Synthesis and Characterization of Monothiosuccinimides

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The synthesis and characterization are described of a series of monothiosuccinimides. These imides are potentially valuable synthetic intermediates, particularly for the preparation of bile pigments. Also described are the synthesis and unusual chemical and spectral behavior of a monothiomaleimide derivative, whose X-ray crystallographic structure was determined.

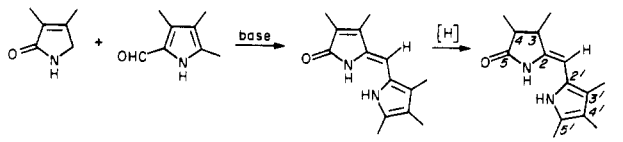
Introduction

In studies directed to the total synthesis of plant bile pigments, improved methods for the construction of variously substituted 3,4-dihydropyrromethenones became imperative. Such intermediates have traditionally been prepared by marginally selective catalytic hydrogenation of the parent pyrromethenone, itself usually made via base-catalyzed condensation of a pyrrolinone and a formylpyrrole (Scheme I).[1-3] This methodology suffers from several drawbacks. The hydrogenation invariably affords a mixture of products resulting from competing reduction at the methine double bond as well as tetrahydro material. The alkaline condensation and reductive conditions are also not compatible with certain desired pyrromethenone substituent patterns, for example the presence of an exocyclic rather than endocyclic double bond at position 3. It would thus be desirable to be in the dihydro oxidation state prior to the coupling reaction. Since pyrrolidinones fail to undergo an analogous coupling reaction with formylpyrroles, the problem centers around devising a completely different ring coupling scheme for the direct generation of dihydropyrromethenones.

Two similar strategies, both involving thioamide chemistry, have been developed to meet these requirements. The first method,[4] an application of sulfide contraction methodology,[5,6] took advantage of the high propensity of a thioamide to undergo S-alkylation. The anion of monothiosuccinimide **1** (Scheme II) was alkylated with bromopyrrole **2**, forming a purported intermediate **3**, which could then be treated with base in the presence of a thiophile to produce the 3-ethylidene-3,4-dihydropyrromethenone **5**. A second method for the synthesis of **5** took advantage of the increased electrophilicity of the sulfur-bearing carbon atom of monothiosuccinimide **1**. Heating **1** and pyrrole ylide **4** together in refluxing toluene produced adduct **5** via a mechanism presumed to be analogous to the Wittig reaction.[7] It had earlier been demonstrated that dioxosuccinimide derivatives undergo Wittig-type alkenylation reactions only under drastic conditions and in low yields,[8] hence the need for activation with sulfur. The thio-Wittig route to **5** was superior to the sulfide contraction pathway both in terms of ease of preparation of the reagents as well as in yield (79% versus 18%).

Our interest in the thio-Wittig reaction centered around the construction of 3,4-dihydropyrromethenones similar to **5**, but differing in the substituent pattern. We recognized early that the success of this coupling reaction was

Scheme I



Scheme II

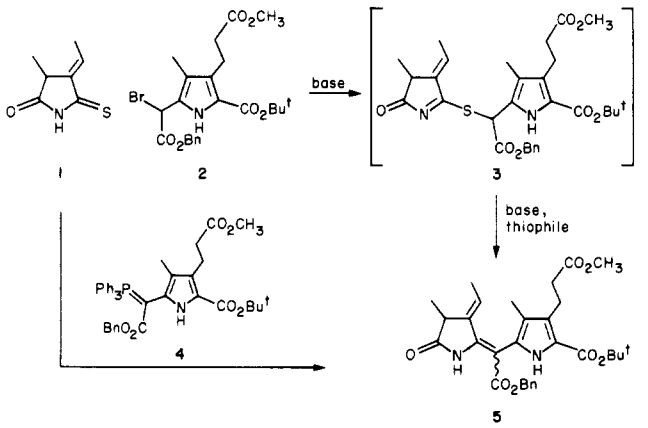
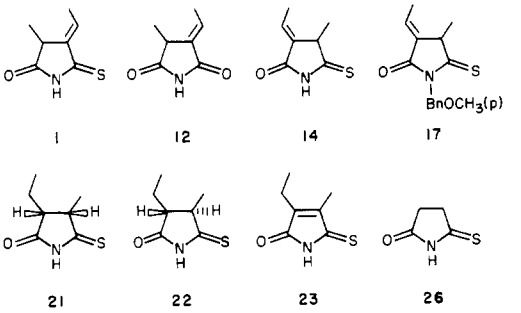


Chart I. Succinimides in Model Study



directly related to the type and position of the substituents attached to the monothiosuccinimide component. When combined with the rather limited literature precedence for the thio-Wittig reaction,[7,9] these peculiarities led us to initiate a comprehensive model study. Our goals were first to experimentally define the structure–reactivity relationships for a series of educts of potential value in tetrapyrrole synthesis, and second to develop a mechanistic

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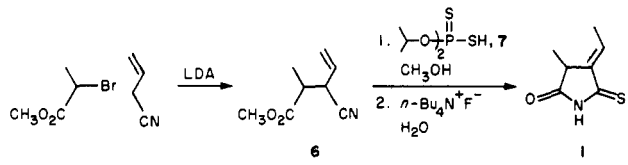
Scheme III



rationale for the reaction and thus to broaden its synthetic applicability.

To meet these goals, we have synthesized a structurally diverse array of succinimides and monitored their reactivity with certain ylides. The surprisingly divergent pattern of reactivity has been correlated to a MNDO[10] analysis of the reaction. We now report the synthesis and characterization of monothiosuccinimides used in the model study; examination of their reactivity toward phosphorus-based ylides will appear in a future communication.[11]

Results and Discussion

The succinimides used in this study are shown in Chart I. Compound **1**, which was shown to successfully couple to ylide **4**,[7] was included to serve as a control. Dioxosuccinimide **12** was also included because it is the direct oxo analogue of **1**. Regioisomer **14**, with transposed methyl and ethylidene groups, was envisioned as a possible precursor to the C/D-ring systems of dilinked bilipeptides.[12,13] The possibility of enhancing thio-Wittig reactivity by protecting the nitrogen atom was also explored, with the *p*-methoxybenzyl (PMB) group, an oxidatively removable amide nitrogen protecting group,[14] as in imide **17**. *cis*- and *trans*-dihydromonothiosuccinimides **21** and **22** were chosen to investigate the roles of unsaturation and stereochemistry. To further define electronic effects, we synthesized monothiomaleimide **23**, in which the double bond now places the thiocarbonyl in conjugation with the electron-withdrawing amide group. For compounds **21**, **22**, and **23**, the regioisomers with the methyl groups adjacent to the thiocarbonyl centers were chosen in order to minimize any steric interactions. Finally, unsubstituted monothiosuccinimide **26** was synthesized in order to correlate the present results with some earlier observations.[9a,b]

The synthesis of (*E*)-2-ethylidene-3-methyl-1-monothiosuccinimide (**1**) has been previously described via two routes. The first involved thiolation with H_2S of an imidate generated from a maleimide derivative.[4] With citraconic acid as the starting material, this nonregiospecific, five-step synthesis afforded a 3% yield of monothiosuccinimide **1**. The second method involved H_2S thiolation of an amidine derivative derived from the alkylation of methyl 2-bromopropionate with diethyl cyanomethylphosphonate.[7] This five-step sequence is reported to result in a 26% overall yield of **1**; however, in our hands, yields were considerably lower.

Scheme III illustrates our two-step route to **1**. The anion of allyl cyanide, generated by treatment with lithium diisopropylamide, was treated with a slight excess of methyl 2-bromopropionate.[15] A complex mixture of products resulted, including **6**, double bond isomers of **6**, a large quantity of unreacted methyl 2-bromopropionate, and oligomers. A much cleaner reaction mixture was obtained by an inverse addition procedure in which the anion of allyl cyanide was added with monitoring of the internal temperature to a cooled solution of the electrophile. After quenching followed by concentrating the organic extracts, a red-colored liquid representing a 92% yield was obtained. The ^1H NMR spectrum was remarkably clean, showing the two diastereomers of **6** and only a trace of double bond isomers. A small (6%) amount of bromine-containing material could be removed by Kugelrohr distillation; however, these thermal conditions resulted in extensive losses as well as double-bond isomerization. Since distilled and undistilled samples of **6** provided comparable yields of **1** in the subsequent reaction, the undistilled, slightly impure material was routinely used.

Numerous methods exist for the conversion of nitriles to thioamides, typically employing vigorous conditions and frequently involving prior conversion of the nitrile to imidate, amidine, or amide derivative. In nitrile **6** a readily isomerized double bond and a hydrolytically labile ester severely restrict application of most of these methods. Although yields were generally low, the *O,O'*-dialkylphosphorodithioic acids, $(RO)_2P(S)SH$, were found to give the best and most reproducible results. Use of these reagents for this purpose has literature precedence; however, experimental protocols are incompletely described.[16,17]

Considerable experimentation was undertaken with different aryl- and alkyl-substituted phosphorodithioic acids. Also, the recently reported[18] diphenylphosphinodithioic acid was applied to nitrile **6** and gave no thioamide product. Best results were obtained by treating **6** with 135 mol % of *O,O'*-diisopropylphosphorodithioic acid **7** and 135 mol % of methanol for 12 h at 55 °C. After quenching with aqueous tetra-*n*-butylammonium fluoride, extraction, and chromatography, **1** was obtained as a geometrically and analytically pure light yellow solid.

The diisopropyl phosphorodithioic acid **7** was synthesized from P_4S_{10} and isopropyl alcohol by variations of a literature procedure[19] and was stored in a cold (5 °C) desiccator.

Although the yield for the conversion of **6** to **1** is low, the sequence described represents an improvement because of its ease, high product purity, reproducibility, and adaptability to large scale.

Regioisomer **14** was synthesized via the sequence shown in Scheme IV. Alkylative coupling of methyl 2-bromopropionate and methyl acetoacetate gave **8** in 72% yield.[20] Reduction of **8** to lactone **9** can be effected with sodium borohydride[21] or with freshly generated platinum oxide.[22] Eliminative ring opening of lactone **9** has been reported, but without experimental details.[23] Thus, treatment of **9** with potassium hydride afforded pure acid *E*-**10** in 39% yield with a remaining 28% yield of a mixture of geometric

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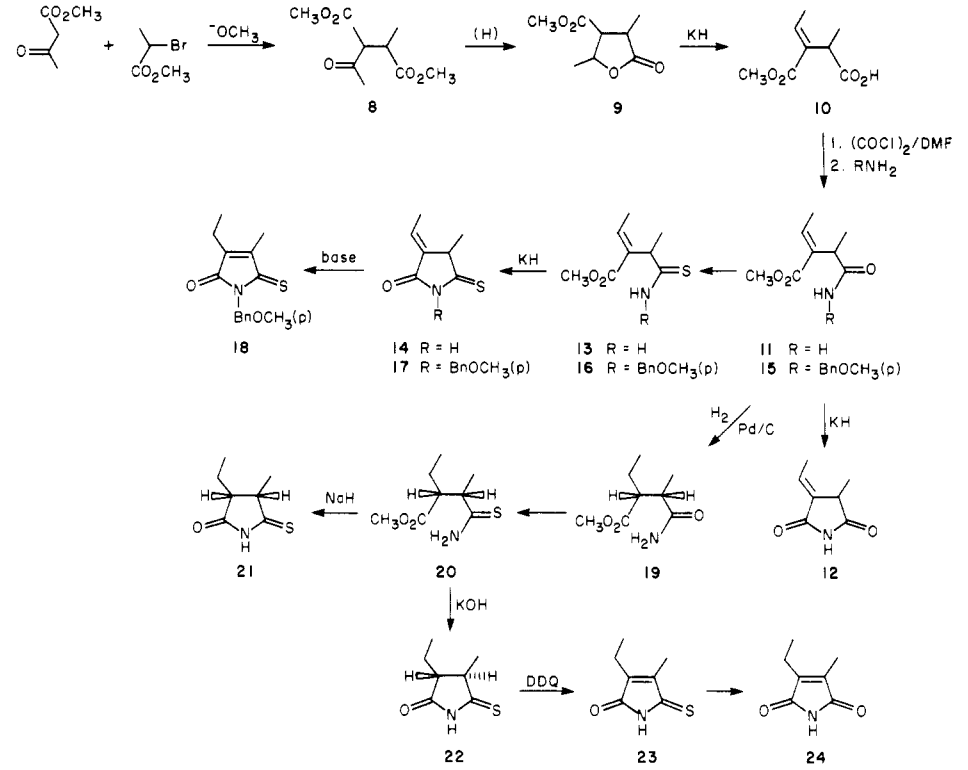
Scheme IV



isomers. Conversion of acid *E*-**10** to the primary amide **11** proceeded through the acid chloride in a temperature-dependent reaction, higher temperatures yielding products resulting from the 1,4-addition of chloride or ammonia.

Dioxosuccinimide **12** was obtained by treatment of intermediate **11** with potassium hydride; the *E* and *Z* isomers were separable by chromatography.

Thiolation of **11** with freshly prepared Lawesson's reagent[24] and subsequent ring closure with potassium hydride gave monothiosuccinimide **14**, which was totally free of the *Z* double bond isomer.

Several attempts were made to introduce the *p*-methoxybenzyl protecting group directly onto the nitrogen atom of succinimide **14** by alkylation with various *p*-methoxybenzyl electrophiles, invariably leading to S-alkylated products. The protecting group had to be introduced earlier in the synthesis, and the *p*-methoxybenzyl-substituted amide **15** was consequently synthesized from acid **10**. Similarly, in a sequence analogous to the production of **14**, the N-protected monothiosuccinimide **17** was generated.

Assignments of double-bond geometry of the four ethylidene succinimides **1**, **12**, **14**, and **17** were made by examining their ^{1}H NMR spectra and applying two previously established criteria.[25] The two geometric isomers were distinguished by the large downfield shift of the vinylic proton in the *E* isomer. All such succinimides showed this resonance at approximately 7 ppm compared with 6 ppm for the *Z* isomers, which were synthesized in parallel from the *E*/*Z* mixture of acid **11**. This difference has been attributed to the deshielding anisotropic effect of the adjacent carbonyl or thiocarbonyl group. The allylic and homoallylic coupling constants are also distinguishable and quite characteristic of *E* or *Z* geometry.[25] The allylic coupling constants for the *E* isomers range from 2.0 to 2.2 Hz while the *Z* isomers consistently show 1.9 Hz. The homoallylic coupling constant difference with the *E* isomers is much greater, 1.0–1.3 Hz, versus 1.7–1.9 Hz for the *Z* isomers.

Saturated succinimides **21** and **22** were obtained by catalytic hydrogenation of the common intermediate **11**. From ^{1}H NMR spectral analysis, succinic amide ester **19** appeared as a single set of diastereomers, hydrogenation being stereoselective and resulting from addition of hydrogen from the side opposite the adjacent methyl group. Thiolation with Lawesson's reagent afforded thioamide **20**, which readily epimerized upon chromatography but could be purified to a single diastereomer by recrystallization. Ring closure with NaH at −22 °C provided the cis dihydro isomer **21**, which, again, easily epimerized. Alternatively, thioamide **20** could be isolated by using aqueous potassium hydroxide, resulting in the trans dihydro diastereomer **22**. Stereochemical assignments were corroborated by comparison of the 2-H/3-H coupling constants with model synthetic 2,3-dihydrobiliverdins, which have an 8.2 Hz coupling constant in the cis isomer and 6.0 Hz in the trans.[3] Succinimides **21** and **22** show this difference as 8.3 and 4.9 Hz, respectively.

Attempts to isomerize exo olefin **14** to maleimide **23** failed under a variety of conditions. Although the corresponding N-protected olefin **17** could be isomerized to its maleimide derivative **18** with alkali, attempted deprotection resulted in complete decomposition. Oxidation of the saturated succinimides **21** or **22**, however, with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) proved successful. Although both succinimides were readily oxidized, preparative quantities of **23** were made via the more readily prepared trans dihydro stereoisomer **22**.

The identity of the product from this oxidation proved to be quite puzzling. After refluxing **22** with DDQ in dry benzene, a spot-to-spot conversion of the yellowish **22** to a purple-colored product was observed by TLC. Upon chromatographic purification a yellowish material similar

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Table I. Crystal and Data Parameters for Monothiomaleimide 23

(A) Crystal Parameters at 25 °C[a,b]	
a, Å	6.3017 (10)
b, Å	7.7199 (10)
c, Å	8.7529 (16)
α, deg	88.234 (11)
β, deg	77.991 (13)
γ, deg	77.979 (11)
V, Å^3	407.3 (2)
crystal size	0.15 × 0.20 × 0.30 mm
space group	$P\bar{1}$
formula weight, amu	155.2
Z, 4	
d_{calcd}, g/cm^3	1.27
μ_{calcd}, cm^{-1}	3.2

(B) Data Measurement Parameters

radiation: Mo Kα (λ = 0.710 73 Å)
monochromator: highly oriented graphite
detector: crystal scintillation counter, with PHA
reflections measured: $+H,\pm K,\pm L$
2θ range: 3 → 45 deg
scan type: $\theta - 2\theta$
scan width: $\Delta\theta = 0.80 + 0.35 \tan\theta$
scan speed: 1.20 → 6.70 (θ, deg/min)
background: measured over 0.25*, ($\Delta\theta$) added to each end of the scan
vertical aperture: 4.0 mm
horizontal aperture: 3.0 + 1.0 tan θ mm
number of reflections collected: 1070
number of unique reflections: 1070
intensity standards: (223), (125), (333); measured over 1 h of X-ray exposure time. Over the data collection period no decrease in intensity was observed.
orientation: three reflections were checked after every 200 measurements. Crystal orientation was redetermined if any of the reflections were offset by more than 0.10° from their predicted positions. Reorientation was performed once during data collection.

[a] Unit cell parameters and their esd's were derived by a least-squares fit to the setting angles of the unresolved Mo Kα components of 24 reflections with 2θ between 24° and 32°. [b] The esd's of all parameters are given in parentheses, right-justified to the least significant digit(s) of the reported value.

in R_f to **22** and a lower R_f UV active spot (**24**) quickly developed. This transformation occurred much more slowly if a rapid flash chromatography was performed followed by immediate concentration and storage of the purple solid residue in the cold. Sublimation of the residue in the dark afforded purple crystals, which, upon elemental analysis, had an empirical composition consistent with **23**. However, fast atom bombardment (FAB) mass spectral analysis showed a strong peak at twice (311) the anticipated parent molecular ion peak (156). Combined with its unusual instability and its unusual electronic spectrum, namely, the presence of a visible absorbance peak at 516 nm, a number of symmetrical, dimerized forms of **23** were considered as possible product structures.

Structural Examination of Monothiomaleimide 23. To distinguish monomer from a symmetrical dimer, crystals suitable for X-ray crystallographic analysis were obtained by slow sublimation at 0.01 mm and 23 °C in the dark, affording purple crystals, which were immediately mounted and coated with black paint. This procedure minimized the compound's exposure to incident light, a factor associated with its decomposition.

The X-ray crystal structure confirmed the identity of monomer **23**. Crystal and data collection parameters are given in Table I. The ORTEP stereodrawing[26] of **23** is

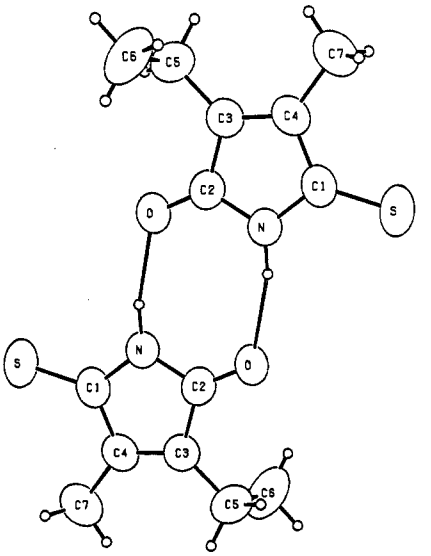

Figure 1. ORTEP stereodrawing of hydrogen-bonded monothiomaleimide **23** (arbitrary numbering scheme).

Table II. Selected Bond Length and Bond Angle Values for Monothiomaleimide 23 Derived from X-ray Crystallography (Arbitrary numbering, corresponding to that in Figure 1)

bond lengths	Å[a]	bond angles	deg[a]
C1–S	1.622 (2)	S–C1–N	125.66 (16)
C1–N	1.373 (2)	S–C1–C4	128.09 (15)
C1–C4	1.479 (3)	N–C1–C4	106.25 (16)
C2–O	1.218 (2)	O–C2–N	124.72 (19)
C2–N	1.386 (2)	O–C2–C3	128.72 (19)
C2–C3	1.480 (3)	N–C2–C3	106.56 (16)
C3–C4	1.332 (3)	C1–N–C2	110.46 (17)
C3–C5	1.497 (3)	C2–C3–C4	107.74 (17)
C5–C6	1.492 (4)	C2–C3–C5	121.16 (19)
C4–C7	1.491 (3)	C4–C3–C5	131.01 (19)
		C1–C4–C3	108.99 (17)
		C1–C4–C7	121.57 (19)
		C3–C4–C7	129.44 (20)
		C3–C5–C6	112.48 (19)

hydrogen bond lengths	Å	hydrogen bond angles	deg
N–H(N)	0.950[b]	C2–O–H(N)	124.7
H(N)–O	1.958[b]	O–H(N)–N	165.3
N–O	2.888		

[a] The estimated standard deviations for all parameters are given in parentheses, right-justified to the least significant digits of the reported value. [b] Calculated from the N–O distance.

presented in Figure 1. Bond lengths and bond angles are given in Table II. The crystal structure consists of pairs of molecules held together by hydrogen bonds around a crystallographic center of inversion. The pairs then stack normally in the crystal lattice. Although **23** may exist in a tautomeric form, with the hydrogen atom attached to sulfur, it is clear from the low values of the residual density on the final difference Fourier map that the hydrogen atom resides on nitrogen. Bond distances and angles are consistent with a localized C3–C4 double bond and a delocalized C1–N–C2 portion of the molecule.

The identity of oxidation product **23** was quite surprising for several reasons. Foremost was the anomalous n → π^* absorption. At 516 nm, this transition is considerably longer in wavelength than most thioamides, which typically absorb between 300 and 430 nm.[27] Also strange was the dimerization observed under a variety of FAB mass

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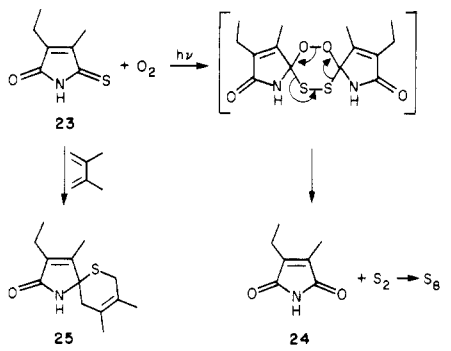
Scheme V. Possible Mechanism for the Conversion of Monothiomaleimide 23 to Dioxomaleimide 24



spectroscopic conditions. Equally perplexing was the short half-life of monothiomaleimide **23**. All of the other thioamides and thiolactams used in this study were stable, usually crystalline, storable substances. When stored in a sealed argon flushed sample vial and placed in a desiccator in the dark, **23** turns from purple crystals to a yellowish solid during the course of several weeks. The change can be accelerated to several hours if the vial is placed on the bench top, exposed to incident fluorescent light. The transformation is even more rapid if the vial is left open. After the disappearance of **23** (TLC), the remaining yellow mass was subjected to flash chromatography. The higher R_f material was identified as molecular sulfur and the low R_f transformation product was identified as maleimide **24**.[25]

The instability of thioketones and thioaldehydes has been well documented. This instability is frequently manifested as oligomerization. It has also been reported that some thioketones can be photooxidized to ketones, an example of which was the transformation of thiobenzophenone to benzophenone using molecular oxygen with concomitant production of elemental sulfur and sulfur dioxide.[28,29] A similar exchange of sulfur for oxygen has been reported for 4*H*-pyran-4-thiones. This reaction, however, required the presence of a sensitizer, methylene blue. It was postulated that singlet oxygen added directly to the thioketone, producing a four-membered ring intermediate, which then collapsed to the ketone and sulfur monoxide.[30] These rather limited observations with thioketones, however, appear to have even less precedent in the thioamide literature.[27,31] The oxidation of thioamides under alkaline conditions with hydrogen peroxide to the corresponding oxo compounds[32] and the photochemical desulfurization of 2-indolinethiones to the corresponding indoles have recently been reported, but even in the presence of atmospheric oxygen, no oxygen-containing products were isolated.[33] No previous examples could be found of the spontaneous conversion of thioamides to amides such as we have observed.

To rationalize this conversion of thioamide **23** to dioxomaleimide **24** we propose that **23** and O_2 react in a 2/1 stoichiometry as illustrated in Scheme V. The dioxodithio six-membered ring intermediate then collapses, forming **24** as well as unstable S_2, which rapidly goes to the more stable S_8. We attempted to detect S_2 in the reaction mixture by trapping it with 2,3-dimethyl-1,3-butadiene to form a dithiacyclohexene, as has been reported,[34] as evidence for S_2 generated from organometallic precursors. For this purpose, the diene was added to a methylene chloride solution of monothiomaleimide **23**, which was kept under oxygen and ambient light. Although the NMR spectrum of the crude product showed minor peaks (3.21, 1.76 ppm) consistent with those reported[34] for the cyclic disulfide (3.21, 1.78 ppm), it could not be isolated. Only minor decomposition to **24** occurred under these conditions, and the major product resulted from addition of the diene to the carbon–sulfur bond of thioamide **23** to form spirocycle **25** (Scheme V) in nearly quantitative yield. Under identical conditions, maleimide **24** was recovered unchanged. Thus the attempt to demonstrate the generation of S_2 was thwarted by the competing reaction of the thioamide **23** with the trapping agent.

The physical and chemical properties of **23** are strikingly similar to those reported for thioketones. This is manifest in the electronic spectrum and as a propensity to dimerize, at least under FAB mass spectroscopic conditions. The observation that monothiomaleimide **23** is so unstable may also explain the absence of reports of thiomaleimides in the literature. This is in marked constrast to the many examples of thiosuccinimides. Should a need for thiomaleimides arise, they might be prepared via stable saturated analogous followed by an oxidative step analogous to the route described.

The remaining succinimide used in the model study, monothiosuccinimide (**26**), was prepared by adding an excess of succinimide to a solution of Lawesson's reagent.

Experimental Procedures

General Methods. P_4S_{10} was purified by soxhlet extraction into CS_2. THF and Et_2O were distilled from Na/benzophenone; acetonitrile, benzene, DMF, diisopropyl amine, toluene, anisole, and isopropyl alcohol were distilled from CaH_2; methanol was distilled from its magnesium salt; final isolation organic solvent solutions were dried over Na_2SO_4. Kieselgel 60 F_{254} plates (E. Merck) were used for thin-layer chromatography while 230–400 mesh silica gel 60 (E. Merck) was used for low-pressure chromatography. Melting points were determined on an open capillary Büchi apparatus, and both melting and boiling points are uncorrected. All NMR spectra were recorded in $CDCl_3$, and chemical shifts are in parts per million (ppm) downfield from internal tetramethylsilane. The $CDCl_3$ peak was calibrated to 77.0 ppm for ^{13}C NMR spectra. ^1H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sep, septet; m, multiplet), number of protons, coupling constant(s) in hertz. Analytical high-performance liquid chromatography (HPLC) was done on a Whatman 9.4 (i.d.) × 150 mm Partisil column (10 μm) in series with a HC Pellosil precolumn (5 × 100 mm), at a flow rate of 3.0 mL/min.

X-ray crystallography was performed at the Chexray Facility and elemental analyses were performed at the Microanalytical Laboratory of the Chemistry Department, University of California, Berkeley, CA.

Methyl 3-Cyano-2-methyl-4-pentenoate (6). To 272 mL of THF and 28.0 mL (0.20 mol) of diisopropylamine at 0 °C was added 132 mL of 1.52 M *n*-butyllithium (100 mol %) dropwise such that the internal temperature did not exceed 5 °C. After addition was complete, the solution was allowed to stir for 20 min at 0–3 °C and then was cooled to −74 °C. Allyl cyanide (16.1 mL, 100 mol %) was then added to the reaction mixture while the internal temperature was maintained at −70 ± 5 °C, and the solution was stirred at −74 °C for an additional 30 min. This solution was added dropwise to 128 mL of THF and 21.2 mL (95 mol %) of methyl 2-bromopropionate cooled to −74 °C such that the internal temperature did not exceed −70 °C. Transfer took

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approximately 40 min, and the mixture was then allowed to stir at −76 °C for 3 h.

The dark red solution was transferred to a separatory funnel, 500 mL of 1 M H_3PO_4 was added, the organic layer was separated, and the aqueous phase was washed with Et_2O (5 × 100 mL). The combined organic layers were washed with 1 M H_3PO_4 (1 × 100 mL), saturated $NaHCO_3$ (1 × 100 mL), H_2O (1 × 100 mL), and saturated NaCl (1 × 100 mL), dried over Na_2SO_4, filtered, and evaporated, leaving 26.82 g (92%) of a dark red liquid. ^1H NMR analysis showed that this residue consisted mainly of a 1/1 mixture of diastereomers of **6**; however, trace amounts of the ethylidene double bond isomers were also present:[7] ^1H NMR (500 MHz) δ 5.71 (m, 1 H, J = 17.0, 10.1, 5.8), 5.53 (dd, 0.5 H, J = 4.5, 1.3), 5.50 (dd, 0.5 H, J = 4.5, 1.4), 5.40 (d, 0.5 H, J = 11.0), 5.37 (dd, 0.5 H, J = 10.2, 1.2), 3.75 (s, 3 H), 3.74 (m, 1 H), 2.88 (dquin, 0.5 H, J = 7.1, 1.0), 2.71 (quin, 0.5 H, J = 7.0), 1.37 (d, 1.5 H, J = 7.0), 1.30 (d, 1.5 H, J = 7.1); high-resolution EI MS calcd for $C_8H_{11}N_1O_2$ (M^+) 153.0790, found 153.0794.

This slightly impure material was used directly in the next reaction but could be further purified by Kugelrohr distillation (1 mm, 45–100 °C), yielding 20.23 g of a yellowish liquid, followed by a more careful fractional distillation. The fraction boiling at 50–55 °C (0.2 mm) was collected, yielding 4.7 g (16%) of a pure, clear liquid. In addition to substantial product decomposition, this purification also resulted in significant double-bond isomerization.

***O,O'*-Diisopropylphosphorodithioic Acid (7).**[19] To 28.57 g (64.3 mmol) of P_4S_{10} in 60 mL of toluene was added isopropyl alcohol (39.4 mL, 800 mol %) at 2.1 mL/min. The temperature was raised to 105–112 °C for 3.25 h, and then the solution was cooled to room temperature, filtered, and evaporated. The residue was purified by Kugelrohr distillation (1.0 mm, 80–110 °C), affording 42.83 g (78%) of a clear liquid (lit.[19] bp 72–74 °C, 0.3 mm): ^1H NMR (250 MHz) δ 4.91 (sep, 1 H, J = 6.3), 1.38 (d, 6 H, J = 6.2). Anal. Calcd for $C_6H_{15}O_2S_2P$: C, 33.6; H, 7.1; S, 29.9. Found: C, 34.3; H, 7.0; S, 29.4.

Exposure to air resulted in discoloration and loss of sulfur; storage was possible in a desiccator at 5 °C for prolonged periods without significant decomposition.

(*E*)-2-Ethylidene-3-methyl-1-monothiosuccinimide (1). A mixture of 27.3 g (178 mmol) of crude nitrile **6**, 51.6 g (135 mol%) of *O,O'*-diisopropylphosphorodithioic acid (**7**), and 9.8 mL of methanol was heated at 55 °C for 12 h and then cooled to room temperature. To the dark red reaction mixture was added 547 mL of 35% (wt/wt) aqueous tetra-*n*-butylammonium fluoride (prepared by adding 25.4 mL of 48% (wt/wt) aqueous HF and 41.1 mL of H_2O to 480.3 mL of 40% (wt/wt) aqueous tetra-*n*-butylammonium hydroxide at room temperature). After stirring for 3 h at room temperature, the solution was extracted with $CHCl_3$ (1 × 400 mL, 4 × 100 mL), and the combined organic layers were washed with saturated NaCl (1 × 150 mL), dried over Na_2SO_4, filtered, and evaporated, affording 134 g of a viscous red oil. This crude material was adsorbed onto approximately 160 g of silica gel and then applied to a 8 × 20 cm low-pressure chromatography column, which had been previously equilibrated with CH_2Cl_2/Et_2O, 19/1. After elution with CH_2Cl_2/Et_2O, 19/1, the product-containing fractions were evaporated and rechromatographed on a 8 × 20 cm column, eluting with hexane/EtOAc, 3/1. The product was homogeneous by TLC (R_f 0.6 in both CH_2Cl_2/Et_2O, 9/1, and hexanes/EtOAc, 1/1). Upon evaporation, 7.46 g of a red oil was obtained, which solidified on standing. This crude solid, contaminated with a red oil, was triturated in 15 mL of hexanes and 3 mL of Et_2O. After sitting at 5 °C for 18 h, the supernatant liquid was removed, leaving 4.14 g of a dark yellow solid, which was further purified by repeating the hexanes/Et_2O wash, affording 2.51 g of an analytically pure light yellow solid, mp 116–117 °C (lit.[4] mp 113–115 °C). The product could be readily sublimed at 0.2 mm (80 °C): ^1H NMR (500 MHz) δ 8.94 (br s, 1 H), 7.15 (dq, 1 H, J = 7.5, 2.0), 3.41 (br q, 1 H, J = 7.6), 1.94 (dd, 3 H, J = 7.5, 1.0), 1.46 (d, 3 H, J = 7.5); UV–vis (MeOH) λ_{max} (log ε), 201, 272 nm (3.9). Anal. Calcd for C_7H_9NOS: C, 54.2; H, 5.8; N, 9.0. Found: C, 54.0; H, 5.9; N, 8.9.

Methyl 3-(Methoxycarbonyl)-2-methyl-4-oxopentanoate (8). To 250 mL of dry methanol was added 17.1 g (0.74 mol) of freshly cut sodium. After hydrogen evolution had ceased, 93 mL (100 mol %) of methyl acetoacetate was added, and the mixture was stirred for 30 min. Methyl 2-bromopropionate (186 mL, 100 mol %) was then added dropwise, and after addition was complete, the mixture was brought to reflux for 3 h. The solution was then evaporated, 200 mL each of H_2O and Et_2O were added, and the layers were separated. The aqueous phase was washed with Et_2O (2 × 100 mL), and the combined organic layers were washed with saturated NaCl (2 × 100 mL) and evaporated, and the residue was fractionated through a 6-cm platinum mesh column. The fraction boiling at 100–114 °C (2 mm) was collected providing 121.0 g (80%) of a clear liquid (lit.[20] bp 146 °C (30 mm)): ^1H NMR (250 MHz; mixture of two sets of diastereomers) δ 3.83–3.90 (m, 1 H), 3.76 (s, 1.5 H), 3.73 (s, 1.5 H), 3.69 (s, 1.5 H), 3.67 (s, 1.5 H), 3.24 (m, 1 H), 2.30 (s, 1.5 H), 2.28 (s, 1.5 H), 1.21 (d, 1.5 H), 1.18 (d, 1.5 H).

2,4-Dimethyl-3-(methoxycarbonyl)-γ-butyrolactone (9). Method A. Keto ester **8** (60.00 g, 0.3 mol) was dissolved in 500 mL of EtOAc, and 0.6 g of freshly prepared platinum oxide[22] was added. The solution was shaken at 45 psi until the consumption of H_2 had ceased; it was then filtered through Celite, and the filtrate was evaporated. The residue was distilled and the fraction boiling at 96–105 °C (1 mm) was collected, yielding 43.94 g (86%) of **9** as a clear liquid.

Method B. Keto ester **8** (105.33 g, 0.52 mol) was dissolved in 200 mL of cold methanol, and portions of sodium borohydride, totaling approximately 30 g (150 mol %), were added with magnetic stirring over 4 h. The reaction was stirred for 2 h, the methanol was evaporated, and 500 mL of EtOAc was added to the residue. After addition of 200 mL of 1 M H_3PO_4, and adjusting the pH to 2 by addition of 85% H_3PO_4, the layers were separated, the aqueous layer was washed with EtOAc (3 × 100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (1 × 250 mL) and saturated NaCl (1 × 100 mL), dried, and evaporated. The residue was distilled as described in method A, yielding 62.7 g (70%) of **9**: ^1H NMR (250 MHz; complex mixture of diastereomers) δ 4.87 (m), 4.5–4.6 (m), 3.79 (s), 3.78 (s), 3.77 (s), 3.76 (s), 3.69 (m), 2.9–3.4 (m), 2.6–2.7 (m), 1.2–1.6 (m). Anal. Calcd for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.8; H, 6.8.

(*E*)-3-(Methoxycarbonyl)-2-methyl-3-pentenoic Acid (*E*-10). Potassium hydride (54.08 g, 35 wt %, in mineral oil suspension, 125 mol %) was washed with hexanes (3 × 150 mL), and then ether (200 mL) and methanol (1 mL) were added. Lactone **9** (64.2 g, 0.38 mol), dissolved in 100 mL of ether, was added dropwise under N_2 with mechanical stirring, and the heterogeneous mixture was refluxed for 4 h, cooled to 0 °C, and quenched by adding 150 mL of 2.5 M H_3PO_4. The solution was then brought to pH 2 with 85% H_3PO_4, the aqueous phase was washed with EtOAc (3 × 200 mL), and the combined organic layers were dried. After evaporation, pure β,γ-unsaturated acid *E*-**10** was obtained as a white powder (25.53 g, 39%) by recrystallization of the resulting residue from EtOAc; an additional 18.26 g (28%) of **10** was obtained from the mother liquors by chromatography (isooctane/EtOAc, 3/1) as a mixture of geometric isomers (*E*/*Z*, 1/1).

^1H NMR (250 MHz; *E* isomer) δ 6.96 (q, 1 H, J = 7.2), 3.74 (s, 3 H), 3.68 (q, 1 H, J = 7.2), 1.86 (d, 3 H, J = 7.2), 1.34 (d, 3 H, J = 7.1). Anal. Calcd for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.9; H, 7.1.

^1H NMR (250 MHz; *Z* isomer) δ 6.23 (dq, 1 H, J = 7.2, 0.8), 3.76 (s, 3 H), 3.51 (br q, 1 H, J = 7.2), 2.06 (dd, 3 H, J = 7.2, 0.5), 1.36 (d, 3 H, J = 7.2).

(*E*)-3-(Methoxycarbonyl)-2-methyl-3-pentenamide (11). To 100 mL of acetonitrile cooled to 0 °C was added 2.0 mL (125 mol %) of oxalyl chloride, followed by 3.5 mL (250 mol %) of DMF. The heterogeneous mixture was stirred for 15 min and cooled to −22 °C, and acid **10** (3.20 g, 18.6 mmol), dissolved in 50 mL of CH_3CN, was added dropwise. After being stirred for 15 min at −22 °C, the mixture was brought to room temperature. A solution containing 1.6 g (500 mol %) of NH_3 in 200 mL of THF was cooled to −76 °C, and the acid chloride solution was added over 5 min. After addition was complete the solution was allowed to warm to room temperature and stirred for 1 h while nitrogen was bubbled through to remove the excess NH_3. The solution was evaporated, the residue was dissolved in 50 mL of $CHCl_3$ and washed with 1 M H_3PO_4 (2 × 25 mL), saturated $NaHCO_3$ (2 × 25 mL), and saturated NaCl (1 × 25 mL), dried, and evaporated. The yellow solid residue was recrystallized from Et_2O/hexanes, resulting in 2.56 g (81%) of *E*-**11**: mp 98–99.5 °C; ^1H NMR (250

MHz, *E* isomer) δ 7.00 (q, 1 H, *J* = 7.3), 5.95 (br s, 1 H), 5.45 (br s, 1 H), 3.76 (s, 3 H), 3.66 (q, 1 H, *J* = 7.2), 1.90 (d, 3 H, *J* = 7.3), 1.38 (d, 3 H, *J* = 7.2). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.6; N, 8.2. Found: C, 56.0; H, 7.6; N, 8.1.

(*E*)-2-Ethylidene-3-methylsuccinimide (12). To potassium hydride (0.84 g, 125 mol %, 35 wt % mineral oil suspension, washed with hexanes, 3 × 10 mL) was added THF (50 mL) followed by 1.00 g (5.84 mmol) of amide **11** as a 1/1 mixture of geometric isomers. The solution was refluxed under N_2 for 24 h, cooled to 0 °C, and then quenched by slowly adding 50 mL of 1 M H_3PO_4. The mixture was extracted with EtOAc (4 × 50 mL), which was washed with 25 mL of saturated NaCl, dried, and evaporated. Chromatography (hexanes/EtOAc, 4/1) of the residue and sublimation (56 °C (0.1 mm)) yielded 0.50 g (62%) of ***E*-12**: mp 101–102 °C (lit.[25] mp 92–95 °C); UV–vis (MeOH) λ_{max} (log ε) 217 (4.2); ^{1}H NMR (500 MHz) δ 9.05 (br s, 1 H), 6.88 (dq, 1 H, *J* = 7.4, 2.2), 3.37 (m, 1 H, *J* = 7.5, 2.2, 1.3), 1.93 (dd, 3 H, *J* = 7.4, 1.3), 1.45 (d, 3 H, *J* = 7.5). Anal. Calcd for $C_7H_9NO_2$: C, 60.4; H, 6.5; N, 10.1. Found: C, 60.2; H, 6.5; N, 10.2.

(*E*)-3-(Methoxycarbonyl)-2-methyl-3-pentenethioamide (13). A solution of amide *E*-**11** (1.86 g, 10.9 mmol), 50 mL of THF, and 1.76 g (40 mol %) of freshly prepared Lawesson's reagent,[24] was stirred for 1 h at room temperature and then evaporated, and the residue was purified by low-pressure chromatography (hexanes/EtOAc, 2/1). Pure ***E*-13** (1.20 g, 59%) was collected as a yellow solid: mp 95–97 °C; ^{1}H NMR (250 MHz, *E* isomer) δ 8.53 (br s, 1 H), 7.83 (br s, 1 H), 6.95 (q, 1 H, *J* = 7.2), 4.20 (q, 1 H, *J* = 7.2), 3.77 (s, 3 H), 1.99 (d, 3 H, *J* = 7.2), 1.51 (d, 3 H, *J* = 7.3). Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.3; H, 7.0; N, 7.5. Found: C, 51.5; H, 6.9; N, 7.3.

(*E*)-3-Ethylidene-2-methyl-1-monothiosuccinimide (14). A suspension of KH (1.84 g, 300 mol %, 35 wt % mineral oil suspension, washed with hexanes, 5 × 10 mL) in THF (10 mL) was cooled to −44 °C, and thioamide **13** (1.00 g, 5.35 mmol) dissolved in 50 mL of THF was added dropwise. The mixture was stirred for 1 h and then brought to room temperature, 50 mL of 1 M H_3PO_4 was added, and the mixture was extracted with ether (5 × 50 mL). The combined organic layers were washed with 50 mL of saturated NaCl, dried, and evaporated to a residue, which was sublimed at 70 °C (0.1 mm) and yielded 0.73 g (88%) of *E*-**14**: mp 95–96 °C; UV–vis (MeOH) λ_{max} (log ε) 204, 228, 282 nm (4.3); ^{1}H NMR (250 MHz, *E* isomer) δ 9.82 (br s, 1 H), 6.82 (dq, 1 H, *J* = 7.4, 2.1), 3.63 (tq, 1 H, *J* = 7.4, 2.0, 1.1), 1.95 (dd, 3 H, *J* = 7.4, 1.1), 1.54 (d, 3 H, *J* = 7.4). Anal. Calcd for C_7H_9NOS: C, 54.2; H, 5.8; N, 9.0. Found: C, 54.3; H, 5.9; N, 8.9.

A mixture of *E*/*Z* isomers was similarly synthesized from the sample of acid **10**, which contained a mixture of geometric isomers: ^{1}H NMR (250 MHz, *Z* isomer) δ 8.63 (br s, 1 H), 6.28 (dq, 1 H, *J* = 7.3, 1.9), 3.52 (br m, 1 H), 2.28 (dd, 3 H, *J* = 7.4, 1.8), 1.50 (d, 3 H, *J* = 7.4).

(*E*)-*N*-(*p*-Methoxybenzyl)-3-(methoxycarbonyl)-2-methyl-3-pentenamide, (15). To a solution of 40 mL of CH_3CN, 1.6 mL of DMF, and 0.6 mL (118 mol %) of oxalyl chloride at −22 °C was added dropwise, over 5 min, *E*-**10** (1.00 g, 5.81 mmol) dissolved in 25 mL of CH_3CN. The mixture was stirred for 20 min at −22 °C, *p*-methoxybenzylamine (2.79 g, 350 mol %) was added dropwise over 3 min, and the mixture was stirred for 5 min at −22 °C followed by 1 h at room temperature. The solvent was evaporated, 100 mL of Et_2O was added, and the solution was washed with 5% aqueous $NaHCO_3$ (50 mL), 1 M HCl (2 × 30 mL), and saturated NaCl (1 × 50 mL) and dried. After evaporation the residue was chromatographed (isooctane/EtOAc, 1/1) and then Kugelrohr distilled (75 °C (0.1 mm)), providing 1.49 g (88%) of *E*-**15** as a viscous yellow oil: ^{1}H NMR (500 MHz) δ 7.17 (d, 2 H, *J* = 8.5), 6.96 (q, 1 H, *J* = 7.2), 6.84 (d, 2 H, *J* = 8.5), 6.21 (br s, 1 H), 4.26–4.44 (m, 2 H), 3.79 (s, 3 H), 3.70 (m, 1 H), 3.69 (s, 3 H), 1.86 (d, 3 H, *J* = 7.2), 1.37 (d, 3 H, *J* = 7.2). Anal. Calcd for $C_{16}H_{21}O_4N$: C, 66.0; H, 7.3; N, 4.8. Found: C, 65.8; H, 7.2; N, 4.7.

(*E*)-*N*-(*p*-Methoxybenzyl)-3-(methoxycarbonyl)-2-methyl-3-pentenethioamide (16). A mixture of amide **15** (1.41 g, 4.84 mmol) and 2.00 g (100 mol %) of freshly prepared Lawesson's reagent in 50 mL of THF was stirred under N_2 for 18 h, the solvent was evaporated, and the residue was chromatographed (isooctane/EtOAc, 1/1) followed by Kugelrohr distillation (75 °C (0.1 mm)). Thioamide **16** was obtained as a yellow oil (0.73 g, 50%). The distillation was found to slowly generate monothiosuccinimide **17** so the material was taken directly into the next step: ^{1}H NMR (250 MHz, *E* isomer) δ 9.17 (br s, 1 H), 7.22 (d, 2 H, *J* = 8.7), 6.89 (q, 1 H, *J* = 7.2), 6.87 (d, 2 H, *J* = 8.7), 4.73 (dq, 2 H, *J* = 21.0, 5.1), 4.32 (q, 1 H, *J* = 7.3), 3.81 (s, 3 H), 3.71 (s, 3 H), 2.00 (d, 3 H, *J* = 7.2), 1.50 (d, 3 H, *J* = 7.3).

(*E*)-*N*-(*p*-Methoxybenzyl)-3-ethylidene-2-methyl-1-monothiosuccinimide (17). Sodium hydride (0.35 g, 300 mol %, 54% active hydride in a mineral oil suspension, washed with 3 × 10 mL of hexanes) in THF (25 mL) was cooled to −44 °C, and thioamide **16** (0.73 g, 2.38 mmol) in 10 mL of THF was added dropwise over 15 min. The solution was stirred for 30 min, quenched with 25 mL of 1 M H_3PO_4, and brought to room temperature. Extraction into Et_2O (4 × 25 mL), drying, evaporation, chromatography (hexanes/EtOAc, 1/1), and Kugelrohr distillation (80 °C (0.1 mm)) yielded 0.56 g (85%) of **17** as an oil: ^{1}H NMR (250 MHz) δ 7.37 (d, 2 H, *J* = 8.6), 6.79 (d, 2 H, *J* = 8.6), 6.79 (m, 1 H, overlapping resonances), 5.06 (s, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.61 (br q, 1 H, *J* = 7.4), 1.91 (dd, 3 H, *J* = 7.4, 1.1), 1.48 (d, 3 H, *J* = 7.4). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.6; H, 6.3; N, 4.9.

A mixture of *E*/*Z* isomers was similarly synthesized from the sample of acid **10**, which contained a mixture of geometric isomers: ^{1}H NMR (250 MHz, *Z* isomer) δ 7.40 (d, 2 H, *J* = 8.5), 6.80 (d, 2 H, *J* = 8.7), 6.28 (dq, 1 H, *J* = 7.4, 1.9), 5.06 (s, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.43 (br q, 1 H, *J* = 7.3), 2.27 (dd, 3 H, *J* = 7.4, 1.7), 1.45 (d, 3 H, *J* = 7.4).

(2*S,3*R**)-3-(Methoxycarbonyl)-2-methylpentanamide (19).** Amide *E*-**11** (3.66 g, 21.44 mmol) was dissolved in 100 mL of EtOAc and hydrogenated at 50 psi in the presence of 0.37 g of 10% Pd/C. The mixture was filtered through Celite and evaporated to yield 3.69 g (99%) of **19** as a white powder: ^{1}H NMR (500 MHz) δ 5.83 (br s, 2 H), 3.71 (s, 3 H), 2.59 (m, 1 H), 2.52 (m, 1 H), 1.61 (m, 2 H), 1.15 (d, 3 H, *J* = 6.8), 0.89 (t, 3 H, *J* = 7.4). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.5; H, 8.7; N, 8.1. Found: C, 55.6; H, 8.7; N, 8.0.

(2*S,3*R**)-3-(Methoxycarbonyl)-2-methylpentanethioamide (20).** Amide **19** (3.69 g, 21.30 mmol), dissolved in 150 mL of THF containing Lawesson's reagent (3.45 g, 40 mol %), was stirred under N_2 for 24 h after which an additional portion of Lawesson's reagent (1.72 g, 20 mol %) was added. After 12 h the mixture was evaporated, chromatographed (isooctane/EtOAc, 6/1), and crystallized from isooctane/EtOAc. Thioamide **20** (0.73 g, 18%) was obtained as a white powder. The mother liquors were concentrated to a yellowish oil (1.31 g, 33%) and were found to contain **20** together with approximately 20% of the epimer. Additional quantities of **20** could be obtained upon enrichment by chromatography followed by recrystallization. Pure **20** epimerized upon exposure to light, heat, or silica gel: ^{1}H NMR (500 MHz) δ 7.43 (br s, 1 H), 7.13 (br s, 1 H), 3.73 (s, 3 H), 2.86 (br quin, 1 H, *J* = 6.7), 2.73 (dt, 1 H, *J* = 9.6, 4.1), 1.6–1.7 (m, 1 H), 1.5–1.6 (m, 1 H), 1.24 (d, 3 H, *J* = 6.6), 0.88 (t, 3 H, *J* = 7.3); high-resolution EI MS *m*/*z* calcd for $C_8H_{15}NO_2S$ (M^+) 189.0824, found 189.0830.

(2*S,3*R**)-3-Ethyl-2-methyl-1-monothiosuccinimide (21).** A suspension of 0.09 g of NaH (230 mol %, 40% suspension in mineral oil, washed with hexanes, 2 × 10 mL, and THF, 2 × 10 mL) in THF (40 mL) was cooled to −22 °C. Pure thioamide **20** (0.13 g, 0.687 mmol), dissolved in 5 mL of THF, was added over 5 min, the mixture was stirred for 1 h at −22 °C, quenched with 20 mL of 1M H_3PO_4, brought to room temperature, extracted into Et_2O (4 × 15 mL), washed with 10 mL of saturated NaCl, dried, and evaporated. Cis monothiosuccinimide **21** was obtained as an orange oil, which epimerized upon chromatography or prolonged exposure to light: yield 0.10 g (93%); ^{1}H NMR (500 MHz) δ 8.13 (br s, 1 H), 3.01 (dq, 1 H, *J* = 8.3, 7.5), 2.80 (dt, 1 H, *J* = 8.1, 6.5), 1.80 (m, 1 H), 1.66 (m, 1 H), 1.27 (d, 3 H, *J* = 7.6), 1.08 (t, 3 H, *J* = 7.4); ^{13}C NMR (126 MHz) δ 217.8, 181.8, 48.9, 47.2, 19.4, 15.4, 12.0; high-resolution EIMS *m*/*z* calcd for $C_7H_{11}NOS$ (M^+) 155.0561, found 155.0566. Anal. Calcd for $C_7H_{11}NOS$: C, 53.5; H, 7.1; N, 8.9. Found: C, 53.3; H, 7.1; N, 8.8.

(2*R,3*R**)-3-Ethyl-2-methyl-1-monothiosuccinimide (22).** A solution of 2.25 g (13.0 mmol) of saturated amide **19** and 3.41 g (65 mol %) of Lawesson's reagent in 100 mL of THF was stirred for 3 h at room temperature. Potassium hydroxide (2.19 g, 300 mol %) in 25 mL of H_2O was added to the reaction mixture, and

the solution was stirred for 30 min and then acidified to pH 2 with 85% H_3PO_4. Extracting into $CHCl_3$ (3 × 100 mL), washing with 50 mL of saturated aqueous NaCl, drying, evaporating, chromatographing (hexanes/EtOAc, 4/1), and subliming (40 °C (0.1 mm)) yielded 3.25 g (88%) of **22**: mp 66–67 °C; UV–vis (MeOH): λ_{max} (log ϵ) 198, 265 nm (4.4); ^{1}H NMR (500 MHz) δ 9.36 (br s, 1 H), 2.80 (dq, 1 H, J = 7.3, 4.9), 2.42 (dt, 1 H, J = 8.0, 5.0), 1.90 (m, 1 H), 1.70 (m, 1 H), 1.47 (d, 3 H, J = 7.2), 1.04 (t, 3 H, J = 7.4). Anal. Calcd for $C_7H_{11}NOS$: C, 53.5; H, 7.1; N, 8.9. Found: C, 53.3; H, 7.1; N, 8.8.

3-Ethyl-2-methyl-1-monothiomaleimide (23). To benzene (45 mL) was added 0.84 g (5.34 mmol) of *trans*-dihydrosuccinimide **22** and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.82 g, 150 mol %, recrystallized from benzene/CH_2Cl_2), and the mixture was refluxed for 12 h in the dark, after which the solution was cooled to room temperature. After the precipitate, which was washed with benzene (2 × 20 mL), was removed, the combined filtrate and washings were evaporated, and the residue was dissolved in EtOAc and chromatographed (hexanes/EtOAc, 1/1). The high R_f purple material was collected, yielding 0.52 g (63%) of **23** as purple plates. A crystal of **23** was grown by slow sublimation at 23 °C (0.01 mm) in the dark and then immediately mounted and coated with black paint for X-ray analysis. The product was very light-sensitive. X-ray crystal structure and data are given in Tables I and II, Figure 1, and the supplementary material: ^{1}H NMR (500 MHz) δ 9.24 (br s, 1 H), 2.39 (q, 2 H, J = 7.6), 2.09 (s, 3 H), 1.15 (t, 3 H, J = 7.6); ^{13}C NMR (126 MHz) δ 202.9, 174.8, 140.8, 136.5, 17.16, 12.4, 10.0; low-resolution FAB MS m/z 311 ($2M^+ + H$), 247 ($2M^+ + H - 2S$), 156 (MH^+); high-resolution EI MS m/z calcd for C_7H_9NOS (M^+) 155.0415, found 155.0404; UV–vis (MeOH) λ_{max} (log ϵ) 202, 293 (4.2) 516 nm (1.1). Anal. Calcd for C_7H_9NOS: C, 54.2; H, 5.9; N, 9.0. Found: C, 54.0; H, 5.9; N, 8.9.

Conversion of 3-Ethyl-2-methyl-1-monothiomaleimide (23) to 3-Ethyl-2-methylmaleimide (24). Upon storage in a sample vial flushed with N_2 and sealed with parafilm, the purple crystalline **23** slowly changed to a yellowish powder, which consisted of a lower and higher spot by TLC (isooctane/Et_2O, 1/1). This transformation could be slowed by storage in a desiccator, in the dark, at 5 °C or accelerated by placing the sample vial in direct sunlight.

The products were purified by chromatography (isooctane/Et_2O, 4/1). The high R_f material was identified as elemental sulfur (Anal. Calcd for S_n: S, 100.0. Found: S, 98.1): low-resolution EI MS m/z 256 (S_8), 224 (S_7), 192 (S_6), 160 (S_5), 128 (S_4), 96 (S_3). The lower R_f material, a white powder, was sublimed (40 °C (0.01 mm)) and was identified as 2-ethyl-3-methylmaleimide (**24**): mp 67–68 °C (lit.[25] mp 66–67 °C); ^{1}H NMR (500 MHz) δ 8.08 (br s, 1 H), 2.41 (q, 2 H, J = 7.6), 1.98 (s, 3 H), 1.15 (t, 3 H, J = 7.6); ^{13}C NMR (126 MHz) δ 172.4, 172.0, 143.3, 137.6, 16.9, 12.5, 8.3; high-resolution EI MS m/z calcd for $C_7H_9NO_2$ (M^+) 139.0633, found 139.0627; UV–vis (MeOH) λ_{max} (log ϵ) 221 (4.2), 272 nm (2.6). Anal. Calcd for $C_7H_9NO_2$: C, 60.4; H, 6.5; N, 10.1; S, 0.0. Found: C, 60.3; H, 6.4; N, 10.0; S, 0.3.

Addition Product 25. 1-Aza-3-ethyl-4,8,9-trimethyl-2-oxo-6-thia-3,4-spiro[4.5]decadiene (25). Monothiomaleimide **23** (200 mg, 1.29 mmol) was dissolved in 10 mL of CH_2Cl_2, and 0.6 mL (400 mol %) of 2,3-dimethyl-1,3-butadiene (stabilized with 100 ppm of hydroquinone) was added. The solution was stirred under O_2 for 7 days at room temperature with continuous exposure to ambient fluorescent light. TLC (EtOAc/hexanes, 1/1) showed only a trace of starting material remaining and one major product (R_f 0.36). After evaporation, the residue was purified by flash chromatography (EtOAc) and sublimation (100 °C (0.1 mm)), affording 280 mg (91%) of **25** as a white solid: mp 169–170 °C; ^{1}H NMR δ 6.74 (br s, 1 H), 3.47 (d, 1 H, J = 16.6), 3.17 (d, 1 H, J = 16.7), 2.78 (d, 1 H, J = 16.1), 2.28 (q, 2 H, J = 7.6), 1.96 (s, 3 H), 1.88 (d, 1 H, J = 16.1), 1.81 (s, 3 H), 1.72 (s, 3 H), 1.09 (t, 3 H, J = 7.6); ^{13}C NMR (126 MHz) δ 172.0, 152.6, 134.6, 125.9, 123.9, 67.0, 41.6, 31.2, 20.5, 19.1, 16.9, 13.0, 10.6; 135° DEPT ^{13}C NMR (126 MHz)[35] δ 41.6*, 31.2*, 20.5, 19.1, 16.9*, 13.0, 10.6. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.8; H, 8.1; N, 5.9; S, 13.5. Found: C, 65.8; H, 8.1; N, 5.9; S, 13.2.

Monothiosuccinimide (26). Succinimide (25.06 g, 0.253 mol) was dissolved in 250 mL of toluene, 20.6 g (20 mol %) of Lawesson's reagent was added, and the mixture was refluxed for 12 h under N_2. The solution was then cooled to 50 °C and filtered, and the filtrate was evaporated. The residue was purified by chromatography (EtOAc) followed by sublimation at 45 °C (0.05 mm), providing 4.80 g of **26** as a yellowish powder: ^{1}H NMR (500 MHz) δ 9.59 (br s, 1 H), 3.16 (t, 1 H, J = 6.9), 2.82 (t, 1 H, J = 6.9); ^{13}C NMR (126 MHz) δ 211.7, 179.5, 39.9, 30.9. Anal. Calcd for C_4H_5NOS: C, 41.7; H, 4.4; N, 12.2. Found: C, 41.7; H, 4.3; N, 12.0.

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Supplementary Material Available: Further crystallographic data for **23** including methods of structure determination, listings of fractional atomic coordinates with their estimated standard deviations, intramolecular distances and angles, least-squares planes, root mean square amplitudes of thermal vibrations, and anisotropic thermal parameters (7 pages). Ordering information is given on any current masthead page.

(35) An asterisk denotes an inverted resonance.