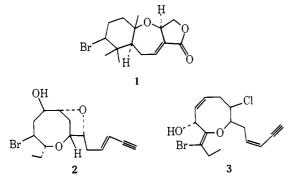


Figure 1.

aplysistatin¹⁰ molecule. The four chiral centers are $C_3(S)$, $C_5(S)$, $C_{12}(R)$, and $C_{14}(S)$.



Since sea hares generally depend upon marine algae for nutrition it may be useful to consider such an exogenous primary source of aplysistatin. In this respect the isomeric substance laurefucin (2) has been isolated from the Japanese marine algae *Laurencia nipponica* Yamada¹¹ and the related chondriol (3) has been obtained from the marine algae *Chondria oppositiclada* Dawson.¹² Presently the antineoplastic effects of aplysistatin are being assessed in the National Cancer Institute's laboratories and we are investigating other new substances from sea hares.

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References and Notes

- Dedicated to Dr. Jonathan L. Hartwell on the occasion of his 70th birthday and retirement from the National Cancer Institute. Part 48 of the series Antlneoplastic Agents. For the preceding contribution see G. R. Pettit, R. B. Von Dreele, D. L. Herald, M. T. Edgar, and H. B. Wood, Jr., J. Am. Chem. Soc., 98, 6742 (1976).
 G. R. Pettit, R. H. Ode, C. L. Herald, R. B. Von Dreele, and C. Michel, J. Am.
- (2) G. R. Pettit, R. H. Ode, C. L. Herald, R. B. Von Dreele, and C. Michel, J. Am. Chem. Soc., 98, 4677 (1976). A recent review of marine animal toxins including those from sea hares has been prepared by P. J. Scheuer, *Lloydia*, 38, 1 (1975). See also M. Watson, *Toxicon*, 11, 259 (1973), and M. Watson and M. D. Rayner, *ibid.*, 11, 269 (1973).
- and M. D. Rayner, *ibid.*, 11, 269 (1973).
 (3) Cf. B. W. Halstead, "Poisonous and Venomous Marine Animals of the World", Vol. 1, U.S. Government Printing Office, Washington, D.C., 1965, p 710.
- (4) Presented as part of the 10th IUPAC Symposium on the Chemistry of Natural

Products, Dunedin, New Zealand, Aug 23-28, 1976.

- (5) G. R. Pettit, C. L. Herald, G. F. Judd, G. Bolliger, and P. S. Thayer, *J. Pharm. Sci.*, **64**, 2023 (1975).
- (6) D. L. Herald, R. H. Ode, and G. R. Pettit, J. Chromatogr. Sci., 14, 356 (1976).
- (7) A revised version of the Alcock analytical absorption program was used for this analysis.
- (8) All calculations other than data reduction and absorption corrections were done using the "CRYSTALS" computing package: R. S. Rollett and J. R. Carruthers, personal communication.
 (9) "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press,
- Birmingham, England, 1974, pp 149–150.
- (10) Aplysistatin represents a new type of sesquiterpene and oxygen heterocyclic system. For this new ring system we suggest the name aplysistane and the numbering system presented by structure i.



- (11) A. Furusaki, E. Kurosawa, A. Fukuzawa, and T. Irie, *Tetrahedron Lett.*, 46, 4579 (1973).
- (12) W. Fenical, K. B. Gifkins, and J. Clardy, Tetrahedron Lett., 16, 1507 (1974).

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Selenium Stabilized Anions. Synthetic Transformations Based on Propargyl Selenoxides

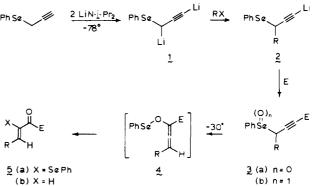
Sir:

Heterosubstituted propargyl and allenyl organolithium reagents have potential as synthetic precursors to highly functionalized 3-carbon fragments.¹ We report here the preparation of the dianion 1,² and reactions of the propargyl selenides derived from it (Scheme I).

Phenyl propargyl selenide is rapidly deprotonated by 2 equiv of lithium diisopropylamide in tetrahydrofuran or glyme at -78 °C to give a pale yellow solution of the dilithium reagent 1.³ Alkyl halides react with 1 exclusively at the α position (>99.5% α -methylation), primary bromides and iodides at -78°C, isopropyl iodide at -40 °C (Table I). The resulting acetylenic lithium reagent 2 can then be protonated, alkylated, or treated with a variety of other electrophiles (E) to give 1.3disubstituted propargyl selenides, **3a**, usually in excellent yield.

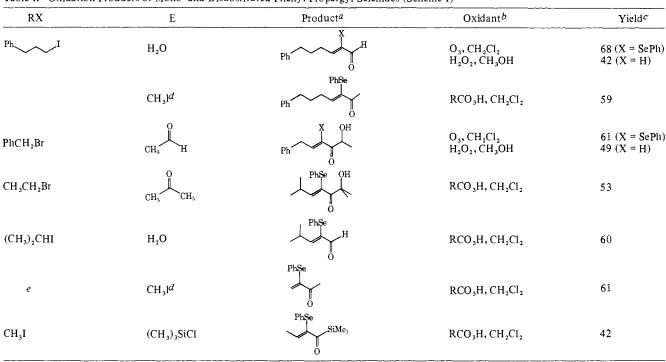
A number of useful transformations of **3a** can be envisaged. Oxidation gives the selenoxide **3b**, which rearranges to α -phenylselenoenone (**5a**)⁴ at -40 to -30 °C, presumably via **4**.⁵ The table shows that a variety of complex enones can be quickly assembled using this technique, including otherwise





Communications to the Editor

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



^{*a*} All selenides and enones were characterized spectrally and by their elemental composition. Mixtures of cis/trans isomers were usually formed (ref 4). ^{*b*} RCO₃H: *m*-chloroperbenzoic acid. ^{*c*} Yields are for materials purified by TLC, based on phenyl propargyl selenide. ^{*d*} Methylation in THF-HMPA (2 equiv) at 25 °C. ^{*e*} The monoanion of phenyl propargyl selenide (LiNH-*i*-Bu, THF, -78 °C) was alkylated.

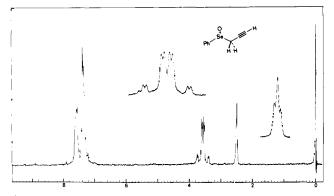
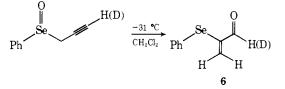


Figure 1. Proton NMR spectrum of phenyl propargyl selenoxide (100 MHz, CDCl₃, -41 °C). The propargyl protons form an ABX pattern: δ 3.63, 3.47 (J_{AB} = 13.8 Hz), 2.46 (J_{AX} = J_{BX} = 2.5 Hz).

poorly accessible compounds. Of a large number of different reaction conditions and potential selenenate trapping reagents tried,⁶ only oxidation with excess hydrogen peroxide in methanol gave moderate yields of the selenium-free enone **5b**.

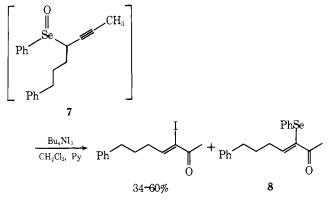
The mechanism of the **3b** to **5a** rearrangement was studied in the parent system. Low temperature ozonolysis of phenyl propargyl selenide gives the selenoxide, as shown by the diastereotopic methylene protons in the NMR spectrum (Figure 1). Above -35 °C a clean first-order isomerization to **6** occurs



 $(k_1 = (10.7 \pm 0.5) \times 10^{-5} \text{ s}^{-1} \text{ at} - 31 \text{ °C})$. No intermediates or by-products can be detected by NMR. The isomerization is at least partially intermolecular, since a mixture of *m*-tri-

fluoromethylphenyl propargyl selenoxide⁷ and deuterated phenyl propargyl selenoxide gave 30% of the crossover product (undeuterated 6). We feel these data are best explained by reaction of the intermediate allenol selenenate ester (4, R = E = H) with some selenenylating species⁸ to give 5a.

These observations suggest that other electrophiles may be capable of trapping the allenol ester. In fact, when selenoxide 7 in dichloromethane is allowed to warm slowly from -50 to 0 °C in the presence of pyridine and excess $n-Bu_4N^+l_3^-$, a cis/trans mixture of an α -iodoenone is formed, together with lesser amounts of α -phenylselenoenone (8).



A number of further transformations of the α -phenylselenoenone 8 have been tried. Addition of dimethyl cuprate is successful but some deselenation occurs (deselenation can be completed by addition of benzenethiol). Oxidation of 8 to the selenoxide followed by warming in the presence of triethylamine gives a γ -hydroxyenone. Presumably α,β - to β,γ -double bond isomerization, followed by [2,3]sigmatropic shift,⁹ occurs.

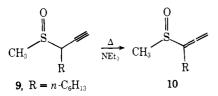
Dianions of propargyl sulfides can be formed and alkylated,¹⁰ but our preliminary efforts to achieve transformations analogous to the selenoxide rearrangement 3b to 5 were unsuccessful. Alkylation of the dianion of methyl propargyl

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Ph
$$(1 - \frac{1}{2} - \frac{1}{PhSH}, B)$$

 (65%)
 $(1 - \frac{1}{2} - \frac{RCO_0H}{PhSH}, B)$
 $(1 - \frac{RCO_0H}{2}, -78 \ ^{\circ}C$
 $(2 - NEt_0)$
 $(2 - NEt_0)$
 $(2 - NEt_0)$
 $(2 - NEt_0)$
 $(3 - NE$

sulfide, followed by oxidation gives the stable sulfoxide 9. The methyl derivative was chosen to avoid the thio-Claisen rearrangements which occur (at 80 °C) with phenyl propargyl sulfoxide.¹¹ Compound 9 decomposes near 100 °C in the presence of $(MeO)_3P$ to give ill-defined mixtures, but no aldehyde. In the presence of triethylamine at 80 °C, allene 10 is formed in low yield.



The dramatic lowering of the [2,3]sigmatropic shift activation energy in the selenium as compared to the sulfur analogue has resulted in interesting and useful chemistry of the selenium system not presently known for the sulfur analogues. The difference in behavior of propargyl selenoxides and sulfoxides is probably a consequence of the greater stability of selenenate vs. selenoxide^{2b.9} (sulfoxides are usually more stable than sulfenates).

Acknowledgment. We thank the National Science Foundation for support of this work.

References and Notes

- (1) (a) S. Hoff, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **87**, 916 (1968); (b) Y. Leroux and C. Roman, *Tetrahedron Lett.*, 2585 (1973); (c) R. M. Carlson, R. W. Jones, and A. S. Hatcher, *ibid.*, 1741 (1975); (d) F. Mercier, N. LeGoff, and R. Epsztein, *C.R. Acad. Sci., Ser. C*, **279**, 525 (1974); (e) B. W. Metcalf and P. Casara, *Tetrahedron Lett.*, 3337 (1975); (f) M. Huche and P. Cresson, *ibid.*, 367 (1975).
- (3) Polylithium reagents derived from propyne and phenylpropyne have been previously prepared: (a) J. Klein and S. Brenner, *Tetrahedron*, **26**, 2345 (1970); J. Org. Chem., **36**, 1319 (1971); (b) T. L. Chwang and R. West, J. Am. Chem. Soc., **95**, 3324 (1973); (c) L. Brandsma and E. Mugge, *Recl. Trav. Chim. Pays-Bas*, **92**, 628 (1973); (d) N. M. Libman, V. I. Zlobina, and G. Kuznetsov, *Zh. Org. Khim.*, **10**, 2057 (1974); (e) F. Scheinmann et al., J. Chem. Soc., Chem. Commun., 1030 (1974), 817 (1975).
- (4) Among the systems tried, a significant amount of selenoxide syn elimination occurs only for 3a, R = PhCH₂, E = Me₃SiCI (38% yield of 1-phenyl-4trimethylsilylbut-1-ene-3-yne).
- (5) Good yields of selencenone 5a are obtained when 3a is oxidized at -78 °C (30 min) with *m*-chloroperbenzoic acid in dichloromethane, 1.5 equiv of pyridine is added, and the reaction mixture is warmed to 0 °C. A mixture of *E* and *Z* isomers is formed, equilibration to *Z* occurs on stirring at room temperature in the presence of pyridine.
- temperature in the presence of pyridine.
 (6) For example, warming 3b (R = (CH₂)₃Ph, X = H) in the presence of HNEt₂, H₂NiBu, P(OCH₃)₃, MeOH, EtOH, HOAc, PhSH/Py, *n*-Bu₄N⁺I⁻, and I₂ did not give useful yields of 5b.
- (7) The *m*-trifluoromethyl substituted selenoxide isomerizes 0.84 times as fast as the unsubstituted compound ($k_{CF_3} = (9.0 \pm 0.5) \times 10^{-5}$ at -31 °C). (8) A related selenenylation reaction has been found to give selenium con-
- (8) A related selenenylation reaction has been found to give selenium containing by-products during the formation of enones by selenoxide syn elimination: H. J. Reich, J. M. Renga, and I. L. Reich, J. Am. Chem. Soc., 97, 5434 (1975).
- [9] [2,3]Sigmatropic rearrangements of allyl selenoxides occur readily:^{2b,d}
 K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); *J. Org. Chem.*, **37**, 3973 (1972).

- W. Reise and H. Waldger, *Pertainbolic Data*, 1000 (1977);
 K. C. Majumdar and B. S. Thyagarajan, *J. Chem. Soc., Chem. Commun.*, 83 (1972); Y. Makisumi and S. Takada, *ibid.*, 848 (1974).
- (12) Alfred P. Sloan Fellow, 1975-1977.

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Electron Density Distribution of the Azide Ion. Quantitative Comparison of Theoretical Calculations with Experimental Measurements

Sir:

Recent progress in the experimental determination of electron density distributions in solids by x-ray (and neutron) diffraction¹ has generated renewed interest in theoretical calculation of the density distribution and in comparison with experiment.² Until now, the experimental difficulties in making measurements on small molecules, for which good theoretical calculations are available, and the computational difficulties in treating larger systems, for which experimental densities have been determined, have prevented comparisons between theory and experiment on the same system. Reported here is a quantitative comparison of the experimental electron density distributions in crystals of NaN₃ and KN₃ with a thermally smeared theoretical density of the azide ion.

The details of the electron density distribution are best visualized in a plot of the deformation density, $\Delta\rho$, given by the difference between the observed density and the density of an assembly of spherical atoms placed at the atomic positions. Values for the atomic positions and thermal vibration parameters unbiased by the valence electron distribution are required. These have been obtained by independent neutron diffraction experiments³ ($\Delta\rho$ (X-N)) and by refinement of high order x-ray data ($\Delta\rho$ (X-X)).

The distribution of errors in the experimental deformation densities has been calculated as described by Rees⁴ considering the contributions from errors in the x-ray intensity measurements, in the refined parameters, and in the x-ray scale factor. Assuming the contributions to be uncorrelated,

$$\sigma^{2}(\Delta \rho) = \sigma^{2}(\rho_{\text{obsd}}) + \sigma^{2}(\rho_{\text{calcd}}) + \rho_{\text{obsd}}^{2}\sigma^{2}(k)/k^{2}$$

where k is the x-ray scale factor. While the first contribution is relatively constant throughout the crystal (except near symmetry elements), the second and third contributions peak at the atomic centers, and differences between densities within about 0.3 Å of the nuclear positions cannot be considered significant.

Sodium azide crystallizes in space group R3m with the N₃⁻ ion on a crystallographic 3m site. X-ray intensity measurements were collected from a single crystal on a Picker cardcontrolled diffractometer with graphite-monochromatized Mo K α radiation.⁵ Anharmonic (third cumulant⁶) thermal parameters were included in a full-matrix least-squares refinement of the structure. Refinement of 139 high order reflections (0.65 < sin θ/λ < 1.25 Å⁻¹) gave R = 2.6% and $R_w = 1.7\%$.⁷ The $\Delta\rho$ (X-X) deformation density was calculated using the full data set (208 reflections with 0.0 < sin θ/λ < 1.25 Å⁻¹), positional and thermal parameters from the high order refinement, and Hartree-Fock atomic scattering factors.⁸ The x-ray scale factor was determined by experimental measurement.⁹

Potassium azide crystallizes in space group I4/mcm with the N₃⁻ ion occupying a site with *mmm* symmetry. Singlecrystal x-ray intensity measurements were collected on a Picker FACS-I diffractometer using Nb-filtered Mo K α radiation. A total of 3463 reflections were measured in the range 0 < sin

⁽¹⁰⁾ W. Kreiser and H. Wurziger, Tetrahedron Lett., 1669 (1975).