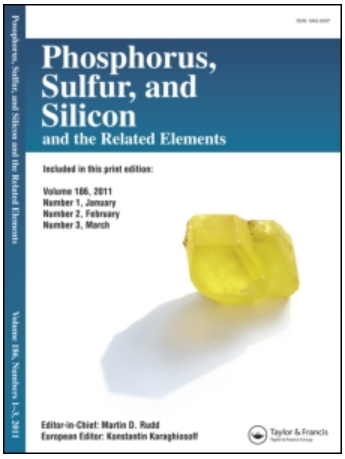


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Recent Advances in the Chemistry of 1,2-Dithiins

Eric Block

To cite this Article Block, Eric(1999) 'Recent Advances in the Chemistry of 1,2-Dithiins', Phosphorus, Sulfur, and Silicon and the Related Elements, 153: 1, 173 — 192
To link to this Article: DOI: 10.1080/10426509908546433
URL: http://dx.doi.org/10.1080/10426509908546433

Phosphorus, Sulfur and Silicon, 1999, Vol. 153-154, pp. 173-192
Reprints available directly from the publisher
Photocopying permitted by license only

Recent Advances in the Chemistry of 1,2-Dithiins*

ERIC BLOCK

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

The natural occurrence, synthesis, reactions and properties of non-anellated 1,2-dithiins are reviewed. Recent results from the author's laboratories are presented.

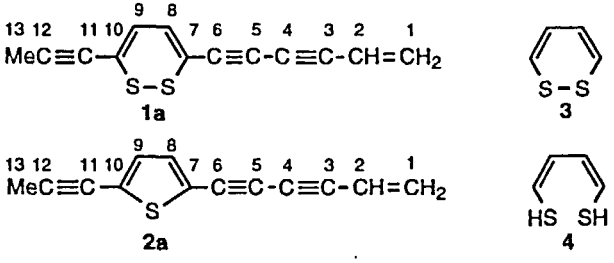
Keywords: 1; 2-dithiins; thiarubrines; thiophenes; sulfur protecting groups; photochemistry

INTRODUCTION

In 1964-5 Mortensen[1] and Bohlmann[2] independently isolated a red, light-sensitive 1,2-dithiin-containing pigment **1a** (3-(5-hexen-1,3-diyn-yl)-6-(1-propynyl)-1,2-dithiin), later[3] called thiarubrine A, from Asteraceae species (see Figure 1 for known thiarubrines), along with the colorless thiophene analog **2a**. The unprecedented cyclic 1,2-dithiin ring in **1a** seemed questionable at the time and various alternative structures were considered. However, also in 1965, Schroth synthesized the parent 1,2-dithiin (**3**) from 1,3-butadiyne, unequivocally favoring the cyclic structure.[4] The synthesis of 1,2-dithiin by Schroth was an indirect result of his interest in (*Z,Z*)-1,4-butadiene-1,4-dithiol (**4**), an isolable precursor in his synthesis of **3**.[5] The apparent simplicity of the 1,2-dithiin ring belies its rich chemistry. The red color of the thi-

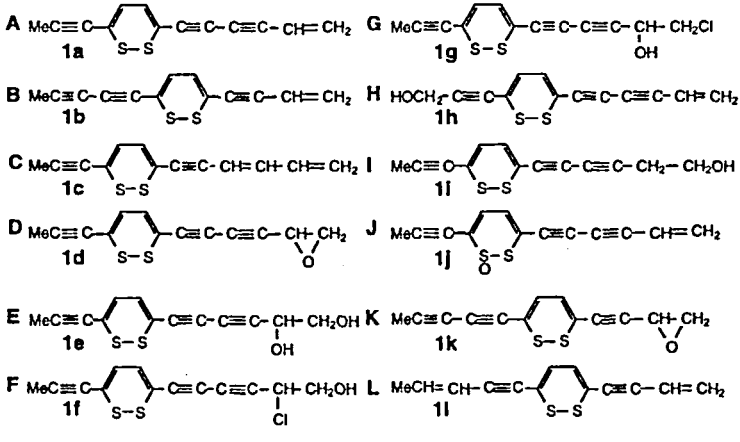
* Dedicated to Professor Werner Schroth on the occasion of his 70th birthday

arubrines and 1,2-dithiin itself, the unusual sensitivity of these compounds to visible light, which leads to thiophene formation, the questions of antiaromaticity, structure and valence tautomerism of the formally 8π-electron 1,2-dithiin ring, the light-dependent biological activity of the thiarubrines, and the challenge of synthesizing the thiarubrines and variously substituted 1,2-dithiins make for a fascinating chapter in organosulfur chemistry. This paper briefly reviews work done on non anellated 1,2-dithiins by the author and by others.[6]



NATURAL PRODUCTS CHEMISTRY

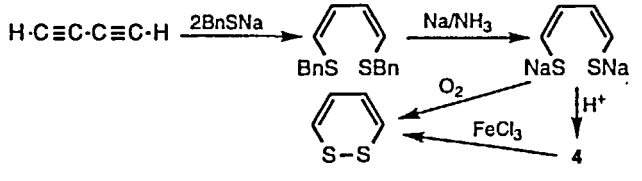
Figure 1: Naturally Occurring Thiarubrines (1,2-Dithia-3,5-cyclohexadiene Polyynes)



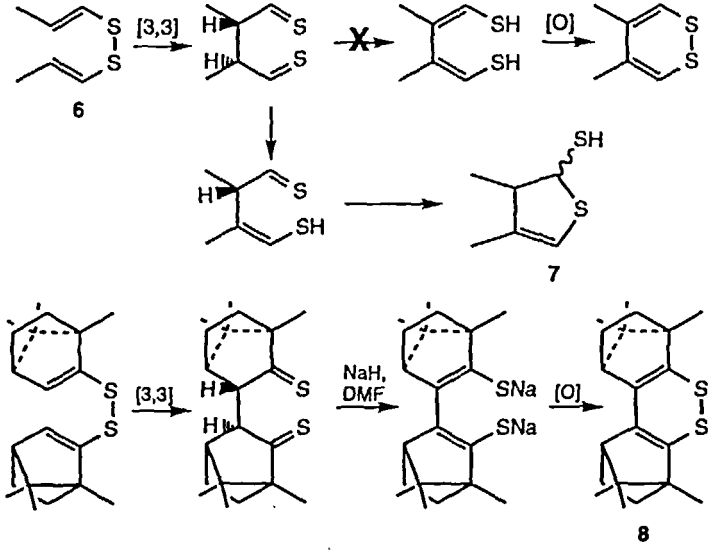
Following the initial report on the natural occurrence of **1a**, a variety of other polyyne 1,2-dithiins **1b-1l**, called thiarubrines B-L (Figure 1), have been found in plants from the species Asteraceae[6b] such as *Rudbeckia hirta* L., the black-eyed Susan, and *Ambrosia trifida* (ragweed). Thiarubrines, along with the corresponding thiophenes, such as **2a**, are formed from straight chain polyacetylenic compounds such as 3,5,7,9,11-tridecapentayne-1-ene by addition of sulfate-derived compounds such as cysteine.[7b] Studies involving $^{35}SO_4^{-2}$ show that dithiin **1a** and thiophene **2a**, are not synthesized sequentially but rather in a parallel manner.[7a] Thiarubrines possess potent in vitro antibiotic, antifungal, antiviral, anti-HIV, and nematocidal activity[8,9] and are toxic against mosquito larvae[10] both in the dark and under visible and near-ultraviolet (UV) irradiation. It was initially postulated that the swallowing of whole leaves of three *Aspilia* (Asteraceae) species by chimpanzees was for the purpose of self-medication associated with nematocidal thiarubines contained in the leaves.[11] However more recent work has established that in fact thiarubrines are not present in leaves from these plants, rendering the hypothesis unsubstantiated.[12]

SYNTHESIS

Schroth's pioneering synthesis of 1,2-dithiin **3** involves two-fold nucleophilic addition of α-toluenethiolate ion to 1,3-butadiyne, Na/NH_3 reductive cleavage of the adduct, and air oxidation.[4] Acidification of the product from Na/NH_3 treatment gave the isolable (*Z,Z*)-1,4-dimercapto-1,3-butadiene (**4**) which afforded **3** on $FeCl_3$ oxidation. Dithiol **4** could be stored as its diacetate derivative **5**. Starting from 1,4-diaryl-1,3-butadiynes various 3,6-diaryl-1,2-dithiins could be prepared.[5]



Initial efforts in our laboratories directed toward synthesis of 1,2-dithiins focussed on dithio-Claisen rearrangement of bis(1-alkenyl) disulfides followed by double thioenolization and oxidation. When this sequence was attempted with bis(1-propenyl) disulfide (**6**), isomers of 2-mercapto-3,4-dimethyl-2,3-dihydrothiophene (**7**) were isolated, likely formed by mono-thioenolization of the 1,4-dithial followed by intramolecular addition of the thiol to the thioaldehyde group.[13] The *dithio-Claisen-double thioenolization approach has been successfully* employed by Schroth in synthesizing diborneno dithiin **8**.[14]

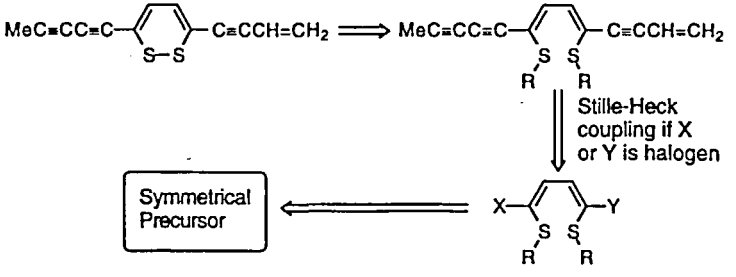


With thiarubrine B (**1b**, 3-(3-buten-1-ynyl)-6-(1,3-pentadiynyl)-1,2-dithiin; see Figure 1) as a synthetic target, we considered methods of constructing unsymmetrical 1,2-dithiins with *different* substituents at the 3- and 6-positions.[15] In view of the instability and reactivity of the 1,2-dithiin ring, it seemed best to defer ring generation until the final step. The key target molecule would then be a 1,3-butadiene with 1,4-(*Z*,*Z*)-bis(benzylthio) (or other protected sulfide sulfur) substitu-

ents. An appealing synthetic strategy, shown in Scheme 1, involves attachment of the acetylenic side chains using Stille-Heck chemistry. If a symmetrical precursor is used, a method is required for differentiating groups X and Y. A serendipitous solution to this challenging problem is given below.

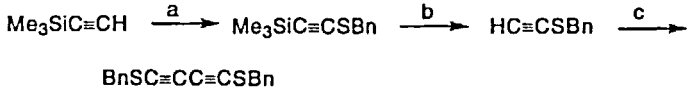
Encouraged by Magriotis' report[16a] that Bu_3SnH cleanly undergoes regio- and stereospecific addition to 1-phenylthioalkynes to give the corresponding (*E*)-1-(tributylstannyl)-1-(phenylthio)-1-alkenes, we examined the reaction of 1,4-bis(benzylthio)-1,3-butadiyne (**9**) with Ph_3SnH.[15] Compound **9** was easily prepared in 93% overall yield as shown in Scheme 2. In the key step, treatment of **9** with 2 equivalents of Ph_3SnH in the presence of $(Ph_3P)_4Pd$ and Et_3B gave crystalline double addition product **10**, whose structure was established by X-ray crystallography (Scheme 3).[15] Regiodifferentiation of **10** was readily achieved by replacement of one Ph_3Sn group with iodine (1.1 equivalent, 0 °C, 3 h), giving compound **11** in 97% yield. Replacement of the remaining tin in **11** with iodine to give (E,E)-1,4-bis(benzylthio)-1,4-diiodo-1,3-butadiene was considerably slower (16 h, 25 °C, 100% yield). A possible explanation for the lesser reactivity of **11** compared to **10** is given in Scheme 4: comparing the resonance forms for addition of I^+ to **10** and **11**, iodine is less able than tin to stabilize an adjacent positive charge.

Scheme 1: Strategy for Thiarubrine Synthesis



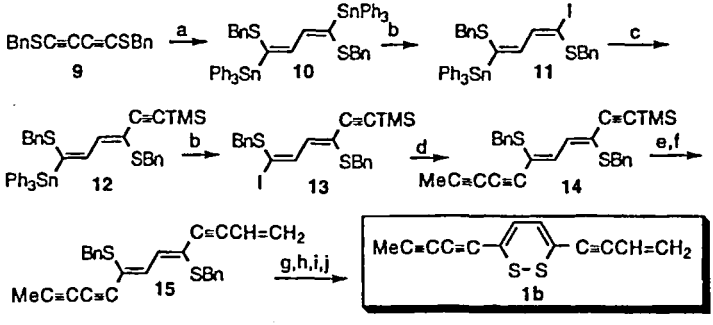
The polyyne side chains were introduced by a series of three Pd(II)-mediated coupling reactions as seen in Scheme 3. Removal of the benzyl groups was achieved by lithium 1-(*N*,*N*-dimethylamino)-naphthalenide (LDMAN),[16b] which avoids Birch reduction seen with Na/NH_3,[16c] followed by trapping with acetyl chloride to give the corresponding bis-thioacetate. The latter compound could be readily converted to thiarubrine B (**1b**) by brief treatment with KOH/MeOH followed by iodine.[15] The bis-thioacetate could be more readily purified than the sensitive **1b**. Anellated 1,2-dithiins have been synthesized employing addition of tin hydride to thioalkynes, as in our conversion of **9** to **10**, as a key step.[16c]

Scheme 2: Synthesis of 1,4-Bis(benzylthio)-1,3-butadiyne



(a) *n*-BuLi; S_8; $PhCH_2Br$; (b)*n*-$Bu_4N^+F^-$; (c) Cu_2Cl_2, TMEDA, O_2, Me_2CO

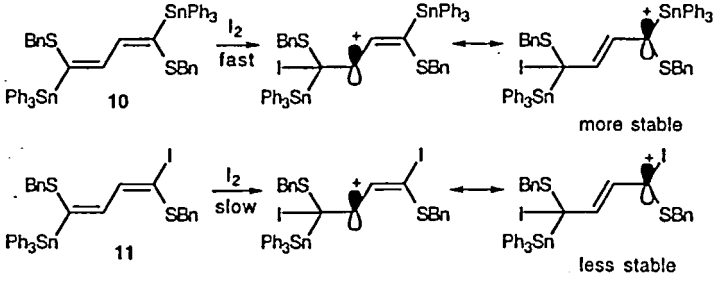
Scheme 3: Total Synthesis of Thiarubrine B



(a) $2Ph_3SnH$, $(Ph_3P)_4Pd$, Et_3B, toluene, -30 to 0 °C, 56%; (b) I_2, CH_2Cl_2, 0 °C, 2 h, 95-97%; (c) TMSC≡CH, CuI-$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 86%; (d) MeC≡CC≡CH, CuI-$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 57%; (e) *n*-Bu_4NF, 86%; (f) CH_2=CHBr, CuI-$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 70%; (g) LDMAN, THF, -80 °C,1.5 h; (h) AcCl; (i) KOH/MeOH; (j) I_2, -30 °C, 17% for four steps.

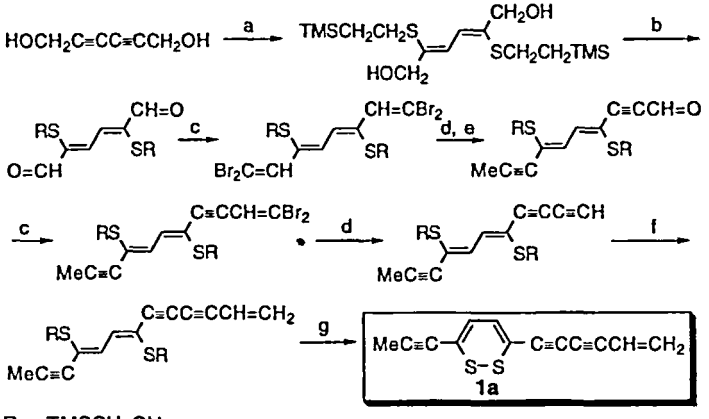
In the course of these studies, a simple synthesis of 1,2-dithiin (**3**) was discovered which entails refluxing 1,4-bis(trimethylsilyl)-1,4-butadiyne with BnSNa, giving (*Z*,*Z*)-1,4-bis(benzylthio)-1,3-butadiene, followed by reductive cleavage and oxidation (Scheme 5).[15] A similar synthesis of **3** was independently developed by Koreeda,[17] who also reported a total synthesis of thiarubrine A (**1a**; Scheme 6).[18] Koreeda's synthesis involves double nucleophilic addition of thiolate to 2,4-hexadiyne-1,6-diol, protection of sulfur with the β-trimethylsilylethyl group (readily removed with fluoride ion), and symmetrical generation of terminal ethynyl groups by a double Corey-Fuchs sequence. The desired unsymmetrical compound was obtained along with symmetrical products. A related approach to 1,2-dithiins uses the base-labile 2-cyanoethyl group for protection of sulfur.[19] Koreeda reports that (*Z*,*Z*)-1,4-bis(tert-butylthio)-1,3-butadiene (**16**), prepared by nucleophilic addition of 2-methyl-2-propanethiol to 1,3-diynes, can be deprotonated, alkylated and then converted to 1,2-dithiins by treatment with iodine, NBS or NIS (Scheme 7).[20]

Scheme 4: Explanation for Differential Rates of Iodinolysis of **10** and **11**



Scheme 5: Simple Synthesis of 1,2-Dithiin

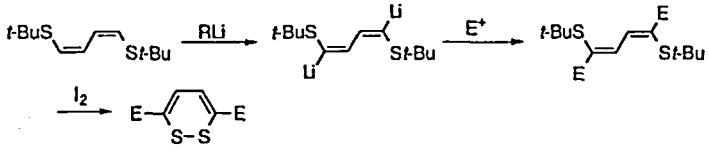
(a) $PhCH_2SNa$, MeOH, reflux, 48 h, 78%; (b) LDMAN, THF, -80 °C,1.5 h; (c) AcCl, 96% (two steps); (d) KOH/MeOH; (e) I_2, -30 °C, 73% (two steps).



R = $TMSCH_2CH_2$

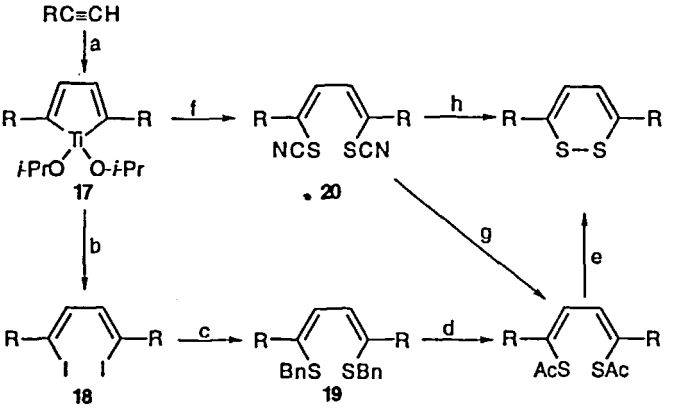
(a) $2TMSCH_2CH_2SH$; (b) Dess-Martin; (c) CBr_4, Ph_3P; (d) BuLi; (e) MeI; DMF; (f) CH_2=CHBr, Pd(0); (g) F^-; I_2

Scheme 7: Synthesis of 3,6-Disubstituted 1,2-Dithiins



The fact that titanacyclopentadienes (**17**, Scheme 8), readily available from terminal alkynes, afford (*Z*,*Z*)-1,4-diiodobutadienes (**18**) when treated with iodine, suggested to us a possible new, simple 1,2-dithiin synthesis. Thus, **18** itself might be directly converted into 1,2-dithiin precursor **19** with the necessary stereochemistry, by replacing the metal with iodine, followed by lithiation and treatment with a sulfur electrophile. Alternatively, this goal might be realized by replacing iodine in the above approach with thiocyanogen, giving **20**. The implementation of these ideas are shown in Scheme 8.[21]

Scheme 8: Titanacyclopentadiene Approach to 1,2-Dithiins



R = *t*-Bu or TMS

a) $Ti(O\text{-}i\text{-}Pr)_4$, *i*-PrMgCl. b) I_2. c) *n*-BuLi; $(BnS)_2$. d) Na/NH_3; AcCl.
e) K_2CO_3, MeOH. f) $(SCN)_2$, CH_2Cl_2. g) $LiAlH_4$; AcCl. h) SmI_2, THF.

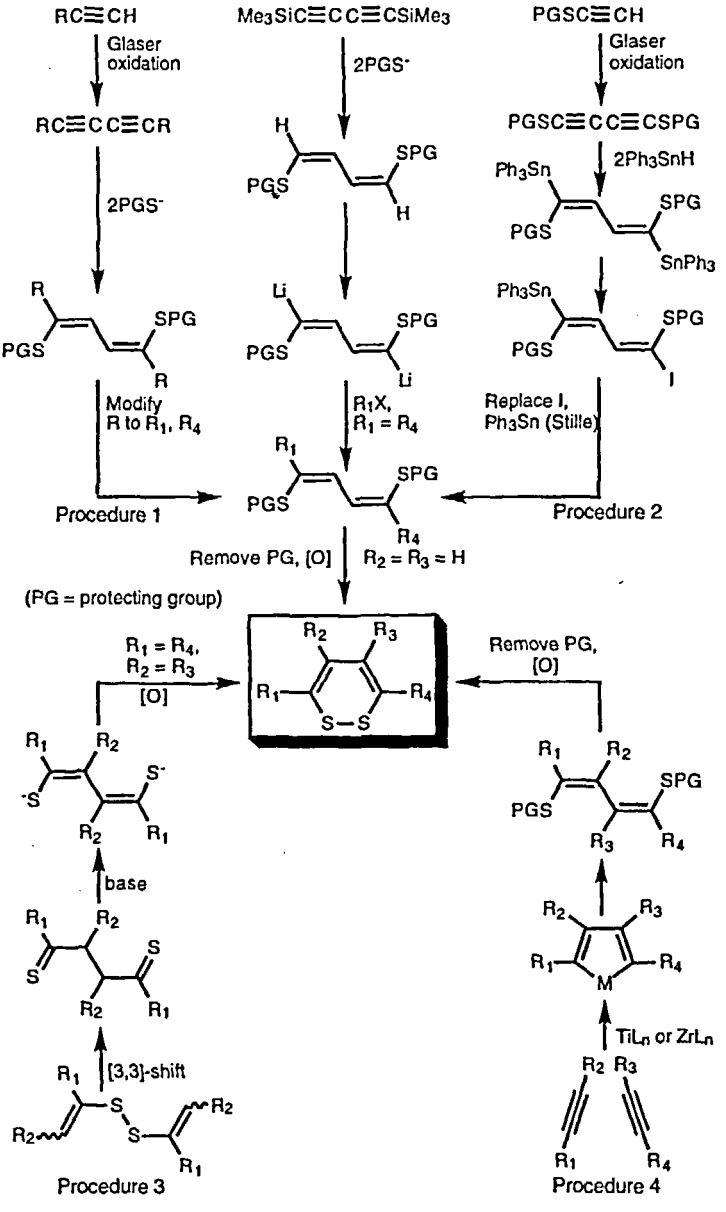
SUMMARY OF SYNTHETIC APPROACHES

Four general synthetic routes to 1,2-dithiins can be identified from the above discussion and are summarized in Scheme 9:

1) Two-fold (anti) nucleophilic addition of thiolate to 1,3-diynes;
2) Two-fold (syn) tin hydride addition to 1,4-dithio-1,3-butadiyne;
3) Dithio-Claisen rearrangement of bis(1-alkenyl) disulfides, then double thioenolization;
4) Dimerization of alkynes to metallocyclopentadienes; retention of double bond stereochemistry by directly replacing metal with sulfur electrophile or by iodine, followed by lithiation/sulfur electrophile or other routes.

A subcategory of procedure 1 involves application to 1,4-bissilyl-1,3-diynes to give (Z,Z)-1,4-bis(*t*-butylthio)-1,3-butadiene followed by double α-lithiation and treatment with electrophiles. While 1,3-diynes are readily available via Glaser-type oxidative coupling of alkynes, only a limited number of 1,3-diynes react twice with thiolate nucleo-

Scheme 9: Summary of Synthetic Approaches to 1,2-Dithiins



philes. The reaction may stop with mono-addition or byproducts may form,[22] limiting the possibilities for double thiolate addition to unsymmetrically substituted 1,3-butadiynes of type RC≡CC≡CR'. Procedure 1 has only been used to prepare precursors to 3,6-disubstituted 1,2-dithiins. Procedure 2 (tin hydride) offers the advantage of regiodifferentiation of substituents introduced into the 3- and 6-positions of 1,2-dithiins. Procedure 3 (thioenolization) is limited to a few special cases, mostly cyclic structures, since the stereochemistry of thioenolization can't be controlled. Procedure 4 offers the prospect of substituting all four ring carbon positions of 1,2-dithiins in a controlled manner utilizing known chemistry of zircona- and titanacyclopentadienes.

While some simple side chain reactions are possible for substituted monocyclic 1,2-dithiins (e.g., acetylation, Williamson ether formation, Dess-Martin oxidation of alcohols to aldehydes),[17] protection of sulfur is required in most syntheses of 1,2-dithiin. Protecting groups must be removable without altering reactive substituents, which is a problem with unsaturated side chains when reductive (e.g. Li/NH_3) deprotection methods are employed.[17,18] Sulfur protecting groups used include benzyl (removed with LDMAN or Li/NH_3),[4,5,14,15,23] carboethoxy (base),[14e] β-trimethylsilylethyl (F^- or NBS),[18,20] β-cyanoethyl (base),[19] *t*-butyl (I_2, NBS, NIS, ArSCl),[20,23e] arylthio (reductive cleavage of one S-S bond),[23e] and cyano (SmI_2 or reductive methods).[21] Various other more serendipitous syntheses of 1,2-dithiins have been reported by routes that cannot be easily generalized.[24] In some of these latter cases[24d,e] it has been established that 1,2-dithiins are in fact not formed[23e] while in other cases the harsh conditions make 1,2-dithiin formation unlikely.[24f,g]

STRUCTURE AND SPECTRA

Microwave and X-ray Structures

The structure of the 1,2-dithiin (**3**; see Scheme 12) in the gas phase was determined by microwave spectroscopy.[25] The molecule has C_2 symmetry corresponding to a twisted conformation about the S-S bond, with dihedral angles ϕ(CSSC) = 53.9° and ϕ(CCCC) = 29.0° bonds length r(S-S) = 2.051(3) Å, r(C-S) = 1.759(4) Å, r(C=C) = 1.353(3) Å, and r(C-C) = 1.451(1) Å, and an electric dipole moment μ_0 = 1.850(1) D. The experimental gas phase structure of **3** is similar to the 1,2-dithiin ring structure found[7,14d,23,26] in anellated 1,2-dithiins and 3,6-(bishydroxymethyl)-1,2-dithiin by X-ray crystallography. For example in the X-ray structures the S–S bond lengths (average value 2.06 Å) are close to the microwave value of 2.05 Å; all the 1,2-dithiin rings have a twisted configuration with ϕ(CSSC) varying from 50.8° to 54.4°, compared to the microwave value of 53.9°. There are larger structural differences in the diene portion of the ring comparing **3** and 3,6-(bishydroxymethyl)-1,2-dithiin (ϕ(CCCC) = 29.0° and 29.9°, respectively) with the annulated 1,2-dithiins (ϕ(CCCC) ranges from 21.45° to 20.2°). The decrease in ϕ(CCCC) makes the the diene portion of the ring more planar, enhancing conjugation with the fused aromatic rings. In the diborneno 1,2-dithiin, ϕ(CSSC) = 46.6° and ϕ(CCCC) = 23.9° and r(S-S) = 2.065 Å.[7] The structure calculated for **3** [27] is in reasonable agreement with experimental results.

NMR and UV Spectra

1,2-Dithiin has ^{1}H and ^{13}C NMR peaks at δ 6.07 (α) and 6.29 (β) ($J_{\alpha\beta}$ = 9.3, $J_{\beta\beta}$ = 5.5, $J_{\alpha\alpha}$ = 1.6 and $J_{\alpha\beta'}$ = -0.1 Hz) and at 119.43 (α) and 129.74 (β), respectively. Thiarubrine A (**1a**; see numbered structure above) has ring protons at δ 6.66 (d, $J_{8,9}$ = 7.0 Hz; H8) and 6.51 (dq, H9) and ring carbons at 118 (C7), 136.1 (C8), 132.3 (C9) and 111

(C10). Thiophene has ^1H and ^{13}C NMR peaks at δ 7.20 (α) and 6.96 (β) ($J_{\alpha\beta}$ = 4.8, $J_{\beta\beta}$ = 3.5, $J_{\alpha\alpha}$ = 2.8 and $J_{\alpha\beta'}$ = 1.0 Hz), at 124.9 (α) and 126.4 (β), respectively, while thiophene A (**2a**) has ring protons at δ 7.27 ($J_{8,9}$ = 4.0 Hz; H8) and 7.05 (H9). The deshielding experienced by thiophene protons compared to those in **3** reflect the aromatic ring current present in the former but absent in the latter. The larger value of $J_{\alpha\beta}$ in **1a** and **3** compared to the value in the analogous thiophenes reflects the twisted six-membered ring conformation [for **3**, ϕ(CCCC) = 29°] present in the former and absent in the planar thiophenes

The UV spectra of **3** (457 nm; log ε 1.98) and 3,6-diphenyl-1,2-dithiin (465 nm, log ε 3.51) can be compared to those of 3,4-benzo-1,2-dithiin (407 nm, log ε 2.48) and colorless dibenzo[c,e][1,2]dithiin (305 nm, log ε 3.46); thiarubrines show UV λ_{max} at 490 (log ε 3.48). The ^{13}C NMR and UV data for **1a** and **3** rule out (*Z*)-2-butenedithione structures since the thiocarbonyl carbon typically shows δ_C 275 ppm and UV λ_{max} at ca. 640 nm.

PHOTOCHEMISTRY

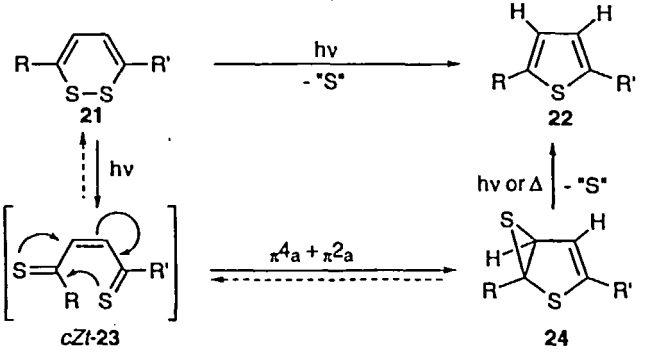
A notable property of 1,2-dithiins is their light sensitivity, with brief exposure to visible or UV light giving the corresponding thiophenes (e.g. **1a** → **2a**).[3] The quantum yield for conversion of 3,6-diphenyl-1,2-dithiin to 2,5-diphenylthiophene is 0.91.[28] Ring opening of 1,2-dithiins to (*Z*)-butenedithione derivatives has been postulated,[2,3,25] and involvement of various valence isomers of 1,2-dithiin in the desulfurization process has been suggested.[23d] As well, direct extrusion of singlet sulfur from **3** is calculated to be disfavored by ca. 80 kcal mol^{-1}.[25] Exposure of **1a** to visible light, leading to desulfurization, results in enhanced biological activity.[9]

Brief irradiation of 1,2-dithiins with visible light at -60 to -75 °C affords in excellent yields 2,6-dithiabicyclo[3.1.0]hex-3-enes (**24**, Scheme 10), a previously unknown class of compounds, identified by

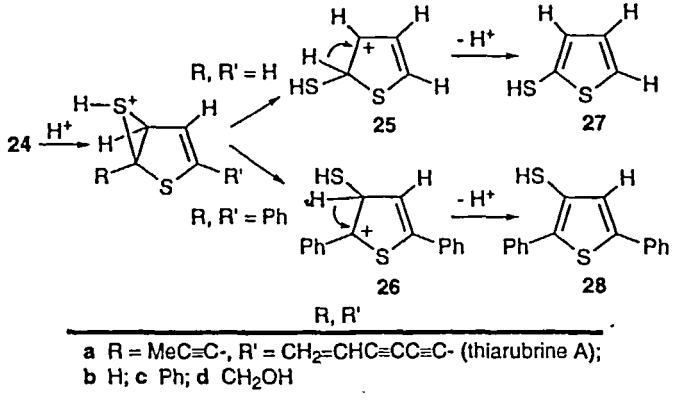
low temperature NMR methods, by LC with a photodiode array detector and by LC-MS. [29] On warming, or on further exposure to light, **24** affords thiophenes **22** and sulfur, while with catalytic acid **24b** and **24c** rearranges to 2- and 3-mercaptothiophenes (**27** and **28**), respectively (Scheme 11). Matrix isolation and flash photolysis techniques were used to identify and determine the lifetime in solution of *s-cis-s-trans*-(Z)-2-butenedithial (*cZt*-**23b**), a presumed intermediate in the formation of **24**, and to define alternative low temperature photochemical pathways available to *cZt*-**23b**, such as rearrangement to thioketene **29** (Scheme 12). We propose that the 2,6-dithiabicyclo[3.1.0]hex-3-ene photoproducts are formed by a thermal $\pi 4_a + \pi 2_a$ rearrangement of the initally photochemically formed (*Z*)-2-butenedithials (**23**). Rearrangement of photoproducts **24b** and **c** to mercaptothiophenes **27** and **28** presumably involves acid catalyzed ring opening giving the most stable carbocation, **25** and respectively.[29]

It is noteworthy that irradiation of unsymmetrically substituted 1,2-dithiins leads to regioselective formation of photoproducts, e.g. **30** → **31a** and not **31b**, **1a** → **32a** favored over **32b**, **1b** → **33a** favored over **33b**, and **1d** → **34a** favored over **34b** (Scheme 13).[30] These obser-

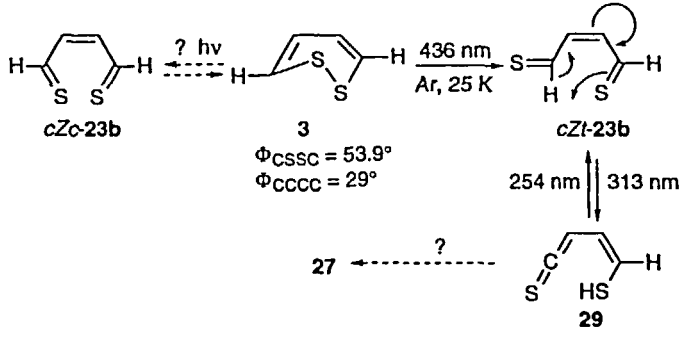
Scheme 10: Photochemical Rearrangement of 1,2-Dithiins



Scheme 11: Acid Catalyzed Rearrangement of 1,2-Dithiin Photoproduct

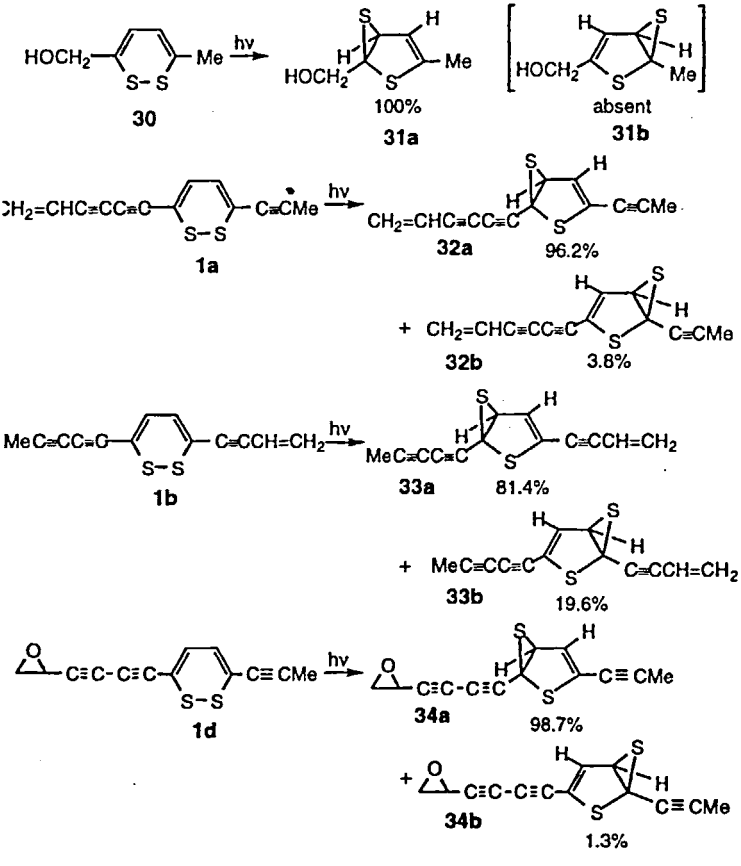


Scheme 12: Matrix Photochemistry of 1,2-Dithiins



vations can be rationalized if it is assumed that in the thermal $\pi 4_a + \pi 2_a$ cyclization of the light-produced (*Z*)-1,4-but-2-enedithiones, like analogous intermolecular $\pi 4_s + \pi 2_s$ cyclizations of thioketones where the HOMO of the diene overlaps with the LUMO of the thioketone, electronic effects on the LUMO of the thioketone are greater than analogous effects on the diene HOMO, and that substituents that lower the LUMO of the thioketone make it a better dieneophile (e.g. $HOCH_2$ better than Me, RC≡CC≡C better than MeC≡C, etc.).[31] It is interesting that deeply colored dibomeno dithiin **8** (λ_{max} 490), which on ring opening cannot achieve the *cZt*-**23** geometry, is stable to light.[14a]

Scheme 13: Regioselective Formation of 1,2-Dithiin Photoproducts



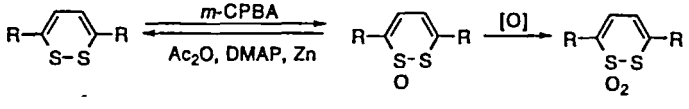
ONE- AND TWO-ELECTRON OXIDATION

Electrochemical oxidation of 1,2-dithiins was studied using cyclic voltammetry.[32] Reversible oxidation occurs at 0.67-0.745 V in CH_3CN and 0.81-0.85 V in CH_2Cl_2 followed by irreversible oxidation at higher potential. For comparison, electrochemical oxidation potentials of 2,5-diphenylthiophene and PhSSPh are 1.13 and 1.34 V, respectively. The lowest gas phase ionization potential of 1,2-dithiin determined by

HeI photoelectron spectroscopy (PES) is 8.16 eV, which is comparable to that of PhSSPh (8.3 eV). The electrochemical oxidation potential of 1,2-dithiin is anomalously low based on its ionization potential (which is only slightly lower than that of PhSSPh). Theoretical calculations suggest that this effect is primarily due to a conformational difference between 1,2-dithiin and its cation radical and dication (the latter two being planar). The time scale of electrolysis allows for flattening of the ring on oxidation while the much shorter time scale of the PES measurement does not.[32] The prominence of M^+ ions in mass spectra of 1,2-dithiins is also consistent with especially stable cation radicals.

Two-electron oxidation of 1,2-dithiins is relatively straightforward using *m*-CPBA or other oxidants. The resulting 1,2-dithiin 1-oxides and 1,1-dioxides are pale yellow compounds which can be reduced back to the 1,2-dithiins using acetic anhydride with DMAP and activated zinc in CH_2Cl_2 at 25° (Scheme 14).[14a,d,27c,33-35] A stable 1,2-dithiin 1,1-dioxide has been prepared by a Diels-Alder route.[36] Oxidation of 3,6-diphenyl-1,2-dithiin with H_2O_2/HOAc gives 1,4-diphenylbutadiene-1,4-disulfonic acid.[4b] Oxidation of unsymmetrical 1,2-dithiins affords pairs of 1,2-dithiin 1-oxides or 1,1-dioxides. Thiarubrine J (**1j**, Figure 1), an *S*-oxide, occurs naturally.

Scheme 14: Oxidation of 1,2-Dithiins



PATENTS

1,2-Dithiin structures and syntheses have been patented because of their potential pharmaceutical applications. Patents include methods for preparing 1,2-dithiins and their precursors,[37a] for synthesizing water-soluble glycosylated 1,2-dithiins,[37b] 1,2-dithiins as antifungal agents,[37c,d], and natural 1,2-dithiins for treatment of candidiasis.[37e]

Acknowledgments

I thank Professor Werner Schroth for sharing unpublished results, warmly thank my coworkers and collaborators, whose names appear in the references, for their many important contributions to this research, and gratefully acknowledge support from NSF, USDA and NIH.

References

[1] J. T. Mortensen, J. S. Sørensen, and N. A. Sørenson, *Acta Chem. Scand.*, **18**, 2392–2394 (1964).

[2] F. Bohlmann and K.-M. Kleine, *Chem. Ber.*, **98**, 3081–3086 (1965).

[3] R. A. Norton, A. J. Finlayson and G. H. N. Towers, *Phytochemistry*, **24**, 356–357 (1985).

[4] a) W. Schroth, F. Billig, and H. Langguth, *Z. Chem.*, **5**, 353–354 (1965); b) W. Schroth, F. Billig, and G. Reinhold *Angew. Chem., Int. Edn. Engl.*, **6**, 698–699 (1967).

[5] W. Schroth, H. Langguth, and F. Billig, *Z. Chem.*, **5**, 352–353 (1965).

[6] Earlier reviews on 1,2-dithiins: a) F. Freeman, D. S. H. L. Kim, and E. Rodriquez, *Sulfur Rep.* **9**, 207–256 (1989). b) F. Balza and G. H. N. Towers, *Methods in Plant Biochem.*, **8**, 551–572 (1993). c) F. Freeman, M. Aregullin, and E. Rodriguez, *Rev. Heteroatom Chem.*, **9**, 1–21 (1993). d) K. Steliou, P.L. Folkins, and D. N. Harpp, in *Advances in Sulfur Chemistry* (E. Block, Ed.), Vol. 1, JAI Press, Greenwich, CT, 1994, p. 114. e) S. M. Ellis, F. Balza, P. Constabel, J. B. Hudson, and G.H. N. Towers, In *Light-Activated Pest Control* (J. R. Heeitz and K. R. Downum, Ed.), ACS Symposium Series 616, ACS, Washington DC, 1995, p. 164–178. f) H. Viola and R. Winkler, *Houben-Weyl*, **E9a** (E. Schaumann, Ed.), 209–249 (1997).

[7] a) C. P. Constabel and G. H. N. Towers, *Phytochemistry*, **28**, 93–95 (1989). b) M. L. Gomez-Barrios, F. J. Parodi, D. Vargas, L. Quijano, M.A. Hjortso, H. E. Flores, and N.H. Fischer, *Phytochemistry*, **31**, 2703 (1991).

[8] G.H.N. Towers, Z. Abramowski, A. J. Finlayson, and A. Zucconi, *Planta Med.*, **51**, 225–229 (1985).

[9] a) C.P. Constabel and G.H.N. Towers, *Planta Med.*, **55**, 35–37 (1989). c) J. B. Hudson, E. A. Graham, R. Fong, A. J. Finlayson, and G. H. N. Towers, *Planta Med.*, **52**, 51–54 (1986). d) J. B. Hudson, E. A. Graham, G. Chen, A. J. Finlayson, and G. H. N. Towers, *Planta Med.*, **52**, 453–457 (1986). b) J. B. Hudson, F. Balza, L. Harris, and G.H.N. Towers, *Photochem. Photobiol.*, **57**, 675–680 (1983).

[10] G. Guillet, B. J. R. Philogéne, J. O'Meara, T. Durst, and J. T. Arnason, *Phytochemistry*, **46**, 495–498 (1997).

[11] E. Rodriguez, M. Aregullin, T. Nishida, S. Uehara, R. Wrangham, Z. Abramowski, A. Finlayson, and G. H. N. Towers, *Experientia*, **41**, 419–420 (1985).

[12] J. E. Page, M. A. Huffman, V. Smith, and G.H.N. Towers, *J. Chem. Ecol.*, **23**, 2211–2226 (1997).

[13] E. Block and S. H. Zhao, *Tetrahedron Lett.*, **31**, 4999–5002 (1990).

[14] a) W. Schroth, E. Hintzsche, R. Spitzner, D. Ströhl, and J. Sieler, *Tetrahedron*, **51**, 13247–13260 (1995). b) M. Bonnat, J.-O. Durand, and M. Le Corre, *Tetrahedron Asymmetry*, **7**, 559–564 (1996). c) P. Salama, M. Poirier, and M. Caissie, *Heterocycles*, **41**, 2481–2485 (1995). d) W. Schroth, E. Hintzsche, H. Viola, R. Winkler, H. Klose, R. Boese, R. Kempe, and J. Sieler, *Chem. Ber.*, **127**, 401–408 (1994). e) W. Schroth, M. Felicetti, E. Hintzsche, R. Spitzner, and M. Pink, *Tetrahedron Lett.*, **35**, 1977–1980 (1994). f) K. Hartke and E. Pfleging, *Liebigs Ann. Chem.*, 933–941 (1988).

[15] E. Block, C. Guo, M. Thiruvazhi, and P.J. Toscano, *J. Am. Chem. Soc.*, **116,** 9403–9404 (1994).
[16] a) P. A. Magriotis, J. T. Brown, and M.E. Scott, *Tetrahedron Lett.*, **32,** 5047–5050 (1991). b) T. Cohen, J. P. Sherbine, J.R. Matz, R. R. Hutchins, B. M. McHenry, and P. R. Willey, *J. Am. Chem. Soc.*, **106,** 3245–3252 (1984). c) W. Schroth, E. Hintzsche, H. Jordan, T. Jende, R. Spitzner, and I. Thondorf, *Tetrahedron*, **53,** 7509–7528 (1997).
[17] M. Koreeda and W. Yang, *Synlett.*, 201–203 (1994).
[18] M. Koreeda and W. Yang, *J. Am. Chem. Soc.*, **116,** 10793–10794 (1994).
[19] D. E. Bierer, J. M. Dener, L.G. Dubenko, R. E. Gerber, J. Litvak, S. Peterli, P. Peterli-Roth, T.V. Truong, G. Mao, and B. E. Bauer, *J. Med. Chem.*, **38,** 2628–2648 (1995).
[20] M. Koreeda and Y. Wang, *J. Org. Chem.*, **62,** 446–447 (1997).
[21] E. Block and C. He, manuscript submitted.
[22] F. Freeman, H. Lu, Q. Zeng, and E. Rodriguez, *J. Org. Chem.*, **59,** 4350–4354 (1994).
[23] a) W. Schroth, E. Hintzsche, M. Felicetti, R. Spitzner, J. Sieler, and R. Kempe, *Angew. Chem., Int. Ed. Engl.*, **33,** 739–741 (1994). b) J. Sieler, E. Hintzsche, and W. Schroth, *Z. Kristallo-gr.*, **208,** 145–147 (1993). c) R. Kempe, M. Pink, E. Hintzsche, and W. Schroth, *Z. Kristallogr.*, **208,** 148–150 (1993). d) M. Tanaka, T. Ishida, T. Nogami, H. Yoshikawa, M. Yasui, and F. Iwasaki, *Bull. Chem. Soc. Jpn.*, **68,** 1193–1199 (1995). e) W. Schroth, S. Dunger, F. Billig, R. Spitzner, R. Herzschuh, A. Vogt, T. Jende, G. Israel, J. Berche, and D. Ströhl, *Tetrahedron*, **52,** 12677–12698 (1996).
[24] a) R. Huisgen, I. Kaalwinsh, J. R. Morán, H. Nöth, and J. Rapp, *Liebigs Ann./Recueil* 1677–1684 (1997). b) K. Hartke and U. Wagner, *Chem. Ber.*, **129,** 663–669 (1996). c) U. Chiacchio, A. Corsaro, A. Rescifina, M.G. Testa, and G. Purrello, *Heterocycles*, **36,** 223 (1993). d) U. M. Dshemilew, F. A. Selimow, W. R. Chafisow, L. M. Chalikow, and G .A. Tolstikow, *Izv. Akad. Nauk SSSR*, 1211–1212 (1986). e) U. M. Dshemilew, N. S. Baibulatowa, T. K. Tkatschenko, and R. W. Kumakowa, *Izv. Akad. Nauk SSSR*, 1918 (1987). f) B. Verkoczy, A. G. Sherwood, I. Safarik, and O.P. Strausz, *Can. J. Chem.*, **61,** 2268–2279 (1983). g) A. Haas, C. Klare, and H.-U. Krächter, *J. Heterocyclic Chem.*, **22,** 1631–1633 (1985). h) H. Behringer and E. Meinetsberger,, *Liebigs Ann. Chem.*, 1729–1750 (1981), *ibid*,315–341 (1982).
[25] J. Z. Gillies, C.W. Gillies, E. A. Cotter, E. Block, and R. DeOrazio, *J. Mol. Spectros.*, **180,** 139–144 (1996).
[26] W. Yang, Ph.D. Dissertation, University of Michigan, Ann Arbor, MI, 1994.
[27] a) M. Mann and J. Fabian, *J. Mol. Struct. (Theochem)*, **331,** 51–61 (1995). b) R. Cimiraglia, J. Fabian, and B.A. Hess, Jr., *J. Mol. Struct. (Theochem.)*, **230,** 287–293 (1991).
[28] Schroth, W.; Jordan, H.; Spitzner, R. *Tetrahedron Lett.* **1995,** *36,*1421–1424 .
[29] a) E. Block, J. Page, J. P. Toscano, C.-X. Wang, X. Zhang, R. DeOrazio, C. Guo, R. Sheridan, and G.H.N. Towers, *J. Am. Chem. Soc.*, **118,** 4719–4720 (1996). b) C.-X. Wang, Ph.D. Dissertation, University of Nevada-Reno, Reno, NV 1995. c) X. Zhang, Ph.D. Dissertation, SUNY-Albany, Albany, NY 1997.
[30] J. E. Page, E. Block and G.H.N. Towers, manuscript submitted.
[31] E. Block, J.E. Page, X. Zhang, R. Sheridan, and G.H.N. Towers, manuscript in preparation.
[32] R. S. Glass, J. R. Pollard, T. B. Schroeder, D. L. Lichtenberger, E. Block, R. DeOrazio, C. Guo, and M. Thiruvazhi, *Phosphorus, Sulfur Silicon Relat. Elem.*, **120/121,** 439–440 (1997).
[33] Y. Wang and M. Koreeda, *Synlett,* 885–886 (1996).
[34] W. Schroth, H. Jordan, and R. Spitzner, *Tetrahedron Lett.*, **36,** 1421–1424 (1995).
[35] F. Balza and G.H. N. Towers, *Phytochemistry,* **29,** 2901–2904 (1990).
[36] J. C. Meslin, Y. T. N'Guessan, H. Quiniou and F. Tonnard, *Tetrahedron,* **31,** 2679–2684 (1975).
[37] a) E. Block and C. Guo, *US 5, 478, 959,* December 26, 1995. b) M. Koreeda, B. K. Shull, and W. Yang, *US 5, 453,500,* September 26, 1995. c) D. E. Bierer, J. M. Dener, J.

Litvak, and L.G. Dubenko, *US 5, 648,354,* August 15, 1997. d) G. H. N. Towers, R.C. Bruening, F. Balza, Z. A. Abramowski, and I. Lopez-Bazzochi, *US 5, 202,348,* April 13, 1993.