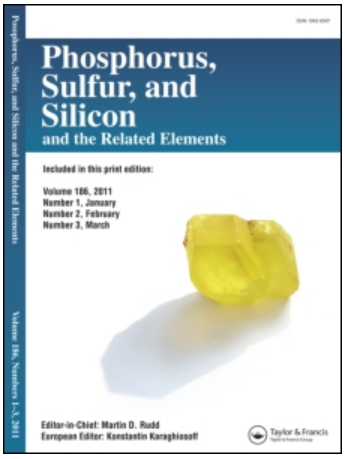


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Chemistry of Analogous Organoselenium and Organosulfur Compounds

Eric Block[a]
[a] Department of Chemistry, SUNY-Albany, Albany, NY, USA

To cite this Article Block, Eric(2001) 'Chemistry of Analogous Organoselenium and Organosulfur Compounds', Phosphorus, Sulfur, and Silicon and the Related Elements, 172: 1, 1 — 23
To link to this Article: DOI: 10.1080/10426500108046637
URL: http://dx.doi.org/10.1080/10426500108046637

Phosphorus, Sulfur and Silicon, 2001, Vol. 172, pp. 1-23
Reprints available directly from the publisher
Photocopying permitted by license only

Chemistry of Analogous Organoselenium and Organosulfur Compounds

ERIC BLOCK

Department of Chemistry, SUNY-Albany, Albany, NY 12222, USA

Selenium analogs of the sulfur-containing flavorant precursors in genus *Allium* spp. (garlic, onion, etc.), *Se*-(alk(en)yl)selenocysteines and γ-glutamyl *Se*-methylselenocysteine, have been synthesized and their oxidation has been studied. While the *S*-(alk(en)yl)selenocysteine *S*-oxides are stable, the analogous Se-oxides undergo a variety of interesting reactions. 1,2-Diselenin and 2-selenathiin have been synthesized and their reactions and properties are compared to those of 1,2-dithiins.

Keywords: selenoamino acids; selenoxides; 1,2-diselenin; 2-selenathiin

INTRODUCTION

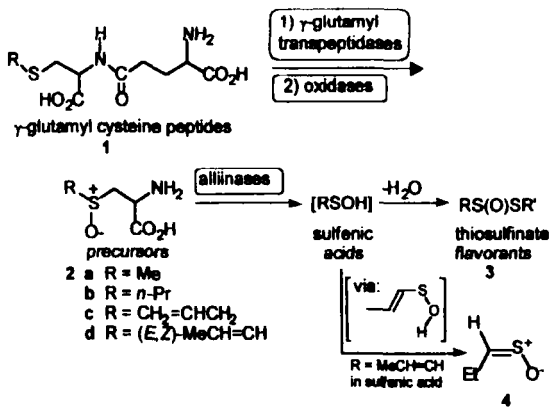
In studying the chemistry of organochalcogen compounds, it can be very informative to compare and contrast the properties and reactions of particular structural types as the chalcogen atom is varied. The names

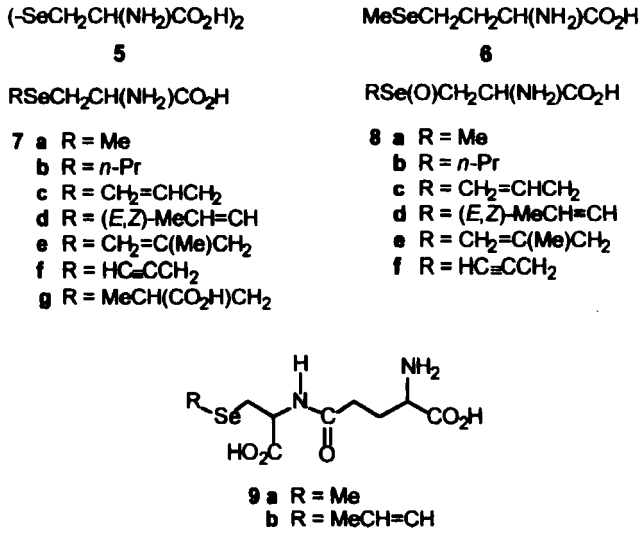
thioalcohols, thioethers, and thioketones for thiols, sulfides and thiones, respectively, reflects the historical, periodic approach to nomenclature as well as to the study of organosulfur compounds. Of course, very significant differences exist between the properties and reactions of alcohols and thiols, ethers and sulfides, and ketones and thiones. On moving down the chalcogen family, it is found that more chemical similarities exist between compounds of sulfur and selenium than between compounds of oxygen and sulfur, although notable differences are often seen in both chemical and biological reactivity of analogous sulfur and selenium compounds. Because the size of selenium and tellurium is similar to that of sulfur, sulfur in biologically active compounds can be replaced with the heavier atom for improved characterization, e.g. by X-ray crystallography or ^{77}Se or ^{99}Te NMR spectroscopy, or for determination of changes in biological activity. Such considerations have led to incorporation of phosphoroselenoate in DNA and selenomethionine in proteins.[1] Comparative studies of two different classes of chalcogen compounds are described below. The first study compares the chemistry of *S*-alk(en)ylcysteine *S*-oxides and *Se*-alk(en)ylselenocysteine *Se*-oxides while the second study compares the chemistry of 1,2-dithiins with that of the selenium homologs, 1,2-diselenin and 2-selenathiin.

ALLIUM SULFUR AND SELENIUM AMINO ACIDS

The sulfur-containing flavorants (e.g. **3**, Scheme 1) of genus *Allium* plants are formed when the plants are cut or crushed through co-mingling of alliinase enzymes with *S*-alk(en)ylcysteines *S*-oxides (**2a-d**,

$RS(O)CH_2CH(NH_2)COOH$; R = Me, *n*-Pr, CH_2=$CHCH_2$ and MeCH=CH), which in turn are derived from γ-glutamyl *S*-alk(en)ylcysteine storage compounds (**1**).[2,3] In the case of onion (*Allium cepa*), the intermediate 1-propenesulfenic acid rearranges to propanethial *S*-oxide (**4**), the onion lachrymatory factor (LF).[2,4] Spåre and Virtanen[5] suggested that selenium-containing analogs of **1** and **2** may also be present in these plants. Thus, analysis of extracts of ^{75}Se-treated onions indicated the possible presence of selenocystine (**5**), selenomethionine (**6**), *Se*-β-carboxypropylselenocysteine (**7g**), *Se*-methylselenocysteine *Se*-oxide (**8a**), *Se*-1-propenylselenocysteine *Se*-oxide (**8d**), and γ-glutamyl *Se*-1-propenylselenocysteine (**9b**). The identity of **5** and **6** was confirmed through comparison with the chromatographic behavior of authentic compounds.[5] In an effort to confirm the identity of the other species, Spåre and Virtanen synthesized *Se*-methyl-, *Se*-propyl- and *Se*-2-propenylselenocysteine (**7a-c**, respectively) but were unsuccessful in their attempts to oxidize **7a-c** to the corresponding *Se*-oxides **8a-c**.





SCHEME 1. Formation of Flavorants in *Allium spp*

Since the seminal studies by Spåre and Virtanen suggesting that there might be a selenium-based flavor chemistry in *Allium* spp. parallel to that based on sulfur, e.g. originating from soil selenate (SeO_4^{-2}) or selenite (SeO_3^{-2}), much progress has been made in Allium organoselenium chemistry and, more broadly, in the natural products chemistry of selenium. Thus, it is possible to enrich garlic (*Allium sativum*) with selenium from the natural level of 0.05 ppm to 100-1355 ppm Se dry weight by fertilizing the crop with selenate and/or selenite salts.[6] Similarly, onions can be enriched to 96-140 ppm Se. Element specific methods of analysis, such as HPLC with inductively coupled plasma-mass spectrometric detection (HPLC-ICP-MS), have been used to characterize a variety of organic selenium compounds from natural sources at levels as low as 20 ng/mL Se in the presence of much larger

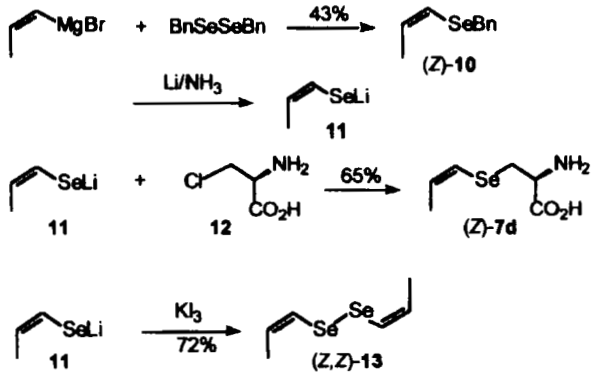
amounts of co-eluting organosulfur and other compounds.[7] Interest in identifying the organoselenium compounds in genus *Allium* plants is heightened by the discoveries that Se-enriched garlic (Se-garlic) is very effective in mammary cancer chemoprevention in the rat model[6,7f,8] and that *Se*-2-propenylselenocysteine (**7c**) is very potent in vivo in inhibiting the development of experimentally induced breast cancer.[8d,e] In addition, Ip and coworkers find that diallyl selenide is significantly more active as an anticancer agent than diallyl sulfide, as shown by the data in Table 1.[8f]

TABLE 1. Comparison of Mammary Cancer Chemoprevention by Diallyl Sulfide and Diallyl Selenide

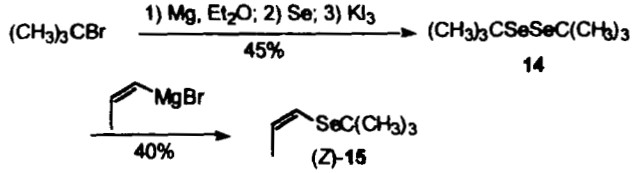
Treatment	Dose (mol/kg b.w.)	Tumor Incidence	Total Tumor Yield
Control	none	Av. 84%	Av. 70
All_2S	0.3×10^{-3}	20/25 (80%)	68
All_2S	0.9×10^{-3}	16/25 (64%)	50
All_2S	1.8×10^{-3}	13/25 (52%)	42
All_2Se	0.6×10^{-5}	10/25 (33%)	16
All_2Se	1.2×10^{-5}	9/25 (30%)	14

In connection with studies of Se-enriched garlic we synthesized **7a-c**,[8d,9] *Se*-(*E,Z*)-1-propenylselenocysteine (**7d**) and γ-glutamyl *Se*-methylselenocysteine (**9a**).[10] Compound **7d** was prepared by alkylation of β-chloro-L-alanine (**12**) with lithium (*E,Z*)-1-propeneselenolate (**11**), in turn prepared from Li-NH_3 reduction of benzyl (*E,Z*)-1-propenyl

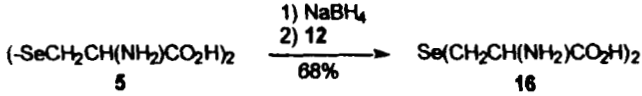
selenide (**10**; Scheme 2; only (Z)-isomers shown). In work to be described below we also required bis(1-propenyl) diselenide **13**, prepared by oxidation of **11**, 2-methyl-2-propyl (*Z*)-1-propenyl selenide (**15**), prepared from bis(2-methyl-2-propyl) diselenide (**14**; Scheme 3), and selenolanthionine (**16**), synthesized by reaction of sodium selenocysteinate with β-chloro-L-alanine (**12**; Scheme 4). γ-Glutamyl *Se*-methylselenocysteine (**9a**) was prepared by condensing *Se*-methyl-L-methylselenocysteinate hydrochloride (**17**) with triethylammonium-*N*-(trityl)-L-γ-glutamate (**18**)[11] in the presence of dicyclohexylcarbodiimide (DCC) and then deprotecting condensation product **19** (Scheme 5).[10] Compounds **7a-d**, **9a** and **16** were used as standards in the HPLC-ICP-MS analysis of Allium extracts.[7]



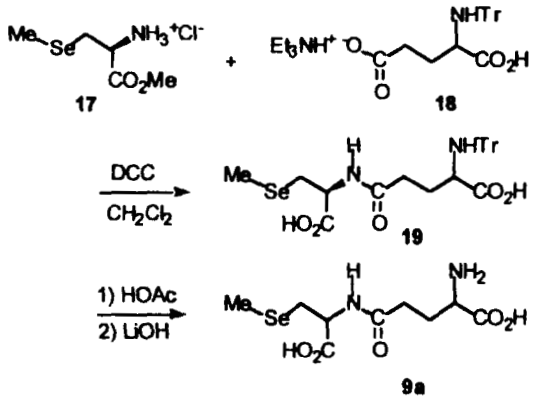
SCHEME 2. Synthesis of (Z)-Se-1-propenylselenocysteine ((Z)-**7b**) and (Z,Z)-bis(1-propenyl) diselenide ((Z,Z)-**13**)



SCHEME 3. Synthesis of 2-methyl-2-propyl (Z)-1-propenyl sulfide ((Z)-**15**)



SCHEME 4. Synthesis of selenolanthionine (**16**)



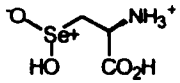
SCHEME 5. Synthesis of γ-Glutamyl *Se*-Methylselenocysteine (**9a**)

OXIDATION STUDIES

Background. Oxidation of selenomethionine (**6**) gives a stable selenoxide **20** or its hydrate **21**,[12] readily reduceable to **6**, e.g.with thiosulfate.[13] Under the same conditions, selenocysteine derivatives afford dehydroalanines by elimination.[12a] Selenomethionine selenoxide (**20**) and/or *Se*-methyl selenocysteine selenoxide (**8a**) are reported to be present in marine phytoplankton,[14] clover,[15] and cabbage.[16] The natural occurrence of 3-seleninoalanine, (**22**, $HO_2SeCH_2CH(NH_2)COOH$; "selenocysteine seleninic acid") and/or 3-seleninoalanine (**23**, $HO_3SeCH_2CH(NH_2)COOH$; "selenocysteic acid") has been proposed without spectroscopic proof or use of authentic samples.[13b,17]

$MeSe(O)CH_2CH_2CH(NH_2)CO_2H$

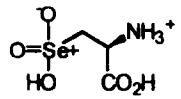
20



22

$MeSe(OH)_2CH_2CH_2CH(NH_2)CO_2H$

21



23

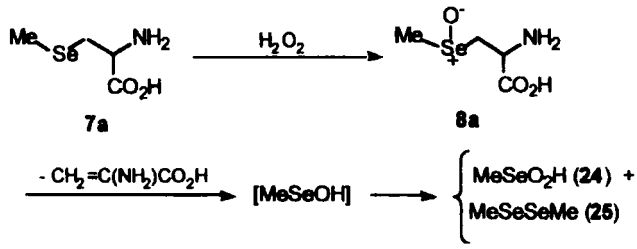
In collaboration with Peter Uden and coworkers, oxidation of selenoamino acids **7a-d** with excess H_2O_2 was investigated using HPLC-ICP-MS.[7e] For each compound oxidized a new selenium- containing peak was produced and the original peak disappeared. The oxidation products eluted at much shorter retention time than their precursors on the reversed-phase (RP) column, consistent with the increased polarity expected for selenoxides. Oxidation of a mixture of (*E/Z*)-*Se*-1-propenyl

selenocysteine (**7d**) led to a pair of new peaks, indicating that geometrical isomerism persisted unchanged in the oxidation products. Treatment of solutions of the oxidized selenoamino acids with thiosulfate restored the original selenoamino acids if the thiosulfate treatment was performed shortly after oxidation, before selenoxide decomposition took place.

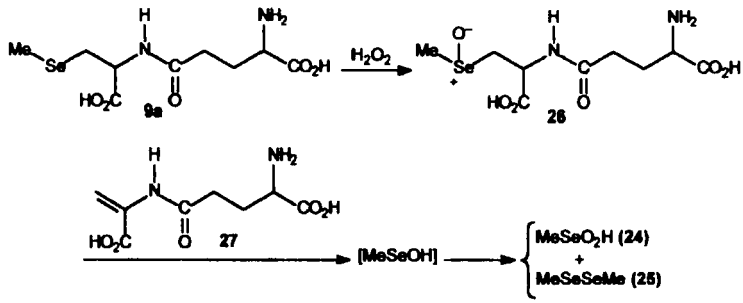
Oxidation of Selenomethionine (6).[10] As monitored by RP-HPLC, addition of an equivalent of H_2O_2 to **6** led to an immediate change in retention time from 7.3 min to 2.2 min. With H_2O_2 at pD 8 in D_2O, the ^1H NMR spectrum showed two singlets at δ = 3.05 and 3.01 replacing the δ 2.02 peak for **6**; similarly, the ^{77}Se NMR spectrum showed two singlets at δ 845 and 838 ppm replacing the δ 75 ppm peak for **6**. These observations are consistent with the conversion of **6** to a pair of diastereomeric selenoxides **20**. Analysis of a solution of oxidized **6** by HPLC-ESI-MS indicated selenoxide hydrate (**21**) at *m/z* 232.

Oxidation of Se-Methylselenocysteine (7a) and γ-Glutamyl-Se-methylselenocysteine (9a).[10] As monitored by RP-HPLC, addition of H_2O_2 to **7a** led to an immediate change in retention time from 3.4 min to 2.0 min. With H_2O_2 at pD 8 in D_2O, the ^1H NMR spectrum showed two singlets at δ = 2.797 and 2.803 replacing the δ 2.05 peak for **7a**; similarly, the ^{77}Se NMR spectrum showed two singlets at δ 853 and 854 ppm replacing the δ 38 peak for **7a**. These observations suggest conversion of **7a** to a pair of diastereomeric selenoxides **8a**. After 24 h the final products were 2:1 methaneseleninic acid (**24**):dimethyl diselenide (**25**) and ammonium pyruvate, as confirmed by NMR and HPLC-ESI-MS (Scheme 6).[7c,d] The results were similar at pD 1 but the reactions were much faster. Similarly, oxidation of **9a** rapidly led to

elimination products **24**, **25** and **27** via selenoxide **26** (Scheme 7). Crystals of **24**, characterized by X-ray crystallography, showed a pyramidal configuration about the selenium atom with Se-C 1.925(8) Å, Se–O 1.672(7) Å, Se–OH 1.756(7) Å, ∠ OSeO 103.0(3)°, ∠ HO-Se-C 93.5(3)° and ∠ OSeC 101.4(3)°.[10] Hydrogen bonds link the molecules together in spirals along the c axis. The structure is isomorphous to that of methanesulfinic acid.[18]



SCHEME 6. Oxidation of *Se*-Methylselenocysteine (**7a**)

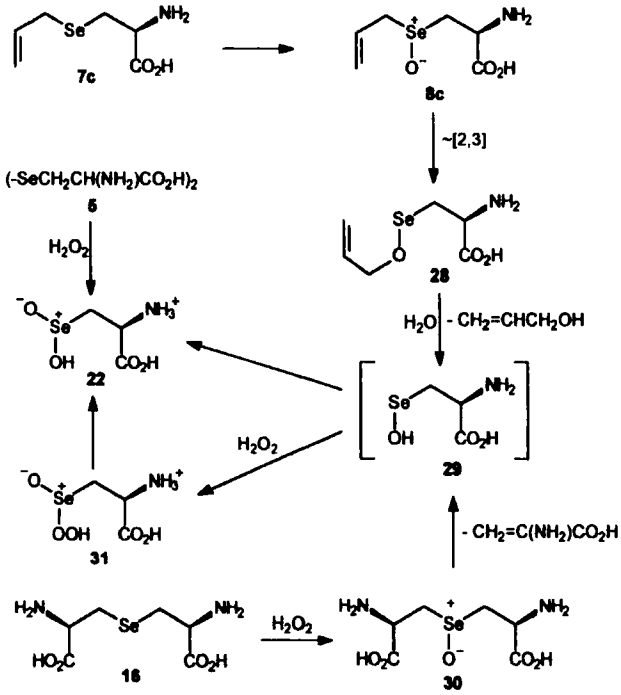


SCHEME 7. Oxidation of g-Glutamyl *Se*-Methylselenocysteine (**9a**)

Oxidation of Se-2-Propenylselenocysteine (7c) and Selenolanthionine (16).[10] Oxidation of **6c** with H_2O_2 at pD 8 in D_2O, led to a reaction which was 95% complete after 1.5 h as judged by NMR, giving allyl alcohol (proven by ^1H NMR and GC-MS) and a selenium-containing compound **22**. The latter compound is also formed on oxidation of selenolanthionine (**16**). Based on the spectroscopic data[10] and on mechanistic grounds (Scheme 8), **22** is identified as 3-seleninoalanine (selenocysteine seleninic acid). Allyl alcohol and **22** are presumably produced by a facile [2,3]-sigmatropic rearrangment of *Se*-2-propenylselenocysteine *Se*-oxide (**8c**)[19] followed by hydrolysis of the resultant selenenic ester **28** to 3-selenenoalanine (**29**), which then undergoes further reactions. The ^{13}C NMR spectrum of **22** indicated two aliphatic carbons (CH, δ 54.9, and CH_2, 53.1) and a COOH carbon at 180.1 ppm. The CH_2 group, which shows ^{77}Se-satellites, is deshielded compared the CH_2 group in selenocystine (**5**)(δ 26.6) but is similar to the chemical shift of the CH_2 group in 3-sulfinoalanine ($HO_2SCH_2CH(NH_3^+)CO_2H$; δ 54.2). The ^1H NMR spectrum of **22** is consistent with a compound of type $X\text{-}SeCH_aH_bCH(NH_3^+)CO_2^-$. The results of oxidation at pD 5 were similar. Using RP-HPLC-ICP-MS and RP-HPLC-ESI-MS within 2 h of addition of H_2O_2, the formation of a short lived, polar selenium-containing oxidation product, most likely **8c** or **28**, was indicated by a peak of *m/z* 226, while a second, more persistent, polar selenium-containing compound was indicated by a peak with the highest mass at *m/z* 185.[7c,d]

We also examined the oxidation of selenolanthionine (**16**) and selenocystine (**5**). We anticipated that the selenoxide **30** of **16** would decompose to pyruvate and **29** (Scheme 8). Oxidation of **5** is reported to

give 3-seleninoalanine (**22**) or 3-selenonoalanine (**23**).[14b] Oxidation of **16** with H_2O_2 gave ammonium pyruvate after 1.5 h. As monitored by RP-HPLC-ICP-MS, addition of H_2O_2 to **16** led to immediate formation of a polar selenium-containing compound with a similar retention time to that of the *m/z* 185 product from oxidation of **7c**.[20] Initially this peak had a (presumed) MH^+ ion at m/z 218, corresponding to selenocysteine perseleninic acid (**31**). After 24 h this peak was replaced with a peak of retention time and a mass spectral pattern (*m/z* 185, 154, 131, 111) identical to that of the *m/z* 185 product from oxidation of **7c**.[20]



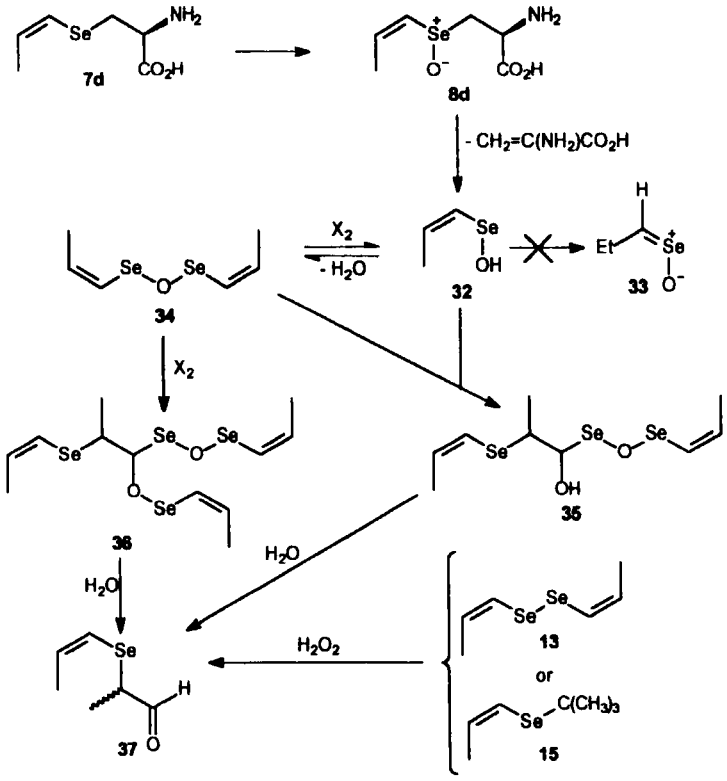
SCHEME 8. Oxidation of Selenocysteine (**5**), *Se*-2-Propenyl selenocysteine (**7c**) and Selenolanthionine (**16**)

While the *m/z* 185 peaks from oxidation of **6c** and **16** might be selenenic acid **29** (perhaps stabilized by intramolecular hydrogen bonding), it is more likely that the *m/z* 185 peak is a fragment ion derived from a heavier parent, e.g. loss of HO• from 3-seleninoalanine (**22**), since under the ESI-MS conditions used, compounds **6a**, **6c** and **6d** show no parent ions but only fragment ions. Furthermore, in the mass spectrum of $MeSeO_2H$ the fragment resulting from loss of HO• is 58% as abundant as the MH^+ ion. It is known that selenenic acids can be oxidized to seleninic acids when generated in the presence of H_2O_2 in addition to undergoing disproportionation to seleninic acids.[21]

During the course of the oxidation of **16**, the ^{77}Se NMR spectrum underwent a change from a single peak in **16** at δ 82 ppm to a pair of peaks at 858 and 865 ppm (presumably selenoxide **30**) to a final product showing a peak at 1195 ppm, which is within the range of chemical shifts reported for seleninic acids (1240-1175 ppm)[22] but distinct from the chemical shifts for selenenic acids (ca. 1143-1066 ppm)[23] and selenonic acids (1022 ppm).[24] In particular, the observed shift of 1195 ppm is quite close to the values of 1188 and 1190 ppm reported for the 3-seleninoalanine component of oxidized selenosubtilisin.[22] Efforts to observe the selenenic acid corresponding to selenosubtilisin were unsuccessful.[22] We also find that oxidation of selenocystine (**5**) with H_2O_2 gives **22**.

Oxidation of Se-(E,Z)-1-Propenylselenocysteine (6d).[10] With formation of methaneselenenic acid, MeSeOH, on oxidation of *Se*-methylselenocysteine (**7a**), it was of interest to determine if a similar process would occur with **7d** giving 1-propeneselenenic acid (**32**; Scheme 9), since the latter might then rearrange to give the unknown

propaneselenal *Se*-oxide (**33**), the selenium analog of the onion lachrymatory factor (**4**, Scheme 1).[4] Oxidation of **7d** at pH 8 with H_2O_2 afforded in 69% yield a yellow oil identified[10] as 2-((*E,Z*)-1-propenylseleno)propanal (**37**).



SCHEME 9. Oxidation of (Z)-*Se*-1-Propenylselenocysteine (**7d**), (Z,Z)-Bis(1-propenyl)diselenide ((Z,Z)-**13**) and 2-Methyl-2-propyl (Z)-1-Propenyl sulfide ((Z)-**15**)

We propose that *Se-(E,Z)*-1-propenylselenocysteine *Se*-oxide (**8d**) undergoes elimination giving 1-propeneselenenic acid (**32**) which is in equilibrium with the corresponding selenenic anhydride (**34**).[23b,25] Compound **34** adds to itself to give intermediate **36** which on hydrolysis gives **37**. Alternatively, addition of **32** to **34** followed by hydrolysis of adduct **35** could also afford **37**. Similar processes are known.[26] In support of this mechanism, oxidation of **13** (which should afford **34**) and **15** (which should yield **32**) both gave **37** in more than 50% yield.

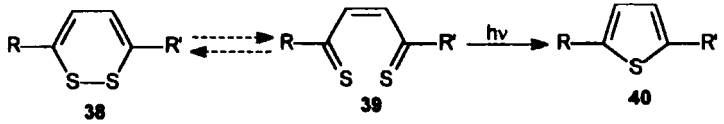
As can be seen, Se-oxides **8** undergo reactions not seen at room temperature with sulfoxides **2**. The enhanced reactivity of the selenoxides is a consequence of the facile elimination and rearrangement seen with these compounds.

1,2-DICHALCOGENINS

Since the discovery[27] that plants of the sunflower (Asteraceae) family contain thiarubrines A and B (**38a,b**, Scheme 10) and related antibiotic pigments,[28] natural and synthetic 1,2-dithiins (**38**, 1,2-dithiacyclohexadienes) have attracted considerable attention.[29] Of particular interest is the potential antiaromaticity of **38** with its 8π electrons,[30] valence tautomerism involving the ring-opened form **39**,[27b] the basis for the red color (λ_{max} 452 nm in **38c** and ca. 480 in **38a,b**) in the absence of a conventional chromophore, and the facile light-induced extrusion of sulfur to form thiophenes **40**.[28,29d,31a,32] Thiarubrines **38a,b** display antibiotic activity both in the light and dark; thiophene **40a** from extrusion of sulfur from **38a** is biologically active only in the light.[28c]

The above features have been explored by theoretical and spectroscopic studies of the parent compound and certain of its derivatives, including **38a,b**.[30]

In connection with a detailed investigation of the chemistry of 1,2-dithiins **38**[33] we have synthesized the previously unknown selenium analogs of **38**, namely 1,2-diselenin (**42a**) and 2-selenathiin (**42c**) and certain of their derivatives.



a: R = CH_2=CHC≡CC≡C-, R' = MeC≡C- (thiarubrine A);
b: R = CH_2CHC≡C-, R' = MeC≡CC≡C- (thiarubrine B);
c: R = R' = H; **d**: R = R' = Ph; **e**: R = R' = CH_2OH;
f: R = R' = Me; **g**: R = R' = t-Bu; **h**: R = R' = i-Pr; **i**: R = R' = TMS

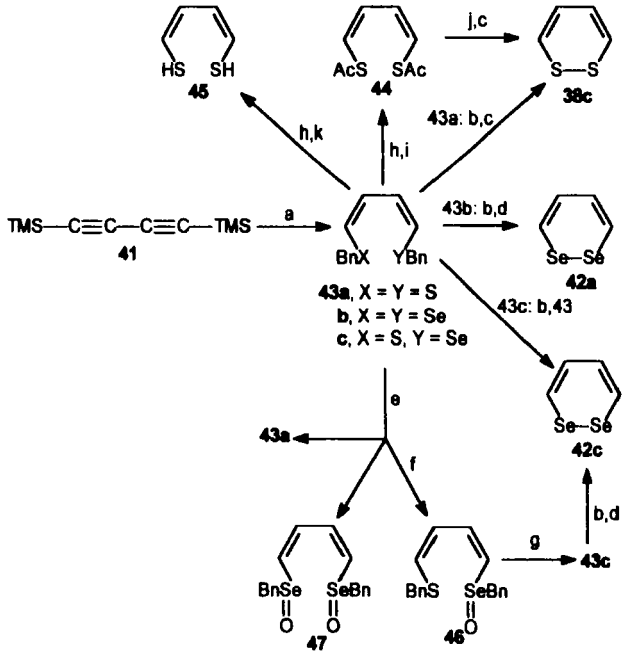
SCHEME 10 Thiarubines and other 1,2-Dithiins

Synthesis of **38c** involves reaction of 1,4-bis(trimethylsilyl)-1,3-butadiyne (**41**) with BnSNa in refluxing methanol, cleavage of the resulting **43a** with lithium 1-(*N*,*N*-dimethylamino)naphthalenide (LDMAN) in THF, and trapping of the resulting dithiolate with acetyl chloride to afford (*Z*,*Z*)-1,3-butadiene-1,4-dithiol *S*,*S*-diacetate (**44**) in good yield[31a]. Compound **44** is a conveniently stored precursor to **38c**, which can then be generated in 73% yield by exposure of **44** to KOH in methanol at 0 °C followed by oxidation with iodine (Scheme 11). Compound **38c** is an orange light sensitive liquid which is stable if stored in the dark at -78 °C. 1,2-Diselenin (**42a**) is similarly prepared by

reaction of **41** with BnSeNa, debenzylation (Li/NH_3) of (*Z,Z*)-1,4-bis(benzylseleno)-1,3-butadiene (**43b**), and air oxidation in the presence of hexane-hexadecane. The volatile but easily polymerized wine-red **42a** is purified, after removal of hexane, by vacuum distillation from hexadecane into a liquid N_2-chilled trap.[33b] Preparation of **42c** is accomplished by reacting **41b** with a mixture of BnSNa and BnSeNa, oxidizing the mixed product with excess H_2O_2, separating the *Se*-oxide (**46**) of (*Z,Z*)-1-benzylseleno-4-benzylthio-1,3-butadiene (**43c**) from bis-(*Se*-oxide) (**47**) and unoxidized **43a**, reducing *Se*-oxide **46** with thiosulfate to **43c**, and treating the latter with Na/NH_3 followed by workup as above. Hexadecane solutions of **42a,c** can be used as sources of these compounds for gas-phase or matrix studies.

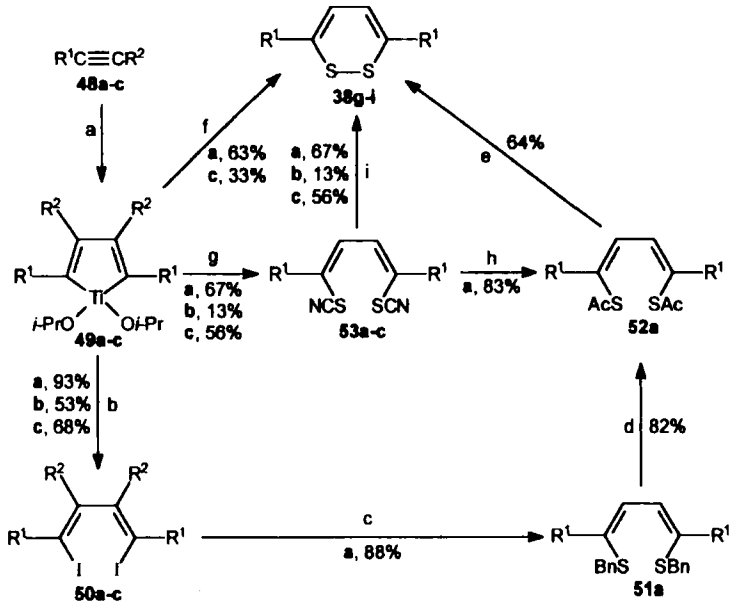
A new synthesis of substituted 1,2-dichalcogenins was developed based upon the chemistry of titanacyclopentadienes developed by Sato and coworkers.[34] The ready availability of *Z,Z*-1,4-diiodo-1,3-butadienes **50** from titanacyclopentadienes **49** (Scheme 12), in turn available from alkynes **48** and (η^2-propene)($Ti(OiPr)_2$,[34c] suggested a useful approach to 1,2-dithiins **38** via lithiation followed by treatment with dibenzyl disulfide (BnSSBn) or other sulfur electrophiles. Terminal alkynes 3,3-dimethylbutyne, 3-methylbutyne, and trimethylsilylethyne (**48a-c**: R^2 = H; R^1 = *t*-Bu, *i*-Pr and TMS, respectively) afford **49a-c**, which give diiodo compounds **50a-c** with I_2. Sequential treatment of **50a** with *n*-BuLi, BnSSBn, lithium dimethylaminonaphthalene (LDMAN), acetyl chloride and KOH/MeOH affords 3,6-bis(*t*-butyl)-1,2-dithiin (e.g. **50a** → **51a** → **52a** → **38g**; 46%). Using thiocyanogen ($(SCN)_2$) instead of I_2 and cyclizing with Bu_4NF or SmI_2,[35] **38g** is obtained from **49a** via **53a** (62%), **38h** from **49b** via **53b** (13%), and **38i** from **49c** via **53c**

(30%). With S_2Cl_2, **49a** gives **38g** (63%) and thiophene **40g** (16%)[36a] while **49c** gives **38i** (33%) and **40i** (33%).[36b] On exposure to light, dithiins **38g-i** give thiophenes **40g-i**.[32] When selenocyanogen ($(SeCN)_2$),[37a] is substituted for thiocyanogen, 3,6-bis(*t*-butyl)-1,2-diselenin (**42b**) could be prepared in 49% yield from **48a** (**48a** → **49a** → **54** → **42b**; Scheme 13), while reaction of selenium diselenocyanate ($Se(SeCN)_2$)[37b] with **48a** affords 2,5-bis(*t*-butyl)selenophene (**55**). On exposure to light, 1,2-diselenin **42b** gives selenophene **55**.



a) BnXNa / BnYNa (X, Y = S or Se). b) Li or Na / NH_3. c) I_2. d) O_2, hexane-hexadecane. e) H_2O_2, THF. f) chromatography, g) $Na_2S_2O_3$, MeOH. h) LDMAN. i), AcCl. j) KOH, MeOH. k) H^+.

SCHEME 11. Synthesis of 1,2-Dithiin, 2-Selenathiin and 1,2-Diselenin



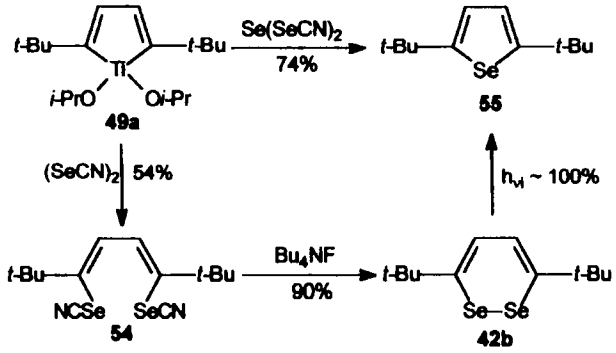
a, R^1 = t-Bu, R^2 = H;
b, R^1 = i-Pr, R^2 = H;
c, R^1 = TMS, R^2 = H.

a) $Ti(OiPr)_4$, *i*-PrMgCl. b) I_2. c) *n*-BuLi; $(BnS)_2$. d) LDMAN; AcCl. e) KOH, MeOH; O_2 or I_2. f) S_2Cl_2. g) $(SCN)_2$, CH_2Cl_2. h) $LiAlH_4$; AcCl. i) Bu_2NF or SmI_2.

SCHEME 12. The Titanacyclopentadiene route to 1,2-Dithiins

The UV maxima for 1,2-diselenin (504 nm) and 2-selenathiin (488 nm) are bathochromically shifted from the maxima of 1,2-dithiin (452 nm) whereas selenophene (249 nm) and thiophene (231 nm) show similar maxima.[33e] Oxidation of 1,2-dithiins and 1,2-diselenins give the corresponding 1-oxide and, with 1,2-dithiins and excess oxidant, 1,1-dioxides; oxidation of 2-selenathiin gives the 2-oxide. In all cases, oxidation of the 1,2-dichalcogenins leads to a hypsochromic shift in the

UV maxima; bathochromic shifts in the UV maxima occur on oxidation of thiophene to its S,S-dioxide.



SCHEME 13. Synthesis of 3,6-Di-*t*-butyl-1,2-diselenin (**42b**)

Due to the instability of the 1,2-diselenin 1-oxides (selenoseleninates) at room temperature, the oxidations were conducted in NMR tubes at -40 °C in CD_2Cl_2 and the ^1H and ^{13}C NMR spectra were obtained immediately.[33e] Electrochemical oxidation of 1,2-dichalcogenins, which have a twisted geometry, affords planar radical cations by an EC mechanism. Theoretical calculations give a flattened or planar structure for the 1,2-dithiin radical cation and a fully planar structure for the 1,2-diselenin radical cation.[33e] The ^{77}Se NMR chemical shifts of 1,2-diselenin (δ 119) are characteristically high-field-shifted with respect to open chain diselenides (PhSeSePh, δ 464; MeSeSeMe, δ 275) and selenophene (δ 565), in good agreement with results of GIAO-DFT calculations based on MP2 and DFT optimum geometries.[33e] On the basis of a detailed analysis of photoelectron spectra, the unusual

colors of 1,2-dichalcogenins are postulated to be associated with low energy HOMO-to-LUMO π/lone pair to chalcogen σ^* transitions.[33f]

ACKNOWLEDGMENT

I am deeply grateful to my coworkers and collaborators whose names appear in the references. This work was supported by grants from NSF, NIH-NCI, and the NRI Competitive Grants Program/USDA (Awards No. 92-37500-8068 and 96-35500-3351).

References

[1] Y. Xu and E. Kool, *J. Am. Chem. Soc.*, **122**, 9040 (2000).
[2] E. Block, *Angew. Chem., Int. Ed. Engl.*, **31**, 1135 (1992).
[3] H.P. Koch and L.D. Lawson, *Garlic. The Science and Therapeutic Applications of Allium sativum L. and Related Species*,William and Wilkens, Baltimore (1996).
[4] E. Block, J.Z. Gillies, C.W. Gillies, A.A. Bazzi, D. Putman, L.K. Revelle, A. Wall, D. Wang, and X. Zhang, *J. Am. Chem. Soc.*, **118**, 7492 (1996).
[5] C. -G. Spåre and A.I. Virtanen, *Acta Chem. Scand.*, **18**, 280 (1964).
[6] C. Ip and D.J. Lisk, *Carcinogenesis*, **16**, 2649 (1995).
[7] (a) M. Kotrebai, S.M. Bird, J.F. Tyson, E. Block, and P.C. Uden, *Spectrochim. Acta B*, **54**, 1573 (1999). (b) M. Kotrebai, M. Birringer, J.F. Tyson, E. Block, and P.C. Uden, *Anal. Commun.*, **36**, 249 (1999). (c) M. Kotrebai, M. Birringer, J.F. Tyson, E. Block, and P.C. Uden, *Analyst*, **125**, 71 (2000). (d) M. Kotrebai, J. F. Tyson, E. Block, and P.C. Uden, *J. Chromatogr. A*, **866**, 51 (2000). (e) P.C. Uden, S.M. Bird, M. Kotrebai, P. Nolibos, J.F. Tyson, E. Block, and E. Denoyer, *Fresenius' J. Anal. Chem.*, **362**, 447 (1998). (f) C. Ip, M. Birringer, E. Block, M. Kotrebai, J.F. Tyson, P.C. Uden, and D.J. Lisk, *J. Agric. Food Chem.*, **48**, 2062 (2000). (g) S. McSheehy, W. Yang, F. Pannier, J. Szpunar, R. Lobinski, J. Auger, and M. Potin-Gautier, *Anal. Chim. Acta*, **421**, 147 (2000).
[8] (a) C. Ip and D. Lisk, *Carcinogenesis*, **15**, 1881 (1994). (b) C. Ip and D. Lisk, *Nutr. Cancer*, **28**, 184 (1997). (c) C. Ip, D. Lisk, and G.S. Stoewsand, *Nutr. Cancer*, **17**, 279 (1992). (d) C. Ip, Z. Zhu, H.J. Thompson, D. Lisk, and H.E. Ganther, *Anticancer Res.*, **19**, 2875 (1999). (e) Z. Zhu, W. Jiang, H.E. Ganther, C. Ip, and H.J. Thompson, *Biochem. Pharmacol.*, **60**, 1467 (2000). (f) K. El-Bayoumy, Y.H. Chae, P. Upadhyaya, and C. Ip, *Anticancer Res.*, **16**, 2911 (1996).
[9] (a) I. Andreadou, W.M.P.B. Menge, J.N.M. Commandeur, E. A. Worthington, and N.P.E. Vermeulen, *J Med Chem.*, **39**, 2040 (1996). (b) J.N.M. Commandeur, I. Andreadou, M. Rooseboom, M. Out, L.J. De Leur, E. Groot, and N.P.E. Vermeulen, *J. Pharmacol. Exp. Ther.*, **294**, 753 (2000).
[10] E. Block, M. Birringer, W. Jiang, T. Nakahodo, H.J. Thompson, P. J. Toscano, H. Uzar, X. Zhang, and Z. Zhu, *J. Agric. Food Chem.*, in press.
[11] G. Amiard, R. Heymes, and L. Velluz, *Bull. Soc. Chim. Fr.*, 698 (1956).
[12] (a) R. Walter and J. Roy, *J. Org. Chem.*, **36**, 2561 (1971). (b) H.A. Zainal, D.E. LaCroix, and W.R. Wolf, *Fresenius J. Anal. Chem.*, **356**, 311 (1996).
[13] (a) A.A. Isab, *Inorg. Chim. Acta*, **80**, L3 (1983). (b) A. Assmann, M. Bonifacic, K. Briviba, H. Sies, and K. -D. Asmus, *Free Rad. Res.*, **32**, 371 (2000).
[14] (a) J.J. Wrench, *Marine Biol.*, **49**, 231 (1978). (b) N.R. Bottino, C.H. Banks, K.J. Irgolic, P. Micks, A.E. Wheeler, and R.A. Zingaro, *Phytochemistry*, **23**, 2445 (1984).

[15] P.J. Peterson and G.W. Butler, *Austral. J. Biol. Sci.*, **15**, 126 (1962).
[16] J.W. Hamilton, *J. Agric. Food Chem.*, **23**, 1150 (1975).
[17] (a) K.A. Caldwell and A.L. Tappel, *Biochemistry*, **3**, 1643 (1964). (b) O.E. Olson, E.J. Novacek, E.I. Whitehead, and I.S. Palmer, *Phytochemistry*, **9**, 1181 (1970). (c) S.E. Ramadan, A.A. Razak, Y.A. Yousseff, and N.M. Sedky, *Biolog. Trace Element Res.*, **18**, 161 (1988). (d) W. Maher, M. Deaker, D. Jolley, F. Krikowa, B. Roberts, *Appl. Organomet. Chem.*, **11**, 313 (1997).
[18] K. Seff, E.G. Heidner, M. Meyers, and K.N. Trueblood, *Acta Crystallogr., Part B*, **25**, 350 (1969).
[19] H.J. Reich, K.E. Yelm, and S. Wollowitz, *J. Am. Chem. Soc.*, **105**, 2503 (1983).
[20] M. Kotrebai, Ph. D. Thesis, University of Massachusetts, Amherst, MA, 2000.
[21] K.B. Sharpless and R.F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).
[22] K.L. House, R.B. Dunlap, J.D. Odom, Z. -P. Wu, and D. Hilvert, *J. Am. Chem. Soc.*, **114**, 8573 (1992).
[23] (a) K. Goto and R. Okazaki, *Liebigs Ann./Recueil*, 2393 (1997). (b) H.J. Reich, W.W. Willis, Jr., and S. Wollowitz, *Tetrahedron Lett.*, **23**, 3319 (1982). (c) T. Saiki, K. Goto, and R. Okazaki, *Angew. Chem. Int. Ed. Engl.*, **36**, 2223 (1997).
[24] M. Iwaoka and S. Tomoda, *J. Am. Chem. Soc.*, **116**, 2557 (1994).
[25] J.L. Kice, F. McAfee, and H. Slebocka-Tilk, *Tetrahedron Lett.*, **23**, 3323 (1982).
[26] H.J. Reich and C.P. Jasperse, *J. Org. Chem.* **53**, 2389 (1988).
[27] (a) J.T. Mortensen, J.S. Sørensen, and N.A. Sørensen, *Acta Chem. Scand.* **1964**, *18*, 2392. (b) F. Bohlmann and K. -M. Kleine, *Chem. Ber.*, **98**, 3081 (1965).
[28] (a) R.A. Norton, A.J. Finlayson, and G.H.N. Towers, *Phytochemistry*, **24**, 356 (1985). (b) E. Rodriguez, In *Biologically Active Natural Products*; Cutler, H.G., Ed.; ACS Symposium Series 380; American Chemical Society: Washington DC, p 432 (1988). (c) S.M. Ellis, F. Balza, J.B. Constabel, and G.H.N. Towers, In *Light-Activated Pest Control*, ACS Symposium Series 616; American Chemical Society: Washington DC, p. 165 (1995). (d) J.E. Page, M.A. Huffman, V. Smith, and G.H.N. Towers, *J. Chem. Ecol.*, **23**, 2211 (1997). (e) G. Guillet, B.J.R. Philogene, J. O'Meara, T. Durst, and J.T. Arnason, *Phytochemistry*, **46**, 495 (1997). (f) S.S. De Viala, B.B. Brodi, E. Rodriguez, and D.M. Gibson, *J. Nematol.*, **30**, 192 (1998) and references therein,.
[29] (a) W. Schroth, E. Hintzsche, H. Jordan, T. Jende, R. Spitzner, and I. Thondorf, *Tetrahedron*, **53**, 7509 (1997). (b) W. Schroth, R. Spitzner, and C. Bruhn, *Eur. J. Org. Chem.*, 2365 (1998). (c) Y. Wang, M. Koreeda, T. Chatterji, and K.S. Gates, *J. Org. Chem.*, **63**, 8644 (1998). (d) E. Block, *Phosphorus, Sulfur, Silicon Rel. Elements*, **153/154**, 173 (1999) and ref. therein.
[30] (a) V. Pitchko and J.D. Goddard, *Chem. Phys. Lett.*, **289**, 391 (1998). (b) T. Ishida, S. Oe, and J. Aihara, *Theochem*, **461–2**, 553 (1999). (c) J. Aihara and T. Ishida, *Bull. Chem. Soc. Jpn.*, **72**, 937 (1999). (d) J. Fabian, M. Mann, and M. Petiau, *J. Mol. Model.*, **6**, 177 (2000), and references therein.
[31] (a) W. Schroth, F. Billig, and G. Reinhold, *Angew. Chem., Int. Edn. Engl.*, **6**, 698 (1967). (b) W. Schroth, F. Billig, and H. Languth, *Z. Chem.*, **5**, 353 (1965). (c) W. Schroth, F. Billig, and G. Reinhold, *Z. Chem.*, **5**, 352 (1965).
[32] (a) E. Block, R. DeOrazio, C. Guo, J. Page, R.S. Sheridan, J. Toscano, G.H.N. Towers, C. -W. Wang, and X. Zhang, *J. Am. Chem. Soc.*, **118**, 4719 (1996). (b) J. Page, E. Block, and G.H.N. Towers, *Photochem. Photobiol.*, **70**, 159 (1999).
[33] (a) E. Block, C. Guo, M. Thiruvazhi, and P.J. Toscano, *J. Am. Chem. Soc.*, **116**, 9403 (1994). (b) J.Z. Gillies, C.W. Gillies, E.A. Cotter, E. Block, and R. DeOrazio, *J. Mol. Spectros.*, **180**, 139 (1996). (c) R.S. Glass, J.R. Pollard, T.B. Schroeder, D.L. Lichtenberger, E. Block, R. DeOrazio, C. Guo, M. Thiruvazhi, *Phosphorus, Sulfur, Silicon Rel. Elements*, **120/121**, 439 (1997). (d) E. Block, M. Birringer, and C. He, *Angew. Chem., Int. Edn. Engl.*, **38**, 1604 (1999). (e) E. Block, M. Birringer, R. DeOrazio, J. Fabian, R.S. Glass, C. Guo, C. He, E. Lorance, Q. Qian, T.B. Schroeder, Z. Shan, M. Thiruvazhi, G.S. Wilson, and X. Zhang, *J. Am. Chem. Soc.*, **122**, 5052 (2000). (f) R.S.

Glass, N.E. Gruhn, D.L. Lichtenberger, E. Lorance, J.R. Pollard, M. Birringer, E. Block, R. DeOrazio, C. He, Z. Shan, and X. Zhang, *J. Am. Chem. Soc.* **122**, 5065 (2000).

[34] (a) F. Sato, H. Urabe, S. Okamoto, *Chem. Rev.*, **100**, 8, 2835 (2000). (b) F. Sato, H. Urabe, S. Okamoto, *Synlett*, **6**, 753 (2000). (c) S. Yamaguchi, R. -Z. Jin, K. Tamao, and F. Sato, *J. Org. Chem*, **63**, 10060 (1998).

[35] X. Jia, Y. Zhang, and X. Zhou, *Tetrahedron Lett.*, **35**, 8833 (1994).

[36] (a) H. Wynberg and U.E. Wiersum, *J. Org. Chem.*, **30**, 1058 (1965). (b) T.J. Barton and G.P. Hussman, *J. Org. Chem.*, **50**, 5881 (1985). (c) J. Yin and W.M. Jones, *Tetrahedron*, **51**, 4395 (1995).

[37] (a) P.T. Meinke, G.A. Krafft, and A. Guram, *J. Org. Chem.*, **53**, 3632 (1988). (b) D.H.R. Barton, D. Bridon, Y. Herve, P. Potier, J. Thierry, and S.Z.A. Zard, *Tetrahedron*, **42**, 4983 (1986).