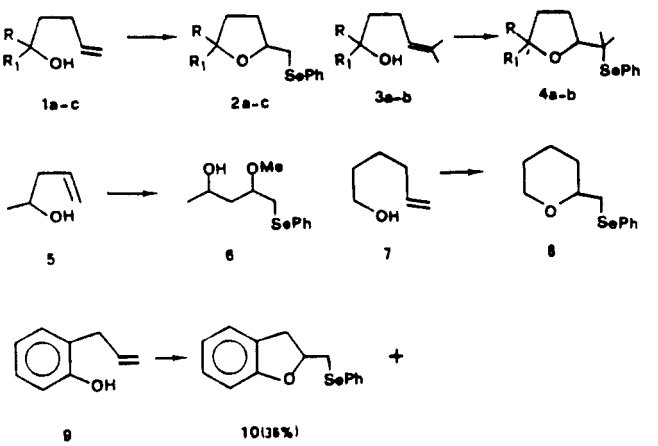




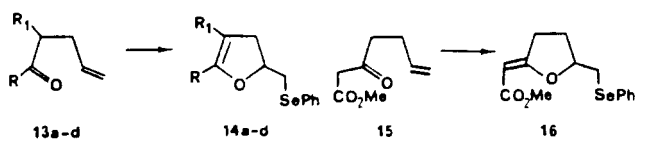
Results and Discussion

We suggest that the oxidation of diphenyl diselenide by peroxydisulfate anions is initiated by an electron transfer or an S_N2 process and produces phenylselenium cations and sulfate anions.[15] The reaction can be effected in methanol as well as in acetonitrile, dioxane, and mixtures of these solvents with water. The choice of the solvent is mainly dictated by the nature of the starting alkene. Two general methods have been employed in the present work. The reaction of PhSeSePh with $(NH_4)_2S_2O_8$ was carried out in refluxing methanol for 1–1.5 h, and to the resulting mixture was added the alkene, after cooling at room temperature (method A). Otherwise, PhSeSePh, $(NH_4)_2S_2O_8$, and the alkene were dissolved in acetonitrile, and the mixture was stirred at room temperature or at 70 °C (method B). In one case a 5:1 mixture of acetonitrile and water was employed.

Scheme I



Scheme II

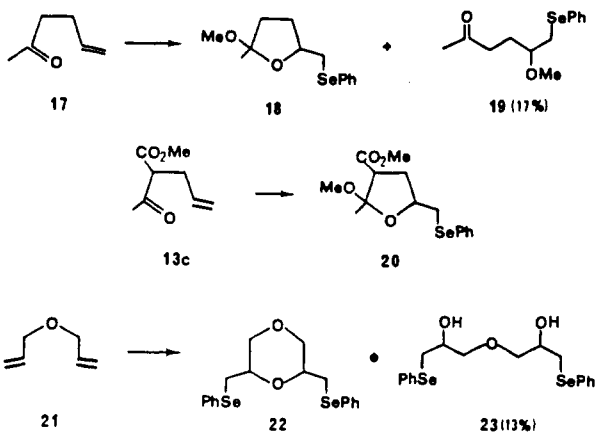


Phenylselenoetherification reactions were investigated starting from unsaturated alcohols and working in methanol (method A). The results obtained are summarized in Scheme I and Table I. The 4-penten-1-ols **1a–c** gave the expected five-membered cyclic selenoethers **2a–c** in good yield. The same type of compounds, **4a–b**, were also obtained from the substituted 4-penten-1-ols **3a–b**. Compound **4a** was contaminated by a tetrahydropyran-type phenylseleno ether. This latter compound was the only product obtained under different experimental conditions.[6] 4-Penten-2-ol, **5**, on the contrary, gave mainly the methoxyphenylselenenylation product **6**, together with small

(15) The mechanistic aspects of this reaction are presently under investigation. The nature of the actual electrophilic selenium species cannot be easily established. When the oxidation of PhSeSePh is carried out in nonnucleophilic solvents, the reactive species can be suggested to be the phenylselenium cation or the product deriving from its association with the sulfate anion; in nucleophilic solvents, other species can be formed by reaction of the initially formed phenylselenium cation with the solvent.

The presently described oxidation of diphenyl diselenide is similar to the previously reported method which employes hydrogen peroxides. In this case however the electrophilic selenium species is produced in the presence of nucleophilic hydroxy anions: Scarborough, R. M., Jr.; Smith, A. B. III; Barnette, W. E.; Nicolaou, K. C. *J. Org. Chem.* **1979**, *44*, 1742.

Scheme III



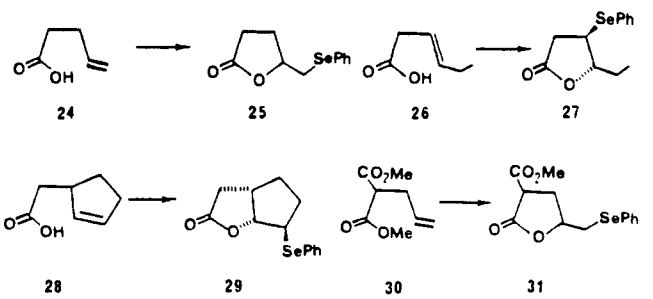
amounts of the cyclized product. The two reaction products could not be separated, and therefore they could not be fully identified. The reaction of **5** in acetonitrile (method B) gave a complex reaction mixture. The 5-hexen-1-ol, **7**, afforded cleanly the six-membered cyclization product **8**. Apart from the case of compound **5**, in all the other cases the methanol employed as solvent did not compete with the hydroxy group in the capture of the seleniranium cation intermediates. This competition occurs in the case of the *o*-allylphenol, **9**, from which a mixture of the three products, **10**, **11**, and **12**, was obtained (Scheme I). As indicated in Table I, the cyclization product **10** could be obtained in good yield by working in acetonitrile.

The allyl derivatives of β-diketones, **13a** and **13b**, β-ketoesters, **13c** and **15**, and of the β-ketonitrile **13d** easily reacted with diphenyl diselenide and ammonium peroxydisulfate in acetonitrile to afford the products of phenylselenoetherification **14a–d** and **16** (Scheme II and Table I). In all these cases the cyclization reaction took place via intramolecular capture of the seleniranium cation intermediate by the oxygen atom of the enolic form of the starting ketones.

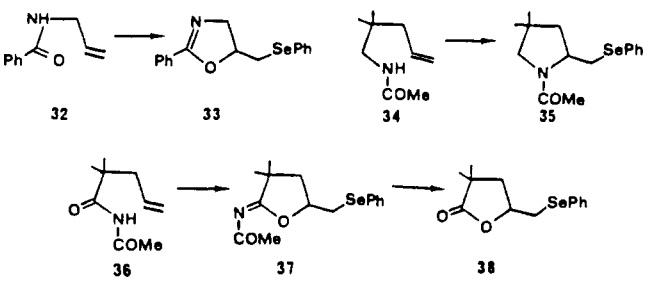
In situ generated hydroxy groups, as in the addition of alcohols to carbonyl compounds, can also participate in phenylselenoetherification type reactions.[16] The results obtained from these kinds of experiments are summarized in Scheme III and in the table. In the reaction of 5-hexen-2-one, **17**, with PhSeSePh and ammonium peroxydisulfate in methanol (method A), participation of the solvent-induced cyclization gave the five-membered ring product **18**, as a mixture of two diastereoisomers which were not separated. In this case the product of methoxyphenylselenenylation of the double bond, **19**, was also formed. A similar ring-closure reaction also occurred in the case of the β-ketoester **13c**, which afforded **20**, as a mixture of diastereoisomers, which could not be separated, but which could be clearly observed by NMR spectroscopy. No cyclization product, **14c**, deriving from the enolic form of **13c** could be observed under these conditions. Thus two completely different ring-closure reactions are taking place selectively, starting from the same compound as a function of the solvent employed.

The reaction of allyl ether, **21**, in acetonitrile and water was selected as an example of hydroxyselenenylation of nonconjugated dienes[17,8] from which cyclic ethers can be

Scheme IV



Scheme V



obtained (Scheme III and Table I). The expected product **22** was indeed obtained in good yield, but this was accompanied by considerable amounts of the product **23**. The formation of this latter compound indicates that, under the conditions employed in the present work, in the second step of the reaction the intramolecular and the intermolecular capture of the seleniranium cation intermediate by the hydroxy group are in competition.

The oxidation of PhSeSePh with ammonium peroxydisulfate was then employed to induce the lactonization of unsaturated acids and esters. The results of these experiments are summarized in Scheme IV and in the table. In the case of 4-pentenoic acid, **24**, the reaction proceeded smoothly in methanol, whereas in the other cases better results were obtained by working in acetonitrile. In every case only γ-lactones were obtained. From the cyclization reactions of **26** and **28**, a single stereoisomer was obtained. On the basis of the assumed S_N2 type mechanism of the intramolecular capture of the seleniranium cation intermediates, structures **27** and **29** were attributed to these compounds. Phenylselenolactonization easily occurred in the case of the malonic ester derivative **30** also. This is not a straightforward reaction. However, lactonization of olefinic carboxylic esters with phenylselenenyl chloride[17,18] and phenylselenenyl triflate[14] have already been reported in the literature.

Finally, some explorative experiments were carried out starting from unsaturated amides and imides. The results obtained are summarized in Scheme V and in the table. From the reaction of the *N*-allylbenzamide, **32**, the dihydrooxazole **33** was obtained in good yield. Under the same conditions the *N*-alkenylacetamide **34** gave the pyrrolidine derivative **35**. The nitrogen atom acts as the nucleophile in this case since the oxygen is unfavorably positioned and its participation would give rise to a seven-membered ring product. Oxygen and nitrogen could in principle compete in the cyclization of the imide **36**. However, the only product observed in this case was the lactone **38**. The formation of this compound can be explained, assuming that the cyclization takes place through

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the oxygen atom to afford the intermediate **37**, which suffers hydrolysis during the workup. This result is not unexpected since closely related selenium-induced cyclizations of *N*-alkylalkenamides afford five-membered cyclic ethers bearing an *exo*-imine substituent.[19]

In conclusion the results described in the present paper indicate that the oxidation of diphenyl diselenide with ammonium peroxydisulfate represents a very simple method of generating phenylselenium cations in the absence of nucleophilic counterions. Most of the cyclization reactions which have been carried out with several types of selenium reagents can be effected with the present method. Thus, this efficient and simple procedure seems to be of general application with considerable advantages over other previously described methods.[20]

Experimental Section

Compounds **1a,c**, **5**, **7**, **9**, **17**, **21**, **24**, **26**, and **28** were commercially available and were used without further purification. Compounds **1b**,[21] **3a**,[22] **3b**,[23] **13a**,[24] **13b**,[25] **13c**,[26] **15**,[27] **30**,[28] **32**,[29] and **34**[30] were prepared as described in the literature. Compounds **13d** and **36** were synthesized as described below. Reaction products were identified by NMR spectroscopy. Proton NMR spectra were recorded on a 90-MHz Varian EM 390 and on a 200-MHz Bruker AC 200 instrument; carbon-13 NMR spectra were recorded at 50.32 MHz on a Bruker AC 200 instrument operating in the Fourier transform mode with proton decoupling throughout. $CDCl_3$ was used as the solvent and TMS as the reference. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. GLC analyses were performed on a Hewlett-Packard 5830 A chromatograph with a 20 in., 10% UCW 982 column. Melting points were determined on a Kofler melting point apparatus and are uncorrected. Silica gel 60 (70–230 mesh) was used for column chromatography and silica gel 60 (230–400 mesh) for flash column chromatography. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254.

2-Benzoyl-4-pentenenitrile (13d). Butyllithium (0.06 mol) was added to a solution of diisopropylamine (0.06 mol) in tetrahydrofuran (30 mL) at 0 °C. Benzoylacetonitrile (0.07 mol) and, after 10 min, allyl bromide (0.08 mol) were added dropwise. The mixture was then stirred at 50 °C for 3 h. The progress of the reaction was monitored by TLC.

After the usual workup, column chromatography with a mixture of petroleum ether and ether (98:2) gave **13d** (33%): ^{1}H NMR δ 8.0–7.9 (m, 2 H), 7.7–7.4 (m, 3 H), 5.85 (ddt, 1 H, J = 7.0, 10.1 and 17.0 Hz), 5.3–5.15 (m, 2 H), 4.42 (dd, 1 H, J = 6.1 and 7.9 Hz), 2.9–2.6 (m, 2 H); ^{13}C NMR δ 189.9, 134.4, 134.1, 131.9, 129.0, 128.7, 119.6, 116.7, 39.6, 33.6. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.82; H, 5.99; N, 7.56. Found: C, 77.74; H, 6.05; N, 7.63.

***N*-(1-Oxo-2,2-dimethyl-4-pentenyl)acetamide (36).** Acetamide (0.05 mol) in THF (10 mL) was treated with NaH (0.07 mol), and to the resulting mixture was added 2,2-dimethyl-4-pentenoyl chloride[31] (0.05 mol) in THF (10 mL) dropwise at room temperature. The mixture was stirred for 15 h. After the usual workup and column chromatography with chloroform as eluant, compound **36** was obtained (80% yield) as a white solid: mp 118–119 °C; ^{1}H NMR δ 8.96 (br s, 1 H), 5.9–5.6 (m, 1 H), 5.2–5.0 (m, 2 H), 2.5 (s, 3 H), 2.35 (d, 2 H, J = 7.0 Hz), 1.25 (s, 3 H), 1.2 (s, 3 H). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.93; H, 8.81; N, 8.36.

Ring-Closure Reactions. General Procedure. Method A. Diphenyl diselenide (0.01 mol) and ammonium peroxydisulfate (0.012 mol) in MeOH (20 mL) were stirred at reflux for 1–1.5 h. The mixture was cooled at 25 °C, and the alkene (0.02 mol) in MeOH (10 mL) was added dropwise. The progress of the reaction was monitored by TLC. After the usual workup the reaction products were purified by column chromatography or flash column chromatography.

Method B. A mixture of diphenyl diselenide (0.01 mol), ammonium peroxydisulfate (0.012 mol), and the alkene (0.02 mol) in CH_3CN (20 mL) were stirred at room temperature or at 70 °C. The progress of the reaction was monitored by TLC. The reaction mixtures were worked up as described above under method A.

Reaction times and yield are reported in the table. Physical and spectral data of the reaction products are reported below.

2-[(Phenylseleno)methyl]tetrahydrofuran (2a): oil;[6] ^{1}H NMR δ 7.6–7.35 (m, 2 H), 7.3–7.05 (m, 3 H), 4.09 (quintet, 1 H, J = 6.9 Hz), 3.9 (q, 1 H, J = 6.9 Hz), 3.75 (q, 1 H, J = 6.9 Hz), 3.12 (dd, 1 H, J = 5.8 and 12.1 Hz), 2.95 (dd, 1 H, J = 6.9 and 12.1 Hz), 2.15–1.8 (m, 3 H), 1.75–1.5 (m, 1 H); ^{13}C NMR δ 132.65, 129.0, 126.8, 78.4, 68.3, 33.1, 31.6, 26.0.

2-Methyl-5-[(phenylseleno)methyl]tetrahydrofuran (2b): oil;[6] ^{1}H NMR δ 7.65–7.55 (m, 4 H), 7.35–7.2 (m, 6 H), 4.4–4.0 (m, 4 H), 3.35–2.55 (m, 4 H), 2.3–1.95 (m, 4 H), 1.85–1.45 (m, 4 H), 1.35 (d, 3 H, J = 7.0 Hz), 1.3 (d, 3 H, J = 7.0 Hz); ^{13}C NMR δ 132.55, 132.5, 130.6, 129.0, 126.7, 78.55, 77.9, 76.0, 75.3, 34.0, 33.55, 33.5, 33.0, 32.3, 31.5, 21.4, 21.2.

5,5-Dimethyl-2-[(phenylseleno)methyl]tetrahydrofuran (2c): oil; ^{1}H NMR δ 7.6–7.5 (m, 2 H), 7.3–7.15 (m, 3 H), 4.3–4.1 (m, 1 H), 3.15 (dd, 1 H, J = 4.8 and 12.0 Hz), 2.95 (dd, 1 H, J = 7.6 and 12.0 Hz), 2.2–2.0 (m, 1 H), 1.9–1.6 (m, 3 H), 1.3 (s, 3 H), 1.2 (s, 3 H); ^{13}C NMR δ 132.4, 128.9, 126.6, 81.4, 77.8, 38.4, 33.7, 31.8, 29.1, 28.0. Anal. Calcd for $C_{13}H_{18}OSe$: C, 57.99; H, 6.74. Found: C, 58.06; H, 6.62.

2-Methyl-5-[1-methyl-1-(phenylseleno)ethyl]tetrahydrofuran (4a): oil; ^{1}H NMR δ 7.65–7.5 (m, 2 H), 7.3–7.15 (m, 3 H), 3.9–3.6 (m, 1 H), 3.1 (dd, 1 H, J = 6.7 and 13.4 Hz), 2.1–1.8 (m, 2 H), 1.65–1.5 (m, 2 H), 1.45 (s, 3 H), 1.3 (s, 3 H), 1.1 (d, 3 H, J = 7.0 Hz); ^{13}C NMR δ 138.4, 134.4, 129.9, 128.4, 128.3, 86.3, 75.6, 35.7, 33.3, 31.8, 30.6, 29.6, 28.9, 26.5, 25.8, 22.3, 20.9. Other absorptions (134.1, 128.9, 127.3, 127.0, 66.3, 66.0, 52.4, 52.0, 27.7, 26.7, 23.7, 22.5, 19.4) are probably due to the tetrahydropyran-type phenylseleno ether. Anal. Calcd for $C_{14}H_{20}OSe$: C, 59.36; H, 7.12. Found: C, 59.24; H, 7.17.

2,2-Dimethyl-5-[1-methyl-1-(phenylseleno)ethyl]tetrahydrofuran (4b): oil;[6] ^{1}H NMR δ 7.7–7.55 (m, 2 H), 7.3–7.1 (m, 3 H), 3.9 (t, 1 H, J = 7.3 Hz), 2.0–1.9 (m, 2 H), 1.75–1.6 (m, 2 H), 1.35 (s, 3 H), 1.3 (s, 3 H), 1.25 (s, 3 H), 1.2 (s, 3 H); ^{13}C NMR δ 138.5, 134.4, 128.4, 128.3, 85.3, 81.0, 49.7, 38.7, 28.6, 28.2, 27.8, 26.4, 25.9.

2-[(Phenylseleno)methyl]tetrahydro-2*H*-pyran (8): oil;[6] ^{1}H NMR δ 7.6–7.35 (m, 2 H), 7.3–7.05 (m, 3 H), 4.2–3.9 (m, 1 H), 3.55–3.35 (m, 2 H), 3.05 (dd, 1 H, J = 6.8 and 12.1 Hz), 2.9 (dd, 1 H, J = 5.8 and 12.1 Hz), 2.0–1.0 (m, 6 H); ^{13}C NMR δ 132.4, 130.9, 128.9, 126.6, 77.1, 68.6, 33.7, 31.7, 25.8, 23.3.

2,3-Dihydro-2-[(phenylseleno)methyl]benzofuran (10): mp 63–64 °C.[32] ^{1}H NMR δ 7.6–7.4 (m, 2 H), 7.3–7.15 (m, 3 H), 7.15–7.0 (m, 2 H), 6.85–6.65 (m, 2 H), 5.1–4.7 (m, 1 H), 3.35–3.32 (m, 2 H), 3.1–2.85 (m, 2 H); ^{13}C NMR δ 159.1, 132.9, 129.4, 129.1, 128.0, 127.1, 126.1, 124.9, 120.45, 109.4, 81.8, 35.4, 32.6.

2-[2-Methoxy-3-(phenylseleno)propyl]phenol (11): oil; ^{1}H NMR δ 8.05 (s, 1 H), 7.6–7.45 (m, 2 H), 7.3–7.2 (m, 3 H), 7.2–6.7

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(m, 4 H), 3.72–3.68 (m, 1 H), 3.35 (s, 3 H), 3.15 (dd, 1 H, J = 4.0 and 12.5 Hz), 3.0 (d, 2 H, J = 5.0 Hz), 2.85 (dd, 1 H, J = 8.4 and 12.5 Hz); ^{13}C NMR δ 155.9, 133.1, 131.7, 129.2, 128.5, 127.4, 124.3, 120.2, 117.2, 83.4, 57.4, 36.9, 29.8. Anal. Calcd for $C_{16}H_{18}O_2Se$: C, 59.82; H, 5.65. Found: C, 59.90; H, 5.76.

2-[3-Methoxy-2-(phenylseleno)propyl]phenol (12): oil; ^{1}H NMR δ 7.65–7.45 (m, 2 H), 7.35–7.2 (m, 3 H), 7.2–7.05 (m, 3 H), 6.95–6.8 (m, 2 H), 3.6–3.45 (m, 3 H), 3.4 (s, 3 H), 3.2–3.05 (m, 2 H); ^{13}C NMR δ 155.2, 134.5, 131.3, 129.1, 128.4, 127.7, 124.4, 120.4, 116.7, 73.8, 58.6, 44.2, 32.6. Anal. Calcd for $C_{16}H_{18}O_2Se$: C, 59.82; H, 5.65. Found: C, 59.74; H, 5.74.

3-Acetyl-4,5-dihydro-2-methyl-5-[(phenylseleno)methyl]furan (14a): oil; ^{1}H NMR δ 7.6–7.45 (m, 2 H), 7.35–7.2 (m, 3 H), 4.77 (ddt, 1 H, J = 5.6, 7.2, and 10.1 Hz), 3.2 (dd, 1 H, J = 5.6 and 12.6 Hz), 3.02 (dd, 1 H, J = 7.2 and 12.6 Hz), 3.08 (ddq, 1 H, J = 1.5, 10.1, and 14.3 Hz), 2.74 (ddq, 1 H, J = 1.5, 7.2, and 14.3 Hz), 2.16 (s, 3 H), 2.14 (t, 3 H, J = 1.5 Hz); ^{13}C NMR δ 194.1, 167.0, 133.2, 129.1, 127.4, 111.7, 81.1, 36.1, 32.6, 29.2, 14.8. Anal. Calcd for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46. Found: C, 57.08; H, 5.35.

3-Benzoyl-4,5-dihydro-2-phenyl-5-[(phenylseleno)methyl]furan (14b): oil; ^{1}H NMR δ 7.65–7.50 (m, 2 H), 7.48–7.4 (m, 2 H), 7.30–6.95 (m, 11 H), 5.02 (ddt, 1 H, J = 5.5, 7.2, and 9.8 Hz), 3.45 (dd, 1 H, J = 9.8 and 15.2 Hz), 3.4 (dd, 1 H, J = 5.5 and 12.6 Hz), 3.2 (dd, 1 H, J = 7.2 and 12.6 Hz), 3.12 (dd, 1 H, J = 7.2 and 15.2 Hz); ^{13}C NMR δ 193.2, 165.0, 139.1, 133.3, 131.1, 130.0, 129.9, 129.3, 129.2, 128.9, 127.7, 127.6, 127.4, 111.7, 81.0, 38.7, 32.7. Anal. Calcd for $C_{24}H_{20}O_2Se$: C, 68.74; H, 4.81. Found: C, 68.63; H, 4.90.

3-Carbomethoxy-4,5-dihydro-2-methyl-5-[(phenylseleno)methyl]furan (14c): oil; ^{1}H NMR δ 7.6–7.45 (m, 2 H), 7.3–7.2 (m, 3 H), 4.76 (ddt, 1 H, J = 5.7, 7.1, and 10.1 Hz), 3.7 (s, 3 H), 3.19 (dd, 1 H, J = 5.7 and 12.5 Hz), 3.1 (ddq, 1 H, J = 1.3, 10.1, and 14.4 Hz), 2.99 (dd, 1 H, J = 7.1 and 12.5 Hz), 2.68 (ddq, 1 H, J = 1.3, 7.1, and 14.4 Hz), 2.12 (t, 3 H, J = 1.3 Hz); ^{13}C NMR δ 167.5, 166.1, 137.6, 137.3, 133.0, 129.0, 127.2, 101.3, 81.0, 50.6, 35.4, 32.6, 13.9. Anal. Calcd for $C_{14}H_{16}O_3Se$: C, 54.03; H, 5.18. Found: C, 54.15; H, 5.23.

3-Cyano-4,5-dihydro-2-phenyl-5-[(phenylseleno)methyl]furan (14d): oil; ^{1}H NMR δ 7.9–7.8 (m, 2 H), 7.6–7.5 (m, 2 H), 7.45–7.3 (m, 3 H), 7.3–7.2 (m, 3 H), 4.96 (ddt, 1 H, J = 5.4, 7.4, and 10.0 Hz), 3.28 (dd, 1 H, J = 5.4 and 12.8 Hz), 3.19 (dd, 1 H, J = 10.0 and 14.9 Hz), 3.06 (dd, 1 H, J = 7.4 and 12.8 Hz), 2.85 (dd, 1 H, J = 7.4 and 14.9 Hz); ^{13}C NMR δ 166.2, 133.4, 131.2, 129.2, 128.7, 128.5, 127.6, 127.0, 117.2, 96.1, 82.0, 37.2, 32.0. Anal. Calcd for $C_{18}H_{15}NOSe$: C, 63.54; H, 4.44; N, 4.12. Found: C, 63.63; H, 4.55; N, 4.04.

2-[Dihydro-5-[(phenylseleno)methyl]-2(3*H*)-furanylidene]acetic acid methyl ester (16): oil;[33] ^{1}H NMR δ 7.56–7.46 (m, 2 H), 7.3–7.15 (m, 3 H), 5.26 (t, 1 H, J = 1.8 Hz), 4.55 (ddt, 1 H, J = 5.4, 6.75, and 7.2 Hz), 3.64 (s, 3 H), 3.3 (dddd, 1 H, J = 1.8, 4.5, 9.0, and 18.0 Hz), 3.2 (dd, 1 H, J = 5.4 and 12.6 Hz), 2.95 (dd, 1 H, J = 7.2 and 12.6 Hz), 2.9 (ddt, 1 H, J = 1.8, 9.0, and 18.0 Hz), 2.25 (dddd, 1 H, J = 4.5, 6.75, 9.0, and 13.5 Hz), 1.82 (ddt, 1 H, J = 6.75, 9.0, and 13.5 Hz); ^{13}C NMR δ 175.7, 168.6, 133.0, 129.1, 127.3, 89.5, 82.9, 50.4, 31.4, 30.2, 29.1.

2-Methoxy-2-methyl-5-[(phenylseleno)methyl]tetrahydrofuran (18): oil; ^{1}H NMR δ 7.6–7.45 (m, 4 H), 7.3–7.15 (m, 6 H), 4.4–4.2 (m, 2 H), 3.3–2.9 (m, 4 H), 3.25 (s, 3 H), 3.2 (s, 3 H), 2.3–1.6 (m, 8 H), 1.45 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR δ 132.7, 132.6, 130.4, 130.0, 129.0, 128.9, 126.8, 126.7, 108.0, 107.9, 79.8, 77.7, 48.5, 48.4, 38.9, 37.7, 34.3, 33.2, 31.0, 30.3, 21.5, 21.4. Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.36. Found: C, 54.68; H, 6.43.

5-Methoxy-6-(phenylseleno)-2-hexanone (19): oil; ^{1}H NMR δ 7.55–7.45 (m, 2 H), 7.3–7.15 (m, 3 H), 3.4–3.3 (m, 1 H), 3.27 (s, 3 H), 3.09 (dd, 1 H, J = 5.0 and 12.4 Hz), 2.94 (dd, 1 H, J = 6.7 and 12.4 Hz), 2.47 (t, 2 H, J = 7.3 Hz), 2.1 (s, 3 H), 1.8 (dt, 2 H, J = 7.3 and 14.6 Hz); ^{13}C NMR δ 207.8, 132.8, 130.5, 129.1, 127.0, 79.6, 56.8, 39.1, 31.5, 29.7, 27.9. Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.36. Found: C, 54.87; H, 6.42.

3-Carbomethoxy-2-methoxy-2-methyl-5-[(phenylseleno)methyl]tetrahydrofuran (20): oil; ^{1}H NMR δ 7.55–7.4 (m, 4 H), 7.3–7.15 (m, 6 H), 4.45–4.15 (m, 2 H), 3.7 (s, 6 H), 3.3–2.6 (m, 6 H), 3.2 (s, 3 H), 3.15 (s, 3 H), 2.4–2.3 (m, 1 H), 1.95–1.8 (m, 1 H), 1.55 (s, 6 H); ^{13}C NMR δ 170.3, 133.1, 132.8, 132.7, 129.1, 129.0, 127.0, 126.9, 107.3, 106.9, 81.0, 78.0, 76.2, 55.2, 54.1, 51.8, 48.7, 48.4, 35.4, 34.3, 33.4, 33.1, 32.6, 32.1, 20.7, 20.2, 13.9. Anal. Calcd for $C_{15}H_{20}O_4Se$: C, 52.49; H, 5.87. Found: C, 52.40; H, 5.96.

2,5-Bis[(phenylseleno)methyl]-1,4-dioxane (22): oil;[17] ^{1}H NMR δ 7.55–7.4 (m, 2 H), 7.3–7.15 (m, 3 H), 4.1–3.4 (m, 3 H), 3.25–2.7 (m, 2 H); ^{13}C NMR δ 132.9, 132.7, 129.1, 127.0, 75.1, 70.1, 69.9, 69.0, 28.2, 27.9.

Bis[2-hydroxy-3-(phenylseleno)-1-propyl] ether (23): oil; ^{1}H NMR δ 7.6–7.45 (m, 2 H), 7.3–7.15 (m, 3 H), 4.0–3.2 (m, 5 H), 3.05–2.95 (m, 1 H); ^{13}C NMR δ 134.5, 132.7, 129.0, 127.8, 127.1, 74.2, 73.9, 72.3, 72.2, 72.1, 72.0, 69.5, 69.4, 63.5, 63.4, 63.3, 46.4, 46.2, 31.7. Anal. Calcd for $C_{18}H_{22}O_3Se_2$: C, 48.66; H, 4.99. Found: C, 48.58; H, 5.05.

Dihydro-5-[(phenylseleno)methyl]-2(3*H*)-furanone (25): mp 44–46 °C; (lit.[34] mp 46–47.7 °C); ^{1}H NMR δ 7.6–7.45 (m, 2 H), 7.3–7.2 (m, 3 H), 4.65 (ddt, 1 H, J = 4.9, 6.6, and 7.8 Hz), 3.25 (dd, 1 H, J = 4.9 and 12.8 Hz), 3.0 (dd, 1 H, J = 7.8 and 12.8 Hz), 2.6–2.3 (m, 3 H), 2.05–1.85 (m, 1 H); ^{13}C NMR δ 176.2, 133.2, 129.3, 129.0, 127.6, 79.2, 32.0, 28.6, 27.6.

Dihydro-5-ethyl-4-(phenylseleno)-2(3*H*)-furanone (27): oil;[35] ^{1}H NMR δ 7.6–7.5 (m, 2 H), 7.35–7.2 (m, 3 H), 4.3 (dt, 1 H, J = 4.3 and 7.6 Hz), 3.51 (dt, 1 H, J = 7.0 and 8.5 Hz), 2.92 (dd, 1 H, J = 8.5 and 18.0 Hz), 2.54 (dd, 1 H, J = 8.5 and 18.0 Hz), 1.9–1.5 (m, 2 H), 0.95 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 174.1, 135.6, 129.3, 128.6, 126.2, 86.8, 38.4, 36.2, 26.6, 9.4.

3-Oxo-8-(phenylseleno)-2-oxabicyclo[3.3.0]octane (29): oil;[34] ^{1}H NMR δ 7.6–7.45 (m, 2 H), 7.35–7.2 (m, 3 H), 4.85 (d, 1 H, J = 7.0 Hz), 3.95–3.8 (m, 1 H), 3.15–3.0 (m, 1 H), 2.8 (dd, 1 H, J = 10.0 and 17.0 Hz), 2.4–2.1 (m, 3 H), 1.95–1.7 (m, 1 H), 1.65–1.45 (m, 1 H); ^{13}C NMR δ 176.3, 133.5, 129.1, 128.6, 127.6, 90.3, 46.1, 37.0, 35.6, 32.2, 30.1.

Dihydro-3-carbomethoxy-5-[(phenylseleno)methyl]-2-(3*H*)-furanone (31): oil; ^{1}H NMR δ 7.6–7.5 (m, 2 H), 7.35–7.2 (m, 3 H), 4.85 (dddd, 1 H, J = 4.7, 6.5, 6.9, and 8.6 Hz), 3.82 (s, 3 H), 3.68 (dd, 1 H, J = 5.2 and 9.5 Hz), 3.26 (dd, 1 H, J = 4.7 and 12.9 Hz), 3.04 (dd, 1 H, J = 8.6 and 12.9 Hz), 2.78 (ddd, 1 H, J = 5.2, 6.9, and 13.3 Hz), 2.21 (ddd, 1 H, J = 6.5, 9.5, and 13.3 Hz); 7.6–7.5 (m, 2 H), 7.35–7.2 (m, 3 H), 4.56 (dddd, 1 H, J = 4.7, 6.5, 7.7, and 8.6 Hz), 3.78 (s, 3 H), 3.62 (dd, 1 H, J = 9.5 and 10.3 Hz), 3.26 (dd, 1 H, J = 4.7 and 12.9 Hz), 3.02 (dd, 1 H, J = 7.7 and 12.9 Hz), 2.67 (ddd, 1 H, J = 6.5, 9.5, and 12.9 Hz), 2.40 (ddd, 1 H, J = 8.6, 10.3, and 12.9 Hz); ^{13}C NMR δ 170.8, 167.9, 133.3, 133.2, 129.3, 128.7, 127.7, 78.5, 78.1, 52.9, 52.8, 47.0, 46.6, 31.8, 31.4, 31.2. Anal. Calcd for $C_{13}H_{14}O_4Se$: C, 49.86; H, 4.51. Found: C, 49.95; H, 4.45.

2-Phenyl-5-[(phenylseleno)methyl]-4,5-dihydrooxazole (33): oil; ^{1}H NMR δ 7.9–7.8 (m, 2 H), 7.6–7.2 (m, 8 H), 4.83 (dddd, 1 H, J = 5.5, 6.9, 7.4, and 9.4 Hz), 4.12 (dd, 1 H, J = 9.4 and 15.0 Hz), 3.78 (dd, 1 H, J = 6.9 and 15.0 Hz), 3.24 (dd, 1 H, J = 5.5 and 12.7 Hz), 3.0 (dd, 1 H, J = 7.4 and 12.7 Hz); ^{13}C NMR δ 163.4, 133.2, 131.0, 129.0, 128.9, 128.1, 128.0, 127.6, 127.2, 78.7, 60.2, 31.8. Anal. Calcd for $C_{16}H_{15}NOSe$: C, 60.77; H, 4.78; N, 4.43. Found: C, 60.69; H, 4.86; N, 4.37.

***N*-Acetyl-2-[(phenylseleno)methyl]-4,4-dimethylpyrrolidine (35)**: oil;[30] ^{1}H NMR δ 7.55–7.45 (m, 2 H), 7.3–7.1 (m, 3 H), 4.33 (dddd, 1 H, J = 3.1, 7.3, 8.3, and 10.4 Hz), 3.44 (dd, 1 H, J = 3.1 and 12.5 Hz), 3.30 (dd, 1 H, J = 7.3 and 12.5 Hz), 3.18 (d, 1 H, J = 10.4 Hz), 3.12 (dd, 1 H, J = 1.24 and 10.4 Hz), 1.92 (ddd, 1 H, J = 1.24, 8.3, and 13.5 Hz), 1.82 (s, 3 H), 1.66 (dd, 1 H, J = 10.4 and 13.5 Hz), 1.12 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR δ 169.3, 133.7, 131.7, 128.8, 126.3, 61.3, 56.4, 44.9, 37.6, 31.4, 26.4, 25.7, 22.7.

Dihydro-3,3-dimethyl-5-[(phenylseleno)methyl]-2(3*H*)-furanone (38): oil; ^{1}H NMR δ 7.6–7.48 (m, 2 H), 7.35–7.2 (m, 3 H), 4.58 (dddd, 1 H, J = 5.2, 6.0, 7.5, and 9.7 Hz), 3.28 (dd, 1 H, J = 5.2 and 12.7 Hz), 3.02 (dd, 1 H, J = 7.5 and 12.7 Hz), 2.28 (dd, 1 H, J = 6.0 and 12.8 Hz), 1.8 (dd, 1 H, J = 9.7 and 12.8 Hz), 1.26 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR δ 180.7, 132.7, 129.0, 128.8, 127.2, 75.3, 42.9, 40.2, 31.8, 24.7, 24.3. Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.69. Found: C, 55.18; H, 5.75.

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Registry No. **1a**, 821-09-0; **1b**, 626-94-8; **1c**, 16744-89-1; **2a**, 65539-72-2; *cis*-**2b**, 113423-56-6; *trans*-**2b**, 113423-55-5; **2c**, 123883-67-0; **3a**, 1569-60-4; **3b**, 6090-15-9; *cis*-**4a**, 123883-68-1; *trans*-**4a**, 123883-69-2; **4b**, 114524-31-1; **5**, 625-31-0; **6**, 123883-70-5; **7**, 821-41-0; **8**, 75526-73-7; **9**, 1745-81-9; **10**, 66558-11-0; **11**, 123883-71-6; **12**, 123883-72-7; **13a**, 3508-78-9; **13b**, 59875-97-7; **13c**, 3897-04-9; **13d**, 123883-65-8; **14a**, 123883-73-8; **14b**, 123883-74-9; **14c**, 123883-75-0; **14d**, 123883-76-1; **15**, 30414-57-4; **16**, 76877-75-3; **17**, 109-49-9; *cis*-**18**, 123883-77-2; *trans*-**18**, 123883-78-3; **19**, 123883-79-4; **20**, 123883-80-7; **21**, 557-40-4; **22**, 75456-42-7; **23**, 123883-81-8; **24**, 591-80-0; **25**, 65234-93-7; **26**, 4219-24-3; **27**, 123883-82-9; **28**, 13668-61-6; **29**, 65234-92-6; **30**, 40637-56-7; *cis*-**31**, 123883-83-0; *trans*-**31**, 123883-84-1; **32**, 10283-95-1; **33**, 123883-85-2; **34**, 101347-54-0; **35**, 101347-60-8; **36**, 123883-66-9; **38**, 123883-86-3; $PhSe^{+}SO_4^{-}$, 123883-87-4; benzoylacetonitrile, 614-16-4; allyl bromide, 106-95-6; acetamide, 60-35-5; 2,2-dimethyl-4-pentenoyl chloride, 39482-46-7; diphenyl diselenide, 1666-13-3.

Reaction of 4-Substituted 2-Azetidinone with Nucleophiles. Existence and Reactivity of 1-Azetin-4-one

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Reaction of 4-acetoxy- or 4-sulfo-2-azetidinone with nucleophiles in the presence of a base has proven to be an elimination-addition process. Intermediate in this process is 1-azetin-4-one, whose free existence in solution, as well as its reactivity and stability, is shown in comparison with a five-member-ring counterpart. A new method for UV determinations of transient species is also described, showing its application to the elusive intermediate.

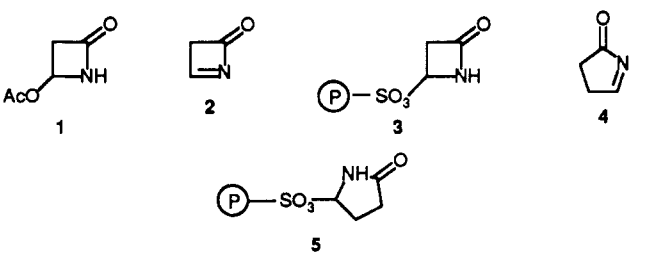
In our research about reactive heterocyclic intermediates[1] we were interested in studying the mechanism of substitution reaction of 4-acetoxy-2-azetidinone (**1**, Chart I) with nucleophiles. This is a very useful reaction in the preparation of a number of antibiotic compounds.[2] 1-Azetin-4-one (**2**) has been postulated by several authors as intermediate in the reactions of azetidin-2-ones in which substituents at position 4 are formally substituted by nucleophiles.[2a,3] In these reactions, the thermodynamic product is always formed, suggesting the reaction proceeds through a planar intermediate. Postulated azetinones of type **2** were also trapped by butadienes.[3b]

If intermediate **2** does exist, the reactions of β-lactams as **1** with nucleophiles will be not a substitution but an elimination-addition process. Thus, the first step in our work was to prepare an adequate precursor from which **2** could be easily obtained. This precursor, similar to **1**, was the polymer-bound 2-azetidinone, **3**.

Results and Discussion

Synthesis of Precursor 3. The synthesis of 4-polymeric sulfonate 2-azetidinone, **3**, was carried out by reaction between the sodium salt of polymeric sulfonic acid and 4-acetoxy-2-azetidinone (**1**). Polymeric sulfonic acid was prepared by hydrolysis of 20% cross-linked chlorosulfonated resin.[4] **3**: IR 1760, 1660, 1630, 1410, 1220-1180 cm^{-1}. Analysis indicated 0.16 mequiv azetidinone/g.

Chart I



The ability of **3** to act as a nonpolymeric analogue of **1**, was checked by reaction with sodium phenoxide. In the same conditions as the ones used by Clauss et al. for 4-acetoxy-2-azetidinone,[5] 4-phenoxy-2-azetidinone was obtained.

Three-Phase Test. The existence and reactivity of 1-azetin-4-one, **2**, was established by using the three-phase test.[4] As trapping agent, a nucleophilic polymer, **6**, was used; **6** was synthesized as shown in Scheme I. The Merrifield's resin reacted with *p*-hydroxybenzoic acid in the presence of triethylamine to give the polymeric ester **6** (IR 3000, 1700, 1600, 1450, 1370, 1260 cm^{-1}).

Polymer **6** was able to react with **1** in the presence of NaOH, as did their nonpolymeric counterparts, yielding **7** (Scheme I). Transesterification of **7** with dimethyl aminoethanol in DMF and then ethanol gave **8** (yield: 80%), identical with the compound obtained by reaction between **1** and *p*-hydroxybenzoic acid ethyl ester. This last reaction gave two different products depending on time. If the reaction time was short (less than 1 h) the product obtained was **8**. But if the reaction time was longer this product experienced a hydrolysis, yielding the acid **9**, after neutralization; **9** could also be obtained from **7** when ethanol was substituted by water during transesterification.

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