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ORGANOSELENIUM-INDUCED CYCLIZATIONS IN ORGANIC SYNTHESIS

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Abstract—A number of organoselenium reagents are introduced as efficient initiators of ring closures leading from unsaturated substrates to lactones, cyclic ethers, cyclic thioethers, N-heterocycles and carbocycles. These cyclizations often proceed with high ring selectivity and stereoselectivity and are accompanied by the incorporation of the phenylseleno group (PhSe) into the final product. Methods are described for the effective removal of this group (PhSe) by oxidation or reduction achieving unsaturation or saturation. Finally the successful application of this Se-based methodology to the synthesis of stable and biologically active prostacyclins is outlined. Representative experimental procedures are included.

In recent times organoselenium chemistry became a very powerful tool in organic synthesis.[1] Of particular importance is the phenylseleno (PhSe) group owing to its rather fertile and easily manipulated nature. Two of the most common and useful transformations of this group are its oxidative and reductive removal to introduce unsaturation and saturation respectively. In these and other organoselenium-based operations the first stratagem is, of course, the introduction of the PhSe group into the organic substrate. For these reasons the design of new reactions and reagents for introducing this group into organic structures became a very important and desirable direction of research in our laboratories in recent years. As a result, a series of organoselenium-based reactions and a number of novel organoselenium reagents were discovered. In this article, we present new synthetic methodology which combines introduction of the PhSe group into organic molecules with simultaneous construction of cyclic systems often with a high degree of regio- and stereoselectivity. Applications to the synthesis of complex biologically active molecules are also included.

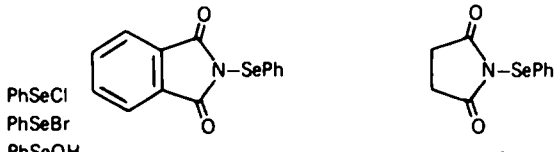
RESULTS AND DISCUSSION

Unsaturated substrates (I Scheme 1) carrying internal nucleophiles (NuX = COOH, OH, SH, SAc, NHCOOEt, CH_2SnMe_3) were found to react smoothly with certain organoselenium reagents according to Scheme 1 to afford cyclic systems (II).

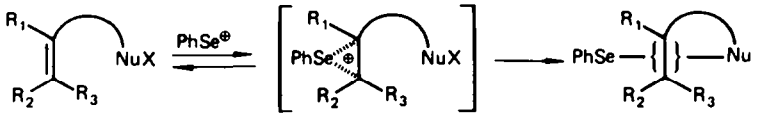
The first reagent to be used in this connection was the commercially available phenylselenenyl chloride, although phenylselenenylbromide also performs similarly in these reactions. Among the various types of cyclic systems to be synthesized according to this general methodology are lactones, ethers, thioethers, nitrogen heterocycles and carbocycles. The synthesis of these classes of compounds and the utilization of the new organoselenium reagents, N-phenylselenophthalimide (N-PSP), N-phenylselenosuccinimide (N-PSS) and phenylselenenic acid (Scheme 2) together with some applications of this selenium-based technology to the construction of biologically active prostacyclins are discussed separately below.

A. *Synthesis of Lactones*

The phenylselenolactonization reaction.[2] The phenylselenolactonization of suitably unsaturated carboxylic acids is illustrated in Scheme 3 for the case of 4-cycloheptene-1-carboxylic acid (**1**) reacting with PhSeCl in methylene chloride at $-78°$ to afford the phenylselenolactone **1a** in quantitative yield. This fast reaction proceeds in the absence or presence of base such as triethylamine, pyridine or anhydrous potassium car-



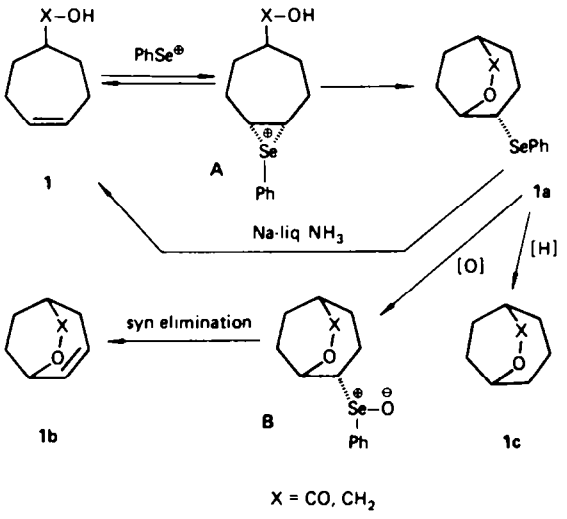
Scheme 2. Organoselenium reagents for cyclizations.



NuX = COOH, OH, SH, SAc, NHCOOEt, CH_2SnMe_3

Scheme 1. Organoselenium-induced cyclizations.

†K. C. Nicolaou is a Fellow of the A. P. Sloan Foundation, 1979–1983 and a recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985.



Scheme 3. Organoselenium-based synthesis of O-heterocycles (lactones and cyclic ethers).

bonate, the choice depending on the particular case. The initial step of this facile cyclization is presumed to be the reversible electrophilic addition of phenylselenonium ion ($PhSe^{\oplus}$) to the double bond of **1** leading to the reactive intermediate **A** which subsequently suffers intramolecular reaction (interception of the positive center by the carboxylic group) furnishing the observed product, phenylselenolactone **1a**. Based on a presumed S_N2 mode of capture of the selenonium ion and by analogy to the related halolactonization reaction, the stereochemistry of the phenylselenolactones was assumed to be *trans*, an assumption verified by an X-ray crystallographic analysis of lactone **8a**[2a] (Table 1).

The generality of this new lactonization method has been demonstrated by a series of unsaturated carboxylic acids undergoing smooth phenylselenolactonization furnishing the corresponding phenylselenolactones in good to excellent yield as indicated in Table 1. In general, the ring closure occurs at the carbon able to sustain the most stable carbonium ion, although subsequent rearrangements are possible. It also appears that 5-membered lactones are preferred over 4- and 6-membered and 6-

Table 1. Phenylselenolactonizations and useful transformation of the products

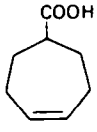
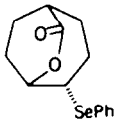
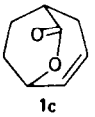
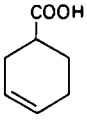
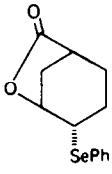
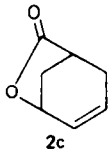
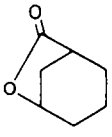
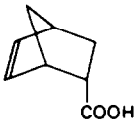
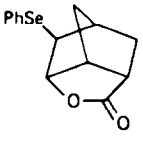
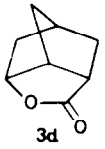
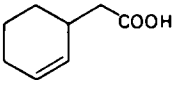
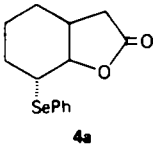
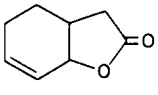
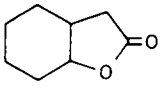
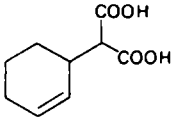
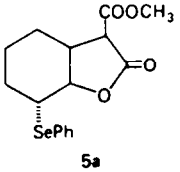
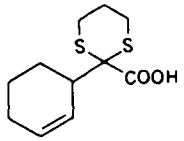
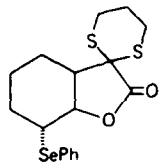
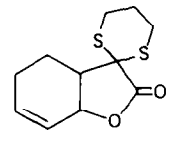
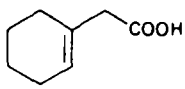
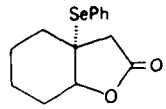
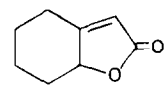
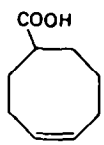
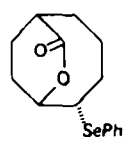
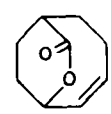
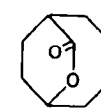
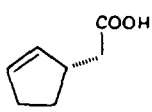
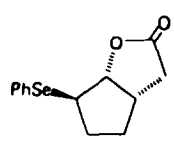
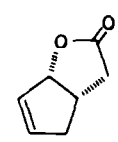
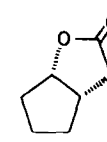
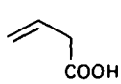
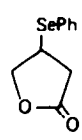
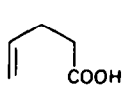
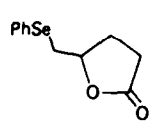
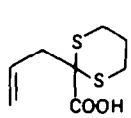
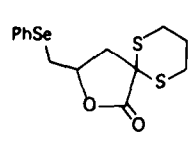
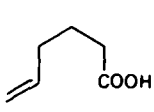
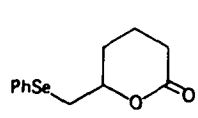
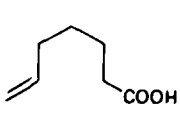
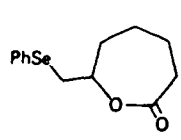
Entry	Unsaturated acid	Reversal yield (percent)	Cyclization product	M.p. (°C)	Yield (percent)	Oxidation product	Yield (percent)	Reduction product	Yield (percent)
1		82	 **1a**	71–71.5	100	 **1c**	90	 **1d**	85,[a] 88[b]
2		77	 **2a**	91–92	90	 **2c**	81	 **2d**	80[a]
3		78	 **3a**	102.5–103.5	95			 **3d**	83,[a] 89[b]
4			 **4a**		93	 **4c**	92	 **4d**	76[a]
5			 **5a**		90				

Table 1 (*Contd*)

Entry	Unsaturated acid	Reversal yield (percent)	Cyclization product	M.p. (°C)	Yield (percent)	Oxidation product	Yield (percent)	Reduction product	Yield (percent)
6			 **6a**	113.5–114.5	98	 **6c**	82	**4d**	73[a]
7			 **7a**	78.5–79	91	 **7c**	87		84 ; 85[c]
8			 **8a**	68–67	93	 **8c**	85	 **8d**[36]	86[b]
9			 **9a**		95	 **9c**	92	 **9d**	97[b]
10			 **10a**		35				
11			 **11a**	46–47.7	80				
12			 **12a**		75				
13			 **13a**		74				
14			 **14a**		70				

[a] Reduction method A (Ra-Ni / H_2). [b] Reduction method B (n-Bu_3SnH).

and 7- are preferred over 7- and 8-membered respectively.

The useful chemical properties of the phenylseleno group was one of the most important and guiding considerations for developing these organoselenium-induced ring closures. One of this group's most versatile and useful transformations is the synthesis of olefins by oxidation. When this process was applied to the phenylselenolactones obtained from the cyclization reactions a series of unsaturated lactones were obtained in good to excellent yields (**1a** → **1b**, Scheme 3, Table 1). The oxidations were carried out with hydrogen peroxide, ozone, chloramine T or *m*-chloroperbenzoic acid and the selenoxides so obtained were allowed to decompose at ambient temperatures in the absence or presence of base such as triethylamine or diisopropylamine.[3] In all cases examined the syn elimination of the phenylselenoxide occurred selectively away from oxygen. This strong directing effect of the oxygen on these eliminations could be explained by the polar nature of the selenoxide function which will tend to align itself antiparallel to the oxygen lone pairs in order to minimize repulsion.[4]

Another very attractive feature of the phenylseleno group is its ability to be reductively removed from organic substrates. This property enhances the usefulness of the phenylselenolactonization reaction for synthetic purposes since this operation converts phenylselenolactones to saturated lactones. Hydrogenolysis of the C-Se bond occurs rapidly with Raney Ni catalyst at room temperature (**1a** → **1c**, Scheme 3, Table 1). The phenylseleno group can also be removed by a milder and more selective method involving tri-*n*-butyltin hydride in toluene at *ca.* 110° in the presence of a radical initiator (azobisisobutyronitrile, AIBN) (**1a** → **1c**, Scheme 3, Table 1).

The phenylselenolactonization reaction can be reversed giving back the starting unsaturated carboxylic acids (e.g. with Na-liqNH_3) thus enhancing even further the power and utility of this methodology (**1a** → **1** Scheme 3, Table 1).

The usefulness of this technology has been demonstrated by the preparation of advanced intermediates for prostaglandin synthesis and the construction of complex molecules in the prostacyclin series.[2a]

B. *Synthesis of cyclic ethers*

The phenylselenoetherification reaction.[5] Several methods have been used in the past[6] for the synthesis of cyclic ethers including the manipulation of furan derivatives and the utilization of unsaturated hydroxy compounds in ring closure reactions induced by oxygen, halogen, mercury, lead and thallium reagents. The majority of these methods, however, suffer from lack of generality, from the drastic nature of some of the reagents and conditions and also from severe limitations in elaborating the products to useful synthetic intermediates and targets. The haloetherification reaction is clearly the most general and useful cyclization leading to cyclic haloethers which can readily be dehalogenated to saturated or unsaturated systems.

We have recently introduced a new, Se-based and versatile method for the construction of O-heterocycles by cyclization of unsaturated hydroxy compounds, a procedure accompanied by the introduction of the PhSe group into the organic framework and leading to cyclic phenylselenoethers.[5] This reaction, termed phenylselenoetherification is illustrated in Scheme 3 for the case of 4-cycloheptene-1-methanol (**1**, $X = CH_2$). Similarly to the phenylselenolactonization this ring closure proceeds rapidly in methylene chloride at −78°, presumably via the intermediate A($X=CH_2$) which is captured intramolecularly by the OH group leading to the formation of the phenylselenoether **1a** ($X=CH_2$) in 95% yield. By analogy to the phenylselenolactones the stereochemistry of the phenylselenoethers formed in this fashion is assigned as *trans*. As indicated in Table 2, primary, secondary and tertiary alcohols as well as phenols enter this reaction. The compatibility of the cyclization conditions with a variety of functionalities including silyl ether, dithiane and carbonyl is worth mentioning and

Table 2. Phenylselenoethers and allylic ethers

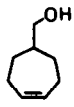
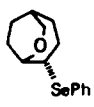
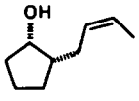
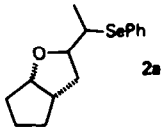
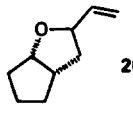
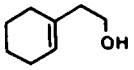
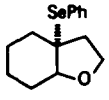
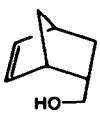
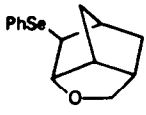
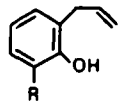
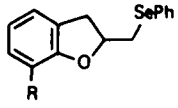
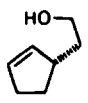
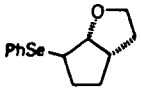
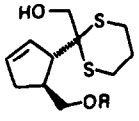
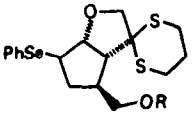
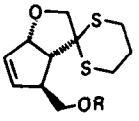
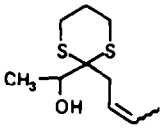
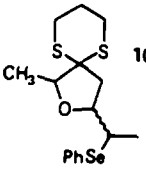
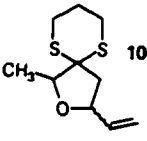
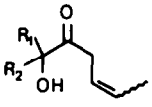
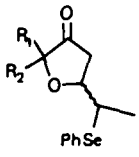
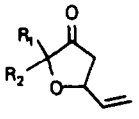
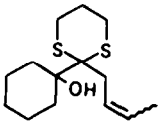
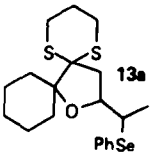
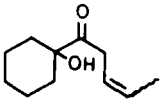
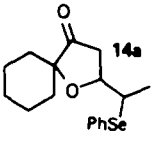
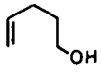
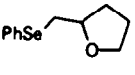
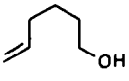
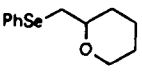
Entry	Unsaturated substrate	Phenylselenoether	Yield (percent)	Allylic ether	Yield (percent)
1		 **1a**	95	 **1b**	87
2		 **2a**	83	 **2b**	84
3		 **3a**	87		
4		 **4a**	93		

Table 2 (*Contd*)

Entry	Unsaturated substrate	Phenylselenoether	Yield (percent)	Allylic ether	Yield (percent)
5	 R = H		5a 85		
6	R = CH_3		6a 82		
7			7a 92		7b 82
8	 R = H		8a 90		8b 75
9	R = Si^tBuMe_2		9a 86		
10			10a 83		10b 83
11	 R_1 = H, R_2 = CH_3		11a 80		11b 82
12	R_1 = R_2 = CH_3		12a 80		
13			13a 83		
14			14a 80		
15			15a 86		
16			16a 90		

clearly enhances the utility of the method in complex instances. The phenylselenoethers so obtained are subject to a variety of transformations, the most useful ones being their conversion to allylic ethers and their reduction to saturated systems as discussed below.

Perhaps the most important and useful characteristic of the phenylselenoetherification reaction is its unique and rather complementary nature to the haloetherification reaction in the synthesis of unsaturated cyclic ethers. Thus, oxidation of phenylselenoether **1a** (X = CH_2, Scheme 3) with hydrogen peroxide (or any other common agent used for the oxidation of selenium) affords smoothly the corresponding selenoxide which suffers *syn*-elimination furnishing the unsaturated cyclic ether **1b** (X=CH_2) in 87% yield. In comparing these two methodologies, two points should be emphasized. First, the introduction of the double bond proceeds under much milder conditions in the case of the selenium procedure and second the *syn*-elimination of the selenoxide occurs selectively away from the oxygen as opposed to the toward-oxygen, base-induced elimination of hydrogen halide from the haloethers. Thus the present methodology represents an excellent and selective procedure for the synthesis of allylic ethers. Table 2 contains a number of examples of cyclic unsaturated ethers synthesized by this new methodology in good to excellent yields.

The readiness of the phenylseleno group to be cleaved reductively from the molecule provides an easy access to cyclic saturated ethers. Scheme 3 summarizes the action of some reducing agents on phenylselenoethers. Thus, hydrogenolysis of the C–Se bond by Raney–Ni occurs at 25° (**1a**→**1c**, X=CH_2, 94% yield), whereas tri-n-butyltin hydride removes the phenylseleno group in the presence of small amounts of azobisisobutyronitrile (AIBN) at 110°. The latter method is particularly useful when selectivity is desired over unsaturation, sulfur or other readily reducible functions.

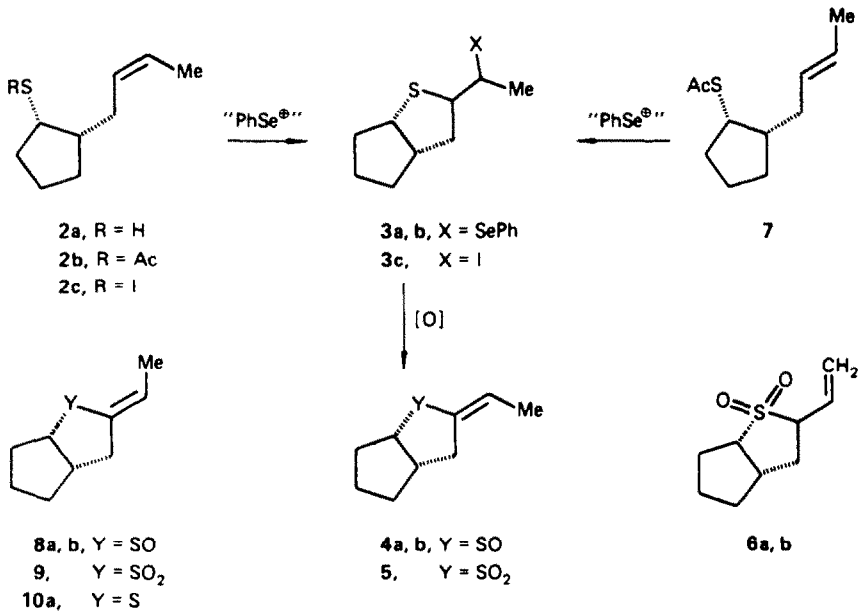
Excess sodium in liquid NH_3 (−78°→−33°) results in reversal of the phenylselenoetherification reaction yielding the starting hydroxy olefin (**1a**→**1**, X=CH_2, 82% yield). This reaction enhances the potential uses of this methodology in synthesis and suggests the phenylselenoether moiety as a possible internal protecting group of the hydroxy olefin system.

C. *Synthesis of* S-*heterocycles and related systems*[5a,7]

As an extension of the Se-induced cyclizations of unsaturated hydroxy substrates and because of the importance of S-heterocyclic systems, the possibility of capturing the phenylselenonium intermediates with strategically positioned internal sulfur nucleophiles was investigated. In many cases this was found to be a successful strategy and leads to cyclic phenyl-selenothioethers, α,β-unsaturated sulfoxides and unsaturated sulfones in a highly selective manner. Scheme 4 and Table 3 demonstrate these reactions and their general applicability.

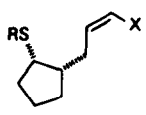
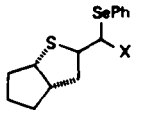
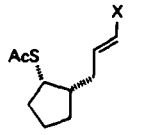
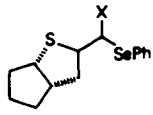
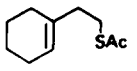
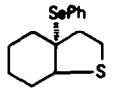
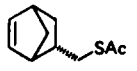
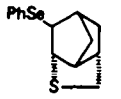
Thiol **2a** (Scheme 4) reacts rapidly with PhSeCl at −78°→25° to afford the cyclic thioether **3a** in 85% yield with incorporation of the PhSe group into the molecule. This ring closure proceeds at least as well with the thioacetate **2b**, a synthetically important observation, since it allows the utilization of a stable, protected form of the often rather unstable unsaturated thiols such as **2a**. Oxidation of the phenylselenothioether **3a** with excess hydrogen peroxide (8 equiv, THF, 25°, Method A) produces a mixture of E sulfone **5** and its unconjugated isomer **6a** (stereochemistry unassigned) in 92% yield (**5**:**6a** *ca* 2:1). However, treatment of **3a** with 1 equiv of *m*-chloroperbenzoic acid (CH_2Cl_2, −78°) followed by another equiv at −20° and warming to 25° (Method B) leads selectively to the formation of two isomeric *E*-sulfoxides **4a** and **4b** (sulfoxide isomerism). Further amounts of *m*-chloroperbenzoic acid (3 equiv total, −78°→25°, Method C) produces directly the *E*-sulfone **5** (95%). Alternatively, a combination of *m*-chloroperbenzoic acid (2 equiv, −78°→25°) and hydrogen peroxide (4 equiv, 25°, 24hr) (Method D) can be used for the formation of the *E*-sulfone **5** in high yield (95%).

The observed oxidation sulfoxide→sulfone is presumably effected by benzeneperoxy seleninic acid (PhSe = OOOH)[8a] produced in *situ* under the reaction



Scheme 4. Organoselenium-based synthesis of S-heterocycles (cyclic thioethers, sulfoxides and sulfones).

Table 3. Organoselenium-induced cyclizations of unsaturated thioacetates and thiols.

Entry	Substrate	Product	Yield[a] (percent)
1, R = H, X = CH_3 2, R = Ac, X = CH_3 3, R = H, X = $(CH_2)_3COOCH_3$ 4, R = Ac, X = $(CH_2)_3COOCH_3$			80 85 77 81
5, X = CH_3 6, X = $(CH_2)_3COOCH_3$			88 80
7			77
8			81

[a] Yield of pure product isolated by preparative tlc or column chromatography (silica gel). Reactions were run on 0.1–1 mmole scale in methylene chloride at −78° C unless otherwise specified.

conditions and represents an excellent means of oxidizing sulfides[5a,7,8b] to sulfoxides and sulfones under very mild conditions and in the presence of double bonds.

The geometry of the double bond in **4a,b** and **5** is based on mechanistic grounds, namely an assumed *trans*-addition during the ring closure and a *syn*-elimination of the selenoxide. As expected from these assumptions the *E*-thioacetate **7** on cyclization with PhSeCl followed by oxidation leads stereoselectively to the *Z* sulfoxides **8a,b** (sulfoxide diastereoisomers) via the selenide **3b** (stereochemistry unassigned) in similarly high yields as above. The same *Z*-sulfoxide **8b** is also obtained by a sequence starting with the *Z*-thioacetate **2b** and (i) cleaving the acetate, (ii) cyclizing with I_2 (CH_2Cl_2, K_2CO_3, −78°) (reaction presumably proceeding via sulfenyl iodide **2c** (undergoing an intramolecular addition to the double bond leading to iodide **3c**), (iii) eliminating with DBU furnishing **10** and (iv) oxidizing with *m*-chloroperbenzoic acid. This sequence provides, in *ca* 30% overall yield, only one sulfoxide (**8a**) presumably due to steric reasons. The β,γ-unsaturated sulfone **6b** (stereochemistry unassigned) was produced as a mixture with its conjugated isomer **9** (**6b**:**9** *ca* 1:3) by oxidation of **3b** according to Method A (87% total yield). The *Z* sulfone **9** can also be formed selectively from **3b** by methods C or D.

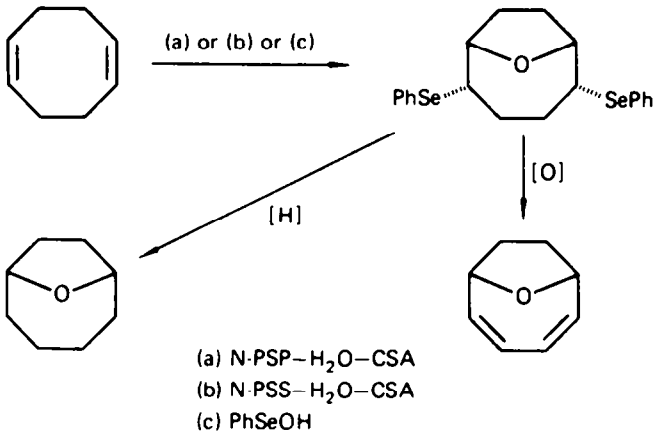
Thus by changing the ring closure initiator, using the correct double bond isomer and choosing the proper oxidizing method, the developed methodology offers versatile and selective routes to *Z* or *E* α,β-unsaturated sulfoxides, sulfones and, in view of the available means for reduction of sulfoxides to sulfides, α,β-unsaturated sulfides as well.

The scope of these ring closures in forming S-heterocycles and related systems is, however, more limited than the corresponding entries into O-heterocycles due to alternative pathways of the organoselenium-induced reaction in cases where the geometry of the substrate and the product are not favorable for ring closure and because of complications in reducing the products in the presence of sulfur. Nevertheless, important applications in the synthesis of complex biologically active molecules have already been demonstrated and will be discussed below.

D. *New organoselenium reagents*

N-*Phenylselenophthalimide* (N-PSP) *and* N-*Phenylselenosuccinimide* (N-PSS). Until very recently, the most commonly used carriers of the phenylseleno group were PhSeCl, PhSeBr and PhSeSePh. Recently, however, a number of new organoselenium reagents have been introduced which are particularly useful in hydroxyselenation of olefins and as inducers of ring closures. Phenylselenenic acid (PhSeOH),[9] N-Phenylselenophthalimide (N-PSP)[10] and N-Phenylselenosuccinimide (N-PSS)[10,11] are three examples that will be discussed here.

Phenylselenenic acid (PhSeOH) first introduced by Sharpless[9a] and Reich[9b] independently is prepared and used in *situ* from diphenyldiselenide (PhSeSePh) and hydrogen peroxide. Besides its use as a hydroxylselenation reagent for olefins it also reacts with certain dienes to form cyclic ethers (Scheme 5).[12] N-Phenylselenosuccinimide (N-PSS) first introduced by Sharpless[11] is prepared from allylphenylselenide and N-chlorosuccinimide and is a colorless crystalline solid. At −20° and under argon, N-PSS is stable although at ambient temperatures and in the air it slowly decomposes turning increasingly yelow due to diselenide formation. N-phenylselenophthalimide (N-PSP) is easily prepared from potassium phthalimide and PhSeCl in high yield and is a perfectly stable colorless crystalline solid.[10] Some of the



Scheme 5. Cyclization of dienes with N-PSP, N-PSS and PhSeOH.

highlights of the chemistry of N-PSP and N-PSS are presented below.

Both N-PSP and N-PSS are excellent reagents for the oxyselenation of olefins in the presence of 2–3 equivalents of water and an acid catalyst (CH_2Cl_2, 25°).[10] Hydroxyselenides are obtained in excellent yield and with considerable selectivity (Table 4) and are readily converted to a variety of useful products including allylic alcohols. Dienes with strategically positioned double bonds such as 1,5-cyclooctadiene (Scheme 5) enter this oxyselenation reaction leading to O-heterocycles with simultaneous introducion of two PhSe groups into the

Table 4. Reaction of N-phenylselenophthalimide (N-PSP) and N-phenylselenosuccinimide (N-PSS) with unsaturated substrates. A. Enes

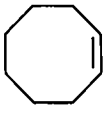
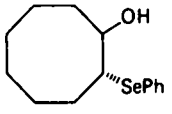
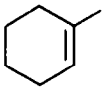
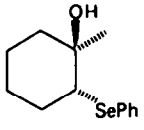
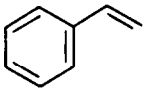
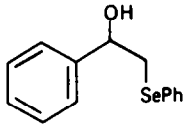
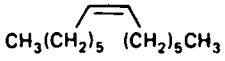
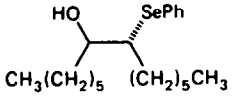
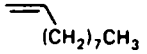
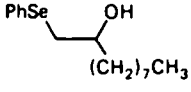
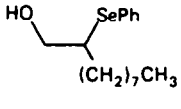
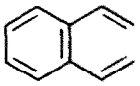
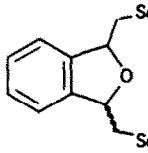
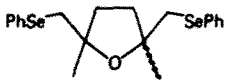
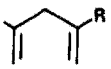
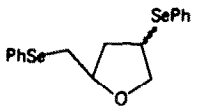
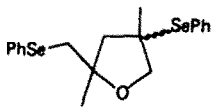
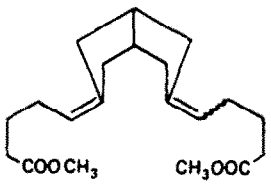
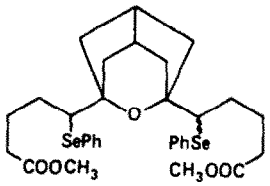
Entry	*Substrate*	*Product*	*Reagent*	*Yield (percent)*
1			N-PSP N-PSS	90 92
2			N-PSP N-PSS	89 84
3			N-PSP N-PSS	80 82
4			N-PSP N-PSS	93 94
5			N-PSP N-PSS	68 64
			N-PSP N-PSS	25 23

Table 5. Reaction of N-phenylselenophthalimide (N-PSP) and N-phenylselenosuccinimide (N-PSS) with unsaturated substrates. B. Dienes

Entry	Substrate	Product	Reagent	Yield (percent)
1			N-PSP N-PSS	97 95
2			N-PSP N-PSS	71 70
3			N-PSS	63
4, R = H			N-PSP	55
5, R = CH_3			N-PSS	24
			N-PSS	53
6			N-PSP	22

cyclic system. Table 5 indicates the formation of tetrahydropyran, tetrahydrofuran and oxetane systems in good to excellent yields and with relatively high regioselectivity. The ring size selectivity in this reaction depends both on the double bond substitution and the relative thermodynamic stability of the products. Some of the useful reactions of these diene-derived O-heterocyclics are demonstrated in Scheme 5 (cyclization, oxidation and reduction) for the case of 1,5-cyclooctadiene.

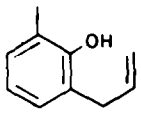
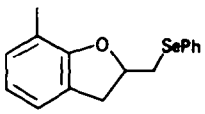
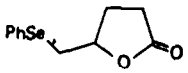
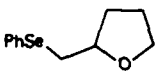
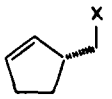
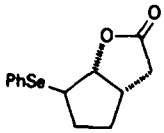
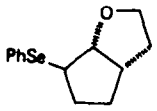
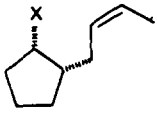
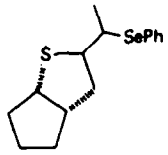
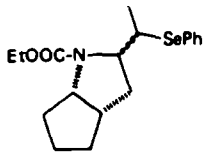
Cyclizations of unsaturated substrates containing internal nucleophiles (carboxylic acids, alcohols, phenols, thioacetates and urethanes) were found to proceed smoothly with N-PSP or N-PSS under the influence of acid catalysis. Excellent yields of O-(lactones, ethers), S-, and N-heterocycles are obtained as shown in Table 6.

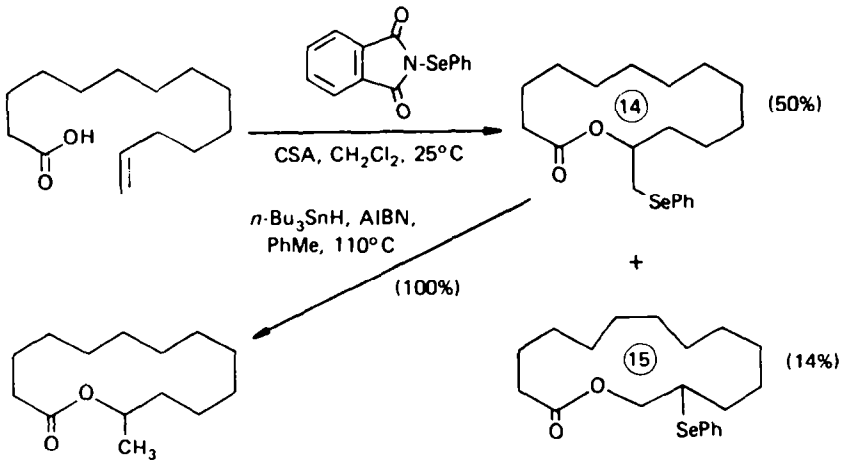
A unique feature of N-PSP and N-PSS is their ability to induce macrolide formation from long chain unsaturated carboxylic acids at 25°.[10] As Scheme 6 outlines exposure of such carboxylic acids to excess N-PSP in the presence of camphorsulfonic acid (CSA) in methylene chloride (0.01 M) at 25° under anhydrous conditions leads to the formation of secondary macrolactones as the major products and their primary regioisomers as minor products.

Macrodiolide formation was also observed, the yields of these products increasing with higher concentrations as expected. It is noteworthy that other organoselenium reagents such as PhSeCl, and PhSeOH fail to induce this reaction, addition of PhSeX across the double bond being the preferred pathway. Removal of the PhSe group under reductive conditions (nBu_3SnH, AIBN, 110°) results in the formation of the corresponding saturated macrolactones (Scheme 6) in high yields (95–100%). As with the C-14 carboxylic acid, the homologous C-16 compound reacted according to Scheme 6 furnishing the corresponding 16- and 17-membered rings.[10] Taking advantage of this technique, two naturally occurring macrolides, exaltolide and 9-decanolide were synthesized.[10]

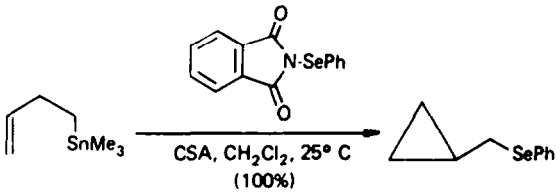
Cyclizations with C–C bond formation can also be induced by N-PSP and N-PSS as exemplified by cyclopropane formation from suitable unsaturated organotin derivatives (Scheme 7).[10] Some other related cyclizations have also appeared.[13]

Table 6. Reaction of N-phenylselenophthalimide (N-PSP) and N-phenylselenosuccinimide (N-PSS) with unsaturated substrates. C. Enes with internal nucleophiles

Entry	Substrate	Product	Reagent	Yield (percent)
1			N-PSP N-PSS	80 90
2, X = COOH			N-PSP N-PSS	100 98
3, X = CH_2OH			N-PSP N-PSS	90 95
4, X = COOH			N-PSP N-PSS	100 98
5, X = CH_2OH			N-PSP N-PSS	83 86
6, X = SAc			N-PSP N-PSS	70 72
7, X = NHCOOEt			N-PSP	90



Scheme 6. Organoselenium-based macrolide synthesis.



Scheme 7. Organoselenium-based cyclopropane synthesis.

Other reactions of N-PSP included the transformation of alcohols into phenylselenides and carboxylic acids to phenylselenoesters or amides.[14]

E. *Applications in the synthesis of prostacyclins*

The described organoselenium-based methodology for inducing facile ring closures arrived very timely and appeared very promising for the construction of prostacyclins.[15] Our results in this area proved very rewarding in that this new methodology provided not only an entry into a series of O- and S-containing prostacyclins but also proved useful in establishing the structures of some of the final products. Scheme 8 outlines the synthesis of some stable O-containing prostacyclins[16,17] whereas Scheme 9 depicts syntheses of two series of S-containing prostacyclins. The details of these works appeared elsewhere.[18,19]

CONCLUSION

We have demonstrated that organoseleniums such as PhSeCl and the novel reagents N-PSP and N-PSS can be used effectively to induce ring closures leading to various cyclic systems often with a high degree of regio- and stereoselectivity and with simultaneous introduction of one or two PhSe groups into the final product. Furthermore, it was demonstrated that the phenylseleno compounds obtained in these cyclizations provide excellent intermediates for elaboration to a variety of products under mild conditions. Notably the PhSe group was removed either oxidatively leading to unsaturated systems of reductively affording saturated products. The usefulness of this new organoselenium-based technology has been proven by its application to the construction of advanced intermediates and in the synthesis of a series of O- and S-containing prostacyclins. Further applications of this mild methodology for ring formation is envisioned to be found in the future.

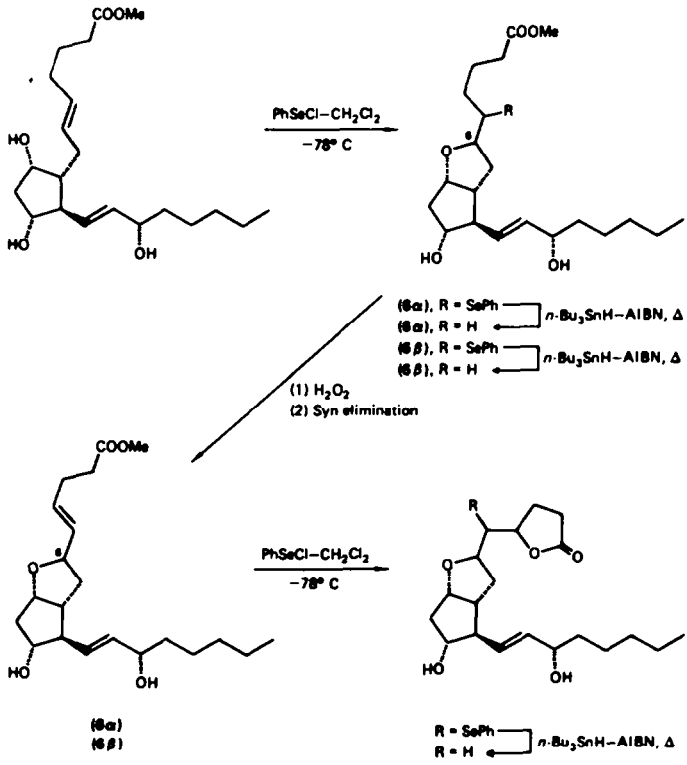
EXPERIMENTAL

Phenylselenolactonization

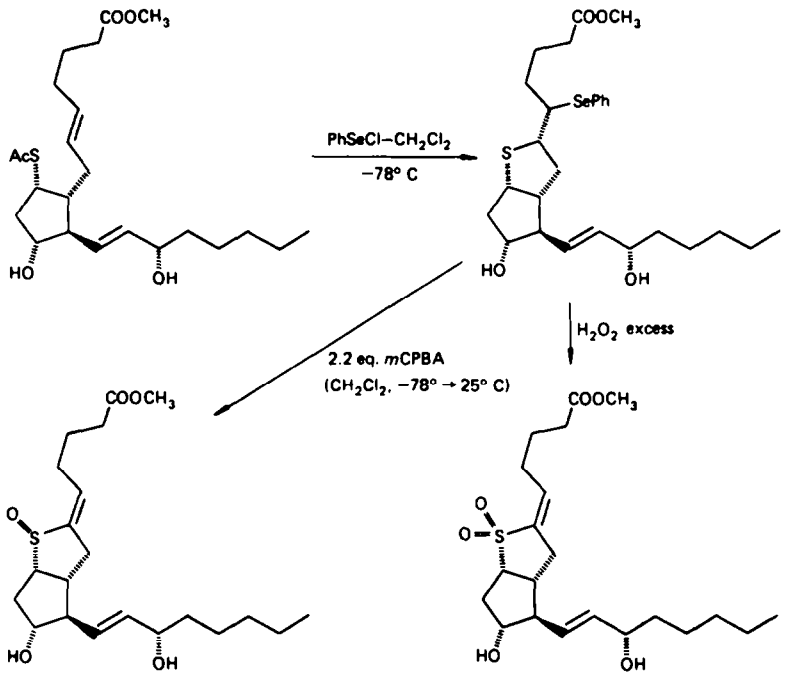
General procedure.[2a] All reactions indicated in Table 1 were carried out on 1-mmol scale in dry CH_2Cl_2 (5 mL) at $-78 \rightarrow 25°$ using commercial (Aldrich) PhSeCl (1.10 mmol) without base (method A) or with triethylamine (method B), pyridine (method C), or anhyd K_2CO_3 (method D). In methods B and C the acid was first stirred with the base (1.10 mmol) at 25° before cooling to $-78°$ and adding the PhSeCl. In method D powdered anhyd K_2CO_3 (2 mmol) was added just prior to the addition of PhSeCl. The phenylselenolactones were isolated after allowing the mixture to reach room temp, concentrating, and chromatographing on silica gel (columns or plates). The procedure is exemplified by the preparation of (1α, 4α, 5α)-4-(phenylseleno)-6-oxabicyclo[3.2.2]nonan-7-one described below.

(1α, 4α, 5α) - 4 - (*Phenylseleno*) - 6 - *oxabicyclo*[3.2.2]*nonan* - 7 - *one* (**1a**, X=CO).

Method A. To a magnetically stirred soln of **1**, (X=CO; 140 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) under argon at $-78°$ was added solid PhSeCl (212 mg, 1.1 mmol) and the mixture stirred at that temp. The completion of the reaction was signaled by the complete dissolution of the red-orange PhSeCl and was confirmed by tlc. The pale yellow soln was then allowed to reach room temp,



Scheme 8. Organoselenium-based synthesis of O-containing prostacyclins.



Scheme 9. Organoselenium-based synthesis of S-containing prostacyclins.

concentrated, and chromatographed on a silica gel-CH_2Cl_2 column. The product was obtained after the elution of trace amounts of diphenyldiselenide. Removal of the solvent from the appropriate fractions furnished 293 mg (100%) of the phenylselenolactone as a pale yellow oil crystallizing on standing. Recrystallization from hexane-ether (3:1) gave analytically pure **1a** (X=CO) as colorless crystals; m.p. 71–71.5° (hexane-ether); R_f 0.19 (silica, CH_2Cl_2); IR (BKr) ν_{max} 1735 cm^{-1} (δ-lactone); ^1H NMR (220 MHz, $CDCl_3$) τ2.35 (m, 2H, aromatic), 2.55 (m, 3H, aromatic), 5.33 (m, 1H, CHO), 6.37 (m, 1H, CHSe), 7.14 (m, 1H, CHCO), 7.66–8.24 (m, 8H, CH_2); mass spectrum *m/e* (rel intensity) 296 ($^{80}Se-M^+$, 26), 95 (base peak). Anal. ($C_{14}H_{16}O_2Se$) C, H, Se.

Oxidative removal of the phenylseleno group

6 - *Oxabicyclo*[3.2.2]*non* - 3 - *en* - 7 - *one* (**1c**, X=CO) (H_2O_2 *method*). A stirred soln of **1b** (X–CO; 295 mg, 1 mmol) in freshly distilled THF (5 mL) was treated dropwise at 0° with a 3% THF soln of H_2O_2 (made from 30% commercial H_2O_2) (275 μL, 1.5 mmol). The mixture was allowed to reach room temp. and stirred for 15 hr before dilution with ether (20 mL) and washing with water (2×5 mL) and sat NaCl aq (5 mL). After drying ($MgSO_4$) and removal of the solvents the product was isolated by column chromatography (silica, CH_2Cl_2). Compound **1c** (X=CO) was obtained as an oil which slowly crystallized on standing (112 mg, 80%). An analytical sample was obtained by recrystallization from pentane, m.p. 42–43° (pentane); R_f0.19 (silica, CH_2Cl_2); IR (liquid film) ν_{max} 1724 cm^{-1} (δ-lactone); ^1H NMR (220 MHz, $CDCl_3$) τ3.90 (m, 1H, olefin), 4.15 (m, 1H, olefin), 5.19 (m, 1H, CHO), 7.04 (m, 1H, CHCO), 7.23–8.50 (m, 6H, CH_2); mass spectrum *m/e* (rel intensity) 138 (M^+, 6), 79 (base peak). Anal. ($C_8H_{10}O_2$) C, H.

Reductive removal of the phenylseleno group

6 - *Oxabicyclo*[3.2.2]*nonan* - 7 - *one* (**1d**, X=CO) (nBu_3SnH *method*). A soln of **1b** (X=CO; 295 g, 1 mmol) in freshly distilled toluene (5 mL) was mixed with tri-n-butyltin hydride (582 mg, 390 μL, 2 mmol) and 0.02 M toluene soln of AIBN, (1 mL, 0.02 mmol). The mixture was degassed with a stream of argon for 15 min, sealed with a plastic cap, and heated to 110° for 1 hr. Removal of the solvent and column chromatography of the residue (silica, CH_2Cl_2) afforded pure **1d** (X=CO; 123 mg, 88%) as an oil crystallizing on standing, m.p. 149.0–150.5° (pentane); R_f0.29 (silica, CH_2Cl_2); IR (CCl_4) ν_{max} 1745 cm^{-1} (δ-lactone); ^1H NMR (220 MHz, $CDCl_3$) τ5.28 (m, 1H, CHO), 7.16 (m, 1H, CHCO), 7.73–8.64 (m, 10H, CH_2); mass spectrum *m/e* (rel intensity) 140 (M^+, 5), 55 (base peak). Anal. ($C_8H_{12}O_2$) C, H.

Phenylselenoetherification[5a]

1α, 4α, 5α - 4 - (*Phenylseleno*)6 - *oxabicyclo* [3.2.2] *nonane* (**1a**, X=CH_2). To a magnetically stirred soln of **1** (X=CH_2; 126 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added solid PhSeCl (212 mg, 1.1 mmol) and the mixture was stirred at that temp. until the red-orange PhSeCl solid dissolved and tlc indicated completion of the reaction. The pale yellow soln was allowed to reach room temp. concentrated, and chromatographed on a silica gel-CH_2Cl_2 column. The product (**1a**, X=CH_2) was obtained after the elution of small amounts of diphenyl diselenide. Compound **1a** (X=CH_2; 269 mg, 95%) as a pale yellow oil; R_f0.33 (silica, CH_2Cl_2); ^1H NMR (220 MHz, $CDCl_3$) τ2.52 (m, 2H, aromatic), 2.80 (m, 3H, aromatic), 6.04 (m, 1H, OCH), 6.16 and 6.35 (d, J = 4.0 Hz, 1H each, $-OCH_2$), 6.47 (m, 1H, –SeCH), 7.70–8.50 (m, 9H, CH_2 and CH); mass spectrum *m/e* (rel intensity) 282 (M^+-PhSe, base peak). Anal. ($C_{14}H_{18}OSe$) C, H.

Preparation of thioselenide **3a**

To a stirring soln of **2b** (198 mg, 1.0 mmol) in abs MeOH (10 mL) at –78° was added PhSeCl (212 mg, 1.1 mmol) under argon. Stirring was continued for 1–2 hr until TLC indicated complete reaction. CH_2Cl_2 (20 mL) was added and the soln was washed with brine (10 mL), 5% $NaHCO_3$ aq, and finally again with brine (10 mL). The organic phase was then dried ($MgSO_4$) and evaporated to afford the crude product which was purified by either flash column or preparative tlc (silica, ether–petroleum ether mixtures). **3a** (85%); Pale yellow oil; R_f0.43 (silica, 5% ether in petroleum ether); ^1H NMR (220 MHz. $CDCl_3$) τ2.41 (m, 2H, aromatic), 2.75 (m, 3H, aromatic), 6.25–6.50 (m, 2H, CHS), 6.64 (m, 1H, CHSe), 7.23 (m, 1H), 7.77 (m, 1H), 8.07–8.60 (m, 10H); ^{13}C NMR (25 MHz, CD_2Cl_2) δ135.33, 135.09, 129.17, 127.77, 58.28, 51.39, 49.25, 44.26, 42.18, 35.90, 31.82, 25.11, 21.64; mass spectrum *m/e* (rel intensity) 312 (M^+, 6), 155 (M^+ – SePh, base peak); high-resolution mass spectrum *m/e* 312.0443 (calcd for $C_{15}H_{20}S^{80}Se$; 312.0451). Anal. ($C_{15}H_{20}SSe$) C, H, S.

Preparation of α,β-unsaturated sulfoxides **4a** *and* **4b**

The thioselenide **3a** (93.6 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was cooled to −78° and treated under argon and with stirring with a soln of *m*-CPBA in CH_2Cl_2 (2.4 mL, 0.125 M, 0.3 mmol). After 15 min at −78° tlc indicated complete conversion to the sulfoxide and at that time another portion of *m*-CPBA (2.4 mL, 0.125 M, 0.3 mmol) was introduced dropwise. The cooling bath was removed and the mixture was allowed to stir at ambient temp. for 12 hr. The mixture was then diluted with CH_2Cl_2 (25 mL) and washed with sat $NaHCO_3$ aq (2 × 20 mL). The organic layer was then washed with 10% $NaHSO_3$ aq (20 mL) and brine (20 mL). The dried ($MgSO_4$) solvent was removed and the residue subjected to preparative layer chromatography to afford the conjugated sulfoxides **4a** (23.5 mg, 46%) and **4b** (21 mg, 41%). α,β-Unsaturated sulfoxide **4a**: colorless oil; R_f 0.37 (silica, 5% MeOH in ether); IR (CCl_4) ν_{max} 1035 cm^{-1} (S=O); ^1H NMR (360 MHz, $CDCl_3$) 3.62 (m, 1H, olefin), 6.63 (m, 1H, CHSO), 6.85 (m, 2H), 7.52 (d, J = 12 Hz, 1H), 7.88 (m, 1H), 8.12 (m, 1H), 8.18 (d, J=6Hz, 3H, CH_3), 8.40 (m, 1H), 8.53 (m, 2H), 8.80 (m, 1H); mass spectrum *m/e* (rel intensity) 171 [$(M+1)^+$, 4], 170 (M^+, 30), 67 (base peak); high-resolution mass spectrum *m/e* 170.0764 (calc. for $C_9H_{14}OS$, 170.0765). α,β-Unsaturated sulfoxide **4b**: colorless oil; R_f 0.47 (silica, 5% methanol in ether); IR (CCl_4) ν_{max} 1038 cm^{-1} (S=O); ^1H NMR (360 MHz, $CDCl_3$) τ3.77 (q, J=6Hz, 1H, olefin), 6.52 (m, 1H, CHSO), 7.18 (m, 1H), 7.30 (m, 1H), 7.42 (m, 1H), 7.77 (m, 1H), 8.17 (m, 6H), 8.30 (m, 1H), 8.53 (m, 1H); mass spectrum *m/e* (rel intensity) 171 [$(M+1)^+$, 7], 79 (base peak); high-resolution mass spectrum *m/e* 170.0762 (calc. for $C_9H_{14}OS$, 170.0765).

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