Selenium-Stabilized Anions.1 Preparation of α,β-Unsaturated Carbonyl Compounds Using Propargyl Selenides. Synthesis of (±)-7-Hydroxymyoporone2

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Abstract: The reaction of alkyl halides, carbonyl compounds, and trimethylsilyl chloride with the mono- and dianion (1) prepared by deprotonation of phenyl propargyl selenide with lithium disopropylamide gives 1- or 3-monomosubstituted or 1,3-disubstituted propargyl selenides (3b). Oxidation to selenoxides (3b) results in rearrangement to 2-(phenylseleno)-1,3-disubstituted propanones.

The rate of rearrangement of propargyl selenoxides increases dramatically when the phenyl group is replaced by a 2-nitrophenyl group, and an intermediate allenyl selenate ester (7e) can be observed by low-temperature NMR. By appropriate modification of oxidation conditions, modest yields of 2-idopropenones (e.g., 10) or the selenium-free enones or enals can be obtained. A synthesis of (±)-7-hydroxymyoporone (15) and its epimer has been carried out by using the dianion 1 to assemble the carbon skeleton. The preparation of α-thiolacetylenyl phenyl selenide (26) has been accomplished, and its reaction with electrophiles has been studied.

Propargylic- and allenyllithium reagents have become increasingly important as synthetic reagents for the introduction of complex functionality. These include a variety of allenic and propargylic ethers1 and thioethers.2,3,4 Since many selenium-substituted carbamions can be conveniently prepared by deprotonation of selenides and selenoxides,1,2 we undertook the study of lithium reagents from propargyl and allenyl selenides. It was anticipated that the products from reaction of such lithium reagents with electrophiles could be transformed to useful selenium-free materials by cleavage of the Se-C bond under oxidative or reductive conditions.6

Allylic selenoxides readily undergo [2,3] sigmatropic rearrangements,7 and adequate precedents exist in sulfur chemistry.8

Table I. Oxidation Products of Mono- and Disubstituted Propargyl Selenides (Scheme I)

<table>
<thead>
<tr>
<th>RUN NO.</th>
<th>RX</th>
<th>E</th>
<th>PRODUCT</th>
<th>YIELD</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H2O</td>
<td>PhSeH</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Br</td>
<td>PhSeBr</td>
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<tr>
<td>3</td>
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<td>CH3</td>
<td>PhSeCH3</td>
<td>59%</td>
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<tr>
<td>4</td>
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<td>Br</td>
<td>PhSeBr</td>
<td>61%</td>
</tr>
<tr>
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<td>Br</td>
<td>H2O</td>
<td>BrH</td>
<td>60%</td>
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<td>7</td>
<td>CH3</td>
<td>SiCl</td>
<td>CH3SiCl</td>
<td>42%</td>
</tr>
<tr>
<td>8</td>
<td>SeMe3</td>
<td>CH3</td>
<td>SeMe3CH3</td>
<td>56%</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>SeMe3</td>
<td>PhSeMe3</td>
<td>38%</td>
</tr>
</tbody>
</table>

* Mixtures of cis-trans isomers were usually formed. Yields are based on phenyl propargyl selenide. Oxidant: ozone in CH2Cl2. Oxidant: H2O2 in methanol. Methylation in THF-HMPA (2 equiv) at 25 °C. Oxidant: m-chloroperbenzoic acid in CH2Cl2. The monosodium (2, R = H) of phenyl proprargyl selenide (LINH-4-Bu, THF, 75 °C). 1-(Trimethylsilyl)but-3-en-1-yne was also formed.

that propargylic and allenic selenoxides will undergo similar rearrangements.
Preparation of α,β-Unsaturated Carbonyl Compounds


Oxidation of the propargyl selenides 3a leads to selenoxides 3b. When these are warmed above -30 °C, they rearrange to the α-(phenylseleno) enones 4a. This isomerization will be discussed in more detail below. The initially formed product 4a is a cis-trans mixture which can be converted into the pure Z isomer by stirring with pyridine in methanol.

A number of oxidizing conditions for the conversion of propargyl selenides (3a) to the selenoxides (3b) have been tried. m-Chloroperbenzoic acid and ozone have been the most useful. In neither case is oxidation of the acetylenic function a significant problem, provided oxidation is performed at low temperature and approximately stoichiometric amounts of reagents are used.

Table I summarizes the enones that have been prepared by using the method outlined in Scheme I. The unique capability of forming two bonds in a one-pot reaction can be used to assemble some unusual functional group combinations. The ability to easily prepare α'-hydroxy α,β-unsaturated ketones (runs 4 and 5) has been used as a key step in the synthesis of 7-hydroxymyoporone and its epimer below. Also noteworthy is the ability to prepare vinyl silyl ketones (runs 8 and 9), for which few other routes have been reported.9-10 Unfortunately, the present procedure is flawed by the tendency of the silylated propargyl selenoxides to undergo syn elimination in competition with [2,3] sigmatropic rearrangement. This is because the trimethylsilyl substituent strongly retards the rearrangement. From approximate rate measurements on 3b (R = H, E = SiMe3) we estimate that it isomerizes at least a factor of 175 slower than the parent selenoxide 6a. It is not known whether steric or electronic effects predominate, but the result is that compound 3b (E = Me,Si, R = CH3Ph) gives enyne as the major product. Here, the syn elimination is especially favored by the conjugating phenyl substituent.11 For compound 3b (E = Me,Si, R = CH3, run 8) approximately equal amounts of rearrangement (the silyl enone) and syn elimination product are observed. Competition between syn elimination and [2,3] sigmatropic rearrangement has also been reported for allyl selenoxides.12a,e

Rearrangement of Phenyl Propargyl Selenoxide. Phenyl propargyl selenoxide (6a) like other allylic selenoxides is stable only at low temperature. Ozonolysis of phenyl propargyl selenide at -78 °C cleanly gives the selenoxide, as shown by the presence of diastereomeric methylene protons in the NMR spectrum.13 Above -35 °C a clean isomerization to α-(phenylseleno)acrolein (8a) occurs. No intermediates or byproducts can be detected by NMR. The rearrangement was found to follow first-order kinetics with a rate constant kobs that is at least 10 times faster than at -31 °C. The rate of formation of 8a is the same as the rate of disappearance of 6a. The transformation appears to be a slow [2,3] sigmatropic rearrangement to give 7a, followed by a rapid isomerization of 7a to 8a. The m-trifluoromethyl)phenyl-substituted selenoxide 6b rearranges about 1.6 times as fast as 6a. This can be compared to the rate acceleration (factor of 1.7) observed for the selenoxide syn elimination of m-trifluoromethyl)phenyl alkyl selenonoid11a and the [2,3] sigmatropic rearrangement (factor of 3.26) of p-trifluoromethyl)phenyl allyl sulfonides1b compared to the phenyl analogues.

The isomerization is at least partially intermolecular as shown by a crossover experiment. When a mixture of 6b and deuterated

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Results and Discussion

Deprotonation and Reactions of Phenyl Propargyl Selenide. Phenyl propargyl selenide is rapidly deprotonated by 1 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran or dioxane at -78 °C to give the acetylenic anion 2 (R = H) and by 2 equiv of LDA to give a pale yellow solution of the di lithium reagent 1. Polylithium reagents derived from a variety of acetylenes including alkoxy- and thio-substituted ones have been prepared previously.9

The diion 1 is a powerful nucleophile as can be seen from the results in Table I. The reaction with primary bromides and iodides proceeds at -78 °C and with isopropyl iodide at -40 °C. Alkyl halides react with 1 at the α-position. Careful examination of the product from reaction of 1 with methyl iodide showed that greater than 99.5% of α-methylation results. Epoxides also react with 1 but higher temperatures and/or longer reaction times are necessary. The reactions of 1 with more reactive electrophiles like ketones and chloroformanes are not as selective.

The monolithium reagents 2 which are the products of the alkylation of 1 can be treated with a second electrophile. Table I presents examples where 2 was alkylated, silylated, protonated, and hydroxylalkylated to give a variety of 1,3-disubstituted propargyl selenides 3a. Although 2 can be sulfonylated with MeSSMe, it could not be cleanly sulfenylated with PhSSPh. More rapid base-catalyzed isomerization due to the greater acidifying effect of the phenylthio group might be responsible for this. Selective oxidation of selenium in the methylsulfonylated product could not be achieved.

The acetylenic lithium reagent 2 (R = H) can be prepared from phenyl propargyl selenide by treatment with 1 equiv of LDA or more conveniently with lithium isobutylamide at -78 °C. We have found that the isomerization (the silyl enone) and syn elimination product can be detected by NMR.

The rearrangement was found to follow first-order kinetics with a rate constant kobs that is at least 10 times faster than at -31 °C. The rate of formation of 8a is the same as the rate of disappearance of 6a. The transformation appears to be a slow [2,3] sigmatropic rearrangement to give 7a, followed by a rapid isomerization of 7a to 8a. The m-trifluoromethyl)phenyl-substituted selenoxide 6b rearranges about 1.6 times as fast as 6a. This can be compared to the rate acceleration (factor of 1.7) observed for the selenoxide syn elimination of m-trifluoromethyl)phenyl alkyl selenonoid11a and the [2,3] sigmatropic rearrangement (factor of 3.26) of p-trifluoromethyl)phenyl allyl sulfonides1b compared to the phenyl analogues.

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References:


6a was allowed to rearrange, 30% of undeuterated 8a was formed. Presumably the selenenate is hydrolyzed, and the allenol so formed is selenenylated. Powerful electrophilic selenium species are generated during selenoxide syn eliminations. A similar selenenylation of enols has been observed when some α-(phenylseleno) ketones are oxidized.

Direct evidence for the intermediacy of allenol selenenate esters was provided by study of the α-nitrophenyl propargyl selenoxide (6c). This compound is much less stable than 6a or 6b (t1/2 = 33 min at −50 °C) and isomerizes about 150 times as fast as does 6a. This isomerization gives a new substance which has been identified as the allene 7c from its low-temperature NMR spectrum (Figure 1) and characteristic IR absorption at 1950 cm⁻¹ (compare 1956 cm⁻¹ for alkyl allenyl ethers). The allene is stable to approximately −10 °C; at higher temperature it rearranges to an aldehyde 8c identical with material prepared by reaction of allenyl 1-ethoxyethyl ether with α-nitrobenzeneselenenyl chloride.

The increased stability of the ortho-nitro-substituted selenenate ester is not unexpected. Selenenic acids and their alkyl esters as well as sulfenic acid derivatives are very much stabilized toward disproportionation and hydrolysis by the introduction of o-nitro groups on the arylseleno or arylthio group.

Attempts To Trap Allenyl Selenenates with Electrophiles. The discovery that the phenylseleneno group in 4a was introduced by an intermolecular reaction suggested that it might be possible to trap the intermediate allenol with other electrophiles. We were encouraged in these efforts by the observation that when 6a was allowed to rearrange in the presence of excess 3,3'-bis(trifluoromethyl)diphenyl diselenide, an 85:15 mixture of 8a and 8b was obtained. Although a number of other trapping reagents were tried, only two were somewhat successful—protonation and iodination.

When several of the propargyl selenides were oxidized with hydrogen peroxide in methanol, moderate yields of selenium-free enones 4b could be isolated (see Table I). Alternatively, if the selenoxide 9 was allowed to warm slowly from −50 to 0 °C in the presence of pyridine and excess n-Bu4N+I− a cis-trans mixture of an α-iodoenone 10 is formed, together with lesser amounts of α-(phenylseleno) enone 11. The iodination was somewhat capricious, and conditions which would reliably convert a variety of propargyl selenides could not be found. A more satisfactory synthesis of certain α-iodo enones using allenyl trimethylsilyl ethers has recently been developed.

Transformations of α-(Phenyrseleno) Enones. A number of further transformations of the easily available α-(phenylseleno) enones 4a have been tried. Addition of dimethyl cuprate is successful but some deselenation occurs. The deselenation can be completed by addition of benzenethiol or benzeneselenol. Oxidation of 11 to the selenoxide at low temperature followed by warming in the presence of triethylamine gives a γ-hydroxy enone. Presumably α,β- to δ,γ-double bond isomerization followed by [2,3] sigmatropic shift occurs. Allylic selenoxides are reported to undergo a rapid [2,3] sigmatropic rearrangement. Similar

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**Figure 1.** Proton NMR spectrum (270 MHz) of 7c at −45 °C in CD2Cl2.

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γ-hydroxylations using the [2,3] sigmatropic rearrangement of a sulfoxide have been reported.15

We have also converted α-(phenylseleno) enones 4a to enones 4b by a deselenation reaction.12 Treatment of 12 by PhSeNa buffered with ammonium acetate results in the formation of enone 14 via the selenoxide.

Synthesis of (±)-7-Hydroxymyoporone. To test the utility of the methodology described here in a somewhat more complex system, we undertook the preparation of 7-hydroxymyoporone (13), isolated and identified by Burka, Bowen, Wilson, and Harris. The plan for the synthesis of 15 is presented in Scheme II.

Initial model experiments were carried out by using the 2-furyl ketone 17. Deprotonation with LDA and reaction with ethylene oxide gave a model compound 16, which was used in a synthesis of a 7-hydroxymyoporone analogue with the side chain in the 2-position. Unfortunately the 3-furyl analogue 18 was deprotonated by LDA or n-BuLi predominantly on the furan ring, as shown by isolation of the methylated compound 19. After several other approaches failed, the 3-substituted dithiane 20 was examined and found to react smoothly and in high yield with ethylene oxide giving compound 21 after tosylation. The preparation of 20 and subsequent reactions are summarized in Scheme III.

The dithiane tosylate 21 was resistant to S₆tos substitution both by the dianion 1 and even by iodide ion. A similar effect had been observed in the model 2-furyloxathiane tosylate derived from 17. In each case the situation was much improved after a transketalization to the ethylene ketal had been performed. Two reagents were found suitable for this reaction in the sensitive furan system: silver trifluoroacetate in ethylene glycol buffered with 2,6-di-tert-butylpyridine and chloramine-T in ethylene glycol.18 The latter reagent was preferred since it is cheaper and gave better yields. The dioxolane tosylate could now be smoothly converted to the iodide 22. Assembly of the carbon skeleton could be carried out in three ways: (1) alkylation of the diianion 25 with 22; (2) one pot alkylation of diianion 1 followed by reaction with isobutyraldehyde as in Scheme III; (3) alkylation of 1 with 22 followed by a separate reaction in which the isobutyraldehyde was introduced. All three procedures proved viable, but (3) gave the highest yield on the basis of 22 since excess diianion 1 could be used in the crucial alkylation step.

Compound 23 was oxidized and allowed to rearrange under the usual conditions to give a cis–trans mixture of enones 24 (some deselenated enone was also formed), which was treated with lithium dimethyl cuprate. Deselenation and ketal hydrolysis completed the synthesis. The product was a 70:30 mixture of two diastereomers which could not be separated chromatographically. The major one was crystalline and could be obtained in pure form. Comparison of the 270-MHz NMR spectra of the synthetic material with that of the natural product19 showed that the minor isomer was (±)-7-hydroxymyoporone, while the major was (±)-epi-7-hydroxymyoporone.

The stereochemistry is introduced during the cuprate addition. Since it did not seem unreasonable to assume that complexation between the inoming cuprate and the alkoxide group in 24 provided some conformational control, it was considered that cis and trans enones 24 might give rise to different diastereomer ratios. While pure (Z)-24 (X = H) did give a different diastereomer ratio (1:1) than did the mixture of E,Z isomers formed during the rearrangement, this approach did not seem promising enough to encourage more extensive studies of the cuprate addition.

α-Lithioallenyl Phenyl Selenide. We have developed three approaches to the lithium reagent 26 and have briefly studied its reactions with representative electrophiles. Alkylation and protonation occurs to give predominantly allenic products (CH₃I, >20:1; PhCH₂Br, 5:1 allenic–acetylenic). The allenyl selenide


(19) We thank Professor Burka for providing us with a sample of 7-hydroxymyoporone.
is smoothly converted to 6-phenylhex-2-yn-1-ol on oxidation with excess hydrogen peroxide under conditions analogous to those used for allylic selenides. The allenic lithium reagent 26 does, however, have lower nucleophilic properties than similar allylithiums since reaction of 26 with 2-phenyl-1-bromomethane gives predominately styrone, whereas the latter gives substitution in good yield.

The reaction of 26 with benzaldehyde gives predominantly acetylenic product. Such reversal in regiochemistry when allenic and allylic lithium reagents react with carbonyl compounds and esters.

The differences in the behavior of propargylic sulfoxides and selenoxides can be ascribed to two factors: the much greater rate of selenoxide syn elimination and the greater ease of cleavage of the Se–O bond of selenenates when compared with the sulfenate bond of selenates. It has been proposed that the allenyl sulfenate ester formed by [2,3] sigmatropic rearrangement undergoes a thio-Claisen rearrangement. In order to avoid this process (which we have not observed in the selenium system), we chose the methyl sulfoxide 27.

Alkylation of the dianion of methyl propargyl sulfide followed by oxidation gives the stable sulfoxide 27. Compound 27 decomposes near 100 °C in the presence of HOAc or (MeO)P to give ill-defined mixtures but no aldehydes. In the presence of triethylamine at 80 °C, allene 28 is formed in low yield presumably by a base-catalyzed proton migration. Thus although dianions of propargyl sulfides can be formed and alkylated, transformation analogous to the selenoxide rearrangement 3b to 4 could not be achieved for sulfoxides.

The differences in the behavior of propargyl sulfoxides and selenoxides can be ascribed to two factors: the much greater rate of [2,3] sigmatropic rearrangement of selenoxides compared with sulfoxides which has its parallel in the greater rate of selenolate syn elimination and the greater ease of cleavage of the Se–O bond of selenenates when compared with the sulfinyl esters.

**Summary.** The lithium reagents 1 and 26 which are the subject of this paper are synthetic equivalents of acrolein dianion 29 and lithiopropargyl alcohol 30, respectively. The two anionic centers of 29 can be utilized separately, although some restrictions on electrophiles do exist as a result of regiochemical and reactivity limitations. A number of acyl anion equivalents related to 29 have been developed. These include lithium reagents derived from 1,3-bis(methylthio)propene and related compounds.

The anion 1 is the only one of the acryl anion equivalents which permits the formation of two C=C bonds in a one-pot reaction. It also has certain other advantages over many of the above in terms of convenience of preparation of the precursor (one step from commercially available materials, high regioselectivity, and mildness of the deprotection step. It suffers from the problems associated with the formation of α-(phenylseleno) enones 4a rather than selenium-free materials (4b).

Sulfur analogues of 1 can be prepared and treated with electrophiles, but conversion to 1,3-disubstituted acryl compounds has not been reported.

Several synthetic equivalents of 30 are known. The simplest is an O-protected propargyl alcohol (the THP derivative has been frequently used). Not enough work has been done with 25 to determine whether it has improved nucleophilic properties compared to the acetylenic anion.

**Experimental Section**

**General Data.** Nuclear magnetic resonance (NMR) spectra were obtained on JEOL MH-100 or PX-60 or Bruker WH-270 spectrometers. Infrared spectra (IR) were obtained on a Perkin-Elmer IR-267 spectrophotometer and mass spectra (MS) on a Hitachi RMU-6 spectrometer. Unless specified otherwise NMR spectra were measured in CDCl₃ solution, and IR spectra of neat liquid between salt plates were recorded. Elemental analyses were performed by Spang Microanalytical Laboratories. Melting and boiling points are uncorrected; all reaction temperatures are measured externally.

Starting materials were commercially available except for diphenyl diselenide, 3-bis(trifluoromethyl)phenyl diselenide, benzene-selenenyl chloride, (2-nitro-4-methylphenyl)selenocyanate, 2,2'-dinitrodiphenyl diselenide and 3-phenylidodopropene were prepared according to literature procedures. Literature procedures. Tetrahydrofuran (THF) was freshly distilled from LiAlH₄ or sodium benzophenone ketyl; 1,2-dimethoxyethane (DME) was freshly distilled from LiAlH₄. Hexamethylphosphoric triamide (HMPA) was distilled from CaH₂ in vacuum and stored under nitrogen. Diisopropylamine and isobutylamine were distilled from KOH and stored over 4 A molecular sieves. Pyridine was stored over KOH. Stock solutions of lithium diisopropylamide (LDA), 1 M in THF-hexane, were prepared as in reference 12 and titrated with diphenylacetic acid. m-Chloroperbenzoic acid (m-CPBA) obtained from various commercial sources was found to contain m-chlorobenzoic acid and water as major impurities. Recrystallization from hexane (3 g/65 mL) is recommended to remove these impurities. All reactions involving organolithium reagents, selenol, or selenolate anions were run under an atmosphere of dry nitrogen. Apparatus for anhydrous reactions was dried in a 110 °C oven for at least 3 h. Preparative thin-layer chromatography (TLC) was carried out by using Merck PF-254 silica gel and dry column chromatography on MC and B 60 silica gel. Gas-liquid chromatographic (GLC) analysis was performed on a Varian 930 gas chromatograph with a thermal conductivity detector. Bulb-to-bulb distillations were carried out with a Kugelrohr apparatus; bath temperatures are reported.

**Normal Workup.** The normal workup procedure involved dilution of the reaction mixture with 20 mL of 50% ether–pentane and addition of the solution to 30 mL of 7% NaHCO₃ solution. The aqueous layer was extracted with 2 × 25 mL of 50% ether–pentane. The combined organic portions were washed with 1.2 N HCl solution and with saturated NaCl solution and dried by filtering through a cone of Na₂SO₄. Solvent was removed on a rotary evaporator.

**Phenyl Propargyl Selenide.** In a 250-mL 3-neck flask equipped with a reflux condenser, an addition funnel, and a gas inlet tube was placed...
Preparation of α,β-Unsaturated Carbonyl Compounds

15 g (48 mmol) of PhSeCl dissolved in 120 mL of EtOH under a nitrogen atmosphere. Sodium formaldehyde sulfoxylate (7.5 g, 49 mmol) was added to this solution followed by NaOH (5.7 g) in 50 mL of water. The resulting solution was stirred for 15 min at 50 °C. The yellow color fades and a white precipitate forms. The oil bath was now replaced by an ice-salt bath. Propargyl bromide (7.95 mL, 100 mmol) was added to this cold solution and the mixture stirred for 3 h at 0 °C. The reaction mixture was warmed to 50 °C and stirred for 15 min at 50 °C. The yellow color fades. After 15 min, 0.27 mL (3.6 mmol) of propargyl bromide was added.

Selenide (18.2 g, 97% yield, bp 62-64 °C (0.07) mm): NMR δ 4.72 (d, J = 7.5 Hz, 1 H), 7.1-7.6 (m, 5 H); IR: 3050, 1940, 1577 cm⁻¹; MS M⁺ 330.0525 (calcd for C₆H₆SeO, 330.0523).

7-Phenyl-(4-phenylseleno)-2-heptyne (Run 3). A solution of LDA (11.1 mmol) was added dropwise to a cooled (dry ice-EtOH) solution of 0.7 mL (5 mmol) of phenyl propargyl selenide in 15 mL of CH₂Cl₂. After 3 min 3-phenyliodopropane (0.75 mL, 5.7 mmol) was added, and the yellow solution was stirred for 0.5 h. Methyl iodide (0.5 mL, 8.2 mmol) was now added to the suspension followed by 1 mL of HMPA. The cold bath was removed, and the reaction mixture was allowed to warm to 25 °C. After 1 h this solution was poured into 1.2 N HCl, work up, and chromatography on silica gel, and was evaporated to give 1.0 g (29% yield) of 4-phenyl-(4-phenylseleno)-2-heptyne: NMR δ 7.17 (d, J = 2.2 Hz, 3 H), 1.7 (m, 4 H), 2.59 (t, J = 7 Hz, 1 H), 3.78 (m, 1 H), 7.0-7.6 (m, 10 H).

2-Hydroxy-2-methyl-4-(phenylseleno)-4-hepten-3-one (31; R. Liedtke, J. Org. Chem., 31, 2117 (1966)). Following the procedure outlined for run 4, 0.28 mL (2.2 mmol) of phenyl propargyl selenide, 0.17 mL (2.2 mmol) of ethyl bromide and 0.15 mL (2.5 mmol) of acetonitrile was added to a solution of 0.502 g (1.6 mmol) of m-CPBA, according to the procedure given (Run 3). A solution of 0.502 g (1.6 mmol) of m-CPBA, 0.3 mL of THF and 0.3 mL of methanol was added dropwise to this suspension followed by 1 mL of HMPA. The cold bath was removed, and the solution was stirred for 1 h and worked up. The concentrated filtrate was distilled (Kugelrohr, bp 63-66 °C/0.01 mm) as a mixture of E and Z isomers: NMR (Z isomer) δ 1.75 (quintet, J = 7.5 Hz, 2 H), 2.18 (s, 3 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.6 (t, J = 7.5 Hz, 2 H), 7.0-7.5 (m, 11 H); NMR (E isomer) δ 1.71 (quintet, J = 7 Hz, 2 H), 2.14 (s, 3 H), 2.33 (q, J = 7 Hz, 2 H), 2.56 (t, J = 7 Hz, 2 H), 6.25 (t, J = 7 Hz, 1 H), 7.0-18 (m, 10 H); MS M⁺ 275.0485 (calcd for C₁₃H₁₇NOSe, 275.0447).

2-Butyllithium (1.52 M in hex.

1-Phenylseleno)-2-butyne (Run 7). n-Butyllithium (1.52 M in hex.

2-Hydroxy-2-methyl-4-(phenylseleno)-4-hepten-3-one (12, Run 5). Following the procedure outlined for run 4, 0.28 mL (2.2 mmol) of phenyl propargyl selenide, 0.17 mL (2.2 mmol) of ethyl bromide and 0.15 mL (2.5 mmol) of acetonitrile was added to a solution of 0.502 g (1.6 mmol) of m-CPBA, according to the procedure given (Run 3). A solution of 0.502 g (1.6 mmol) of m-CPBA, 0.3 mL of THF and 0.3 mL of methanol was added dropwise to this suspension, resulting in a pale yellow solution. After 3 min, 1 mL of methyl iodide was added followed by 1 mL of HMPA. The cold bath was removed, and the solution was stirred for 1 h and worked up. The concentrated filtrate on distillation (Kugelrohr, bp 63-66 °C/0.01 mm) gave 1.93 g (98%) of 1-phenylseleno)-2-butyne: NMR δ 2.78 (t, J = 7 Hz, 3 H), 3.36 (q, J = 7 Hz, 2 H), 7.0-7.7 (m, 5 H); IR 3060, 2920, 2230, 1580 cm⁻¹; MS M⁺ 298.0465 (calcd for C₁₃H₂₂OSe, 298.0427).

1-Phenylseleno)-2-butene (Run 7). n-Butyllithium (1.52 M in hex.

6-phenyl-(2-phenylseleno)-1-hexyne (Run 1). A solution of 0.504 g (1.61 mmol) of 6-phenyl-(2-phenylseleno)-1-hexyne in 10 mL of meth.

2. (Phenylselenilo)-1-[(trimethylsilyl)propen-1-one (Run 9). To a solution of 5.0 mL (35 mmol) of phenyl propargyl selenide in 30 mL of THF at -78 °C was added 39.6 mL of a 0.93 M solution of LDA (37 mmol). After 10 min, 5.2 mL (41 mmol) of chlorotrimethylsilane was added, and after 10 min, the flask was warmed to 0 °C and stirred 45 min. The crude was extracted with chloroform (20 mL) and ether (20 mL), and the combined organic layers were washed with 3% NaHCO₃, dried (Na₂SO₄), and evaporated. The residue was chromatographed by preparative TLC (20% ether–pentane) to give 0.176 g (56% yield) of 10 as a mixture of E and Z isomers: NMR (200 MHz) δ 1.72 (quintet, J = 7 Hz, 2 H), 2.32 (q, J = 7 Hz, 2 H); IR (CCl₄) 2960, 1610, 1580, 1256, 862 cm⁻¹; MS M+ 284.0314 (calcd for C₁₂H₁₆O₇Si, 284.0128). TWO recrystallizations from 95% ethanol gave yellow crystals, mp 53.5–54.5 °C (decomposition).

Analog. Calc'd for C₁₂H₁₆O₇Si: C, 50.87; H, 5.70. Found: C, 50.92; H, 5.33.

Preparation and Rearrangement of 2-Nitrophenyl Propargyl Selenoxide (6c). An oxygen–oxygen stream was calibrated by oxidizing Ph₂Se₂ to Ph₂SeO₃ at -78 OC (3 equiv of O₃/molecule). Dry ozone (0.13 mmol) and 2-(phenylseleno)-1-(trimethylsilyl)propen-1-one (0.25 mL, 1.5 mmol) was dissolved in CH₂Cl₂ (5 mL) and slowly warmed to -30 OC. Yellow precipitates (MeCu) appeared at this point. This solution was warmed to 0 °C and stirred 45 min. The solution was further warmed to 0 °C and poured into 10% Na₂S₂O₃ solution, and the mixture was extracted with ether–pentane. The combined organic extracts were treated with 2% NaHCO₃, 1.2 N HCl, and saturated NaCl solution, dried, concentrated, and purified by preparative TLC (20% ether–pentane) to give 0.176 g (56% yield) of 10 as a mixture of E and Z isomers: NMR (200 MHz) δ 1.81 (quin, J = 7 Hz, 2 H), 2.36 (s, 3 H), 2.27, 2.21 (3 H, 2 H), 5.83 (d, J = 7 Hz, 1 H); IR 3440, 3040, 2935, 1677, 1630 cm⁻¹; MS M⁺ 204.1136 (calcd for C₁₃H₁₄O₇S, 204.1150).

4-Methyl-7-phenyl-3-hepten-2-one. Methylithium (0.1 mL, 1.1 M) was added dropwise to a stirred mixture of 63 (4.0 mL, 1.9 mmol) at -78 OC, and the solution became yellow. After being left sitting overnight, the solution was filtered, giving (after vacuum drying) a yellow oil which isomerized at -31 °C and observed by 270-MHz NMR. The rate followed first-order kinetics: k = 6.5 × 10⁻⁵ s⁻¹; the selenoxide was briefly observable even at room temperature (t₁/₂ ≈ 3 min).

3-Iodo-7-phenyl-3-hepten-2-one (10). To a stirred cooled (-78 °C) solution of 0.323 g (1 mmol) of 7-phenyl-4-(phenylselenilo)-2-heptyne in 5 mL of CH₂Cl₂ was added a CH₂Cl₂ (2 mL) solution of 0.203 g (1 mmol) of m-CPBA. Iodine (0.254 g 1 equiv) was dissolved in a solution of 0.37 g (1 mmol) of n-Bu₄N⁺BF₄⁻ in 4 mL of CH₂Cl₂. This dark brown solution was added to the reaction mixture after 0.5 h. The reaction mixture was now warmed to -30 °C in 15 min and kept between -30 °C and -20 °C for 0.5 h. The solution was further warmed to 0 °C and poured into 10% Na₂S₂O₃ solution, and the mixture was extracted with ether–pentane. The combined organic extracts were treated with 2% NaHCO₃, 1.2 N HCl, and saturated NaCl solution, dried, concentrated, and purified by preparative TLC (20% ether–pentane) to give 0.176 g (56% yield) of 10 as a mixture of E and Z isomers: NMR (200 MHz) δ 1.81 (quintet, J = 7 Hz, 2 H), 2.36 (s, 3 H), 2.27, 2.21 (3 H, 2 H), 5.83 (d, J = 7 Hz, 1 H); IR 3440, 3040, 2935, 1677, 1630 cm⁻¹; MS M⁺ 204.1136 (calcd for C₁₃H₁₄O₇S, 204.1150).

5-Hydroxy-7-phenyl-3-hepten-2-one. To a cooled (-78 °C) solution of 0.343 g (1 mmol) of 11 in 4 mL of THF was added 0.203 g (1 mmol) of m-CPBA. After this solution was stirred for 0.5 h, 0.310 mL (2.2 mmol) of NEt₃ was added, and the reaction mixture was allowed to warm to 0 °C during 30 min, poured into 10% Na₂S₂O₃ solution, and the mixture was filtered. Yellow precipitates (MeCu) appeared at this point. This solution was stirred for 5 min, and 0.1 mL of H₂O was added. The solution was slowly warmed to 0 °C, poured into 1.2 N HCl, extracted with saturated NaCl solution, and dried. The crude product was purified by chromatography by using 20% ether–pentane to give 0.1 g of carboxylic product.

Ph₃Se (60 mg) in 3 mL of EtOH was heated under N₂ with powdered NaBH₄ until the solution was clear. Acetone (0.03 mL) was added to remove excess NaBH₄. The carboxylic product obtained above in 1 mL of EtOH was added to this reaction mixture. After 1 h, 20 mg of chloroacetic acid was added to remove excess Ph₃Se. The solution was stirred for 10 min, worked up, and purified by preparative TLC to give 53 mg (65% yield) of 4-methyl-7-phenyl-2-heptanone: NMR δ 0.86 (d, J = 7 Hz, 3 H), 1.26 (m, 2 H), 1.59 (q, J = 7 Hz, 2 H), 2.02 (s, 3 H), 2.19 (d, J = 5 Hz, 2 H), 2.45 (d, J = 7 Hz, 1 H), 7.0–7.4 (m, 7 H); IR 3450, 3040, 2935, 1677, 1630 cm⁻¹; MS M⁺ 204.1136 (calcd for C₁₃H₁₄O₂, 204.1150).

2-Hydroxy-2-methyl-4-hepten-3-one (14). NaBH₄ was added to an EtOH (5 mL) solution of 0.5 g (1.6 mmol) of Ph₃Se and 0.2 g (2.6 mmol) of NH₂OAc under N₂ until the solution was pale yellow. After 0.5 h, 10 mg of Ph₃Se was added to remove excess NaBH₄. The solution of 2-Me-Ph₃Se was stirred for 1 h. The yellow color of Ph₃Se was developed after addition of 12. The reaction mixture was added to 5% Na₂CO₃ solution and worked up.

The crude product (13) was dissolved in 10 mL of CH₂Cl₂. Pyridine (0.25 mL, H₂O (0.6 mL), and H₂O₂ (30%, 0.6 mL) were added. After the reaction mixture was stirred for 0.5 h, it was poured into 10% Na₂CO₃ solution and extracted with ether–pentane. The combined organic extracts were worked up and dried. The concentrated filtrate upon preparative TLC gave 96 mg (73% yield) of 14: NMR δ 1.1 (t, J = 7 Hz, 3 H), 1.31 (s, 2 H), 2.33, 2.31 (3 H, J = 7 Hz, 2 H), 3.60 (br, s), 3.63 (m, 2 H, J = 5 Hz, 1 H), 7.12 (dt, J = 14.5 and 7 Hz) (3 H, 1 H); IR 3480, 2980, 1685, 1632 cm⁻¹; MS M⁺ 142.0994 (calcd for C₆H₁₀O₂, 142.0994).


3-Furanmethanol. In a 500-mL three-neck flask was placed 2.3 g of 2-phenylpropenal (40 mmol). To a solution of 0.03 mL of H₂O (0.6 mL) and 0.30 mL of freshly distilled THF. A solution of 3.04 g (25 mmol) of LiAlH₄ and 250 mL of freshly distilled THF. A solution of 3-furic acid (4.28 g, 38.2 mmol) in 40 mL of THF was then dripped in cautiously, and the gray mixture was refluxed for 22 h. After being cooled to 25 °C, Glauber's Salt (Na₂SO₄–H₂O) was carefully added until the mixture became white. This was vacuum filtered and the granular
solid was washed twice with hot THF. The combined filtrates were concentrated under reduced pressure, and the residue was distilled at 0.4 mm, maximum temperature 60 °C to give 3.12 g of clear liquid (83% yield). NMR (CDCl3) δ 3.90 (t, 3 H), 7.28 (m, 2 H).

3-Furancarboxaldehyde. In a 500-mL three-neck flask was placed 300 mL of CH2Cl2 and 19.5 mL (240 mmol) of pyridine. To this was added 3.0 mmol of 1,2-propanediol (THF solution) and 186 mg (0.52 mmol) of seleno alcohol 23. After cooling to 25 OC and allowing to stir for 20 min. This crude mixture was decanted into a separatory funnel, the black residue was washed twice with ether, and the combined organics were washed thrice with 5% NaOH and then with 5% Na2S2O3 solution. The solvent was removed slowly by evaporation under reduced pressure, and the residue was distilled at 0.4 mm, maximum temperature 60 °C (bath temperature 120-140 °C). A colorless syrup, 2.85 g (12.4 mmol), was thus obtained (95% yield): NMR (CDCl3) δ 6.82 (s, 1 H), 7.56 (s, 1 H), 8.32 (s, 1 H), 10.02 (s, 1 H); IR (CDCl3) 3150, 2850, 1720, 1690, 1570, 1520, 1415, 1385, 1285, 1170, 1160 °C; MS M+ 96.0209 (calcd for C6H8O2, 96.0211). 1-3-Furanyl)-1,3-dithiane (20). In a 50-mL flask equipped with a Dean-Stark trap was placed 3-Furanmethanol in 10 mL of CH2Cl2 and was added while stirring was carefully continued and allowed to stir for 20 min. This crude mixture was decanted into a separatory funnel, the black residue was washed twice with ether, and the combined organics were washed thrice with 5% NaOH and then with 5% Na2S2O3 solution. The solvent was removed slowly by evaporation under reduced pressure, and the residue was distilled at 0.028 mm, maximum temperature 50 °C, to afford 1.0 g of clear, sweet-smelling liquid (80% yield): NMR (CDCl3) δ 6.82 (s, 1 H), 7.56 (s, 1 H), 8.32 (s, 1 H), 10.02 (s, 1 H); IR (CDCl3) 3150, 2850, 1720, 1690, 1570, 1520, 1415, 1385, 1285, 1170, 1160 °C; MS M+ 96.0209 (calcd for C6H8O2, 96.0211).

1-3-Furanyl)-1,3-dithiane (20). An analytical sample, recrystallized from ether-pentane-CH2C12 (3:3:1), was obtained as white needles in 60% yield: mp 62-63 °C (lit., 60-61 °C). To this was added 0.5 mmol of the crude seleno alcohol 23 from the two-pot sequence and 0.150 mL of 2,6-di-tert-butylpyridine. The reaction mixture was stirred for 2 h at -78 °C (after 10 min a precipitate began to form and the reaction mixture lightened) and was then poured into dilute NaHCO3. The layers were separated and the aqueous layer was extracted three times with ether-pentane (1:1); IR (CDCl3) 3320 (s, 1 H), 1690, 1560, 1460, 1435, 1375, 1350, 1290, 1170, 1160 °C; MS M+ 230.0433 (calcd for C10H14O2S2, 230.0435); major fragments 294 (l.0), 227 (1.2), 155 (4.4), 140 (11.2), 139 (100), 95 (83.8), 77 (5.0). 1-3-Furanyl)-4-(phenylseleno)-5-hexyn-1-one, Ethylene Ketals. A 25-mL flask charged with 12 mL of DMF and 0.250 mL (1.71 mmol) of phenyl propargyl selenide was flushed with nitrogen, cooled to -78 °C and 2.18 g (20 mL) of 1 M LDA was added slowly. The resulting dark green solution was stirred for 2 h and 0.5 mmol of m-CPBA. After 45 min 0.09 mL of 3-Furancarboxaldehyde (1.0 g, 10.4 mmol) was added in 2 mL of DME. This was stirred for 2 h at -78 °C (after 10 h a precipitate began to form and the reaction mixture lightened) and was then poured into dilute NaHCO3. The layers were separated and the aqueous layer was washed three times with ether-pentane (1:1). The organic solutions were combined and shaken with brine and then filtered through Na2SO4. Solvent removal left an oil which was purified by preparative TLC (22% ether-pentane) to give 21 mg of iodide (Rf0.48) and 100 mg of 2,6-di-tert-butylpyridine (Rf 0.85). The iodide 22 was obtained as a low-melting white solid in 51% overall yield from the dithiane tosylate 21: NMR (CDCl3) δ 2.55 (m, 2 H), 3.10 (m, 2 H), 3.90 (m, 4 H), 6.32 (s, 1 H), 7.38 (m, 2 H); IR 3150, 2960, 2890, 1585, 1550, 1390 cm-1; MS M+ 293.9752 (calcd for C17H14O2Se, 293.9762); major fragments 294 (l.0), 227 (1.2), 155 (4.4), 140 (11.2), 139 (100), 95 (83.8), 77 (5.0). 1-3-Furanyl)-4-(phenylseleno)-7-hydroxy-8-methyl-5-nonyl-1-one, Ethylene Ketals (23). In an oven-dried flask was placed the purified selenide prepared above (186 mg, 0.52 mmol) and 5 mL of DMF. After being flushed with N2, the solution was cooled to -78 °C and 0.52 mL of 1 M LDA was added. After 10 min, 0.06 mL of isobutyltrityl chloride (excess) was added by syringe and the reaction mixture was heated to 54 °C, and the resulting solution was kept at 6 OC tightly stoppered for 40 h. The flask then contained long white needles (pyridine-HCl) and orange liquid. Additional 30 mL of water and fourfold extraction with 1:1 ether-pentane gave an organic extract which was shaken vigorously with 10% HCl four times and once with saturated NaHCO3 and brine. After filtration through Na2SO4 and removal of solvent under reduced pressure, a white solid remained: 4.72 g (12.3 mmol, 99% yield); mp 57-58 °C.

1-3-Furanyl)-3-iodo-1-propanone, Ethylene Ketals (22). Anhydrous chloramine-T (350 mg, 1.54 mmol) was dissolved in 3 mL of ethylene glycol, 1.2 mL of THF and 150 mg (0.39 mmol) of tosylate 21 was added, and the mixture was stirred until homogeneous and then for 1 h longer. The pale yellow solution was decanted into 5% NaOH and extracted three times with 1:1 ether-pentane. The organic extracts were combined, washed with brine, and dried by passing through Na2SO4, and the solvent was removed. The residue was nearly pure ethylene ketal tosylate (95% conversion), which was used directly in the next reaction: NMR (CDCl3) δ 8.23 (J, J = 8 Hz, 2 H), 2.46 (J, J = 8 Hz, 2 H), 4.19 (J, J = 8 Hz, 2 H), 6.30 (m, 1 H), 7.35 (m, 4 H), 7.79 (d, J = 8 Hz, 2 H).

In 1.5 mL of reagent grade acetone was dissolved 190 mg of crude tosylate and 0.150 mL of 2,6-di-tert-butylpyridine. To this was added, under N2, 270 mg of Na (a yellow color develops). After 90 minutes and then obviated, and the only contaminant remaining is pyridine. The workup procedure has been developed wherein the crude reaction mixture is filtered through a short column of Florisil. The base extractions are then evaporated, and the only contaminant remaining is pyridine. The workup procedure has been developed wherein the crude reaction mixture is filtered through a short column of Florisil. The base extractions are then evaporated, and the only contaminant remaining is pyridine.

warm to 25 °C during 1 h. Dilution with 1:1 ether-pentane (10 mL) followed by washing with 10% HCl twice with saturated Na2CO3 once with brine, and filtration through Na2SO4 gave after removal of solvent and preparative TLC with 50% ether-pentane (Rf 0.05-0.53) 198 mg of a mixture of (Z)- and (E)-24, X = H and SePh (87% yield based on 1-(3-furlyl)-4-(phenylseleno)-5-hexyn-1-one; IR 3580, 3100, 1765(sh), 1720, 1620, 1530, 1580, 1490 cm⁻¹). A sample of the stereochemically pure (E)-24 (X = H) was prepared by deselenation of the mixture prepared above by using the same procedure as for the conversion of 12 to 14 (1 PhSeNa/NEt3/MeOH; 2 H2Oz): NMR (CDCl3, 270 MHz) δ 6.9 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6.9 Hz, 3 H), 2.1 (m, 3 H), 2.38 (br q, J = 7 Hz, 2 H), 3.95 (symm m, 4 H), 4.24 (d, J = 2.2 Hz, 1 H), 6.22 (dt, J = 15.6, 1.5 Hz, 1 H). 6.32 (m, 1 H), 7.05 (dt, J = 15.6, 7.0 Hz, 1 H), 7.4 (m, 2 H).

1-(3-Furyl)-4,8-dimethyl-7-hydroxy-1,6-nonanedione

An oven-dried flask was flushed with N2, and 741 mg of CuI (3.88 mmol) was added, followed by 40 mL of ether and 0.29 mL of dimethyl sulfide. After being stirred for 1.25 h, the reaction mixture was diluted with 5% NaOH and then worked up. The crude 3-(methylthio)-1-nonyne was added, followed by 40 mL of ether and 0.3 mL of PhSH, and 0.4 mL of MeOH and 0.3 mL of PhSH, and 0.4 mL of Na2S04 Solvent removal left 185 mg of semisolid crude material. The crude product was purified by preparative TLC with 50% ether-pentane (Rf center 0.30, containing 160 mg of the desired ketal (66% yield, mp 70.5-71.5 °C)) was prepared by deselenation of the mixture prepared above by using the same procedure as for the conversion of 12 to 14 (1 PhSeNa/NEt3/MeOH; 2 H2Oz):

Frontier-Controlled Pericyclic Reactions of Cyclooctatetraene with Cyclopentadienones. First Example of Exo [4 + 6]π Cycloadduct by Effective Secondary Orbital Control and Its Molecular Structure

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Abstract: Pericyclic reactions of cyclooctatetraene with 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (1a), 2-oxo-1,3-bis(ethoxycarbonyl)-2H-cyclopentalenylacenaphthylene (1b), and 2-oxo-1,3-diphenyl-2H-cyclopentalenylphenanthrene (1c) were investigated. The cycloaddition reactions of cyclooctatetraene with 1a and 1b afforded the novel exo [4 + 6]π cycloadducts together with bis-Diels–Alder cycloadducts. The configuration of the exo [4 + 6]π cycloadduct was assigned by the spectral data and verified by X-ray crystallography. The reactions are discussed on the kinetic and molecular orbital calculation data together with X-ray structural determination of the exo [4 + 6]π and bis-Diels–Alder cycloadducts.